Notes & Notes

For MRCP part I & 11

By

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Always Remember (The Devil is in the Details)

The main Sources of this Notes & Notes

Passmedicine	BMJ OnExamination
PasTest Dedicated to your success	NICE National Institute for Health and Care Excellence
Patient Trusted medical information and support	SIGN
BMJ Best Practice	UpToDate
Medscape	Medical Masterclass The MRCP(UK) revision package from the RCP Part 1 → Part 2 → PACES

The contents

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Neurology

Updated

2017

Contains:

1/ Passmedicine 2017

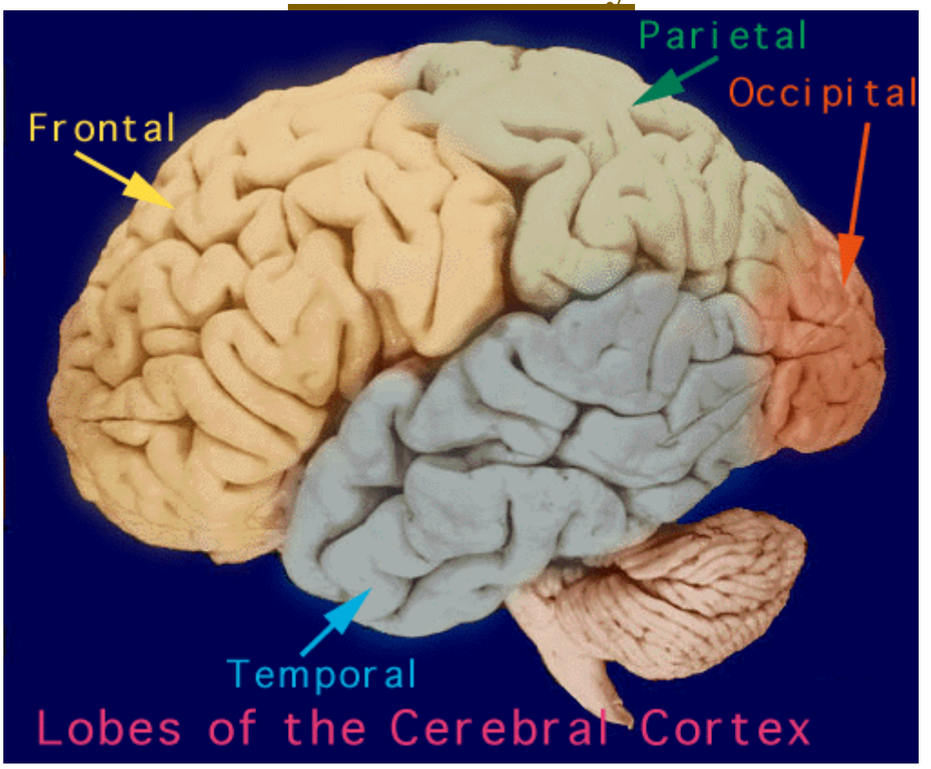
2/ On examination 2017

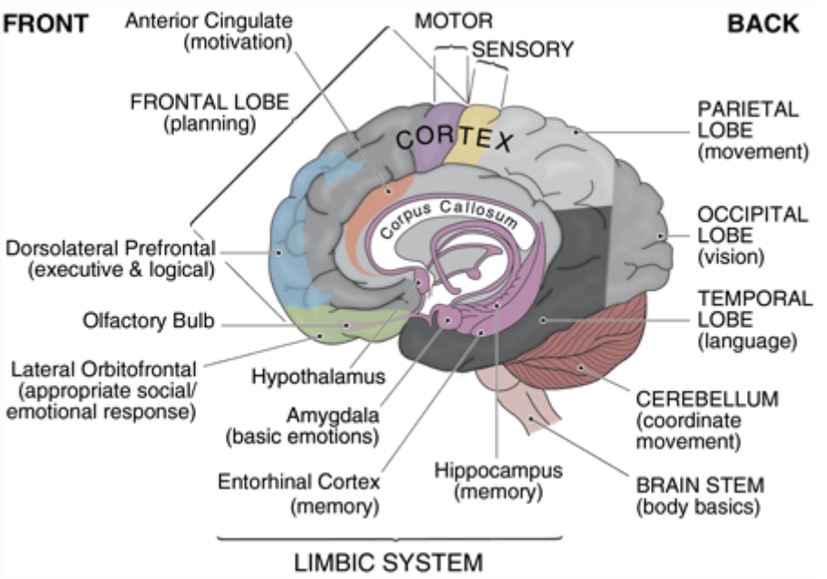
3/ Pastest 2017

4/ **Red fonts --> previous exams**

5/ Other updated UK sources

CNS anatomy


Parietal
Occipital
Frontal
Temporal
Lobes of the Cerebral Cortex


FRONT
BACK
Anterior Cingulate (motivation)
MOTOR
SENSORY
FRONTAL LOBE (planning)
CORTEX
PARIETAL LOBE (movement)
Corpus Callosum
OCCIPITAL LOBE (vision)
Dorsolateral Prefrontal (executive & logical)
Olfactory Bulb
TEMPORAL LOBE (language)
Lateral Orbitofrontal (appropriate social/ emotional response)
Hypothalamus
CEREBELLUM (coordinate movement)
Amygdala (basic emotions)
Entorhinal Cortex (memory)
Hippocampus (memory)
BRAIN STEM (body basics)
LIMBIC SYSTEM

Foramina of the skull

Questions asking about foramina of the skull have come up in the exam in previous years. Below is a brief summary of the major foramina:

Foramen	Bone	Vessels	Nerves
Optic canal	Sphenoid	Ophthalmic artery	Optic nerve (II)
Superior orbital fissure	Sphenoid	Superior ophthalmic vein Inferior ophthalmic vein	Oculomotor nerve **(III)** Trochlear nerve **(IV)** lacrimal, frontal and nasociliary branches of ophthalmic nerve **(V: V_1)** Abducent nerve **(VI)**
Inferior orbital fissure	Sphenoid and maxilla	Inferior ophthalmic veins Infraorbital artery Infraorbital vein	Zygomatic nerve and infraorbital nerve of maxillary nerve (V2) Orbital branches of pterygopalatine ganglion
Foramen rotundum	Sphenoid	-	Maxillary nerve (V2)
Foramen ovale	Sphenoid	Accessory meningeal artery	Mandibular nerve (V3)
Jugular foramen	Occipital and temporal	**Posterior meningeal artery** **Ascending pharyngeal artery** Inferior petrosal sinus Sigmoid sinus Internal jugular vein	**Glossopharyngeal nerve (IX)** **Vagus nerve (X)** **Accessory nerve (XI)**

- **Right jugular foramen lesion:**
  - palatal weakness and swallowing difficulties (**IX/X**),
  - shoulder and sternocleidomastoid weakness (due to accessory nerve (**XI**) involvement.

Anatomy

- **hindbrain** comprises:
  - myel**encephalon** (medulla oblongata and lower part of the fourth ventricle)
    - medulla oblongata opens into the fourth ventricle.
  - met**encephalon** (pons, cerebellum and intermediate part of fourth ventricle), and
  - Isthmus rhomb**encephalon**.
- **Cranial nerve nucleus**
  - All the nuclei except that of the trochlear nerve (CN IV) supply nerves of the same side of the body.
- **nucleus ambiguous**
  - **gives rise to fibres of the glossopharyngeal (IX), vagus (X), and accessory (XI) nerves.**
- **Solitary nucleus**
  - embedded in the **medulla oblongata**,
  - purely sensory nuclei
  - receives inputs from cranial nerves: facial (**VII),** glossopharyngeal **(IX)** and vagus **(X)**.
    - involved in the reflexes initiated through the vagus or glossopharyngeal nerves (e.g., carotid sinus reflex, gag reflex, etc.).
  - specifically receives:
    - **Taste** information from the facial nerve (anterior 2/3 of the tongue), glossopharyngeal nerve (posterior 1/3) and **vagus nerve (small area on the epiglottis)**
    - general visceral sensory inputs from the chemoreceptors in the **carotid body** (via glossopharyngeal nerve) and **aortic body** (via vagus nerve) and baroreceptors in the **carotid sinus** (via glossopharyngeal nerve)
    - general visceral sensory inputs from mechanoreceptors and chemoreceptors located in the heart, lungs and gastrointestinal tract (via vagus nerve).

- **Nucleus locus coeruleus**
  - located in the **pons**
  - involved with the physiological **responses to stress and panic**.
  - the principal site for brain **synthesis of norepinephrine** (noradrenaline).
    - Norepinephrine also released from the adrenal medulla.
  - **Melanin granules** inside the neurons contribute to its **blue colour**.
  - In opiate withdrawal:
    - Opioids inhibit the firing of neurons in the locus coeruleus.
    - opiate withdrawal → increased activity of the locus coeruleus →withdrawal symptoms.
      - **clonidine** (**alpha2** adrenoceptor **agonist**) is used to **counteract this withdrawal** effect by **decreasing adrenergic neurotransmission from the locus coeruleus**

Brain lesions

The following neurological disorders/features may allow localisation of a brain lesion:

Frontal lobes lesions

- Difficulties with task sequencing and executive skills
- Expressive (Broca's) aphasia:
  - located on the posterior aspect of the frontal lobe, in the inferior frontal gyrus.
  - Speech is non-fluent, laboured, and halting
- Disinhibition
- Perseveration
- **Anosmia**
- primitive reflexes (positive grasp, pout and palmomental reflexes)
- inability to generate a list
- Changes in personality.

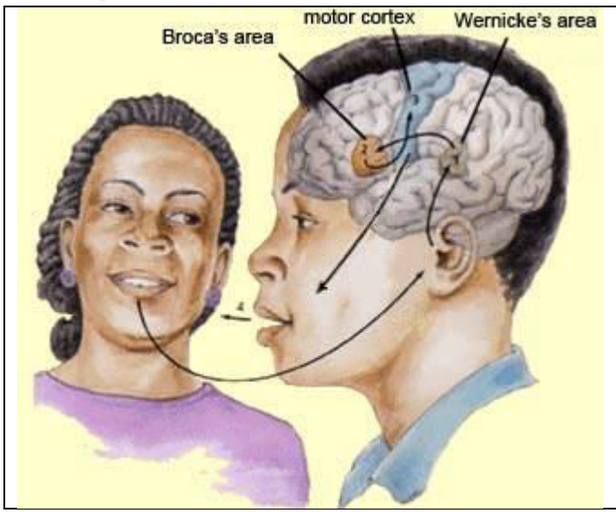
Parietal lobes lesions

- sensory inattention (contralateral hemihypesthesia)
- apraxias
- astereognosis (tactile agnosia)
- **inferior homonymous quadrantanopia**
- Neglect
- mild hemiparesis
- parietal ataxia
- Acalculia (inability to perform mental arithmetic).
- **Gerstmann's syndrome** (lesion of dominant parietal):
  - Alexia (inability to read), acalculia, finger agnosia and right-left disorientation
- unilateral impairment of optokinetic nystagmus.
  - **Optokinetic nystagmus** is a **nystagmus** that occurs in response to a rotation movement. It is present normally.

Visual-spatial awareness deficit

Damage to the right parietal lobe leads to visual-spatial deficits that result in patients being unable to navigate around locations, especially places that are new to them, but also familiar locations.

Temporal lobes lesions



Homonymous quadrantanopias

PITS

(Parietal-Inferior, Temporal-Superior)

- Wernicke's aphasia:
  - this area 'forms' the speech before 'sending it' to Broca's area.
  - Lesions result in word substitution, neologisms but speech remains fluent
- **superior homonymous quadrantanopia**
- auditory agnosia
- prosopagnosia (difficulty recognising faces)
- Memory impairment.

Occipital lobes lesions

- homonymous hemianopia (with macula sparing)
  - may present as **Anton syndrome** where there is blindness but the patient is unaware or denies blindness.
- cortical blindness
- visual agnosia
- visual illusions and elementary visual hallucinations.

May 2010 exam: A patient diagnosed with a glioma in the parietal lobe. Which feature is most likely to develop? Acalculia

Cerebellum lesions

- midline lesions:
  - gait and truncal ataxia
- hemisphere lesions:
  - intention tremor,
  - past pointing,
  - dysdiadokinesis (inability to perform rapid, alternating movements),
  - nystagmus

More specific areas

Area	Associated conditions
Medial thalamus and **mammillary bodies** of the hypothalamus	Wernicke and Korsakoff's syndrome
Subthalamic nucleus of the basal ganglia	**Hemiballism**
Striatum (**caudate nucleus**) of the basal ganglia	Huntington **chorea**
Substantia nigra of the basal ganglia	Parkinson's disease
Amygdala	**Kluver-Bucy syndrome:** • hypersexuality, • hyperorality (insertion of inappropriate objects in the mouth) • hyperphagia, • visual agnosia **increased activation** to the amygdala is associated with **depression**
Hippocampus pathology	**Short term memory impairment** (for example, **Alzheimer's** disease).
Lateral geniculate nucleus pathology	visual field defect.
Red nucleus	**tremor**, which is present both at rest and during action (for example, multiple sclerosis tremor).
Prefrontal cortex damage	**disinhibition** and **problems with social interaction** and judgement and has been implicated in **schizophrenia**. **Left prefrontal cortex → Depression**

The anterior hypothalamic nucleus plays a crucial role in thermoregulation and circadian rhythms. It is situated at the inferior border of the paraventricular nucleus.

Transient ischaemic attack (TIA)

Antiplatelets
- TIA: clopidogrel
- ischaemic stroke: clopidogrel

Definition

- temporary, focal cerebral ischemia that results in brief neurologic deficits **lasting < 24 hours**

Stroke risk assessment

- **ABCD2 prognostic score**
  - **ABCD^2 score** is used to determine the **risk for stroke** in the days **following a (TIA)**
  - This gives a total score ranging from 0 to 7.

	Criteria	Points
A	**A**ge >= 60 years	1
B	**B**lood pressure >= 140/90 mmHg	1
C	**Clinical features** - Unilateral weakness - Speech disturbance, no weakness	 **2** 1
D	**D**uration of symptoms **- > 60 minutes** - 10-59 minutes	 **2** 1
	Patient has diabetes	1

  - **Interpretation of ABCD2 risk score**
    - **If the ABCD2 risk score is 4 or above → high risk of stroke**
      - should have:
        - aspirin (300 mg daily) started immediately
        - specialist assessment and investigation **within 24 hours** of onset of symptoms
        - measures for secondary prevention introduced as soon as the diagnosis is confirmed, including discussion of individual risk factors
  - **If the ABCD2 risk score is 3 or below → low risk of stroke**
    - specialist assessment **within 1 week** of symptom onset, including decision on brain imaging
    - if vascular territory or pathology is uncertain, refer for brain imaging
  - People with crescendo TIAs (two or more episodes in a week) should be treated as being at high risk of stroke, even though they may have an ABCD2 score of 3 or below.
  - The risk for stroke can be estimated from the ABCD2 score as follows:

	2 day risk	7 day risk
Score 1-3 (low)	1.0%	1.2%
Score 4-5 (moderate)	4.1%	5.9%
Score 6–7 (high)	8.1%	11.7%

The Risk of future ischemic stroke after a TIA
- overall **annual** risk is 3–4%,
- **over the next 7 days is 11%**
- over the **following 5 years** is 24–29%.

Ref: emedicine.medscape.com Updated: Sep 11, 2017
https://emedicine.medscape.com/article/1910519-overview

A 77-year-old man presented after a single episode of unilateral weakness of the left arm that lasted for 2 hours. 170/100 mmHg. **What is his chance of having a stroke in the first week? 11%**
Ref: www.mrcpuk.org/ Acute Medicine Specialty Certificate Examination/ sample questions

Investigations (NICE guidelines. Last updated: March 2017)

- **Most specific and sensitive for TIA**
  - **MRI is superior to CT** in detecting the small ischemic lesions occurring after TIA and minor stroke.
    - Identifies ischemia earlier than CT (within 3–30 minutes after onset)
      - Non-contrast cranial CT (gold standard and most important initial imaging **in stroke**):
        - detects acute hemorrhage **but cannot reliably identify early ischemia**
    - CT scanning should only be used if MRI is contraindicated
  - Although the definition of TIA is "a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction," **up to 50% of TIA show ischemic changes in imaging.**
  - MRI findings of ischemia
    - T1: hypointense
    - T2: hyperintense
  - Time of image:
    - $ABCD^2$ score ≥ 4 → urgent brain imaging **within 24 hours** (preferably diffusion-weighted **MRI**)
      - **the most appropriate next step → Admit for MRI neuroimaging, initiate anti-platelet therapy**
    - $ABCD^2$ score ≤ 4 → brain imaging (preferably diffusion-weighted **MRI**) **within 1 week**
- **Duplex ultrasound of carotid stenosis**
  - **the most appropriate next step if bruits in the neck are heard upon auscultation.**
  - If ultrasound is not available, a CTA or MRA may be used.

Treatment

- **Antithrombotic therapy** (2012 Royal College guideline)
  - clopidogrel is recommended first-line (as for patients who've had a stroke)
  - aspirin + dipyridamole should be given to patients who cannot tolerate clopidogrel

2016 Royal College guideline
- Patients with a confirmed diagnosis of TIA should receive clopidogrel (300 mg loading dose and 75 mg daily thereafter) and high intensity statin therapy (e.g. atorvastatin 20-80 mg daily) started immediately.

January 2013 exam: Which factor is most associated with an increased risk of going on to have a stroke in a patient presented with TIA? Duration of his TIA

Stroke

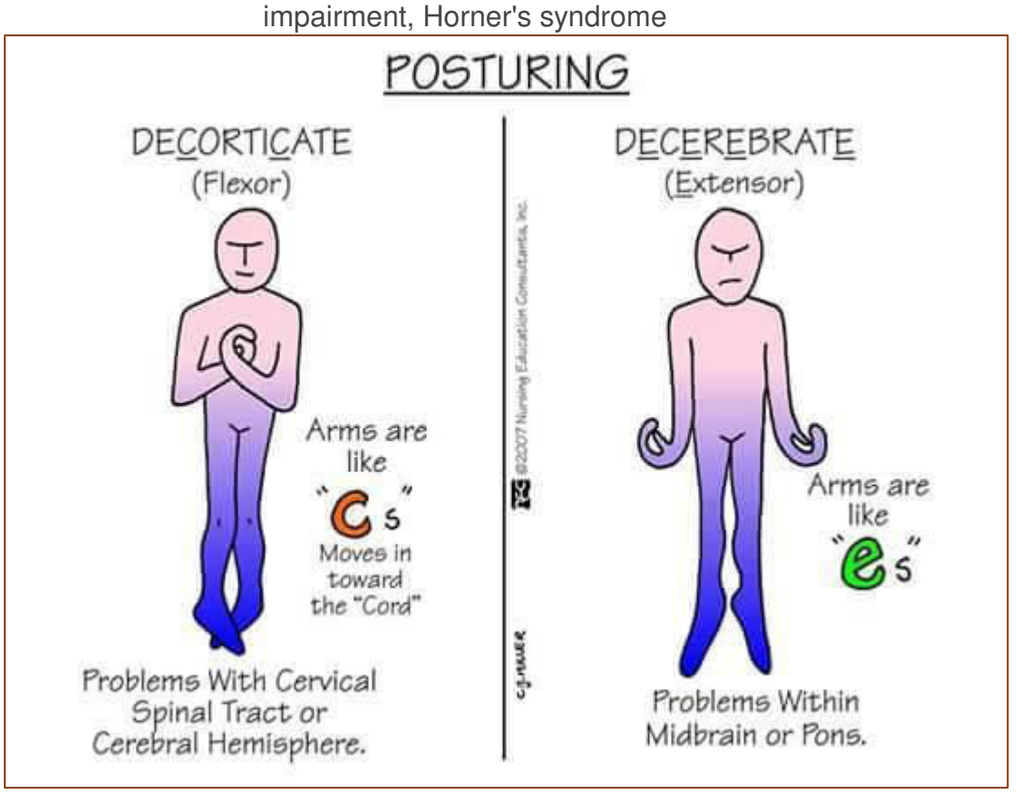
Etiology

- 35% - atherosclerosis of the extracranial vessels (carotid atheroma)
- 30% - cardiac and fat emboli, endocarditis
- 15% - lacunar
- 10% - parenchymal hemorrhage
- 10% - subarachnoid hemorrhage

Presentation

- Edema occurs 2-4 days post-infarct.
- Watch for symptoms
  - decorticate (cortical lesion): flexion of arms
  - decerebrate (midbrain or lower lesion): extension of arms
  - cerebellar: ataxia, nystagmus, abnormal finger-nose and heel-shin

- Other stroke syndromes
  - lateral medullary infarct (Wallenburg syndrome)
    - loss of pain and temp on ipsilateral face and contralateral body, vestibulocerebellar impairment, Horner's syndrome



Imaging

- **CT without contrast** for acute presentation
  - **the next best step in the management of stroke**
  - to rule out hemorrhage
  - Contrast head CT is not used in the diagnosis of acute stroke.
- if the CT is negative → **MRI**, specifically diffusion-weighted imaging and others, is the most widely used.
  - MR studies may show which brain regions are already infarcted and which are at risk of infarction if perfusion is not restored.
  - An acute ischemic stroke is diagnosed by diffusion weighted MRI or by using the clinical history (i.e. don't delay tPA just to get an MRI if there is strong clinical suspicion and no evidence of bleed).

Management

- If an ischemic stroke suspected clinically and CT is negative for evidence of a hemorrhagic stroke, the recommended treatment is to give IV tPA if the presentation is within 3-4.5 hours.
  - Of note, a contraindication to tPA is systolic BP > 185 or diastolic BP > 110 mm Hg.
- For embolic disease and hypercoagulable states give warfarin or aspirin only once the hemorrhagic stroke has been ruled out.

Stroke by anatomy

Site of the lesion	Associated effects
Anterior cerebral artery	Contralateral hemiparesis and sensory loss, **lower extremity > upper**
Middle cerebral artery	Contralateral hemiparesis and sensory loss, **upper extremity > lower** Contralateral homonymous hemianopia Aphasia **(global aphasia)**
Posterior cerebral artery	Contralateral homonymous hemianopia with macular sparing Visual agnosia Other possible findings: • Cortical blindness • Visual hallucinations • Thalamic syndrome, and • Claude's and Weber's syndromes.
Weber's syndrome (branches of the posterior cerebral artery that supply the **midbrain**) **Or branches of the basilar artery**	Ipsilateral CN III palsy Contralateral weakness
Posterior inferior cerebellar artery (**PICA**)(lateral medullary syndrome, **Wallenberg syndrome**) **lesion to dorsolateral medulla**	**Ipsilateral**: facial pain and temperature loss **Contralateral**: limb/torso pain and temperature loss. Ataxia, nystagmus
Anterior inferior cerebellar artery (**lateral pontine syndrome**)	Symptoms are similar to Wallenberg's (see above), but: **Ipsilateral**: facial **paralysis** and **deafness**
Retinal/ophthalmic artery	Amaurosis fugax
Basilar artery	'Locked-in' syndrome

Middle cerebral artery (MCA) occlusion

For individuals aged up to 60 years who suffer an acute MCA territory ischaemic stroke complicated by massive cerebral oedema, surgical decompression by hemicraniectomy should be offered within 48 hours of stroke onset.

- **Divisions**
  - **Superior division**
    - Occlusion of the superior division of the MCA results in:
      - contralateral hemiparesis that affects the face, hand and arm, but spares the leg
      - contralateral hemisensory deficit in the same distribution
      - **no homonymous hemianopia**
      - If the dominant hemisphere is involved, there is also **expressive aphasia**
  - **Inferior division**
    - Occlusion of the inferior division of the middle cerebral artery results in:
      - **contralateral homonymous hemianopia**
      - marked impairment of cortical sensory functions, such as graphaesthesia and stereognosis on the contralateral side of the body
      - disorders of spatial thought, including
        - lack of awareness that a deficit exists (anosognosia)
        - neglect of and failure to recognise the contralateral limbs
        - neglect of the contralateral side of external space

- ⇨ dressing apraxia
- ⇨ constructional apraxia

❖ Involvement of the dominant hemisphere also causes **receptive aphasia**

- ➢ acute confusional state may occur if the non-dominant hemisphere is affected

- **Neurosurgery in treatment of MCA (decompressive hemicraniectomy)**
  - ➢ Current clinical guidelines recommend that patients who are **under 60 years** of age with **large** cerebral infarctions arising in the **MCA** territory should be considered for **decompressive hemicraniectomy.**
  - ➢ **Decompressive hemicraniectomy** involves removing part of the skull in order to reduce intracranial pressure and should be carried out **within 48 hours** of the index event.
  - ➢ **Eligibility** is based on
    1. Clinical and radiological evidence of a stroke affecting this territory,
    2. Radiological evidence that **more than 50% or 145 cm^3 of the MCA territory is involved** and
    3. Being classified as having a moderate to severe stroke according to the National Institute of Health stroke scale.

September 2010 exam: Right sided sensory loss affecting arms more than the legs + right sided homonymous hemianopia. What area is the stroke most likely to have affected?
Middle cerebral artery

Lacunar strokes

Lacunar strokes is defined by one of:

- Unilateral weakness (and/or sensory deficit) of face and arm, arm and leg or all three.
- Pure sensory stroke.
- Ataxic hemiparesis

- The term 'lacune' refers to a small deep infarct resulting from occlusion of a penetrating branch
- Lacunar infarcts occur in areas supplied by small perforating vessels and result from:
  - ➢ atherosclerosis
  - ➢ hypertension
  - ➢ diabetes
- present with either isolated hemiparesis, hemisensory loss or hemiparesis with limb ataxia
- **strong association with hypertension**
- common sites include the basal ganglia, thalamus and internal capsule
- **The putamen is the commonest site for hypertensive intracerebral haemorrhage**

Lateral medullary syndrome

Lateral medullary syndrome - PICA lesion - cerebellar signs, contralateral sensory loss & ipsilateral Horner's

- also known as **Wallenberg's syndrome**,
- occurs following occlusion of the **Posterior Inferior Cerebellar Artery → lesion to dorsolateral medulla**
- **Features**
  - ➢ **Cerebellar features**
    - ▪ ataxia
    - ▪ nystagmus
  - ➢ **Brainstem features**
    - ▪ ipsilateral: dysphagia, facial numbness, cranial nerve palsy e.g. Horner's
    - ▪ contralateral: limb sensory loss
- **Damage to:**
  - ➢ vestibular nucleus → nystagmus and vomiting
  - ➢ inferior cerebellar peduncle → ipsilateral limb ataxia
  - ➢ spinothalamic tract → contralateral loss of pain and temperature sensation
  - ➢ IXth and Xth nerve nuclei → ipsilateral palatal, pharyngeal and vocal cord paralysis
  - ➢ nucleus and tract of the Vth nerve → ipsilateral loss of facial pain and temperature sensation
  - ➢ descending sympathetic fibres → ipsilateral Horner syndrome
- **Diagnosis**

- MRI will be better able to visualise cerebellar infarction.

September 2009 exam: Lateral medullary syndrome is caused by occlusion of which vessel? Posterior inferior cerebellar artery

May 2012 exam: H/O unsteady feet, right-sided Horner's syndrome and horizontal nystagmus, sensory loss on the left side. Where is the lesion most likely to be? Posterior inferior cerebellar artery

Pontine stroke

Diplopia + hemiparesis + lower motor neurone facial nerve lesion → pontine stroke

- Rapidly deteriorating level of consciousness, impaired extraocular movement and extensive sensorimotor deficits are clinical clues to pontine haemorrhage.
- **Decerebrate state is most likely a pontine lesion.**

- **Millard-Gubler syndrome**; a **pontine lesion** that produces:
  - **ipsilateral** VIth and VIIth nerve palsy
  - **contralateral** hemiparesis

Crossed neurological signs (ipsilateral motor and sensory cranial nerve signs and contralateral hemiplegia) → localise to the brainstem (midbrain, pons or medulla).

- **Pons → (ipsilateral abducens and facial nerves palsy, contralateral hemiplegia)**
- **Midbrain → (ipsilateral oculomotor nerve palsy , contralateral hemiplegia)**

Weber's syndrome

- ipsilateral III palsy
- contralateral weakness

Cerebellar haemorrhage

- **The most common symptoms are of severe nausea, vomiting and ataxia.**
- Headache may be severe.
- Patients with cerebellar haemorrhage can rapidly become comatose within hours after the onset from herniation, because of its limited space in the posterior fossa.

Hypoperfusion strokes

- Hypoperfusion tends to cause brain injuries at 'watershed' areas that are border zones between the major cerebral arteries.

Arteries aneurysms

anterior communicating artery aneurysms → The most common aneurysm in circle of Willis

- Most anterior artery communicating aneurysms are asymptomatic unless they rupture, and so they are usually found either incidentally or when a patient presents with SAH.

Posterior communicating artery aneurysm will cause → compression of the third nerve, and therefore : → isolated **ipsilateral painful** third nerve palsy

- Pupillary involvement (pupil dilation) from compression of the parasympathetic fibres that run on the outside of the third nerve
- Other features of a third nerve palsy include ptosis, and a 'down and out' eye.
- Cerebral aneurysms may be associated with polycystic kidney disease.

Stroke: types

- The **Oxford Stroke Classification** (also known as the Bamford Classification) classifies strokes based on the initial symptoms
  - The following criteria should be assessed:
    1. unilateral hemiparesis and/or hemisensory loss of the face, arm & leg
    2. homonymous hemianopia
    3. higher cognitive dysfunction e.g. dysphasia
  - **Total anterior circulation infarcts** (TACI, c. 15%)
    - involves middle and anterior cerebral arteries
    - all 3 of the above criteria are present
  - **Partial anterior circulation infarcts** (PACI, c. 25%)
    - involves smaller arteries of anterior circulation e.g. upper or lower division of middle cerebral artery
    - 2 of the above criteria are present
  - **Lacunar infarcts** (LACI, c. 25%)
    - involves perforating arteries around the internal capsule, thalamus and basal ganglia
    - presents with 1 of the following:
      - unilateral weakness (and/or sensory deficit) of face and arm, arm and leg or all three.
      - pure sensory stroke.
      - ataxic hemiparesis
  - **Posterior circulation infarcts** (POCI, c. 25%)
    - involves vertebrobasilar arteries
    - presents with 1 of the following:
      - cerebellar or brainstem syndromes
      - loss of consciousness
      - isolated homonymous hemianopia

Stroke: assessment

- **FAST screening tool** (**F**ace/**A**rms/**S**peech/**T**ime):
  - widely known by the general public following a publicity campaign.
  - It has a positive predictive value of 78%.

- **ROSIER score**
  - **useful for medical professionals.**
  - **It is validated tool recommended by the Royal College of Physicians.**
  - Exclude hypoglycaemia first, then assess the following:

Assessment	Scoring
Loss of consciousness or syncope	- 1 point
Seizure activity	- 1 point
New, acute onset of:	
• asymmetric facial weakness	+ 1 point
• asymmetric arm weakness	+ 1 point
• asymmetric leg weakness	+ 1 point
• speech disturbance	+ 1 point
• visual field defect	+ 1 point

  - **stroke is likely if > 0**

- **Scores ad scales used in stroke**

score	Used in
"ABCD2" score	predicts the risk of stroke following a transient ischaemic attack
Barthel Index	measures a person's daily functioning, e.g ability to bath, feed
"CHADS2-Vasc"	assesses stroke risk in patients with non-valvular atrial fibrillation
Modified Rankin Scale	measures the degree of disability, after a stroke
NIHSS Score (**N**ational **I**nstitute of **H**ealth **S**troke **S**cale)	is a tool used acutely to assess the degree of stroke-related neurologic deficit and hence determine appropriate treatment e.g. thrombolysis

  - **Barthel index**
    - used to assess disability following a stroke
    - The Barthel index correlates well with other prognostic scales.
    - It has very good concurrent and predictive validity.
    - It is very sensitive and it only takes 10 minutes to perform.
    - **The most limitation of the Barthel index is floor and ceiling effects**.
      - It basically means that a disabled person can score a maximum score of 100 and still not be independent.
      - It is poor at differentiating disability in patients who function at a higher level.
      - It also has floor effects as it may incorrectly score patients low who are initially bed bound following a stroke.
- **WHO International Classification of Functioning, Disability and Health (ICF)**
  - The NICE guidelines on stroke suggest that we use **terminology to describe the type of impairment** in accordance with the WHO International Classification of Functioning, Disability and Health.
    - **'impairment of body function'**
      - **Symptoms and signs like hemiparesis are classified as.**
    - **'activity limitation'**
      - difficulties in executing certain activities, for example communication impairment in patients with aphasia following a stroke or the inability to pick up a cup in the affected hand.
    - **'participation restriction'**
      - problems in social roles - for example as a spouse or parent.
    - **'pathology'**
      - the diagnosis/disease.

Stroke: management

Hypertension should not be treated in the initial period following a stroke

Stroke thrombolysis - only consider if less than 4.5 hours and haemorrhage excluded

- **Initial management**
  - blood glucose, hydration, oxygen saturation and temperature should be maintained within normal limits
  - **Blood pressure**
    - should not be lowered in the acute phase unless there are complications e.g. Hypertensive encephalopathy.
  - **Aspirin**

- 300mg orally or rectally should be given as soon as possible **if a haemorrhagic stroke has been excluded**

- **Thrombolysis**
  - Thrombolysis should only be given if:
    - administered within 4.5 hours of onset of stroke symptoms
    - haemorrhage has been definitively excluded (i.e. Imaging has been performed)
  - Alteplase is currently recommended by NICE.
    - blood pressure should be reduced to **below 185/110** mmHg before alteplase treatment
  - Patients treated with thrombolysis should be started on an antiplatelet agent **after 24 hours** once significant haemorrhage has been excluded.
  - **Contraindications to thrombolysis:**

Absolute	Relative
• Previous intracranial haemorrhage • Seizure at onset of stroke • Intracranial neoplasm • Suspected subarachnoid haemorrhage • Stroke or traumatic brain injury in preceding 3 months • Gastrointestinal haemorrhage in preceding 3 weeks • Lumbar puncture in preceding 7 days • Active bleeding • Oesophageal varices • Uncontrolled hypertension >200/120mmHg	• Concurrent anticoagulation (INR >1.7) • Haemorrhagic diathesis • Active diabetic haemorrhagic retinopathy • Suspected intracardiac thrombus • Major surgery / trauma in preceding 2 weeks • Pregnancy • **Active pancreatitis.**

  - patients with severe strokes only have an 8% likelihood of achieving clinically significant improvement with tPA alone.
- **Intra-arterial clot retrieval** (Mechanical thrombectomy)
  - Advantages
    - safe and effective
    - Mechanical thrombolytic devices can remove a clot in a matter of minutes, whereas pharmaceutical thrombolytics, even those delivered intra-arterially, may take as long as 2 hours to dissolve a thrombus.
  - patients should undergo the procedure **within 6 hours** of symptom onset.
  - Indications
    - large vessel occlusion (usually in addition to IV thrombolytic therapy)
      - proximal **MCA** or
      - **distal internal carotid artery** or
      - **basilar artery** occlusion.
    - Patients who are **ineligible for IV thrombolysis** who present within the appropriate time-frame with large vessel occlusion.
- **Surgical treatment → decompressive hemicraniectomy**
  - **Indications**
    - Patient with middle cerebral artery infarction who meet all of the criteria below:
      1. **Aged 60 years or under.**
      2. Clinical deficits suggestive of infarction in the territory of the middle cerebral artery, with a score on the National Institutes of Health Stroke Scale **(NIHSS) of above 15**.
      3. Decrease in the level of consciousness to give a **score of 1 or more** on item 1a of the **NIHSS.**
      4. Signs on CT of an infarct of at least **50% of the middle cerebral artery** territory

- **Secondary prevention**
  - **clopidogrel** is now recommended by NICE

- aspirin plus MR dipyridamole is now recommended after an ischaemic stroke only if clopidogrel is contraindicated or not tolerated, but treatment is no longer limited to 2 years' duration
- MR dipyridamole alone is recommended after an ischaemic stroke only if aspirin or clopidogrel are contraindicated or not tolerated, again with no limit on duration of treatment

➢ **Aspirin**
- Start aspirin after excluding intracerebral haemorrhage by brain imaging
- aspirin 300 mg orally if they are not dysphagic or if they are dysphagic → aspirin 300 mg rectally or by enteral tube.
- aspirin 300 mg should be continued until 2 weeks after the onset of stroke, at which time definitive long-term antithrombotic treatment should be initiated.

➢ **Anticoagulation treatment for other comorbidities** (e.g: atrial fibrillation):
- should not be started until brain imaging has excluded haemorrhage,
- usually **after 14 days** from the onset of an **ischaemic stroke.**
  - ischaemic stroke + atrial fibrillation → aspirin 300 mg for the first 2 weeks before considering anticoagulation treatment.
- cerebral infarction in patient with prosthetic valves and who are at significant risk of haemorrhagic transformation,→ **anticoagulation treatment should be stopped for 1 week and aspirin 300 mg substituted.**
- ischaemic stroke and symptomatic proximal DVT or PE → should receive anticoagulation treatment in preference to treatment with aspirin
- haemorrhagic stroke and symptomatic DVT or PE → prevent further PE using either **anticoagulation or a caval filter.**

➢ **Statin treatment**
- Immediate initiation of statin is not recommended in acute stroke
  - Many physicians will delay treatment until after at least 48 hours due to the risk of haemorrhagic transformation
- If already on statins should continue their statin
- **all patients who are diagnosed with stroke or TIA should be commenced on statin therapy irrespective of the cholesterol level.**(passmedicine 2017 part 2)

➢ **Glycaemic management during the inpatient enteral feeding of stroke patients with diabetes:**
- The Joint British Diabetes Society 2012 guidelines recommend a target BM of between 6 and 12 mmol/l for hyperglycaemic patients on NG feed with insulin to be started when BM over 12 mmol/l.
- The insulin regime of choice is a biphasic insulin such as humulin M3, with a mixture of intermediate and short acting insulin, prescribed twice daily, at the start and middle of the NG feed.
  - **the optimal management of hyperglycaemia → Prescribe biphasic insulin twice daily**
- Patients with hyperglycaemia should never be prescribes PRN actrapid nor should the NG feed be stopped

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Spontaneous intracerebral haemorrhage

Current management of spontaneous intracerebral haemorrhage (bmj.com 2017)

http://svn.bmj.com/content/2/1/21

- **The most common locations of hypertensive ICH are** the putamen, thalamus, subcortical white matter, pons and cerebellum
- **Common risk factors**
  - HTN, (**the most common risk factor**)
  - age,
  - history of heavy alcohol,
  - methamphetamine or cocaine use,
  - education at less than a high school level and
  - genetic alleles associated with cerebral amyloid.

- Classification by location
  - lobar versus non-lobar and supratentorial versus infratentorial.
  - **Lobar ICH**
    - commonly due to **cerebral amyloid angiopathy** (CAA).
      - **Amyloid deposition** in small-sized to medium-sized cortical perforators may lead to the rupture of these vessels,
  - **Non-lobar ICH**
    - commonly due to **long-standing high blood pressure** resulting in **lipohyalinosis of small perforating arteries** of the basal ganglia, thalamus, pons and cerebellum, leading to deep haemorrhages, often with extension into the ventricles.
- **Feature**
  - ICH should be suspected in any patient with severe headache, vomiting, elevated systolic blood pressures or decreased level of consciousness.
  - Fever is common
    - Sustained fever after ICH is an independent prognostic factor for worse outcome.
- **Diagnosis**
  - **non-contrast head CT** is highly sensitive and specific
- **Treatment**
  - Stabilisation of airway, breathing and circulation **(ABCs)**
    - **Intubation** for airway protection is indicated in patient with **GCS ≤8** or significant respiratory distress.
  - Patient with a decreased level of consciousness from **intraventricular haemorrhage with hydrocephalus**, mass effect or brainstem herniation should receive:
    - **ventriculostomy**,
    - hyperosmolar therapy with **mannitol** 0.5–1 g/kg or **hypertonic saline** (HTS) infusion.
  - **In patients with an intracerebral haemorrhage, intervention to control the blood pressure is required only when the systolic BP exceeds 170 mmHg.**
  - **Intensive lowering of systolic blood pressure to <140 mm Hg is proven safe by two recent randomised trials**.
    - the 2015 update to the AHA/ASA Guidelines for the Management of Spontaneous ICH recommend that for patients presenting with SBP between 150 and 200, acute lowering of SBP to 140 mm Hg is safe and may be effective for improving functional outcome.
    - aggressive blood pressure reduction with continuous antihypertensive drug intravenous infusion and frequent monitoring
    - Intravenous calcium channel blockers (eg, **nicardipine**) and β-blockers (eg, **labetalol**) are the **treatment of choice** for early BP reduction, given their short half-life and ease of titration.
    - **During acute phase**, patients may have **resistant HTN due to sympathetic surge**. A few weeks later, they may require fewer medications and be at risk of hypotension unless the doses of medications are adjusted promptly

- In patients with **small haematoma without significant mass effect**, there is no indication for routine use of mannitol or hypertonic saline (HTS) → **Observe**
- However, for patients with large ICH (volume > 30 cbic centmetre) or symptomatic perihaematoma oedema, it may be beneficial to keep serum sodium level at 140–150 mEq/L for 7–10 days to minimise oedema expansion and mass effect.
- Mannitol and hypertonic saline (HTS) can be used emergently for worsening cerebral oedema, elevated intracranial pressure (ICP) or pending herniation.
- Ventriculostomy is indicated for patients with severe intraventricular haemorrhage, hydrocephalus or elevated ICP.
- **Reversal of coagulopathies**
  - 12–20% of patients presenting with ICH are taking oral anticoagulants.
  - For all patients taking **vitamin K antagonists (eg, warfarin)**
    - for patients with INR ≥1.4:
      - vitamin K 10 mg and 3-factor or 4-factor **prothrombin complex concentrates (PCCs)**

- ⇨ PCC is an inactivated concentrate of factors **II, IX** and **X,** with variable amounts of factor **VII**.
- ⇨ Variation in factor VII concentrations in PCC has led to their classification as either 3- or 4-factor.

❖ PCC is preferred over FFP

❖ **Recombinant Factor VIIa (rFVIIa)** has been associated with relatively high thrombosis rates and should **only be considered in patients who will not accept blood products (eg, Jehovah's witness).**

- ➢ **Direct thrombin inhibitors** (**DTI**s; eg, **dabigatran**, **argatroban** and **bivalirudin**)
  - reversal of coagulopathy is indicated if patient presents within 3–5 half-lives (or beyond in patient with renal insufficiency).
  - **haemorrhage associated with dabigatran** → **Idarucizumab** (5 g intravenous divided into two doses)
  - If idarucizumab is not available, or if the haemorrhage is associated with a **DTI other than dabigatran**, **PCC** is recommended.
  - Haemodialysis can also be considered in patients with dabigatran-associated ICH and renal insufficiency, especially if continued haemorrhage despite first-line therapies.
- ➢ For patients taking Factor **Xa** inhibitors (eg, rivaro**xaban**, api**xaban** and edo**xaban**):
  - **PCC** is recommended if the haemorrhage occurred within 3–5 half-lives of drug exposure (or in context of liver failure).
  - If presenting within 2 hours of drug exposure, activated charcoal can be administrated to prevent further drug absorption.
  - Laboratory testing is unlikely to be helpful in guiding treatment; therefore, reversal should be guided by bleeding (major or intracranial) instead.
- ➢ **low-molecular-weight heparin** (low molecular weight heparin (LMWH); eg, enoxaparin, dalteparin, nadroparin and tinzaparin)
  - → **protamine** should be administered.
- ➢ For **thrombolytic** (eg, recombinant tissue plasminogen activator (rtPA)) reversal:
  - 1st line → **cryoprecipitate** administration.
  - 2nd line (If cryoprecipitate is contraindicated or unavailable), → tranexamic acid (anti-fibrinolytic agent)
- ➢ For patients taking antiplatelet agents (eg, aspirin, clopidogrel and abciximab):
  - platelet transfusion is not recommended routinely, regardless of antiplatelet agent, platelet function testing, haemorrhage volume or neurological examination.
  - Platelet transfusion seems inferior to **standard care** for patients taking antiplatelet therapy before ICH
  - Platelet transfusion should be considered for patients with aspirin- or adenosine diphosphate receptor (ADP) inhibitor-associated ICH **who will undergo a neurosurgical procedure.**

❖ Platelet function testing prior to platelet transfusion should be performed if possible and timely results available. If platelet function is within normal limits or patient has documented antiplatelet resistance, platelet transfusion should be avoided.

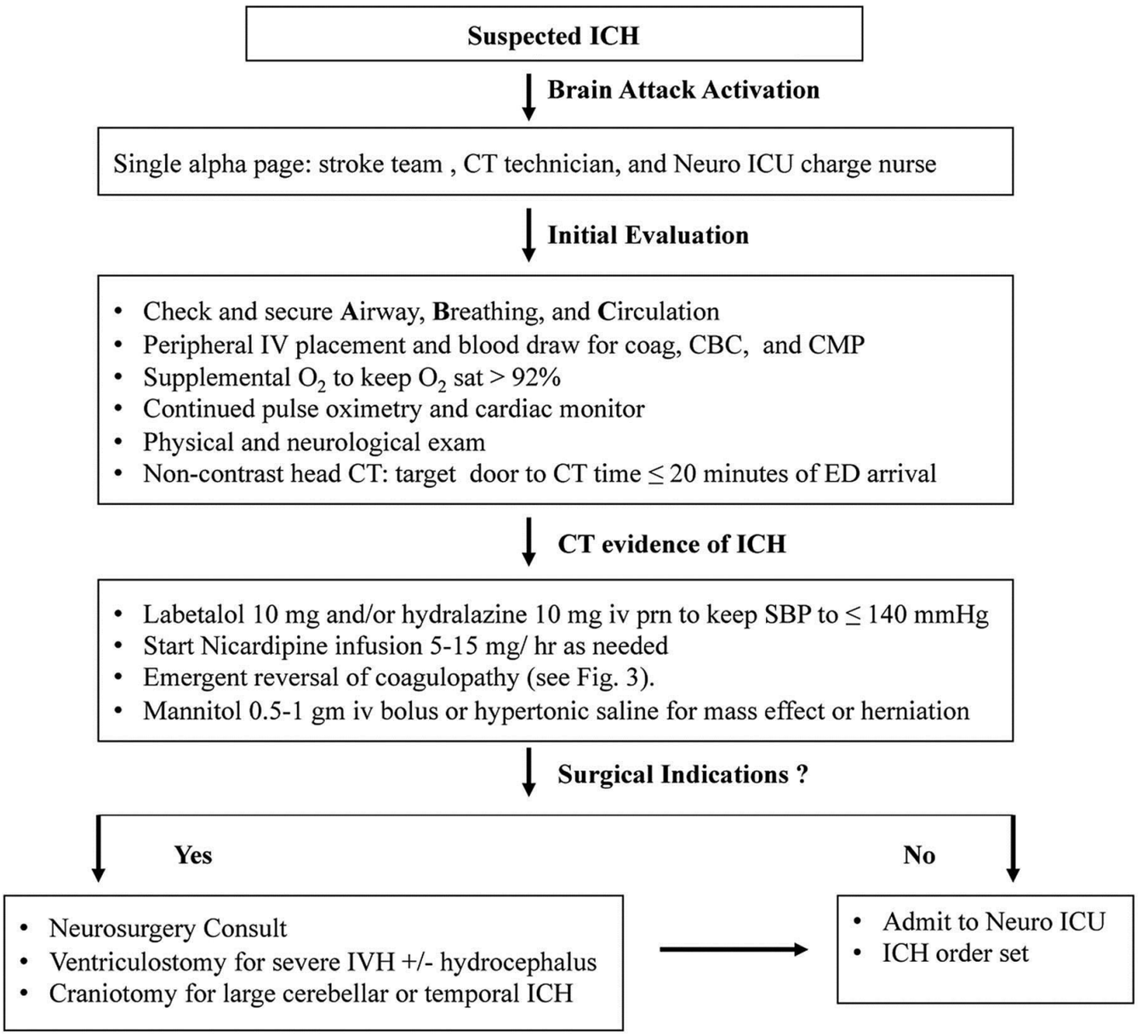
- **Management of intraventricular haemorrhage (IVH) and hydrocephalus**
  - ➢ (IVH) occurs in up to 45% of patients with ICH.
  - ➢ External ventricular drain (EVD) placement should be considered in:
    - any patient with GCS ≤ 8,
    - significant IVH,
    - hydrocephalus or
    - evidence of transtentorial herniation
  - ➢ Elevated ICP (>20 mm Hg) should be treated with hyperosmolar therapy (HTS and/or mannitol), cerebrospinal fluid drainage or sedation, though none of these therapies has been shown to improve outcomes
- **Surgical intervention**
  - ➢ no benefit for early haematoma evacuation in patients with **supratentorial ICH**

- Unlike supratentorial ICH, **cerebellar ICH** is considered a neurosurgical emergency and evacuation is recommended per current guidelines given the high morbidity from rapid development of **brainstem compression**
  - Surgical indications include:
    - haematoma size >3 cm in diameter,
    - brainstem compression or
    - hydrocephalus.

- **Management of peri-haematoma oedema (PHE)**
  - (PHE) develops within the first few days after ICH and may cause elevated ICP, mass effect, midline shift and brain herniation
  - **asymptomatic PHE** require **no specific treatment** except maintaining a normal sodium goal.
  - symptomatic cerebral oedema and elevated ICP → mannitol and hypertonic saline (HTS) are the first-line
    - Mannitol is an osmotic diuretic. It increases water excretion by the kidneys and reduces cerebral oedema and ICP.
    - HTS **increases plasma osmolarity** and the flow of excess water from cerebral tissue to the blood **via the osmotic gradient**.
    - HTS vs mannitol:
      - A meta-analysis performed in 2011 showed that **HTS** is slightly **more effective than mannitol** for the treatment of elevated ICP.
      - A recent analysis of the INTERACT2 data showed that **mannitol** seems safe, but **might not improve outcome** in patients with acute ICH
      - According to patient's medical history:
        - ⇨ patients with **congestive heart failure** should receive a bolus of **mannitol** or **23.4% of HTS**,
        - ⇨ whereas continuous infusion of **3% of HTS** can be used for patients with **dehydration or decreased urine output**.
- **Patients with DVT or PE + ICH:**
  - consider anticoagulation depending on stability of the haematoma, cause of haemorrhage and time since presentation.
  - If systemic anticoagulation is contraindicated, **inferior vena cava filter** placement should be considered
- **Prophylactic management**
  - prophylaxis of venous thromboembolism (VTE):
    - risk of (DVT) is 1–5%.
    - Start mechanical VTE prophylaxis **at the time of admission**
      - preferably with **intermittent pneumatic compression (IPC)** devices
        - ⇨ cuffs around the legs that fill with air and squeeze legs → ↑blood flow through the leg veins → prevent blood clots.
      - If (**IPC)** devices are unavailable, **graduated compression stockings (GCS)** can be utilised.
      - Early aggressive comprehensive care may **improve survival** and functional recovery.
    - Prophylactic doses of subcutaneous unfractionated heparin or LMWH should be started in patients with stable haematomas **within 48 hours of admission**.
      - Mechanical VTE prophylaxis should be continued after initiation of pharmacological prophylaxis.
  - There is no benefit for seizure prophylaxis or aggressive management of fever or hyperglycaemia.

Intracerebral haemorrhage in association with anticoagulants (royal college guidelines 2016):

intracerebral haemorrhage in association with	reversed with
vitamin K antagonist treatment	combination of prothrombin complex concentrate and intravenous vitamin K.
dabigatran	idarucizumab
factor Xa inhibitor	prothrombin complex concentrate



The 2016 RCP stroke guidelines state: Patients with primary **intracerebral haemorrhage** who present within 6 hours of onset with a systolic blood pressure above 150mmHg should be treated urgently using a locally agreed protocol for **blood pressure lowering to a systolic blood pressure of 140 mmHg** for at least 7 days, unless:

- the Glasgow Coma Scale score is 5 or less
- the haematoma is very large and death is expected
- a structural cause for the haematoma is identified
- immediate surgery to evacuate the haematoma is planned.

January 2013 exam: Which medications should be given following an ischaemic stroke (i.e. after 14 days)? Clopidogrel + statin

September 2009 exam: A 62-year-old man admitted 5 hours after left hemiplegia. ECG confirms atrial fibrillation. A CT head is normal. What is the most appropriate initial management? Aspirin (He is outside the thrombolysis window so alteplase is not an option. anticoagulation should be commenced 14 days after an ischaemic stroke.)

Paradoxical embolisation

- For a right-sided thrombus (e.g. DVT) to cause a left-sided embolism (e.g. stroke) it must obviously pass from the right-to-left side of the heart.
- The following cardiac lesions may cause such events
  - patent foramen ovale
    - present in around 20% of the population
    - **Transoesophageal echocardiography (TOE) is the investigation of choice** to investigate for a patent foramen ovale,
    - transthoracic echocardiography with contrast may be an alternative.
    - TOE offers better views of the anatomical area.
  - atrial septal defect - a much less common cause

Cerebral venous thrombosis (CVT)

Patients with a hypercoagulable state (e.g pregnancy) and papilloedema with neurological signs should be investigated for cerebral venous thrombosis.

Basics

- Structure
  - reflections in dura matter where meningeal and periosteal layers split
- Function
  - return blood from cerebral veins to internal jugular vein
- veins contains **NO** valves

Epidemiology

- more common in young women
  - Sex: ♀ > ♂, 3:1
  - Age of onset: ≤ 40 years

Pathophysiology

- The underlying problem is a thrombosis and the **petechial haemorrhages are caused by venous outflow blockage**.
- Thrombogenesis occurs in the cerebral venous system, → ↓ cerebral drainage → ↑ intracranial pressure → clinical features (see below)
- Additionally, thrombus formation → congestion within the venous system of the brain → blood stasis → ↓ oxygenated blood in brain tissue → cerebral edema and/or infarcts/stroke.

Types

- The dural sinuses are grouped into:
  - sagittal,
  - lateral (including the transverse, sigmoid, and petrosal sinuses), and
  - cavernous sinuses.
    - Because of its complex neurovascular anatomic relationship, it is the **most important** of any intracranial septic thrombosis.
- **50% of patients have isolated sagittal sinus thromboses**
  - the remainder have coexistent lateral sinus thromboses and cavernous sinus thrombosis

Risk factors and etiology

- local infection
  - *Staphylococcus aureus* is the most common
  - sinusitis
    - Frontal sinuses are the most common source of infection
  - local infection midface infection
    - most commonly a furuncle
- diabetes mellitus
- hypercoagulable states:

- pregnancy, post-partum period ,
  - **It typically presents with headache, seizures and focal neurological deficit two to three weeks postpartum (but is also seen earlier.**
- Malignancy
- clotting disorders (e.g., factor V Leiden, protein C and S deficiencies, antiphospholipid syndrome)
- polycythemia

- intracranial hypotension
- lumbar puncture
- Minor head trauma
- medications
  - **Oral contraceptive pill**, including the third-generation formulations
  - Corticosteroids
  - Epsilon-aminocaproic acid
  - Thalidomide
  - Tamoxifen
  - Erythropoietin
  - Phytoestrogens
  - L-asparaginase
  - Heparin - Heparin therapy has been reported to produce thrombotic thrombocytopenia with associated venous sinus thrombosis

Features

- Raised intracranial pressure (ICP):
  - **headache**
    - **The most common presenting symptom**
  - nausea & vomiting
    - Vomiting in the morning is characteristic of raised ICP as it follows a period of lying flat.
  - Bending over, coughing or straining causes a transient increase in already raised ICP→ ↑optic nerve compression → visual disturbance.
  - Papilloedema
- **Cranial nerve symptoms**
  - (e.g., diplopia, tinnitus, unilateral deafness, facial palsy)
  - Cranial nerves III, IV and VI palsies
- Ocular chemosis
- Proptosis
- Seizures
  - Focal or generalized seizures are frequent, occurring in up to 40% of patients.
- rare cause of stroke,

Investigations

- If CVT is suspected, D-dimer levels and imaging studies are first steps of diagnosis
  - D-dimers: > 500 µg/L
  - Imaging:
    - CT/MRI (with or without venography): **tests of choice to confirm the diagnosis**
    - Plain CT/MRI help detect only edema and/or infarcts, but the **thrombus itself can be visualized by means of venography**.
    - CT
      - Hypodense structures indicate ischemic event
      - Thrombus can appear as a hyperdense vein or sinus
      - CT venography shows a **filling defect** in a vein or sinus
    - MRI
      - Thrombus is isointense on T1 and hypointense on T2 early in the disease
      - Cerebral edema can be identified
      - MR venography demonstrates a **lack of flow**
- Evaluation for possible causes
  - ↑ ESR and antibody studies

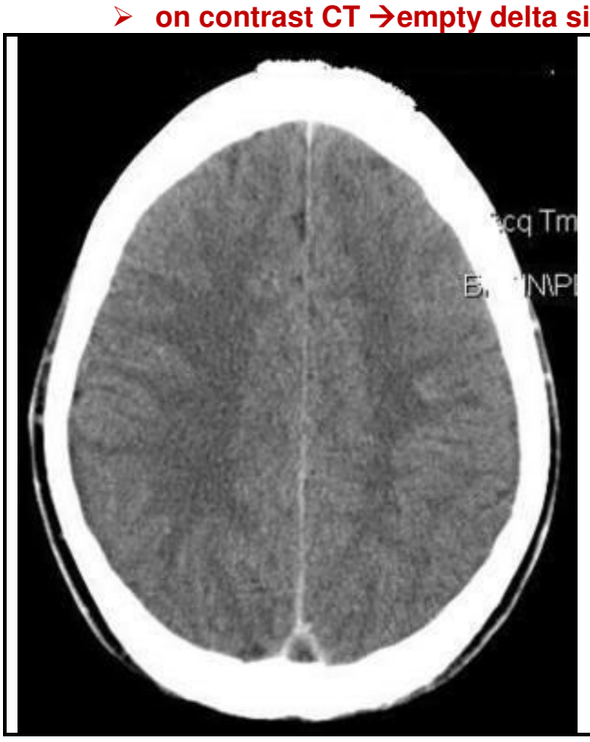
- CBC, CRP
- Tests for clotting disorders (e.g., Leiden factor V mutation)
  - Thrombophilia screen should be performed.

Treatment of cerebral venous thrombosis

- If primary→ anticoagulants (full-dose heparin then warfarin).
- Secondary thrombosis (usually secondary to infection)→ should be treated or drained if possible.
- Dexamethasone can be used to reduce cerebral oedema.
- Surgical therapy
  - Indications
    - Progressive neurologic worsening (despite adequate anticoagulation)
    - Acute rise in intracranial pressure
    - Impending herniation
  - Surgical options
    - Blood clot removal
    - Vessel recanalization
    - Shunt placement

Sagittal sinus thrombosis

- **the most frequently affected sinus**
  - **Superior sagittal sinus thrombosis (SSST) is the most common type of dural venous sinus thrombosis**
- **Features**
  - Anterior occlusion is usually asymptomatic,
  - posterior occlusion can present with:
    - raised intracranial pressure (headache, vomiting), and papilloedema
    - involvement of the upper hemispheres (paraplegia).
    - may present with seizures and hemiplegia
    - disorder of the oculomotor nerve by affecting the oculomotor (Edinger-Westphal) nuclei.
    - parasagittal biparietal or bifrontal haemorrhagic infarctions are sometimes seen
    - The territory of the affected sinus usually shows congestive oedema, which can progress to haemorrhagic venous infarction.
  - **on contrast CT →empty delta sign (is a specific to the superior sagittal sinus)**

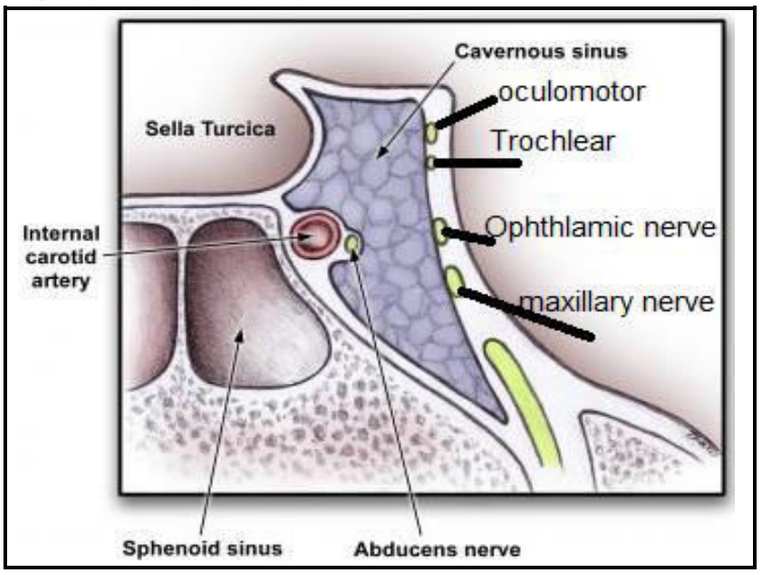


Empty delta sign → superior sagittal sinus thrombosis

- **CT with contrast demonstating a superior sagittal sinus thrombosis showing the typical empty delta sign.**
- **Look at the 'bottom' of the scan for the triangular shaped dural sinus.**
- **This should normally be white due to it being filled with contrast.**
- **The empty delta sign occurs when the thrombus fails to enhance within the dural sinus and is outlined by enhanced collateral channels in the falx.**
- **This sign is seen in only about 25%-30% of cases but is highly diagnostic for sagittal sinus thrombosis**

Cavernous sinus thrombosis (CST)

Cavernous sinus contents



Structures passes through the cavernous sinus:

- internal carotid artery with its surrounding sympathetic plexus
- third, fourth, and sixth cranial nerves are attached to the lateral wall of the sinus.
- Ophthalmic (V1) and maxillary (V2) divisions of the fifth cranial nerve are embedded in the wall
  - **The mandibular branch of the trigeminal nerve (V3) does not travel in the cavernous sinus and would therefore not be affected.**
    - **V3 innervates the lower face. (NO lower face symptoms)**

Other features of cavernous sinus syndrome

- peri-orbital oedema (Chemosis, oedema and cyanosis of the upper face occur due to obstruction of the ophthalmic vein)
  - **Eye swelling begins as a unilateral process and spreads to the other eye within 24-48 hours via the intercavernous sinuses**. This is **pathognomonic for CST**.
  - Periorbital edema may be the **earliest** physical finding.
- ophthalmoplegia:
  - 6th nerve damage typically occurs before 3rd & 4th
    - Lateral gaze palsy (patient cannot abduct eye) (isolated cranial nerve VI) is usually seen first
    - since CN VI lies freely within the sinus in contrast to CN III and IV, which lie within the lateral walls of the sinus.
  - Ptosis, mydriasis, and eye muscle weakness from cranial nerve III dysfunction
  - **Patients typically have double vision on looking upward**
- trigeminal nerve involvement may lead to hyperaesthesia of upper face and eye pain
- central retinal vein thrombosis
- Signs of increased intraocular pressure (IOP) may be observed.
  - Pupillary responses are sluggish.
  - Decreased visual acuity is common

Which group of nerves run through the cavernous sinus?
→ III, IV, (V-1, V-2), and VI

September 2012 exam: Left-sided eye pain & diplopia for the past 2 days + 6th & 3rd cranial nerve palsy on the left side + hyperaesthesia of the upper face on the left side. Where is the likely lesion? Cavernous sinus

superior orbital fissure syndrome

- is similar to the cavernous sinus syndrome except for the presence of proptosis.

Lateral sinus thrombosis

- 6th and 7th cranial nerve palsies

Lesions at the jugular foramen

Causes of jugular foramen syndromes

- Nasopharyngeal carcinoma is the commonest cause.
- Other are → neurofibromas, metastatic tumours, jugular vein thrombosis, Paget's disease of the bone, and basal skull fractures.

Affected CN → 9,10,11

- CN IX (Glossopharyngeal nerve) & CN X (Vagus nerve) → palatal weakness and swallowing difficulties , **Laryngeal muscle paralysis would result in bovine cough and husky voice.**
- CN XI (Accesory nerve) → shoulder and sternocleidomastoid weakness

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Cervical vascular dissection

Stroke provoked by minimal trauma (e.g: exercise) is likely due to **Cervical vascular dissection** until proven otherwise

- **Mechanism of ischaemia**
  - Most ischaemic symptoms (85-95%) of cases are caused by emboli from the site of the dissection.
  - (5-15%) due to vessel narrowing (subintimal tears → intramural haematomas → protrude inward and narrow the vessel lumen)

- **Feature**
  - sudden-onset weakness and numbness provoked by exercise
    - When an ischaemic event occurs in the context of exercise, the possibility of a Valsalva manoeuvre precipitating embolism from a patent foramen ovale should also be considered.However, an arterial dissection should be considered most likely until proven otherwise
  - Horner's sign may be present
  - two-thirds of patients have head or neck pain, the remainder present painlessly

- **Investigation** → (magnetic resonance angiography)

Carotid artery stenosis

- **Epidemiology**
  - Carotid artery stenosis causes 10% to 15% of all ischaemic strokes.
  - the annual risk of stroke in patients with asymptomatic carotid disease is between 1% and 2%
- **Pathophysiology**
  - Atherosclerotic plaque in the cervical carotid artery is the most common cause.
  - Plaque disruption and athero-embolisation into the intracranial circulation is the most common mechanism for stroke.
  - The most common site of carotid Atherosclerosis:
    - usually at the fork where the common carotid artery divides into the internal and external carotid artery.
- **Features**

Carotid artery atherosclerosis is an important cause of ipsilateral amaurosis fugax.

  - The majority of carotid artery stenosis are asymptomatic.
  - cervical bruit
  - plaques rupture → embolism to :
    - intracranial arteries → (TIA or stroke) or
    - retinal arteries → (amaurosis fugax or retinal strokes).
- **Diagnosis**
  - **Duplex ultrasonography** is the preferred mode of diagnosis;
    - sensitivity of 99%, specificity of 86%
    - stepwise diagnostic work-up:
      - carotid duplex for screening purposes.

- If the stenosis is less than 50%, → no further imaging is needed.
- If the stenosis **>** 50%,→ CTA or MRA should be considered for more detailed plaque characterization.

- CT or magnetic resonance **angiography** helps to define the anatomy if intervention is indicated.
  - **computed tomography angiography (CTA)**
    - sensitivity is 85% and specificity 93%
    - requires exposure to ionising radiation, and the iodinated contrast is a hazard in patients with renal insufficiency.
    - faster and less expensive than MRA.
    - less susceptible than (MRA) to overestimate the stenosis
  - **magnetic resonance angiography (MRA)**
    - Less commonly performed than CTA
    - sensitivity 88% and specificity 84%
    - has a tendency to overestimate stenosis severity.
    - does not require ionising radiation.
- NICE guidelines state that a patient with a TIA should receive a CT/MRI head and **carotid duplex within a week.**
- **cervical angiography**
  - The **definitive test** for identifying and quantifying the degree of stenosis in the carotid artery
  - however, it is infrequently ordered as it is **invasive** (requiring catheterisation of the aortic arch and carotid artery) and carries a **risk of atheroembolic stroke**.
  - Generally ordered when non-invasive tests show a suspicion of a string sign (i.e., ≥95% stenosis).

- **Management**
  - Initial management → antiplatelet therapy, and risk factor modification.
  - endarterectomy
    - Indications
      - if carotid stenosis **>** 70% according ECST criteria (European Carotid Surgery Trial' Collaborative Group)
      - or **> 50% according to NASCET** (North American Symptomatic Carotid Endarterectomy Trial) **criteria**.
        - **2016 Royal College guideline** recommend that : The degree of carotid artery stenosis should be reported **using the (NASCET) method**.
    - If carotid endarterectomy is deemed necessary then **surgery should be performed within two weeks**. ("urgent" endarterectomy within 2 weeks)
    - It **reduces the risk of disabling stroke or death by 48%** in a person with severe symptomatic carotid stenosis (>70%) who has had a TIA.
    - The peri-operative risk of disabling stroke or death is approximately 3%.
    - **The benefit of endarterectomy is prevention of future stroke.**
      - **Surgery will be appropriate if there is a TIA or resolving stroke.**
      - **with dense strokes, if there is no recovery, the benefits are greatly reduced due to end-organ damage.**
    - Contraindications:
      - 100% carotid stenosis
        - ⇨ usually requires a **bypass** procedure, as risk of endarterectomy outweighs benefit.
      - previous stroke with persistent neurological symptoms
  - Carotid stenting
    - used as an alternative to endarterectomy.
    - less invasive revascularisation strategy, and uses an embolic protection device.
    - There seems to be a similar early risk of death or stroke, and similar long-term benefits.
    - Indications
      - **Restenosis**.

- **Previous radiotherapy to the neck** may make endarterectomy difficult, and stenting may be preferred.
  - Revascularisation would have the risk of reperfusion haemorrhage.
  - Risk is higher in elderly patients, possibly due to vascular tortuosity and calcification.

Question

left-sided hemiparesis of more than 8 hours' duration. carotid ultrasound scan, shows 80% stenosis of the left carotid artery, **50% stenosis of the right** carotid artery. What is the most appropriate treatment for long-term stroke prevention?

➔ **Clopidogrel**

- endarterectomy is not recommended in:
  - ❖ significant stenosis but asymptomatic side (left carotid in this case)
  - ❖ symptomatic side but there is less than 70% (right carotid in his case).

Carotid artery stenosis management

- Symptomatic (TIA, stroke, and amaurosis fugax)
  - ipsilateral carotid stenosis **≥** 50% (NASCET criteria) → carotid endarterectomy **+** antiplatelet therapy and cardiovascular risk reduction
  - ipsilateral carotid stenosis **<** 50% → antiplatelet therapy and cardiovascular risk reduction
- Asymptomatic
  - asymptomatic carotid stenosis <70% → antiplatelet therapy and cardiovascular risk reduction
  - **asymptomatic carotid stenosis ≥ 70% :**
    - **1st line → antiplatelet therapy and cardiovascular risk reduction**
      - ❖ **the best course of action? → Discharge and outpatient follow up**
    - Adjunct → carotid endarterectomy
- Bilateral carotid stenosis:
  - asymptomatic bilateral stenoses **≥** 70% (NASCET criteria)
    - the higher-grade stenosis is addressed surgically first.
    - In the case of equal degrees of stenosis, handedness is considered. (eg, the left carotid would be surgically treated first in a right-handed person).
  - symptomatic found to have carotid stenosis in a contralateral carotid artery, the asymptomatic carotid stenosis is treated
- Carotid restenosis: → antiplatelet therapy **±** revascularisation
  - The causes of restenosis:
    - within 30 days of the carotid intervention → Residual stenosis.
    - within the first 2 years after surgery → neointimal hyperplasia
    - 2 years after surgery → new atherosclerotic plaque
  - perform carotid artery re-**stenting** when the stenosis reaches **≥** 70% (NASCET criteria) in asymptomatic patients and **≥** 50% (in symptomatic patients).

Ref: bestpractice.bmj.com 2017

Carotid artery dissection

The classic triad of symptoms of carotid dissection are:

1. unilateral (ipsilateral) headache
2. **ipsilateral Horner's syndrome** and
3. **contralateral** hemisphere signs (aphasia, neglect, visual disturbance, **hemiparesis**).

- The two commonest causes of **young onset stroke** (less than 40 years) are:
  - cardio-embolism and
  - carotid artery dissection.
- Dissection of the internal carotid artery can occur intracranially or extracranially
  - Extracranially is more common
  - 75% of carotid dissections affect the internal carotid artery (that is, extracranially)
- **Causes**
  - mechanical forces (eg, trauma, blunt injury, and stretching)
  - arteriopathies (eg, Ehlers-Danlos syndrome IV and other connective tissue disorders)
- **Features**

- **Pain** is the initial symptom
  - Headache (including neck and facial pain)
  - ipsilateral to the dissected artery.
  - It usually precedes a cerebral ischemic event, unlike headache associated with stroke, which usually follows or accompanies the ischemic event.
  - 25% of patients have isolated ipsilateral neck pain.
- Ischaemic neurological features (transient or completed **strokes**) are found in 30-80%
- Pulsatile **tinnitus** is common, (25%)
- **syncope**
- partial **Horner** syndrome (Ptosis with miosis)
  - usually **painful** when caused by internal carotid artery dissections
  - The term partial Horner syndrome is used for the oculosympathetic palsy because **anhydrosis is absent**.
    - Because the **sympathetic fibers innervating the facial sweat glands** are anatomically **located on the external** rather than the internal **carotid artery**
- **amaurosis fugax**.
  - Transient episodic blindness
  - caused by decreased blood flow to the retina
- Decreased taste sensation (**hypogeusia**)

- **Diagnosis**
  - The current **gold standard** for diagnosis of carotid artery dissection, **contrast arteriography (the single best investigation of choice)** should be strongly considered, if there is:
    - mono or hemiparesis with normal mental state,
    - signs or history of major cervical trauma with abnormal neurology,
    - or basilar skull fracture in a patient with altered mental status.
  - Magnetic resonance angiography (MRA) replaced conventional angiography
    - MRA may fail to detect intramural hematoma within the first 24-48 hours after the occurrence of carotid artery dissection.
  - **Helical computed tomography angiography (CTA)**
    - 100% sensitivity and specificity
    - (CTA) is rapidly replacing conventional angiography and possibly MRA as **the diagnostic modality of choice.**
    - Helical CTA is fast and noninvasive
    - **CTA may be the first (or even the only) modality used for screening and diagnosis for carotid artery dissection in trauma patients**
    - The hallmark of injury to the internal carotid artery on CTA is a **change in the caliber of the vessel.**
    - Non-contrast CT is not an adequate screening or diagnostic test for internal carotid artery dissection.
  - **Conventional angiography**
    - It was the standard diagnostic modality
    - Now it is no longer considered the diagnostic modality of choice
    - it is invasive, resource-intensive, and costly;
    - it may miss dissections when the false lumen does not opacify with contrast medium.
    - should be reserved for high suspicion negative results with other imaging
    - The pathognomonic finding for a carotid artery dissection is an intimal flap and double lumen, secondary to an intramural hematoma. **This finding is rarely detected.**
    - **The most common angiographic finding** is termed the **string sign**, which is a long, tapered, narrowing column of contrast material in the distal segment of the internal carotid artery.
  - **Doppler ultrasonography (DUS)**
    - With its improving resolution, ready applicability, speed, and ease of use, DUS can now be used for the **initial assessment of patients** with suspected carotid artery dissection.
      - In trauma cases, it usually is already at the bedside for focused assessment with sonography for trauma (FAST).
    - DUS has the lowest cost and the highest safety profile.
    - sensitivity is high as 96%

        - The **pathognomonic DUS finding** for carotid artery dissection is the **demonstration of a membrane in the longitudinal and axial view**.
        - The most common DUS finding in carotid artery dissection is a **high-resistance flow pattern** or the **absence of signal in a totally occluded artery**.
        - Unlike angiography, DUS is able to demonstrate a false lumen even if it is thrombosed.
        - have a **31% false-negative** rate in patients with carotid artery dissection who presented with **Horner syndrome**.
        - Whenever abnormalities are found by DUS, follow-up with another imaging modality is always indicated.
    - in practice many trusts will require a CT head **first**.
    - in the **absence of arteriography**, duplex scanning or MRI with MRA may be considered **the next best tests.**
- **Management**
    - antithrombotic treatment provides the best outcome.
        - Do not initiate anticoagulation in trauma patients without first ruling out intracranial hemorrhage
    - Surgery has a limited role
- **Prognosis**
    - When the condition is diagnosed early, the prognosis is usually good.
    - Healing usually takes 3-6 months
    - 75% of patients making a good recovery.
    - mortality is less than 5%.

Carotid dissection

- Younger age group <50 years.
- Neck pain.
- Associated with vigorous exercise or event that sustains severe neck movement (e.g., roller coaster ride, motor vehicle accident).
- May have Horner's syndrome or history of genetic collagen abnormality.

Carotico-cavernous fistula

- Caroticocavernous fistula is a high pressure shunt of blood between the intracavernous carotid artery and the cavernous sinus.
- It is usually traumatic and may occur secondary to open or closed head trauma.
- Feature
    - Patients usually complain of **pain in the eye**.
    - **The most striking sign is pulsatile proptosis.**
    - Patients also have **palsies of the IIIrd, IVth and Vth nerve** palsies,
    - **injection and chemosis** due to raised episcleral venous pressure.
    - **orbital bruit** can be heard .

Vertebral artery dissection

The typical presentation of vertebral artery dissection is a **young person** (average age 40 years) with severe **occipital headache** and **neck pain** following a **recent head or neck injury**. The trauma is often trivial, but is usually associated with some form of cervical distortion.

- About 85% of patients develop focal neurological signs due to ischaemia of the brain stem or cerebellum.
- The commonest neurological manifestations are symptoms attributable to lateral medullary dysfunction (that is, Wallenberg's syndrome).
- **Common symptoms and signs** include:
    - ipsilateral facial pain and/or numbness (the most common symptom)
    - vertigo (very common)
    - dysarthria or hoarseness (CN IX and X)
    - ipsilateral loss of taste (nucleus and tractus solitarius)
    - hiccups
    - nausea and vomiting
    - diplopia or oscillopsia (image movement experienced with head motion), and
    - dysphagia (CN IX and X).
- Depending upon which areas of the brain stem or cerebellum are affected, clinical signs may include:

- limb or truncal ataxia
- nystagmus
- ipsilateral Horner syndrome (up to 1/3 patients affected)
- ipsilateral impairment of fine touch and proprioception
- contralateral impairment of pain and thermal sensation in the extremities (that is, spinothalamic tract)
- contralateral hemiparesis
- lateral medullary syndrome
- tongue deviation to the side of the lesion (impairment of CN XII), and
- internuclear ophthalmoplegia (lesion of the medial longitudinal fasciculus).

- **Risk factors** associated with the development of vertebral artery dissection include:
  - judo
  - yoga
  - ceiling painting
  - nose blowing
  - minor neck trauma
  - chiropractor manipulation
  - hypertension
  - oral contraceptive use, and
  - female sex.

Localisation of speech problems

- The speech area is in the left, dominant side of the brain in about 99% of right-handed people
- Thus, impairment of the speech area with a stroke, causing left-sided weakness, is rare. It will occur in virtually no right-handers and in only 30% of left-handers.
- As a general rule, a lesion of the left hemisphere will cause dysphasia whilst, in the right hemisphere, it will cause neglect, visuo-spatial and cognitive problems
- Wernicke's aphasia and pure aphasia (that is, without alexia) are middle cerebral artery.

Common types of aphasia

	Comprehension	fluency	repetition	localisation
Sensory (Wernicke's) aphasia	Deficits ✗	Intact ✓	Deficits ✗	left posterior perisylvian region**(posterior, superior temporal lobe)**
Production (Broca's) aphasia	Intact ✓	Deficits ✗	Deficits ✗	left pre-central areas **(inferior frontal lobe)**
Mixed aphasia	Deficits ✗	Deficits ✗	Intact ✓	**Damage that isolates the language areas (Broca's, Wernicke's, and the arcuate fasiculus) from other brain regions.**
Transcortical sensory aphasia	Deficits ✗	Intact ✓	Intact ✓	Temporal-occipital-parietal junction, located behind Wernicke's area.
Transcortical motor aphasia	Intact ✓	Deficits ✗	Intact ✓	anterior superior frontal lobe
conduction (arcuate fasciculus)aphasia	Intact ✓	Intact ✓	Deficits ✗	Arcuate fasciculus, posterior parietal and temporal regions.
Global aphasia	Deficits ✗	Deficits ✗	Deficits ✗	Left perisylvian region, white matter, basal ganglia and thalamus.

Dr.Yousif 2015

Comprehension, fluency and repetition are the three main variables that allow for localisation of speech problems

The three, general, areas are:

1. **Wernicke's area (posterior, superior temporal lobe) - lesions produce normal fluency, impaired comprehension, impaired repetition**

- receptive aphasia
- They are unaware of their language difficulties

2. conduction (arcuate fasciculus) - lesions produce normal fluency, normal comprehension, diminished repetition
3. Broca's area **(inferior frontal lobe)**
   - lesions produce impaired fluency, intact comprehension, impaired repetition.
   - **Unlike Wernicke's aphasia, Broca's patients are aware of their language difficulties.**

Mixed aphasia

- **Mixed aphasia** (or transcortical mixed aphasia) is not a complete 'global aphasia'.
  - In global aphasia there is receptive and expressive dysphasia.
- **With mixed aphasia, patients can often repeat words but not understand commands**, name objects or have intelligible spontaneous speech. 'Mixed aphasia' is not specific for stroke, although it can be caused by it.
- It may be **caused by** the following:
  - Alzheimer's disease
  - Bilateral cerebral damage
  - Tumours, and
  - Thalamic lesions.

Transcortical sensory aphasia

Transcortical sensory aphasia involves poor comprehension with fluent speech and repetition.

- The main problem lies within the brain in a region known as the **temporal-occipital-parietal junction**, located behind Wernicke's area.
- The patient has **intact repetition but is unable to follow verbal commands**. He has fluent grammatical speech.
- It is characterised by impaired auditory comprehension with intact repetition and fluent speech, and is caused by damage to the temporal lobes.
- It differs from Wernicke's aphasia in that patients still have **intact repetition**, and exhibit cholalia (the compulsive repetition of words)

Nomic aphasia or nominal aphasia

- **Anomic aphasia or nominal aphasia results in word finding difficulties.**
- On closer examination there may also be repetition problems and comprehension problems but these are typically mild compared to other aphasia syndromes.

Aphemia

- Aphemia is a type of aphasia in which there is **severe dysarthria and impairment of verbal output.**
- There is intact comprehension.
- It is believed to be the result of pars opercularis, inferior pre-Rolandic gyrus or subcortical lesions.

January 2008 exam: H/O difficulty in finding the right words whilst speaking. With normal comprehension. Where is the likely lesion? Posterior frontal lobe (expressive aphasia due to a lesion in Broca's area, located on the posterior aspect of the frontal lobe, in the inferior frontal gyrus)

Pupil conditions

Basic principle

- **oculomotor nerve carries parasympathetic efferents to the sphincter pupillae muscle.**
- **optic nerve carries sympathetic postganglionic fibres to the dilator pupillae muscle.**

- parasympathetic fibers lead to pupillary constriction (miosis)
  - light enters the eye → retinal ganglion → optic nerve → optic chiasm → optic tract → **pretectal nucleus→ Edinger-Westphal nucleus** → ciliary ganglion → pupillary constrictor muscles → causing uniform bilateral miosis
- sympathetic fibers lead to pupillary dilation (mydriasis)

  - hypothalamic nuclei → T1 and T2 spinal cord levels → paravertebral sympathetic chain (via the white ramus) → superior cervical ganglion → pupillary dilator muscle
- **Causes of small pupils include:**
  - Horner's syndrome
  - Old age
  - **Pontine haemorrhage**
  - Argyll Robertson pupil
  - Drugs, and
  - Poisons (opiates, organophosphates).
- **Causes of dilated pupils include:**
  - Holmes-Adie (myotonic) pupil
  - Third nerve palsy
  - Drugs, and
  - Poisons (atropine, CO, **ethylene glycol**).

PUPIL	LESION
Slightly smaller but reactive	Early stage of thalmic damage
Fixed dilated(7mm) pupil (non- reactive)	Oculomotor nerve lesion
Fixed midsized pupils(5mm)	Mid brain lesion
Pinpoint pupils(1-1.5mm)	Pontine lesion,opioid overdose
Asymmetrical pupils	Normal in 20 % of population but reactive.. If one pupil is sluggish to react than the other think mid brain or oculomotor lesion

Hippus

- Hippus is papillary athetosis.
  - athetosis → abnormal muscle contraction causes involuntary writhing movements.
- It is typically a benign finding.
- **It is a spasmodic rhythmical dilation and contraction of the pupil.**
- It is particularly noticeable when pupils are tested with a light, but is independent of eye movements or light.
- Pathological hippus is rare but is recognised with aconite poisoning, trauma, cirrhosis and renal disease (possibly due to frontal lobe dysfunction).

Tonic pupil (Holmes-Adie pupil) (HAS)

Holmes-Adie → dilated pupil

Overview

- tonic pupil or Holmes-Adie pupil is a **di**lated pupil caused by parasympathetic damage.
- characteristically seen in young women

Pathophysiology

- degeneration of parasympathetic nerves in the cilliary ganglion which leads to denervation of the pupil and hence hypersensitvity to dilute pilocarpine drops.
- usually occurs after a herpes zoster infection

Features

- At the beginning of the condition the pupil is large, (abnormally large pupil poorly reactive to light with a normal near reflex), but over time (years) it gradually diminishes in size to be smaller than the non-affected pupil. becomes small and poorly reactive.
- absence of deep tendon reflexes, usually in the Achilles tendon.

Association

- **Ross's syndrome: triad of:**
  1. abnormal pupil size,
  2. loss of deep tendon reflexes, and
  3. excessive sweating
- Sjogren's syndrome
- migraine.

Diagnosis

- Slit lamp examination may reveal small worm like contractions of the iris, but **the usual diagnostic test is to use weak pilocarpine eye drops**, which induce vigorous pupil contraction on the affected side, but only weak contraction of the pupil on the unaffected side.

Treatment

- In adults it tends to be a benign condition and is simply **observed**, however infants are usually referred because of an association with familial dystonias.
- The loss of deep tendon reflexes is permanent
- For impaired vision in the affected eye
  - reading glasses to compensate, and pilocarpine drops to be applied 3 times daily to constrict the dilated pupil.
  - For most individuals, pilocarpine drops and glasses will improve vision.
- Thoracic sympathectomy is the definitive treatment for excessive sweating.

The combination of these 3 symptoms – abnormal pupil size, loss of deep tendon reflexes, and excessive sweating – is usually called **Ross's syndrome**, although some doctors will still diagnose the condition as a **variant of HAS**.

Argyll Robertson Pupil (ARP)

Argyll-Robertson: small irregular pupils that do not react to light but react to accommodation. Referred to as the "Whore's Eye" because of the association with tertiary syphilis and because of the convenient mnemonic that, like a prostitute, they "accommodate but do not react"

Causes: **neurosyphilis,** Multiple Sclerosis, Sarcoidosis, DM

Accommodation Reflex Present

ARP

Pupillary Reflex Absent

- **bilateral small pupils**
- **"prostitute's pupils"→ that reduce in size on a near object (they "accommodate"), but do *not* constrict when exposed to bright light (they do not "react" to light).**
- **They are a highly specific sign of neurosyphilis, and might also be a sign of diabetic neuropathy.**

Pupillary Defect	Comments
Argyll Robertson pupil	• A type of light-near dissociation where ➢ the eye does not constrict in response to light as much as it does with accomodation ➢ pupil has an absent light reflex • Associated with neurosyphilis
Adie's myotonic pupil	• A type of light-near dissociation where ➢ the eye does not constrict in response to light as much as it does with accomodation ➢ light reflex is merely reduced • Secondary to ➢ degeneration of the ▪ ciliary ganglion ▪ postganglionic parasympathetic neurons

Visual field defects

Visual field defects:
- left homonymous hemianopia means visual field defect to the left, i.e. lesion of right optic tract
- homonymous quadrantanopias: PITS (Parietal-Inferior, Temporal-Superior)
- incongruous defects = optic tract lesion; congruous defects= optic radiation lesion or occipital cortex

Bitemporal hemianopia
- lesion of optic chiasm
- upper quadrant defect > lower quadrant defect = inferior chiasmal compression, commonly a pituitary tumour
- lower quadrant defect > upper quadrant defect = superior chiasmal compression, commonly a craniopharyngioma

The main points for the exam are:
- left homonymous hemianopia means visual field defect to the left, i.e. Lesion of right optic tract
- homonymous quadrantanopias: PITS (Parietal-Inferior, Temporal-Superior)
- incongruous defects = optic tract lesion; congruous defects = optic radiation lesion or occipital cortex

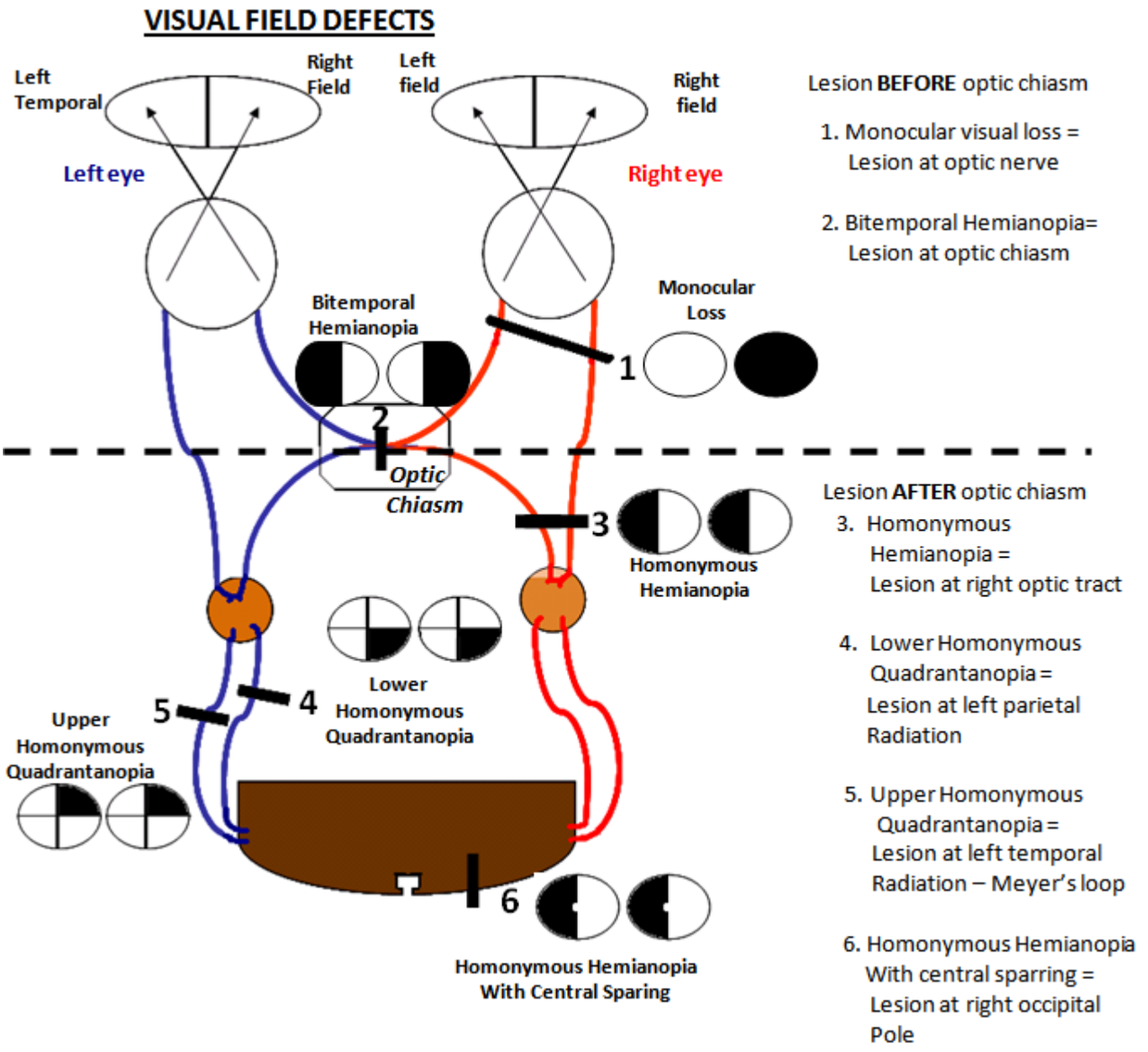
A congruous defect simply means complete or symmetrical visual field loss and conversely an incongruous defect is incomplete or asymmetric. Please see the link for an excellent diagram.

Homonymous hemianopia
- incongruous defects: lesion of optic tract
- congruous defects: lesion of optic radiation or occipital cortex
- macula sparing: lesion of occipital cortex

Homonymous quadrantanopias*
- superior: lesion of temporal lobe
- inferior: lesion of parietal lobe
- **mnemonic = PITS (Parietal-Inferior, Temporal-Superior)**

Bitemporal hemianopia
- **lesion of optic chiasm**
- upper quadrant defect > lower quadrant defect = inferior chiasmal compression, commonly a pituitary tumour

- lower quadrant defect > upper quadrant defect = superior chiasmal compression, commonly a craniopharyngioma



Bilateral internal carotid artery displacement can cause binasal incongruous hemianopia if the optic nerves are compressed.

September 2012 exam: What sort of visual field defect is expected following an operation to remove a meningioma in left temporal lobe? Right superior homonymous quadrantanopia

January 2009 exam: In a left congruous homonymous hemianopia. Where is the lesion most likely to be? Right occipital cortex

Cortical blindness

- The visual cortex is located in the occipital lobes, receiving its blood supply from the posterior cerebral arteries.
- The area for macular vision is in a small area adjacent to the calcarine sulcus.
- Bilateral occlusion or infarction of the vessels supplying this area results in cortical blindness:
- the visual pathways as far as the cortex are normal and as a result pupillary reactions and fundoscopy are normal.
- **Patients with cortical blindness frequently have visual hallucinations and occasionally deny that they are blind.**

Drop attacks

- Drop attacks describes the sudden falling to one's knees **without loss of consciousness** and without warning. Recovery is immediate.
- Often the attacks spontaneously stop after a year or two.
- The aetiology of drop attacks is uncertain.
- Over 90% of drop attacks occur in women although men can develop the problem.
- The average age of onset is between 45 and 55
- **textbooks suggest that vertebrobasilar ischaemia is the cause**

Features

- sudden fall to the ground while standing or walking
- Patients with functional drop attacks normally can't remember the fall itself but are aware of the impact on the ground (or within seconds of falling). This is different to a mechanical fall when people often do remember the fall (often in detail). Its also different to a dissociative attack (non-epileptic attack) where there is an actual 'blackout'.
- Unlike an epileptic seizure or a faint, people with drop attacks can usually get up again quite quickly
- Injury is a common consequence

Klüver–Bucy syndrome

- Klüver–Bucy syndrome is a syndrome resulting from bilateral lesions of the medial temporal lobe (including **amygdaloid** nucleus).
- Herpes simplex virus-1 can cause bilateral amygdala lesions leading to Klüver–Bucy syndrome.
- may present with
  - compulsive eating,
  - **hypersexuality**,
  - **insertion of inappropriate objects in the mouth (hyperorality),**
  - visual agnosia, and docility.

Cranial nerves

Cranial Nerve	Fibres	Structures Innervated	Functions	Brainstem Nucleus
I Olfactory	Sensory	Olfactory epithelium (via olfactory bulb)	Olfaction	----------
II Optic	Sensory	Retina	Vision	----------
III Oculomotor	Motor	Superior/middle/inferior rectus, inferior oblique, levator palpebrae.	Movement of eye ball	Oculomotor nucleus
	Parasympathetic	Pupillary constrictor, cillary muscle of eyeball. Both via the ciliary ganglion	Pupillary constriction and accommodation	Oculomotor nucleus
IV Trochlear	Motor	Superior oblique	Movement of eyeball	Trochlear nucleus
V Trigeminal	Sensory	Face, scalp, cornea, nasal and oral cavities, cranial dura mater.	General sensation	Trigeminal sensory nucleus
	Motor	Muscles of mastication	Opening/closing mouth	Trigeminal Motor nucleus
		Tensor Tympani muscle	Tension of tympanic membrane	Trigeminal Motor nucleus
VI Abducens	Motor	Lateral rectus	Movement of eyeball	Abducens nucleus
VII Facial	Sensory	Anterior 2/3 of tongue	Taste	Nucleus Solitarius
	Motor	Muscles of facial expression	Facial Movement	Facial Motor nucleus
		Stapedius Muscle	Tension of ossicles	Facial Motor Nucleus
	Parasympathetic	Salivary and lacrimal glands via submandibular and pterygopalatine ganglia	Salivation and Lacrimation	Superior Salivaroty Nucleus
VIII Vestibulocochlear	Sensory	Cochlea	Hearing	Cochlear Nucleus
		Vestibular apparatus	Proriception of head, balance.	Vestibular nucleus
IX Glossopharyngeal	Sensory	Eustachian tube, middle ear	General Sensation,	Trigeminal Sensory nucleus
		Caroitd Body, and sinus	Chemo/baroreception	
		Pharynx, posterior 1/3 of tongue	Taste	Nucleus Solitarius
	Motor	Styropharyngeous	Swallowing	
	Parasympathetic	Salivary glands via the otic ganglion	Salivation	Inferior Salivatory nucleus
X Vagus	Sensory	Pharynx, larynx, oesophagus, external ear	General Sensation	Trigeminal Sensory nucleus
		Aortic bodies and arch	Chemo/baroreception	
		Thoracic and abdominal viscera	Visceral Sensation	Nucleus Solitarus
	Motor	Soft Palate, larynx, pharynx, upper oesophagus	Speech, swallowing	Nucleus Ambiguus
	Parasympathetic	Cardiovascular, respiratory and gastrointestinal systems.	Control of these systems	Dorsal Motor nucleus of Vagus
XI Accessory	Motor	Sternomastoid, trapezius	Movement of head and shoulders	Nucelus Ambiguus, cranial nerves
XII Hypoglossal	Motor	Intrinsic and extrinsic muscles of tongue	Movement of tongue	Hypoglossal nucleus

Brain stem (Mid brain, Pons, Medulla Oblongata) lesions are typically characterized by ipsilateral cranial nerve involvement and contralateral body involvement.

- Lesions of the **cerebellopontine angle** causes compression of cranial nerves **V (**trigeminal), **VII** (facial) **and VIII** (vestibulocochlear).
- The **cavernous sinus syndrome** consists of variable involvement of
  - Oculomotor **(III)**
  - Trochlear **(IV)**
  - Abducens **(VI)**
  - Trigeminal (ophthalmic and maxillary division) **(V)** and
  - Oculo-sympathetic nerves.
- The **superior orbital fissure** syndrome is similar to the cavernous sinus syndrome except for the presence of **proptosis**.
- **petrous apex lesion**
  - **features**
    - **abducens nerve palsy**
      - **horizontal diplopia**
    - **ipsilateral Facial pain** or sensory disturbance (**numbness**) in the trigeminal nerve distribution
      - occurs secondary to involvement of the trigeminal nerve at the Meckel cave.
  - causes
    - meningioma or nasopharyngeal carcinoma of the petrous apex.
      - The most common cause now
    - petrous osteitis (Gradenigo syndrome)

- In the pre-antibiotic era

Optic nerve

- The optic and olfactory nerves lie entirely within the **supra-tentorial fossa**, unlike the rest of the cranial nerves.
- **The optic nerve is part of the central nervous system, hence its myelin sheaths are derived from oligodendrocytes**, not Schwann cells.
- Accordingly, diseases of the peripheral nervous system and radiculopathies don't target the optic nerve.
- The physiological blind spot results from absence of photoreceptors in the area of the retina where the optic nerve leaves the eye.
- It leaves the eye through the optic canal. It forms the afferent pathway of the direct and consensual pupillary reflexes.

Oculomotor Third (III) nerve palsy

Features

- divergent squint - affected eye deviated **'down and out'**.
- ptosis
- dilated pupil (sometimes called a 'surgical' third nerve palsy)
- **Unreactive pupil to light**

Causes

- diabetes mellitus
- vasculitis e.g. temporal arteritis, SLE
- false localizing sign due to uncal herniation through tentorium if raised ICP
- posterior communicating artery aneurysm (pupil dilated)
- cavernous sinus thrombosis
- Weber's syndrome: ipsilateral third nerve palsy with contralateral hemiplegia -caused by midbrain strokes
- other possible causes: amyloid, multiple sclerosis

Ipsilateral 3rd CN palsy + contralateral hemiplegia → Weber's syndrome
Ipsilateral 3rd CN palsy + contralateral hemiataxia → Benedikt syndrome
Ipsilateral 3rd CN palsy + ipsilateral hemiparesis + Contralateral homonymous hemianopsia → Uncal herniation

Painful third nerve palsy = posterior communicating artery aneurysm

Fourth nerve (IVth) palsy

Overview

- supplies superior oblique (depresses eye, moves inward)
- Head trauma (including minor head injuries) can result in a trochlear nerve palsy as it is compressed against the tentorial edge or along another part of the pathway.
- **The fourth cranial nerve palsy → superior oblique palsy →vertical diplopia → (eg: missing steps when walking down the stairs, bumping head when trying to get out of a car)**

Features

- **vertical diplopia**
- classically noticed when reading book or going down stairs
- The trochlear nerve would lead to **nystagmus on looking down and out**.

Trigeminal neuralgia

Trigeminal neuralgia - carbamazepine is first-line

- Sensation over the face is supplied by the trigeminal nerve
- Trigeminal neuralgia is a pain syndrome characterised by severe unilateral pain.

- **Causes**
  - idiopathic (The vast majority)
  - compression of the trigeminal roots by tumours or vascular problems
- The International Headache Society defines trigeminal neuralgia as:
  - unilateral disorder characterised by brief **electric shock-like pains**, abrupt in onset and termination, limited to one or more divisions of the trigeminal nerve
  - the pain is commonly evoked by light touch, including washing, shaving, smoking, talking, and brushing the teeth (**trigger factors**), and frequently occurs spontaneously
  - small areas in the nasolabial fold or chin may be particularly susceptible to the precipitation of pain (**trigger areas**)
  - the pains usually remit for variable periods
- **Management**
  - carbamazepine is first-line
  - failure to respond to treatment or atypical features (e.g. < 50 years old) should prompt referral to neurology

January 2015 exam: History of electric shock like pains on the right side of the face. around 10-20 episodes a day which, each lasting for around 30-60 seconds. What is the most suitable first-line management? Carbamazepine

What is the nerve supply to the angle of the jaw?

- **The angle of the jaw is supplied by nerve roots C2/C3 and not the trigeminal nerve.**
- In patients with non-organic sensory loss, that loss usually extends to the edge of the jaw.

abducens (VIth) nerve palsy

- The VIth nerve is motor to the lateral rectus muscle.
- **It is responsible for abduction of the ipsilateral eye.**
- In the neutral position the affected eye is deviated medially due to unopposed action of the medial rectus.
- **In patients with diplopia the 'cover test' can be used to determine the eye that has the problem.**
  - **On covering the affected eye the outermost image disappears.**
  - Eg : **diplopia on right horizontal gaze , improved on covering the right eye → the right abducens is affected**
- After finding a VIth nerve palsy the cause should always be looked for, it is not a diagnosis in itself.
- Due to the long course and anatomy of the VIth nerve it can be damaged in any condition causing raised intracranial pressure. It can therefore be a 'false localising sign'.

Facial (VII) nerve

Facial nerve branches (mnemonic)
(superior to inferior) as they exit the anterior border of the parotid gland: **T**o **Z**anzibar **B**y **M**otor **C**ar

1. **T:** temporal
2. **Z:** zygomatic
3. **B:** buccal
4. **M:** mandibular
5. **C:** cervical

Facial Palsy + convergent squint
↓
lesion in Pons
as VI th is encircled by VII th

Supply - 'face, ear, taste, tear'

- face: muscles of facial expression
- ear: nerve to stapedius **(Hyperacusis is due to paralysis of stapedius)**
- taste: supplies anterior two-thirds of tongue
- tear: parasympathetic fibres to lacrimal glands, also salivary glands
- **Orbicularis oculi** is affected causing inability to blink/close eyelids.

Causes of bilateral facial nerve palsy

1. sarcoidosis
2. Guillain-Barre syndrome
3. polio,
4. Lyme disease

Causes of unilateral facial nerve palsy - as above plus

Lower motor neuron	Upper motor neuron
• **Bell's palsy** • **Ramsay-Hunt syndrome (due to herpes zoster)** • **acoustic neuroma** • **parotid tumours** • **HIV** • **multiple sclerosis*** ➢ may also cause an UMN palsy • **diabetes mellitus**	• **stroke**

LMN vs. UMN

- upper motor neuron lesion 'spares' upper face i.e. forehead
- lower motor neuron lesion affects all facial muscles

Bell's palsy

Definition

- acute, unilateral, idiopathic, facial nerve paralysis.

Causes

- unknown
- although the role of the herpes simplex virus has been investigated previously.

Epidemiology

- The peak incidence is 20-40 years
- more common in pregnant women.

Features

- lower motor neuron facial nerve palsy - forehead affected
- other features
  - post-auricular pain (may precede paralysis),
  - altered taste,
  - dry eyes,
  - hyperacusis (seen in around a third of patients)

Management

- **prednisolone 1mg/kg for 10 days should be prescribed for patients within 72 hours of onset of Bell's palsy**.
- **Adding in aciclovir gives no additional benefit**
- eye care is important - prescription of artificial tears and eye lubricants should be considered

Prognosis

- if untreated around 15% of patients have permanent moderate to severe weakness

January 2012 exam: Which features would be most consistent with a diagnosis of Bell's palsy? Hyperacusis

May 2010 exam: What is the current evidenced base approach to the management of Bell's palsy? Prednisolone

Ramsay Hunt syndrome

Aetiology

- Ramsay Hunt syndrome (herpes zoster oticus) is caused by the **reactivation** of the varicella zoster virus in the **geniculate ganglion** of the seventh cranial nerve.

Features

- **auricular pain** is often the **first feature**
- facial nerve palsy
- **vesicular rash around the ear**
- other features include vertigo and tinnitus

Management

- oral aciclovir and corticosteroids are usually given

Acoustic neuroma

Loss of corneal reflex - think acoustic neuroma

- Acoustic neuromas (more correctly called vestibular schwannomas)
- account for 5% of intracranial tumours and 90 % of cerebellopontine angle
- **Features can be predicted by the affected cranial nerves**
  - cranial nerve V: absent corneal reflex
  - cranial nerve VII: facial palsy
  - cranial nerve VIII: **hearing loss**, vertigo, **tinnitus**
- Bilateral acoustic neuromas are seen in **neurofibromatosis type 2**
- **MRI of the cerebellopontine angle is the investigation of choice**

Other notes

- The lacrimal gland is supplied by the facial nerve.
- The glossopharyngeal nerve supplies the parotid salivary gland controlling salivary secretions.
- The trochlear nerve supplies the superior oblique muscle.
- The oculomotor nerve innervates the superior rectus.
- **The vagus nerve supplies the palatal muscles.**

Holmes tremor

Holmes tremor → lesion in the red nucleus

- Holmes tremor is caused by a lesion in the red nucleus.
- This is most commonly due to a previous stroke of this area.
- It is classically an irregular low frequency tremor which is a combination of resting, postural and action tremor.
- It may also arise from any underlying structural disorders including multiple sclerosis, tumors, haemorrhage, trauma, neuroleptic agents, radiation.
- Treatments include:
  - medical therapy such as levodopa
  - however thalamotomy or chronic thalamic stimulation have also shown to play a role in managing this condition.

Movement disorders

Movement disorders in order of least speed to fastest (DACB)

- Dystonia - fixated position
- Athetosis - Snake-like writhing (slow)
- Choreiform - Like a dance choreographer
- Ballistic/Ballismus/Hemiballismus - Fast flinging movements, can injure themselves or others 'like a ballistic missile' (memorisation method)

Chorea

Chorea is caused by damage to the basal ganglia, in particular the Caudate nucleus

- Chorea describes involuntary, rapid, jerky movements which often move from one part of the body to another ('dance-like').
  - Slower, sinuous movement of the limbs is termed athetosis.
- **Chorea is caused by damage to the basal ganglia, especially the caudate nucleus.**

Causes of chorea

- **Inherited causes** such as:
  - Huntington's chorea
  - Wilson's disease
  - ataxic telangiectasia
- **Acquired causes** include:
  - Drugs - antipsychotics, anticonvulsants, amphetamines, oral contraceptive pill, L-dopa, dopamine agonists in patients with Parkinson's disease
  - Toxins - carbon monoxide, cyanide, opiates, mercury
  - Immune - post-streptococcal (rheumatic fever) (Syndenham's chorea), SLE, anti-phospholipid syndrome, vasculitis (PAN, Behcet's disease)
  - Infectious - meningitis, encephalitis, cerebral toxoplasmosis, new variant Creutzfeldt-Jakob disease
  - Vascular - stroke, polycythaemia, moyamoya
  - Hormonal - hypoparathyroidism, pregnancy, OCP, HRT, hyperthyroidism
  - Metabolic - hyper/hyponatraemia, hypo/hyperglycaemia, hypomagnesaemia, hypocalcaemia, B1 and B12 deficiency. thyrotoxicosis
  - Paraneoplastic - small cell lung carcinoma, renal cell carcinoma, ovarian carcinoma, lymphoma polycythaemia rubra vera
  - CNS - trauma, tumours, senile chorea. neuroacanthocytosis

- pregnancy: **chorea gravidarum**
  - often in patients who have had rheumatic fever.
  - usually begins in 1st trimester and **resolves spontaneously after delivery.**
  - If treatment before delivery is necessary because chorea is severe, **barbiturates** are indicated because they have fewer fetal risks than other drugs used to manage chorea.
  - Rarely, a similar disorder occurs in women taking oral contraceptives.

September 2012 exam: (SLE) presents with continuous jerky, irregular movements, which move from one limb to another. Where is the lesion most likely to be? Caudate nucleus

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Cerebellar syndrome

Unilateral cerebellar lesions cause ipsilateral signs

Causes

- Friedreich's ataxia, ataxic telangiectasia
- neoplastic: cerebellar haemangioma
- stroke
- alcohol
- multiple sclerosis
- hypothyroidism
- drugs: phenytoin, lead poisoning
- paraneoplastic e.g. secondary to lung cancer

A history of vertigo, nystagmus, Slurred speech, intention tremor and past pointing, as well as ataxia, suggest the cerebellum as the site of injury.

Oppenheim's sign is seen when scratching of the inner side of leg leads to extension of the toes. It is a sign of cerebral irritation

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Inferior cerebellar vermis lesion

A patient has: 1. A staggering gait 2. Truncal instability 3. Normal arm and leg coordination 4. Spontaneous nystagmus 5. A rotated head posture

In children the commonest cause is a medulloblastoma.

Abnormal gait

- **lesions of cerebellar vermis cause → truncal ataxia and tendency to fall backwards.**
- Basal ganglia disease causes→ extrapyramidal signs with Parkinsonism (festinant gait, marche à petits pas).
- Proximal myopathy causes → a waddling gait.
- **Phenytoin toxicity → broad-based ataxic gait**

Gait disturbance may occur for a variety of reasons:

- Sensory ataxia in B_{12} deficiency and tabes dorsalis
- Pyramidal signs in B_{12} deficiency and SLE
- Cerebellar ataxia in cerebrotendinous xanthomatosis.

Nystagmus

Upbeat nystagmus → cerebellar vermis lesions
Downbeat nystagmus → foramen magnum lesions (Arnold-Chiari malformation)

- Nystagmus is defined as involuntary oscillations of the eyes.
- This may be pendular when the oscillations are equal in rate and amplitude, or jerking when there are quick and slow phases. (The quicker phase is used to define the direction.)
- Nystagmus may be caused by:
  - Visual disturbances
  - Lesions of the labyrinth
  - The central vestibular connections
  - Brain stem or cerebellar lesions.
- Pendular nystagmus is due to:
  - usually due to loss of macular vision,

  - may be seen in diffuse brain stem lesions.
- **Jerking nystagmus which is of constant direction regardless of the direction of gaze**, suggests → a labyrinthine or cerebellar lesion.
- **Nystagmus which changes with the direction of gaze** suggests widespread central involvement of **vestibular nuclei.**
- **Jerking nystagmus presents only on lateral gaze**, the fast component of which is in the direction of gaze and indicates a **lesion of the brain stem or cerebellum.**
- Nystagmus confined to one eye suggests:
  - a peripheral lesion of the nerve or muscle,
  - or a lesion of the medial longitudinal bundle.
- Nystagmus restricted to the abducting eye on lateral gaze (ataxic nystagmus) is due to a **lesion of the medial longitudinal bundle** between the pons and mid-brain as in multiple sclerosis (MS).
- Nystagmus occurring on upward gaze with the fast component upwards (upbeat nystagmus) may be due to a **lesion in the mid-brain** at the level of the superior colliculus.
- **Downbeat nystagmus (fast phase downwards) suggests a lesion in the lower part of the medulla. It is therefore typical of the Arnold-Chiari malformation (Chiari type I malformation).**
- Wernicke's encephalopathy is another rare cause.
- Horizontal nystagmus occurs in unilateral disease of the cerebral hemisphere, with the fast phase directed to the side of the lesion.
- Lateral cerebellar lesions classically cause pronounced nystagmus, whereas this is rarer and much more subtle with midline lesions.

May 2007 exam: Which one of the following is most associated with downbeat nystagmus? Arnold-Chiari malformation

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Spinocerebellar ataxia

- Spinocerebellar ataxias are a group of autosomal dominant disorders which are associated with the progressive development of ataxic features such as gait disturbance, nystagmus and tremor.
- The majority of affected patients develop symptoms within the 3rd and 4th decade.

Hemiballism

Hemiballism is caused by damage to the subthalamic nucleus

The presence of severe flinging movements affecting proximal muscles and following no particular pattern is typical for hemiballism.

- damage to the subthalamic nucleus of the basal ganglia → Hemiballism → decreased suppression of involuntary movements.
- Ballisic movements are involuntary, sudden, jerking movements which occur contralateral to the side of the lesion.
- The ballisic movements primarily affect the proximal limb musculature whilst the distal muscles may display more choreiform-like movements
- It is always unilateral, but it is common for arms and legs to move together.
- Bilateral ballismus is rare and implicates a metabolic cause, usually non-ketotic hyperosmolar coma.
- **Symptoms may decrease whilst the patient is asleep.**
- The movements worsens with activity, and decrease with relaxation.

Causes

- vascular events (stroke). **infarction being the commonest cause**.
- traumatic brain activity
- amyotrophic lateral sclerosis
- hypergylcaemia
- malignancy

- vascular malformations
- tuberculomas, and
- demyelinating plaques.

Treatment

- Anti-dopaminergic agents (e.g. Haloperidol) are the mainstay of treatment.
- Topiramate can be used, as can intrathecal baclofen, botulinum toxin and **tetrabenazine**.
- Functional neurosurgery can be used for cases which have failed to respond to other treatment.

Prognosis

- Usually the flinging movements stop spontaneously in the next four to eight weeks

September 2012 exam: H/O involuntary, jerking movements of arms, resolved during asleep. Damage to which structure may lead to hemiballism? Subthalamic nucleus

Epilepsy

Epilepsy classification

Basics

- two main categories are generalised and partial seizures
- partial seizures may progress to general seizures
- other types: myoclonic, atypical absence, atonic and tonic seizures are usually seen in childhood

Generalised - no focal features, consciousness lost immediately

- grand mal (tonic-clonic)
- petit mal (absence seizures)
- myoclonic: brief, rapid muscle jerks
- **Lennox-Gastaut syndrome**
  - Occurs in 1 – 5 in every 100 children with epilepsy.
  - The most common cause of intractable (difficult to treat) childhood epilepsy.
  - The most common time for it to start is between three and five years of age.
  - The most common type of seizures is atonic seizures or ‘drop attacks’.
- partial seizures progressing to generalised seizures

Partial - focal features depending on location

- simple (no disturbance of consciousness or awareness)
- complex (consciousness is disturbed)
- **jacksonian seizure**
  - also known as a focal (partial) motor seizure.
  - In this condition an uncontrolled, spontaneous discharge of electricity from one motor cortex presents with contralateral motor signs.
  - The patient has preserved consciousness as it is a partial seizure
  - after the seizure it is common to have a Todd's paralysis where the limb is weak.
- **Temporal lobe epilepsy** presents with the sensation of déjà vu or an unreal feeling and can progress to hallucinations and altered conscious level.
- **Rolandic epilepsy** is a benign partial epilepsy associated with centro-temporal spikes. There is an excellent prognosis.
- **aversive seizures** are a form of simple partial seizure, consisting of head turning and conjugate eye movements.

Complex partial seizures

- Temporal lobe epilepsy can take the form of automatisms such as chewing and swallowing repeatedly, scratching the head or searching for an object.
- Some people may even undress.
- Spread of the seizure activity to the contralateral temporal lobe impairs memory of the event in the complex partial form of temporal lobe epilepsy.
- They can occur as a result of seizure activity in any part of the brain but **most commonly arise in the temporal lobes**.
- The commonest finding is **hippocampal sclerosis**
- **MRI is an appropriate investigation**

Epilepsy: treatment

Epilepsy medication: first-line

- generalised seizure: sodium valproate
- partial seizure: carbamazepine

Patients cannot drive for 6 months following a seizure

Most neurologists now start antiepileptics following a second epileptic seizure. NICE guidelines suggest starting antiepileptics after the first seizure if any of the following are present:

- the patient has a neurological deficit
- brain imaging shows a structural abnormality
- the EEG shows unequivocal epileptic activity
- the patient or their family or carers consider the risk of having a further seizure unacceptable

Sodium valproate is considered the first line treatment for patients with generalised seizures with carbamazepine used for partial seizures

Generalised tonic-clonic seizures

- sodium valproate
- second line: lamotrigine, carbamazepine

Absence seizures* (Petit mal)

- sodium valproate or **ethosuximide**
- sodium valproate particularly effective if co-existent tonic-clonic seizures in primary generalised epilepsy
- *carbamazepine may actually exacerbate absence seizure

Myoclonic seizures

- sodium valproate
- second line: clonazepam, lamotrigine
- (carbamazepine and phenytoin may **worsen** myoclonic seizures).

Partial seizures

- carbamazepine
- second line: lamotrigine**, sodium valproate
  - **the 2007 SANAD study indicated that lamotrigine may be a more suitable first-line drug for partial seizures although this has yet to work its way through to guidelines

Stopping of anti-epileptic drugs (AED) (2004 NICE guidelines)

- **Can be considered if seizure free for > 2 years, with AEDs being stopped over 2-3 months**
- Benzodiazepines should be withdrawn over a longer period.

AED cessation can be considered if seizure free for > 2 years – Stop AEDs over 2-3 months

January 2015 exam: Which one of the antiepileptic drugs is most associated with weight gain? Sodium valproate

September 2012 exam: What is the most appropriate first-line antiepileptic for myoclonic seizures? Sodium valproate

Absence seizures

Absence seizures - good prognosis: 90-95% become seizure free in adolescence

- Absence seizures (petit mal) are a form of generalised epilepsy that is mostly seen in children.
- The typical age of onset of 3-10 years old and girls are affected twice as commonly as boys.

Features

Absence seizure (petit mal) presents with a blank stare, **3 Hz** brain waves and do not show postictal confusion.

- absences last a few seconds and are associated with a quick recovery
- seizures may be provoked by hyperventilation or stress
- the child is usually unaware of the seizure
- they may occur many times a day
- EEG: bilateral, symmetrical 3Hz spike and wave pattern

Management

- sodium valproate and ethosuximide are first-line treatment
  - **Absence seizures** are best treated by drugs that specifically target **T-type calcium currents**, which are believed to be involved in providing the pacemaker current for **thalamic neurons**, which then generate the generalized rhythmic discharge in the cortex during absence attacks.
    - The only two drugs listed that **target the T-type calcium current** are ethosuximide and valproic acid .
    - **Ethosuximide has much better safety profile than valproic acid, and thus is considered first-line treatment**

Prognosis

- good prognosis - 90-95% become seizure free in adolescence

Juvenile myoclonic epilepsy

Juvenile myoclonic epilepsy is the **most common** primary generalised epilepsy, but is underdiagnosed due to lack awareness of the condition by doctors

- is a common form of idiopathic generalised epilepsy, representing 10% of all patients with epilepsy.
- typically first manifests itself **between the ages of 10 and 18** with brief episodes of involuntary muscle twitching occurring early in the morning.
- **Genetic**
  - The condition is genetically linked to the short arm of chromosome 6.
- **Presentation**
  - Absence seizures in childhood (which may be remain undiagnosed)
  - Myoclonic jerks, especially of the upper limbs, which predominantly occur in the mornings shortly after waking (and may be so subtle as to be interpreted as 'clumsiness' when eating breakfast)
  - Generalised tonic-clonic seizures, which often present for the first time between the ages of 13 and 18 years (usually provoked by sleep deprivation and/or excessive alcohol intake)
  - There may be a positive family history
- **Precipitating factors include:**
  - alcohol,
  - menstruation and
  - sleep deprivation.
- **Investigations**

  - Interictal EEG is diagnostic showing → generalised spike- and polyspike-wave activity; a photosensitive response may also be present
- **Management**
  - responds extremely well to **sodium valproate**
  - other options include, lamotrigine and topiramate.
  - but may be exacerbated by some other antiepileptic drugs including carbamazepine
  - Lifelong drug treatment is usually necessary to avoid relapses in patients who achieve seizure-free status on medication.
- **Prognosis**
  - Prognosis is extremely favourable if the condition is treated correctly, with many patients becoming seizure-free.

Epilepsy in children: syndromes

Infantile spasms (West's syndrome)

- brief spasms beginning in first few (4-6) months of life; M>F
- 1. Flexion of head, trunk, limbs → extension of arms (Salaam attack); last 1-2 secs, repeat up to 50 times
- 2. Progressive mental handicap
- 3. EEG: hypsarrhythmia
- usually 2nd to serious neurological abnormality (e.g. TS, encephalitis, birth asphyxia) or may be cryptogenic
- poor prognosis
- vigabatrin/steroids

Typical (petit mal) absence seizures

- onset 4-8 yrs
- duration few-30 secs; no warning, quick recovery; often many per day
- EEG: 3Hz generalized, symmetrical
- sodium valproate, ethosuximide
- good prognosis: 90-95% become seizure free in adolescence

Lennox-Gastaut syndrome

- may be extension of infantile spasms (50% have hx)
- onset 1-5 yrs
- atypical absences, falls, jerks
- 90% moderate-severe mental handicap
- EEG: slow spike
- ketogenic diet may help

Benign rolandic epilepsy

- most common in childhood, M>F
- paraesthesia (e.g. unilateral face), usually on waking up

Juvenile myoclonic epilepsy (Janz syndrome)

- onset: teens; F:M = 2:1
- 1. Infrequent generalized seizures, often in morning
- 2. Daytime absences
- 3. Sudden, shock like myoclonic seizure
- usually good response to sodium valproate

Neonatal period - try vitamin B6

- 2nd: hypoglycaemia, meningitis, head trauma
- pyridoxine dependency (AR, IV B6)
- benign familial neonatal seizures (AD)
- benign neonatal convulsions (5th day)

Gelastic seizures

- **Gelastic seizures should be suspected in cases of erratic laughing or crying.**
- The term Gelastic originates from the Greek word "Gelos" which means laughter
- **typically arise from hypothalamic hamartomas**
- It can be hard to identify in young children but there is usually associated automatisms such as fidgeting or lip smacking or change in sensorium.

Status epilepticus

- Status epilepticus is traditionally defined as **continuous convulsion lasting longer than 30 minutes**, or the occurrence of serial convulsions between which there is no return of consciousness.
- It may be generalised (tonic clonic, absent) or partial (simple, complex, or with secondary generalisation). Generalised tonic clonic seizures predominate.
- This is a medical emergency. The priority is termination of seizure activity, which if prolonged will lead to irreversible brain damage.
  - Approximately 20 minutes of status epilepticus produces regional oxygen sufficiency deficiency promoting cell damage and necrosis. This is, therefore, used as the threshold in children.
  - Cell death thus results in increased metabolic demands from continually discharging neurones. Vulnerable areas include the hippocampus, the mid to low cerebellum, middle cortical areas, and thalamus.
- The relationship between neurological outcome and duration of status epilepticus is unknown
- The most common cause in a child less than 3 years is a prolonged febrile seizure. Sleep deprivation and drug withdrawal can also precipitate it.
- There are three major sub-types:
  1. prolonged febrile seizures.
  2. idiopathic status epilepticus (no underlying central nervous system [CNS] lesion or insult).
  3. symptomatic (longstanding neurological disorder or metabolic abnormality).

Management

- **General treatment**
  - Initial management begins with ABC.-**Maintain airway and circulation with intubation**
  - Remember "DEFG" (Don't Ever Forget Glucose): Hypoglycaemia should be excluded as it is easily and rapidly treatable (if present 3-5 ml/kg of 10% dextrose is given by IV infusion),
  - blood obtained for full blood count, electrolytes including calcium and magnesium, glucose, creatinine, anticonvulsant levels. Blood and urine may be obtained for toxicology. Arterial blood gases should be done, and consideration given to lumbar puncture.
- **Anticonvulsant therapy**
  - **First-line** drugs are benzodiazepines such as diazepam or lorazepam.
    - Lorazepam is preferred because of long duration of anti-epileptic effect.
    - This is effective in ~80% cases.
    - If the patient does not respond, the regime may be repeated after 5-10 minutes using the same or a different benzodiazepine.
    - If ineffective within 10 minutes it is appropriate to start a **second-line** agent
  - **Second-line**
    - If seizures recur or fail to respond after 30 minutes a parenteral anti-epileptic agent should be started.
    - such as **phenytoin**, sodium valproate, levetiracetam, or phenobarbital.
      - phenytoin may be given as a loading dose followed by an infusion.
      - **Fosphenytoin**:
        - Fosphenytoin is a pro-drug of phenytoin - metabolised in the body to phenytoin and endogenous phosphates.
        - has several advantages over phenytoin:
          - ✓ it can be given IV or IM (phenytoin can only be given IV)
          - ✓ can be given at infusion rates three times faster than phenytoin
          - ✓ therapeutic levels are achieved within 10 minutes,
          - ✓ it has a lower incidence of adverse events than phenytoin.
        - If the patient is already taking phenytoin, either IV phenytoin or fosphenytoin should still be given: it is likely that plasma levels are subtherapeutic.
  - **Third-line**
    - If no response within 30 minutes from onset, then the best way to achieve rapid control of seizure activity is induction of **general anaesthesia**.
      - The anaesthetic agents **thiopental** and **propofol** may be effective (unlicensed indication) but should only be done with full intensive care support.

If a patient in generalised status epilepticus does not respond to lorazepam and adequate doses of intravenous phenytoin, what is the next step in their management?

➔ **Transfer to an Intensive Therapy Unit**

The use of phenytoin is not recommended in patients with underlying liver impairment therefore not used in status epilepticus secondary to alcohol withdrawal.

Drug therapy

- **Only start after a minimum of two fits.**
- **Only use one drug at a time, and begin with a small dose, and gradually increase it, until control is achieved, toxic affects occur, or the maximum dose is reached.**

Drug	Mechanism	Side effects	Clinical uses
Phenobarbital	**Inhibits sodium channels**, thus reducing action potential propagation. **Does not lower the seizure threshold.**	**Sedation,** impairment of motor and cognition systems after long term use, megaloblastic anaemia	Rarely used due to sedation – been superceeded by**phenytoin**
Phenytoin	**Inhibits sodium channels**, thus reducing action potential propagation. Acts on voltage dependent channels, and selectively binds when they are in the open state.	Vertigo, nystagmus,headaches, megaloblasticanaemia, hypersensitivity,confusion and cognition problems (high dose).**Teratogenic, gum hypertrophy,** arrythmias	Partial and generalised attacks, but **not in absence.** High doses my precipitate attacks
Carbamazepine	**Inhibits sodium channels**, thus reducing action potential propagation. Acts on voltage dependent channels, and selectively binds when they are in the open state.	Ataxia, **drowsyness,**dizziness, GI disturbance, cardio effects, water rention (and subsequenthyponatraemia), **altermetabolism of other drugs,skin rash**	**First line for partial seizures** Also often tried as a 2nd or third line drug, when other treatments have been unsuccessful.
Lamotrigine	**Inhibits sodium channels**, thus reducing action potential propagation.	Nausea, dizziness, ataxia	**Generalised seizures –** 2nd line treatment
Ethosuximide	**Calcium channel inhibitor –**inhibits calcium channels of the T-type – thought to be involved in the 3Hz rhythmic discharge seen in absence seizures	Dizziness, nausea, anorexia, lethargy. Can precipitate tonic/clinic attacks	Useful for **absence seizures**
Sodiumvalproate	**Increases GABA concentration** **Inhibits sodiumchannels** **Inhibits glutamate decarboxylase**	**Very few side effects.** **Highly teratogenic** 10% will have hair loss **Reduces efficacy of contraceptive pill**	**First line treatment for: Absence seizures Generalised seizures second line treatment for partial seizures**

Which antiepileptic drugs does not have interactions with warfarin?

- **Lamotrigine has no effect on liver enzymes and is the treatment of choice for patient taking warfarin**
- Phenytoin, carbamazepine, primidone and phenobarbital are liver enzyme inducers
- Sodium valproate is a liver enzyme inhibitor

What is the likelihood of being seizure-free after a second or third antiepileptic is added?

- A study of patients with previously untreated epilepsy demonstrated that 47% achieved control of seizures with the use of their first single drug.
- **14 % became seizure-free during treatment with a second or third drug.**

September 2008 exam: H/O complex partial seizures, not able to tolerate either carbamazepine or sodium valproate. What is the most appropriate next line drug? Lamotrigine

What is the likelihood of controlling seizures in a patient never previously on anti-epileptic medication?

A study of patients with previously untreated epilepsy demonstrated that:

- **With a single first-line anti-convulsant agent → 47% achieved control of seizures**
- Fourteen per cent became seizure-free during treatment with a second or third drug.
- An additional 3% became seizure-free with the use of two drugs simultaneously.

Epilepsy: pregnancy and breast feeding

Epilepsy + pregnancy = 5mg folic acid

- The risks of uncontrolled epilepsy during pregnancy generally outweigh the risks of medication to the fetus.
- All women thinking about becoming pregnant should be advised to take folic acid 5mg per day well before pregnancy to minimise the risk of neural tube defects.
- Around 1-2% of newborns born to non-epileptic mothers have congenital defects. This rises to 3-4% if the mother takes antiepileptic medication.

Other points

- aim for monotherapy
- there is no indication to monitor antiepileptic drug levels
- **Sodium valproate** (November 2013 Drug Safety Update)
  - **Sodium valproate should not be used during pregnancy and in women of childbearing age unless clearly necessary**.
  - associated with neural tube defects
  - New evidence showing a significant risk of neurodevelopmental delay in children following maternal use of sodium valproate.
  - Women of childbearing age should not start treatment without specialist neurological or psychiatric advice.
  - Because of relatively short half-life, it should be taken 2-3 times per day.
  - It can result in pancreatitis (and severe abdominal pain).
- **carbamazepine**: often considered **the least teratogenic of the older antiepileptics**
- **phenytoin**:
  - associated with cleft palate
  - It is advised that **pregnant women taking phenytoin are given vitamin K in the last month of pregnancy to prevent clotting disorders in the newborn.**
- **Lamotrigine**:
  - the rate of congenital malformations may be low.
  - The dose of lamotrigine may need to be increased in pregnancy
- **Breast feeding** is generally considered safe for mothers taking antiepileptics with the possible exception of the barbiturates

Prescribing in patients with epilepsy

- The following drugs may worsen seizure control in patients with epilepsy:
  - alcohol, cocaine, amphetamines
  - ciprofloxacin, levofloxacin
  - aminophylline, theophylline
  - buproprion
  - methylphenidate (used in ADHD)
  - mefenmic acid
- Some medications such as benzodiazipines, baclofen and hydroxyzine may **provoke seizures whilst they are being withdrawn.**
- **P450 enzyme inducers** will decrease the drug level and therefore **increase the failure rate of** oestrogen and progesterone containing **contraceptives.**
  - Carbamazepine
  - Oxcarbazepine
  - Phenytoin
  - Phenobarbitone
  - Primidone
  - Topiramate
- Other medications may worsen seizure control by **interfering with the metabolism of anti-epileptic drugs** (i.e. P450 inducers/inhibitors).
- Lamotrigine
  - is not a P450 inducer.
  - Levels of lamotrigine are reduced by oral contraceptives containing ethinylestradiol, increased seizure frequency may therefore occur.
  - There is no evidence that progestogen-only methods affect lamotrigine levels.

Pseudoseizures

Suspected psychogenic non-epileptic seizures→ do Video-EEG recording

- Pseudoseizures are commonly misdiagnosed as true seizures and treated inappropriately with anti-epileptic drugs.

Factors favouring pseudoseizures

- pelvic thrusting
- family member with epilepsy
- more common in females
- **crying after seizure**
- don't occur when alone
- gradual onset
- **prolonged nature of the attacks (15-30 minutes)**
- Violent shaking,
- resistance to passive eye opening
- normal vital signs

Urinary incontinence can also occur in pseudoseizures but tongue biting is rare.

Factors favouring true epileptic seizures

- tongue biting
- raised serum prolactin*
  - *why prolactin is raised following seizures is not fully understood. It is hypothesised that there is spread of electrical activity to the ventromedial hypothalamus, leading to release of a specific prolactin regulator into the hypophyseal portal system

Diagnosis

- **Video telemetry is useful for differentiating**

Treatment

- Simple **observation** is the appropriate management.

Somatosensory seizures

- Spread of symptoms ('marching') **in seconds**
- Example → tingling sensation starts in fingers and spreads **in seconds** to affect the whole arm and leg
- The usual source of somatosensory seizures is the **parietal lobe**.

- **Positive symptoms** (jerking, tingling) usually signify **epilepsy**.
- **Negative symptoms** (weakness, numbness) are usually caused by transient focal **ischaemia**.
- **Spread of symptoms** ('marching') indicates **migraine (in 5-20 minutes)** or **seizures (in seconds).**

Rett syndrome

- Rett syndrome is a neurodevelopmental disorder of the grey matter
- mostly affecting girls.
- related to the MECP2 gene on the X chromosome
- **Feature**
  - Small hands and feet with deceleration of head growth.
  - Epileptic → **repetitive hand movements** such as **hand wringing**.
  - GI problems, such as constipation.

Tourette syndrome

- Definition
  - a chronic neurologic disorder that manifests with motor and vocal tics
- Epidemiology
  - Tourette syndrome presents before 18 years of age and many children grow out of it.
  - more common in males (4:1)
- Pathogenesis
  - due to genetic, environmental, and social factors resulting in an abnormality in the **mesolimbic spinal system**
  - the condition is familial in most cases
- Features
  - The motor tics often have a build up that the patient is aware of, like an itch.
  - **Commonly they involve blinking, throat clearing or shoulder shrugging.**
  - Shouting of swear words is a typical vocal tic of Tourette's.
- Associated conditions:
  - 90% of patients have a comorbid psychiatric disorder such as:
    - attention deficit hyperactivity disorder (~60% of cases)
    - obsessive compulsive disorder (~27% of cases)
- Diagnosis
  - The criteria for diagnosis require multiple motor and one or more vocal tics, showing themselves over a year, with not more than three consecutive months tic free.
  - MRI and EEG are typically normal
- Prognosis
  - tics typically decline during adolescence and may resolve around 18 years of age (~50% of children)
- management
  - Cognitive behavioural approaches (e.g., comprehensive behavioural intervention for tics [CBIT], which includes habit reversal therapy) are considered **first-line** interventions for patients with mild to moderate tics.
  - Medication should be recommended only when behavioural intervention has not been effective or is not available.
    - First-line pharmacotherapy is generally an **alpha-2 agonist** (e.g., clonidine and guanfacine).

Huntington's disease

Genetics

- autosomal dominant, neurodegenerative genetic disorder
- trinucleotide repeat disorder: repeat expansion of CAG
- results in degeneration of cholinergic and GABAergic neurons **in the striatum of the basal ganglia**
- due to defect in huntingtin gene on short arm of chromosome **4**
- The disease may develop earlier in life in each successive generation

Features: typically appear between 30 and 50 years of age.

- chorea
- personality changes (e.g. irritability, apathy, depression) and intellectual impairment (The earliest symptom)
- lack of coordination and an unsteady gait
- dystonia
- saccadic eye movements
- The disease leads eventually to dementia and premature death.

Diagnosis

- **DNA analysis is the most useful diagnostic test**
  - (e.g., via PCR)
  - trinucleotide CAG repeat expansion in the Huntington gene is diagnostic
- **MRI → caudate nucleus atrophy**
  - Atrophy of the caudate nucleus, putamen, and deep cerebral cortex are the hallmark features of Huntington's disease.
  - The role of neuroimaging is primarily to rule out other intracranial causes of a patient's symptoms, rather than to diagnose HD.

Treatment

- **Tetrabenazine works as a VMAT-inhibitor (vesicular monoamine transporter 2),** involved in transportation of monoamines. It is indicated for Huntington's chorea to reduce hyperkinetic movements.

Prognosis

- progressive and incurable condition
- typically results in death 20 years after the initial symptoms develop.
- Average life span after clinical onset is about 15 years.

Subclavian Steal Syndrome

- is associated with retrograde flow in the vertebral artery due to proximal subclavian artery stenosis.
- Neurological symptoms are precipitated by vigorous exercise with the arm above the head, such as painting a wall.
- Diagnosis is often confused with transient ischemic attacks or epilepsy.
- Duplex ultrasound and MRA are the investigations of choice.
- Endarterectomy and stenting are common surgical methods involved in relieving symptoms associated with this condition.

Headache

Trigeminal autonomic cephalalgias (TAC)

- **Trigeminal autonomic cephalalgias (TACs)**
  - cluster headache
    - attacks have a frequency between one every other day and 8 per day and last 15-180 minutes.
  - paroxysmal hemicranias
    - attacks have a frequency above five per day and last 2-30 min. The condition responds absolutely to indomethacin
  - hemicrania continua

        - a constant form of paroxysmal hemicrania (no headache-free periods). Also responds absolutely to indomethacin.
    - short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT syndrome)
    - short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA)
        - could get 20 attacks in a day, each last around 1600 seconds.
- hemicrania continua and paroxysmal hemicrania clearly are the two that completely resolve with indomethacin.
- Notice the differences between how long each lasts and how many attacks there can be per day. The rest of the features are quite similar to each other between the headaches, so learn the general features of a TAC then memorise how long each should last and its frequency to help you differentiate them.

the most likely to aid in making a diagnosis →a trial of indomethacin

Cluster headache

Cluster headache - acute treatment: subcutaneous sumatriptan + 100% O2

Epidemiology

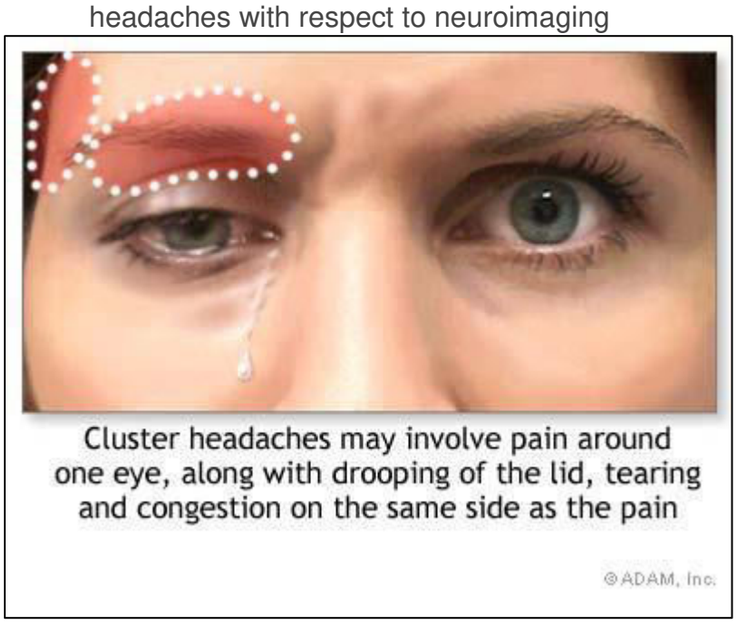
- Cluster headaches are more common in men (5:1) and smokers.
- **more common in younger males below the age of 40**

Features

- pain typical occurs once or twice a day, each episode lasting **15 mins - 2 hours**
- clusters typically last 4-12 weeks
- intense pain around one eye (recurrent attacks 'always' affect same side)
- The attacks are often nocturnal and are associated with parasympathetic overactivity.
- patient is restless during an attack
- accompanied by redness, lacrimation, lid swelling
- nasal stuffiness
- miosis and ptosis in a minority

Management

- **Acute**: 100% oxygen, subcutaneous or a **nasal triptan**
    - the use of 100% oxygen at least 12 litres per minute via a non-rebreathable mask
    - It is not recommended to offer paracetamol, NSAIDS, opioids, ergots or oral triptans for the acute treatment of a cluster headache.
- **prophylaxis: First line → verapamil**, prednisolone , with other options including lithium, sodium valproate and gabapentin
- NICE recommend seeking specialist advice from a neurologist if a patient develops cluster headaches with respect to neuroimaging



Differential diagnosis

- The main differential is between cluster headaches and **chronic paroxysmal hemicrania** (CPH; which is treated with indomethacin).
  - Features that distinguish CPH are
    - Shorter duration of attacks (2-45 mins)
    - Increased frequency of attacks
    - Female preponderance and
    - Selective response to treatment with indomethacin.

Distinguishing cluster headaches and Chronic Paroxysmal Hemicrania

Cluster headache	Chronic Paroxysmal Hemicrania
more common in males	more common in females
frequency of 1-4 (maximum 8) in 24 hours.	the **frequency** of attacks is **higher**, usually more than 15 in 24 hours
The duration of headaches is (15-60 min).	The **duration** of headaches is **shorter** (2-25 min)
Not responds to indomethacin	**responds very well to indomethacin**

Distinguishing cluster headaches and SUNCT (short lasting unilateral neuralgiform headache with conjunctival injection or tearing):

cluster headaches	SUNCT
more prevalent in younger males below the age of 40	more common in older patients above the age of 40.
typically onset at night	can occur at any time of day
last from 15 minutes to 3 hours	typically lasts for seconds to minutes.
rarely onset more than 3 times per day	has been described in up to 75 times per day.
A transient Horners syndrome is typical	Horners may be lacking in SUNCT
classically, but not always, triggered by alcohol	not triggered by alcohol

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Migraine

Diagnostic criteria

The International Headache Society has produced the following diagnostic criteria for **migraine without aura:**

Point	Criteria
A	At least 5 attacks fulfilling criteria B-D
B	Headache attacks **lasting 4-72 hours*** (untreated or unsuccessfully treated)
C	Headache has at least two of the following characteristics: • 1. unilateral location • 2. pulsating quality (i.e., varying with the heartbeat) • 3. moderate or severe pain intensity • 4. aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D	During headache at least one of the following: • 1. nausea and/or vomiting • 2. photophobia and phonophobia
E	Not attributed to another disorder (history and examination do not suggest a secondary headache disorder or, if they do, it is ruled out by appropriate investigations or headache attacks do not occur for the first time in close temporal relation to the other disorder)

- NICE suggests migraines may be unilateral or bilateral

Migraine with aura

- seen in around 25% of migraine patients
- tends to be easier to diagnose with a typical aura being progressive in nature
- may occur hours prior to the headache.
- Typical aura include:
  - transient hemianopic disturbance or a spreading scintillating scotoma ('jagged crescent').
  - **Spreading (over minutes) sensory and motor symptoms**
  - Word-finding difficulties are also a common migraine aura symptom.
  - autonomic symptoms such as a Horner syndrome

- may occur with or without headache
- NICE also give more detail about **typical auras**:
  - are fully reversible
  - develop over at least 5 minutes
  - last 5-60 minutes
- The following aura symptoms are atypical and may prompt further investigation/referral;
  - motor weakness
  - double vision
  - visual symptoms affecting only one eye
  - poor balance
  - decreased level of consciousness.

- **Complicated migraine**
  - **Complicated migraine** is one which results in hemi sensory or hemi motor findings associated with a typical migraine presentation.
- **Confusional migraine** involves alteration in sensorium rather than limb involvement.

Other features:

- family history of similar headaches is common
- Bilateral fortification spectra
  - Fortification spectra (jagged lines resembling battlements) and teichopsia (flashes) are common features of migraine.
- Precipitation by oral contraceptives (contraindicated in migraine with aura)
- Frequency reduced by tricyclic antidepressants (can be useful in the prophylaxis of migrain)
- Third nerve palsy
  - seen in **ophthalmoplegic migraine**
  - ophthalmoplegic migraine was reclassified as a **cranial neuralgia** in the most recent International Headache Society classification.
  - most commonly affects the third nerve,
  - the deficits can be permanent.
  - A subset of these patients will have gadolinium enhancement of the cisternal segment of the cranial nerve
  - it is thought some of these patients actually have a demyelinating neuropathy.

Migraine: management

Migraine
- acute: triptan + NSAID or triptan + paracetamol
- prophylaxis: topiramate or propranolol

acute → 5-HT **ago**nists
prophylaxis: β-blocker, 5-HT2 antagonist

- 5-HT receptor agonists are used in the acute treatment of migraine
- 5-HT receptor antagonists are used in prophylaxis.

Acute treatment

- first-line:
  - combination of oral triptan and NSAID, **OR** oral triptan and paracetamol
    - for young people aged 12-17 years: **nasal triptan** is preferred than oral triptan
- if the above measures are not effective or not tolerated offer a non-oral preparation of metoclopramide* or prochlorperazine and consider adding a non-oral NSAID or triptan
  - *caution should be exercised with young patients as acute dystonic reactions may develop with metoclopramide.

Prophylaxis (NICE 2015)

- prophylaxis should be given if patients are experiencing 2 or more attacks per month.
- Modern treatment is effective in about 60% of patients.
- NICE advise either **topiramate** or **propranolol** or **amitriptyline** 'according to the person's preference, comorbidities and risk of adverse events'.
  - **Propranolol** should be used **in preference to topiramate** in **women of child bearing age** as it may be **teratogenic** and it can **reduce the effectiveness of hormonal contraceptives**
- if these measures fail NICE recommend 'a course of up to 10 sessions of **acupuncture** over 5-8 weeks'
- gabapentin are not recommended now because evidence shows that it is not effective in preventing migraine. (NICE 2015)
- NICE recommend: 'Advise people with migraine that **riboflavin** (400 mg once a day) may be effective in reducing migraine frequency and intensity for some people'
  - **riboflavin** also known as **vitamin B_2**
    - safe during pregnancy.
- for women with **predictable menstrual migraine** treatment:
  - NICE recommend either frova**triptan** (2.5 mg twice a day) or zolmi**triptan** (2.5 mg twice or three times a day) as a type of 'mini-prophylaxis'
- pizotifen is no longer recommend.
  - Adverse effects such as weight gain & drowsiness are common

Efficacy of Paracetamol in migraine

- **Migraine → ↓ gastric empting → ↓Paracetamol absorption → ↓Paracetamol effects**
- **Metoclopramide may be useful in accelerating gastric emptying.**
- paracetamol absorption technique is used to study gastric emptying.

January 2006 exam: Which type of medication would be most appropriate to reduce the frequency of migraine attacks? Beta-blocker (Topiramate is also recommended by NICE as first-line prophylaxis against migraine. However, a beta-blocker is a better choice in a female of child-bearing age)

Migraine: pregnancy, contraception and other hormonal factors

Migraine during pregnancy

- paracetamol 1g is first-line
- aspirin 300mg or ibuprofen 400mg can be used second-line in the first and second trimester

Migraine and the combined oral contraceptive (COC) pill

- if patients have migraine with aura then the COC is absolutely contraindicated due to an increased risk of stroke (relative risk 8.72)

Migraine and menstruation

- many women find that the frequency and severity of migraines increase around the time of menstruation
- SIGN recommends that women are treated with mefanamic acid or a combination of aspirin, paracetamol and caffeine. Triptans are also recommended in the acute situation

Migraine and hormone replacement therapy (HRT)

- safe to prescribe HRT for patients with a history of migraine but it may make migraines worse

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Triptans

- Triptans are specific **5-HT1 agonists** used in the acute treatment of migraine.
- They are generally used first-line in combination therapy with an NSAID or paracetamol.

Prescribing points

- should be taken as soon as possible after the onset of headache, rather than at onset of aura
- oral, orodispersible, nasal spray and subcutaneous injections are available

Adverse effects

- 'triptan sensations' - tingling, heat, tightness (e.g. throat and chest), heaviness, pressure

Contraindications

- patients with a history of, or significant risk factors for, ischaemic heart disease or cerebrovascular disease

Epilepsy is not a contraindication to the use of triptans

Idiopathic intracranial hypertension(IIH)

Obese, young female with headaches / blurred vision think idiopathic intracranial hypertension

Suspected Idiopathic intracranial hypertension → lumbar puncture to confirm the diagnosis is the next step

- also known as pseudotumour cerebri and formerly benign intracranial hypertension
- classically seen in young, overweight females.

Features

- headache
- blurred vision,
  - Diplopia is common due to sixth nerve palsy.
- papilloedema (usually present)
- **enlarged blind spot**
- Reduction in colour vision is common
- sixth nerve palsy may be present
- normal appearances of the magnetic resonance imaging (MRI). Normal ventricular size, anatomy and position. Normal CSF cell count and protein content.
- **plantars are flexor**
  - Extensor plantars suggest alternative diagnosis.
- **Absence of retinal venous pulsations**

Risk factors

- obesity
- female sex
- pregnancy
- drugs*: **oral contraceptive pill (eg: Dianette)**, **steroids**, **tetracycline**, **vitamin A**, Nalidixic acid
  - *if intracranial hypertension is thought to occur secondary to a known causes (e.g. Medication) then it is of course not idiopathic

Diagnosis

- the diagnosis is confirmed by finding an **elevated CSF opening pressure** (more than 20 cm H_2O). CSF protein, glucose and cell count will be normal.
- CT and MRI scans are often normal

Management

- weight loss
- diuretics e.g. acetazolamide
- topiramate is also used, and has the added benefit of causing weight loss in most patients
- repeated lumbar puncture
- surgery:
  - A lumboperitoneal or ventriculoperitoneal shunt may also be performed to reduce intracranial pressure
  - optic nerve sheath decompression and fenestration may be needed to prevent damage to the optic nerve.
    - **In progressive visual loss → Lumbo-peritoneal (LP) shunt is the treatment of choice.**

- ❖ Optic nerve fenestration is an alternative.
- ❖ There are no comparative studies between the two interventions.

Complication

- Progressive visual loss and optic atrophy

September 2008 exam: Sudden loss of vision in left eye + headaches + bilateral papilloedema. Which drug is most likely to be responsible? Prednisolone → intracranial hypertension

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Spontaneous intracranial hypotension (SIH)

Strong postural relationship with the headache generally much worse when upright. Patients may therefore be bed-bound

- Low (CSF) pressure headache, that is seen most frequent following lumbar puncture, but may also occur either following an episode of possible minor trauma to meninges (eg sports injury to neck or back) or without apparent cause (SIH).
- The lower limit of the normal range for CSF pressure is 10 cm H2O
- **Mechanism**: CSF leak leads to → low CSF pressure → orthostatic headache in association with one or more of the following symptoms:
  - ➢ nausea, vomiting
  - ➢ horizontal diplopia
  - ➢ unsteadiness or vertigo
  - ➢ altered hearing
  - ➢ neck pain/stiffness
  - ➢ interscapular pain
  - ➢ visual field abnormalities
- **Diagnosis**
  - ➢ may be confirmed by measuring **CSF opening pressure** at lumbar puncture: by very definition, the opening CSF pressure is low, below 60 mm H_2O, and often a 'dry' tap is encountered
  - ➢ However, the pressure may be normal
  - ➢ CSF fluid analysis is normal
  - ➢ **MRI** studies typically reveal diffuse pachymeningeal enhancement, frequently in association with 'sagging' of the brain, tonsilar descent and posterior fossa crowding
- **Treatment**
  - ➢ conservative measures are often undertaken **first** (bed rest, analgesia, increased fluid intake)
  - ➢ **epidural blood patch is the treatment of choice**

Medication overuse headache

Medication overuse headache
- simple analgesia + triptans: stop abruptly
- opioid analgesia: withdraw gradually

- Medication overuse headache is one of the most common causes of chronic daily headache.
- may affect up to **1** in **50** people

Features

- present for 15 days or more per month
- developed or worsened whilst taking regular symptomatic medication
- patients using opioids and triptans are at most risk
- may be psychiatric co-morbidity

Management (from 2008 SIGN guidelines)

- simple analgesics and triptans should be withdrawn abruptly (may initially worsen headaches)
- opioid analgesics should be gradually withdrawn

- Withdrawal symptoms are likely to occur, including worsening headache, nausea, agitation and sleep disturbance. These usually settle within seven days, and headaches should stop within approximately three weeks.

Thunderclap headache

- Thunderclap headache describes a sudden (reaches maximum severity within seconds to minutes of onset) and severe headache.

Causes

- subarachnoid hemorrhage
- cerebral venous sinus thrombosis
- internal carotid artery dissection
- pituitary apoplexy
- reversible cerebral vasoconstriction syndrome
- primary sexual headache
- posterior reversible leucoencephalopathy syndrome

Parkinsonism

Causes:

- Parkinson's disease
- drug-induced e.g. antipsychotics, metoclopramide
- progressive supra-nuclear palsy
- multiple system atrophy
- Wilson's disease
- post-encephalitis
- dementia pugilistica (secondary to chronic head trauma e.g. boxing)
- toxins: carbon monoxide, MPTP

Drugs causing Parkinsonism

- phenothiazines: e.g. chlorpromazine, prochlorperazine
- butyrophenones: haloperidol, droperidol
- metoclopramide
  - Domperidone does not cross the blood-brain barrier and therefore does not cause extra-pyramidal side-effects

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Parkinson's disease

Parkinson's disease - most common psychiatric problem is depression

- Parkinson's disease is a progressive neurodegenerative condition caused by degeneration of dopaminergic neurons in the substantia nigra.
- After approximately 50% of the dopamine neurons, and 75-80% of striatal dopamine is lost patients start to exhibit the classical signs of bradykinesia, resting tremor and rigidity.
- **The characteristic microscopic finding in Parkinson's disease is the Lewy body**

Epidemiology

- around twice as common in men
- mean age of diagnosis is 65 years

Pathophysiology

- **Decreased dopamine impairs movement by which mechanisms?**
  - ➔ **Decreased activation of the D1 and D2 receptors**
- **pathway involved in conscious motion, and how that pathway becomes interrupted in Parkinsonian patients:**
  - There are two pathways in the brain that promote motion:
    - the direct, stimulatory pathway and
    - the indirect, inhibitory pathway.

- In normal circumstances, the stimulatory pathway is activated while the inhibitory pathway is deactivated, allowing for smooth motion.
- The substantia nigra produces dopamine, which binds the D1 receptors in the striatum, inhibiting the globuspallidus, leading to activation of the thalamus and allowing movement.
- Also, dopamine binds the D2 receptor, inhibiting the inhibitory pathway. This allows for activation of the subthalamic nucleus, inhibition of the globus pallidus internus and activation of the thalamus, leading to movement.
- Inhibition of the globus pallidus is necessary to promote thalamic function. In Parkinsonian patients, decreased dopamine leads to increased globus pallidus internus output and decreased motion.
- Parkinson → ↓ dopamine → ↑ **globus pallidus internus** output → ↓thalamic function →↓motion.
- Parkinson → ↓ dopamine → ↓activity at the **D1** receptor → ↓**excitatory** pathway,
- Parkinson → ↓ dopamine → ↓ activity at the **D2** receptor → **disinhibiting the inhibitory** pathway → ↑ **globus pallidus internus** output → ↓thalamic function →↓motion.

- **Which mechanism underlying the neurodegeneration seen in Parkinson's?**
  - → **Impaired protein degradation**
    - Mutations in either the **parkin gene or UCHL1** lead to impaired protein degradation.
  - **Alpha-synuclein** is a synaptic protein accumulates in Lewy body dementia and Parkinson's disease,

Features

The classic triad of features: bradykinesia, tremor and rigidity.

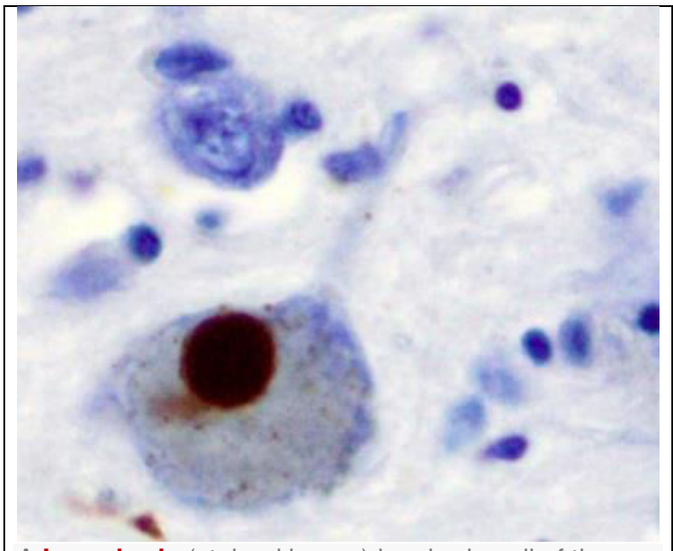
The symptoms of Parkinson's disease are characteristically asymmetrical.

- **Bradykinesia**
  - poverty of movement also seen, sometimes referred to as hypokinesia
  - short, shuffling steps with reduced arm swinging
  - difficulty in initiating movement
- **Tremor**
  - **most marked at rest, 3-5 Hz**
  - worse when stressed or tired
  - typically 'pill-rolling', i.e. in the thumb and index finger
  - The tremor of parkinsonism only disappears during REM sleep.
- **Rigidity**
  - lead pipe
  - cogwheel: due to superimposed tremor
- **Other characteristic features**
  - mask-like facies
  - flexed posture
  - micrographia
  - drooling of saliva
  - psychiatric features:
    - **depression is the most common feature (affects about 40%);**
    - dementia, psychosis and sleep disturbances may also occur
  - impaired olfaction
  - **REM sleep behaviour disorder**
    - **The most early feature**
    - Imperfect abolition of muscle tone during REM sleep.
    - Caused by lesion in the area of the pons responsible for REM sleep atonia.
    - Patient may seen to kick, laugh, punch or fight invisible enemies during REM sleep.
    - Interestingly, the side most affected by Parkinson's appear to adopt near normal movement during REM sleep.
  - **Intestinal pseudo-obstruction**
    - common feature of advanced Parkinson's

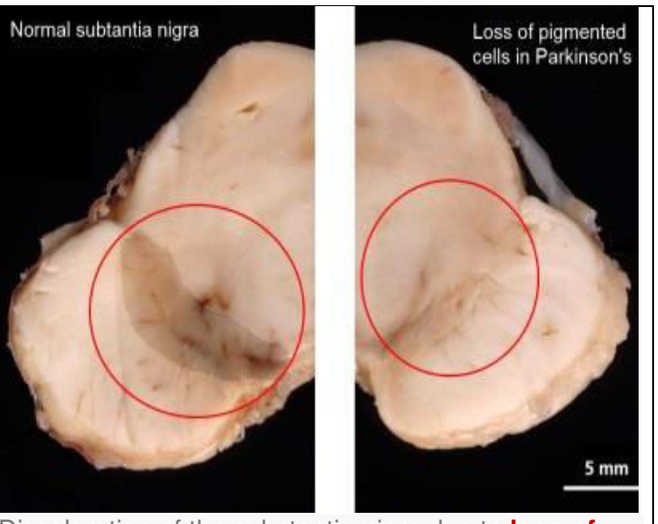
- results in symptoms of **intermittent abdominal bloating and vomiting**.

Drug-induced parkinsonism has slightly different features to Parkinson's disease:

- **motor symptoms are generally rapid onset and bilateral**
- **rigidity and rest tremor are uncommon**



A **Lewy body** (stained brown) in a brain cell of the substantia nigra in Parkinson's disease. The brown colour is positive immunohistochemistry staining for alpha-synuclein.



Discoloration of the substantia nigra due to **loss of pigmented nerve cells**.

Diagnosis

Parkinson's Disease Society Brain Bank diagnostic criteria for Parkinson's disease

- **Step 1. Diagnosis of a parkinsonian syndrome**
  - Bradykinesia and at least one of the following:
    - Muscular rigidity
    - Rest tremor (4-6 Hz)
    - Postural instability unrelated to primary visual, cerebellar, vestibular, or proprioceptive dysfunction
- **Step 2. Exclusion criteria for Parkinson's disease**
  - History of:
    - Repeated strokes with stepwise progression
    - Repeated head injury
    - Antipsychotic or dopamine-depleting drugs
    - Definite encephalitis or oculogyric crises on no drug treatment
    - More than one affected relative
    - Sustained remission
    - Negative response to large doses of levodopa (if malabsorption excluded)
    - Strictly unilateral features after 3 years
    - Other neurological features: supranuclear gaze palsy, cerebellar signs, early severe autonomic involvement, Babinski sign, early severe dementia with disturbances of language, memory, or praxis
    - Exposure to known neurotoxin
    - Presence of cerebral tumour or communicating hydrocephalus on neuroimaging
- **Step 3. Supportive criteria for Parkinson's disease**
  - Three or more required for diagnosis of definite Parkinson's disease:

- Unilateral onset
- Excellent response to levodopa
- Rest tremor present
- Severe levodopa-induced chorea
- Progressive disorder
- Levodopa response for over 5 years
- Persistent asymmetry affecting the side of onset most
- Clinical course of over 10 years.

Investigations

- **Single photon Emission Computed Tomography (SPECT)**
  - **The investigation of choice**
  - for people with tremor if essential tremor cannot be clinically differentiated from parkinsonism.

Feature most strongly suggest idiopathic Parkinson's disease → The asymmetry of tremor

Parkinson's disease: management (NICE guidelines 2017)

- there is no proven neuroprotective or disease-modifying therapy.
- **First-line treatment:**
  - if the motor symptoms are affecting the patient's quality of life → **levodopa**
  - if the motor symptoms are not affecting the patient's quality of life → dopamine agonist (non-ergot derived), levodopa or monoamine oxidase B (MAO-B) inhibitor
- **Do not offer ergot-derived dopamine agonists as first-line** treatment for Parkinson's disease.
- **second line**
  - **Adjuvant treatment of motor symptoms**(dyskinesia and/or motor fluctuations) if not responded **despite optimal levodopa therapy** → Add non-ergot-derived dopamine agonists, MAO-B inhibitors or catechol-O-methyl transferase (COMT) inhibitors
- **Third line** :
  - If dyskinesia is not adequately managed by modifying existing therapy, consider **amantadine**
- for advanced Parkinson's disease, whose symptoms are not adequately controlled by best medical therapy → **deep brain stimulation.**
- Whilst all drugs used to treat Parkinson's can cause a wide variety of side-effects NICE produced tables to help with decision making:

	Levodopa	**Dopamine agonists**	**MAO-B inhibitors**
Motor symptoms	More improvement in motor symptoms	Less improvement in motor symptoms	Less improvement in motor symptoms
Activities of daily living	More improvement in activities of daily living	Less improvement in activities of daily living	Less improvement in activities of daily living
Motor complications	More motor complications	Fewer motor complications	Fewer motor complications
Adverse events	Fewer specified adverse events*	More specified adverse events*	Fewer specified adverse events*

* excessive sleepiness, hallucinations and impulse control disorders

- If a patient continues to have symptoms despite optimal levodopa treatment or has developed dyskinesia then NICE recommend the addition of a dopamine agonist, MAO-B inhibitor or catechol-O-methyl transferase (COMT) inhibitor as an adjunct.

- NICE summarise **the main points in terms of decision making**:

	Dopamine agonists	**MAO-B inhibitors**	**COMT inhibitors**	**Amantadine**
Motor symptoms	Improvement in motor symptoms	Improvement in motor symptoms	Improvement in motor symptoms	No evidence of improvement in motor symptoms
Activities of daily living	Improvement in activities of daily living	Improvement in activities of daily living	Improvement in activities of daily living	No evidence of improvement in activities of daily living
Off time	More off-time reduction	Off-time reduction	Off-time reduction	No studies reporting this outcome
Adverse events	Intermediate risk of adverse events	Fewer adverse events	More adverse events	No studies reporting this outcome
Hallucinations	More risk of hallucinations	Lower risk of hallucinations	Lower risk of hallucinations	No studies reporting this outcome

Specific points regarding Parkinson's medication

- Antiparkinsonian medicines **should not be withdrawn abruptly** or allowed to fail suddenly due to poor absorption (for example, gastroenteritis, abdominal surgery) to avoid the potential for acute **akinesia** or **neuroleptic malignant syndrome**.
- The practice of withdrawing people from their antiparkinsonian drugs (so called 'drug holidays') to reduce motor complications should not be undertaken because of the risk of neuroleptic malignant syndrome.

Management of non-motor symptoms of Parkinson's disease (NICE 2017)

- **Excessive daytime sleepiness**
  - Consider modafinil
- **Rapid eye movement sleep behaviour disorder**
  - Consider clonazepam or melatonin
- **Nocturnal akinesia**
  - Consider levodopa or oral dopamine agonists
  - If neither is effective, consider rotigotine
- **Postural hypotension**
  - review the person's existing medicines to address possible pharmacological causes, including:
    - antihypertensives (including diuretics)
    - dopaminergics
    - anticholinergics
    - antidepressants
  - first line → **midodrine**
    - **alpha agonist**
    - monitor for **supine hypertension.**
  - Second line → **fludrocortisone**
    - If midodrine is contraindicated, not tolerated or not effective.
- **Psychotic symptoms (hallucinations and delusions)**
  - Do not treat if they are well tolerated.
  - Reduce the dosage of any Parkinson's disease medicines
  - Consider **quetiapine** in people without cognitive impairment.
  - If standard treatment is not effective, offer clozapine
    - Lower doses of **quetiapine** and **clozapine** are needed for people with Parkinson's disease than in other indications
  - **Do not** offer olanzapine
- **Dementia**

  - cholinesterase inhibitor (rivastigmine, donepezil, or galantamine capsules or rivastigmine patches)
  - if cholinesterase inhibitors are not tolerated or contraindicated → Consider memantine
- **Drooling**
  - Consider glycopyrronium bromide
    - Anticholinergic
    - reduce excessive saliva (sialorrhea)
    - does not cross the blood–brain barrier → no central effects.
  - If glycopyrronium bromide is not effective, not tolerated or contraindicated, consider referral for botulinum toxin
- **Parkinsonian malignant syndrome**
  - Triggered by **abrupt withdrawal from anti-parkinsonian medication**.
  - The presentation is **similar of neuroleptic malignant syndrome** (pyrexia, rigidity, tachycardia) but without a history of neuroleptic drug use.
  - **Re-initiation of Parkinson's therapy is curative**.

Parkinson's medication

Levodopa

- **precursor to dopamine**, **can penetrate the blood brain barrier** and be converted to dopamine by amino acid decarboxylase (or dopa decarboxylase) enzyme.
  - peripherally administered **dopamine** cannot penetrate the blood brain barrier
- usually combined with a **decarboxylase inhibitor** (e.g. carbidopa or benserazide) to prevent peripheral metabolism of levodopa to dopamine
  - levodopa alone →peripheral conversion of levodopa to dopamine →significant **GI side effects such as nausea and vomiting**.
- Levodopa, coupled with carbidopa, remains the gold standard of symptomatic treatment for Parkinson disease.
- reduced effectiveness with time (usually by 2 years)
- side effects:
  - nausea & vomiting
  - dyskinesia (involuntary writhing movements),
  - dry mouth,
  - anorexia,
  - cardiac arrhythmias → palpitations,
  - postural hypotension,
  - drowsiness
  - reddish discolouration of urine upon standing
  - psychosis,
  - **hallucinations (usually visual).**
    - usually appear late (more than two years after initiation of treatment).
    - The risk for developing psychiatric symptoms increases with:
      - age,
      - other psychiatric conditions,
      - **long duration of levodopa treatment**, and
      - high doses.
- no use in neuroleptic induced parkinsonism
- 'on-off' effect,
  - **On/off phenomena may be considerably improved either by the addition of cabergoline (a dopamine agonist) or a subcutaneous infusion of apomorphine.**
    - Liquid forms of l-dopa may also be helpful as they allow closer titration of dose, and splitting meals into smaller snacks and one larger evening meal also affects the pharmacokinetics (PK) of l-dopa positively.

Dopamine receptor agonists

Ropinirole - dopamine receptor agonist

- **Non-ergot**
  - Ropinirole
  - Apomorphine
  - Pramipexole
  - Rotigotine
- **Ergot-derived dopamine receptor agonists**
  - eg: bromocriptine, cabergoline, pergolide
  - not recommended as first-line treatment for Parkinson's disease.
  - Side effects:
    - **pulmonary**, **retroperitoneal** and **cardiac fibrosis**.
      - echocardiogram, ESR, creatinine and chest x-ray should be obtained prior to treatment and patients should be closely monitored
      - pergolide was withdrawn from the US market in March 2007 due to increased incidence of valvular dysfunction
    - **impulse control disorders**
      - The different types of impulse control disorders (for example, compulsive gambling, hypersexuality, binge eating and obsessive shopping).
      - more common with:
        - dopamine agonist therapy
        - history of previous impulsive behaviours
        - history of alcohol consumption and/or smoking
      - can also develop while taking dopaminergic therapies other than dopamine agonists.
      - Treatment
        - gradually reducing any dopamine agonist.
        - Monitor for improvement and symptoms of dopamine agonist withdrawal.
        - if modifying dopaminergic therapy is not effective → cognitive behavioural therapy
    - excessive daytime somnolence
      - **If excessive daytime sleepiness develops then:**
        - patients should not drive.
        - Medication should be adjusted to control symptoms.
        - **Modafinil** can be considered if alternative strategies fail.
    - Psychotic symptoms (hallucinations and delusions) (more likely than levodopa).
    - Nasal congestion
    - postural hypotension.
      - **If orthostatic hypotension develops then:**
        - medication review for potential causes should be done.
        - If symptoms persist then **midodrine** (acts on peripheral alpha-adrenergic receptors to increase arterial resistance) can be considered.

MAO-B (Monoamine Oxidase-B) inhibitors

- e.g. Selegiline
- inhibits the breakdown of dopamine secreted by the dopaminergic neurons

Amantadine

- mechanism
  - not fully understood, probably increases dopamine release and inhibits its uptake at dopaminergic synapses
  - Amantadine is a **weak antagonist of the NMDA-type glutamate receptor**, increases dopamine release, and blocks dopamine reuptake
- indications

  - Amantadine is not a powerful anti-Parkinsonian medication. It is used only in idiopathic Parkinson's disease
  - if no clinical response is noted, the medication should be withdrawn gradually, not stopped abruptly.
- side-effects
  - **ataxia,**
  - slurred speech,
  - confusion, dizziness
  - **livedo reticularis**
  - **peripheral edema** and weight
    - should be avoided in congestive heart failure

COMT (Catechol-O-Methyl Transferase) inhibitors

- e.g. Entacapone, tolcapone
- COMT is an enzyme involved in the breakdown of dopamine, and hence may be used as an adjunct to levodopa therapy
  - blocks conversion of dopamine to 3-methoxytyramine.
- used in conjunction with levodopa in patients with established PD

Antimuscarinics

- block cholinergic receptors
- now used more to treat drug-induced parkinsonism rather than idiopathic Parkinson's disease
- help tremor and rigidity
- e.g. procyclidine, benzotropine, trihexyphenidyl (benzhexol)
- Do not offer anticholinergics to people with Parkinson's disease who have developed dyskinesia and/or motor fluctuations.
- **Anticholinergic drugs such as benzhexol remain the treatment of choice in parkinsonian tremor.**

January 2011 exam : H/O schizophrenia , developed parkinsonism secondary to his antipsychotic medication. Which drug is most useful in the management of tremor? Benzhexol

January 2008 exam: What is the mechanism of action of selegiline in Parkinson's disease. ? Monoamine Oxidase-B inhibitor

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Progressive supranuclear palsy

Progressive supranuclear palsy: parkinsonism, impairment of vertical gaze

The triad of parkinsonism, vertical gaze palsy and cognitive impairment

Overview

- aka **Steele-Richardson-Olszewski syndrome**
- a 'Parkinson Plus' syndrome

Features

- impairment of vertical gaze (down gaze worse than up gaze - patients may complain of difficultly reading or descending stairs)
- parkinsonism
- falls
- slurring of speech
- cognitive impairment
- also cause pyramidal signs, dementia or frontal lobe syndrome.

Management → poor response to L-dopa

Prognosis→ Median survival is about seven years.

Multiple system atrophy

- Shy-Drager syndrome is a type of multiple system atrophy.
- The average age of onset is 50 years (earlier than in Parkinson's disease)
- the median survival six to nine years.
- It runs a briefer course than Parkinson's disease.

Pathophysiology

- Multi-system atrophy includes three syndromes that usually overlap
  1. Strionigral degeneration leading to parkinsonism
  2. Autonomic failure
  3. Olivopontocerebellar degeneration.

Features

- parkinsonism
- **autonomic disturbance (atonic bladder, postural hypotension)**
- cerebellar signs
- The unifying **pathologic hallmark is** the **presence of a-synuclein-positive inclusions** located in various brain regions.

May 2012 exam: A 67-year-old increasing clumsiness + ataxic gait + ↑↑upper limb tone with cog-wheel rigidity. Blood pressure is 135/80 lying and 95/70 standing. What is the most likely diagnosis? Multiple system atrophy

Normal pressure hydrocephalus (NPH)

Urinary incontinence + gait abnormality + dementia = normal pressure hydrocephalus

- Normal pressure hydrocephalus is a **reversible cause of dementia** seen in elderly patients.

Mechanism

- It is thought to be secondary to **reduced CSF absorption at the arachnoid villi**.

Causes

- These changes may be secondary to:
  - head injury,
  - subarachnoid haemorrhage or
  - meningitis

The classical triad of features is

1. urinary incontinence
2. dementia and bradyphrenia
3. gait abnormality (may be similar to Parkinson's disease)

What is the underlying cause of urinary incontinence in NPH?

➔ **Inability to suppress voiding**

- The symptoms of NPH are caused by an underlying compression of the periventricular white matter tracts → loss of central inhibition of the detrusor muscle → strong voiding reflex that cannot be suppressed (**urge incontinence**).
- The urge incontinence is potentially exacerbated by the functional frontal lobe impairment that results from compression, which prevents recognition of the urinary urge.

Imaging

- hydrocephalus with an enlarged fourth ventricle

Management

- **the most likely helpful initial managements steps is CSF drainage via repeated lumbar puncture**
- ventriculo-peritoneal shunting

Acute confusional state

- Acute confusional state is also known as delirium or acute organic brain syndrome.
- It affects up to 30% of elderly patients admitted to hospital.

Features - wide variety of presentations

- memory disturbances (loss of short term > long term)
- may be very agitated or withdrawn
- disorientation
- mood change
- visual hallucinations
- disturbed sleep cycle
- poor attention

Diagnosis

- The Confusion Assessment Method (**CAM**) is the most effective tool in identifying delirium.

Management

- treatment of underlying cause
- modification of environment
- the 2006 Royal College of Physicians publication 'The prevention, diagnosis and management of delirium in older people: concise guidelines' recommended haloperidol 0.5 mg as the first-line sedative
- the 2010 NICE delirium guidelines advocate the use of haloperidol or olanzapine

January 2011 exam: An elderly patient admitted for UTI, became agitated and aggressive. What is the most appropriate management? Haloperidol 0.5 mg orally

Dementia

Presence of the e4 allele of apo-lipoprotein E → Alzheimer's disease
Loss of GABA is seen in → Parkinson's disease.
Peri-vascular mononuclear inflammation is seen in → multiple sclerosis.
Loss of Betz cells is seen in → motor neurone disease.

- Dementia affect over 700,000 people in the UKT
- **DP43 is a protein that has recently been found to be involved in a multitude of neurodegenerative diseases** including **dementia** and motor neuron disease.

Common causes of dementia

- **Alzheimer's disease** (the most common) (50-75%)
- cerebrovascular disease: multi-infarct dementia (c. 20-30% %)
- Lewy body dementia (c. 10-20%)

Rarer causes (c. 5% of cases)

- Huntington's
- CJD
- Pick's disease (atrophy of frontal and temporal lobes)
- HIV (50% of AIDS patients)

Important differentials, potentially treatable

- hypothyroidism, Addison's
- B12/folate/thiamine deficiency
- syphilis
- brain tumour
- normal pressure hydrocephalus
- subdural haematoma
- depression
- chronic drug use e.g. Alcohol, barbiturates

Features

- diagnosis can be difficult and is often delayed
- the mini-mental state examination is widely used. A score of 24 or less out of 30 suggests dementia

- Short term memory impairment is the commonest clinical presentation of Alzheimer's disease. **The best way to test short term memory is to ask the patient to recall new information in the next few minutes.**
- Long term memory is usually intact.
- Usually patients are fully orientated in time, person and place.

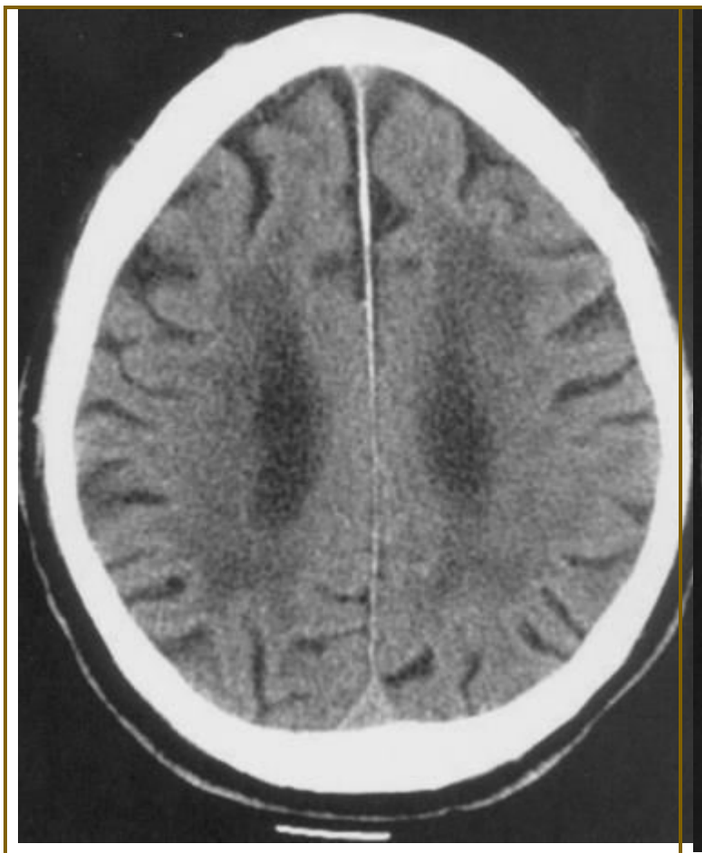
Distinguishing between normal aging and dementia

- Memory impairment, occasional difficulties in word finding, and slower cognitive processing are normal effects of aging.
- An important distinguishing factor between normal aging and forms of dementia is the degree to which independence with everyday activities is impaired. In normal aging, **independence in daily activities** is preserved.
- cognitive exams are within normal limits in aging.
- Alzheimer's disease is often accompanied by behavioral changes (such as aggression, depression, insomnia)

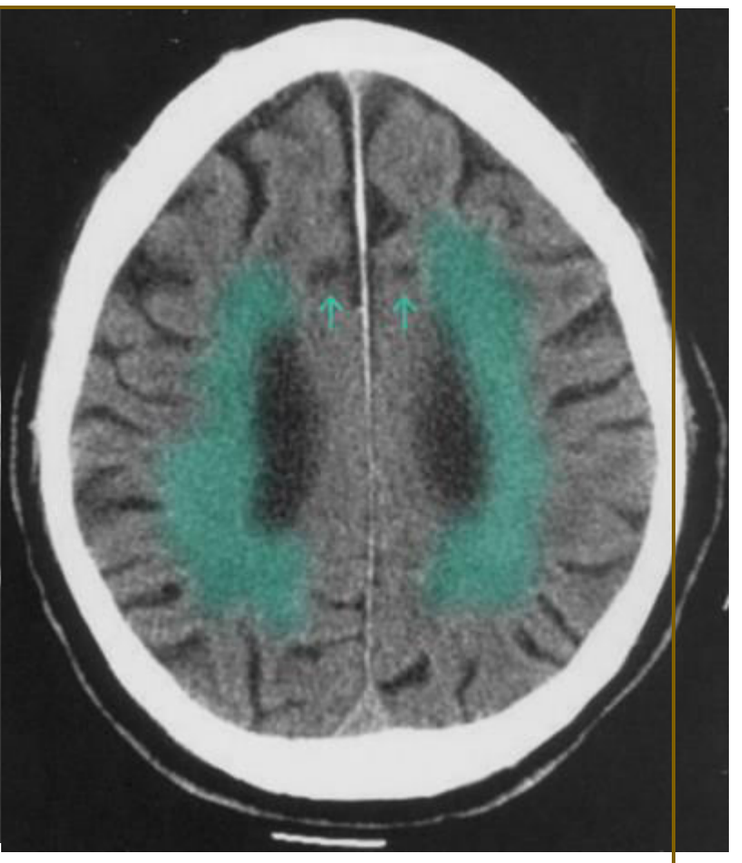
Investigations

Neuroimaging is required to diagnose dementia

- in the 2011 NICE guidelines structural imaging was said to be essential in the investigation of dementia
- **MRI** to exclude other cerebral pathologies and to help establish the subtype diagnosis.(CT could be used, but MRI is better)
- Perfusion hexamethylpropyleneamine oxime (HMPAO) single-photon emission computed tomography **(SPECT) should be used to differentiate Alzheimer's disease, vascular dementia and frontotemporal dementia if the diagnosis is in doubt.**
  - **Vascular dementia**
    - typically occurs in those with **widespread vascular disease**.
    - The course is typically fluctuating with stepwise progression.
    - Differentiation from Alzheimer's disease can be difficult, although **a history of strokes or the presence of focal neurological signs are very suggestive**.
    - CT or MRI will show → multiple lacunar infarcts
    - does not respond to acetylcholinesterase inhibitors such as donepezil.
    - Vascular dementia caused by lipohyalinosis or microatheroma formation and **NOT thromboemboli.** Therefore, anticoagulation is not indicated.
    - **Memory therapy is the best next step in management for this patient's confirmed vascular dementia.**
      - treatment specific to vascular dementia also includes reduction of cardiovascular risk factors and, in some cases, anticoagulation.



Progressive impairment in an individual with cardiovascular disease, hypertension, hypercholesterolemia, and focal neurological deficits is suggestive of vascular dementia.



The CT scan of the head confirms this diagnosis and shows lacunar infarcts in the frontal region as well as hypodense periventricular lesions.

subcortical arteriosclerotic encephalopathy (Binswanger's disease) with microangiopathic lesions, which are primarly hypodense perventricular lesions (shaded areas). The arrows point to two lacunar infarcts (marginated hypodense areas) in the frontal region.

- People with Down's syndrome may show SPECT abnormalities throughout life that resemble those in Alzheimer's disease, so this test is not helpful in this group.
- Cerebrospinal fluid examination should be used if Creutzfeldt–Jakob disease or other forms of rapidly progressive dementia are suspected.

Assessing the severity of dementia

- For people with learning disabilities, tools used:
  - Cambridge Cognitive Examination (CAMCOG)
  - Modified Cambridge Examination for Mental Disorders of the Elderly (CAMDEX)
  - DMR
  - Dementia Scale for Down Syndrome (DSDS), which can be useful in diagnosis of dementia in people with learning disabilities who do not have Down's syndrome.
- For others → cognition score

Management

- in primary care a blood screen is usually sent to exclude reversible causes (e.g. Hypothyroidism). NICE recommend the following tests: FBC, U&E, LFTs, calcium, glucose, TFTs, vitamin B12 and folate levels. Patients are now commonly referred on to old-age psychiatrists (sometimes working in 'memory clinics').

- in secondary care neuroimaging is performed* to exclude other reversible conditions (e.g. Subdural haematoma, normal pressure hydrocephalus) and help provide information on aetiology to guide prognosis and management
- **memory therapy** is an important component of treatment for all dementias,
  - Memory therapy is individualized treatment for dementia that involves improving cognitive abilities through image recognition, solving math problems, and past memory recall.
- For the management of Alzheimer's disease, **behavioral and environmental regulation**, such as **adhering to a regular sleep schedule**, should always be attempted prior to resorting to pharmacologic treatment.
- Frequent travel has been shown to worsen the symptoms of Alzheimer's disease. Maintaining a consistent environment will help orient the patient.

Pharmacological treatment

(1) acetylcholinesterase (AChE) inhibitors

- The three **acetylcholinesterase (AChE) inhibitors** **donepezil**, **galantamine** and **rivastigmine** are recommended for managing **mild to moderate Alzheimer's** disease
- The only role for cholinesterase inhibitors is to **improve some cognitive function and improvement in activities of daily living**.
- There is no role for cholinesterase inhibitors in advanced Alzheimer's disease.
- NICE guidelines recommend discontinuation of cholinesterase inhibitors once the mini mental state examination has fallen **below 12.**
  - **The best option would be to withdraw donepezil and possibly consider memantine, which is licensed for use in moderate to severe dementia.**
- **Side-effects** of cholinesterase inhibitors **(donepezil)**
  - GIT: nausea, vomiting or diarrhea
  - Cardiac: **bradycardia** and, rarely, AV block
  - bladder outflow obstruction
  - rarely, hepatitis

(2) N-methyl-D-aspartate (NMDA)-receptor antagonist (Memantine)

- **Memantine**, is a novel N-methyl-D-aspartate (NMDA)-receptor antagonist affects the transmission of glutamate
- **Memantine** is recommended for managing Alzheimer's disease for people with:
  - moderate Alzheimer's disease who are intolerant of or have a contraindication to AChE inhibitors or
  - **severe Alzheimer's** disease.
- It has numerous **drug interactions**:
  - Other NMDA-receptor antagonists (eg ketamine, **amantadine**): increased risk of psychosis
  - Dopamine agonists, L-dopa and anticholinergics: enhanced effects
  - Antispasmodics (eg baclofen): enhanced effects, as memantine has some antispasmodic effects
  - Drugs excreted by cationic transporters in the kidney (eg quinine, cimetidine, ranitidine): reduced excretion, therefore higher plasma concentrations
    (It inhibits renal excretion of ranitidine)

Control of violence, aggression and extreme agitation

- oral medication should be offered before parenteral medication
- If parenteral treatment is necessary, (IM) route should be preferred because it is safer than (IV).
- (IM) lorazepam, haloperidol or olanzapine should be used.

Reversible causes of impaired memory:

- Serum Vitamin B12 levels and
- thyroid function tests

Alzheimer's disease

- Alzheimer's disease is a progressive degenerative disease of the brain
- accounting for the majority of dementia seen in the UK
- typically first affects the temporal and parietal lobes
  - **Temporal lobe** degeneration results in memory loss (misplaced keys, leaving the stove on) and language deficits (word-finding difficulties),
  - **whereas parietal** lobe degeneration results in spatial navigation problems (getting lost during walks outside)

Genetics

- most cases are sporadic
- 5% of cases are inherited as an autosomal dominant trait
- mutations in the (APP gene) **A**myloid **P**recursor **P**rotein (chromosome 21), presenilin 1 (chromosome 14) and presenilin 2 (chromosome 1) genes are thought to cause the inherited form
- apoprotein E allele E4 - encodes a cholesterol transport protein

What is the primary anatomical target of Alzheimer's disease? → Cerebral cortex

- Alzheimer's disease is a form of **"cortical" type** of dementia that targets primarily the central cholinergic nuclei (e.g., the nucleus basalis of Myenert).
- The **"sub-cortical type"** of dementia occurs in Huntington's disease, advanced Wilson's disease, and advanced multiple sclerosis

Pathological changes

- **What kind of pathological deposits are most likely to be present in the brain of Alzheimer's? → Amyloid plaques**
- macroscopic: widespread cerebral atrophy, particularly involving the cortex and **hippocampus**
- microscopic: cortical plaques due to deposition of type A-Beta-amyloid protein and intraneuronal neurofibrillary tangles caused by abnormal aggregation of the tau protein
- biochemical: there is a deficit of acetylecholine from damage to an ascending forebrain projection
- Patients with Alzheimer disease have **reduced production of choline acetyl transferase,** leading to → a decrease in acetylcholine synthesis and impaired cortical cholinergic functioning.
- evidence shows that excessive activation of the NMDA (N-methyl-D-aspartate) receptor may play a role in the pathogenesis of AD.

Neurofibrillary tangles

- **Neurofibrillary tangles are a pathological feature of Alzheimer's**
- paired helical filaments are partly made from a protein called tau
- in AD are tau proteins are excessively phosphorylated

Features

- The amnestic presentation is the most common syndromic presentation of AD dementia.
  - The deficits should include:
    1. impairment in learning and recall of recently learned information,
    2. **and** a deficit from another domain, such as the **visuospatial domain** (recognizing a family member). For example, he was unable to learn/recall a major family event.

Investigation

- MRI scan in Alzheimer → symmetrically **increased size of the lateral ventricles** along with **cerebral cortical atrophy** in a mainly frontal and parietal distribution.

Management

- NICE now recommend the three acetylcholinesterase inhibitors (donepezil, galantamine and rivastigmine) as options for managing mild to moderate Alzheimer's disease
  - **A well-known side effect of rivastigmine is AV block**
- memantine (a NMDA receptor antagonist) is reserved for patients with moderate - severe Alzheimer's

Mild cognitive impairment (MCI) is typically someone forgetting things and then remembering later in the day. Some patients may describe it as the 'ageing process', and the complaints are typically vague. The presence of a second domain such as deficit of the **visuospatial domain** suggest a diagnosis of Alzheimer's disease and rules out MCI.

Aggression in Alzheimer's disease

- Ideally, aggression in Alzheimer's disease should be managed with non-drug approaches, aiming to identify and avoid triggers and finding behavioural techniques which manage the symptoms. However, sometimes drug treatment is required.
- Atypical neuroleptics, such as quietapine, and haloperidol are not recommended as there is an increased risk of death or stroke. There is also concern that these agents may contribute to cognitive decline, and it is recognised that symptoms often relapse after cessation of haloperidol.
- However, **risperidone has been tested in this setting and is licensed for 6 weeks treatment of persistent aggression in those with moderate to severe Alzheimer's disease**, providing that non-pharmacological alternatives have been tried and there is a risk of harm.
- Valproate has been widely used for its calming effects in this situation, but there is little evidence of the efficacy of valproate.
- Benzodiazepines are not recommended, as they can impair alertness and increase daytime sleepiness (thereby increasing the risk of falls), and are also associated with worsening cognitive decline.

Lewy body dementia

Alpha-synuclein(AS) is a protein that is abundant in the human brain. It is found mainly in the pre-synaptic terminals of neurones; it is found in particularly high levels in the substantia nigra. Lewy bodies are aggregates of AS that occur in cells affected by Parkinson's disease.

- Lewy body dementia is an increasingly recognised cause of dementia, accounting for up to 20% of cases.
- The characteristic pathological feature is alpha-synuclein cytoplasmic inclusions (Lewy bodies) in the substantia nigra, paralimbic and neocortical areas
- The relationship between Parkinson's disease and Lewy body dementia is complicated, particularly as dementia is often seen in Parkinson's disease. Also, up to 40% of patients with Alzheimer's have Lewy bodies
- It should be distinguished from Parkinson's disease with dementia (PDD), which is diagnosed when the dementia onset is more than a year after the onset of Parkinson's. **Lewy body dementia is diagnosed when the cognitive symptoms begin at the same time or within a year of Parkinsonism.**
- **Neuroleptics should be avoided in Lewy body dementia**, as patients are extremely sensitive and may develop irreversible parkinsonism.
    - Questions may give a history of a patient who has deteriorated following the introduction of an antipsychotic agent
        - The most appropriate therapeutic strategy with respect to maintaining his mobility is → **Stop dopamine-blocking drugs (causing significant parkinsonism) eg: quetiapine**

Features

- progressive cognitive impairment
- parkinsonism
- visual hallucinations (other features such as delusions and non-visual hallucinations may also be seen)

Other feature

- Intermittent confusion
- Myoclonus, and
- Marked sensitivity to neuroleptic treatment.

Diagnosis

- usually clinical
- single-photon emission computed tomography (SPECT) is increasingly used. It is currently commercially known as a DaTscan. Dopaminergic iodine-123-radiolabelled 2-carbomethoxy-3-

(4-**iodo**phenyl)-N-(3-fluoropropyl) nortropane (123-I FP-CIT) is used as the radioisotope. The sensitivity of SPECT in diagnosing Lewy body dementia is around 90% with a specificity of 100%

Haloperidol ➔ contra-indicated in Lewy body dementia

Treatment

- The treatment of choice is rivastigmine, which improves both the visual hallucinations, and cognitive impairment.

September 2013 exam: A 78-year-old man with memory impairment, hallucinations, resting tremor, festinating gait and an expressionless face. He scores 12 / 30 on the mini-mental state examination (MMSE). which test is most likely to confirm the diagnosis? SPECT scan (Lewy body dementia)

September 2006 exam: H/O parkinsonian symptoms + agitation. deteriorated after prescribing haloperidol. What is the most likely underlying diagnosis? Lewy body dementia

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Frontotemporal lobar degeneration

- Frontotemporal lobar degeneration (FTLD) is the third most common type of cortical dementia after Alzheimer's and Lewy body dementia.
- Characterised by loss of 'executive' functions and multi-infarct state, usually has a step-wise history.
- **Although frontotemporal dementia is associated with chromosome 17, when there is motor neurone disease (MND) associated the chromosome linked to the disorder is 9.**
  - **FTD-MND or FTS-ALS has been linked to chromosome 9.**
- **C9ORF72 is associated with an autosomal dominant inheritance of motor neurone disease and frontotemporal dementia**
- **Frontotemporal dementia (FTD) start initially in the orbitofrontal cortex and anterior cingulate regions of the frontal lobes**

- There are three recognised types of FTLD
  - Frontotemporal dementia (Pick's disease)
  - Progressive non fluent aphasia (chronic progressive aphasia, CPA)
  - Semantic dementia

Common features of frontotemporal lobar dementias
Onset before 65
Insidious onset
Relatively preserved memory and visuospatial skills
Personality change and social conduct problems

Pick's disease

- This is the most common type of frontotemporal dementia
- characterised by **personality change and impaired social conduct.**
- Other common features include hyperorality, disinhibition, increased appetite, and perseveration behaviours.
- Focal gyral atrophy with a knife-blade appearance is characteristic of Pick's disease.
- **Macroscopic changes** seen in Pick's disease include:-
  - Atrophy of the frontal and temporal lobes
- **Microscopic changes** include:-
  - Pick bodies - spherical aggregations of **tau protein** (silver-staining)
  - Gliosis
  - Neurofibrillary tangles
  - Senile plaques

CPA

- Here the chief factor is non fluent speech. They make short utterances that are agrammatic.

- Comprehension is relatively preserved.

Semantic dementia

- Here the patient has a fluent progressive aphasia. The speech is fluent but empty and conveys little meaning.
- Unlike in Alzheimer's **memory is better for recent rather than remote events.**

Frontal lobe syndrome

- Frontal lobe syndrome usually presents with
  - Personality changes
  - Urinary and faecal incontinence
  - Anosmia
  - Expressive dysphasia (dominant lobe)
  - Release of primitive reflexes (positive grasp, pout and palmomental reflexes) and
  - Epilepsy.
- 50% of patients presenting with status epilepticus (with no previous history of seizures) have frontal lobe tumour.
- It can mimic dementia.

Permanent vegetative state (PVS)

Definition

- defined as a state of 'wakefulness without awareness'.
- The condition typically occurs when there is irreversible damage to the cerebral hemispheres but the brain stem remains intact.

Causes include

- Head injury
- Hypoxic injury (cardiac arrest, carbon monoxide poisoning)
- Stroke
- Hypoglycaemia
- Intracranial infection
- End-stage degenerative brain disease (for example, Alzheimer's).

Features

- The patient breathes spontaneously without mechanical support, is haemodynamically stable and has cycles of eye closure and opening that resemble a normal sleeping pattern but the patient is inattentive and unaware of his/her surroundings.
- Patients may have spontaneous movements (moaning, grunting, teeth grinding, roving eye movements) and may also smile, laugh and cry without any apparent reason.
- Although there may be eye movement, the eyes do not track a moving object.
- Patients may respond to painful stimuli and may have myoclonus in response to startling stimuli.
- Primitive reflexes may be present.
- Posture may become decorticate
- plantar responses are commonly extensor.

Creutzfeldt-Jakob disease (CJD)

Definition

- Creutzfeldt-Jakob disease (CJD) is **rapidly progressive** neurological condition caused by prions that are resistant to degradation by proteases due to misfolding into beta-pleated sheets.
  - **prion** is an **incorrectly folded protein** that causes misfolding of other proteins.

Epidemiology

- CJD is the most common prion disease in humans.

Types

1. Sporadic (~ 85%): no identifiable cause
2. Familial (~ 10–15%): various mutations in the PRNP gene
3. Acquired (< 1%)
   - **Iatrogenic CJD**: transmission during medical procedures (e.g., via organ transplantation, blood transfusion)
   - **Variant CJD (vCJD):** by ingestion of beef infected with bovine spongiform encephalopathy (BSE)

- (BSE is a transmissible prion disease occurring in cattle. Infection leads to vCJD in humans.)

Pathophysiology

- Caused by prion proteins.
  - These proteins induce the formation of amyloid folds resulting in tightly packed beta-pleated sheets resistant to proteases.
  - Prions proteins lead to neurodegeneration
    - results from the **conversion of an a-helix in a normal protein, termed prion protein (PrPc), to a ß-pleated form.** The new ß-pleated protein (PrPSc) resists degradation and facilitates conversion of normal proteins to the abnormal form.
    - accumulation of abnormal ß-pleated prion protein (PrPSc) results in "spongiform encephalopathy,"
  - the 'prion protein' is encoded on chromosome 20 - it's role is not fully understood
  - methionine homozygosity at codon 129 of the prion protein is a risk factor for developing CJD - all patients who have so far died have had this
- iatrogenic CJD cases in 1985 resulting from:
  - cadaveric tissue product (**cadaveric human growth hormones**)
  - infected neurosurgical instrumentation
    - Change in practice has caused a fall in the numbers of iatrogenic CJD, although with **possible incubation up to 30 years, cases may still present.**

What is the agent responsible for variant Creutzfeldt-Jakob disease (CJD)?
➔ **Proteinaceous infectious particle (prion protein)**

Features

Rapidly progressive dementia and **myoclonic jerks** are the hallmarks of Creutzfeldt-Jakobdisease

- progressive mental deterioration (100%); dementia (rapid onset)
- **myoclonus** or movement disorder (100%);
- cerebellar signs (70%);
- pyramidal weakness (62%); and
- behavioural abnormality (55%).

Differential diagnosis

- distinguished from other causes of dementia by its rapidly progressive course (patients usually die within one year of symptom onset), prominent myoclonus (especially provoked by startle), and prominent gait disturbance.

Investigation

- CSF is usually normal
  - 14-3-3 protein analysis may be useful in confirming a diagnosis of sporadic CJD.
  - elevation of **IgG**
- **EEG: biphasic, high amplitude sharp waves** (only in sporadic CJD)
  - EEG is usually normal in new variant CJD.
- **MRI**: **hyperintense signals** in the basal ganglia and thalamus
- Brain biopsy
  - diagnostic for CJD, but the combination of MRI, EEG and lumbar puncture is usually sufficient to make the diagnosis in life.
  - the main histologic features are:
    - spongiform change,
    - neuronal loss without inflammation,
    - accumulation of the abnormal prion protein,
    - **Amyloid plaques (vCJD)**

- ❖ Histologic features that **distinguish vCJD from CJD** include the presence of amyloid plaques staining for PrP^{sc}, which have eosinophilic centers and pale peripheries.

Sporadic CJD

The rapidly progressive neurological impairment, with myoclonus and hyper-reflexia coupled with EEG abnormality and MRI changes in the caudate and putamen, is most consistent with sporadic CJD.

- Sporadic CJD has an annual incidence of around 1 per million.
- accounts for **85%** of cases
- 10-15% of cases are familial
- mean age of onset is **65 years**
- Presence of 14-3-3 protein in cerebrospinal fluid would support this diagnosis.

New variant vCJD

- younger patients (average age of onset = 25 years)
- **psychological symptoms** such as anxiety, withdrawal and dysphonia are **the most common presenting features**
- Ataxia and involuntary movements (for example, myoclonus) usually appear at an interval of about six months after the initial symptoms.
- associated primarily with change in the posterior thalamus on MRI.
- **Diagnosis**
  - ➢ **MRI brain typically shows bilateral pulvinar (posterior thalamic nuclei) high signals.**
  - ➢ EEG is usually normal in new variant CJD.
  - ➢ Testing for the 14-3-3 protein marker in (CSF) has a diagnostic sensitivity of around 80%
  - ➢ Sometimes, it is possible to isolate prion proteins from tonsillar tissue
  - ➢ produces a characteristic abnormality in brain tissue called "**florid plaques**"
- Prognosis
  - ➢ median survival = 13 months

Other prion diseases

- kuru
- fatal familial insomnia
- Gerstmann Straussler-Scheinker disease

The characteristic neuropathologic profile of variant CJD in both the cerebellum and cerebrum, by immunohistochemical analysis:

➔ **numerous kuru-type amyloid plaques surrounded by vacuoles and prion protein (PrP).**

Treatment

- No curative therapy available
- Symptomatic treatment and eventually palliative care

Prognosis

- Following disease manifestation, most patients die within 12 months, usually from complications such as pneumonia

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Cerebro-tendinous xanthomatosis

- inherited condition,
- associated with accumulation of cholesterol in tissues including brain, peripheral nerve and tendons
- **clinical picture** :
  - ➢ Early onset dementia
  - ➢ Gait ataxia
  - ➢ Loss of vibration sense
  - ➢ Cataracts
  - ➢ Large tendon xanthomata.

- **Diagnosis**
  - there is a deficiency in sterol storage,
  - diagnosis is based on high serum (and tendon) **cholesTANOL**.
    - **cholestanol** is a derivative of cholesterol.
  - Serum cholesterol may be normal or low.
- **Treatment**
  - It is eminently treatable by the oral administration of **chenodeoxycholic acid.**

Transient global amnesia

Overview

- presents with transient loss of memory function
- patients may appear anxious and repeatedly ask the same question
- patients have no recall of events after the attack
- aetiology is unknown, thought to be due to transient ischaemia to the thalamus (in particular the amygdala and hippocampus)

Risk factors

- usually affects people over the age of 50
- Migraine in younger patients (<55y)
- Psychological and vascular risk factors
- after a venous congestion in the context of insufficient jugular-vein valves.
- Epilepsy can present with discreet episodes of amnesia. This syndrome is called **transient epileptic amnesia.**
  - Features that suggest epilepsy are;
    - shorter duration (should be less than 1 hour),
    - multiple attacks,
    - onset on waking from sleep
    - accompanying epileptic features - e.g. motor automatism, stereotyped behaviours, limb shaking.

Diagnostic criteria are as follows;

- discrete episode lasting for a few hours (always less than 24 hours) of anterograde amnesia, retrograde amnesia,
- repetitive questioning
- **Normal perception**
- absence of other cognitive or neurological impairments.
- absence of head trauma or loss of consciousness at the onset
- preserved personal identity
- absence of epileptic features.
- Patients are usually disoriented in time and place, but not usually person.
- Attack is often associated with headache, nausea and dizziness.
- Other associated features are chills, fear of death, paraesthesia, emotional upset and chest pain.
- Recurrence is unusual.

Management

- **the best line of management → Admit for observation**
- The great majority of patients recover within 24 hours and do not get further such episodes.
- No treatment is needed except observation until recovery.
- Imaging is considered if amnesia does not resolve after 24 hours.

Restless legs syndrome

Restless leg syndrome - management includes dopamine agonists such as ropinirole

- Restless legs syndrome (RLS) is a syndrome of spontaneous, continuous lower limb movements that may be associated with paraesthesia.
- It is extremely common, affecting between 2-10% of the general population.

- Males and females are equally affected and a family history may be present

Clinical features

- uncontrollable urge to move legs (akathisia). Symptoms initially occur at night but as condition progresses may occur during the day. Symptoms are worse at rest
- paraesthesias e.g. 'crawling' or 'throbbing' sensations
- movements during sleep may be noted by the partner - periodic limb movements of sleeps (PLMS)

Causes and associations

- there is a positive family history in 50% of patients with idiopathic RLS
- iron deficiency anaemia **(a low serum ferritin is most likely to be a cause of secondary restless legs syndrome)**
  - associated with nutritional deficiencies of folate, magnesium, iron
- uraemia (end stage renal failure),
- diabetes mellitus
- pregnancy
- COPD,
- gastric surgery,
- chronic venous insufficiency,
- hypothyroidism
- drugs such as beta-blockers, H2 antagonists or neuroleptics.
  - It can be exacerbated by diuretics, tricyclics, phenytoin and calcium antagonists.

Diagnosis is clinical although bloods to exclude iron deficiency anaemia may be appropriate

- Although no specific tests exist for the diagnosis it is based on the international restless legs syndrome study group four basic criteria for diagnosing RLS:
  1. A desire to move the limbs, often associated with paraesthesias or dysaesthesias
  2. Symptoms that are worse or present only during rest and are partially or temporarily relieved by activity
  3. Motor restlessness, and
  4. Nocturnal worsening of symptoms.

Management

- simple measures: walking, stretching, massaging affected limbs
- **treat any iron deficiency**
- **dopamine agonists** are first-line treatment (e.g. Pramipexole, **ropinirole**)
- Anti-convulsants such as sodium valproate being effective second line agents.
- benzodiazepines
- gabapentin
- Pramipexole and rotigotine are also licensed for moderate to severe restless legs.

Essential tremor

Essential tremor is an AD condition that is made worse when arms are outstretched, made better by alcohol and propranolol

Essential tremor (previously called benign essential tremor) is an autosomal dominant condition which usually affects both upper limbs

Features

- postural tremor: worse if arms outstretched
- improved by alcohol and rest
- most common cause of titubation (head tremor)

Management

- propranolol is first-line
- primidone is sometimes used

January 2013 exam: H/O involuntary movements of the head, worse on movement and during stress and relieved by alcohol and sleep. What is the most likely diagnosis? Essential tremor (Essential tremor is the most common cause of titubation (head tremor).

January 2015 exam: H/O tremor of the arms, which is worse when arms are outstretched. His father suffered from a similar complaint. What is the most suitable first-line treatment? Propranolol

Friedreich's ataxia

Genetics

- **autosomal recessive**,
- **trinucleotide repeat disorder**
  - characterised by a **GAA** repeat in the **X25 gene** on **chromosome 9** (**frataxin**).
- Friedreich's ataxia is unusual amongst trinucleotide repeat disorders in **not demonstrating the phenomenon of anticipation.**

Epidemiology

- the most common early-onset hereditary ataxias.
- The typical age of onset is 10-15 years old.

Pathophysiology

- The posterior columns, corticospinal and spinocerebellar tracts are affected leading to cerebellum dysfunction, spastic paraparesis and absent reflexes in lower limbs.
- Gait ataxia and kyphoscoliosis are the most common presenting features.

Neurological features

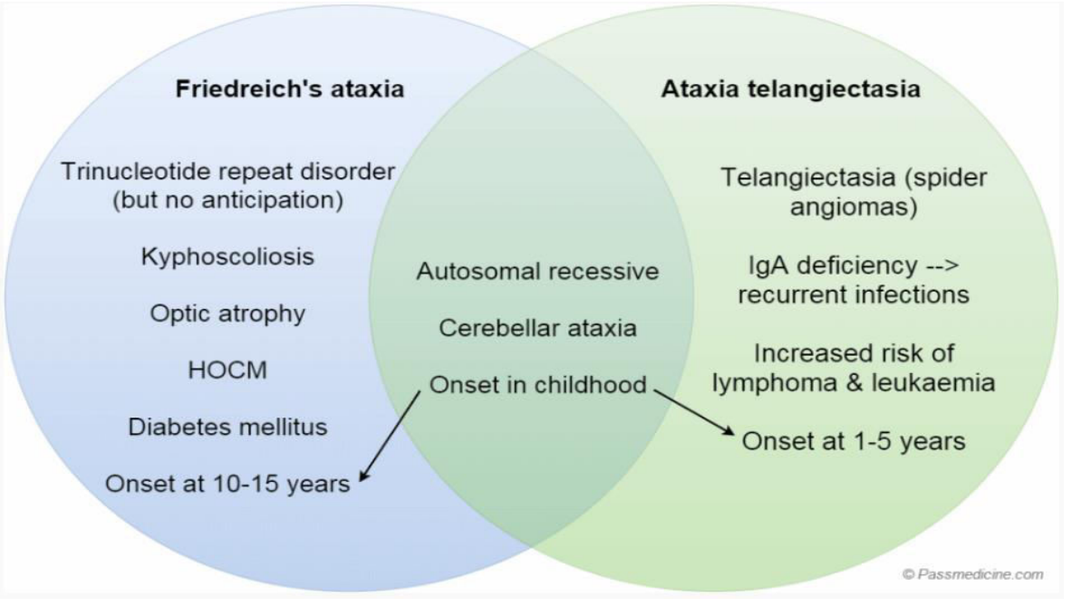
- absent ankle jerks/extensor plantars
- cerebellar ataxia
- optic atrophy
- spinocerebellar tract degeneration

Other features

- hypertrophic obstructive cardiomyopathy (90%, most common cause of death)
- diabetes mellitus (10-20%)
- high-arched palate
- Bilateral pes cavus
- kyphoscoliosis

Diagnosis

- definitive diagnosis → Genetic testing for **expansion of the GAA triplet repeat** in the FXN gene
- Other diagnostic tests suggestive of Friedreich ataxia include:
  - nerve conduction studies showing absent or reduced sensory nerve action potentials,
  - MRI of the brain and spinal cord revealing cervical spine atrophy with minimal cerebellar atrophy.



Ataxic telangiectasia

- autosomal recessive disorder
- caused by a defect in the **ATM gene** which encodes for **DNA repair enzymes**.
- It is one of the inherited combined immunodeficiency disorders.
- It typical presents in early childhood with abnormal movements. oculomotor apraxia and choreoathetosis developing later.

Features

- cerebellar ataxia
- telangiectasia (spider angiomas)
- **IgA deficiency** resulting in recurrent chest infections → **bronchiectasis**
- 10% risk of developing malignancy, lymphoma or leukaemia, but also non-lymphoid tumours

Diagnosis

- Elevated **serum alpha-fetoprotein**, at least two standard deviations above the normal range, is diagnostic of ataxia-telangiectasia
- confirmed by the identification of mutations on the ATM gene.

Prognosis

- Death in the late teens or 3rd decade from **bronchiectasis** is typical.

Sleep

Sleep Stage	Description	EEG Waveform
	• Awake and alert	• Beta
	• Awake and eyes closed	• Alpha
Stage N1	• Light sleep	• Theta
Stage N2	• Deeper sleep	• Sleep spindles and K complexes
Stage N3	• Deepest non-REM sleep • Sleepwalking • Night terrors • Bedwetting	• Delta
REM	• Dreaming	• Beta

- Suprachiasmastic nucleus of the hypothalamus is involved in circadian rhythm regulation
- GABA agonists (alcohol, benzodiazepines, and barbiturates) reduce REM and delta sleep
- **REM Sleep:**
  - Physiology
    - rapid eye movement
    - same EEG pattern as when awake

        - erection
        - ↑ and variable pulse and blood pressure
        - loss of muscle tone
    - Timing
        - occurs every 90 min
        - duration ↑ with every cycle
        - amount of REM sleep ↓ with age
    - acetylcholine is the principle neurotransmitter
    - norepinephrine, serotonin, and histamine suppress REM sleep
        - therefore, certain antidepressants (eg, SSRI, SNRI) can pharmacologically suppress REM sleep

Sleep paralysis

- Mechanism is believed to involve a dysfunction in REM sleep.
- Epidemiology
    - Between 8% and 50% of people experience sleep paralysis at some time.
    - 5% of people have regular episodes.
    - Males and females are affected equally.
- Feature
    - aware but unable to move.
    - may include
        - hallucinations
        - fear.
- Episodes generally last less than a couple of minutes.
- Associations
    - may occur in those who are otherwise healthy,
    - narcolepsy
    - familial
    - can be triggered by sleep deprivation, psychological stress, or abnormal sleep cycles
- Diagnosis is based on a person's description.
- Differential diagnosis
    - narcolepsy,
    - atonic seizure, and
    - hypokalemic periodic paralysis.
- Treatment
    - reassured that the condition is common and not serious.
    - Other options that may be tried include sleep hygiene, cognitive behavioral therapy, and antidepressants.

Narcolepsy

- **Pathophysiology**
    - Due to loss of orexin (hypocretin) neuropeptides
        - normally produced in the **lateral hypothalamus.**
        - associated with wakefulness
    - About one-third of all patients have a family history of the disorder.
    - There is a strong HLA association; about 95% of white people with narcolepsy are positive for the DRw16 subtype of DR2.
    - The MSLT will demonstrate rapid eye movement (REM) sleep at sleep onset, or shortly after the onset of sleep, in those with narcolepsy.
- **Triad of:**
    1. **sleep paralysis,**
    2. **excessive daytime somnolence and**
    3. **cataplexy.**
        - About 5% of patients with narcolepsy have cataplexy.
- may include hallucinations
    - hypnagogic
        - just before sleep
    - hypnopompic
        - just before awakening
- **Diagnosis**

- Diagnosis is a clinical one, supported by an **overnight polysomnogram** **and** **multi sleep latency test.**

- **Treatment**
  - **Non**-amphetamine based stimulants, such **modafinil,** are the treatment of choice.

Cataplexy

- Cataplexy describes the sudden and transient loss of muscular tone caused by strong emotion (e.g. laughter, being frightened).
- Features range from buckling knees to collapse.
- Longer episodes can be associated with hallucinations.
- Around two-thirds of patients with narcolepsy have cataplexy.

Head injury

Head injury: NICE guidance

CT head immediately (**within the one hour**)

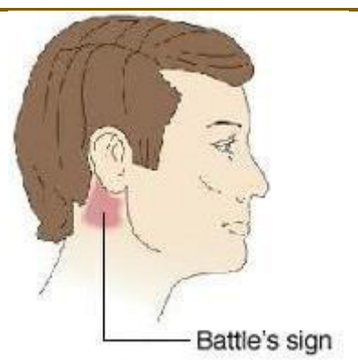
- GCS < 13 on initial assessment
- **GCS < 15 at 2 hours post-injury**
- suspected open or depressed skull fracture.
- any sign of basal skull fracture (haemotympanum, 'panda' eyes, cerebrospinal fluid leakage from the ear or nose, Battle's sign).
- post-traumatic seizure.
- focal neurological deficit.
- more than 1 episode of vomiting

CT head scan within 8 hours of the head injury - for adults with any of the following risk factors who have experienced some loss of consciousness or amnesia since the injury:

- age 65 years or older
- any history of bleeding or clotting disorders
- dangerous mechanism of injury (a pedestrian or cyclist struck by a motor vehicle, an occupant ejected from a motor vehicle or a fall from a height of greater than 1 metre or 5 stairs)
- more than 30 minutes' retrograde amnesia of events immediately before the head injury
- **If a patient is on warfarin perform a CT head scan within 8 hours of the injury regardless of whether he have risk factors for an intracranial injury.**

Battle's sign (mastoid ecchymosis)

- bruising over the mastoid process, as a result of extravasation of blood along the path of the posterior auricular artery.
- is an indication of fracture of middle cranial fossa of the skull,
- take at least one day to appear after the initial traumatic basilar skull fracture



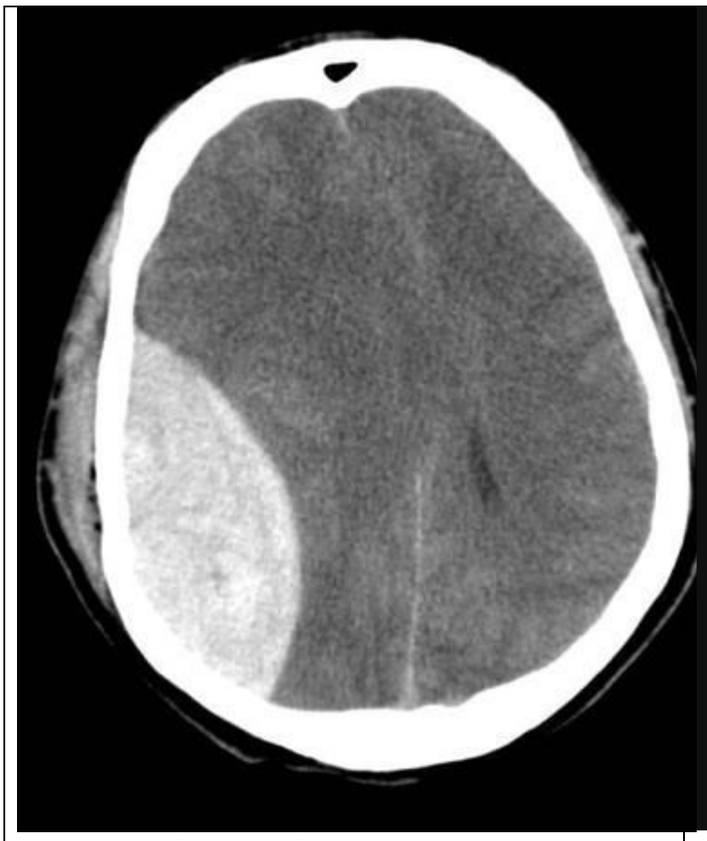
Head injury: types of traumatic brain injury

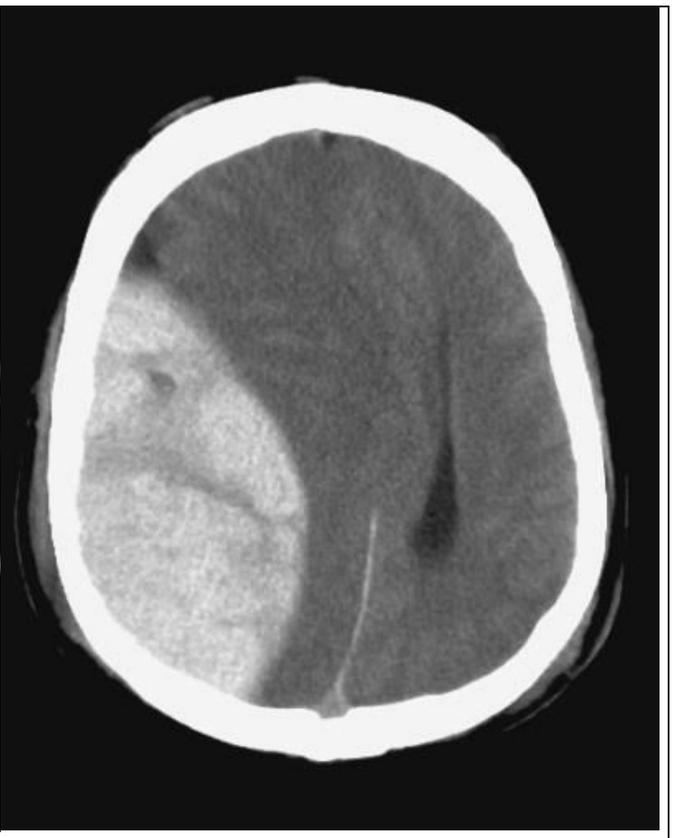
Basics

- primary brain injury may be focal (contusion/haematoma) or diffuse (diffuse axonal injury)
- diffuse axonal injury occurs as a result of mechanical shearing following deceleration, causing disruption and tearing of axons

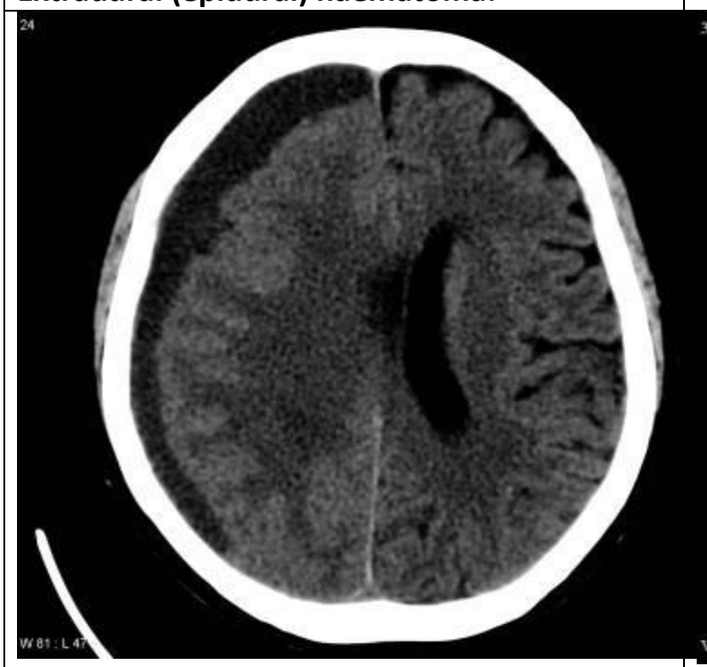
- intra-cranial haematomas can be extradural, subdural or intracerebral, while contusions may occur adjacent to (coup) or contralateral (contre-coup) to the side of impact
- secondary brain injury occurs when cerebral oedema, ischaemia, infection, tonsillar or tentorial herniation exacerbates the original injury.
- The normal cerebral auto regulatory processes are disrupted following trauma rendering the brain more susceptible to blood flow changes and hypoxia
- the Cushings reflex (hypertension and bradycardia) often occurs late and is usually a pre terminal event

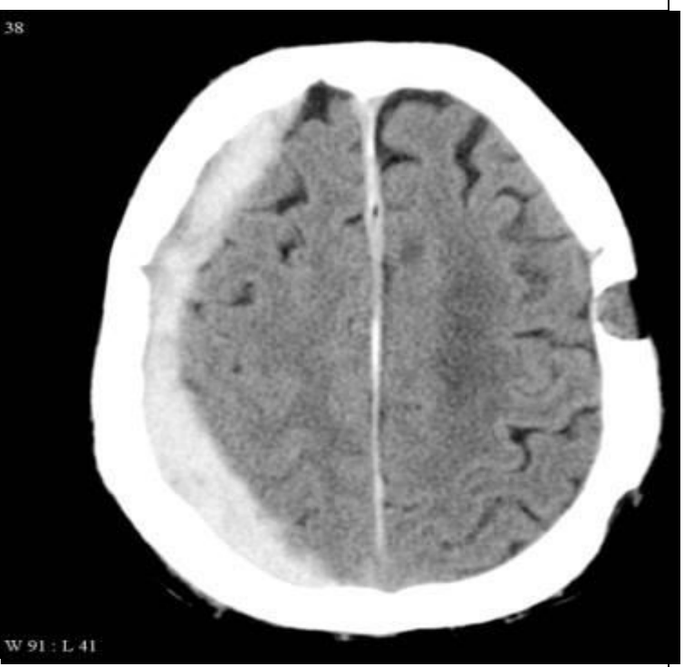
Type of injury	Notes
Extradural (epidural) haematoma	➢ Bleeding into the space between the dura mater and the skull. ➢ Often results from acceleration-deceleration trauma or a blow to the side of the head. ➢ The majority of epidural haematomas occur in the temporal region where skull fractures cause a **rupture of the middle meningeal artery**. **Features** Epidural haematoma - lucid interval ➢ features of raised intracranial pressure ➢ some patients may exhibit a lucid interval (apparent recovery from the initial concussion, but deterioration is usually within 15-30 minutes).
Subdural haematoma	Bleeding into the outermost meningeal layer. Most commonly occur around the frontal and parietal lobes. Risk factors include old age, alcoholism and anticoagulation. Slower onset of symptoms than a epidural haematoma.
Subarachnoid haemorrhage	Usually occurs spontaneously in the context of a ruptured cerebral aneurysm but may be seen in association with other injuries when a patient has sustained a traumatic brain injury





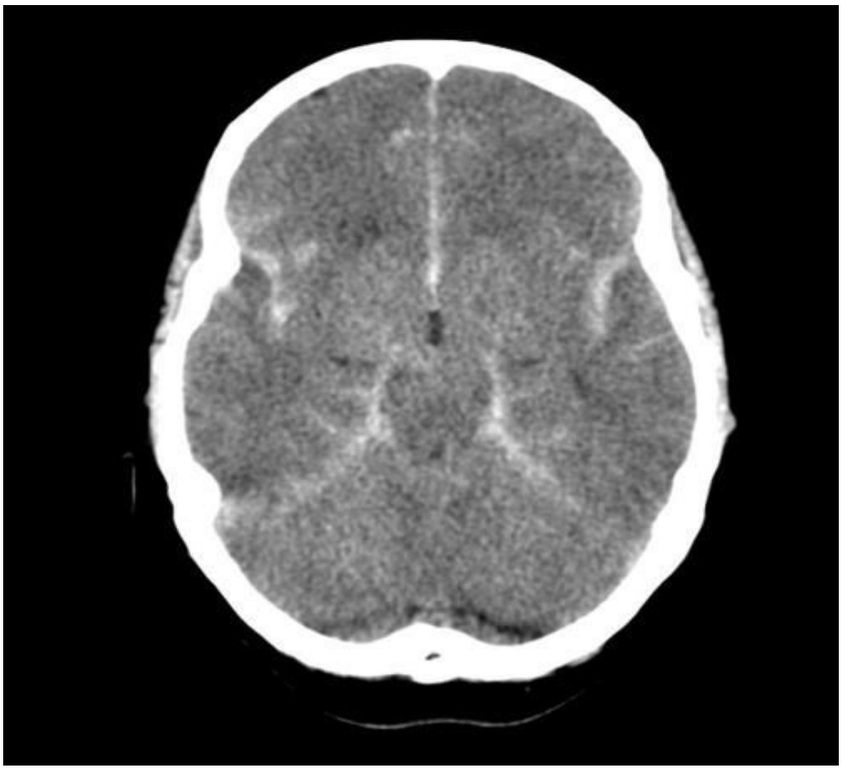
Extradural (epidural) haematoma:





Subdural haematoma

Subarachnoid haemorrhage:



Subdural haemorrhage

Fluctuating consciousness = subdural haemorrhage

The history of progressive 'confusion' and unsteadiness for some weeks followed by an acute exacerbation is a typical presentation of a subdural haematoma in the elderly population.

Basics

- most commonly secondary to trauma e.g. old person/alcohol falling over
- initial injury may be minor and is often forgotten
- caused by bleeding from damaged bridging veins between cortex and venous sinuses
- The phrase 'fluctuating conscious level' is common in questions and should always bring to mind subdural haemorrhage
- The combination of falls, alcohol excess, fluctuating episodes of confusion and focal neurology points towards a diagnosis of subdural haemorrhage.

Features

- headache (The most common presenting symptom , seen in up to 80% of patients)
- classically fluctuating conscious level
- raised ICP → bilateral papilloedema

Other common symptoms are:

- fatigue
- memory impairment
- confusion
- nausea and vomiting
- impaired vision, and
- seizures.
- Hemiparesis, or paralysis is also possible.

Treatment

- needs neurosurgical review ? burr hole

Acute subdural haematoma

- usually results from acute head trauma
- The haematoma accumulates between the surface of the brain and the dura mater.
- The mortality rate ranges between 50% and 90%.
- A good outcome is most likely if surgical evacuation of the haematoma is prompt and secondary brain injury is prevented.
- Mortality is less likely in:
  - younger adults
  - patients with a GCS score above 6 or 7
  - those with pupil reactivity, and
  - those without cerebral contusions or uncontrolled rises in intracranial pressure.

Subarachnoid haemorrhage (SAH)

- **Vascular malformations and aneurysms typically bleed in the subarachnoid space.**

Causes

- 85% are due to rupture of berry aneurysms (conditions associated with berry aneurysms include adult polycystic kidney disease, Ehlers-Danlos syndrome and coarctation of the aorta)
- AV malformations (**Cerebral aneurysms are associated with polycystic kidney disease**)
- trauma
- tumours

Investigations

- If SAH is suspected, obtain a head CT without contrast.
- If CT is ⊖, LP is mandatory.

- CT: negative in 5%
- **lumbar puncture: done after 12 hrs (allowing time for xanthochromia to develop)**
- Lumbar puncture (LP) is not usually required unless the history is suggestive and the **CT is normal.**
- **If CT image shows blood in the subarachnoid space, the most appropriate next investigation is → CT cerebral angiography** to look for an underlying aneurysm or vascular malformation which may be amenable to neurosurgical intervention.

Intracranial hemorrhage → ECG changes:

- **deep symmetrical T- wave inversion**
- **prolonged QT interval**

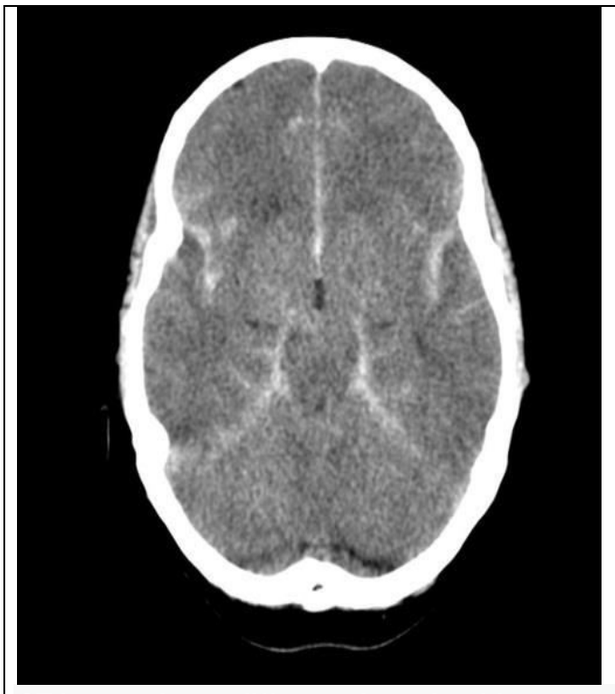
Complications

- rebleeding (in 30%)
- obstructive hydrocephalus (due to blood in ventricles)
- vasospasm leading to cerebral ischaemia

Management

What is the most appropriate minimum interval between neurological observations in the first instance? Answer → 30 min

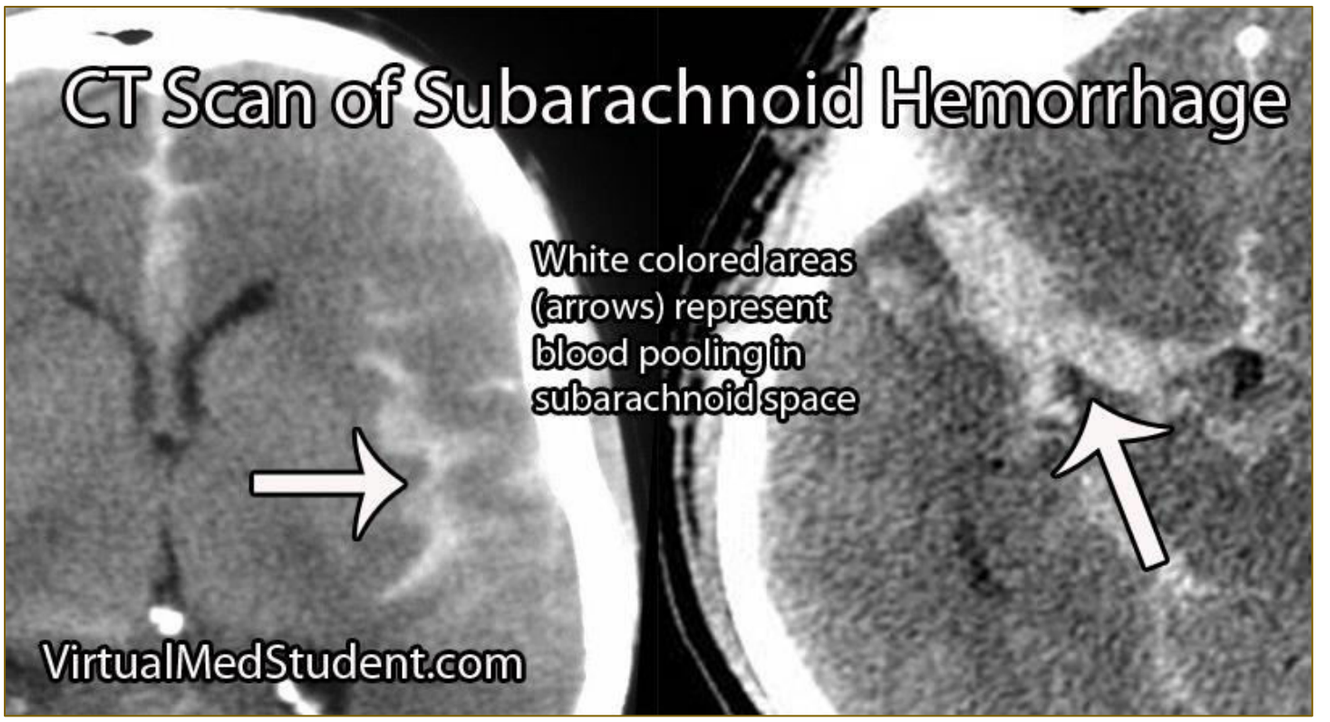
- neurosurgical opinion: no clear evidence over early surgical intervention against delayed intervention
- Patients presenting following sub arachnoid haemorrhage may suffer from cerebral vasospasm. Vasospasm occurs in approximately 30% of patients. it may result in further ischemia due to a reduction in distal blood flow. All patients are prescribed a calcium channel blocker (eg Nimodipine) to prophylactically prevent this.
- post-operative nimodipine (e.g. 60mg / 4 hrly, if BP allows) has been shown to reduce the severity of neurological deficits but doesn't reduce rebleeding*
  - *the way **nimodipine** works in subarachnoid haemorrhage is not fully understood. It has been previously postulated that it **reduces cerebral vasospasm** (hence maintaining cerebral perfusion) but this has not been demonstrated in studies



CT image shows diffuse subarachnoid haemorrhage in all basal cisterns, bilateral sylvian fissures and the inter-hemispheric fissure. This case demonstrates the typical distribution that takes the blood into the subarachnoid space in a subarachnoid hemorrhage.

Conditions associated with berry aneurysms that can* MAKE *an* SAH *more likely:

Marfan's syndrome
Aortic coarctation
Kidney disease (autosomal dominant, polycystic)
Ehlers-Danlos syndrome
Sickle cell anemia
Atherosclerosis
History (familial)



Comparison of Intracranial Haemorrhage

Feature	**Subarachnoid**	**Subdural**	**Extradural**
Location	The inner most layer around the brain tissue	Between the dura mater and arachnoid mater	The outermost layer, between the skull and dura mater
Mechanism	Usually due to rupture of a blood vessel (e.g. berry aneurysm or AVM). Pain typically felt at the back of the head	Usually due to trauma causing damage to one of the ***bridging veins.*** Trauma may be minor and could be many months ago. Can be acute or chronic.	Due to direct moderate / severe head trauma. Typically around the eye, causing fracture of the temporal or parietal bone, resulting in laceration of the middle meningeal artery and/or vein
Pain	Sudden onset, painful	Possible dull headache	Likely, and often severe, but not sudden onset
Consciousness	May become impaired quickly – if so, a very bad prognostic indicator	Fluctuates, often over weeks or even months	Classically, an initial lucid period, followed by impaired consciousness
Neurological signs	May be present; are a poor prognostic indicator	Often insidious. May involve memory impairment, epilepsy, drowsiness, dizziness. Often occur weeks / months after injury	Typically after a ***lucid period,*** severeheadache, impaired consciousness. Vomiting, seizures, drowsyness,confusion, and later, coma.
Investigations	CT – should show irregular shaped bleed. If absent, and still suspicious, do LP to confirm (blood in CSF, CSF turn yellow when left to stand – *xanthochromia)*	CT / MRI – classically shows a***crescent*** of blood around the brain tissue, and midline shift	CT / MRI – described as a ***lens shaped***lesion – meaning it is **biconvex.** **LP is contraindicated!** **X-ray** may show skull fracture
Management	If few symptoms, surgical clipping of platinum coiling of aneursm, or if AVM then balloon therapy and stening are beneficial. Give ***Nimodipine*** to reduce risk of vasospasm (and ↑ survival) as long as BP can be maintained.	Burr hole or craniotomy	Surgery to evacuate blood and ligate bleeding vessels

Brain stem herniation

The sudden onset of headache, ataxia and vomiting suggest → an intracranial haemorrhage, which leads to → mass effect and → subsequent **brain stem herniation**.

- Brain herniation often causes false localising signs due to compression of various areas of the brain.
- it usually follows two patterns:
  1. **uncal herniation** : presented with:
     - **third nerve paresis**
       - (ipsilateral dilated pupil, abnormal external ocular movements, including nystagmus)

- The third nerve paresis occurs due to compression of the parasympathetic fibres around the third nerve, which results in unopposed sympathetic response.

- **contralateral hemiparesis**
  - which can lead to ipsilateral hemiparesis.
  - Contralateral hemiparesis occurs with compression of the cerebral peduncle.
  - Ipsilateral hemiparesis and third nerve palsy occur late when the lateral translation is so great that it compresses the contralateral third nerve and peduncle.

2. **central herniation**:presents with:
   - confusion and drowsiness,
   - followed by impaired vertical gaze,
   - small pupils,
   - impaired oculocephalic reflexes
   - Bilateral corticospinal tract signs including increased tone and Babinski signs.
   - signs of raised intracranial pressure:
     - bradycardia,
     - hypertension,
     - irregular breathing (Cushing response)
     - and a sixth-nerve palsy.
   - The sixth nerve is usually the first to be compressed due to its long extracerebral intracranial course.
   - Diplopia from either a third or sixth nerve palsy can cause nystagmus.

- **Treatment**
  - immediate intensive care support, with intubation and hyperventilation.
  - The case should be discussed urgently with neurosurgeons, and their advice sought regarding the possibility of operative intervention.
  - Intravenous mannitol and other hyperosmolar solutions are often indicated, and should be considered.

Brain stem death tests include:
- Pupillary light response - CN II and III
- Corneal reflex, response to supraorbital pressure - CN V and VII
- Vestibulo-ocular reflex - CN III and VIII
- Gag reflex - CN IX and X
- **Cough reflex - CN X**
- Absence of respiratory effort.

Post-concussion syndrome

The most common symptoms are headache and neck discomfort; changes in memory, concentration, and attention; dizziness; irritability, depression or anxiety; and sleep disturbance, among other symptoms.
There is:
- Disturbance of thought
- Poor concentration span and
- Subjects are easily distracted.
- **Anxiety is common**

Encephalitis

Encephalitis may be caused by:

- **Direct invasion** by a neurotoxic virus (encephalitis).
  - most commonly caused by enteral viruses, herpes simplex virus (HSV) 1 and 2, varicella, cytomegalovirus (CMV), and Epstein-Barr virus (EBV).
  - occasionally caused by respiratory viruses, human herpes virus 6 (HHV6), rubella, or mumps.

- **Post-infectious** encephalopathy: delayed brain swelling because of an immunological response to the antigen, i.e. a neuroimmunological response.
    - **caused by measles** or varicella zoster (cerebellar ataxia).
- **Slow virus infection**, for example, human immunodeficiency virus (HIV) or subacute sclerosing panencephalitis (SSPE).

Herpes simplex encephalitis

CT head showing temporal lobe changes - think herpes simplex encephalitis

- Herpes simplex (HSV) encephalitis is a common topic in the exam. The virus characteristically affects the temporal lobes - questions may give the result of imaging or describe **temporal lobe signs** e.g. aphasia.
- **Temporal lobe involvement is common (limbic encephalitis), in particular the anterior temporal lobes. These abnormalities are visible on CT or MRI.**
- Winter is the peak incidence.
- It has peaks of presentation in the young and old.

Types

Both herpes simplex virus type 1 and type 2 can cause encephalitis.

- **Herpes simplex type 1** is the virus associated with encephalitis in older children and adults.
- **Herpes simplex type 2** is characterised by generalised brain involvement, but is almost exclusively seen in neonates who acquire the virus during delivery.

Herpes simplex encephalitis presents with:

- **Behavioural changes or psychiatric disturbance**
- **Focal seizures**
- **Fever and**
- **Alteration in consciousness.**

Features

- fever, headache, psychiatric symptoms, **seizures**, vomiting
- focal features e.g. aphasia
- peripheral lesions (e.g. cold sores) have no relation to presence of HSV encephalitis

Pathophysiology

- HSV-1 responsible for 95% of cases in adults
- typically affects temporal and inferior frontal lobes

Investigation

- CSF: **lymphocytosis**, elevated protein, mildly raised red cells and a normal or low glucose.
- **PCR for HSV on (CSF) is a highly specific test.**
- CT: medial temporal and inferior frontal changes (e.g. petechial haemorrhages) - normal in one-third of patients
- MRI is better
    - CT scan of the brain may be normal, but MRI may reveal the diagnosis.
- **EEG pattern: lateralised periodic discharges at 2 Hz**

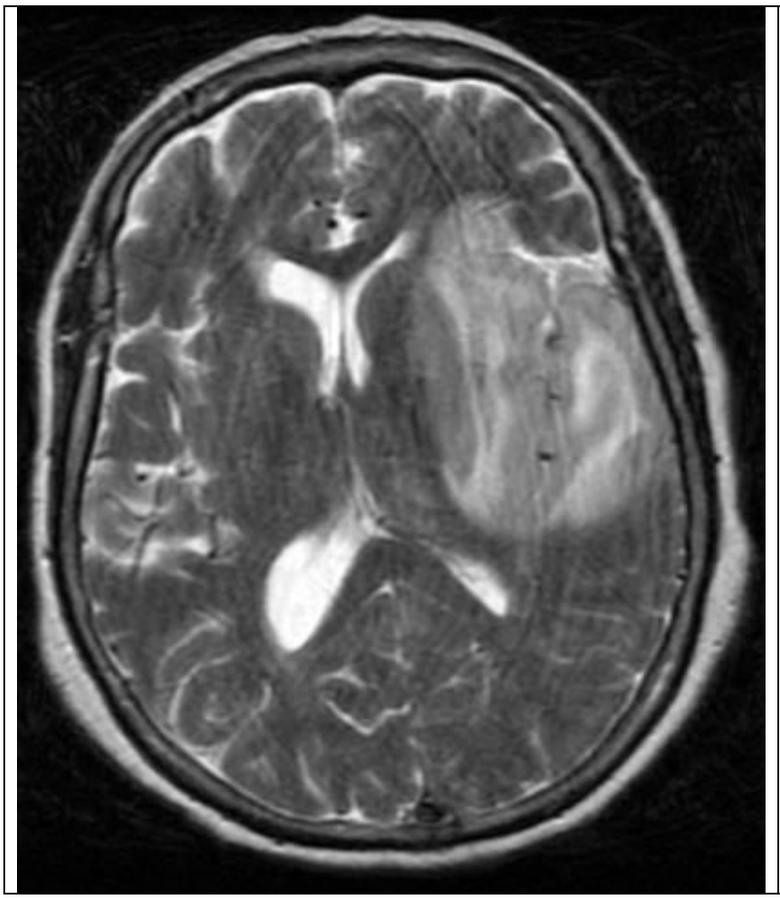
Treatment

- intravenous aciclovir
    - Immediate treatment is required on clinical suspicion - do not wait
    - continued until CSF PCR is negative, or for at least 14 days.
    - **Intravenous fluids and aciclovir is the best option here.**

prognosis

- The prognosis is dependent on whether aciclovir is commenced early.
    - If treatment is started promptly the mortality is 10-20%.

- Left untreated the mortality approaches 80%



MRI of a patient with HSV encephalitis. There is hyperintensity of the affected white matter and cortex in the medial temporal lobes and insular cortex.

January 2012 exam: H/O Confusion, headache and fever + seizure. MRI shows patchy haemorrhagic changes in the temporal lobe. Given the likely diagnosis, what is the treatment of choice? Supportive treatment + intravenous acyclovir. (Δ Herpes simplex encephalitis)

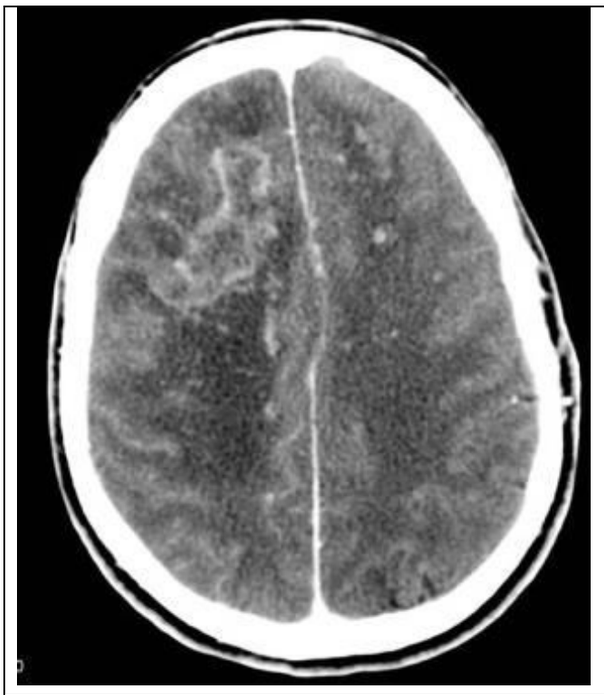
HIV: neurocomplications

Focal neurological lesions

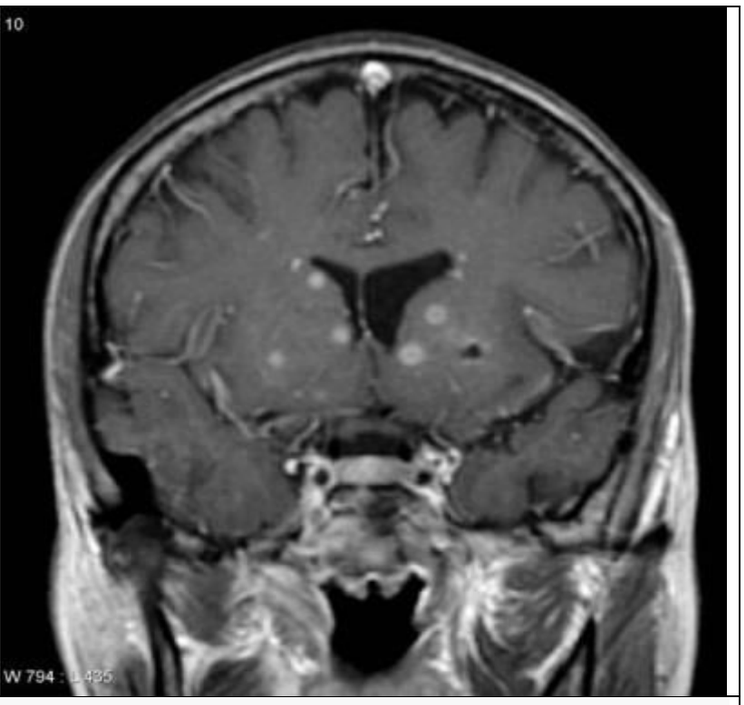
Toxoplasmosis

HIV - multiple ring enhancing lesions = toxoplasmosis

- the **most common** neurological infection seen in HIV,
- occurring in up to 10% of patients
- accounts for around **50%** of cerebral lesions in patients with HIV
- occurring at CD4 counts of less than 100 cells/mm^3.
- constitutional **symptoms**, headache, confusion, drowsiness
- **CT**: usually single or multiple ring enhancing lesions, mass effect may be seen
- **management: sulfadiazine and pyrimethamine**



Cerebral toxoplasmosis: CT scan with contrast showing multiple ring enhancing lesions



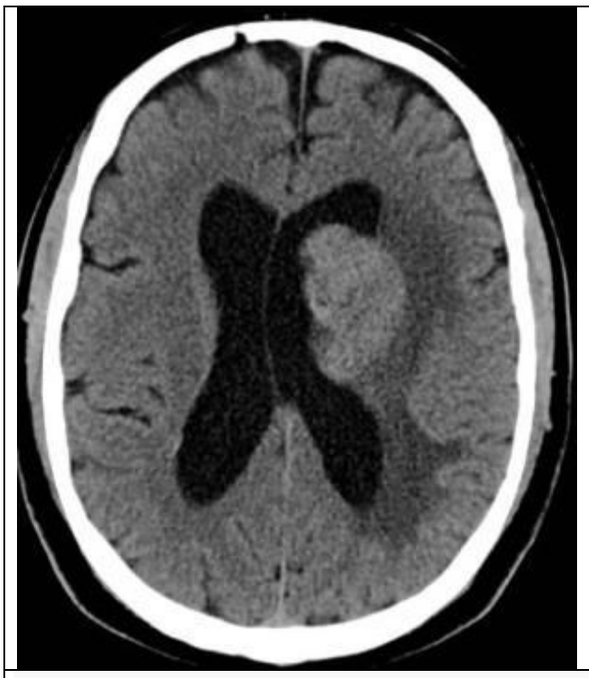
Cerebral toxoplasmosis: MRI (T1 C+) demonstrates multiple small peripherally enhancing nodules located predominantly in the basal ganglia as well as the central portions of the cerebellar hemispheres. Only a small amount of surrounding oedema is present.

The differential diagnosis of ring-enhancing lesions on CT in a patient with AIDS include:

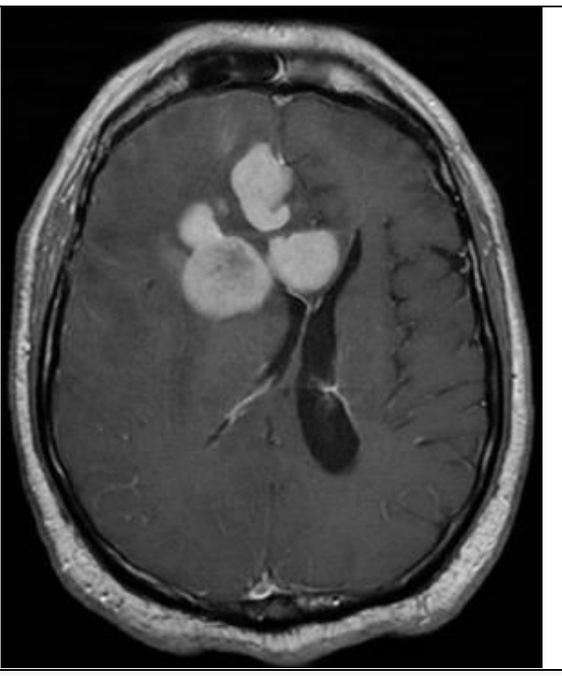
- Cerebral toxoplasmosis
- Abscesses
- Metastases
- Atypical CNS lymphoma.

Primary CNS lymphoma

- accounts for around 30% of cerebral lesions
- associated with the Epstein-Barr virus
- CT: single or multiple homogenous enhancing lesions
- treatment generally involves steroids (may significantly reduce tumour size), chemotherapy (e.g. methotrexate) + with or without whole brain irradiation. Surgical may be considered for lower grade tumours



Primary CNS lymphoma: Non-contrast CT demonstrates a hyper-attenuating mass adjacent to the left lateral ventricle, with no calcification or haemorrhage.



Primary CNS lymphoma: MRI (T1 C+) demonstrates a large multilobulated mass in the right frontal lobe. It homogeneously enhances and extends to involve the caudate and the periventricular area. There is significant mass effect.

Differentiating between toxoplasmosis and lymphoma is a common clinical scenario in HIV patients. The table below gives some general differences.

Condition	CT finding
Toxoplasmosis	▪ **Multiple** lesions ▪ Ring or nodular enhancement ▪ **Thallium SPECT negative**
Lymphoma	▪ **Single** lesion ▪ Solid (homogenous) enhancement ▪ **Thallium SPECT positive**
Tuberculosis	single enhancing lesion
Encephalitis	oedematous brain
Cryptococcus	meningeal enhancement, cerebral oedema
Progressive multifocal leukoencephalopathy (PML)	single or multiple lesions, **no mass effect**, **don't usually enhance**
AIDS dementia complex	cortical and subcortical atrophy

Given the more limited availablity of SPECT compared to CT many patients are treated empirically on the basis of **scoring systems**, for example there is a 90% likelihood of toxoplasmosis if all of the following criteria are met:

- toxoplasmosis IgG in the serum
- CD4 < 100 and not receiving prophylaxis for toxoplasmosis
- multiple ring enhancing lesions on CT or MRI

Tuberculosis

- much less common than toxoplasmosis or primary CNS lymphoma
- CT: single enhancing lesion

Generalised neurological disease

Encephalitis

- may be due to CMV or HIV itself
- HSV encephalitis but is relatively rare in the context of HIV
- CT: oedematous brain

Cryptococcus

- most common fungal infection of CNS
- typically there is a sub-acute onset of symptoms and the disease is associated with raised intracranial pressure (leading to the papiloedema and the falsely localising 6th nerve palsy).
- headache, fever, malaise, nausea/vomiting, seizures, focal neurological deficit
- CSF: high opening pressure, India ink test positive
- CT: meningeal enhancement, cerebral oedema
- meningitis is typical presentation but may occasionally cause a space occupying lesion
- raised intracranial pressure (ICP) is thought to be caused by the yeast cells and fungal polysaccharides forming microscopic plugs and blocking CSF resorption in the subarachnoid villi.
- **management**
  - **The best management would be intravenous anti-fungal agents, such as amphotericin B and flucytosine.**
  - Therapeutic lumber puncture is also advocated to reduce ICP.
  - Anti-retroviral (ARV) therapy should not be started immediately, as there is a very high risk of the patient developing IRIS (immune reconstitution inflammatory syndrome). Instead, ARVs should be delayed for several weeks or months after initiating treatment.

Progressive multifocal leukoencephalopathy (PML)

- widespread demyelination
- rare and fatal opportunistic infection of the central nervous system caused **by (JC) virus**.
- **seen in advanced HIV/AIDS**
- Associated with infection of oligodendrocytes by JC virus (papova-virus) (a polyoma DNA virus) , **hence associated with high CD4 lymphocyte count**
- **Natalizumab has a black-box warning of increased risk of developing (PML**),
- Three risk factors have been clearly identified in **patients with multiple sclerosis** which predispose them to the future developing PML:
  1. positive anti-JC viral serum antibodies,
  2. prior use of immunosuppressants, and
  3. increased duration of **natalizumab treatment** and its number of infusions (25-49 infusions).

Features

- subacute onset :
- Behavioural changes, speech, motor, visual impairment
- Ataxia
- Head tremor
- Focal neurology progressing **over a period of months** to paresis and even coma.

Diagnosis

- CT: single or multiple lesions, **no mass effect**, **don't usually enhance**.
- MRI is better - **high-signal demyelinating white matter lesions are** seen
- It can be diagnosed via **CSF PCR for the JC virus.**

AIDS dementia complex

- caused by HIV virus itself
- symptoms: behavioural changes, motor impairment
- CT: cortical and subcortical atrophy
- progresses over a longer time period than progressive multifocal leukoencephalopathy (PML).
- **Differential diagnosis**
  - Patients with **cryptococcal meningitis** present with headache, fever, vomiting and few neurological signs.
  - **PML** can present at any CD4 count with ataxia, behavioural changes and focal neurological signs, **often progressing over a period of months** to paresis or even coma.
  - **Toxoplasmosis** presents with headache, fever and seizures. It has a typical CT head scan with ring enhancing lesions.

January 2010 exam: H/O HIV positive, admitted following a seizure + headaches, night sweats and poor appetite. CD4=89 u/l. CT head =Single homogenously-enhancing lesion in the right parietal lobe . What is the most likely diagnosis? Primary CNS lymphoma

January 2014 exam: HIV positive, admitted with confusion, drowsiness and headache. temperature is 37.2ºC. CT brain (with contrast): Multiple hypodense regions predominantly in the basal ganglia which show ring enhancement. Minimal surrounding oedema. No mass effect. What is the most likely diagnosis? Cerebral toxoplasmosis (HIV - multiple ring enhancing lesions = toxoplasmosis)

Motor neuron disease (MND)

Progressive motor weakness and pseudo-bulbar palsy + normal sensations + normal brain imaging → always think of amyotrophic lateral sclerosis.
Electromyography is the best investigation to carry out next.

- Motor neuron disease is a neurological condition of unknown cause which can present with both upper and lower motor neuron signs.
- **the primary defect is in the anterior horn cells**

Epidemiology

- Sex: ♂ > ♀
- It rarely presents before 40 years

Types

1. **Amyotrophic lateral sclerosis (50% of patients)**
   - typically LMN signs in arms and UMN signs in legs
     - **anterior motor horn degeneration** leads to **lower** motor neuron signs.
     - **lateral corticospinal tract degeneration** leads to **upper** motor neuron signs.
   - **Causes**
     - un known in 90 % (sporadic)
     - inherited (10%)
       - **polygenic inheritance**
       - A defect on **chromosome 21**, which codes for **superoxide dismutase 1 (SOD1)**, is associated with about 20% of familial cases of ALS, or about 2% of ALS cases overall.
   - characterized by stiff muscles, muscle twitching, and gradually worsening weakness due to muscles decreasing in size. This results in difficulty speaking, swallowing, and breathing.
   - **20% of patients present with bulbar onset.**
     - most often a **late** clinical feature and suggests a **poor** prognosis
   - **Onuf nucleus is preserved**, thus the **bladder and rectal sphincters remain normal** through the course of the disease.
     - Onuf nucleus is **located** in the ventral part of laminae IX of the **anterior horn of spinal cord segments S1-S4**, and is composed of alpha motor neurons.
2. **Primary lateral sclerosis**
   - UMN signs only
3. **Progressive muscular atrophy**
   - **LMN** signs only
   - affects **distal** muscles before proximal
   - carries **best** prognosis
4. **Progressive bulbar palsy**
   - Epidemiology
     - accounts for ~ 0.2% of all motor neuron diseases
     - Age: 75–80 years
   - palsy of the tongue, muscles of chewing/swallowing and facial muscles due to loss of function of brainstem motor nuclei
   - carries **worst** prognosis

- Most common cause of death is respiratory complications secondary to recurrent aspiration(e.g., pneumonia).

	Upper motor neuron lesion	Lower motor neuron lesion
Symptoms noticed by patient	May be long before clinical evidence	Short
Muscle wasting	Mild	Marked
Fasciculations (visible **spontaneous** contraction of groups of muscle fibres)	No	Yes
Tone	Increased[a]	Decreased/Normal
Weakness	Pyramidal Upper limb – extensor weakness Lower limb – flexor weakness	Either root/peripheral nerve
Reflexes	↑ ± clonus	↓/**absent**
Plantar responses	Extensor or normal	Normal
Superficial reflexes	Absent (abdominal reflexes lost in lesions above T9)[b]	

[a] In the *acute* phases of stroke or in spinal shock, for example, there may be flaccid tone and depressed reflexes, and it takes days to weeks for the tone and reflexes to increase.

[b] Only relevant in young, thin patients with an unscathed abdomen.

Features

- **Clues, which point towards a diagnosis of motor neuron disease:**
  - **fasciculation**
  - absence of sensory signs/symptoms*
    - *vague sensory symptoms may occur early in the disease (e.g. limb pain) but 'never' sensory signs
  - lower motor neuron signs in arms and upper motor neuron signs in legs
  - wasting of the small hand muscles/tibialis anterior is common
- **Other features**
  - doesn't affect external ocular muscles
  - no cerebellar signs
  - abdominal reflexes are usually preserved and sphincter dysfunction if present is a late feature
  - 10 % of patients with MND have dementia (**fronto-temporal**).
  - **Respiratory involvement** is thought to be present in up to **50% of MND** cases at presentation, although symptoms may be subtle.
    - bilateral **diaphragmatic weakness causing orthopnea and exertional dyspnoea** particularly during exertion, or on lying down, when the raised abdominal pressure causes lung compression.
    - Respiratory failure is the commonest cause of death in this condition.

Features NOT compatible with MND are:

- sensory impairment
- Optic atrophy and
- bladder dysfunction.

Diagnosis

- The diagnosis of MND is clinical
- **Electromyography** shows:
  - reduced number of action potentials
  - increased amplitude.
- Nerve conduction studies:
  - usually normal

  - to **exclude** a neuropathy.
- MRI
  - to **exclude** the differential diagnosis of cervical cord compression and myelopathy
- creatine kinase → increased

Management

Motor neuron disease - treatment: NIV is better than riluzole

Motor neuron disease - riluzole

- **Riluzole**
  - prevents stimulation of glutamate receptors → **decreasing presynaptic glutamate release** (thereby limiting cytotoxic effects of this neurotransmitter)
  - used mainly in amyotrophic lateral sclerosis
  - prolongs life by about **3 months**
  - **side effects:**
    - Common side effects are:
      - nausea,
      - asthenia,
      - abdominal pain,
      - dizziness,
      - asymptomatic elevation in liver enzymes.
    - Rare life-threatening side effects such as:
      - **pancreatitis**,
      - hepatitis, and
      - neutropenia
- **Respiratory care**
  - Non-Invasive Ventilation (NIV)(usually BIPAP) is used at night
    - **have the greatest effect on survival**
    - studies have shown a survival benefit of around **7 months**

Prognosis

- poor: 50% of patients die within 3 years
- The median survival time for motor neurone disease from onset of symptoms is three to five years.
- Poor prognostic factors include:
  - low forced vital capacity (FVC) and
  - older age.

Bulbar palsy

- Bulbar palsy results from bilateral impairment of function of the IXth, Xth and XIIth cranial nerves.
- This gives rise to dysarthria, dysphagia (often with choking episodes and nasal regurgitation of fluids), dysphonia and poor cough, and susceptibility to aspiration pneumonia.
- The lowermost part of VII may, infrequently, be involved.
- The disturbance is of the motor nuclei rather than of the corticobulbar tracts.
- It is distinguished from pseudobulbar palsy by the presence of lower motor neurone signs.
- Autonomic features are uncommon.

Causes of bulbar palsy include:

- motor neurone disease
- Guillain Barre syndrome
- syringobulbia
- poliomyelitis
- diphtheria
- myasthenia gravis
- neurosyphilis

Features

- atrophy and fasciculations in bulbar muscles:
- tongue appears wasted and folded; fasciculations are prominent and produce a writhing appearance
- orbicularis oris is often affected at the same time as the tongue; orbicularis oculi and other facial muscles tend to be affected later and less severely
- the palate and the extrinsic muscles of the pharynx and larynx are affected after the tongue
- protrusion of the tongue is weakened and lost
- dysarthria and dysphonia - from paresis of the lips, tongue and palate; nasal speech is typical
- dysphagia - food may regurgitate through the mouth; may be most noticeable with fluids
- jaw jerk and gag reflex are absent

Comparison of bulbar and pseudobulbar palsy

Pseudobulbar Palsy	Bulbar Palsy
degeneration of corticobulbar pathways to **V**,VII,X,XI,XII	disturbance to X, XI, XII, sometimes VII, rather than the corticobulbar tracts
lower motor neurone signs **absent**	lower motor neurone signs **present**
gag reflex (+/n)	gag reflex (-)
spastic tongue	wasted tongue, fasciculations
jaw jerk (+)	jaw jerk (n)
spastic dysarthria	nasal speech
labile emotions	normal emotions
bilateral UMN	signs in limbs

+ = increased; - = reduced; n = normal

Benign fasciculation syndrome

- benign fasciculation syndrome is a condition associated with a reduced threshold for action potentials at the neuromuscular junction and entirely benign.
- **Typically the patients are health professionals as they translate fasciculations to mean motor neurone disease.**
  - The general public often do not pay any attention to muscle twitches particularly when they feel well.
- In the absence of clinical and electromyographic findings of neurogenic disease, the diagnosis of benign fasciculations is made.
- the most effective approach to treatment is to treat any accompanying anxiety.
- No treatments have been found that completely control the symptoms.

Opercular syndrome (OPS)

- Opercular syndrome, also known as Foix-Chavany-Marie syndrome,
- is a paralysis of the facial, pharyngeal, masticatory, tongue, laryngeal, and brachial muscles.
- It is a rare cortical form of pseudobulbar palsies **caused by vascular insults to bilateral operculum.**
- caused by multiple strokes
- Its clinical presentations include anarthria, weakness of voluntary muscles involving face, tongue, pharynx, larynx, and masticatory muscles.
- However, **autonomic reflexes and emotional activities of these structures are preserved.**
- presented with symptoms and signs limited to bulbar and masticatory muscles, especially for voluntary actions. **Involuntary movement of these muscles, like yawning, are preserved**.

- Also, there are no long tract signs like extensor plantar or increased DTR.
- Differential diagnosis
  - Pseudobulbar paralysis in OPS is clinically distinguished from **bulbar paralysis**, disorders of the cranial nerves and neuromuscular junction (e.g., **botulism** and **myasthenia gravis**) by:
    - normal eye movements,
    - preserved or hyperactive brainstem reflexes (e.g., jaw jerk),
    - the dissociation of automatic and volitional movements of the bulbar muscles with preservation of automatic movements,
    - absence of atrophy and fasciculations of the lower motor neuron-innervated muscles
- **Prognosis**
  - poor
  - Chewing, swallowing, and speech functions do not usually recover completely.
  - have a significant risk for aspiration pneumonia.

Cerebral palsy

- Cerebral palsy is a disorder of movement and posture due to a non-progressive lesion of the motor pathways in the developing brain.
- clinical manifestations tend to evolve with age.
- incidence is 2 per 1000 live births
- the most common motor disability in children.

Risk factors:

- **Preterm birth and low birth weight are the most important risk factors for cerebral palsy,**
- Other risk factors include intrauterine infections, multiple pregnancies, kernicterus (very rare in developed countries), and/or structural brain abnormalities.

Features:

- **Epilepsy in 40%**
- Squints in 30%
- Hearing loss and visual impairment in 20%, and
- Speech and language disorders.
- behavioural problems.
- Learning difficulties in cerebral palsy can be absent, mild, moderate or severe (45% incidence of learning impairment, with 25% classified as severe (IQ <50).

Investigations

- cerebral palsy is primarily a clinical diagnosis, cranial ultrasound and/or MRI may help identify a causative lesion.
- MRI of the head shows periventricular leukomalacia.

Fasciculations

are a *lower* motor neurone finding

Fasciculations may be seen in otherwise normal individuals with no muscular weakness/atrophy. If pronounced and combined with muscle atrophy, they usually signify motor neurone disease.

They may also be seen in diseases that involve:

- Spinal cord grey matter
- Lesions of anterior roots
- Peripheral neuropathies.

They may also be seen with:

- Severe metabolic disturbance
- Dehydration
- Thyrotoxicosis.

However, they are not seen in demyelinating disease of the central nervous system.

Multifocal motor neuropathy with conduction block

- It is a very important differential diagnosis of motor neurone disease because it is treatable
- It is usually slowly progressive, sometimes mimicking mononeuritis multiplex
- Sensation is normal

- Nerve conduction studies support the diagnosis of multifocal motor neuropathy with → **conduction block**
- **The treatment of choice is intravenous immunoglobulins**

Multiple sclerosis (MS)

- Demyelinating CNS condition clinically defined by 2 episodes of neurological dysfunction (brain, spinal cord, or optic nerves) that are separated in space and time.
- Classically presents in white women, aged between 20 to 40 years, with temporary visual or sensory loss. However, may affect either sex and any age or ethnic group
- Associated with **HLA-DR2**

Features

- age → often under 50
- **non-specific features**
  - eg: lethargy(75%). .
- **Visual**
  - optic neuritis: common presenting feature
    - loss or reduction of vision in 1 eye with painful eye movements
    - **any patient with isolated optic neuritis → refer to a neurologist for further assessment**
      - **The cumulative probability of developing MS by 15 years after onset of optic neuritis was 50%**
  - optic atrophy
  - Uhthoff's phenomenon: worsening of vision following rise in body temperature
  - internuclear ophthalmoplegia
- **Sensory**
  - pins/needles
  - numbness
  - trigeminal neuralgia
  - Lhermitte's syndrome: paraesthesiae in limbs on neck flexion
    - classically associated with multiple sclerosis
    - suggests a lesion of the dorsal columns of the cervical cord or of the caudal medulla.
    - Other causes of Lhermitte's sign:
      - Radiation myelopathy
      - If following radiotherapy it usually resolves in two to three months.
- **Motor**
  - ***upper* motor neurone findings only.**
  - spastic weakness: most commonly seen in the legs
- **Cerebellar**
  - ataxia: more often seen during an acute relapse than as a presenting symptom
  - tremor
- **Others**
  - urinary incontinence
  - sexual dysfunction
  - intellectual deterioration

Classification

- Relapsing–remitting MS
  - lesions have developed at different times and are in different anatomical locations
- Primary progressive MS.
  - progressive neurological deterioration over 1 year or more

Investigations

- **MRI** : Do not diagnose MS on the basis of findings alone.
- **Visual evoked potentials (VEPs)** are averaged cerebral potentials evoked by visual stimuli (a flash or black-and white checkerboard pattern) and detected by scalp electrodes placed over the occiput

- **is highly sensitive for detecting demyelination of the optic nerve** and central visual pathways
- In multiple sclerosis, **VEPs may demonstrate abnormality when the MRI is normal**, because the optic nerves are often involved early and may be asymptomatic

Diagnosis

- the diagnosis of MS on the basis of established up-to-date criteria, such as the revised 2010 **McDonald criteria**

McDonald criteria (2010 revision) - MRI findings

- **Dissemination in space (DIS):**
  - One or more T2 lesions in at least 2 of the 4 MS-typical regions of CNS (periventricular, juxtacortical, infratentorial, or spinal cord).
- **Dissemination in time (DIT):**
  - Simultaneous presence of asymptomatic gadolinium(Gd)-enhancing and non-enhancing lesions at any time, or
  - New T2 and/or Gd-enhancing lesion on follow-up MRI, irrespective of timing with reference to baseline scan.

Management

- There is no cure.
- Treatment of the condition can be divided into 3 parts:
  1. treatment of the acute attack;
  2. prevention of future attacks by reducing triggers and use of disease-modifying therapies;
  3. symptomatic treatments of neurological difficulties such as spasticity, pain, fatigue, and bladder dysfunction.

Acute relapse

- High dose steroids (e.g. IV methylprednisolone) may be given for 3-5 days to shorten the length of an acute relapse.
- It should be noted that **steroids shorten the duration of a relapse and do not alter the degree of recovery (i.e. whether a patient returns to baseline function)**

Disease modifying drugs

- **Beta-interferon** has been shown to reduce the relapse rate by up to 30%.
  - Certain criteria have to be met before it is used:
    - relapsing-remitting disease + 2 relapses in past 2 years + able to walk 100m unaided
    - secondary progressive disease + 2 relapses in past 2 years + able to walk 10m (aided or unaided)
  - reduces number of relapses and MRI changes, however doesn't reduce overall disability
  - **side effect** : The **risk of thyroid disease** (both, hyper- and hypothyroidism) seems related to interferon beta-1b treatment **during the first year only**, particularly in patients with pre-existing thyroiditis; the resulting thyroid dysfunction is generally transient, mild in degree, and needs no replacement therapy with L-thyroxine.
    - **Keep thyroid function tests under review**

Other drugs used in the management of multiple sclerosis include:

- **glatiramer** acetate: immunomodulating drug - acts as an 'immune decoy'
  - **generally regarded as safe in pregnancy**
    - Beta interferon 1alpha and 1beta, fingolimod, natalizumab, and dimethyl fumarate are category C in pregnancy
- natalizumab: a recombinant monoclonal antibody that antagonises Alpha-4 Beta-1-integrin found on the surface of leucocytes, thus inhibiting migration of leucocytes across the endothelium across the blood-brain barrier
- Alemtuzumab is an anti-CD52 antibody used in the treatment of MS.
- **fingolimod**:
  - the primary mode of action→ **sphingosine 1-phosphate receptor modulator,**
  - **additional actions of fingolimod:**
    - **Ceramide synthase inhibitor**
    - cannabinoid receptor antagonist
  - prevents lymphocytes from leaving lymph nodes. It is an immunomodulator, which sequesters lymphocytes in lymph nodes.

- It has been shown to reduce the rate of relapses in relapsing-remitting MS by over half.
- An oral formulation is available

Some specific problems

Spasticity

- **Baclofen** and gabapentin are first-line.
- Consider tizanidine or dantrolene as a second-line
- Consider benzodiazepines as a third-line
- physiotherapy is important
- cannabis and botox are undergoing evaluation

Oscillopsia (loss of natural image stabilization)

- Consider **gabapentin** as a first-line
- Consider memantine as the second-line

Bladder dysfunction

- may take the form of urgency, incontinence, overflow etc
- guidelines stress the importance of getting an ultrasound first to assess bladder emptying - anticholinergics may worsen symptoms in some patients
  - if significant residual volume → intermittent self-catheterisation
  - if no significant residual volume → anticholinergics may improve urinary frequency

MS-related fatigue

- usually described as physical exhaustion that is unrelated to the amount of activity performed.
- seen in 78% of patients.
- often aggravated by heat and humidity.
- Offer **amantadine to treat fatigue in people with MS.**
- Consider mindfulness-based training, cognitive behavioural therapy
- exercises including yoga may be helpful.

Prognostic features

Good prognosis features

- female sex
- young age of onset
- relapsing-remitting disease
- sensory symptoms
- long interval between first two relapses

Ways of remembering prognostic features

- the typical patient carries a better prognosis than an atypical presentation

Chances of developing MS in patient presented with acute isolated optic neuritis

Determined by presence or absence of demyelinating lesions on MRI

➔ with normal baseline MRI → the 10-year risk is 22%

➔ **with at least one MRI T2 > 3 white-matter lesion → the 10-year risk is 56 %**

pregnancy

- relapse rates may **reduce during pregnancy** and may **increase 3–6 months after childbirth** before returning to pre-pregnancy rates
- **Only glatiramer acetate is thought to be safe in pregnancy.**
  - Beta interferon 1alpha and 1beta, fingolimod, natalizumab, and dimethyl fumarate are category C;
  - Mitoxantrone is category D; teriflunamide is category X.

Internuclear ophthalmoplegia (INO)

Overview

- a cause of horizontal disconjugate eye movement
- due to **a lesion in the medial longitudinal fasciculus**, which connects the IIIrd, IVth and VIth cranial nuclei in the pons
- It is due to a lesion in the medial longitudinal fasciculus, which connects optic brainstem nuclei on either side of the brainstem. Thus, conjugate movements, but not unilateral movement, is affected.

Features

- impaired adduction of the eye on the same side as the lesion
- horizontal nystagmus of the abducting eye on the contralateral side
- When covering one eye, unilateral movements will be normal. But when together, the adducting eye will not move past the midline.
- the patient may complain of horizontal diplopia.

Causes

- **multiple sclerosis (characteristic of MS)**
- Tumour of the brainstem (glioma, for example)
- Brainstem vascular lesions, or
- Wernicke's encephalopathy.

INO - Internuclear Ophthalmoplegia

Chronic progressive external ophthalmoplegia (CPEO)

- CPEO is an eye movement disorder characterized by slowly progressive inability to move the eyes and eyebrows. which is **often associated with mitochondrial disease.**
- CPEO is the most common manifestation of mitochondrial myopathy (in two-thirds of all cases).
- It is associated with cytochrome deficiency.
- typically presents in young adults, but may affect all ages.
- **Feature:**
  - bilateral ptosis (the initial sign), often unnoticed by the patient until the lid droops to the point of producing a visual field defect.
  - Fatigue
  - limitation to eye- movements in all directions. but downward gaze often less so.
    - Ophthalmoplegia or the inability/difficulty to move the eye is usually symmetrical.
    - Weakness of extraocular muscle groups, such as orbicularis oculi and facial muscles, can be present in 25% of patients.
  - Visual acuity is affected in 95% of patients, but the deficit is usually mild.
- Other diseases like Graves' disease, myasthenia gravis and glioma that may cause an external ophthalmoplegia must be ruled out.
- It is important to have a dilated eye exam to determine if there is pigmentary retinopathy that may signify Kearns-Sayre syndrome which is associated with cardiac abnormalities.
- **Diagnosis**
  - muscle biopsy, which shows an accumulation of enlarged mitochrondria.
  - PCR can also determine a mutation of mitochondrial DNA.
- **Treatments**
  - no specific treatment currently,
  - surgery can be used to correct ptosis
  - prisms can be used to help with ophthalmoplegia.

Miosis

Ptosis + dilated pupil → third nerve palsy	Ptosis + constricted pupil → Horner's

Causes of miosis (small pupil)

- Horner's syndrome
- Argyll-Robertson pupil
- senile miosis
- pontine haemorrhage
- congenital

Drugs causes

- opiates
- parasympathomimetics: pilocarpine
- organophosphate toxicity

Causes of dilated pupils include:

- Holmes-Adie (myotonic) pupil
- Third nerve palsy
- Drugs, and
- Poisons (atropine, CO, ethylene glycol).

Ptosis

Ptosis may be unilateral or bilateral

Causes of bilateral ptosis:

- myotonic dystrophy
- myasthenia gravis*
- syphilis
- congenital

Causes of unilateral ptosis, as above plus:

- third nerve palsy
- Horner's

*ptosis is much less common in Lambert-Eaton syndrome than myasthenia gravis

Horner's syndrome

Horner's → ptosis, miosis and anhydrosis

Horner's syndrome - anhydrosis determines site of lesion:

- head, arm, trunk = central lesion: stroke, syringomyelia
- just face = pre-ganglionic lesion: Pancoast's, cervical rib
- absent = post-ganglionic lesion: carotid artery

- Horner's syndrome develops following disruption of the sympathetic chain.

Features

- miosis (small pupil)
- ptosis
- enophthalmos* (sunken eye)
  - *in reality the appearance is due to a narrow palpebral aperture rather than true enophthalmos
- anhydrosis (loss of sweating one side)

Distinguishing between causes

- **heterochromia (difference in iris colour) is seen in congenital Horner's**
- anhydrosis: see below

Types

- There are three separate forms of Horner's syndrome, depending on what level the sympathetic fibres are affected at:
  1. **First-order sympathetic fibres**
     - originate in the hypothalamus and descend through the brainstem to their synapse with the preganglionic sympathetic fibres at C8-T2.
     - First-order lesions can be caused by:
       - strokes,
       - multiple sclerosis and
       - basal meningitis.
  2. **Second-order (preganglionic) fibres**
     - leave the cord at T1 and ascend in the sympathetic chain over the lung apex. They synapse in the superior cervical ganglion at the level of C3-C4, at the bifurcation of the common carotid artery.
     - Lesions affecting these fibres can be caused by:
       - apical lung tumours,
       - lymphadenopathy and
       - lower brachial plexus trauma.
  3. **Third-order (postganglionic) fibres**
     - pass along the internal carotid artery, with branches passing to the blood vessels and sweat glands of the face. They pass through the cavernous sinus and superior orbital fissure, where they joint the long ciliary nerves to supply the iris dilator and Muller's muscle.
     - **Because the sympathetic plexus accompanying the internal carotid artery innervates sweat glands only to the medial forehead, facial anhydrosis is only partial when Horner's syndrome is caused postganglionic lesions.**
     - These lesions can be caused by:
       - internal carotid artery dissection or
       - herpes zoster infection.

Central lesions	Pre-ganglionic lesions	Post-ganglionic lesions
Anhydrosis of the face, arm and trunk	Anhydrosis of the face	No anhydrosis
Stroke **S**yringomyelia Multiple **s**clerosis Tumour Encephalitis	Pancoast's **t**umour **T**hyroidectomy **T**rauma Cervical rib	**C**arotid artery dissection **C**arotid aneurysm **C**avernous sinus thrombosis **C**luster headache

- Sweat glands are controlled by the sympathetic nervous system, for example, anhydrosis in Horner's syndrome.

Myasthenia gravis (MG)

- Myasthenia gravis is an autoimmune disorder resulting in insufficient functioning acetylcholine receptors.
- Antibodies to acetylcholine receptors are seen in 85-90% of cases.
  - antibodies are less commonly seen in disease limited to the ocular muscles
- more common in women (2:1)

Feature

- muscle fatigability (the key feature)
  - muscles become progressively weaker during periods of activity and slowly improve after periods of rest.
- extraocular muscle weakness:
  - **diplopia**
  - ptosis
- proximal muscle weakness: face, neck, limb girdle

- dysphagia (that is **worse with liquids than solids** in contrast to achalasia which typically affects solids more than liquids, or solids and liquids equally)
  - **Acetyl choline receptors antibodies is the most appropriate investigation**
  - No abnormality would be expected on chest x-ray, barium swallow or gastroscopy.
  - Nasal regurgitation, coughing and choking episodes during meals, dysphagia that is worse with liquids than solids and dysarthria indicate neurogenic dysphagia (eg: myasthenia gravis and motor neuron disease).
    - Nasal regurgitation and dysarthria are not usually accompanying features of mechanical dysphagia.

Associations

- thymic hyperplasia in 50-70%
- thymomas in 15%
- autoimmune disorders: pernicious anaemia, autoimmune thyroid disorders, rheumatoid, SLE

Investigations

- **Single fibre electromyography (EMG):**
  - **High sensitivity** (92-100%)
  - It simultaneously records the variability in potentials of two muscle fibres innervated by an individual axon: jitter.
  - **Electrical recordings of single motor unit activity commonly reveal variation in the latency of the various muscle fibre responses (jitter)**
  - Although **abnormal jitter** is not specific for MG and may occur in polymyositis and amyotrophic lateral sclerosis (ALS), a large degree of jitter with minimal other abnormalities is suggestive of the diagnosis.
  - **Jitter is the most sensitive EMG index in MG but is not specific of the condition.**
  - The nerve conductions and EMG studies are usually normal in myasthenia gravis, but the repetitive stimulation of a nerve may demonstrate decrements of the muscle action potential (far less than 98%).
  - An increase in decrement on stimulation at 3Hz is detectable in some patients.
- CT thorax to exclude thymoma
- CK normal
- **autoantibodies**:
  - around 85-90% of patients have **antibodies to acetylcholine receptors**.
  - In the remaining patients, about 40% are positive for **anti-muscle-specific tyrosine kinase (MuSK)** antibodies
    - patients with **(MuSK)** antibodies are much less likely to have thymic hyperplasia or a thymoma,
    - may be less responsive to anticholinesterase drugs,
    - may require more aggressive early immunotherapy than patients who have AChR antibodies.
- **Tensilon test**: IV edrophonium reduces muscle weakness temporarily - not commonly used anymore due to the risk of cardiac arrhythmia
  - Tensilon (edrophonium) challenge test can be used to diagnose MG, or distinguish it from cholinergic crisis.
  - Edrophonium given at increasing doses should produce improvement in muscle strength within a minute.
  - It does this by blocking the breakdown of acetylcholine by cholinesterase and temporarily increases the level of acetylcholine at the neuromuscular junction.
  - However, a positive response is not specific and may occur in amyotrophic lateral sclerosis.
  - There is a risk of bradycardia, asystole and heart block and atropine should therefore be available.
  - Airway support should be used as respiratory weakness can be exacerbated after the edrophonium wears off.
  - Although improved muscle strength after edrophonium is seen, it is not diagnostic but depends more on the clinical presentation and presence of AChR ab.

Management

- **in mild cases**
  - **long-acting anticholinesterase e.g. pyridostigmine**

        - Pyridostigmine → cholinesterase inhibitors →increased ACh at neuromuscular junctions.
- In more severe disease (with limb weakness or bulbar dysfunction)
    - immunosuppression:
        - prednisolone initially
        - addition of steroid-sparing agents such as mycophenolate mofetil, ciclosporin or azathioprine if necessary.
- In patients with **congenital myasthenia**, anticholinesterase drugs and immunomodulating treatments are not beneficial and **should be avoided.**
- Thymectomy
    - improves symptoms in cases associated with thymoma, and may also be beneficial in young patients with recent onset of symptoms, but would not be used as an initial treatment option.
    - should also be considered in non-thymomatous generalised myasthenia in patients with antibodies to acetylcholine receptor who are aged under 50.
    - Biopsy is not generally required prior to surgery.
    - **thymectomy is not indicated if:**
        1. **patients have antibodies to MUSK (muscle specific tyrosine kinase)**
        2. late onset disease or
        3. purely ocular disease

Management of myasthenic crisis

- intravenous immunoglobulins
- plasmapheresis
    - Plasmapheresis usually works quicker but involves more expensive equipment
- **Intubation and assisted ventilation: Elective intubation should be considered if the vital capacity show values are less than 20 mL/kg.**
    - Ventilatory assistance should consist of endotracheal intubation with positive pressure mechanical ventilation.
    - endotracheal intubation can often be performed as an **"elective"** procedure rather than as an emergency response to precipitous respiratory collapse. (medical-masterclass.com. 2017 part 2)

Myasthenia gravis: exacerbating factors

- The most common exacerbating factor is exertion resulting in fatigability, which is the hallmark feature of myasthenia gravis . Symptoms become more marked during the day

The following drugs may exacerbate myasthenia:

- **Penicillamine**
    - **penicillamine toxicity → nephrotic syndrome and myasthenic syndrome.**
- quinidine, procainamide
- **beta-blockers,** calcium channel blockers, verapamil, propafenone,.
- lithium
- phenytoin
- antibiotics: **gentamicin**, macrolides, quinolones, tetracyclines
    - **Aminoglycoside-induced neuromuscular blockade**
        - Aminoglycosides may impair neuromuscular transmission and should not be given to patients with myasthenia gravis;
        - **large doses given during surgery have been responsible for a transient myaesthenic syndrome in patients with normal neuromuscular function.**

Cholinergic crisis due to overuse of pyridostigmine

- overuse of pyridostigmine → **cholinergic crisis** (like organophosphate poisoning)
- Excessive intake of pyridostigmine → potentiates cholinergic activity → bradycardia, hypotension, bronchospasm, abdominal cramping, diarrhea, and **flaccid paralysis of the extremities.**
- Differentiating a myasthenic crisis from a cholinergic crisis is difficult, but the **edrophonium test is your clue.**
    - Edrophonium is a short-acting acetylcholinesterase inhibitor.

- In myasthenia gravis, this will lead to a temporary relief of symptoms.
- **In a cholinergic crisis, this will have no effect (or worsen the situation).**

- history of increased medication usage, worsening symptoms, and negative edrophonium test, → cholinergic crisis precipitated by overuse of an acetylcholinesterase inhibitor.
- **Atropine would be indicated to antagonize cholinergic activity.**

Ref → Pastest – USMLE 2017 – step 1

Lambert-Eaton syndrome

	Myasthenia gravis	Lambert-Eaton
muscle weakness	proximal muscle weakness: face, neck, limb girdle	affects lower limbs first
muscle power following exercise	becomes weaker	Temporary increase
reflexes	normal or brisk	absence of reflexes or hyporeflexia
Antibodies	Antibodies to acetylcholine receptors	antibody directed against pre-synaptic voltage gated calcium channel
Commonly associated tumor	thymomas or thymic hyperplasia	small cell lung cancer

- Lambert-Eaton myasthenic syndrome is seen in association with small cell lung cancer, and to a lesser extent breast and ovarian cancer.
- It may also occur independently as an autoimmune disorder.
- Lambert-Eaton myasthenic syndrome is caused by an antibody directed against pre-synaptic voltage gated calcium channel in the peripheral nervous system

Features

- **repeated muscle contractions lead to increased muscle strength* (in contrast to myasthenia gravis)**
- limb girdle weakness (affects lower limbs first).Proximal lower limb weakness is the most consistent neurological feature causing **difficulty in standing from a seated position and climbing stairs.**
- hyporeflexia (but normalise with repetitive muscle contraction)→ The weakness improves with exercise and the reflexes return.**The absence of reflexes is characteristic, in contrast to myasthenia gravis where the reflexes are normal or brisk**
- autonomic symptoms: dry mouth, impotence, difficultly micturating
- ophthalmoplegia and ptosis not commonly a feature (unlike in myasthenia gravis)

Diagnosis

the most likely to confirm the diagnosis → Voltage gated calcium channels antibodies

EMG

- incremental response to repetitive electrical stimulation

Management

- treatment of underlying cancer
- immunosuppression, for example with prednisolone and/or azathioprine
- 3,4-diaminopyridine is currently being trialled**
- intravenous immunoglobulin therapy and plasma exchange may be beneficial

May 2013 exam: A patient of small cell lung carcinoma presents with muscle weakness, spreading from legs to arms + hyporeflexia . C/O dry mouth & erectile dysfunction. Antibodies to which one are most likely to be responsible for these findings? Voltage gated calcium channels

*in reality this is seen in only 50% of patients and following prolonged muscle use muscle strength will eventually decrease

**works by blocking potassium channel efflux in the nerve terminal so that the action potential duration is increased. Calcium channels can then be open for a longer time and allow greater acetylcholine release to the stimulate muscle at the end plate

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Neurofibromatosis

NF1: chromosome 17 - as neurofibromatosis has 17 characters
NF2: chromosome 22 - all the 2's
Lisch nodules are seen in neurofibromatosis

Genetics

- autosomal dominant
- In 50% of cases there will be no family history as there is a high incidence of new mutations.
  - ➢ 50% inherited and 50% sporadic mutations

Types

- There are two types of neurofibromatosis, NF1 and NF2.
  1. **NF1**
     - also known as von Recklinghausen's syndrome.
     - caused by a gene mutation on chromosome **17** (*NF1* gene) which encodes **neurofibromin**
       - ❖ tumor suppressor that inhibits ras activity via stimulating GTPase
     - most common type of neurofibromatosis
       - ❖ affects around 1 in 4,000
     - half of all cases give no family history and are new mutations.
     - To be given the **diagnosis of NF1**, an individual must have at least two of the following features:
       1) **six or more café-au-lait spots**
          - ❖ each over 5 mm in diameter in pre-pubertal individuals and
          - ❖ over 15 mm in post-pubertal individuals.
       2) two or more neurofibromas or a plexiform neurofibroma
       3) axillary freckling (can also be present in the groins)
       4) optic glioma
       5) lisch nodules (visible within the iris), or
       6) family history.
  2. **NF2**
     - caused by gene mutation on chromosome 22
     - affects around 1 in 100,000

Pathophysiology

- Mutation of tumor suppressor gene → loss of function → ↑ risk of cancer development
  - ➢ Neurofibromatosis I: *neurofibromin 1 gene* (*NF1*) affected; **encodes *neurofibromin protein*** on chromosome 17
  - ➢ Neurofibromatosis II: *neurofibromin 2* gene (*NF2*) affected; **encodes *Merlin protein*** (tumor suppressor protein) on chromosome 22

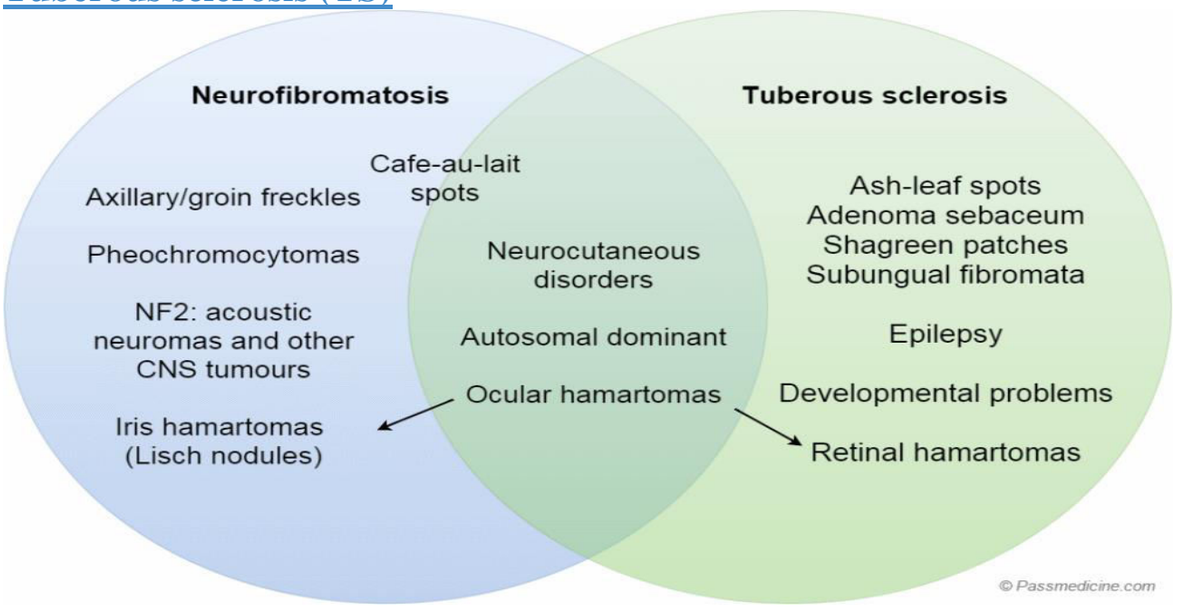
Features

NF1	NF2
• Cafê-au-lait spots (≥ 6, 15 mm in diameter) • Axillary/groin freckles • Peripheral neurofibromas • **Iris harmatomas (Lisch nodules) in > 90%** • Scoliosis • Pheochromocytomas	• Bilateral acoustic neuromas (the hallmark feature) • Multiple intracranial schwannomas, mengiomas and ependymomas

Complications

- increased lifetime cancer risk

Tuberous sclerosis (TS)



- **autosomal dominant** condition.
- TS affects about 1 in 10,000 people in the general population
- It is the second most frequent neurocutaneous syndrome, with neurofibromatosis being the most common.
- Like neurofibromatosis, the majority of features seen in TS are neuro-cutaneous
- **The responsible defects having been identified on both chromosome 9 and chromosome 16.**
  - **caused by a mutation in the TSC1/TSC2 genes.**
  - This gene produces the **hamartin** and **tuberin** proteins.
    - ***TSC1*** **(**encodes **hamartin** on chromosome **9**) and ***TSC2*** (encodes **tuberin** on chromosome **16**)
    - These proteins are responsible for control of cell growth.
- Most of the tumours which are produced in tuberous sclerosis are **hamartomas**

Cigarettes and coffee with a rough stupid person with a butterfly on his nose while he is dancing

Cutaneous features

- Ash-leaf macules, which are discrete areas of hypopigmentation, often present at birth
  - fluoresce under UV light
- Shagreen patches
  - roughened patches of skin over lumbar spine
  - skin with a texture similar to shark (سمك القرش) skin
- adenoma sebaceum:
  - butterfly distribution over nose (angiofibromas of the face).
- fibromata beneath nails (subungual fibromata)
- dental pits
- caf-au-lait spots* may be seen
  - *these of course are more commonly associated with neurofibromatosis but also found in 28% of patients.

Neurological features

- developmental delay
- epilepsy (infantile spasms or partial)
  - infantile spasm is the most common type of seizure at initial diagnosis
  - hypsarrythmia on EEG

  - vigabatrin, an irreversible GABA transaminase inhibitor, is particularly effective for infantile spasms
- autism
- intellectual impairment
- Fibromas may also develop within the central nervous system, where they calcify typically in the periventricular area.

Also

- retinal hamartomas: dense white areas on retina (phakomata)
- rhabdomyomas of the heart
  - Rhabdomyomas affect 50% to 60% of TS
  - generally regress during early childhood without the need for intervention.
- gliomatous changes can occur in the brain lesions
- polycystic kidneys, renal angiomyolipomata
- lymphangioleiomyomatosis: multiple lung cysts
  - it is identified in females only
  - arises from metastases from renal angiomyolipomas.

Treatment (BMJ best practice 2017)

- **Angiofibromas or collagen plague**
  - ≤ 2 mm → laser therapy
  - 2 mm → dermabrasion or surgical resection
- **Ungula fibroma** → clipping
- **Angiomyolipoma**
  - 3-6 cm
    - First line → surveillance
    - 2nd line → mTOR inhibitor (Everolimus)
  - ≥ 3- 6 cm
    - First line → mTOR inhibitor (Everolimus)
    - 2nd line → embolisation of the artery supplying a lesion + mTOR inhibitor (Everolimus)
    - 3rd line → Partial renal-sparing nephrectomy may be performed if embolisation is unsuccessful

January 2010 exam: Generalised seizure + patches of hypopigmented skin + fibromata under finger nails. What is the most likely diagnosis? Tuberous sclerosis

May 2007 exam: H/O hypovolaemic shock. CT abdomen reveals a haemorrhagic lesion in the right kidney. biopsy shown it to be an angiomyolipomata. What is the most likely underlying diagnosis? Tuberous sclerosis

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Paraneoplastic syndromes affecting nervous system

Lambert-Eaton myasthenic syndrome

- associated with small cell lung cancer (also breast and ovarian)
- antibody directed against pre-synaptic voltage gated calcium channel in the peripheral nervous system
- can also occur independently as autoimmune disorder

Anti-Hu

- associated with small cell lung carcinoma and neuroblastomas
- sensory neuropathy - may be painful
- cerebellar syndrome
- encephalomyelitis

Anti-Yo

- associated with ovarian and breast cancer
- cerebellar syndrome

Anti-GAD antibody

- associated with breast, colorectal and small cell lung carcinoma
- stiff person's syndrome or diffuse hypertonia

Anti-Ri
- associated with breast and small cell lung carcinoma
- ocular opsoclonus-myoclonus

Anti-Purkinje cell antibodies
- subacute cerebellar degeneration
- peripheral neuropathy due to a remote (autoimmune) effect of gynecologic or breast carcinoma.

(**GM1 antibodies)** (Glycolipid ganglioside-monosialic acid) associated with
- Lower motor neuron syndromes
- Amyotrophic lateral sclerosis
- Multiple sclerosis
- Other multifocal neuropathies and
- Systemic lupus erythematosus (SLE) with central nervous system involvement.

May 2009 exam: Ovarian cancer + unsteadiness, nystagmus and past-pointing. Which antibody is most likely to be present? Anti-Yo

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Kennedy's disease

Aetiology
- The gene abnormality responsible for Kennedy's disease is an abnormal increase in the trinucleotide CAG repeats in the region of the androgen-receptor gene
- It is inherited in an X-linked recessive fashion, with the mother of an affected male patient being an obligate carrier

Presentation
- Characteristic symptoms include prominent muscle cramps, difficulty walking and limb-girdle muscle weakness
- Dysarthria and dysphagia occur in less than half of patients
- Reflexes are depressed or absent
- Facial and particularly perioral fasciculations are highly characteristic of this condition
- Gynaecomastia is present in up to 90% of cases
- Endocrine abnormalities, such as infertility, testicular atrophy and diabetes mellitus, are common

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Meningitis (see infectious diseases)

Brain tumours

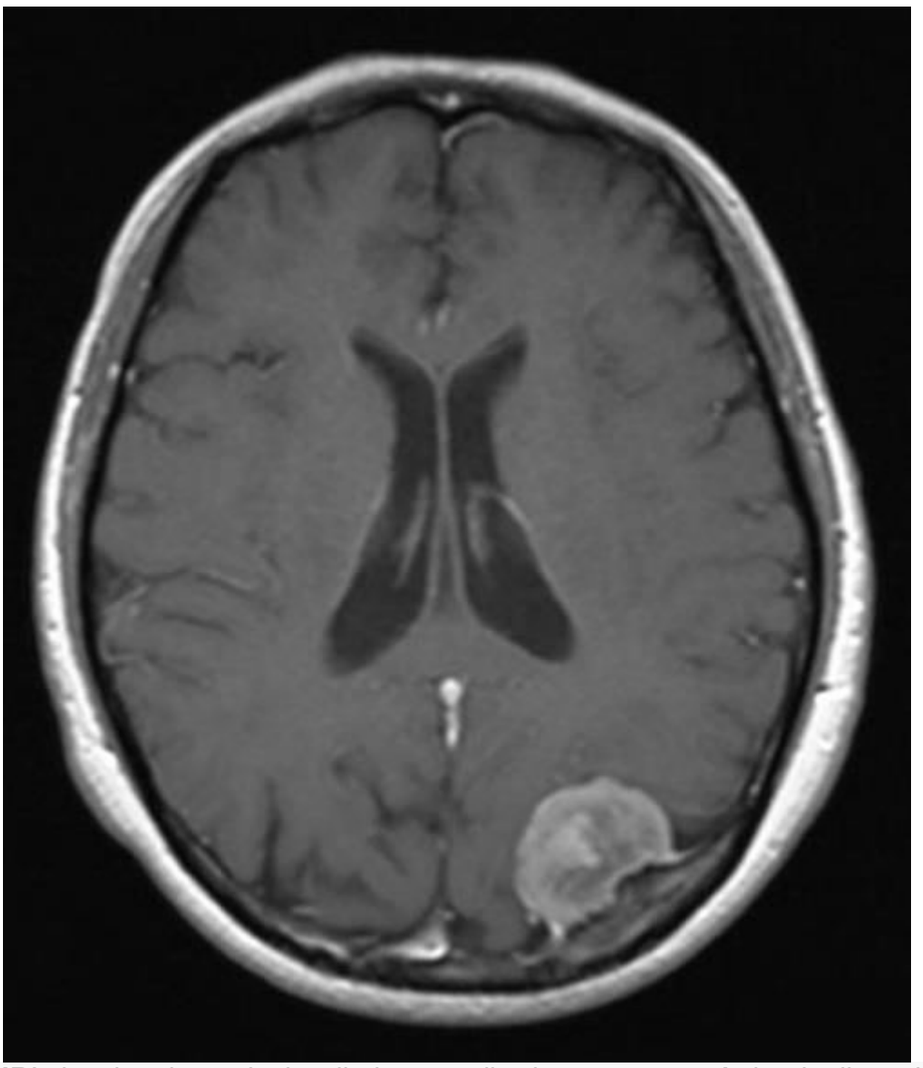
The majority of adult tumours are supratentorial, where as the majority of childhood tumours are infratentorial.

Type of tumour	Features
Glioblastoma multiforme	**• The most common primary brain tumour in adults.** • Histology: Pleomorphic tumour cells border necrotic areas
Meningioma	• The second most common primary brain tumour in adults • Histology: Spindle cells in concentric whorls and calcified psammoma bodies
Schwannoma	• Often seen in the cerebellopontine angle: acoustic neuroma • Bilateral schwannoms are seen in neurofibromatosis • Histology: Antoni A or B patterns are seen. Verocay bodies (acellular areas surrounded by nuclear palisades)
Pilocytic astrocytoma	• The most common primary brain tumour in children • Histology: Rosenthal fibres (corkscrew eosinophilic bundle)
Medulloblastoma	• More common in children • Found exclusively in the posterior fossa • Metatases through the CSF • Histology: Small, blue cells. Rosette pattern of cells with many mitotic figures

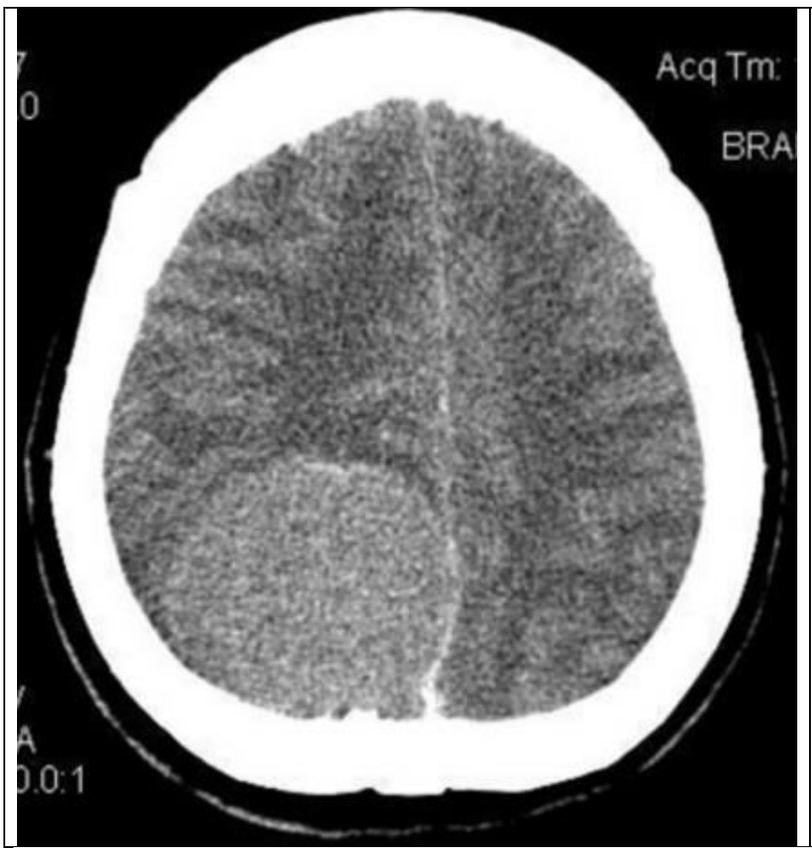
Type of tumour	Features
Ependymoma	• Commonly seen in the 4th ventricle • May cause hydrocephalus • Histology: perivascular pseudorosettes
Oligodendroma	• Benign, slow-growing tumour common in the frontal lobes • Histology: Calcifications with 'fried-egg' appearance
Haemangioblastoma	• Vascular tumour of the cerebellum • Associated with von Hippel-Lindau syndrome • Histology: foam cells and high vascularity
Pituitary adenoma	• Most common type is a prolactinoma • May present with bitemporal hemianopia
Craniopharyngioma	• Most common paediatric supratentorial tumour • Histology: Derived from remnants of Rathke pouch
Metastases	• Most common type of brain tumour

Craniopharyngioma

- slow-growing, calcified cystic tumour arising from the remnants of the craniopharyngeal duct.
- It compromises 4.2% of all childhood tumours.
- It is slightly more common in males than females.
- The symptoms develop very slowly and usually become manifest once the tumour has attained a diameter of 3 cm.
- The commonest presentation in young patients is growth failure and delayed puberty.
- The radiological hallmark of a craniopharyngioma is the presence of a suprasellar calcified cyst, with calcification being more common in children than in adults.
- Using imaging studies, CTS is most useful in demonstrating the calcifications whereas MRI is essential for defining the local anatomy prior to surgical intervention.
- Surgery is the management of choice and may attempt to resect the tumour in total, or to reduce the size followed by postoperative radiotherapy treatment.

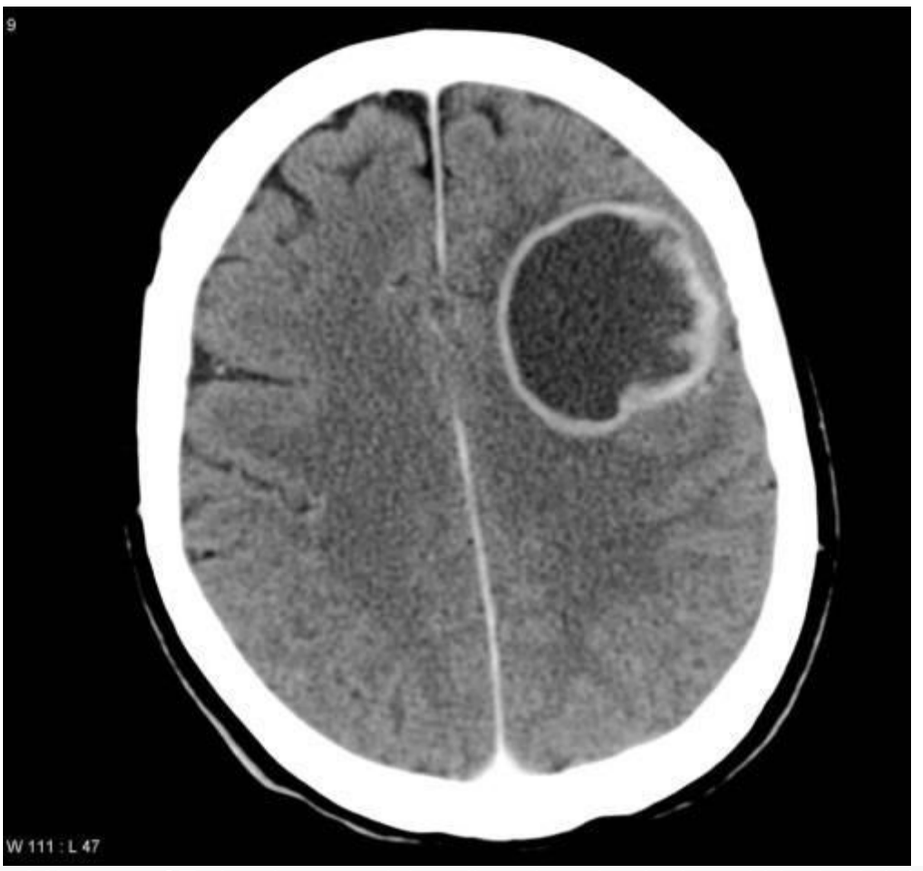


Meningioma - MRI showing the typical well-circumscribed appearance. A dural tail can be where the tumour 'connects' to the dura. It is seen in around 65% of **meningiomas.**



The CT shows a well defined spherical mass in the right posterior falx cerebri consistent with a meningioma.

There is mild oedema and mass effect on the right lateral ventricle. The tumour is straddling the inferior surface of the falx.



Glioblastoma multiforme - CT showing a peripherally enhancing lesion within the left frontal lobe. Note the contrast to the **more homogenous** (مُتَجَانِس) meningioma above.

A glioblastoma multifome would normally have a **more heterogenous** (مُتَبَايِن) appearance than

Brain metastases

- Approximately 20% of people who die from cancer have brain metastases. These can be solitary or multiple.
- The most common sites that metastasise to the brain are:
  - **lung (44%)**
  - breast (10%)
  - kidney (7%)
  - gastrointestinal tract (6%), and
  - melanoma (skin 3%).
- Therefore a **chest x ray would be the initial investigation of choice**, with the greatest chance of finding the primary.
- Management
  - **Start dexamethasone immediately**
  - Surgical resection is usually only recommended if a single cerebral lesion is found.
  - Anticonvulsant prophylaxis is unnecessary if seizures are not a problem and are not effective in preventing first seizures in patients with newly diagnosed brain tumours.

Spinal cord conditions

Cerebrospinal fluid

- **What type of cells produce cerebrospinal fluid?**
  - **Ependymal cells**
    - lines the ventricles and other CSF-filled spaces
- Approximately 500ml of cerebrospinal fluid is produced each day.
- It is absorbed into the circulation via the arachnoid villi.
- CSF is largely similar to plasma in composition, but has much lower levels of protein.

Normal values of cerebrospinal fluid (CSF) are as follows:

- pressure = 60-150 mm (patient recumbent)
- protein = 0.2-0.4 g/l
- glucose = > 2/3 blood glucose
- cells: red cells = 0, white cells < 5/mm³

The following conditions are associated with raised lymphocytes

- viral meningitis/encephalitis
- TB meningitis
- partially treated bacterial meningitis
- Lyme disease
- Behcet's, SLE
- lymphoma, leukaemia

The following conditions are associated with raised protein levels

- Guillain-Barre syndrome
- tuberculous, fungal and bacterial meningitis
- spinal block (Froin's syndrome*)
  - *describes an increase in CSF protein below a spinal canal blockage (e.g. tumour, disc, infection)
- viral encephalitis

Vertebral level and corresponding structure

- The **aortic** opening is at **T12**.
- Hyoid bone → C4
- **Bifurcation of common carotid → C4**
- Thyroid cartilage → C5
- Carotid pulse palpated → C5
- Cricoid cartilage →C6
- Beginning of trachea → C6
- Beginning of esophagus → C6
- Sternal notch →T2
- Arch of aorta → T2
- Sternal angle →T4
- Junction of superior and inferior mediastinum →T4
- Bifurcation of trachea →T4
- **Inferior vena caval hiatus** (opening in the diaphragm) **→T8**
- Xiphisternal joint →T9
- **Esophageal hiatus** (opening in the diaphragm) **→ T10**
- Upper pole of left kidney →T11
- Upper pole of right kidney →T12
- **Aortic hiatus** (opening in the diaphragm) **→ T12**
- Umbilicus → L3
- Iliac crest → L4
- Bifurcation of aorta → L4
- Beginning of sigmoid colon → S1
- End of dural sac (and CSF) → S2
- End of sigmoid colon → S3

The spinal cord terminates at lower border of L1 vertebra

Post-lumbar puncture headache

- **Epidemiology**
  - Headache following lumbar puncture (LP) occurs in approximately **one-third** of patients.
  - more common in **young females** with a **low body mass index**
- **Pathophysiology**
  - **Leaking of cerebrospinal fluid from the dura** is the most likely explanation.

Typical features

- usually develops within 24-48 hours following LP but may occur up to one week later
- may last several days
- worsens with upright position
- improves with recumbent position

Factors which may contribute to headache	Factors which do not contribute to headache
Increased needle size Direction of bevel Not replacing the stylet Increased number of LP attempts **Use of a Quincke (sharp) needle**	Increased volume of CSF removed Bed rest following procedure Increased fluid intake post procedure Opening pressure of CSF Position of patient

What is the most appropriate type of needle to use in lumbar puncture?

⇨ **20G Sprotte® (atraumatic) needle**

❖ Studies show that smaller atraumatic needles reduce the risk of post-lumbar puncture headache.

Management

- supportive initially (analgesia, rest)
- if pain continues for more than 72 hours then specific treatment is indicated, to prevent subdural haematoma
- treatment options include: blood patch, **epidural saline** and intravenous caffeine

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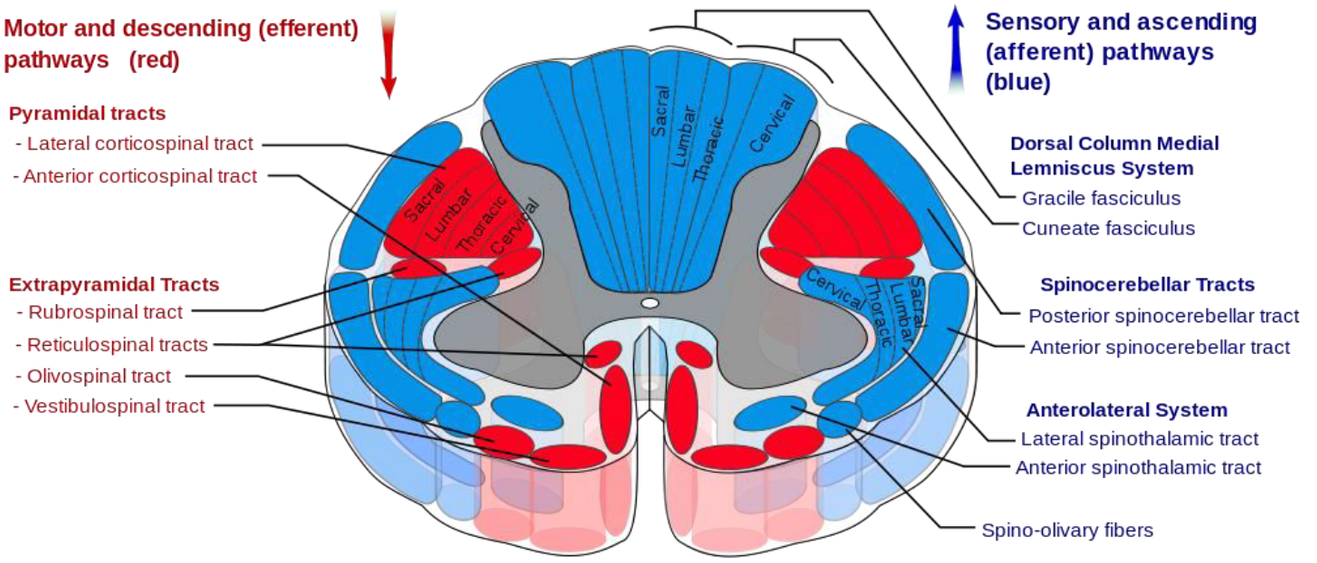
Spinal cord lesions

The diagram below shows cross-section view of the spinal cord:



Disorder	Tracts affected	Clinical notes
Brown-Sequard syndrome (spinal cord hemisection)	1. Lateral corticospinal tract 2. Dorsal columns 3. Lateral spinothalamic tract	1. **Ipsilateral spastic paresis** below lesion 2. **Ipsilateral loss of proprioception and vibration sensation** 3. **Contralateral loss of pain and temperature sensation**
Subacute combined degeneration of the spinal cord (vitamin B12 & E deficiency)	1. Lateral corticospinal tracts 2. Dorsal columns 3. Spinocerebellar tracts	1. Bilateral spastic paresis 2. Bilateral loss of proprioception and vibration sensation 3. Bilateral limb ataxia
Friedrich's ataxia	Same as subacute combined degeneration of the spinal cord (see above)	Same as subacute combined degeneration of the spinal cord (see above)
Anterior spinal artery occlusion	1. Lateral corticospinal tracts 2. Lateral spinothalamic tracts	1. Bilateral spastic paresis 2. Bilateral loss of pain and temperature sensation
Syringomyelia	1. Ventral horns 2. Lateral spinothalamic tract	1. Flacid paresis (typically affecting the intrinsic hand muscles) 2. Loss of pain and temperature sensation
Multiple sclerosis	Asymmetrical, varying spinal tracts involved	Combination of motor, sensory and ataxia symptoms

Sensory lesions

Disorder	Tracts affected	Clinical notes
Neurosyphilis (tabes dorsalis)	1. Dorsal columns	1. Loss of proprioception and vibration sensation

Spinal lesion localisation

- **A lesion at left side of C5 will cause weakness of the left leg**
  - **At** the pyramidal decussation (lower medulla), 85% fibres cross over forming the lateral corticospinal tract, the remaining forming the ventral corticospinal tract, the fibres of which eventually cross the cord. Hence, **a lesion at left side of C5 will cause weakness of the left leg.**
- **Central spinal cord lesions** destroy:
  - Contiguous structures like the anterior horn cells (lower motor neurone signs)
  - Decussating sensory fibres (pain and temperature) and
  - The lateral corticospinal tracts (upper motor neurone signs).
- **Conus medullaris lesion** causes:
  - Wasting and weakness of leg muscles with fasiculations (lower motor neurone signs)
  - Hyper-reflexia especially distally (upper motor neurone signs) supplied by the lower sacral segments (glutei).
  - sensory loss of buttocks and perineum.

Spinal cord compression

Epidemiology

- Spinal cord compression is an oncological emergency and affects up to **5% of cancer patients**.

Causes

- Extradural compression accounts for the majority of cases, usually due to vertebral body metastases.

- It is more common in patients with lung, breast and prostate cancer

Features

- back pain
  - the earliest and most common symptom
  - may be worse on lying down and coughing
- lower limb weakness
- sensory changes: sensory loss and numbness
- neurological signs depend on the level of the lesion.
  - **Lesions above L1** usually result in upper motor neuron signs in the legs and a sensory level.
  - **Lesions below L1** usually cause lower motor neuron signs in the legs and perianal numbness. Tendon reflexes tend to be increased below the level of the lesion and absent at the level of the lesion

Diagnosis

- **The definitive investigation in this case is an MRI** of the vertebral column to look for vertebral collapse or other vertebral disease.

Management

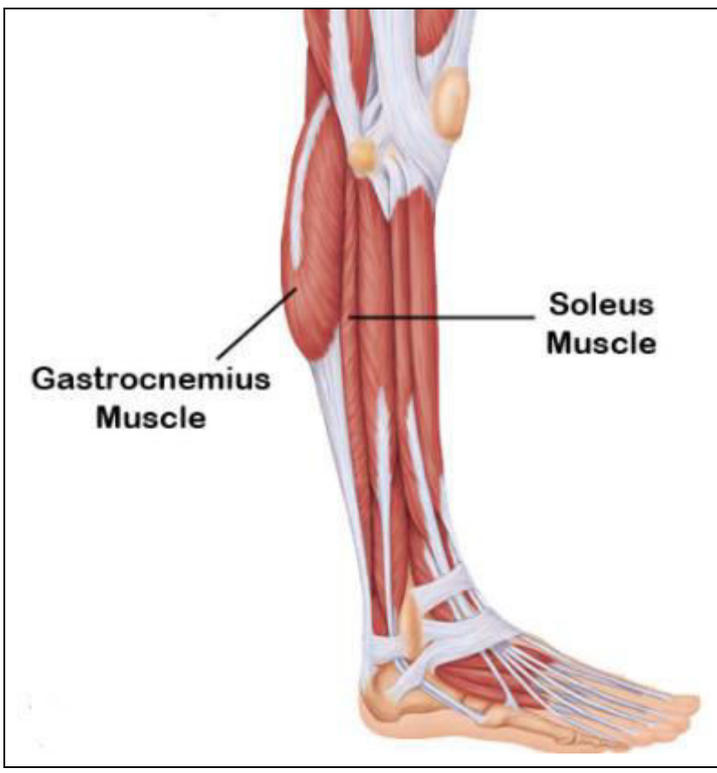
- high-dose oral **dexamethasone**
  - **Corticosteroids should be started immediately**, even before the diagnosis is confirmed radiologically,
  - usually with dexamethasone 16mg STAT followed by 8mg BD (either oral or IV is acceptable).
  - temporarily reduce oedema related to the underlying tumour and thus have a positive impact on neurological deficit,
  - the response to steroids predicts neurological response to subsequent definitive treatment which should be started within 24 hours.
- urgent oncological assessment for consideration of radiotherapy or surgery
  - **Urgent radiotherapy is the definitive treatment**, although neurosurgical opinion should be sought in order to ensure that surgical decompression is not required.
  - Treatment is effective in 90% of patients if the diagnosis is made early.

Prognosis

- **Pre-treatment ambulatory function is the best determinant of post treatment gait function**
  - 80% of patients will maintain mobility if ambulatory function is good at presentation.

This table demonstrates the expected features according to the level of compression

Level of compression	features
L3 nerve root compression	• **Sensory loss** from anterior thigh to **medial aspect of lower leg** • Weak quadriceps • ↓ knee reflex • Positive femoral stretch test
L4 nerve root compression	• Caused by L3/4 disc prolapse • **Sensory loss** over the thigh and **anterior aspect of knee** • Weak quadriceps • ↓ knee reflex • Positive femoral stretch test
L5 nerve root compression	• Caused by L4/5 disc prolapse • **Sensory loss dorsum of foot** and lateral aspect of leg • Weakness in foot and big toe dorsiflexion ('foot drop') • Reflexes intact • Positive sciatic nerve stretch test
S1 nerve root compression	• Caused by L5/S1 disc prolapse • **Sensory loss** posterolateral aspect of leg **(posterior calf and the plantar surface of the foot)** and lateral aspect of foot • Weakness in plantar flexion of foot • ↓ ankle reflex • Positive sciatic nerve stretch test



L5/S1 disc prolapse → **S1 nerve root compression causing**:

- Sensory loss to the posterior calf and the plantar surface of the foot
- Motor loss to **gastrocnemius** and **soleus**
- Loss of ankle jerk.

gastrocnemius muscle meaning "stomach of leg" (referring to the bulging shape of the calf)

gastrocnemius and **soleus** forms the calcaneal tendon or **Achilles Tendon** and inserts onto the posterior surface of the calcaneus, or heel bone.

Disc prolapse

- **Loss of sensation in the upper outer thigh is consistent with nerve root compression caused by a prolapsed vertebral disc.**

- 'Disc prolapse' actually refers to herniation of the nucleus pulposus, which is usually contained by the annulus fibrosus.

- The herniation of the nucleus pulposus is most commonly in the **posterolateral direction as it is the weakest part** of the surrounding annulus fibrosus.
- **commonly secondary to disc degeneration**, but can also be traumatic.
- **most often occurs in the lumbar spine**, especially **L5/S1** which results in sciatica.
- usually occurs on one side, rather than bilaterally
- Symptoms:
  - unilateral leg pain in the distribution of the affected nerve (which is often more severe than the back pain)
    - Pain is typically better with rest (although prolonged sitting can worsen it) –
    - if it is **unremitting or worse on resting** you should **consider other causes** such as bony **metastases** or infection.
  - numbness
  - paraesthesia
  - weakness and/or loss of tendon reflexes in the same distribution.

Cauda equina syndrome (CES)

- cauda equina syndrome (CES), the lumbosacral roots, **from L1 down to S5** are bilaterally damaged, symmetrically or asymmetrically, depending on the underline cause
- **Causes**
  - herniation of a lumbar disc (at L4/L5 and L5/S1)
  - tumour (metastases, lymphoma, primary spinal tumours)
  - trauma
  - infection (epidural abscess).
  - Others: ankylosing spondylitis, Paget's disease, and congenital spinal stenosis.
- **Features:** CES is a form of radiculopathy and is a **lower motor neuron lesion,** hence it **presents with:**
  - **flaccid paraplegia**
  - unilateral or bilateral lower limb motor and/or sensory abnormality
  - areflexia
  - low back pain
  - Whilst classically patients present with a sensory level, this is variable in clinical practice.
  - flexor plantar reflexes
  - bladder retention and **overflow incontinence** (bowel and/or bladder dysfunction with saddle and perineal anaesthesia)
  - saddle anesthesia.
    - Patients usually describe numbness and/or "pins-and-needles" sensations of the groin and inner thighs which would contact a saddle when riding a horse. This reflects involvement of the S3-S5 roots.
- **Diagnosis:**
  - **MRI is the investigation of choice**
- Determining the presence of bowel dysfunction (with reduced anal tone and sensation) can be helpful prognostically, but does not assist with the differential diagnosis.

Conus medularis syndrome

Conus medullaris syndrome is caused by compression of the T12-L2 cord and nerve roots, and therefore results in a mix of upper and lower motor neuron signs.

- Conus medularis syndrome presents with **mixed upper and lower motor neurone signs**.
  - These include bilateral distal weakness with increased tone and hyper-reflexia, fasciculation.
  - Because of the anatomy of the spinal cord if there is compression at the level of the conus medullaris some of the cord is compressed to cause upper motor (UMN) signs and some of the nerves are compressed to give lower motor signs.
    - Cauda equina would give just LMN signs, and so would not have positive Babinski sign and clonus.
- **Sensory loss is most marked in the perianal region**.

- In Amyotrophic lateral sclerosis (the commonest form of motor neurone disease), There would be a mixture of UMN and LMN signs; however they do not have any sensory signs or incontinence.

- It is much rarer than cauda equina syndrome.

	Conus Medullaris Syndrome	Cauda Equina Syndrome
Presentation	Sudden and bilateral	Gradual and may be unilateral leg signs initially
Reflexes	Knee jerks preserved, ankle jerks affected	Both knee and ankle jerks affected
Radicular pain	Less severe	More severe
Sensory	Numbness often localised to perianal area, dissociation can occur, usually bilateral and symmetrical	Numbness often localised to the saddle area, may be asymmetrical and unilateral, sensory loss often dermatomal
Motor	Symmetrical, hyperreflexic disal paresis, less marked than cauda equina, may be fasciculations	Areflexic paraplegic, may be asymmetric, more marked than conus medullaris, fasciculations rare, atrophy more common
Impotence	Frequent	Often less marked
Sphincter dysfunction	Urinary retention and atonic anal sphincter present early in disease (can cause overflow urinary incontinence)	Urinary retention, usually presents later in course of disease
Low back pain	More marked	Less marked

Autonomic dysreflexia

- This clinical syndrome **occurs in patients who have had a spinal cord injury at, or above T6 spinal level.**
- poorly understood condition associated with abnormal control of the autonomic nervous system in quadriplegic patients.
- It affects approximately 85% of patients with a lesion above C6 and may be triggered by cystitis, retention of urine or a blocked catheter as in this case, or constipation.
- Briefly, afferent signals, most commonly triggered by faecal impaction or urinary retention (but many other triggers have been reported) cause a sympathetic spinal reflex via thoracolumbar outflow.
- The increased sympathetic activity results in vasoconstriction and hypertension with stimulation of the carotid and aortic baroreceptors. These in turn respond via the vasomotor centre with increased vagal tone resulting in a bradycardia but reduced sympathetic tone with vasodilatation not possible due to the cord damage.
- The usual, centrally mediated, parasympathetic response however is prevented by the cord lesion.
- **The result is** an unbalanced physiological response, characterised by :
  - extreme hypertension , may leads to complications
  - flushing and sweating above the level of the cord lesion
  - Agitation
- **Treatment**
  - recognition and removal of the noxious stimulus.
  - Vasodilators such as calcium antagonists may be used to treat the hypertension.

Spastic paraparesis

Spastic paraparesis describes a upper motor neuron pattern of weakness in the lower limbs

Causes

- demyelination e.g. multiple sclerosis
- cord compression: trauma, tumour
- parasagittal meningioma
- **tropical spastic paraparesis**
  - **classic presentation → HTLV-1 positive patient presenting with paraparesis and urinary retention due to Adult T-cell lymphoma (ATL) caused by human T-lymphotropic virus type 1 (HTLV-I)**
- transverse myelitis e.g. HIV
- syringomyelia
- hereditary spastic paraplegia
- osteoarthritis of the cervical spine

Absent ankle jerks, extensor plantars

Typically caused by lesion producing both upper motor neuron (extensor plantars) and lower motor neuron (absent ankle jerk) signs

Causes

- Absent ankle jerks may occur in conditions associated with neuropathy (B_{12} deficiency, systemic lupus erythematosus [SLE], cerebrotendinous xanthomatosis) and dorsal root disease (tabes dorsalis).
- subacute combined degeneration of the cord
- motor neuron disease
- Friedreich's ataxia (usually presents by age 30)
- Syringomyelia
- taboparesis (syphilis)
- HIV
- Spinal AVM
- conus medullaris lesion

Which neurological finding is most helpful in differentiating subacute combined degeneration of the cord from multiple sclerosis?

➔ **Absent ankle jerk**

Subacute combined degeneration of spinal cord

Basics

- due to vitamin B12 deficiency
- dorsal + lateral columns affected
- **joint position and vibration sense lost first** then distal paraesthesia
- upper motor neuron signs typically develop in the legs, classically extensor plantars, brisk knee reflexes, **absent ankle jerks** (Knee reflexes in SACDC may be increased, normal or absent)
- Lhermitte's phenomenon is typically present in multiple sclerosis, but may also occur in sub-acute combined degeneration of the cord.
- **MRI** typically shows **increased signal on T2~weighted imaging** in the dorsal columns
- if untreated stiffness and weakness persist

Transverse myelitis

- Characterised by acute or subacute motor, sensory and autonomic spinal cord dysfunction.
- **Causes** of transverse myelitis
  - viral infections: varicella zoster, herpes simplex, cytomegalovirus, Epstein-Barr, influenza, echovirus, human immunodeficiency virus
  - bacterial infections: syphilis, Lyme disease
  - post-infections or vaccination (immune mediated)
  - first symptom of multiple sclerosis (MS) or neuromyelitis optica (NMO)
- **Signs** (develop over hours to days, and are usually bilateral):
  - Sensory level is characteristic.
  - Midline or dermatomal neuropathic pain can be present.
  - Urinary incontinence or retention,
  - bowel incontinence or constipation,
  - and sexual dysfunction are common but vary in severity.

- **Investigation**
  - MRI is indicated to rule out the presence of structural lesions, and determine the presence of myelitis, which enhances with gadolinium in the acute phase.
  - There may be more than one area of myelitis, and the lesions usually span at least two vertebral segments.
  - In the acute phase the MRI may be normal.
- **Treatment**
  - Corticosteroids are first line, and are initially given in high doses intravenously.
  - Plasma exchange can be given to those who fail to respond.
  - Patients with demyelinating disease can be started on long term immunosuppression.
- **prognosis**
  - **predictors of poor prognosis**
    - rapidly progressive course
    - severe weakness
    - hypotonia
    - areflexia
  - improvement can take three months and longer to develop
  - 50% - 70% of patients have partial or complete recovery.

Syringomyelia

Syringomyelia - spinothalamic sensory loss (pain and temperature)

Syringomyelia typically causes loss of reflexes, spinothalamic sensory loss (pain and temperature), and weakness. It can be asymmetrical initially

Definition

- Syringomyelia is a **degenerative** disease of the spinal cord that is characterized by a fluid-filled cavity within the cervical spinal cord.

Pathophysiology

- development of cavity (syrinx) within the spinal cord
- Syrinx (fluid-filled cavitation) in the central spinal cord, usually cervical. This can elongate and enlarge, causing → compression of the corticospinal and spinothalamic tracts and anterior horn cells.
- if extends into medulla then termed syringobulbia
- Most of the cavities in syringomyelia lie between the **second cervical** and the **ninth thoracic** vertebrae.
  - most commonly affecting the cervical region
- collection of fluids within the central canal of the spinal cord →enlargement spinal canal, leading to damage of the crossed fibers (anterior white commissure) of the spinothalamic tract → loss of pain and temperature sensation in the upper extremities

Epidemiology

- more common in men than women
- usually presents in the 20s and 30s although it can present later in life.

Causes

- Arnold-Chiari malformation type I → impaired cerebrospinal fluid circulation
  - **The most common cause**
- arachnoiditis,
- meningeal carcinomatosis,
- space-occupying lesions
- **Post-traumatic syringomyelia**
  - complicate up to 4% of spinal cord injury
  - **often presents with pain, which spreads upwards from the initial injury site.**
- idiopathic.

Features

- maybe asymmetrical initially
- **slowly progressive** sensory and motor symptoms, possibly over years

- motor: wasting and weakness of arms
- sensory: spinothalamic sensory loss (pain and temperature)
  - bilateral loss of pain and temperature sensation in the upper extremities.
  - fine touch sensation, vibration and proprioception are preserved
- loss of reflexes, bilateral upgoing plantars
- Horner's syndrome,
  - seen in advanced syringomyelia due to disruption of sympathetic trunk neurons.
- Bladder, bowel and sexual dysfunction can develop

Investigations

MRI is the investigation of choice

- MRI of the spinal cord
  - **the diagnostic modality of choice**.
  - MRI enhanced with gadolinium has more sensitivity than regular MRI.
- Myelography
  - used to confirm the diagnosis but was associated with more deterioration

Localization of the lesion :

- At syrinx (there is anterior horn cell involvement) → lower motor neuron pattern of weakness.
- At central decussating fibres (spinothalamic tract) → dissociated sensory loss with late development of neuropathic arthropathy.
- At corticospinal tracts below the level of the syrinx results in spastic paraparesis.

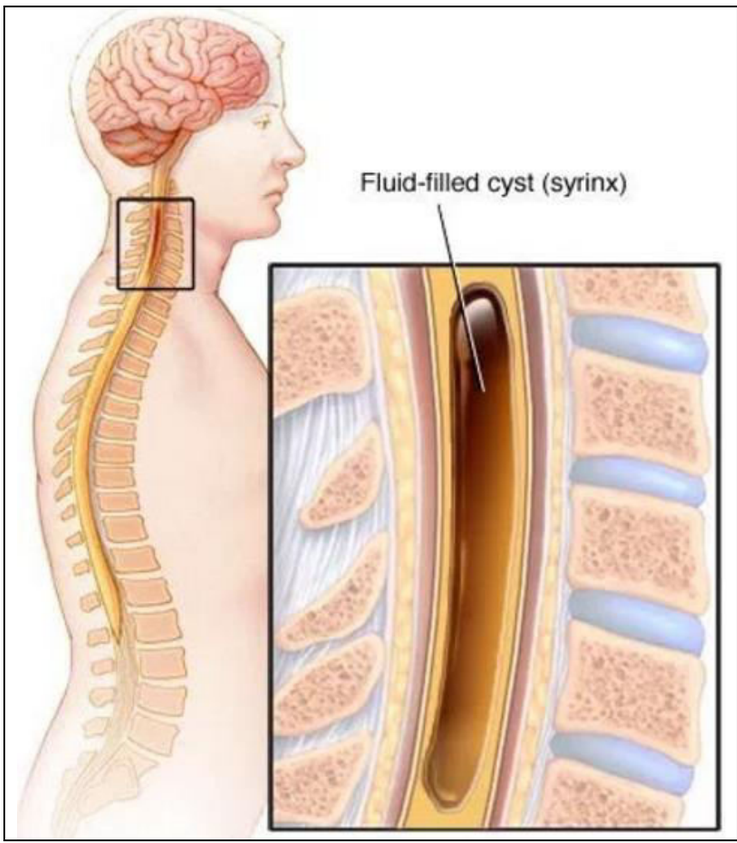
Defferntial diagnosis

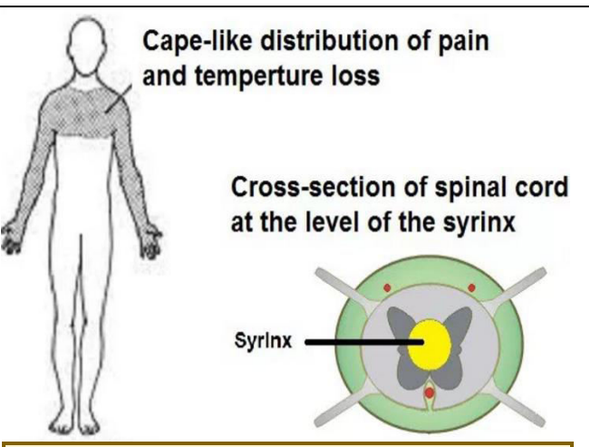
- Amyotrophic lateral sclerosis → NO sensory deficits.
- Anterior spinal artery thrombosis
  - characterised by loss of motor function **below the level of injury**, loss of pain and temperature sensations, and preservation of proprioception, fine touch and vibration.
- Post-traumatic spinal stenosis
  - result in neurological changes **below the level** of stenosis.

Management

- The mainstay of the treatment of is surgery.

May 2010 exam: feature of weakness & wasting of the small muscles of the hand. Which one of the following features would most support a diagnosis of syringomyelia? Loss of temperature sensation in the hands





The presence of loss of pain and temperature sensation in a 'cape like' distribution is highly suggestive of syringomyelia.

A fluid filled cavity within the cord develops, typically between C2 to T9, compressing the cord from inside to out.

Arnold-Chiari malformation

- Arnold-Chiari malformation describes the downward displacement, or herniation, of the cerebellar tonsils through the foramen magnum.
- Malformations may be congenital or acquired through trauma.

Pathophysiology

- Symptoms of Arnold-Chiari malformation, type I develop as a result of **three pathophysiological consequences** of the disordered anatomy:
  1. compression of the medulla and upper spinal cord,
  2. compression of the cerebellum,
  3. disruption of cerebrospinal fluid flow through the foramen magnum.

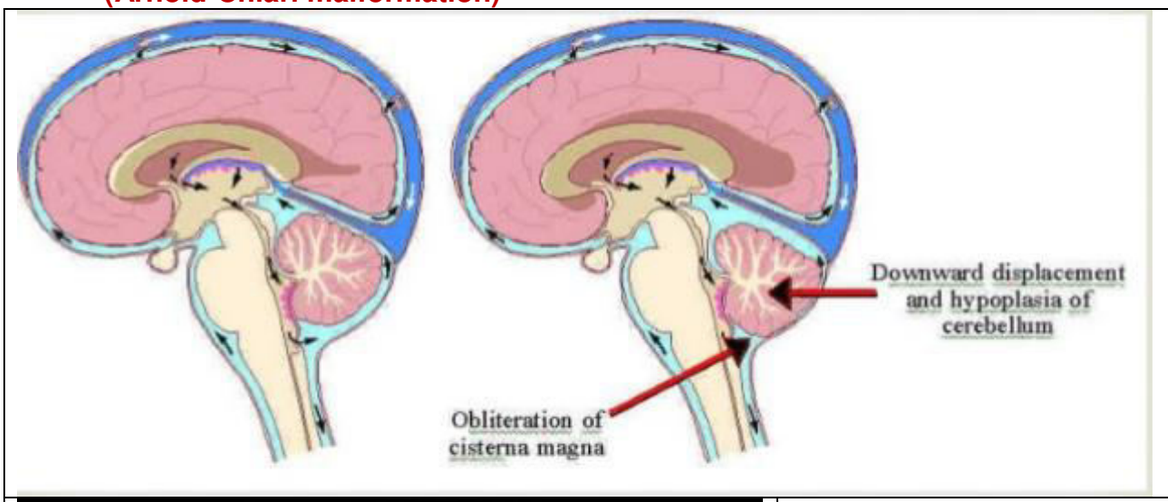
Classification

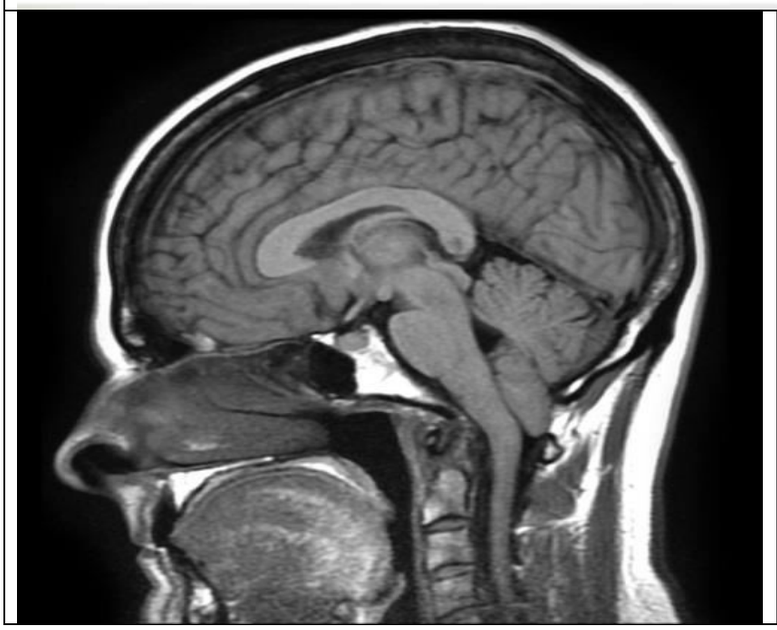
- classified by extent with which parts of the brain protrude into the spinal canal.
  - **Chiari I malformation**,
    - the only type that can be acquired or can remain asymptomatic until late childhood or early adulthood.
    - characterized by:
      - the time of onset (late childhood/early adulthood) and
      - the downward herniation of cerebellar tonsils, without the involvement of brainstem tissue.
    - symptoms due to obstruction of cerebrospinal fluid flow.
  - more severe types of Chiari malformations would involve additional herniation of brainstem tissue (Types II and III) or incomplete development of the cerebellum as a whole (Type IV).

Features

- non-communicating hydrocephalus may develop as a result of obstruction of cerebrospinal fluid (CSF) outflow
- neck pain
- headache
  - exacerbated by cough, valsalva maneuver and exercise.
- changes in balance, and poor hand coordination
- Syringomyelia

- **Downbeat nystagmus is classically associated with lesions at the foramen magnum (Arnold-Chiari malformation)**





MRI showing herniation of the cerebellar tonsils through the foramen magnum consistent with a Chiaria I malformation

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Anterior spinal artery thrombosis

Anterior spinal artery thrombosis → **Sudden paralysis and loss of pain and temperature sensation** below the level of the lesion.

- it supplies, roughly the anterior 2/3 of the cord.

Sequelae

- Occlusion of the anterior spinal artery infarcts the ventral portion of the cord.
- affects the structures found at the front of the spine
  - corticospinal tracts (motor neurons)
  - spinothalamic tracts (pain/temperature sensation).

Feature

- **Light-touch sensation and proprioception** are preserved because these are carried in the dorsal columns that are **supplied by the posterior spinal artery**.
- Power is reduced below the hips
- Pain and temperature sensation are lost to the waist.
- Vibration and joint-position sense are normal (found on posterior columns)
- In the acute stage reflexes are diminished, in keeping with "spinal shock", this may last for several days
- Injury level

- Anterior spinal cord lesions above **cervical vertebra 6** will result in **tetraplegia** with involvement of the upper and lower extremities.
- injuries from **T1-T6** have normal upper extremity, although abdominal and chest muscles may be affected with diminished respiratory excursion.
- The region of **thoracic vertebra 6** is the thoracic watershed (نقطة تحول) zone; lesions below this level result in loss of bowel, bladder, and sexual functions.

Anterior spinal arteries supply corticospinal and spinothalamic tracts, and anterior horns of the grey matter.

What is the diagnostic possibilities of a lesion involve the anterior two thirds of the spinal cord which **spares light touch, vibration and position sense**, but causes loss of pain and temperature sensation distally?.
The diagnostic possibilities include :
1- anterior spinal artery occlusion → **sudden onset**
2- and intramedullary spinal cord metastasis

Types of incomplete spinal cord syndromes

- All types present with dissociated sensory loss: a pattern of selective sensory loss ("dissociation of modalities"); suggests a focal lesion of a single tract within the spinal cord

	Affected spinal tracts	**Etiology**	**Clinical features**
Central cord syndrome (most common)	Bilateral **central corticospinal tracts** and **lateral spinothalamic tracts**	• Hyperextension injury (e.g., car crash) associated with chronic cervical spondylosis • Spinal cord compression	• **Bilateral paresis: upper** > lower extremities
Anterior cord syndrome	Corticospinaland sp inothalamic tracts	• Trauma (e.g., penetrating injury, burst fracture of vertebra) • Occlusion of **anterior spinal artery**	• Bilateral motor paralysis, loss of pain and temperature sensation, and autonomic dysfunction below the level of the lesion
Posterior cord syndrome	Bilateral posterior columns	• Trauma (e.g., penetrating injury) • Occlusion of the posterior spinal artery • Multiple sclerosis	• Ipsilateral loss of proprioception, vibration, and touch sensationbelow the level of the lesion
Brown-Séquard syndrome(hemi section syndrome)	Hemisectionof the cord	• Trauma (e.g., penetrating injury) • Spinal cord compression	• **Ipsilateral** ➢ **Loss of proprioception, vibration, and tactile**discrimination below the level of the lesion ➢ Segmental flaccid paresis at the level of the lesion, spastic paralysis below the level of the lesion , and ipsilateral Babinski sign • **Contralateral**: **loss of pain and temperature sensation** one or two levels below lesion

Para- spinal abscess

Risk factors

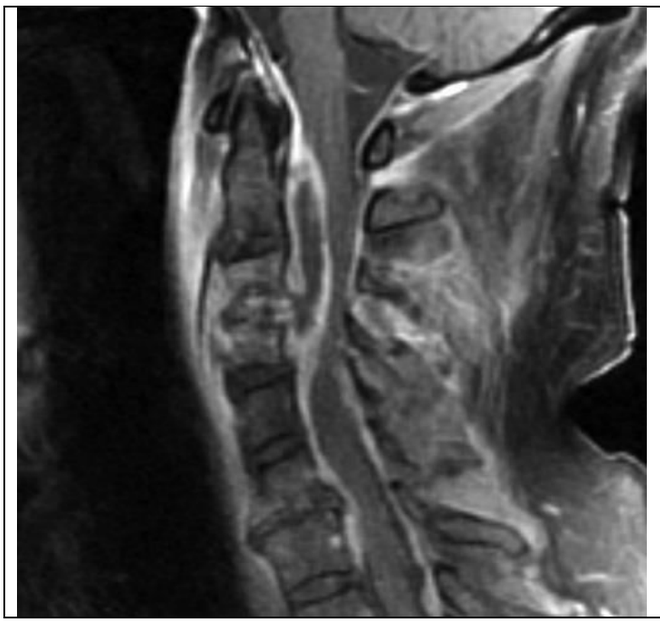
- often associated with infection in an intravenous (IV) line, which may or may not be apparent as cellulitis.
  - usually due to seeding of Staphylococcus aureus, endocarditis is a possibility.

Features

- spinal pain
- fever
- neurological deficit

Diagnosis

- MRI neck is the investigation of choice
  - MRI of the neck should delineate the anatomy of the abscess, which will not be seen on a CT scan of the head.
- CSF should show an elevated protein with raised white cells, and a low/normal glucose.



- MRI demonstrates an epidural collection with peripheral contrast enhancement. The cord is displaced posteriorly and to the right.
- Features are consistent with an epidural abscess.
- There are associated changes at the C3/4 level consistent with advanced discitis osteomyelitis.

Brown-Séquard's syndrome

- Thoracic spinal cord lesion produced by a hemisection of the spinal cord.
- Causes include:
- trauma,
- tumours, and
- multiple sclerosis.
- Presented with
  - **ipsilateral weakness**
  - ipsilateral loss of position and vibration below the lesion (dorsal column dysfunction)
  - **Contralateral loss of pain and temperature.**

Lower back pain

Lower back pain (LBP) is one of the most common presentations seen in practice. Whilst the majority of presentations will be of a non-specific muscular nature it is worth keeping in mind possible causes which may need specific treatment.

Red flags for lower back pain

- age < 20 years or > 50 years
- history of previous malignancy
- night pain
- history of trauma
- systemically unwell e.g. weight loss, fever

The table below indicates some specific causes of LBP:

Facet joint	**May be acute or chronic** **Pain worse in the morning and on standing** **On examination there may be pain over the facets. The pain is typically worse on extension of the back**
Spinal stenosis	Usually gradual onset Unilateral or bilateral leg pain (with or without back pain), numbness, and weakness which is worse on walking. pain is worse with walking downhill and less with walking uphill. Resolves when sits down. Pain may be described as 'aching', 'crawling'. Relieved by sitting down, leaning forwards and crouching down Clinical examination is often normal Requires MRI to confirm diagnosis
Ankylosing spondylitis	Typically a young man who presents with lower back pain and stiffness Stiffness is usually worse in morning and improves with activity Peripheral arthritis (25%, more common if female)
Peripheral arterial disease	Pain on walking, relieved by rest Absent or weak foot pulses and other signs of limb ischaemia Past history may include smoking and other vascular diseases

Wernicke's encephalopathy

- Wernicke's encephalopathy is a neuropsychiatric disorder caused by **thiamine deficiency**, which is most commonly seen in alcoholics.
- **Rarer causes include**:
  - persistent vomiting,
  - stomach cancer,
  - dietary deficiency.
- **A classic triad of:**
  - nystagmus,
  - ophthalmoplegia
  - and ataxia
- In Wernicke's encephalopathy petechial haemorrhages occur in a variety of structures in the brain including the mamillary bodies and ventricle walls

Features

- nystagmus (the most common ocular sign)
- ophthalmoplegia
- ataxia
- confusion, altered GCS
- peripheral sensory neuropathy
- Sometimes bilateral wrist drop but more frequently bilateral foot drop with pain or pressure over the long nerves.

Investigations

- decreased red cell transketolase
- MRI

Treatment is with urgent replacement of **thiamine (Pabrinex (Intravenous))**

Relationship with Korsakoff syndrome

Inability to acquire new memories and confabulation suggests the development of Korsakoff's syndrome

- If not treated Korsakoff's syndrome may develop as well. This is termed Wernicke-Korsakoff syndrome and is characterised by the addition of antero- and retrograde amnesia and

confabulation in addition to the above symptoms.
- MRI finding → **mammillary body degeneration**

Marchiafava Bignami syndrome: Corpus callosum degeneration from chronic alcohol excess

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Acute disseminated encephalomyelitis

- Acute disseminated encephalomyelitis (ADEM) is an autoimmune demylinating disease of the central nervous system. It may also be termed post infectious encephalomyelitis.
- The aetiology is not fully understood and it can occur following infection with a bacterial or viral pathogen. Common infections include measles, mumps, rubella, varicella and small pox, however this list is not exhaustive.
- After a lag time of between a few days to 2 months there is an acute onset of multifocal neurological symptoms with rapid deterioration.
- Non-specific signs such as headache, fever, nausea and vomiting may also accompany the onset of illness.
- Motor and sensory deficits are frequent and there may also be brainstem involvement including occulomotor defects.
- There are no specific biomarkers for the diagnosis of ADEM. MRI imaging may show areas of supra and infra-tentorial demylination.
- Management involves intravenous glucocorticoids and the consideration of IVIG where this fails.

Anti-NMDA receptor encephalitis

- Anti-NMDA receptor encephalitis is a paraneoplastic syndrome, presenting as prominent psychiatric features including agitation, hallucinations, delusions and disordered thinking; seizures, insomnia, dyskinesias and autonomic instability.
- Ovarian teratomas are detected in up to half of all female adult patients, particularly prevalent in Afro-Carribean patients.
- MRI head can be normal but abnormalities can be visualised on FLAIR sequences in the deep subcortical limbic structures.
- CSF may demonstrate pleiocytosis but can be normal initially.
- Anti-MuSK is an autoantibody specific to muscle kinase in myasthenia gravis with no evidence of a thymoma and without antibodies to acetylcholine receptors.
- Anti-GM1 is an autoantibody specific to acute inflammatory demyelinating polyneuropathy (AIDP) variant of Guillain-Barre syndrome.
- Treatment of anti-NMDA encephalitis is based of immunosuppresion with intravenous steroids, immunoglobulins, rituximab, cyclophosphamide or plasma exchange, alone or in combination. Resection of teratoma is also therapeutic.

Autoimmune encephalitis

Types of autoimmune encephalitis include:
- autoimmune limbic encephalitis (paraneoplastic and non-paraneoplastic)
- Rasmussen's encephalitis
- anti-NMDAR (NR1) encephalitis
- glycine-receptor mediated encephalitis
- Bickerstaff brainstem encephalitis

Reye's syndrome

- Reye's syndrome is a severe, progressive encephalopathy affecting children that is accompanied by **Microvesicular fatty infiltration** of the liver, kidneys and pancreas.
- **The aetiology** of Reye's syndrome is not fully understood although there is a known association with aspirin use and a viral cause has been postulated
- The peak incidence is 2 years of age,
- **Features** include:

  - may be history of preceding viral illness
  - encephalopathy: confusion, seizures, cerebral oedema, coma
  - fatty infiltration of the liver, kidneys and pancreas
  - hypoglycaemia
- **Management** is supportive
- **Prognosis** although has improved over recent years there is still a mortality rate of 15-25%.

CADASIL

Overview

- Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)
- A family history is almost always present, as it is an autosomal dominant condition, **located to chromosome 19**.

Features

- rare cause of multi-infarct dementia
- **patients often present with migraine**
- Recurrent ischaemic events (transient or permanent) & Severe mood disorders

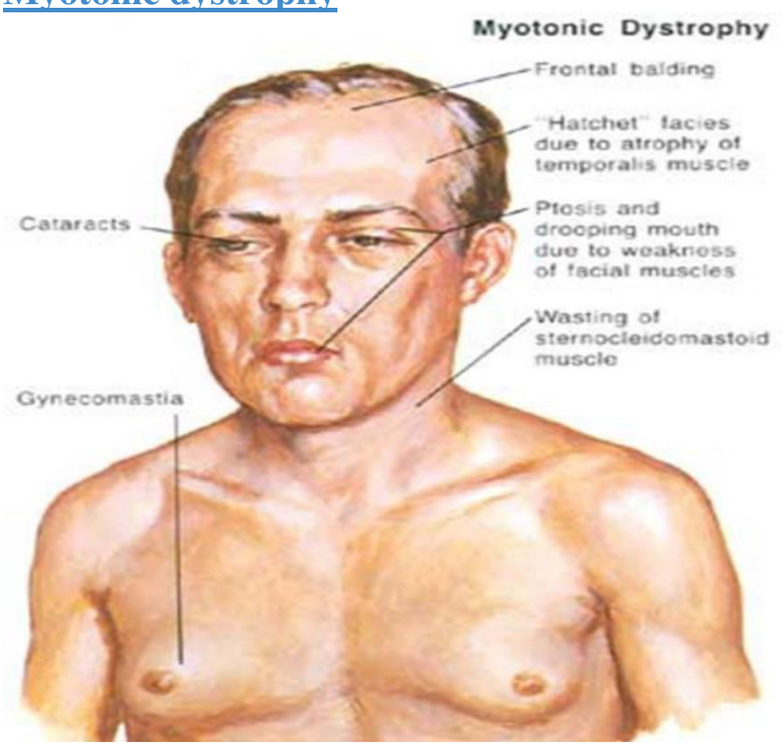
Diagnosis

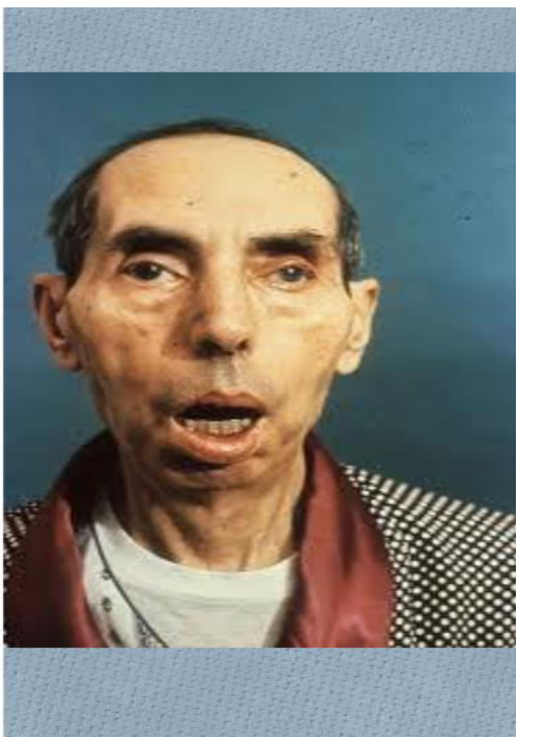
- Characteristic MRI changes include T2 weighted hyperintensity of the periventricular white matter.
- **DNA testing** for the **notch-3 gene mutation** confirms the diagnosis.

Treatment

- the **oral contraceptive pill should be stopped**, given its association with stroke in migraine.

Myotonic dystrophy





Dystrophia myotonica - DM1

- distal weakness initially
- autosomal dominant
- diabetes
- dysarthria

- Myotonic dystrophy (Steinert's disease) (also called dystrophia myotonica) is an inherited myopathy
- the most common **adult** muscular dystrophy.
- It affects skeletal, cardiac and smooth muscle.

- results in a **selective atrophy of type I muscle fibers**
- features developing at around 20-30 years old.
- There are two main types of myotonic dystrophy, DM1 and DM2.
- Congenital myotonic dystrophy is a more severe form of the disease that occurs in **children born to mothers who have established myotonic dystrophy**. **Babies are hypotonic and frequently require assisted ventilation.**

Genetics

- autosomal dominant
- a trinucleotide repeat disorder
- DM1 is caused by a CTG repeat at the end of the DMPK (Dystrophia Myotonica-Protein Kinase) gene on chromosome 19
- DM2 is caused by a repeat expansion of the ZNF9 gene on chromosome 3

The key differences are listed in table below:

DM1	DM2
- DMPK gene on chromosome 19 - Distal weakness more prominent	- ZNF9 gene on chromosome 3 - Proximal weakness more prominent - Severe congenital form not seen

General features

- myotonic facies (long, 'haggard' appearance)
- frontal balding
  - some women have hair loss
- Atrophy of temporalis, masseters and facial muscle
- bilateral ptosis
- cataracts

Other features

- myotonia (tonic spasm of muscle)
  - Neck muscles, including sternocleidomastoid, are involved early in the course of disease.
- weakness of arms and legs (distal initially)
  - Distal weakness is often more marked than proximal weakness
- mild mental impairment
- diabetes mellitus (Insulin resistance)
- testicular atrophy
- **slow-relaxing grip** may be noticed on initial hand-shake with the patient and is **typical** of myotonic dystrophy.
- Dysarthric speech secondary to myotonia of the tongue and pharynx
- cardiac involvement: heart block, cardiomyopathy
- dysphagia
- Cataracts are common

Diagnosis

- **Diagnosis can be made on electromyogram (EMG)**
  - **The most appropriate next step to confirm the diagnosis**
  - EMG changes are found in almost any muscle
    - **Wasxing and waning of potentials , termed the "dive bomber effect"**
  - Genetic testing can confirm the diagnosis

Evaluation

- Serology → increased serum CK

Treatment (mostly symptomatic)

- for weakness - which is the main cause of disability- → There is no treatment
- for myotonia → phenytoin, quinine or procainamide may be useful
- for cardiac abnormalities → pacemaker
- for obstructive sleep apnea (common) → CPAP

Dystrophinopathies

Overview

- **X-linked recessive**
  - Affected father (Y, **X**):
    - All sons will not be affected and not carriers (His sons will get the X chromosome from their mother)
    - All his daughters will be carriers
  - Carrier mother (X , **X**):
    - **50% of sons will be affected** (there is a 1 in 2 chance (50:50) of passing the gene on to their sons.)
- due to mutation in the gene encoding dystrophin, **dystrophin gene on Xp21**
- dystrophin is a protein in muscle which connects the muscle membrane to actin, part of the muscle cytoskeleton

Diagnostic investigations

- **1st investigations to order**
  - **serum CK**
    - 50 to 100 times normal level consistent with Duchenne muscular dystrophy
  - **genetic testing**
    - DNA analysis → **Xp21 mutation** → may present in both Duchenne and Becker muscular dystrophies
- Investigations to consider
  - EMG
    - EMG can distinguish between neuropathic and myopathic pathology.
    - **myopathic reading** with **fast firing**, **short duration** but **polyphasic** and **decreased amplitude** motor units with **early recruitment** in the affected muscles
  - **muscle biopsy**
    - absence of dystrophin → Duchenne muscular dystrophy
    - diminished quantity or quality of dystrophin → Becker muscular dystrophy

Duchenne muscular dystrophy (DMD)

- most common and most rapidly progressive muscular dystrophy
- there is a **frameshift mutation** resulting in one or both of the binding sites are lost leading to a **severe form**
- progressive proximal muscle weakness **from 5 years**
  - Usually, there is severe progression with wheelchair dependence by the age of 12 on average
  - Death usually occurs as a teenager or in the early 20s from respiratory failure.
- calf pseudohypertrophy
- Gower's sign: child uses arms to stand up from a squatted position
- intellectual impairment (30%)
- urinary and bowel incontinence (common)
- DMD patients tend to be hyperactive and have difficulty in focusing attention.

Becker muscular dystrophy

- there is a **non-frameshift insertion** in the dystrophin gene resulting in both binding sites being preserved leading to a **milder form**
- develops after the age of 10 years
- **Similar type of disease to Duchenne's, with a later onset (average age at presentation 12 years), milder phenotype and longer life expectancy**
- intellectual impairment much less common
- Occasionally, patients present with CHF and cardiac arrhythmias before complaining of muscle weakness and before diagnosis.

Facio-scapulo-humeral muscular dystrophy

- Facioscapulohumeral muscular dystrophy (FSHMD) is an autosomal dominant form of muscular dystrophy.
- As the name suggests it stypically affects the face, scapula and upper arms first.

- Symptoms typically presents by the age of 20 years.
- may go unrecognised until later life
- The presence of distal wasting and **pes cavus** (indicates a very **chronic neuromuscular disorder** with axonal loss)

Foster-Kennedy syndrome

Foster Kennedy's syndrome is a combination of optic atrophy and central scotoma, contralateral papilloedema and anosmia.

- Foster-Kennedy syndrome describes a series of symptoms and signs associated with frontal lobe lesions.
- It is caused by optic and olfactory nerve compression and raised intracranial pressure.
- This is **often secondary to a mass such as an olfactory groove meningioma**.

Features

- optic atrophy in the ipsilateral eye
- central scotoma in the ipsilateral eye
- papilloedema in the contralateral eye
- anosmia
- symptoms of raised intracranial pressure such as nausea and vomiting,
- frontal symptoms such as emotional lability and memory loss.

Hypokalaemic periodic paralysis

Pathophysiology

- autosomal dominant disorder
- The underlying defect is a **mutation in muscle voltage-gated calcium channels**.

Features

- **Episodes of paralysis,**
  - Symptoms begin with stiffness and heaviness of the limbs followed by weakness , Examination during an attack will demonstrate weakness with hyporeflexia
  - Occasionally the respiratory and bulbar muscles may be involved.
    - Age → Onset usually in adolescence
    - Time →Typically occur at night.
    - Duration →Attacks can last from several minutes to hours, although they may last for up to 3 days
  - **Attacks may be precipitated by:**
    - Carbohydrate meals.
    - **Exercise**
    - sodium-rich meals followed by exertion
- may associate with thyrotoxicosis
  - **with thyrotoxicosis called →Thyrotoxic hypokalaemic periodic paralysis**
  - Without thyrotoxicosis called →hypokalaemic periodic paralysis.

Epidemiology

- The prevalence is much higher in patients with thyrotoxicosis of Chinese origin versus Caucasians, (13-14% vs. 0.1-0.2%).
- occurs in 10% of young Latin American or Asian men **with thyrotoxicosis** (of whatever aetiology).

Diagnosis

- **documentation of hypokalaemia during an attack**

Management

- **Potassium infusion → provide immediate relief from symptoms**
- lifelong potassium supplementation
- continuous cardiac monitoring
- The periodic paralysis resolves when the thyrotoxicosis is treated.

Mental Capacity Act

- Mental capacity includes the ability to make decisions affecting daily life, healthcare and financial issues.
- It applies to adults over the age of 16 and sets out who can take decisions if a patient becomes incapacitated (e.g. following a stroke).
- **The Act contains 5 key principles:**
    1. A person must be assumed to have capacity unless it is established that he lacks capacity
    2. A person is not to be treated as unable to make a decision unless all practicable steps to help him to do so have been taken without success
    3. A person is not to be treated as unable to make a decision merely because he makes an unwise decision
    4. An act done, or decision made, under this Act for or on behalf of a person who lacks capacity must be done, or made, in his best interests
    5. Before the act is done, or the decision is made, regard must be had to whether the purpose for which it is needed can be as effectively achieved in a way that is less restrictive of the person's rights and freedom of action

Assessment of capacity

- An adult can only be considered unable to make a particular decision if:
    1. has an 'impairment of, or disturbance in, the functioning of the mind or brain' whether permanent or temporary AND
    2. unable to undertake any of the following

        a) understand the information relevant to the decision
        b) retain that information
        c) use or weigh that information as part of the process of making the decision
        d) communicate the decision made by talking, sign language or other means
- No individual can be labelled 'incapable' simply as a result of a particular medical condition.
- a lack of capacity cannot be assumed by a person's age, appearance, or any condition or aspect of a person's behaviour

Best interests

The following should be considered when assessing what is in someone's best interests:

- 1. Whether the person is likely to regain capacity and can the decision wait.
- 2. How to encourage and optimise the participation of the person in the decision.
- 3. The past and present wishes, feelings, beliefs, values of the person and any other relevant factors
- 4. Views of other relevant people

Lasting Powers of Attorney (LPAs)

- The Act allows a person to appoint an attorney to act on their behalf if they should lose capacity in the future, replacing the current Enduring Power of Attorney (EPA).
- In addition to property and financial affairs the Act also allows people to empower an attorney make health and welfare decisions.
- The attorney only has the authority to make decisions about life-sustaining treatment if the LPA specifies that.
- Before it can be used an LPA must be registered with the Office of the Public Guardian

Advance decisions

- Advance decisions can be drawn up by anybody with capacity to specify treatments they would not want if they lost capacity.
- They may be made verbally unless they specify refusing life-sustaining treatment (e.g. Ventilation) in which case they need to be written, signed and witnessed to be valid.
- Advance decisions cannot demand treatment

Neuromyelitis optica

Neuromyelitis optica is a demyelinating disease involving the optic nerves and spinal cord but sparing the brain. The specific test for this is the NMO antibody which is against aquaporin 4.

- Neuromyelitis optica (NMO) is monophasic or relapsing-remitting demyelinating CNS disorder
- Although previously thought to be a variant of multiple sclerosis, it is now recognised to be a distinct disease
- particularly prevalent in Asian populations
- typically involves the **optic nerves** and **cervical spine**, with **imaging of the brain frequently normal**.
- Vomiting is also a common presenting complaint.
- **Diagnosis** is requires bilateral optic neuritis, myelitis and 2 of the follow 3 criteria
    1. Spinal cord lesion involving 3 or more spinal levels
    2. Initially normal MRI brain
    3. **Aquaporin 4 positive serum antibody**

Oculopharyngeal muscular dystrophy

Features

- ptosis
- weakness of the extraocular muscles
- dysphagia
- tongue atrophy

Superficial siderosis

Superficial siderosis describes the chronic deposition of iron in neurons of the central nervous system. The most common cause is chronic bleeding secondary to either a subarachnoid haemorrhage or subdural haemorrhage.

Features

- sensorineural hearing loss
- ataxia
- dementia
- anosmia
- anisocoria

Vertigo

The table below lists the main characteristics of the most important causes of vertigo

Disorder	Notes
Labyrinthitis	Recent viral infection or head trauma Sudden onset Nausea and vomiting typically has associated tinnitus and a history of infection. Hearing may be affected
Vestibular neuritis	Recent viral infection Recurrent vertigo attacks lasting hours or days No hearing loss
Benign paroxysmal positional vertigo	Gradual onset Triggered by change in head position Each episode lasts 10-20 seconds
Meniere's disease	Associated with hearing loss, tinnitus and sensation of fullness or pressure in one or both ears
Vertebrobasilar ischaemia	Elderly patient Dizziness on extension of neck
Acoustic neuroma	Hearing loss, vertigo, tinnitus Absent corneal reflex is important sign Associated with neurofibromatosis type 2

- Cerebellar stroke may present in a similar fashion to vestibular neuritis.
  - Clinically, vertical nystagmus is suggestive of a central cause of vertigo.
  - Additionally, patients usually cannot stand without support, even with the eyes open, whereas a patient with acute vestibular neuritis is usually able to do so.

Other causes of vertigo include

- trauma
- multiple sclerosis
- ototoxicity e.g. gentamicin
- Migraine is a another common cause of vertigo

Benign paroxysmal positional vertigo

- Benign paroxysmal positional vertigo (BPPV) is one of the most common causes of vertigo encountered.
- It is characterised by the sudden onset of dizziness and vertigo triggered by changes in head position.
- The average age of onset is 55 years and it is less common in younger patients.

Features

Vertigo and nausea, with nystagmus, fit best with benign paroxysmal positional vertigo, which occurs due to otolith detachment into the semicircular canals of the inner ear.

- vertigo triggered by change in head position (e.g. rolling over in bed or gazing upwards)
- may be associated with nausea
- each episode typically lasts 10-20 seconds
- positive Dix-Hallpike manoeuvre

Treatment:

- Symptomatic relief may be gained by:
  - Epley manoeuvre (successful in around 80% of cases)

- teaching the patient exercises they can do themselves at home, for example Brandt-Daroff exercises
- Medication is often prescribed (e.g. Betahistine) but it tends to be of limited value.

Prognosis: BPPV has a good prognosis and usually resolves spontaneously after a few weeks to months.

May 2013 exam: H/O vertigo and dizziness precipitated by a change in head position. What is the most appropriate next step to confirm the diagnosis? Dix-Hallpike manoeuvre

Meniere's disease

- Meniere's disease is a disorder of the inner ear of unknown cause.
- It is characterised by excessive pressure and progressive dilation of the endolymphatic system.
- It is more common in middle-aged adults but may be seen at any age.
- has a similar prevalence in both men and women.

Features

- recurrent episodes of vertigo, tinnitus and hearing loss (sensorineural). Vertigo is usually the prominent symptom
- a sensation of aural fullness or pressure is now recognised as being common
- other features include nystagmus and a positive Romberg test
- episodes last minutes to hours
- typically symptoms are unilateral but bilateral symptoms may develop after a number of years

Natural history

- symptoms resolve in the majority of patients after 5-10 years
- the majority of patients will be left with a degree of hearing loss
- psychological distress is common

Management

- ENT assessment is required to confirm the diagnosis
- patients should inform the DVLA. The current advice is to cease driving until satisfactory control of symptoms is achieved
- acute attacks: buccal or intramuscular prochlorperazine. Admission is sometimes required
- prevention: betahistine may be of benefit

May 2013 exam: H/O recurrent attacks of 'dizziness' + 'roaring' sensation in the left ear. Weber's test localises to the right ear. What is the most likely diagnosis? Meniere's disease

Neuropathy

- **Definitions**
  - **Allodynia**: **pain** caused by a **stimulus** that does not normally cause pain (e.g. light touch, contact with clothing)
  - **Dysesthesia**: abnormal **spontaneous** sensations (burning, stinging, stabbing) **from activities** that do not normally cause pain)
  - **Paresthesia**: an abnormal skin sensation **in the absence of a stimulus** (described as burning, prickling, itching, tingling)
  - **Hyperesthesia**: increased sensitivity to sensory stimuli
  - **Hypoesthesia**: decreased sensitivity to sensory stimuli

Peripheral neuropathy

- neuropathy is classified into:
  - mononeuropathy commonly due to entrapment or trauma;
  - mononeuropathy multiplex commonly due to leprosy and vasculitis; and
  - polyneuropathy due to systemic, metabolic or toxic etiology.
- Peripheral neuropathy may be divided into conditions which predominately cause a motor or sensory loss

Predominately motor loss	Predominately sensory loss
• Guillain-Barre syndrome • porphyria • lead poisoning • hereditary sensorimotor neuropathies (HSMN) - Charcot-Marie-Tooth • chronic inflammatory demyelinating polyneuropathy (CIDP) • diphtheria	• diabetes • **uraemia** • leprosy • alcoholism • vitamin B12 deficiency • amyloidosis • Sjogren's syndrome

Types

- **Large-fibre neuropathy**
  - ➢ generally causes glove and stocking sensory loss and **loss of reflexes**.
- **Small-fibre neuropathy**
  - ➢ typically presents with pain and loss of temperature sensation, with relative preservation of other sensory modalities and muscle strength.
    - General neurological examination and reflexes are usually normal
  - ➢ not detectable on conventional nerve conduction studies, which can only investigate large fibres.
  - ➢ **Causes** of small fiber neuropathy
    - **Diabetes**
      - ❖ is a **common** cause and should be excluded in any patient with a painful peripheral neuropathy.
      - ❖ Conditions in which the small fibres are preferentially affected in the early stages include **diabetes** and **amyloidosis**. In the later stages however the neuropathy in these conditions also affects large fibres.
    - **Amyloidosis**
    - Fabry's disease
      - ❖ X-linked lysosomal storage disorder
      - ❖ causes a painful peripheral neuropathy, due to deposition of glycosphingolipids within small sensory fibres.
      - ❖ Nerve conduction studies are typically normal as large fibres are unaffected.
    - Tangier's disease
    - Hereditary sensory and autonomic neuropathy
    - Sjogren's syndrome
      - ❖ **pure sensory** neuropathy (ganglionopathy).
    - Chronic idiopathic small fiber sensory neuropathy

Small-fibre neuropathy	Large-fibre neuropathy
Loss of pain and temperature	Loss of touch, vibration and position sense Sensory ataxia
Preservation of reflexes and motor function	Reflexes lost early and motor functions impaired
Electrophysiological test is silent Skin biopsy are used	Impaired nerve conduction velocity

- ➢ **Skin punch biopsy** can be done if a **small-fiber neuropathy** is suspected;
  - loss of nerve endings supports that diagnosis.
- ➢ **Nerve biopsy** is occasionally done to help differentiate demyelinating from vasculitic **large-fiber neuropathies.**
- ➢ If vasculitis is a consideration, the **biopsy specimen should include skin and muscle** to increase the likelihood of a definitive diagnosis.
- ➢ If all limbs are affected, **MRI** can be done to rule out cervical **spinal cord compression**.

- **Lead neuropathy**
  - **purely motor neuropathy**
  - affecting mainly the **upper limbs**.

- Thalamic infarcts
  - commonly cause late-onset of severe neuropathic pain weeks to months after the stroke.
  - The pain is intractable to analgesics.
  - **The treatment of choice for neuropathic pain is amitriptyline/gabapentin.**

Alcoholic neuropathy

Epidemiology

- Alcohol abuse and diabetes are the commonest causes of peripheral neuropathy in the United Kingdom.

Pathophysiology

- Typically, **all fibre types are affected** and it is seen with a higher alcohol consumption more than 30 units.
- affects mainly the spinothalamic pathway.
- secondary to both direct toxic effects and reduced absorption of B vitamins (**thiamine deficiency**)

Features

- slowly progressive
- sensory symptoms typically present prior to motor symptoms
- Pain is usually a more dominant feature

Treatment

- **thiamine** and **cessation of alcohol use**

Neuropathy of Vitamin B12 deficiency

- leads to demyelination
- usually causes a more rapidly progressive neuropathy with dorsal column involvement (joint position and vibration involvement with sensory ataxia and pseudoathetosis of upper limbs).
- most commonly involves the peripheral nerves, but can also result in subacute degeneration of the spinal cord.
  - Peripheral involvement results in loss of vibration sense and proprioception.
  - Cord involvement then affects the posterior columns and corticospinal tracts resulting in loss of reflexes, weakness, spasiticity, Babinski's responses and ataxia.

Course of the neuropathy (http://emedicine.medscape.com)

- Early in the course, poor joint position and vibration sense predominate.
  - **dorsal column usually affected first (joint position, vibration**) prior to distal paraesthesia
- Typically, the legs are affected before the arms.
- On presentation, 50% of patients have absent ankle reflexes with relative hyperreflexia at the knees.
- Plantars are initially flexor and later extensor.
- As the disease progresses, ascending loss of pinprick, light touch, and temperature sensation occurs.
- Later, depending on the predominance of posterior column versus cortical spinal tract involvement, ataxia or spastic paraplegia predominates.
- Then, PNS involvement causes distal limb atrophy.

Peripheral neuropathy: axonal vs. demyelinating

Peripheral neuropathy	Causes	Nerve conduction studies (NCS)
Axonal	• alcohol • isoniazid • Simvastatin • diabetes mellitus* • vasculitis • vitamin B12 deficiency* • Renal failure • hereditary sensorimotor neuropathies (HSMN) **type II** (*may also cause a demyelinating picture)	• normal conduction velocity • **reduced amplitude**
Demyelinating	• **Guillain-Barre syndrome** • chronic inflammatory demyelinating polyneuropathy (CIDP) • Paraproteinaemia • Amiodarone (Amiodarone can cause a mixed demyelinating and axonal picture) • Refsum's disease • hereditary sensorimotor neuropathies (HSMN) **type I** (Charcot-Marie-Tooth disease) • Leukodystrophies.	• **reduced conduction velocity** • normal amplitude

- Nerve conduction studies (NCS) are useful in determining between axonal and demyelinating pathology
- Segmental demyelination is a feature seen in axons in the central nervous system with **multiple sclerosis**.

Wallerian degeneration

- **Wallerian degeneration is degeneration of the portion of the nerve distal to the injury.**
- **It occurs following axonal injury in both the peripheral and central nervous systems**
- **usually begins within 24-36 hours of injury.**

Chronic inflammatory demyelinating polyneuropathy (CIDP)

Chronic inflammatory demyelinating polyneuropathy is clinically similar to Guillain-Barre syndrome (hyporeflexia or areflexia, paraesthesia and mild sensory deficits in the upper and lower extremities, weakness) **except that it follows a chronic progressive course.**

- CIDP is characterised by progressive weakness and impaired sensory function in the upper and lower limbs.
- **subacute** sensory and motor peripheral neuropathy
- The cause of the demyelination is not understood,
- More common in young adults and in men.
- mainly causes motor impairment (distal and proximal).
- presents with
  - weakness of the limbs
  - **areflexia**
  - abnormal sensation (which typically begins distally)
  - fatigue.
  - **(CIDP) causes a large fibre peripheral neuropathy (Joint position sense and vibration are carried through large fibres)**
  - **Autoantibodies against GM1 gangliosides**
- **Differential diagnosis**

1. CIDP is closely linked to **Guillain-Barré syndrome (GBS**), and is thought by some to be its chronic counterpart.
    - Both CIDP and GBS can affect motor and sensory nerves
    - (GBS) is an **acute** (which reaches its peak in severity **within six weeks**), post-infectious neuropathy
    - Whereas CIDP is **subacute (several months history)**
2. **Hereditary motor and sensory neuropathy (HMSN)** is normally a **very chronic** neuropathy developing **over many years** and usually with a family history of the condition.

- **Treatment**
    - Corticosteroids
    - plasmapheresis
    - intravenous immunoglobulin
    - Physiotherapy

Electromyogram (EMG)

- A pattern of rapidly recruited low amplitude short duration motor units on the electromyogram (EMG) would be considered to represent myopathic changes rather than de-innervation.

Multifocal motor neuropathy (MMN)

- Acquired autoimmune demyelinating motor neuropathy
- Associated with motor conduction block (Multifocal motor neuropathy with conduction block (MMN-CB)

Feature:

- Features of MMN-CB may resemble motor neuron disease but in contrast MMN-CB may **respond well to intravenous immunoglobulin.**
- Slowly progressive, distal motor neuropathy which progresses over many years
- **asymmetric** muscle weakness, which is **slowly progressive**, and **without sensory signs**.
- Weakness **without wasting** is another typical feature.
- Differential weakness of finger extension is a typical presentation, and reflects a pathological process which selectively affects particular motor fibres within a peripheral nerve (eg: posterior interosseous branch of the radial nerve).

Investigations

- Nerve conduction studies show areas of conduction block outside usual areas for compression.
- Anti-GM1 antibodies frequently raised

Differential diagnosis

- motor neuron disease (MND)
    - bulbar weakness is common in MND but rare in MMN.
    - variable upper motor neuron signs may occur in MND, contrary to MMN which is a purely lower motor neuron condition occurring in a distribution correlating with named peripheral nerves.
    - whereas MND is usually fatal within 5 years, MMN is slowly progressive over decades and does not typically cause respiratory failure.
- Chronic inflammatory demyelinating polyneuropathy(CIDP)
    - (CIDP) typically causes a progressive sensory and motor neuropathy with loss of reflexes.
    - CSF protein is elevation and nerve conduction studies show evidence of demyelination.
- Inclusion body myositis
    - characteristically causes weakness of finger flexion, as well as knee extension and ankle dorsiflexion.
    - Affected muscles are wasted,
    - fasciculations do not occur as there is no denervation.

Treatment:

- Intravenous immunoglobulin can produce a rapid improvement in weakness.

Diabetic neuropathy (see endocrinology system)

Neuropathic pain

- Neuropathic pain may be defined as pain which arises following damage or disruption of the nervous system.
- It is often difficult to treat and responds poorly to standard analgesia.

Examples include:

- diabetic neuropathy
- post-herpetic neuralgia
- trigeminal neuralgia
- prolapsed intervertebral disc

Management of neuropathic pain (NICE guidance 2013):

- first-line treatment*: amitriptyline, duloxetine, gabapentin or pregabalin
  - *please note that for some specific conditions the guidance may vary. For example carbamazepine is used first-line for trigeminal neuralgia
- if the first-line drug treatment does not work try one of the other 3 drugs
- tramadol may be used as 'rescue therapy' for exacerbations of neuropathic pain
- topical capsaicin may be used for localised neuropathic pain (e.g. post-herpetic neuralgia)
- pain management clinics may be useful in patients with resistant problems

January 2012 exam: severe 'shooting' pains after blistering rash. What is the most appropriate next step in management? Amitriptyline

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Drugs causing peripheral neuropathy

Drugs causing a peripheral neuropathy

- antibiotics: nitrofurantoin, metronidazole
- amiodarone
- **isoniazid**
- vincristine
- tricyclic antidepressants

Autonomic neuropathy

Features

- impotence, inability to sweat, postural hypotension
- postural hypotension e.g. drop of 30/15 mmHg
- loss of decrease in heart rate following deep breathing
- pupils: dilates following adrenaline instillation

Causes

- diabetes
- Guillain-Barre syndrome
- multisystem atrophy (MSA), Shy-Drager syndrome
- Parkinson's
- infections: HIV, Chagas' disease, neurosyphilis
- drugs: antihypertensives, tricyclics
- craniopharyngioma

Hereditary sensorimotor neuropathy (HSMN)

Mixed motor and sensory symptoms, slowly progressing initially in the lower limbs and then to the upper limbs, together with a family history suggests a diagnosis of Hereditary sensorimotor neuropathy (HSMN)

- Hereditary sensorimotor neuropathy (HSMN) is a relatively new term which encompasses **Charcot-Marie-Tooth disease** (also known as peroneal muscular atrophy).
- Over 7 types have been characterised - however only 2 are common to clinical practice

1. HSMN type I: primarily due to demyelinating pathology
2. HSMN type II: primarily due to axonal pathology

HSMN type I

- autosomal dominant
- due to defect in PMP-22 gene (which codes for myelin)
- features often start at puberty
- motor symptoms predominate
- distal muscle wasting, pes cavus, clawed toes
- foot drop, leg weakness often first features

Diagnosis

- Genetic testing usually reveals the diagnosis
- **neurophysiology** : **E**lectro**m**yo**g**raphy (EMG) and **n**erve **c**onduction **s**tudies (NCS) may distinguish between the demyelinating (type 1) and axonal (type 2) forms.

September 2007 exam: A woman with Charcot-Marie-Tooth disease (type 1), how likely her children will get the disease? 50% (autosomal dominant)

Critical illness polyneuropathy

Prolonged periods in the Intensive Therapy Unit, irrespective of the underlying pathology, are associated with a risk of developing critical illness polyneuropathy

- This is an axonal neuropathy and thus muscle wasting may occur
- It may be predominantly sensory, predominantly motor or mixed
- Nerve conduction studies and electromyography may be indicated to confirm the diagnosis and exclude any other condition that may require specific therapy (eg Guillain-Barre syndrome)
- A patient with a previous history of chronic alcohol misuse, diabetes or another condition predisposing to neuropathy may be more prone to developing significant critical illness polyneuropathy

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Mononeuritis multiplex

- Causes of mononeuritis multiplex include
  - Vasculitis
  - Diabetes
  - Sarcoidosis
  - paraneoplastic syndrome
  - amyloidosis
- **nerve biopsy should be performed to confirm the diagnosis**
- Treatment includes prednisolone and cyclophosphamide

Vasculitic neuropathy

- **The presence of nail fold infarcts and the multifocal nature of the neuropathy indicate that a vasculitic cause is most likely**
- Hepatitis C infection may be associated with cryoglobulinaemia, which causes a vasculitic syndrome including neuropathy

Other conditions associated with vasculitic neuropathy include

- Polyarteritis nodosa
- Churg-Strauss syndrome
- rheumatoid arthritis
- systemic lupus erythematosus
- systemic sclerosis
- Wegener's granulomatosis

Treatment include one or several of the following

- high-dose intravenous steroids
- plasma exchange
- intravenous immunoglobulins

Guillain-Barre syndrome

FVC is used to monitor respiratory function in Guillain-Barre syndrome

- also known as **Post-infectious polyradiculopathy**

Definition

- Guillain-Barre syndrome describes an immune mediated demyelination of the peripheral nervous system often triggered by an infection :
  - classically *Campylobacter jejuni*
  - **cytomegalovirus**

Pathogenesis

- cross reaction of antibodies with gangliosides in the peripheral nervous system
- correlation between anti-ganglioside antibody (e.g. anti-GM1) and clinical features has been demonstrated
- **anti-GM1 antibodies in 25%** of patients

Miller Fisher syndrome

Miller Fisher syndrome - areflexia, ataxia, ophthalmoplegia

- variant of Guillain-Barre syndrome
- associated with ophthalmoplegia, areflexia and ataxia. **The eye muscles are typically affected first**
- usually presents as a descending paralysis rather than ascending as seen in other forms of Guillain-Barre syndrome
- **anti-GQ1b antibodies are present in 90% of cases**

Features

- **characteristic features**
  - progressive weakness of all four limbs. The weakness is classically ascending i.e. the lower extremities are affected first, however it tends to affect proximal muscles earlier than the distal ones.
  - Sensory symptoms tend to be mild (e.g. distal paraesthesia) with very few sensory signs. However, a sensory level is NOT a feature and would suggest cervical myelopathy
  - symmetrical involvement is typical, asymmetry present in only 9% of patients.
  - Some patients experience back pain in the initial stages of the illness.
- **Other features**
  - areflexia
  - cranial nerve involvement e.g. diplopia
  - autonomic involvement: e.g. urinary retention
  - Muscle wasting is typical with prolonged illness.
  - **Bulbar involvement occurs in 50%,** with a risk of aspiration and respiratory insufficiency
  - urinary incontinence or retention (in 20% of cases).
- **Less common findings**
  - papilloedema: thought to be secondary to reduced CSF resorption

Investigations

- **(CSF) protein elevated, with normal glucose and no pleocytosis.**
  - CSF cell counts are usually within normal limits,
  - a rise in CSF protein doesn't peak until the second or third week of the illness.
- MRI may be indicated to rule out spinal cord lesions, peripheral neuropathis and neuromuscular junction disorders.

Management

- **IV immunoglobulins (IVIG):**
  - **First line therapy.**
  - as effective as plasma exchange. No benefit in combining both treatments.

  - IVIG may be easier to administer and tends to have fewer side-effects
- plasma exchange
- steroids and immunosuppressants have not been shown to be beneficial
- FVC regularly to monitor respiratory function .
  - **FVC of less than 1 litre would be an indication for immediate ventilation**
  - **Forced vital capacity of 1.4 L is most likely to predict the need for invasive ventilation**
  - FVC of less than 15ml/kg (or less than 30% of FVC predicted) or a rising $PaCO_2$ are indications for mechanical ventilation.

Prognosis

- 20% suffer permanent disability, 5% die

Poor prognostic features

- age > 40 years
- poor upper extremity muscle strength
- **previous history of a diarrhoeal illness (specifically *Campylobacter jejuni*)**
- high anti-GM1 antibody titre
- need for ventilatory support

There is currently contradictory evidence as to whether a gradual or rapid onset of GBS is associated with a poor outcome

Botulism

- **The clinical presentation of descending weakness with autonomic dysfunction (fixed dilated pupils) is typical of botulism.**
- It is a neuromuscular junction disorder and therefore nerve conduction studies and EMG are normal.
- Repetitive nerve stimulation shows incremental responses, which is diagnostic of botulism.
- Cerebrospinal fluid analysis is usually normal.

May 2012 exam: a patient developed weakness in his legs extended to his arms after viral illness. ↓↓ power, reflexes and sensation in his lower limbs. Developed SOB &↓↓ (FVC). Given the likely diagnosis, what is the treatment of choice? Intravenous immunoglobulin
(Guillain-Barre syndrome (GBS) secondary to a viral illness, possibly the **Epstein-Barr virus**)

May 2010 exam: H/O double vision & ↓↓ eye movement + unsteadiness + ↓↓ reflexes + past-pointing. What is the most likely diagnosis? Miller Fisher syndrome

January 2008 exam: Regarding nerve conduction studies for suspected Guillain-Barre syndrome. Which finding would be most consistent with this diagnosis? Reduced conduction velocity

Bickerstaff's encephalitis

- This is a rare immune disorder affecting the brainstem.
- usually preceded by an infection, typically *Campylobacter jejuni*.
- associated with autoantibodies against gangliosides, typically anti-GQ1b IgG, in the serum.
- It causes drowsiness, ophthalmoparesis, ataxia and brisk reflexes.
- **The drowsiness and brisk reflexes can be used to differentiate it from Miller-Fisher.**
- It may be seen on MRI as hyperintensities in the brain stem on T2 weighted images.

Tinnitus

Causes of tinnitus include:

Meniere's disease	**Associated with hearing loss, vertigo, tinnitus and sensation of fullness or pressure in one or both ears**
Otosclerosis	Onset is usually at 20-40 years Conductive deafness Tinnitus Normal tympanic membrane* ➢ *10% of patients may have a 'flamingo tinge', caused by hyperaemia Positive family history
Acoustic neuroma	Hearing loss, vertigo, tinnitus Absent corneal reflex is important sign Associated with neurofibromatosis type 2
Hearing loss	Causes include excessive loud noise and presbycusis
Drugs	Aspirin Aminoglycosides Loop diuretics Quinine

The combination of sensorineural deafness, facial nerve palsy and cranial nerve V involvement suggests a cerebellopontine angle tumour, for example, acoustic neuroma.

Other causes include

- impacted ear wax
- chronic suppurative otitis media

Glomus jugulare tumours

- Glomus jugulare tumours tend to present with **pulsatile tinnitus** and **conductive deafness**.
- Cranial nerves **IX, X and XI which run through the jugular foramen** are also commonly affected to varying degrees.
- Cranial nerves VII and XII may be affected if the tumour enlarges sufficiently.

Meniere's disease

Definition

- Meniere's disease is a **disorder of the inner ear** of unknown cause.
- characterised by excessive pressure and progressive dilation of the endolymphatic system.

Epidemiology

- more common in middle-aged adults but may be seen at any age.
- similar prevalence in both men and women.

Features

- Recurrent episodes of vertigo,
  - ➢ Vertigo is usually the prominent symptom
- tinnitus and **hearing loss (sensorineural).**
- sensation of aural fullness or pressure
- nystagmus
- positive Romberg test
- episodes last minutes to hours
- typically symptoms are unilateral but bilateral symptoms may develop after a number of years

Natural history

- symptoms resolve in the majority of patients after 5-10 years
- the majority of patients will be left with a degree of hearing loss

- psychological distress is common

Management

- ENT assessment is required to confirm the diagnosis
- patients should inform the DVLA. The current advice is to cease driving until satisfactory control of symptoms is achieved
- acute attacks: buccal or intramuscular prochlorperazine.
- Restriction of salt and fluid may hasten resolution.
- prevention: betahistine may be of benefit

Hearing loss

	Conductive hearing loss	Sensorineural hearing loss
Age of Onset	• commonly in **childhood** or young adulthood	• commonly in **middle or late age**
Etiology	• **Otosclerosis** • **Otitis media** • Ear barotrauma • **Cerumen Impaction** • External auditory canal atresia	• **Ménière's disease** • **Acoustic neuroma** • Noise-induced hearing loss • Internal ear infections • **Presbycusis**
Pathophysiology	• **External** or **middle** ear pathology that **disrupts conduction of sound** into the inner ear	• **Inner ear**, **cochlear**, or **auditory nerve** pathology that **impairs neuronal transmission** to the brain
Clinical Features	• **Hearing improves in noisy environments** • Volume of voice remains normal because inner ear and auditory nerve are intact • Sound normally is not distorted • Features of external auditory canal pathology (e.g., cerumen impaction)	• **Hearing worsens in noisy environments** • Volume of voice may be loud because nerve transmissions are impaired • Tend to lose higher frequencies preferentially, such that sounds may be distorted • Absent features of external auditory canal pathology
Weber Test(unilateral hearing loss)	• **Lateralization to impaired ear** (cannot hear ambient room noise well, so detection of vibration is greater)	• **Lateralization to good ear** (sound is not transmitted by damage inner ear or auditory nerve)
Rinne Test(unilateral hearing loss)	• **Bone conduction > air conduction** (vibrations bypass blockage to reach the cochlea)	• **Air conduction > bone conduction** (the inner ear or auditory nerve cannot transmit sound information well regardless of how vibrations reach the cochlea)

Diagnostics

- **Whispered voice test**:
  - ➢ screening to determine extent of hearing loss
- **Rinne test and Weber test**:
  - ➢ to classify hearing loss as **conductive** or **sensorineural**
- **Pneumoscopy**
  - ➢ (evaluates the mobility of the tympanic membrane):
  - ➢ for conductive hearing loss
- **Audiometry**
  - ➢ for all patients without any obvious cause to hearing loss
- **Laboratory tests**

  - (e.g., blood glucose, CBC with differential, TSH, and/or syphilis testing depending on the suspected etiology):
  - for patients with unexplained sensorineural hearing loss
- **MRI or CT scan** (of the posterior fossa)
  - indicated in patients with unilateral, gradual sensorineural hearing loss to exclude **acoustic neuroma**

Rinne's and Weber's test

- Performing both Rinne's and Weber's test allows differentiation of conductive and sensorineural deafness.
- **Rinne's test**
  - tuning fork is placed over the mastoid process until the sound is no longer heard, followed by repositioning just over external acoustic meatus
  - air conduction (AC) is normally better than bone conduction (BC)
  - if BC > AC then conductive deafness
- **Weber's test**
  - tuning fork is placed in the middle of the forehead equidistant from the patient's ears
  - the patient is then asked which side is loudest
  - in unilateral sensorineural deafness, sound is localised to the unaffected side
  - in unilateral conductive deafness, sound is localised to the affected side

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Sensorineural hearing loss

- Sensorineural hearing loss is caused by lesions in the cochlea or the auditory nerve or central connections.
- It may be unilateral or bilateral.
- The overall incidence is about 2 in 1000 children.
- Language acquisition and secondary educational difficulties follow, with social isolation, and an increased risk of mental health problems.

The risk factors for sensori-neural deafness include:

- NICU admission - low birth weight, less than 32 weeks gestation, prolonged ventilation, prolonged jaundice, ototoxic drugs, hypoxic ischaemic encephalopathy, neonatal meningitis
- Congenital infection (rubella, CMV)
- Dysmorphic syndromes (affecting head and neck)
- Family history of a close relative needing a hearing aid below the age of 5 years
- Infections - acute bacterial or TB meningitis, mumps
- **Down syndrome - some 10%-15% of children with Down syndrome develop sensorineural deafness.**

If all risk factors are considered only around 50% of cases could be identified by testing between 5 and 10% of all babies.

Conductive hearing loss

- Conductive hearing loss is related to **middle ear** pathology.
- This is commoner in:
  - **Down syndrome**
    - In Down syndrome: 60%-70& of children develop conductive deafness **due to glue ear.**
    - The eustachaian tube is small and glue ear may begin before the age of 1.
  - cleft palate,
  - Turner's syndrome,
  - facial malformation syndromes.

Motion sickness

Motion sickness - hyoscine > cyclizine > promethazine

- Motion sickness describes the nausea and vomiting which occurs when an apparent discrepancy exists between visually perceived movement and the vestibular systems sense of movement

- **Management**
  - the BNF recommends hyoscine (e.g. transdermal patch) as being the most effective treatment.
    - Use is limited due to side-effects
  - non-sedating antihistamines such as cyclizine or cinnarizine are recommended in preference to sedating preparation such as promethazine

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DVLA: neurological disorders

DVLA advice post CVA: cannot drive for 1 month

DVLA advice post multipler TIAs: cannot drive for 3 months

- The guidelines below relate to car/motorcycle use unless specifically stated.
- For obvious reasons, the rules relating to drivers of heavy goods vehicles tend to be much stricter

Specific rules

- **first seizure**: **6 months** off driving*.
  - *previously rule was 12 months. It is now 6 months off driving if the licence holder has undergone assessment by an appropriate specialist and no relevant abnormality has been identified on investigation, for example EEG and brain scan where indicated

- For patients with **established epilepsy** they must be fit free for **12 months** before being able to drive
- **stroke or TIA**: **1 month** off driving
- **multiple TIAs** over short period of times: **3 months** off driving
- **craniotomy** e.g. For meningioma: **1 year** off driving
  - if the tumour is a **benign meningioma** and there is **no seizure** history, licence can be reconsidered **6 months** after surgery if remains seizure free
- pituitary tumour:
  - craniotomy: 6 months;
  - trans-sphenoidal surgery 'can drive when there is no debarring residual impairment likely to affect safe driving'
- narcolepsy/cataplexy:
  - cease driving on diagnosis,
  - can restart once 'satisfactory control of symptoms'
- chronic neurological disorders e.g. multiple sclerosis, motor neuron disease:
  - DVLA should be informed,
  - complete PK1 form (application for driving licence holders state of health)
- **Syncope**
  - simple faint: no restriction
  - single episode, explained and treated: 4 weeks off
  - single episode, unexplained: 6 months off
  - two or more episodes: 12 months off

Susac syndrome

- Susac syndrome presents with the **triad of:**
  - **Encephalopathy**
  - **branch retinal artery occlusion**
  - **and hearing loss**

due to involvement of the pre-capillary arterioles of the brain, retina and cochlea.

- Most commonly women in the age range 20-40 years are afflicted.
- Encephalopathy is often severe and associated with MRI changes due to corpus callosum micro infarcts.

- Branch retinal artery occlusion in Susac is associated with retinal arterial wall plaques (Gass plaques) on fundoscopy and distinctive patterns of arterial wall hyper-fluorescence on fluorescein angiography.
- Hearing loss is of low or middle frequencies and can be profound and require cochlear implants.
- The aetiology of the microangiopathy in Susac syndrome remains unproven. Recent literature highlights the similarity between the microvascular changes observed in Susac syndrome and juvenile dermatomyositis, with preliminary evidence that that Susac syndrome pathogenesis may be associated with anti-endothelial cell antibodies.
- No clinical trials of treatment in Susac syndrome have been conducted. Reported treatment strategies involve steroids followed by immunosuppressive therapy including cyclophosphamide, mycophenalate mofetil, azathioprine, cyclosporin, immunoglobulins or plasma exchange.

Glasgow coma scale (GCS)

- The Glasgow coma scale (GCS) can be useful as a predictor of outcome and a way to measure and monitor patients with reduced consciousness.
- It is made up of three components: eye opening, best verbal response and best motor response. Each of these is scored, as shown below.

Eye opening:

Spontaneously	4
To speech	3
To painful stimulus	2
No response	1

Best verbal response:

Orientated	5
Disorientated	4
Inappropriate words	3
Incomprehensible sounds	2
No response	1

Best motor response:

Obeys verbal commands	6
Localises painful stimuli	5
Withdrawal to pain	4
Flexion to pain	3
Extension to pain	2
No response	1

- The GCS defines coma as E = 2, V = 2, M = 4 or less.
- The GCS is meaningless unless it is broken down into its components.
- It is important to note that the GCS is unreliable and should not be applied to patients who are inebriated, intubated or who have a therapeutic or traumatic paralysis.

Altitude related disorders

Types

- There are three main types of altitude related disorders:
- All three conditions are due to the chronic hypobaric hypoxia which develops at high altitudes
    1. **acute mountain sickness (AMS),**
        - **Features** of AMS start to occur above 2,500 - 3,000m,
        - developing gradually over 6-12 hours and potentially last a number of days
            - headache
            - nausea
            - fatigue
        - Prevention and treatment of AMS
            - the risk of AMS may actually be positively correlated to physical fitness
            - gain altitude at no more than 500 m per day
            - acetazolamide (a carbonic anhydrase inhibitor) is widely used to prevent AMS and has a supporting evidence base
        - Treatment:
            - Descent
            - generally a self-limiting condition.
    2. **high altitude pulmonary edema (HAPE)**
        - A minority of people above 4,000m go onto develop high altitude pulmonary oedema (HAPE)
        - potentially fatal conditions
        - HAPE presents with classical pulmonary oedema features
        - Management of HAPE
            - descent
            - nifedipine, dexamethasone, acetazolamide, phosphodiesterase type V inhibitors
                - ⇨ All seem to work by reducing systolic pulmonary artery pressure
            - oxygen if available
    3. **high altitude cerebral edema (HACE).**
        - A minority of people above 4,000m go onto develop high altitude cerebral oedema (HACE),
        - potentially fatal conditions
        - HACE presents with headache, ataxia, papilloedema
        - Management of HACE
            - descent
            - dexamethasone

Complex regional pain syndrome (CRPS)

- (CRPS) is the modern, umbrella term for a number of conditions such as reflex sympathetic dystrophy and causalgia.
- (CRPS) is a chronic pain condition that can affect any area of the body, but often affects an arm or a leg, and occurs after an injury or rarely after a sudden illness such as a heart attack or stroke.
    - ➢ typically occur following surgery or a minor injury.
- The condition can sometimes appear without obvious injury to the affected limb.
- 3 times more common in women.
- CRPS may have three stages (acute, dystrophic, and atrophic), with variable progression from one stage to another.

There are two types of CRPS:

- **type I (most common): there is no demonstrable lesion to a major nerve**
- type II: there is a lesion to a major nerve

Character of the pain

- intense and burning
- disproportionate to the original injury
- worse over time

- Spreads beyond the site of injury and
- associated with hyperalgesia, hyperpathia or allodynia on examination. These features do not occur in DVT, osteomyelitis, or cellulitis.

Features

- progressive, disproportionate symptoms to the original injury/surgery
- allodynia
- temperature and skin colour changes
- oedema and sweating
- motor dysfunction
- the Budapest Diagnostic Criteria are commonly used in the UK

Diagnosis

- clinical diagnosis
- **Plain radiographs** may show soft tissue swelling, peri-articular osteoporosis, and rarely erosions
- **MRI** may also show bone marrow oedema apart from these changes
  - ➢ In the atrophic phase, imaging may show contractures.
- 99mTc bone scan shows hypervascularity in the acute phase, and hypovascularity in the

Management

- early physiotherapy is important
- neuropathic analgesia in-line with NICE guidelines
- specialist management (e.g. Pain team) is required

Cheyne-Stokes breathing

- Cheyne-Stokes is a type of central sleep apnoea in which there is loss of chest and abdominal movements and crescendo-decrescendo breathing in a repetitive fashion.
- **Two-thirds of cases of Cheyne-Stokes breathing appear to have heart failure.(the most common finding in Cheyne-Stokes breathing)**
- Stroke and metabolic dysfunction can also result in Cheyne-Stokes apnoea but are not as common as heart failure.
- Treatments include diuretics and non-invasive ventilation.

Orbital apex syndrome

- **The combination of optic neuropathy, proptosis, chemosis, Horner syndrome, ophthalmoplegia and involvement of the first branch of the trigeminal nerve is typical of orbital apex syndrome**
- The presence of proptosis, with swelling of eyelids and chemosis (swelling of the ocular surface membrantes),indicates significant mass extension within the orbit
- The orbital apex syndrome (involvement of cranial nerves II, III, IV and V1) is a superior orbital fissure syndrome with loss of vision

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Causes of absent ankle reflexes and extensor plantars include

- Subacute combined degeneration of the cord (posterior column signs, positive Romberg's sign, anaemia, splenomegaly)
- Syphilitic taboparesis
- Friedreich's ataxia
- Motor neurone disease.

Prolonged neuromuscular junction (NMJ) blockade

- may be exacerbated by both corticosteroids and magnesium.
- This condition was originally described with suxamethonium due to hereditary reductions in plasma cholinesterase activity.
- However, drugs and electrolyte abnormalities may exacerbate this.

Neuromyelitis optica

- Neuromyelitis optica is a demyelinating disease involving the optic nerves and spinal cord but sparing the brain.
- **The specific test for this is the NMO antibody which is against aquaporin 4.**

Neurodegenerative disease

- TAR DNA-binding protein 43 **(TDP-43) is associated with neurodegenerative diseases** including dementia and motor neuron disease.

Balint's syndrome

- triad of:
  1. (simultanagnosia) → inability to perceive the visual field as a whole
  2. (oculomotor apraxia) → difficulty in fixating the eyes (difficultly shifting gaze)
  3. (optic ataxia) inability to move the hand to a specific object by using vision
     - **Examining for optic ataxia can be done by Controlling hand-eye coordination** asking the patient to reach out and touch an object.
     - Unlike cerebellar problems there is no tremor.
     - The patient clearly grabs in the wrong part of space and does not attempt to correct unlike cerebellar lesions.

Dystonia

Definition:

- involuntary sustained or spasmodic muscle contractions

Types

- **Focal dystonias**
  - Involves a single body part
  - Cervical dystonia, or torticollis, is the most common focal dystonia.
  - In 20-30% of patients, focal dystonias become segmental or multifocal.
  - **writer's cramp dystonia** or musician's dystonia
    - A common upper limb dystonia
    - This task-specific dystonia, manifesting as hyperextension or hyperflexion of the wrist and fingers, → **unable to write**
    - may be triggered by repetitive activities such as writing and attempting to play the piano or other musical instruments.
  - often relieved by a geste antagoniste, in which palpation of another unaffected part of the body leads to relief of symptoms, thought to be a result of alternative sensory input to cortical networks with altered plasticity.
- segmental
  - Affects 2 or more contiguous regions of the body
- Multifocal dystonia - Consists of abnormalities in noncontiguous body parts
- generalised dystonias, which involve a greater number of muscle groups.
  - involves the trunk and limbs.

Cervical dystonia (torticollis)

- The term *torticollis* is derived from the Latin words *tortus* for twisted neck
- Torticollis is a fixed or dynamic tilt, rotation, or flexion of the head and/or neck.
- involuntary neck movements
- commonly affects women
- Secondary causes need to be excluded such as drugs (eg neuroleptics) and cervical spine abnormalities
- **Botulinum toxin injection is the first-line treatment for cervical dystonia (torticollis)**

Botulinum toxin

- **Botulinum toxin is produced by Clostridium botulinum, a Gram-positive, spore-forming, obligate anaerobe**
- Botulinum toxin type A (or trade name Botox®)

Action

- The primary action of the toxin is to block acetylcholine release at the neuromuscular junction and so to produce muscle weakness.
- myasthenia gravis would be expected to **worsen** with this treatment

Indications

- **Botulinum toxin is the treatment of choice for focal dystonia (such as torticollis, and hemi-facial spasm) and focal dystonia.**
- Botulinum toxin injections are also used in patients with:
  - hemifacial spasm
  - blepharospasm
  - spasticity
    - spasticity associated with stroke
    - spasticity associated with cerebral palsy
  - Primary axillary hyperhidrosis
  - Strabismus
  - Cervical dystonia.

Side effects

- Occasionally **systemic absorption of the toxin can affect distal muscles causing symptoms such as diplopia and dysphagia.**
- The main side-effect is excessive weakness in the treated muscle

Contra-indications

- myasthenia gravis
- other generalised muscle conditions

Paraneoplastic cerebellum syndrome

- **The patient with progressive ataxia and dysarthria following malignancy**
- features include ataxia, dysarthria, vertigo, oscillopsia, nystagmus and dysmetria
- Associated malignancies are lung cancer, breast cancer, ovarian cancer and lymphoma
- Brain imaging and CSF analysis are either normal or show non-specific changes
- Serum and CSF may contain anti-Purkinje-cell antibodies
- Occasionally patients respond to steroids, immunoglobulins or plasmapheresis.

Glioblastoma multiforme

- Glioblastoma multiforme (or anaplastic astrocytoma) is the highest grade (most malignant) form of astrocytoma,
- **accounts for about 20% of all cerebral tumours**
- often remain clinically silent until they have reached a large size
- About half occupy more than one hemisphere at presentation, and some are multicentric
- **Feature** : headache, seizure, hemiparesis
- CT brain scan shows → multicentric mass lesion with surrounding vasogenic oedema and some hemisphere shift.
- Biopsy shows high cellularity with mitoses, pleomorphism and vascular hyperplasia
- **Prognosis** is extremely poor with only 20% surviving beyond 1 year and 10% beyond 2 years
- **Treatment** may consist of surgical debulking, external-beam radiotherapy and chemotherapy
- Recent research has focused on the possibility of gene therapy
- A UK trial of intratumoural injections of modified herpes simplex virus, aiming to create local tumour necrosis, is underway

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Parinaud's Syndrome

- also known as **dorsal midbrain syndrome** and **vertical gaze palsy**,
- **results from dorsal midbrain lesion**
- It is caused by a **tumor of the pineal gland** which compresses the vertical gaze center at the rostral interstitial nucleus of medial longitudinal fasciculus (riMLF).
- **Feature**
  - **Inability to move the eyes up**. Downward gaze is usually preserved
  - convergent nystagmus (Attempts at upward gaze often produce this phenomenon),
  - mydriasis
  - impaired pupillary reflexes

- **Eyelid retraction (Collier's sign):** sclera can be seen above the cornea, and further upgaze increases the distance between the eyelids and irises

Peripheral nerves

Upper limb anatomy

The information below contains selected facts which commonly appear in examinations:

Nerve	Motor	Sensory	Typical mechanism of injury & notes
Musculocutaneous nerve (C5-C7)	Elbow flexion (supplies biceps brachii) and supination	Lateral part of the forearm	Isolated injury rare - usually injured as part of brachial plexus injury
Axillary nerve (C5,C6)	**Shoulder abduction (deltoid muscle)**	Inferior region of the deltoid muscle	Humeral neck fracture/dislocation Results in **flattened deltoid**
Radial nerve (C5-C8)	**Extension** (forearm, wrist, fingers, thumb)	Small area between the dorsal aspect of the 1st and 2nd metacarpals	Humeral midshaft fracture Palsy results in **wrist drop**
Median nerve (C6, C8, T1)	LOAF* muscles Features depend on the site of the lesion: • wrist: paralysis of thenar muscles, opponens pollicis • elbow: loss of pronation of forearm and weak wrist flexion	Palmar aspect of lateral **3** and half fingers	Wrist lesion → carpal tunnel syndrome
Ulnar nerve (C8, T1)	Intrinsic hand muscles except LOAF* Wrist flexion	Medial **1**and half fingers	Medial epicondyle fracture Damage may result in a **'claw hand'**
Long thoracic nerve (C5-C7)	**Serratus anterior**		Often during sport e.g. following a blow to the ribs. Also possible complication of mastectomy **Damage results in a winged scapula**

*__LOAF muscles__

- **L**ateral two lumbricals
- **O**pponens pollis
- **A**bductor pollis brevis
- **F**lexor pollis brevis

Erb-Duchenne palsy ('waiter's tip')

- due to damage of the upper trunk of the brachial plexus (C5,C6)
- may be secondary to shoulder dystocia during birth
- the arm hangs by the side and is internally rotated, elbow extended

Radial nerve

Overview

- arises from the posterior cord of the brachial plexus **(C5-8)**

Motor to

- **extensor muscles (forearm, wrist, fingers, thumb)**
- The radial nerve supplies:
  - Triceps
    - myotome of **tri**ceps and extensor digitorum is **C7**
    - Both radial nerve palsy and C7 radiculopathy can cause an absent triceps jerk
  - brachioradialis,
    - myotome of brachioradialis is **C6**
  - extensor carpi radialis longus (extensor digitorum profundus)
  - extensor muscles of the forearm (via the **posterior interosseous nerve**).
    - **The posterior interosseous nerve**
      - **innervates the extensor carpi ulnaris, extensors of the metacarpo-phalangeal joints and thumb extensors**
      - pure motor nerve

Sensory to

- dorsal aspect of lateral 3 1/2 fingers
- The commonest site of sensory loss is at the **anatomical snuffbox**
  - small area between the dorsal aspect of the 1st and 2nd metacarpals

Patterns of damage

- **wrist drop** with hand pronation and thumb adduction
- sensory loss to small area between the dorsal aspect of the 1st and 2nd metacarpals

Axillary damage

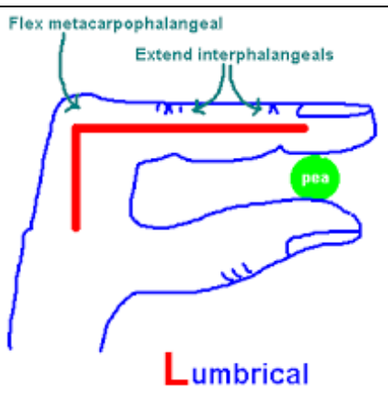
- as above
- paralysis of triceps

Site of lesion	Sensory symptoms	Motor symptoms
Axilla	• All below	• All below • Paralysis of triceps m
Mid-arm	• All below • Numbness, paresthesia, pain along lateral posterior arm	• All below • **Wrist drop** ➢ weakness of extensors (hand, finger and wrist joint).
Elbow (radial tunnel)	• Pain and tenderness following extension or repetitive pronation/supination	• Sometimes weakness of extension and supination, secondary to pain (not to missing innervation)
Deep Forearm (posterior interosseous nerve)	• **None**	• Paralysis of the finger extensors (**no true wrist drop**)
Superficial forearm and wrist (superficial radial nerve)	• Deficits on the radial side of the dorsum of the hand (thumb, index finger, and the radial half of the middle finger)	• **None**

Median nerve

Overview

- arises from lateral and medial cords of the brachial plexus (C6-8, T1)
- Motor to (LOAF)



When look at hand in this position, can see this makes an "L" shape, since L Lumbrical.

- **L**ateral two lumbricals
- **O**pponens pollicis → rotates and flexes the thumb
- **A**bductor pollicis brevis → **Ab**duction and opposition of the thumb
- **F**lexor pollicis brevis → Flexes the thumb at the first metacarpophalangeal joint

- the above three form the **thenar eminence muscles**
- also supplies flexor muscles of the forearm

Sensory to

- palmar aspect of lateral (radial) 3 1/2 fingers

Patterns of damage

- **Damage at wrist**
  - e.g. carpal tunnel syndrome
  - paralysis and wasting of thenar eminence muscles
  - sensory loss to palmar aspect of lateral (radial) 3 1/2 fingers
- **Damage at elbow, as above plus:**
  - unable to pronate forearm
  - **weak wrist flexion**
  - **ulnar deviation of wrist**
- **Anterior interosseous nerve** (branch of median nerve)
  - leaves just below the elbow
  - results in loss of pronation of forearm and weakness of long flexors of thumb and index finger

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Carpal tunnel syndrome

Carpal tunnel syndrome is caused by **compression of median nerve in the carpal tunnel**.

Causes

- idiopathic
- pregnancy
- oedema e.g. heart failure
- lunate fracture
- **rheumatoid arthritis**

History

- pain/pins and needles in thumb, index, middle finger
- unusually the symptoms may 'ascend' proximally
- patient shakes his hand to obtain relief, classically at night

Examination

- weakness of thumb abduction (abductor pollicis brevis)
- wasting of thenar eminence (NOT **hypo**thenar → supplied by ulnar nerve)
- **T**inel's sign: **t**apping causes paraesthesia
- **Ph**alen's sign: **f**lexion of wrist for 60 seconds causes symptoms
- **Which area supplied by the median nerve will be spared if the problem is at the carpal tunnel?**

- **the skin over the thenar eminence**
  - **The palmar cutaneous branch of the median nerve** lies superficial to the flexor retinaculum and does not pass through the carpal tunnel. It supplies the skin over the thenar eminence, which is therefore spared in carpal tunnel syndrome.

Electrophysiology

- **The most appropriate further investigation → Electromyogram (EMG)/nerve conduction studies**
  - (EMG)/nerve conduction study is useful for confirming clinical diagnosis prior to actual surgery.
  - nerve conduction studies show:
    - **decreased conduction velocity** in the median nerve.
    - **prolongation of the action potential**

Treatment

- In patients with mild carpal tunnel syndrome the management should be behavior modification.
- corticosteroid injection
- wrist splints at night
- surgical decompression (flexor retinaculum division)

Pronator teres syndrome

Definition

- entrapment of the **median nerve** between the two heads of the pronator teres muscle **at the elbow**

Features

- **The characteristic physical finding is tenderness over the proximal median nerve, which is aggravated by resisted pronation of the forearm.**

Diagnosis

- Examination involves excluding carpal tunnel syndrome and pronation of the affected forearm against resistance, which brings on the pain.
  - Unlike carpal tunnel syndrome, the median nerve proximal to the wrist may be tender to palpation.

Treatment

- Injection of corticosteroids into the pronator teres muscle may produce relief of symptoms, but a strong response to a steroid injection would be more consistent with carpal tunnel syndrome

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Anterior interosseous syndrome

Definition

- Anterior interosseous syndrome or **Kiloh-Nevin syndrome** is a damage to the anterior interosseous nerve (AIN),
- The anterior interosseous nerve is a **motor branch of the median nerve**, which **arises just below the elbow**. It passes distally in the anterior interosseous membrane and **innervates the long flexor muscles of the thumb** (Flexor pollicis longus) **(FPL), index and middle finger** (flexor digitorum profundus) **(FDP).**

Causes

- neuritis (inflammation of the nerve) in most cases
- compression of the AIN can happen.
- Trauma to the median nerve

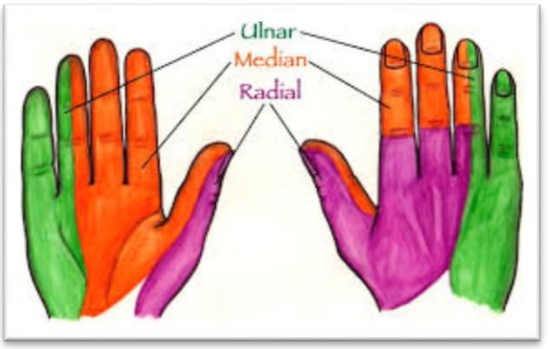
Feature

- pain in the forearm
- **characteristic weakness of the pincer movement of the thumb and index finger.**
- If asked to make the "OK" sign, patients will make a triangle sign instead.
  - This 'Pinch-Test' exposes the weakness of the Flexor pollicis longus muscle and the flexor digitorum profundus leading to weakness of the flexion of the distal phalanges of the thumb and index finger.
- **difficulty picking up a small item, such as a coin, from a flat surface**

Diagnosis

- Electromyography (EMG) is generally most useful and will reveal abnormalities in the flexor pollicis longus, flexor digitorum profundus I and II and pronator quadratus muscles.

Ulnar nerve



Overview

- arises from medial cord of brachial plexus **(C8, T1)**

Motor to

- medial two lumbricals
- adductor pollicis → **Adduction of the thumb**
- interossei
- hypothenar muscles: opponens digiti minimi, abductor digiti minimi, flexor digiti minimi
- flexor carpi ulnaris

Sensory to

- medial 1 1/2 fingers (palmar and dorsal aspects)

Patterns of damage

- **Damage at wrist**
  - 'claw hand' - hyperextension of the metacarpophalangeal joints and flexion at the distal and proximal interphalangeal joints of the 4th and 5th digits
  - wasting and paralysis of intrinsic hand muscles (except lateral two lumbricals)
  - wasting and paralysis of hypothenar muscles
  - sensory loss to the medial 1 1/2 fingers (palmar and dorsal aspects)
- **Damage at elbow**
  - **the commonest site** for entrapment of ulnar nerve
  - may be due to chronic pressure, leaning on the elbows, and direct trauma.
  - results in numbness in the 5th finger, the medial aspect of the ring finger and the dorsum of the hand over the 5th finger.
  - weakness of the small muscles of the hand and, if allowed to progress, a **claw hand** develops where the little and ring fingers curl into the palm.
  - radial deviation of wrist
- **ulnar neuropathy is a common complication with ill patients in hospital.**
- **Nerve conduction studies will confirm the site of the lesion.**

MRCPUK-part-1-sep 2017: H/O dropping things on a frequent basis and muscle wasting at the back of the right hand. On examination, you note wasting of the dorsal interossei. What is the nerve supply of the dorsal interossei?

→ C8/T1

Neuralgic amyotrophy (Brachial neuritis)

- Neuralgic amyotrophy is an inflammatory process that affects the **brachial plexus**

Precipitating factors:

- Recent trauma, (minor trauma)
- **infection**, usually proceeded by an **upper respiratory tract infection**
- surgery, or even vaccination.
- Rarely it may be hereditary.

Feature

- usually presents with severe **pain** (pain over the deltoid region) for days to weeks followed by **weakness** and **sensory loss** over the corresponding **territory of the brachial plexus** **(more commonly C5-7).**
  - winging of the scapula (**C 5, 6, 7**)
  - shoulder abduction weakness (**C 5**)
  - sensory loss over the lateral aspect of the shoulder (**C 5**)
  - absent triceps reflex (**C 7**)
  - Weakness of elbow extension (**C7**)
- There may be subsequent rapid wasting of the arm muscles in accordance to which nerve is involved.

Investigations

- **Electrical studies** confirm denervation in affected muscles
- The **CSF** is usually normal but may show a **slightly elevated protein** level and a **small lymphocytosis**

Treatment

- It is **self-limiting** condition but recovery may be slow (**years**).
- The **prognosis** is usually **good except when the phrenic nerve is involved** since this can result in significant **breathlessness**.

Klumpke's paralysis (damage to the T1 nerve root) → median & ulnar damage

- due to damage of the lower trunk of the brachial plexus (C8, T1)
- This root eventually supplies the median and ulnar nerves.
- The ulnar nerve supplies all of the intrinsic hand muscles except for those of the thenar eminence and the **first and second lumbricals which are innervated by the median nerve.**
- **Causes**
  - sudden upward jerk of the hand
  - associated with Horner's syndrome
  - may be secondary to shoulder dystocia during birth.
- **Feature**
  - **global wasting of the small hand muscles,**
  - **sensory loss over the medial border of the forearm around the elbow.**
  - sensory disturbance affecting the medial half of the ring finger and little finger.

Stretching injury of the arm

- Sudden upward movement of the abducted arm (fall that has been stopped by grasping a fixed object with one hand) → causes features of an ulnar nerve palsy which is supplied by the **lower brachial plexus** roots C8 and T1 (Klumpke's paralysis)

Common peroneal nerve lesion (L5, S1)

The commonest cause of acute foot drop after prolonged bed rest is entrapment common peroneal neuropathy at the neck of fibula.

Anatomy:

The sciatic nerve divides into the tibial and common peroneal nerves in the popliteal fossa.

Common peroneal nerve divides into a superficial and a deep branch

- deep peroneal nerve supplies muscles, which **dorsiflex the foot and toes**:
  - tibialis anterior
  - extensor hallucis longus
  - extensor digitorum longus
- superficial nerve supplies the muscles, which **evert the foot**
  - peroneus longus and brevis

Injury often occurs at the neck of the fibula.

Features:

- The most characteristic feature of a common peroneal nerve lesion is **foot drop**
- **Other features include:**
  - weakness of foot dorsiflexion
  - weakness of foot eversion

- weakness of extensor hallucis longus
- **Sensory loss over the dorsum of the foot and the lower lateral part of the leg with sparing of the fifth toe.**
- wasting of the anterior tibial and peroneal muscles

foot-drop is usually due to either a L4-5 radiculopathy or a common peroneal nerve palsy (eversion and dorsiflexion are weak with both whilst **ankle inversion is spared with the latter**)

Meralgia paraesthetica

Burning thigh pain - ? meralgia paraesthetica - lateral cutaneous nerve of thigh compression

Basics

- caused by compression of lateral cutaneous nerve of thigh
- typically burning sensation over antero-lateral aspect of thigh
- pure sensory loss
- It is usually a consequence of **entrapment at the lateral inguinal ligament** or less likely, trauma, ischaemia, or a retroperitoneal lesion.

May 2006 exam: **A patient presents with a burning sensation over antero-lateral aspect of thigh. Which nerve is most likely to be affected? Lateral cutaneous nerve of thigh**

Sciatic nerve palsy

- Sciatic nerve palsy is a known complication of a total hip replacement (femoral nerve palsy can occur but is much less common).
- It causes **global weakness of the ankle** due to the involvement of both of its branches: tibial nerve (plantaflexion and inversion) and common peroneal nerve (dorsiflexion and eversion).
- **ankle jerk is absent due to tibial nerve involvement**.
- Sensory loss is variable but most commonly occurs around the dorsum of the foot and lateral aspect of the leg

Other notes

- Obturator nerve palsy causes → weakness of hip adduction

Femoral nerve palsy (L234)

Causes:

- Psoas haematoma (due to anticoagulant therapy or haemophilia), Psoas abscess
- Diabetic amyotrophy (proximal neuropathy, seen in patients with diabetes, causes burning pain in the hip and thigh and wasting of thigh muscles)
- Trauma - hip or pelvic fractures
- Tumours - eg: Synovial cyst, Sarcoma
- Iatrogenic: eg: Hip arthroplasty, Pelvic surgery, Coronary angiography.

Feature

- instability of the knee (often described as 'buckling') on climbing stairs.
- weakness of **knee extension** (quadriceps) and **hip flexion** (iliopsoas)
- **absent knee jerk**
- The weakness is typically acute or subacute, (in contrast to that caused by myopathy, in which the onset is often gradual and usually bilateral).
- Decreased sensation in anterior thigh (anterior femoral cutaneous nerve) (meralgia paraesthetica) and medial distal leg(saphenous nerve)

lumbosacral plexopathy

The patient presents with generalised weakness of the right leg associated with pelvic pain, leg oedema and autonomic dysfunction. The most likely diagnosis is a lumbosacral plexopathy.

- Anatomically, the lumbosacral plexus consists of lumbar (L1-L4) and sacral (L5-S5) portions, which are connected by the lumbosacral trunk (L4-L5).
- **Upper lumbar plexus** lesion will cause weakness of hip flexion and adduction of the thigh and extension of the leg with anaesthesia over the anterior thigh and leg.
- **Lower plexus lesions** will weaken the posterior thigh and foot muscles. Lesions affecting the entire plexus will affect all muscle groups causing weakness or paralysis of the leg, areflexia and anaesthesia from the toes, to involve the perianal area.

Diabetic Lumbosacral Plexopathy (diabetic amyotrophy)

- Pathology → immune vasculopathy
- pain in the hip and thigh.
- asymmetrically weakness and wasting of the thigh muscles,
- lumbar puncture results may show elevated (CSF) proteins.
- Management
  - Good glycemic control
  - Physiotherapy
- Prognosis
  - Good functional recovery within 12-24 months is expected in 60%

Neoplastic lumbosacral Plexopathy

- incidence is 0.71%.
- most commonly due to intra-abdominal tumor extension (73% of cases)
  - The most prevalent types of tumors are colorectal tumors (20%)
- occurs less commonly with growth from metastases, lymph nodes, or bone structures.
  - The most common distant metastatic lesions are caused by breast cancer.
- The lower (sacral) plexus is involved most frequently
- characterized by significant pain and sensorimotor deficits.
- diagnosis is confirmed by (MRI) or (CT) scanning of the affected areas.
  - MRI is preferred because it is more sensitive and provides better detail than CT
- Treatment
  - Medical or surgical treatment of the carcinoma when possible is the first treatment of choice.
  - The most commonly used treatment with such plexopathy involves radiation treatment.
    - improvement noted in 85%
  - Neuropathic pain may respond to nerve stimulation, antidepressants, and antiepileptics.

Radiation-Induced Lumbosacral Plexopathy

- The mechanism may be related to a combination of localized ischemia and subsequent soft-tissue fibrosis due to microvascular insufficiency.
- noted in 1.3% of patients after abdominal irradiation and in 0.32% of patients after pelvic irradiation.
- The median symptom-free interval for radiation-induced lumbosacral plexopathy, from treatment to the initial neurologic symptom, is 5 years
  - most commonly present with painless weakness
  - Weakness is asymmetrical
  - commonly are bilateral (80%) and asymmetrical.
- Treatment
  - tricyclic antidepressants or antiepileptic agents (eg, gabapentin, carbamazepine).

Saphenous nerve

- **The saphenous nerve supplies the skin over the anteromedial side of the knee, leg and medial malleolus.**
- can be injured in such procedures as:
  - femoral artery catheterization for angiography,
  - saphenous vein harvest for coronary artery bypass grafting or
  - long saphenous vein stripping for varicose veins.

Tarsal tunnel syndrome

- also, known as posterior tibial neuralgia
- **Caused by entrapment of the posterior tibial nerve** as it travels through the tarsal tunnel, this tunnel is found along the inner leg behind the medial malleolus → painful foot

Lower limb anatomy

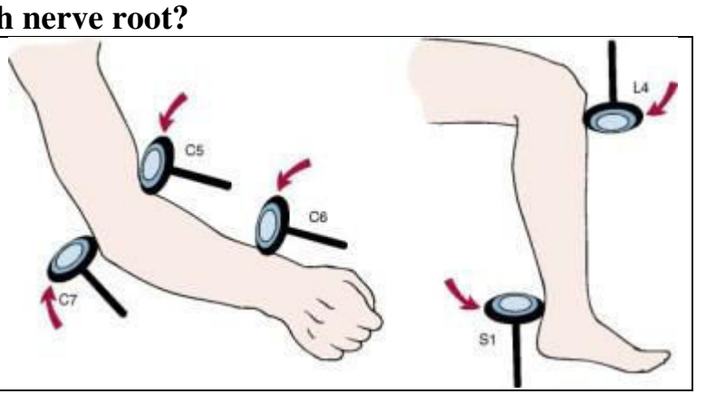
The information below contains selected facts which commonly appear in examinations:

Nerve	Motor	Sensory	Typical mechanism of injury & notes
Femoral nerve	Knee extension, thigh flexion	Anterior and medial aspect of the thigh and lower leg	Hip and pelvic fractures Stab/gunshot wounds
Obturator nerve	**Thigh adduction**	Medial thigh	**Anterior hip dislocation**
Lateral cutaneous nerve of the thigh	None	Lateral and posterior surfaces of the thigh	Compression of the nerve near the ASIS → meralgia paraesthetica, a condition characterised by pain, tingling and numbness in the distribution of the lateral cutaneous nerve
Tibial nerve	Foot plantarflexion and inversion	Sole of foot	Not commonly injured as deep and well protected. Popliteral lacerations, posterior knee dislocation
Common peroneal nerve	Foot dorsiflexion and eversion Extensor hallucis longus	Dorsum of the foot and the lower lateral part of the leg	Injury often occurs at the neck of the fibula Tightly applied lower limb plaster cast Injury causes foot drop
Superior gluteal nerve	Hip abduction	None	Misplaced intramuscular injection Hip surgery Pelvic fracture Posterior hip dislocation **Injury results in a positive Trendelenburg sign**
Inferior gluteal nerve	Hip extension and lateral rotation	None	Generally injured in association with the sciatic nerve Injury results in difficulty rising from seated position. Can't jump, can't climb stairs

Nerve roots

Deep tendon reflexes: which test for which nerve root?

C5 – Biceps
C6 – Biceps, Brachioradialis
C7 – Triceps
L4 – Patellar (knee jerk)
S1 – Achilles (ankle jerk)



- Brachioradialis is the "supinator" reflex and it is mediated by C5/6.
- Deltoid is supplied by C5/6.
- Ankle reflex (tibial nerve mediated)
- knee reflex (femoral nerve mediated)

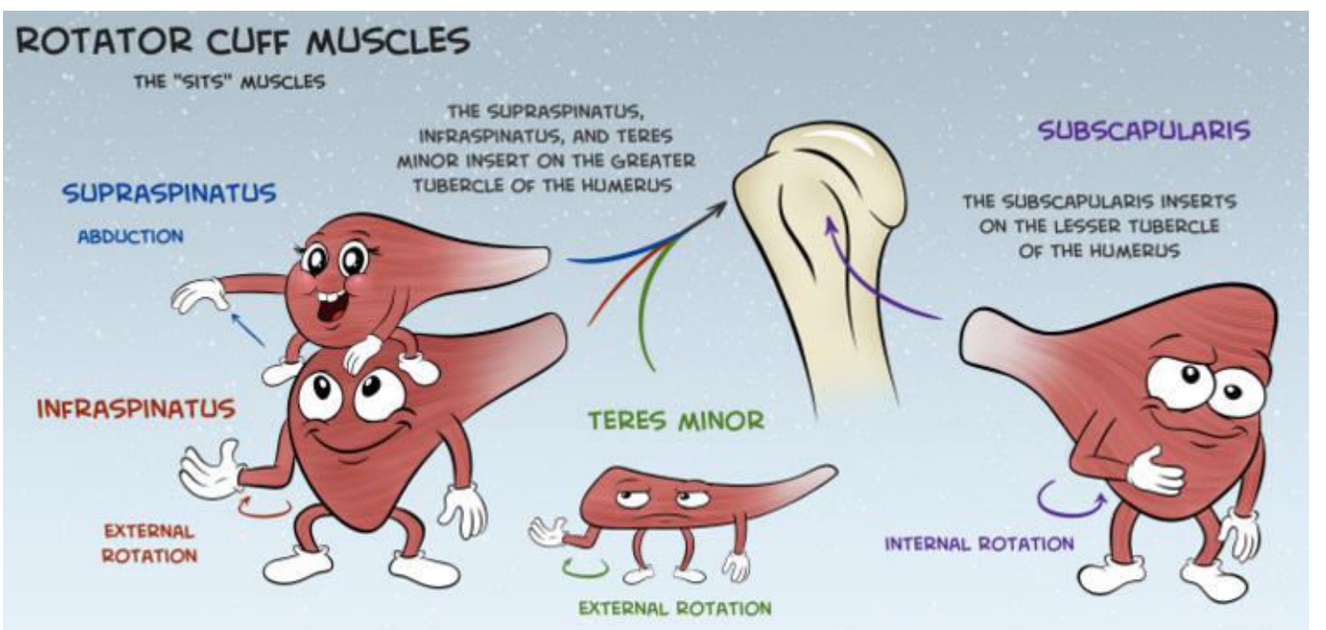
- **spinal lesion at the level of C8**→ Weakness of finger flexion
  → Loss of sensation over the **medial** aspect of the arm; forearm and hand (**Lateral** aspect of arm is **C5**)

Winging of the scapula is caused by paralysis of the long thoracic nerve to serratus anterior (C5, 6, 7).

Which nerve (and its nerve root) are you tested in triceps reflex?
➔ Radial nerve C7

Rotator cuff muscles

Muscle	Notes
Supraspinatus	aBDucts arm before deltoid Most commonly injured
Infraspinatus	Rotates arm laterally
teres minor	aDDucts & rotates arm laterally
Subscapularis	aDDuct & rotates arm medially



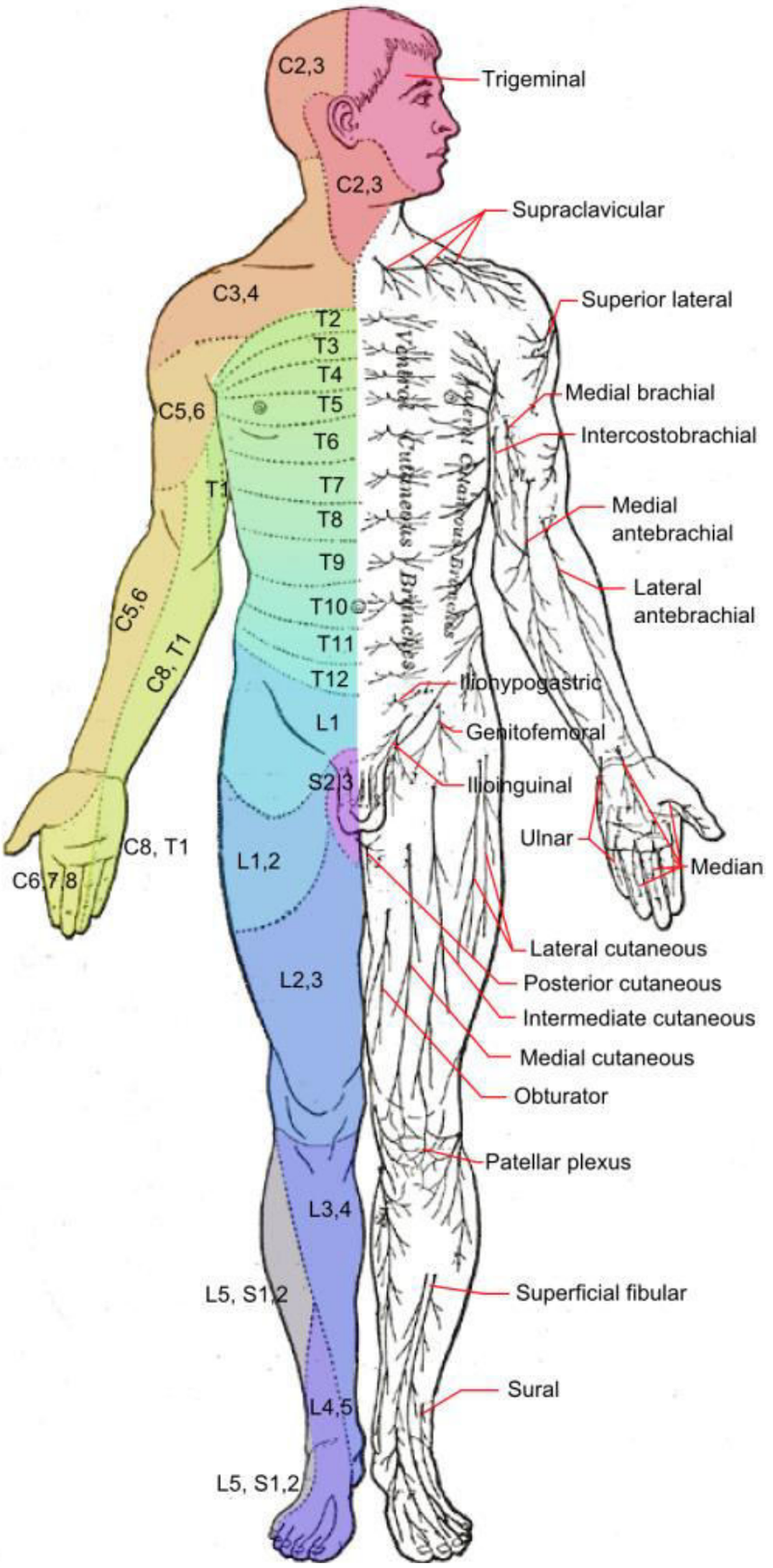
Dermatomes

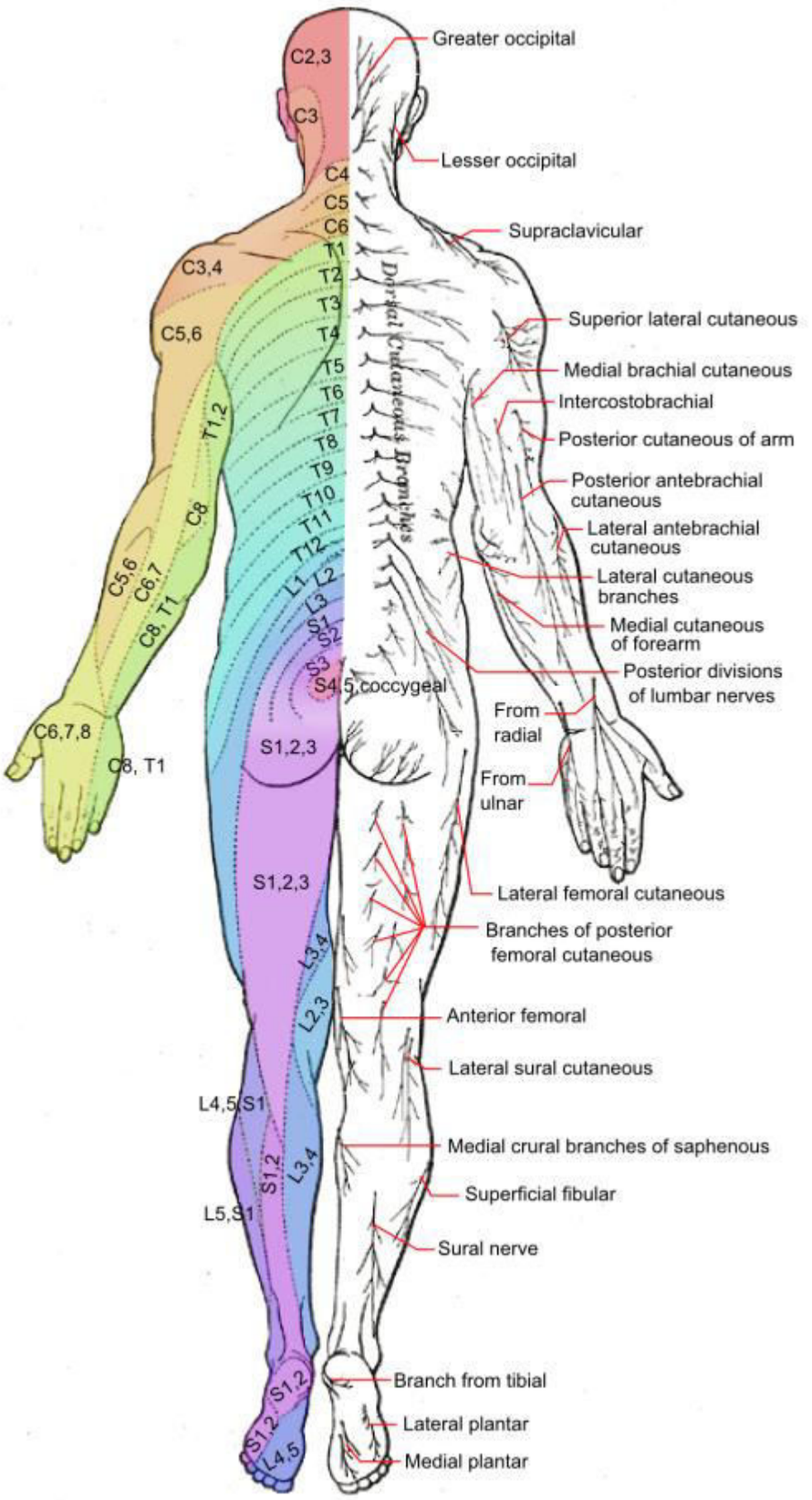
The table below lists the major dermatome landmarks:

Nerve root	Landmark	Mnemonics
C2	Posterior half of the skull (cap)	
C3	High turtleneck shirt	
C4	Low-collar shirt	
C5, C6	Thumb + index finger	**Make a 6 with your left hand by touching the tip of the thumb & index finger together - C6**
C7	Middle finger + palm of hand	C7 gives the finger to heaven (as in middle finger)
C8	Ring + little finger	
T4	**Nipples**	**T4 at the Teat Pore**
T5	Inframammary fold	
T7	Xiphoid process	
T10	**Umbilicus**	**BellybuT-TEN**
L1	Inguinal ligament	**L for ligament, 1 for 1nguinal**
L4	Knee caps	**Down on aLL fours - L4**
L5	Big toe, dorsum of foot (except lateral aspect)	**L5 = Largest of the 5 toes** **L5 root has no lower limb deep tendon reflex representation. Therefore, an acute lumber disc prolapse resulting in L5 radiculopathy is commonly misdiagnosed as malingering.**
S1	Lateral foot, small toe	**S1 = the smallest one**
S2, S3	Genitalia	

Symptoms and signs of a C6 root lesion include

- Paraesthesias in the thumb or lateral distal forearm
- Weakness of brachioradialis, biceps, or triceps and
- Diminished biceps and brachioradialis reflexes in conjunction with an increased triceps reflex.


C2,3
Trigeminal
C2,3
Supraclavicular
C3,4
Superior lateral
T2
T3
T4
T5
T6
T7
T8
T9
T10
T11
T12
L1
S2,3
C5,6
T1
C5,6
C8, T1
C8, T1
C6,7,8
L1,2
L2,3
L3,4
L5, S1,2
L4,5
L5, S1,2
Medial brachial
Intercostobrachial
Medial antebrachial
Lateral antebrachial
Ilionypogastric
Genitofemoral
Ilioinguinal
Ulnar
Median
Lateral cutaneous
Posterior cutaneous
Intermediate cutaneous
Medial cutaneous
Obturator
Patellar plexus
Superficial fibular
Sural


C2,3
C3
C4
C5
C6
T1
T2
T3
T4
T5
T6
T7
T8
T9
T10
T11
T12
L1
L2
L3
S1
S2
S3
S4,5,coccygeal
C3,4
C5,6
T1,2
C8
C5,6
C6,7
C8, T1
C6,7,8
C8, T1
S1,2,3
S1,2,3
L3,4
L2,3
L4,5,S1
S1,2
L3,4
L5,S1
S1,2
S1,2
L4,5
Dorsal Cutaneous Branches
Greater occipital
Lesser occipital
Supraclavicular
Superior lateral cutaneous
Medial brachial cutaneous
Intercostobrachial
Posterior cutaneous of arm
Posterior antebrachial cutaneous
Lateral antebrachial cutaneous
Lateral cutaneous branches
Medial cutaneous of forearm
Posterior divisions of lumbar nerves
From radial
From ulnar
Lateral femoral cutaneous
Branches of posterior femoral cutaneous
Anterior femoral
Lateral sural cutaneous
Medial crural branches of saphenous
Superficial fibular
Sural nerve
Branch from tibial
Lateral plantar
Medial plantar

Which spinal dermatome is responsible for the initial vague periumbilical discomfort in appendicitis?

- **T10**
  - **Visceral afferents from the appendix** enter the spinal cord at the level of the **10th** thoracic vertebra , the **same level as the somatic afferents** from the anterior abdominal wall in the region of the **umbilicus**.
  - **Hence the initial pain associated with this condition is vague**, poorly localized, and in the periumbilical region.
  - As the **parietal peritoneum adjacent to the appendix becomes inflamed**, **somatic nerves** are activated **and localized pain occurs** in the right lower quadrant.
  - **T12** dermatome is inferior to the umbilicus, and may be **responsible for pain once appendicular inflammation of the peritoneum has occurred.**

Cervical roots

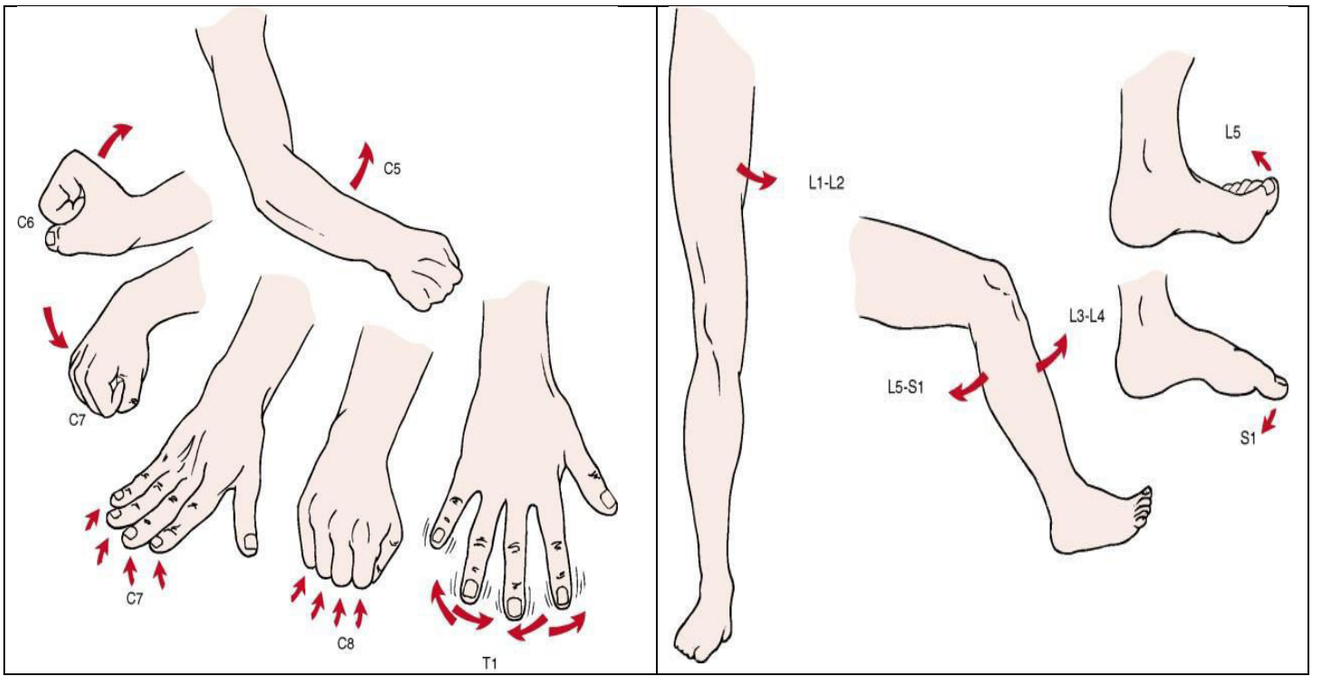
Root	Dermatome distribution	Myotome distribution	Tendon reflex
C4	Upper outer shoulder	Shoulder abduction	Nil
C5	Outer arm, forearm	Shoulder abduction, elbow flexion	Bicep
C6	Index and thumb	Wrist extension	Supinator
C7	**Middle finger centre of palm**	**Finger and elbow extension**	**Triceps**
C8	**Little finger, ulnar border of hand**	**Wrist/finger flexion**	Finger jerk

Lumber and sacral roots

Root	Dermatome distribution	Myotome distribution	Tendon reflex
L1	Skin above, and below the inguinal ligament	None	Nil
L2	Upper anterior, and medial thigh	Psoas hip abductors	Nil
L3	Mid anterior, and medial thigh	Psoas quadriceps	Patella (L3-4)
L4	Medial aspect of leg, front of knee, and lower lateral thigh	Tibialis anterior, extensor hallucis	Patella (L3 - 4)
L5	Lateral aspect of leg and dorsum of foot (except for the lateral border which is supplied by S1)	Extensor halluces, peroneal, gluteus medius, dorsiflexors, hamstrings	Plantar (L5, S1-2)
S1	Posterior lateral thigh and calf	Peroneal, plantar flexors	Ankle (S1-2)
S2	Popliteal fossa	Many, in combination with other nerve roots - including knee flexors	Ankle (S1-2)
S3 - 5	Medial buttock and perianal skin in a concentric manner with S3 most lateral, and s5 closest to the anus	Bladder, rectum	Nil

- The L5 reflex is tested by tapping the medial hamstrings, but is typically cumbersome to do and not tested. It is the asymmetry which is important as it is not necessarily present.
- S2-4 reflex is part of the anocutaneous reflex or anal wink.

L5 lesion features = loss of foot/big toe dorsiflexion + sensory loss dorsum of the foot



September 2013 exam: H/O neck & arm pain like 'electric shocks', worse on turning head + decreased sensation on the dorsal aspect of the thumb and index finger. What is the most likely underlying diagnosis? C6 radiculopathy

H/O pain affecting buttock region and the lateral border and sole of his foot, in association with paraesthesiae of the sole on walking. What is the correct nomenclature for the nerve root from which these symptoms have arisen? → **S1**(The S1 nerve root is mapped to the sole of the foot)

Ref: mrcpuk.org SCE sample question

Notes & Notes

For MRCP part 1 & 11

By

Dr. Yousif Abdallah Hamad

Endocrinology

Updated

2017

Contains:

1/ Passmedicine 2018

2/ On examination 2018

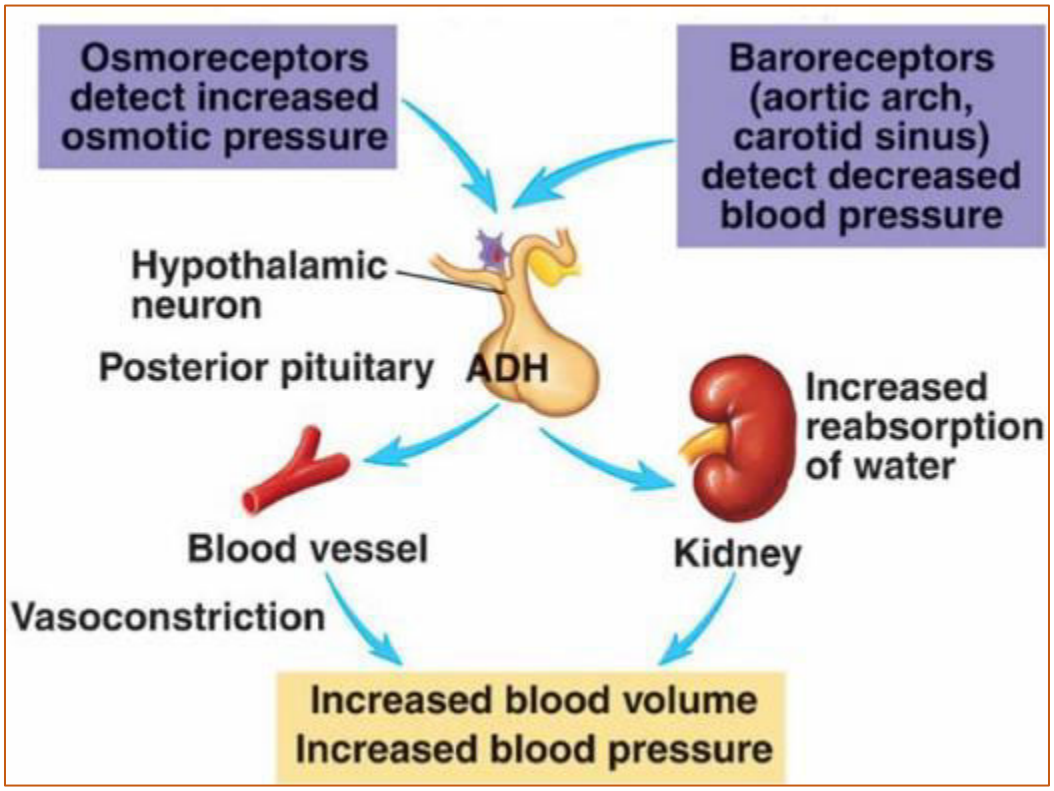
3/ Pastest 2018

4/ **Red fonts --> previous exams**

5/ Other updated UK sources

Pituitary gland conditions

Antidiuretic hormone (ADH) (Vasopressin)



Overview:

- Synthesized in the supraoptic nucleus of the hypothalamus.
- Stored and secreted from the **posterior pituitary** gland
- it contains arginine, so called **arginine vasopressin** (**AVP**) or **argipressin**

Functions:

1) Antidiuresis
   - retain water in the body: (It acts on the collecting ducts improving water permeability and hence water retention).
     - By **acting on V2 receptors** → ↑↑ transcription and **insertion of water (Aquaporin-2) channels** into the apical membrane of distal convoluted tubule and collecting duct epithelial cells → ↑↑ water permeability → water reabsorption → excretion of more concentrated urine, i.e., antidiuresis.
2) Vasoconstriction
3) **Increase platelet aggregation**, (prothrombotic at high dose).
4) **Increase factor VIII production**, and as such may be of utility in treating some patients with haemophilia A.

5) It leads to uterine and GI **smooth muscle contraction** and indirectly leads to a reduction in coronary artery blood flow.

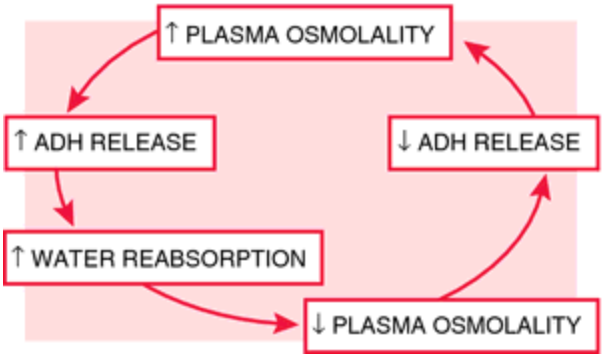
Vasopressin receptors

Receptor	Second messenger	Location	Action	Agonist
V 1	Phosphatidyl-inositol/calcium	Vascular smooth muscle	Vasoconstriction	♦**Terlipressin** → ↑ splanchnic VC → ↓ esophageal varices bleeding. ♦ Felypressin → prolong the action of local anesthesia (safer than epinephrine in cardiac patients)
V2	Adenylate cyclase/cAMP	Renal	Anti-diuresis (Insertion of aquaporin-2 channels)	♦ Vasopressin (weak , short acting , given SC or IM) ♦ **Desmopressin** (more potent, long acting, given intra-nasally)
		Extra renal (vascular endothelium)	↑↑ release of von Willebrand & factor VIII.	**Desmopressin** (used for haemophilia A & Von Willebrand disease)

- The **V_1** receptor for antidiuretic hormone on vascular smooth muscles is coupled to **phospholipase C** by a **G_q protein**.
- The **V_2** receptor for antidiuretic hormone on late distal tubule and collecting duct is coupled to **adenylyl cyclase** by a **G_s protein**.

ADH regulation

- **Feedback mechanism of ADH:**
  - Receptors in the hypothalamus measure plasma osmolality (measuring system).
  - If the osmolality exceeds a set point, the neural pituitary gland excretes ADH (controlled variable).
  - ADH increases renal reabsorption of water (process unit).
  - Receptors in the hypothalamus detect falling osmolality and reduce ADH secretion, which decreases the amount of water reabsorption in the kidneys.



- factors **increase secretion** of vasopressin (<u>stimulatory</u> factors):

- **Increased osmolality of plasma** (**The main stimulus**).
- Reduced extracellular volume (less sensitive stimulus).
- Angiotensin II
- **Hypoglycemia**
- Increased pain
- Opiates
- Nicotine
- Antineoplastic drugs
- **Carbamazepine**

- Factors **decreases secretion** of vasopressin (inhibitory factors):
  - Ethanol (alcohol) → ↓↓ calcium-dependent secretion of AVP
  - Atrial natriuretic peptide,
    - by inhibiting Angiotensin II-induced stimulation of AVP secretion
  - Cortisol

Scenario **(MRCPI-part-1- January 2018)**
(hypovolemic hyponatremia)
H/O RTA + rapid pulse and low BP + low Na.

- **What is the most likely explanation for this patient's hyponatremia?**
  - **Physiologic ADH (vasopressin) secretion**
    - **Hyponatremia that develops after massive hemorrhage is likely dilutional.**
    - When baroreceptors detect decreases in effective arterial volume, such as after massive blood loss, they cause antidiuretic hormone (ADH) to be released from the pituitary gland to increase renal reabsorption of free water, diluting serum sodium levels and causing hyponatremia.
- **What is the appropriate management of this patient?**
  - **normal saline.**
    - Management of **hypovolemic hyponatremia** includes volume repletion with normal saline.
    - Correction of hypovolemia removes the stimulus to release ADH, causing free water excretion by the kidneys, which leads to rapid correction of serum sodium levels.
    - volume repletion with normal saline must occur at a slow rate, because rapid correction of hyponatremia can cause central pontine myelinolysis.

Scenario (May 2016 exam -part-1)
Which adaptive mechanism that prevent dying from dehydration?

- **Increase of aquaporin-2 in the collecting duct.**
  - ADH (vasopressin) → ↑ **aquaporin-2** expression → ↓ water excretion → protect against dehydration

Syndrome of inappropriate ADH secretion (SIADH) (↑↑ ADH)

Causes

Category	Examples
Malignancy	• **small cell lung cancer** **(The most common cause)** • also: pancreas, prostate
Neurological	• stroke • subarachnoid haemorrhage • subdural haemorrhage • meningitis/encephalitis/abscess
Infections	• tuberculosis • pneumonia
Drugs	• Sulfonylureas , • Thiazides • SSRIs, tricyclics, mon-amine oxidase uptake inhibitors, phenothiazines • **carbamazepine** • vincristine , vinblastine • cyclophosphamide, chlorpropamide • **omeprazole**
Other causes	• positive end-expiratory pressure (PEEP) • porphyrias (**SIADH is associated with acute intermittent porphyria)**

Mechanisms:

- ↑↑ (ADH)→ ↑↑ water retention → **Euvolemic hyponatraemia** (dilutional effects) → low plasma osmolality + high urine osmolality with an elevated urine sodium (above 20 mmol/L)
- Osmotic fluid shifts → Cerebral edema and ↑ intracranial pressure

Features

- Symptoms of hyponatremia
  - usually asymptomatic until the sodium level falls below 120 mmol/l
    - Mild: anorexia, nausea, vomiting, headache, muscle cramps
      - **The earliest symptoms** of acute hyponatremia are **nausea and vomiting.**
    - Moderate: muscle weakness, lethargy, confusion
    - Severe: seizures, altered consciousness
- Normotensive

- Symptoms of the underlying condition

Diagnostic criteria: SIADH can only be diagnosed when the following criteria are satisfied:

1. The patient is clinically euvolaemic (no clinical evidence of fluid overload (oedema) or dehydration)
2. **↓ plasma sodium (<134 mmol/l) & osmolality (<280 mosmol/kg)**
3. ↑ urine sodium (>20 mmol/l) and osmolality **(>100 mosmol/kg),**
4. Normal adrenal, thyroid and renal function.

which finding would most suggest a diagnosis of (SIADH)?

➔ **concentrated urine relative to plasma**

- because normally, low plasma osmolality should suppress (ADH) secretion and lead to dilute urine.
- The low plasma osmolality reflects the hyponatraemia, since sodium is the principal determinant of extracellular fluid osmolality. It does not reveal information about the underlying cause.

SIADH patients are usually euvolemic, normotensive, and have no edema. A hyponatremic patient with edema should raise suspicion of other conditions (e.g. congestive heart failure)

Management

Restriction of water intake is the initial treatment of choice for hyponatraemic patients with SIADH who are not at imminent risk of seizures or coma. This precipitates a gradual rise in serum sodium, not greater than the recommended maximum of 8–10 mmol/day.

- **sever acute symptomatic hyponatraemia:**
  - hypertonic (3%) saline given via continuous infusion
    - Infusion of hypertonic (3%) saline is **reserved for patients with acute severe life-threatening hyponatraemia**, usually where **sodium is less than 120 mmol**/l and there are significant neurological features **(i.e. seizures or GCS less than 11).**
    - If severe: consider adding a loop diuretic (e.g., furosemide) to hypertonic saline. Most effective if urine osmolality is > 2x the serum osmolality (typically urine osmolality > 500 mOsmol/kg)
  - correction must be done slowly to avoid precipitating central pontine myelinolysis
    - The sodium serum levels may increase by a maximum of 10 mmol/L within 24 hours or 0.5 mmol/L per hour.
  - acute treatment should be interrupted once any of three end points is reached:
    (1) the patient's symptoms are abolished
    (2) a safe serum [Na+] level (generally ≥120 mmol/L) is achieved;
    (3) a total magnitude of correction of 18 mmol/L is achieved

- **Mild acute OR chronic hyponatraemia:** (Na+ ≥ 120 and NO neurological signs)
  - 1st line → **fluid restriction** (**the initial treatment of choice**)
    - Restriction of fluid to a **daily intake of 700–1000 ml** redresses the hyponatraemia.
    - the degree of restriction depends on urine output plus insensible fluid loss (generally fluids should be limited to 500 mL/day below the average daily urine volume);
    - several days of restriction are usually necessary before a significant increase in plasma osmolality occurs
  - 2nd line → **demeclocycline**
    - it is a semi-synthetic tetracycline antibiotic that can be used off-licence for the treatment of hyponatraemia caused by SIADH
    - **reduces the responsiveness of the collecting tubule cells to ADH (by inducing nephrogenic diabetes insipidus)**
    - treatment must be continued for several days to achieve maximal diuretic effects; consequently, one should wait 3 to 4 days before deciding to increase the dose
    - Side effects include:
      - diabetes insipidus
      - photosensitive rash.
      - reversible azotaemia
      - nephrotoxicity, especially in patients with cirrhosis
  - 3rd line → ADH (vasopressin) receptor antagonists have been developed (ie. tolvaptan)

Diabetes insipidus (↓↓ADH)

Diabetes insipidus is characterised by a high plasma osmolality and a low urine osmolality

Definition:

- The passage of large volumes (>3 L/24 hr) of dilute urine (< 300 mOsm/kg).
- characterised by either:
  1. deficiency of antidiuretic hormone (ADH) → (cranial DI) (**most common form**)
  2. Insensitivity to (ADH) → (nephrogenic DI) (**rare**)

Causes of cranial DI

- idiopathic
- post head injury
- pituitary surgery
- craniopharyngiomas
- histiocytosis X
- DIDMOAD is the association of cranial Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness (also known as **Wolfram's syndrome**)

Causes of nephrogenic DI

- genetic: two forms:
  1. **vasopressin-2 receptor** (V2 ADH) mutation
     - the more common form
     - X linked
     - This fits best with only **male** members of the family being affected by the condition.

2. mutations in the aquaporin-2 gene
    - the less common form
    - Autosomal recessive
    - leading to reduced water reabsorption in the distal tubule.

- electrolytes:
    - hypercalcaemia,
    - hypokalaemia
        - hypokalemia → desensitization of renal tubules to (ADH) → increased water excretion
- drugs: the commonest precipitants
    - **tetracycline** (demeclocycline)
    - **lithium**,
        - **Lithium inhibits signalling pathways that involve glycogen synthase kinase type 3 beta (GSK3beta),** → dysfunction of aquaporin-2 water channel → nephrogenic DI.
- tubulo-interstitial disease:
    - obstruction,
    - **Sickle cell trait**
    - pyelonephritis

Features

- polyuria
    - Diabetes insipidus (DI) is suspected when the urine output is > 50 ml/kg per day (3000 ml for a 60-kg female).
    - Nocturia → Restless sleep, daytime sleepiness
        - **In the absence of nocturia, diabetes insipidus is very unlikely**
- Polydipsia

Investigation

In suspected DI the most appropriate next investigation is → Urine and plasma osmolality (non-invasive first step)

- high plasma osmolality,
    - **plasma osmolality >305 mOsmol/kg**
    - serum [Na] >145 mmol/L, and
- low urine osmolality
    - **urine osmolality <200 mOsm/kg**
    - urinary [Na] 20-60 mmol/L
    - urinary specific gravity <1.005.
- water deprivation test
    - nephrogenic diabetes insipidus
        - **the investigation most likely to reveal the underlying diagnosis**
        - low urine osmolality and elevated serum osmolality, with **no significant response to desmopressin.**

- If CDI is diagnosed, a CT scan or MRI of the head should be conducted to rule out brain tumors

Management

- **Central (CDI)**
  - desmopressin is the drug of choice.
    - synthetic vasopressin without vasoconstrictive effects
    - side effect: hyponatremia
  - increase oral water intake.
    - In the unconscious patient, nasogastric water and/or intravenous 5% dextrose can be administered.
  - Synthetic ADH can be given intra-nasally or intravenously if the urine output continues to be greater than 250 ml/hr.
- **Nephrogenic (NDI)**
  - congenital nephrogenic DI
    - congenital nephrogenic DI is generally unresponsive to exogenous ADH.
    - **Sildenafil**, a phosphodiesterase inhibitor, has been shown to substantially reduce urine output in patients with **congenital x-linked nephrogenic diabetes** insipidus
  - lithium – induced **nephrogenic DI**:
    - cessation of lithium.
    - **If there is hypovolaemic hypernatraemia ((hypotension, tachycardia, poor skin turgor)):**
      - **The first step is to restore volume with isotonic fluids (0.9% saline).**
        - ⇨ Isotonic fluid is not usually used in hypernatraemia, but it is recommended in patients with marked volume depletion and haemodynamic instability.
        - ⇨ Once euvolaemic, the fluid can be switched to a hypotonic fluid (5% dextrose preferred over 0.45% saline) for free water supplementation.
        - ⇨ The serum sodium should be corrected by 0.5 mmol/l/hr without exceeding 12 mmol/l in 24 hours. Cerebral oedema can occur if the sodium is corrected too quickly.
    - **If fail to respond to cessation of lithium.**
      - **thiazide diuretics**
        - ⇨ **Amilioride (block ENaC channel in cortical collecting duct where lithium enter and causes DI)**
      - NSADs:
        - ⇨ **indomethacin**

Fluid status in DI

- Total body water: decrease,
- Extracellular fluid: increase,

- Intracellular fluid: decrease

DI → losing hypotonic fluid in the urine →↑ osmolarity of the extracellular fluid → water will flow out of the intracellular compartment and into the extracellular compartment → ↑extracellular fluid volume and ↓intracellular fluid volume.

January 2013 exam: A mutation in the gene that encodes aquaporin 2 is most likely to result in…? Diabetes insipidus

Which part of the nephron is most affected in diabetes insipidus?
→ Cortical and medullary collecting tubules

Water deprivation test

A dramatic improvement in the ability of the kidneys to concentrate urine following the administration of DDAVP points towards a diagnosis of cranial diabetes insipidus

- The diagnostic test to confirm DI is a water deprivation test.
- Normal plasma osmolality is 285-305 mosmol/kg.
- The normal 24-hour urine osmolality is, on average, **500-800 mOsm**/kg of water.

Method

- prevent patient drinking water
  - ➢ patients are deprived of fluids for a period of 8 h or until 5% of body weight is lost.
- ask patient to empty bladder
- Patients should be weighed hourly.
- Test urine volume and osmolality every hour
- Test sodium and plasma osmolality every two hours
- Water deprivation continues until one of the following occurs:
  1. Urine osmolality rises and reaches a normal value (> 600 mOsmol/kg) → **DI ruled out** and **primary polydipsia** confirmed
     - **Where urine osmolality reaches levels above 600 mOsmol/kg without desmopressin, then the diagnosis is primary polydipsia.**
  2. No change in urine osmolality despite a rising plasma osmolality (> 290 mOsmol/kg)
  3. Plasma osmolality> 295–300 mOsmol/kg or sodium ≥ 145 meq/L
- In the latter two situations → **administer desmopressin** (a synthetic ADH analog) 2 µg intramuscular
  - ➢ Monitor urine osmolality testing every 30 minutes for 2 hours
    - In **CDI**: Urine osmolality rises (> 600) after desmopressin administration (renal ADH receptors are intact).
    - In **NDI**: Urine osmolality remains low after desmopressin administration (defective renal ADH receptors).

	Primary polydipsia (psychogenic polydipsia)	CDI	NDI
Lab findings on presentation	• **Hyponatremia** (< 137 meq/L) • Plasma osmolality: low- normal (255–280 mOsmol/kg) • Very low urine osmolality (< 250 mOsmol/kg)	• **Mild hypernatremia** (> 150 mEq/L) • High-normal plasma osmolality(280–290 mOsmol/kg) or slightly elevated • Low urine osmolality ➢ Partial DI: 300–500 mOsmol/kg ➢ Complete DI: < 300 mOsmol/kg	
Water deprivation test results	• Plasma osmolality: normal (275–290 mOsmol/kg) • **Urine osmolality: rises, reaches normal value** (> 600 mOsmol/kg) This result shows that both ADH release and effect are intact.	• Plasma osmolality: rises (> 290 mOsmol/kg) • **Urine osmolality: no change**	
Desmopressin administration results	• Water deprivation test results confirm diagnosis; **no need to administer desmopressin**	• Plasma osmolality: normalizes (275–290 mOsmol/kg) • **Urine osmolality rises**	• Plasma osmolality remains elevated • Urine osmolality remains low

- Differentiate **psychogenic polydipsia** from **CDI** and **NDI:**
  - Patients with this disorder ingest and excrete up to 6L of fluid/day and are often emotionally disturbed.
  - **Unlike patients with CDI and NDI, they do not have nocturia, nor does increased thirst wake them at night.**
  - Patients with **acute psychogenic** polydipsia can concentrate their urine during a water deprivation test but chronic water intake diminishes medullary tonicity in the kidney.
  - Patients with **long-standing polydipsia** are not able to concentrate their urine to maximal levels during water deprivation, a response similar to that of patients with partial central diabetes insipidus.
    - However, **unlike central diabetes insipidus, patients of psychogenic polydipsia show no response to exogenous ADH after water deprivation.** This response resembles nephrogenic diabetes insipidus, but ADH levels are low in psychogenic polydipsia and high in nephrogenic polydipsia.

Wolfram's syndrome or the DIDMOAD syndrome is characterised by diabetes insipidus, diabetes mellitus, optic atrophy, and deafness

Hypopituitarism

Definition

- ↓↓ secretion of one or more of the eight hormones normally produced by the pituitary gland.
- Hypopituitarism becomes symptomatic when more than 80% of pituitary cells are damaged.

Etiology

- Intrasellar/parasellar **masses**
  - **Nonsecretory pituitary macroadenomas (≥ 10 mm in diameter) are the most common cause of hypopituitarism among adults (~ 40% of cases).**
  - Less common: internal carotid artery aneurysms, meningiomas, craniopharyngiomas,
- **Pituitary apoplexy**
  - **results in acute hypocortisolism and hypothyroidism, can present with sudden hypotension and hypovolemic shock**
- Sheehan syndrome: postpartum necrosis of the pituitary gland. Usually occurs following postpartum hemorrhage, but can also occur even without clinical evidence of hemorrhage.
- Traumatic brain injury (especially around the skull base)
- Infiltration of the pituitary and/or hypothalamus
  - Hemochromatosis
  - Infections: meningitis, TB
- Congenital deficiency of hypothalamic hormones
  - GnRH deficiency (Kallman syndrome)

Features - mix (depends on which hormone is deficient).

- **The most common** problem is insufficiency of follicle-stimulating hormone (**FSH**) and/or luteinizing hormone (**LH**) leading to sex hormone abnormalities.
- **growth hormone deficiency**
  - **The first hormone to fall is the growth hormone**
    - in children would produce short stature,
    - in adults it causes:
      - lassitude (tiredness)
      - **increased fat mass** (weight gain)
      - poor concentration
      - low IGF-1 concentration.
      - low peak growth hormone levels in response to insulin-induced hypoglycaemia
- Low ACTH:
  - tiredness,
  - postural hypotension. **(Postural hypotension is related to adrenal failure regardless of cause)**

- low gonadotrophins: amenorrhoea
- low TSH: (the last hormone to fall) → constipated
  - the typical thyroid function tests of a hypopituitarism are with a low thyroid-stimulating hormone and therapy would be guided by monitoring the free thyroxine (T4) concentration.

Investigations

- **Dynamic pituitary function tests**
  - **Used to** assess patients with suspected primary pituitary dysfunction
  - **Method:**
    - Insulin, TRH and LHRH are given to the patient following which the serum glucose, cortisol, growth hormone, TSH, LH and FSH levels are recorded at regular intervals. Prolactin levels are also sometimes measured
    - A normal dynamic pituitary function test has the following characteristics:
      - GH level rises > 20mu/l
      - cortisol level rises > 550 mmol/l
      - TSH level rises by > 2 mu/l from baseline level
      - LH and FSH should double
- **Insulin stress test**
  - **Basics**
    - used in investigation of hypopituitarism
    - IV insulin given, GH and cortisol levels measured
    - with normal pituitary function GH and cortisol should rise
  - **Contraindications**
    - epilepsy
    - ischaemic heart disease
    - adrenal insufficiency

Management

- **Hydrocortisone**
  - **the most important replacement therapy to be started first → Hydrocortisone**
    - to avoid the possibility of precipitating an adrenal crisis.
  - Fludrocortisone is only necessary in patients with adrenal insufficiency who are unable to maintain normal blood pressure control.
- Thyroxine replacement
  - should be begun after commencing hydrocortisone because levothyroxine increases the clearance of cortisol and may precipitate an adrenal crisis
- GH therapy:
  - licensed for treatment of symptoms with reduced quality of life on adult growth hormone deficiency assessment (AGHDA) questionnaire score.
- **Testosterone**
  - **the most appropriate treatment to prevent the progression of bone loss → Add testosterone therapy**

Patients with TSH deficiency should not be treated with levothyroxine until ACTH deficiency has been ruled out and/or treated because levothyroxine increases the clearance of cortisol and may precipitate an adrenal crisis

Growth hormone (GH)

- Anabolic hormone secreted by somatotroph cells of the anterior lobe of the pituitary gland.
- Growth hormone releasing hormone (**GHRH**) release from the hypothalamus stimulates the somatotrophs in the anterior pituitary gland to release GH.
  - **GHRH** uses (two second messengers) **cAMP and IP3/Ca2+** to stimulate growth hormone release.
- **Which signaling pathways does growth hormone (GH) use?**
  - **A tyrosine kinase receptor that uses the JAK/STAT pathway**
    - GH, like prolactin, uses tyrosine kinase receptor followed by activation of Janus kinase (JAK) followed by signal transduction and activation of transcription (STAT).
    - The other tyrosine kinase receptor hormones:
      - PDGF (platelet-derived growth factor),
      - FGF (fibroblast growth factor),
      - IGF-1 (insulin-like growth factor 1)

Mechanism of action

- **Direct** action on target tissues, such as skeletal muscle, liver, or adipose tissue,
  - it uses **tyrosine kinase-associated receptors** (transmembrane receptors).
- **Indirect** action via insulin-like growth factor 1 (IGF-1), primarily secreted by the liver
  - Many of the effects of growth hormone (GH) are mediated through insulin-like growth factor (IGF)-1 the concentrations of which are high in acromegaly.

Functions

- Direct effects of GH:
  - ↓ Glucose uptake into cells → ↑ insulin resistance → ↑Blood insulin levels
  - ↑ Lipolysis
  - ↑ Protein synthesis in muscle
  - ↑ Production of IGF

Growth hormone (GH) counteracts in general the effects of insulin on glucose and lipid metabolism, but shares protein anabolic properties with insulin.

GH along with cortisol and adrenalin (called counter-regulatory hormones) tell the body to increase the availability of glucose – so it counters the effect of insulin.

Regulations

GH release is increased by: (anything ↓ glucose)	**GH release is inhibited by:** (anything ↑ glucose)
• Deep sleep • Fasting → **Hypoglycaemia** • Alpha adrenergic activity • Stress • **Exercise** • **Hypoglycaemia** • Ghrelin. the "hunger hormone" • **Amino** acids (**Arginine**) • Thyroxine • Sex steroids (estrogen or testosterone)	• **Somatostatin** • Cortisol • Beta adrenergic activity • Hyperglycaemia (DM) • Obesity • Free **fatty** acids • Hypothyroidism • IGF-1 • **pregnancy**

- Glucocorticoid (acutely – within 3 hours stimulates GH; chronically - by 12 hours suppresses GH secretion)

Conditions associated with GH disorders

- GH deficiency: resulting in short stature
- excess GH: acromegaly

Insulin-like growth factor 1 (IGF-1)

- also called **somatomedin C**
- Polypeptide hormone produced **mainly by the liver** in response to the **indirect** action of growth hormone
  - GH → activation of liver GH receptor, → promotes IGF-I synthesis which, in turn, is released to the circulation
  - Although it is mainly produced by the liver, virtually every tissue is able to secrete IGF-I for autocrine/paracrine purposes
- IGF-1 is structurally related to insulin, and is even capable of binding the insulin receptor (**tyrosine kinase receptor**), albeit at lower affinity than insulin.
- 80% of circulating IGF-1 is carried by **IGF binding protein-3** (IGFBP-3)

Regulation:

- Pituitary (GH) and liver (IGF-I) establish negative feedback mechanisms
  - IGF-I inhibits GH secretion acting on the hypothalamus by two feedback mechanisms: firstly, inhibiting GH gene expression and secondly by stimulating the secretion of somatostatin that inhibits GH production.
- **Causes of increased IGF-1**
  - ↑GH
- **Causes of Reduced IGF-1**
  - ↓GH

- Cirrhosis of the liver → reduced synthesis

Function

- growth in childhood and continues anabolic effects in adults.

Action

- Binding to the IGF1R, a receptor tyrosine kinase, → initiates intracellular signaling; → activate of the AKT signaling pathway, → ↑ cell growth and proliferation,+ ↓ programmed cell death .

Conditions associated with IGF-I deficiency:

1. Laron Syndrome, in children;
2. advanced liver cirrhosis, in adults;
3. intrauterine growth restriction
4. Aging including cardiovascular and neurological diseases associated to aging.
5. higher probability of hepatocarcinoma and poorer prognosis in patients requiring liver surgery. As a result IGF-I levels are considered of prognostic value regarding survival in cirrhotic patients

Clinical uses

- IGF-1 levels can be **used as marker of growth hormone levels, but are not diagnostic**.
  - IGF-1 levels may remain within normal ranges despite growth hormone deficiency in up to 50% of patients, and therefore a normal result does not exclude growth hormone deficiency.
- A synthetic analog of IGF-1, mecasermin, is used for the treatment of growth failure

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Growth hormone deficiency (GHD)

Causes

- **The most common cause is pituitary tumors.**
- Complication of pituitary tumors treatment with surgery, radiation therapy
- Traumatic brain injury
- idiopathic, isolated growth hormone deficiency in childhood

Features

- Infancy
  - The primary manifestations in infancy are **hypoglycemia** and micropenis.
- Child hood
  - The primary manifestation in early childhood is growth failure.
    - causes premature fusion of the epiphyseal portion of the bone.
- Adult
  - ↓↓quality of life (QoL) especially **reduced energy** levels
  - ↓↓bone mineral density → osteopenia/osteoporosis
  - ↓↓ sweating → Dry skin
  - ↓↓ muscle strength and exercise capacity

- ↓↓ extracellular fluid volume
- ↓↓ cardiac function.
- lipid abnormalities (↑↑ LDL cholesterol) (**increased fat mass, especially in the trunk**)
- **insulin resistance**
- ↑↑ thickness of the intima media of blood vessels
- ↑↑ levels of fibrinogen and plasminogen activator inhibitor

Investigations

- decreased serum insulin-like growth factor-1 (**IGF-1**) levels.
  - normal IGF-I level does not exclude the diagnosis of GHD
- **insulin-induced hypoglycaemia**
- arginine stimulation test

Diagnosis (Endocrine Society guideline 2011)

- there is a significant false-positive error rate in the response to a single GH stimulation test, we suggest the use of **two tests** before making this diagnosis.

Treatment

- subcutaneous injections of recombinant human growth hormone.

MRCP-UK. SCE .Sample question

patients with childhood-onset GHD who are candidates for GH therapy after adult height achievement. What is the most appropriate next step in management?

➔ **should be retested for GHD**

Criteria for GH treatment

- Recombinant human growth hormone (somatropin) treatment is recommended for the treatment of **adults** with growth hormone (GH) deficiency only if they fulfil **all three of the following criteria.**
  1- Severe GH deficiency, defined as a peak GH response of less than 9 mU/litre (3 ng/ml) during an insulin tolerance test.
  2- impairment of **Q**uality **o**f **L**ife (**QoL**), as demonstrated by a reported score of **at least 11** in the disease-specific 'Quality of life assessment of growth hormone deficiency in adults' (QoL-AGHDA) questionnaire.
  3- They are already receiving treatment for any other pituitary hormone deficiencies as required.

Side effects associated with treatment with recombinant human growth hormone (hGH).

- Headache
- arthralgia (joint pain), myalgia (muscle pain)
- fluid retention (peripheral oedema),
- mild hypertension,
- carpal tunnel syndrome
- visual problems
- nausea and vomiting,
- paraesthesia,
- antibody formation,
- reactions at the injection site.
- slipped upper femoral epiphysis

- **Idiopathic intracranial hypertension (IIH)**
  - result from antidiuretic effect of hGH
  - Most common in association with impaired renal homeostasis.
  - In patients with intact homeostatic mechanisms, hGH→ ↑plasma renin & aldosterone which counteracts the antidiuretic effect.
  - If **IIH** is diagnosed, hGH treatment should be interrupted and reinstated at a lower dose if **IIH** resolves.

(SUFE),
- malignancies,
- gynaecomastia
- impaired glucose metabolism.
- **↑Lean body mass &** ↓ body fat
- ↓Serum total cholesterol & (LDL) & triglycerides **but** ↑ lipoprotein(a)

GH treatment is contraindicated in:

- evidence of tumour activity
  - In patients with tumours, anti-tumour therapy must be completed before starting GH therapy.
- critically ill patients
- Pregnancy and lactation.

The golden notes

Growth hormone deficiency (GHD)

- **Prevalence** of adult-onset GH deficiency is 1 in 10,000 of the adult UK population.
- **Causes**
  - Adult onset, GH deficiency→commonly due to **pituitary tumours or their treatment,** (e.g cranial irradiation)
    - **Sheehan's syndrome is post-delivery infarction of the pituitary and growth hormone deficiency is typical.**
  - Childhood-onset GH deficiency → is often idiopathic
    - only around 8% of referred patients will have GH deficiency.
- **Diagnosis:**
  - **Insulin tolerance test (ITT) is the gold standard for the diagnosis of GHD,**
    - **insulin-induced hypoglycaemia → GH response of less than 9 mU/L (3 ng/ml)**
    - **When the ITT is contraindicated (eg: in epilepsy) other tests – such as response to GH-releasing hormone, arginine or glucagon – can be used.**
- **Management:** replacement therapy with biosynthetic human GH (somatropin).

growth hormone deficiency in the newborn may present with hypoglycemia, micropenis, exaggerated jaundice.

Management of idiopathic, isolated growth hormone deficiency:

- Most individuals with idiopathic, isolated growth hormone deficiency in childhood have normal growth hormone secretion during late adolescence or young adulthood,

- presumably because of the stimulatory effects of gonadal steroid hormones on the hypothalamic-pituitary axis for growth hormone secretion.
- At completion of linear growth (growth rate <2cm/year), **growth hormone replacement therapy can be safely discontinued if biochemical assessment demonstrates normal growth hormone secretion.**
  - **Stop rhGH therapy for 2–3 months and undertake biochemical assessment of growth hormone secretion**
- However, if severe growth hormone deficiency persists, continuation of growth hormone therapy at adult doses may be considered until adult peak bone mass is achieved, usually around 25 years of age.
- Continuation beyond this point is only recommended if the individual has ongoing severe growth hormone deficiency and a perceived impairment of quality of life which improves with rhGH treatment.

Acromegaly (excess growth hormone ''GH'')

Acromegaly: increased sweating is caused by sweat gland hypertrophy

Approximately 30% of growth hormone (GH) secreting pituitary tumours is associated with mutation of the Gs protein alpha subunit

Epidemiology

- Age of onset: 3rd decade of life (mean age at diagnosis usually 40–45 years)

Causes

- Pituitary adenoma (95%)
- ectopic GHRH or GH production by tumours e.g. pancreatic
  - mechanism: GH secreting tumours → **mutation in the alpha sub-unit of the stimulatory guanosine triphosphate (GTP) binding protein** → persistent **elevation of cyclic adenosine monophosphate (cAMP)** → production of excess growth hormone.

Features

- coarse facial appearance, spade-like hands, increase in shoe size
- large tongue, prognathism, interdental spaces
- excessive sweating and oily skin
- **Pseudogout** is a recognised association of acromegaly; gout is not.
- Hypertension, heart failure and cardiomyopathy may occur.
- Goitre is seen in 20%, along with other soft tissue swelling.
- **Phosphate levels** are elevated but calcium levels are not significantly increased.
- features of pituitary tumour: hypopituitarism, headaches, bitemporal hemianopia
- raised prolactin in 1/3 of cases → galactorrhoea
  - There are 2 Mechanism of ↑ prolactin:
    1. damaged pituitary stalk → ↓dopamine suppression signal → ↑ prolactin

2. pituitary tumour → hypopituitarism →↓ TSH → ↑ thyrotropin-releasing hormone (TRH) → ↑ prolactin

- 6% of patients have MEN-1

Complications

- hypertension
- Diabetes (>10%)
- cardiomyopathy
- colorectal cancer

Investigations

The diagnostic test for acromegaly is an oral glucose tolerance with growth hormone measurements

- Growth hormone (GH) levels vary during the day and are therefore not diagnostic.
- **Serum insulin-like growth factor 1 (IGF-1)**
  - may also be used as a **screening test** and is sometimes used to monitor disease
  - **IGF-1 measurement is the most appropriate initial investigation**
  - Normal IGF-1 levels rule out acromegaly
  - Growth hormone stimulates the production of (IGF-1), and IGF-1 has a long half-life, so it is the ideal measure of growth hormone secretion.
  - If ↑ IGF-1 → conduct OGTT with baseline GH → measure GH after 2 hours
    → if GH suppressed → acromegaly ruled out
    → if GH not suppressed: confirmed acromegaly → conduct pituitary MRI
  - Insulin-like growth factor binding protein 3 **(IGFBP-3)** is the main circulating binding protein for IGF and might be useful in the future as a screening test for acromegaly.
- **Oral glucose tolerance test (OGTT) with serial GH measurements.**
  - **The definitive test**
  - GH secretion is part of the counter-regulatory defence against hypoglycaemia and physiological GH secretion is inhibited by hyperglycaemia.
  - In normal patients GH is suppressed to < 2 mu/L with hyperglycaemia. This is because **insulin and GH are antagonistic hormones.**
  - in acromegaly there is no suppression of GH
  - may also demonstrate impaired glucose tolerance which is associated with acromegaly
- **Pituitary MRI**
  - May demonstrate a pituitary tumour.
  - Pituitary tumours in acromegaly are usually **macro**adenomas.
    - If normal → screen for an extrapituitary cause (e.g., CT scan of the chest and abdomen, measure GHRH)

In active acromegaly with associated diabetes mellitus → There is insulin resistance

Acromegaly → ↑risk of colon cancer → regular colonoscopy screening, starting at the age of 40 years.

- colonoscopic screening with three yearly colonoscopy in the presence of either elevated IGF-1 or adenomas at initial screening.
- High risk features are detection of adenomas or elevated IGF-1 which should prompt three yearly follow-up, otherwise colonoscopy can be deferred for five years.

British Society of Gastroenterology (May 2010)

Management

Trans-sphenoidal surgery is first-line treatment for acromegaly in the majority of patients

- **Surgery: transsphenoidal adenomectomy**
- Medication
  - Somatostatin analogs (e.g., octreotide, lanreotide)
    - **first line medical therapy.**
    - effective in 50-70% of patients
    - may be used as an adjunct to surgery
    - may improve glycaemic control.
  - Dopamine agonists (e.g., **bromocriptine**, cabergoline)
    - Dopamine agonists are less effective in the treatment of acromegaly
    - Its use now superseded by somatostatin analogues
  - GH receptor antagonists (e.g., pegvisomant)
    - once daily s/c administration
    - very effective - decreases IGF-1 levels in 90% of patients to normal
    - doesn't reduce tumour volume therefore surgery still needed if mass effect
    - the major use of pegvisomant is in patients who have an inadequate response to surgery or radiotherapy (is a third-line treatment when surgery, radiotherapy and somatostatin analogues are not effective.)
    - Growth hormone antagonists used prior to surgery improve metabolic risk factors for surgery, such as hypertension and hyperglycaemia
- Radiotherapy
  - Conventional fractionated radiotherapy
  - Stereotactic radiosurgery (e.g., Gamma Knife, Cyber Knife, proton beam)

  Danger of hypopituitarism following surgery or radiotherapy

Long acting somatostatin analogue, Somatuline LA

- → **Mode of action → ↓↓meal-time related superior mesenteric artery blood flow**
- → One intra-muscular injection should be given every 14 days.
- → **Common side effects :** pain at injection site, GIT disturbances , Cholelithiasis, Sinus bradycardia , Hypoglycaemia, hyperglycaemia

Which test is the best way to monitor for recurrence after trans-sphenoidal surgery for resection of a growth hormone-secreting pituitary adenoma?
⇨ **Insulin-like growth factor 1(IGF-1) or growth hormone level**

- The aim of therapy is to keep the growth hormone level below 5 mU/l or the insulin-like growth factor 1 (IGF-1) levels within normal limits.
- Growth hormone levels above 5 mU/l are associated with a worse prognosis.

Prognosis

- Cardiomegaly progressing to CHF is the most common cause of death

What is the most likely cause of death if treatment is unsuccessful?
⇨ **Left ventricular failure**

January 2015 exam: A 45-year-old man presents with bitemporal hemianopia and spade-like hands. What is the definite test to confirm the diagnosis? Oral glucose tolerance test with growth hormone measurements

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Laron's syndrome

- Definition
  - an autosomal recessive disorder characterized by an insensitivity to (GH), usually caused by a mutant growth hormone receptor.
- Pathophysiology
  - mutations in the gene for the GH receptor.
  - autosomal recessive condition
- Features
  - short stature
  - reduced incidence of acne, cancer and diabetes.
  - Seizures are frequently seen secondary to hypoglycemia.
  - low levels of insulin-like growth factor (IGF-1) and its principal carrier protein, insulin-like growth factor binding protein 3.
- Treatment
  - injections of recombinant IGF-1.
  - Not respond to growth hormone treatment due to a lack of GH receptors.

Nelson's syndrome

- occurs in approximately 30% of **patients adrenalectomised for Cushing's disease.**
- bilateral adrenalectomy as a second line procedure is much rarer than formerly in the treatment of Cushing's disease
- It is probably due to the clinical progression of the pre-existing pituitary adenoma after the restraint of hypercortisolism on adrenocorticotropic hormone (ACTH) secretion is removed.
- **Pigmentation** arises from the MSH products of the proteolysis of POMC, which also produces ACTH.
- **Plasma ACTH levels are markedly elevated.**
- Pituitary magnetic resonance imaging (MRI) defines the extent of the tumour.

- Nelson's tumours can be aggressive and locally invasive, and prophylactic pituitary radiotherapy after adrenalectomy is favoured by many.
- Monitoring is with ACTH levels and serial pituitary imaging.

Macroglossia: Causes

- hypothyroidism
- **acromegaly**
- amyloidosis
- Duchenne muscular dystrophy
- mucopolysaccharidosis (e.g. Hurler syndrome)
- Down's syndrome → apparent macroglossia due to a combination of mid-face hypoplasia and hypotonia

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Pituitary adenoma

classifications

- Type of tumor according to size:
  - Microadenoma: ≤ 10 mm
  - Macroadenoma: > 10 mm
- Types of tumor according to hormone secretion
  - Secretory pituitary adenomas (60%): hormone secretion → **hyperpituitarism**
    - Most secrete one pituitary hormone.
    - The presence of multiple pituitary hormones should also raise the suspicion of atypical pituitary adenomas or pituitary carcinomas.
  - Non-secretory pituitary adenomas 'chromophobe'
    - A chromophobe adenoma refers to no uptake of dye within the tumourous specimen.

Type of secretory pituitary adenomas	**Relative frequency** (as a percentage of all pituitary adenomas)	**Pathophysiology**
Lactotroph adenoma(prolactinoma)	~ 40%	Hyperprolactinemia
Somatroph adenoma	~ 15%	↑ Growth hormone → acromegaly/gigantism
Corticotroph adenoma(Cushing's disease)	~ 5%	↑ ACTH → secondary hypercortisolism
Thyrotroph adenoma	~ 1%	↑ TSH →secondary hyperthyroidism

Prolactinomas are the most common pituitary adenomas

Features
The symptoms depends on the tumor size and whether the tumor produces hormones

Type of pituitary adenoma	Secretory adenomas	Non-secretory adenomas
Microadenomas	• The pituitary hormone which is produced in excess is determined by the histopathology of the pituitary adenoma (see hyperpituitarism).	• **Asymptomatic**
Macroadenomas	• The hormone which is produced in excess is determined by the histopathology of the pituitary adenoma (see hyperpituitarism); • other pituitary hormones may be deficient as a result of pituitary destruction. • **Mass effects** (e.g., headache, **bitemporal hemianopsia**, diplopia)	• **Hypopituitarism** • Mass effects(e.g., headache, bitemporal hemianopsia, diplopia)

- **Mass effects**
  - **Superior extension** of the tumour can lead to compression of firstly the optic apparatus and later the hypothalamus.
  - **Lateral extension** of the tumour with compression or invasion of the cavernous sinus can compromise third, fourth, or sixth cranial nerve functions, manifest as diplopia in 5 to 15% of pituitary tumour patients.

Diagnostics
- Cranial contrast MRI (initial test) : reveals an intrasellar mass
  - CT scan may be considered
- Hormone assays
  - Basal prolactin levels
  - Insulin-like growth factor-1 (IGF-1)
  - 24-hour urine cortisol
  - Thyroid function tests
- Perimetry: to assess visual field defects

Treatment
- **Prolactinomas**
  - First-line: dopamine agonists (e.g., bromocriptine, cabergoline), which cause the pituitary adenoma to shrink.
  - Second-line: transsphenoidal hypophysectomy ± adjuvant radiotherapy
- **Non-secretory pituitary microadenomas** (incidentalomas):
  - no treatment (only follow-up with serial MRI)
- **Other pituitary adenomas**
  - First-line: transsphenoidal hypophysectomy
  - Second-line: pituitary irradiation

Differentiate between non-functioning adenoma and macroadenoma:

- **Although stalk compression with a non-functioning tumour may cause hyperprolactinaemia the concentrations of prolactin are usually below 2000 mU/L and galactorrhoea would be rare.**

Except Prolactinomas, all other functioning adenomas are treated primarily by surgery (i.e; for secondary hyperthyroidism, acromegaly etc).

Scenario

- **If the CT scan shows a pituitary tumour with suprasellar extension, Which structures is likely to be compressed?**
  - **Optic chiasm**
    - The optic chiasm lies 5-10 mm above the diaphragm sellae and anterior to the stalk.
    - Adenomas **>** 1.5 cm frequently have suprasellar extension, and (MRI) will show compression and upward displacement of the optic chiasm.

Incidentalomas

Definition

- small pituitary tumors (microadenomas < 1 cm) that are detected on MRI or CT scans done for other reasons.

Features

- asymptomatic

Approach

- first rule out Function (i.e; hormone production).
  - first - do prolactin level, Dexamethasone suppression test, ACTH level, TSH and IGF-1

Management

- **The most appropriate strategy would be observation and repeat scanning.**

Pituitary apoplexy

- Caused by acute haemorrhage or infarction of the pituitary gland.
- A pituitary adenoma usually pre-exists, which may be asymptomatic before presentation.
- **Predisposing factors** include:
  - bromocriptine,
  - head injury,
  - pregnancy,
  - irradiation and
  - endocrine stimulation tests.

- **The combination of sudden-onset retro-orbital headache, vomiting, visual disturbance and hormonal dysfunction should lead you to consider a diagnosis of pituitary apoplexy**
- The visual symptoms include reduced acuity, visual field impairment and ocular motility dysfunction. This is due to involvement of the optic nerve, chiasm and cavernous sinus.
- Ocular paresis occurs in up to 80% of patients, with third nerve palsy the commonest finding.
- The expanding mass can compress the cavernous sinus with the Ocular nerves and the trigeminal nerve can also be affected.
- The mild hyponatraemia may be a consequence of the either syndrome of inappropriate antidiuretic hormone (SIADH) or secondary hypoadrenalism.
- The main initial problem is ↓↓ (ACTH), → ↓↓ cortisol → features of an 'Addisonian crisis', i.e. hypotension, hyponatraemia, hyperkalaemia and hypoglycaemia. Subacutely, there can be ↓ (TSH) and gonadotropins (LH and FSH).
- Diagnosis → Magnetic resonance imaging
- **Treatment**
  - Urgent steroid replacement
  - Consideration of neurosurgical decompression.
  - Over the long-term → corticosteroid, testosterone and thyroid hormone replacement.

Sheehan syndrome

- Incidence: 1 in 10,000 deliveries.
- Occur in women who have had a postpartum haemorrhage and hypovolaemic shock,
- **Risk factors** increase with
  - type 1 diabetes who have microvascular disease
  - sickle cell anaemia
- **management**
  - immediate steroid therapy
  - full endocrine assessment
  - replacement of pituitary-dependent hormones (eg thyroxine) as required.
- Subsequent conception can be difficult and require pulsed gonadotropin therapy to restart ovulation.

Hyperprolactinaemia

Prolactin and galactorrhoea

Prolactin inhibits GNRH. If there is no GNRH, the body cannot release LH and FSH.

The first test to do when seeing anyone with hyperprolactinaemia is to exclude pregnancy, as it is the most common cause.

Prolactin

- secreted by the anterior pituitary gland

- **Regulation**
  - thyrotropin-releasing hormone (TRH) stimulates prolactin release
  - Hypothalamic **dopamine inhibits prolactin**
    - dopamine agonists such as bromocriptine may be used to control galactorrhoea.
- **Functions**
  - **Prolactin is important for development of the fetal lung**
  - lactation and breast development during pregnancy.

Epidemiology

- **Sex: ♀ > ♂**
- Hyperprolactinemia is the most common form of hyperpituitarism.

Pathophysiology

- ↑ Prolactin → galactorrhea and suppression of GnRH → ↓ LH, ↓ FSH → ↓ estrogen, ↓ testosterone (hypogonatrophic hypogonadism)

Causes

Causes of raised prolactin - the p's
- pregnancy
- prolactinoma
- physiological
- polycystic ovarian syndrome
- primary hypothyroidism
- phenothiazines, metoclopramide, domperidone

1. Hypothalamic stimulation:

- **primary hypothyroidism** (due to thyrotrophin releasing hormone (TRH) stimulating prolactin release)
- Adrenal insufficiency.
- Certain types of focal epilepsy: directly after temporal lobe seizures, due to close proximity to the hypothalamus.

2. Medications (inhibit dopamine release, leading to reduced inhibition and therefore higher prolactin release):

- **Levels less than 1000 are most likely to be drug related**
  - **metoclopramide (most common)**, domperidone
  - Neuroleptics - phenothiazines, haloperidol
  - Antihypertensives - calcium-channel blockers, methyldopa
  - Psychotropic agents - tricyclic antidepressants , SSRI

- Anti-ulcer agents - Hs antagonists
- Opiates and opiate antagonists.

3. Neurogenic (via autonomic nervous system):

- Chest wall injury
- Breast stimulation
- Breast feeding.

4. Physiological causes (via oestrogen stimulation):

- Pregnancy
- Coitus
- Exercise
- Sleep
- Stress.

5. Increased prolactin production:

- Ovarian: polycystic ovarian syndrome
- Pituitary tumours
  - Prolactin-secreting pituitary adenomas (**Prolactinomas**),
    - **Pituitary adenomas are the most common cause (~ 50%) of pathological hyperprolactinemia**
  - hypothalamic stalk interruption,
  - hypophysitis ,
  - **acromegaly (1/3 of patients)**
    - **The grossly elevated prolactin concentration is most suggestive of a microprolactinoma.**
    - **The presence of hyperprolactinaemia with hypogonadotrophic hypogonadism (↓↓ sex hormones) suggests a diagnosis of a microprolactinoma**
    - **In case of combination between microprolactinoma and recurrent dyspepsia (→** gastro-entero-pancreatic tract tumours (gastrinomas, insulinomas, carcinoid)**), a diagnosis of multiple endocrine neoplasia (MEN) type 1 should be considered.**
    - Microprolactinoma is associated with levels of prolactin of 1,000-3,000 mU/L.
    - In macroprolactinomas, the prolactin concentration is greater than 3000 mU/L.
    - Combined oral contraceptives can lead to mild rises in serum prolactin, and therefore should only be used with caution in patients with prolactinomas.
    - In males, the decreased libido and erectile dysfunction are the result of decreased FSH, LH, and testosterone due to the **upstream inhibition of GnRH**, which would normally result in the release of these hormones from the anterior pituitary.
    - inhibitory effect of prolactin on GnRH → ↓ FSH, LH, and testosterone → decreased libido and erectile dysfunction

6. Reduced prolactin elimination:

- **Renal failure**
- Hepatic insufficiency

7. idiopathic hyperprolactinaemia

- **over time prolactin levels stay the same around 50% of the time.**
- A reduction in prolactin levels occurs in around a third of people presenting with idiopathic hyperprolactinaemia.
- A further increase in prolactin is seen in the remainder

Features of excess prolactin

- men: impotence, loss of libido, galactorrhoea
- women: amenorrhoea, galactorrhoea

Hormonal changes	Clinical features	
	Female	**Male**
↑ **Prolactin**	• **Galactorrhea**	• Galactorrhea is rare.
↓ **LH + ↓ FSH**	• Primary and/or secondary amenorrhea, or **irregular menses** • Infertility	• Clinical features of ↓ testosterone (see below)
↓ **Testosterone**	• Loss of libido	• Loss of libido, erectile dysfunction • Gynecomastia
↓ **Estrogen**	• Atrophic endometrium and vaginal atrophy (menopausal symptoms) • **Osteoporosis** (after several years)	• Little to no noticeable effects

The presence of amenorrhea, galactorrhea, and vaginal atrophy in a woman with new-onset headaches and blurry vision should raise suspicion of which diagnosis?

- ➢ **prolactinoma.**

- **The most likely hormonal result will be?**
  - ➢ **↑Prolactin ↓FSH ↓LH**
    - elevated FSH leads to a normal/high estrogen and would not be consistent with vaginal atrophy, which is a sign of decreased estrogen.

Investigations

- serum prolactin

Levels of prolactin

- **<** 1000 → **drug-induced prolactinaemia**
- 1000 -- 3000 mU/l → **microprolactinoma**.
- **>** 3000 → **macroprolactinoma.**

- ➢ HOOK EFFECT:

  - Very high prolactin concentrations can interfere with immunoassay systems resulting in falsely low prolactin determination. this is due to "hook effect" which describes the inhibition of immune complex formation by excess antigen concentrations.
  - this is an important consideration in patients with large pituitary adenomas when the clinical suspicion of prolactinoma is strong, as in patients with amenorrhoea-galactorrhoea or longstanding hypogonadism.
  - appropriate dilution of the serum in such cases helps in accurate estimation of serum prolactin concentration.
- Dopamine antagonist tests using metoclopramide may also be used in the investigation of hyperprolactinaemia.
  - A normal response is at least a twofold rise in prolactin.
  - A blunted prolactin response suggests a prolactinoma
- MRI
  - **The most accurate diagnostic test is an MRI of the brain.**
  - Be aware MRIs do not rule out small microadenomas

Hyperprolactinaemia → ↓ GRH → ↓ LH & FSH

Treatment of prolactinomas

Prolactinoma management - medical therapy is almost always first-line

- **dopamine agonist therapy (cabergoline and Bromocriptine)**
  - effective in most patients
  - they are able to normalize the prolactin levels, restore gonadal function and reduce tumor size
  - If patient is asymptomatic, there is no absolute requirement for treatment.
  - Indications for treatment are adverse effect of tumour size or effects of prolactinaemia.
  - Contraindications to treatment are cardiac valve fibrosis and pulmonary fibrosis.
  - **A meta-analysis suggested that cabergoline is more efficacious than bromocriptine in normalising prolactin and has a better side effect profile, and is therefore the treatment of choice.**
    - Both pergolide and **cabergoline may be associated with pericarditis,** cardiac valve regurgitation, pericardial effusion and pulmonary hypertension.
      - ropinirole may be an appropriate alternative in this case, otherwise surgery would be the next most appropriate step.
  - **If possible, dopamine agonists can be held during pregnancy but if treatment is required bromocriptine has the most safety data.**
    - **Bromocriptine is the first drug of choice in symptomatic pregnant.**
    - Cabergoline may be considered if the adenoma does not respond to bromocriptine
  - **Women should stop her bromocriptine once she knows she is pregnant .**

- It is advisable to stop the use of Dopamine agonists (DAs) immediately once pregnancy is confirmed, except in the case of women with invasive macroprolactinomas or pressure symptoms.
- There is no evidence that bromocriptine is teratogenic, but Once pregnancy is established, bromocriptine is not necessarily required, and so most physicians recommend stopping it for the duration.

- If Prolactin Producing Macroadenomas are associated with mass effect → Still bromocriptine must be tried first. Only if no response, Surgery (trans sphenoidal resection) is done.
  - Remember that prolactinomas even when large and causing symptoms , they can shrink with dopamine agonists.
- **Pituitary surgery** is rarely required in prolactinomas and is generally reserved for patients intolerant of or resistant to dopamine agonist therapy. Radiotherapy can be used to reduce the chance of tumour recurrence, but is rarely required.

Cabergoline	**Bromocriptine**
higher affinity and selectivity for D2 dopamine receptors.	D2 receptor agonist with agonist and antagonistic properties on D1 receptors.
has long duration of action allowing administration once or twice weekly with better tolerability and patient compliance	required multiple dosing throughout the day because of its short half life

Which hormones are expected to be low in hyperprolactinaemia?

- Hyperprolactinaemia suppresses the release of gonadotropin-releasing hormone **(GRH),** which leads to reduced production of luteinising hormone **(LH)** and follicle-stimulating hormone **(FSH).**
- There can also be a direct effect of prolactin itself on the ovary to disrupt LH and FSH signalling.

Prolactinomas in pregnancy

- During pregnancy, the pituitary gland undergoes global hyperplasia due to a progressive increase in serum estrogens level that may lead to increase of the tumor volume with potential mass effect and visual loss
- The risk of tumor enlargement during pregnancy is found to depend on tumor size:
  - 3% for microprolactinomas,
  - 32% for macroprolactinomas that were not previously operated on
- In case the patient becomes symptomatic with visual disturbance or progressive headaches, an MRI without gadolinium (not a CT) should be performed to assess changes in tumor size.
- pregnancy is not recommended in women with **drug resistant large macro**prolactinomas and they should not conceive even if the tumor is intrasellar, until the size is reduced by transsphenoidal surgery.

Cranial irradiation may **initially** cause **hyperprolactinaemia** but a **low PRL** is typical **after a year**.

A patient presented with **elevated oestradiol** and **prolactin** with suppressed (LH/FSH) and recent

amenorrhoea. what is the most likely diagnosis?
➔ **Pregnancy**

Bromocriptine

- **Action**
  - Bromocriptine is an ergotamine dopamine agonist that leads to activation of D2 receptors
    - Agonist at central and peripheral D2 receptors
- **Indications**
  - used to inhibit prolactin release from the anterior pituitary
  - preferred in women who are looking to get pregnant or are having unprotected sex.
    - *Bromocriptine has less teratogenicity than cabergoline.*
- **Side effects**
  - **Common**
    - nausea
    - nasal congestion
    - constipation
  - **Uncommon**
    - Dizziness (orthostatic hypotension.)
    - dyskinesia
  - **Rare**
    - **Tinnitus**
    - Excessive sleepiness (it is seen more commonly with modern agents such as ropinirole).
    - Pulmonary fibrosis
    - diarrhoea
    - vasospasm in the peripheral circulation
      - Higher doses may cause cold-induced peripheral digital vasospasm (**Raynaud's phenomenon**).
    - hallucinations and psychosis
      - exacerbation or unmasking of depression and psychosis.
      - only at very high drug doses

TSH-producing pituitary tumour (secondary hyperthyroidism)

If free T4 and T3 are high, but TSH is normal or high, a pituitary MRI should be done to look for a pituitary mass (TSH-secreting adenoma).

The diagnosis should be suspected when TSH concentrations are not suppressed in the presence of hyperthyroidism.

Definition

- **secondary hyperthyroidism** due to a pituitary tumour (thyrotrophinoma) that is producing thyroid-stimulating hormone (TSH). **with elevated tri-iodothyronine (T3) and thyroxine (T4) and inappropriately *normal* or high (TSH).**

Epidemiology

- rare approximately less than 1% of all pituitary adenomas,

Features

- features of thyrotoxicosis: sweating, weight loss, lethargy, tachycardia
- Clinical examination: There is a diffuse, smoothly enlarged thyroid due to TSH stimulation.

Investigations

- **free T4 and T3 are high**
- **TSH is normal or high**
- **Alpha subunit is also secreted in large amounts**
  - measurement of this should yield an **elevated alphaSU: TSH ratio** (usually 1:1).
- **Pituitary MRI**
  - **the next investigation of choice**
  - to look for a pituitary mass (TSH-secreting adenoma).

Differential diagnosis

- If there is no pituitary mass, but there is end-organ evidence of hyperthyroidism, a careful family pedigree should be obtained as well as genetic testing for the possibility of **thyroid hormone resistance.**

Treatment

- Trans-sphenoidal resection of the tumour is the therapy of choice.

Thyroid and parathyroid conditions

Physiological effects of thyroid hormones

- **Thyroid hormones production**
  - The thyroid utilises tyrosine and iodine to manufacture thyroxine and T3.
  - Iodide is taken into the thyroid follicular cells by active transporters and then oxidised to iodine by thyroid peroxidase.
  - Organification occurs when iodine is attached to tyrosine molecules which themselves are attached to thyroglobulin, forming monoiodotyrosine (MIT) and diiodotyrosine (DIT). The coupling of 2 molecules of DIT forms thyroxine.
- **T4 vs T3**
  - More T4 is produced than T3 but T4 is less potent.
  - A **deiodinase** in the blood converts T4 to the biologically active T3.T4 is therefore a hormonal precursor (prohormone).
  - **Peripheral metabolism of thyroxine is the only source of T3.**
  - The half-life of T3 is about one day (~ 20 hours), whereas the half-life of T4 is about one week (~ 190 hours). This **longer half-life** makes T4 suitable for use as a depot form that can be used replacement therapy.
- **Thyroid hormone receptor**
  - **The thyroid hormone receptor is a nuclear receptor.**

- **Functions of thyroid hormones**
  - **Enhancement of**:
    - insulin-dependent entry of glucose into cells **(Enhance insulin sensitivity**)
    - myocardial oxygen consumption
    - nerve conduction
    - gluconeogenesis, and
    - oxidation of fatty acids.

➔

What is the defect Which responsible for thyroid hormone dyshormonogenesis?

- **Defect in iodine organification**

Calcitonin

- polypeptide hormone
- produced by the parafollicular cells (also known as C-cells) of the thyroid,
- acts to reduce blood calcium (Ca^{2+}), opposing the effects of parathyroid hormone (PTH).
- **Calcitonin-gene related peptide causes vasodilatation.**
- Secretion of calcitonin is stimulated by:
  - an increase in serum [Ca2+]
  - gastrin and pentagastrin.
- calcitonin lowers blood Ca2+ levels in two ways:
  1. Major effect: Inhibits osteoclast activity in bones
  2. Minor effect: Inhibits renal tubular cell reabsorption of Ca2+ and phosphate, allowing them to be excreted in the urine
- calcitonin receptor,
  - found on **osteoclasts**, and in the kidney and regions of the brain,
  - is a G protein-coupled receptor, which is coupled by G_s to adenylate cyclase and thereby to the generation of cAMP in target cells.
  - It may also affect the ovaries in women and the testes in men.
- **Despite high serum calcitonin levels, which mechanism best explains the normal calcium levels in a patient with thyroid nodule ?**
  - **High levels of calcitonin down regulates its receptor**
    - Calcitonin's primary function is to act on osteoclasts and decrease serum calcium levels.
    - Huge amounts of calcitonin are secreted in medullary carcinoma of the thyroid, or when calcitonin is used therapeutically to treat certain medical conditions, such as Paget's disease, osteoporosis, and hypercalcemia. Its effects on osteoclasts disappear after one week of therapy. This is called the **'calcitonin escape phenomenon'**.
    - The biochemical basis for the 'calcitonin escape phenomenon' is the down regulation of its receptor.
    - Whenever the levels of calcitonin become high, they down regulate the receptor by rapid and prolonged down regulation of calcitonin receptor messenger RNA.

Thyroid disorders and respiratory physiology

Compared with normal subjects, hyperthyroid patients show significantly lower resting arterial CO_2 tension, tidal volume and significantly higher mean inspiratory flow and Pao_2.

Thyroid function tests: The interpretation of thyroid function tests is usually straightforward:

Diagnosis	TSH	Free T4	Notes
Thyrotoxicosis (e.g. Graves' disease)	Low	High	In T3 thyrotoxicosis the free T4 will be normal
Primary hypothyroidism (primary atrophic hypothyroidism)	High	Low	
Secondary hypothyroidism	Low	Low	Replacement steroid therapy is required prior to thyroxine
Sick euthyroid syndrome*	Low**	Low	Common in hospital inpatients T3 is particularly low in these patients
Subclinical hypothyroidism	High	Normal	
Poor compliance with thyroxine	High	Normal	
Steroid therapy	Low	Normal	

*now referred to as non-thyroidal illness

**TSH may be normal in some cases

Thyrotropin is a glycoprotein hormone (glycosylated)

Thyroid disorders: a very basic introduction

- Disorders of thyroid function are very commonly encountered in clinical practice. Around 2% of the UK population has hypothyroidism (an under active thyroid gland) whilst around 1% have thyrotoxicosis (an over active gland).
- Both hypothyroidism and hyperthyrodism (also known as thyrotoxicosis) are around 10 times more common in women than men.

Structure and function

- The thyroid gland is one of the largest endocrine organs in the body. It is a bi-lobed structure which is found in the anterior neck. As with many endocrine organs it is part of a hypothalamus-pituitary-end organ system with negative feedback cycles to main.
- On a simple level the hypothalamus secretes thyrotropin-releasing hormone (TRH) which stimulates the anterior pituitary to secrete thyroid-stimulating hormone (TSH). This then acts on the thyroid gland increasing the production of thyroxine (T4) and triiodothyronine (T3), the two main thyroid hormones. These then act on a wide variety of tissues, helping to regulate the use of energy sources, protein synthesis, and controls the body's sensitivity to other hormones.

How are thyroid problems classified?

- Hypothyroidism may be classified as follows

- primary hypothyroidism: there is a problem with the thyroid gland itself, for example an autoimmune disorder affecting thyroid tissue (see below)
- secondary hypothyroidism: usually due to a disorder with the pituitary gland (e.g.pituitary apoplexy) or a lesion compressing the pituitary gland
- congenital hypothyroidism: due to a problem with thyroid dysgenesis or thyroid dyshormonogenesis

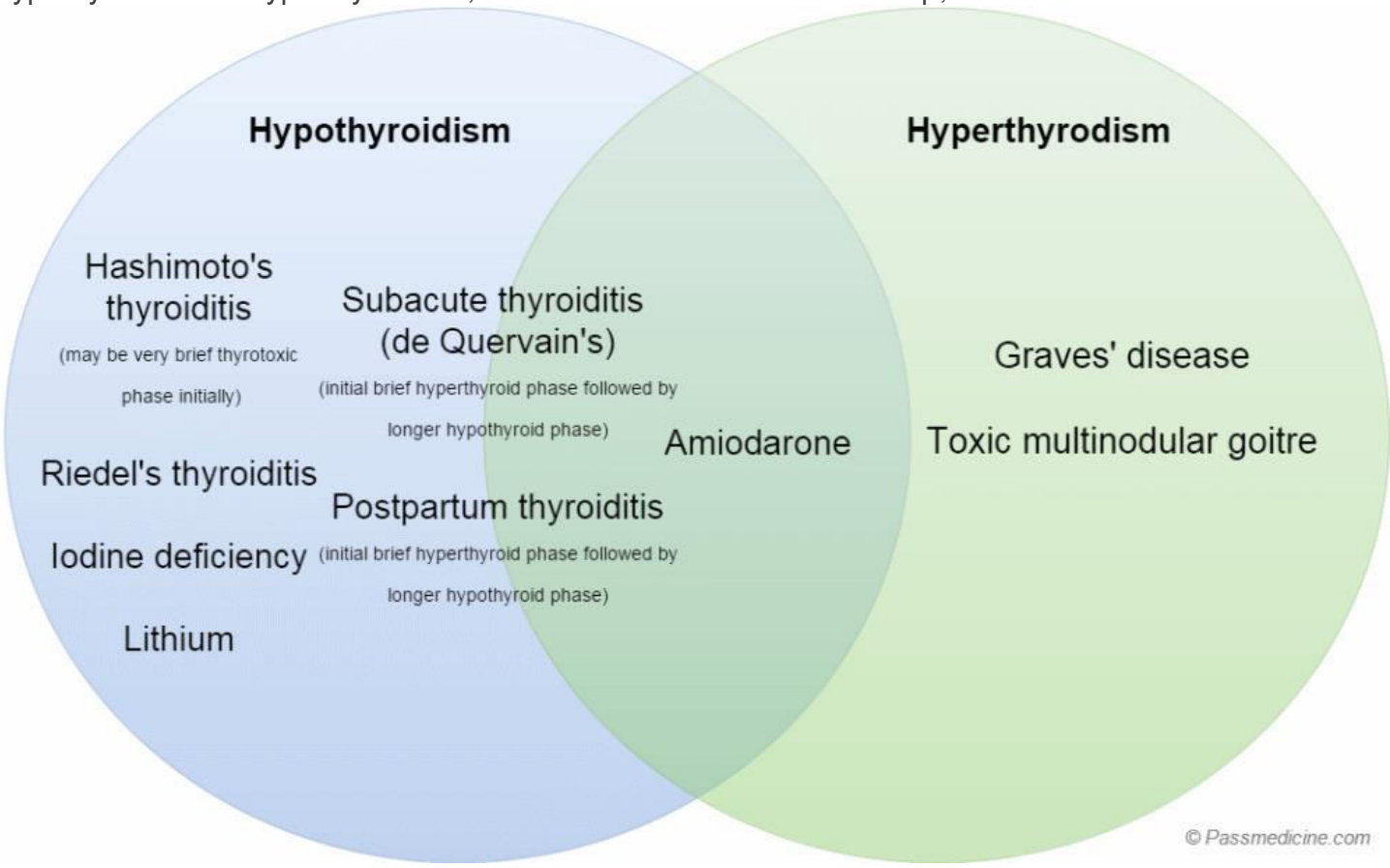
What causes thyroid problems?

- The majority of thyroid problems seen in the developed world are a consequence of autoimmunity.

The table below shows the different autoimmune problems which cause thyroid dysfunction:

	Hypothyroidism	**Thyrotoxicosis**
Most common cause	Hashimoto's thyroiditis • most common cause • autoimmune disease, associated with type 1 diabetes mellitus, Addison's or pernicious anaemia • may cause transient thyrotoxicosis in the acute phase • 5-10 times more common in women	Graves' disease • most common cause of thyrotoxicosis • as well as typically features of thyrotoxicosis other features may be seen including thyroid eye disease
Other causes	Subacute thyroiditis (de Quervain's) • associated with a painful goitre and raised ESR Riedel thyroiditis • fibrous tissue replacing the normal thyroid parenchyma • causes a painless goitre Postpartum thyroiditis Drugs • lithium • amiodarone Iodine deficiency • the most common cause of hypothyroidism in the developing world	Toxic multinodular goitre • autonomously functioning thyroid nodules that secrete excess thyroid hormones Drugs • amiodarone

It should be remembered that a lot of the conditions mentioned above don't always cause either hypothyroidism or hyperthyroidism, there is sometimes some overlap, as shown below:



Venn diagram showing how different causes of thyroid dysfunction may manifest. Note how many causes of hypothyroidism may have an initial thyrotoxic phase.

Symptoms and signs

Thyroid disorders can present in a large variety of ways. Often (but not always) the symptoms present are the opposite depending on whether the thyroid gland is under or over active, for example hypothyroidism may result in weight gain whilst thyrotoxicosis normally leads to weight loss

Feature	Hypothyroidism	Thyrotoxicosis
General	**Weight gain**	**Weight loss**
	Lethargy	'Manic', restlessness
	Cold intolerance	Heat intolerance
Cardiac	Bradycardia	**Palpitations**, may even provoke arrhythmias e.g. atrial fibrillation
Skin	Dry (anhydrosis), cold, yellowish skin	Increased sweating
	Non-pitting oedema (e.g. hands, face)	Pretibial myxoedema: erythematous, oedematous lesions above the lateral malleoli
	-	Thyroid acropachy: clubbing
Hair	Dry, coarse (خشن) scalp hair, loss of lateral aspect of eyebrows	Fine (ناعم)
Gastrointestinal	Constipation	Diarrhoea
Gynaecological	Menorrhagia	Oligomenorrhea
Neurological	Decreased deep tendon reflexes Carpal tunnel syndrome	**Anxiety** **Tremor**

Investigations and diagnosis

The principle investigation is 'thyroid function tests', or TFTs for short:

- these primarily look at serum TSH and T4 levels

- T3 can be measured but is only useful clinically in a small number of cases
    - Note that T3 concentrations are of no value when evaluating hypothyroidism because the T3 values are often normal due to increased T4 to T3 conversion.
- remember that TSH and T4 levels will often be 'opposite' in cases of primary hypo- or hyperthyroidism. For example in hypothyroidism the T4 level is low (i.e. not enough thyroxine) but the TSH level is high, because the hypothalamus/pituitary has detected low levels of T4 and is trying to get the thyroid gland to produce more
- TSH levels are more sensitive than T4 levels for monitoring patients with existing thyroid problems and are often used to guide treatment

The table below shows how thyroid function tests are interpreted:

Diagnosis	TSH	Free T4	Notes
Thyrotoxicosis (e.g. Graves' disease)	Low	High	
Primary hypothyroidism (e.g. Hashimoto's thyroiditis)	High	Low	
Secondary hypothyroidism	Low	Low	
Sick euthyroid syndrome	Low	Low	Common in hospital inpatients. Changes are reversible upon recovery from the systemic illness and no treatment is usually needed
Subclinical hypothyroidism	High	Normal	This is a common finding and represents patients who are 'on the way' to developing hypothyroidism but still have normal thyroxine levels. Note how the TSH levels, as mentioned above, are a more sensitive and early marker of thyroid problems
Poor compliance with thyroxine	High	Normal	Patients who are poorly compliant may only take their thyroxine in the days before a routine blood test. The thyroxine levels are hence normal but the TSH 'lags' and reflects longer term low thyroxine levels

Different patterns on thyroid function test:

Situation	TSH	fT4	fT3
Over-replacement with thyroxine	**Low**	**High**	**Normal/High**
Sick euthyroid syndrome	Normal/ High	Low	Normal/Low
Subclinical hypothyroidism	High	Normal	Normal
TSH-secreting tumour	High	High	High
Untreated hypopituitarism	Low/Low normal	Low/Low normal	Low/Low normal

A number of thyroid autoantibodies can be tested for (remember the majority of thyroid disorders are autoimmune). The 3 main types are:

- Anti-thyroid peroxidase (anti-TPO) antibodies
  - present at high titre, in Hashimoto's thyroiditis
  - low titre in Graves' disease, De Quervain's thyroiditis,
  - 8% of males, and 10% of females without thyroid disease.
- TSH receptor antibodies
- Thyroglobulin antibodies

There is significant overlap between the type of antibodies present and particular diseases, but generally speaking TSH receptor antibodies are present in around 90-100% of patients with Graves' disease and anti-TPO antibodies are seen in around 90% of patients with Hashimoto's thyroiditis

Other tests include:

- nuclear scintigraphy; toxic multinodular goitre reveals patchy uptake

Anti-TPO antibodies are present in 10% females without thyroid pathology

Treatment

- This clearly depends on the cause.
  - **For patients with hypothyrodism:** thyroxine is given in the form of levothyroxine to replace the underlying deficiency.
  - **Patients with thyrotoxicosis may be treated with:**
    - propranolol: this is often used at the time of diagnosis to control thyrotoxic symptoms such as tremor

- carbimazole: blocks thyroid peroxidase from coupling and iodinating the tyrosine residues on thyroglobulin → reducing thyroid hormone production. Agranulocytosis is an important adverse effect to be aware of
- radioiodine treatment

A history of an acutely painful, left-sided goitre in euthyroid and apyrexial patient with normal labs and no prior history of thyroid disease ?

➔ **Haemorrhage into a cyst**

Hypothyroidism: causes

Hypothyroidism affects around 1-2% of women in the UK and is around 5-10 times more common in females than males.

- **Primary atrophic hypothyroidism**
  - most common cause
  - autoimmune disease, associated with IDDM, Addison's or pernicious anaemia
  - 5 times more common in women

- **Hashimoto's thyroiditis**
  - autoimmune disease with goitre (positive microsomal antibodies)
  - may cause transient thyrotoxicosis in the acute phase
  - 10 times more common in women
- **After thyroidectomy or radioiodine treatment**
- **Drug therapy** (e.g. lithium, amiodarone or anti-thyroid drugs such as carbimazole)
  - "The common clinical side effects of the lithium are goitre in up to 40% and hypothyroidism in about 20%. Lithium increases thyroid autoimmunity if present before therapy. Treatment with levothyroxine is effective and lithium therapy should not be stopped."
- **Dietary iodine deficiency**
  - **Iodine deficiency** is extremely unlikely in the United Kingdom
  - **common in parts of central Africa,** where the diet is poor in iodine and access to sea fish is relatively difficult.
  - It may present as goitre without hypothyroidism, or in severe cases can progress to frank hypothyroidism.
- **Secondary hypothyroidism (rare)**:From pituitary failure
- **Other associated conditions**
  - Down's syndrome
  - Turner's syndrome
  - coeliac disease
  - **Hyperprolactin (hyperPRL) hypogonadism:**
    - Hypothyroidism → ↑↑TRH (thyrotropin-releasing factor) → act as prolactin-releasing factor → release of prolactin and hyperprolactinaemia.
  - slightly raised bilirubin:

- In hypothyroidism, the activity of bilirubin UDP-glucuronyl transferase is decreased, resulting in a reduction in bilirubin excretion.

➢ **Dyslipidaemia: may well resolve following the appropriate replacement with thyroxine.**

➢ **Hypercarotenaemia** (high blood levels of beta-carotene)

- **Carotonemia is yellowing of the skin (xanthoderma) associated with beta-carotene excess and can be seen in hypothyroidism**.
- It occurs because of a decrease in conversion from carotene to vitamin A.
- decreased consumption of vitamin A in hypothyroidism.
- thyroxine, normally speeds the conversion of beta-carotene to retinol.
- ↓ thyroxine → ↑Beta-carotene
- Beta-carotene is more prominent in areas where the stratum corneum is thickened (palms and soles).
- Carotenemia is most commonly seen in young children who are fed excessive amounts of **beta-carotene rich foods** (squash, sweet potatoes, carrots).
- It may also be seen in some instances of diabetes mellitus, hyperlipidemia, anorexia nervosa or hepatic and renal disease.

- **Low thyroid hormone means reduced use of glucose and FFAs as fuel. This is why glucose intolerance and hyperlipidemia occur in hypothyroidism.**
- **Low thyroid = Decreased metabolic rate = Weight gain**

Feature

- Constipation,
- dry skin,
- Menorrhagia
- Weight gain
- **Clinically silent pericardial effusion is common in untreated hypothyroidism**
- The predominant lipid picture in hypothyroidism is mixed dyslipidaemia (↑LDL , ↑ **triglycerides**)

Thyroxine in patient receiving oestrogen/progesterone (HRT):

- Thyroxine is mostly bound to thyroxine binding globulin in the circulation.
- Oestrogen therapy is associated with elevation of thyroxine binding globulin in the serum.
- Thus the **total serum thyroxine** may be misleading in this case, and **serum free thyroxine will confirm whether this patient is hypothyroid or euthyroid.**

confusion and coldness with erythema ab igne suggest a diagnosis of hypothyroidism.

Which laboratory tests is most likely to confirm the diagnosis of hypothyroidism?

⇨ **Serum thyroid-stimulating hormone (TSH) measurement**

- TSH levels usually rise above normal before serum thyroxine(T4) and serum triiodothyronine

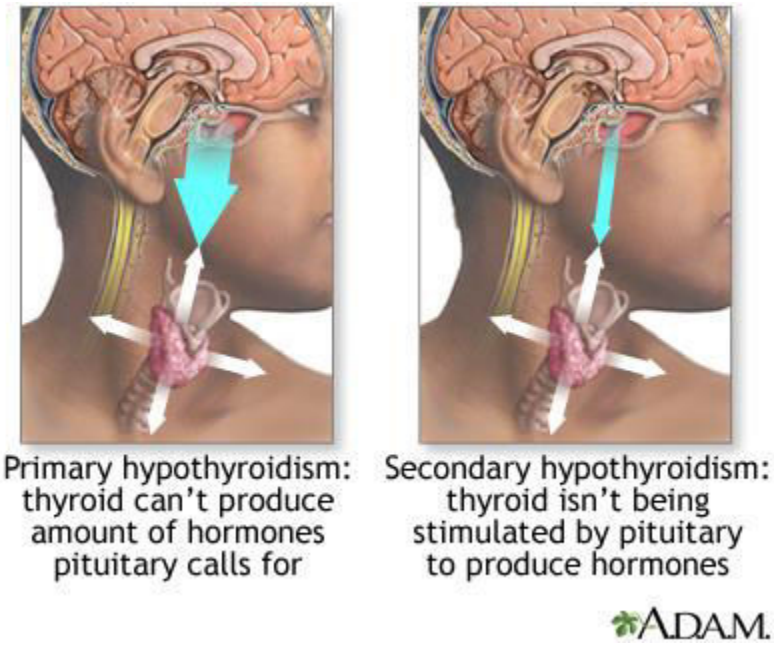
(T3) levels do, even in mild cases of hypothyroidism.
- anti-thyroid antibodies is characteristic of chronic thyroiditis, which is the most common cause of hypothyroidism. However, detection of these antibodies would not indicate that hypothyroidism was present.

Myxoedema coma
- usually occurs in the elderly who are typically non-compliant.
- can be the initial presentation of hypothyroidism, but more usually occurs against a background of long-standing disease where patients are unable to comply with their thyroxine replacement.
- carries a high mortality
- The clues toward this diagnosis are:
  - 'yellowish hue' (referring to carotinaemia)
  - obesity
  - bradycardia
  - hypothermia, and
  - coma.
- Facial features include general coarsening with periorbital oedema and hair thinning.
- **should be treated initially with IV thyroid hormone - either T4 or T3 - and IV hydrocortisone even before results are obtained.**
  - Treatment with hydrocortisone is recommended until Addison's disease can be excluded, as just **giving thyroid hormone alone may precipitate an adrenal crisis.**
- Other treatment includes rewarming.
  - should be rewarmed **slowly** in order to improve the chance of neurological recovery.
- IV fluids should be used cautiously, as these patients are typically fluid overloaded.

High dose aspirin may affect interpretation of free T4 values, but low dose aspirin and clopidogrel are not known to interfere with thyroid function testing.

A number of agents are known to interfere with thyroxine absorption. These include binding agents such as cholestyramine and sevelamer, iron sulphate, and proton pump inhibitors.

Primary vs secondary hypothyroidism



primary vs secondary hypothyroidism

- **primary hypothyroidism**
  - menorrhagia,
  - skin will be coarse,
  - macroglossia will be severe,
  - diastolic BP elevated,
  - delayed relaxation of deep tendon reflexes.
  - High TSH, low T4, low T3
- **secondary hypothyroidism**
  - skin and hair which are dry but not very coarse,
  - skin depigmentation,
  - only minimal macroglossia,
  - **atrophic breasts**,
  - **low blood pressure**,
  - **normal or low TSH, low T4, low T3**
- Amenorrhea, menorrhagia and other menstrual irregularities are all associated with both primary and secondary hypothyroidism.

Hypothyroidism: management

Iron reduces the absorption of thyroxine

Key points

- initial starting dose of levothyroxine should be lower in elderly patients and those with ischaemic heart disease. The BNF recommends that for patients with cardiac disease, severe hypothyroidism or patients over 50 years the initial starting dose should be 25mcg od with dose slowly titrated. Other patients should be started on a dose of 50-100mcg od
- following a change in thyroxine dose thyroid function tests should be checked after 8-12 weeks
- the therapeutic goal is 'normalisation' of the thyroid stimulating hormone (TSH) level. As the majority of unaffected people have a **TSH value 0.5-2.5 mU/l it is now thought preferable to aim for a TSH in this range**
- women with established hypothyroidism who become pregnant should have their dose increased 'by at least 25-50 micrograms levothyroxine due to the increased demands of pregnancy. The TSH should be monitored carefully, aiming for a low-normal value
- there is no evidence to support combination therapy with levothyroxine and liothyronine
- Over-replacement can lead to accelerated bone loss and osteoporosis, particularly in women so regular monitoring of TSH is recommended.

Monitoring of thyroid status
Thyroid-stimulating hormone (TSH) is the most sensitive indicator of thyroid status.
• **Normal TSH** result **suggests→ adequate thyroxin replacement & euthyroidism** • **↑↑ (TSH) with normal (T4) suggest → poor compliance** • **↓↓ (TSH) with normal - high (T4) suggests → over-replacement**

Side-effects of thyroxine therapy

- hyperthyroidism: due to over treatment
- reduced bone mineral density
- worsening of angina
- atrial fibrillation

Interactions: Drugs interfere with absorption of thyroxine → leading to a hypothyroid crisis.

- **rifampicin**
- calcium supplements
- Amiodarone
- and ferrous sulphate (give at least 2 hours apart)

Overdoses of thyroxine

- are relatively rare,
- In reality, patients may be partially protected from thyroid hormone excess by production of reverse T3.

- **The vast majority can be managed with regular propranolol to alleviate symptoms of tachycardia and anxiety.**
- **In severe cases**,
  - plasmapheresis to remove protein bound thyroxine,
  - and cholestyramine to reduce enterohepatic circulation of thyroxine

In which situation is it most important to increase the thyroxine dose very gradually?

Increased age

In the older population, the recommended initial dose of levothyroxine is 25 µg once daily, adjusted in steps of 25 µg every four weeks according to response. This is because of significantly increased risk of cardiac arrhythmia in older patients.

Hashimoto's thyroiditis

Hashimoto's thyroiditis = hypothyroidism + goitre + anti-TPO

Hashimoto's thyroiditis is associated with thyroid lymphoma

- Hashimoto's thyroiditis is an autoimmune disorder of the thyroid gland.
- It is typically associated with hypothyroidism although there may be a transient thyrotoxicosis in the acute phase.
- **Early in the course of disease, T4 and TSH levels are normal and there are high levels of thyroid peroxidase antibodies** and, less commonly, anti-thyroglobulin antibodies. **Thyroid radioiodine uptake may be increased** because of defective iodide organification, together with a gland that continues to trap iodine.
- **Later in the course of the disease**, patients develop hypothyroidism with decreased T4, decreased radioiodine uptake, and increased TSH.
- **It is the most common hypothyroidism in UK**, Irrespective of gender.
- It is 10 times more common in women
- **Commonly associated with Turner's syndrome.**

Features

- features of hypothyroidism (eg hair loss, hoarse voice and periorbital oedema)
- goitre: firm, non-tender
- antibodies
  - anti-thyroid peroxidase (anti TPO) also known as (**Anti-microsomal antibodies)**
  - anti-thyroglobulin antibodies (anti-Tg)

Hashimoto's encephalopathy

- Hashimoto's encephalopathy is extremely rare.
- **result in altered mental state, myoclonus and ataxia.**

- Should be suspected in TSH derangement however there may be no clinical evidence of thyroid dysfunction.
- **the next laboratory tests should be → Anti-thyroid peroxidase antibodies**
- It is a steroid responsive encephalopathy

January 2009 exam: Feature of feeling tired and cold + firm, non-tender goiter. TSH = 24.2 mU/l, Free T4 = 5.4 pmol/l. What is the most likely diagnosis? Hashimoto's thyroiditis

September 2009 exam: A patient diagnosed with autoimmune thyroiditis. Which type of thyroid cancer is she predisposed to developing? Lymphoma

September 2009 exam: Which one of the following is most likely to be found in a patient with Hashimoto's thyroiditis? Anti-thyroid peroxidase antibodies.

Profound hypothyroidism

Presentation

- **greatly reduced free T4 concentration,**
- hypothermic
- unconscious
- evidence of associated heart failure.

Management

- T3 is usually given via a nasogastric tube or by intravenous injection at the rate of 2.5-5 pg every 8 hours, with conversion to T4 after the patient regains consciousness.
- There is a risk of precipitating heart failure if larger doses are given in the initial period.

Prognosis

- Mortality associated with this condition used to be as high as 50%, but survival has improved with modern intensive-care management.

Pendred's syndrome Autosomal recessive disorder of defective iodine uptake

signs of deafness and hypothyroidism → Pendred's syndrome

Features

- **sensorineural deafness**
- The patients tend to present with :
  - progressive hearing loss
  - delay in academic progression.
  - Often head trauma tends to make the sensorineural deafness worse, leading to patients having to avoid contact sports.
  - goitre
- euthyroid or mild hypothyroidism
- Thyroid function tests are also often normal, requiring the perchlorate discharge test to aid diagnosis.
- **diagnosed** via **:**

  - **genetic testing** (Pendred syndrome **(PDS) gene**, **chromosome 7**),
  - audiometry and MRI imaging to look for **characteristic one and a half turns in the cochlea**, compared to the normal two and a half turns.
- **Treatment** with:
  - thyroid hormone replacement
  - cochlear implants.

Sick euthyroid syndrome

- In sick euthyroid syndrome (now referred to as non-thyroidal illness) it is often said that everything (TSH, thyroxine and T3) is low.
- In the majority of cases however the TSH level is within the normal range (inappropriately normal given the low thyroxine and T3).

Pathology

- down regulation of type 1 deiodinase, reducing the peripheral conversion of T4 to T3 and thus reducing the basal metabolic rate during periods of stress.
- Upregulation of type 3 deiodinase to inactive (reverse) T3 also aids to reducing basal metabolic rate.

Causes

- myocardial infarctions,
- starvation,
- burns, trauma, surgery,
- malignancy,
- diabetic ketoacidosis,
- any organ failure **(particularly common in patients with chronic renal failure)**
- inflammatory conditions.

Features: Typically:

- Thyroid-stimulating hormone (TSH) decreases during the acute phase of the illness and increases during recovery.
- Free tri-iodothyronine (fT3) is low due to reduced peripheral conversion of thyroxine (T4) to T3 by deiodinase enzymes. Similar issues can occur in chronic nutritional deficiency, poorly controlled diabetes mellitus and drug treatment with hydrocortisone or beta blockers.
- Reverse T3 (rT3) is made instead of normal T3.
- T4 is often normal or slightly low.
- Thyroid binding proteins.

Management

- Changes are reversible upon recovery from the systemic illness.
- **the most appropriate next step in management → repeat thyroid function tests in 3 months**

September 2012 exam: A patient admitted to ITU with a severe pneumonia. Thyroid function tests are most likely to show:? TSH normal / low; thyroxine low; T3 low

Skin disorders associated with thyroid disease

Skin manifestations of hypothyroidism

- dry (anhydrosis), cold, yellowish skin
- non-pitting oedema (e.g. hands, face)
- dry, coarse scalp hair, loss of lateral aspect of eyebrows
- eczema
- xanthomata

Skin manifestations of hyperthyroidism

- pretibial myxoedema:
  - erythematous, oedematous lesions above the lateral malleoli
  - It can occur anywhere, but typically it occurs on the shins and dorsum of feet.
  - treatment:
    - No treatment is usually required, → **Reassurance**
    - when there is more severe localised pain, then patients may be considered for local use of a potent corticosteroid such as fluocinolone.
      - **Topical fluocinolone is the first line treatment for pretibial myxoedema, but usually only when there is significant pain and discomfort.**
    - Systemic steroids are only rarely used for very severe disease, usually in conjunction with compression bandaging.
- thyroid acropachy: clubbing
- scalp hair thinning
- increased sweating

Pruritus can occur in both hyper- and hypothyroidism

Subclinical hypothyroidism

Basics

- TSH raised but T3, T4 normal
- no obvious symptoms

Significance

- risk of progressing to overt hypothyroidism is 2-5% per year (higher in men)
- risk increased by presence of thyroid autoantibodies

Treat if

- **TSH > 10**
- thyroid autoantibodies positive
- other autoimmune disorder
- previous treatment of Graves' disease
- For patients with atherosclerotic cardiovascular disease
- Pregnancy or pregnancy planned in the near future

Frequency of TFT testing :

- **if anti-TPO antibodies are negative and asymptomatic → Review every 3 years with thyroid function tests**
- Where antibodies are positive, a 1-year testing interval is recommended for patients without symptoms of hypothyroidism.

Pregnancy: thyroid problems

Physiological changes

- thyroid gland hypertrophy
  - The thyroid gland needs to produce 50% more thyroid hormone during pregnancy to maintain a euthyroid state.
- increase in thyroid-binding globulin and albumin due to increased hepatic synthesis.
  - **pregnancy → ↑↑ thyroxine-binding globulin (TBG)→ ↑↑ total thyroxine but does not affect the free thyroxine level**
  - Thyroid-binding globulin has a twofold increase in concentration during pregnancy as a result of reduced hepatic clearance and increased synthesis under oestrogen stimulus
- **Increase in total T3 and T4**
  - **in normal pregnancy (T_3) and T_4 levels show a slight increase with suppressed (TSH) in the first trimester due to the partial thyroid-stimulating action of human chorionic gonadotrophin (beta-HCG).**
  - **Free T3 and T4 remains within normal ranges**
  - HCG → activation of the TSH receptor → **transient gestational hyperthyroidism.**
  - TSH may be mildly suppressed in up to 13.5% of pregnancies during the first trimester, and 4.5% of women in the second trimester, and this is considered a normal variant.
  - HCG levels will fall in second and third trimester

Daily requirement of iodine

- Maternal thyroid hormone is needed for neuronal development until 12-13 weeks, and recent research has shown children of mothers with hypothyroidism may have a lower IQ than those born to women with normal thyroid function.
- **American Thyroid Association's 2017 Guidelines recommends:**
  - all pregnant women should ingest approximately 250 micrograms of iodine daily.
  - In most countries, women who are planning pregnancy or currently pregnant, should supplement their **diet with a daily oral supplement that contains 150 micrograms** of iodine in the form of **potassium iodide**. This is optimally **started 3 months before conception.**

Thyrotoxicosis

- Untreated thyrotoxicosis increases the risk of fetal loss, maternal heart failure and premature labour

- When there are TSH receptor antibodies present at high concentration they may cross the placenta.
- Fetal hyperthyroidism occurs in children born to mothers with Graves' disease due to circulating thyroid stimulating antibodies which can cross the placenta.
- **A pregnant woman with positive thyroid antibodies but who is euthyroid has a higher risk of spontaneous abortion.** A meta-analysis confirms the association between anti-TPO antibodies and premature foetal loss.
- Graves' disease is the most common cause of thyrotoxicosis in pregnancy.
- **Investigations**
  - Serum TSH can exclude primary thyrotoxicosis.
  - Confirm diagnosis with free T4 levels.
  - If TSH is suppressed but free T4 levels are normal then, if not previously supplied, free T3 level is necessary (T3 toxicosis occurs in 5% of patients).
  - It is important to remember that the ranges of TSH, T3 and T4 are different in pregnancy:
  - **TSH - levels are trimester-dependent:**
    - 0.2-2.5 mIU/L in the first trimester.
    - 0.3-3.0 mIU/L in the second trimester.
    - Up to 3.5 mIU/L in the third trimester.
  - **TRAb** can cross the placenta, stimulating the fetal thyroid, so it is important to measure during pregnancy.
- **Management**

Due to the small risk of fetal abnormalities with carbimazole it is recommended to use PTU in the first trimester during organogenesis and then carbimazole in trimester 2 + 3.

  - **Early pregnancy (1st trimester)**
    - **Due to the small risk of fetal abnormalities with carbimazole it is recommended to use PTU in the first trimester during organogenesis and then carbimazole in trimester 2 + 3.**
    - **Propylthiouracil** is more highly protein bound and is ionized at pH 7.4, thus making it **less likely to cross the placenta or breast milk.**
    - PTU may be more protein bound and so less is transmitted to the fetus, but compliance with carbimazole is generally better.
    - Carbimazole has rarely been associated with aplasia cutis of the neonate
  - **Late pregnancy (2nd + 3rd trimester):**
    - **Carbimazole is the recommended option in late pregnancy because of reports of hepatotoxicity associated with Propylthiouracil.**
    - Despite this some endocrinologists use carbimazole and the BNF states both drugs may be used in pregnancy.
  - **Postpartum Patients:**
    - Postpartum Patients may continue to breast-feed

- the risk of propylthiouracil and carbimazole being secreted into breast milk is negligible.
- PTU has the advantage of being excreted to a lesser extent than carbimazole in breast milk.
- **PTU is the most appropriate treatment for pregnant who plan to breast-feed her baby after delivery.** **(medical-masterclass.com 2017 part 2)**
- However, neonatal thyroid function should be checked regularly.

➢ **Investigations and targets**
- maternal free thyroxine levels should be kept in the upper third of the normal reference range to avoid fetal hypothyroidism
- thyrotrophin receptor stimulating antibodies should be checked at 30-36 weeks gestation - helps to determine risk of neonatal thyroid problems

➢ **Contraindications:**
- block-and-replace regimes should not be used in pregnancy
- radioiodine therapy is contraindicated

Hypothyroidism

- **Overview**
  - Hypothyroidism is the commonest pre-existing endocrine disorders in pregnancy
  - occurs in 2.5% of pregnant women.
  - most commonly caused by Hashimoto's thyroiditis.
- **Monitoring**
  - thyroid function tests should be assessed at 6-8 weeks gestation, 16-20 and at 28-32 weeks (each trimester and 6-8 weeks post-partum)
  - Thyroid function tests should be measured every 8-12 weeks if stable, and 4-6 weeks if medication is changed.
- **Thyroxine**
  - **safety**
    - thyroxine is safe during pregnancy and breast feeding
  - **dose adjustment**
    - **Patients with established hypothyroidism**
      - at the first prenatal visit the dose is usually increased by 30-50%
      - **During pregnancy, the average thyroxine requirements typically increase by 25-50 mcg.**
      - The patient normally returns to their original dose of levothyroxine straight after delivery.
    - **Patients newly diagnosed with hypothyroidism whilst pregnant**
      - treatment commenced immediately with a starting dose of 100 microgram daily.
      - thyroxine dose should be adjusted to reach and maintain serum TSH concentrations in the low normal range (0.4 - 2.0mU/L) in the first trimester (or trimester specific normal TSH values)
- **Complications**
  - Hypothyroidism consequences for mother

        - congestive cardiac failure,
        - megacolon,
        - adrenal crisis,
        - psychosis,
        - myxoedema coma
        - hyponatraemia.
        - pre-eclampsia,
        - placental abruption
    - consequences for the foetus:
        - miscarriage
        - low birth weight,
        - increase in stillbirth rate
- **Prognosis for mother and foetus**
    - excellent with appropriate treatment.

September 2007 exam: Pregnant lady investigated for excessive sweating and tremor. Blood tests reveal the following: TSH < 0.05 mu/l. T4 =188 nmol/l.What is the most appropriate management?
Propylthiouracil

Post-partum thyroiditis

Definition

- thyroid dysfunction occurring **within the first 6 months after delivery.**

Course of disease

- Hyperthyroid status followed by a hypothyroid phase at three to six months, followed by spontaneous recovery in one third of cases. In the remaining two-thirds, a single-phase pattern or the reverse occurs.

Pathophysiology

- The exact aetiology is unknown but **lymphocytic infiltration of the thyroid is typical**, suggesting auto-immunity.

Prevalence

- occurs in approximately 5-7% of females

Risk factors

- Common in whom thyroid peroxidase (TPO) antibodies were positive prior to delivery
- twice common in patients with type 1 diabetes mellitus.

Three stages

- 1. Thyrotoxicosis
- 2. Hypothyroidism
- 3. Normal thyroid function (but high recurrence rate in future pregnancies)

Investigations

- **Thyroid peroxidase (TPO) antibodies** are found in 90% of patients

Management

- the thyrotoxic phase is not usually treated with anti-thyroid drugs as the thyroid is not overactive.
    - ➢ Symptomatic treatment using → **beta-blockers** for relief of tremor or anxiety.
        - **Propranolol is typically used for symptom control**
- the hypothyroid phase is usually treated with **thyroxine**
    - ➢ **withdrawal period after 6 months** to measure recovery of thyroid function.

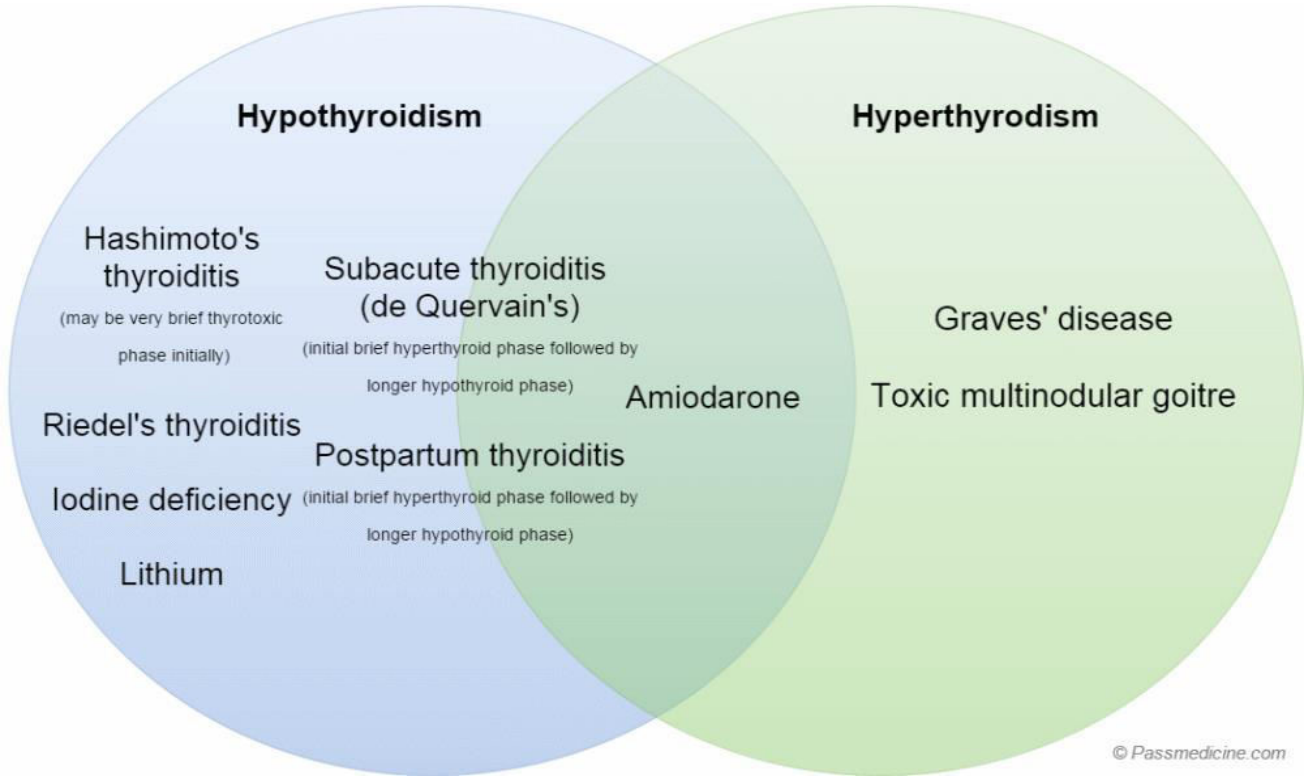
Prognosis

- Recurrence of thyroiditis is common in subsequent pregnancies
- in up to 40% permanent hypothyroidism develops.

Subacute (De Quervain's) thyroiditis

Thyrotoxicosis with tender goitre = subacute (De Quervain's) thyroiditis

- Subacute thyroiditis also known as De Quervain's thyroiditis and subacute **granulomatous** thyroiditis
- Occur after viral infection
- The thyroid gland will be firm, enlarged bilaterally or unilaterally **due to extravasation of colloid from the follicles causing a granulomatous reaction.**
- typically presents with hyperthyroidism
- **It is associated with HLA-B35**



Features

Tender goitre, hyperthyroidism and raised ESR + globally reduced uptake on technetium thyroid scan is typical (De Quervian)

- Hyperthyroidism
  - As the condition resolves patients become hypothyroid and then euthyroid.
- painful goitre, raised temperature
  - The thyroid enlargement is typically rapid, occurring over a period of days.
- raised ESR (>50 and usually 100)
- **globally reduced uptake on iodine-131 scan**
  - **the most helpful investigation in establishing the diagnosis → Radioactive iodine uptake scan**
  - Radioiodine uptake is typically less than 1% at 24 hours (Tc 99m uptake is similarly low).

Management

- usually self-limiting - most patients do not require treatment
- **The most appropriate treatment of de Quervain's thyroiditis is symptomatic control.**
- thyroid pain may respond to aspirin or other NSAIDs
- in more severe cases **steroids (Prednisolone)** are used, particularly if hypothyroidism develops

Prognosis

- The hypothyroidism is usually mild but persists for two to four months.
- A few patients (~5%) remain hypothyroid and need longterm thyroid hormone replacement.
- Recurrences are uncommon.

May 2012 exam: H/O palpitations and heat intolerance. O/E pulse is 90/min & a small, diffuse goitre is noted which is tender to touch. TFT: Free T4=24 pmol/l. TSH< 0.05 mu/l. What is the most likely diagnosis? De Quervain's thyroiditis

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Subclinical hyperthyroidism

It is defined as:

- normal serum free thyroxine and triiodothyronine levels
- with a thyroid stimulating hormone (TSH) below normal range (usually < 0.1 mu/l)

Causes

- multinodular goitre, particularly in elderly females
- excessive thyroxine may give a similar biochemical picture

The importance in recognising subclinical hyperthyroidism lies in the potential effect on the cardiovascular system (atrial fibrillation) and **bone metabolism (osteoporosis).** It may also impact

on quality of life and increase the likelihood of dementia

Management

- TSH levels often revert to normal - therefore levels must be persistently low to warrant intervention
- a reasonable treatment option is a therapeutic trial of low-dose antithyroid agents for approximately 6 months in an effort to induce a remission

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Thyrotoxicosis

The PTH level in primary hyperparathyroidism may be normal

Causes

- Graves' disease (50-60% of cases of thyrotoxicosis)
- toxic nodular goitre
- subacute (de Quervain's) thyroiditis
- post-partum thyroiditis
- acute phase of Hashimoto's thyroiditis (later results in hypothyroidism)
- toxic adenoma (Plummer's disease)
- amiodarone therapy
- **factitious hyperthyroidism**
  - **diagnosis of factitious hyperthyroidism→ undetectable thyroglobulin.**
    - thyroglobulin is the precursor of thyroid hormones, therefore if undetectable, indicates an external source of thyroid hormone has been administered.
  - **Which of the investigation is likely most to differentiate between self-administration of thyroid hormone and endogenous causes of thyrotoxicosis?**
    - **Radioactive uptake thyroid scan**
      - **endogenous causes of thyrotoxicosis → increased radioactive uptake**
      - **In thyrotoxicosis factitia, uptake is globally reduced.**
- **Excess iodine ingestion**
  - **Kelp is a very rich source of iodine.**
  - In patients with pre-existing thyroid hyperplasia or adenoma, the ingestion of largeamounts of iodine can precipitate thyrotoxicosis.
  - Treatment is withdrawal of the kelp with monitoring of thyroid function.
- **struma ovarii**
  - a rare cause of hyperthyroidism which is due to thyroglobulin production by ectopic thyroid tissue in an ovarian teratoma (also known as dermoid cysts).
  - Teratomas include tissues from all three germ layers and commonly have hair, teeth, and sebum.
  - **negative neck ultrasound and neck exam in the setting of hyperthyroidism** and low radioiodine uptake.
  - can be visualized with a **pelvic ultrasound** or abdominal CT.

Feature

- **Lid retraction and lag are signs of sympathetic overactivity, and occur in any thyrotoxic state (thyroxine potentiates the action of catecholamines).**
- **Decreased libido**
- High bone turnover and **osteoporosis** may be associated with thyrotoxicosis. Bone turnover involves increased osteoclastic and osteoblastic activity, leading to **elevated alkaline phosphatase levels** derived from bone.
- AF occurs in 10% to 25% of patients with hyperthyroidism, more commonly in men and the elderly than in women or patients less than 75-years-old.
    - AF generally caused by increased beta-adrenergic tone. Propranolol is effective in controlling all symptoms prior to initiation of specific therapy (e.g. carbimazole, which will have a more delayed effect on symptoms).

Metabolic changes

- Serum glucose levels typically increase in patients with hyperthyroidism.
- Hypocholesterolemia due to increased LDL receptor expression.

Investigation

- TSH down, T4 and T3 up
    - The most sensitive test to diagnosis hyperthyroidism is TSH level.
    - In primary hyperthyroidism the TSH should always be suppressed by negative feedback
    - **Non-suppressed (TSH)** suggests → excessive TSH production by the pituitary gland,→ the possibility of a thyrotroph adenoma → do **MRI scan pituitary gland**
- thyroid autoantibodies
- other investigations are not routinely done but includes isotope scanning

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Toxic multinodular goitre (TNG) (Plummer's disease)

- Toxic multinodular goitre describes a thyroid gland that contains a number of autonomously functioning thyroid nodules that secrete excess thyroid hormones.
- TNG is the second most common cause of hyperthyroidism in the Western world, after Graves disease. In elderly individuals and in areas of endemic iodine deficiency, TNG is the most common cause of hyperthyroidism.
- Mechanism: related to iodine deficiency.
    - Iodine deficiency → ↓ T4 → thyroid cell hyperplasia to compensate for the low levels of T4 → ↑thyroid cell replication → somatic mutations of the TSH receptor → further growth → clonal proliferation → multiple nodules.
    - Somatic mutations of the TSH receptors and G α protein → activation of cyclic adenosine monophosphate (cAMP) cascade of the inositol phosphate pathways →functional autonomy of the thyroid
    - Endothelin-1 (ET-1) production may be involved in thyroid gland growth and vascularity.
- usually occurs in women aged over 55 years

Investigations

- Evidence of hyperthyroidism (↓TSH + ↑ or normal free T4)

- Nuclear scintigraphy reveals → **patchy uptake**
  - Toxic nodular goiter (TNG) → patchy uptake
  - Graves disease → homogeneous diffuse uptake.
  - Thyroiditis → low uptake.
- CT of the chest → is the investigation of choice to determine the degree of retrosternal involvement
- Ultrasonography is a highly sensitive to detect nodules that are not palpable during thyroid examination.
  - helpful when correlated with nuclear scans to determine the functionality of nodules.
  - Dominant cold nodules should be considered for fine-needle aspiration biopsy prior to definitive treatment of a TNG.
  - Fine-needle aspiration is not usually indicated in an autonomously functioning (ie, hot) thyroid nodule. The risk of malignancy is quite low.
  - Perform a fine-needle aspiration biopsy if a dominant cold nodule is present in a multinodular goiter.

Treatment

- **The treatment of choice is radioiodine therapy**
  - In patients with uptake of less than 20%, pretreatment with lithium, PTU, or recombinant TSH can increase the effectiveness of iodine uptake and treatment.
- Surgical therapy is usually reserved for young individuals, patients with 1 or more large nodules or with obstructive symptoms, patients with dominant nonfunctioning or suspicious nodules, patients who are pregnant, patients in whom radioiodine therapy has failed, or patients who require a rapid resolution of the thyrotoxic state.

Radioiodine treatment

- Anti-thyroid drugs can be recommenced after radioiodine administration, but treatment should be withdrawn gradually and guided by 6-8-weekly thyroid function testing.
- Early post-radioiodine hypothyroidism might be transient.
- Mild thyrotoxic symptoms after radioiodine occur in about one-third of patients, and about 4% of patients develop a clinically significant radiation-induced thyroiditis. These patients should be treated symptomatically with beta blockers.
- (TSH) level should be monitored every 6 months after radioiodine therapy to detect late hypothyroidism.
- **Patients should not have close contact with children under the age of 11 years for about 2 weeks after treatment**

September 2010 exam: H/O thyrotoxicosis. O/E goitre containing multiple irregular nodules. Nuclear scintigraphy with technetium 99m reveals patchy uptake. What is the treatment of choice? Radioiodine (ΔToxic multinodular goitre)

Graves' disease

Graves' disease is the most common cause of thyrotoxicosis

Basics

- Graves' disease is the most common cause of thyrotoxicosis.
- typically seen in women aged 30-50 years.
- genetic susceptibility to Graves' disease is **associated with the presence of HLA-DR3 and HLA-B8**

Mechanism

- Graves' disease, an autoimmune disorder in which there are antibodies to the TSH receptor mimicking the action of endogenous TSH. Binding to the TSH receptor then activates adenyl cyclase and results in increased secretion of thyroid hormones.
    - **Antibodies overstimulating adenyl cyclase**

Features

- typical features of thyrotoxicosis
- specific signs limited to Grave's

Features seen in Graves' but not in other causes of thyrotoxicosis

- eye signs (30% of patients): exophthalmos, ophthalmoplegia
- **pretibial myxedema** (commonly described as **orange peel skin present on both shins**) → pathognomonic
    - Infiltrative dermopathy
    - raised, indurated pinkish patches.
    - characterized by non-pitting infiltration by proteinaceous ground substance, usually in the pretibial area.
    - It can occur anywhere, but typically it occurs on the shins and dorsum of feet.
    - It is often found with acropachy and ophthalmopathy and a high titre of thyroid-stimulating hormone (TSH) receptor antibodies would be expected.
    - It rarely occurs in the absence of ophthalmopathy.
    - It rarely occurs in the absence of ophthalmopathy.
    - The lesion is often pruritic and erythematous in the early stages, and subsequently becomes brawny.
    - may appear years before, or after, hyperthyroidism.
- **Thyroid acropachy** (a dermopathy characterized by soft-tissue swelling of the hands and clubbing of the fingers.
    - Radiographic imaging of affected extremities typically demonstrates periostitis, most commonly the metacarpal bones)
- thyroid bruit
- tachycardia
- Globally increased uptake on thyroid scan.

The most likely associate of Graves' disease is vitiligo occurring in approximately 7% of cases.

Investigations

Laboratory tests in hyperthyroidism

- Both thyroxine (T4) and triiodothyronine (T3) levels are raised. However, **T3 is more sensitive** because occasional cases of isolated T3 toxicosis can occur
- thyroid-stimulating hormone (TSH) level is suppressed, but there are rare instances of TSH hypersecretion
- **increased** levels of sex hormone-binding globulin **(SHBG)**

Which blood tests is most sensitive in establishing whether there is excess thyroid activity?
⇨ **Free T3 level**

Autoantibodies

- **anti-TSH receptor stimulating antibodies (90%)** (specific for Graves' disease)
- anti-thyroid peroxidase antibodies (50%)

Management

TSH is used to assess the response of patient to carbimazole for treating Grave's

- Despite many trials there is no clear guidance on the optimal management of Graves' disease.
- Treatment options include titration of anti-thyroid drugs (ATDs, for example carbimazole), block-and-replace regimes, radioiodine treatment and surgery.
- Propranolol is often given initially to block adrenergic effects
  - Propranolol, a nonselective beta blocker, may help to lower the heart rate, control tremor, reduce excessive sweating, and alleviate anxiety. Propranolol is also known to reduce the conversion of T4 to T3.
  - In patients with underlying asthma, beta-1 selective antagonists, such as atenolol or metoprolol, would be safer options.
  - In patients with contraindications to beta blockers (eg, moderate to severe asthma), calcium channel antagonists (eg, diltiazem) may be used to help control the heart rate.

ATD titration

- carbimazole is started at 40mg and reduced gradually to maintain euthyroidism
- typically continued for 12-18 months
- patients following an ATD titration regime have been shown to suffer fewer side-effects than those on a block-and-replace regime
- **Long-term remission following antithyroid drugs is of the order of 15%**, with **the vast majority relapsing.** Thus, frequently, radio-iodine is advocated as a primary treatment - particularly for multi-nodular or toxic solitary nodules.

Block-and-replace

- carbimazole is started at 40mg
- thyroxine is added when the patient is euthyroid
- treatment typically lasts for 6-9 months

Radioiodine iodine (RAI) treatment

- contraindications include pregnancy (should be avoided for 4-6 months following treatment) and age < 16 years.
- Thyroid eye disease is a relative contraindication, as it may worsen the condition
- **Hypothyroidism is the most common adverse effect.** the proportion of patients who become hypothyroid depends on the dose given, but as a rule the majority of patient will require thyroxine supplementation after 5 years
    - **approximately 80% will have long-term hypothyroidism following radio-iodine.**
- There is no evidence of increased risk of thyroid neoplasia or gastric neoplasia following radioactive iodine (RAI).
- Goitre shrinkage may occur in up to 30% following RAI.

Carbimazole

- Carbimazole is used in the management of thyrotoxicosis.
- It is typically given in high doses for 6 weeks until the patient becomes euthyroid before being reduced.

Mechanism of action

- The active metabolite of carbimazole, methimazole, reduces the synthesis of new thyroid hormones by inhibiting the iodination of tyrosine
- blocks thyroid peroxidase from coupling and iodinating the tyrosine residues on thyroglobulin (**Inhibition of the iodination of tyrosine**) → reducing thyroid hormone production
- It also has an immunosuppressive action leading to a reduction in serum thyroid-stimulating hormone (TSH) receptor antibody (TRAb) concentrations
- There is a subjective improvement within 10-14 days of starting carbimazole but euthyroid levels are reached only after 3-4 weeks, since the synthesis rather than the release of hormones is affected
- in contrast propylthiouracil as well as this central mechanism of action also has a peripheral action by inhibiting 5'-deiodinase which reduces peripheral conversion of T4 to T3

Adverse effects

- Carbimazole-induced agranulocytosis (The major complication)
    - **defined as neutrophil count less than 0.5 $\times 10^9$/L**
    - the incidence of leukopenia/neutropenia with carbimazole is **less than 1%.**
    - **should be stopped if neutrophil count below 1.5 $\times 10^9$/L (1.5-7).**
    - In fact a mild decrease in WBC can also occur with hyperthyroidism.
    - **If neutrophil count are just below normal → The most appropriate treatment would be to continue the carbimazole.**
    - Treatment
        - Thionamides should be withdrawn,
        - infection treated with appropriate antibiotics (broad spectrum cephalosporin)
        - and occasionally, granulocyte colony-stimulating factor (G-CSF) is required when white count fails to respond.

- crosses the placenta, but may be used in low doses during pregnancy
  - (also Propylthiouracil does cross the placenta , although thyroxine does not)
- Neonatal hypothyroidism will occur in approximately 10% of babies, because carbimazole crosses the placenta and switches off the fetal thyroid axis. The goitre that occurs is transient and will disappear following delivery

Interaction

- **carbimazole effect is potentiated by the liver enzyme-inhibitor (eg: erythromycin)**

January 2013 exam: H/O a smooth, non-tender goiter , thyrotoxicosis and exophthalmos + ↑↑Anti-thyroid peroxidase antibodies. What is the most appropriate management? Carbimazole (Radioiodine treatment should be avoided given the presence of thyroid eye disease)

January 2012 exam: H/O weight loss & palpitations in a 35-year-old female.TSH < 0.05 mu/l, T4=178 mmol/l. Which feature would most suggest a diagnosis of Grave's disease? Pretibial myxedema (Pretibial myxoedema is not seen in other causes of thyrotoxicosis and points towards a diagnosis of Graves')

January 2006 exam: A 30-year-old female is started on carbimazole 20mg bd following a diagnosis of Grave's disease. What is the best biochemical marker to assess her response to treatment? TSH

September 2011 exam: H/O eye pain & ↓↓ visual acuity following the initiation of treatment for recently diagnosed Grave's disease. Which treatments is likely to have been started? Radioiodine treatment
(Radioiodine treatment → ↑↑ thyroid eye disease in 15% of patients with Grave's disease)

May 2015 exam: What is the mechanism of action of carbimazole? Blocks thyroid peroxidase from coupling and iodinating the tyrosine residues on thyroglobulin

Propylthiouracil (PTU)

Propylthiouracil (PTU) vs carbimazole

- Propylthiouracil (PTU) and carbimazole are derivatives of thiourea
- Both inhibit the organification of iodine at the thyroid gland as their major mechanism of action
- PTU, but not carbimazole, is an inhibitor of thyroxine to tri-iodothyronine, giving it a modest therapeutic advantage over the latter agent because it reduces the proportion of active thyroid hormone as well as reducing the total amount of T4
- Carbimazole is approximately 15 times as potent as PTU

Cautions

- Both PTU and carbimazole are excreted in very small quantities in breast milk, so breast feeding is not advised with either

Side-effects

- Thiourea derivatives have several side-effects including a maculopapular rash, hepatocellular damage and vasculitis

- The most serious side-effect of both agents is agranulocytosis, although it is more common to see a fall in, rather than total absence of, white cells

Advantages

- its risk of fetal abnormalities when used in pregnant women is lower than that of methimazole.
- the medication of choice in the first trimester of pregnancy

Contraindications

- **contraindicated in patients with liver dysfunction**
  - PTU has a documented risk of hepatotoxicity.

Thyrotoxic periodic paralysis (TPP)

Features

- abrupt onset of paralysis of the lower extremities,
- often associated with hypokalaemia, with thyrotoxicosis.
  - increase Na^+/K^+-ATPase activity → shift of potassium into tissues
- It is **most commonly seen in Asian** men in their third to fifth decades,

Differential diagnosis

- The neuromuscular presentation of both TPP and autosomal dominant **familial periodic paralysis (FPP**) is identical, thus confirmation of **family history** and features of hyperthyroidism should be sought.
  - FPP :
    - **more common in Caucasian** populations
    - may be triggered by:
      - strenuous exercise followed by abrupt rest,
      - high-carbohydrate or high-salt meals,
      - temperature change and
      - emotional stress.

Treatment

- It is curable once euthyroidism is achieved.
- non-selective beta-blocker such as propranolol blunts the hyperadrenergic stimulation of Na+/K+-ATPase and thus prevents intracellular shift of potassium and phosphate.
- Potassium replacement should be given in low dose to reduce the chance of rebound hyperkalaemia.
- Definitive therapy is with anti-thyroid medication, radioiodine or surgery to achieve euthyroidism.

Thyroidectomy

Post-thyroidectomy hypocalcaemia

- **Up to 10% of patients who undergo subtotal thyroidectomy suffer transient hypocalcaemia due to local trauma at the time of surgery**. Thankfully, it becomes permanent hypoparathyroidism in fewer than 1% of patients.
- Features:

- usually presents 24-48 hours postoperatively
- perioral tingling, twitching or tetany. This may progress to seizures.
- ventricular arrhythmias .ECG may show a prolonged QT interval (QTc is prolonged if >440 ms in men or >460 ms in women.) is associated with increased risk of torsades de pointes

- Treatment for serum calcium levels <2 mmol/L is urgent intravenous calcium (10 ml of 10% calcium gluconate) followed by an infusion if necessary.

Thyroidectomy complications

- **transient hypoparathyroidism** occur in 8% of cases **(the most likely post-operative complication)**
- permanent hypoparathyroidism seen in 1-2%
- Infection is seen in 1-2%
- Bleeding is less common, seen in around 0.5% or less
- Permanent recurrent laryngeal nerve palsy occurs in 1% of patients;
  superior laryngeal nerve palsy affects more patients (3-4% in case series).

What is the most common postoperative complication following subtotal thyroidectomy?

⇨ **Hypothyroidism** occurs in about 10% of patients within 1 year of surgery.

Which structures is most closely related to the recurrent laryngeal nerve?

➔ **Inferior thyroid artery**

- The nerve is found deep to the inferior thyroid artery in 40%, superficially in 20%, and between branches of the artery in 35%.
- The position between nerve and artery on one side of the neck is similar to that found on the other side in only 17% of the population.

The **superior** thyroid artery runs closest to the **superior** laryngeal nerve.

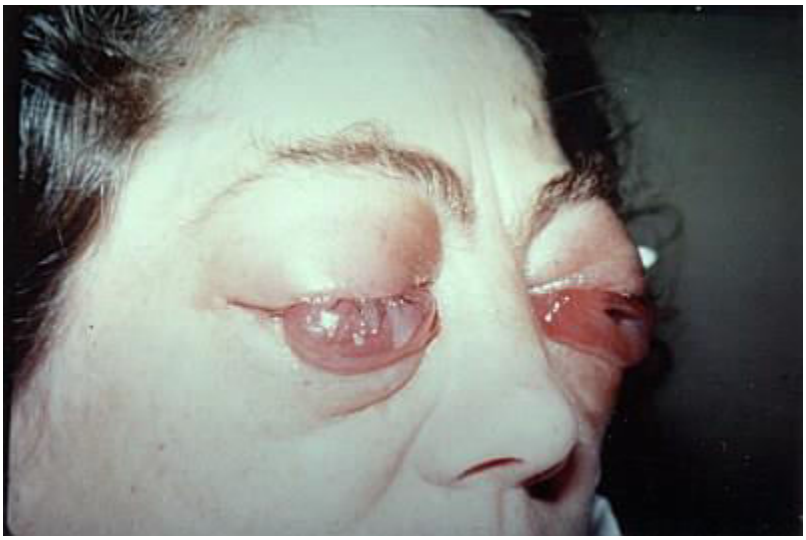
Thyroid eye disease

Feature	Assessment	Frequency
Lid lag / lid retracted	Measure lid fissure width	50-60%
Grittyness, discomfort, periorbital oedema, pain, excessive tears.	Self-assessment score by patient	40%
Proptosis (aka exophthalmos) **this is where the eye bulges out of its socket.**	Exopthalmometry **or evaluation on MR/CT scan.**	20%
Extraocular muscle dysfunction –typically causes diplopia (double vision) when looking up and out.	Hess chart + CT/MR to detect muscle size	10%
Corneal involvement, causing exposure keratitis	Flourescin staining	<5%
Loss of sight due to optic nerve compression	Visual acuity tests, visual field tests. CT/MR scan	<1%

- also called Graves' Ophthalmopathy or Graves' eye disease
- **Thyroid eye disease affects between 25-50% of patients with Graves' disease.**
- **In about 10% of patients, the signs will only be unilateral.**

- **can occur with normal thyroid function.**
    - The diagnosis can be made by thyroid stimulating receptor antibody in the serum.
- Ophthalmopathy **may occur before the onset of hyperthyroidism**, or as late as 20 years afterward.
- definition of lid retraction: When looking at the patient from the side, you see that the eyes are proptosed.
- definition of lid lag: When the patient follows your finger, moving downwards from above, the sclera can temporarily be seen above the iris.

Graves' eye disease can occur in euthyroid, hypothyroid or hyperthyroid setting.



The slide shows characteristic features of severe Graves' eye disease - termed '**malignant exophthalmos'** in this case - proptosis, chemosis, palpebral oedema and periorbital swelling. It may require orbital decompression.

Pathophysiology

- it is thought to be caused by an autoimmune response against an autoantigen, possibly the TSH receptor → retro-orbital inflammation
- the inflammation results in glycosaminoglycan and collagen deposition in the muscles
- The levator palpebrae superioris is the muscle that lifts the eyelid, innervated by the third cranial nerve. Hyperthyroidism stimulates the beta receptors of the third cranial nerve. High thyroid levels pull up the eyelid by stimulating the levator muscle.
- The ophthalmoplegia is thought to be the result of an increased proliferation of retro-orbital connective tissues and local edema due to the increased secretion of glycosaminoglycans like hyaluronic acid.
- It **most commonly affects the inferior rectus**, but usually results in a complex pattern of gaze restriction bilaterally.
- The pathogenesis of infiltrative ophthalmopathy, which is responsible for exophthalmos may result from immunoglobulins directed against specific receptors in the orbital fibroblasts and

fat. This results in release of proinflammatory cytokines, inflammation, and accumulation of glycosaminoglycans.

- **the most likely underlying pathogenesis → Excessive fibroblast proliferation**

Which eye signs are specific to Graves' disease?

Eye signs found in most thyrotoxic states	eye signs specific to Graves' disease:
Both lid lag and lid retraction reflect enhanced sensitivity to circulating catecholamines, and may therefore be found in most thyrotoxic states.	• proptosis • ophthalmoplegia • chemosis • **periorbital oedema**

Prevention

smoking is the most important modifiable risk factor for the development of thyroid eye disease

- **Radioiodine treatment → ↑↑ thyroid eye disease** → malignant exophthalmos
- Prednisolone may help reduce the risk
  - patients with thyroid eye disease are generally treated with steroids for one to two weeks prior to starting radioiodine therapy.
  - In patients with thyroid eye disease undergoing radioiodine treatment, **post-radioiodine hypothyroidism should be avoided,** because of the risk of **worsening Grave's eye disease**. For this reason patients are stabilised on a block replace regimen before moving to radioiodine therapy.

Features

- the patient may be eu-, hypo- or hyperthyroid at the time of presentation
- exophthalmos
- conjunctival oedema
- optic disc swelling
- ophthalmoplegia
- inability to close the eye lids may lead to sore, dry eyes. If severe and untreated patients can be at risk of exposure keratopathy

Management

- topical lubricants to prevent corneal inflammation caused by exposure
- steroids (the mainstay of initial therapy).
- **Block replace with high dose carbimazole and full dose thyroxine replacement is the optimal step**. (may be continued for up to 18 months until thyroid eye disease is stable).
  - Stability of thyroid function → ↓↓progression of thyroid eye disease.
    - Periods of hypothyroidism → worsen peri-orbital oedema → symptoms related to optic nerve compression.
- Radiotherapy
  - Radioiodine is a definitive treatment option for relapsed Graves' thyrotoxicosis.
  - There is concern that radioiodine could exacerbate Graves' ophthalmopathy.

  - Patients with active Graves' ophthalmopathy receiving radioiodine treatment should be offered steroid cover.
  - Radioiodine treatment can safely be given to patients with inactive Graves' ophthalmopathy provided hypothyroidism is avoided.
- **For sight-threatening** (malignant exophthalmos, diplopia and loss of colour vision)
  - **the initial treatment is IV glucocorticoids** (methylprednisolone 500 mg once weekly and subsequently tapering down).
  - surgical orbital decompression may be necessary.
    - performed 1-2 weeks after IV glucocorticoids if the response is poor.

The following symptoms/signs should indicate the need for urgent review by an ophthalmologist:

- unexplained deterioration in vision
- awareness of change in intensity or quality of colour vision in one or both eyes
  - (**Impaired perception of colour implies → acute progressive neuropathy**)
- history of eye suddenly 'popping out' (globe subluxation)
- obvious corneal opacity
- cornea still visible when the eyelids are closed
- disc swelling

Thyroid storm (crisis)

- Thyroid storm is a rare but life-threatening complication of thyrotoxicosis.
- Associated with a significant mortality rate (30-50%)
- It is typically seen in patients with established thyrotoxicosis and is rarely seen as the presenting feature.
- Iatrogenic thyroxine excess does not usually result in thyroid storm.

Precipitating factors

- Any acute stressful condition such as surgery
- acute infections
- postpartum
- when antithyroid drugs are being withdrawn.

Clinical features include:

- fever > 38.5C
- tachycardia
- confusion and agitation
- nausea and vomiting
- hypertension
- heart failure
- abnormal liver function test

Diagnosis

- The points system of **Burch and Wartofsky** is sometimes used for clinical diagnosis of thyroid storm. In presence of a previous hyperthyroid state, the following point system is used to arrive at a clinical score. Here the score is 60.
  - A score of >45 is highly suggestive of thyroid storm.

- 25-44 is suggestive of “impending” storm
- score below 25 is unlikely to represent thyroid storm.

Criteria	Observation	Point
Atrial fibrillation	Absent	0
Atrial fibrillation	Present	10
Precipitating event	Absent	0
Precipitating event	Present	10
Pulse rate	90–109	5
Pulse rate	110–119	10
Pulse rate	120–129	15
Pulse rate	130–139	20
Pulse rate	≥140	25
GI symptoms	Absent	0
GI symptoms	Moderate	10
GI symptoms	Severe jaundice	20
CNS effects	Absent	0
CNS effects	Mild	10
CNS effects	Moderate (incl. delirium)	20
CNS effects	Severe (seizure/coma)	30
Temperature	99–99.9	5
Temperature	100–100.9	10
Temperature	101–101.9	15
Temperature	102–102.9	20
Temperature	103–103.9	25
Temperature	≥104	30

CCF	Absent	0
CCF	Mild	5
CCF	Moderate	10
CCF	Severe	15

Management

- **Transfer the patient to the Intensive Therapy Unit**
- symptomatic treatment e.g. Paracetamol
- Chlorpromazine can be used to treat agitation and, because of its effect in inhibiting central thermoregulation, it can be useful in treating the hyperpyrexia.
- treatment of underlying precipitating event
- propranolol
- anti-thyroid drugs: e.g. methimazole or propylthiouracil
- Lugol's iodine used in conjunction with Carbimazole → more rapid resolution.
  - Iodine: Blocks uptake of iodine into the thyroid gland and blocks the release of hormone.
- dexamethasone - e.g. 4mg IV qds - **blocks the conversion of T4 to T3**
- Plasmapheresis and peritoneal dialysis can be effective in cases resistant to pharmacological measures.

Thyroid cancer

there are five main types of thyroid carcinoma and their properties are given below:

Cell type	Frequency	Behaviour	Spread	Prognosis
Papillary	70%	**Often young females** present as "cold nodules" on isotope scanning	Local – sometimes bone / lung secondaries	**excellent** prognosis
Follicular	20%	More common in females	Lung / Bone	**Good** if resectable
Medullary cell	5%	**Often familial.** Cancer of parafollicular cells (c cell), **secrete calcitonin**, part of MEN-2	Local and mets	**Poor,** but often very slow course
Anaplastic	<5%	Aggressive, Not responsive to treatment, can cause **pressure symptoms**	Locally invasive	**Very Poor**
lymphoma	2%	*almost always non-Hodgkin lymphomas * **Associated with Hashimoto's** *often elderly women.	Locally invasive	**Poor** – but sometimes responds to radiotherapy

Types

- **Papillary thyroid carcinoma**
  - the commonest type of thyroid cancer,
  - histopathology
    - **The presence of Orphan-Annie nuclei is pathognomonic of papillary thyroid neoplasms.**
    - large thyrocytes and psammoma bodies are features typically seen on histology.
  - Abnormalities are often multi-focal, with local spread via lymphatics being seen.
- **Follicular thyroid carcinoma (FTC)**
  - **(FTC)** is a well-differentiated tumour. In fact, FTC resembles the normal microscopic pattern of the thyroid.
  - originates in follicular cells
  - the second most common cancer of the thyroid after papillary carcinoma.
- **Medullary thyroid carcinoma**
  - occurs in conjunction with MEN2
  - Medullary thyroid carcinoma is the most important diagnosis to confirm, with the **pentagastrin stimulation test** the best way to do this.
    - It measures calcitonin levels at 2 and 5 minutes, however, and a rise in calcitonin is suggestive of medullary thyroid carcinoma.
- **Anaplastic thyroid carcinoma**
  - rapidly growing
  - occurs most commonly in the elderly.

Risk factors of developing thyroid cancer

- Females are three times more likely to develop thyroid cancer than males.
- Endemic goitre, Hashimoto's thyroiditis and thyroid adenoma
- Family history of familial adenomatous polyposis (FAP)
  - FAP is caused by an APC gene mutation on chromosome 5

Features

- The most common presentation of thyroid cancer is an asymptomatic thyroid mass, or a nodule, that can be felt in the neck.
- Features of hyperthyroidism or hypothyroidism are not commonly seen in patients with thyroid malignancies as they rarely secrete thyroid hormones

Investigations

- **Ultrasound scanning thyroid**
  - **The initial investigation of choice in small non-symptomatic thyroid mass**
  - can show cystic lesions 2 mm wide and solid lesions 3 mm wide.
  - It is far more sensitive than palpation alone, and only 4-7% of nodules detected by US are clinically palpable.
- **Fine needle aspiration cytology** (FNA)
  - The appropriate investigation after ultrasound
  - FNA is the most important investigation once a lesion is recognised as solitary.

- diagnostic in over 85% of cases.

- Excision biopsy is required for equivocal lesions on fine needle aspiration.
- Radioisotope scanning confirms uptake by one or more nodules in the thyroid; nodules which take up the isotope are less likely to be malignant.
- **Exclusion of phaeochromocytoma is crucial before considering thyroidectomy → Abdominal MRI.**
  - Medullary thyroid carcinoma (MTC) and pheochromocytoma are associated in MEN type 2A and MEN type 2B.
  - Pheochromocytoma has to be ruled out before thyroidectomy, because any major surgery can **precipitate hypertensive crisis due to release of massive amounts of catecholamines.**

The association of Horner's syndrome and a thyroid nodule suggest invasion of the sympathetic chain and suggest that this thyroid nodule is malignant.

Which familial condition that carries an increased risk of papillary carcinoma of the thyroid ?

- **Gardner's syndrome** (intestinal tumours & lipomas. Also Osteomas & fibromas).
  → **carries an increased risk of papillary carcinoma**

Papillary carcinoma

- **Histologically,** papillary thyroid carcinoma appears as “ground glass” or “Orphan Annie” nuclei with **psammoma bodies** (calcified spherical bodies).
- **Thyroid cancer associated with Graves' disease is not uncommon and usually due to papillary carcinoma** and must be considered in suspicious/expanding nodules rather than attributing purely to Graves' disease.
  - **hyperthyroidism with prominent nodule which is 'cold' on uptake scanning is highly suggestive of thyroid carcinoma and the mostly likely diagnosis is Graves' disease (periorbital puffiness and thyroid bruit) associated with papillary thyroid carcinoma.**

Which proto-oncogenes is most associated with papillary carcinoma of the thyroid?

- **Trk is a proto-oncogene, mutation of which leads to activation of tyrosine kinase receptors.**
- **Trk activation is thought to play a role in the pathogenesis of papillary thyroid carcinoma**

Management of papillary and follicular cancer

- total thyroidectomy with thyroxine replacement
- followed by radioiodine (I-131) to kill residual cells
- yearly thyroglobulin levels to detect early recurrent disease

Prognosis

- Papillary → 5-year survival rate is only 5%
- Follicular → 5-year survival rate is 80%

Factors that suggest a poor prognosis in thyroid cancer

- increasing age
- **male sex**
- poorly differentiated histological features, and
- distant spread.

Thyroid neoplasms–

The most Popular is Papillary:

Papillae (branching)
Palpable lymph nodes
"**P**upil" nuclei ("Orphan Annie" nuclei)
Psammoma bodies within lesion (often)
Also has a **P**ositive **P**rognosis

Which test is most useful in the assessment of airflow obstruction due to the retrosternal goitre?

- **Flow volume curve**
  - airflow obstruction may be present in up to 40% of patients with retrosternal goitre
  - symptoms arises after at least 50% obstruction of the airway

Staging

- The staging of well-differentiated thyroid cancers is related to age for the first and second stages but not related for the third and fourth stages.
- **Younger than 45 years:**
  - Stage I - Any T, any N, M0 (Cancer is in the thyroid only).
  - Stage II - Any T, any N, M1 (Cancer has spread to distant organs).
- **Older than 45 years:**
  - Stage I - T1, N0, M0 (Cancer is in the thyroid only and may be found in one or both lobes).
  - Stage II - T2, N0, M0 and T3, N0, M0 (Cancer is in the thyroid only and is larger than 1.5 cm).
  - Stage III - T4, N0, M0 and any T, N1, M0 (Cancer has spread outside the thyroid but not outside of the neck).
  - Stage IV - Any T, any N, M1 (Cancer has spread to other parts of the body).

Management

- **Surgery is the definitive management of thyroid cancer.**
- Various types of operations may be performed.

- **Lobectomy with isthmectomy** is the minimal operation for a potentially malignant thyroid nodule.
  - Patients less than 40 years who have FTC nodules less than 1 cm, well defined, minimally invasive, and isolated may be treated with hemithyroidectomy and isthmectomy.
- If feasible, subtotal thyroidectomy (small part of contralateral lobe retained) is preferable since it carries a lower incidence of complications (for example, hypoparathyroidism, superior and/or recurrent laryngeal nerve injury).
- Total thyroidectomy
  - Approximately 10% of patients who have had total thyroidectomy (removal of all thyroid tissue preserving the contralateral parathyroid glands) demonstrate cancer in the contralateral lobe.
  - Total thyroidectomy should be performed in patients who are more than 40 years with FTC and in any patient with bilateral disease. Total thyroidectomy is recommended for any patient with a thyroid nodule and a history of irradiation. Some studies show lower recurrence rates and increased survival rates in patients who have undergone total thyroidectomy. This surgical procedure also facilitates earlier detection and treatment of recurrent or metastatic carcinoma.

- Patients receive radioiodine four to six weeks after thyroidectomy to detect and destroy any metastases and any residual tissue in the thyroid.
- Following thyroidectomy, patients will need to take thyroid replacement therapy.
- External beam radiation is used in the management of FTC if the cancer cannot be resected, or if there is extension into adjacent structures. Radiotherapy may also be administered postoperatively to reduce the risk of local-regional recurrence. It may also be used palliatively to treat pain from bone metastases.

marker of thyroid cancer recurrence after thyroidectomy

- **Thyroglobulin**
  - thyroid is the only source of thyroglobulin.
  - Normal or elevated serum thyroglobulin values indicate the presence of residual normal or cancerous thyroid tissue

The most appropriate investigation at annual follow-up for papillary thyroid cancer.

- **Ultrasound scan is the most sensitive investigation for the detection of locally recurrent papillary carcinoma.**
- Other investigations should be considered if ultrasound scan is negative or distant metastases are suspected.

Riedel's thyroiditis

- Riedel's thyroiditis is often confused with thyroid carcinoma.
- **It is characterised by marked fibrous infiltration of the thyroid gland.**
- Hypothyroidism &Thyroid autoantibodies are negative.
- The cause of this remains unidentified.
- Treatment is with thyroxine replacement.

T3 thyrotoxicosis and factitious thyrotoxicosis

- The patient has symptoms and signs of thyrotoxicosis and a suppressed thyroid-stimulating hormone (TSH), but with low thyroid-stimulating hormone (T4) and fT4.
- The main differentials are between triiodothyronine (T3) thyrotoxicosis and factitious thyrotoxicosis (purposeful or inadvertent ingestion of large quantities of thyroid hormone).
- (T3) thyrotoxicosis associated with around **5%** of cases of thyrotoxicosis.
- The diagnosis of **T3 toxicosis** should be suspected in patients presenting with:
  - symptoms of thyrotoxicosis (including a goitre)
  - serum T4 and fT4 are normal or low
  - **RAIU is increased.**
- In **factitious thyrotoxicosis**, the proportions of T3 and T4 depend on the preparation of the thyroid hormone replacement tablets.
  - Both T3 and T4 concentrations will be increased if the preparation contains both hormones;
  - serum T3 is elevated and T4 depressed in those taking T3;
  - T4 elevated and T3 suppressed in those taking T4.
  - However, **radioactive iodine uptake (RAIU) and plasma thyroid-binding globulin (TBG) will be depressed and a goitre will not be palpable.**

Thyrotoxicosis factitia (thyroxin abuse**)** The combination of **low thyroglobulin,** decreased uptake on scintigraphy and raised T4 can only really be thyrotoxicosis fatitia.

Calcium metabolism

The two hormones which primarily control calcium metabolism are:

- parathyroid hormone (PTH)
- 1,25-dihydroxycholecalciferol (calcitriol, the active form of vitamin D)

Other hormones include

- calcitonin: secreted from the parafollicular cells (C-cells) of the thyroid gland
- thyroxine
- growth hormone

Actions of parathyroid hormone

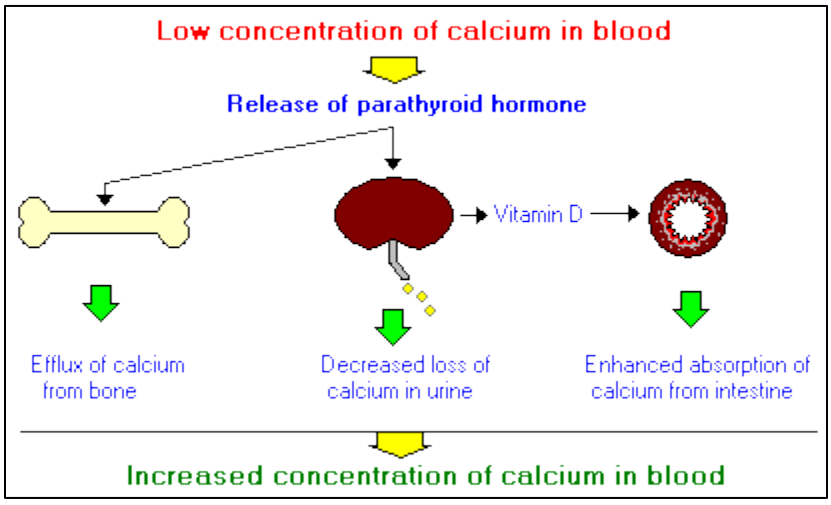
- increases plasma calcium, decreases plasma phosphate
- increases renal tubular reabsorption of calcium
- increases osteoclastic activity
- increases renal conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol
- decreases renal phosphate reabsorption

Actions of 1,25-dihydroxycholecalciferol

- increases plasma calcium and plasma phosphate
- increases renal tubular reabsorption and gut absorption of calcium
- increases osteoclastic activity
- increases renal phosphate reabsorption

Actions of the Hormones Involved in Calcium Homeostasis

HORMONE	*EFFECT ON BONES*	*EFFECT ON GUT*	*EFFECT ON KIDNEYS*
Parathyroid hormone↑Ca^{++}, ↓PO_4 levels in blood	Supports osteoclast resorption	Indirect effects via↑calcitriol from 1-hydroxylation	Supports Ca^{++}resorption and PO_4excretion, activates 1-hydroxylation
Calcitriol (vitamin D)↑Ca^{++},↑PO_4 levels in blood	No direct effects	↑Ca^{++} and PO_4absorption	No direct effects
Calcitonin causes ↓Ca^{++}, ↓PO_4 levels in blood when hypercalcemia is present	Inhibits osteoclast resorption	No direct effects	Promotes Ca^{++} and PO_4 excretion



Absorption

- **The intestinal absorption of calcium is facilitated by →1,25 dihydroxy-vitamin D**, which stimulates the microvillous membrane of the enterocyte to synthesise the calcium-binding carrier protein necessary for active calcium ion absorption.
- In serum, most of the calcium ion is bound to albumin
- Low albumin levels can affect the total serum calcium level.
- Less than 50% of calcium is in the ionised form in serum, the rest being bound to protein and other anions such as phosphate and citrate
- The ionised form is most important in regulation of body functions
- 99% of filtered calcium is reabsorbed in the kidneys, around 55% in the proximal convoluted tubule

Excretion

- Calcitonin is the most important factor regulating calcium excretion.
- Calcitonin is secreted by the parafollicular cells of the thyroid gland and responds to raised calcium levels by inhibiting bone resorption and increasing renal excretion

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Hypercalcaemia: causes

Thiazides cause hypercalcaemia

The most common causes of hypercalcemia are primary hyper-parathyroidism and malignancy (90 %).

In the presence of hypercalcaemia and hypophosphataemia, is highly suggestive of hyperparathyroidism.

The most common causes of hypercalcaemia are:

1. primary hyperparathyroidism (**Thyrotoxicosis**) due to increased bone turnover.
   - The most useful investigation is → Sesta **MIBI** scan of the neck
2. malignancy (bone metastases, myeloma, PTHrP from squamous cell lung cancer)
   - **In malignancy, roughly 80% of cases are due to parathyroid-hormone-related peptide release.** The vast majority of remaining cases are due to osteolysis, and some due to calcitriol-mediated hypercalcaemia and ectopic PTH secretion.
   - Raised alkaline phosphatase associated with hypercalcaemia is more likely to be due to bony metastases;
   - Normal alkaline phosphatase raises the possibility of underlying myeloma.
     - The LFTs show increased globulin fraction (TP-ALB) indicating the possibility of myeloma.
     - In myeloma, hypercalcaemia is primarily due to increased osteolysis and high-dose steroids - e.g. prednisolone 40 mg od can rapidly reduce the calcium level.
   - **malignancy should be considered in hypercalcaemia without hypophosphataemia.**
   - **the best initial investigation to contribute to the underlying diagnosis → Skeletal survey**

Other causes include

- **Tertiary hyperparathyroidism**
  - in a patient with chronic renal failure with prolonged hypocalcaemia the parathyroids become autonomous, even if renal function is improved with transplantation. This can **lead to hypercalcaemia.**
  - Tertiary hyperparathyroidism occurs when PTH production becomes autonomous and levels do not fall once serum calcium is corrected with supplementation of calcium and vitamin D.
    - Note that secondary hyperparathyroidism is a response to hypocalcaemia, not a cause of hypercalcaemia.
- Sarcoidosis (**Granulomatous disease** - sarcoidosis, leprosy, TB and histoplasmosis)
  - Increased intestinal absorption is the main cause for raised calcium levels in sarcoidosis due to increased production of 1,25-OH vitamin D from activated pulmonary macrophages
    - Sarcoidosis → activated pulmonary macrophages → ↑vitamin D →↑intestinal absorption of Ca → ↑Ca
- vitamin D intoxication
  - **Increased sun exposure** results in increased vitamin D production.
  - Patients often drink more cola drinks whilst on holiday, leading to increased phosphate intake.
  - The combination of increased vitamin D and phosphate availability in the presence of sarcoidosis is thought to lead to hypercalcaemia.
- acromegaly
- **Milk-alkali syndrome**
  - **Milk-alkali syndrome** - the triad of hypercalcaemia, metabolic alkalosis and renal impairment secondary to the ingestion of large amounts of calcium and absorbable alkali (such as sodium bicarbonate for the treatment of peptic ulcer disease).
  - **The age of the patient, the dyspeptic symptoms and the raised bicarbonate level suggest the most likely diagnosis is the milk-alkali syndrome, caused by the ingestion of antacids.**
  - The condition can lead to mild renal impairment, but this may well return to normal once calcium intake is reduced.
- drugs:
  - thiazides, → reduce excretion → hypercalcaemia.
    (Furosemide → hypocalcaemia but thiazides → hypercalcaemia).
  - calcium containing antacids
  - **lithium**,
  - vitamin D overdose,
  - vitamin A toxicity (including analogs used to treat acne)
- dehydration
- Addison's disease
- Paget's disease of the bone**
  - **usually normal in this condition but hypercalcaemia may occur with prolonged immobilisation
- **Infections**: HIV, histoplasmosis

- **Williams' syndrome** - a rare genetic disease affecting chromosome 7 and characterised by hypercalcaemia in infancy, anxiety and learning disability.
- **Familial hypercalcaemic hypocalciuria** - autosomal dominant mutations in the calcium sensing receptor gene, leading to calcium hyposensitivity, compensatory hypercalcaemia and hypocalciuria.

Secretion of which substances by the tumour is most likely to cause hypercalcaemia?

➔ In patients with solid tumours, **non-metastatic hypercalcaemia is most frequently the result of secretion of parathyroid hormone-related peptide (PTHrP) by the tumour** and is reported in association with gastric cancer. Non-parathyroid secretion of PTH itself is very rare.

mild hypercalcaemia + Normal parathyroid hormone (PTH) → primary hyperparathyroidism.

- **(PTH) is inappropriately normal as it should, by homeostatic mechanisms, be suppressed if the hypercalcaemia were a consequence of another disorder.**
- **Also low phosphate concentration is typical of PHPTH.**

Differentiate between hypercalcaemia in primary hyperparathyroidism and malignancy:

- **in primary hyperparathyroidism**
  - **Parathyroid hormone is elevated or normal**
  - calcium level is often < 3 mmol/l
  - Hypercalcaemia is often asymptomatic and might have been present for months or years.
- **in malignancy**
  - patients are usually acutely ill
  - often with neurological symptoms
  - calcium level is usually > 3 mmol/l
  - **Parathyroid hormone is suppressed**
  - Cancer (eg lung, breast or myeloma) is often clinically apparent.

Features

Features include the classic mnemonic, "**bones, stones, groans, and moans**":

- **Bones** - bone pain, especially if the PTH is elevated
- **Stones** - renal calculi
- **Groans** - constipation and likely subsequent abdominal pain
- **Pyschic moans** - depression and confusion

- Musculoskeletal manifestations (**Bones**)
  - Bone pain
  - Malaise , fatigue, muscle weakness
  - Osteoporosis of cortical bone, such as the wrist, is mainly associated with primary hyperparathyroidism.

  - Excess PTH also can result in subperiosteal resorption, leading to osteitis fibrosa cystica with bone cysts and brown tumors of the long bones.
- Renal manifestations (**Stones**)
  - polydipsia and polyuria
    - due to a type of nephrogenic diabetes insipidus - modification of the renal response to antidiuretic hormone causing dehydration.
  - Dehydration → thirst
  - nephrolithiasis resulting from hypercalciuria.
  - nephrocalcinosis.
- Gastrointestinal manifestations (**Groans**)
  - **abdominal pain,**
  - Nausea, anorexia, dyspepsia,
  - constipation
  - peptic ulcer disease
    - Calcium stimulates gastrin release and promotes increased secretion of gastric acid.
  - pancreatitis
- Neurological manifestations (**Pyschic moans**)
  - impaired concentration, confusion,
  - **Hyporeflexia**
  - corneal calcification,
  - depression
- Cardiovascular manifestations
  - hypertension,
  - vascular calcification
  - Cardiac arrhythmias are rare.
  - ECG changes include:
    - **Short QT interval →** significantly increases the risk of cardiac arrhythmias.
    - PR prolongation (but is much less common than QT shortening).
    - Bradycardia
    - Ventricular fibrillation has been reported in extreme cases.
    - widened T waves
    - In severe hypercalcaemia J (osborn) waves can be seen.
- Others
  - Itching
  - Keratitis, conjunctivitis
  - Hypokalaemia
    - hypercalcaemia → ↓ reabsorption of potassium, promoting its loss in the urine.

MECHANISM OF VOLUME DEPLETION IN HYPERCALCEMIA

- High calcium levels inhibit the effect of ADH on the collecting duct, inducing nephrogenic diabetes insipidus.
- High calcium filtration also promotes osmotic diuresis.

Presentation of Hypercalcaemia		
At levels <2.8 mmol/L	At levels <3.5 mmol/L	At levels >3.5 mmol/L
• Polyuria and polydipsia • Dyspepsia - due to calcium-regulated release of gastrin • Depression • Mild cognitive impairment	All of the previous plus: • Muscle weakness • Constipation • Anorexia and nausea • Fatigue	All of the previous plus: • Abdominal pain • Vomiting • Dehydration • Lethargy • Cardiac arrhythmias, shortened QT interval • Coma • Pancreatitis

Interpreting Laboratory Values in Hypercalcaemia					
Condition	**Serum Phosphate**	**Serum Alkaline Phosphatase**	**Urine Calcium**	**Urine Phosphate**	**PTH**
Hyperparathyroidism	Low	Normal-high	High (in 67% of patients)	High	High
Vitamin D excess	Normal-high	Low	High	High	Low
Malignancy	Often low	High (except in haematological malignancy, when normal)	Variable	High	Variable

Interpreting Laboratory Values in Hypercalcaemia					
Granulomatous disease	Normal-high	Normal-high	High	Normal	Low
Calcium alkali syndrome	Normal-high	Normal	Normal	Normal	Low
Familial hypocalciuric hypercalcemia	Normal or low	Normal	Low (<200 mg/day)	Normal	High

Hypercalcaemia: management

- **The initial management of hypercalcaemia is rehydration with normal saline, typically 3-4 litres/day.**
  - **The most appropriate management is with 0.9% sodium chloride.**
  - **If the sodium level were 150 or above an initial treatment would be with 0.45% sodium chloride reverting to 0.9% sodium chloride when the sodium concentration fell below 150.**
  - gentle hydration with intravenous saline may be enough but if congestive heart failure ensues or if more rapid lowering of serum calcium is desired, a loop diuretic will enhance calcium excretion
    - ECF volume depletion must be avoided because this will worsen hypercalcaemia
    - in a setting of renal insufficiency, higher doses of loop diuretics are needed
    - intravenous saline plus a loop diuretic should decrease the serum calcium rapidly, usually by 0·25-0·75 mmol/L in 1 or 2 days. if this reduction is insufficient bisphosphonate may be required.

- Following rehydration bisphosphonates may be used. They typically take 2-3 days to work with maximal effect being seen at 7 days
  - **If calcium is still elevated despite adequate hydration with saline. The most appropriate next step is to give pamidronate, a bisphosphonate, to inhibit bone resorption and formation, thus reducing bone turnover.**

In the context of hypercalcaemia secondary to malignancy the below advice is suggested by NICE:

- **Advice about maintaining good hydration (drinking 3 - 4 L of fluid per day),** provided there are no contraindications (such as severe renal impairment or heart failure).
- Reassure that a low calcium diet is not necessary, as intestinal absorption of calcium is usually reduced.
- Advise the person to avoid any drugs or vitamin supplements that could exacerbate the hypercalcaemia.
- Encourage mobilization where possible to avoid exacerbating the hypercalcaemia.

- Advise the person to report any symptoms of hypercalcaemia.

Other options include:

- **calcitonin - quicker effect than bisphosphonates**
  - If hydration and furosemide do not control the calcium and you need something faster than a bisphosphonate, then calcitonin is the answer.
  - Calcitonin use is limited by its association with anaphylaxis.
- Non-steroidal anti-inflammatory drugs (NSAIDs) should not be prescribed in patients with hypercalcaemia as they reduce renal blood flow thus inhibiting urinary calcium excretion.
- steroids in sarcoidosis
- There is a limited role for the use of furosemide in hypercalcaemia. It may be useful in patients who cannot tolerate aggressive fluid rehydration
- loop diuretics such as furosemide increase urine calcium excretion but may also induce ECF volume depletion, increasing renal calcium resorption and worsening the hypercalcaemia

Parathyroidectomy:

NICE guidelines clearly stipulate the circumstances under which parathyroidectomy should be considered in primary hyperparathyroidism. These are listed below:

- **Age under 50 years.**
- Adjusted serum calcium concentration that is 0.25 mmol/L or more above the upper end of the reference range.
- Estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m2 although this threshold depends on other factors, such as age.
- creatinine clearance reduced by 30% or more
- Renal stones or presence of nephrocalcinosis on ultrasound or CT.
- 24 hour total urinary calcium excretion greater than 10 mmol
- Presence of osteoporosis or osteoporotic fracture.
  - bone mineral density T-score less than −2.5 at any site
- Symptomatic disease
- unwillingness of patient to follow advice of medical surveillance.

Pseudohypercalcaemia

- **heat cramps**
  - (painful muscular cramping during or after exertion in hot environments).
  - The patient developed haemoconcentration and elevated protein (and albumin), leading to a phenomenon of pseudohypercalcaemia.
  - In this condition, the total serum calcium is high but the ionised calcium should be normal.
  - As a rule of thumb, the first step in the diagnostic evaluation of hypercalcaemia (and more often hypocalcaemia) should be to make sure that the "abnormality" in the total serum calcium levels is not due to abnormal albumin concentrations. In cases of abnormal albumin level, adjusted calcium might better reflect the correct calcium level.

- Only ionised (or free) calcium is physiologically active and should be checked if in doubt, such as in patients with very abnormal albumin level. Extensive investigation, such as protein electrophoresis, should be omitted if pseudohypercalcaemia is confirmed.
- Pseudohypercalcaemia is asymptomatic and should not affect the ECG.
- **the most appropriate immediate management → Intravenous saline infusion and check ionised calcium**.

Familial benign hypocalciuric hypercalcaemia (FHH)

- FHH is a rare, benign, **autosomal dominant** disorder
- due to a defect in the calcium sensing receptor
- pattern of inheritance with complete penetrance.
- The mutation causes a reduced ability of the calcium sensor to detect hypercalcaemia, so the body tolerates levels of serum calcium that would usually be said to be outside the normal range.
- It leads to reduced calcium excretion and consequent mild to moderate hypercalcaemia.

Feature

- asymptomatic hypercalcaemia (often diagnosed incidentally)
- Affected heterozygous patients typically present in childhood with the incidental discovery of:
  - mild hypercalcemia
  - hypocalciuria
  - a normal PTH level, and
  - high-normal to frankly elevated serum magnesium levels. can present with renal stones.
- Rarely, can be associated with episodes of acute pancreatitis.
  - **Management**
    - Mild → adequate hydration to reduce the risk of stone formation.
    - Total parathyroidectomy effective **for recurrent severe pancreatitis.**

Diagnosis

- We recommend a two-step diagnostic procedure (The diagnostic sensitivity of this setup is 98%)
  - First, the calcium/creatinine clearance ratio is measured from a 24-h urine.
  - Second, all patients with calcium/creatinine clearance ratio of 0.020 or less are tested for mutations in the **CASR gene**.

Treatment

- In general, FHH does not require treatment.
- individuals with FHH are typically advised to avoid parathyroidectomy

Hypocalcaemia

Parathyroid hormone is the single most useful test in determining the cause of hypocalcaemia

Causes

- ↓↓ calcium and phosphate + ↑↑alkaline phosphatase → **Osteomalacia**
- **normal** calcium and phosphate + ↑↑alkaline phosphatase → **Paget's disease**
- Serum biochemistry is normal in **osteoporosis**, although alkaline phosphatase can be elevated following a fracture.

- vitamin D deficiency (osteomalacia) **(Osteomalacia causes hypocalcaemia associated with a low serum phosphate, rather than a raised phosphate level)**
- chronic renal failure
- hypoparathyroidism (e.g. post thyroid/parathyroid surgery)
- pseudohypoparathyroidism (target cells insensitive to PTH) (short fourth finger, round face, and mental retardation)
- rhabdomyolysis (initial stages)
- magnesium deficiency (due to end organ PTH resistance)
  - Magnesium is needed to release PTH from the gland.
  - Patients with **ileostomies** can lose large amounts of magnesium through their stomas; hypomagnesaemia → ↓↓PTH → hypocalcaemia that is resistant to an increased provision of calcium
- Acute hyperphosphatemia: Phosphate binds with the calcium and lowers it.
- Fat malabsorption: This binds calcium in the gut.
- massive blood transfusion
  - anticoagulant **citrate** in the bags → **citrate accumulation** in blood → chelates (binds to) circulating ionized calcium (iCa) → ↓plasma iCa.
- Acute pancreatitis may also cause hypocalcaemia.
- Contamination of blood samples with EDTA may also give falsely low calcium levels

Features

Hypocalcaemia: Trousseau's sign is more sensitive and specific than Chvostek's sign

As extracellular calcium concentrations are important for muscle and nerve function many of the features seen in hypocalcaemia seen a result of neuromuscular excitability

Features

- tetany: muscle twitching, cramping and spasm
- **perioral paraesthesia**
- Carpopedal spasm (wrist flexion and fingers drawn together)
- Muscle cramps.

- Hyperreflexia
- Bronchospasm
- Laryngospasm
- Seizures
- if chronic: depression, cataracts
- **Trousseau's sign**
  - carpal spasm if the brachial artery occluded by inflating the blood pressure cuff and maintaining pressure above systolic
  - wrist flexion and fingers drawn together
  - seen in around 95% of patients with hypocalcaemia and around 1% of normo-calcaemic people
- **Chvostek's sign**
  - tapping over parotid causes facial muscles to twitch
  - seen in around 70% of patients with hypocalcaemia and around 10% of normo-calcaemic people
- ECG changes are associated with hypocalcaemia:
  - Common: Corrected QT interval prolongation
  - Rare: Atrial fibrillation or torsade de pointes

Management

- acute management of severe hypocalcaemia is with intravenous replacement. The preferred method is with intravenous calcium gluconate, 10ml of 10% solution over 10 minutes
- intravenous calcium chloride is more likely to cause local irritation
- ECG monitoring is recommended
- further management depends on the underlying cause

Vitamin D

Vitamin D is a fat soluble vitamin that plays a key role in calcium and phosphate metabolism.

Sources

- vitamin D2 (ergocalciferol): plants
- vitamin D3 (cholecalciferol): dairy products, can be synthesised by the skin from sunlight

Functions

- increases plasma calcium and plasma phosphate
  - stimulates intestinal absorption of magnesium and phosphate
  - increases renal tubular reabsorption of calcium and phosphate
- **Calbindin is an intestinal transporter of calcium**, and **by upregulating calbindin expression**, vitamin D leads to increased calcium absorption from the small intestine.
- increases osteoclastic activity
- **Suppression of synthesis of type 1 collagen.** This is balanced by upregulation of osteocalcin, the balance of these changes is an increase in bone mineralisation.
- Vitamin D is recognised to modulate cytokine production and may have a role in the treatment of inflammatory disorders in the future. One example is **decreased production of IL6** in response to vitamin D supplementation.

- stimulate calcium deposition in the extracellular matrix of bone.

Consequences of vitamin D deficiency:

- rickets: seen in children
  - Radiographs of the limbs will demonstrate **epiphyseal widening with metaphyseal fraying.**
- Osteomalacia: seen in adults
  - **It classically presents in the female Asian population whose clothing offers little exposure to sunlight.**
  - **Proximal myopathy is often a presenting feature of osteomalacia**
  - The phosphate and calcium are usually low normal, and the alkaline phosphatase is high

Diagnosis

Measurement of serum 25-OH vitamin D is the best way of estimating vitamin D status.

Optimal: > 75nmol/l
Adequate: 50--75nmol/l
Insufficiency: 30-49nmol/l
Deficiency: < 30nmol/l

Treatment (Load with vitamin D and then continue on maintenance).

- Serum 25OHD < 30 nmol/l: treatment recommended
- Serum 25OHD 30-50 nmol/l: treatment is advised in patients with: fragility fracture, osteoporosis, symptoms suggestive of vitamin D deficiency, reduced exposure to sunlight, raised PTH, conditions associated with malabsorption
- Serum 25OHD > 50 nmol/l: provide reassurance and give advice on maintaining adequate vitamin D levels through safe sunlight exposure and diet
- In patients with good calcium intake and normal serum calcium, giving oral calcium may actually be detrimental. This is due to evidence suggesting adverse cardiovascular outcomes, which is thought to be related to accelerated tissue and vascular calcification.

Vitamin D supplementation

The following groups should be advised to take vitamin D supplementation:

- all pregnant and breastfeeding women should take a daily supplement containing 10µg of vitamin D
- all children aged 6 months - 5 years. Babies fed with formula milk do not need to take a supplement if they are taking more than 500ml of milk a day, as formula milk is fortified with vitamin D
- adults > 65 years
- 'people who are not exposed to much sun should also take a daily supplement'

Testing for vitamin D deficiency

The NOS guidelines specify that testing may be appropriate in the following situtations:

- patients with bone diseases that may be improved with vitamin D treatment e.g. known osteomalacia or Paget's disease
- patients with bone diseases, prior to specific treatment where correcting vitamin deficiency is appropriate e,g, prior to intravenous zolendronate or denosumab
- patients with musculoskeletal symptoms that could be attributed to vitamin D deficiency e.g. bone pain ?osteomalacia

Testing for vitamin D deficiency is not necessary in:

- Patients with osteoporosis → should always be given calcium/vitamin D supplements
- People at higher risk of vitamin D deficiency → should be treated anyway

January 2015 exam: elderly woman with osteoporosis. Prescribed vitamin D supplementation. Which benefits will vitamin D result in? Increased calcium absorption in the gut

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Hyperparathyroidism

Pathophysiology

- PTH indirectly stimulates osteoclasts by binding to its receptor on osteoblasts, inducing RANK-L and M-CSF synthesis

Epidemiology

- occurs in 0.1% of the population
- 90% result from a single adenoma
- remaining 10% from parathyroid hyperplasia
- parathyroid carcinoma accounts for less than 1% of all cases

Classification

	Serum Ca	*Serum Phos*	*Serum PTH*
Primary	↑	↓	↑
Secondary	normal or ↓	↑	↑
Tertiary	↑	↑	↑

- **Primary**
  - typically the result of hypersecretion of PTH by a parathyroid adenoma/hyperplasia
  - may result in osteitis fibrosa cystica
    - breakdown of bone
    - common involves the jaw
- **Secondary**
  - secondary parathyroid hyperplasia as compensation from hypocalcemia or hyperphosphatemia
    - ↓ gut Ca^{2+} absorption
    - ↑ phosphorous
  - Pathophysiology
    - CRF → ↓ phosphate excretion → hyperphosphatemia.

- CRF → Impaired renal conversion of 25-hydroxycholecalciferal to 1,25-dihydroxycholecalciferol (vitamin D, calcitriol) → ↓ intestinal absorption of calcium.
- ↑serum phosphate + ↓ vitamin D production → hypocalcemia → ↑PTH levels.
- As a consequence of prolonged hypocalcemia, parathyroid chief cell hyperplasia occurs and PTH secretion increases.
- secondary and tertiary HPT primarily result from four gland hyperplasia

➢ Causes
- most commonly "secondary" to chronic renal failure (CRF)
  - ❖ 90% of patients with CRF develop this disease by the time hemodialysis is initiated
  - ❖ CRF → ↓ vit D → ↓ Ca^{2+} absorption
- Other causes of secondary HPT include osteomalacia, rickets, and malabsorption.

➢ Features
- **hypocalcemia** or normocalcemia
- decreased vitamin D.
- **hyperphosphatemia.**
- extremely elevated PTH

➢ complications
- progressive bone disease,
  - ❖ osteitis fibrosa cystica,
  - ❖ soft-tissue calcifications.

➢ Management
- predominantly medical,
  - ❖ Supplementation of calcium using oral calcitriol and vitamin D is usually sufficient
- alternative therapies **If become refractory to replacement of calcium and vitamin D,**
  - ❖ These agents are designed to bridge patients to r**enal transplant, the optimal treatment for secondary HPT.**
  - ❖ calcimimetics, such as **cinacalcet**,
    - ✓ It works as an agonist at the site of the calcium sensor on the parathyroid gland. This leads to a suppression of PTH levels.
    - ✓ Cinacalcet may currently be used in patients on renal replacement therapy as an adjunct to vitamin D or phosphate binders.
    - ✓ used to treat secondary hyperparathyroidism.
    - ✓ It mimics the effect of calcium on the parathyroid glands (and elsewhere) with the intention of limiting parathyroid hormone (PTH) production and deleterious effects on bone architecture.
  - ❖ new phosphate binders, and
  - ❖ vitamin D analogues that are less likely to result in hypercalcemia.
- About 1–2% of patients with secondary HPT require parathyroidectomy each year
- indication for parathyroidectomy
  - ❖ The most life threatening indication is calciphylaxis

- ✓ occurs in only 4% of patients undergoing surgery.
- ✓ Calciphylaxis results in expanding, painful, cutaneous, purpuritic lesions that cause tissue calcification and ischemic necrosis which lead to dry gangrene if untreated
- ✓ surgery has been shown to help avoid amputation, decrease pain, and reduce the use of narcotics

- **Tertiary**.
  - parathyroid glands become dysregulated after secondary hyperparathyroidism
  - secrete PTH regardless of Ca2+ level
  - classically caused by hyperplasia of all four glands
  - Causes
    - most commonly in the setting of renal transplant where patients with secondary HPT continue to have elevated PTH levels after receiving a renal allograft
      - ❖ After correction of the primary disorder (CRF) by renal transplant, the hypertrophied parathyroid tissue fails to resolute and continues to over-secrete PTH.
      - ❖ occurs in up to 30% of kidney transplant recipients
    - other causes: after any long-standing period of hypocalcemia such as those seen with chronic dialysis or gastrointestinal malabsorption.
  - Features
    - normal or **elevated serum calcium**
    - decreased vitamin D
    - **decreased serum phosphate**
    - moderately elevated PTH
    - elevated alkaline phosphatase
  - complications
    - bone pain or fractures,
    - pruritus,
    - nephrolithiasis,
    - pancreatitis,
    - soft tissue or vascular calcifications,
    - mental status changes.
  - Management
    - treatment of patients with tertiary HPT is surgical.
    - medical treatment is not curative and, generally, not indicated.
    - tertiary HPT requiring surgical intervention occurs in 1–5% of patients with HPT after undergoing kidney transplant.

Investigations

- Serology
  - primary
    - hypercalcemia
    - ↑ PTH
  - secondary
    - hypocalcemia/normocalcemia

        - ↑ PTH
    - malignancy
        - ↓ PTH
    - ↑ alkaline phosphatase
    - normal anion gap metabolic acidosis
        - ↓ renal reclamation of bicarbonate
- Urinalysis
    - primary
        - hypercalciuria (renal stones)
        - ↑ cAMP
- Radiograph
    - cystic bone spaces ("salt and pepper")
        - often in the skull
    - loss of phalange bone mass
        - ↑ concavity
    - subperiosteal thinning (cortical resorption)
- EKG
    - shortened QT

Thiazide diuretics might unmask underlying primary hyperparathyroidism (PHPT), as they cause mild hypercalcemia by reducing urinary calcium excretion.

Primary hyperparathyroidism

MECHANISM OF PARATHYROID HORMONE (PTH) EFFECT

- **Reabsorbs** calcium **at distal tubule**
- **Excretes phosphate at proximal tubule**
    - A mnemonic to remember this is **PTH** = "**P**hosphate **T**rashing **H**ormone."
- Activates vitamin D from 25 to the 1,25 dihydroxy form
    - increased activity of renal **1-α-hydroxylase** (which converts inactive 25-hydroxycholecalciferol into active 1, 25-dihydroxycholecalciferol),
- Reabsorbs both calcium and phosphate from bone

In exams primary hyperparathyroidism is stereotypically seen in elderly females with an unquenchable thirst and an inappropriately normal or raised parathyroid hormone level.

- the most common cause of hypercalcemia
- most commonly found in women between 50 and 60 years of age
- Two to three times more common in women than men.
- **most commonly due to a solitary adenoma**
- **Parathyroid carcinoma is more likely when PTH is grossly elevated**

Causes of primary hyperparathyroidism

- 80%: solitary adenoma
- 15%: hyperplasia
- 4%: multiple adenoma
- 1%: carcinoma

Parathyroid hormone has a number of direct effects:

- it enhances the release of calcium from bones by binding to osteoblasts which stimulates the formation of osteoclasts, and
- **it enhances reabsorption of calcium in the distal tubules.**

Features - 'bones, stones, abdominal groans and psychic moans'

The PTH level in primary hyperparathyroidism may be normal

- polydipsia, polyuria (Chronic hypercalcaemia can compromise the renal concentrating ability leading to polydipsia and polyuria from nephrogenic diabetes insipidus).
- peptic ulceration/constipation/pancreatitis
- bone pain/fracture (kyphosis due to osteoporosis)
- renal stones → calculi-induced hydronephrosis → Renal impairment
- depression , Confusion
- hypertension, Short QT syndrome on the ECG

Associations

- hypertension
- multiple endocrine neoplasia: MEN I and II
    - **The association of primary hyperparathyroidism and a gastrinoma would suggest a diagnosis of multiple endocrine neoplasia type 1.**

MECHANISM OF NEURAL INHIBITION IN HYPERCALCEMIA

- ↑ calcium levels →↓ depolarization of excitable tissue such as nerves.
- ↑ calcium moves the threshold for depolarization away from the resting membrane potential.
- Bowels are a long muscular tube.
- ↑ calcium → ↓ smooth muscle contraction → constipation
- Low calcium = Hyperexcitable

Investigations

- raised calcium, low phosphate
    - **Hypophosphataemia is due to → reduced renal reabsorption of phosphate.**
    - **PO_4^{3-} is usually elevated or normal in Bone metastases (this clue could differentiate primary hyperparathyroidism from cancer metastases)**
- PTH may be raised or normal **(A high or even normal PTH concentration in the presence of hypercalcaemia would support the diagnosis of hyperparathyroidism)**
- technetium-MIBI subtraction scan
    - Technetium (99mTc) sestamibi scanning has a high specificity and sensitivity for parathyroid adenoma.
    - **Sestamibi (Technetium-99m sestamibi) scanning** is most likely to inform on location of any adenoma prior to a surgical approach.
        - **The most sensitive and specific technique for tumor localization**
        - has a sensitivity of 90.7% and specificity of 98.8%.
        - Sestamibi is a derivative of technetium that avidly incorporates into mitochondria.
        - The large amounts of **mitochondria** in hyperactive parathyroid glands allow for more intense labeling of parathyroid tumors relative to the surrounding tissue.

- 24 hour urinary calcium may be useful if used in comparison to the serum calcium in order to distinguish familial hypocalciuric hypercalcaemia from primary hyperparathyroidism.
- Urinary cAMP increases, because PTH works on the G protein pathway, Gs, which uses cAMP as a secondary messenger.

The effect of PTH on calcium and phosphate

Mechanism	calcium	Phosphate
Excretion by kidneys	↓	↑
Absorption from gut	↑	↑
Absorption from bone	↑	↑
Net Serum concentration	↑	↓

Hyperparathyroidism: Types

Type	PTH	Calcium	Causes
Primary	Normal	High	Tumour of the parathyroid gland (parathyroid adenoma)
Secondary	High	Low	A low level of Ca2+ induces the parathyroid gland to produce large amounts of PTH. **Low levels of Ca2+ are commonly due to renal failure.** Can also be caused by: • **insufficient vit D,** • **insufficient Ca2+ in the diet,** • **excessive Mg2+ in the diet**
Tertiary	High	High	occurs after years of secondary hyperparathyroidism, but then the secondary cause is resolved. The parathyroid gland secretes high levels of PTH even though levels of Ca2+ are now responsive to PTH. There is **hyperplasia of the glands, and loss of response to ca2+. PTH is raised, calcium is raised and so is phosphate, whilst eGFR is significantly deceased .** **Cinacalcet** should be only offered in patients who are unfit for surgery.

- Patients with renal disease however are not treated for hyperparathyroidism until the PTH level breaches twice the upper limit of the normal range. This is because of the risk of precipitating adynamic bone disease.
- Usual first line therapy is weekly 1-alphacalcidol.

Treatment

- total parathyroidectomy

Indications for parathyroidectomy:

- markedly elevated corrected serum calcium (above 3 mmol/l),
- Serum albumin-adjusted calcium greater than 0.25 mmol/L above the normal range
- 24 hour total urinary calcium excretion greater than 10 mmol (400 mg)
- impaired renal function, Creatinine clearance reduced by 30% or more
- **Bone mineral density T-score less than −2.5 at any site** (at any site)

- Age less than 50
- Unwillingness of patient to follow advice of medical surveillance. (Patient request; adequate follow-up unlikely).

indications for surgery in hyperparathyroidism,

- previous marked hypercalcaemic episode,
- renal stones,
- reduced bone mineral density.

Patients with hyperparathyroidism kept under observation require;

- annual plasma calcium, renal function and blood pressure checks, repeat bone mineral density check every 2–3 years and renal ultrasound scan.

Familial isolated hyperparathyroidism (FIHP)

- autosomal dominant
- It is closely related to MEN1 but the development of other tumours is not seen over the course of many years
- Parathyroidectomy is the treatment of choice.

Hyperparathyroidism jaw tumour syndrome

- is a syndrome of hyperparathyroidism and fibro-osseous tumours of the jaw.
- It is described as having increased incidence in Romany families.

Secondary hyperparathyroidism

- Raised PTH, low calcium, **high phosphate**, high alkaline phosphatase
- Due to chronic renal failure.

Feature

- Raised parathyroid hormone (PTH) (low calcium increases PTH release from the parathyroid glands)
- Low serum calcium (kidneys are involved in the activation of vitamin D)
- Raised serum phosphate (kidneys normally excrete phosphate so levels of the latter increase in renal failure)
- High alkaline phosphatase (renal osteodystrophy).

Mechanism

- occurs because of loss of tubules and decreased calcium absorption. Calcium wasting causes a reactive elevation in parathyroid hormone.
- kidneys are involved in the activation of vitamin D

Management

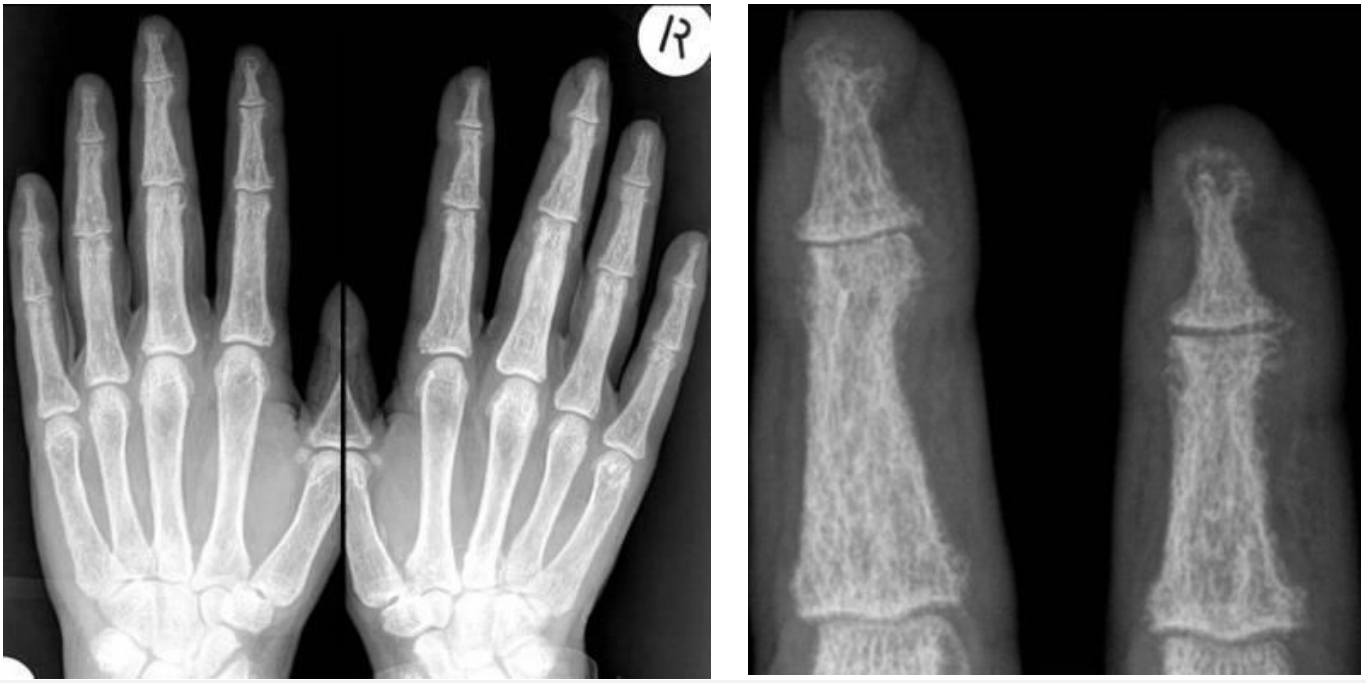
- **vitamin D replacement** (Alphacalcidol) normally given dose twice per week.
- Surgery may be considered if parathyroidism does not respond to medical management.
- NICE guidelines suggest only using cinacalcet in patients with end stage renal failure on renal replacement or in those who are unable to undergo surgery.

Osteitis fibrosa cystica

- The cystic bone spaces seen on radiography are most likely osteitis fibrosa cystica, a condition in which brown, fibrous tissue fills bone cysts.
- most commonly associated with parathyroid adenoma, the most common cause of hyperparathyroidism.

Hungry bone syndrome

- Hungry bone syndrome is an uncommon entity but can occur after parathyroidectomy if the hyperparathyroidism has been long standing.
- The mechanism is thought to be thus: high pre-operative levels of parathyroid hormone provide a constant stimulus for osteoclast activity creating the hypercalcaemic state by de-mineralizing the bones.
- This process can result in x-ray changes very similar to metastatic lytic lesions if left untreated. Upon removal of the parathyroid adenoma the hormone levels fall rapidly (they have a very short half life) and the osteoclast activity is subsequently diminished and the bones rapidly begin re-mineralisation - 'hungry bone syndrome'.
- This process can be uncomfortable and also result in systemic hypocalcaemia.



Bilateral hand radiographs in a middle-aged woman demonstrating generalised osteopenia, erosion of the terminal phalyngeal tufts (acro-osteolysis) and sub-periosteal resorption of bone particularly the radial aspects of the 2nd and 3rd middle phalanges. These changes are consistent with a diagnosis of hyperparathyroidism.

Hypoparathyroidism

Primary hypoparathyroidism

- decrease PTH secretion
  - e.g. secondary to thyroid surgery
  - **Frequency increased in alcoholics**, **particularly in association with hypomagnesaemia**.
    - Alcohol → Hypercalciuria & hypermagnesuria → hypocalcemia and hypomagnesemia → hypoparathyroidism (↓PTH & ↓Ca)
- low calcium, high phosphate
- treated with alfacalcidol

The main symptoms of hypoparathyroidism are secondary to hypocalcaemia:

- tetany: muscle twitching, cramping and spasm
- perioral paraesthesia
- Trousseau's sign: carpal spasm if the brachial artery occluded by inflating the blood pressure cuff and maintaining pressure above systolic
- Chvostek's sign: tapping over parotid causes facial muscles to twitch
- if chronic: depression, cataracts
- ECG: prolonged QT interval

Pseudohypoparathyroidism

Pathophysiology

- Pseudohypoparathyroidism is caused by target cell insensitivity to parathyroid hormone (PTH) due to a mutation in **alpha subunit of** the G-protein.
- It is an autosomal dominant condition and is due to defects in the gene (GNAS1) encoding the alpha subunit of the stimulatory G protein (Gsa)
- **The G-protein-coupled receptor for parathyroid hormone (PTH) becomes unresponsive to the hormone, hence patients become hypocalcaemic in the face of normal or elevated PTH levels.**

Epidemiology

- occurs twice as frequently in females as in males.

Types

- **type I: there is a complete receptor** defect
- type II : the cell receptor is intact.

Bloods

- **PTH: high**
- **calcium: low**
- **phosphate: high**
- alkaline phosphatase: high

Features

- **short fourth and fifth metacarpals**
- short stature
- obesity
- round face
- subcutaneous calcification

- cognitive impairment, low IQ
- dental hypoplasia
- **Slipped femoral epiphysis**

Investigation

- Diagnosis is made by measuring **urinary cAMP** and **phosphate** levels following an **infusion of PTH.**
  - In **hypoparathyroidism** this will cause an increase in both cAMP and phosphate levels.
  - In **pseudohypoparathyroidism type I** neither cAMP nor phosphate levels are increased
  - whilst in **pseudohypoparathyroidism type II** only cAMP rises.

Radiographic features

- **Musculoskeletal manifestations**
  - soft tissue calcification
  - exostoses: short metaphyseal or more central and perpendicular to long axis of bone
  - broad bones with coned epiphyses
- **CNS / head and neck manifestations**
  - basal ganglia calcification
  - sclerochoroidal calcification
  - deep white matter calcification

Management

- **Calcium and vitamin D supplementation**

Pseudopseudohypoparathyroidism

- similar phenotype to pseudohypoparathyroidism but normal biochemistry

Pseudohypoparathyroidism is when the defect is inherited from the **mother** while **pseudopseudohypoparathyroidism** is inherited from the **father**.

Adrenal gland conditions

Adrenal cortex

Adrenal cortex mnemonic: GFR - ACD

Adrenal cortex (mnemonic **GFR - ACD**)

- zona **G**lomerulosa (on outside): mineralocorticoids, mainly **A**ldosterone
- zona **F**asciculata (middle): glucocorticoids, mainly **C**ortisol
- zona **R**eticularis (on inside): androgens, mainly **D**ehydroepiandrosterone (DHEA)

Adrenal medulla

The adrenal medulla secretes →

➔ **all the adrenaline in the body**
➔ Small amounts of noradrenaline.

It essentially represents an enlarged and specialised sympathetic ganglion

noradrenaline metabolism

The action of noradrenaline released at sympathetic nerve endings is terminated by which mechanism?

➔ The majority are **Re-uptaked by the axonal terminals** ➔ **into the neurosecretory granules**

- small amount is metabolised by monoamine oxidase (MAO).
- smaller quantities that escape into the circulation are metabolised by catechol-O-methyl transferase (COMT).

De-hydro-epi-androsterone (DHEA)

- Dehydroepiandrosterone is the most abundant circulating adrenal steroid.
- Adrenal glands are the main source of dehydroepiandrosterone in females - loss of functioning adrenal tissue as in Addison's disease may result in symptoms secondary to androgen deficiency, such as loss of libido.
- Research is ongoing as to whether routine replacement of DHEA is beneficial

May 2008 exam: Addison's disease C/O a decrease in her libido. On examination there is a slight loss of pubic hair. What is the most likely cause? Dehydroepiandrosterone (DHEA) deficiency

---

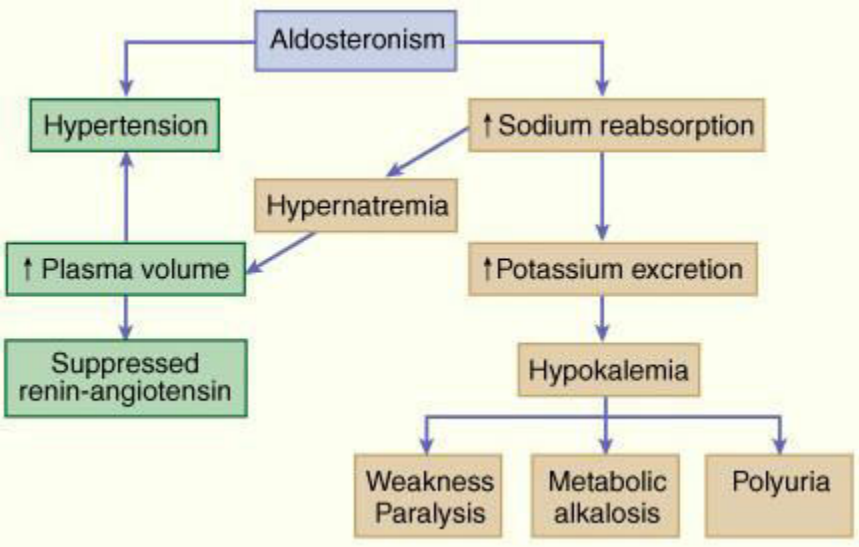
Cortisol

Cortisol levels are increased in:

- **pregnancy**
- conditions of physical and emotional stress
- oestrogens
- oral contraceptives
- amphetamines
- cortisone
- spironolactone.

Primary hyperaldosteronism

Bilateral idiopathic adrenal hyperplasia is the most common cause of primary hyperaldosteronism



Prevalence

- with the wide diffusion of the aldosterone to renin ratio (ARR) as a screening test, the estimated prevalence of primary aldosteronism (PA) has risen from 1 to **10–30% of all forms of hypertension**

Causes

1. **The most common → Bilateral idiopathic adrenal hyperplasia (70% of cases).**
2. Common → adrenal adenoma, termed Conn's syndrome.
3. rare → Adrenal carcinoma
4. Glucocorticoid deficiency - also called glucocorticoid-remediable aldosteronism → high ACTH levels → increased aldosterone production.

Features

- Hypertension
  - The most common cause of hypertension,(**(up to 12%) of hypertension**, and as such should always be considered.
  - May present with untreated or resistant hypertension
- Hypokalaemia , may leads to:
  - fatigue, muscle weakness, cramping, headaches, and palpitations.
  - polydipsia and polyuria from hypokalemia-induced nephrogenic diabetes insipidus.
  - Abdominal distention (ileus from hypokalemia)
- elevated aldosterone and low renin.
  - (aldosterone-to-renin ratios are typically ≥ 20).
- Low magnesium and normal/high sodium.
- Metabolic alkalosis
  - resulting from the **action of aldosterone on the renal distal convoluted tubule (DCT**) (ie, enhancing sodium reabsorption and potassium and hydrogen ion excretion).
- Patient with **adrenal adenoma** do not have features of hyperandrogenaemia like hirsutism as benign adrenal tumours produce cortisol but not the androgens. **Absence of hirsutism and**

virilisation in a patient with other features of Cushing's syndrome favours adrenal adenoma but needs further investigations.

Screening for hyperaldosteronism (using aldosterone / renin ratio) **should be considered for**:

- Hypertensive patients with hypokalaemia (not due to treatment),
- those with marked diuretic-induced hypokalaemia (<3.0)
- and those with refractory hypertension (failure to respond to three or more agents).

Investigations

- high serum aldosterone
- low serum renin
- high-resolution CT abdomen with contrast
  - (the initial radiologic investigation) and better than MRI .
  - sensitivity greater than 90%
  - If CT or MRI is normal in a patient with primary aldosteronism, a 6- to 12-month treatment trial with aldosterone antagonists is recommended, after which the imaging studies should be repeated.
- adrenal vein sampling
  - its greatest utility when adrenal imaging is normal despite biochemical evidence for primary aldosteronism
- If aldosterone/renin ratios is ↑↑ → definitive confirmation or exclusion of diagnosis → suppression testing with measurement of aldosterone response to fludrocortisone or to salt loading.
- genetic testing for the hybrid gene causing familial hyperaldosteronism type I (glucocorticoid-remediable aldosteronism).
  - A negative genetic test should be followed by adrenal CT and adrenal venous sampling to differentiate unilateral from bilateral forms.

Aldosterone: renin ratio

- causes of **false-positive** results:
  - ingesting large amounts of sodium,
  - renal impairment,
  - **beta-blockers**

- causes of **false-negative** results
  - Salt-restriction,
  - ACE inhibitors and angiotensin-receptor blockers,
  - spironolactone and other diuretics

- **The aldosterone concentration is usually higher when the patient is erect than when supine** (in bilateral hyperplasia)
- **(ACEi), ARB, diuretics, calcium-channel blockers and β-blockers all ideally require a washout period of 2 weeks to make the aldosterone: renin ratio assay meaningful.** While it may seem dangerous to wash out, a definitive diagnosis is impossible if you do not.
- Spironolactone requires a washout period of 6 weeks.
- A high aldosterone: renin ratio is suggestive of primary hyperaldosteronism.

- The blood sample should be taken in the morning, standing, and with a normalised potassium concentration (using supplementation) if possible.
- Alpha-blockers (for example, doxazosin) and calcium channel blockers (for example, amlodipine) are the hypertensives of choice in patients undergoing renin/aldosterone ratio measurements.
- **Alpha blockers such as doxazosin have the lowest effect on the renin-angiotensin system; thus can be continued during the renin/aldosterone ratio test .**

The effect of drugs on renin and angiotensin is seen below:

Drug	Renin	Aldosterone	Effect
Non-dihydropyridine CCB	Minimal	Minimal	**No effect**
Dihydropyridine CCB	Minimal	Decreased/minimal	**No effect**
Alpha-blockers	**Nil**	**Nil**	**No effect**
Hydralazine	Minimal	Minimal	**No effect**
ACE inhibitors & ARBs	Increased	Decreased	**False negative**
Diuretics	Increased markedly	Increased	**False negative**
Minoxidil	Increased	Minimal	**False negative**
Beta-blockers	Decreased	Minimal	**False positive**
Methyldopa	Decreased	Minimal	**False positive**

- **Differential diagnosis**
  - Hypertension is also a feature of Liddle syndrome and steroid 11β-hydroxylase deficiency**, but aldosterone concentrations are low**.
  - In secondary aldosteronism, aldosterone secretion is increased secondary to an increase in renin secretion, and **plasma renin activity is normal or increased.**
  - **Adrenal hyperplasia can be differentiated from adrenal adenoma by measuring aldosterone levels on awakening, and 2-4 hours later while standing:**
    - **In adenoma, aldosterone levels decline on standing 2-4 hours later.**

- **in hyperplasia, levels increase.**

Management

- adrenal adenoma: surgery
  - Surgery is the treatment of choice for Conn's adenoma and leads to resolution of hypertension in around 70% of patients.
  - For hypertension
    - **Aldosterone inhibition with spironolactone will bring the greatest additional reduction in blood pressure**.
- bilateral adrenocortical hyperplasia: aldosterone antagonist e.g. **spironolactone**

Prognosis

- After removal of the adenoma the blood pressure is normal in 70% of patients at 1 year;
- 50% of patients are still normotensive after 5 years.

January 2016 exam: A 24-year-old woman with BP: 170/100 mmHg during a routine medical check. Blood tests show: Na+ =140 mmol/l. K+ = 2.6 mmol/l. Bicarbonate = 31 mmol/l. Urea = 3.4 mmol/l. Creatinine =77 µmol/l. Which one of the following investigations is most likely to be diagnostic? **Renin:aldosterone ratio** (Δ Conn's syndrome)

Bilateral hyperplasia vs adrenal adenoma:

bilateral hyperplasia	adrenal adenoma
idiopathic adrenal hyperplasia (IAH)	Aldosterone-producing adenomas (APAs)
Commonest	common
higher prevalence in African Americans, persons of African origin, and, potentially, other blacks.	have more severe hypertension, hypokalemia, and higher urinary aldosterone than IAH.
4 times more prevalent in men than in women	more common in women than in men, with a female-to-male ratio of 2:1.
peaking in the sixth decade of life	The typical patient with an APA is a woman aged 30-50 years.
renin-angiotensin system (RAS)–mediated **increase** in aldosterone level occurs **with upright posture.**	**decrease** in the aldosterone level **with upright posture**
Loss of normal circadian rhythm of aldosterone secretion (normally: lowest around midnight, and highest in early morning)	preserved of normal circadian rhythm of aldosterone secretion

aldosterone-producing adrenal adenomas are commoner in young women, whereas bilateral adrenal hyperplasia tends to occur later and is commoner in men.

Congenital adrenal hyperplasia (CAH)

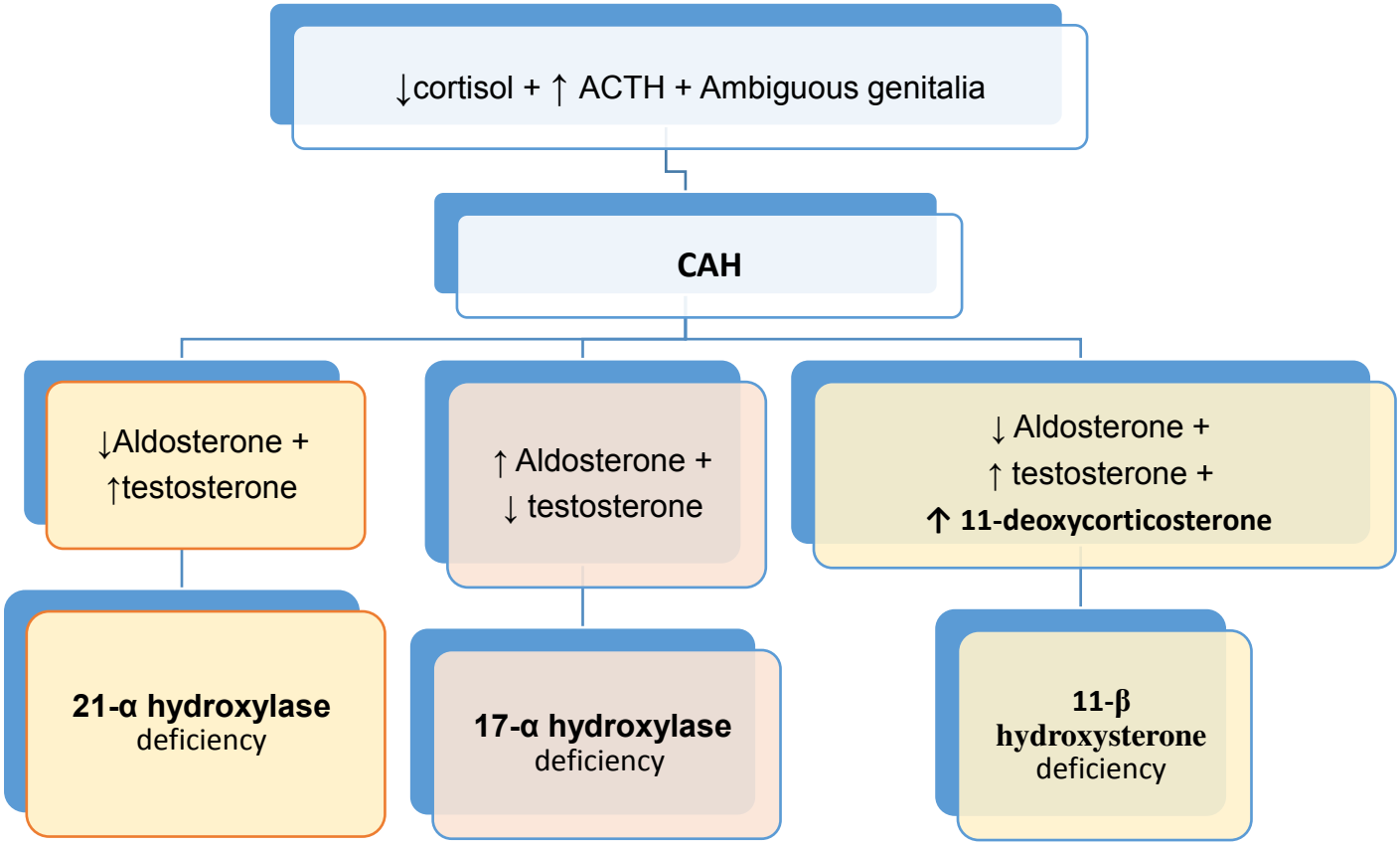
Overview

- group of autosomal recessive disorders
- Congenital adrenal hyperplastia is caused by an inherited defect in the cortisol and/or aldosterone biosynthetic pathways. Non-classical forms result from milder enzyme dysfunction and therefore manifest later in life (adolescence or adulthood).
- **associated with HLA B47**
- affect adrenal steroid biosynthesis
- affects males and females in equal numbers.
- Results from a defect in the biosynthetic pathway of cortisol and/or aldosterone.
- in response to resultant low cortisol levels the anterior pituitary secretes high levels of ACTH
- ACTH stimulates the production of adrenal androgens that may virilize a female infant

Cause

- **21-hydroxylase deficiency (90%) most common cause**
  - due to mutation of the CYP21A2 gene **on chromosome 6**
  - ↓ aldosterone
  - ↑ **testosterone**
  - All forms of CAH cause → ↓ cortisol + ↑ ACTH
- 11-beta hydroxylase deficiency (5%)
  - ↓ aldosterone
  - patients with 11β-hydroxylase will present with increased blood pressure, hypokalemia and increased androgen levels, differentiating it from 17α-hydroxylase deficiency.
  - ↑ **testosterone**
  - ↑ **11-deoxycorticosterone , ↑ 11-Deoxycortisol**
    - 11 Beta-hydroxylase is responsible for conversion of 11-deoxycorticosterone and 11-deoxycortisol to corticosterone and cortisol. As this enzyme is not active in patients with 11-beta hydroxylase deficiency, levels of these steroids accumulate in patients suffering from the disorder.
    - Whilst levels of 17-OH steroids are elevated in those with 11-beta hydroxylase deficiency, the elevation seen is not as great as that seen with 21-hydroxylase deficiency, occasionally an incorrect diagnosis of 21-hydroxylase deficiency may however be made.
- 17-hydroxylase deficiency (very rare):
  - ↑ **mineralocorticoids (aldosterone) → hypertension and hypokalemia**
  - ↓ **testosterone**
  - amenorrhea, no secondary sexual characteristics,
  - Pathophysiology
    - This enzyme converts progesterone to 17-α-hydroxyprogesterone, which subsequently is converted to androstenedione, testosterone, and finally estradiol.

- ↓estradiol results in a failure of development of the estrogen-dependent menstrual cycle and the appearance of normal secondary sexual characteristics.
- Progesterone accumulates and is pushed off into the aldosterone pathway. This increased synthesis of mineralocorticoids then results in hypertension and hypokalemia as a result of Na^+ retention, K^+ expulsion, and fluid retention.



Feature

- **Premature epiphyseal closure**
- Under- and over-treatment of CAH → risk of **short stature:**
  - over-treatment → glucocorticoid-induced inhibition of the growth axis.
- ACTH excess → hyperpigmentation
- Cortisol deficiency
- aldosterone deficiency → **salt-losing crises**
- androgen excess →
  - **in boys → ambiguous genitalia, precocious puberty**
  - **in girls → virilism, hirsutism, clitoromegaly and primary amenorrhoea.**
- Hyperreninaemia due to sodium loss and hypovolaemia.

Diagnosis

- 17-OH progesterone is elevated because of the enzyme deficiency.
  - **Measurement of 17-OHP levels, can help to distinguish between PCOS and non-classical CAH.**
    - The clinical presentation may be indistinguisable from polycystic ovarian syndrome, with hirtusism being a dominant feature.The synacthen stimulation test can evaluate adrenal gland function, and when 17-OHP levels are measured concurrently, can help to distinguish between PCOS and non-classical CAH.
  - Diagnosis is by finding raised serum 17-hydroxyprogesterone levels that show a hyper-responsiveness to adrenocorticotropic hormone (ACTH).
  - The ACTH stimulation test (synacthen stimulation test)is the best screening evaluation, and can diagnose 21-OH deficiency when the plasma 17-OH progesterone are more than 30 nmol/L.

Treatment

- glucocorticoid replacement
  - the drug of choice?
    - hydrocortisone
      - it minimises growth suppression in children.
  - The dose?
    - The lowest dose of glucocorticoid that suppresses (not totally) adrenal androgens, whilst maintaining normal growth and weight gain.
    - Hydrocortisone has a relatively short half-life and must therefore be administered twice daily.

Monitoring of treatment

- **Efficacy of treatment is best monitored by 17-OH progesterone and androstenedione levels**
- Renin activity levels can be used to monitor the adequacy of mineralocorticoid and sodium replacement.
- Over treatment with mineralocorticoids leads to hypertension, suppressed plasma rennin activity and possibly growth retardation.

Non-classic congenital adrenal hyperplasia (NCAH)

classical CAH (C-CAH)	Nonclassical CAH (NC-CAH)
• The SEVERE form • begins in early fetal life, usually detected in the newborn period or in early childhood. • Have a partial enzyme deficiency • Less common • Lack of both cortisol and aldosterone predispose 3/4 of severely affected individuals with CAH to "adrenal crises" • characterized by ambiguous genitalia in girls. • Severely affected girls may be mistaken for boys at birth. • Affected boys have no genital malformations at birth, but continued androgen excess causes unusually fast body growth.	• The milder form • Have a partial enzyme deficiency • usually asymptomatic at birth and typically present in late childhood, adolescence, or adulthood • may cause symptoms at any time from infancy through adulthood. • NC-CAH 21-OH deficiency is much **more common** than C-CAH • In adolescent and adult females, the symptoms of hyperandrogenism include hirsutism, acne, menstrual irregularity, androgenic alopecia, and impaired fertility • not characterized by ambiguous genitalia in girls.

- **Genetics**
  - autosomal recessive disorder
  - due to P450c21 **(21-hydroxylase) deficiency**
  - **due to mutations in the *CYP21A2* gene.**
  - Non-classical forms are characterised by milder enzyme dysfunction, and therefore usually only manifest in adolescence or adulthood.
- **Incidence:**
  - Non-classic congenital adrenal hyperplasia is a cause of hyperandrogenism in up to 1 in 1000 females, particularly those of Hispanic, Yugoslavian or Eastern European **Jewish descent**.
- **Feature**
  - Patients might complain of no other symptoms apart from **primary amenorrhoea**.
  - The clinical presentation may be indistinguisable from polycystic ovarian syndrome, with hirtusism being a dominant feature.
  - **Normal ultrasound scan will rules out other causes of primary amenorrhoea (Turner syndrome and testicular feminization).**
- **Diagnosis**
  - 17-OHP concentration above 33 nmol/L would be diagnostic.
- **Management**
  - glucocorticoid supplementation **in juveniles**,
  - Flutamide (used as an anti-androgen) **in adults** with mild symptoms.
  - If the main concern is infertility, ovulation induction is the treatment of choice.
  - **If hirsutism is the presenting problem then anti-androgens (such as flutamide) should be used.**

Glucocorticoid remediable aldosteronism (GRA)

- **autosomal dominant**
- mutation leads to ACTH responsive aldosterone production from the zona fasciculata rather than the zona glomerulosa.
  - ectopic expression of aldosterone synthase and novel steroids in the adrenal zona fasciculata under the regulation of ACTH.
- It occurs because the regulatory portion of the 11b-OH gene binds to the aldosterone synthase gene.

Features

- **strong family history**
  - family history of early hypertension and haemorrhagic strokes is characteristic.
- **resistant hypertension**,
- **hypokalaemia**,
  - **potassium is normal in more than one-half of cases** of GRA in contrast to the hypokalaemia frequently seen in primary aldosteronism
- **responsive to corticosteroid therapy**,

Treatment

- physiologic doses of a glucocorticoid will correct the overproduction of aldosterone by suppressing ACTH.

Pseudohyperaldosteronism

Definition

- Pseudohyperaldosteronism is characterized by a clinical picture of hyperaldosteronism with suppression of plasma renin activity and aldosterone.

Feature:

- hypertension,
- salt retention
- hypokalaemia
- low renin and aldosterone concentrations.

Causes

- Direct mineralocorticoid effect, as with desoxycorticosterone, fluorohydrocortisone, fluoroprednisolone, estrogens, and the ingestion of high amounts of glycyrrhetinic acid.

- **inhibition of 11 beta hydroxysteroid dehydrogenase (11 bHSD)**
  - 11bHSD is responsible for the conversion of cortisol to the inactive cortisone, preventing activation of the mineralocorticoid receptor by cortisol but permitting activation by aldosterone.
  - Both **liquorice** and carbenoxolone inhibit 11bHSD and produce pseudohyperaldosteronism
  - Licorice has aldosterone-like properties and prevents inactivation of cortisol, resulting in a syndrome of apparent mineralocorticoid excess.

- Liddle syndrome, which is due to a mutation of the gene encoding for beta and gamma subunits of the sodium channels.

Apparent mineralocorticoid excess (AME)

- (AME) is a rare form of pseudohyperaldosteronism characterized by very early-onset and severe hypertension, associated with low renin levels and hypoaldosteronism.

Causes

- Autosomal recessive mutation in the ***HSD11B2*** gene (16 q 22) which encodes the kidney isozyme of **11β-H**ydroxy-**S**teroid **D**ehydrogenase type **2** (11-beta-HSD2)
- acquired reduction of the activity of the **(11 bHSD)** enzyme caused by:
  - glycyrrhetinic acid,
  - carbenoxolone,
  - grapefruit juice.
  - (rarely)↑ **liquorice** consumption → inhibition of 11-hydroxysteroid dehydrogenase type 2 → ↑ cortisol → AME. (Liquorice**:** black substance produced from the root of a plant used in midicine and sweets)

Pathophysiology

- Normally **11-hydroxysteroid dehydrogenase type 2 → converts cortisol into inactive cortisone at the renal parenchyma** (In order to prevent cortisol activation of the mineralocorticoid nuclear receptor and subsequent hyperaldosteronism)
- ↓11β-hydroxysteroid dehydrogenase type 2 →↑ cortisol in the kidney → activate the mineralocorticoid receptor → aldosterone-like effects in the kidney → hypokalemia, hypertension, and hypernatremia

Feature:

- usually diagnosed within the first years of life
- polyuria and polydipsia,
- failure to thrive,
- hypokalemia, hypertension, and hypernatremia
- low renin and aldosterone levels
- metabolic alkalosis
- nephrocalcinosis.
- Stroke has been observed before the age of 10 years in untreated children.

Diagnosis:

- ↑ ratio of free urinary cortisol to free urinary cortisone. (AME patients create less cortisone)
- differentiate between AME and Liddle's Syndrome by administering a potassium-sparing diuretic:
  - Liddle's syndrome: **only** respond to a diuretic that binds the ENaC channel,
  - AME: respond to a diuretic that binds to ENaC or mineralcorticoid receptor.

Treatment: Two main strategies:

1. blockade of the mineralocorticoid receptor by spironolactone (2-10 mg/kg/day), combined with thiazides to help to normalize blood pressure and reduce hypercalciuria and nephrocalcinosis.

2. administration of exogenous corticoids to block ACTH and suppress the endogenous secretion of cortisol.

Phaeochromocytoma

Phaeochromocytoma: do 24 hr urinary metanephrines, not catecholamines

PHaeochromocytoma - give PHenoxybenzamine before beta-blockers

The 5 P's of pheochromocytoma:

Pressure (BP)
Pain (headache)
Perspiration
Palpitations
Pallor/diaphoresis

Pheochromocytoma rule of 10's:

10% extra-adrenal
10% bilateral
10% malignant
10% occur in children
10% familial

Pheochromocytoma = Episodic hypertension

Pheochromocytoma is part of MEN II.

- Phaeochromocytoma is a rare catecholamine secreting tumour.
- The tumors arise from the chromaffin cells of the adrenal medulla
  - **Chromaffin cells are modified post-ganglionic sympathetic cells** that release catecholamines after stimulation by pre-ganglionic sympathetics.
- The peak incidence is between ages 20 to 40.
- About 10% are familial
- may be **associated with**:
  - MEN type II.
  - Neurofibromatosis.
  - von Hippel-Lindau syndrome.

Basics

- bilateral in 10%
- malignant in 10%

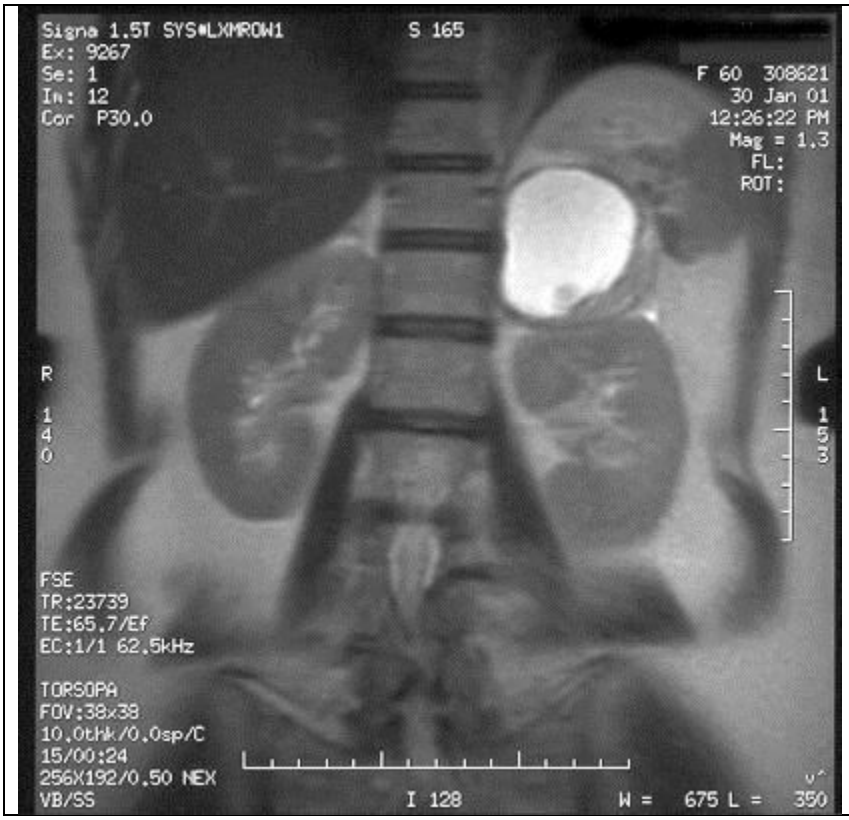
- extra-adrenal in 10% (most common site = organ of Zuckerkandl, adjacent to the bifurcation of the aorta)

Features are typically episodic

- hypertension (around 90% of cases, may be sustained)
  - it can also present with severe hypotension from catecholamine-induced cardiomyopathy
- headaches**(80%) the most common presenting feature**
- Palpitations (70%)
- sweating Hyperhidrosis (60%)
- anxiety
  - (sense of impending doom)
- symptoms occur primarily at night
- Hyperglycemia or glycosuria may be present.
- **Paroxysmal attacks may be provoked by:**
  - palpation of the tumor,
  - abdominal compression or massage,
  - postural changes,
  - induction of anesthesia,
  - emotional trauma,
  - micturition if the tumor is in the bladder.
- **Drugs that exacerbate or unmask the symptoms** (drugs that inhibit catecholamine reuptake)
  - unopposed beta blocker
  - tricyclic antidepressants
  - cocaine

Tests

- **24 hr urinary collection of metanephrines (sensitivity 97%)**
  - this has replaced a 24 hr urinary collection of catecholamines (sensitivity 86%)
  - False positive urinary metanephrines can occur as a result of:
  - hypoglycaemia, **stress**, exercise, drugs such as methyldopa, dopamine agonists or ganglion-blocking antihypertensives, and also various foodstuffs including coffee, chocolate, bananas and citrus fruits.
- the definitive methods for localisation →
  - **Magnetic resonance imaging** and meta-iodo-benzyl guanidine **(MIBG) scanning**
  - Scanning with (MIBG) demonstrates specific uptake in sites of sympathetic activity, **particularly useful with extra-adrenal tumours**.
  - A scan with ^{131}iodine-labelled metaiodobenzylguanidine (MIBG) is used in cases where a tumour is confirmed biochemically but cannot be identified on computerized tomography (CT) or magnetic resonance imaging (MRI) scanning.
  - The presence of noradrenaline alone usually indicates an **extra-adrenal tumour**.



The image reveals a large left suprarenal mass. The appearances are typical of a which, unlike most other adrenal tumours, demonstrates a distinctive 'bright white' signal on T2-weighted MRI.

Management

definitive management → Surgery.

Initial management →The patient must first however be stabilized with medical management:

- alpha-blocker (e.g. phenoxybenzamine), **given first, before a beta-blocker.**
  - β-blockade without first adequate α-blockade will result in significantly increased blood pressure
  - to avoid a **hypertensive crisis** upon **tumor manipulation at the time of surgery**.
- beta-blocker (e.g. propranolol)
- It is also important to fill patients well with intravenous fluids prior to surgery in order to prevent a sudden loss of vascular tone **in the postoperative period** as a result of a **sudden fall in catecholamines** leading to **profound hypotension**. These are important anesthetic considerations.
- **Management of phaeochromocytoma in pregnancy → (initiate alpha-blockade and arrange delivery by C-section)**
  - Alpha blockade (phenoxybenzamine) should be started as soon as the diagnosis is made, and should be given for 10-14 days.
    - Doxazosin is also safe in pregnancy but can be displaced by high levels of endogenous catecholamines.
    - Unopposed beta blockade should not be used in the management of phaeochromocytoma because of the **risk of paradoxical increases in blood pressure**
  - Laparoscopic adrenalectomy is indicated if the tumour mass is less than 7 cm

- However, after 24 weeks of gestation surgical removal is recommended after an elective caesarean section.
- Vaginal delivery carries a higher mortality rate of 31%, compared to 19% with C-section.
- The anaesthetic approach is extremely important, as anaesthetia can precipitate a hypertensive crisis. General anaesthesia is recommended.

Preoperative and intraoperative precautions to be undertaken in patients with pheochromocytoma:

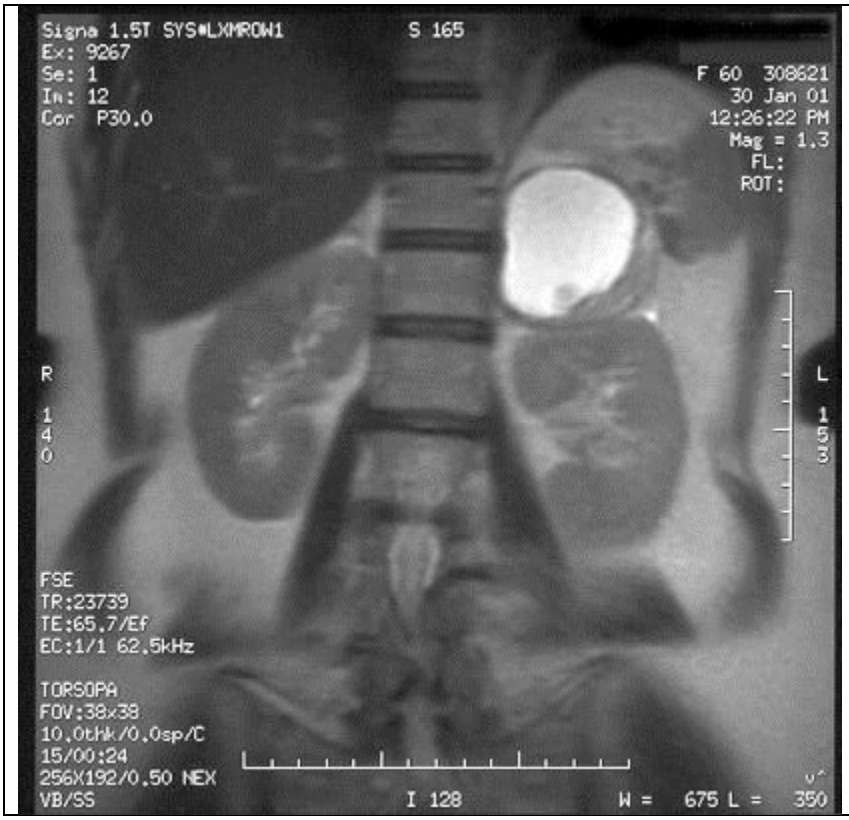
- Anesthesia should be induced with a non-arrhythmogenic drug like thiopentone
- Anesthesia should be continued with enflurane
- If muscle relaxants are needed, drugs that do not release histamine are preferred
- Atropine should not be used preoperatively

Prognosis:

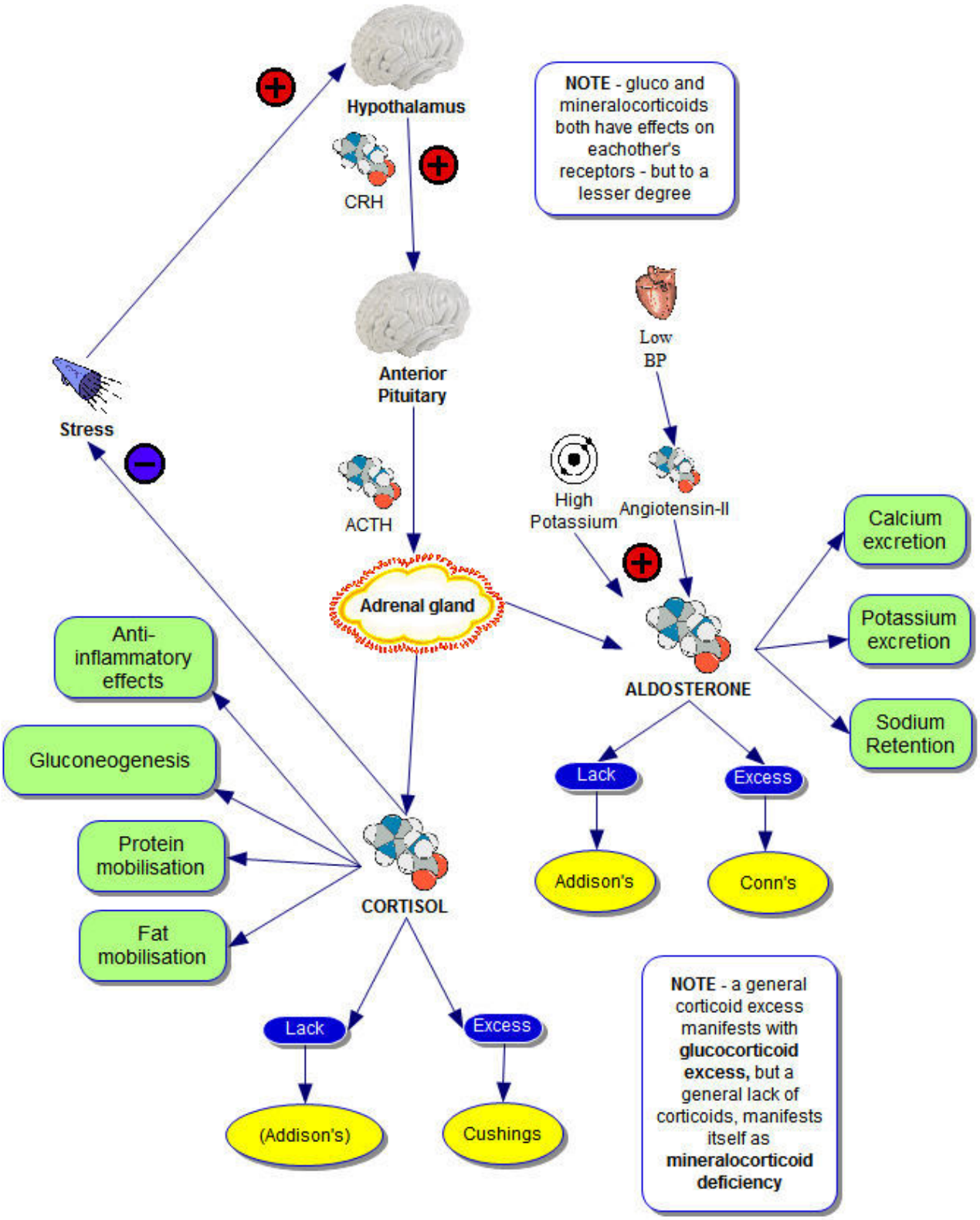
- benign phaeochromocytoma →The 5-year survival rate is 95%
- malignant phaeochromocytoma → The 5-year survival rate is 40%
- Phaeochromocytomas are three times more likely to be malignant in women.

May 2013 exam : A 43-year-old man is found to have a phaeochromocytoma. Which anti-hypertensive medication should be started first? Phenoxybenzamine

January 2015 exam: A 41-year-old patient C/O recurrent headaches, sweating and palpitations. BP: 210/110 mmHg. Given the likely diagnosis, what is the most appropriate next test? 24 hour urinary collection of metanephrines (∆ Phaeochromocytoma)



The image reveals a large left suprarenal mass. The appearances are typical of a phaeochromocytoma which, unlike most other adrenal tumours, demonstrates a distinctive 'bright white' signal on T2-weighted MRI.


Hypothalamus
CRH
Anterior Pituitary
ACTH
Stress
Adrenal gland
Low BP
High Potassium
Angiotensin-II
ALDOSTERONE
Calcium excretion
Potassium excretion
Sodium Retention
Lack
Excess
Addison's
Conn's
Anti-inflammatory effects
Gluconeogenesis
Protein mobilisation
Fat mobilisation
CORTISOL
Lack
Excess
(Addison's)
Cushings
NOTE - gluco and mineralocorticoids both have effects on eachother's receptors - but to a lesser degree
NOTE - a general corticoid excess manifests with glucocorticoid excess, but a general lack of corticoids, manifests itself as mineralocorticoid deficiency

Hypoadrenalism

Primary hypoadrenalism (Addison's disease)

Addison's disease is associated with a metabolic acidosis

Definition

- A disorder caused by the destruction of the adrenal cortices
  - involves all three layers of the cortex
  - results in ↓ production of glucocorticoid (cortisol), mineralcorticoids (aldosterone), and steroids
- clinical findings are noted after 90% of the adrenal cortex has been destroyed.
- Addison's disease (primary hypoadrenalism) is associated with:
  - Low aldosterone secretion (leading to salt wasting)
  - High plasma renin
  - High adrenocorticotrophic hormone (ACTH)
  - High lipotropin
  - Elevated plasma vasopressin, and Angiotensin II.

Prevalence

- Prevalence is around 5 per 100,000.
- There is a female: male preponderance of 2:1

Pathophysiology

- (aldosterone insufficiency)leads to loss of salts an water(kidneys) → blood volume decreases so does the cardiac work → hypotension. also K+ and H+ renal secretion is impaired → hyperkalemia and metabolic acidosis.
- insufficiency of glucocorticoids leads to hypoglycemia and inability of kidney to excrete a water load (hyponatremia)

Causes

- Autoimmune
  - **Autoimmune destruction of the adrenal glands is the commonest cause of hypoadrenalism in the UK, accounting for 80% of cases**
  - **70% of patients have circulating anti-adrenal antibodies.**
- infectious (eg, mycobacterial, fungal),
  - Tuberculosis
    - accounts for a further 15% of cases.
    - the predominant cause of Addison disease in developing countries.
    - In case with high ESR, TB adrenalitis should be considered
    - **the best investigation to establish the diagnosis in this patient → CT abdomen**
      - absence/shrinkage or enlargement of the adrenals may be seen.

- ❖ Although a CXR would be an appropriate initial investigation this may be normal despite the possibility of TB.
- ➢ The differential diagnosis for a pyrexia of unknown origin and bilateral adrenal swelling would be lymphoma, tuberculosis, or histoplasmosis.
- ➢ Acute meningococcal sepsis due to *Neisseria meningitidis* can lead to sepsis, disseminated intravascular coagulation (DIC), endotoxic shock, and acute primary adrenal insufficiency, also known as **Waterhouse-Friderichsen syndrome**.
  - ▪ ***Neisseria meningitidis* is a gram-negative diplococcus that grows on chocolate agar.**
  - ▪ The adrenal insufficiency is secondary to acute adrenal hemorrhage which may be attributable to DIC or an endotoxin-mediated process.
  - ▪ **purpuric rash** classically appears on the trunk and extremities secondary to the DIC
- ➢ HIV

- neoplastic (eg, primary, metastatic),
  - ➢ (e.g. bronchial carcinoma)
- vascular (eg, hemorrhage, emboli, thrombus),
  - ➢ **anti-phospholipid syndrome (Hughes' syndrome)**
    - ▪ precipitate adrenal infarction and haemorrhage through adrenal vein thrombosis.
  - ➢ Anticoagulant overdose
    - ▪ bilateral hemorrhage in the adrenal glands resulting in severe acute adrenal insufficiency.
    - ▪ Flank pain, **hypotension refractory to resuscitative efforts**, and hypoglycemia indicate acute adrenal insufficiency due to heparin overdose.
- traumatic, iatrogenic (eg, surgery, medication),
- metabolic (eg, amyloidosis)

Features

- lethargy, weakness, anorexia,
- Nausea, vomiting, and diffuse abdominal pain are present in approximately 90% of patients and usually represent an impending addisonian crisis.
- weight loss,
- 'salt-craving'
- **hyperpigmentation** (present in 95% of patients) **(especially palmar creases**), **Buccal pigmentation**
  - ➢ ↑ ACTH → melanocyte stimulating hormone (MSH) → hyperpigmentation
  - ➢ **Oral mucous membrane hyperpigmentation is pathognomonic for the disease.**
  - ➢ **Increased tanning during winter is particularly suggestive and due to the action of excess ACTH on melanocytes.**
- vitiligo,
- loss of pubic hair and axillary in women,
  - ➢ Women may have loss of androgen-stimulated hair, such as pubic and axillary hair, because androgens are produced in the adrenal cortex.

- Men do not have hair loss because androgens in males are produced primarily in the testes.

- Hypotension
  - marked postural drop in blood pressure,
- crisis: collapse, shock, pyrexia

Associations with Addison's → Other autoimmune conditions such as

- **pernicious anaemia**
- **thyroid disease**
- Type 1 diabetes
- Vitiligo
- Chronic active hepatitis.

Investigations

The short synacthen test is the best test to diagnose Addison's disease

- ACTH stimulation test (**short Synacthen test**): is the **definitive diagnostic test**
  - Plasma cortisol is measured before and 30 minutes after giving Synacthen 250ug IM.
  - Cosyntropin (synthetic ACTH) stimulation test: You measure the level of cortisol before and after the administration of cosyntropin. If there is adrenal insufficiency, there will be no rise in cortisol level.
- **Adrenal autoantibodies such as anti-21-hydroxylase may also be demonstrated.**
  - 21 hydroxylase is the enzyme involved in the cholesterol steroid pathway
  - present in approximately 80% of cases.
- serum cortisol: If a ACTH stimulation test is not readily available (e.g. in primary care) then sending a 9 am serum cortisol can be useful:
  - 500 nmol/l makes Addison's very unlikely
  - < 100 nmol/l is definitely abnormal
  - 100-500 nmol/l should prompt a ACTH stimulation test to be performed
- Serum electrolyte: Associated electrolyte abnormalities are seen in around one-third of undiagnosed patients:
  - **Hyponatraemia** (90%)
    - due to both loss of sodium in the urine (due to aldosterone deficiency) and to movement into the intracellular compartment.
  - **Hyperkalaemia** (65%)
    - Caused by a combination of aldosterone deficiency, impaired glomerular filtration (due to hypotension) and acidosis.
    - Hyperkalemia with a mild metabolic acidosis from the inability to excrete either H+ or K+ because of the loss of aldosterone.
  - **Hypoglycaemia**
    - (due to loss of the glucogenic effect of glucocorticoids)
    - (↓ cortisol-stimulated gluconeogenesis)

  - Mild to moderate **hypercalcaemia** occurs in 10-20% patients, the cause of which is uncertain.
- Modest **hyperprolactinaemia** is reported in Addison's disease and is glucocorticoid-responsive.
- High plasma renin and angiotensin II.
- High adrenocorticotrophic hormone (ACTH)
- High lipotropin
- Elevated plasma vasopressin
- metabolic acidosis
  - due to ↓ bicarbonate
- normocytic normochromic anaemia is often present,
- eosinophilia, lymphocytosis, and neutropenia
  - due to ↓ cortisol
    - normally suppresses levels of eosinophils and lymphocytes
    - normally de-marginates a portion of the neutrophil population which results in ↑ measurable neutrophil count

This patient has buccal pigmentation which raises the possibility of adrenal insufficiency,

Addisonian crisis

Causes

- sepsis or surgery causing an acute exacerbation of chronic insufficiency (Addison's, Hypopituitarism)
- adrenal haemorrhage eg Waterhouse-Friderichsen syndrome (fulminant meningococcemia)
- steroid withdrawal
- Sick euthyroidism is a recognised feature of Addison's disease and **treatment with thyroxine may exacerbate the condition and precipitate acute hypoadrenalism.**

Signs/symptoms of Addisonian crisis:

Neurological	Haemodynamic	Biochemical
• syncope • confusion • lethargy • convulsions	• hypotension • hypothermia	• hyponatraemia • hyperkalaemia • hypoglycaemia

Management of Addisonian crisis (medical emergency):

- intravenous fluids
  - 1 litre normal saline infused over 30-60 mins or with dextrose if hypoglycaemic
- corticosteroids (e.g iv dexamethasone)
  - hydrocortisone 100 mg im or iv
  - Note: iv dexamethasone is often preferred as this will not interfere with cortisol assays needed for a short synacthen test, unlike hydrocortisone.
  - continue hydrocortisone 6 hourly until the patient is stable. No fludrocortisone is required because high cortisol exerts weak mineralocorticoid action
  - oral replacement may begin after 24 hours and be reduced to maintenance over 3-4 days

Wolman's syndrome is characterised by primary adrenal failure, hepatosplenomegaly, and steatorrhoea.

Waterhouse-Friderichsen syndrome is bilateral adrenal haemorrhage occurring due to massive septicaemia, often associated with severe, life-threatening meningococcal disease. It can present, with tiredness, lethargy and postural hypotension a short period after discharge from hospital following the precipitating illness.

Conditions associated with hyponatraemia and hyperkalaemia:

- Carbenoxolone therapy due to pseudohypoaldosteronism through inhibition of the enzyme 11 beta hydroxysteroid dehydrogenase.
- Type IV renal tubular acidosis is associated with hyporeninaemic hypoaldosteronism and both hyponatraemia and hyperkalaemia can occur.
- Hypoadrenalism
- Co-amilofruse, the combination of amiloride and furosemide
- cardiac failure, hepatic and renal failure.

Secondary hypoadrenalism

- **Definition**
  - adrenal hypofunction due to a lack of adrenocorticotropic hormone (ACTH)
- **Causes**
  - panhypopituitarism,
    - pituitary tumors
    - craniopharyngioma (in youngers)
    - irradiation
  - Exogenous glucocorticoid therapy (by any route, including high doses of inhaled, intra-articular, or topical), or after corticosteroids are stopped.

- Patients receiving corticosteroids for > 4 wk may have insufficient ACTH secretion during metabolic stress to stimulate the adrenals to produce adequate quantities of corticosteroids, or they may have atrophic adrenals that are unresponsive to ACTH. These problems may persist for up to 1 yr after corticosteroid treatment is stopped.

➢ Inadequate ACTH can also result from failure of the hypothalamus to stimulate pituitary ACTH production, which is sometimes called tertiary adrenal insufficiency.

- **Feature**
  - ➢ Symptoms and signs are similar to those of Addison disease
  - ➢ **Differentiating features** include:
    - absence of hyperpigmentation
    - relatively normal electrolyte and BUN levels; hyponatremia, if it occurs, is usually dilutional.
    - Patients with panhypopituitarism have depressed thyroid and gonadal function and hypoglycemia.
      - ❖ Adrenal crisis is likely if a patient is treated with thyroxine, without hydrocortisone replacement.
- **Diagnosis**

Confirmatory Serum Testing for Secondary Adrenal Insufficiency	
Test	**Result**
ACTH	Low (< 5 pg/mL)
Cortisol	Low (< 5 µg/dL [138 nmol/L])
ACTH stimulation test	Normal or subnormal
Prolonged (24-h) ACTH stimulation test	Cortisol should continue to rise for 24 h

  - ➢ **ACTH stimulation testing**
    - done by injecting cosyntropin (synthetic ACTH) 250 mcg IV or IM followed by measurement of serum cortisol levels.
    - Some authorities believe that in patients with suspected secondary adrenal insufficiency, a low-dose ACTH stimulation test using 1 mcg IV instead of the standard 250 mcg-dose should be done because such patients may react normally to the higher dose.
    - Patients taking glucocorticoid supplements or spironolactone should not take them on the day of the test.
    - A normal response to cosyntropin may occur in secondary adrenal insufficiency. However, because pituitary failure may cause adrenal atrophy (and hence failure to respond to ACTH), the patient may need to be primed with long-acting ACTH 1 mg IM once/day for 3 days before the ACTH stimulation test if pituitary disease is suspected.
    - **prolonged ACTH stimulation test** (sampling for 24 h)
      - ❖ may be used to diagnose secondary (or tertiary, ie, hypothalamic) adrenal insufficiency.
      - ❖ Cosyntropin 1 mg IM is given, and cortisol is measured at intervals for 24 h, typically at 1, 6, 12, and 24 h.

- ❖ Results for the first hour are similar for both the short (sampling stopped after 1 h) and prolonged tests,
  - in Addison disease there is no further rise beyond 60 min.
  - In secondary and tertiary adrenal insufficiency, cortisol levels continue to rise for ≥ 24 h.
- ❖ Only in cases of prolonged adrenal atrophy is adrenal priming (with long-acting ACTH) necessary.
- ❖ **The simple short test is usually done initially**, because a normal response obviates the need for further investigation.
- ❖ If adrenal crisis is suspected, confirmation of Addison disease by ACTH stimulation testing is deferred until the patient has recovered. If ACTH stimulation testing is done, elevated ACTH levels together with low cortisol levels confirm the diagnosis.

➢ CT or MRI of the brain to rule out a pituitary tumor or pituitary atrophy.

Corticosteroids

Patients on long-term steroids should have their doses doubled during intercurrent illness

Mechanism of action

- Corticosteroids are hydrophobic small molecules and thus freely pass through cell membranes. They bind to inactive cytosolic glucocorticoid receptors, which then translocate to the nucleus to **act as nuclear transcription regulators.**

The relative glucocorticoid and mineralocorticoid activity of commonly used steroids is shown below:

Minimal glucocorticoid activity, very high mineralocorticoid activity,	**Glucocorticoid activity, high mineralocorticoid activity,**	**Predominant glucocorticoid activity, low mineralocorticoid activity**	**Very high glucocorticoid activity, minimal mineralocorticoid activity**
Fludrocortisone	Hydrocortisone	Prednisolone	Dexamethasone Betmethasone

Side-effects

- The side-effects of corticosteroids are numerous and represent the single greatest limitation on their usage.
- Side-effects are more common with systemic and prolonged therapy.
- **Glucocorticoid side-effects**
  - ➢ endocrine:

        - impaired glucose regulation,
        - increased appetite/weight gain,
        - hirsutism,
        - hyperlipidaemia
        - Cushing's syndrome: moon face, buffalo hump, striae
    - musculoskeletal:
        - osteoporosis,
        - proximal myopathy,
        - avascular necrosis of the femoral head
    - immunosuppression:
        - increased susceptibility to severe infection,
        - reactivation of tuberculosis
    - psychiatric:
        - insomnia,
        - mania,
        - depression,
        - psychosis
    - gastrointestinal:
        - peptic ulceration,
        - acute pancreatitis
    - ophthalmic:
        - glaucoma,
        - cataracts
    - suppression of growth in children
    - intracranial hypertension
- **Mineralocorticoid side-effects**
    - fluid retention
    - hypertension

The pathogenesis of corticosteroid induced osteoporosis is multifactorial:

1. Corticosteroids **reduce osteoblastic activity**, and the resulting osteoblast/osteoclast imbalance causes loss of bone.
2. **Corticosteroids reduce intestinal calcium absorption** and lower circulating sex steroid levels.

Selected points on the use of corticosteroids:

- patients on long-term steroids should have their doses doubled during intercurrent illness
    - For milder concurrent illnesses oral prednisolone is usually doubled for a few days.
    - **For sever illness convert prednisolone temporarily to IV glucocorticoids**, conventionally 50-100 mg of hydrocortisone six hourly.
    - **Mineralocorticoid dose is always left unchanged.**

- the BNF suggests gradual withdrawal of systemic corticosteroids if patients have: received more than 40mg prednisolone daily for more than one week, received more than 3 weeks treatment or recently received repeated courses
- **Low dose i.v hydrocortisone ➔ improve outcome in sepsis**
  - More recent randomised controlled trials have suggested that there is a benefit in sepsis when lower physiological doses of steroids are given.
- **Lactose-containing methylprednisolone preparations should not be used in patients with cows' milk allergy**
- Corticosteroids are recognised to **inhibit osteoblast activity and increase osteoblast apoptosis**. This is thought to be a more important component in bone loss with respect to steroid induced osteoporosis versus any effect on osteoclasts.
- Whilst corticosteroids do increase osteoclast activity, it is thought to be their effect on osteoblast activity which has a greater impact on bone mineral density.

Steroid induced hypogonadism

- Body builders may be involved in the illicit use of anabolic and androgenic steroids. These results are consistent with ongoing use of androgens.
- The hypogonadism, if persistent, may be treated with human chorionic gonadotropin.

Relative potencies of the glucocorticoids

- It is important to know the relative potencies of the glucocorticoids.
- **1 mg prednisolone is equivalent to 4 mg of hydrocortisone**
- Dexamethasone for instance is roughly 30 times more potent than hydrocortisone.

Steroid doses equivalence

- 1mg prednisolone = 4mg hydrocortisone
- 1mg dexamethasone = 7mg prednisolone
- Dexamethasone is roughly 30 times more potent than hydrocortisone.

May 2012 exam: Which effect is linked to long-term steroid use? Avascular necrosis (Long-term corticosteroid use is linked to osteopaenia and osteoporosis, rather than osteomalacia)

Anabolic steroids

- Anabolic steroids can be taken orally (eg stanozolol) or may have to be injected because of their high first-pass metabolism (eg testosterone enantate)
- Among their many unwanted effects, they increase the risk of cardiovascular disease:
  - blood pressure is elevated
  - blood lipid profiles change, with increased LDL-cholesterol and decreased HDL-cholesterol
  - haematocrit is increased, leading to a prothrombotic tendency, although there is a protective **decrease in plasma fibrinogen concentrations with prolonged use**

Abuse of androgenic steroids

- The abuse of androgenic steroids amongst people who practise certain sports is quite common.

- **side effects**
  - **Paranoid delusions**
  - **aggressive behaviour.**
  - Other side effects of these illicit drugs include:
  - Acne
  - Gynaecomastia (also increase in breast cancer risk)
  - Hypertension
  - Hypercholesterolaemia, and
  - Hepatic tumours.

Cushing's syndrome (Hypercortisolism)

The overnight dexamethasone suppression test is the best test to diagnosis Cushing's syndrome

Cushing's syndrome - hypokalaemic metabolic alkalosis

Pathological definition

- Cushing's syndrome → hypercortisolism from any cause.
- Cushing's disease → hypercortisolism caused by ACTH-secreting pituitary adenoma→the most common cause of Cushing's syndrome (80% of cases).

Causes

- **ACTH dependent causes** (also called Secondary hypercortisolism)
  - **pituitary ACTH**: Cushing's disease (80%): pituitary tumour secreting ACTH producing adrenal hyperplasia
  - **ectopic ACTH** production (5-10%): e.g. small cell lung cancer
    - **weight loss suggests there is an underlying malignancy → ectopic (ACTH)**
    - Ectopic ACTH secretion (e.g. secondary to small cell lung cancer) is characteristically associated with very low potassium levels.
- **ACTH independent causes** (also called Primary hypercortisolism)
  - adrenal adenoma (5-10%) → **Undetectable serum adrenocorticotropic hormone (ACTH) level**
  - **adrenal carcinoma (rare)**
    - Serum **potassium** is most likely to be **low** in cases of ectopic ACTH or adrenal carcinoma.
    - features of **virilisation** (development of male physical characteristics (such as muscle bulk, body hair, and deep voice) in a female or precociously in a boy, typically as a result of excess androgen production)
    - **abnormal liver function tests (LFTs)** suggest metastases

        - Abdominal ultrasound/CT is a most appropriate next investigation.
    - **iatrogenic: steroids**
        - **Most common cause of hypercortisolism**
        - exogenous corticosteroids that causes Cushing syndrome results in decreased ACTH, which in turn causes **bilateral adrenal atrophy**.
    - Carney complex: syndrome including cardiac myxoma
    - micronodular adrenal dysplasia (very rare)
- **Pseudo-Cushing's**
    - often due to alcohol excess or severe depression (**Obese patients who consume alcohol to excess over a prolonged period can acquire a cushingoid appearance**) **(alcohol-induced Cushing's syndrome)**
        - mechanism may be due to increased CRH secretion or impaired hepatic metabolism of cortisol.
        - **raised MCV is helpful in this context**.
        - usually mild and disappears rapidly during abstinence from alcohol. .
    - causes false positive dexamethasone suppression test or 24 hr urinary free cortisol
    - **insulin stress test** is used to differentiate between true Cushing's and pseudo-Cushing's
        - in pseudo-Cushing's the insulin tolerance test will demonstrate hypoglycaemia with a rise in ACTH and cortisol.
        - In Cushing's syndrome, this hypoglycaemia induced response is lost.
        - insulin tolerance test is contraindicated in epilepsy, ischaemic heart disease, or hypoadrenalism.
    - Management → lifestyle measures to promote weight loss, and strict control of alcohol intake.

Endogenous Cushing's syndrome

Types	Primary hypercortisolism (ACTH-independent Cushing's syndrome)	Secondary hypercortisolism	
		Pituitary ACTH production (Cushing's disease)	Ectopic ACTH production
frequency	• 5–10%	• ~ 75%	• ~ 15%
Sex	• ♂ < ♀ (1:4)	• ♂ < ♀ (1:4)	• ♂ = ♀
Causes	• Autonomous overproduction of cortisol by the adrenal gland →ACTH suppression • **Adrenal adenomas** • Adrenal carcinoma • Macronodular adrenal hyperplasia	• **Pituitary adenomas** → ACTH secretion	• Paraneoplastic syndrome → ACTH secretion ➢ **Small cell lung cancer** ➢ Renal cell carcinoma

Features

- **Fat redistribution:** Truncal obesity, “moon face,” buffalo hump, thin arms and legs
- **Proximal myopathy**, **easy bruising** and **thin skin** are clinical features that are most suggestive of Cushing's syndrome.
  - **Cortisol breaks down proteins so the free amino acids can be used to make sugar**. Specifically, bone and skin proteins are broken down and made into sugar. This leads to bruising, striae, muscle wasting, and osteoporosis.
- **Necrosis of the femoral head due to osteoporosis.**
- **Osteoporosis may lead to → Vertebral collapse**
- elevated corticosteroid levels can lead to early development of **cataracts**.
  - Most commonly → **Posterior subcapsular cataract**
  - The predominant feature of a posterior subcapsular cataract is glare when looking into bright lights, either from the sun or car headlights.
- Hyperglycemia (Diabetes mellitus may occur in 30%).
  - Cortisol → ↑gluconeogenesis (from protein break down → free amino acids) → ↑glucose levels
- hyperlipidemia
- Hypertension: From fluid and sodium retention
- Hirsutism: From increased adrenal androgen levels
- hypokalaemic metabolic alkalosis
  - caused by increased urinary loss of H+ (acid)
- Leukocytosis
- low oestradiol
  - in deferential diagnosis: The low oestradiol excludes pregnancy and PCOS
    - in pregnancy oestradiol will be elevated
    - typically in PCOS oestradiol is normal or elevated.

Investigations

Disorder	Investigation of choice
Cushing	Overnight Dexamethasone Test
Cushing- vs. Pseudo-cushing	Insulin Stress Test
Addison	Short Synacthen Test
Pheochromocytoma	24H Urinary metanephrines
Acromegaly	Oral Glucose Tolerance Test

- Investigations are divided into confirming Cushing's syndrome and then localising the lesion.
- **Tests to confirm Cushing's syndrome (hypercortisolism)** : The two most commonly used tests are:
    1. **overnight dexamethasone suppression test (ODST) (most sensitive)**
        - The ODST has a **sensitivity and specificity of 98%**
        - Failure to suppress cortisol below 50 nmol/L on this test is highly suggestive of Cushing's
        - **sensitivity and specificity 75-80% in obese subjects therefor (UFC) will be best than (ODST) in obese**
        - If cortisol is not suppressed by the low or high dose dexamethasone suppression test then either
            - **primary adrenal Cushing's syndrome** (low/undetectable ACTH)
            - or **ectopic ACTH** is the cause (high ACTH).
        - If cortisol is not suppressed by low dose dexamethasone but is by high dose then **Cushing's disease** is the likely cause.
        - **Interactions with the test:**
            - **cytochrome p450 inducers →false-positive ODST** (meaning that a diagnosis of Cushing is suggested incorrectly).
                - Dexamethasone is metabolised by the cytochrome p450 system, specifically by the CYP3A4 isoenzyme.
            - Patients need to be off all oestrogen-containing medication for six weeks prior to any measurements of serum cortisol
        - If (ODST) is not offered in a question then 24 hour urinary free cortisol is the next best answer
    2. **24 hr urinary free cortisol (UFC)**
        - **An ideal initial test** because it can be done as an outpatient and is non-invasive.
        - this test is more likely to give a false negative than an overnight dexamethasone suppression test.
        - Because the false-negative rate approaches 10%, it is never used alone as a **screening** test for Cushing syndrome and **should be followed by an overnight dexamethasone suppression test**.
        - **If both of these tests** are normal, then Cushing syndrome could be ruled out.

It is a difficult choice between an overnight dexamethasone suppression test and the urine free cortisol estimation and there are no clear national guidelines regarding which is best.
However, **a recent BMJ article states that** if the clinical suspicion of endogenous Cushing's syndrome is high then either a 24 hour urinary free cortisol (if the patient has normal renal function) or a late night salivary cortisol are the most likely to make a diagnosis.

Localisation tests

source of the hypercortisolism:

- **The first step is to measure ACTH level:**
  - **ACTH level low**: This means **the origin is in the adrenal gland** → Scan the gland with a CT or MRI.
  - **ACTH level high**: This means the origin is either in the **pituitary** gland or from the **ectopic** production of ACTH.
- The next step is a high-dose dexamethasone suppression test.
  - **If high-dose dexamethasone suppresses the ACTH**, the origin is the **pituitary**. Scan the pituitary.
  - **If high-dose dexamethasone does not suppress the ACTH**, the origin is an **ectopic** production of ACTH or a cancer that is making ACTH. Scan the chest for lung cancer or carcinoid.

If a 24-hour urine free cortisol is elevated, and there is an inadequate suppression on 1 mg overnight dexamethasone test in a patient suspected of Cushing syndrome, **the next step** would be to measure **ACTH.**

After the 1 mg overnight test and the 24-hour urine test confirm the presence of hypercortisolism, then we must determine the location or origin to treat it.
The first-line localisation is 9 am and midnight **plasma ACTH** (and cortisol) levels. If ACTH is suppressed then a non-ACTH dependent cause is likely such as an adrenal adenoma

- **High-dose dexamethasone suppression test**
  - mechanism
    - High doses of dexamethasone send a negative feedback response to the brain to decrease ACTH production. Since the pituitary is receptive to negative feedback loops but ectopic foci are resistant to negative feedback, cortisol levels will decrease to **< 50% of baseline** following high doses of dexamethasone if the patient has Cushing's disease, but will be relatively unchanged in ectopic ACTH production.
    - In the high dose dexamthasone suppression test, classically, the cortisol should suppress to 50% of the level found after low dose dexamethasone in cases of pituitary dependent CS.
      - However 50% suppression is found on less than 80% of occasions and so is far from diagnostic.
  - Explanation
    - if cortisol suppressed → pituitary source
    - if no change in cortisol → ectopic/adrenal
- **CRH stimulation**
  - if cortisol rises → pituitary source
  - if no change in cortisol → ectopic/adrenal
- **Inferior Petrosal sinus sampling** (IPSS)

- (**IPSS**) **is the only test with sufficient diagnostic accuracy to differentiate Cushing's disease from ectopic ACTH production**
- high gradient of ACTH from sinus compared with a peripheral sample is diagnostic of pituitary dependent disease.
- Patients with an IPSS central/peripheral gradient >2:1 or 3:1 after corticotrophin-releasing hormone (CRH) stimulation → Cushing's disease
- Patients without an IPSS central/peripheral gradient >2:1 or 3:1 → ectopic ACTH → do CT of the chest, abdomen, and pelvis to look for a tumour secreting ACTH.
  - CT scan and octreotide scintigraphy should be employed when results of IPSS suggest an ectopic source.
  - The most common tumours that secrete ACTH are bronchial or thymic carcinoids.
- Up to 40% of patients with Cushing's disease will not have visible lesions on pituitary/sellar MRI.
- Patients without definitive lesions on MRI should undergo inferior petrosal sinus sampling

Serum cortisol levels would remain unchanged with both low-level and high-level dexamethasone testing due to the lack of glucocorticoid receptors to facilitate negative feedback **on the ectopic cells producing the ACTH.** Anterior pituitary corticotrophs do have these receptors and, therefore, will be suppressed by any dose of dexamethasone.

Diagnostic steps

- After exclusion of exogenous corticosteroid use, patients with suspected Cushing's syndrome should be tested for hypercortisolism with 1 of 4 high-sensitivity tests
  1) late-night salivary cortisol;
  2) 1 mg overnight low-dose dexamethasone suppression testing,
  3) 24-hour urinary free cortisol; or
  4) 48-hour 2 mg dexamethasone suppression testing.
- At least 1 additional test should be used to confirm hypercortisolism in patients with a positive initial screening test.
- Once endogenous hypercortisolism is confirmed, **plasma (ACTH)** should be measured.
  - If ACTH is suppressed, diagnostic testing should focus on the adrenal glands.
  - If ACTH is not suppressed, pituitary or ectopic disease should be sought.

The differentiation between Cushing's disease and ectopic ACTH secretion is made by carrying out low- and high-dose dexamethasone suppression tests. With Cushing's disease, the pituitary usually remains susceptible to feedback by glucocorticoids but is less sensitive, low-dose dexamethasone does not suppress cortisol secretion but high-dose dexamethasone does. In cases of ectopic ACTH secretion (and also adrenal tumors), there is usually no response to dexamethasone because pituitary ACTH secretion is already maximally suppressed by the high plasma cortisol levels.

Classically pituitary dependent Cushing's disease is differentiated from ectopic ACTH production and non-ACTH dependent Cushing's by:

- measurement of plasma ACTH levels and
- suppression of plasma cortisol by 50% from baseline after 48 hours of high dose dexamethasone.
  - In a normal individual, plasma cortisol suppresses to < 50 nmol/l after 48 hours of dexamethasone 0.5 mg 6 hourly.
  - When differentiating pseudo-Cushing's from Cushing's syndrome a cut off of 38 nmol/l at this time point gave 100% specificity for diagnosing Cushing's syndrome
  - Approximately 10% of subjects with pituitary dependent Cushing's may fail to suppress however, and a few people with ectopic ACTH production also will.

Which techniques is the best in differentiating between ectopic Cushing's syndrome and pituitary dependent Cushing's disease?

- ➔ **Inferior petrosal sinus sampling**
- It samples venous blood draining from the pituitary gland, using a femoral approach.
- A raised ACTH from here compared to the periphery suggests a pituitary cause.
- complication rate is low and is most commonly only groin haematoma.
- The high-dose dexamethasone suppression test can differentiate between the two forms of Cushing's syndrome, but is not as accurate as inferior petrosal sinus sampling.

The following table summarizes the characteristics of the 3 sources of Cushing disease.

	Pituitary Tumor	Ectopic ACTH Production	Adrenal Adenoma
ACTH	High	High	Low
High-dose dexamethasone	Suppression	No suppression	No suppression
Specific test	MRI Petrossal vein sampling	Scan chest and abdomen	Scan adrenals
Treatment	Removal		

Which feature would favour benign adrenal adenoma as the cause of Cushing's syndrome over the other causes?

➔ **Absence of hirsutism and virilisation** (adrenal adenoma produces cortisol but not the androgens)

Treatment

- the initial treatment of choice →Trans-sphenoidal hypophysectomy/adenomectomy
- Laparoscopic adrenalectomy would be advised where pituitary surgery has failed.
- **Ketoconazole may be an effective treatment for patients unfit for surgery.**
- The recurrence rate for Cushing's disease after surgery is of the order of 20-30% in most series and depends on the size of the tumour with macroadenomas having a higher rate of relapse.

Which drug is most appropriate to improve metabolic parameters prior to surgery in pituitary-dependent Cushing's?

➔ **Metyrapone**

- Metyrapone → **inhibits 11-beta hydroxylase** → inhibits cortisol production.
- It has rapid onset of action and as such may be of value pre-operatively in improving BP and glycaemic control without associated weight gain of other options such as insulin.
  - Metyrapone can be used as short-term treatment for Cushing's syndrome before definitive treatment.
  - Metyrapone blocks cortisol synthesis by inhibiting 11 β-hydroxylase.
    - This blockade can be measured by the urinary increase of the metabolites of cortisol precursors in the urine (17-hydroxycorticosteroids [17-OHCS] and 17-ketogenic steroids [17-KGS]).

What is the optimum time for the administration of hydrocortisone to a patient undergoing bilateral adrenalectomy for Cushing's disease?

⇨ **Immediately following the removal of both adrenal glands.**

May 2008 exam: A 62-year-old man is investigated for hypertension and proximal myopathy. On examination he is noted to have abdominal striae. Which one of the following is most associated with ectopic ACTH secretion? Small cell lung cancer

Small cell lung cancer accounts 50-75% of case of ectopic ACTH

Glucocorticoid resistance syndrome

- rare
- due to a mutation of the glucocorticoid receptor.
- Subjects have **high ACTH levels and high cortisol** levels because of lack of negative feedback via the glucocorticoid receptors.
- Women may demonstrate the **virilising effects of excess androgen secretion under the influence of increased ACTH**,
- may have **hypertension** due to the action of salt retaining steroids,
- but fail to demonstrate the other features of Cushing's syndrome such as thinning of the skin and myopathy

Diabetology

Basics

Pancreatic Hormones

- Islet **A** cells produce **glucagon**
- **Islet beta cells produce:**
  1. **insulin**
  2. **C peptide**
  3. **pro-insulin**
  4. **amylin**
  5. **GABA**
- Islet **D** cells produce **somatostatin**
- **F** cells produce **pancreatic polypeptide**

Glucose transporters

Sodium/glucose cotransporter (SGLT)

- Glucose uptake into the enterocyte from the lumen of the GI tract occurs primarily via the sodium-dependent **SGLT-1** secondary active transport mechanism.
  - SGLT-1 is a transporter found predominantly in the gut, and is responsible for glucose absorption.
  - The Na+-glucose cotransporter also transports galactose. Thus, when the cotransporter is congenitally defective, the resulting glucose and galactose malabsorption causes severe diarrhea that can be fatal if glucose and galactose are not removed from the diet.
- Function
  - **transport glucose actively across lumen against concentration gradient**
    - energy provided by transport of sodium down its concentration gradient
- location
  - **small intestine (SGLT1)** → 2:1 Na^+:Glu

- **proximal tubule of nephron (SGLT2)** → 1:1 Na^+:Glu
- Glucose exit from the enterocyte into the extracellular fluid occurs by facilitated diffusion and is mediated by the membrane transporter, **Glut-2**.

GLUT-1

- function
  - basal glucose uptake (GLUT1 and GLUT3 continually transport glucose into cells at an essentially constant rate.)
    - high affinity
      - transporters saturated at normal blood glucose levels
      - ensures glucose entry to cells
- location
  - wide distribution in tissues in the body (brain, erythrocytes, endothelial cells, cornea **etc.)**
  - especially expressed in cells with barrier functions, such as Blood- Brain barrier, blood-retinal barrier, blood placental barrier, blood testes barrier
  - **most importantly it is expressed in erythrocytes.**

GLUT-2

- GLuT 2 is a glucose transporter expressed in **pancreatic beta cells**.
- It is a fundamental part of the glucose sensing apparatus in the pancreatic beta cells and helps trigger insulin release in response to increasing glucose concentrations in the extracellular fluid.
- GluT 2 is also expressed in hepatocytes and may act as a glucose sensor in the portal vein system.
- It may have a role in regulating glucagon secretion and feeding behaviour.
- function
  - **low affinity glucose uptake** (high-capacity but a low affinity transporter)
    - in the fasting state glucose does not enter cells
    - mediates glucose surplus storage in liver when blood glucose levels rise
    - **facilitates insulin release in β-cells**
- location
  - hepatocytes
  - **pancreatic β-cells**
  - kidney
  - small intestines

In healthy individuals, which glucose transporter is required for triggering insulin secretion in response to elevated blood glucose concentration?

- **GluT 2**

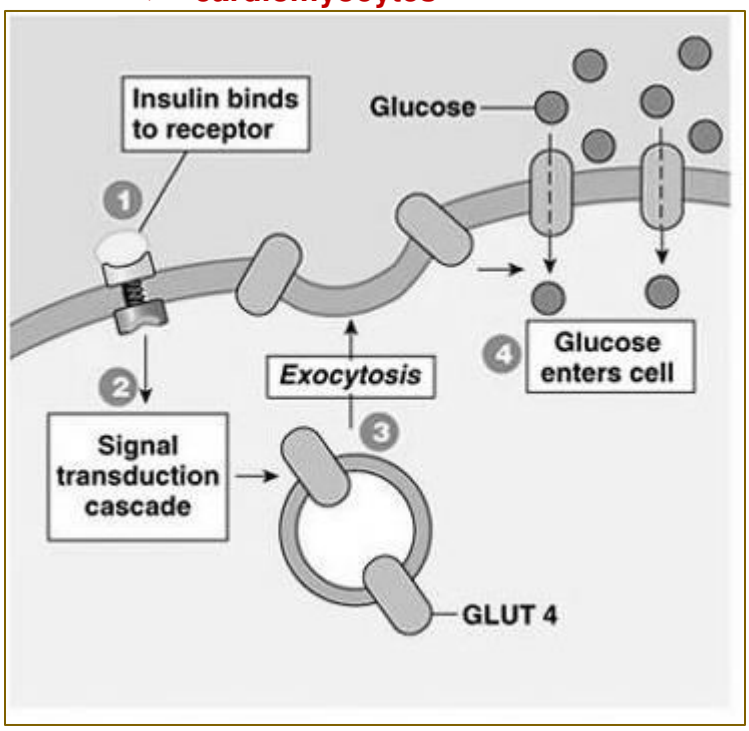
GLUT-3

- function
  - high affinity glucose uptake
    - glucose preferentially accessed by neurons in low-glucose states

- location
  - **brain**
  - **neurons**

GLUT-4

- **GLUT-4 is the only glucose transporter that is responsive to circulating insulin levels.**
  - ↑plasma glucose concentration → ↑**circulating insulin** → ↑expression of GLUT-4 → ↑glucose transport into the cell.
  - The other types of glucose receptors (GLUT-1,2,3,&5) are not responsive to circulating insulin levels
  - exogenous insulin in the treatment of diabetes mellitus results in increased glucose uptake **via the GLUT-4 transporter.**
  - This high-affinity glucose transporter plays a crucial role in avoiding postprandial hyperglycemia, since insulin secreted by the pancreatic beta cells promotes glucose uptake into myocytes.
- function
  - **insulin-controlled uptake of glucose**
  - basal level of glucose intake without insulin
    - presence of insulin ↑ translocation of transporters to the cell membrane
      - ↑↑↑ glucose uptake
      - **also stimulated by exercise**
- **location**
  - **adipocytes**
  - **myocytes**
  - **cardiomyocytes**



Which glucose transporter is responsible for assisting glucose across the plasma membrane in myocytes?

➔ **GLUT 4**

Glut-5

- located on the apical portion of the enterocyte
- function: entry of **fructose** into the cell.

- **Glut-1 and Glut-3** have a very low Km (less than 1 mM). It means that they have high affinity for glucose ,so **even in situation of relative hypoglycemia they can continue transporting glucose to the brain.**
- **Glut 2**, in liver, has a Km of about 15 mM, so it **works properly when glucose concentration in blood is high** (like in postpandrial situations; recall that after meals blood arrives first to liver through the portal system).
- GLUT-1 = BBB (Blood- Brain barrier)
- GLUT-3 = "Brain"

Glycaemic index

- The glycaemic index (GI) describes the capacity of a food to raise blood glucose compared with glucose in normal glucose-tolerant individuals.
- Foods with a high GI may be associated with an increased risk of obesity and the post-prandial hyperglycaemia associated with such foods may also increase the risk of type 2 diabetes mellitus.

Classification	Examples
High GI	White rice (87), baked potato (85), white bread (70)
Medium GI	Couscous (65), boiled new potato (62), digestive biscuit (59), brown rice (58)
Low GI	Fruit and vegetables, peanuts

The glycaemic index is shown in brackets. Glucose, by definition, would have a glycaemic index of 100

Metabolic syndrome

The cardinal features of the metabolic syndrome include:

- the hypertension
- central adiposity
- hyperlipidaemia
- fatty liver
- pre-diabetes.

Pathophysiology

- It is thought that the key pathophysiological factor is insulin resistance.

Diagnostic criteria

- **SIGN** recommend using criteria similar to those from the **American Heart Association**. The similarity of the International Diabetes Federation criteria should be noted.
- For a diagnosis of metabolic syndrome at least 3 of the following should be identified:
    1. elevated waist circumference: men > 102 cm, women > 88 cm
    2. elevated triglycerides: > 1.7 mmol/L
    3. reduced HDL: < 1.03 mmol/L in males and < 1.29 mmol/L in females
    4. raised blood pressure: > 130/85 mmHg, or active treatment of hypertension
    5. raised fasting plasma glucose > 5.6 mmol/L, or previously diagnosed type 2 diabetes
- The **International Diabetes Federation** produced a consensus set of diagnostic criteria in 2005, which are now widely in use.
    - These require the presence of central obesity (defined as waist circumference > 94cm for Europid men and > 80cm for Europid women, with ethnicity specific values for other groups) plus any two of the following four factors:
        1. raised triglycerides level: > 1.7 mmol/L, or specific treatment for this lipid abnormality
        2. reduced HDL cholesterol: < 1.03 mmol/L in males and < 1.29 mmol/L in females, or specific treatment for this lipid abnormality
        3. raised blood pressure: > 130/85 mm Hg, or active treatment of hypertension
        4. **raised fasting plasma glucose > 5.6 mmol/L**, or previously diagnosed type 2 diabetes
- In 1999 the **World Health Organization** produced diagnostic criteria which required
    - the presence of diabetes mellitus, impaired glucose tolerance, impaired fasting glucose or insulin resistance, AND two of the following:
        1. blood pressure: > 140/90 mmHg
        2. dyslipidaemia: triglycerides: > 1.695 mmol/L and/or high-density lipoprotein cholesterol (HDL-C) < 0.9 mmol/L (male), < 1.0 mmol/L (female)
        3. central obesity: waist:hip ratio > 0.90 (male), > 0.85 (female), and/or body mass index > 30 kg/m2
        4. microalbuminuria: urinary albumin excretion ratio > 20 mg/min or albumin:creatinine ratio > 30 mg/g

- **The ATP III criteria (2001):** three of these five criteria must be present to diagnose metabolic syndrome.

NECP ATP IIIM	Male	Female
Waist circumference	≥ 102 cm	≥ 88 cm
Blood pressure	≥ 130/85 mmHg	≥ 130/85 mmHg
HDL	≤1.03 mmol/L	≤1.29 mmol/L
	≤40 mg/dL	≤ 50 mg/dL
Triglyceride	≥ 1.7 mmol/L	≥ 1.7 mmol/L
	≥ 150 mg/dL	≥ 150 mg/dL
Fasting glucose	≥ 6.1 mmol/L	≥ 6.1 mmol/L
	≥ 110 mg/dL	≥ 110 mg/dL

- **Other associated features include:**
  - raised uric acid levels
  - non-alcoholic fatty liver disease
  - polycystic ovarian syndrome

Management

- **the most appropriate strategy to reduce the future risk of developing diabetes mellitus is → Treatment with orlistat and diet**
  - The XENDOS study revealed that orlistat, in combination with diet, will reduce the risk of diabetes in these obese patients by 38% more than just diet alone plus placebo.

Pre-diabetes and impaired glucose regulation (IGR)

	normal	Prediabetes	Diabetes mellitus
Fasting glucose	**≤ 6 mmol/l**	**≥ 6.1 – 6.9 mmol/l impaired fasting glucose (IFG)**	**≥ 7 mmol/l**
2h glucose during an OGTT	**< 7.8 mmol/l**	**7.8 -n 11 mmol/l Impaired glucose tolerance (IGT)**	**≥ 11.1 mmol/l**
HA1c	**< 42 mmol/mol < 6%**	**42 – 47 mmol/mol (6.0 – 6.4%)**	**≥ 6.5%**

NICE however classifies those at "High Risk" of Type 2 Diabetes as:

- **fasting plasma glucose of 5.5-6.9 mmol/l or**
- **HbA1c of 42-47 mmol/mol [6.0-6.4%]**

Prediabetes

- **Definition**:
  - impaired glucose levels which are above the normal range but not high enough for a diagnosis of diabetes mellitus.
  - Includes impaired fasting glucose (IFG) and impaired glucose tolerance (IGT).
- **Terminology**
  - Diabetes UK currently recommend using the term prediabetes when talking to patients and impaired glucose regulation (IGR) when talking to other healthcare professionals
- **Types:**
  - **Impaired fasting glucose (IFG)**
    - Definition → fasting glucose greater than or equal to 6.1 but less than 7.0 mmol/l
    - Mechanism → **due to hepatic insulin resistance**
    - people with IFG should then be offered an oral glucose tolerance test (OGTT) to rule out a diagnosis of diabetes.
  - **Impaired glucose tolerance (IGT)**
    - Definition → fasting plasma glucose less than 7.0 mmol/l and OGTT 2-hour value greater than or equal to 7.8 mmol/l but less than 11.1 mmol/l
    - Mechanism → due to **muscle** insulin resistance
    - patients with IGT are more likely to develop T2DM and cardiovascular disease than patients with IFG
    - **The risk of progression from (IGT) to frank diabetes is 20- 30% within 5 years.**
- **Incidence:**

- Diabetes UK estimate that around **1 in 7** adults in the UK have prediabetes.

- **Prognosis**
  - Many individuals with prediabetes will progress on to developing type 2 diabetes mellitus (T2DM) and they are therefore at greater risk of microvascular and macrovascular complications.
  - **What would be the risk of developing type 2 diabetes in patient with (IGT)?**
    - **60% over 6 years**
      - This increased to 64.5% if individuals had both (IGT) and (IFG).

- **Identification of patients with prediabetes**
  - Who should be assessed for the risk of type 2 diabetes?
    - all adults aged 40 and over,
    - people of South Asian and Chinese descent aged 25-39,
    - adults with conditions that increase the risk of type 2 diabetes:
      - cardiovascular disease, stroke, hypertension,
      - obesity,
      - polycystic ovary syndrome,
      - history of gestational diabetes
      - mental health problems.

- **Management**

The best way to reduce the incidence of type 2 diabetes in individuals with IGT is → Intensive lifestyle change

- lifestyle modification: weight loss, increased exercise, change in diet
  - intensive diet and lifestyle change (that results in loss of approximately 5% of initial body weight) can reduce progression from impaired fasting glucose (or impaired glucose tolerance) to frank type 2 diabetes **by approximately 50%.**
- at least yearly follow-up with blood tests is recommended
- NICE recommend metformin for adults at high risk *'whose blood glucose measure (fasting plasma glucose or HbA1c) shows they are still progressing towards type 2 diabetes, despite their participation in an intensive lifestyle-change programme'*
- As well as demonstrating a reduction in risk of new onset type 2 diabetes of 25%, **acarbose** was associated in the STOP-NIDDM study with a **49% reduction in cardiovascular events.**
- Metformin and pioglitazone have not been shown to reduce cardiovascular disease in impaired glucose tolerance.

Which drug classes is most well known as a cause of impaired glucose tolerance?
⇨ **Atypical antipsychotics**

Both typical antipsychotics and antihypertensives (thiazides and beta blockers), have been shown in meta-analyses to be associated with impaired glucose tolerance and increased risk of type 2 diabetes.
The risk is relatively larger for risperidone than thiazides & β.blocker

September 2009 exam: The fasting glucose of asymptomatic patient comes back as 6.5 mmol/l. The test is repeated and reported as 6.7 mmol/l. How should these results be interpreted? Impaired fasting glycaemia

Diabetes mellitus

Types of diabetes mellitus

Type	Notes
Type 1 diabetes mellitus (T1DM)	• 5–10% of cases • Caused by autoimmune B-cell destruction.
Type 2 diabetes mellitus (T2DM)	• 90% of cases • caused by a relative deficiency of insulin • defective insulin secretion, usually with defective insulin action.
Prediabetes	• patients who don't yet meet the criteria for a formal diagnosis of T2DM to be made but are likely to develop the condition over the next few years.
Gestational diabetes	• raised glucose levels during pregnancy.
Maturity onset diabetes of the young (MODY)	• Genetic defects of B-cell function • Results in younger patients developing symptoms similar to those with T2DM, i.e. asymptomatic hyperglycaemia with progression to more severe complications such as diabetic ketoacidosis
Latent autoimmune diabetes of adults (LADA)	• patients who develop autoimmune DM later in life. • often misdiagnosed as having T2DM

Type	Notes
Ketosis-prone diabetes (KPD)	• presents with DKA or ketosis, but insulin requirements decline over weeks l months, and insulin can often be stopped. • Most commonly seen in patients of African origin who are antibody –ve. • Patients should be advised that they may develop ketosis again during illness and be given ketone-monitoring equipment.
Secondary diabetes	• Diseases of the exocrine pancreas ➢ Pancreatitis, trauma, pancreatectomy, neoplasia, ➢ pancreatic destruction (including cystic fibrosis and haemochromatosis) • Drug-induced: ➢ **Corticosteroids** ➢ **Thiazide diuretics** ➢ **Beta-blockers** ➢ **Antipsychotics** ➢ **Statins** ➢ thyroid hormone, ➢ diazoxide, may act directly to increase glucose production and inhibit glucose uptake. ➢ G-interferon → **chronic type 1 diabetes** ➢ antiretroviral treatment (HIV). • Polycystic ovary syndrome (PCOS) • Cushing's syndrome • Infections: Congenital rubella, cytomegalovirus (CMV), others.
Genetic syndromes associated with diabetes	• Down's syndrome, Klinefelter's syndrome, Turner's syndrome, • Wolfram syndrome (or DIDMOAD—diabetes insipidus, DM, optic atrophy, and sensorineural deafness), • Friedreich's ataxia, Huntington's chorea, Lawrence–Moon–Biedl syndrome, myotonic dystrophy, Prader–Willi syndrome, others.

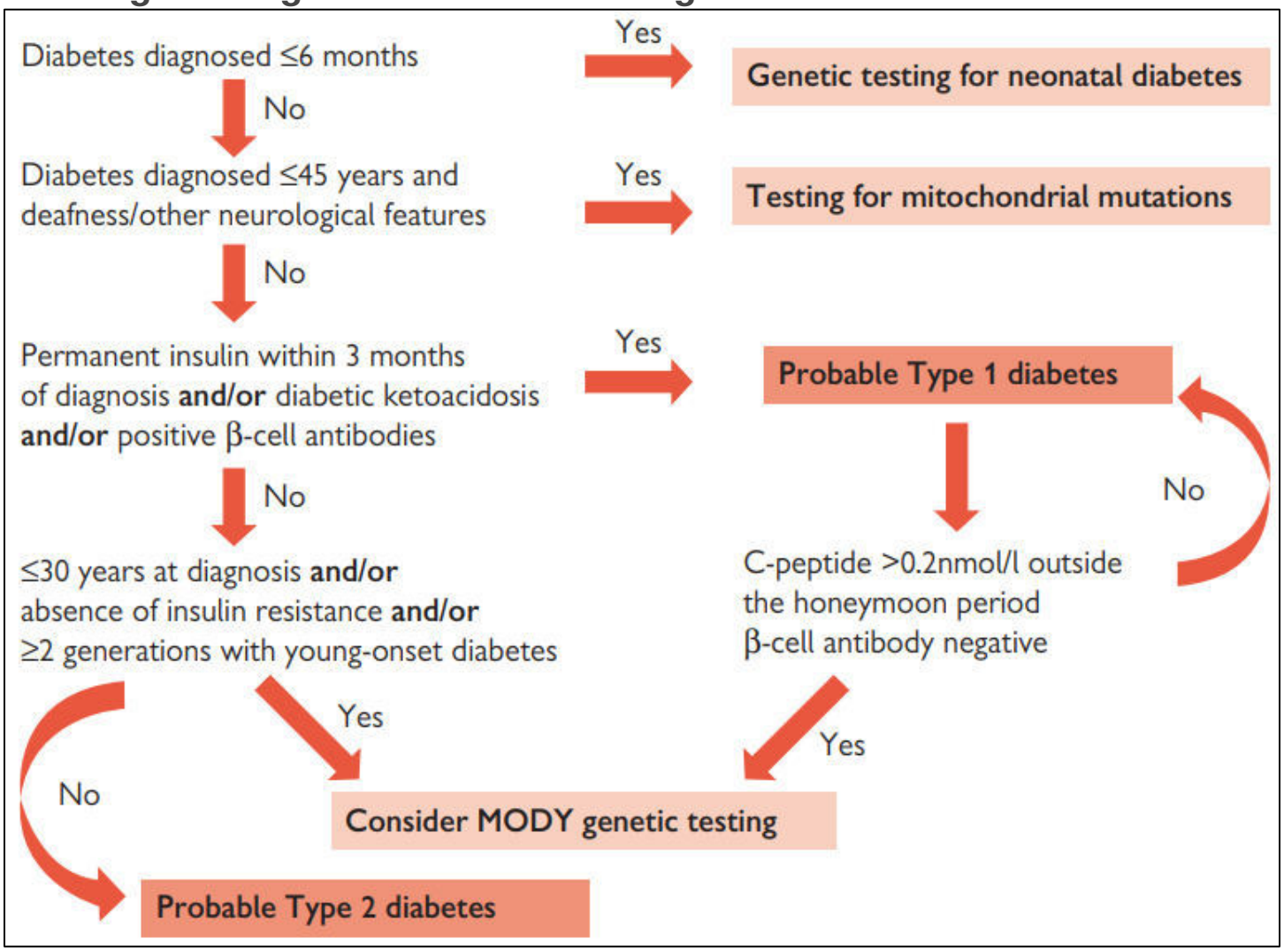
Symptoms and signs

Type 1 DM	Type 2 DM
• Weight loss • Polydipsia • Polyuria	• Often picked up incidentally on routine blood tests • Polydipsia

Type 1 DM	Type 2 DM
• May present with diabetic ketoacidosis ➢ abdominal pain ➢ vomiting ➢ reduced consciousness level	• Polyuria

- Remember that the polyuria and polydipsia is due to water being 'dragged' out of the body due to the osmotic effects of excess blood glucose being excreted in the urine (glycosuria).

Aetiological diagnosis in diabetes diagnosed



Type 1 DM

- **Epidemiology**
  - Type 1 diabetes accounts for about 5% to 10% of all patients with diabetes.
  - more common in Europeans and less common in Asians.
- **Mechanism**
  - autoimmune disease
  - antibodies against beta cells of pancreas
  - primarily T cell mediated disorder.
  - **Type 1 diabetes becomes clinically evident upon destruction of approximately 70-80 % of beta cell mass.**
  - HLA DR4 > HLA DR3
  - **Enteroviruses may play a role in both protection from and susceptibility to type 1 diabetes.**
  - **antibodies** detected in patients who later go on to develop type 1 DM:
    - glutamic acid decarboxylase **(GAD)** antibody
      - **found in 70-90% of type1 diabetics.**
      - The presence of GAD autoantibodies signifies a 10 fold increased risk of developing IDDM.
      - 10% of adults who have been classified as having type 2 diabetes may have circulating islet cell antibodies or antibodies to glutamic acid decarboxylase (GAD), indicating autoimmune destruction of beta cells.
    - islet cell antibodies (ICA)
    - antibodies to insulin (IAA)
    - ZnT8 is found within the beta cell; whilst ZnT8 autoantibodies are often positive in patients with type 1 diabetes, it is not invariable.
- **Risk of development of diabetes over a five year period.**
  - The presence of autoantibodies such as IA2 and ZnT8 is associated with around a 50% risk of development of diabetes over a five year period. This is less than the risk of development of diabetes with loss of first phase insulin response, which is nearer to 100% over two years.
  - Conventionally, anti-GAD and anti-IA2 antibodies are measured to support the diagnosis.
  - **Which feature is most closely associated with the imminent development of type 1 diabetes?**

    Loss of first phase insulin response
    - 100% of subjects with loss of first phase insulin response and anti-IA2 antibodies progressing to type 1 diabetes within 2 years.
    - When weighing up which of the possible answers has the greatest contribution to the risk of diabetes development, it's important to remember that **individuals may remain antibody positive for many years before developing T1DM,** but the **loss of first phase insulin**

response is an indicator of significant impending beta cell destruction.

- Loss of second phase insulin response is associated with a risk of diabetes intermediate between autoantibodies alone, and loss of first phase insulin response.

- **Genetics**
  - Only 10% of patients have a positive family history
  - **Genetic risks for developing diabetes**
  - if your mother has type 1 diabetes → 2-3%
  - if your father has type 1 diabetes → 3–6%
  - **the risk of Type 1 diabetes in offspring in families where both parents have the disease → around 40%.**
    - Offspring of parents who both have Type 1 diabetes have a tendency to develop the disease at a younger age than their parents.
  - if a sibling (brother or sister) has type 1 diabetes → 5–6%
  - **if one identical twin has type 1 diabetes, the risk in the unaffected twin → 30-50%.**

- **Features**
  - ketosis
  - rapid weight loss
  - age of onset below 50 years
  - BMI below 25 kg/m^2
  - Personal and/or family history of autoimmune disease.

- **Investigations**
  - Consider C-peptide and/or diabetes-specific autoantibody titres if:
    - atypical features (for example, age 50 years or above, BMI of 25 kg/m^2 or above, slow evolution of hyperglycaemia or long prodrome) or
    - suspicion of monogenic form of diabetes (MODY) (test may guide the use of genetic testing)
      - ↓ C-peptide levels indicate an absolute insulin deficiency → type 1 diabetes
      - ↑ C-peptide levels may indicate insulin resistance and hyperinsulinemia → type 2diabetes

  - **HbA1c**
    - should be monitored every 3-6 months
    - adults should have a target of HbA1c level of 48 mmol/mol (6.5%) or lower.
      - NICE do however recommend taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation and history of hypoglycaemia

- **Prognosis**
  - A diagnosis of type 1 diabetes can still reduce the life expectancy of patients by 13 years and the micro and macrovascular complications are well documented.

Diabetes mellitus: management of type 1 (NICE guidelines 2015)

In newly diagnosed adults with type 1 diabetes, the first-line insulin regime should be a basal–bolus using twice-daily insulin detemir

- **Diet**
  - Do not advise adults with type 1 diabetes to follow a low glycaemic index diet for blood glucose control.

- **Frequency of self-monitoring of blood glucose**
  - recommend testing at least 4 times a day, including before each meal and before bed.
  - more frequent monitoring is recommended if frequency of hypoglycaemic episodes increases; during periods of illness; before, during and after sport; when planning pregnancy, during pregnancy and while breastfeeding.
- **Referral indication for islet or pancreas transplantation**
  - type 1 diabetes with recurrent severe hypoglycaemia that has not responded to other treatments
  - type 1 diabetes with suboptimal diabetes control who have had a renal transplant and are currently on immunosuppressive therapy.
- ***Awareness of hypoglycaemia***
  - Assess awareness of hypoglycaemia at each annual review. Use the Gold score or Clarke score to quantify awareness of hypoglycaemia
- ***Thyroid disease monitoring***
  - Measure (TSH) levels in adults with type 1 diabetes at annual review.
- **Targets**

Test	Targets
HbA1c	≤ 48 mmol/mol (6.5%)
fasting plasma glucose	5–7 mmol/litre **on waking**
	4–7 mmol/litre **before meals**
plasma glucose at least 90 minutes after eating	**5–9 mmol/litre**
during surgery or acute illness	5–8 mmol/litre
blood pressure	135/85 mmHg

- **Type of insulin**
  - **offer multiple daily injection basal–bolus insulin regimens, rather than twice-daily mixed insulin regimens, as the insulin injection regimen of choice for all adults**

- **twice-daily insulin detemir is the regime of choice.** Once-daily insulin glargine or insulin detemir is an alternative
- offer rapid-acting insulin **analogues** injected before meals, rather than rapid-acting soluble human or animal insulins, for mealtime insulin replacement for adults with type 1 diabetes

- insulin dose
  - normal insulin requirements are around 0.5–0.6 units/kg/day, split equally between background (basal) and mealtime (bolus) requirements
- dose adjustments
  - Reduce evening basal insulin after alcohol or exercise by 25–50%.
- **Metformin**
  - NICE recommend considering adding metformin if the BMI ≥ 25 kg/m²

Type 2 DM

- **Epidemiology**
  - greater incidence among those of black and South Asian origin.
  - Most are over 40yrs, but teenagers are now getting type 2 DM
- **Pathophysiology**
  - Caused by a relative deficiency of insulin and the phenomenon of insulin resistance.
  - **The presence of amyloid polypeptide on pancreatic histology is highly suggestive of type 2 diabetes.**
    - **amyloid deposition is associated with reduced islet cell number and function.**
  - **↑Plasminogen activator inhibitor 1 (↑in obesity & ↓ in weight loss → insulin resistance → type 2 diabetes mellitus.**
  - Haemochromatosis is an example of secondary diabetes
  - **Adiponectin secretion by adipocytes tends to be reduced** and peripheral resistance to its actions increases among obese individuals.
    - Adiponectin is secreted by adipocytes and is involved in lipid catabolism, improved insulin response, decreased risk of atherosclerosis, and reduced inflammatory markers in diabetic patients.
    - It is inversely correlated with the risk for diabetes and lower levels are present with worsening levels of insulin resistance in diabetic patients.
- **Risk factors**
  - Age, obesity and ethnicity are important risk factors.
- **Genetics**
  - Genetic risks for developing diabetes
    - **Concordance between identical twins is higher in type 2 diabetes mellitus than type 1**
    - **if one identical twin has type 2 diabetes, the risk in the unaffected twin → 60 – 100 %.**
  - No HLA associations.

- TCF7L2 (**T**rans**c**ription **f**actor **7**-**l**ike **2** protein) in chromosome 10q has the largest effect on type 2 diabetes risk

Beta cell mass

- **Compared with subjects with normoglycaemia,**
  - **beta cell mass is reduced by 50% in subjects with Impaired Fasting Glucose,**
  - **by 65% in subjects with Type 2 diabetes, and**
  - **over 90% in subjects with type 1 diabetes.**

Immunosuppression in poorly controlled diabetes

- Immunosuppression with susceptibility to infection is an inevitable consequence of poorly controlled diabetes mellitus.
- **Impaired neutrophil chemotaxis and phagocytosis is the most important mechanism of immunosuppression in diabetes** and would certainly cause an increased propensity for bacterial infections, such as the recurrent UTIs

Polyuria:

- Polyuria is urine excretion of **more than 40 mL/kg** body weight per day.
- Polydipsia is defined as water intake of more than 100 mL/kg/day.

Causes

Common (>1 in 10)	Infrequent (1 in 100)	Rare (1 in 1000)	Very rare (<1 in 10 000)
• diuretics, caffeine & alcohol • diabetes mellitus • lithium • heart failure	• hypercalcaemia • hyperthyroidism	• chronic renal failure • primary polydipsia • hypokalaemia	• diabetes insipidus

There are four **mechanisms**, which can cause polyuria.

1. Increased intake of fluids as in psychogenic causes, stress and anxiety
2. Increased GFR as in hyperthyroidism, fever, hypermetabolic states
3. Increased output of solutes as occurs in DM, hyperthyroidism, hyperparathyroidism, use of diuretics (which present more solute at the DCT)
4. Inability of the kidney to reabsorb water in DCT as in CDI, NDI, drugs and chronic renal failure (CRF).

thiazide diuretic abuse → polyuria and polydipsia of recent onset + high calcium, glucose and hypokalaemia, with an elevated bicarbonate. ↑Serum Osmolality > 300

Diabetes mellitus (type 2): diagnosis

Diabetes diagnosis: fasting > 7.0, random > 11.1 - if asymptomatic need two readings

- The diagnosis of type 2 diabetes mellitus can be made by either a plasma glucose or a HbA1c sample.
- Diagnostic criteria vary according to whether the patient is symptomatic (polyuria, polydipsia etc) or not.
  - **If the patient is symptomatic:**
    - fasting glucose greater than or equal to 7.0 mmol/l
    - random glucose greater than or equal to 11.1 mmol/l (or after 75g oral glucose tolerance test)
  - **If the patient is asymptomatic,**
    - the above criteria apply but must be demonstrated on two separate occasions.
  - **If the fasting or random values are not diagnostic, the two hour value should be used.**
    - Diabetes UK suggests :'People with IFG should then be offered an oral glucose tolerance test to rule out a diagnosis of diabetes. A result below 11.1 mmol/l but above 7.8 mmol/l indicates that the person doesn't have diabetes but does have IGT.'
- WHO guidance on the use of HbA1c on the diagnosis of diabetes:
  - a HbA1c of greater than or equal to 6.5% (48 mmol/mol) is diagnostic of diabetes mellitus
  - a HbAlc value of less than 6.5% does not exclude diabetes (i.e. it is not as sensitive as fasting samples for detecting diabetes)
  - in patients without symptoms, the test must be repeated to confirm the diagnosis
  - it should be remembered that misleading HbA1c results can be caused by increased red cell turnover (see below)
- **Conditions where HbA1c may not be used for diagnosis:**
  - haemoglobinopathies
  - haemolytic anaemia
  - untreated iron deficiency anaemia
  - suspected gestational diabetes
  - children
  - HIV
  - chronic kidney disease
  - patients who are acutely ill,

- patients taking steroids or antipsychotics (which can cause a rapid glucose rise),
- patients with acute pancreatic damage

- **Impaired fasting glucose and impaired glucose tolerance.**
  - A fasting glucose greater than or equal to 6.1 but less than 7.0 mmol/l implies impaired fasting glucose (IFG)
  - Impaired glucose tolerance (IGT) is defined as fasting plasma glucose less than 7.0 mmol/l and OGTT 2-hour value greater than or equal to 7.8 mmol/l but less than 11.1 mmol/l

- **The relationship between type 2 diabetes and colonic cancer?**
  - Type 2 diabetes is associated with a 40-60% increase in the risk of cancer of the large bowel. This increase is linked to changes in $HbA1_c$.
  - No association has been found between colonic malignancy and type 1 diabetes, nor gestational diabetes.
  - **Increased concentrations of C peptide are a marker of increased colorectal cancer risk**

Which lipid abnormalities are most likely to be detected in a patient with type 2 diabetes?
→Small dense LDL molecules

- small dense LDL is more atherogenic, able to be oxidised more readily and penetrate endothelium and macrophages.
- LDL is not typically elevated in type 2 diabetes
- HDL is typically low in the patient with type 2 diabetes.
- Triglycerides are often elevated with poor glycaemic control.

The OGTT

- Used to diagnose diabetes.
- Particularly useful in cases of borderline diabetes or gestational diabetes.
- The test requires:
  - Overnight fast prior to the test
  - Normal eating the previous day
  - Baseline sample for glucose using a fluoride tube
  - 75 g oral anhydrous glucose usually washed down in 250-300 ml water (if hydrous glucose is used, the same weight represents a lower proportion of glucose in molar measurement)
  - Further glucose sample taken at 120 minutes
  - Plasma tubes, such as fluoride oxalate, must be used as the test results have not been validated using serum samples
  - Serum samples without additives allow further metabolism of the glucose by the red

cells and may give a falsely low value. Fluoride oxalate prevents further metabolism of glucose.

Glycosylated haemoglobin

Diabetes mellitus - HbA1c of 6.5% or greater is now diagnostic (WHO 2011)

- Glycosylated haemoglobin (HbA1c) is the most widely used measure of long-term glycaemic control in diabetes mellitus.
- HbA1c is produced by the glycosylation of haemoglobin at a rate proportional to the glucose concentration.
- HbA1c is generally thought to reflect the blood glucose over the previous '2-3 months' although there is some evidence it is weighed more strongly to glucose levels of the past 2-4 weeks
- The level of HbA1c therefore is dependant on
  - red blood cell lifespan
  - average blood glucose concentration
- HbA1c is affected by many factors:
  - Elevated HbA1c can occur in iron deficiency, vitamin B_{12} deficiency, alcohol dependence, chronic renal failure, hyperbilirubinaemia and splenectomy
  - Reduced HbA1c can occur in chronic liver disease, hypertriglyceridaemia, some haemoglobinopathies, splenomegaly, rheumatoid arthritis and certain medications, including iron or vitamins B_{12}, C or E, antiretrovirals and dapsone.

A number of **conditions can interfere with accurate HbA1c interpretation:**

Lower-than-expected levels of HbA1c(due to reduced red blood cell lifespan)	**Higher-than-expected levels of HbA1c(due to increased red blood cell lifespan)**
Sickle-cell anaemia GP6D deficiency Hereditary spherocytosis	Vitamin B12/folic acid deficiency Iron-deficiency anaemia Splenectomy

A new internationally standardised method for reporting HbA1c has been developed by the International Federation of Clinical Chemistry (IFCC). This will report HbA1c in mmol per mol of haemoglobin without glucose attached.

HBA1c (%)	Average plasma glucose (mmol/l)	IFCC-HbA1c (mmol/mol)
5	5.5	
6	7.5	42
7	9.5	53
8	11.5	64
9	13.5	75
10	15.5	
11	17.5	
12	19.5	

From the above we can see that

average plasma glucose = (2 * HbA1c) - 4.5

When is the first time that HbA_{1c} is likely to be accurate post blood transfusion?

⇨ **3 months**

September 2011 exam: What is the minimum time period after which the HbA1c should be repeated?
3 months (A more accurate answer would probably be 2 months but this is not given as an option)

September 2013 exam: A Fasting glucose of one patient is = 7.7 mmol/l, but his HA1c is = 31 mmol/mol (5.0%).Which would explain the discrepancy between the HbA1c and fasting glucose levels? Sickle-cell anaemia

Diabetes mellitus: management of type 2 (NICE 2015)

> It's worthwhile thinking of the average patient who is taking metformin for T2DM, you can titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%), but should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)

Why is the management of diabetes mellitus so important?

- The main focus of diabetes management now is reducing the incidence of macrovacular (ischaemic heart disease, stroke) and microvascular (eye, nerve and kidney damage) complications.

The new changes of NICE guidance on the management of type 2 diabetes mellitus (T2DM) in 2015 include:

- HbA1c targets have changed. They are now dependent on what antidiabetic drugs a patient is receiving and other factors such as frailty
- there is more flexibility in the second stage of treating patients (i.e. after metformin has been started) - you now have a choice of 4 oral antidiabetic agents

Dietary advice

- encourage high fibre, low glycaemic index sources of carbohydrates
- include low-fat dairy products and oily fish
- control the intake of foods containing saturated fats and trans fatty acids
- limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake
- discourage use of foods marketed specifically at people with diabetes
- initial target weight loss in an overweight person is 5-10%

HbA1c targets

- individual targets should be agreed with patients to encourage motivation
- HbA1c should be checked every 3-6 months until stable, then 6 monthly
- NICE encourage us to consider relaxing targets on *'a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes'*
- in 2015 the guidelines changed so HbA1c targets are now dependent on treatment:

Lifestyle or single drug treatment

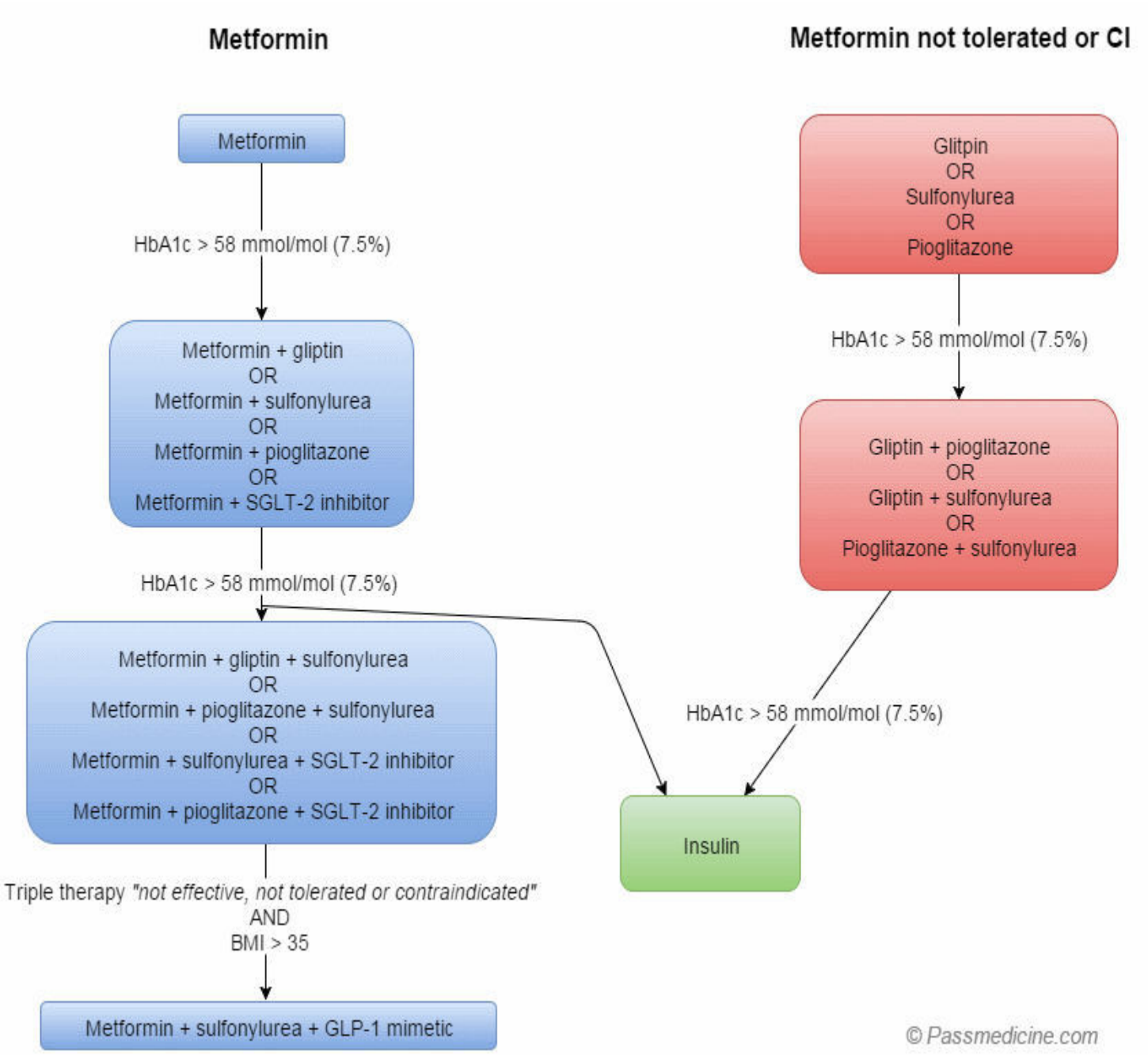
Management of T2DM	HbA1c target
Lifestyle	48 mmol/mol (6.5%)
Lifestyle + metformin	48 mmol/mol (6.5%)
Includes any drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea)	53 mmol/mol (7.0%)
Already on one drug, but HbA1c has risen to 58 mmol/mol (7.5%)	53 mmol/mol (7.0%)

Practical examples

- a patient is newly diagnosed with HbA1c and wants to try lifestyle treatment first. You agree a target of 48 mmol/mol (6.5%)
  - many local protocols now recommend starting metformin upon diagnosis
- you review a patient 6 months after starting metformin. His HbA1c is 51 mmol/mol (6.8%). You increase his metformin from 500mg bd to 500mg tds and reinforce lifestyle factors
- you review an established type 2 diabetic on maximum dose metformin. Her HbA1c is 55 mmol/mol (7.2%). You do not add another drug as she has not reached the threshold of 58 mmol/mol (7.5%)
- a type 2 diabetic is found to have a HbA1c of 62 mmol/mol (7.8%) at annual review. They are currently on maximum dose metformin. You elect to add a sulfonylurea

Drug treatment

- First line
  - **titrate up metformin** and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%),
  - **If gastrointestinal side effects are not tolerated, then a trial of modified release metformin would be appropriate.**
  - If metformin is not tolerated at all then a dipeptidyl peptidase-4 inhibitor, sulfonylurea or pioglitazone would be indicated.
- Second line
  - **should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)**
  - there is more flexibility in the second stage of treating patients (i.e. after metformin has been started) - you now have a choice of 4 oral antidiabetic agents
- There are essentially two pathways, one for patients who can tolerate metformin, and one for those who can't:



Tolerates metformin:

- metformin is still first-line and should be offered if the HbA1c rises to 48 mmol/mol (6.5%)* on lifestyle interventions
- if the HbA1c has risen to 58 mmol/mol (7.5%) then a **second drug** should be added from the following list:
    1. → sulfonylurea
    2. → gliptin
    3. → pioglitazone
    4. → SGLT-2 inhibitor

- if despite this the HbA1c rises to, or remains above 58 mmol/mol (7.5%) then **triple therapy** with one of the following combinations should be offered:
  - → metformin + gliptin + sulfonylurea
  - → metformin + pioglitazone + sulfonylurea
  - → metformin + sulfonylurea + SGLT-2 inhibitor
  - → metformin + pioglitazone + SGLT-2 inhibitor
  - → OR insulin therapy should be considered

Criteria for glucagon-like peptide1 (GLP1) mimetic (e.g. exenatide)

- if triple therapy is not effective, not tolerated or contraindicated then NICE advise that we consider combination therapy with metformin, a sulfonylurea and a glucagonlike peptide1 (GLP1) mimetic if:
  - → BMI ≥ 35 kg/m² and specific psychological or other medical problems associated with obesity or
  - → BMI < 35 kg/m² and for whom insulin therapy would have significant occupational implications or Weight loss would benefit other significant obesity related comorbidities
- only continue if there is a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months
- Exenatide should be used only when insulin would otherwise be started, obesity is a problem (BMI > 35 kg/m^2) and the need for high dose insulin is likely.

Cannot tolerate metformin or contraindicated

- if the HbA1c rises to 48 mmol/mol (6.5%) on lifestyle interventions, consider one of the following:
  - → sulfonylurea
  - → gliptin
  - → pioglitazone
- if the HbA1c has risen to 58 mmol/mol (7.5%) then a one of the following combinations should be used:
  - → gliptin + pioglitazone
  - → gliptin + sulfonylurea
  - → pioglitazone + sulfonylurea
- if despite this the HbA1c rises to, or remains above 58 mmol/mol (7.5%) then consider insulin therapy

Starting insulin

- if HbA1c > 58 mmol/mol (DCCT = 7.5%) then consider human insulin
- Metformin should be continued. In terms of other drugs NICE advice: *'Review the continued need for other blood glucose lowering therapies'*
- NICE recommend starting with human NPH insulin (isophane, intermediate acting) taken at bed-time or twice daily according to need
- if the patient is at risk from hypoglycaemia (or the consequences of) then a DPP-4 inhibitor or thiazolidinedione should be considered rather than a sulfonylurea
- meglitinides (insulin secretagogues) should be considered for patients with an erratic lifestyle
- **However, you can consider using sitagliptin or a thiazolidinedione instead of insulin if there would be employment (eg: truck driver), social, recreational or personal issues.**

- In patients with diabetes starting thyroxine, doses of antidiabetic drugs including insulin may need to be increased.

Risk factor modification

- **Blood pressure**
  - target is < 140/80 mmHg (or < 130/80 mmHg if end-organ damage is present)
  - ACE inhibitors are first-line
- **Antiplatelets**
  - should not be offered unless a patient has existing cardiovascular disease
- **Lipids**
  - following the 2014 NICE lipid modification guidelines only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin. The first-line statin of choice is atorvastatin 20mg on

Which laboratory test results would be most significantly associated with an increased incidence of cardiovascular disease in type 2 diabetics? → Raised proinsulin levels

January 2013 exam: A taxi driver with type 2 DM , on metformin and the dose was titrated up. His HbA1c one year ago was 75 mmol/mol (9%) and is now 69 mmol/mol (8.5%). His BMI 33 kg/m². What is the most appropriate next step in management? Add sitagliptin (because DPP-4 inhibitors are weight neutral & no risk of hypoglycaemia)

September 2010 exam: H/O (T2DM) & bladder cancer on gliclazide and atorvastatin. A recent trial of metformin was unsuccessful due to gastrointestinal side-effects. He works as an accountant, is a non-smoker his BMI is 31 kg/m². HisHbA1c = 62 mmol/mol (7.8%) What is the most appropriate next step in management? Add sitagliptin (Pioglitazone is contraindicated in bladder cancer and may contribute to his obesity. he does not meet the NICE body mass index criteria of 35 kg/m².)

Metformin

Metformin should be titrated slowly, leave at least 1 week before increasing dose

- Metformin is a biguanide used mainly in the treatment of type 2 diabetes mellitus.
- metformin is now sometimes used in pregnancy, for example in women with polycystic ovarian syndrome
- It has a number of actions which improves glucose tolerance (see below).
- Metformin is the only oral hypoglycaemic shown to reduce **macro**vascular complications and death
- The UKPDS (United Kingdom Prospective Diabetes Study) showed that metformin was superior to sulphonylureas or insulin in terms of macrovascular risk, showing a statistically significant risk reduction for myocardial infarction
- Unlike sulphonylureas it does not cause hypoglycaemia and weight gain and is therefore first-line, particularly if the patient is overweight.
- Metformin is also used in polycystic ovarian syndrome and non-alcoholic fatty liver disease

- Mutations in organic cation transporters are known to be associated with differences in metformin response

Mechanism of action

- increases insulin sensitivity
- **decreases hepatic gluconeogenesis**
- may also reduce gastrointestinal absorption of carbohydrates

Adverse effects

High dose (> 2 gm daily) **interferes with enterohepatic circulation of the bile salts** (Bile salt malabsorption) → diarrhoea

- gastrointestinal upsets are common (nausea, anorexia, diarrhoea), intolerable in 20%
  - GIT side-effects are more likely to occur if metformin is not slowly titrated up.
  - The BNF advises leaving at least 1 week before increasing the dose.
  - modified release preparations reduce the risk further.
  - High dose metformin is thought to interfere with the enterohepatic circulation of bile salts, leading to **reduced reabsorption of bile salts from the ilieum →chronic diarrhoea .**
- **vitamin B_{12} deficiency**
  - rarely a clinical problem
  - Long-term treatment with metformin increases the risk of **vitamin B_{12} deficiency**.
  - The possibility of metformin-associated B_{12}deficiency should be considered in patients on metformin who suffer cognitive impairment, peripheral neuropathy, subacute combined degeneration of the cord or anaemia.
  - Regular measurement of vitamin B_{12} concentrations during long term metformin treatment should be strongly considered.
- **lactic acidosis** with severe liver disease or renal failure
  - it is now increasingly recognised that lactic acidosis secondary to metformin is rare, although it remains important in the context of exams
  - **factors increases the risk of metformin lactic acidosis**:
    - Raised serum creatinine
      - Drugs causes kidney injury:
        - contrast media,
          - Metformin should therefore be stopped before, and for 48 h after, contrast radiography.
        - cyclosporin
        - aminoglycosides.
    - Excess **alcohol** intake
    - Cimetidine
      - Metformin is excreted by the renal tubules and this process can be inhibited by cimetidine, but not the other H2 receptor antagonists.
  - **The mainstay of treatment is rehydration.**
  - Despite aggressive treatment, mortality still 50%.

Contraindications

- chronic kidney disease:
  - NICE recommend that the dose should be reviewed if the creatinine is > 130 mmol/l (or **eGFR < 45** ml/min) (reduce the those and monitor renal function every three months) and stopped if the creatinine is > 150 mmol/l (or eGFR < 30 ml/min)
  - In regards to metformin and renal impairment, guidance has recently been revised to support metformin initiation at glomerular filtration rate as low as **45ml/min.**
  - The drug should be stopped once eGFR falls to less than 30 mL/min/1.73 m^2 (creatinine more than 150 µmol/L).
- metformin may cause lactic acidosis if taken during a period where there is tissue hypoxia. Examples include a recent myocardial infarction, sepsis, acute kidney injury and severe dehydration
- **Metformin should be stopped in patients who have an unstable circulation post-MI**
- **The British National Formulary (BNF) states that there should be a six week "cooling off" period post-MI before the commencement or recommencement of metformin.**
- **In controlled heart failure, metformin may be used with caution.**
- **iodine-containing x-ray contrast media:** examples include peripheral arterial angiography, coronary angiography, intravenous pyelography (IVP); there is an increasing risk of provoking renal impairment due to contrast nephropathy; **metformin should be discontinued on the day of the procedure and for 48 hours thereafter**
- sepsis
- alcohol abuse is a relative contraindication
  - **alcohol intake → increases the risk of lactic acidosis in diabetic patients on metformin**

Action of metformin in polycystic ovary syndrome ➔increasing peripheral glucose uptake

- Lowering serum insulin concentrations with metformin ameliorates hyperandrogenism by reduction of ovarian enzyme activity that results in ovarian androgen production.
- Clinical studies have shown that metformin reduces insulin resistance and have demonstrated a fall in serum androgens, luteinising hormone and weight.
- The reduced insulin resistance is associated with reduced insulin drive to the insulin sensitive ovary in polycystic ovarian syndrome and hence reduces androgen production.

Metformin overdose (medical-masterclass.com 2017 part 2)

- Metformin classically causes a type-B lactic acidosis in overdose, **especially in patients who have co-ingested alcohol** or who have underlying renal or hepatic dysfunction.
- **Feature**
  - gastrointestinal upset
  - severe lactic acidosis.
  - Hypoglycaemia is not often seen in metformin overdose.

- **Prognosis**
  - If lactic acidosis occurs following overdose, **mortality is usually greater than 50%.**
- **Management**
  - gastric decontamination and use of activated charcoal
  - **correction of acidosis with 8.4% sodium bicarbonate**.
  - Patients with **resistant acidosis** should be considered for **haemodialysis, which also clears metformin.**

Sulphonylureas

Action

- **blocks potassium channels.**
- acts by blocking ATP-dependent potassium channels in the beta cells of the pancreas. Membrane depolarization results in influx of calcium and release of insulin.
- Act by enhancing pancreatic islet cell function → promotes insulin release
- Also, act on the liver, stimulating the glycolytic pathway and inhibiting the production of glucose.
- On a molecular level they bind to an ATP-dependent K^+(K_{ATP}) channel on the cell membrane of pancreatic beta cells.

Side effects

- Common adverse effects
  - Hypoglycaemia (more common with long acting preparations such as chlorpropamide)
  - **weight gain**
- Rarer adverse effects
  - syndrome of inappropriate ADH secretion (SIADH)
  - bone marrow suppression
  - liver damage (cholestatic)
  - photosensitivity
  - peripheral neuropathy
  - Of the sulphonylureas, **chlorpropamide is the main drug associated with facial flushing following alcohol intake**, although a lesser reaction may be seen with other sulphonylureas. This disulfiram-like reaction is also seen with metronidazole.

Contraindications:

- Pregnancy and breast feeding

Interaction

- As a result of drug interaction **hypoglycaemia** may be potentiated when a sulfonylurea is used concurrently with agents such as:
  - Long-acting sulfonamides
  - Tuberculostatics
  - Phenylbutazone
  - Clofibrate
  - Monoamine oxidase (MAO) inhibitors

- Coumarin derivatives
- Salicylates
- Probenecid
- Propranolol
- Cimetidine
- Disopyramide, and
- Angiotensin converting enzyme inhibitors.
- **Fluconazole** has a low level of plasma protein binding and it is excreted by the kidney. However, it is also a potent inhibitor of CYP2C8 and CYP2C9 and can thus interact with gliclazide and other sulphonylureas (for example, glimepiride, glibenclamide, tolbutamide and glipizide).

Further notes:

- Although sulphonylurea therapy was proved by the UK Prospective Diabetes Study to provide **micro**vascular benefits, **NO benefit was demonstrated for macrovascular outcomes** (cardiovascular disease), in contrast to metformin.
- **Glibenclamide**
  - long-acting sulfonylurea,
  - associated with a greater risk of hypoglycaemia
    - therefore should be avoided in the elderly, and shorter-acting alternatives, such as gliclazide or tolbutamide, should be used instead
  - metabolism
    - cleared by hepatic metabolism but has two active metabolites, 4-trans-hydroxyglibenclamide and 3-cis-hydroxyglibenclamide, which are both renally excreted.
    - **Renal impairment therefore increases the risk of hypoglycaemia in patients taking glibenclamide.**
      - with moderate CKD (eGFR 60-90 mL/min) → (reduced dose, frequent monitoring due to increased risk of hypoglycemia).
      - contraindicated in stage ≥ 3 CKD (eGFR < 60 mL/min)
- **Gliclazide**
  - intermediate half-life of around 11 hours.
  - causes less hypoglycemia than other sulfonylureas.
  - Metabolism
    - extensively metabolised within the liver by CYP2C9. Within the circulation, gliclazide is highly bound to plasma proteins, about 94%.
    - Renal clearance accounts for only 4% of total drug clearance.
    - In CKD stage 1, 2, 3 (eGFR > 30 mL/min) gliclazide can be used safely.
      - in patients with severe CKD → reduced dose can be used

- Therefore **gliclazide action can be potentiated predominantly by two mechanisms:**
  - Displacement of the drug from plasma proteins to give more free (unbound) drug - some agents such as **aspirin** can do this, and
  - Interference with the hepatic metabolism of the drug.(e.g fluconazole)

- **Glipizide**
  - **Glipizide is the best choice of sulfonylureas in a patient with renal impairment.**
  - does not need dose adjustment in severe and moderate renal disease
  - It is metabolized by the liver into inactive metabolites and therefore, renal insufficiency does not affect the drug's clearance.
- **Chlorpropamide**
  - is a first generation sulfonylurea.
  - may produce a syndrome of inappropriate anti-diuretic hormone (ADH) secretion.
  - It has a higher side effect profile

Meglitinides(**glinides**) (e.g. repaglinide, nateglinide)

Meglitinides - stimulate insulin release - good for erratic lifestyle

Meglitinides (nateglinide and repaglinide) → increase postprandial insulin release specifically

Action

- insulin secretagogues
- like sulfonylureas they bind to an ATP-dependent K^+(K_{ATP}) channel on the cell membrane of pancreatic beta cells but have a weaker binding affinity and faster dissociation from the SUR1 binding site (**acts by closure of the β-cell K+-ATP channel**)
- It is short-acting

Indications

- often used for patients with an erratic lifestyle
- particularly useful for post-prandial hyperglycaemia or an erratic eating schedule, as patients take them shortly before meals
- taken to coincide with meals.

Advantages

- The shorter action of duration appears to result in less weight gain compared to traditional sulphonylureas.
- Nateglinide is more expensive than sulphonylureas but offers advantages **for shift workers and patients who tend to fast for a period of time** because doses can be skipped when meals are missed.In these patient groups there may be a lower incidence of hyperglycaemia.
- Repaglinide can be used even in CKD stages 4 and 5 without dose reduction.

Adverse effects

- weight gain and hypoglycaemia (less so than sulfonylureas)

Thiazolidinediones (pioglitazone)

Peroxisome **P**roliferator **A**ctivated **R**eceptor **(PPAR) gamma agonists** have been shown to reduce bone mineral density.

Glitazones are agonists of PPAR-gamma receptors, reducing peripheral insulin resistance

(PPAR-γ) agonists increase the metabolism of free fatty acids

A major function of peroxisomes is beta-oxidation of fatty acids

- **The PPAR-gamma receptor is:**
  - **an intracellular nuclear receptor.**
  - Its natural ligands are free fatty acids
  - it is thought to control adipocyte differentiation and function.
  - **activated by:**
    - **free fatty acids** and
    - thiazolinediones such as pioglitazone.
- **Pioglitazone, a PPAR gamma agonist**, is an insulin sensitiser.
- It upregulates genes for enzymes which deal with the metabolism of free fatty acids.
- lead to increased peripheral insulin sensitivity, and improve glucose uptake.
- **The main cytochrome P450 enzyme pathway responsible for pioglitazone metabolism is CYP2C8**
- **Advantages**
  - reduces HbA1c by between 1 and 1.3%.
  - raises HDL cholesterol by around 10%,
- **MOA**
  - They are agonists to the PPAR-gamma receptor → ↑fatty acid metabolism → ↓ visceral obesity → reduce peripheral insulin resistance.
    - Metformin also boosts insulin sensitivity, but **pioglitazone has more effect on peripheral insulin resistance.**
  - **They act at the peroxisome proliferator-activated receptor-gamma (PPAR-gamma) receptor site, promoting binding as a heterodimer with the retinoid X-receptor to DNA**
  - This then leads to → ↑↑ lipid metabolism → ↓↓ free fatty acids → reduction in hepatic insulin resistance, a rise in adiponectin and improved peripheral insulin sensitivity.
  - **activate adiponectin**

- **Adverse effects**
  - Weight gain (caused by a combination of fat accumulation and fluid retention).
  - liver impairment: monitor LFTs
  - **Fluid retention**: therefore contraindicated in heart failure.

- in 10% of patients,
- mechanism: by means of an action on the collecting ducts of the kidney so promoting sodium and water retention.
- Rosiglitazone was withdrawn in 2010 following concerns about the c **The risk of fluid retention is increased if the patient also takes insulin** , or other drugs that cause fluid retention (for example, **NSAIDs**, **calcium antagonists**)
- ardiovascular side-effect profile.

➢ **increased risk of osteoporotic fractures**
- due to reduced bone mineral density.
- The underlying mechanism is thought to be due to bone cell precursors differentiating into adipocytes rather than osteoblasts.

➢ **bladder cancer**: recent studies have showed an increased risk of bladder cancer in patients taking pioglitazone (hazard ratio 2.64)

- **NICE guidance on thiazolidinediones**
  - ➢ only continue if there is a reduction of > 0.5 percentage points in HbA1c in 6 months

MRCPUK- part-1-January 2007 : Which one of the following problems is most likely to be caused by pioglitazone? Peripheral oedema

MRCPUK- part-1-January 2013: What is the mechanism of action of thiazolidinediones? PPAR-gamma receptor agonist

Insulin therapy

- Insulin is released by beta cells **as a result of increased intracellular calcium.**
- Insulin is released in pulses about every 9-13 minutes.This pulsing release mechanism is important because it is thought that this keeps cells sensitive to insulin. this is one of the first things that disappears when insulin sensitivity disappears.
- **Action**
  - ➢ Insulin inhibits gluconeogenesis by **inhibiting pyruvate carboxylase**. It increases glycolysis by inducing the synthesis of glucose-6-phosphate dehydrogenase. Both pyruvate dehydrogenase and glycogen synthetase are activated by insulin.
  - ➢ Insulin induces the synthesis of phosphofructokinase, which increases glycolysis, and stimulates acetyl-CoA carboxylase **to increase the synthesis of fatty acids.**
  - ➢ It acts via a similar mechanism to cell surface receptors.
  - ➢ Insulin binding to its receptor results in receptor autophosphorylation on tyrosine residues and the tyrosine phosphorylation of insulin receptor substrates (IRS-1, IRS-2 and IRS-3) by the insulin receptor tyrosine kinase.
  - ➢ It is synthesised in the beta cells of the islets of Lagerhans.
  - ➢ It causes an increased glucose-protein transport on the endoplasmic reticulum
- **C-peptide**
  - ➢ is a protein that is cleaved from proinsulin when it is activated.

  - This has a much longer half-life than insulin itself, and thus is a useful measure of insulin secretion (it is more accurate than measuring insulin itself).
  - The level of this can be measured in the urine.
- GLUT-4 is the main insulin responsive glucose transporter.
- **Enzymes and insulin**
  - **Insulin inhibits Pyruvate carboxylase, an enzyme involved in gluconeogenesis**
  - Insulin stimulate glycogen synthetase → increases glycogenesis in the liver and muscle
  - Insulin activates the hexose monophosphate (HMP) shunt by inducing the synthesis of glucose 6-phosphate dehydrogenase
  - Both acetyl-CoA carboxylase and ATP citrate lyase are stimulated to increase the synthesis of fatty acids.

the most appropriate initial insulin regime for young patient after being diagnosed with new onset Type1 DM → Meal time Actrapid and insulatard at night.

Classification of insulin

- **By manufacturing process**
  - porcine: extracted and purified from pig pancreas
  - human sequence insulin: either produced by enzyme modification of porcine insulin (emp) or biosynthetically by recombinant DNA using bacteria (crb, prb) or yeast (pyr)
  - analogues
- **By duration of action**

	Onset	Peak	Duration
Rapid-acting insulin analogues	5 mins	1 hour	3-5 hours
Short-acting insulin	30 mins	3 hours	6-8 hours
Intermediate-acting insulin	2 hours	5-8 hours	12-18 hours
Long-acting insulin analogues	1-2 hours	Flat profile	Up to 24 hours
Premixed preparations	-	-	-

  - **Rapid-acting insulin analogues**
    - the rapid-acting human insulin analogues act faster and have a shorter duration of action than soluble insulin (see below)
    - may be used as the bolus dose in 'basal-bolus' regimes (rapid/short-acting 'bolus' insulin before meals with intermediate/long-acting 'basal' insulin once or twice daily)
    - insulin aspart: NovoRapid
    - insulin lispro: Humalog

- If there is a pre-lunch ↑↑ glucose, that means there is a significant post-breakfast peak in glucose levels. As such, **the best way to manage this is with a breakfast time injection of rapid acting insulin.**

➢ **Short-acting insulins**
- soluble insulin examples: Actrapid (human, pyr), Humulin S (human, prb)
- may be used as the bolus dose in 'basal-bolus' regimes

➢ **Intermediate-acting insulins**
- isophane insulin
  - ❖ NICE guidelines advise that, in general, a **humane isophane insulin (also referred to as a Neutral Protamine Hagedorn [NPH] insulin) is the first-line recommended insulin to use in a type 2 diabetic.** These are intermediate acting insulins usually used once daily at night or twice a day.
- many patients use isophane insulin in a premixed formulation with

➢ **Long-acting insulins**
- insulin determir (Levemir): given once or twice daily
- insulin glargine (Lantus): given once daily
- A long-acting insulin analogue might be useful in someone who struggles to inject a twice a day NPH insulin to reduce the frequency of injections to once a day (e.g. someone who requires assistance to inject from a carer or district nurse).

➢ **Premixed preparations**
- combine intermediate acting insulin with either a rapid-acting insulin analogue or soluble insulin
- Novomix 30: 30% insulin aspart (rapid-acting), 70% insulin aspart protamine (intermediate-acting)
- Humalog Mix25: 25% insulin lispro (rapid-acting), 75% insulin lispro protamine (intermediate-acting); Humalog Mix50: 50% insulin lispro, 50% insulin lispro protamine
- Humulin M3: biphasic isophane insulin (human, prb) - 30% soluble (short-acting), 70% isophane (intermediate-acting)
- Insuman Comb 15: biphasic isophane insulin 9human, prb) - 30% soluble (short-acting), 70% isophane (intermediate-acting)
- A biphasic 'mixed' preparation is recommended if an individual's diabetic control is especially poor (HbA_{1c} > 75 mmol/mol).

Advantages of Short-acting insulin analogue VS short-acting soluble insulins.

- Short-acting insulin analogue, like lispro-insulin, aspart insulin and glulisine insulin have a **rapid onset of action** and a **shorter duration of action** than conventional short-acting soluble insulins.
- Consequently studies reveal **reduced post-prandial glucose excursions** versus soluble insulin and potentially a reduced incidence of hypoglycaemia although the evidence for this is debated.

Types of Insulin

Insulin[a]	Onset	Peak Effect	Duration
Regular	30–60 minutes	2–4 hours	5–8 hours
Humalog (lispro)	5–10 minutes	0.5–1.5 hours	6–8 hours
NovoLog (aspart)	10–20 minutes	1–3 hours	3–5 hours
Apidra (glulisine)	5–15 minutes	1.0–1.5 hours	1.0–2.5 hours
NPH	2–4 hours	6–10 hours	18–28 hours
Levemir (detemir)	2 hours	No discernible peak	20 hours
Lantus (glargine)	1–4 hours	No discernible peak	20–24 hours

[a] Combination preparations mix longer-acting and shorter-acting types of insulin together to provide immediate and extended coverage in the same injection (e.g., 70 NPH/30 regular = 70% NPH + 30% regular).

Insulin analogues

Insulin lispro:

- short-acting insulin →
- The first insulin analogue to be developed, by reversing the position of two amino acids (**lys**ine and **pro**line) in the B chain of human insulin.
- This allows larger amounts of prandial insulin to be available soon after injection and **reduces the chance of between-meal hypoglycaemia.**
- Short-acting analogues are useful for **reducing postprandial hypoglycaemia** because their profile is more in keeping with physiological insulin release.

Insulin glargine

- long-acting insulin analogue (up to 24-hour duration of action)
- produced by **r**ecombinant DNA technology utilizing a non-pathogenic laboratory strain of **Escherichia coli (K12)** as the production organism.
- Insulin glargine differs from human insulin in that the amino acid asparagine at position A21 is replaced by **glycine** and two **arginines** are added to the C-terminus of the B-chain.

- the main advantage → **Reduced nocturnal hypoglycaemia**
  - in which situations does insulin glargine have the clearest advantage over isophane?
    - → **In patients with type-1 diabetes who have significant nocturnal hypoglycaemia on isophane**
- suitable for providing a basal level of insulin which attempts to mimic the normal physiological state.
- and when given at night, provides good control of the fasting blood glucose.
- Unlike crystalline suspensions, insulin glargine does not need to be mixed thoroughly prior to injection, thus making it easier to use.
- NICE have reviewed use of long acting insulin analogues and they are only appropriate in cases of significant hypoglycaemia.
  - NICE only recommends use of insulin glargine in patients - with type-2 diabetes - who have significant hypoglycaemia on isophane insulin
- Glargine and detemir are insulin analogues, as such they are considered by NICE to be **only suitable in cases:**
  - nocturnal hypoglycaemia is a problem on isophane (NPH) insulin
  - morning hyperglycaemia on isophane (NPH) insulin results in difficult day-time blood glucose control
  - rapid-acting insulin analogues are used for meal-time blood glucose control.

Administration of insulin

- The vast majority of patients administer insulin subcutaneously.
- It is important to rotate injection sites to prevent lipodystrophy.
- Insulin pumps are available ('continuous subcutaneous insulin infusions') which delivers a continuous basal infusion and a patient-activated bolus dose at meal times.
- Intravenous insulin is used for patients who are acutely unwell, for example with diabetic ketoacidosis.
  - **Intravenous insulin is the optimal management of high blood sugar in acute myocardial infarction.**

Insulin prescription

- **Starting dose**
  - The guidelines recommend starting with either morning or evening long-acting insulin, or with **bedtime intermediate acting insulin.**
  - **0.2 U/kg or a flat dose of 10 U is the recommended starting dose for intermediate acting insulin.**
- **Targets**
  - The ADA/EASD consensus 2006 recommends a target of between 3.9 and 7.2 mmol/L for fasting and pre-prandial glucose levels.
- **Monitoring**
  - **Generally, if patients are not using insulin, sulphonylureas or glinides (repaglinide or netaglinide), then the ADA/EASD consensus does not recommend self-monitoring of blood glucose levels.**

- Once daily long-acting insulin taken at night is monitored using pre-breakfast fasting glucose measurements. A fasting glucose level of 4-7 mmol/L is the ideal aim.
- If fasting levels are in range yet the HbA_{1c} is elevated, post-prandial monitoring is recommended, aiming for glucose levels of less than 10 mmol/L.

- **Dose adjustment**
  - At least three consecutive, self-monitored fasting glucose readings should be used to adjust doses (i.e. three days minimum between dose adjustments).
  - Up-titration
    - If the fasting plasma glucose is more than 10 mmol/L, then a more aggressive uptitration schedule of 4 U every three days can be considered.
    - increase 2 U of insulin every three days until fasting glucose is in the target range of 3.9-7.2 mmol/L.
    - Use the '10% rule' for up-titration of insulin.
  - Down-titration
    - If fasting glucose is less than 4, then the insulin dose should be reduced. **A good general rule of thumb is that when reducing the insulin doses you should do so in steps of 20%.**
    - Reduce insulin dose in steps of 20% if hypoglycaemia occurs.
- **Insulin in renal failure**
  - The kidneys carry out one third of exogenous insulin degradation.
  - The dose of exogenous insulin is reduced 25% when eGFR is 10-50 mL/min and 50% when eGFR is < 10 mL/min

Insulin therapy: side-effects

Hypoglycaemia

- patients should be taught the signs of hypoglycaemia: sweating, anxiety, blurred vision, confusion, aggression
- conscious patients should take 10-20g of a short-acting carbohydrate (e.g. a glass of Lucozade or non-diet drink, three or more glucose tablets, glucose gel)
- every person treated with insulin should have a glucagon kit for emergencies where the patient is not able to orally ingest a short-acting carbohydrate
- patients who have frequent hypoglycaemic episodes may develop reduced awareness. If this develops then allowing glycaemic control to slip for a period of time may restore their awareness
- beta-blockers reduce hypoglycaemic awareness

Lipodystrophy

- typically presents as atrophy of the subcutaneous fat
- can be prevented by rotating the injection site

Other notes

- **insulin-related worsening of heart failure and fluid overload**
  - occurs because insulin itself promotes salt and water retention and increased sympathetic drive .
  - Management
    - furosemide to promote salt and water excretion,

- Once fluid status is stable, if he still has symptoms of heart failure, addition of a cardioselective beta blocker such as bisoprolol may be of value.

- **Insulin detemir** has been associated with less weight-gain or even slight weight-loss compared with other insulins.

Types of insulin	Effect	Application	Special features
Rapid-acting insulin			
Insulin lispro **Insulin aspart** **Insulin glulisine**	• Onset: 5–30 min • Peak: 30 min–3 h • Duration: 3–5 h	• Intensified conventional insulin therapy	• Injected before a meal time • Used in combination with longer-acting insulin
Short-acting insulin			
Regular insulin	• Onset: ~30 min • Peak: 2.5–5 h • Duration: 4–24 h	• "Standard insulin" for lowering blood glucose levels **in an acute setting** • Conventional insulin therapy • Intensified conventional insulin therapy	• Mandatory interval between injections and meal times: ~30 min • Used in combination with longer-acting insulin • **Intravenous therapy available** (only for this type of insulin)
Intermediate-acting insulin			
NPH insulin	• Onset: 1–2 h • Peak: 4–12 h • Duration: 14–24 h	• Conventional insulin therapy • Component of basal supported oral therapy (BOT) for treatment-resistant type 2 diabetes mellitus	• Crystalline suspension • Mandatory interval between injections and meal times: 30–60 min • Used in combination with rapid or short-acting insulin • Usually administered twice daily
Long-acting insulin			
Insulin glargine **Insulin detemir** **Insulin**	• Onset: 1.5–4 h • Peak: flat; not defined • Duration: ~ 24 h	• Intensified conventional insulin therapy • Component of basal supported oral therapy (BOT)	• Insulin analogs • More consistent efficacy profile and longer duration of effect compared to NPH insulin • Used in combination with rapid or short-actinginsulin

Types of insulin	Effect	Application	Special features
degludec **Ultralente insulin**		for treatment-resistant type 2 diabetes mellitus	• Administered once or twice daily
Mixed insulin			
Mixed insulin	• Biphasic effect • Short-term effect like that of regular insulin/lispro/aspart • Long-term effect like that of NPH insulin	• Conventional insulin therapy	• Contains regular insulin and NPH insulin mixed according to a defined ratio • Example: Actraphane® 30/70, contains 30% regular insulin and 70% NPH insulin • Administered two or three times a day

Mixtard- associated nocturnal hypoglycemia

- Diabetics often have hypoglycaemic attacks at night. This is a common scenario in someone on a twice-daily mixed regime.
- The patient has a hypoglycaemic attack at about 0200 h in the morning. This is because the insulatard component of the Mixtard peaks about 6 h after it has been given. This, along with some residual actrapid activity, gives an excess of insulin in the middle of the night, leading hypoglycaemia.
- If the evening dose of Mixatard is split up in to its component insulins, taking the actrapid pre-evening meal and the insulatard taken before bed, hypoglycaemia is normally avoided.
  - ➢ **Split evening insulin so take actrapid before evening meal and insulatard before bedtime**

September 2011 exam: A diabetic patient on simvastatin, gliclazide and metformin, admitted with acute MI. How should his diabetes be managed whilst in CCU? Stop metformin & gliclazide + intravenous insulin

Hypoglycaemic episodes which occur during the day in a patient takes a basal bolus insulin regime of long-acting insulin (Insulatard®) and short- acting insulin (Actrapid®) with each meal:

- the most appropriate next step → Refer for Dose Adjustment for Normal Eating education (**DAFNE**)
- the next step after DAFNE, should hypos persist, would be **continuous glucose monitoring**, to learn more about fluctuations in serum blood glucose over the course of the day.
- those patients who have problems with **nocturnal hypoglycaemia** → changing Insulatard to insulin glargine

Counselling a diabetic started on insulin about what to do if they are unwell (eg: they have a pneumonia)

- **For type 1 diabetics, if they are unwell:**
  - test their blood glucose and ketones at least every 4 hours.
    For this question we have used the TREND UK and Leicestershire NHS insulin guidelines.
  - The TREND UK guidance (Training, research and education for nurses in diabetes UK) advises that if blood glucose is less than 13 mmol/L and no ketones are present then insulin should be taken as normal;
  - if blood glucose is more than 13 mmol/L and ketones are present then insulin adjustment is needed.
    - **add 10% of the daily insulin dose as rapid acting insulin every four hours, and then four hourly glucose and ketone monitoring** to guide ongoing dosage/management.
  - The Leicestershire NHS guidance is identical aside from it using a cut-off of 11 mmol/L rather than 13 mmol/L.
- For type 2 diabetics, if they are unwell:
  - they should test their blood glucose at least every 4 hours.
  - if blood glucose is more than 13 mmol/L then insulin adjustment is needed.
  - if blood glucose is more than 13 mmol/L then insulin adjustment is needed.
    - add two units of insulin to each dose and continue to monitor the glucose levels **every four hours.**

Diabetes mellitus: GLP-1 and the new drugs

Incretins increase insulin release and decrease glucagon secretion from the pancreas. DPP-IV metabolizes GLP. Inhibiting DPP-IV maintains high levels of GLP.

- glucagon-like peptide-1 (GLP-1), a hormone released by the small intestine in response to an oral glucose load
- In normal physiology an oral glucose load results in a greater release of insulin than if the same load is given intravenously - this known as the **incretin effect**. This effect is largely mediated by GLP-1 and is known to be decreased in T2DM.
- **The two hormones responsible** for the incretin effect, glucose-dependent insulinotropic hormone (GIP) and glucagon-like peptide-1 (GLP-1), are secreted after oral glucose loads and augment insulin secretion in response to hyperglycaemia.
- **TCF7L2 mutations may be associated with a reduced incretin response**

- Increasing GLP-1 levels, either by the administration of an analogue (glucagon-like peptide-1, GLP-1 mimetics, e.g. exenatide) or inhibiting its breakdown (dipeptidyl peptidase-4 ,DPP-4 inhibitors - the gliptins), is therefore the target of two recent classes of drug.

GLP is a confusing misnomer: Glucagon raises glucose and FFA levels. GLP decreases glucagon.

Incretin response in type 1 DM

In new onset type 1 diabetes, a paradoxical incretin response to mixed meal testing is seen, where **a rise in glucagon occurs**. **Elevated glucagon** and consequent gluconeogenesis and glycogenolysis is thought to drive further negative impact on remaining beta cells, accelerating their demise

Glucagon-like peptide-1 (GLP-1) mimetics (e.g. exenatide)

Exenatide = Glucagon-like peptide-1 (GLP-1) mimetic

Exenatide causes vomiting

GLP analogs such as exenatide, liraglutide, slow gastric emptying, promote weight loss and lower glucose

- **Example**
  - **Exenatide, Liraglutide**
- **Metabolic effects**
  - increase insulin secretion
  - inhibit glucagon secretion.
  - inhibits glucose production in the liver,
  - slows gastric emptying
  - **Suppresses appetite**

- **Indications**
  - **NICE state that:** *Consider adding exenatide to metformin and a sulfonylurea if:*
    - ***BMI >= 35 kg/m*** *in people of European descent and there are problems associated with high weight, or*
    - *BMI < 35 kg/m and insulin is unacceptable because of* ***occupational implications*** *or weight loss would benefit other comorbidities.*

- **Advantages**
  - **typically result in weight loss**, in contrast to many medications such as insulin, sulfonylureas and thiazolidinediones.
    - promote approximately 3% weight loss over a 6 month period.
    - weight loss of approximately 6% at 6 months can be achieved with liraglutide 1.8 mg.
  - **improving glycaemic control, with modest weight loss, without increasing the risk of hypoglycaemia compared with uptitration of insulin.**
    - reduce HbA1c by similar levels to basal insulin, without increasing the risk of hypoglycaemia,
- **Advantages of liraglutide over exenatide**
  - liraglutide is only needs to be **given once a day** (long-acting).
    - exenatide must be given by subcutaneous injection within 60 minutes before the morning and evening meals. It should not be given after a meal.
  - **liraglutide can be used in renal impairment with an estimated glomerular filtration rate [eGFR] as low as 30 mL/min/1.73 m2.**
    - **exenatide are not recommended in patients with severe renal impairment**
- **Administration**
  - administered subcutaneously.
  - **Combination of GLP-1 and DPP- 4 inhibitors**
    - **trials of DPP- 4 inhibitor and GLP-1 together suggest no added efficacy versus GLP-1 alone.**
  - Both exenatide and liraglutide may be combined with metformin and a sulfonylurea.
  - Standard release exenatide is also licensed to be used with basal insulin alone or with metformin.
- **Ongoing prescription of GLP-1 mimetics**
  - NICE like patients to have achieved a 1% reduction in HbA1c and 3% weight loss after 6 months to justify the ongoing prescription of GLP-1 mimetics.
  - **nice advice that this should only be continued if after six months HbA1c reduces by at least 11 mmol/mol**
- **Adverse effects**
  - nausea and vomiting (the major adverse effect).
  - severe **pancreatitis** in some patients.
  - **Liraglutide** is associated with an approximately 7 beats per minute **increase in heart rate** versus control in diabetes

The preferred pathway for glucose management according to the NICE guidelines is to add insulin to the combination of metformin and a sulphonylurea. However, **where weight is of particular concern (BMI >35), exenatide may be considered as an alternative**. **It can also be used where insulin would interfere with a patient's occupation**.

When to choose exenatide as an alternative to insulin or sulphonylurea as first choice add-in options to metformin?
→ morbid obesity
→ **or risk of hypoglycaemia, (eg : HGV drivers)**

Current NICE guidance suggests the use of GLP-1 mimetics only if BMI is above 35 and there are specific medical or psychological problems associated with high body weight.

Dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g. Vildagliptin, sitagliptin)

Gliptins = Dipeptidyl peptidase-4 (DPP-4) inhibitors

- **Members**
  - Vildagliptin, Sitagliptin, Saxagliptin, Linagliptin and Alogliptin
- **Action**
  - **Dipeptidyl peptidase-4 (DPP-4) inhibitors**
  - **induce Glucose dependent glucagon suppression**
- Indications
  - only recommended as **second-line** therapy with metformin **if patients are at significant risk of hypoglycaemia** or its consequences (e.g. older patients, those working at heights or heavy machinery, isolated patients) or if a sulphonylurea is not tolerated or contraindicated.
- **NICE guidelines on DPP-4 inhibitors**
  - continue DPP-4 inhibitor only if there is a reduction of > 0.5 percentage points in HBA1c in 6 months
  - NICE suggest that a DPP-4 inhibitor might be preferable to a thiazolidinedione if further weight gain would cause significant problems, a thiazolidinedione is contraindicated or the person has had a poor response to a thiazolidinedione
- **Advantages**
  - oral preparation
  - well tolerated with no increased incidence of hypoglycaemia
  - do not cause weight gain
  - We can use them all in CKD but with dose adjustment (**Only linagliptin does not need dose adjustment in any stage of CKD**)
- **Side effects**
  - **GI disturbance** is reported across a range of sitagliptin studies, including nausea, flatulence, diarrhoea and constipation.
    - This is not surprising given that GLP-1, the degradation of which is blocked by sitagliptin, a DPPIV inhibitor, delays gastric emptying.

SGLT2 inhibitors (- gliflozin)

- Examples include cana**gliflozin**, dapa**gliflozin** and empa**gliflozin**
- **Mode of action**
  - **reversibly** inhibit sodium-glucose co-transporter 2 (SGLT2) **in the renal proximal convoluted tubule** to reduce glucose reabsorption and increase urinary glucose excretion.
- **Advantages**
  - **promotes greater weight loss (**modest calorie spillage into the urine)
    - **there for it is better than gliptins in obese patient who not achieve control by metformin**
  - has positive effects on blood pressure control.
    - **Sodium loss → the most likely cause of the fall in blood pressure** some four weeks after therapy initiation**.**
  - associated with positive cardiovascular outcomes.
  - reduce uric acid, which may over the longer term reduce nephropathy progression
- **Adverse effects**
  - glycosuria
    - urine dip sticks will test positive for glucose.
    - ↑ glucose in the urine → predispose to bacterial growth.
      - **recurrent urinary infections**
      - genital infection
        - these medications are **contra-indicated in patients with recurrent thrush**.
  - diabetic ketoacidosis
    - **may contribute to developing diabetic ketoacidosis**
    - **patients may present with euglycaemic ketoacidosis**
  - **increased risk of bone fracture**
    - SGLT-2 inhibitors → ↑**PTH** → ↑bone turnover →↑ risk of bone fracture.
    - SGLT-2 inhibitors → ↑ fibroblast growth factor (FGF-23) → ↓vitamin D → ↓bone mineralisation.

Alpha-glucosidase inhibitors

- These are **acarbose** and **miglitol.**
- **MOA**
  - **inhibits intestinal α-glucosidase**, which therefore delays the digestion and absorption of starch and sucrose.
  - **has a modest effect on the absorption of sugars from the gut,**
- **Advantage of acarbose**
  - in impaired glucose tolerance:
    - reduction in risk of new onset type 2 diabetes of 25%
    - **reduction in cardiovascular events of 49%**
- **Side effects**

- They can lead to diarrhea, abdominal pain, bloating, and **flatulence** in much the same way as lactose intolerance.
- MECHANISM OF DIARRHEA WITH GLUCOSIDASE INHIBITORS
  - When acarbose and miglitol block glucose absorption, the sugar remains in the bowel, available to bacteria. When bacteria eat the glucose, they cast off gas and acid. Using glucosidase inhibitors is like making a person lactose intolerant.

Diabetic ketoacidosis (DKA)

Epidemiology

- **Approximately 25% of patients with type 1 diabetes will first present in diabetic ketoacidosis**

Pathophysiology

- **What is the primary cause of ketoacidosis in type 1 diabetes?**
  - ➔ **Lipolysis**
- **Precipitating factors leading to diabetic ketoacidosis (DKA) are:**
  - Infection (30-40%) The most common precipitating factor
  - **Non-compliance with treatment (25%)**
  - Alterations to insulin dose (13%)
  - Newly diagnosed diabetes (10-20%)
  - Myocardial infarction (< 1%)

- **The drugs implicated in precipitating diabetes as well as diabetic ketoacidosis.**
  - **atypical antipsychotics such as olanzapine**
  - thiazide diuretics
  - beta sympathomimetics, and
  - steroids.

Features

- abdominal pain
- polyuria, polydipsia, dehydration
- Kussmaul respiration (deep hyperventilation)
- Acetone-smelling breath ('pear drops' smell)
- **serum sodium** is **falsely low** due to the osmotic load of glucose.

Diagnostic criteria

American Diabetes Association (2009)	Joint British Diabetes Societies (2013)	Nice guidelines (2015)
• glucose > 13.8 mmol/l • pH < 7.30 • serum bicarbonate <18 mmol/l • anion gap > 10 • ketonaemia	• glucose > 11 mmol/l or known diabetes mellitus • pH < 7.3 • bicarbonate < 15 mmol/l • ketones > 3 mmol/l or urine ketones ++ on dipstick	• acidosis (indicated by blood pH < 7.3 or bicarbonate < 18 mmol/l) **and** • ketonaemia (indicated by blood beta-hydroxybutyrate **>** 3 mmol/l) **or** ketonuria **≥ ++** • Diagnose severe DKA if pH **<** 7.1.

A raised amylase in the absence of frank pancreatitis is common in patients with diabetic ketoacidosis (DKA), No specific management is required and amylase falls with rehydration and control of blood glucose.

Very high glucose artificially drops sodium level → Pseudohyponatremia

Mechanism of hyperkalemia in DKA

- Hyperkalemia is from transcellular shift of potassium out of the cell in exchange for hydrogen ions going into the cell. The cells "suck up acid" as a way of compensating for the severe metabolic acidosis and release potassium in exchange.
- Also, insulin drives potassium into cells with glucose.
- Although plasma potassium is significantly elevated in DKA, total body potassium stores are depleted. This is due to transcellular shift of potassium from intracellular sites to the plasma, resulting in excess loss of solutes with water in the urine, which may lead to hypovolemic shock.
- Note that acidemia can also cause hyperkalemia via exchange of potassium for protons in the serum. The mechanism for this is not entirely clear.

- Cause of hyperkalemia → transcellular shift of potassium out of the cell in exchange for hydrogen.
- Cause of ↓ total body K stores → excess loss of solutes with water in the urine.
- Cause of hypokalemia during DKA treatment → insulin drives potassium into cells with glucose.

MECHANISM OF INCREASED ANION GAP

- In the absence of insulin, glucose can't enter, and cells look for an alternate fuel source. The alternate fuel is FFA and ketones.
- Ketones are negatively charged acids, so using them as fuel drives down the level of bicarbonate.

Acidosis = Hyperkalemia
Alkalosis = Hypokalemia

In a patient with DKA, the total body level of potassium is low. Chronic hyperkalemia depletes the potassium of the body.

Parameters indicate severe DKA: (suggest intensive care admission)

- pH < 7
- Blood ketone > 6 mmol/L
- Bicarbonate < 5 mmol/L
- Anion gap >16 mmol/l
- **Potassium < 3.5 mmol/L on admission**
- Tachycardia or bradycardia
- Systolic blood pressure <90 mmHg
- Oxygen saturation <92% on air
- GCS < 12

Management

- **Fluid replacement:**
  - ❖ Assume a 5% fluid deficit in children and young people in mild or moderate DKA (indicated by a blood pH of 7.1 or above)
  - ❖ Assume a 10% fluid deficit in children and young people in severe DKA (indicated by a blood pH below 7.1)

  - ➢ Most patients with DKA are deplete around 5-8 litres. **The typical fluid deficit associated with DKA is approximately 6 litres.**
  - ➢ Isotonic saline is used initially
  - ➢ The initial half of this amount is derived from intracellular fluid and precedes signs of dehydration, while the other half is from extracellular fluid and is responsible for clinical signs of dehydration.
  - ➢ Appropriate fluid replacement requires 1 litre of normal saline over the first 1/2 hour, then 1 litre over the next hour, then 1 litre over the next two hours followed by 1 litre every 4 hours depending on the degree of dehydration.

- Nice 2015 recommend: When calculating the fluid requirement for people with DKA, assume:
  - a 5% fluid deficit in mild to moderate DKA (indicated by a blood pH of 7.1 or above)
  - a 10% fluid deficit in severe DKA (indicated by a blood pH below 7.1).
- Calculate the maintenance fluid requirement
  - if they weigh less than 10 kg, give 2 ml/kg/hour
  - if they weigh between 10 and 40 kg, give 1 ml/kg/hour
  - if they weigh more than 40 kg, give a fixed volume of 40 ml/hour.
- Aim to replace the fluid deficit over the first 48 hours because faster rehydration is associated with an increased risk of cerebral oedema.
- Use 0.9% sodium chloride until the plasma glucose is below 14 mmol/litre.
- all fluids (except any initial bolus) administered with 40 mmol/litre potassium chloride, unless they have renal failure.
- Change fluids to 0.9% sodium chloride with 5% glucose and 40 mmol/litre potassium chloride once the plasma glucose concentration falls below 14 mmol/litre
- **JBDS example of fluid replacement regime for patient with a systolic BP on admission 90mmHg and over:**

Fluid	Volume
0.9% sodium chloride 1L	1000ml over 1st hour
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours

Fluid	Volume
0.9% sodium chloride 1L with potassium chloride	1000ml over next 6 hours

- Note that slower infusion may be indicated in young adults (aged 18-25 years) as they are at greater risk of cerebral oedema.

- **Insulin**:
  - Root and dose?
    - an intravenous soluble infusion should be started at 0.1 unit/kg/hour.
  - best time for starting?
    - nice 2015 recommend: Start an intravenous insulin infusion 1–2 hours after beginning intravenous fluid therapy
  - Rate?
    - Latest guidance recommends use of a **fixed rate insulin regime**, **not a sliding scale**.
      - 0.1 unit/kg/hr based on estimate of weight
      - 50 units human soluble insulin (Actrapid or Humulin S) made up to 50 ml with 0.9% sodium chloride solution
      - Once blood glucose is < 15 mmol/l an infusion of 5% dextrose should be started
      - If patient normally takes **long acting insulin analogue (Lantus, Levemir) continue at usual dose and time.**
    - Guidelines suggest that **insulin infusion rate should only be increased if blood ketones are not falling at >0.5 mmol/h.**
    - Do not give bolus doses of intravenous insulin.

pH >7.3 and ketones <0.3 mmol/L define resolution of DKA, at which time a patient can be converted back to subcutaneous insulin.

- **correction of hypokalaemia**

JBDS potassium guidelines

Potassium level in first 24 hours (mmol/L)	Potassium replacement in mmol/L of infusion solution
Over 5.5	Nil
3.5-5.5	40
Below 3.5	Senior review as additional potassium needs to be given

- **Bicarbonate:**
  - The role of bicarbonate in DKA is controversial.
  - The acidosis usually corrects itself once the fluid and electrolyte balance is restored.
  - Some physicians administer bicarbonate if there is severe acidosis (pH < 7). However, rapid correction of acidosis might impair cardiac function.
  - There is no evidence to support bicarbonate use in a patient with a pH greater than 7.0.
  - Intravenous bicarbonate should be given **if the blood pH is lower than 6.9.**
  - In practice for DKA, sodium bicarbonate is only really considered in the peri-arrest situation.
- **S/c low-molecular weight heparin**
  - DKA → increased risk of venous thromboembolism because of volume depletion, hyperglycaemia and their decreased conscious level.

Complications of DKA and its treatment

- gastric stasis
- **cerebral oedema**
  - the leading cause of death in children with DKA
  - The risk is highest in paediatric (1%) and adolescent patients, and is rarer in adults.
  - Exact pathogenic mechanism remains unknown – multifactorial
  - May be iatrogenic due to incorrect fluid therapy
  - ↑glucose → ↑osmolar gradient results in water shift from the intracelluar fluid (ICF) to the extracellular fluid (ECF) space and contraction of cell volume. Correction with insulin and I.V fluids → rapid reduction in osmolarity → reversal of the fluid shift → cerebral edema.
  - Thus the warning signs of cerebral oedema - headache, lethargy, confusion, reduced conscious level, incontinence, pupillary changes - must be considered in this patient group.
  - early manifestations:
    - headache
    - agitation or irritability
    - unexpected fall in heart rate
    - increased blood pressure.
  - treatment with mannitol (20%, 0.5–1 g/kg over 10–15 minutes) **or** hypertonic sodium chloride (2.7% or 3%, 2.5–5 ml/kg over 10–15 minutes).
  - Immediately treat for cerebral oedema if person with DKA develops any of these signs:
    - deterioration in level of consciousness
    - abnormalities of breathing pattern, for example respiratory pauses
    - oculomotor palsies
    - pupillary inequality or dilatation.
- thromboembolism
- acute respiratory distress syndrome
- arrhythmias secondary to hyperkalaemia/iatrogenic hypokalaemia

- acute kidney injury

Prognosis

- Whilst DKA remains a serious condition mortality rates have decreased from 8% to under 1% in the past 20 years.
- **The mortality associated with the modern management of diabetic ketoacidosis ➔ 1-2%**
- Specifically, mortality relates to cerebral oedema.

January 2008 exam: A patient weighs 80 kg. Presented with a feature of DKA. One litre of 0.9% saline is infused and an intravenous insulin pump is set-up. What rate should insulin be initially given? 8 unit / hour (The Joint British Diabetes Societies produced guidelines in 2010 recommending starting the insulin infusion at a rate of 0.1 unit/kg/hour)

Hypoglycaemia

- Hypoglycaemia is defined as a plasma glucose concentration < 2.5 mmol/l

Causes

- **↑ Insulin with ↓ C-Peptide level points to a diagnosis of insulin abuse**
- **C-Peptide level ↑ with Sulfonylurea abuse**
- insulinoma - increased ratio of proinsulin to insulin
- self-administration of insulin/sulphonylureas
  If C peptide is undetectable → Exogenous insulin administration (as the C peptide is released with endogenous insulin)
- liver failure
- Addison's disease
- Alcohol
- Glucokinase activators may lead to both enhanced insulin release and glycogen storage in the liver, as such they are known to cause hypoglycaemia. No glucokinase activators have yet made it to the clinic.
- **Other possible causes in children**
  - nesidioblastosis - beta cell hyperplasia

features

- **nocturnal hypoglycaemia → vivid dreams** → REM sleep disruption → daytime weakness and somnolence

Standard work-up for hypoglycaemia should include:

- Laboratory (not test-strip) blood glucose measurement
- Liver function tests to rule out significant liver dysfunction
- Blood alcohol and alcohol history
- Cortisol levels, with or without Synacthen testing
- Insulin and C-peptide levels taken during an attack
- Chest X-ray to exclude occult malignancy

- In health, **serum insulin concentration** falls to low values during fasting: the combination of fasting hypoglycaemia and hyperinsulinaemia suggests that insulin is causing the hypoglycaemia.
- Measurement of **C-peptide** is important to exclude a diagnosis of self-administration of insulin: insulin for therapeutic use does not contain C-peptide, which is released from pancreatic islet cells during insulin secretion.

Management

- For patient who are able to swallow, give fast-acting form of glucose.
- **Large-bore venous access should be achieved and blood samples taken for serum glucose, liver function, ethanol, Cortisol, insulin, C-peptide, proinsulin and sulphonylurea levels.**
- **If the patient's Glasgow Coma Score (GCS) is under 13, then 60-80 ml 20% glucose should be given intravenously.**
- If a patient's Glasgow Coma Scale Score is reduced oral routes of glucose replacement are likely to be inappropriate due to the risk of aspiration.
- 50% intravenous dextrose is contra-indicated due to difficulties with intravenous access, the intravenous flow of 50% dextrose, and risks of phlebitis.
- **The most appropriate treatment to correct hypoglycemia is treatment with 10% intravenous dextrose.**
- **Glucagon** (1 mg intramuscularly) can be administered if no intravenous access can be obtained.
  - Can be given by a family member or friend
  - Glucagon acts mainly on the liver by **Activates adenylate cyclase** → increases glycogenolysis and gluconeogenesis
  - Activation of **adenylate cyclase** is responsible for rapid correction of hypoglycaemia
  - Glucagon acts also via cyclic AMP to stimulate lipolysis in adipose tissue, producing free fatty acids that can act as a major source of energy.

September 2011 exam: An 18-year-old girl is admitted with hypoglycaemia (RBS: 1.9 mmol). her father who has type 2 DM describes a number of similar episodes.Insulin15 mg/ml (6-10 mg/ml)Proinsulin22% (22-24%) C-peptide 0.15 nmol/l (0.2-0.4 nmol/l).What is the most likely diagnosis? Insulin abuse (The raised insulin with low c-peptide level points to a diagnosis of insulin abuse. C-peptide levels would be raised in a patient following sulfonylurea abuse)

Somogyi effect vs Dawn phenomenon

- Somogyi effect: Nocturnal hypoglycemia leading to a surge of counterregulatory hormones, leading in turn to hyperglycemia in the morning.
- Dawn phenomenon: Nocturnal secretion of GH leading to early-morning hyperglycemia
- Somogyi: high dose insulin → hypoglycemia at midnight → body adjusts it by releasing Epinephrine, Norepinephrine, Cortisol, glucagon → Hyperglycemia in the morning → treatment by insulin dose modification.
- Dawn phenomenon: normal nocturnal glycemia, but hyperglycemia due to increased GH in the morning → no treatment.

Differentiate between them by:

- Nocturnal glycaemia: low → Somogyi, normal is Dawn. Both have hyperglycemia in the morning.
- DECREASE the insulin at night: Then check morning glucose:
  - If the glucose ↑↑ → Dawn Phenomenon. (not enough Insulin or not the right type at pm)
  - If the glucose is normal or ↓↓ → Somogyi.
    (NEVER INCREASE the Insulin dose, because if the patient has Somogyi, we could end up putting him in a coma)

Hypoglycaemia unawareness

- Hypoglycaemia unawareness is more common in patients with **intensively controlled diabetes** of long duration, but can occur in any person with diabetes **as a consequence of diminished counter-regulatory responses to recurrent hypoglycaemia.**
- **Alcohol inhibits gluconeogenesis, decreases peripheral hypoglycaemic responses and impairs perception of symptoms of hypoglycaemia.**
- There is no evidence to suggest that beta-blockers cause hypoglycaemia unawareness.
- Glucose sensing occurs in the hypothalamus, and there is evidence to suggest that chronic, and recurrent hypoglycaemia may have deleterious effects on higher cerebral function.
-

Factitious hypoglycaemia

- **↑↑ insulin + normal C-peptide → abuse of exogenous insulin**
- if C-peptide levels also elevated, then the logical **next step** → urine test for the metabolites of sulphonylurea

Hypoglycaemic episodes after regular exercise in patient who takes BD mixed insulin:

- **the most appropriate next step in his management is → transfer to a basal bolus regime**
  - change to a basal bolus regime where he can alter his short acting insulin dose just prior to planning exercise.

Hyperosmolar hyperglycaemic state (HHS)

- Hyperosmolar hyperglycaemic state (HHS) is **a complication of type 2 diabetes**
- In general **there is enough insulin in patients with type 2 diabetes to suppress ketogenesis,** but insufficient to prevent hyperglycaemia and the hepatic resistance to glucagon.
- Two-thirds of people with Hyperosmolar hyperglycaemic state are presenting with type 2 diabetes mellitus for the first time.
- The risk of mortality in HHS is 10-20%, with a strong predilection to thrombotic events.

- In general, HHS results in osmotic fluid shift to the intravascular space.
- Urinalysis reveals increased specific gravity denoting dehydration.

Confirmed by:

- Dehydration
- Osmolality >320mosmol/kg
  - calculated osmolality of mOsm/kg = [2(Na+K) + glucose + urea]
- Hyperglycaemia >30 mmol/L with pH >7.3, bicarbonate >15mmolL and no significant ketonenaemia <3mmol/L

Management

- Fluid management is essential
  - The initial goal is repletion of extracellular volume; the **1 litre of 0.9% saline** will start to restore this, as it remains in the extracellular compartment; this is suggested by the mild hypotension and absent postural drop - if these were still persistent that would indicate a need for further volume expansion.
  - Once this has been achieved in patients who are hyperosmolar given the hypernatraemia, the appropriate agent is **0.45% saline** which replaces intra and extracellular fluid loss, which is similar in composition to the fluid lost during the osmotic diuresis.
  - 5% dextrose should be added when blood glucose reaches 15 mmol/L.
  - Electrolytes should be checked 2-4 hourly, aiming a decrease of Na of no quicker than 10 mmol/day, and patients managed in a high care environment.
- Insulin
  - **The aim is to reduce glucose levels by approximately 3 mmol/hour.**
  - Patients with HONK are often sensitive to insulin replacement and doses can be much lower than those required for DKA.
  - insulin replacement of 0.15 IU/kg/hour is recommended as an initial guide.
  - After getting over their episode of hyperosmolar hyperglycaemic state it is likely that their insulin requirement will fall. Hence as a starting insulin dose it would be most sensible to **begin with around 2/3rds of the total dose required during the episode of hyperosmolar hyperglycaemic state**, split morning and evening.

Diabetes mellitus: hypertension management

Antihypertensive therapy is the single intervention most likely to reduce the overall risk of both microvascular and macrovascular events

- **Lipid** lowering therapy → prevent **macrovascular** events, but has no effect on microvascular events.
- **Lowering HbA_{1c}** only resulted in → a significant reduction in **microvascular** events

- **Hypertension in type 2 diabetes is primarily associated with hyperinsulinaemia and insulin resistance**

Pathophysiology

- Hyperinsulinaemia directly stimulates sympathetic nervous system activity, increasing renal sodium reabsorption and promoting vascular smooth-muscle proliferation.
- Insulin resistance is also associated with the reduced activity of nitric oxide synthase, leading to reduced vasodilation in response to vascular stress.
- Red cell sodium-lithium countertransport activity abnormalities are associated with the early development of hypertension in type 1 diabetes.

NICE recommend the following blood pressure targets for type 2 diabetics:

- **targets for type 2 diabetics**
  - if end-organ damage (e.g. renal disease, retinopathy) < 130/80 mmHg
  - otherwise < 140/80 mmHg
- Patients who were more tightly controlled had a slightly reduced rate of stroke but otherwise outcomes were not significantly different.
- Because ACE-inhibitors have a renoprotective effect in diabetes they are the first-line antihypertensives recommended for NICE.
- Patients of African or Caribbean family origin should be offered an ACE-inhibitor plus either a thiazide diuretic or calcium channel blocker.
- Further management then reverts to that of non-diabetic patients, as discussed earlier in the module.
- Remember that autonomic neuropathy may result in more postural symptoms in patients taking antihypertensive therapy.
- The routine use of beta-blockers in uncomplicated hypertension should be avoided, particularly when given in combination with thiazides, as they may cause insulin resistance, impair insulin secretion and alter the autonomic response to hypoglycaemia.

ACE inhibitors are first-line for hypertension in diabetics, irrespective of the patients age

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Diabetes associated with pancreatitis is due to damage to the endocrine pancreas and associated lack of insulin. the patient's presentation: thin, with symptoms of insulinopaenia. As such, **exogenous insulin replacement is the only appropriate intervention**

Diabetic nephropathy

Basics

- commonest cause of end-stage renal disease (ESRD) in the western world
- In type 1 diabetes microalbuminuria usually occurs 5-15 years after the diagnosis of diabetes mellitus.
- **The peak incidence of frank albuminuria is 17 years after diagnosis of type 1 diabetes**

- The majority of patients with diabetic nephropathy have type 2 diabetes, however this is due to higher prevalence of type 2, rather than higher incidence of nephropathy (as incidence is in fact higher in type 1 DM).
- Diabetic nephropathy develops in approximately 40% of patients with type 1 diabetes and in 5% to 40% of patients with type 2 diabetes.
- It is reasonable to expect a fall in the glomerular filtration rate (GFR) of 1 ml/minute per month once the serum creatinine level has reached around 200 pmol/l.
- 40% of deaths of patients with nephropathy are due to cardiovascular disease.
- **Glomerulosclerosis the most common renal complication of DM**
  - Typically, there is thickening of the glomerular basement membrane and glomerulosclerosis that may be diffuse or nodular (Kimmelstiel-Wilson disease)
  - Kimmelstiel-Wilson disease is characterised by hyaline masses in the mesangial core of the glomerular lobules.These masses consist of lipids and fibrin
    - **What is the renal biopsy finding would be diagnostic of diabetic related kidney injury?**

➔ **Kimmelstiel-Wilson lesion**

Pathophysiology is poorly understood, however:

- changes to the haemodynamics of the glomerulus is thought to be key, which leads to an increased glomerular capillary pressure
- **histological changes** include: basement membrane thickening, capillary obliteration, mesangial widening. Nodulular hyaline areas develop in the glomuli - Kimmelstiel-Wilson nodules
  - **Kimmelstiel-Wilson lesion is the only biopsy finding that is specific & diagnostic to diabetic related kidney disease.**

MECHANISM OF GLOMERULAR DAMAGE

- Uncontrolled diabetes removes the negative charge from the filtration slits of the glomerular basement membrane.
- Normally, negative charges repel (يمنع) the filtration of albumin, which is also negatively charged.
- Loss of negative charges allows albumin to pass through the glomerulus.
- ACE inhibitors decrease intraglomerular hypertension by dilating the efferent arteriole. This protects the glomerulus from the damage caused by intraglomerular hypertension.

Risk factors for developing diabetic nephropathy

Modifiable	Non-modifiable
Hypertension Hyperlipidaemia Smoking Poor glycaemic control Raised dietary protein	Male sex Duration of diabetes Genetic predisposition (e.g. ACE gene polymorphisms)

Screening

- all patients should be screened annually
- albumin:creatinine ratio (ACR) in early morning specimen
- ACR > 2.5 = microalbuminuria

Diabetic nephropathy: stages occurring in five stages*:

Stage	Description
Stage 1	• hyperfiltration: increase in GFR • may be reversible
Stage 2 (silent or latent phase)	• most patients do not develop microalbuminuria for 10 years • GFR remains elevated
Stage 3 (incipient nephropathy)	• microalbuminuria (albumin excretion of 30 - 300 mg/day, dipstick negative)
Stage 4 (overt nephropathy)	• persistent proteinuria (albumin excretion > 300 mg/day, dipstick positive) • hypertension is present in most patients • histology shows diffuse glomerulosclerosis and focal glomerulosclerosis (Kimmelstiel-Wilson nodules)
Stage 5	• end-stage renal disease, GFR typically < 10ml/min • renal replacement therapy needed

*The timeline given here is for type 1 diabetics. Patients with type 2 diabetes mellitus (T2DM) progress through similar stages but in a different timescale - some T2DM patients may progress quickly to the later stages

Management

Optimal glycaemic and blood pressure control is the most important step

The best therapeutic option to prevent progression of renal disease → Treat with ACEI (superior to glycaemic control)

- dietary protein restriction
  - ➢ Do not offer low-protein diets (dietary protein intake less than 0.6–0.8 g/kg/day) to people with CKD. [new 2014] nice guidelines
  - ➢ The evidence for a low protein diet exists for overt proteinuria but not microalbuminuria.
- tight glycaemic control
  - ➢ The evidence for good glycaemic control in the treatment of microalbuminuria in patients with type 1 diabetes suggests no clear benefit
- BP control: aim for < 130/80 mmHg

- benefits independent of blood pressure control have been demonstrated for ACE inhibitors (ACE-i) and angiotensin II receptor blockers (A2RB).
  - ACEi or A2RBs are the treatment of choice for hypertension in diabetic nephropathy
  - Combinations of ACE-i and A2RB are not recommended → ↑side effects → worse outcomes.
  - ACEi can potentiate the hypoglycaemic effect of insulin and oral antidiabetic agents, especially during the first few weeks of use.
  - ACEi should be used under specialist supervision if the creatinine concentration is > 150 pmol/l, and the renal function and potassium levels should be monitored.
- Non-dihydropyridine calcium antagonists, eg diltiazem, may have additional effects in reducing proteinuria
  - amongst the calcium antagonist class, only **diltiazem** has been shown to impact significantly on proteinuria.
- control dyslipidaemia e.g. Statins

Prognosis

- Without intervention nephropathy is likely to deteriorate with the development of macroalbuminuria. In association with the latter, renal function declines about 10% per year, ending in end-stage renal disease.
- **The deterioration in GFR/year if BP is well controlled is 4 ml/min/year.**
- Proteinuria in the absence of reduced GFR is associated with approximately 20% progression to nephropathy over five years.
- End-stage renal failure is said to occur some 7-10 years after diagnosis of albuminuria, but improved management of hyperglycaemia and hypertension might stretch this period a little.
- 33% of patients with type 1 diabetes mellitus have diabetic nephropathy by the age of 40 years
- approximately 5-10% of patients with type 1 diabetes mellitus develop (ESRD)
- percentage of diabetics with diabetic nephropathy would be expected to progress to ESRD
  Type 1 ➔ 50%.
  Type 2 ➔ 15%

Diabetic retinopathy

- The most common cause of blindness in adults aged 35-65 years-old.
- **About 80% of patients with type I diabetes will have retinopathy 10 years after presentation. By contrast, in type II diabetes, where the time of onset is uncertain, up to 25% of patients will have retinopathy at the time of diagnosis.**
- **the most likely cause of blurred vision in a newly diagnosed diabetic who was previously fit and well is → Osmotic changes in the lens**
- **Rapid improvement in blood glucose levels may be associated with worsening of diabetic eye disease.**

Pathogenesis

- Hyperglycaemia → ↑ retinal blood flow & abnormal metabolism in the retinal vessel walls → damage to endothelial cells & pericytes

- Endothelial dysfunction → ↑ vascular permeability → exudates (seen on fundoscopy).
- **Pericyte dysfunction** → predisposes to the formation of **microaneurysms.**
- retinal ischaemia → **production of growth factors** → **Neovasculization**

Classification

The earliest sign of diabetic retinopathy is the presence of microaneurysms on fluorescein angiography.

Recently a new classification system has been proposed, dividing patients into those with non-proliferative diabetic retinopathy (NPDR) and those with proliferative retinopathy (PDR):

Traditional classification	New classification
Background retinopathy • microaneurysms (dots) • blot haemorrhages (<=3) • hard exudates **Pre-proliferative retinopathy** • cotton wool spots (soft exudates; ischaemic nerve fibres) • > 3 blot haemorrhages • venous beading/looping • deep/dark cluster haemorrhages • more common in Type I DM, treat with laser photocoagulation	**Mild NPDR** • 1 or more microaneurysm **Moderate NPDR** • microaneurysms • blot haemorrhages • hard exudates • cotton wool spots, venous beading/looping and intraretinal microvascular abnormalities (IRMA) less severe than in severe NPDR **Severe NPDR** • blot haemorrhages and microaneurysms in 4 quadrants • venous beading in at least 2 quadrants • IRMA in at least 1 quadrant

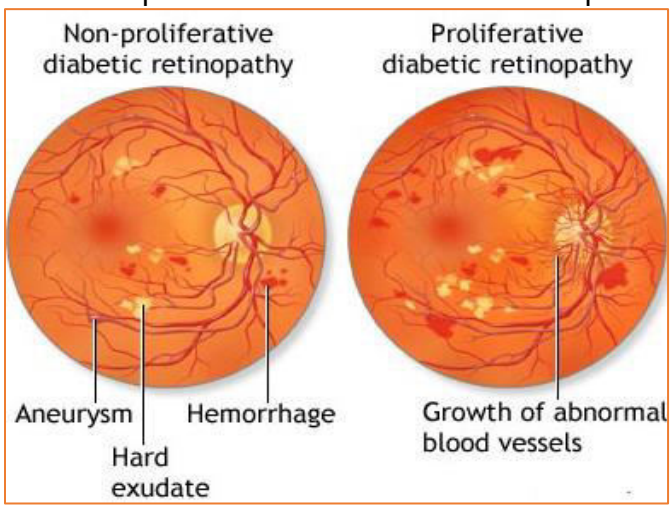
Proliferative retinopathy⟶ (**urgent referral to an ophthalmologist for pan-retinal photocoagulation**)

- retinal neovascularisation - may lead to vitrous haemorrhage
- fibrous tissue forming anterior to retinal disc
- more common in Type I DM, 50% blind in 5 years
- **Normal visual acuity is seen in proliferative retinopathy**
- **urgent referral to an ophthalmologist (seen within one week) is required if there is proliferative retinopathy or there is evidence of clinically significant macular oedema (hard exudates at the fovea).**

Maculopathy

- based on location rather than severity, anything is potentially serious
- hard exudates and other 'background' changes on macula
- The exudates can be arranged in **a ring (circinate exudates)** surrounding a point of capillary leakage.

- This can be shown on fluorescein angiography
- check visual acuity
- more common in Type II DM
- responds to laser treatment at the point of leakage.



- **Cotton wool spots (CWS) represent infarcts of the nerve fibre layer of the retina,** since multiple CWS are a pre-proliferative sign.
- Haemorrhages (or hard exudates) close to the fovea represent a risk of macular oedema and are therefore sight threatening.
- Hard exudates (HE) are collections of exudated lipid and protein.
- Macular oedema is associated with micro-aneurysms and hard exudates and is due to fluid leakage but is not necessarily a feature pre-proliferative or proliferative retinopathy although it may still require laser photocoagulation.
- Microaneurysms (MA) are capillary aneurysms.
- **Venous beading, loops and soft exudates (cotton wool spots) are characteristic of the ischaemia associated with preproliferative diabetic retinopathy.**
- **Soft exudates are a feature of pre-proliferative retinopathy, and despite quite marked new vessel disease the visual acuity may be normal.**

- **New vessels suggest proliferative retinopathy.**
- **Feature necessitate immediate referral to the ophthalmologist**
  → **New vessels anywhere in the fundus**

Treatment

- **Achievement of target HbA1c of 47.54 mmol/mol (6.5%) would be associated with significantly reduced progression of retinopathy.**
- Progression may be slowed with improved **glycaemic and hypertensive control but the latter has been shown to be more effective at reducing progression**

- **Indications for emergency referral to ophthalmologist:**
  - sudden loss of vision
  - rubeosis iridis
  - pre-retinal or vitreous haemorrhage
  - retinal detachment.

- **Indication for urgent referral to the ophthalmologist (seen within one week)**
  - **Hard exudates in the macular region (**evidence of clinically significant macular oedema**)**
  - proliferative retinopathy
  - **Vitreous haemorrhage**
- Laser destroys ischaemic - but viable- retina to reduce the secretion of angiogenic growth factors and allow new vesel regression. it is not applied directly to new vessels as this would cause bleeding.

NHS Diabetic Eye Screening Programme (2015):

- Screening for diabetic retinopathy is offered to all people **aged 12 and over** with type 1 or type 2 diabetes.
- For diabetics at low risk of sight loss, the interval between screening tests should change from one year to two years. The current one year interval should remain unchanged for the remaining people at high risk of sight loss.

Prognosis

The approximate percentage of eyes that will lose useful vision irretrievably within 5 years if not treated :

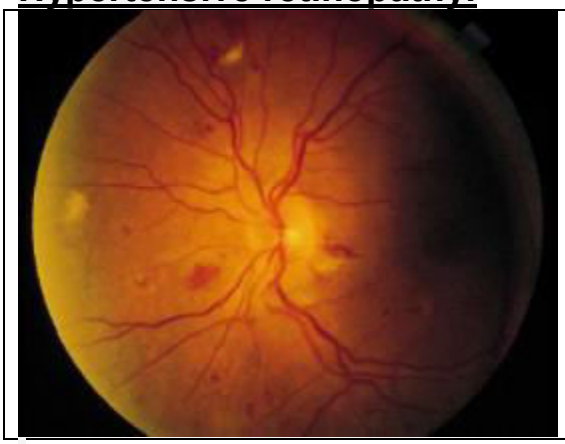
- 3% in those with background retinopathy
- 20% for those with exudative
- 30% for those with pre-proliferative,
- **50% for those with proliferative retinopathy.**

Asymmetric diabetic retinopathy

Asymmetric DM Retinopathy → suspect ocular ischemia (carotid artery disease)

- **Asymmetric diabetic retinopathy** should always raise the suspicion that there is some other cause of ocular ischaemia on the worst-affected side, such as unilateral or asymmetrical carotid artery disease → do **Carotid Doppler**

Hypertensive retinopathy.



The presence of flame and blot haemorrhages, cotton wool spots and blurring of the optic disc margins are typical of the retinal changes that are seen in advanced hypertensive retinopathy.
Whilst some of these findings are also observed in diabetic eye disease (e.g. dot and blot haemorrhages, cotton wool spots), the absence of other features (e.g. hard exudates, venous beading) should alert the clinician to other possible diagnoses.

Diabetic neuropathy

MECHANISM OF NEUROPATHY IN DIABETES

- Nerves have a supply of blood vessels. Diabetes damages small blood vessels, starving off the nerves

- pain and temperature sensation carried through **small fibres** →affected first
- Joint position sense and vibration are carried through **large fibres**, and are therefore affected later.
- Sensory nerves are affected more than motor so often **reflexes remain intact**.
- **Diabetic peripheral neuropathy** usually goes in parallel with retinopathy and nephropathy.
- It is also slowly progressive and affects mainly the spinothalamic pathway.

Treatment: NICE updated it's guidance on the management of neuropathic pain in 2013. Diabetic neuropathy is now managed in the same way as other forms of neuropathic pain:

- first-line treatment: amitriptyline, duloxetine, gabapentin or pregabalin
  - Duloxetine
    - **Duloxetine is preferred to amitryptiline because it is associated with a lower risk of urinary retention.**
    - Duloxetine is first line therapy for neuropathy except where it is **contraindicated** due to:
      - previous hypersensitivity
      - history of glaucoma
      - patients already taking a serotonergic agent, such as **tramadol**, because of the associated risk of serotonin syndrome.
  - Amitriptyline

- Amitriptyline is recommended by NICE as an option for second line therapy in patients for whom home duloxetine is unsuitable.
- Doses of 10-75 mg amitriptyline are usually appropriate, but again is contraindicated here due to history of glaucoma.
- **glaucoma and left bundle branch block are contraindications to TCA use.**

➢ Pregabalin or gabapentin
- Pregabalin or gabapentin can be considered as second or third line monotherapy or in combination.
- **However where there is renal impairment, pregabalin is preferable over gabapentin.**
- **Peripheral neuropathy** with H/O **glaucoma** and on **tramadol** for chronic back pain, what is the best treatment?
  - **Pregabalin**

- if the first-line drug treatment does not work try one of the other 3 drugs
- tramadol may be used as 'rescue therapy' for exacerbations of neuropathic pain
- topical capsaicin may be used for localised neuropathic pain (e.g. post-herpetic neuralgia)
- pain management clinics may be useful in patients with resistant problems

Acute painful neuropathy of rapid improvement of blood glucose control

- rapid improvement of blood glucose control → Acute painful neuropathy (self-limiting) → Simple analgesics (paracetamol, aspirin) and local measures (bed cradles) are recommended as a first step

- **Duloxetine is the standard first line therapy for neuropathy**
  - ➢ The starting dose is 60 mg daily, may be increased up to 120 mg/day.
  - ➢ It cannot be used in patients with a history of acute narrow angle glaucoma.
- Amitriptyline is an alternative option to duloxetine if it is contraindicated; a dose of 10-75 mg/day is recommended.
- pregabalin is recommended either as a second line agent or in combination with amitriptyline.

September 2009 exam: H/O type 2 DM and benign prostatic hypertrophy (BPH) presents with burning pain in his feet. He tried duloxetine but no benefit. What is the most suitable initial management?
Pregabalin (Amitriptyline is first choice but given H/O BPH, it is better to avoid amitriptyline due to the risk of urinary retention).

Diabetic autonomic neuropathy

Features

- marked postural drop (recurrent falls)
- gastrointestinal tract neuropathy → diarrhoea - particularly at night - and intractable vomiting.
- impotence.
- tachycardia

- impaired cardiovascular response to the Valsalva manoeuvre.
- atonic bladder, painless urinary retention and recurrent urinary tract infections.

Gastroparesis

- occurs in 10–20% of diabetics after 10 years.
- **mechanism**
  - The major stimulant for gastric motility is "stretch."
  - In patients with longstanding diabetes, there is impaired ability to perceive stretch in the GI tract and impaired motility.
- **symptoms** include
  - erratic blood glucose control,
  - bloating and vomiting
  - abdominal fullness, constipation.
- **diagnosis**
  - may be confirmed with a **gastric-emptying scan**, but this is often unnecessary.
    - **Isotope gastric motility studies are the most appropriate way to assess gastric emptying**
- **management** options include
  - metoclopramide, domperidone
    - **Domperidone is now the initial intervention of choice**, with metoclopramide having fallen out of favour because of long-term neurological sequelae associated with its use.
    - prokinetic drug has the added effects of increasing locally released acetylcholine at the myenteric plexus.
  - or erythromycin (**prokinetic agents**)
    - Erythromycin increases the release of "motilin," a pro-motility GI hormone.

Impotence

- Autonomic nerve dysfunction is one of the commoner causes of impotence in a person with diabetes
- **The combination of DM and hypogonadotrophic hypogonadism (HH) (low testosterone & FSH)) is compatible with a diagnosis of haemochromatosis and measuring ferritin would be a reasonable investigation.**
- diabetes and impotence associated with high ferritin → haemochromatosis
  - **The next investigation would be measurement of transferrin saturation,**
  - and then, if elevated (above 45%), genotyping (homozygosity for C282y mutations) would next be considered and would be expected to clinch the diagnosis.
- hypotestosteronaemia
  - Hypogonadism is not unusual in the **obese diabetic** nor indeed in the metabolic syndrome and seems to arise as a consequence of a combination of tertiary and primary hypogonadism.

- Low testosterone + normal TSH and LH
- In the first instance, to improve sexual function together with libido, it is probably worthwhile starting transdermal testosterone, probably gel.
- **the most appropriate treatment for this man's erectile dysfunction → Transdermal testosterone**
- If sexual dysfunction persists then sildenafil or any other phosphodiesterase inhibitor would be an appropriate adjunct.

Diabetic amyotrophy

Leg pain, weakness and reduced knee reflexes with an impaired fasting glucose concentration suggests a diagnosis of diabetic amyotrophy → should be confirmed with OGTT.

- Diabetic amyotrophy is also known as **proximal diabetic neuropathy.** The latter term is probably more useful as it describes more accurately the aetiology of the condition.
- Caused by occlusion of the vasa nervorum of the proximal lumbar plexus and/or femoral nerve.
- It is a mixed motor and sensory proximal neuropathy that can cause severe pain (which is responsible for the anorexia and weight loss).
- Occur most commonly in men in their 50s with type 2 diabetes treated with oral hypoglycaemic agents.
- Is not uncommonly a presenting feature of diabetes in the elderly.
- Often associated with poor diabetic control
- May improve with good control (although it often self-resolves with time).
- often affects the femoral nerve, lumbosacral plexus or lumbar roots.

Features

- pain is usually the first symptom, often in the thigh, hips or buttocks
- this is followed by weakness, for example difficulty getting out of a chair
- Often asymmetrical (although it can be bilateral).
- loss of knee reflexes
- Tender & wasting of proximal muscles with diminished reflexes.
- The plantars can become extensor, but this is unusual.
  - Plantar responses may be flexor or extensor.
- There is often little sensory loss.

Investigations

- EMG shows multifocal denervation in paraspinous & leg muscles.

Treatment

- **The mainstay of treatment is supportive care and transference to insulin therapy.**

Post prandial pain in diabetics

- Diabetes, especially Type 2 diabetes, is associated with macrovascular disease.
- Smoking is a further risk factor for macrovascular atherosclerosis.
- **After a meal splanchnic blood flow is increased. If the mesenteric artery is occluded the lack of blood flow to the bowel will produce ischaemic type pain.**

Diabetic foot

2% of patients with diabetes in the community develop new foot ulcers each year

Diabetic foot ulcers can be divided into:

1. **Neuropathic foot**
   - Warm
   - Well perfused with palpable pulses
   - sweating is decreased and the skin may be dry and prone to fissures.
   - typical **neuropathic ulcer**,
     - callus forming the edge
     - clean base.
     - commonly found on the pressure points (i.e. metatarsal heads and the heel).
     - Painless
       - These ulcers are the result of continuous trauma due to the lack of pain..
     - 10% of people have absent dorsalis pedis pulses. Therefore, their absence does not indicate ischaemia.
2. **Ischaemic foot**
   - cool
   - pulseless
   - thin, shiny skin which often lacks hair
   - There may be atrophy of the subcutaneous tissues,
   - Intermittent claudication and rest pain may be absent due to co-existent neuropathy.
   - Ischaemic ulcers found on the dorsa or edges of the feet.
   - the nails are in poor condition.
   - Arterial ulcers typical present in patients with severe atherosclerosis or peripheral vascular disease.
   - Normally, the ulcer starts as a small injury that doesn't heal due to poor blood supply.

Other types of ulcers

- Infected ulcers are mal-odorous and often exude pus.
- **Venous ulcers**
  - usually found on the gaiter area of the ankle.
  - Venous stasis ulcers typically present in the area around the ankle and result from venous reflux.
    - The venous reflux causes congestion and dilated veins, which impair the transport of fresh blood to the area.
  - **Multi-layer bandaging** is most useful in reducing lower limb oedema and improving the chances of healing of venous ulcers.
    - **An ankle brachial pressure index (ABPI) measurement is essential before beginning bandaging**, as if there is significant arterial insufficiency, blood supply to the lower limb may be threatened.

Manifestations

(Range in severity from superficial paronychia to deep infection and gangrene)

- Cellulitis
- Myositis
- Abscesses
- Necrotising fasciitis
- Septic arthritis
- Tendonitis, and
- Osteomyelitis.

Risk factors of foot ulceration in diabetics

- Neuropathy
- vascular insufficiency
- reduced neutrophil function

Factors associated with an increased risk of plantar ulceration,

- neuropathy disability score, loss of 10-g monofilament sensation
- foot deformity
- **However, the strongest predictive factor with respect to future risk of ulceration is either active ulceration or a history of a previous ulcer.**
- **Callus formation at pressure areas is an important predictor of ulceration**
- Plantar ulceration is usually a consequence of neuropathy and minor skin trauma is probably the most common initiating event.

Local signs of wound infection

- Granulation tissue that becomes increasingly friable
- Yellow or grey moist tissue at the base of the ulcer
- Purulent discharge, and
- An unpleasant odour.

Pathogens

- The most common pathogens in acute, previously untreated superficial ulcers in diabetic patients are aerobic Gram positive bacteria (**particularly *Staphylococcus aureus*** and beta-haemolytic *Streptococci*).

- In patients who have recently received antibiotics or who have deep tissue involvement, infection is usually caused by a mixture of aerobic Gram positive, Gram negative (for example, *Escherichia coli*,*Proteus*, *Klebsiella*) and anaerobic organisms (for example, *Bacteroides*, *Clostridium*).
- Methicillin-resistant *Staphylococcus aureus* (MRSA) is more common in patients who have been previously hospitalised or who have received antibiotic therapy, although increasingly it is community acquired.

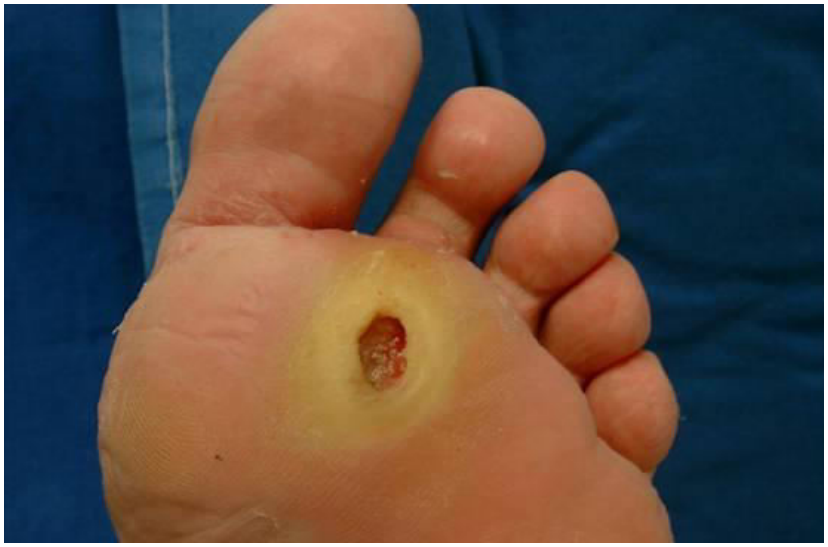
Treatment

- Many leg ulcers have a mixed etiology so arterial and venous function should also be assessed here.
- If infection is suspected, deep swab and tissue samples should be sent for culture and broad-spectrum antibiotics started. The presence of deep infection with abscess, cellulitis gangrene or osteomyelitis is an indication for hospitalisation.
- Indications for urgent surgical intervention are:
  - A large area of infected sloughy tissue
  - Localised fluctuance and expression of pus
  - Crepitus in the soft tissues on radiological examination, and
  - Purplish discolouration of the skin (which indicates subcutaneous necrosis).
- Antibiotic treatment should subsequently be tailored according to the clinical response, culture results and sensitivity.
- If osteomyelitis is present, surgical resection should be considered and antibiotics continued for four to six weeks.
- Blood flow is often decreased with autonomic neuropathy hence sympathectomy may be performed to improve skin blood flow.

Neuropathic & ischaemic picture:

neuropathic foot	ischaemic foot
often warm	Cold foot
Painless or abnormal neuropathic pain.	causes rest pain
bounding pulses	nearly pulseless foot
ulceration tends to occur on the plantar surface	Ulceration tends to be painful and often presents in the heal area
It can be high arched, with toe clawing.	there is often gravity-dependent reddening of the foot, which disappears on elevation of the foot.

The two conditions can coexist, with a mixed ischaemic/neuropathic picture.



This is a typical **neuropathic ulcer**, with callus forming the edge and a clean base.

Adhesive capsulitis

- Adhesive capsulitis (frozen shoulder) is a common cause of shoulder pain. aetiology of frozen shoulder is not fully understood.
- **Adhesive capsulitis is a recognised musculoskeletal complication of diabetes**.
- 40% of diabetic patients developing this problem at some stage.
- occurs more commonly in women after age 50

Feature (typically develop over days)

- Pain (Night pain may interfere with sleep).
  - patients typically have a painful freezing phase, an adhesive phase and a recovery phase
- Restricted both active and passive movement of the shoulder, usually in the absence of intrinsic shoulder disease.
  - The restricted active and passive movements confirm that this patient's problems are either capsular or articular in origin rather than periarticular tendon problems where active movements are generally more restricted than passive movements.
  - external rotation is affected more than internal rotation or abduction
- The shoulder is tender to palpation,
- bilateral in up to 20% of patients
- the episode typically lasts between 6 months and 2 years

Diagnosis:

- Radiographs of the shoulder show osteopenia.

- **The diagnosis is confirmed by arthrography.**

Management

- no single intervention has been shown to improve outcome in the long-term
- treatment options include NSAIDs, physiotherapy, oral corticosteroids and intra-articular corticosteroids

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Charcot's foot (Charcot's arthropathy)

In patients with long-standing diabetes and peripheral neuropathy, a **red hot swollen foot** should raise suspicion of Charcot neuroarthropathy after exclude infection.

- A Charcot joint is also commonly referred to as a neuropathic joint.
- It describes a joint which has become badly disrupted and damaged secondary to a loss of sensation.

Incidence

- Occur in 1 in 750 people with diabetes mellitus, although this increases to 5 in 100 diabetics with documented neuropathy.

Causes

- **The most common cause is diabetes mellitus**):
- Other causes
  - syringomyelia (20-40%)
  - long-standing syphilis(tabes dorsalis) (5-10%)
  - poliomyelitis,
  - rheumatoid arthritis

Pathophysiology

- **The pathophysiology** is thought to start with peripheral neuropathy. The lack of pain sensation may mean that patients subject the foot joints (commonly the midfoot) to stress injuries that lead to the Charcot process.
- Charcot's is thought to occur due to increased blood flow as a result of neuropathy. This results in increased osteoclast activity and bone turnover; the foot is then susceptible to often very minor trauma and destructive changes take place.
- **The pathology of this condition is thought to be due to sympathetic dysfunction, excessive blood flow to the joint and osteoclast activity**

Features

- The majority of patients are in their 50-60s, and they often present in the latter stages of the disease.
- the foot and ankle is typically swollen, red and warm
  - infection is important to exclude.
  - normal C-reactive protein and white blood cell count → make osteomyelitis unlikely
- typically less painful than would be expected given the degree of joint disruption due to the sensory neuropathy. However, 75% of patients report some degree of pain

Stages: Four stages of Charcot neuropathy are recognised:

- **Stage 0** (inflammation): characterised by erythema and oedema, but no structural changes

- **Stage 1** (development): bone resorption, fragmentation and joint dislocation. Swelling, warmth and erythema persist but there are also radiographic changes such as debris formation at the articular margins, osseous fragmentation and joint disruption
- **Stage 2** (coalescence): bony consolidation, osteosclerosis and fusion are all seen on plain radiographs
- **Stage 3** (reconstruction): osteogenesis, decreased osteosclerosis, progressive fusion. Healing and new bone formation occur, and the deformity becomes permanent.

Investigation

- **X-ray :**
  - plain radiographs can be normal in the early stages
  - later on they show joint destruction, osteolysis, joint reorganisation and subluxation.
- Although not widely available, an **indium-labelled white cell scan is the best way to differentiate between infective causes of this clinical presentation and Charcot's arthropathy.**

Complications

- Chronic untreated Charcot's foot results in either
  - 'rocker-bottom' foot due to downward displacement and subluxation of the tarsus,
  - or medial convexity due to talonavicular joint displacement
  - or dislocation of the tarsometatarsal joints.

Management

- **the most effective treatment is a period of immobilisation in a specially made cast**
  - **Immobilisation in a cast for 3–6 months is the treatment of choice**
- this is thought to be complemented by use of bisphosphonates.
  - The reduction in bone reabsorption associated with bisphosphonates is thought to accelerate healing.
- In stages 0 and 1 the treatment is:
  - immediate immobilisation
  - avoidance of weight-bearing
  - A total-contact cast is worn until the redness, swelling and heat subside (generally 8-12 weeks, changed every 1-2 weeks to minimise skin damage)
  - After this the patient should use a removable brace for a total of four to six months.
    - Intravenous bisphosphonate treatment can benefit some patients.
    - tight glycaemic control,
    - Surgery is reserved for severe deformities that are susceptible to ulceration, and where braces and orthotic devices are difficult to use.
- Good control of blood glucose to reduce the risk of microvascular complications is associated with decreased incidence of Charcot's arthropathy, although once established, it cannot be reversed.

Diabetic cheiroarthropathy

- **Diabetic cheiroarthropathy is a condition of limited joint mobility that occurs in subjects with diabetes.**
- characterised by thickening of the skin resulting in contracture of the fingers.
- causes limited motion of the fingers that the affected individual is unable to extend the fingers to flatten the hand fully.
- Typically both hands are affected.
- reported in over half of patients with insulin-dependent diabetes and approximately three quarters of those with non-insulin-dependent diabetes.
- occurs more frequently in those with a longer history of diabetes.
- Treatment includes pain relief and/or anti-inflammatory drugs, physiotherapy and tight glycaemic control.

Diabetic cheiroarthropathy

Skin lesions in diabetes

Necrobiosis lipoidica diabeticorum

- Definition
  - a disorder of collagen degeneration with a granulomatous response, thickening of blood vessel walls, and fat deposition.
- Causes
  - occurs in patients with type 1 diabetes,
  - It is usually related to diabetes, but **can also occur in patients with rheumatoid arthritis**
  - may precede symptoms and signs of diabetes by several months.
- Epidemiology
  - more common in females
  - presents in young adults or in early middle life.

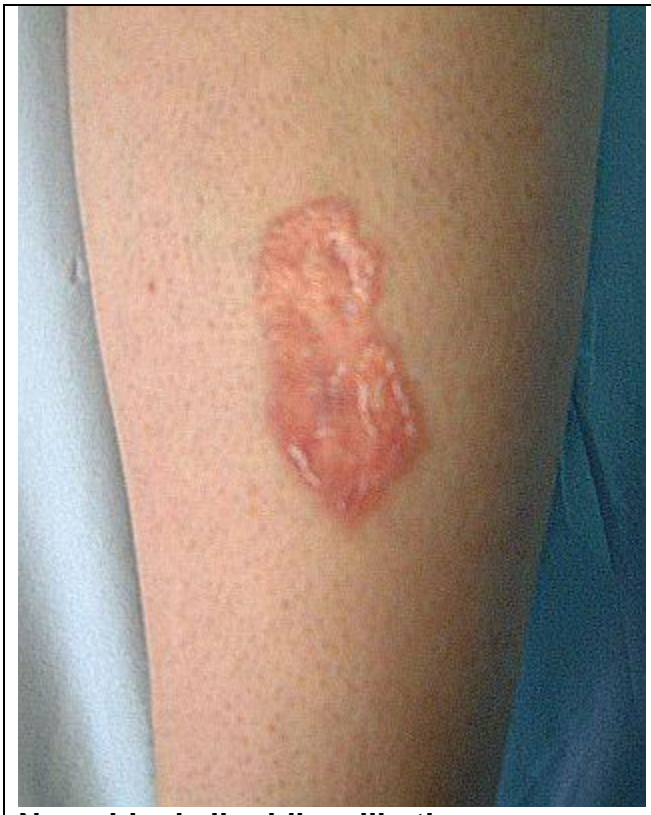
- Pathophysiology
  - The exact cause is unknown, but the leading theory has focused on diabetic microangiopathy.
- Features
  - typically painless.
  - **Beginning as a patch of erythema that spreads across the shin, begins to yellow and can then ulcerate.**
- Diagnosis
  - Biopsy reveals granuloma formation with infiltration of lymphocytes, plasma cells and eosinophils.
- Differential diagnosis
  - Necrobiosis is often mistaken for eczema but rather than responding to steroids may actually deteriorate.
- Treatment
  - usually managed with support bandaging and the use of topical steroids.
  - **Topical steroids is the most appropriate treatment to the non-atrophied areas**
    - the areas of already atrophied skin respond poorly to steroid therapy.
  - Small trials support the use of both Ciclosporin and Hydroxychloroquine as second line agents.

Acanthosis nigricans

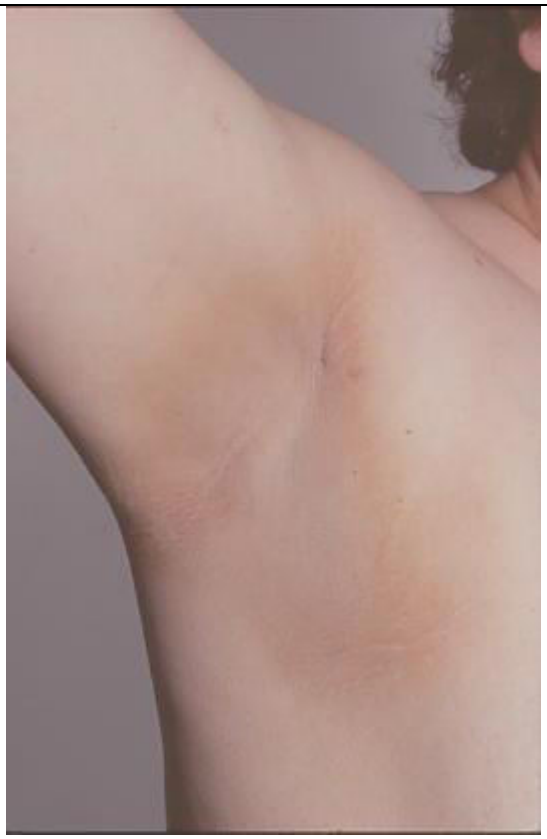
- Definition
  - Acanthosis nigricans has a characteristic hyperpigmented, velvety surface.
- Sites of lesions
  - It frequently occurs in the axillae, groins and in the skin fold of the neck and occasionally on the dorsum of the hand.
- Causes
  - endocrine disease (acromegaly, Cushing's syndrome, **insulin resistant diabetes mellitus**)
  - polycystic ovary syndrome, and
  - paraneoplastic phenomenon (usually tumours of the GI tract, especially adenocarcinoma of the stomach).

Granuloma annulare

- normally diffuse in diabetes and occurs as a ring of papules.



Necrobiosis lipoidica dibeticorum



Acanthosis nigricans

Bullous disease of diabetes or 'bullosis diabeticorum'

- Recurrent, dermal blisters containing sterile proteinaceous fluid with no inflammatory component, in patients with diabetes.
- It is rare, with a prevalence of 0.5%,
- twice as common in males as in females.
- The cause is unknown, although as they tend to occur on the acral surfaces a number of theories are postulated including trauma and microangiopathy.
- It tends to occur in patients with longstanding diabetes and multiple complications, many of whom will have neuropathy and nephropathy.
- Blisters **usually heal spontaneously after 2–6 weeks**, although they often recur in the same place and can be complicated by secondary infection, which may lead to further complications such as ulceration, osteomyelitis, and amputation.
- **Correct management is to leave the blister intact to reduce the risk of secondary infection.**

Diabetes mellitus: Ramadan

During Ramadan, one-third of the normal metformin dose should be taken before sunrise and two-thirds should be taken after sunset

If a patient with type 2 diabetes mellitus does decide to fast:

- they should try and and eat a meal containing long-acting carbohydrates prior to sunrise (Suhoor)
- patients should be given a blood glucose monitor to allow them to check their glucose levels, particularly if they feel unwell
- **for patients taking metformin the expert consensus is that the dose should be split one-third before sunrise (Suhoor) and two-thirds after sunset (Iftar)**
- expert consensus also recommends switching once-daily sulfonylureas to after sunset. For patients taking twice-daily preparations such as gliclazide it is recommended that a larger proportion of the dose is taken after after sunset
- no adjustment is needed for patients taking pioglitazone

May 2012 exam: H/O type 2 diabetes on metformin500 mg tds, asks for advice regard his medication because he is due to start fasting for Ramadan soon. What is the most appropriate advice? 500 mg at the predawn meal + 1000 mg at the sunset meal

DVLA: diabetes mellitus

Patients on insulin may now hold a HGV licence if they meet strict DVLA criteria

Type 2 vehicles (lorries, HGV)

- A recent change in the DVLA guidelines of May 2012 allows HGV drivers to retain their license even if taking insulin, providing they are able to meet a stringent set of criteria.
- **Criteria regarding driving for patient on insulin** (and also apply to patients using other hypoglycaemic inducing drugs such as sulfonylureas):
    1) having no episodes of hypoglycaemia requiring the assistance of another person within the preceding 12 months
    2) **evidence of good glycemic control - demonstrated by review of 3months of BM readings on insulin**
        - to demonstrate adequate control, applicants will need to have used blood glucose meters with a memory function to measure and record blood glucose levels for at least 3 months prior to submitting their application
    3) close BM monitoring (at least BD)

4) full hypoglycaemia awareness,
5) the ability to manage hypoglycaemia independently.
6) here are no other debarring complications of diabetes
    - no visual field impairments.

- From a practical point of view patients on insulin who want to apply for a Group 2 (HGV) licence need to complete a D2 form. They may will also be required to produce a D4 Medical examination report.

Type 1 vehicles (cars, motorcycles)

- if on insulin then patient can drive a car as long as they:
    - have hypoglycaemic awareness,
    - not more than one episode of hypoglycaemia requiring the assistance of another person within the preceding 12 months
    - no relevant visual impairment.
    - Drivers are normally contacted by DVLA
- if on diet controlled alone , tablets or exenatide no need to notify DVLA.

hypoglycaemic episodes

- If a patient has **two or more episodes** of **severe hypoglycaemia** then they need to inform the DVLA and not drive.
    - If a patient needs help to correct the hypoglycaemic episode then it is termed severe hypoglycaemia.
    - When the DVLA is informed, the **patient should be advised to inform the DVLA themselves** rather than breaking patient confidentiality, but if the patient repeatedly fails to follow this advice then **the doctor should inform the DVLA** after telling the patient that he or she is doing so.

Jobs that not allowed to subjects with insulin dependent diabetes

- armed forces,
- working offshore or aboard ships,
- air pilot,
- **Police, Fire or driving in the post office (Traffic police driver)**
- driving emergency vehicles.
- Offshore work (البحرية)

- **Patient with diabetes who have had two hypoglycaemic episodes requiring help needs to surrender (تسليم) their driving licence**
- **If a patient needs help to correct the hypoglycaemic episode then it is termed severe hypoglycaemia**
- **If a patient has two or more episodes of severe hypoglycaemia then they need to inform the DVLA and not drive.**

Insulinoma

Insulinoma is diagnosed with supervised prolonged fasting

An insulinoma is a neuroendocrine tumour deriving mainly from pancreatic Islets of Langerhans cells

Basics

- most common pancreatic endocrine tumour
- incidence of 1-2/million/year,
- commoner in women
- may be associated with the MEN-1 syndrome in around 10%;
- 10% malignant, 10% multiple
- of patients with multiple tumours, 50% have MEN-1
- 90% of them are less than 2 cm in size.
- More of the insulin released by an insulinoma remains as pro-insulin, so that pro-insulin levels are often raised as a proportion of total insulin levels.

Features

Whipple triad is the clinical presentation of **pancreatic insulinomas** and consists of:

1. fasting hypoglycemia
2. symptoms of hypoglycemia
3. immediate relief of symptoms after the administration of IV glucose

- features of hypoglycaemia: typically early in morning or just before meal, e.g. diplopia, weakness , sweating, Tachycardia/palpitations etc
- Memory loss
- Seizures
- Hunger
- rapid weight gain may be seen
  - Patients eat in an attempt to avoid hypoglycaemia
  - and may avoid physical activity because this is also recognised as a trigger.
- high insulin, raised proinsulin:insulin ratio
- high C-peptide

Diagnosis

- supervised, prolonged fasting (up to 72 hours)
  - If the patient develops symptoms, then a plasma glucose is measured and if low, insulin and C-peptide is then collected and the fast terminated.
  - After a 15 h fast, the cut-off normal limits for glucose are 2.5 mmol/l and 5 mU/l for insulin.
  - By 24 h, fasting leads to a detection rate of 78% for insulinoma. If the fast is extended to 72 h, this detection rate increases to 98%.
- CT pancreas
- To exclude possible drug administration, a **sulphonylurea screen should be undertaken**.

Management

- surgery
- diazoxide and somatostatin if patients are not candidates for surgery

September 2010 exam: H/O gained 10 kg in weight in the past 3 months + early morning sweating & double vision What is the most likely diagnosis? Insulinoma

January 2010 exam: H/O weight gain & recurrent 'dizzy' episodes. blurred vision, sweating, headaches and palpitations. blood sugar 1.4 mmol/l. What is the single most useful test? Insulin + C-peptide levels during a hypoglycaemic episode (Δ insulinoma. Whilst supervised fasting is the investigation of choice, **if this option is not given** then insulin + C-peptide levels during an acute hypoglycaemic episode are useful)

Glucagon

- Action and function
  - stimulates glycogenolysis, at the same time inhibiting glycolysis and activating gluconeogenesis.
  - **stimulates lipolysis.**
  - stimulation of catecholamine secretion.
  - delays gastric emptying
  - reduces pancreatic exocrine secretions.

Glucagonoma

- Glucagonomas are small tumours, almost always found in the pancreas, and frequently malignant.
- Very rare, with an annual incidence of 1 in 20 million,
- **They present with**
  - secondary diabetes mellitus
    - Over 90% of glucagonomas are associated with impaired glucose tolerance as a result of **insulin antagonism**
  - weight loss due to protein catabolism.
  - Neuropsychiatric features.
  - venous thrombo-embolism
  - **necrolytic migratory erythema**
    - in 75% of cases
    - Red, blistering rash.
    - The lesion starts as an indurated erythema at the perineum, face and nose.
    - Within a few days blisters will cover the surface of the skin, which then crust and heal, leaving hyperpigmented skin.
    - This process takes 7-14 days, with lesions developing in one area while others are resolving.
- At least 50% are metastatic at presentation, so prognosis is poor.
- **Measure plasma glucagon levels**
- **Management**

- surgical cure rate is only 5% because these tumours have often metastasised many years before the patient presents.
- Octreotide improves the skin rash but can have a detrimental effect on glucose control.
- Combination chemotherapy with streptazocin and 5-fluorouracil (5FU) gives good palliative results, as does hepatic embolisation.

Maturity-onset diabetes of the young (MODY)

Definition

- characterised by the development of type 2 diabetes mellitus in patients < 25 years old.
- It is an important diagnosis as the therapy may be different compared with T1DM and T2DM.
  - MODY3 is particularly important to diagnose as many patients initially treated with insulin can in fact be managed with sulphonylurea.

Epidemiology

- MODY is the commonest cause of **monogenic** B-cell dysfunction
- It is thought that around 1-2% of patients with diabetes mellitus have MODY, and around 90% are misclassified as having either type 1 or type 2 diabetes mellitus.

Genetic

- autosomal dominant condition.

General features

- typically develops in patients < 25 years
- absence of autoimmune markers,
- absence of insulin resistance
- remains C-peptide +ve, even if insulin-treated.
- **a family history of early onset diabetes is often present**
- ketosis is not a feature at presentation
- patients with the most common form are very sensitive to sulfonylureas, insulin is not usually necessary

Types

- **MODY 3** (**HNF1A-MODY**)
  - the **commonest** form of MODY, 60% of cases
  - due to a defect in the **HNF-1 alpha** gene (hepatic nuclear factor-1)
  - characterised by:
    - ↑(HDL) cholesterol levels
    - Preserved insulin sensitivity
    - Low renal threshold for glucose (glycosuria)
  - Sulphonylureas is the initial drug of choice
- **MODY 2 (GCK-MODY)**
  - The second commonest MODY variant after MODY3
  - 20% of cases
  - due to a defect in the **glucokinase gene (*GCK* gene)**

- This gene helps the body to recognise how high the blood glucose level is in the body. When this gene isn't working properly the body allows the level of blood glucose to be higher than it should be.
- Blood glucose are typically only slightly higher than normal, generally between 5.5-8mmol/l.
- often picked up through routine testing (eg during pregnancy).
- 90% of MODY2 patients are controlled on diet therapy alone.
- Patients do not tend to get diabetes complications and do not require treatment.
- All types of MODY apart from glucokinase carry a risk of the long-term complications of diabetes

- **MODY 5 (HNF1B-MODY)**
  - **Defect in HNF-1 beta gene.**
  - **associated with renal cysts**, uterine abnormalities and gout as well as diabetes.
  - Often the renal cysts can be detected in the womb before a baby is born.
    - **bilateral renal cysts + ↑ glucose → MODY related cyst formation**
  - insulin treatment is usually necessary

HNF4-alpha is associated with macrosomy, and with hypoglycaemia in the neonatal period. It is an uncommon form of MODY.

subacute presentation & negative antibodies suggests that → a diagnosis of MODY most likely than type 1 diabetes

September 2011 exam: Which one of the following statements regarding maturity-onset diabetes of the young (MODY) is true? There is usually a strong family history

September 2012 exam: A 25-year-old male develops type 2 diabetes mellitus. Which gene is most likely to be responsible? HNF-1 alpha

Latent autoimmune diabetes of adulthood (LADA)

Definition

- adult-onset, presence of diabetes associated autoantibodies, and no insulin treatment requirement for a period after diagnosis.

Epidemiology

- constitutes approximately 10% of patients incorrectly labelled as type 2 diabetic.

Feature

- **features consistent with type 1 diabetes (eg: weight loss)**
- despite the presence of islet antibodies at diagnosis of diabetes, the progression of autoimmune -cell failure is slow.

- In contrast to type 2 diabetes, patients are typically younger and without an increased body habitus.
- In contrast to type 1 diabetes, insulin is not usually required in the early stages of the disease.

Diagnosis

- may be aided through a Glutamic Acid Decarboxylase (GAD) Autoantibodies test and evidence of other autoimmune diseases.

Pregnancy: diabetes mellitus (NICE 2015)

The oral glucose tolerance test remains the investigation of choice for gestational diabetes

- Diabetes mellitus may be a pre-existing problem or develop during pregnancy, gestational diabetes.
- It complicates around 1 in 40 pregnancies.

Risk factors for gestational diabetes

1) BMI of > 30 kg/m
2) previous macrosomic baby weighing 4.5 kg or above
3) previous gestational diabetes
4) first-degree relative with diabetes
5) family origin with a high prevalence of diabetes (South Asian, black Caribbean and Middle Eastern)

Importance of planning pregnancy

- use contraception until blood glucose is controlled (assessed by HbA1c level)
- Control will reduce the risk of miscarriage, congenital malformation, stillbirth and neonatal death.
- glucose target ranges as recommended for all people with type 1 diabetes:
  - a fasting plasma glucose level of 5–7 mmol/litre on waking **and**
  - a plasma glucose level of 4–7 mmol/litre before meals at other times of the day.
  - HbA1c level below 48 mmol/mol (6.5%)

Screening for gestational diabetes

- Women who've previously had gestational diabetes:
  - oral glucose tolerance test **(OGTT) should be performed as soon as possible** after booking and at 24-28 weeks if the first test is normal.
  - NICE also recommend that early self-monitoring of blood glucose is an alternative to the OGTTs
- women with any of the other risk factors should be offered an OGTT at 24-28 weeks
- Be aware that glycosuria of 2+ or above on 1 occasion or of 1+ or above on 2 or more occasions detected by reagent strip testing during routine antenatal care may indicate undiagnosed gestational diabetes. If this is observed, consider further testing to exclude gestational diabetes.

Diagnostic thresholds for gestational diabetes

- these have recently been updated by NICE, gestational diabetes is diagnosed if either:

- fasting glucose is ≥ 5.6 mmol/l
- 2-hour glucose is ≥ 7.8 mmol/l
- **If fasting blood glucose between 5.5 and 7.0 mmol/l then proceed to → 75-g oral glucose tolerance test**

Management of gestational diabetes

- newly diagnosed women should be seen in a joint diabetes and antenatal clinic within a week
- women should be taught about self-monitoring of blood glucose
- advice about diet (including eating foods with a low glycaemic index) and exercise should be given
- Aspirin should also be considered given the increased risk of pre-eclampsia.
- **if the fasting plasma glucose level is < 7 mmol//l:**
  - **trial of diet and exercise should be offered**
  - if glucose targets are not met within 1-2 weeks of altering diet/exercise metformin should be started
  - if glucose targets are still not met insulin should be added to diet/exercise/metformin
  - glibenclamide should only be offered for women who cannot tolerate metformin or those who fail to meet the glucose targets with metformin but decline insulin treatment.
- **if at the time of diagnosis the fasting glucose level is ≥ 7 mmol/l:**
  - **insulin should be started**
- if the plasma glucose level is **between 6-6.9 mmol/l**, and there is evidence of **complications** such as macrosomia or hydramnios:
  - **insulin should be offered**
- **fasting blood glucose should be checked 6 -13 weeks postpartum**

Management of pre-existing diabetes

- weight loss for women with BMI of > 27 kg/m^2
- stop oral hypoglycaemic agents, apart from metformin, and commence insulin
- folic acid 5 mg/day from pre-conception to 12 weeks gestation
- detailed anomaly scan at 20 weeks including four-chamber view of the heart and outflow tracts
- tight glycaemic control reduces complication rates
- treat retinopathy as can worsen during pregnancy
  - It is advised, however, if the patient has not had **retinal screening within the last six months** to offer this **urgently** as there can be rapid development of diabetic retinopathy in pregnancy.
- In diabetes, patients should achieve good diabetic control prior to planning for pregnancy.
  - If this has not been achieved, then NICE advises contraception and to offer termination if pregnancy does occur due to increased risks in pregnancy.

Patients with diabetes should have increased frequency of retinal screening during pregnancy due to increased risk of retinopathy

Targets for self-monitoring of pregnant women (pre-existing and gestational diabetes)

Time	Target
Fasting	5.3 mmol/l
1 hour after meals	7.8 mmol/l, or:
2 hour after meals	6.4 mmol/l

Prognosis

- Abnormal glucose tolerance occurs as a de novo event in around 2–3% of pregnant women, unfortunately their **long-term risk of subsequent type 2 diabetes is as high as 40-50%.**
  - Women should be offered a further glucose tolerance test at the 6 week check, to rule out the possibility of continued abnormal glucose tolerance or type 2 diabetes.

May 2009 exam: H/O 26 weeks pregnant has (OGTT): 14 mmol/l. ultrasound shows that the fetus is large for dates. What is the most appropriate management? Start insulin (due to ↑↑ glucose & macrosomia. Aspirin should also be considered as she is at increased risk of pre-eclampsia)

Lipids and obesity problems

Obesity hormones

Obesity hormones
- Leptin Lowers appetite
- Ghrelin Gains appetite

Food intake regulation (ghrelin and leptin):

- ghrelin → "hunger hormone"
- regulate appetite → **stimulates hunger**
- empty stomach → ↑↑ghrelin
- stretched stomach → ↓↓ghrelin
- **secreted by GIT**(mainly by the fundus of the stomach and the pancreas), **acts on hypothalamus** to ↑↑ hunger, ↑↑gastric acid secretion and ↑↑GIT motility
- **acts synergistically with GnRH to stimulate growth hormone release**
- Leptin - the satiety hormone - has opposite effects from ghrelin.

Leptin (the satiety hormone)

- **synthesised within the adipocyte**
- plasma concentrations are directly related to adipocyte (fat) mass.
- **acts on** receptors within the **arcuate nucleus within the hypothalamus** to **produce satiety**.
- when patients reach a certain peripheral fat mass, leptin acts as a lipostat to reduce food intake.
- However, leptin resistance is seen, hence patients can continue to accumulate weight and addition of leptin does not curb food intake.

Adiponectin

Adiponectin—a unique adipokine with anti-atherogenic, anti-inflammatory and insulin-sensitizing properties

- **adiponectin** is a recently described **adipokine** that has been recognized as a key regulator of **insulin sensitivity** and tissue inflammation.
- It is produced by adipose tissue (white and brown)
- Actions
  - improve hepatic insulin sensitivity,
    - via AdipoR2 receptor
  - increase fuel oxidation [via up-regulation of adenosine monophosphate-activated protein kinase (AMPK) activity]
    - via AdipoR1 receptor
  - decrease vascular inflammation.
    - Via T-cadherin (adiponectin-binding protein)
- In contrast to other adipokines, adiponectin levels are inversely proportional to body fat content.
- Levels are reduced in metabolic syndrome, diabetes and coronary artery disease.
- Adiponectin antagonizes many effects of tumour necrosis factor-alpha(TNF-alpha) and this, in turn, suppresses adiponectin production.
- adiponectin secretion from adipocytes is enhanced by thiazolidinediones (which also act to antagonize TNF-alpha effects).
- PPAR-gamma upregulates HMW adiponectin and PPAR-alpha upregulates adiponectin receptors (AdipoRs)
- adiponectin may be the common mechanism by which TNF-alpha promotes, and the thiazolidinediones suppress, insulin resistance and inflammation.
- under pathophysiological conditions, such as **obesity** and **diabetes**, only **high molecular weight (HMW) adiponectin** was **decreased**; therefore, strategies to increase only HMW

adiponectin may be a logical approach to provide a novel treatment modality for obesity-linked diseases, such as insulin resistance and type 2 diabetes.

Obesity: therapeutic options

The management of obesity consists of a step-wise approach:

1. conservative: diet, exercise
   - Diet and exercise have been shown to be ineffective **over the long term**.
     - More than 90% of people who attempt to lose weight gain it all back.
2. medical
3. surgical

Dietary fat intake

- **The average daily energy consumption of a male is 2500 kcal and 2000 kcal for a female.**
  These values are important when determining the dietary calorie restriction.
- The current recommendations in the UK for fat intake are that:
  - **Total fat intake should be restricted to less than 30% of dietary energy.**
  - Monounsaturated fats should provide around 12% of dietary energy.
  - Polyunsaturated fats should provide around 6% of dietary energy.
  - Saturated fats should provide no more than 10% of dietary energy.

anti-obesity drugs

- Indications:
  - body mass index (BMI) **≥** 30 kg/m2 in whom **at least three months** of managed care involving supervised diet, exercise and behaviour modification fails.
  - BMI **≥** 28 kg/m2 **+ risk factors** (eg: diabetes mellitus, coronary heart disease, hypertension and obstructive sleep apnoea)
- Discontinuation: Anti-obesity drug treatment should be **discontinued** :
  - If weight loss is less than 5% after the first 12 weeks.
  - **If the individual regains weight at any time whilst receiving drug treatment**
- Contraindications:
  - Combination drug therapy is contraindicated
  - drugs should never be used as the sole element of treatment (should only be prescribed as part of an overall plan for managing obesity).

Orlistat

- **Action**
  - pancreatic lipase inhibitor,
  - blocks the breakdown and hence the absorption of dietary fat.
  - used in the management of obesity.
- **Adverse effects**
  - faecal urgency/incontinence and flatulence.

- If patients taking orlistat do not maintain a low-fat diet then they can suffer distressing, oily diarrhoea. This is why it is essential to combine orlistat therapy with an effective patient support programme.

- A lower dose version is now available without prescription ('Alli').
- NICE have defined criteria for the use of orlistat:
  - It should only be prescribed as part of an overall plan for managing obesity in adults who have:
    - BMI of 28 kg/m^2 or more with associated risk factors ((eg: diabetes mellitus, coronary heart disease, hypertension and obstructive sleep apnoea))
    - **BMI of 30 kg/m^2 or more** in whom at least three months of managed care involving supervised diet, exercise and behaviour modification fails.
    - continued weight loss e.g. 5% at 3 months
    - orlistat is normally used for < 1 year

Sibutramine

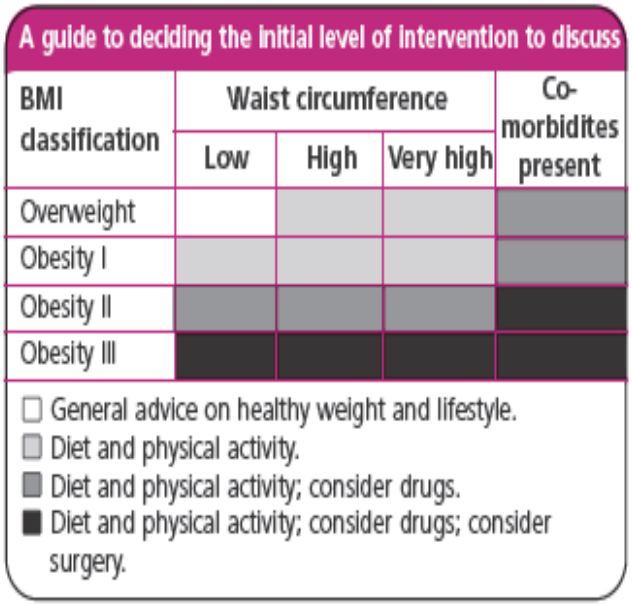
- **withdrawn** January 2010 by the European Medicines Agency due to an increased risk of cardiovascular events
- centrally acting appetite suppressant (inhibits uptake of serotonin and noradrenaline at hypothalamic sites that regular food intake)
- adverse effects include hypertension (monitor blood pressure and pulse during treatment), constipation, headache, dry mouth, insomnia and anorexia
- contraindicated in psychiatric illness, hypertension, IHD, stroke, arrhythmias

Rimonabant,

- was **withdrawn** in October 2008 after the European Medicines Agency warned of serious psychiatric problems including suicide
- a specific CB1 cannabinoid receptor antagonist,

NICE recommendations are first to classify the level of obesity.

Classification	BMI kg/m^2
Healthy weight	18.5-24.9
Overweight	25-29.9
Obesity I	30-34.9
Obesity II	35-39.9
Obesity III	40 or more



Obesity: bariatric surgery

Obesity - NICE bariatric referral cut-offs
- with risk factors (T2DM, BP etc): > 35 kg/m^2
- no risk factors: > 40 kg/m^2

Benefits
- It is now recognised that for many obese patients who fail to lose weight with lifestyle and drug interventions **the risks and expense of long-term obesity outweigh those of surgery**.
- **Reduces cardiovascular mortality**

Indications (NICE guidelines):
- BMI **≥** 40 kg/m^2 ,
- BMI **≥** 35 kg/m^2 **and** other significant disease (eg: type 2 DM, hypertension, sleep apnea)
  - **If all appropriate non-surgical measures have failed to achieve or maintain adequate clinically beneficial weight loss for at least 6 months**
  - they are receiving or will receive intensive specialist management
  - they are generally fit for anaesthesia and surgery
  - they commit to the need for long-term follow-up
- BMI > 50 kg/m2
  - Consider surgery as a **first-line option** for adults with a BMI of more than 50 kg/m2 in whom surgical intervention is considered appropriate;
  - consider orlistat before surgery if the waiting time is long

Types of bariatric surgery:
- primarily restrictive: laparoscopic-adjustable gastric banding (LAGB) or sleeve gastrectomy
- primarily malabsorptive: classic biliopancreatic diversion (BPD) has now largely been replaced by biliopancreatic diversion with duodenal switch
- mixed: Roux-en-Y gastric bypass surgery

Which operation?
- LAGB produces less weight loss than malabsorptive or mixed procedures but as it has fewer complications it is normally the first-line intervention in patients with a BMI of 30-39kg/m^2
- patients with a BMI > 40 kg/m^2 may be considered for a gastric bypass or sleeve gastrectomy. The latter may be done as a sole procedure or as an initial procedure prior to bypass
- primarily malabsorptive procedures are usually reserved for very obese patients (e.g. BMI > 60 kg/m^2)

Post-operative mortality
- ranges from 0.1-2%.
- The rate of post operative complications following bariatric surgery is no greater than other elective major abdominal operations

Specific post bariatric complications deoend on the procedure used:

- Laparoscopic adjustable gastric band - band slippage, erosion, infection, pouch dilatation, band/tubing leak, megaoesophagus.
- Laparoscopic roux en y gastric bypass - stomal stenosis, internal hernia, malnutrition.
- Laparoscopic sleeve gastrectomy - reflux, staple line leak, sleeve dilatation and weight gain.

Lipid disorders

Etiology

- **Congenital (less common)**
  - Hyperchylomicronemia
  - Familial hypercholesterolemia
  - Familial Combined Hyperlipidaemia
  - Remnant hyperlipidaemia (dysbetalipoproteinaemia)
  - Familial hypertriglyceridemia
- **Acquired (more common)**
  - Obesity
  - Diabetes mellitus
  - Physical inactivity
  - Alcoholism
  - Hypothyroidism
  - Nephrotic syndrome
  - Cholestatic liver disease
  - Cushing's disease
  - Drugs:
    - oral contraceptive pill,
    - high-dose diuretic use,
    - metoprolol

Genetic dyslipidemias

WHO/Fredrickson classification:

- Classification was devised before the importance of **HDL** as a prognostic indicator was recognized.
- **High triglycerides** are a component of each of these dyslipidemias **except** Fredrickson type **IIa** (familial hypercholesterolemia).
- The **2 most common** dyslipidemias are Fredrickson type II**b** (familial com**b**ined hyperlipidemia) and type IV (familial hypertriglyceridemia). Together, these 2 dyslipidemias account for 85% of familial dyslipidemias.

Types:

WHO/Fredrickson classification:

Classification	Name	Lipid profile	Etiology	Notes
Type 1	Familial Hyper-chylomicronaemia	↑ chylomicrons	**Deficiency of Apo CII or LPL** (lipoprotein lipase)	typically presents with **eruptive xanthoma** and abdominal colic.
Type 11A	**Familial hypercholesterolaemia**	↑TC > 7.5 ↑LDL-C > 4.9	LDL-receptor deficiency	**Heterozygous** type is Common **Associated with tendon xanthoma**
Type 11B	**Familial Combined Hyperlipidaemia**	↑ LDL ↑VLDL ↑TG	**overproduction of apo B-100 &(VLDL) by the liver**	**The commonest type** (two thirds). Associated with glucose intolerance.
Type 111	Remnant hyperlipidaemia (dysbetalipoproteinaemia)	↑ IDL	**Abnormal ApoE**	**palmar xanthoma is diagnostic** fibrates are first line treatment
Type 1V	**Familial hypertriglyceridaemia**	↑TG ↑VLDL	Overproduction or↓catabolism of VLDL (**due to ↓ LPL**)	often "polygenic". **Common**

Chylomicronaemia (type I)

- **The episodes of abdominal pain, eruptive xanthoma and strong family history should lead you to think of a form of familial hyperlipidaemia.**
- **Chylomicrons** are lipoprotein particles that consist of triglycerides (85–92%), phospholipids (6–12%), cholesterol (1–3%), and proteins (1–2%)
- Chylomicrons are **formed in** the endoplasmic reticulum in the absorptive cells (enterocytes) of the small intestine.
- The lymphatic vessels carry the chyle to the venous return of the systemic circulation. From there the chylomicrons supply the tissue with fat absorbed from the diet.
- unlike the carbohydrates and proteins, the lipids from the diet bypass the hepatic portal system, meaning the liver does not get "first crack" at them.
- **Function**: Chylomicrons transport lipids absorbed from the intestine to adipose, cardiac, and skeletal muscle tissue, where their triglyceride components are hydrolyzed by the activity of the lipoprotein lipase, allowing the released free fatty acids to be absorbed by the tissues.

- Chylomicronaemia is due to a circulating inhibitor of lipoprotein lipase **(type 1c hyperlipidaemia**).

- **It typically presents with eruptive xanthoma and abdominal colic.**
- Associated particularly with severe hypertriglyceridaemia and not with large elevations in cholesterol.
- There is no increased risk of atherosclerotic disease.
- **Complications** include
  - retinal vein occlusion,
  - acute pancreatitis,
  - steatosis
  - and lipidaemia retinalis.

The following table shows the apolipoproteins present on the surface of various lipoproteins:

Lipoproteins	apolipoproteins
Chylomicron	Apo CII & Apo B48
Chylomicron remnant	**Apo E**
VLDL	Apo CII & Apo B100
LDL	**Apo B100**
IDL	Apo E & Apo B100
HDL	Apo A1

Which protein deficiency is most likely to be associated with very high levels of plasma chylomicrons? → Apolipoprotein CII

Familial hypercholesterolaemia (FH) (type IIa)

Tendon xanthomata are diagnostic hallmarks of heterozygous familial hypercholesterolaemia (FH)

- **autosomal dominant** on the short arm of chromosome 19
- **Heterozygous** familial hypercholesterolaemia is one of the most common familial conditions, with a prevalence of about 1 in 500.
- Homozygous familial hypercholesterolaemia is exceedingly rare - most patients die in their teenage years from a myocardial infarction.
- Heterozygotes rarely present before age 30.
- caused by mutations in the gene which encodes the LDL-receptor protein → **LDL-receptor deficiency**
- manifests by increased low density lipoprotein (LDL) concentrations (not chylomicrons) due to constitutional abnormalities and reduced numbers of the LDL receptor.
- results in high levels of LDL-cholesterol which, if untreated, may cause early cardiovascular disease (CVD).
- **Tendon xanthomata are characteristic**
- **genetic factor mechanisms**
  - **Failure to produce any LDL receptors**

- **Failure of the LDL receptors to move to the cell surface**
- **Abnormal receptor binding to LDL**
- **Inability to internalise LDL for metabolism**

Clinical diagnosis is now based on the **Simon Broome criteria**:

- in adults total cholesterol (TC) > 7.5 mmol/l and LDL-C > 4.9 mmol/l or children TC > 6.7 mmol/l and LDL-C > 4.0 mmol/l, plus:

    1. **for definite FH**: **tendon xanthoma** in patients or 1st or 2nd degree relatives or DNA-based evidence of FH
    2. **for possible FH**: family history of myocardial infarction below age 50 years in 2nd degree relative, below age 60 in 1st degree relative, or a family history of raised cholesterol levels

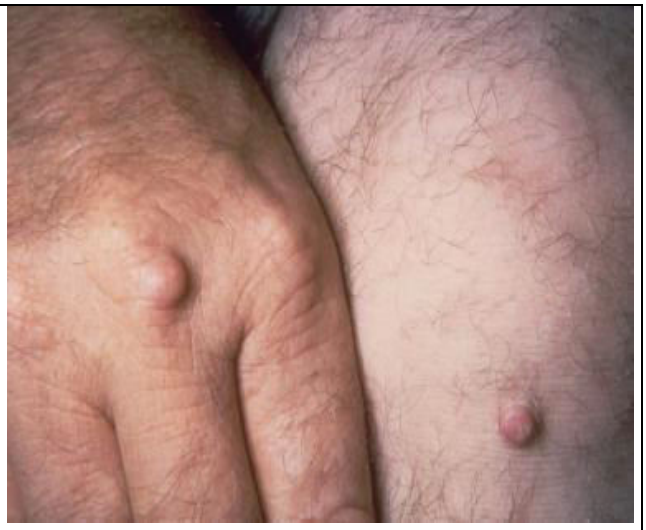
Management

Which of the following reflects the mode of action of evolocumab?

Prevents low-density lipoprotein receptor degradation

Evolocumab is a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor. It binds selectively to PCSK9 and prevents circulating PCSK9 from binding to the low-density lipoprotein receptor (LDLR) on the surface of liver cells, thus preventing PCSK9-mediated LDLR degradation.

- the use of CVD risk estimation using standard tables is not appropriate in FH as they do not accurately reflect the risk of CVD
- the maximum dose of potent statins are usually required
- first-degree relatives have a 50% chance of having the disorder and should therefore be offered screening. This includes **children who should be screened by the age of 10 years if there is one affected parent**
- statins should be discontinued in women 3 months before conception due to the risk of congenital defects



The golden notes

Familial hypercholesterolaemia (FH) (type IIa)

- **autosomal dominant,** on chromosome 19
- prevalence → 1 in 500 (the second most common).
- Usually **Heterozygous (because homozygous die in teenage years by MI)**
- caused by → **LDL-receptor deficiency**
- **diagnosis** based on the **Simon Broome criteria**:
  - in adults total cholesterol (TC) > 7.5 mmol/l and LDL-C > 4.9 mmol/l or children TC > 6.7 mmol/l and LDL-C > 4.0 mmol/l, plus:
    1. **for definite FH**: **tendon xanthoma** in patients or 1st or 2nd degree relatives or DNA-based evidence of FH
    2. **for possible FH**: family history of myocardial infarction below age 50 years in 2nd degree relative, below age 60 in 1st degree relative, or a family history of raised cholesterol levels
- management
  - statin (usually maximum dose)
  - screening for 1st degree (children by the age of 10 years)

Question

A Fasting lipid profile shows an elevated cholesterol, reduced HDL-cholesterol, and normal triglyceride, in a patient with negative family history for any hereditary lipid disorder. Which is the most likely cause of the observed disturbance in his lipid profile?

Answer → Reduced tissue LDL uptake

- Serum cholesterol is carried in:
  - In the fasting state → in LDL, VLDL, HDL
  - After a meal → chylomicrons
- VLDL additionally contains triglyceride.
- This patient's fasting lipid profile has shown a reduced HDL cholesterol and normal triglyceride. Therefore, the elevated serum cholesterol in this patient is most likely due to an increase in the level of LDL, not VLDL (because the triglyceride concentration is normal).

Familial Combined Hyperlipidaemia (FCHL) (type IIB)

- Epidemiology
  - **The commonest type (two thirds)**
  - affect around **1** person in every **100**.
- Etiology
  - It is autosomal dominant,
- More likely it is caused by a **combination of genes** working individually or together to affect the levels of blood fats.
- caused by overproduction of hepatically-derived apo B-100 associated with very low density lipoprotein (VLDL)
- Apo B levels are strongly correlated with LDL phenotype B in FCHL families
- Total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels are all elevated.
- Triglycerides and cholesterol may not be raised until the age of 20 or 30. Only 20% of children have elevated triglycerides before the age of 25.
- Low levels of HDL-C are often associated with raised TG levels (eg, in familial combined hyperlipidaemia and in dyslipidaemia in type 2 diabetes).
- can be diagnosed only on family studies
- **associated with:**
  - Obesity,
  - insulin resistance,
  - hyperinsulinaemia,
  - **glucose intolerance,**
  - and hyperuricaemia
- **Pattern of raised blood fats**
  People with FCH have a unique pattern of raised blood fats which put them at high risk of cardiovascular disease. This includes:
  - raised levels of VLDL particles – these are **triglyceride** rich particles produced by the liver
  - elevated ApoB levels (each VLDL particle contains one particle of ApoB, so more VLDL means more ApoB)
  - fasting **triglyceride** levels above 1.5mmol/l
  - LDL cholesterol particles that are smaller and more compact (dense) than normal

Large LDL vs small

- Increased **large** buoyant low density lipoprotein (LDL) is seen in response to increased insulin sensitivity. It is thought to be less atherogenic than **small** dense LDL.

Which feature suggests a diagnosis of familial combined hyperlipidaemia (FCHL) rather than heterozygous familial hypercholesterolaemia (FH)?

➔ **Presence of glucose intolerance**

HDL

- Increased high density lipoprotein (HDL) is seen with exercise and modest alcohol consumption.
- Diabetes causes low HDL
- **They contain apolipoprotein B-100**
- Increased oestrogen levels, as caused by the contraceptive pill, lead to higher HDL levels.
  - Women have naturally higher HDL levels compared to men, due to higher oestrogen levels.
  - Low levels of HDL are associated with an increased risk of ischaemic heart disease

The golden notes

Familial Combined Hyperlipidaemia (FCHL) (type IIB)

- commonest type (two thirds)
- prevalence → 1%
- caused by → ↑apo B-100 & &(VLDL)
- associated with: Obesity, glucose intolerance, and hyperuricaemia
- feature → ↑ LDL, ↑VLDL, ↑TG
- **→ premature cardiovascular disease**
- **treatment → atorvastatin**

Remnant hyperlipidaemia (type III)

A significantly elevated TG, despite normal VLDL and chylomicron concentrations, simply implies increased concentrations of IDL and chylomicron remnants. This can be due to apoE deficiency which results in the accumulation of IDL and chylomicron remnants in the plasma. Normally, these particles have apoE on the surface through which they are taken up by the liver.

Palmar xanthomas are pathognomonic of dysbetalipoproteinaemia (type III hyperlipoproteinaemia).

Overview

- rare cause of mixed hyperlipidaemia (raised cholesterol and triglyceride levels)
- also known as Fredrickson **type III hyperlipidaemia**, broad-beta disease and dysbetalipoproteinaemia.

Genetic

- Autosomal recessive with variable penetrance
- **caused by mutation in apoprotein E** (apo-e2 homozygosity)
- usually requires a secondary exacerbating metabolic factor for expression of the phenotype. Therefore, secondary causes of hyperlipidaemia such as hypothyroidism, obesity, diabetes mellitus, renal insufficiency, unhealthy diet (high-calorie, high-fat diet) or alcohol are often encountered at diagnosis,

Pathophysiology

- Plasma TG is mainly transported by chylomicron (in the postprandial state) and VLDL (in the fasting state) as well as intermediate-density lipoprotein (IDL) cholesterol.
- After being released into the circulation by the intestinal tract and liver, chylomicron and VLDL are subject to hydrolysis by capillary lipoprotein lipase (cLPL), mostly in the adipose tissue and muscles.
- By losing its TG content, the chylomicron is converted to chylomicron remnant.
- VLDL is converted to IDL and then to low-density lipoprotein (LDL) cholesterol.
- Normally, these particles (**IDL and chylomicron remnants)** have apoE on the surface through which they are taken up by the liver.
  - **Decreased or lack of apolipoprotein E-containing lipoproteins → results in the accumulation of IDL and chylomicron remnants in the plasma.**
- Remnant hyperlipidaemia is due to a **combination of:**
  1) **abnormal ApoE receptor function and**
  2) **metabolic disorder** such as diabetes, obesity or hypothyroidism.
     - Affected homozygotes may be asymptomatic until an additional insult occurs affecting lipoprotein metabolism, such as the development of obesity or diabetes mellitus.

Features

- **Yellow palmar creases (palmar xanthoma is diagnostic)**
- tuberous xanthomas
- Hypercholesterolaemia, typically 8-12 mmol/L
- Hypertriglyceridaemia, typically 5-20 mmol/L
- Normal ApoB concentration

Consequences include:

- premature cardiovascular disease and
- **pancreatitis.**

Diagnosis

- Definitive diagnosis can be made by **lipoprotein electrophoresis** or **genotyping of apoprotein E.**

Management

- **fibrates are first line treatment**
  - **mode of action → Increased lipoprotein lipase activity via PPAR-alpha**

- The effect of fibrates on the metabolism of triglyceride-rich lipoproteins is due to a PPAR-alpha-dependent stimulation of lipoprotein lipase and of apolipoprotein (apo)A-V, and to an inhibition of apoC-III expression.
- The increase in plasma HDL-cholesterol depends partly on an overexpression of apoA-I and apoA-II.

Familial hypertriglyceridaemia (type IV)

- autosomal dominant condition
- **Affects 1 in 300 people.**
- Usually due to polygenic factors
- May also be due to **lipoprotein lipase deficiency**
- can be exacerbated by alcohol, glucocorticoids and thiazide diuretics

Features:

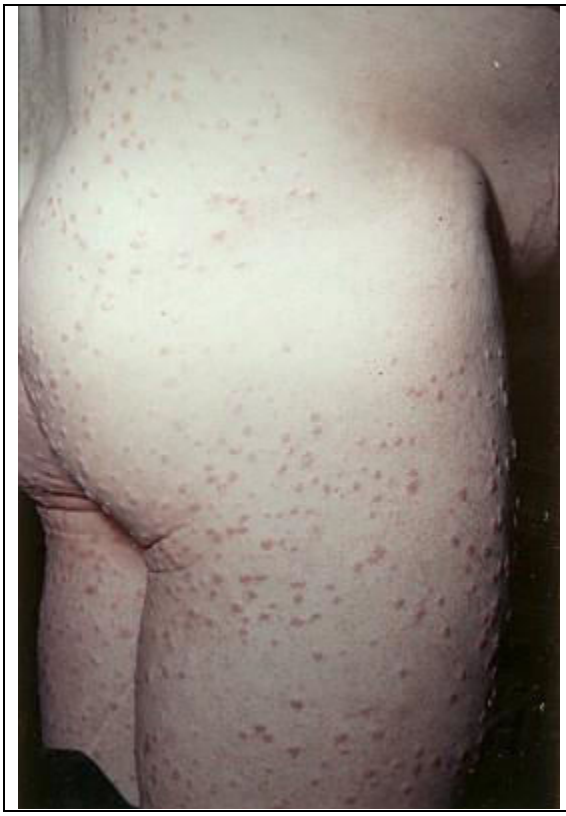
- severe hypertriglyceridemia > 5.6 mmol/l (>500 mg/dL) may cause pancreatitis
- **eruptive xanthomas**
  - 1- to 3-mm yellow papules that can erupt anywhere but are usually seen on the back, chest, and proximal extremities.
- **Lipaemia retinalis → is a sign consistent with isolated hypertriglyceridaemia** :
  - visualization of lipemic blood in the retinal blood vessels → pale pink milky appearance to the retinal vessels or even to the retina itself.
- **raised very-low-density lipoprotein (VLDL) and triglyceride levels.**
- total cholesterol and LDL levels are typically normal

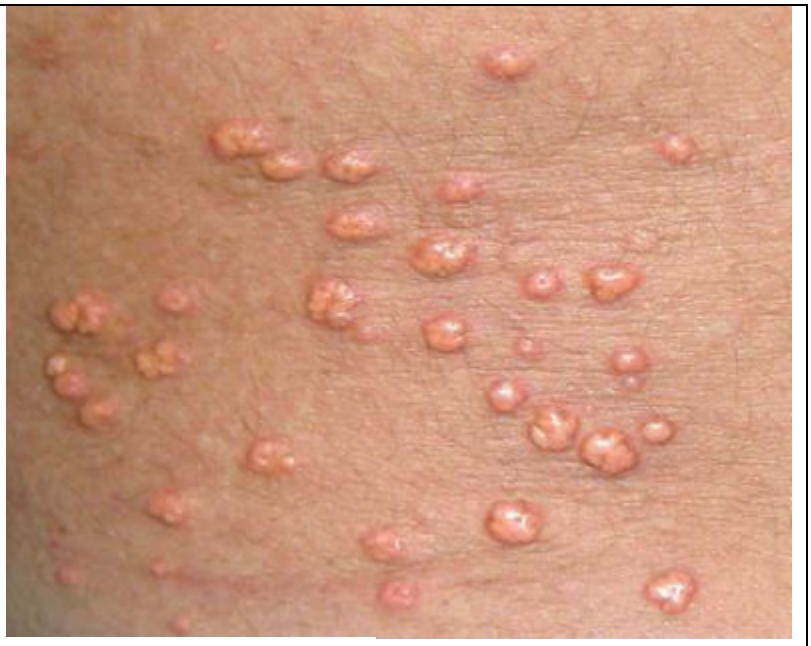
Management

- fibrates are generally used first-line
  - **the best option to reduce triglyceride is fibrate or omega 3 fatty acids**
- statins do reduce triglyceride levels and they may be indicated, particularly if there is mixed hyperlipidaemia

Which lipid abnormalities are most likely to be detected in a patient with type 2 diabetes?

- **Small dense LDL molecules** (LDL is not typically elevated in type 2 diabetes)
- ↓↓ HDL
- ↑↑Triglycerides





Eruptive xanthomata

Hypertriglyceridaemia (NICE 2015)

The commonest cause of a mild hypertriglyceridaemia is obesity secondary to a reduced efficacy of lipoprotein lipase activity and overproduction of VLDL.

Alcohol consumption is a common cause of hypertriglyceridaemia.

- Hypertriglyceridaemia may be primary (familial) or secondary.
- **Secondary causes** include:
  - high alcohol intake
  - type 2 diabetes mellitus
    - Lipoprotein lipase hydrolyzes triglycerides in chylomicrons and very low-density lipoprotein (VLDL), releasing free fatty acids. This pathway is affected in diabetes, **because lipoprotein lipase requires insulin for full activity.**
    - **Bad diabetic control (↑↑ HbA_{1c}) leads to → hypertriglyceridaemia. As such the first priority in this patient is to improve the glucose control with a second oral agent.**
    - Hepatic fat content is a determinant of postprandial triglyceride levels in type 2 diabetes, and increased hepatic fat is associated with elevated triglyceride levels.

- JBS2 guidelines suggest that all patients with type 2 diabetes should be prescribed a statin, even if their cholesterol is within the target range, although statin therapy impacts most on low-density lipoprotein (LDL) cholesterol.
- In patients with type 2 diabetes who have hypertriglyceridaemia despite optimal glucose control and statin therapy, treatments targeted for triglyceride reduction, such as niacin, fibrates or omega-3 fatty supplementation should be considered.
- **High triglycerides and low high-density lipoprotein (HDL) cholesterol are the commonest lipid abnormality seen in type 2 diabetes, and both are associated with increased cardiovascular risk.**
- Studies indicated that elevated triglyceride levels are associated with increased cardiovascular risk, particularly in the presence of low HDL cholesterol, a situation seen most commonly in patients with type 2

Hypertriglyceridaemia is often present in non-alcoholic steatohepatitis, but this condition is typically (though not always) associated with obesity.

hypertriglyceridaemia and raised transaminases are suggestive of increased hepatic fat → associated with Non-alcoholic steatohepatitis (NASH)

- renal disease
- **drugs** (cyclosporin, oestrogens, corticosteroids)

Medications That Elevate Triglycerides
Atypical anti-psychotics
Beta blockers
Bile acid binding resins
Estrogen (in higher dose oral contraceptives and unopposed oral estrogen)
Glucocorticoids
Immunosuppressants
Isotretinoin
Protease inhibitors
Tamoxifen
Thiazides

- bulimia nervosa
- pregnancy

Complications

- **Triglycerides above 1.7 are thought to be associated with around a 30% relative increase in cardiovascular disease events.**

- **Triglycerides were seen as the strongest independent risk factor for cardiovascular death in a patient with impaired glucose tolerance, ahead of other more established risk factors such as smoking, body weight or blood pressure.**

- Triglyceride levels greater than 11.2 mmol/l (1000 mg)increase the risk of acute pancreatitis
  - to prevent pancreatitis → reduce triglyceride levels to < 5.6 mmol/l (500 mg/dL).
- **elevated triglycerides associated with Increased insulin resistance**
  - **Triglyceride/HDL ratio is most predictive of insulin resistance.**
  - TG/HDL can be used to stratify both future risk of the development of cardiovascular disease and future risk of diabetes mellitus.

Management

For people with a TG concentration > 20 mmol/l that is not a result of excess alcohol or poor glycaemic control, refer for urgent specialist review (i.e at a regional lipid clinic).

- For people with a triglyceride concentration between 10 and 20 mmol/L:
  - Repeat the triglyceride measurement with a fasting test (following a meal, the chylomicron level rises in the serum which will lead to a rise in triglyceride levels)
  - Review for potential secondary causes of hyperlipidaemia
  - Address lifestyle factors: encourage weight loss, healthy diet and exercise
    - **Disordered free fatty acid handling is associated with increased central fat**, increased cardiovascular risk, and hepatic steatosis. Weight loss is an important treatment option in this case.
  - Commence high-potency statins (atorvastatin, rosuvastatin) if unable to address the triglyceride level through lifestyle measures. Monitor liver function tests and creatine kinase in these patients
    - Statins result in only a modest reduction in triglycerides versus their impact on LDL cholesterol.
  - Fibrates can also be used (for example fenofibrate). These lower triglycerides through **increasing the activity of lipoprotein lipase**
    - However, fibrates have not been shown to reduce cardiovascular events in the presence of diabetes, while statins have. Thus, **an isolated hypertriglyceridaemia in the presence of significant cardiovascular risk factors, in a patient not currently on a statin, should be managed with the introduction of a statin.**
    - **Fenofibrate increases HDL-C by 10-15% and reduces plasma TG by 15-20%.**
    - Concomitant fibrate-statin use is associated with an increased risk of myopathy so evaluation of combination therapy for safety and tolerability is important.
  - **Omega-3**-acid ethyl esters and nicotinic acid are other pharmacological options
    - **Trials of omega 3 supplementation suggest that it is associated with triglyceride reduction of up to 38%.**
    - **OMACOR (omega-3-acid ethyl esters) : Mode of action → Increases peroxisomomal beta-oxidation of fatty acids in the liver**
  - **Nicotinic acid**
    - it lower both cholesterol and triglyceride concentrations by inhibiting synthesis and increases HDL-cholesterol when used in doses of 1.5-3g daily.

- It is recommended for use by specialists in combination with a statin, where a statin alone has failed to adequately control dyslipidaemia.
- **Add of nicotinic acid → raise HDL cholesterol level by great amount**
- the value of nicotinic acid is limited by its side-effects (especially vasodilatation)
- **may increase blood glucose in some patients. many mechanisms have been suggested for this**:
  - Since **nicotinic acid inhibits triglyceride synthesis**, it may be that the increased availability of free fatty acids stimulates hepatic glucose output by increasing gluconeogenesis or replacing glucose as the primary energy source.
  - Higher levels of fatty acids may also block glucose uptake by skeletal muscle.
  - Direct effects on beta-cell function have also been postulated.

- For people with a triglyceride concentration between 4.5 and 9.9 mmol/L, optimize the management of other CVD risk factors present.

Treatment Guidelines for Hypertriglyceridemia.

- Initiate therapeutic lifestyle changes (weight loss/exercise) first
- Reduce triglyceride level to less than 500 mg/dL to prevent pancreatitis
- Primary aim of medical therapy is to reach LDL goal
- Secondary aim of therapy is to reach non-HDL goal
- In patients with CHD or CHD risk equivalents, tertiary aim of therapy is to reach HDL goal.

Lipoprotein lipase deficiency

Pathogenesis:

- Dietary triglycerides in cholesterol are packaged by gastrointestinal epithelial cells into large lipoprotein particles called chylomicrons.
- chylomicrons bind to the enzyme lipoprotein lipase, which is located on endothelial surfaces.

- This enzyme is activated by a protein contained in the chylomicron, apolipoprotein CII, liberating free fatty acids and monoglycerides, which then pass through the endothelial cells and enter adipocyte or muscle cells.
- Complete inactivation of either lipoprotein lipase or apolipoprotein CII results in an accumulation of chylomicrons (type I lipoprotein elevation) due to failure of conversion to the chylomicron remnant particle.

Presentation:

- usually present in infancy with recurrent attacks of abdominal pain caused by pancreatitis.
- eruptive xanthomas resulting from triglyceride deposition.

Treatment

- life- long low-fat diet

This milky looking serum sample is due to hyperchylomicronaemia/hypertriglyceridaemia and is a consequence of deficiency of lipoprotein lipase (LPL).

- **Causes:**
  - primary condition (rare) : autosomal recessive loss of LPL
  - secondary to diseases (more common) such as:
    - Pancreatitis
    - Hypothyroidism
    - Type 1 diabetes
    - Alcoholism, and
    - Cushing's syndrome.
- Apolipoprotein C-II deficiency (rare autosomal recessive hereditary disorder) is an inhibitor to lipoprotein lipase and may cause this type of appearance, but is extremely rare and manifests in childhood.

Question

Analysis of a patient lipoprotein profile shows a deficiency of apolipoprotein C-II. All other lipoproteins are normal.

Which lipid profile is most likely to be shown?

Answer → **Elevated levels of both chylomicrons and VLDLs**

- Apolipoprotein C-II (Apo C-II) is an essential co-factor of lipoprotein lipase, which hydrolyzes triglyceride in chylomicrons and VLDLs.

Hyperlipidaemia: xanthomata

The presence of tendon xanthomata and ↑LDL, ↑T.chol ≡ HDL meet the diagnostic criteria for familial hypercholesterolemia.

Xanthomas

- **Tuboeruptive xanthomas** occur in type III hyperlipoproteinaemia
- **Eruptive xanthomas** are associated with hyperchylomicronaemia (type I and type V hyperlipoproteinaemia)
- **Xanthoma tendinosum**, which are nodular swellings of tendons, usually occur in type II hyperlipoproteinaemia

Characteristic xanthomata seen in hyperlipidaemia:

Palmar xanthoma

- **remnant** hyperlipidaemia
- may less commonly be seen in familial hypercholesterolaemia

Eruptive **xanthoma** are due to high triglyceride levels and present as multiple red/yellow vesicles on the extensor surfaces (e.g. elbows, knees)

Causes of **eruptive** xanthoma

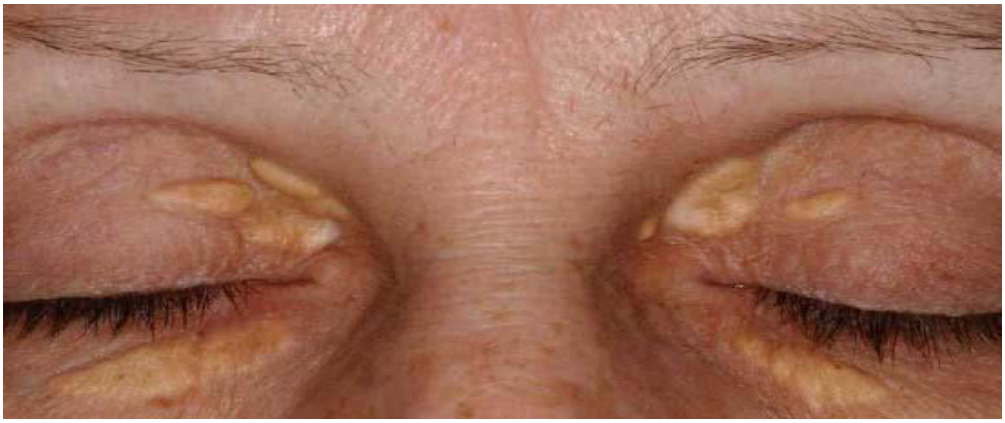
- familial hyper**triglyceride**aemia
- lipoprotein lipase deficiency

Tendon xanthoma, tuberous xanthoma, xanthelasma

- familial hyper**cholesterol**aemia
- remnant hyperlipidaemia

Xanthelasma

- xanthomas that appear on the eye are called xanthelasmas
- Xanthelasmas are yellow plaques on the medial aspects of the eyelids and are commonly bilateral.
- causes
  - **familial hypercholesterolemia**
  - primary biliary cirrhosis
  - also seen without lipid abnormalities
- Management of xanthelasma, options include:
  - surgical excision
  - topical trichloroacetic acid
  - laser therapy
  - electrodesiccation



xanthelasma

Hyperlipidaemia: secondary causes

Hypercholesterolaemia rather than hypertriglyceridaemia: nephrotic syndrome, cholestasis, hypothyroidism

Causes of predominantly hypertriglyceridaemia

- diabetes mellitus (types 1 and 2)
- obesity
- alcohol
- chronic renal failure
- drugs: thiazides, non-selective beta-blockers, unopposed oestrogen
- liver disease

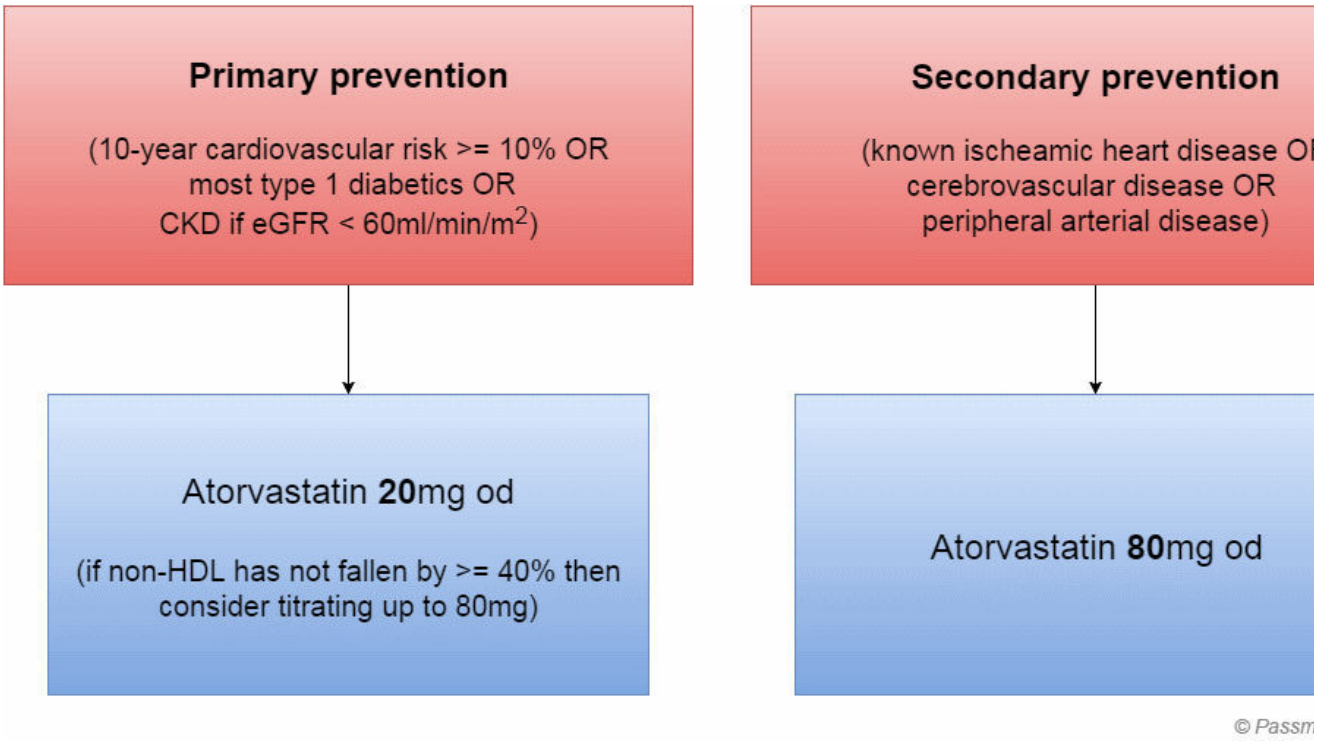
Causes of predominantly hypercholesterolaemia

- nephrotic syndrome
- cholestasis
- **hypothyroidism**
  - Frank hypothyroidism is said to occur in 4% of patients with dyslipidaemias;
  - **a raised thyroid-stimulating hormone (TSH)** & normal free T4 occur in 10% of patients with dyslipidaemia
  - Total cholesterol often improves to some degree with thyroxine therapy but statins might be required as well.

Hyperlipidaemia: management (NICE 2014)

In the primary prevention of CVD using statins aim for a reduction in non-HDL cholesterol of > 40%

Graphic showing choice of statin.



Statins reduce all-cause mortality (not just cardiovascular mortality) in primary prevention

Primary prevention - who and how to assess risk

- A systematic strategy should be used to identify people aged over 40 years who are likely to be at high risk of cardiovascular disease (CVD), defined as a 10-year risk of **10%** or greater.
- NICE recommend we use the **QRISK2** CVD risk assessment tool for patients aged <= 84 years. Patients >= 85 years are at high risk of CVD due to their age.
- QRISK2 should not be used in the following situations as there are more specific guidelines for these patient groups:
  - type 1 diabetics
  - patients with an estimated glomerular filtration rate (eGFR) less than 60 ml/min and/or albuminuria
  - patients with a history of familial hyperlipidaemia
- NICE suggest QRISK2 may underestimate CVD risk in the following population groups:
  - people treated for HIV
  - people with serious mental health problems
  - people taking medicines that can cause dyslipidaemia such as antipsychotics, corticosteroids or immunosuppressant drugs
  - people with autoimmune disorders/systemic inflammatory disorders such as systemic lupus erythematosus

Measuring lipid levels

- When measuring lipids both the total cholesterol and HDL should be checking to provide the most accurate risk of CVD.
- A full lipid profile should also be checked (i.e. including triglycerides) before starting a statin. The samples does not need to be fasting.

- When monitoring for dyslipidaemia in people with type 2 diabetes, Confirm dyslipidaemia using a **repeat sample** (fasting or non-fasting) before deciding on further management strategies. **[new 2015]**
- In the vast majority of patient the cholesterol measurements will be fed into the QRISK2 tool. If however the patient's cholesterol is very high we should consider familial hyperlipidaemia.
- NICE recommend the following that we should consider the possibility of familial hypercholesterolaemia and investigate further if the total cholesterol concentration is > 7.5 mmol/l and there is a family history of premature coronary heart disease.
- They also recommend referring people with a total cholesterol > 9.0 mmol/l or a non-HDL cholesterol (i.e. LDL) of > 7.5 mmol/l even in the absence of a first-degree family history of premature coronary heart disease.

Interpreting the QRISK2 result

- Probably the headline changes in the 2014 guidelines was the new, lower cut-off of 10-year CVD risk cut-off of 10%.
- **NICE now recommend we offer a statin to people with a QRISK2 10-year risk of >= 10%**
- Lifestyle factors are of course important and NICE recommend that we give patients the option of having their CVD risk reassessed after a period of time before starting a statin.
- Atorvastatin 20mg should be offered first-line.

Special situations

- **Type 1 diabetes mellitus**
  - NICE recommend that we 'consider statin treatment for the primary prevention of CVD in all adults with type 1 diabetes'
  - atorvastatin 20 mg should be offered if type 1 diabetics who are:
    → older than 40 years, or
    → have had diabetes for more than 10 years or
    → have established nephropathy or
    → have other CVD risk factors
- **Chronic kidney disease (CKD)**
  - atorvastatin 20mg should be offered to patients with CKD
  - increase the dose if a greater than 40% reduction in non-HDL cholesterol is not achieved and the eGFR > 30 ml/min. If the eGFR is < 30 ml/min a renal specialist should be consulted before increasing the dose
- **Secondary prevention**
  - All patients with CVD should be taking a statin in the absence of any contraindication.
  - Atorvastatin 80mg should be offered first-line.

- **LDL should be treated to the secondary prevention target of <2.0 mmol/L and triglycerides to the 1.7 mmol/L target.**

Follow-up of people started on statins

- NICE recommend we follow-up patients at 3 months
- repeat a full lipid profile
- if the non-HDL cholesterol has not fallen by at least 40% concordance and lifestyle changes should be discussed with the patient
- NICE recommend we consider increasing the dose of atorvastatin up to 80mg

Lifestyle modifications

Cardioprotective diet

- total fat intake should be <= 30% of total energy intake
- saturated fats should be <= 7% of total energy intake
- intake of dietary cholesterol should be < 300 mg/day
- saturated fats should be replaced by monounsaturated and polyunsaturated fats where possible
- replace saturated and monounsaturated fat intake with olive oil, rapeseed oil or spreads based on these oils
- choose wholegrain varieties of starchy food
- reduce their intake of sugar and food products containing refined sugars including fructose
- eat at least 5 portions of fruit and vegetables per day
- eat at least 2 portions of fish per week, including a portion of oily fish
- eat at least 4 to 5 portions of unsalted nuts, seeds and legumes per week

Physical activity

- each week aim for at least 150 minutes of moderate intensity aerobic activity or 75 minutes of vigorous intensity aerobic activity or a mix of moderate and vigorous aerobic activity
- do muscle strengthening activities on 2 or more days a week that work all major muscle groups (legs, hips, back, abdomen, chest, shoulders and arms) in line with national guidance for the general population

Weight management

Alcohol intake: males drink no more than 3-4 units/day and females no more than 2-3 units/day

Smoking cessation

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lipid-lowering agents

mechanism of action and adverse effects

The following table compares the side-effects of drugs used in hyperlipidaemia:

Drugs	Mechanism of action	Adverse effects
Statins	HMG CoA reductase inhibitors	Myositis, deranged LFTs

Drugs	Mechanism of action	Adverse effects
Ezetimibe	Decreases cholesterol absorption in the small intestine	Headache
Nicotinic acid	Decreases hepatic VLDL secretion	Flushing, myositis
Fibrates	**Agonist of PPAR-alpha therefore increases lipoprotein lipase expression**	Myositis, pruritus, cholestasis
Cholestyramine	Decreases bile acid reabsorption in the small intestine, upregulating the amount of cholesterol that is converted to bile acid	GI side-effects

PPAR-α agonists (The fibrate) → ↓serum triglyceride levels and ↑ HDL-cholesterol
PPAR-γ agonists (the glitazones) → ↓free fatty acid levels → ↓insulin resistance → ↓blood glucose levels

Statins

Statins inhibit HMG-CoA reductase, the rate-limiting enzyme in hepatic cholesterol synthesis

Action

- Statins inhibit the action of HMG-CoA reductase, the rate-limiting enzyme in hepatic cholesterol synthesis

Indication

- **Statins are the first-line therapy for hypercholesterolemia**

Metabolism

- **Simvastatin, atorvastatin** and **lovastatin** are mainly metabolized by cytochrome **P450 (CYP) 3A4**,
- **fluvastatin** and **rosuvastatin** is metabolized by **CYP2C9**,
- **pravastatin** is excreted largely **unchanged**.

Adverse effects

- myopathy:
  - includes myalgia, myositis, rhabdomyolysis and asymptomatic raised creatine kinase.
  - It is important to check the CK in all patients with statin related muscle symptoms to exclude these serious causes.

- Statins decrease the synthesis of coenzyme Q_{10} and impair energy production within the muscle
- Risks factors for myopathy include:
  - advanced age,
  - female sex,
  - low body mass index
  - presence of multisystem disease such as diabetes mellitus.
- Statin-associated myopathy occurs in up to 5% of those treated with statins and may be exacerbated by the co-prescription of other drugs (see interaction blow)
- Myopathy is more common in lipophilic statins (simvastatin, atorvastatin) than relatively hydrophilic statins (rosuvastatin, pravastatin, fluvastatin)
- Myalgia (muscle pain): continue treatment as long as creatinine phosphokinase (CK) remain normal
- Statin-associated myopathy
  1. Muscle pain and weakness
  2. ↑ CK
  3. May progress to rhabdomyolysis: rare but severe side-effect that may lead to myoglobulinuria → AKI (↑ BUN and ↑ creatinine)
- Management of cardiovascular risk in case of statin-induced myalgia**.**
  - Myalgia can gradually improve with time, dose reduction, or changing to an alternative statin.
  - Myalgia is a side effect of all statins but the **incidence is probably less with rosuvastatin and pravastatin.**
  - Pravastatin and rosuvastatin are metabolised via different pathways when compared to simvastatin and atorvastatin.
  - Pravastatin may be suitable for primary prevention, **but in high-risk secondary prevention patient, a stronger agent is required such as rosuvastatin.**
  - Rosuvastatin can be effective at even low doses (5-10 mg).
    - Starting at a low dose and gradually titrating up can also minimise the risk of side effects: for example, start at 5 mg of rosuvastatin.

- Hepatotoxicity:
  - (~ 2% of patients)
  - ↑ LFTs due to the involvement of cytochrome P450 systems (CYP3A4 and CYP2C9) in the breakdown of statins
  - the 2014 NICE guidelines recommend checking LFTs at baseline, 3 months and 12 months.
  - Treatment should be discontinued if serum transaminase concentrations rise to and persist at **3 times** the upper limit of the reference range.
  - **If LFT are raised but less than twice the upper limit of normal.**
    - The options are to reduce the dose or consider an alternative statin.
    - **NICE advises reducing the dose in the first instance.**

        - Fibrates and ezetimibe are generally not recommended in patients with type 2 diabetes.
        - NICE suggests referral to a specialist if statins are completely not tolerated.
    - If there is a history of statin-related hepatitis or rhabdomyolysis, statins should generally be avoided in the future if possible.
- statins may increase the risk of intracerebral haemorrhage in patients who've previously had a stroke.
    - This effect is not seen in primary prevention.
    - For this reason the Royal College of Physicians recommend avoiding statins in patients with a history of intracerebral haemorrhage

Maintain a high index of suspicion for rhabdomyolysis if muscle pain occurs after administering statins

Who should receive a statin?

- all people with established cardiovascular disease (stroke, TIA, ischaemic heart disease, peripheral arterial disease)
- following the 2014 update, NICE recommend anyone with a 10-year cardiovascular risk >= 10%
- patients with type 2 diabetes mellitus should now be assessed using QRISK2 like other patients are, to determine whether they should be started on statinsStatins should be taken at night as this is when the majority of cholesterol synthesis takes place. This is especially true for simvastatin which has a shorter half-life than other statins

Current guidelines for lipid lowering*

	Total cholesterol (mmol/l)	LDL cholesterol
Joint British Societies	< 4.0	< 2.0
National Service Framework for CHD	< 5.0	< 3.0
SIGN 2007	< 5.0	< 3.0

*current NICE guidelines do not recommend a target cholesterol in primary prevention

Drug interactions with statins

P450 inhibitors ↑ CK and myopathy

- Other lipid-lowering agents
    - Fibrates and Nicotinic acid

    - Both agents may also cause myopathy → concomitant use with statins further increases the risk of myopathy
- CYP3A4 inhibitors
    - HIV/HCV protease inhibitors
    - Macrolides (especially erythromycin and clarithromycin)
    - Azole antifungals
    - **Cyclosporine**
    - Macrolides (especially erythromycin and clarithromycin)
    - azole antifungal
    - Antacid and antifungal agents are known to interact with atorvastatin.
- **Warfarin** and **digoxin** have well-recognised interactions with atorvastatin and simvastatin.
- **Antacid** and **antifungal** agents are known to interact with atorvastatin.
- **Agents which can precipitate Myopathy or rhabdomyolysis**
    - **calcium channel blockers**,
    - macrolide antibiotics,(eg: **Erythromycin**)
    - fibrates,
    - Amiodarone
    - **grapefruit juice.**
        - Grapefruit juice → reducing the CYP3A4-mediated first-pass (a member of the cytochrome P450 system.) → ↑ serum statins.
        - **Bergamottin** is a constituent of grapefruit juice and is metabolised by the cytochrome p450 3A4 pathway.

What to do in case of atorvastatin intolerance?

- NICE guidance currently recommends starting high-dose statins in patients with type 2 diabetes and established cardiovascular disease (atorvastatin 80 mg).
- If patient has been intolerant of atorvastatin at its maximum dose with myalgia or raised liver function tests (LFT less than twice the upper limit of normal),The options are:
    - **NICE advises reducing the dose in the first instance.**
    - NICE suggests referral to a specialist if statins are completely not tolerated (LFT ≥ twice the upper limit of normal)
    - Myalgia is a side effect of all statins but the incidence is probably less with rosuvastatin and pravastatin.
    - Starting at a low dose and gradually titrating up can also minimise the risk of side effects: for example, start at 5 mg of rosuvastatin.

- Normally in **pregnancy, cholesterol can increase by up to 50%**
- Omega-3 fatty acids can be used safely in pregnancy as monotherapy, and function to decrease maternal TG levels.
- With the exception of the bile acid sequestrants (BAS) such as cholestyramine , cholesterol-lowering medications should be stopped prior to pregnancy
- (NICE) guidelines recommend stopping cholesterol-lowering medications 3 months before attempting to conceive.

Which statin is associated with the lowest risk of rhabdomyolysis?

➔ **Fluvastatin**

- The lipophilic statins, simvastatin, lovastatin and cerivastatin are all associated with a higher incidence of rhabdomyolysis compared to hydrophilic statins.
- It is possible that the lipophilic statins have a greater ability to cross the myocyte cell membrane and cause direct effects on intracellular organelles.
- Cerivastatin has been withdrawn from the market as the risk of rhabdomyolysis was considered unacceptably high.

Contraindications

1. Active liver disease
2. Muscle disorder
3. Pregnancy, breastfeeding

Fibrates

Agents:

- bezafibrate, fenofibrate, and gemfibrozil

Mechanism of action:

- **activation of** the peroxisome proliferator-activated receptor alpha **(PPAR–α)** → ↓ LDL, ↑ HDL, ↓↓↓ triglyceride
  - ↑LDL receptor-mediated clearance of LDL → ↓ LDL
  - **increase high-density lipoprotein (HDL) synthesis.**
  - This leads to a corresponding fall in triglycerides due to a fall in very low-density lipoprotein (VLDL), and a rise in HDL.
- **enhance lipoprotein lipase activity,**
  - fibrates inhibit the secretion of triglycerides from the liver and stimulates the clearance of triglycerides by activating lipoprotein lipase.
- In total, they reduce triglycerides by 20–60%, LDL by 5–25%, and increase HDL by 15–30%.

Indication:

- second-line drug of choice in hyperlipidemia, most effective for lowering triglycerides

Contraindications

- Renal insufficiency
- Liver failure
- Gall bladder diseases

Side effects

- Dyspepsia
- Myopathy
- **Cholelithiasis** (Cholesterol gallstones)
- ↑ LFTs (hepatotoxicity)

Interactions:

- enhance the effect of other drugs by inhibiting hepatic CYP450 (e.g., sulfonylureas, warfarin)

Ezetimibe

Ezetimibe→ reduces the absorption of cholesterol through the gut.

Mechanism of action:

- selective inhibition of cholesterol reabsorption at the brush border of enterocytes (cholesterol transporter NPC1L1) → ↓ LDL
  - **blocks cholesterol reabsorption at small intestine brush border via inhibiting NPC1L1 in the gut lumen.**

Indication

- Monotherapy: in contraindications or statin intolerance
  - When used as a monotherapy at a dose of 10 mg daily, ezetimibe reduces LDL cholesterol by around 20%. Increasing the dose further generally does not improve efficacy.
- Combination therapy (statin and ezetimibe): in insufficient LDL cholesterol reduction by statins
  - When used in conjunction with statins much greater LDL cholesterol reductions are seen.

Side effects (especially in combination therapy, otherwise rare):

- ↑ liver enzymes,
- angioedema,
- diarrhea,
- myalgia

Contraindication:

- coadministration with a statin during active liver disease

Nicotinic acid (niacin)

Nicotinic acid increases HDL levels

Mechanism of action:

- inhibits lipolysis and fatty acid release in adipose tissue → ↓ triglyceride and LDL synthesis, ↑ HDL
- Niacin lowers LDL-C and increases HDL-C by:
  - ↓ hepatic VLDL synthesis and secretion into circulation,
  - ↓ lipolysis in peripheral adipose tissue.

Indication:

- high LDL cholesterol and lipoprotein(a) levels (> 50 mg/dL) despite statin and ezetimibe therapy (or if statins are contraindicated)
- **Nicotinic acid is highly effective at raising high density lipoprotein (HDL) cholesterol**

Adverse effects

- **Flushing**
  - **NSAIDs (e.g., aspirin, ibuprofen) taken 30–60 minutes before niacin can prevent flushing by inhibiting prostaglandin synthesis.**
  - **Aspirin is commonly given as a pretreatment to alleviate niacin-induced flushing.**
  - Alternatively, the use of an extended-release niacin formulation, which is associated with less flushing, can considered.
  - This flushing is thought to be mediated by prostaglandin release.
  - sometimes accompanied by paresthesias such as tingling or itching.
  - The flushing typically begins within an hour of niacin intake.
  - Niacin-induced flushing often subsides over a few weeks as a result of tachyphylaxis.
- **Hyperglycemia** (impaired glucose tolerance)
  - **Nicotinic acid → may increase blood glucose → ↑ HA1c in diabetics**
  - suggested mechanisms for this:
    - nicotinic acid →↓ triglyceride synthesis → ↑free fatty acids:
      - ⇨ ↑free fatty acids →stimulates hepatic glucose output by increasing gluconeogenesis or replacing glucose as the primary energy source.
      - ⇨ ↑free fatty acids → block glucose uptake by skeletal muscle.
    - Direct effects on beta-cell function have also been postulated.
- irritates the gastric mucosa, exacerbates gastroesophageal reflux.
  - It is **contraindicated in patients with active peptic ulcer disease**
- Myositis
- **Hyperuricemia** → precipitates acute gout
- ↑ LFTs

Contraindications

- Liver failure
- Gout
- Hemorrhage
- Gastric ulcer
- Cardiovascular instability

Cholestyramine

Mechanism of action

- bile acid sequestrant
- bind bile acids in the intestine to prevent reabsorption and recycling
  - forces liver to consume cholesterol in the process of making more bile salts
  - binds bile acids in the intestine → interruption of enterohepatic circulation (↓ bile acid absorption and ↑ bile acid excretion) → lowers cholesterol
- The main effect on lipid profile → reduce LDL cholesterol (↓ unbound LDL),

- causes ↑ in LDL-receptor synthesis

Indications

- management of hyperlipidaemia.
  - Combination treatment with statins in hypercholesterinemia
- Digitoxin overdose
- Pruritus associated with elevated bile acid levels (cholestasis)
- Bile acid diarrhea
- Bowel obstruction
- occasionally used in Crohn's disease for treatment resistant diarrhoea.

Adverse effects

- abdominal cramps and constipation
- **decreases absorption of fat-soluble vitamins (e.g: vitamin D absorption will be reduced)**
- cholesterol gallstones
- ↑ LFTs
- Myalgia
- may raise level of triglycerides

Contraindications

- **Hypertriglyceridemia** > 300–500 mg/dL
- Hypertigylceridemia-induced pancreatitis

Drug interactions

- warfarin, digoxin, fat-soluble vitamins

OMACOR (omega-3-acid ethyl esters) → Increases peroxisomomal beta-oxidation of fatty acids

- omega-3 fatty acids make up only 30–50% of many fish oil supplements, whereas Omacor has 90% omega-3 fatty acids.

Action

- decreased serum triglyceride concentrations by 25-30%.
- The synthesis of triglycerides is inhibited through reduced production of triglycerides in the liver, as EPA and DHA are poor substrates for the enzymes responsible for triglyceride synthesis.
- EPA and DHA also inhibit esterification of other fatty acids.
- Omacor increases peroxisomomal beta-oxidation of fatty acids in the liver.

unwanted effects

- ↑ LDL-C levels

Tangier disease

- Tangier disease is an extremely rare autosomal recessive metabolic disorder.
- Characteristics of Tangier disease include:
  - Decreased levels or even a complete absence of high-density lipoproteins (HDL) concentrations in the plasma
  - Low cholesterol levels in the plasma
  - Increased cholesteryl esters in the tonsils, spleen, liver, skin and lymph nodes.
  - One easily seen characteristic usually found in children with Tangier disease is the presence of enlarged, yellow-orange tonsils.

Abetalipoproteinemia

- rare **autosomal recessive** disorder

Pathophysiology

- the microsomal triglyceride transfer protein is absent.
- **Deficiency of apolipoprotein B-48 and B-100.**
  - both necessary for chylomicron formation and fat absorption.
  - leads to deficiency of LDL, VLDL and chylomicrons.

Features

- fat malabsorption (chylomicrons accumulate in intestinal villi and prevent absorption)
  - deficiency of fat-soluble vitamins (A,D,E,K).
    - low calcium and phosphate levels, suggestive of vitamin D deficiency.
  - frothy or foul-smelling stools (Steatorrhoea)
  - Fatty liver.
- **neurologic symptoms**: ataxia, cognitive decline
  - **deficiency of vitamin E, especially, is responsible for the neurologic symptoms**
    - crucial substance for **myelin** formation and **antioxidant** properties
  - Hypocholesterolaemia syndrome resembling Friedreich's ataxia
- low visual acuity, caused by:
  - Retinitis pigmentosa
    - **fundoscopy reveals retinitis pigmentosa.**
  - Vitamin A deficiency.
- acanthocytosis,
  - seen in the peripheral smear (irregularly distributed spicule in red blood cells).
- hemolytic anemia
- failure to thrive
- muscle weakness.

Treatment

- **high-dose vitamin E** and
- restriction of long-chain fatty acids.

Gynaecomastia

- Gynaecomastia describes an abnormal amount of breast tissue in males and is usually caused by an **increased oestrogen: androgen ratio**.
- It is important to differentiate the causes of galactorrhoea (due to the actions of prolactin on breast tissue) from those of gynaecomastia

Causes of gynaecomastia

- physiological: normal in puberty
- syndromes with androgen deficiency: Kallman's, **Klinefelter's (47, XXY karyotype)**
- testicular failure: e.g. mumps
- liver disease
- testicular cancer e.g. **seminoma** secreting hCG
- ectopic tumour secretion
- **hyper**thyroidism
- haemodialysis
- starvation/refeeding
- drugs: see below

Drug causes of gynaecomastia (10-25% of cases)

Relatively Common causes

- **spironolactone (most common drug cause)**
- cimetidine
- **digoxin**
- cannabis
- diamorphine
- cyproterone
- finasteride
- gonadorelin analogues e.g. Goserelin, buserelin
- oestrogens, anabolic steroids

Very rare drug causes of gynaecomastia

- tricyclics
- isoniazid
- calcium channel blockers
- heroin
- busulfan
- methyldopa

September 2010 exam: H/O developed excessive amounts of breast tissue bilaterally. Which one of the following drugs is most likely to be responsible? Goserelin (Zoladex)

Pregnancy: physiological changes – endocrine

pregnancy → ↑ oestradiol & prolactin + ↓ LH/FSH.

The elevated oestradiol with suppressed luteinising hormone/follicle-stimulating hormone (LH/FSH) and an elevated prolactin concentration. With the recent amenorrhoea, the most likely diagnosis is pregnancy.

Progesterone

- during the first 2 weeks stimulates the fallopian tubes to secrete the nutrients the zygote/blastocyst requires
- placenta starts production at 6 weeks and takes over at 12 weeks
- progesterone inhibits uterine contractions by:
  - Inhibiting production of prostaglandins
  - Decreasing sensitivity to oxytocin
- stimulates development of lobules and alveoli

Oestrogen

- oestriol is major oestrogen (not oestradiol)
- stimulates the continued growth of the myometrium
- stimulates the growth of the ductal system of the breasts

Prolactin

- increase during pregnancy probably due to oestrogen rise
- initiates and maintains milk secretion of the mammary gland
- essential for the expression of the mammotropic effects of oestrogen and progesterone
- oestrogen and progesterone directly antagonises the stimulating effects of prolactin on milk synthesis

hCG

- secreted by syncitiotrophoblast, stimulated by GnRH produced in adjacent cytotrophoblast
- can be detected within 9 days, peak secretion at 9 weeks
- mimics LH, thus rescuing the corpus luteum from degenerating and ensuring early oestrogen and progesterone secretion
- stimulates production of relaxin
- may inhibit contractions induced by oxytocin
- **Beta-HCG has a degree of thyroid stimulating activity → ↓↓ (TSH).** No intervention is necessary

Thyroid hormones

- **Elevated total T4 is a normal finding at third trimester** of pregnancy due to increased thyroid binding globulin.
- Elevated thyroid hormones with suppression of TSH may be considered a normal variant in the early stages of pregnancy if there is a history of hyperemesis.
- **TSH** falls in the first and second trimester, and increases in the third trimester.
- Thyroid binding globulin increases during pregnancy.
- There is an increases in triiodothyronine (T3) and thyroxine (T4), but free T4 and T3 fall in the third trimester.

Also

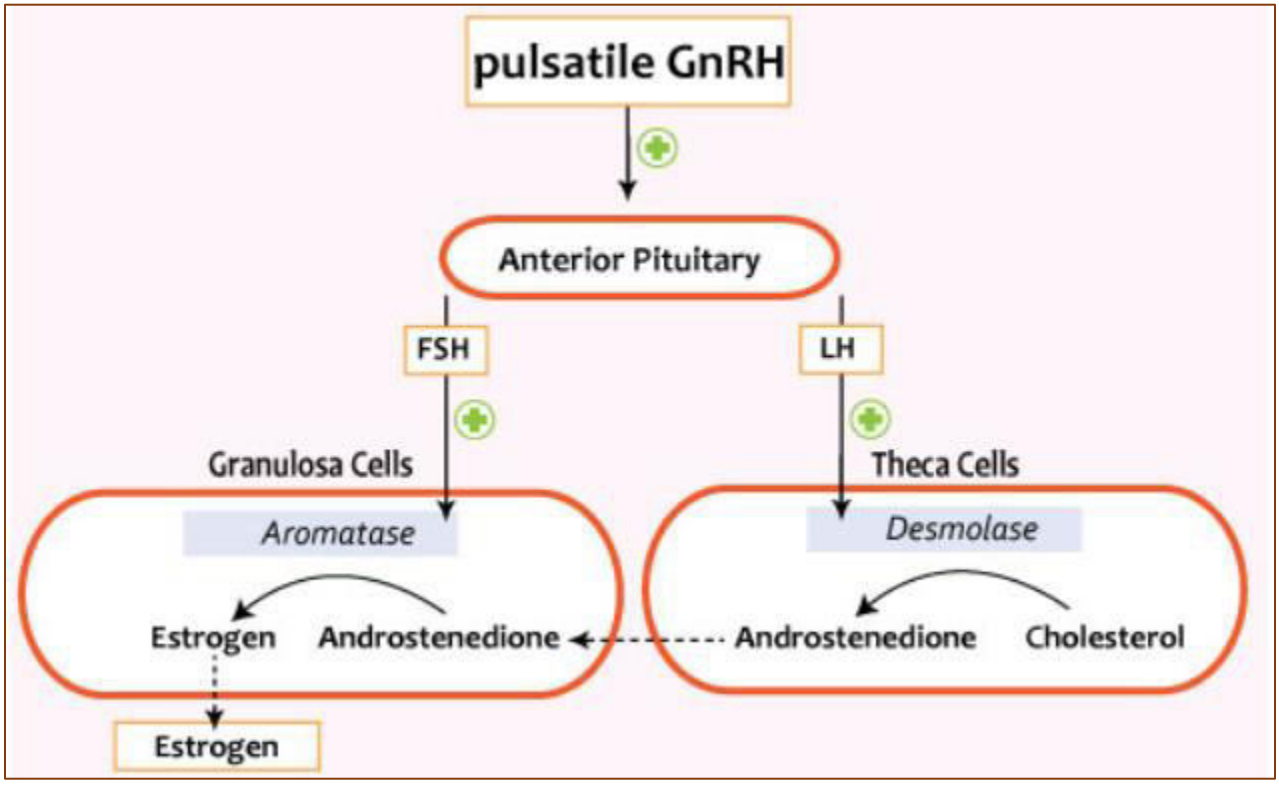
- Relaxin: suppresses myometrial contractions and relaxes the pelvic ligaments and pubic symphysis
- **Human placental lactogen** (**hPL**): has lactogenic actions (insignificant with respect to prolactin) - antagonises insulin, therefore making less glucose available to the mother - enhances protein metabolism

Telogen phase

- The telogen phase is the resting phase of the hair follicle.
- Due to extreme stress → shedding of hair leading to loss of thickness → loss of hair.
- **It occurs as a normal phenomenon one to three months after pregnancy.**
- No treatment is required (**only reassurance**) and hair thickness eventually recovers without further intervention.

Physiological effects of LH, FSH, and sex hormones

- ♀: **Ovaries**
  - **FSH:** follicular maturation → ↑ **estrogen** (see effects of estrogen and associated diseases)
  - **LH:** ↑ estrogen, **ovulation**, and ↑ **progesterone**
- ♂: **Testicles**
  - **FSH:** production of sperm, ↑ **inhibin**
  - **LH:** stimulation of Leydig cells → ↑ **production of testosterone**
    - Effects of testosterone
      - Development of male sexual characteristics during puberty
      - Spermatogenesis
      - **Increased libido**
      - **Anabolic effects**
        - Bone formation, growth
        - Muscle-building effects



Dihydrotestosterone (DHT)

- **Testosterone is a steroid hormone and can be converted to oestradiol.**
- It binds to **intracellular receptors** and is mostly bound to sex-hormone binding globulin.
- **LH** stimulates testosterone production and **FSH** spermatogenesis
- Testosterone is responsible for the development of internal genitalia and spermatogenesis.
- It is converted to dihydrotestosterone (DHT) in the body by the enzyme 5α-reductase.
- **DHT is a more active compound than testosterone and is involved in the expression of male secondary sex characteristics.**
- The absence of 5α-reductase or the absence of DHT receptors leads to testicular feminisation.
- Dihydrotestosterone (DHT) is responsible for the differentiation of the penis, scrotum and prostate during fetal development and early life.
- In late adulthood, DHT is responsible for prostate growth, male pattern baldness, and sebaceous gland activity.
- Testosterone is converted by the enzyme 5α-reductase to DHT to allow for the development of male external genitalia. Patients with 5α-reductase deficiency will have ambiguous genitalia at birth until they reach puberty, when the testosterone surge causes growth of external male genitalia, however, these patients are otherwise healthy.
- **obesity → lowered sex hormone binding globulin (SHBG) concentrations →low testosterone**
  - insulin downregulates SHBG expression and secretion and thus the hyperinsulinaemia of obesity leads to lower SHBG levels.
  - Measurement of his SHBG would confirm low levels and imply that free testosterone concentrations are normal
  - some people use a 'free androgen index' for the calculated free testosterone though there is debate about its utility in this situation.
- **↓ testosterone is due to either**
  1. ↓ free level
     - Due to ↓ production (Leydig and pituitary dysfunction)
     - Lead to ↑ synthesis of SHBG
  2. ↓ activity at receptor
     - often due to androgen receptor deficiency
- **testosterone therapy: side effects**
  - Erythrocytosis leading to **elevated haematocrit**
    - Haematocrit should be measured 3-6 months after initiating therapy and yearly thereafter.
    - Guidelines suggest that if haematocrit is increased and no other underlying cause is found, the dose should be down-titrated.
  - PSA, haematocrit, LFTs, and lipid levels need to be monitored serially.
  - Androgen replacement therapy is contraindicated in patients with prostate cancer and breast cancer.

testosterone secreting tumour of either ovarian or adrenal origin would typically cause a testosterone concentration above 7 nmol/L and would switch off LH/FSH with consequent hypo-oestrogenism.

Hormonal changes in weight-restricting adults

- ↑↑ GH
- ↓↓ LH
- Normal Prolactin
- T3 and T4 are often low-normal, with a normal (TSH).
- ↑↑ **Cortisol ,** often fail to suppress with dexamethasone.
- The most likely reason for the elevation in Cortisol is a stress response related to starvation.
- Weight gain will lead to a restoration of the normal menstrual cycle.

Polycystic ovarian syndrome (PCOS)

Polycystic ovarian syndrome - ovarian cysts are the most consistent feature

Infertility in PCOS - clomifene is superior to metformin

- PCOS is a complex condition of ovarian dysfunction thought to affect between 5-20% of women of reproductive age.
- The aetiology of PCOS is not fully understood. **Both hyperinsulinaemia and high levels of luteinizing hormone** are seen in PCOS and there appears to be some overlap with the metabolic syndrome.

Features

- Oligo/amenorrhoea 70%
- hirsutism, acne (due to hyperandrogenism) 60%
- obesity 35%
- subfertility and infertility 30%.
  - Chronic anovulation is the mechanism for infertility
- **acanthosis nigricans** (due to insulin resistance)
- psychological symptoms
- Clitoromegaly is seen occasionally in PCOS but is normally associated with very high androgen levels. **If clitoromegaly is found then further investigations to exclude an ovarian or adrenal androgen secreting tumour are required.**

Investigations

- pelvic ultrasound: multiple cysts on the ovaries
  - transvaginal ultrasound is said to have 91% diagnostic sensitivity
  - The presence of more than eight follicular cysts of less than 10 mm and increased ovarian stroma is sufficient to make the diagnosis.

- FSH, LH, prolactin, TSH, and testosterone are useful investigations:
  - **FSH will be normal or low, while LH will be elevated.**
    - Increased LH causes hyperplasia of ovarian theca cells.
    - Increased LH causes increased testosterone and androstenedione
  - **Raised LH:FSH ratio is a 'classical' feature** but is no longer thought to be useful in diagnosis.
    - LH/FSH ratio is normally about 1:1 in premenopausal women, but with PCOS a ratio of greater than 2:1 or 3:1 may be considered diagnostic.
  - Prolactin may be normal or mildly elevated.
    - 10% of patients with PCOS have hyperprolactinaemia, the aetiology of which is uncertain
  - **Testosterone may be normal or mildly elevated** however, **if markedly raised consider other causes**
    - **The appropriate initial biochemical investigation**
    - Normal or elevated testosterone, but with a low sexhormone-binding globulin (SHBG) level, resulting in a high free androgen index.
      - The significance of the sex hormone binding protein is that Sex hormone binding globulin is lower in PCOS. The reasons include that androgens reduce the globulin production, whereas oestrogen promotes production. It is a protein for transport of hormones in the blood.
  - hyperestrogenism
    - Increased androstenedione/testosterone in PCOS can be peripherally converted in adipose tissue to estrone by aromatase.
    - increased circulating levels of estrone → endometrial hyperplasia which is a precursor to endometrial carcinoma

- check for impaired glucose tolerance
  - **hyperinsulinaemia** (insulin resistance → high circulating insulin levels due to peripheral insulin resistance).
  - 10% develop frank type 2 diabetes mellitus.

long term complication of PCOS:
- **risks of diabetes** (due to peripheral insulin resistance),
- sleep apnoea,
- **endometrial cancer,**
- mental health disorders.

Diagnostic criteria

- According to the Rotterdam Consensus, **two** of the following three criteria are required for the diagnosis of the PCOS:
  1. oligo-/anovulation
  2. hyperandrogenism
     - clinical (hirsutism or less commonly male pattern alopecia) or

- **biochemical (raised free androgen index or free testosterone)**

3. polycystic ovaries on ultrasound.

Management

General

- Weight reduction
  - **the gold-standard treatment for PCOS**, and improves ovulation, androgen levels, hirsuitism and metabolic features associated with insulin resistance.
  - A loss in weight of only 5% reduces hirsuitism by up to 40%.
- if a women requires contraception then a combined oral contraceptive (COC) pill may help regulate her cycle and induce a monthly bleed (see below)

Hirsutism and acne

- **For associated hirsutism → Dianette® (cyproterone acetate) combined oral contraceptive pill (COC) is the most effective,** along with cosmetic treatments like waxing, shaving, plucking or electrolysis.
  - Possible options include a **third generation COC** which has fewer androgenic effects or **co-cyprindiol** which has an anti-androgen action. Both of these types of COC may carry an increased risk of venous thromboembolism
  - **Co-cyprindrol** because it contains cyproterone, an anti-androgen, **may be more effective than the COCP** in controlling acne and hirsuitism and acne in PCOS.
- **if doesn't respond to COC then topical eflornithine may be tried**
- spironolactone, flutamide and finasteride may be used under specialist supervision
  - used for its anti-androgenic properties
- A Cochrane meta-analysis has suggested that metformin is not effective in controlling hirsuitism and acne versus other options such as the COCP or co-cyprindrol

Infertility

- NICE guidelines from 2013 recommend **weight loss as the most important initial step.**
- anti-oestrogen therapies such as **clomifene** → the most effective treatment
  - work by occupying hypothalamic oestrogen receptors without activating them. This interferes with the binding of oestradiol and thus prevents negative feedback inhibition of FSH secretion
- metformin is also used, either combined with clomifene or alone, particularly in patients who are obese but is not a first line treatment
- gonadotrophins: usually reserved for patients who are resistant to clomifene

Other notes

- Surgical intervention with wedge ovarian resection can reduce androgen secretion and symptoms.

May 2009 exam: H/O infertility with PCOS. Apart from advising her to lose weight, which intervention is most effective in increasing her chances of conceiving? Clomifene (if clomifene – the first line - is not an option, metformin – the second line - is the right answer)

September 2009 exam: Which finding is most consistently seen in polycystic ovarian syndrome? Ovarian cysts on ultrasound

January 2012 exam: What is the mechanism of action of metformin in PCOS? Increases peripheral insulin sensitivity

Hirsutism and hypertrichosis

- hirsutism is often used to describe androgen-dependent hair growth in women
- hypertrichosis used for androgen-independent hair growth

Hirsutism

- **Definition**
  - Excessive male pattern hair growth in women (e.g., on the chin, above the upper lip, and around the umbilicus)
- **causes**
  - idiopathic (the most common)
  - excess androgen (10% of cases)
    - ⇨ Although hirsutism is generally associated with hyperandrogenemia, **one-half of women with mild symptoms** have **normal androgen levels**.
    - Polycystic ovarian syndrome is **the most common causes of hirsutism**
      - accounting for three out of every four cases.
    - Cushing's syndrome
    - congenital adrenal hyperplasia
    - androgen therapy
    - obesity: due to peripheral conversion oestrogens to androgens
    - adrenal tumour
    - androgen secreting ovarian tumour
      - Rapid onset of hirsutism
      - Virilization (e.g., clitoromegaly, increased muscle mass, loss of female body contour)
      - Palpable abdominal or pelvic mass
      - Early morning total testosterone level greater than200 ng per dL (6.94 nmol per L)
    - drugs

- **Features of hyperandrogenemia**
  - hirsutism,
  - could be asymptomatic
  - acne,
  - menstrual dysfunction,
  - alopecia,
- **Assessment of hirsutism**
  - Ferriman-Gallwey scoring system: 9 body areas are assigned a score of 0 - 4, a score > 15 is considered to indicate moderate or severe hirsutism
- **Work-up**

- evaluation is focused on testing for endocrinopathies and neoplasms, such as polycystic ovary syndrome, adrenal hyperplasia, thyroid dysfunction, Cushing syndrome, and androgen-secreting tumors.
- Women with mild hirsutism and normal menses do not require laboratory workup and can be treated empirically.
- Any patient with rapid onset of hirsutism, obvious signs of virilization, or a palpable abdominal or pelvic mass should undergo a thorough workup for a possible androgen secreting tumor.
- For patients with moderate or severe symptoms,
  - an early morning **total testosterone** level should be obtained,
  - if moderately elevated, it should be followed by a plasma **free testosterone** level.
    - A total testosterone level greater than 200 ng per dL (6.94 nmol per L) should prompt evaluation for an androgen-secreting tumor.
  - Further workup is guided by history and physical examination, and may include:
    - thyroid function tests,
    - prolactin level,
    - 17-hydroxyprogesterone level, and
    - corticotropin stimulation test.

- **Management of hirsutism**
  - advise weight loss if overweight
  - hair removal
    - Shaving is effective but needs to be repeated often.
    - Evidence for the effectiveness of electrolysis and laser therapy is limited.
    - cosmetic techniques such as waxing/bleaching - not available on the NHS
  - pharmacologic measures
    - combined oral contraceptive pills
      - **first-line pharmacologic treatment** in patients who are not planning a pregnancy
      - such as co-cyprindiol (Dianette) or ethinylestradiol and drospirenone (Yasmin).
      - Co-cyprindiol should not be used long-term due to the increased risk of venous thromboembolism
    - facial hirsutism: topical eflornithine - contraindicated in pregnancy and breast-feeding
  - Treatment response should be monitored for at least six months before making adjustments.

Hypertrichosis

- **Definition**
  - excessive **hair growth above the normal** for the age, sex and race of an individual, in contrast to **hirsutism**, which is excess hair growth **in women** following a male distributionpattern.

- **Causes of hypertrichosis**
  - drugs:

- **phenytoin**
- **minoxidil** (antihypertensive vasodilator. also used to treat androgenic alopecia → slows hair loss and promotes hair regrowth)
- **ciclosporin**
- diazoxide

➢ congenital hypertrichosis lanuginosa, congenital hypertrichosis terminalis
➢ metabolic disorders:
- thyroid dysfunction,
- porphyria cutanea tarda
- anorexia nervosa

- **Treatment**
  - ➢ Hair removal

Amenorrhoea

Primary amenorrhoea

- **Definition**
  - ➢ failure to start menses by the age of 16 years
- **Causes**
  - ➢ Turner's syndrome
  - ➢ testicular feminisation
  - ➢ congenital adrenal hyperplasia
  - ➢ congenital malformations of the genital tract

Secondary amenorrhoea

- **Definition**
  - ➢ absence of menses for more than 3 months (in women with previously regular cycles) or 6 months (in women with previously irregular cycles)
- **Causes**
  - ➢ Pregnancy → most common cause of secondary amenorrhea
  - ➢ hypothalamic amenorrhoea (e.g. Stress, **excessive exercise**) → ↓ FSH
    - **Weight-related amenorrhoea**
      - ❖ amenorrhoea can even be seen at the lower end of the normal range.
      - ❖ often seen in ballet dancers, who maintain a **low weight** and undergo periods of extreme physical exercise.
      - ❖ Gaining body weight to above the 50th centile for height normally results in the restoration of menstruation, but if this cannot be achieved oestrogen replacement might be considered.
  - ➢ polycystic ovarian syndrome (PCOS)
  - ➢ hyperprolactinaemia
  - ➢ premature ovarian failure → ↑ FSH
  - ➢ thyrotoxicosis (hypothyroidism may also cause amenorrhoea)
    - Hypothyroidism (↓ T3/T4 → ↑ TRH → ↑ prolactin → ↓ GnRH → ↓ estrogens)

- Sheehan's syndrome
- Asherman's syndrome (intrauterine adhesions)

Initial investigations

- exclude pregnancy with urinary or serum bHCG
- gonadotrophins: low levels indicate a hypothalamic cause where as raised levels suggest an ovarian problem (e.g. Premature ovarian failure)
- prolactin
- androgen levels: raised levels may be seen in PCOS
- oestradiol
- thyroid function tests

Primary ovarian failure means that the patient never has a normal menstrual cycle, and has the **triad of**

1- amenorrhea,
2- hypergonadotropinism,
3- and hypoestrogenism.

Premature ovarian failure (Premature ovarian insufficiency)

The history of prolonged cessation of menses with a normal weight, normal thyroid function tests and a history of coeliac disease is pointed to a diagnosis of premature ovarian failure

Criteria for diagnosis *(NICE guidelines: November 2015)*

1. age under 40 years
2. menopausal symptoms (including no or infrequent periods)
3. **and** elevated FSH levels **on 2 blood samples** taken 4–6 weeks apart.

Epidemiology

- It occurs in around 1 in 100 women.

Causes

- idiopathic - the most common cause
- chemotherapy
- **autoimmune**
  - Autoimmune disease is responsible for 20% of cases.
    - It occurs in 10% of women with Addison's disease
    - and in 25% of women with autoimmune thyroid disease.
- radiation

Features

- **prolonged amenorrhoea**
- climacteric symptoms: hot flushes, night sweats
- infertility
- secondary amenorrhoea
- raised FSH, LH levels
  - **↑↑ (FSH), + ↓↓oestradiol**

    - FSH levels above 30 IU/L are generally considered post menopausal.
    - Levels above 12 are considered raised in a woman still having periods.
- sex hormone releasing hormones would be elevated in an attempt to drive LH and follicle-stimulating hormone (FSH) release.
- Testosterone levels vary in women and are increased in women who are overweight because of peripheral conversion to androgens in fat, and in patients with polycystic ovarian syndrome.

Treatment

- Spontaneous recovery of fertility is unlikely (occurs in only 5%).
- Require hormone replacement therapy (HRT) to protect against osteoporotic fracture.
    - HRT or a combined hormonal contraceptive
    - HRT may have a beneficial effect on blood pressure when compared with a combined oral contraceptive
    - both HRT and combined oral contraceptives offer bone protection
    - HRT is not a contraceptive.

Menopause (NICE guidelines: November 2015)

Definitions of perimenopause and menopause

- Peri-menopause → aged over 45,vasomotor symptoms and irregular periods
- menopause → aged over 45, no period for at least 12 months and are not using hormonal contraception

Symptoms associated with menopause

- vasomotor symptoms (for example, hot flushes and sweats)
    - hot-flashes **occur due** to erratic vasodilation of blood vessels in the skin, resulting in intense sweating.
    - Hot flashes are caused by low oestrogen which results in dysfunction of thermoregulation in the hypothalamus.
    - inappropriate peripheral vasodilatation and sweating lead to rapid heat loss and a drop in core temperature leading to shivering.
- musculoskeletal symptoms (for example, joint and muscle pain)
- effects on mood (for example, low mood)
- urogenital symptoms (for example, vaginal dryness)
    - vaginal atrophy can lead to vaginal dryness and dyspareunia as well as loss of libido and low mood.
- Sexual difficulties (for example, low sexual desire).
- Women with **obesity** tend to suffer from **fewer symptoms** in menopause due to **peripheral conversion of androgens to estrogen** in adipose tissue.

Consequences of menopause

- ↓↓ bone mineral density → osteoporotic fractures.
- ischaemic heart disease,
- ↓↓ insulin sensitivity
- ↑↑ thrombotic tendency.
- **Increased possibility of developing Alzheimer's dementia**
  - Oestrogen deficiency might play a role in the development of dementia.

Investigations

- androstenedione is produced by ovarian stromal cells and the adrenal glands.
- ↓ HDL (high-density lipoprotein) + ↑ total cholesterol levels
- ↑ FSH and LH
- ↓ estradiol + ↑ GnRH
  - Decreased estradiol release by the ovaries in menopause results in **increased release of gonadotropin-releasing hormone** from the hypothalamus.
  - **Estrone** is the dominant form of estrogen in menopausal women as it is produced by aromatase from androstenedione in adipose cells.

Management

- ***Vasomotor symptoms → hormone replacement therapy (HRT)***
  - women with a uterus → oestrogen and progestogen
  - Women without a uterus → Oestrogen alone.
    - Oestrogen only replacement is only appropriate for patients whose uterus has been removed due to the increased risk of endometrial cancer.
- **Psychological symptoms → low mood or anxiety →** HRT & CBT
  - women with low sexual desire → testosterone supplementation if HRT alone is not effective.
- **Urogenital atrophy →** vaginal oestrogen (including those on systemic HRT), also in whom systemic HRT is contraindicated.
  - If vaginal oestrogen does not relieve symptoms of urogenital atrophy, consider increasing the dose

Hormone replacement therapy (HRT)

Main indication for HRT: control of vasomotor symptoms

HRT: unopposed oestrogen increases risk of endometrial cancer

HRT: adding a progestogen increases the risk of breast cancer

- Hormone replacement therapy (HRT) involves the use of a small dose of oestrogen, combined with a progestogen (in women with a uterus), to help alleviate menopausal symptoms.

Unopposed oestrogen therapy is most appropriate for patient who had a hysterectomy and combined hormone replacement therapy (HRT) is unnecessary.

Indications

- **vasomotor symptoms such as flushing, insomnia and headaches (**The main indication**)**
- Premature menopause: should be continued until the age of 50 years. Most important reason is preventing the development of osteoporosis
- The other indications such as reversal of vaginal atrophy should be treated with other agents as first-line therapies

Advantages of hormone replacement therapy (HRT)

1. improvement in menopausal symptoms
2. protection against fractures of the wrist, spine and hip secondary to osteoporosis.
3. reduced incidence of colorectal cancer
4. reductions in the incidence of Alzheimer's

- **Hormone replacement therapy and effects on bone mass**
  - Reduction in total-body bone mass **begins in women in their late twenties**
  - This loss is accelerated at the menopause
  - Both trabecular bone loss at the level of the vertebrae and cortical bone loss at the radius are prevented by oestrogen therapy
  - The risk of osteoporotic fractures is reduced, but not eliminated, by oestrogen therapy
  - If the uterus has been removed in a patient, there is no need for additional progesterone therapy
  - **The effect of oestrogens on bone loss may be reduced after 10 years of oestrogen therapy**

Combined OCP:
↑ Risk of breast cancer
↑ Risk of DVT
↓ Risk of endometrial ca.

HRT long term adverse effects (NICE guidelines: November 2015)

- ***Venous thromboembolism*** *(VTE)*
  - **↑ risk of (VTE)**
  - VTE risk is greater for oral than transdermal preparations
  - the risk associated with transdermal HRT given at standard therapeutic doses is no greater than baseline population risk.
  - Consider transdermal rather than oral HRT for menopausal women who are at increased risk of VTE, including those with a BMI over 30 kg/m^2.
  - **Risk of DVT is 2–4 times higher in women on HRT**
- **Cardiovascular disease**
  - HRT does not increase cardiovascular disease risk when started in women **aged under 60 years**
  - HRT with **oestrogen alone** is associated with no, or reduced, risk of coronary heart disease
  - HRT with **oestrogen and progestogen** is associated with **little** or no increase in the risk of coronary heart disease.
  - taking oral (but not transdermal) **oestrogen** is associated with a small increase in the risk of **stroke**.
  - increased risk of ischaemic heart disease if taken more than 10 years after menopause

- ***Breast cancer*** *(increased by the addition of a progestogen)*
  - *HRT with **oestrogen alone** is associated with **little** or no change in the risk of breast cancer*
  - *HRT with **oestrogen and progestogen** can be associated with an **increase in the risk** of breast cancer and reduces after stopping HRT.*
  - the increased risk relates to duration of use
  - breast cancer incidence is higher in women using combined preparations compared to oestrogen-only preparations
  - the risk of breast cancer begins to decline when HRT is stopped and by 5 years it reaches the same level as in women who have never taken HRT
  - Women with mutated BRCA genes or existing breast cancer should not receive hormone replacement therapy during menopause.
- **Endometrial cancer**
  - increased risk of endometrial cancer: reduced by the addition of a progestogen but not eliminated completely. The BNF states that the additional risk is eliminated if a progestogen is given continuously

Combined treatment with oestrogen and progesterone increases the risk of VTE, stroke, breast cancer, and cardiovascular disease. Protective effects include reduction in osteoporosis and colorectal cancers.

Short term Side-effects

- Nausea
- breast tenderness
- fluid retention and weight gain
- unscheduled vaginal bleeding is a common side effect of HRT within the first 3 months of treatment

Effects of reducing and stopping of HRT

- gradually reducing HRT may limit recurrence of symptoms in the **short term**
- gradually reducing or immediately stopping HRT makes no difference to their symptoms in the **longer term**.

synthetic oestrogen - ethinyl oestradiol, for oestrogen replacement is not detectable on the traditional oestradiol assay. So this is why the oestradiol concentration is unrecordable and is also the reason why oestradiol should not be requested (but unfortunately is) whilst patients are taking the combined OCP.

Selective Estrogen Receptor Modulators (SERMs)

Raloxifene

- **Mechanism of action**
  - estrogen **antagonist** in **breast** and **endometrium**
    - (preventing endometrial/breast hyperplasia).
    - It differs from tamoxifen in this regard, because tamoxifen (another SERM) acts as a partial agonist at the endometrium, so can promote endometrial hyperplasia.
  - **agonist** in bone
    - to increase mineralisation
- **Clinical use**
  - osteoporosis in menopausal women
  - breast cancer prevention in women high risk for breast cancer
- **Toxicity**
  - ↑ risk of venous thromboembolism
  - induces menopause

- hot flashes

Tamoxifen

- **Mechanism of action**
  - estrogen **antagonist** in **breast**
  - estrogen **agonis**t in endometrium and **bone**
- **Clinical use**
  - estrogen and progesterone receptor positive breast cancer
  - breast cancer prevention in women high risk for breast cancer
- **Toxicity**
  - ↑ risk of venous thromboembolism
  - **↑ risk of endometrial cancer**
    - secondary to agonist activity
  - induces menopause
    - hot flashes

Androgen insensitivity syndrome

The testosterone which is in the male range, the history of hernias as a baby and absence of acne or secondary sexual hair are all pointers towards androgen insensitivity syndrome.

The presence of **breast development** in the **absence of secondary sexual hair**, with a history of **hernias** as a child is suggestive of a diagnosis of **androgen insensitivity syndrome**. It is likely that the hernias were related to **undescended testes**. The vagina is blind ended, and there are no ovaries.

- **X-linked recessive**
- due to end-organ resistance to testosterone causing genotypically male children (46XY) to have a female phenotype.
- Complete androgen insensitivity syndrome is the new term for testicular feminisation syndrome

Features

- primary amennorhoea
- undescended testes causing groin swellings, Crypt**orchidism** (absence of one or both testes from the scrotum)
- External genitalia ranges from normal female, to female with clitoromegaly, to under-developed male (hypospadias).
- **Associated with abdominal hernias.**
- breast development may occur as a result of conversion of testosterone to oestradiol

- The **feminisation** is a consequence of:
  - increased testicular secretion of oestradiol
  - **peripheral conversion of androgens to oestradiol**.

Diagnosis

- **high levels of LH**
- borderline/elevated levels of testosterone (with lack of virilization)
- **buccal smear** or chromosomal analysis to reveal 46XY genotype

Management

- counselling - raise child as female
- bilateral orchidectomy (increased risk of testicular cancer due to undescended testes)
  - typically performed after puberty
- oestrogen therapy

Azoospermia

- absence of spermatozoa after centrifugation of complete semen
- causes of Azoospermia:
  1. reproductive tract obstruction (Obstructive azoospermia)
     - congenital (absence of the vas deferens, idiopathic epididymal obstruction) or
     - acquired (from infection, vasectomy, trauma).
  2. inadequate production of spermatozoa.
- Investigations
  - hormonal analysis (FSH, testosterone) to define the cause of azoospermia.
    - provide a >90% prediction of the type of azoospermia (obstructive v. non-obstructive).
  - testicular biopsy
  - Couples in whom the man has **congenital reproductive tract obstruction** should have **cystic fibrosis gene mutation analysis** for both partners, as there is a high risk of the male being a CF carrier.
- Treatment
  - Acquired obstruction of the genital tract
    - can be treated using microsurgical reconstruction.
    - Alternatively, sperm can be retrieved from the testes and subsequently used for assisted reproduction.
  - The cause of non-obstructive azoospermia needs to be identified prior to any treatment.

Erectile dysfunction

- **Epidemiology**
  - Erectile dysfunction occurs in approximately 10% of all men and in > 50% of men over the age of 70 years.
- **Common causes**
  - psychological factors (20%),
  - drugs (25%) and

- endocrine causes.

- **the commonest cause in healthy younger age group is → Psychological factors**

Menstrual cycle

The menstrual cycle may be divided into the following phases:

	Follicular phase (proliferative phase) (from day 1 until day 14)	**Luteal phase (secretory phase)** (From day 15 until day 28)
Ovarian histology	• A number of follicles develop. • One follicle will become dominant around the mid-follicular phase	• Corpus luteum
Endometrial histology	• Proliferation of endometrium	• Endometrium changes to secretory lining under influence of progesterone
Hormones	• A rise in FSH results in the development of follicles which in turn secrete oestradiol • When the egg has matured, it secretes enough oestradiol to trigger the **acute release of LH. This in turn leads to ovulation** • **Graafian follicle** is a large mature tertiary follicle containing an oocyte that is ready to be ovulated. • Ovulation occurs 14 days before menses, regardless of cycle length. • estradiol stimulates the growth of the endometrium. • Progesterone levels are low • **FSH activates aromatase within granulosa cells, increasing estradiol production.** • The main hormone controlling the follicular phase is estradiol, secreted by Granulosa cells.	• corpus luteum produces (3 hormones) estrogen, inhibin, and progesterone. • **progesterone** is **significantly higher** than in other phases of the menstrual cycle. • If fertilisation does not occur the corpus luteum will degenerate and progesterone levels fall
Cervical mucus	• Following menstruation the mucus is thick and forms a plug across the external os • Just prior to ovulation the mucus becomes clear, acellular, low viscosity.	• Under the influence of progesterone it becomes thick, scant, and tacky

	Follicular phase (proliferative phase) (from day 1 until day 14)	Luteal phase (secretory phase) (From day 15 until day 28)
	It also becomes 'stretchy' - a quality termed spinnbarkeit	
Basal body temperature	• **Falls** prior to ovulation due to the influence of oestradiol	• **Rises** following ovulation in response to higher progesterone levels

- The normal menstrual cycle typically lasts 28 to 35 days.
- The length of the follicular phase can vary, but the luteal phase lasts for 14 days following ovulation.
- **Endometrial biopsy**
  - Endometrial biopsy is still performed as an indicator of ovulation and adequate progesterone secretion in the luteal phase.
  - **The presence of proliferative endometrium indicates that ovulation has not occurred.**
  - Proliferative endometrium is seen in the follicular phase before ovulation.
  - Secretory endometrium is the hallmark of ovulation: the endometrium thickens and contains more tortuous glands that secrete mucus.
  - Aplastic cells would be seen in neoplasia of the endometrium.
  - In pregnancy, the secretory endometrium would be much thicker (decidua).
- **Anovulation**
  - is the failure of the ovary to release ova.
  - common causes is:
  - hypothalamic dysfunction, characterized by failure of the pituitary gland to produce LH and FSH hormones needed for ovulation. This is common in women who are:
    - underweight,
    - **exercise excessively**, or
    - have delayed menarche.
  - Diagnosis of anovulation is difficult and is often done by temperature charting or measuring hormone levels.
- **Follicle stimulating hormone (FSH)**
  - **In women**,
    - FSH stimulates folliculogenesis during the follicular stage of the menstrual cycle to prepare for the next ovulation cycle.
    - FSH also stimulates granulosa cell hypertrophy and cell division as well as the enzyme aromatase within the granulosa cells, which converts androstenedione to estradiol.
  - **In men**,
    - binds to receptors on the basal membrane of **Sertoli cells**, leading to increased cAMP levels and activation of protein kinase. This, in turn, causes the Sertoli cells to **increase production of androgen binding proteins**.

- FSH also stimulates spermatogenesis.
- Men without or with low levels of FSH are unable to produce sperm and can be diagnosed with secondary hypogonadism.

Which hormone levels would be most likely to indicate the occurrence of ovulation?
➔ **Luteinising hormone**

At which point in the menstrual cycle do progesterone levels peak?
➔ **Luteal phase**
- Progesterone is secreted by the corpus luteum following ovulation.

Which mechanism is most likely responsible for the missed period in early pregnancy?
➔ **Syncytiotrophoblast produces human chorionic gonadotropin (hCG), which stimulates progesterone production by the corpus luteum.**

Ovarian hyperstimulation syndrome (OHSS)

- **Definition**
  - potentially life-threatening conditions that occurs as a result of fertility medications enlarging the ovaries and causing a fluid shift.
- **Causes**
  - clomiphene treatment or
  - following in-vitro fertilization(IVF), but **pathogenesis does not occur unless a dose of injectable hCG is given.**
- **Pathophysiology**
  - Effectively, OHSS results from disruption of the hypothalamic-pituitary-ovarian feedback system of the normal menstrual cycle.
  - Neovascularization due to follicular production of VEGF creates highly permeable vessels. These leaky vessels allow fluid to escape, leading to third-spacing in the abdomen. This third-spacing can manifest as ascites, edema, and pericardial effusion.
- **Risk factors:**
  - prior episodes of OHSS,
  - larger or more numerous follicles,
  - polycystic ovarian syndrome (PCOS).
- **Symptoms:**
  - typically begin within 10 days of treatment,
  - abdominal pain,
  - nausea, vomiting,
  - bloating,
  - sudden weight gain.

- **Signs of severe OHSS** include:
  - severe pain,
  - shortness of breath,
  - arterial and venous thromboembolisms, and
  - reduced liver function.

Hypogonadism

Primary hypogonadism (Hypergonadotropic hypogonadism)

- **Definition**:
  - insufficient sex steroid production in the gonads
- **Pathophysiology**
  - gonadal insufficiency → insufficient sex steroid production (↓ testosterone, ↓ estrogen) → increased gonadotropin secretion (↑ FSH and ↑ LH) from the anterior pituitary → lack of negative feedback from the impaired gonads → further ↑ FSH and ↑ LH levels
- **Causes**
  - Congenital abnormalities: (Primary gonadal insufficiency):
    - Turner syndrome (females),
      - webbed neck, short stature
    - Klinefelter syndrome (males),
      - gynecomastia
    - androgen insensitivity syndrome,
    - Mutation in the FSH and LH receptor genes
    - Cryptorchidism
    - Varicocele
    - Myotonic dystrophy.
  - Acquired diseases: (Secondary gonadal insufficiency) →(damage to leydig cells or ovarian tissue):
    - Medications (Radiation, chemotherapy, Ketoconazole, Glucocorticoids, Environmental toxins)
    - trauma/surgery,
    - autoimmune disease,
    - infections (**mumps**, tuberculosis)
    - **Testicular tumour, infiltration**
    - Chronic systemic illnesses (eg: Hepatic cirrhosis, Chronic renal failure)
    - Ageing
    - primary testicular failure (**idiopathic failure**).
- **Investigations**
  - (↑(LH) & (FSH) + ↓ testosterone + ↓ sperm count)
    - loss of negative feedback of testosterone results in ↑ LH
    - **FSH** levels are variable based on presence of inhibin
      - ↑ FSH if seminiferous tubule dysfunction is also present
      - inhibin normally released by Sertoli cells to inhibit FSH
      - if damaged that feedback is lost

- ❖ normal FSH if dysfunction is limited to Leydig cells
- ▪ ↓ function of Leydig cells → ↓ **testosterone** synthesis
  - ❖ any dysfunction isolated to Sertoli cells/seminiferous tubules does not result in ↓ testosterone synthesis
  - ❖ if testes are cryptorchid, testosterone production is normal because Leydig cells are not affected by ↑ temperature

➢ **Testicular ultrasound**
- ▪ **ultrasonic evaluation of the testes is the most appropriate investigation.**

Andropause is the term for the gradual decrease in serum testosterone concentration with age, but does not occur, usually, until after the age of 50.

Secondary hypogonadism (hypogonadotrophic hypogonadism)

- **Definition**:
  - ➢ insufficient gonadotropin-releasing hormone (GnRH) and/or gonadotropin release at the hypothalamic-pituitary axis
- **Pathophysiology**
  - ➢ In Kallmann syndrome:
    - ▪ impaired migration of GnRH cells and defective olfactory bulb → ↓ GnRH in hypothalamus → ↓ FSH and ↓ LH → ↓ testosterone and ↓ estrogen
  - ➢ In hypothalamic and/or pituitary lesions:
    - ▪ ↓ pituitary gonadotropins (↓ FSH and ↓ LH) → ↓ testosterone and ↓ estrogen
- **Causes**
  - ➢ Genetic disorders
    - ▪ **Kallmann's syndrome**
      - ❖ congenital GnRH deficiency
      - ❖ Other associated abnormalities include **anosmia**, midline defects particularly cleft palate, colour blindness, and deafness.
    - ▪ Idiopathic hypogonadotropic hypogonadism (IHH): genetic disorder characterized by a defect in GnRH production/action in the absence of anosmia
    - ▪ Prader-Willi syndrome
      - ❖ muscular hypotonia, short stature, facial dysmorphia
    - ▪ Gaucher's disease
      - ❖ hepatomegaly, splenomegaly, painful bone crisis
  - ➢ Hypothalamic and/or pituitary lesions due to:
    - ▪ Neoplasm (e.g. prolactinoma, craniopharyngioma, astrocytoma)
    - ▪ Trauma, surgery, irradiation
    - ▪ Infection
  - ➢ Eating disorders
  - ➢ associated with type 2 diabetes and obesity.
- **Investigations**
  - ➢ serum **testosterone** and **sperm count** are **subnormal** + **normal or reduced LH and FSH**

- **Prolactin level**
  - **Hyperprolactinaemia may be associated with a hypogonadotrophic hypogonadism** and signs such as galactorrhoea may be present. **This should be excluded.**
- measure of **free testosterone**
  - as total testosterone can be low due to SHBG being decreased in obesity and with ageing.
- pituitary MRI would be the best imaging technique to exclude other pituitary pathology.

Clinical features

- **Delayed puberty**
  - ♂
    - Testicular hypoplasia
    - ↓ Body hair growth (e.g., absent facial hair)
    - High-pitched voice
    - Smooth skin (no acne)
    - ↓ Lean body mass
  - ♀: primary amenorrhea
- Developmental abnormalities with genitalia (undescended testes, hypospadias)
- Infertility (↓ sperm count), impotence, and/or ↓ libido
- Secondary amenorrhea

Routine tests

- ↓ Serum testosterone levels and ↓ serum estrogen levels (in females)
- Determine if the source is primary or secondary hypogonadism.
  - Hypergonadotropic hypogonadism: ↑ GnRH, ↑ LH/FSH
  - Hypogonadotropic hypogonadism: ↓ GnRH, ↓ LH/FSH
- Bone scan may support the diagnosis of hypogonadism (↓ bone density (osteoporosis) or delayed epiphyseal closure).

Further tests: based on suspected etiology

- Genetic testing (for Klinefelter syndrome, Turner syndrome, Kallmann syndrome)
- Serum prolactin (↑ in prolactinoma)
- Pelvic ultrasound (e.g., gonadal dysgenesis in Klinefelter syndrome)
- Brain MRI (for CNS lesion or Kallmann syndrome)
- Adrenocorticotropic hormone stimulation test (ACTH stimulation test): to exclude congenital adrenal hyperplasia

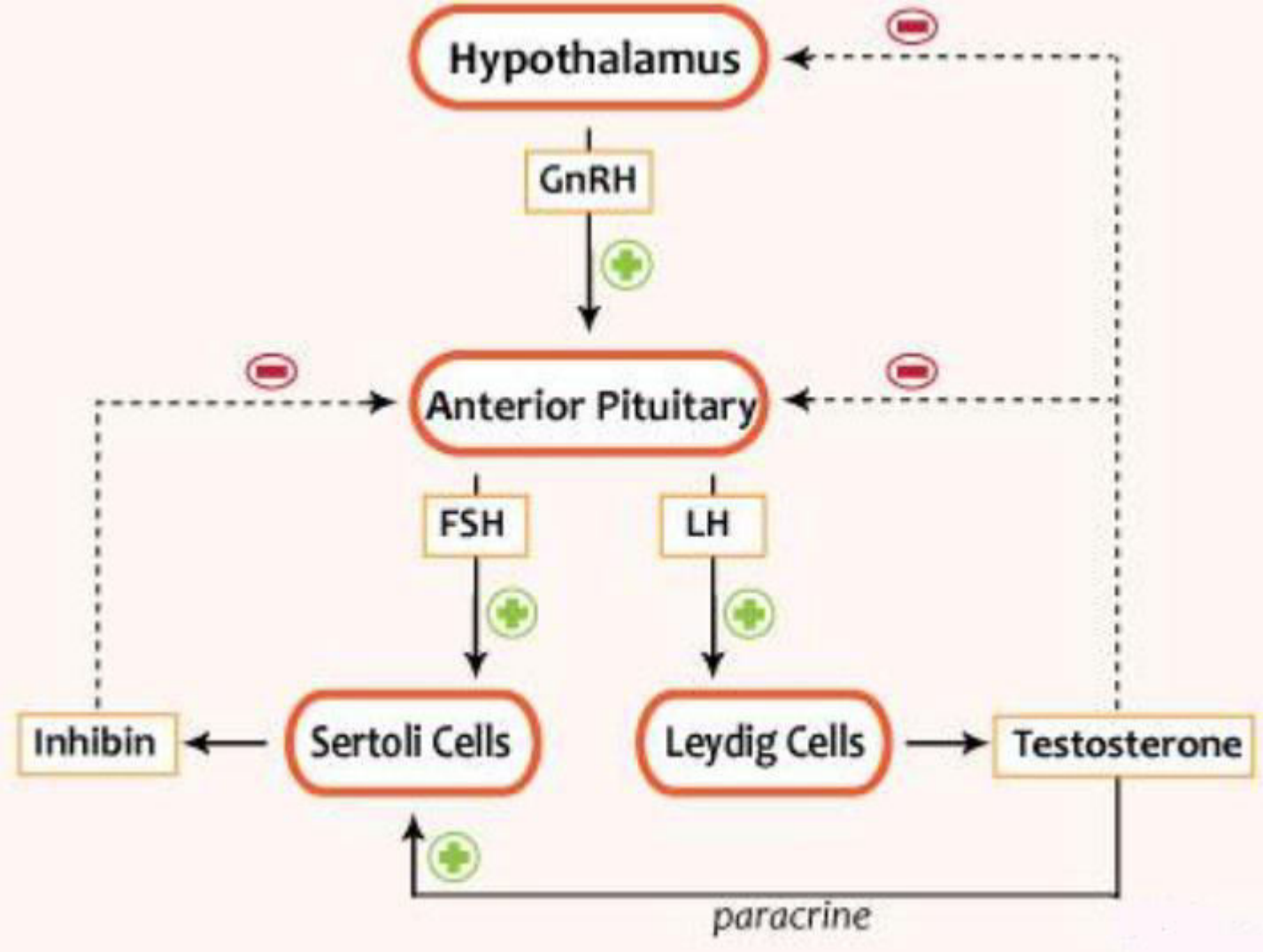
Treatment

- Treat underlying cause: e.g., surgical excision of tumors, pharmacotherapy for prolactinomas
- Hormone replacement therapy

Tip to remember
Testosterone and LH levels can help distinguish between different causes of abnormal sexual

development:

- High testosterone and high LH: defective androgen receptor (androgen insensitivity syndrome)
- High testosterone and low LH: testosterone-secreting tumor
- Low testosterone and high LH: primary hypogonadism
- Low testosterone and low LH: hypogonadotrophic hypogonadism



Contraception

Mechanisms of action:

- **Estrogen**
  - Hypothalamus: ↓ release of GnRH
  - Pituitary: ↓ LH → inhibits ovulation, ↓ FSH → prevents ovarian folliculogenesis
- **Progestin**
  - Endometrial atrophy, changes in cervical mucus (↓ volume and ↑ viscosity), and impaired fallopian tube peristalsis → inhibition of sperm ascension and egg implantation
  - Inhibits follicular maturation; ovulation may be suppressed (not consistent).

- **Antiprogestin**
  - inhibits or delays ovulation by inhibiting the progesterone receptor

Emergency contraception

- Most effective when taken within 3 days of intercourse
- Typically administered as a single dose or as two doses over one day
- Significantly less effective in patients who are obese or overweight
- **What is the action of emergency contraception in preventing conception following unprotected sexual intercourse.?**
  - **Decreasing tubal motility and ciliary activity** thereby preventing sperm from reaching the oocyte in the ampulla of the tube.
    (levonorgestrel 1.5 mg)
- **The rate of pregnancy is ≤ 3.0% if emergency contraception is taken within 72 hours** after unprotected sexual intercourse. The earlier it is takes, the lower the likelihood of pregnancy

Side-effects of the oral contraceptive pill

- **Breakthrough bleeding is most commonly associated with low-dose combined oral contraceptive pills, especially those containing 20 micrograms ethinylestradiol.**
- Nausea and vomiting are less with this dose.
- Migraine can occur in susceptible women, irrespective of the dosage.
- There is no appreciable increase in clotting risk or pregnancy rate with these pills.

Contraindications to the combined oral contraceptive pill

As well as age > 35 years, other absolute contraindications to the combined oral contraceptive pill (OCP) include a history of:

- Heart disease
- Pulmonary hypertension
- Arterial or venous thrombosis
- Cerebrovascular disease
- Liver disease
- Severe migraine
- Breast or genital tract cancer

Studies have shown that women taking estrogen- progestin combination OCPs before menopause have an increased risk of cervical carcinoma but a decreased risk of endometrial and ovarian carcinoma.

Progestin-only pills

- **Indications**
  - women who are unable to take regular oral contraceptives due to their side-effects or to the exacerbation of existing conditions like migraine.
  - breastfeeding women:
    - estrogen-containing combined contraceptives should be avoided in early postpartum period :
      - estrogen → inhibition of prolactin activity → reduce breast milk production.

- Estrogens → increased risk of thromboembolic events in the early postpartum period.

- **Action**
  - **Main contraceptive mechanism → thickens the cervical mucus, preventing the entry of sperm.**
    - Although it decreases tubal motility, this is more related to the occurrence of ectopic pregnancy.
    - The dose of progesterone is not sufficient to inhibit ovulation or reduce luteinising hormone (LH) secretion.

An entirely normal 16-year-old girl is very tall and would like to stop growing. What is the most appropriate treatment for her?

→ **Oral contraceptive pill**

- **The oral contraceptive pill used in this context would be associated with fusion of long-bone growth plates, and subsequent cessation of longitudinal growth.**
- Although ideally she should be encouraged not to receive medical intervention at all, in this situation use of the OCP represents the lowest-risk option.

Puberty

Physiology:

- The primary event of puberty is the initiation of a pulsatile secretion pattern of gonadotropin-releasing hormone.
- unknown initial trigger → ↑ activators and/or ↓ inhibitors of GnRH secretion → ↑ GnRH pulsing → ↑ FSH and ↑ LH levels

Puberty in girls

- **The sequence of pubertal events in girls:**
  1. **breast development** (thelarche) usually marks the first stage of puberty and is indicated by the presence of breast budding.
     - This begins between the ages of 9 years and12 years and continues to 12-18 years.
  2. Thelarche is typically followed by pubic hair growth (pubarche) secondary to production of adrenal androgens (adrenarche).
     - Pubic hair growth occurs at ages 9-14 years, and is complete at 12-16 years.
     - Adrenarche, the appearance of pubic and axillary hair during female puberty, depends on increased levels of adrenal androgens.
  3. Thelarche and pubarche are followed by acceleration of growth to maximum growth rate (growth spurt),
     - Peak height velocity is reached earlier (10-13 years) and growth is completed much earlier than in boys
  4. finally the onset of menses (menarche).
     - Menarche occurs relatively late (age 11-15 years).
     - Started with irregular menses (usually related to anovulatory cycle)

The first visible sign of puberty in males is testicular enlargement, while in females it is breast development.

Precocious puberty

Central precocious puberty has a central cause (e.g., hypothalamic lesions) and high GnRH levels; precocious pseudopuberty has a peripheral cause (e.g., germ cell tumors), without elevated GnRH levels

- **Definition:**
  - the appearance of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys
- **Classification**
  - **Central precocious puberty** (gonadotropin-dependent precocious puberty, true precocious puberty)
  - **Peripheral precocious puberty** (gonadotropin-independent precocious puberty, peripheral pseudopuberty, peripheral precocity)
- **Clinical features**
  - Precocious puberty may manifest with either development of all the secondary sexual features or occasionally as isolated premature thelarche, adrenarche, or menarche.
  - Accelerated growth and early skeletal maturity
  - Central precocious puberty (CPP): Premature sexual development typically follows the normal pattern of puberty, except that it is early.
  - Peripheral precocious puberty: may not follow the normal developmental pattern; may exhibit possible features of underlying condition (e.g., café-au-lait spots in neurofibromatosis, testicular mass in Leydig cell tumor)

Central precocious puberty

- **Definition:**
  - precocious puberty with elevated GnRH levels
- **Etiology**
  - Idiopathic or constitutional (most cases)
  - CNS lesions
    - midline hamartoma of the hypothalamus.
  - Pituitary gonadotropin-secreting tumors (rare)
  - Systemic conditions: tuberous sclerosis, neurofibromatosis
  - Obesity-related precocious sexual development due to increased levels of leptin in obesity
    - Obesity causes compensatory hyperinsulinemia (due to increased insulin resistance) and higher levels of leptin, which both lead to earlier development of sexual characteristics.
- **Pathophysiology:**
  - premature activation of the hypothalamo-hypophyseal axis → abnormally early initiation of pubertal changes → early development of secondary sexual characteristics and gonadarche

- **Diagnosis**
  - Laboratory tests
    - Basal LH and FSH (**The best initial lab test**): increased
    - GnRH stimulation test (**gold standard**): Gonadotropin (LH and FSH) levels increase after intravenous administration of GnRH.
    - Sex hormones
      - ♂: ↑ serum testosterone
      - ♀: ↑ serum estradiol
  - Imaging
    - Brain MRI/CT with contrast
    - X-ray of the left hand
- Therapy
  - GnRH agonist (e.g., leuprolide, buserelin), with close monitoring of therapy
  - Manage underlying cause

Peripheral precocious puberty

- **Definition:**
  - precocious puberty without elevated GnRH levels
- **Etiology**
  - ↑ Androgen production, e.g.:
    - **Ovarian cyst (most common cause)**
    - Congenital adrenal hyperplasia (CAH)
    - Virilizing ovarian and adrenocortical tumors
    - Leydig-cell tumor
  - ↑ Estrogen production, e.g.:
    - HCG-secreting germ cell tumors (e.g., granulosa cell tumor)
    - Rarely: adrenal gland tumors that produce estrogen
    - **McCune-Albright syndrome**
      - **McCune-Albright syndrome** is established on clinical grounds, with the presence of:
        - ⇨ precocious puberty,
        - ⇨ bony fibromas leading to possible pathological fractures,
        - ⇨ thyrotoxicosis, and
        - ⇨ café au lait spots
  - ↑ β-HCG production: e.g.,
    - Hepatoblastoma
    - pinealoma
      - Pinealoma is a tumor of the pineal gland.
      - The pineal gland produces the hormone melatonin which plays a role in regulating circadian rhythms.
      - can lead to paralysis of conjugate vertical gaze by the compression of superior colliculi , resulting in vertical gaze palsy
      - present as precocious puberty in males due to increased beta-human chorionic gonadotropin production
  - Primary hypothyroidism
  - Obesity-related precocious sexual development due to compensatory hyperinsulinemia (caused by increased insulin resistance in obesity)

- **Diagnosis**
  - Imaging: **ultrasound** of the pelvis, testicles, and abdomen
  - Laboratory tests
    - ↑ Estrogen/testosterone (depending on the tumor), ↓ FSH, ↓ LH
    - Tests to detect primary underlying causes: e.g., TSH, FT3, β-HCG, CT/MRI
- **Therapy**
  - Precocious puberty caused by excessive hormonal production from a tumor in the body: surgical removal
  - Precocious puberty caused by CAH: cortisol replacement
  - Ovarian cysts: No intervention is necessary, as spontaneous resolution of ovarian cysts is common.

Delayed puberty

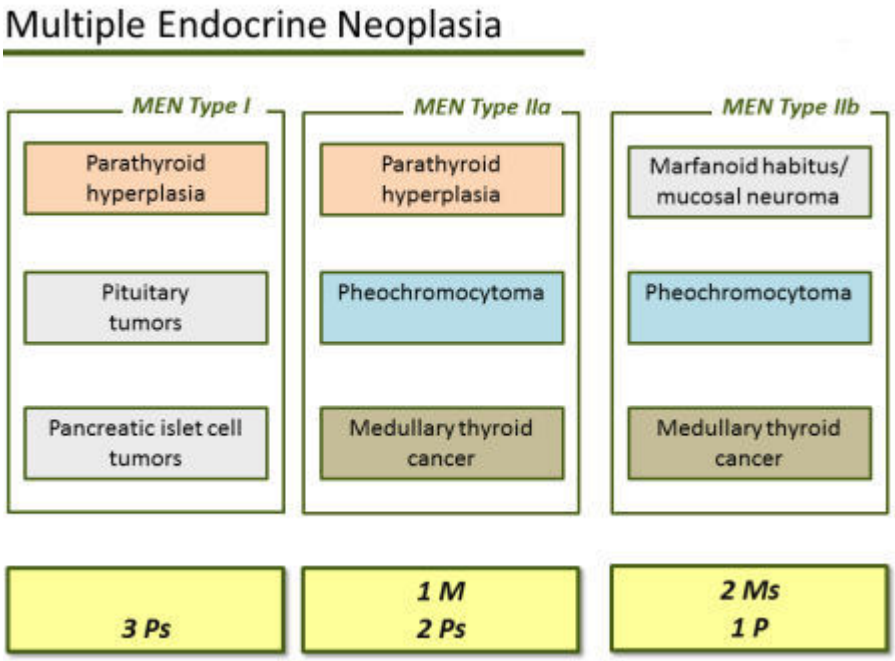
- **Causes**
  - **Constitutional growth delay (most common cause of delayed puberty)**
    - Definition:
      - a temporary delay in growth and onset of puberty that is not caused by any pathological process
    - Etiology:
      - may be inherited as an autosomal dominant, recessive, or X-linked trait
    - Diagnosis:
      - X-ray showing a bone age that is less than the individual's chronological age
    - Treatment:
      - No treatment is needed, as catch-up growth eventually occurs and the individual reaches a normal adult height.
  - hypogonadotrophic causes such as:
    - low weight / malnutrition,
    - Kallman's syndrome
  - hypergonadotrophic causes such as Turner's syndrome.
  - Other causes include:
    - pituitary lesions like craniopharyngioma,
    - co-morbidities such as severe asthma, or inflammatory bowel disease.
- **Signs of delayed puberty in girls include:**
  - Absence of breast development by age 14 years
  - Pubic hair absent by age 14
  - More than five years between the start and completion of breast growth
  - **Menarche has not occurred by age 16.**
- **Signs of delayed puberty in boys include:**
  - No testicular enlargement by age 14 years
  - Pubic hair absent by age 15
  - More than five years between the start and completion of growth of the genitalia.
- **Investigations**
  - X-ray of the hand
    - Allows association between skeletal maturation and chronological age

        - Shows delayed bone age
    - Basal LH and FSH
    - In the case of primary amenorrhea → also measure TSH and prolactin
- **Therapy**
    - Treatment of the underlying disease
    - Watchful waiting: careful serial growth measurements at frequent intervals ~ every 6 months
    - When pubertal delay is severe: gonadal steroids

Multiple endocrine neoplasia

Genetic inheritance

- autosomal dominant disorder, high penetrance



The table below summarises the three main types of multiple endocrine neoplasia (MEN)

MEN type I	MEN type IIa	MEN type IIb
3 P's Parathyroid (95%): hyperparathyroidism due to parathyroid hyperplasia Pituitary (70%) Pancreas (50%): e.g. insulinoma, gastrinoma (leading to recurrent peptic ulceration) Also: adrenal and thyroid	Medullary thyroid cancer (70%) 2 P's Parathyroid (60%) Phaeochromocytoma	Medullary thyroid cancer 1 P Phaeochromocytoma Marfanoid body habitus Neuromas
MEN1 gene Most common presentation = hypercalcaemia	RET oncogene	RET oncogene

	MEN 1	MEN 2	
		MEN 2A	MEN 2B
	Wermer syndrome	Sipple syndrome	
Genetics	• Altered **menin** protein expression	• Altered expression of the ***RET* proto-oncogene** → elevated tyrosine kinase activity	
Main disease	• **Primary hyperparathyroidism** (~ 90% of cases)	• **Medullary thyroid carcinoma** (95–100% of cases)	
Further	• **Endocrine pancreatic**	• **Pheochromocytoma** (~ 40% of cases)	

	MEN 1	MEN 2	
		MEN 2A	MEN 2B
	Wermer syndrome	Sipple syndrome	
manifestations	**tumors** (~ 50–80% of cases) such as **gastrinoma (60%)** (**most common**) and **insulinoma (30%)** • **Pituitary adenoma** (~ 30–50% of cases) • Carcinoid tumors (~ 10–15% of cases)	• **Primary hyperparathyroidism**(~ 20–30% of cases)	• **Marfanoid habitus** (> 95%) • **Multiple neuromas** (mucosal neuroma, intestinal ganglioneuromatosis)
Mnemonics	3 "**P**"s = **P**arathyroid, **P**ancreas, **P**ituitary gland	**1 "M", 2 "P"s = M**edullary thyroid carcinoma**, P**heochromocytoma**, P**arathyroid	**2 "M"s, 1 "P" = M**edullary thyroid carcinoma, **M**arfanoid habitus/Multiple neuromas, **P**heochromocytoma
Management	• **Parathyroidectomy** • Excision of pancreatic tumor • Transsphenoidal surgery for pituitary adenoma	• **Thyroidectomy** including cervical lymph nodes ➢ Pheochromocytoma should first be ruled out (e.g., measuring urine metanephrines) or treated before undergoing surgery • If pheochromocytoma removal (**adrenalectomy**) • If hyperparathyroidism: (**parathyroidectomy**)	

Type 1 multiple endocrine neoplasia (MEN 1)

- **Genetic**
  - ➢ Menin is a tumor suppressor gene implicated in multiple endocrine neoplasia 1.
  - ➢ The ***MEN1* gene** on **chromosome 11** codes for the tumor suppressor protein **menin**,
- **Features**
  - ➢ Hyperparathyroidism is the most common manifestation in MEN 1(or Werner syndrome).
  - ➢ Prolactinomas are most common in the pituitary gland.
  - ➢ The pancreas is the second most commonly involved organ in MEN 1.
    - **60% of pancreatic endocrine tumours are gastrinomas (most common).**
    - About 30% of pancreatic tumours are insulinomas.
    - Somatostatinoma, ViPoma and glucagonomas are much rarer than the two commonest types.
    - Duodenal microgastrinomas may also occur, and can be multiple, although they make up less than 10% of MEN-1 related pancreatic tumours.
    - **Pancreatic tumours are associated with:**
      - ❖ pancreatic polypeptide (75-85%)

- gastrin (Zollinger—Ellison syndrome) - recurrent peptic ulcers
- insulinoma - hypoglycaemia
- glucagonoma - hyperglycaemia and skin rash (necrolytic migratory erythema)
- VIPoma (vasoactive intestinal peptide-secreting tumour) - Verner-Morrison syndrome or watery diarrhoea hypokalaemia achlorhydria (WDHA syndrome).

Type 2 multiple endocrine neoplasia (MEN 2)

When differentiating between MEN 2A and 2B, it is worth remembering that MEN 2B has similar characteristics as MEN 2A (Thyroid carcinoma's, Adrenal tumours, Parathyroid hyperplasia) but in addition typically have a Marfanoid appearance and mucosal neuromas, as well as the absence of hyperparathyroidism.

- **Pathogenesis**
  - **A point mutation in the RET oncogene**
    - **The RET oncogene encodes a receptor tyrosine kinase**
    - mutation on the long arm of chromosome 10 (mutations at 10q11)
- **Subtypes**
  - **MEN Type 2a**
    - **also called Sipple syndrome**
    - associated with parathyroid hyperplasia, pheochromocytoma and medullary thyroid cancer.
    - medullary thyroid carcinoma in MEN-2a tends to be less aggressive than in 2b
    - **young-onset hypertension with feature of hyperparathyroidism (↑ Ca & ↓ P) → MEN Type 2a**
  - **MEN-2b**
    - MEN-2b present earlier than 2a
    - **MEN-2 is strongly associated with a family history of unexplained death in childbirth**
    - Feature of MEN-2b:
      - Intestinal ganglioneuromatosis affects around 75% of cases.
      - Neuromas involve the autonomic nerves of both the myenteric and submucosal plexi and can cause poor suckling with failure to thrive, constipation, diarrhoea, recurrent pseudo-obstruction and toxic megacolon.
      - marfanoid habitus, visceral and intestinal ganglioneuromas (which can occur around the lips and tongue)
      - Adrenal tumours leading to Cushing syndrome and phaeochromocytoma (70% bilateral) can occur.
- **Management**
  - For underlying phaeochromocytoma.

- **full alpha blockade with an agent such as phenoxybenzamine is essential** whilst investigations are undertaken to rule out medullary thyroid carcinoma (as part of MEN) as a cause of her hypercalcaemia.
- **the most appropriate additional medication to control blood pressure is → phenoxybenzamine**
- Beta blockade without first alpha blocking raises the possibility of rebound hypertension due to unopposed action of the alpha vasoconstrictors; as such it is inadvisable to consider bisoprolol or atenolol.

➢ **Screening in case of family history**

- Biochemical screen with annual calcium, calcitonin and urinary metaphrines, and MRI adrenals every three years are needed
- The best screen for phaeochromocytoma is 24-hour urinary catecholamine estimation.
- Screening is recommended for people with MEN 2:
- The pentagastrin test is used to screen for medullary thyroid carcinoma.
  - ❖ (Total thyroidectomy in childhood is often recommended for those with a known gene defect.)
- **Annual testing of calcium and PTH from the age of 10 is recommended for child with family history of MEN-2**

- **Prognosis**
  - ➢ the 10-year survival rate is around 65%.

Which of the manifestations of MEN-2 has the most malignant potential?

➔ C cell hyperplasia

- C cell hyperplasia eventually undergoes malignant transformation, leading to → medullary carcinoma of the thyroid.
- If patients with MEN-2 are not identified by screening, often at the time of presentation medullary thyroid carcinoma with metastases to cervical lymph nodes has already occurred.

Which finding in a blood test will be the most characteristic in (MEN 2B) patient?

⇨ Elevated metanephrines

Multiple endocrine neoplasia type II is due to mutation in which sort of receptor?

Membrane-bound tyrosine kinase receptor

January 2008 exam: A 25-year-old man with a family history of multiple endocrine neoplasia type 1 is reviewed in clinic. What is the single most useful investigation to monitor such patients? Serum calcium

Autoimmune polyendocrinopathy syndrome (APS) (Polyglandular syndrome)

Type	**Polyglandular syndrome type 1**	**Polyglandular syndrome type 2** Also called (Schmidt's disease)
inheritance	• autosomal recessive • caused by mutation of **AIRE1** gene on chromosome **21**	• polygenic inheritance • linked to HLA DR3/DR4.
Epidemiology	• rare • usually begins in childhood.	• **more common**
feature	• Mucocutaneous candidiasis (100%) • **Hypoparathyroidism (in around 90%)** • Adrenal insufficiency (in around 60%) • gonadal failure • Primary hypothyroidism • Hypopituitarism/diabetes insipidus (rarely) • There might be associated malabsorption, pernicious anaemia, chronic active hepatitis or vitiligo.	• Adrenal insufficiency (in all patients) • Hypothyroidism • Type-1 diabetes • Gonadal failure • Diabetes insipidus (rare) • Associated conditions include vitiligo, myasthenia gravis, alopecia, immune thrombocytopenic purpura and pernicious anaemia.
diagnosis	(2 out of 3 needed) 1. **chronic mucocutaneous candidiasis (typically first feature as young child) (100%)** 2. **primary hypoparathyroidism (90%),** 3. **Addison's disease (60%)**	Patients have Addison's disease **plus** either: 1. type 1 diabetes mellitus 2. autoimmune thyroid disease

Primary HYPOparathyroidism is usually the first endocrine manifestation of type 1 autoimmune POLYendocrinopathy syndrome. While (MEN) → hyperparathyroidism is a common finding

- **Tryptophan hydroxylase autoantibodies** may be found in autoimmune polyendocrine syndrome associated with an autoimmune malabsorption.

May 2005 exam: H/O recurrent painful oral ulceration. Examination reveals signs of oral *Candida*l infection. Which one of the following would most suggest type 1 polyglandular syndrome? Hypocalcaemia

Somatostatin

Source	Action	Regulation	Notes
• D cells (pyloric antrum, and duodenum mucosa) • delta cells (pancreas) • ventromedial nucleus of the hypothalamus.	• ↓ gastric H^+ and pepsinogen secretion • ↓ pancreatic and small intestine fluid secretion • ↓ gallbladder contraction • ↓ insulin and glucagon release • ↓ GH release	• ↑ by H^+ • ↓ by vagal stimulation	• Inhibitory hormone • Antigrowth hormone effects (digestion and absorption of substances needed for growth) • Produce **vasoconstriction of the splanchnic system**. • Somatostatin is treatment for VIPoma and carcinoid tumors

- **Mechanism of action**
  - Somatostatin receptor is linked to adenylyl cyclase by Gi protein, which inhibits cAMP production and reduces secretion of hormones.

Somatostatinoma

- Annual incidence → 1 in 40 million.
- **Associations:**
  - Impaired glucose tolerance (IGT) or diabetes mellitus (95%)
  - Gallstones (68%)
  - Weight loss (25%)
  - Anaemia (14%)
  - Multiple endocrine neoplasia type 1 (7%)
  - Diarrhoea
- **Diagnosis**:
  - The tumours are often multisecretory → ↑↑ **Somatostatin, adrenocorticotropic hormone (ACTH) and calcitonin**
  - Contrast spiral computed tomography scanning is effective for detecting the primary tumour in only 50% of cases;
  - Radiolabeled octreotide or endoscopic ultrasound scanning are often be required.
- **Treatment**:
  - surgery is rarely possible due to presence of metastases,
  - hepatic embolisation can be helpful for symptom control.

Carney complex

- autosomal dominant
- **Caused by an inactivating mutation of protein kinase A on chromosome 17**.
- Carney complex is diagnosable if there are **two features** out of the following:
    1. Spotty skin pigmentation
    2. Myxoma
    3. Endocrine tumours:
        - the commonest is primary pigmented nodular adrenocortical disease,
        - others
            - Sertoli cell tumours,
            - growth hormone- or prolactin-producing pituitary adenomas,
            - thyroid adenomas
            - ovarian cysts
    4. Psammomatous melanotic schwannoma (PMS)
- It is also diagnosable in the presence of one feature and an affected first-degree relative.

Notes & Notes

For MRCP part 1 & 11

By

Dr. Yousif Abdallah Hamad

Cardiology

Updated

2017

Contains:

1/ Passmedicine 2017

2/ On examination 2017

3/ Pastest 2017

4/ **Red fonts --> previous exams**

5/ Other updated UK sources

Anatomy of the heart

- The right ventricle lies anterior to the left ventricle
- **The tricuspid valve is the most anterior valve of the heart and is the most common to be injured during a stabbing attack**
- The left atrium is the most posterior chamber of the heart, the right atrium is just anterior and to the right of the left atrium.
- The left atrial appendage is not readily seen on transthoracic echocardiography and requires transoesophageal echocardiography.
- **The aortic valve is tricuspid**

Arterial anatomy

- internal thoracic artery arises from the subclavian artery.
- **The subscapular artery arises from the axillary** and is its largest branch, eventually anastomosing with the lateral thoracic and intercostal arteries.

Anatomical relations

- **descending aorta lies behind (posterior to) the left main bronchus.**
- ascending aorta is anterior to the pulmonary trunk.
- left pulmonary artery is anterior to the left main bronchus.
- right main bronchus should be beside the left following bifurcation of the trachea.
- superior vena cava can be found next to the ascending aorta.
- oesophagus is also a posterior structure to the left main bronchus.

Valvular anatomy

- **left atrial enlargement can result in mitral regurgitation by affecting which leaflet?**
  - **posterior leaflet**
    - anterior leaflet is not affected, because of its attachment to the root of the aorta.

Coronary arteries

- Basic understanding of coronary anatomy is important as this is predictive of problems following MI. For example:
  - the **right coronary artery** supplies the AV node, so heart block following inferior MI is common. **However, heart block following anterior MI is a grave prognostic marker as this indicates a large anterior wall infarct.**
  - The right coronary system also supplies the right ventricle, hence problems relating to a **right ventricular infarct are commonly associated with an inferior MI.**
  - right coronary artery supplies the inferior myocardium and occlusion causes ST elevation in II, III and aVF.

- **Posterior descending artery**
  - a branch of the right coronary artery in 85% of people (a branch of the circumflex in the remaining population).
    - The concept of **coronary dominance** refers to **which coronary artery supplies the posterior descending coronary artery.**
      - 85% of patients having a dominant right coronary artery
      - 15% of patients having a dominant left circumflex.
  - supplies the posterior left ventricular myocardium
  - occlusion causes **posterior MI** (ST depression in V1-V4 with a dominant R wave in V1).
- **Circumflex**: lateral
  - Occlusion produces ST elevation in V5, V6, I and aVL.
- **Left anterior descending**: anterior and septum
  - **Occlusion → ST segment elevation in leads V1-V4**
  - **Right bundle branch block in acute anterior myocardial infarction suggests obstruction prior to the first septal branch of the left anterior descending coronary artery**
- **Left main stem**:
  - branches into the left anterior descending artery and circumflex and supplies most of the left ventricle.
  - Complete left main stem occlusion is invariably fatal.
  - Occlusion of the left main stem has the same effect as occlusion of the left circumflex and anterior descending simultaneously (given that they are both branches of the above). It

would produce extensive ST elevation across all the chest leads, I and aVL and possibly aVR, too.

- **Obtuse marginal**: one of the branches of the circumflex and supplies the 'high lateral' region of the left ventricle (ECG leads I and aVL).

Coronary circulation

Arterial supply of the heart

- left aortic sinus → left coronary artery (LCA)
- right aortic sinus → right coronary artery (RCA)
- LCA → LAD + circumflex
- RCA → posterior descending
- RCA supplies SA node in 60%, AV node in 90%
  - The sinus node artery is a branch of the right coronary artery in 60% of cases.

Venous drainage of the heart

- coronary sinus drains into the right atrium

Other notes

- **Adenosine is an important mediator of metabolic vasodilatation**
  - Adenosine has a particularly short half-life,
  - acts on specific adenosine cell surface receptors (A1 and A2)
  - inactivated by adenosine deaminase.
  - It results in coronary vasodilatation and depression of sinus node automaticity and AVN conduction.
- Coronary blood flow is dependent on myocardial oxygen consumption and is pretty independently maintained throughout the ranges of blood pressure.
- Increasing O2 demands are met by increased blood supply facilitated by vasodilatation brought about by adenosine production.

Pulmonary circulation

The normal pulmonary circulation is characterised by:

- **low pressures,**
- **low flow rates,**
- **high compliance vessels.**

Internal jugular vein

- originates at the jugular foramen.
- It initially lies posterior to the carotid artery, as it descends in the carotid sheath it lies lateral first to the internal then the common carotid artery within the carotid sheath.
  - **Lies lateral to the common carotid artery**
- It passes anterior to the subclavian artery to join the subclavian vein and then form the brachiocephalic vein; the left and right brachiocephalic veins unite to form the superior vena cava.
- The internal jugular vein receives a lymphatic trunk at its union with the subclavian vein.

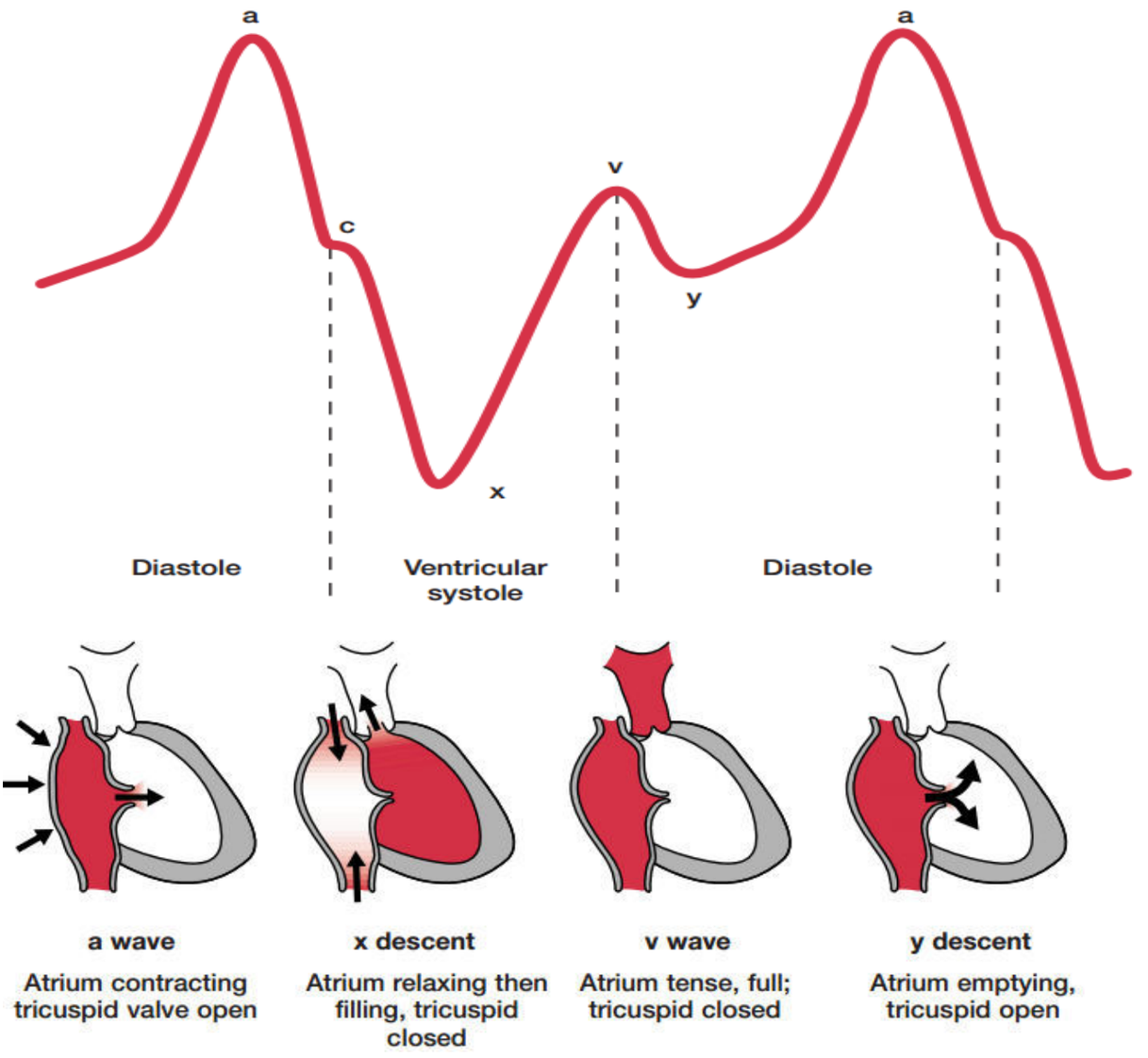
Waveforms of the jugular venous pressure

JVP: C wave - closure of the tricuspid valve

JVP: x descent = fall in atrial pressure during ventricular systole

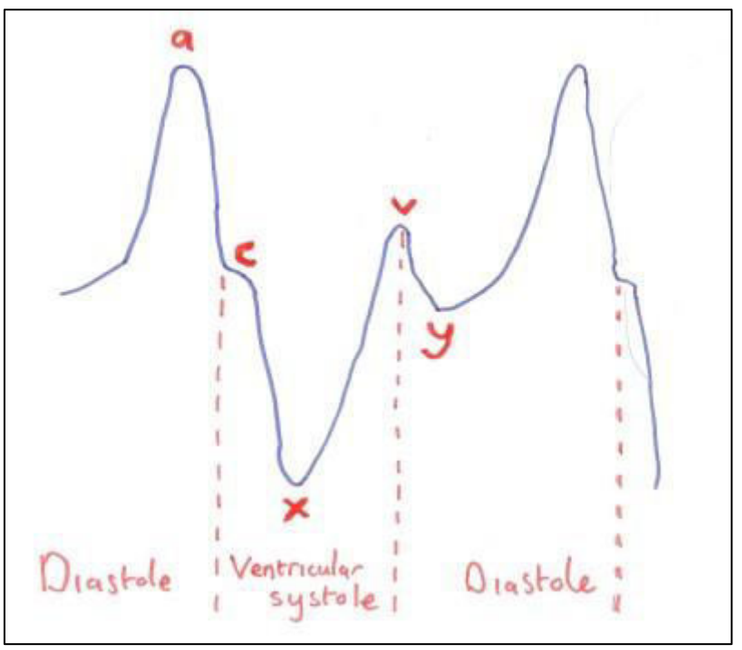
JVP: y descent = opening of tricuspid valve

JVP: giant v waves in tricuspid regurgitation



Jugular venous pulse

As well as providing information on right atrial pressure, the jugular vein waveform may provide clues to underlying valvular disease. A non-pulsatile JVP is seen in superior vena caval obstruction. Kussmaul's sign describes a paradoxical rise in JVP during inspiration seen in constrictive pericarditis.



'a' wave = atrial contraction

- large if atrial pressure e.g. tricuspid stenosis, pulmonary stenosis, pulmonary hypertension

- absent if in atrial fibrillation

Cannon 'a' waves

- caused by atrial contractions against a closed tricuspid valve
- are seen in complete heart block, ventricular tachycardia/ectopics, nodal rhythm, single chamber ventricular pacing

'c' wave

- closure of tricuspid valve
- not normally visible

'v' wave

- due to passive filling of blood into the atrium against a closed tricuspid valve
- giant v waves in tricuspid regurgitation

'x' descent = fall in atrial pressure during ventricular systole
'y' descent = opening of tricuspid valve

JVP: cannon waves

Caused by the right atrium contracting against a closed tricuspid valve. May be subdivided into regular or intermittent

Regular cannon waves

- ventricular tachycardia (with 1:1 ventricular-atrial conduction)
- atrio-ventricular nodal re-entry tachycardia (AVNRT)

Irregular cannon waves

- complete heart block

Subclavian vein

- Each **subclavian vein is a continuation of the axillary vein and runs from the outer border of the first rib** to the medial border of anterior scalene muscle. From here it joins with the internal jugular vein to form the brachiocephalic vein (also known as "innominate vein"). The angle of union is termed the venous angle.
- The subclavian vein follows the subclavian artery and is separated from the subclavian artery by the insertion of anterior scalene. Thus, the subclavian vein lies anterior to the anterior scalene while the subclavian artery lies posterior to the anterior scalene (and anterior to the middle scalene).
- The subclavian and internal jugular vein unite to form the brachiocephalic vein, subsequently the left and right brachiocephalic veins unite to form the superior vena cava.
- The thoracic duct enters the left subclavian.
- **Right or left subclavian is regarded as the cleanest site for central venous access. It also the most tolerated by patients.**
- However the incidence of subclinical pneumothorax even in the hands of experienced clinicians has led to it falling out of favour.
- Compared with femoral site access, internal jugular or subclavian access was associated with a lower risk of catheter-related bloodstream infections (CRBSIs) in earlier studies, but subsequent studies (since 2008) found no significant differences in the rate of CRBSIs between these three sites.
- The subclavian approach remains the most commonly used blind approach for subclavian vein cannulation. Its advantages include consistent landmarks, increased patient comfort, and lower potential for infection or arterial injury compared with other sites of access.

You are planning a procedure to insert a subclavian venous catheter

Where is the optimal point of needle insertion?

1 cm inferior to the junction of the middle and medial third of the clavicle

which vessel would become important for transporting blood from the lower to upper parts of the body in the event of complete occlusion of the inferior vena cava?

➔ **Ascending lumbar vein**

A left sided internal jugular central venous catheter has been inserted and you are reviewing the chest radiograph to check the position of the tip of the catheter. What is the safest position to leave the catheter tip?

➔ **In the lower superior vena cava**

- If the catheter tip is above the carina on a post-procedure radiograph then it is generally accepted that the catheter lies outside the right atrium in the lower superior vena cava (SVC).
- It is also recommended that the catheter tip should lie in the long axis of the SVC without acute abutment to the vein wall.
- Left sided catheters are more likely to erode the vessel wall if they lie in the innominate veins or the upper SVC due to the abutment of the catheter tip to the vessel wall.
- They are also more likely to cause pain on injection, thrombosis and infection if the tip lies in the innominate veins.
- It is considered negligent to site the catheter tip in the right atrium as this may lead to arrhythmias, tricuspid valve disfunction and placement in the coronary sinus.

Subclavian steal syndrome

- characterized by **retrograde flow** into the vertebral or internal thoracic arteries, **due to stenosis and/ or occlusion of the subclavian artery.**

Symptoms:

- Many patients are asymptomatic.
- Upper extremity symptoms include fatigue, aching, coolness of the affected arm and numbness.
  - **The most common symptoms** of subclavian steal syndrome are those related to **upper limb ischemia.**
    - **arm pain and numbness, especially during exertion.**
- Neurological symptoms
  - occur in around 25% of patients.
  - may include vertigo, diplopia, decreased vision, nystagmus and gait unsteadiness
- **blood pressure is different between the upper limbs by at least 15 mmHg.**
- can present with the manifestations of cardiac ischemia in patients with internal mammary bypass graft.
- Symptoms may be precipitated by:
  - extreme exercise on the affected side, such as cricket bowling, use of an underarm crutch or **painting a wall**.

Pathophysiology:

- Subclavian steal **produces symptoms by flow-related phenomena** rather than embolic.
- **atherosclerotic lesion** in the proximal subclavian artery → significant stenosis, → collateral vessels enlargement from subclavian artery distal to obstruction
- The upper extremity becomes dependent on these collaterals
- The collateral vessels serve as points of re-entry for blood flowing retrograde into the arm from the head, shoulder and neck, thereby providing the extremity with adequate perfusion.
- **When the arm is exercised,** the blood vessels dilate to enhance perfusion to the ischaemic muscle, thus lowering the resistance in the outflow vessels.
- Blood is siphoned from the head, neck and shoulder through collateral vessels to supply this low-resistance vascular bed, satisfying increased oxygen demand by the exercising muscles of the upper extremity.
- This results in **posterior cerebral circulation neurological symptoms**.
- **What is the most likely mechanism that maintains blood flow to the affected extremity?**

- Blood from the **contralateral vertebral artery** is shunted away from the basilar artery (away from the brainstem) and **retrograde into the ipsilateral vertebral artery** to supply the affected arm .

Diagnosis

- non-invasive arterial flow studies, Doppler and arteriography.
  - **Duplex ultrasound** is **the best initial** radiological test
  - The **most accurate** test is **angiography** of the subclavian vessels.

Management:

- Most patients require no intervention,
- surgical reconstruction may be required where symptoms are severe.

Physiological notes

- The **sinoatrial node** has the **fastest firing rate** of all potential pacemakers in the heart.
- Sinoatrial node impulses must occur at a rate **slower than 200 impulses per minute** to be considered in normal sinus rhythm.
- **Endothelin**
  - preferentially **constricts renal afferent arterioles.**
    - **Efferent** arteriole **vasoconstriction** is particularly **mediated by angiotensin-II,** to defend GFR in states of generalised vasoconstriction and reduced blood flow.
      - efferent arteriole vasodilation will occur when angiotensin-II levels fall.
  - Stimulates the renin-angiotensin-aldosterone system
  - Leads to release of atrial natriuretic peptide
  - Inhibits the action of vasopressin
  - Two types of endothelin receptor have been characterised, A and B.
    - Binding of endothelin to the A receptor induces vasoconstriction,
    - binding to the B receptor leads to nitric oxide release and hence vasodilatation.

Pulses

Pulsus parodoxus

- greater than the normal (10 mmHg) fall in systolic blood pressure during inspiration → faint or absent pulse in inspiration
- severe asthma, cardiac tamponade

Slow-rising/plateau

- aortic stenosis

Collapsing

Patent ductus arteriosus - collapsing pulse

- aortic regurgitation
- patent ductus arteriosus
- hyperkinetic (anaemia, thyrotoxic, fever, exercise/pregnancy)

Pulsus alternans

Pulsus alternans - seen in left ventricular failure

- regular alternation of the force of the arterial pulse
- severe LVF
- **It is found in association with a third heart sound**

Bisferiens pulse

- 'double pulse' - two systolic peaks
- mixed aortic valve disease

'Jerky' pulse

- hypertrophic obstructive cardiomyopathy*

*HOCM may occasionally be associated with a bisferiens pulse

Atrial natriuretic peptide

Basics

- secreted mainly from myocytes of right atrium and ventricle in response to increased blood volume

- secreted by both the right and left atria **(right >> left)**
- synthesis increased by thyroid hormones, glucocorticoids, endothelin-1, angiotensin-II, and tachycardia, independent of the haemodynamic effects of these factors.
- 28 amino acid peptide hormone, which acts via cGMP
- degraded by endopeptidases

Actions

- natriuretic, i.e. promotes excretion of sodium
- lowers BP
- reduced pre-load due to relaxing effects on vascular smooth muscle.
- antagonises actions of angiotensin II, aldosterone

B-type natriuretic peptide

BNP - actions:
- vasodilator
- diuretic and natriuretic
- suppresses both sympathetic tone and the renin-angiotensin-aldosterone system

- B-type natriuretic peptide (BNP) is a hormone produced mainly by the **left ventricular** myocardium in response to strain.

Causes of raised BNP levels

- heart failure is the most obvious cause
  - The stimulus for BNP release is myocyte stretch, rather than transmural pressure load.
- any cause of left ventricular dysfunction such as myocardial ischaemia or valvular disease
- chronic kidney disease (due to reduced excretion).
- BNP synthesis is increased by thyroid hormones as well as glucocorticoids, endothelin-1, angiotensin-II, and tachycardia, independent of the haemodynamic effects of these factors.

Factors which reduce BNP levels

- treatment with ACE inhibitors, angiotensin-2 receptor blockers and diuretics.

Effects of BNP

- Vasodilator
  - **arterial and venous smooth muscle vasodilatation**
  - BNP → relaxing effects on vascular smooth muscle (vasodilatation) → reduced pre-load → reduced blood pressure,
- Diuretic and natriuretic
  - In the kidney, BNP causes increased glomerular filtration rate (GFR) and inhibition of sodium reabsorption, leading to natriuresis and diuresis.
- suppresses both sympathetic tone and the renin-angiotensin-aldosterone system

Clinical uses of BNP

- Diagnosing patients with acute dyspnoea
  - a low concentration of BNP(< 100pg/ml) makes a diagnosis of heart failure unlikely, but raised levels should prompt further investigation to confirm the diagnosis
    - Levels >400 pg/ml warrant urgent specialist assessment and echocardiography;
    - intermediate levels (100-400 pg/ml) should be investigated within six weeks.
  - NICE currently recommends BNP as a helpful test to rule out a diagnosis of heart failure
- Prognosis in patients with chronic heart failure
  - initial evidence suggests BNP is an extremely useful marker of prognosis
- Guiding treatment in patients with chronic heart failure
  - effective treatment lowers BNP levels
- Screening for cardiac dysfunction
  - not currently recommended for population screening

Micro-anatomical structures

- **T tubules and calcium channels**
  - tubular network formed by the invagination of the sarcolemma of the myocyte
  - Sarcolemmal calcium channels are located on the T tubules
  - There are two main types of channels
    - T (transient) channels do not interact with conventional calcium-channel blockers
    - **L-type calcium channels do interact with calcium-channel blockers**
- **Titin**
  - Titin tethers the myosin molecule to the Z line, and its elasticity explains the stress-strain elastic relation of striated muscle
  - It is the largest protein molecule yet described
- **Tropomyosin**
  - The thin actin filaments intertwine and are carried on a heavier tropomyosin molecule that functions as a backbone
  - At regular intervals along this structure is a group of three regulatory proteins called the 'troponin complex', which is composed of troponin C, I and M

Cardiovascular physiology

- The basic muscle unit of the myocardium → Sarcomere
- **What is the normal resting cell membrane potential of a cardiac myocyte?** → **- 90 mV**

Left ventricular ejection fraction (LV EF)

- The left ventricle pumps only a fraction of the blood it contains.
- The ejection fraction is the amount of blood pumped (stroke volume) divided by the amount of blood the ventricle contains (end diastolic volume).
  - **ejection fraction = (Stroke volume/end diastolic volume)** * 100%
  - stroke volume = end diastolic volume − end systolic volume
- normal ejection fraction is more than 55% of the blood volume.
  - in systolic dysfunction, EF is low.
  - In diastolic dysfunction, EF is normal (called HF with preserved LV EF)
    - **e.g:** hypertrophy heart failure occur due to diastolic dysfunction. heart muscle is big, so less blood can come to the heart during the diastole. say 40 ml of blood can come to the heart (40 ml is the total blood volume end of the diastole) but heart pump 30 ml in each beat. so EF 30/40=75%.
- **Which echocardiographic measures is mandatory in calculating ejection fraction?**
  - **Left ventricular end diastolic diameter**
- One way of measuring ejection fraction (EF) is estimated by the ratio between the M-mode readings of the left ventricular end diastolic volume (EDV) and the end systolic volume (ESV), using the formula [(EDV - ESV) / EDV] x 100 = EF (%).

Cardiac output (CO)

- The Cardiac output measure how much blood ejected by the heart in one minute.
- CO= Stroke volume (SV) (volume pumped in each beat) x Heart rate (HR)
- Changes in CO
  - ↓ SV in ventricular tachycardia
    - if HR is too high, diastolic filling is incomplete and CO decreases
  - exercise
    - CO maintained by **SV** in **early** stages of exercise
    - CO maintained by **HR** in **late** stages of exercise
- cardiac output studies
  - **PiCCO (pulse contour cardiac output)**
    - PiCCO gives indications of cardiac output, extravascular lung water, **intravascular filling**
    - only requires a central line and a PiCCO femoral arterial line and as such is relatively simple to use.

Stroke Volume (SV)

- SV = CO/HR = End-Diastolic Volume (EDV) - End-Systolic Volume (ESV)
- volume of blood ejected per heart beat
  - SV ~ 70 mL

Pulse pressure

- Pulse pressure = Systolic Pressure - Diastolic Pressure
- Factors which **increase pulse pressure**

  - **less compliant** aorta (this tends to occur with advancing age)
  - increased stroke volume
- Factors which reduced pulse pressure
  - Reduced stroke volume,
  - high aortic compliance,
  - reduced venous return, and
  - reduced peripheral resistance

Cardiovascular physiology response to blood loss

Stroke volume (SV) is decreased because of hypovolaemia

The compensation mechanisms to sudden hypovolaemia include:

- Cardiac output (CO) can increase, decrease, or stay the same (CO = HR × SV).
- Heart rate (HR) can increase **due to decreased (parasympathetic) vagal stimulation and enhanced sympathetic stimulation with adrenaline**.
- Total peripheral resistance can increase **due to increased sympathetic drive**. This causes peripheral vasoconstriction and preserves blood flow to essential organs, such as the brain, heart and kidneys.
- Venous return increases if sympathetic output increases, and this is related to the peripheral vasoconstriction. Less blood can pool in the peripheral vessels so it is transported back to the central circulation quickly. This increases venous return and maximises stroke volume.

Physiological C.V changes during pregnancy

- **Heart rate:**
  - **increases by 10-20 bpm**
- cardiac output
  - cardiac output and blood volume increase from the second month up to the thirtieth week to 30 - 50% above the normal levels.
  - The average increase in blood volume during pregnancy amounts to 1600 ml
  - The increase in cardiac output is mediated via **increase in both stroke volume** and to a lesser extent **heart rate**, along with a dramatic **fall in total peripheral vascular resistance**.
  - stroke volume and cardiac output increase
- venous pressure
  - venous pressure should remain the same due to a 25% reduction in systemic and pulmonary vascular resistance.
- Blood pressure:
  - should drop in the first and second trimester and then climb to pre-pregnancy levels by the third trimester.
  - **Lowered diastolic blood pressure due to vasodilatation: this is responsible for the fading of the aortic regurgitation murmur**
- The increase in blood volume and increased cardiac output lead to **all stenosic murmurs becoming more prominent** (there is increased flow across the valve, with more turbulence and pressure gradient, leading to a louder sound).
- Typically, an **ASD** is associated with fixed splitting of the second heart sound; if a murmur is present it has **arisen from increased pulmonary valvular flow**, and hence is increased during pregnancy.
- metabolic workload
  - there is also an increased metabolic workload
- apex beat
  - The apex beat is displaced, because of cardiomegaly and a raised diaphragm
- The increased blood flow may produce a **pulmonary systolic murmur** and a **third heart sound**.

Which murmur is diminished during pregnancy?

➔ **Aortic regurgitation**

- The fall in diastolic blood pressure during pregnancy leads to a reduction in the murmur of aortic regurgitation.
- Murmurs follow pressure gradients – if the blood pressure is lower, then the difference between the aortic pressure and LV pressure is less, making the murmur quieter.

Valsalva manoeuvre

The Valsalva manoeuvre describes a forced expiration against a closed glottis. This leads to increased intrathoracic pressure which in turn has a number of effects on the cardiovascular system.

Uses

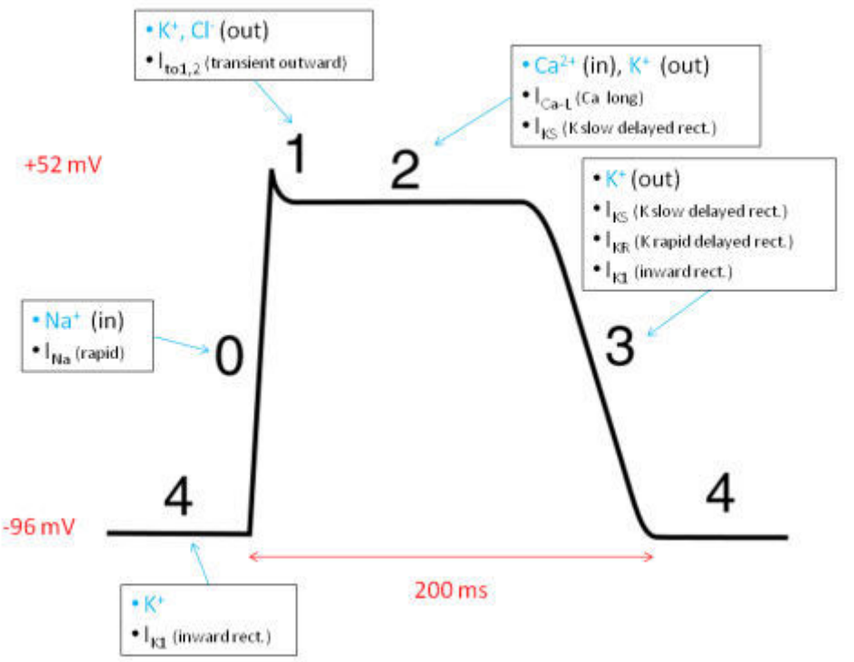
- to terminate an episode of supraventricular tachycardia
- normalizing middle-ear pressures

Stages of the Valsalva manoeuvre

- 1. Increased intrathoracic pressure
- 2. Resultant increase in venous and right atrial pressure reduces venous return
- 3. The reduced preload leads to a fall in the cardiac output (Frank-Starling mechanism)
- 4. When the pressure is released there is a further slight fall in cardiac output due to increased aortic volume
- 5. Return of normal cardiac output

Cardiac action potential

Cardiac action potential



Phase	Description	Mechanism
0	Rapid depolarisation	Rapid sodium influx These channels automatically deactivate after a few ms
1	Early repolarisation	Efflux of potassium
2	Plateau	Slow influx of calcium
3	Final repolarisation	Efflux of potassium
4	Restoration of ionic concentrations	Resting potential is restored by Na^+/K^+ ATPase There is slow entry of Na^+ into the cell decreasing the potential difference until the threshold potential is reached, triggering a new action potential

NB cardiac muscle remains contracted 10-15 times longer than skeletal muscle

Conduction velocity

Site	Speed
Atrial conduction	Spreads along ordinary atrial myocardial fibres at 1 m/sec
AV node conduction	0.05 m/sec
Ventricular conduction	Purkinje fibres are of large diameter and achieve velocities of 2-4 m/sec (this allows a rapid and coordinated contraction of the ventricles

Which physiological change associated with age during exercise?

- **Reduced tachycardic response**
  - There is a reduced tachycardic response during exercise associated with age.
  - The heart has to compensate by increasing stroke volume and failure to do so will reduce aerobic capacity.
  - Some fit, healthy elderly men can compensate for this by increasing left ventricular filling and thus stroke volume (Starling's law).

Physiological changes associated with age. They occur, irrespective of whether a patient exercises or not.

- Decrease elasticity and compliance of the aorta → increased resistance to ejection of blood from the left ventricle → increased ventricular afterload.
- Diastolic dysfunction and reduced stroke volume
- ↓↓diastolic pressure (the pressure responsible for subendocardial perfusion) → subendocardial ischemia and interstitial fibrosis. (These changes are related to an increase in the magnitude of the L-type Ca^{++})
- Higher systolic arterial pressure and increased impedance to left ventricular ejection
- **↑ systolic + ↓ diastolic → ↑ pulse pressure**
- Increased sino-atrial conduction time
  - Because of the delayed LV relaxation and the stiffer left ventricle, the force of left atrial contraction increases and the contribution of the atrial contraction to LV end-diastolic volume increases
- There is apoptosis of atrial pacemaker cells with a loss of 50%-75% of cells by age 50. The number of atrioventricular nodal cells is preserved and there is fibrosis and cellular loss in the His bundle
- Left ventricular hypertrophy

Heart sounds

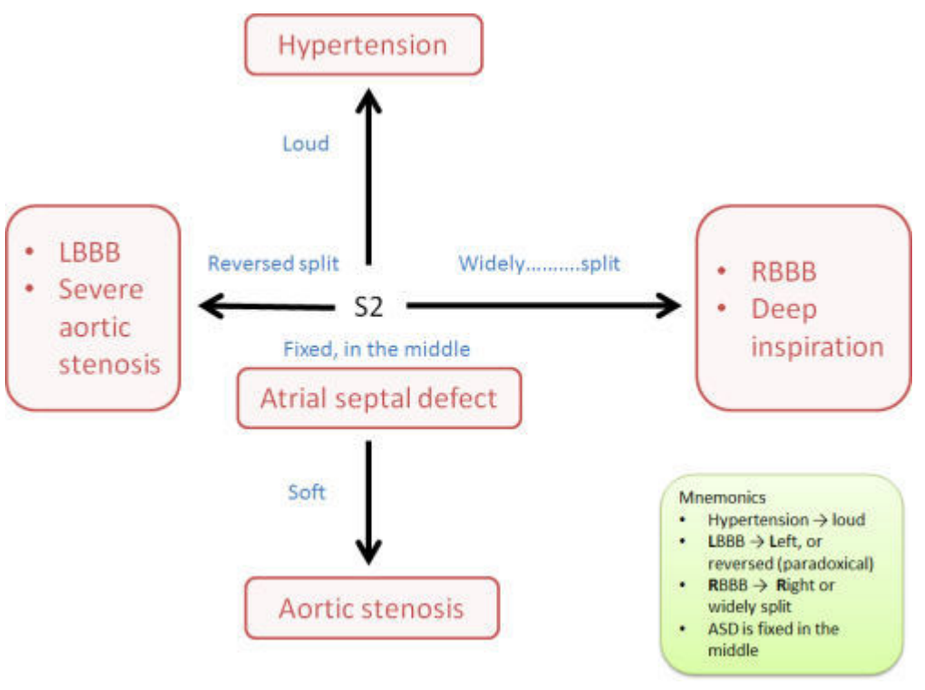
First heart sound (S1)

- Caused by closure of mitral and tricuspid valves
- **Causes of a loud S1**
  - mitral stenosis
  - left to right shunts
  - short PR interval, (shortened diastole) **atrial premature beats**
  - hyperdynamic states
- **Causes of a quiet S1**
  - mitral regurgitation
  - long PR

Second heart sound (S2)

Second heart sound (S2)
- loud: hypertension
- soft: AS
- fixed split: ASD
- reversed split: LBBB

- The second heart sound consists of the closure of the aortic valve (A_2) followed by the closure of the pulmonary valve (P_2).
- splitting during inspiration is normal
  - inspiration causes negative intrathoracic pressure, increasing return of blood from the body into the right atrium and ventricle. This slightly prolongs systole in the right ventricle and therefore delays closure of the pulmonary valve, causing an appreciably split second heart sound.
- **Causes of a loud S2**
  - hypertension: systemic (loud A2) or pulmonary (loud P2)
  - hyperdynamic states
  - atrial septal defect without pulmonary hypertension
- **Causes of a soft S2**
  - aortic stenosis
- **Causes of fixed split S2**
  - **atrial septal defect (ASD)**
    - ASD →↑ blood volume in the right atrium, → overloads the right ventricle,→ delayed closure of the pulmonary valve.
    - As the flow of blood from the left to the right is relatively unaffected by respiration, it results in a fixed, widely split second heart sound.
  - right heart failure
  - **Right bundle-branch block with heart failure**
    - right bundle-branch block widens the split, and heart failure makes the split fixed.
  - pulmonary hypertension
- **Causes of a widely split S2**
  - deep inspiration
    - S2 is split during inspiration, and synchronous during expiration.
    - This is because during inspiration there is increased venous return to the right heart, which delays the closure of the pulmonary valve (P2) relative to the aortic valve (A2).
  - RBBB
    - RBBB (delayed electrical activation of the right ventricle) → delayed pulmonary valve close → wide physiological splitting of S2
  - pulmonary stenosis
  - severe mitral regurgitation
- **Causes of a reversed (paradoxical) split S2 (P2 occurs before A2)**
  - LBBB
  - severe aortic stenosis
  - hypertrophic obstructive cardiomyopathy
  - right ventricular pacing
  - WPW type B (causes early P2)
  - patent ductus arteriosus



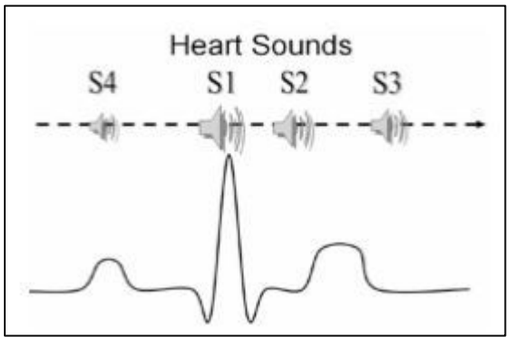
Third heart sound (S3)

Gallop rhythm (S3) is an early sign of LVF

- caused by diastolic filling of the ventricle
- The mechanism of an S3 gallop is rapid ventricular filling during diastole. As soon as the mitral valve opens, blood rushes into the ventricle, causing a splash sound
- considered normal if < 30 years old (may persist in women up to 50 years old)
- heard in left ventricular failure (e.g. dilated cardiomyopathy), constrictive pericarditis (called a pericardial knock)

Fourth heart sound (S4)

- caused by **atrial contraction** against a stiff ventricle
  - **P wave on ECG**
- It is heard just before S1
- occurs with: (any type of left ventricular hypertrophy):
  - aortic stenosis,
  - hypertension
  - HOCM,
    - in HOCM a double apical impulse may be felt as a result of a palpable S4



Splitting			
Normal splitting	Inspiration → drop in intrathoracic pressure → ↑ venous return → ↑ RV filling → ↑ RV stroke volume → ↑ RV ejection time → delayed closure of pulmonic valve. ↓ pulmonary impedance (↑ capacity of the pulmonary circulation) also occurs during inspiration, which contributes to delayed closure of pulmonic valve.	Expiration Inspiration	| || S1 A2 P2 | | |
Wide splitting	Seen in conditions that delay RV emptying (e.g., pulmonic stenosis, right bundle branch block). Delay in RV emptying causes delayed pulmonic sound (regardless of breath). An exaggeration of normal splitting.	Expiration Inspiration	| | | S1 A2 P2 | | |
Fixed splitting	Seen in ASD. ASD → left-to-right shunt → ↑ RA and RV volumes → ↑ flow through pulmonic valve such that, regardless of breath, pulmonic closure is greatly delayed.	Expiration Inspiration	| | | S1 A2 P2 | | |
Paradoxical splitting	Seen in conditions that delay aortic valve closure (e.g., aortic stenosis, left bundle branch block). Normal order of valve closure is reversed so that P2 sound occurs before delayed A2 sound. Therefore on inspiration, P2 closes later and moves closer to A2, thereby "paradoxically" eliminating the split.	Expiration Inspiration	| | | S1 P2 A2 | ||

Murmurs

Most murmurs of stenosis or regurgitation are exaggerated during squatting and get softer with the Valsalva manoeuvre. **The exceptions are HOCM where the opposite occurs (↑ by valsalva & ↓ by squatting)** and mitral valve prolapse where the murmur gets longer.

Relation between murmurs intensity and respiration:

- Murmurs that **increase** in intensity with **inspiration** originate from the **right side of the heart** (tricuspid or pulmonary)
- Murmurs that **increase** in intensity with **expiration** originate from the **left side of the heart** (mitral or aortic).

Mnemonic: RILE (Right Inspiration, Left Expiration)

Ejection systolic

- aortic stenosis, HOCM
- pulmonary stenosis
- ASD
  - **(ASD with pulmonary hypertension → prominent left precordium with an ejection murmur)**
- Fallot's

Holosystolic (pansystolic)

- mitral/tricuspid regurgitation (high-pitched and 'blowing' in character)
- VSD ('harsh' in character)

Late systolic

- mitral valve prolapse
- coarctation of aorta

Early diastolic

- aortic regurgitation (high-pitched and 'blowing' in character)
- Graham-Steel murmur (pulmonary regurgitation, again high-pitched and 'blowing' in character)

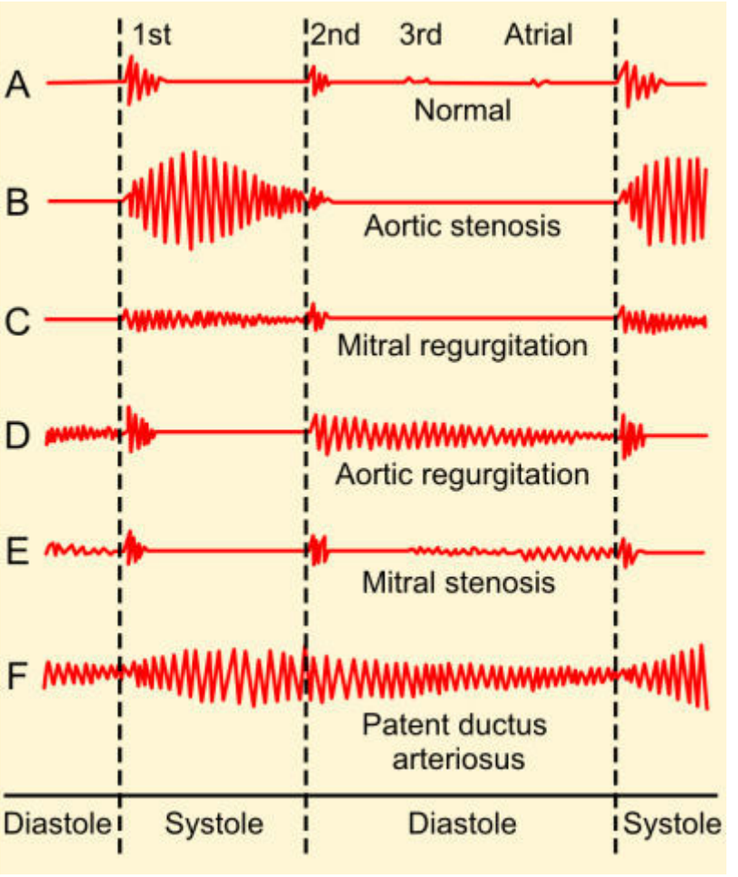
Mid-late diastolic

- mitral stenosis ('rumbling' in character)
- **Austin-Flint murmur** (severe aortic regurgitation, again is 'rumbling' in character)

- **It is a low frequency mid/late diastolic murmur which may show pre-systolic accentuation** and is virtually indistinguishable from that of mitral stenosis.
- It is due to partial closure of the anterior leaflet of the mitral valve by the regurgitant jet.

Continuous machine-like mumur

- patent ductus arteriosus



Murmurs and the Effects of Maneuvers

Lesion	Squatting/ leg raising	Standing/ Valsalva
Mitral and aortic stenosis	Increases both	Decreases both
Mitral and aortic regurgitation	Increases both	Decreases both
Mitral valve prolapse	Decrease	Increase
HOCM	Decrease	Increase

More blood increases **all** murmurs except MVP and HOCM.

Standing and Valsalva **decrease** venous return to the heart.

BEDSIDE MANEUVER	EFFECT
Inspiration (↑ venous return to right atrium)	↑ intensity of right heart sounds
Hand grip (↑ afterload)	↑ intensity of MR, AR, VSD murmurs ↓ hypertrophic cardiomyopathy murmurs MVP: later onset of click/murmur
Valsalva (phase II), standing up (↓ preload)	↓ intensity of most murmurs (including AS) ↑ intensity of hypertrophic cardiomyopathy murmur MVP: earlier onset of click/murmur
Rapid squatting (↑ venous return, ↑ preload	↓ intensity of hypertrophic cardiomyopathy murmur ↑ intensity of AS murmur MVP: later onset of click/murmur

Murmurs in pregnancy

- **The intensity of Aortic regurgitation murmur diminishes during pregnancy.**
- Diastolic blood pressure is lower due to vasodilatation, and this is responsible for the fading of the aortic regurgitation murmur
- **All stenotic murmurs become more prominent**

Mitral murmurs are heard best during expiration and while the patients lies on the left side.

All right-sided heart murmurs are intensified during deep inspiration.

Syncope (Nice guidelines 2014) and (ESC guidelines 2009)

- Syncope is a transient loss of consciousness due to transient global cerebral hypoperfusion, characterised by rapid onset, short duration, and spontaneous complete recovery.
- in the majority of patients, the cause of syncope is relatively benign, and a strategy based on patient education and prevention of recurrences is sufficient.
- Syncope can be classified as
    1. neurally-mediated (reflex syncope)
    2. secondary to orthostatic hypotension
    3. secondary to cardiac causes.
- In older patients, non-cardiovascular causes (such as vasovagal or orthostatic episodes) are twice as common as cardiovascular causes (such as arrhythmias or ischaemia).
- **situational syncope**: provoked by straining during micturition (usually while standing) or by coughing or swallowing.
- The initial evaluation after T-LOC consists of:
    - a careful history
    - physical examination, including orthostatic blood pressure measurements
    - electrocardiogram (ECG).
    - Based on these findings, simple additional examinations such as, carotid sinus massage, echocardiogram, ECG monitoring or orthostatic challenge can be indicated.
- The initial evaluation can define the cause of syncope in 23-50% of patients and should answer three key questions:
    - Is it a true syncopal episode or not?
    - Has the aetiological diagnosis been determined?
    - Are there findings suggestive of a high risk of cardiovascular events or death?
- It is important to distinguish exercise-induced syncope occurred **during exercise** (when a cardiac arrhythmic cause is probable) from those whose syncope occurred **shortly after stopping exercise** (when a vasovagal cause is more likely).
- For people who have experienced syncope **during exercise**:
    - offer urgent (within 7 days) exercise testing, unless there is a possible contraindication (such as suspected aortic stenosis or hypertrophic cardiomyopathy requiring initial assessment by imaging).
    - Advise the person to refrain from exercise until informed otherwise following further assessment.
    - If the mechanism for exercise-induced syncope is identified by exercise testing, carry out further investigation or treatment as appropriate in each individual clinical context.

  - Otherwise, carry out further investigations assuming a suspected cardiac arrhythmic cause.
- For people with a suspected cardiac arrhythmic cause of syncope, offer an ambulatory ECG and do not offer a tilt test as a first-line investigation.
- For all people with unexplained syncope → offer ambulatory ECG. Do not offer a tilt test before the ambulatory ECG.
- The type of ambulatory ECG offered should be chosen on the basis of the person's history and frequency of TLoC.
  - **TLoC at least several times a week**, → offer Holter monitoring (up to 48 hours)
    - If no further TLoC occurs during the monitoring period, → offer external event recorder that provides continuous recording with the facility for the patient to indicate when a symptomatic event has occurred.
  - **TLoC every 1–2 weeks** → offer an external event recorder.
    - If the person experiences further TLoC outside the period of external event recording, → offer an implantable event recorder.
  - **TLoC infrequently (less than once every 2 weeks)** → offer an implantable event recorder. A Holter monitor should not usually be offered unless there is evidence of a conduction abnormality on the 12-lead ECG.
- For people with suspected **carotid sinus syncope** and for people with unexplained syncope who are aged 60 years or older, → offer **carotid sinus massage as a first-line investigation.**
  - This should be conducted in a controlled environment, with ECG recording, and with resuscitation equipment available.
  - Diagnose carotid sinus syncope if carotid sinus massage reproduces syncope due to marked bradycardia/asystole and/or marked hypotension.
  - Do not diagnose carotid sinus syncope if carotid sinus massage causes asymptomatic transient bradycardia or hypotension
- **tilt test**
  - Do not offer a tilt test to people who have a diagnosis of vasovagal syncope on initial assessment.
  - For people with suspected **vasovagal syncope with recurrent episodes of TLoC** adversely affecting their quality of life, or representing a high risk of injury, → consider a tilt test **only to assess whether the syncope is accompanied by a severe cardioinhibitory response (usually asystole).**
- If a person has persistent TLoC, consider psychogenic **non-epileptic seizures (PNES)** or **psychogenic pseudosyncope** if:
  - the nature of the events changes over time
  - there are multiple unexplained physical symptoms
  - there are unusually prolonged events.
- **Driving**
  - must not drive while waiting for a specialist assessment.
  - Following specialist assessment →report the TLoC event to (DVLA)

Implantable loop recorder (ILR)
- subcutaneous, single-lead, (ECG) monitoring device
- used for diagnosis in patients with recurrent unexplained episodes of palpitations or syncope,
- The device is typically implanted in the left parasternal region and is capable of storing ECG data automatically in response to a significant bradyarrhythmia or tachyarrhythmia or in response to patient activation.
- It is particularly useful either when symptoms are infrequent (and thus not amenable to diagnosis using short-term external ECG recording techniques) or when aggregate long-term data (eg, burden of AF) are required.

Vasovagal syncope (VVS)

- Vasovagal syncope (VVS) is the most common type of syncope.

Causes
- features suggestive of uncomplicated vasovagal syncope (**the 3 'P's**):
  - **P**osture – prolonged standing, or similar episodes that have been prevented by lying down
  - **P**rovoking factors (such as pain or a medical procedure)
  - **P**rodromal symptoms (such as sweating or feeling warm/hot before TLoC).
- **Vasovagal syncope** is common during dental procedures, mainly induced by pain (as the dentist started drilling).

Feature

- VVS is usually preceded by a prodrome of symptoms such as dizziness, nausea, and diaphoresis.
  - The syncope lasts briefly, but nausea, warmth and sweating may persist for some time.
- Twitching and jerking are often seen with vasovagal or cardiac syncope, which can be differentiated from rhythmic jerking of all the limbs in tonic-clonic seizures.
- **It is common to have jerking of limbs due to brain hypoxia.**
- **Incontinence of urine can occur, but not biting of the tongue**.

Diagnosis

- Recover very quickly supports the diagnosis of syncope.
- ECG is always normal.
- **Tilt table test is a useful test to support the diagnosis**
  - If structural heart disease is excluded and syncope is reproduced on tilt table testing along with fall in blood pressure and heart rate, then this is diagnostic of vasovagal syncope.

Treatment

- Midodrine may be indicated in patient with VVS refractory to life style management
  - Midodrine is a prodrug of Desglymidodrine
  - a sympathomimetic (alpha receptor agonist) that acts on the blood vessels to raise blood pressure.

Postural hypotension

- **Causes: mnemonic (*HANDI*)**
  - H = Hypovolemia, Hypopituitarism (dehydration, bleeding)
  - A = Addison's disease
  - N = Neuropathy (autonomic due to diabetics, amyloidosis)
  - D = Drugs (Vasodialators, TCA, antipsychotic, Diuretics etc.)
  - I = Idiopathic orthostatic hypotension
- **Management of postural hypotension**
  - if the standing BP is clearly acceptable (110 systolic) , **the most obvious first step is stopping the causative drug (eg: indapamide)** and monitoring his blood pressure over the subsequent 2-4 weeks.
  - If he still has significant postural hypotension then **the next steps** would be to add elastic stockings, **then** fludrocortisone.
  - The history of pre-syncope is much more suggestive of changes in blood pressure rather than changes in blood glucose.

Sudden cardiac death

- **The most common cause of sudden cardiac death in those aged greater than 35 years, is ischemic heart disease.**
- Up to 80% of individuals who suffer sudden cardiac death have coronary heart disease.
- In those under the age of 35 years of age, HOCM is the most common cause of sudden cardiac death, coronary artery disease being the second most common cause.
- In competitive athletes <35 years of age HOCM is by far the most common cause of sudden cardiac death (prevalence is 1 in 500).
- arrhythmogenic right ventricular dysplasia (ARVD).
  - the second most common cause of sudden cardiac death in the young after HOCM.
- Catecholaminergic polymorphic ventricular tachycardia (CPVT)
  - an autosomal dominant inherited cardiac disease
  - prevalence of around 1:10,000.
- Brugada syndrome
  - an autosomal dominant inherited cardiovascular disease.
  - prevalence of 1:5,000-10,000.
  - more common in Asians.

Exercise: physiological changes

Blood pressure

- **systolic increases, diastolic decreases**
  - Diastolic BP remains the same and may decrease slightly
- leads to increased pulse pressure
- in healthy young people the increase in MABP is only slight

Cardiac output

- increase in cardiac output may be 3-5 fold
- results from venous constriction, vasodilation and increased myocardial contractibility, as well as from the maintenance of right atrial pressure by an increase in venous return
- heart rate up to 3-fold increase
- stroke volume up to 1.5-fold increase.

arrhythmias in athletes

- A variety of arrhythmias occur in athletes, most of which are benign and do not require further evaluation.
- Sinus pauses and arrests less than 3 seconds are common and do not necessarily indicate an underlying structural heart disease.
- Wandering atrial pacemaker and atrial ectopics are common and reflect high resting vagal tone.
- Atrial flutter in the absence of Wolf-Parkinson-White syndrome is rare and should be evaluated further.
- **Sustained or non-sustained VT is never normal and almost always occurs in the context of underlying structural heart disease.**

Exercise tolerance tests

Indications: Exercise tolerance tests (ETT, also exercise ECG) are used for a variety of indications:

- assessing patients with suspected angina - however the 2010 NICE Chest pain of recent onset guidelines do not support the use of ETTs for all patients
- risk stratifying patients following a myocardial infarction
  - the best predictor of mortality post-STEMI → exercise capacity
  - **Above average exercise capacity → good prognosis after a STEMI**
- assessing exercise tolerance
- risk stratifying patients with hypertrophic cardiomyopathy

Sensitivity and specificity of ETT: (high number of false positives and false negatives)

- **ETT has a sensitivity of around 80% and a specificity of 70% for ischaemic heart disease**. Thus, a negative test may not necessarily be true and further testing may be adviced.
  - Exercise ECG testing has a **relatively high sensitivity but only moderate specificity for the diagnosis of CAD.**
- Diagnostic accuracy is poor in women and this may relate to smaller heart size.

Heart rate:

- maximum predicted heart rate = 220 - patient's age
- the target heart rate is at least 85% of maximum predicted to allow reasonable interpretation of a test as low-risk or negative

Contraindications

- myocardial infarction less than 7 days ago
- unstable angina
- uncontrolled hypertension (systolic BP > 180 mmHg) or hypotension (systolic BP < 90 mmHg)
- Any condition where left ventricular output is reduced - eg, aortic stenosis or hypertrophic obstructive cardiomyopathy (HOCM).
- Abnormal baseline ECG (eg, bundle branch block patterns or left ventricular hypertrophy); these make interpretation of the ETT difficult.

Stop if:

- exhaustion / patient request
- 'severe', 'limiting' chest pain
- > 3mm ST depression
- > 2mm ST elevation.Stop if rapid ST elevation and pain
- systolic blood pressure > 230 mmHg
- systolic blood pressure falling > 20 mmHg
- attainment of maximum predicted heart rate
- heart rate falling > 20% of starting rate
- arrhythmia develops

Interpreting the exercise tolerance test

- The patient is normally considered to have been adequately 'stressed' if they achieve 85% or more of their maximum heart rate (calculated as 220 - age in years for men and 210 - age for women).
- **If ECG criteria for inducible ischaemia (chest pain is not mandatory).The next step is → Coronary angiography**
  - this will define the coronary anatomy and give a better guide to prognosis.

- If an inadequate test was performed, further non-invasive investigations may be indicated, such as myocardial perfusion scanning, cardiac MRI, or stress echocardiogram.

Notes

- Beta-blockers and digoxin can interfere with the results so are usually stopped before the ETT.
  - If ETT performed on beta blocker and there is an **adequate rise in heart rate (85% of (220 − age))** → so there is no indication for stopping beta blocker and repeat the test

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PiCCO (pulse contour cardiac output)

Which method is an appropriate of measuring adequate intravascular filling?

- **PiCCO (pulse contour cardiac output)**
- PiCCO gives indications of cardiac output, extravascular lung water, intravascular filling and only requires a central line and a PiCCO femoral arterial line and as such is relatively simple to use.

Cardiac enzymes and protein markers

Myoglobin rises first following a myocardial infarction

Key points for the exam

- myoglobin is the first to rise
- CK-MB is useful to look for reinfarction as it returns to normal after 2-3 days (troponin T remains elevated for up to 10 days)

	Begins to rise	Peak value	Returns to normal
Myoglobin	1-2 hours	6-8 hours	1-2 days
CK-MB	2-6 hours	16-20 hours	2-3 days
CK	4-8 hours	16-24 hours	3-4 days
Trop T	4-6 hours	12-24 hours	7-10 days
AST	12-24 hours	36-48 hours	3-4 days
LDH	24-48 hours	72 hours	8-10 days

Troponin

Troponin C: Binds to calcium to activate actin: myosin interaction
Troponin **T**: Binds to **t**ropomyosin
Troponin **I**: Blocks or **i**nhibits actin: myosin interaction

- Troponin is a **component of thin filaments** (along with actin and tropomyosin), and is the protein to which calcium binds to accomplish this regulation.
- Troponin has three subunits, TnC, TnI, and TnT.
- When calcium is bound to specific sites on TnC, the structure of the thin filament changes in such a manner that myosin (a molecular motor organised in muscle thick filaments) attaches to thin filaments and produces force and/or movement.
- In the absence of calcium, tropomyosin interferes with this action of myosin, and therefore muscles remain relaxed.
- Both troponin I and T are highly sensitive and specific for cardiac damage, and are of equal clinical value.
- Baseline troponin (I or T) should be done on admission. This troponin is not used immediately for interpretation of the cause of chest pain, but can be used to show a rise in patients who have an elevated baseline troponin (for example those with renal impairment).

- A second blood sample is taken for troponin I or T 10-12 hours after the onset of symptoms. A myocardial infarct can be diagnosed when there is a rise and/or fall of troponin (with at least one value abouve the 99th percentile of the upper reference limit)
- The 99th percentile thresholds for troponin I and T may differ between sexes.
- There is probability of chronically elevated troponin levels in some people
- **Diagnosis of ischaemia**
  - What is the significant level?
    - A level of > 0.1 ng/ml is considered as a significant rise
  - What is the next step after detecting a high level before confirming the diagnosis of ACS?
    - a detectable troponin on the **first high-sensitivity test** does not necessarily indicate that they have had an MI.
    - perform a **second high-sensitivity troponin test** if the first troponin test at presentation is positive.
    - When a raised troponin level is detected in people with a suspected ACS, reassess to exclude other causes for raised troponin (for example, myocarditis, aortic dissection or pulmonary embolism) before confirming the diagnosis of ACS.
  - What is the time for increasing after event?
    - Levels rise about 4 hours after the onset of chest pain
    - 100% of patients are positive for troponin at 12 hours after the onset of pain
  - **Levels act as a prognostic factor following an acute coronary syndrome**
- **Other causes of an elevated troponin are:**
  - Trauma
  - Cardioversion
  - Rhabdomyolysis
  - Pulmonary embolism
  - Pulmonary hypertension
  - Hypertension
  - Hypotension, especially with arrhythmias
  - Hypertrophic obstructive cardiomyopathy
  - Myocarditis including Kawasaki's disease
  - Sepsis
  - Burns
  - Subarachnoid haemorrhage and stroke
  - Infiltrative/autoimmune disorders including sarcoidosis, amyloidosis, haemochromatosis and scleroderma.
  - Drugs including
    - Adriamycin, **Herceptin** and 5-fluorouracil.

Serum creatine kinase

- Creatine kinase (CK) rises to a peak at about 24 h after a myocardial infarction and usually returns to baseline by72 h
- **serum CK activity in Afro-Caribbean people is often up to three times the upper limit of normal for white populations**
- other causes of high CK: hypothyroidism, heavy exercise and statins

Other notes

- LDH-1 isoenzyme is predominantly found in cardiac muscle so a high LDH-1:LDH-2 ratio can indicate myocardial damage.
- **Glycogen phosphorylase isoenzyme BB (GPBB)**
  - GPBB exists in heart and brain tissue.
  - **rise significantly by three hours post mi. As such it is an appropriate marker for early cardiac muscle injury.**
  - **Rise earlier than myoglobin**
    - GPBB levels increase 1–3 h after the event.
    - Myoglobin levels increase significantly 2 h after ischaemia.
- Cardiac enzymes may be elevated in pulmonary embolism (PE), aortic dissection, renal failure and sepsis.

ECG

ECG: axis deviation

Left axis deviation (LAD)

- Left axis deviation (≥ - 30 degrees) is the most common "abnormality" in adults occurring in over 8%. It can be part of the criteria for LVH but in isolation it has little significance.
- Marked LAD (≥ - 45 degrees) is called left anterior hemiblock or left anterior fascicular block.
- **Recommendations:** If left axis deviation is present:
  - Exclude hypertension. If borderline → ambulatory BP monitoring.
  - check for borderline indicators of LVH (i.e., the voltage criteria and left atrial enlargement).
  - Note whether diagnostic inferior Q waves are present since an inferior MI can cause LAD.
- **Causes of left axis deviation (LAD)**
  - left anterior hemiblock
  - left bundle branch block
  - Wolff-Parkinson-White syndrome* - right-sided accessory pathway
  - hyperkalaemia
  - congenital: ostium primum ASD, tricuspid atresia
  - minor LAD in obese people

Right axis deviation (RAD)

- QRS axis between +90° and + 180°
- **Causes of right axis deviation (RAD)**
  - right ventricular hypertrophy
  - left posterior hemiblock
  - chronic lung disease → cor pulmonale
  - pulmonary embolism
  - ostium secundum ASD
  - Wolff-Parkinson-White syndrome* - left-sided accessory pathway
    - *in the majority of cases, or in a question without qualification, Wolff-Parkinson-White syndrome is associated with left axis deviation
  - normal in children or thin adults
  - normal in youngsters (less than 21 years of age) and in athletes.
  - minor RAD in tall people

ECG: coronary territories

The table below shows the correlation between ECG changes and coronary territories:

	ECG changes	Coronary artery
Anteroseptal	V1-V4	Left anterior descending
Inferior	II, III, aVF	Right coronary
Anterolateral	V4-6, I, aVL	Left anterior descending or left circumflex
Lateral	I, aVL +/- V5-6	Left circumflex
Posterior	Tall R waves V1-2	Usually left circumflex, also right coronary

high lateral wall MI

- **ST segment elevation in leads I and aVL → High lateral wall MI**
- usually due to occlusion of the first diagonal branch of the left anterior descending artery, though occlusion of other arteries like branches of the left circumflex or a short left anterior descending artery may cause the same picture.

Postero-lateral MI → prominent R wave in lead V1 and ST depression in V1-V3 + ST elevation in leads V5 and V6.

posterior MI (ESC guidelines 2017)

- posterior wall (now termed inferobasilar), usually supplied by the posterior descending artery — a branch of the **right coronary artery** in 80% of individuals.
- isolated ST-segment depression ≥ 0.5 mm in leads V_1–V_3 represents the dominant finding. These should be managed as a STEMI.
- The use of additional posterior chest wall leads [elevation V_7–V_9 ≥ 0.5 mm (≥1 mm in men, 40 years old)] is recommended.

The presence of ST depression ≥ 1 mm in six or more surface leads, coupled with ST-segment elevation in aVR and/or V_1, suggests **multivessel ischemia** or **left main coronary artery obstruction**, particularly if the patient presents with haemodynamic compromise. (ESC guidelines 2017)

Left main stem (LMS)

- LMS occlusion typically presents dramatically with cardiogenic shock.
- ECG findings include ST elevation in aVR with diffuse ST depression in other leads.

Which ECG changes may be seen earlier in ischaemia ?
→ hyper-acute T-waves, which may precede ST-segment elevation.

ECG criteria for STEMI (ESC guidelines 2017)

- ST-segment elevation (measured at the J-point) is considered suggestive of ongoing coronary artery acute occlusion in the following cases:
  - **Numbers of leads**: at least two contiguous leads with ST-segment elevation
  - ST-segment elevation:
    - **≥** 2.5 mm in men **<** 40 years,
    - **≥** 2 mm in men **≥** 40 years, or
    - **≥** 1.5 mm in women in leads V_2–V_3 and/or
    - **≥** 1 mm in the other leads
  - In patients with **inferior MI,** it is recommended to record right precordial leads (V_3R and V_4R) seeking ST-segment elevation, to identify **concomitant right ventricular (RV) infarction.**
  - Likewise, ST-segment depression in leads V_1–V_3 suggests myocardial ischaemia, especially when the terminal T-wave is positive (ST-segment elevation equivalent), and confirmation by concomitant ST-segment elevation ≥ 0.5 mm recorded in leads V_7–V_9 should be considered as a means to identify **posterior MI** (circumflex occlusion).

ECG: digoxin

ECG features

- down-sloping ST depression ('reverse tick')
- flattened/inverted T waves
- short QT interval
- arrhythmias e.g. AV block, bradycardia

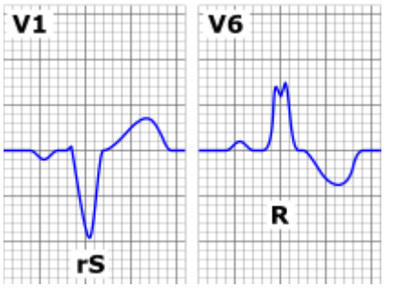
ECG: hypothermia

The following ECG changes may be seen in hypothermia

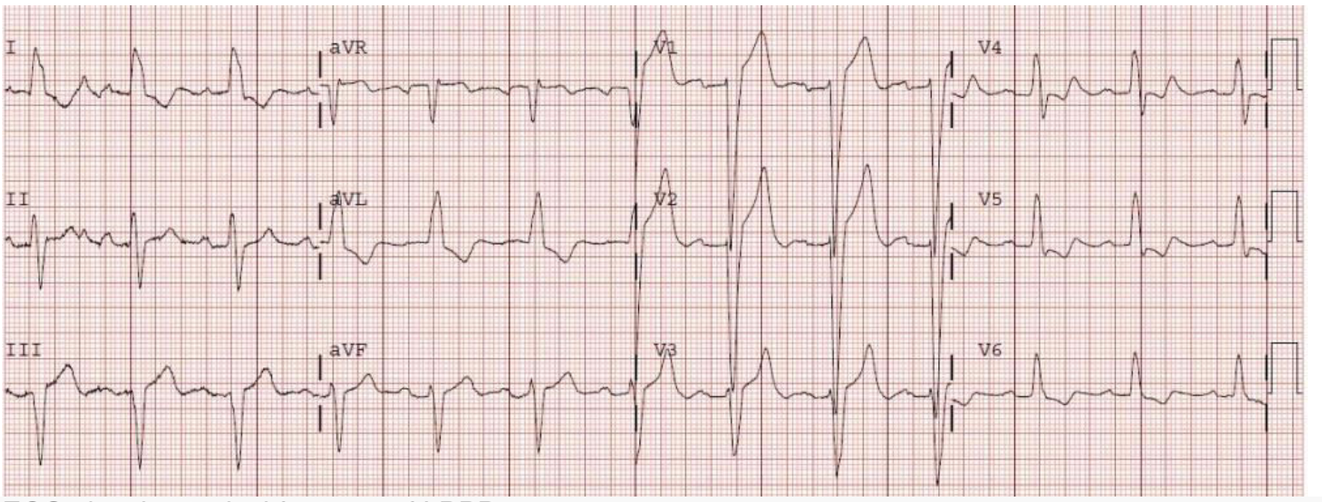
- bradycardia
- 'J' wave - small hump at the end of the QRS complex
- first degree heart block
- long QT interval
- atrial and ventricular arrhythmias

ECG: left bundle branch block

- The diagram below shows the typical features of left bundle branch block (LBBB):



- The ECG would show:
  - broad QRS complex (>120ms),
  - tall R waves in the lateral leads (I, V5-6) and deep S waves in the right precordial leads (V1-3)
  - usually leads to left axis deviation.
- One of the most common ways to remember the difference between LBBB and RBBB is WiLLiaM MaRRoW
  - WiLLiaM : in LBBB there is a 'W' in V1 and a 'M' in V6
  - MaRRoW: in RBBB there is a 'M' in V1 and a 'W' in V6



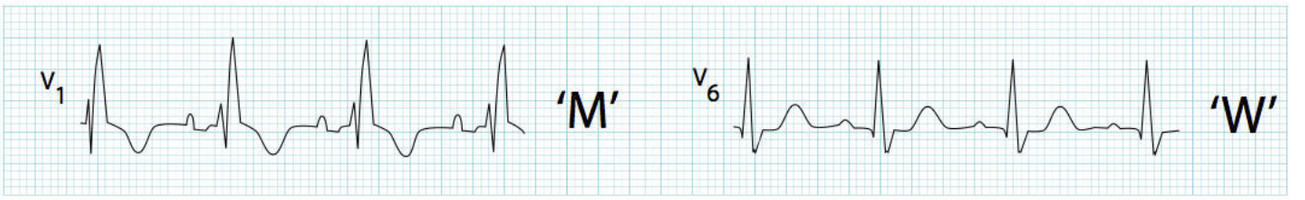
ECG showing typical features of LBBB

- Causes of LBBB
  - ischaemic heart disease
  - hypertension
  - aortic stenosis
  - cardiomyopathy
  - rare: idiopathic fibrosis, digoxin toxicity, hyperkalaemia

Right bundle branch block (RBBB)

- **Patients with MI and right bundle branch block (RBBB) have a poor prognosis.** (ESC guidelines 2017)
  - It may be difficult to detect transmural ischaemia in patients with chest pain and RBBB.

- Therefore, persistent **ischaemic symptoms** occur in the presence of **RBBB** → primary **PCI** strategy (emergent coronary angiography and PCI if indicated) **should be considered**



Trifascicular block

The evidence of trifascicular block (RBBB, LAD and prolongation of the PR interval) in the context of dizziness and collapses. This is an indication for dual chamber (DDDR) pacing for likely complete heart block.

- trifascicular block is not strictly an ECG diagnosis but is a term used for the combination of:
  1. right bundle branch block,
  2. left hemiblock (typically left anterior hemiblock (LAHB)) (LAHB is diagnosed because the net QRS deflection in lead II is negative).
  3. long PR interval.
- **the site of the lesion →AV node and Purkinje fibres**
- The most common pattern referred to as "trifascicular block" is the **combination of bifascicular block with 1st degree AV block.**
- It implies that the bundle branches (Purkinje fibres) are blocked in the right bundle and one of the left hemibundles.
- The 'third' bundle is also delayed or partially blocked hence the name. However, the delay (long PR interval) is usually at the AV node.
- Clinically it means there is extensive disease of the conduction system and, in a patient such as this, would be an indication for permanent pacemaker.

ECG: normal variants

The following ECG changes are considered normal variants in an athlete:

- sinus bradycardia
- junctional rhythm
- first degree heart block
- Wenckebach phenomenon

ECG: PR interval

Causes of a **prolonged PR interval**

- idiopathic
- ischaemic heart disease
- digoxin toxicity
- hypokalaemia*
  - *hyperkalaemia can rarely cause a prolonged PR interval, but this is a much less common association than hypokalaemia
- rheumatic fever
- aortic root pathology e.g. abscess secondary to endocarditis
- Lyme disease
- sarcoidosis
- myotonic dystrophy
- A prolonged PR interval may also be seen in athletes

short PR interval is seen in Wolff-Parkinson-White syndrome

ECG: ST depression

Causes of ST depression

- secondary to abnormal QRS (LVH, LBBB, RBBB)
- ischaemia

- digoxin
- hypokalaemia
- syndrome X

Q waves

- A Q wave is any negative deflection that precedes an R wave on the ECG.
- The evolution of Q waves is the most suggestive of an infarct. **(more specific than ST elevation and cardiac enzyme for MI)**
  - **the most specific for a diagnosis of myocardial infarction**
- Small Q-waves are normal in most leads, and they can be prominent in leads III and aVR as a normal variant, but should not be seen in leads V1-V3.
- They are **considered pathological if** they are:
  - more than 1mm wide,
  - more than 2mm deep,
  - more than 25% of the depth of the QRS complex, or
  - seen in leads V1-V3.
- Such pathological Q-waves usually indicate prior full thickness myocardial infarct.

ECG: ST elevation

Causes of ST elevation

- myocardial infarction
- pericarditis
- normal variant - 'high take-off'
- left ventricular aneurysm
- Prinzmetal's angina (coronary artery spasm)
- rare: subarachnoid haemorrhage, part of spectrum of changes in hyperkalaemia

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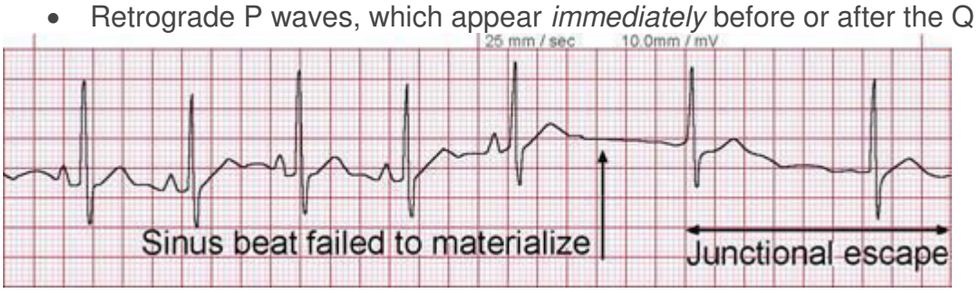
TQ Interval

- The TQ interval is the time between the end of the T wave and the onset of the **next QRS** complex.
- **It represents the ventricular diastole**
- T wave corresponds with ventricular repolarization (when contraction stops) and QRS corresponds with ventricular depolarization (when it contracts).
- which phase of the cardiac cycle shortens the most with increasing heart rate?: it is diastole.
- Diastole is usually the longest portion of the cardiac cycle, and its duration diminishes the most (more than the reduction seen in the duration of systole) with increasing heart rate.
- **Which ECG interval will show the greatest reduction during ECG stress test?**
  - **TQ interval**

ECG: Junctional escape rhythm

- Junctional escape rhythm describes an abnormal heart rhythm that arises within the AV node or from an adjacent area.
- There is a slow, regular pulse rate.
- Common after a pause in the underline rhythm
- ECG shows absent P waves, narrow QRS complexes, and a heart rate of 40 to 60 bpm.
- Retrograde P waves, which appear *immediately* before or after the QRS complex may be seen.



Cardiac amyloidosis

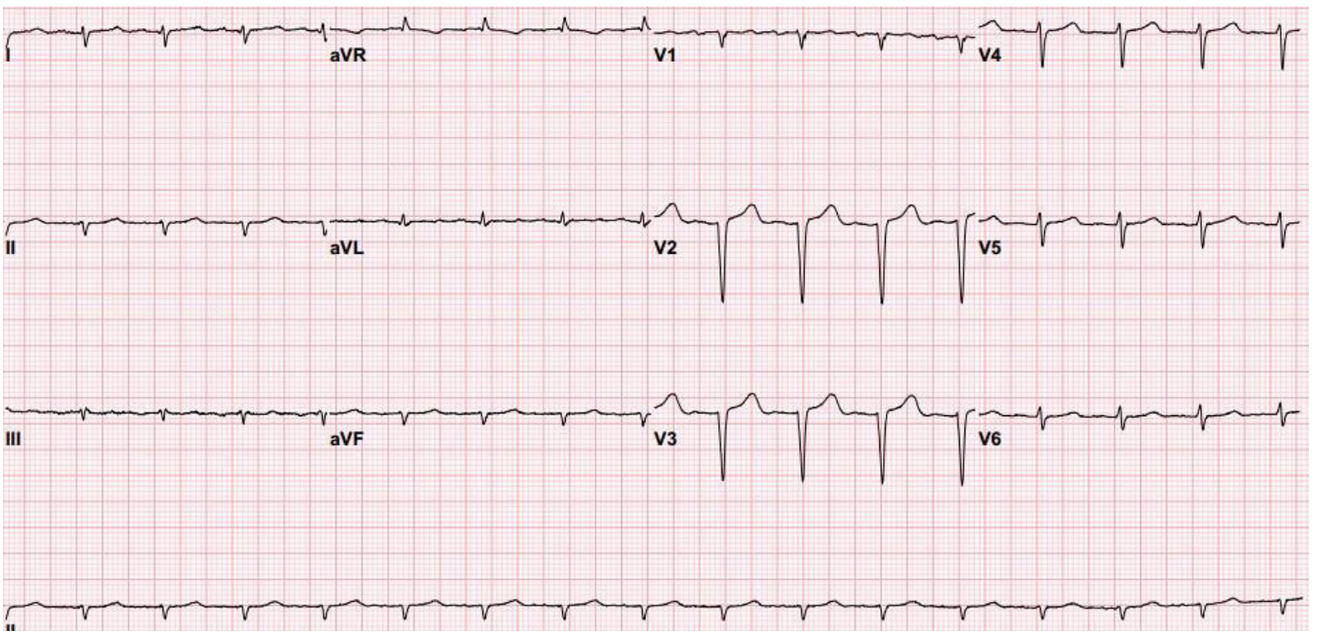
Amyloid

- Low-voltage EKG
- Speckled pattern on echo

- Cardiac amyloidosis most commonly presents as restrictive cardiomyopathy.
- The clinical findings are those of right heart failure, i.e. jugular venous distension and peripheral oedema, whereas orthopnoea and paroxysmal nocturnal dyspnoea are typically absent.
- In more advanced stages, systolic dysfunction also occurs. Postural hypotension can occur as a result of poor ventricular filling or associated autonomic neuropathy.
- **The combination of low-voltage ECG and thickened ventricular walls is one of the characteristic features of cardiac amyloidosis.**
- echocardiographic abnormalities include atrial dilatation, thickened interatrial septum, diastolic dysfunction and small-volume ventricles.
- The most distinctive feature of cardiac amyloidosis is a sparkling, granular appearance of the myocardium, but this is a relatively insensitive feature occurring only in about 25% of cases.

- The history of rheumatoid arthritis and the echocardiographic finding of bi-atrial dilatation, ventricular hypertrophy and a speckled appearance to the myocardium make amyloidosis the most likely underlying cause.
- **Digoxin is contraindicated in amyloid patients as the digoxin binds irreversibly to the amyloid fibrils.**

The ECG typically shows low-voltage complexes with poor R wave progression in the chest leads (a pseudoinfarction pattern).



Cardiac amyloidosis is associated with a 'global speckled' pattern on echo.

ECG: Wrong leads

- They are normally labelled red (right arm) and yellow (left arm). The other leads are green (left leg) and black (right leg).
- If the wires to the right and left arms have been accidentally swapped over → It gives the appearence of abnormal T wave inversion in the lateral leads I and aVL.
- The clue to recognising it is the **inverted P waves in lead I** and the **upright aVR which** are both highly unusual for a 12-lead ECG.
  - **The correct course of action → Repeat the ECG again**

Early repolarization variant

- It is expresses as an early uptake of the ST segment before the descending limb of the R wave has reached the baseline**.**
- **Features of early repolarization variant are:**
  - **Classically the ST segment elevation during early exercise returns to normal as heart rate increases further**

- It is common in black males
- Clinical evaluation is entirely normal
- ST elevation is usually seen in the precordial leads

ECG: U wave

Causes of prominent U waves are:

- Hypokalaemia
- Cardiovascular drugs, e.g. digitalis, quinidine, amiodarone
- Psychotropic drugs, e.g. phenothiazines, tricyclic antidepressants.

Cardiac investigations

Cardiac catheterisation and oxygen saturation levels

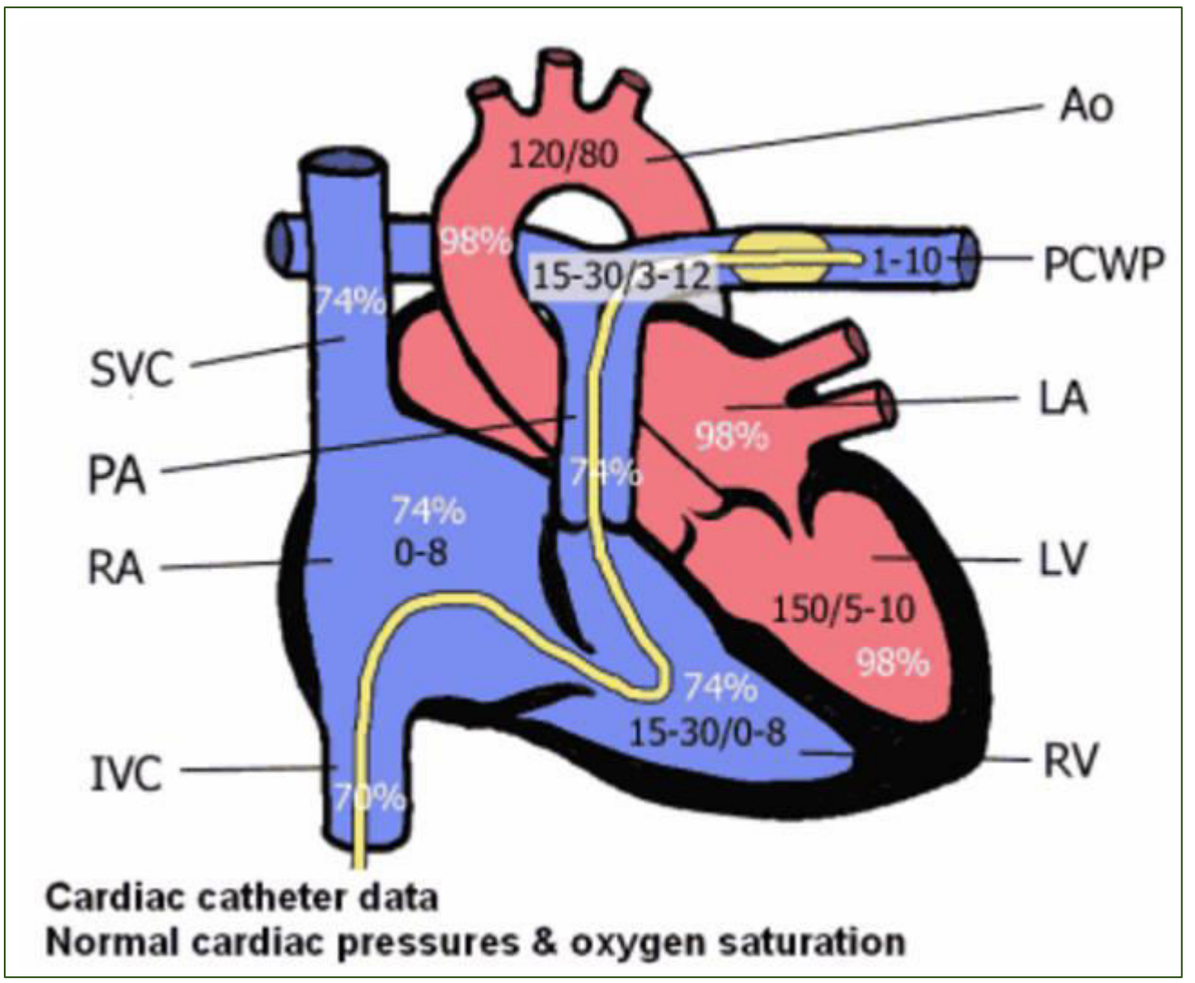
- Questions regarding cardiac catheterisation and oxygen saturation levels can seem daunting at first but a few simple rules combined with logical deduction can usual produce the answer.

Let's start with the basics:

- deoxygenated blood returns to the right side of the heart via the superior vena cava (SVC) and inferior vena cava (IVC). It has an oxygen saturation level of around **70%**. The right atrium (RA), right ventricle (RV) and pulmonary artery (PA) normally have oxygen saturation levels of around 70%
- the lungs oxygenate the blood to a level of around **98-100%**. The left atrium (LA), left ventricle (LV) and aorta should all therefore have oxygen saturation levels of 98-100%

Some examples:

Diagnosis & notes	RA	RV	PA	LA	LV	Aorta
Normal	70%	70%	70%	100%	100%	100%
Atrial septal defect (ASD) The oxygenated blood in the LA mixes with the deoxygenated blood in the RA, resulting in intermediate levels of oxygenation from the RA onwards	85%	85%	85%	100%	100%	100%
Ventricular septal defect (VSD) The oxygenated blood in the LV mixes with the deoxygenated blood in the RV, resulting in intermediate levels of oxygenation from the RV onwards. The RA blood remains deoxygenated	70%	85%	85%	100%	100%	100%
Patent ductus arteriosus (PDA) Remember, a PDA connects the higher pressure aorta with the lower pressure PA. This results in only the PDA having intermediate oxygenation levels	70%	70%	85%	100%	100%	100%
VSD with Eisenmenger's	70%	70%	70%	100%	85%	85%
PDA with Eisenmenger's	70%	70%	70%	100%	100%	85%
ASD with Eisenmenger's	70%	70%	70%	85%	85%	85%



Guidelines for the Interpretation of Cardiac Catheter Data

- Right-heart saturations do not exceed 75%. Saturations more than this are suggestive of a left-to-right shunt.
- **Atrial septal defect (ASD) : The oxygen saturation in the RA and SVC should be the same. But in ASD there is a step-up in oxygen saturation at the level of the RA.** This can only result from the addition of oxygenated blood to the deoxygenated blood in the right heart circulation, that is, an abnormal connection between the right and left sides of the heart.
  - **Primum ASD:**
    - The location of the step-up is suggestive of a primum defect since these lesions **occur low down in the A-V septum, lying immediately above the atrioventricular valves.**
    - These lesions can affect the function of the anterior leaflet of the mitral valve, causing mitral regurgitation.
    - **high pressures of Right ventricular are more likely to occur with primum ASDs**.
- **Patent ductus arteriosus (PDA)**
  - **unexpected step-up in oxygen saturation between the RV and PA.**
  - **high pulmonary artery pressures**
  - high wedge pressure.
  - **The change in O_2 saturation between the ascending and descending aorta strongly suggests the presence of a patent ductus.**
  - Unfortunately the extremely elevated right sided pressures are indicative of advanced disease, not amenable to surgical correction. In late disease the machinery murmur said to be characteristic of the disease may well not be audible.
- Left-heart saturations vary from 96–98%. Saturations less than this are suggestive of a right-to-left shunt.

- In right-to-left shunts, the arterial saturations do not change with inspired high-concentration oxygen.
- **Ventricular septal defect (VSD)**
  - **There is a step-up in the oxygen saturation between the RA and RV.** This can only occur when there is an abnormal connection between these two chambers, that is, via a VSD.
  - This is confirmed by the **raised right ventricular pressures.**
  - **VSD with Eisenmenger's syndrome**
    - the **pressures in the RV and PA are markedly elevated**, but RA pressure is normal.
    - **The left ventricular oxygen saturation is low**, which raises the possiblity of a right to left cardiac shunt mixing desaturated RV blood with LV saturated blood (due to right ventricular pressures exceeding left ventricular pressure).
  - post-MI VSD and papillary rupture are difficult to distinguish clinically.
    - The diagnosis is established by demonstration of a left to right shunt.
      - if there is a step-up in the oxygen saturation between the RA and PA → VSD
      - if there is no step-up, → papillary muscle rupture.
- **Fallot's tetralogy**
  1. **VSD:** step-down in oxygen saturation between LA and LV, indicating right to left shunt at the level of the ventricles.
  2. **Pulmonary stenosis**: there is ↑mmHg gradient across the pulmonary valve (RV systolic - PA systolic).
  3. **RVH**: Right ventricular pressures are high and there is a right to left shunt, which indicated by the oxygen saturations.
  4. **Over-riding aorta**:
     - **there is a further step-down in oxygen saturation between the LV and aorta.**
     - This could occur in either Fallot's or with a patent ductus arteriosus with right to left shunting.
     - However, given the other features of Fallot's, this is most likely to be caused by an over-riding aorta with reduced saturations due to a mixture of deoxygenated blood from the RV entering the left heart circulation.
     - The over-riding aorta recieves a mixture of blood from the left and right ventricles as is formed above a VSD.
- Pulmonary hypertension does not occur in Fallot's tetralogy due to narrowing of the right ventricular outflow tract/ subpulmonary valve stenosis.
- A VSD with a right-to-left shunt and pulmonary stenosis can be differentiated from Fallot' s tetralogy by examining the oxygen saturation in the left ventricle and the ascending aorta.
  - **In the case of a VSD**, the saturations in the left ventricle and the aorta will both be low and very similar.
  - **In the case of Fallot' s tetralogy**, the aortic oxygen saturation will be much lower than the oxygen saturation in the left ventricle because the right ventricle pumps most of the deoxygenated blood into the overriding aorta.
- A pulmonary artery pressure exceeding 35 mmHg is suggestive of **pulmonary hypertension**.
- A pressure drop of more than 10 mmHg across the aortic or pulmonary valve is suggestive of **aortic or pulmonary stenosis**, respectively.
- The diagnosis of **mitral regurgitation** cannot be made unless you are given the PCWP 'v-wave'. A v-wave higher than 20 mmHg is highly suggestive of mitral regurgitation.
- The right and LVEDP and the left and right atrial pressures are roughly equal in pericardial constriction
- When interpreting right heart catheter data, remember the saturation should decrease gradually as the venous blood reaches the pulmonary capillary wedge saturation, which should be equal to arterial blood.
- In Ebsteins anomaly there should be elevated RA pressure due to significant tricuspid regurgitation.
- **Hypertrophic cardiomyopathy**

- **Left ventricular pressures are high with a steep drop-off between the LV and aortic systolic pressures.**

- Anomalous pulmonary venous drainage to SVC
  - normally oxygenation in the superior vena cava should always be lower than the inferior vena cava, due to the high oxygen demands from the brain.
  - If SVC sats is markedly higher than the IVC, sugest a diagnosis of **anomalous pulmonary venous drainage** of more highly oxygenated blood into the SVC (left to right shunt).

What is meaning of "valve gradient" ?

- The valve's gradient describes the severity of the narrowing of the valve by the increase in pressure behind it.
- It helps to measure the amount of blood that is able to pass through the valve.
- It also indicates whether the "velocity" (or speed of movement) of the blood flow is increased because of the increased pressure behind the narrowed valve.

Diagnosis of tricuspid stenosis

- mean gradient by echocardiogram or cardiac catheterisation of 2 mmHg or greater, but is usually found to be >7 to 10 mmHg in severe TS

Diagnosis of pulmonary hypertension

- If the pulmonary arterial pressure is greater than the normal one-fifth of systolic measurements → pulmonary hypertension is present.

Diagnosis of right ventricular failure

- The right atrial pressure is grossly elevated, with a normal wedge pressure.
  - Normal right atrial pressure = (4–8) mmHg.
  - Normal indirect left atrial mean pressure (wedge) = (5–10) mmHg.
    - normal wedge pressure excludes acute left ventricular failure or acute mitral regurgitation.

Diagnosis of aortic stenosis

- a greater than 25mmHg gradient across the aorta valve, demonstrating moderate aortic stenosis.
- systolic gradient of ↑ mmHg across the aortic valve (LV systolic pressure - aortic systolic pressure), indicating critical aortic stenosis.
- Hypertrophic cardiomyopathy may result in similar pressure differences, but given the clinical information, aortic stenosis is far more likely than hypertrophic obstructive cardiomyopathy (HOCM) in an old patient.
- A guide to determining the severity of aortic stenosis is given below:

Severity of aortic stenosis	Severity Valve area (cm^2)	Mean gradient (mmHg)
Mild	>1.5	<25
Moderate	1.0-1.5	**25-50**
Severe	<1.0	>50
Critical	<0.7	>80

Diagnosis of mitral stenosis

- A normal mitral valve expects less than 5mmHg pressure difference.
- Using these inferences, the mitral valve gradient is calculated by the capillary wedge pressure of mmHg (same as the left atrial pressure) minus the diastolic left ventricular pressure of mmHg: **the mmHg difference more than 5 demonstrates mitral stenosis**.
- The PCWP is equal to the LVEDP. When the PCWP exceeds the LVEDP, the diagnosis of **mitral stenosis** should be considered.
- **The gradient across the mitral valve (LA pressure - LV end diastolic pressure); it is usual to use the PCWP as a surrogate for LA pressure.**
- There is also evidence of right ventricular hypertrophy, with **markedly elevated RV pressures due to secondary pulmonary hypertension**.

- The severity of mitral stenosis can be graded:

Severity of mitral stenosis	Severity Valve area (cm^2)	Gradient (mmHg)
Mild	1.6-2.0	<5
Moderate	1.0-1.5	**5-10**
Severe	<1.0	>10

Aortic incompetence

- Aortic regurgitation is diagnosed by a wide pulse pressure in the aortic pressure.
- There is a wide pulse pressure in the aorta
- accompanied by a very high left ventricular end-diastolic pressure (LVEDP).LVEDP greater than 20 mmHg is suggestive of irreversible LV dysfunction.
- All left heart valve diseases can ultimately cause elevated right heart pressures

coarctation of the aorta

- **There is a steep systolic gradient between the left ventricle and the femoral artery**

Pulmonary artery floatation catheter findings:

- **if the pulmonary artery occlusion pressure is low with a relatively low cardiac index, suggesting the patient is hypovolaemic,** even in spite of high right atrial pressure.
  - A fluid challenge should be performed and values re-measured to assess response.
  - In a fluid replete patient the occlusion pressure would be higher (usually >13 mmHg)
- if the Pulmonary artery occlusion pressure is high and cardiac index low (i.e. <2.5 $L/min/m^2$) this would be more suggestive of cardiogenic shock.

Hyperthyroidism and cardiac catheterisation:

- Cardiac catheterisation requires the use of an iodine-containing contrast.
- This may worsen hyperthyroidism caused by toxic multinodular goitre, whereas it may improve the symptoms in patients with Grave's disease (Wolff–Chaikoff effect).
- **The most reliable diagnostic method is a radionuclide (99Tcm, 123I or 131I) scan of the thyroid, which will distinguish the diffuse, high uptake of Grave's disease from nodular thyroid disease.**
- If a toxic multinodular goitre or toxic adenoma is detected, the patient should receive an antithyroid drug before undergoing catheterisation.
- The antithyroid medication must be continued for at least 2 weeks after the procedure.

Pulmonary capillary wedge pressure

- Pulmonary capillary wedge pressure (PCWP) is measured using a balloon tipped Swan-Ganz catheter which is inserted into the pulmonary artery.
- The pressure measured is similar to that of the left atrium (normally 6-12 mmHg).
- The PCWP provides an indirect measurement of the left atrial pressure, and since the left atrial pressure is increased, the PCWP will also be increased.
- One of the main uses of measuring the PCWP is determining whether pulmonary oedema is caused by either heart failure or acute respiratory distress syndrome.
- In many modern ITU departments PCWP measurement has been replaced by non-invasive techniques.

Which method is an appropriate of measuring adequate intravascular filling?

- **PiCCO (pulse contour cardiac output)**
  - PiCCO gives indications of cardiac output, extravascular lung water, intravascular filling and only requires a central line and a PiCCO femoral arterial line and as such is

relatively simple to use.

Cardiac imaging: non-invasive techniques excluding echocardiography

Nuclear imaging

- These techniques use radiotracers which are extracted by normal myocardium.
- Examples include:
  - Thallium
    - Nuclear isotopes are picked up by the Na/K ATPase of normal myocardium.
    - If cardiac tissue is alive and perfused, it will pick up the nuclear isotope.
    - To the myocardium, thallium looks like potassium.
    - Decreased uptake = Damage
  - technetium (99mTc) sestamibi:
    - a coordination complex of the radioisotope technetium-99m with the ligand methoxy-iso-butyl isonitrile (MIBI), used in 'MIBI' or cardiac Single Photon Emission Computed Tomography (SPECT) scans
  - **fluorodeoxyglucose (FDG):**
    - **used in Positron Emission Tomography (PET) scans**
      - Cardiac PET is predominately a research tool at the current time

SPECT

- The primary role of SPECT is to assess myocardial perfusion and myocardial viability.
- Two sets of images are usually acquired. First the myocardium at rest followed by images of the myocardium during stress (either exercise or following adenosine / dipyridamole).
- By comparing the rest with stress images any areas of ischaemia can classified as reversible or fixed (e.g. Following a myocardial infarction).

MUGA

- Multi Gated Acquisition Scan, also known as radionuclide angiography
- radionuclide (technetium-99m) is injected intravenously
- the patient is placed under a gamma camera
- may be performed as a stress test
- can **accurately measure left ventricular ejection fraction**.
- Typically used before and after cardiotoxic drugs are used

Cardiac Computed Tomography (CT)

- Cardiac CT is useful for **assessing suspected ischaemic heart disease**, using two main methods:
  - **calcium score:**
    - there is known to be a correlation between the amount of atherosclerotic plaque calcium and the risk of future ischaemic events.
    - Cardiac CT can quantify the amount of calcium producing a 'calcium score'
  - **contrast enhanced CT**:
    - allows visualisation of the coronary artery lumen
- If these two techniques are combined cardiac CT has a **very high negative predictive value** for **ischaemic heart disease**.
- The updated NICE guidelines recommends that **cardiac CT** is the **first-line investigation** for patients presenting with **new-onset chest pain due to suspected CAD**.

Cardiac MRI

- Cardiac MRI (commonly termed CMR) has become the gold standard for providing **structural images of the heart**.
- It is particularly **useful in**:
  - assessing congenital heart disease,
  - determining right and left ventricular mass and
  - differentiating forms of cardiomyopathy.
  - Myocardial perfusion can also be assessed following the administration of gadolinium.
- Currently CMR provides limited data on the extent of coronary artery disease.

Valvular diseases

Mitral stenosis

Causes:

- **Common → rheumatic fever**
  - Rheumatic valve disease is increasing uncommon in the UK, but can still be seen in other parts of the world.
  - The physiological stress of pregnancy can exacerbate the features of rheumatic mitral stenosis.
- **Rare →** mucopolysaccharidoses, carcinoid and endocardial fibroelastosis

Features

- **tapping apex beat**
- mid-**late** diastolic murmur (with pre-systolic accentuation) (best heard in expiration)
- loud S1
- opening snap
  - **suggests that the mitral valve is mobile**
  - **opening snap is not heard when the mitral valve is heavily calcified**
  - snap occurs when the superior systolic bowing of the **anterior mitral valve leaflet is rapidly reversed towards the left ventricle in early diastole**, owing to the high left atrial pressur
- low volume pulse
- malar flush
- atrial fibrillation
- leads to left atrial enlargement, but the **left ventricle is usually small.**
- **enlarged left atrium may lead to pressure posteriorly on the oesophagus.**

Features of severe MS

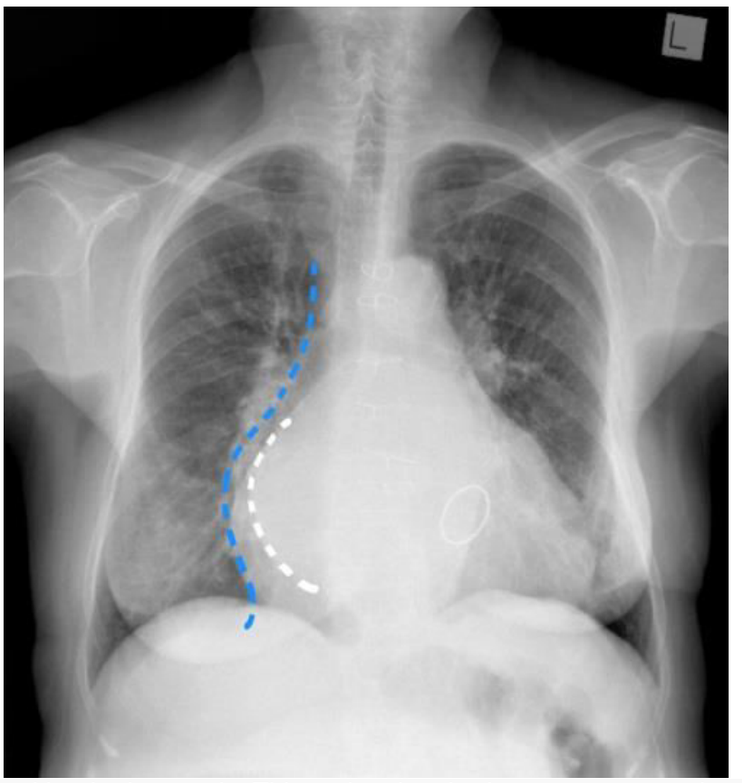
- length of murmur increases
- opening snap becomes closer to S2.
  - **opening snap is characteristically lost with heavy valvular calcification**

Chest x-ray

- left atrial enlargement may be seen

Echocardiography

- the normal cross sectional area of the mitral valve is 4-6 sq cm. A 'tight' mitral stenosis implies a cross sectional area of < 1 sq cm



Chest x-ray from a patient with mitral stenosis. This patient has had a sternotomy and a prosthetic mitral valve. There is splaying of the carina with elevation of the left main bronchus, a double right heart border and cardiomegaly. The features are those of left atrial enlargement. Although the entire heart is enlarged, a double contour is seen through the right side of the heart. The more medial line is the enlarged left atrium (white dotted line) and the heart heart border is more lateral (blue dotted line).

Mitral stenosis in pregnancy:

- Mitral stenosis is poorly tolerated in pregnancy due to volume overload.
- Pregnancy can unmask previously undiagnosed obstructive valvular heart disease and intervention should be performed with adequate shielding of the fetus.
- Pregnant women with mitral stenosis may develop symptoms in the second trimester, when the demand for cardiac output increases by around 70%.
- A diuretic is given to control mild symptoms.
- **Percutaneous mitral balloon valvuloplasty (PMBV) should be carried out for severe mitral stenosis in patients who remain symptomatic despite medical therapy**.

MECHANISM OF OPENING SNAP EARLIER IN WORSENING MS

- The mitral valve opens when LA pressure > LV pressure. Worse MS = Higher LA pressure. Higher LA pressure pushes the mitral valve open earlier.

Lutembacher syndrome

- **characterised by both mitral stenosis and atrial septal defect (ASD).**
- Both conditions may be congenital and occur concurrently, or the mitral stenosis may occur as a result of rheumatic fever or some other cause.
- Incidence is higher in women due to the greater incidence of congenital ASD.
- Cardiac signs are mixed due to the two concurrent lesions.
- Presentation is typically in later life, with fatigue or atrial fibrillation.
- **mid-diastolic tricuspid murmur** fits with increased tricuspid valve flow, consistent with a shunt because of an ASD
- Ideally, surgery should be performed as early as possible due to the risks of Eisenmenger syndrome in untreated patients.

Mitral regurgitation (MR)

- **Myxomatous degeneration of the mitral valve is by far the most common cause of MR in the United Kingdom.**

Features

- pan-systolic murmur
- soft S1, split S2

Which feature suggests more severe mitral regurgitation?

- As mitral regurgitation becomes more severe, the left ventricle enlarges and the **apex beat displaces** and a **systolic thrill** can develop.

Mitral valve prolapse (MVP)

Epidemiology

- common, occurring in around 5-10 % of the population.
- more common in females.

Causes

- usually idiopathic
- may be **associated with**:
  - congenital heart disease: PDA, ASD
  - cardiomyopathy
  - Turner's syndrome
  - Marfan's syndrome,
  - Fragile X
  - osteogenesis imperfecta
  - pseudoxanthoma elasticum
  - Wolff-Parkinson White syndrome
  - long-QT syndrome
  - Ehlers-Danlos Syndrome
  - polycystic kidney disease

Features

The late systolic murmur with mid systolic click is indicative of mitral valve prolapse where the posterior leaflets bulge during systole.

- patients may complain of atypical chest pain or palpitations
- mid-systolic click (occurs later if patient squatting)
- late systolic murmur (longer if patient standing)

Complications:

- mitral regurgitation,
- arrhythmias (including long QT),
- emboli,
- sudden death

Treatment

- mild to moderate mitral regurgitation
  - follow-up in clinic with repeat echocardiograms to monitor progression.
- Mitral valve replacement is only indicated in:
  - severe mitral regurgitation or
  - if there are signs of concomitant LV compromise (reduced ejection fraction or new dilatation of the LV).
- if a surgical mitral valve replacement are indicated, coronary angiogram should be part of the pre-op work-up for potential concomitant coronary artery bypass grafting.

Aortic dissection

Aortic dissection
- type A - ascending aorta - control BP(IV labetalol) + surgery
- type B - descending aorta - control BP(IV labetalol)

- It is most common between the ages of 50-70, being rare below the age of 40.

Stanford classification

- type **A** - **A**scending aorta, (immediately above of the aortic valve) → **2/3 of cases**
- type B - descending aorta, (after the aorta arch) distal to left subclavian origin, 1/3 of cases

DeBakey classification

- type I - originates in ascending aorta, propagates to at least the aortic arch and possibly beyond it distally
- type II - originates in and is confined to the ascending aorta
- type III - originates in descending aorta, rarely extends proximally but will extend distally

Associations

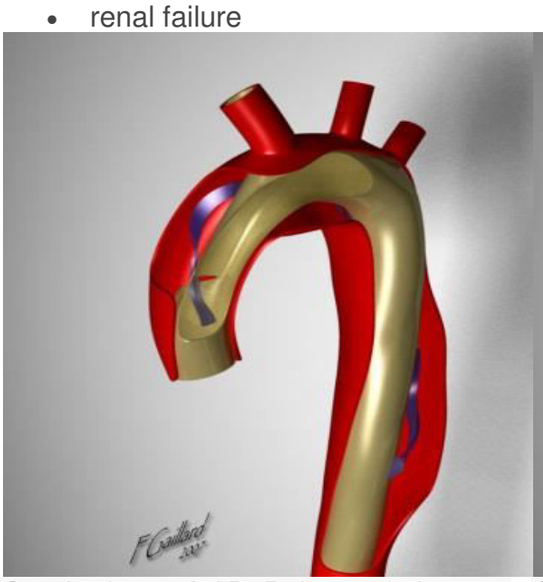
- hypertension (The most common risk factor)
- trauma (direct blunt chest trauma)
- collagens: Marfan's syndrome, Ehlers-Danlos syndrome
- bicuspid aortic valve
- Turner's and Noonan's syndrome
- pregnancy
- syphilis
- Drugs (such as cocaine)

Complications of backward tear

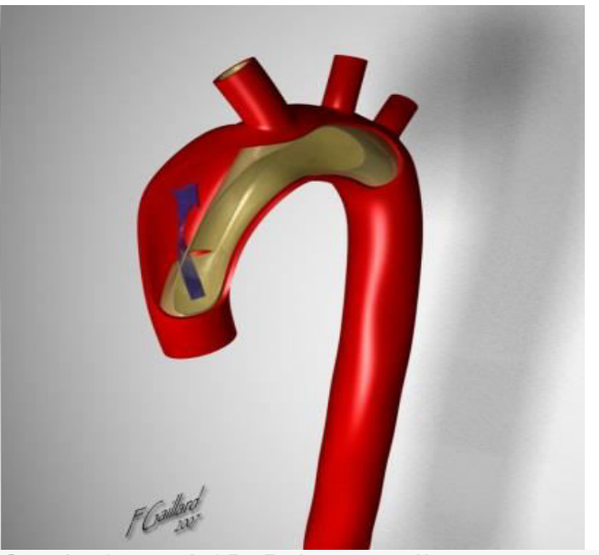
- aortic incompetence/regurgitation
- MI: inferior pattern often seen due to right coronary involvement

Complications of forward tear

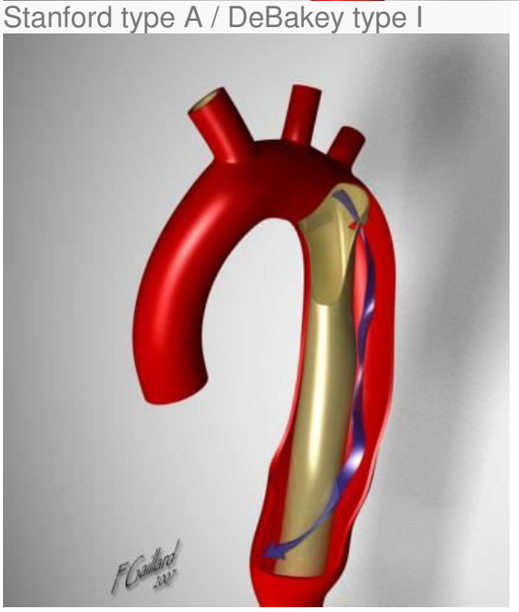
- unequal arm pulses and BP
- stroke
- renal failure



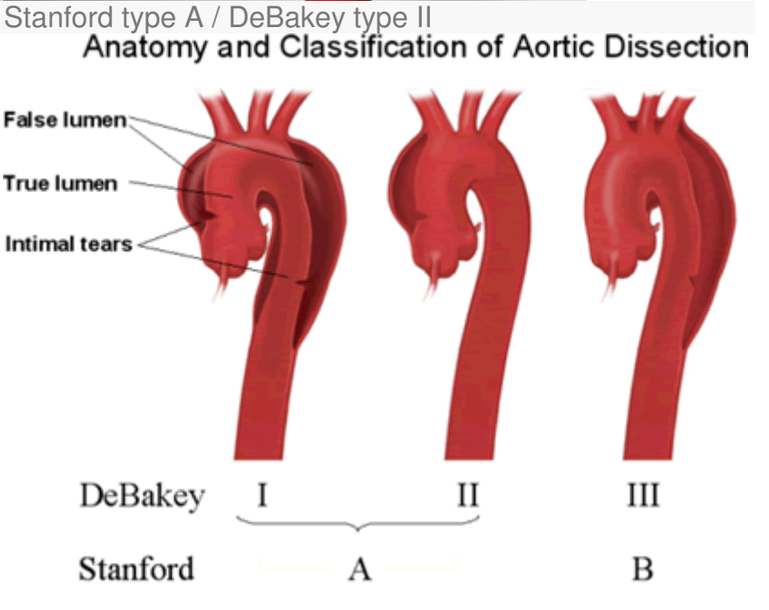
Stanford type A / DeBakey type I



Stanford type A / DeBakey type II



Stanford type B / DeBakey type III

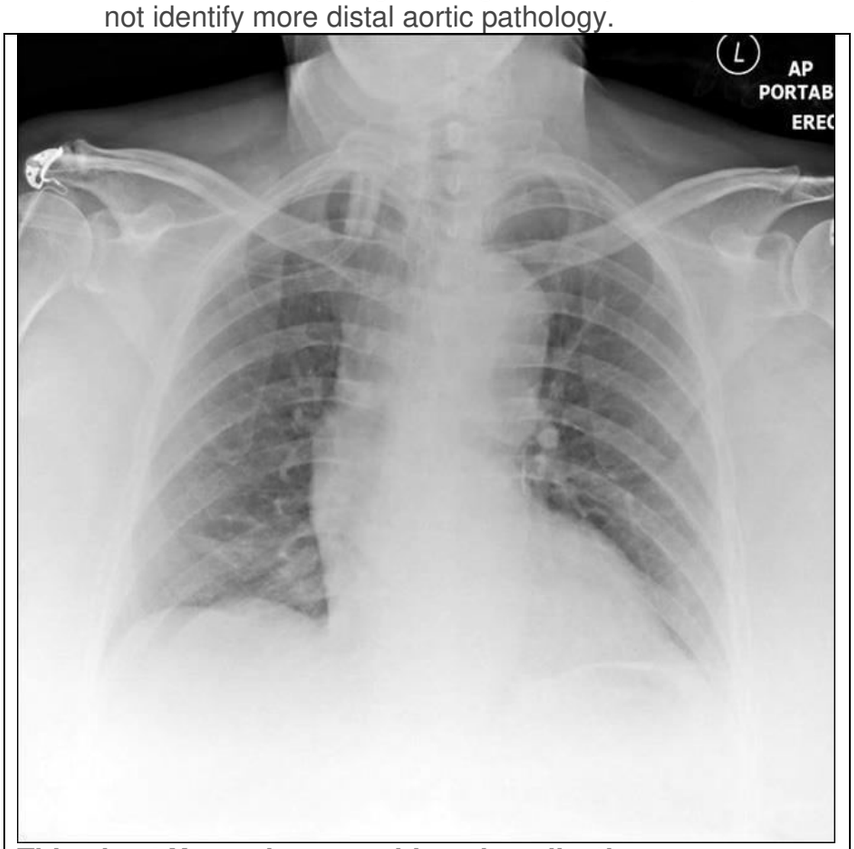


Investigation

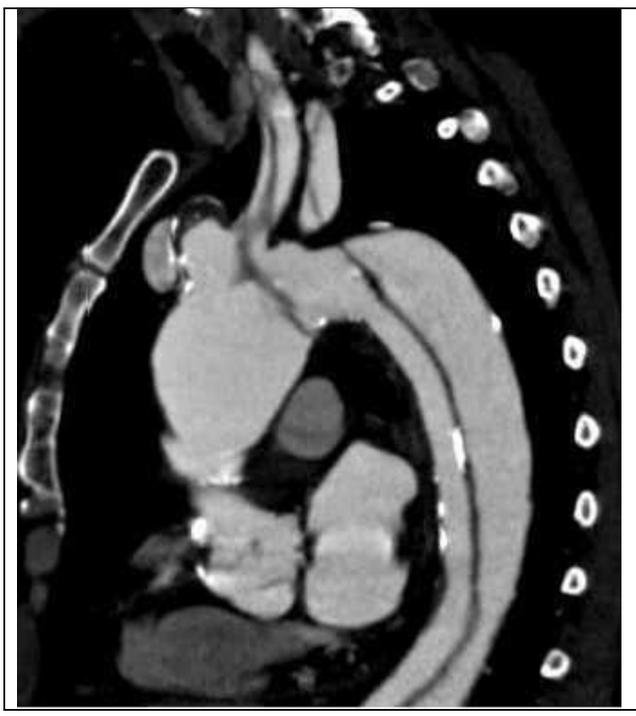
- **The best investigation is a CT chest with IV contrast (CT aortogram)** because the IV contrast will be able to best demonstrate the size and extent of the false lumen.
- Chest X-ray:
  - is a useful **first line** investigation because its readily available it is, and useful for ruling out many other conditions.
  - The chest X-ray may show a **widened mediastinum,**

- but unfortunately it is not a sensitive or specific investigation as 20% of patients present with normal chest X-ray and there are many causes of a widened mediastinum.
- Looking for a separation of the intimal calcification from the outer aortic soft tissue border by 10 mm is an indication of the presence of a dissection.

- **In a man with low blood pressure and vague abdominal pain, always be mindful of the possibility of dissection or aneurysmal rupture.**
- Occasionally, there is involvement of the right coronary artery in the dissection process giving rise to the acute electrocardiographic changes.
- MRI has the best sensitivity (98%) and specificity (98%) for aortic dissection.
- Whilst an echocardiogram might identify disruption of the aortic root in a backwards tear, it would not identify more distal aortic pathology.



This chest X-ray shows a widened mediastinum



This computerised tomography (CT) scan demonstrates an obvious **flap in the thoracic aorta indicating aortic dissection.** The flap is in the middle of the descending aorta (the dark line) which separates the true lumen anteriorly from the intimal flap posteriorly. The aortic regurgitant murmur would alert the examiner to this and mediastinal widening may be seen on x ray.

Differential diagnosis

- **Myocardial infarction and aortic dissection: an important differential diagnosis**
  - The ECG changes of inferior myocardial infarct suggest that the aneurysm has dissected the right coronary artery at its ascending aortic ostium.
  - An inferior myocardial infarct is high in the differential; however thrombolysis will kill a patient with an aortic dissection. (delayed diagnosis and surgical treatment)
  - up to 85% of patients with dissections may not receive appropriate medical treatment in the first hours of treatment due to an incorrect diagnosis
  - pain onset
    - pain in aortic dissection is abrupt in onset and maximal at the time of onset.
    - pain associated with **MI** starts slowly and gains in intensity with time.
  - Pain character
    - In dissection although tearing is the classical description, the pain is described as sharp more often than tearing, ripping, or stabbing.
    - In MI it is usually more oppressive and dull.
  - Pain site
    - with distal dissections the pain location is between the scapulae and in the back.
- **Oesophageal rupture**
  - **Features that favor oesophageal rupture over aortic dissection include:**
    - The history of onset while eating
    - Blood pressure equal in both arms
    - No diastolic murmur
    - Good peripheral pulses, and
    - Presence of a pleural effusion.

the history of chest pain **radiating to the back** is concerning., **early diastolic murmur** suggesting aortic valve regurgitation, **ECG changes in the inferior territory** and indicating occlusion of the right coronary artery. These features combined suggest that the **aortic dissection has tracked back to the heart** itself. The enlarged heart on chest X-ray may suggest a **haemopericardium**, and the patient should be assessed for **cardiac tamponade** given his **low blood pressure**. This patient is highly unstable and requires urgent cardiothoracic involvement . **the most appropriate next step in the management → Bedside echocardiogram and urgent cardiothoracic review**

Management

- **Type A**
  - surgical management, but blood pressure should be controlled to a target systolic of 100-120 mmHg whilst awaiting intervention
  - The most appropriate management strategy is to provide adequate analgesia and urgently reduce the blood pressure with intravenous antihypertensives: beta-blockers first line, and then nitroprusside. Then the cardiothoracic surgeons should be contacted.
  - perioperative management of patients undergoing high risk vascular surgery
    - prophylactic beta blockers for high risk vascular surgery (including those **patients with COPD).**
      - Bisoprolol is the best clinical choice
      - **Atenolol is next best choice**; it is cardioselective and long acting, reducing risk of postoperative myocardial ischaemia and tachycardia.
- **Type B***
  - conservative management
    - bed rest
    - reduce blood pressure IV labetalol to prevent progression
  - *endovascular repair of type B aortic dissection may have a role in the future

Complication

- **haemopericardium and cardiac tamponade**
  - If the dissection (involving the ascending aorta (Stanford type A) results in a tear of the tunica externa, aortic blood can leak into the pericardium.
  - **Management of aortic dissection complicated by haemopericardium and cardiac tamponade**
    - acute type A aortic dissection complicated by haemopericardium and cardiac tamponade:
      - **Relatively stable patient → immediate surgical repair and surgical evacuation of haemopericardium.**

- ❖ Pericardiocentesis in these patients can increase the intra-aortic pressure and reopen the closed communication between false lumen and pericardium. This can lead to recurrent cardiac tamponade that may be lethal.
- marked hypotension or electromechanical dissociation → pericardiocentesis

Prevention

- The management of patients with predisposing inherited diseases such as Marfan's syndrome and Ehlers-Danlos syndrome should include:
  - Periodic aortic diameter screening.
  - Lifelong beta-blockade.
  - Consideration of prophylactic replacement of the aortic root if dilated.
  - Moderate restriction of physical activity.

Prognosis

- Mortality for untreated aortic dissection is 25–30% at 24 h and 65–70% at 2 weeks
- dissections confined to the descending aorta are associated with better survival (80%).

Aortic aneurysms (NICE 2009)

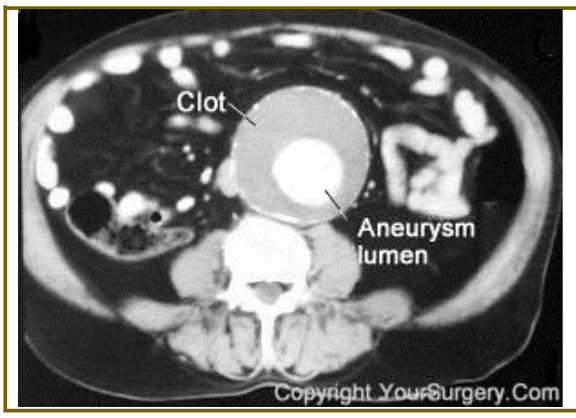
The nice guidelines state that an aortic aneurysm of greater than 5.5 cm in diameter should be treated. Below this size, the risk of dissection is outweighed by the risk of surgery.

- **Most common cause of aneurysms → atherosclerosis**
- most common site of **aneurysms** →lower part of the abdominal aorta, below the kidney (infra-renal).
- **abdominal aortic aneurysm (AAA)**
  - Definition
    - enlargement of the aorta of at least 1.5 times its normal diameter or **greater than 3 cm diameter in total.**
  - Incidence
    - more common in men than in women (3:1)
  - Risk factors
    - increasing age
    - high blood pressure,
    - smoking
    - family history
  - Features
    - most are asymptomatic (detected by chance during clinical investigation (for example, ultrasound or X-ray))
    - pulsating sensation in the abdomen,
    - back pain and abdominal pain that may spread to the back.
  - Investigations
    - diagnostic gold standard → Ultrasound
    - the best modality to determine anatomy and size → CT
    - for definitive diagnosis → Aortogram
  - Treatment
    - Elective surgery is recommended for →
      - ❖ **aneurysms > 5.5 cm**
      - ❖ aneurysms **>** 4.5 cm that have increased by **>** 0.5 cm in the past 6 months.
    - Endovascular stent-grafts are recommended as a possible treatment if: → the aneurysm is below their kidney **and** has not burst.
  - Follow up
    - symptomatic aneurysms < 4.5 cm → ultrasonography every 6 months.
    - aneurysms of 4.5–5.5 cm → every 3 or 6 months.
  - prognosis

- without surgery the 5-year survival rate for patients with aneurysms larger than 5 cm is about 20%.
- aneurysms larger than 6 cm in diameter have an annual risk of rupture of 25%.
- Among patients with a ruptured AAA the mortality rate is about 80%; even when they undergo emergency surgery, only about half survive beyond 30 days.

Peri-operative management of patients undergoing high-risk vascular surgery

- The ESC guidelines in 2009 for peri-operative management of patients undergoing high risk vascular surgery recommends prophylactic beta-blockers for high risk vascular surgery (including those patients with COPD).
- **Bisoprolol is probably the best clinical choice in this case, but is not available, atenolol is the best alternative** - it is cardio-selective and long acting - reducing risk of postoperative myocardial ischaemia and tachycardia.



This CT reveals leakage of a large aortic aneurysm with contrast extravasating into the mural thrombus of the aortic aneurysm.

The aortic aneurysm has not yet ruptured.

The likely cause of this is atherosclerotic

Aortic regurgitation (AR)

Turner's syndrome - most common cardiac defect is bicuspid aortic valve

Causes

- **due to valve disease**
  - bicuspid aortic valve
    - **the most common cause of chronic AR in a young patient is a congenital bicuspid valve.**
    - Bicuspid valve is also a common cause of early-onset aortic stenosis.
  - infective endocarditis
    - the vegetations prevent the valve from creating a proper seal to prevent backflow during diastole.
  - rheumatic fever
  - connective tissue diseases e.g. RA/SLE
- **due to aortic root disease**
  - aortic dissection
  - Spondyloarthropathies (e.g. **ankylosing spondylitis**)
    - Ankylosing spondylitis is strongly associated with aortic regurgitation (occurs in 4% of cases).
    - An aortitis leads to aortic root dilatation with subsequent failure of leaflet coaptation.
  - hypertension
  - syphilis
  - Marfan's,
  - Ehler-Danlos syndrome

Causes of acute aortic regurgitation:

- ascending aortic dissection,
- infective endocarditis,
- **collagen vascular disorders such as Marfan's**
- trauma,

- dehiscence of a prosthetic valve.

Features

- early diastolic murmur
  - heard along the left sternal border
  - heard best while the patient is leaning forward on deep expiration.
- collapsing pulse
- wide pulse pressure
- mid-diastolic Austin-Flint murmur
  - **It is a low frequency mid/late diastolic murmur**
  - due to partial closure of the anterior mitral valve cusps caused by the regurgitation streams.
  - There is no correlation between the presence of murmur and severity of AR, or aetiology.
- Note that there is often an aortic systolic flow murmur because there is an increased volume of blood in the LV due to the regurgitation.
- **Isolated LV dilatation (other chambers are normal) on ECHO due to volume overload**
  - (AS, HOCM & ↑ BP → hypertrophy and a smaller LV cavity)
- Pulsus bisferiens; increased pulse pressure; visible, forceful, and bounding peripheral pulses (water hammer)
- Corrigan's pulse - visible and vigorous arterial pulsations in neck
- **Musset's sign - Bobbing of the head,** due to the arterial pulsations in the neck
- Quincke's sign - Capillary pulsations of the nail bed
- Muller's sign - Pulsations of the uvula
- Traube's sign - Loud systolic sound over femoral arteries ('pistol-shot' femorals)
- Duroziez sign - diastolic murmur proximal to femoral artery compression (due to flow reversal).

Severity is indicated by the presence of:

- collapsing pulse,
- a wide pulse pressure and
- pulmonary oedema.

Investigations

- **Echocardiogram** (the most important test)
  - **Echocardiographic markers of severe AR**
    - Regurgitant volume of >60 mL/beat
    - pressure half time of <250 ms .
- Cardiac catheterisation
  - may be performed if there is doubt over the severity of the regurgitation;
  - severity is estimated by the degree of contrast that fills the ventricles after injection into the aortic root.

Treatment

- **asymptomatic → ACEI**
  - **ACEI improve the prognosis in asymptomatic left ventricular dysfunction.**
- Beta blockers **should be avoided** as these prolong diastole and therefore would increase the regurgitant fraction.
- Surgery is indicated in symptomatic patients with severe aortic regurgitation.
- **Indications for surgery in asymptomatic aortic regurgitation** are:
  - **LV ejection fraction under 50%**
  - LV end diastolic diameter greater than 7 cm
  - LV end systolic diameter greater than 5 cm.

Under current **ACC/AHA guidelines**, aortic valve surgery is recommended for patients with chronic severe AR under the following circumstances;

- Patient is symptomatic
- Patient is asymptomatic, with a resting EF of < 55%
- Patient is asymptomatic, with LV dilatation (LV end-systolic dimension >55 mm)
- Additional circumstances in which aortic valve surgery may be reasonable include the following:
  - Patient has moderate AR and is undergoing coronary artery bypass surgery or other surgery involving the ascending aorta
  - Patient has severe AR with no symptoms, normal EF, and less severe LV dilation (LV

end-systolic dimension >50 mm or LV end-diastolic dimension >70 mm)
- if the patient experiences:
  - progressive LV dilation on serial imaging studies;
  - deteriorating exercise tolerance, or
  - abnormal hemodynamic responses to exercise, such as inability to augment blood pressure during a treadmill study

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Aortic stenosis

Aortic stenosis - most common cause:
- younger patients < 65 years: bicuspid aortic valve
- older patients > 65 years: calcification

Angiodysplasia is associated with aortic stenosis

Aortic stenosis - S4 is a marker of severity

Epidemiology
- Aortic stenosis (AS) is the **most common valve problem** in the United Kingdom.

Causes
- degenerative calcification (tricuspid aortic valve calcification)
  - most common cause in older patients > 65 years
- **congenital bicuspid aortic valve (BAV)**
  - most common cause in younger patients < 65 years
  - BAV is the most common form of congenital heart disease in adults (1-2% of population).
  - The European Society of Cardiology states that there is an estimated 10% chance of a first degree relative being affected, which increases to 20-30% if you consider aortopathy. NOTCH1 gene mutations may be responsible.
    - It is possible that up to a third of relatives of patients with a bicuspid valve have valve or aortic abnormalities (often a dilated aorta).
    - NOTCH1 gene mutations may be responsible.
  - **most helpful in establishing a diagnosis of congenital bicuspid valve as the aetiology is → Systolic ejection click** (best heard at the apex)
  - **aortic valve replacement is eventually likely to be required**
    - Only 15% of patients with a bicuspid aortic valve will have a normally functioning valve in the fifth decade, and this often continues to deteriorate with age.
- William's syndrome (supravalvular aortic stenosis)
- post-rheumatic disease → fibrosis → Commissural fusion on ECHO
- subvalvular: HOCM

Pathophysiology
- **Pathophysiological response in aortic stenosis**
  - **The LV hypertrophies increase (in the size of myocytes) in a concentric - rather than an eccentric (asymmetric) - manner in response to the increase in afterload.**
  - There is also an increase in interstitial collagen and little fibrosis

The triad of angina, left ventricular failure and syncope is classical to aortic stenosis.

Features of severe aortic stenosis
- **Symptoms**
  - heart failure
  - **SAD**
    - **S**yncope
    - **A**ngina or chest pain (most common)
    - **D**yspnea
- **Physical exam**
  - ejection systolic murmur (ESM)

- crescendo-decrescendo murmur
- typically a mid-systolic ejection murmur
- heard best with the diaphragm of the stethoscope in the 2nd intercostal space in a patient who is sitting upright leaning forward.
  - ❖ in the elderly the more high frequency components of aortic stenosis may be heard best at the apex, the so called (Gallavardin phenomenon)
- may have ejection click
- **radiates to carotid arteries** (left often louder than right). radiate to the right neck
- decreases with standing, Valsalva, or handgrip
- increases with amyl nitrate, squat, or leg raise
- The **intensity of the systolic murmur does not correspond to the severity of aortic stenosis**;
  - ❖ As LV contractility decreases in critical AS, the murmur becomes softer and shorter. The intensity of the murmur may therefore be misleading in these circumstances.
- **the timing of the peak and the duration of the murmur correspond to the severity of aortic stenosis.**
  - ❖ The more severe the stenosis, the longer the duration of the murmur and the more likely it peaks at late systole.

➢ **S4** heart sound
- from stiff or hypertrophic ventricle

➢ **S2 (Character of S2)**
- soft/absent S2
- paradoxical splitting of S2
  - ❖ heard on **expiration** rather than inspiration

➢ pulse
- narrow pulse pressure
- slow rising pulse
- pulsus parvus et tardus
  - ❖ weak pulses with a delayed peak

➢ thrill

Associated conditions
- hemolytic anemia

In a patient with aortic stenosis, what will lead to an overestimation of the severity of the problem when assessed by echocardiography?
➔ **Aortic regurgitation**
- due to large volumes of blood passing over the valve at high velocities

Which condition is most associated with quietening of the aortic stenotic murmur?
➔ **Atrial fibrillation**
- Where the R-R interval is particularly short, such as in atrial fibrillation, flow across the valve is reduced, as such the intensity of the murmur is variable and may be significantly reduced.
- Aortic regurgitation has no effect on the intensity of the murmur, such that in patients with mixed aortic valve disease, the stenotic murmur is still clearly audible.

Conditions which leads to accentuation of the murmur → increased flow across the murmur.
- High output cardiac failure
- severe thyrotoxicosis

The predominant component of mixed aortic valve disease is determined by the murmur that is louder (ejection systolic murmur in aortic stenosis and mid diastolic murmur for aortic regurgitation).

Evaluation
- Severe AS is defined by a valve area of less than 1.0 cm^2.
- **distinguish patients with true severe (AS) with secondary LV dysfunction from those who have a falsely low calculated aortic valve area because of low cardiac output.**
  - ➢ calculated valve area in patients with severe left ventricular (LV) dysfunction can be falsely low because low cardiac output reduces the valve opening forces.

- It is important to distinguish patients with true severe (AS) with secondary LV dysfunction from those who have a falsely low calculated aortic valve area because of low cardiac output.
- **An important method of distinguishing between the two conditions is to assess the haemodynamics after increasing the cardiac output by dobutamine infusion during echocardiography or cardiac catheterisation.**
  - Patients with truly severe AS manifest an increase in trans-aortic pressure gradient while the valve surface area remains the same during dobutamine infusion;
  - those with falsely low calculated valve area manifest an increase in calculated valve surface area.
- Dobutamine echocardiography is also important to assess LV contractile reserve.
  - Patients who have 20% or more increase in stroke volume after dobutamine infusion have a much better prognosis after surgery compared to those who do not have LV contractile reserve.

What is the difference between aortic stenosis and aortic sclerosis?

- Both aortic stenosis and aortic **sclerosis** is :
  - senile degeneration of the valve
  - **there is an ejection systolic murmur**,
- Unlike aortic stenosis, **aortic sclerosis** have:
  - Occur in > 25% of > 65 year of age
    - Aortic stenosis occur in > 2% of > 65 year of age
  - **Absence of stenosis**
    - **no carotid radiation**,
    - **normal pulse** (character and volume)
    - **normal S2**.

Investigations

- Echocardiography
  - transthoracic echocardiogram (TTE) initially
  - transesophageal echocardiogram (TEE) is more accurate
- Left heart catheterization
  - most accurate diagnostic test
  - to assess pressure gradient across the valve
  - only indicated to confirm the diagnosis if echocardiography is unclear
  - findings
    - elevated pressure gradient (**>** 30 mmHg)
      - In the context of poor LV function, the aortic valve gradient may be normal or only mildly raised in the presence of a severely narrowed aortic valve area.
- **The next step in management after diagnosis → Coronary angiography**
  - Coronary artery disease (CAD) is common in patients with AS
  - Progressing straight to aortic valve replacement is not advised; significant coronary artery disease should be ruled out first, as CABG may be required at the same time as valve replacement.

Patients undergoing open surgical valve replacement should first undergo coronary angiography to exclude any coronary stenosis that could simultaneously be treated with bypass grafting.

Management

Aortic stenosis management: AVR if symptomatic, otherwise cut-off is gradient of 50 mmHg

- if asymptomatic then observe the patient is general rule
- if symptomatic then valve replacement
  - **The patient's symptomatology is the most important determinant in terms of the decision to operate**

There are three important factors to consider regarding management of aortic stenosis:

- 1. Presence of symptoms
- 2. The gradient across the valve on echocardiogram
- 3. Evidence of left ventricular dysfunction.

- **Symptomatic patient**
  - Fit for surgery → aortic valve replacement
    - **the best treatment option in an older person who can undergo the surgery.**
  - Not fit for aortic valve replacement →
    - **Transcatheter aortic valve implantation (TAVI)**
      - The catheter-delivered device produces similar one-year survival as aortic valve replacement but a higher risk of stroke, TIAs and vascular complications.
    - Balloon valvuloplasty
      - Balloon aortic valvuloplasty is a palliative procedure prone to restenosis for patients unsuitable for other interventions.
- **Asymptomatic patient**
  - **with severe stenosis (transvalvular gradient > 50 mmHg, valve area <1 cm^2) but has an ejection fraction of less than 50%.**
    - **should be referred for aortic valve replacement or TAVI if unsuitable.**
  - with severe stenosis but has an ejection fraction is greater than 50%.
    - Exercise testing would be recommended
      - If pass exercise testing then → reviewed in six months.

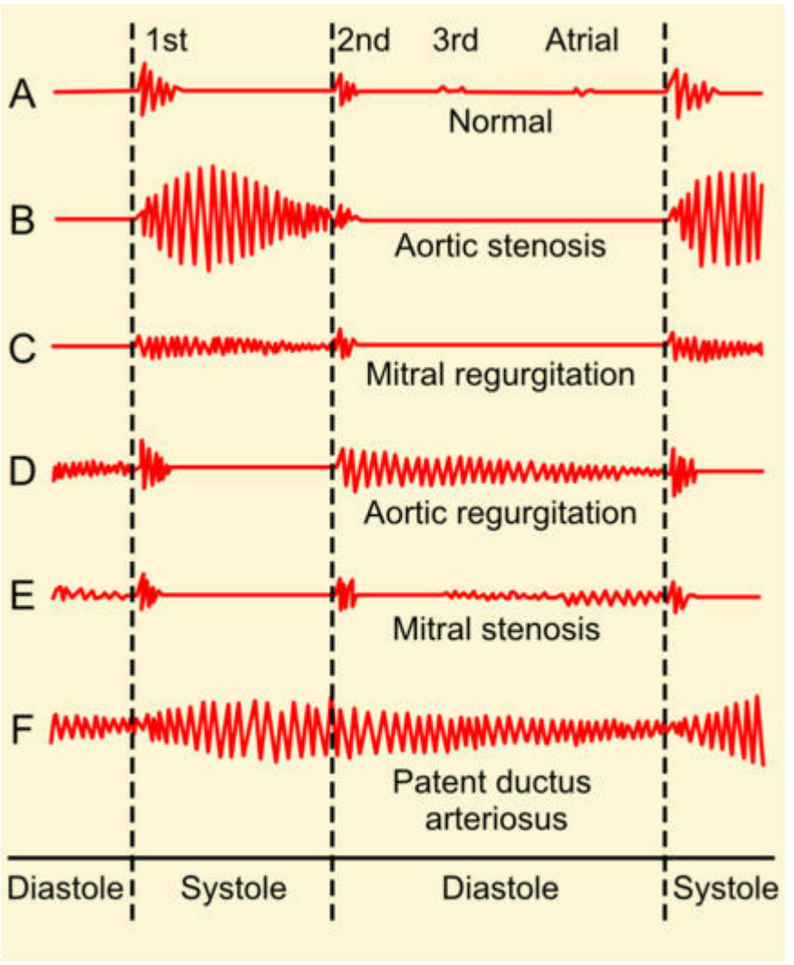
What is the most appropriate treatment for a **pregnant** lady with **symptomatic** congenital bicuspid aortic valve, If she **wishes to start a family**?

➔ **Refer for a porcine valve replacement before pregnancy**

- metal valve replacements require warfarinisation, and warfarin is teratogenic in early pregnancy and not advised in late pregnancy because of the risk of haemorrhage.
- Presence of a metallic valve would therefore necessitate switching to LMW heparin at some stage in pregnancy.
- This leaves a porcine valve replacement before pregnancy as the best option.
- Untreated aortic stenosis has an average five-year survival rate of only 40%.

Indicator of poor prognosis

- **Clinical features of left ventricular failure**
  - deteriorating LV function (ejection fraction less than 40%)
- Symptomatology
  - exertional breathlessness or presyncope/syncope
- Increasing gradient across the valve (above 70 mmHg)
- Age of patient



Phonocardiograms from normal and abnormal heart sounds

Heyde's syndrome

- **association between microcytic anaemia and calcific aortic stenosis.**
- Heyde syndrome refers to a **triad of**
  1. aortic stenosis,
  2. acquired coagulopathy (von Willebrand syndrome type 2A) and
  3. anaemia due to bleeding from intestinal angiodysplasia or from an idiopathic site.
     - Angiodysplasia most commonly occur in the ascending colon, particularly the **caecum**.
- Pathophysiology
  - the mechanism is thought to be due to destruction of von Willebrand's factor as the platelets traverse the stenosed valve resulting in bleeding per rectum.
- Investigation
  - The investigation of choice after valve replacement is mesenteric angiography as the bleeding vessels are poorly visualised on colonoscopy.
    - This would look for the presence of angiodysplasia, which may be associated with aortic stenosis.
  - All patients with aortic stenosis should be screened for iron deficiency anaemia.
- Treatment
  - replace the valve
  - Resection of the diseased bowel has also been described as a treatment.
- There is an association with jaundice and aortic stenosis; this is thought to be due to microangiopathic haemolysis.

Coarctation of the aorta

Definition:

- congenital narrowing of the descending aorta, most commonly at the site of insertion of the ductus arteriosus

Overview

- more common in males (despite association with Turner's syndrome)
- **site of coarctation:**
  - **distal** to the origin of the left subclavian artery
    - **The commonest site**
    - The systolic BP in the arms exceeds that in the leg.
  - **proximal** to the origin of the left subclavian artery
    - occurs in 15% of cases of coarctation
    - **if the systolic BP in the right arm is higher than that of the left arm by more than 30 mmHg, the left subclavian is involved in the coarctation (ie coarctation is proximal to the origin of the subclavian)**

Features

- Most patients are asymptomatic
- infancy: heart failure
- claudication of the calf muscles.
  - pain in calves is almost certainly due to poor distal blood supply.
- Hypertension
  - the **most common** presenting feature in adults
- headache and nose bleeds occur due to hypertension proximal to the coarctation,
- differential blood pressures between the right and left arms
- radio-femoral delay
- mid systolic murmur, and thrill
  - maximal over back.
  - **continuous** murmur over the thoracic spine usually originates **from small, tight coarctation (< 2 mm).**
- apical click from the aortic valve

Complications

- Secondary hypertension
- development of cerebral aneurysms
  - may present with intracranial haemorrhage from a ruptured berry aneurysm
- Left ventricular failure,
- Bacterial endocarditis.

Associations

- **Bicuspid aortic valve**
  - **the commonest associated congenital abnormality**
  - occurs in 50% of the coarctations.
- patent ductus arteriosus (PDA)
- Turner's syndrome
  - Female patients diagnosed with coarctation of the aorta should have a **karyotype analysis** to rule out Turner syndrome.
- berry aneurysms
- neurofibromatosis

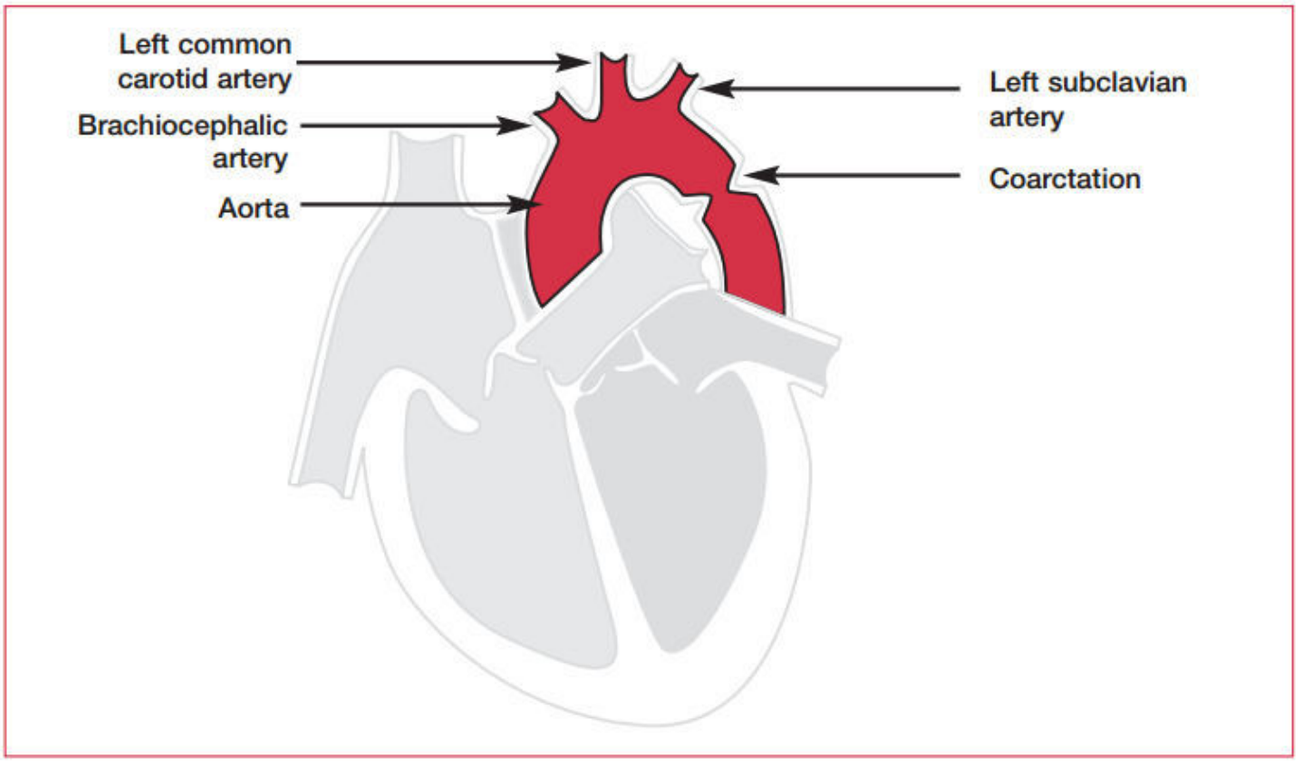
Investigations

- Radiograph
  - Cardiomegaly
  - ↑ pulmonary vascular markings
  - rib notching
    - notching of the **inferior border of the ribs** (**due to collateral vessels**)
    - usually manifests in adults and older children, as it takes time to develop.
  - may demonstrate an indentation of the aortic shadow at the site of the coarctation.
  - rib notching is not seen in young children
- **Echocardiography with doppler** (**confirmatory test**):
  - location and extent of stenosis;
  - concurrent anomalies

Treatment

- Balloon angioplasty and stenting is
  - the preferred intervention in adults.
  - surgical correction is indicated if the **pressure gradient across the coarctation is above 20 mmHg**, even without associated hypertension.

- Prostaglandin E1 should be administered to neonates with aortic coarctation to keep the ductus arteriosus open.



Coarctation of the aorta.

Differences in blood pressure between arms:

- up to 10 mmHg difference → **Normal variant (physiological)**
- difference of greater than 10 mmHg: → abnormal**:**
  - **+** radio-radial or **radio-femoral delay** (NO Leg claudication) → **proximal coarctation** of the aorta (involves the left subclavian artery origin)
  - **+ arm claudication**, intermittent vertigo, ataxia or diplopia, or facial sensory symptoms (NO Leg claudication) →**Subclavian steal syndrome**
  - **+ Leg claudication** (chronic intermittent leg pain, exacerbated by exercise and relieved by rest) → **Peripheral vascular disease**

Bicuspid aortic valve

Overview

- occurs in 1-2% of the population
- Bicuspid aortic valve tends to be sporadic although there is a reported familial incidence of approximately 9%.
- usually asymptomatic in childhood
- the majority eventually develop aortic stenosis or regurgitation

associated with:

- left dominant coronary circulation (the posterior descending artery arises from the circumflex instead of the right coronary artery)
- Turner's syndrome
- coarctation of the aorta (around 5% of patients)

Complications

- aortic stenosis/regurgitation as above
- higher risk for aortic dissection and aneurysm formation of the ascending aorta

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Tricuspid regurgitation

Signs

- pan-systolic murmur
- giant V waves in JVP
- pulsatile hepatomegaly

- left parasternal heave

Causes

- right ventricular dilation
- pulmonary hypertension e.g. COPD
- rheumatic heart disease
- infective endocarditis (especially intravenous drug users)
- **Ebstein's anomaly**
- carcinoid syndrome

Prosthetic valves

Prosthetic heart valves - mechanical valves last longer and tend to be given to younger patients

Prosthetic heart valves - antithrombotic therapy:
- bioprosthetic: aspirin
- mechanical: warfarin + aspirin

Mechanical valves - target INR:
- aortic: 2.0-3.0
- mitral: 2.5-3.5

- The most common valves which need replacing are the aortic and mitral valve.
- There are two main options for replacement: biological (bioprosthetic) or mechanical.

Biological (bioprosthetic) valves	**Mechanical valves**
Usually bovine or porcine in origin	The most common type now implanted is the bileaflet valve. Ball-and-cage valves are rarely used nowadays
advantages : not requiring Long-term anticoagulation Warfarin may be given for the first 3 months depending on patient factors. Low-dose aspirin is given long-term.	**advantages :** have a low failure rate
disadvantages calcification over time. must be replaced within 5 to 10 years. Most older patients (> 65 years for aortic valves and > 70 years for mitral valves) receive a bioprosthetic valve	**disadvantages** ↑ risk of thrombosis meaning long-term anticoagulation is needed. Aspirin is normally given in addition unless there is a contraindication. Target INR • aortic: 2.0-3.0 • mitral: 2.5-3.5

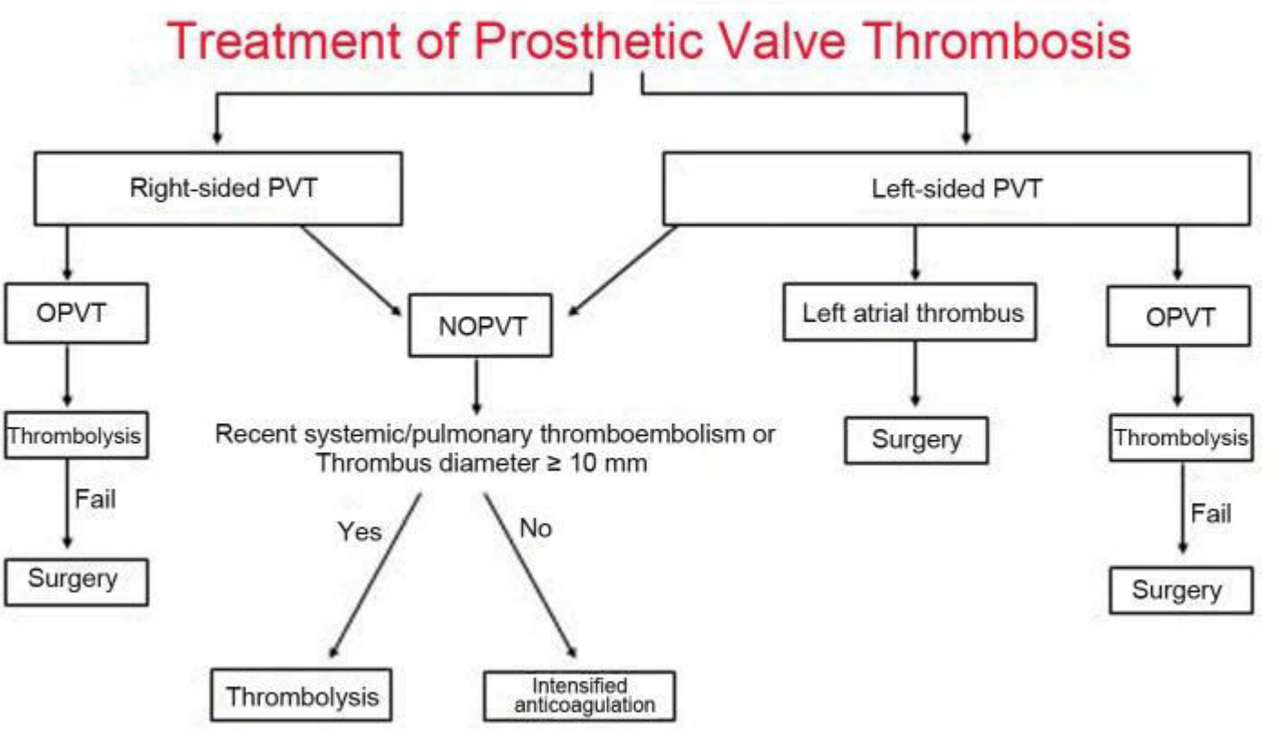
Following the 2008 NICE guidelines for prophylaxis of endocarditis → **antibiotics are no longer recommended for common procedures such as dental work.**

Which pathological findings in the bioprosthesis has most likely led to the need for replacement?

➢ **Calcification with stenosis**

Complications

- **prosthetic valve thrombosis (PVT)** resulting in shock.
  - occurs in 0.03–5.5% annually
  - The incidence is higher for mechanical than for biological heart valves (right-sided > left-sided, mitral > aortic).
  - Non-obstructive thrombi are more frequently observed than obstructive thrombi
  - high-risk situations
    - early postoperative period,
    - interruption of anticoagulant therapy for non-cardiac surgery,
    - pregnancy
    - sub-therapeutic anticoagulation (the most important factor)
  - Diagnosis
    - The initial diagnostic work-up includes:
      - transthoracic echocardiogram (TTE) and
      - cinefluoroscopy of mechanical valves.
        - this technique will not be helpful in identifying non-obstructive PVT or differentiating pannus from thrombus. Hence, additional diagnostic procedures are often necessary.
        - Suggestive findings **include** reduced or absent leaflet mobility, elevated transprosthetic gradients, decreased effective orifice area and thrombus visualization
    - TOE will often be performed to complete the investigation.
      - can differentiate thrombi from pannus formation or strands.
      - TOE is also important in guiding treatment
  - **Treatment**
    - **first-line → Thrombolysis**
      - Tissue plasminogen activator (tPA)
      - Thrombolytic therapy can be a safe alternative to surgery even during pregnancy.
    - **If the patient is haemodynamically unwell (ie pulmonary oedema or hypotension) and no immediate surgery is available, thrombolytic therapy should be given (IV alteplase).**
  - Follow up:
    - When thrombolysis is contemplated, then TEE and Doppler echocardiography are the preferred modalities to assess serially the hemodynamic success of fibrinolysis.
    - Doppler echocardiography is the most accurate method for detecting and quantifying the degree of transvalvar gradient increase and is useful in the follow-up of patients during thrombolysis.



OPVT: obstructive prosthetic valve thrombosis; NOPVT: non-obstructive prosthetic valve thrombosis.

Arrhythmias

Supraventricular tachycardia (SVT)

- Whilst strictly speaking the term supraventricular tachycardia (SVT) refers to any tachycardia that is not ventricular in origin the term is generally used in the context of paroxysmal SVT.

Causes

- atrioventricular **nodal** re-entry tachycardia (AVNRT).
  - the most common supraventricular tachycardia,
  - twice as common in females as in males
  - the incidence is 1–3 per 1000.
  - Small elevations in troponin are occasionally seen in this situation, but there are no ECG changes to suggest a myocardial infarction.
- atrioventricular re-entry tachycardias (AVRT)
- junctional tachycardias.

Paroxysmal SVT would start and stop suddenly, **not gradually.**
Panic attacks → breathlessness and palpitations start and stop **gradually.**

Acute management

- vagal manoeuvres: e.g. Valsalva manoeuvre
  - **Carotid sinus massage is contraindicated in patients with carotid vascular disease**
- intravenous adenosine 6mg → 12mg → 12mg
  - contraindicated in asthmatics - verapamil is a preferable option
- electrical cardioversion

Prevention of episodes

- **beta-blockers**
  - **Prophylaxis for SVT in pregnancy → Metoprolol,**
    - the most appropriate option for SVT in pregnancy
    - although can cause intra-uterine growth restriction, is seen as the safest as toxicity is usually associated with higher doses in treatment of gestational hypertension.
    - It is a short acting β blocker and a TDS regimen is required.
- radio-frequency ablation

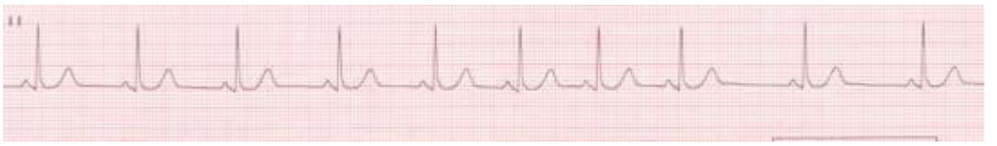
SVT in pregnancy

- Tachyarrhythmias may increase during pregnancy although the causes are not entirely clear.
- Regarding the termination of **acute SVT**, **adenosine appears to be safe in pregnancy.**

- In the case of the **prevention of recurrent SVT** then verapamil or beta-blockers have data supporting their use.
- **Current AHA/EHA criteria for the treatment of SVTs in pregnancy do suggest using metoprolol (level of evidence 1B) rather than verapamil (C), although they recommend avoiding the former in the first trimester.**

Sinus arrhythmia

- The (ECG) shows normal P wave, PR interval, QRS complex and each P wave conducted to ventricles.
- **There is a gradual decrease in R–R interval and then an increase again. This slight beat-to-beat variation (rhythmic and cyclical variation) is termed as sinus arrhythmia.**
- the most common cause is respiration.
  - Respiratory sinus arrhythmia is thus heart rate variability in synchrony with respiration, and is normal in children and young adults.
  - The R–R interval decreases with inspiration and increases with expiration.
- Anxiety →reassured.



Premature ventricular ectopic (PVEs)

Beta blockade is the initial treatment of choice for palpitations precipitated by premature ventricular ectopics (PVEs).

- usually seen in normal hearts;
- palpitations are described as an early beat with a pause followed by an unusually strong or 'pounding' beat, or simply as a 'flip-flop';
  - Symptoms are usually worse at rest and may disappear with exercise.
    - Symptoms which increase on exercise are more worrying and significant.
- may be associated with caffeine intake
- Investigations
  - baseline ECG without symptoms: typically normal
  - ambulatory ECG: isolated wide QRS complexes
    - If symptoms are short-lived but frequent (>2-3 times per week), use a 24-hour Holter monitor
    - If symptoms are short-lived and infrequent (<1 per week), use an event monitor or transtelephonic recorder
  - Exercise stress testing
    - the relation of extrasystoles to exercise may have prognostic importance.
  - Echocardiography - to assess LV function and heart structure.
- For PVE to be **significant** they have to meet the following criteria:
  - Occurring frequently (6 or more beats/min)
  - PVE in bigeminal rhythm
  - PVE in short runs of ventricular tachycardia
  - PVE exhibiting R-on-T phenomenon

- PVE associated with serious organic heart disease and left ventricular decompensation.

- **Treatment**
  - **Not significant PVE → Reassurance**
  - **Significant PVE**
    - **beta-blockers**
    - Radiofrequency catheter ablation of the ectopic focus
      - Curative with good outcome

Ventricular extrasystoles are the most common type of arrhythmia that occurs after myocardial infarction.

Management of symptomatic atrial extrasystoles
- beta-blockers (atenolol or metoprolol).
- Atrial extrasystoles arising from the pulmonary veins may be treatable by the procedure of pulmonary vein isolation.

Arrhythmogenic right ventricular cardiomyopathy (ARVC)

- Arrhythmogenic right ventricular cardiomyopathy (ARVC, also known as arrhythmogenic right ventricular dysplasia or ARVD) is a form of inherited cardiovascular disease which may present with syncope or sudden cardiac death.
- It is generally regarded as **the second most common cause of sudden cardiac death** in the young after hypertrophic cardiomyopathy.
- Although ARVC was initially described in the right ventricle, most patients have biventricular involvement.

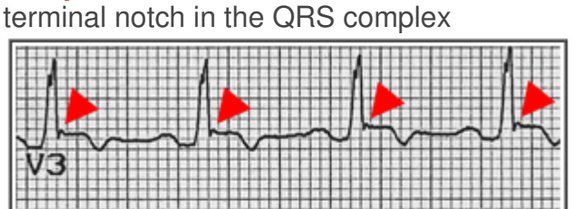
Pathophysiology
- inherited in an autosomal dominant pattern with variable expression
- the right ventricular myocardium is replaced by fatty and fibrofatty tissue
- around 50% of patients have a mutation of one of the several genes which encode components of desmosome

Presentation
- palpitations
- syncope
- sudden cardiac death

Investigation

epsilon potential is seen on the ECG of patients with → Right ventricular dysplasia

- ECG abnormalities in V1-3:
  - Typically, T wave inversion.
  - An **epsilon wave** is found in about 50% of those with ARV - this is best described as a terminal notch in the QRS complex



The epsilon wave

The epsilon wave (marked by red triangle), seen in ARVD.

- echo changes are often subtle in the early stages but may show an enlarged, hypokinetic right ventricle with a thin free wall
- magnetic resonance imaging is useful to show fibrofatty tissue

Management

- drugs: sotalol is the most widely used antiarrhythmic
- catheter ablation to prevent ventricular tachycardia
- implantable cardioverter-defibrillator:

Naxos disease

- an autosomal recessive variant of ARVC
- a triad of ARVC, palmoplantar keratosis, and woolly hair

Atrial fibrillation (AF)

Overview

- AF is the most commonly encountered cardiac arrhythmia.
- Hypertension is the most common risk factor for AF.
- In 15% of cases, AF is idiopathic
- AF **most commonly originates from** the **roots of the pulmonary veins**. (**longitudinal smooth muscle fibres in the pulmonary vein**)

classification

Definition	Duration of atrial fibrillation
Paroxysmal	Up to 7 days
Persistent	Longer than 7 days
Permanent	Cardioversion failed or not attempted

Classification of atrial fibrillation.

classification of atrial fibrillation (AF): AF classified into 3 patterns:

1. **first detected episode** (irrespective of whether it is symptomatic or self-terminating)
2. **recurrent episodes**, when a patient has 2 or more episodes of AF:
   - **paroxysmal AF**:
     - episodes of AF terminate spontaneously.
     - episodes last less than 7 days (typically < 24 hours).
   - **persistent AF**
     - the arrhythmia is not self-terminating.
     - episodes usually last greater than 7 days
3. **permanent AF**
   - there is continuous atrial fibrillation which cannot be cardioverted or if attempts to do so are deemed inappropriate.
   - Treatment goals are therefore rate control and anticoagulation if appropriate

Symptoms and signs

- Symptoms
  - Palpitations
  - Dyspnea
  - chest pain
- Signs
  - irregularly irregular pulse

Complications

- AF is poorly tolerated in elderly and often leads to **pulmonary oedema** even in the presence of a relatively normal left ventricle (LV).

Investigations

- An ECG is essential to make the diagnosis as other conditions can give an irregular pulse, such as ventricular ectopics or sinus arrhythmia.

Treatment

- There are two key parts of managing patients with AF:
  1. Rate/rhythm control
  2. Reducing stroke risk

- **Rate vs. rhythm control**
  - There are two main strategies in dealing with atrial fibrillation:
    - **Rate control**:
      - accept that the pulse will be irregular, but slow the rate down to avoid negative effects on cardiac function
      - now the majority of patients are managed with a rate control strategy.
    - **Rhythm control**:
      - try to get the patient back into, and maintain, normal sinus rhythm. This is termed cardioversion.
      - Drugs (pharmacological cardioversion) and synchronised DC electrical shocks (electrical cardioversion) may be used for this purpose
      - indications of **Rhythm control** :
        - coexistent heart failure,
        - first onset AF or
        - where there is an obvious reversible cause.

Do not use rhythm control therapy in asymptomatic AF patients, nor in patients with permanent AF.

Rhythm control has no survival benefit over a rate control strategy

Reducing stroke risk → anticoagulation

Young man with AF, no TIA or risk factors, no treatment is now preferred to aspirin (NO treatment)

Do not use antiplatelet therapy for stroke prevention in AF.

- Some patients with AF are at a very low risk of stroke whilst others are at a very significant risk.
- NICE in 2014 suggest using the **CHA_2DS_2-VASc** score to determine the most appropriate anticoagulation strategy

	Risk factor	Points
C	Congestive heart failure	1
H	Hypertension (or treated hypertension)	1
A_2	Age >= 75 years	2
	Age 65-74 years	1
D	Diabetes	1
S_2	Prior Stroke or TIA	2
V	Vascular disease (including ischaemic heart disease and peripheral arterial disease)	1
S	Sex (female)	1

The table below shows a suggested anticoagulation strategy based on the score:

Score	Anticoagulation
0	No treatment
1	Males: Consider anticoagulation Females: No treatment (this is because their score of 1 is only reached due to

Score	Anticoagulation
	their gender)
2 or more	Offer anticoagulation

Atrail fibrilation related to mitral stenosis

- **atrial fibrillation related to valvular heart disease → Warfarin**
  - In patients with **non-valvular atrial fibrillation**, **novel oral anticoagulants** have the same efficacy as warfarin in preventing stroke.
- NICE guidelines suggest that valvular disease have high risk for thromboembolic events, and would benefit from anticoagulation.
- Mitral stenosis patients were excluded from the studies developing the CHADS-VASC score.
- None of the 'novel' anticoagulants currently available (rivaroxaban, apixaban, dabigatran) are indicated or licensed for atrial fibrillation related to valvular heart disease.

CHADS2-VASc scoring is generally used as a tool to assess need to anticoagulate a patient with AF. However, the following are **conditions that, if present, may trump the decision to anticoagulate:**

1. **valvular heart disease**
2. prior peripheral embolism, and
3. intracardiac thrombus.

The risk of stroke without anticoagulation

- In order to be counselled correctly on the risks and benefits of anticoagulation, patients should be aware of their stroke risk based on their risk factors - as outlined below:

CHA2DS2-VASc Score	Ischaemic Stroke Rate (per year)
0	0.2%
1	0.6%
2	2.2%
3	**3.2%**
4	4.8%
5	7.2%
6	9.7%
7	11.2%
8	10.8%
9	12.2%

- The MRCP examiners would not expect knowledge of the precise figures, however you should know that :
  - scores of 0-1 convey an annual risk of <1%,
  - while scores of 2 and above give an annual risk roughly equivalent to the score, increasing at scores over 5.
  - It is important to know that this risk is annual, rather than 10-year or lifetime.
  - Generally, risk is more readily understood by patients if expressed as a '1 in x' rather than a percentage.

Bleeding risk assessment (using the HASBLED scoring system)

- NICE recommend that we offer patients a choice of anticoagulation, including warfarin and the novel oral anticoagulants (NOACs).
- Aspirin is no longer recommended for reducing stroke risk in patients with AF
- Doctors have always thought carefully about the risk/benefit profile of starting someone on warfarin.
- A history of falls, old age, alcohol excess and a history of previous bleeding are common things that make us consider whether warfarinisation is in the best interests of the patient.
- NICE now recommend we formalise this risk assessment using the HASBLED scoring system.

	Risk factor	Points
H	Hypertension, uncontrolled, systolic BP > 160 mmHg	1
A	Abnormal renal function (dialysis or creatinine > 200) Or Abnormal liver function (cirrhosis, bilirubin > 2 times normal, ALT/AST/ALP > 3 times normal	1 for any renal abnormalities 1 for any liver abnormalities
S	Stroke, history of	1
B	Bleeding, history of bleeding or tendency to bleed	1
L	Labile INRs (unstable/high INRs, time in therapeutic range < 60%)	1
E	Elderly (> 65 years)	1
D	Drugs Predisposing to Bleeding (Antiplatelet agents, NSAIDs) Or Alcohol Use (>8 drinks/week)	1 for drugs 1 for alcohol

- There are no formal rules on how we act on the HAS-BLED score although **a score of >= 3 indicates a 'high risk' of bleeding**, defined as intracranial haemorrhage, hospitalisation, haemoglobin decrease >2 g/L, and/or transfusion.

Atrial fibrillation: post-stroke (NICE guidelines 2006)

- following a stroke or TIA warfarin should be given as the anticoagulant of choice.
- Aspirin/dipyridamole should only be given if needed for the treatment of other comorbidities
- cerebral infarction are subject to the risk of haemorrhagic transformation within the acute period , so in acute stroke patients, in the absence of haemorrhage, anticoagulation therapy should be commenced after 2 weeks. If imaging shows a very large cerebral infarction then the initiation of anticoagulation should be delayed
- The use of aspirin and/or low dose heparin/LMWH for venous thromboembolism (VTE) prophylaxis can be considered within 24 hours of symptom onset.

Atrial fibrillation: cardioversion

Atrial fibrillation - cardioversion:

- **if no structural heart disease → flecainide**
- **With structural heart disease → amiodarone**

offer rate or rhythm control if the onset of the arrhythmia is less than 48 hours, and start rate control if it is more than 48 hours or is uncertain

- **Cardioversion indications**
  - Haemodynamically unstable patient → electrical cardioversion (DC cardioversion 200J → 360J → 360J)
    - Adverse signs necessitating DC cardioversion are:
      - Blood pressure (BP) ≤90 mmHg
      - Chest pain
      - Heart failure

- Impaired consciousness, and
- Heart rate ≥ 200 bpm.

- **Elective procedure** where a rhythm control strategy is preferred → electrical or pharmacological cardioversion
  - **Onset < 48 hours**
    - Anticoagulation
      - patients should be heparinised.
      - Patients who have risk factors for ischaemic stroke should be put on lifelong oral anticoagulation.
    - Cardioversion method:
      - electrical - 'DC cardioversion'
      - pharmacology:
        - amiodarone if structural heart disease,
        - flecainide or amiodarone in those without structural heart disease
    - Post-cardioversion:
      - further anticoagulation is unnecessary
  - **Onset > 48 hours**
    - **prior to cardioversion:**
      - anticoagulation
        - **for at least 3 weeks prior to cardioversion. OR**
        - exclude a left atrial appendage (LAA) thrombus by transoesophageal echo (TOE). If excluded patients may be heparinised and cardioverted immediately.
      - If there is a high risk of cardioversion failure (e.g. Previous failure or AF recurrence) then it is recommend to have at least **4 weeks amiodarone or sotalol** prior to electrical cardioversion
      - If the patient has a **slow ventricular response of AF** in the absence of anti-arrhythmic drugs, cardioversion should be performed after the **insertion of a temporary transvenous-pacing catheter**
    - Cardioversion method:
      - NICE recommend electrical cardioversion, rather than pharmacological.
      - The initial shock strength should be 100 J, followed by a second 200-J shock and a third 360-J shock
      - If AF persists, a second 360-J shock with the paddles in the anteroposterior position can be attempted
    - Post-cardioversion:
      - Following electrical cardioversion patients should be **anticoagulated for at least 4 weeks**. After this time decisions about anticoagulation should be taken on an individual basis depending on the risk of recurrence

- **The success of cardioversion depends on:**
  - the duration of AF
  - transthoracic impedance
  - left atrial size
  - the age of the patient
- **Catheter AF ablation**
  - **Radiofrequency pulmonary vein isolation with ablation**
    - **the treatment of choice for patients who remain poorly controlled despite medical therapy,**
    - in selected patients as first-line therapy for symptomatic paroxysmal AF
    - Anticoagulation for stroke prevention should be continued indefinitely in patients at high risk of stroke, **even after apparently successful ablation of AF.**
- **Surgical AF ablation**
  - Ablation can be performed in symptomatic patients during cardiac surgery for other reasons, or by stand-alone surgery either using open-chest techniques or by thoracoscopy.
  - Anticoagulation for stroke prevention should be continued indefinitely in patients at high risk of stroke, even after apparently successful ablation of AF.

The enlarged left atrial size suggests that a repeat DC cardioversion is unlikely to work for a sustained period.
H/O AF + enlarged left atrial size with previous DC cardioversions. the best long term treatment option → Refer for consideration of atrial fibrillation ablation → longer term good result.

AV node ablation:
- AV node ablation is reserved for those patients where pharmacological rate control is unsuccessful or not tolerated.
- The procedure is invasive and requires permanent pacemaker implantation.
- **Patients who are candidates for this therapy include those with tachycardia induced cardiomyopathy despite pharmacologic efforts** at rate control and intolerable symptoms despite aggressive attempts at pharmacologic therapy (in some cases, much of the symptom burden is due to medications rather than AF itself).

Do not perform cardioversion or catheter ablation without anticoagulation, unless an atrial thrombus has been ruled out by transoesophageal echocardiogram.

Amiodarone or **vernakalant** have been efficient in converting post-operative AF to sinus rhythm.

Vernakalant
- A Novel agent for the Termination of Atrial Fibrillation
- blocks sodium channels
- **more prominent in vernakalant's mechanism of action is its ability to block certain potassium channels.**
- **Specifically, it blocks the atrial-selective potassium current, I_{Kur}, which is involved in atrial repolarization.**

Atrial fibrillation: pharmacological cardioversion

Atrial fibrillation - cardioversion: amiodarone + flecainide

- **Agents with proven efficacy in the pharmacological cardioversion of atrial fibrillation**
  - amiodarone
  - **flecainide (if no structural heart disease)**
    - with large doses of **oral agents** or with intravenous agents.
    - Large single doses of flecainide (300 mg) or propafenone (450-600 mg) given orally have been shown to convert patients to sinus rhythm.
    - Flecainide and propafenone are not used in people with :
      - known or suspected ischaemic heart disease,
      - individuals who are already on antiarrhythmic therapy,
      - those with a prolonged QT interval because these agents may have pro-arrhythmic effects (torsade de pointes).
  - others (less commonly used in UK): quinidine, dofetilide, ibutilide, propafenone
- **Less effective agents**
  - beta-blockers (including sotalol)
  - calcium channel blockers
  - digoxin
  - disopyramide
  - procainamide

1.

Atrial fibrillation: rate control and maintenance of sinus rhythm

Atrial fibrillation: rate control - beta blockers preferable to digoxin

The patient with very recent onset of atrial fibrillation is more likely to stay in sinus rhythm

- **Agents used to control rate** in patients with atrial fibrillation
  - Beta-blockers
    - should be used **first line for rate control.**
    - cardioselective beta-blockers should be tried in patients with left ventricular systolic dysfunction **even if they have a diagnosis of:**
      - Chronic obstructive pulmonary disease (COPD)
      - Peripheral vascular disease
      - Diabetes
      - Erectile dysfunction, or
      - Interstitial pulmonary disease.
    - Beta-blockers should not be commenced in the setting of acute exacerbations of COPD or cardiac failure
    - If one drug does not control the rate adequately NICE recommend combination therapy with diltiazem or digoxin
  - calcium channel blockers (diltiazem)
  - digoxin:
    - not considered first-line anymore as they are less effective at controlling the heart rate during exercise.
    - they are the preferred choice if the patient has coexistent **heart failure**
  - If the duration of AF is unknown caution should be used when considering the use of drugs which may cardiovert the patient - amiodarone and flecainide.

- **Agents used to maintain sinus rhythm** in patients with a history of atrial fibrillation
  - sotalol
  - amiodarone
  - flecainide
  - others (less commonly used in UK): disopyramide, dofetilide, procainamide, propafenone, quinidine
- The table below indicates some of the factors which may be considered when considering either a rate control or rhythm control strategy

Factors favouring rate control	Factors favouring rhythm control
• Older than 65 years • History of ischaemic heart disease	• Younger than 65 years • Symptomatic • First presentation • Lone AF or AF secondary to a corrected precipitant (e.g. Alcohol) • Congestive heart failure

Atrial flutter

Tachycardia with a rate of 150/min ?atrial flutter

Overview

- Atrial flutter is a form of supraventricular tachycardia characterised by a succession of rapid atrial depolarisation waves.
- usually caused by a single **macro**reentrant rhythm within the atria.
- **What is the differences between atrial flutter** and **focal atrial tachycardia**?
  - Atrial flutter is caused mechanistically by **macro**- reentry and has atrial rate (P wave/flutter morphology) **usually >250 bpm.**
  - Focal atrial tachycardia is caused mechanistically by micro-reentry or increased automaticity and has atrial rates of 100-250 bpm.

Epidemiology

- Sex: ♂ > ♀ (5:2)
- Peak incidence: risk of atrial flutter increases with age

Etiology:

- similar to atrial fibrillation

ECG findings

- Regular, narrow QRS complexes
- flutter waves, which are a **saw-tooth pattern** of atrial activation
  - **most prominent in leads II, III, aVF, and V1.**
- as the underlying atrial rate is often around 300/min the ventricular or heart rate is dependent on the degree of AV block. For example if there is 2:1 block the ventricular rate will be 150/min
- flutter waves may be visible following carotid sinus massage or adenosine

Management

- is similar to that of atrial fibrillation although medication may be less effective
- atrial flutter is more sensitive to cardioversion however so lower energy levels may be used
- Anticoagulate patients with atrial flutter similar to AF.
- **Catheter ablation** is **the definitive treatment** for atrial flutter.
  - **radiofrequency ablation of the tricuspid valve isthmus** is **curative** for most patients

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Multifocal atrial tachycardia

- Multifocal atrial tachycardia (MAT) may be defined as a irregular cardiac rhythm caused by at least three different sites in the atria, which may be demonstrated by morphologically distinctive P waves.
- It is more common in elderly patients with chronic lung disease, for example COPD
- **Management**
  - correction of hypoxia and electrolyte disturbances
  - rate-limiting calcium channel blockers are often used first-line
  - cardioversion and digoxin are not useful in the management of MAT

Atrial myxoma

Atrial myxoma - commonest site = left atrium

Overview

- Benign cardiac tumor
- the most common primary cardiac tumors in adults.
  - (rhabdomyoma is the most common primary cardiac tumor in pediatric patients and strongly associated with tuberous sclerosis).
- 75% occur in left atrium , arising from a pedicle on the fossa ovalis.
- more common in females
  - Three-quarters of cases of atrial myxoma occur in females
- Although most cases of atrial myxoma are sporadic, an **autosomal dominant** variety may also exist within families.
- 10% are inherited

Features

- One third present with emboli
- One third with systemic inflammation (ESR ↑↑ in 1/3)
- One third are asymptomatic when detected.
- constitutional symptoms:
  - fatigue, weight loss, fever, clubbing
- Dyspnoea,
  - Exertional dyspnoea is present in three-quarters of patients.
- Dizziness or syncope
  - results from the atrial myxoma obstructing the mitral valve.
    - **Mitral valve obstruction is the most likely complication**
    - Myxomas are more likely to have a stalk and be freely mobile.
- emboli
- atrial fibrillation
- mid-**diastolic** murmur, 'tumour plop'
- Elevated left atrial pressures cause dilatation.
- echo: pedunculated heterogeneous mass typically attached to the fossa ovalis region of the interatrial septum
- on histology
  - gelatinous appearance
  - abundant ground substance.

Treatment

- surgical removal by median sternotomy.

Prognosis

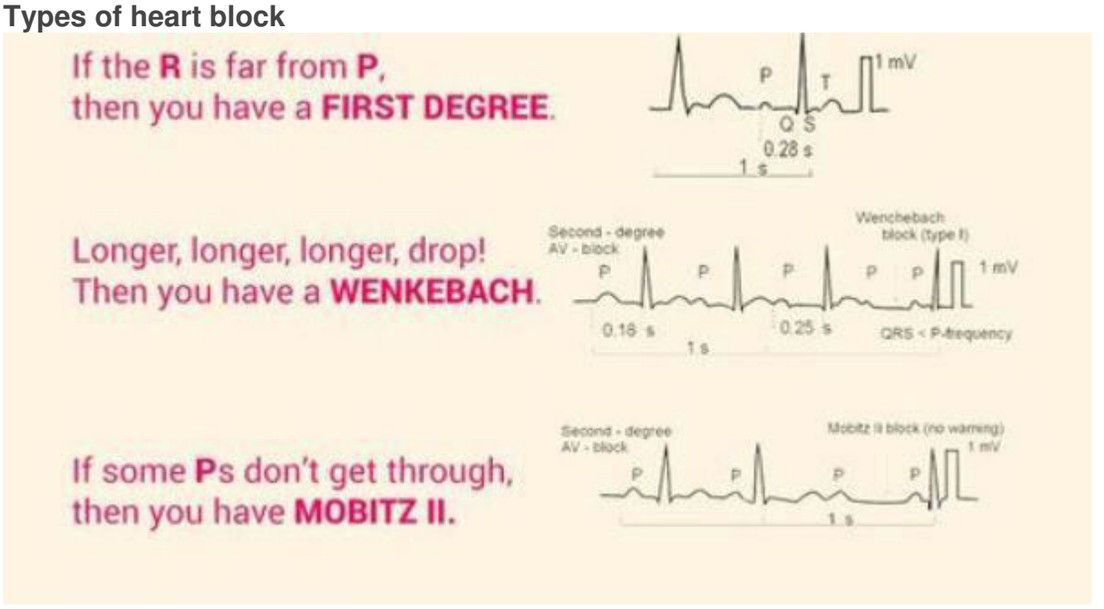
- sudden death may occur in 15% of patients.

Carney's complex is a familial multiple neoplasia and lentiginosis syndrome, associated with

1. **Primary adrenal hypercortisolism**
2. Lentigines and naevi of the skin
3. Various tumours including **myxoma.**

Heart block

Types of heart block



First-degree heart block

- PR interval > 0.2 seconds
- Causes:
  - Increased vagal tone (such as in trained athletes)
  - Ischaemic heart disease
  - Rheumatic fever
  - Hyperkalaemia
  - Hypokalaemia, and
  - Drug therapy such as digoxin or beta-blockers.
- A long PR interval on the ECG may also be caused by structural abnormalities such as an atrial septal defect.
- No treatment is usually required.

Second-degree heart block

- **type 1 (Mobitz I, Wenckebach):**
  - progressive prolongation of the PR interval until a dropped beat occurs
  - Mobitz Type I with symptoms is a **relative indication** for a permanent pacemaker
  - **Asymptomatic → NO treatment → Discharge him from the clinic**
    - The risk of progression to complete heart block with Mobitz type I in an asymptomatic man is very low, unlike in Mobitz type II.
- **type 2 (Mobitz II):**
  - PR interval is constant but the P wave is often not followed by a QRS complex
  - **the most appropriate next management step → Transvenous cardiac pacing**
  - Mobitz type II or complete heart block does not respond to atropine. Atropine may be useful for sinus or junctional bradycardia.
- **Second-degree heart block with RBBB implies that this patient has a significantly increased risk of complete heart block.**
  - prior to committing to pacemaker insertion, **repeat tape is the most likely next step, with an electronic patient diary to see if the recorded arrhythmia corresponds to her symptoms.**
- **murmurs**

Third degree (complete) heart block

- there is no association between the P waves and QRS complexes

- **Complete heart block (whether symptomatic or not) is an absolute indication for a permanent pacemaker**

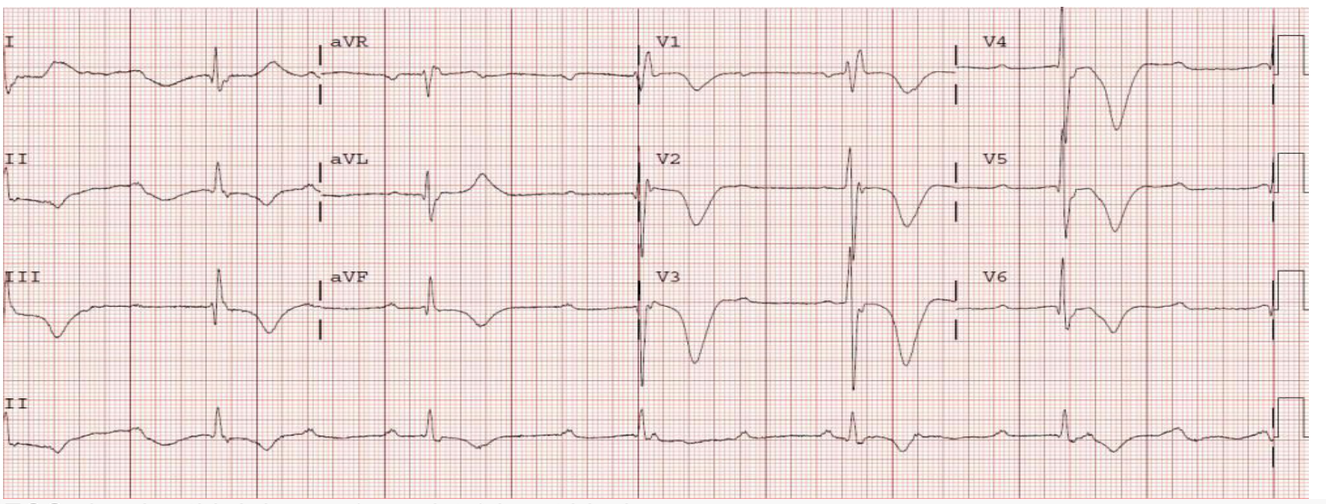
Complete heart block

Complete heart block causes a variable intensity of S1

- Complete heart block is related most to right coronary artery occlusion because this commonly involves both the AV nodal artery and the right superior descending artery.
  - Prognosis is favourable, and revascularisation normally leads to restoration of sinus rhythm.
  - **As the AV nodal artery arises proximally from the right ventricular artery, distal right coronary artery occlusion is not commonly associated with complete heart block.**
  - **the artery most likely to be affected → Proximal right coronary**
- Left coronary artery occlusion leads to anterior myocardial infarction. As it is less commonly associated with complete heart block, when it does occur, the prognosis is very poor.

Features

- Syncope
- heart failure
- regular bradycardia (30-50 bpm) that does not vary with exercise
- wide pulse pressure
- JVP: **irregular** cannon waves in neck
- variable intensity of S1
- compensatory increase in stroke volume with a large-volume pulse and **systolic flow**



ECG showing third degree (complete) heart block

Treatment

- Whilst **arrangements are being made for temporary pacing**, the options to be considered, prior to **temporary transvenous pacing**, in this context are:
  1. **Atropine** 0.5-1.0 mg intravenous bolus, repeated as required.
  2. Isoprenaline, intravenous infusion at 2-10 microg/min.
     - it is a non-selective β agonist that is analog of epinephrine (adrenaline)
  3. External cardiac pacing.
- Intravenous aminophylline is useful in complete heart block, as the heart block is often mediated by adenosine which aminophylline inhibits

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Carotid sinus hypersensitivity (CSH)

- CSH demonstrating an exaggerated response to carotid sinus stimulation.
- The diagnosis is only made after ischaemic heart disease or rhythm disturbance have been excluded.
- CSH may be predominantly cardioinhibitory (resulting in bradycardia), vasodilatory (resulting in hypotension), or a mixture of the two.

- Management:
  - **Cardioinhibitory CSH is usually managed with insertion of a dual-chamber pacemaker.**
  - vasodilatory CSH is managed with support stockings, fludrocortisone and midodrine (available on a named-patient basis in the UK).

Pacemakers

Definition

- A permanent pacemaker is an implanted device that provides electrical stimuli, thereby causing cardiac contraction when intrinsic myocardial electrical activity is inappropriately slow or absent.

Conditions definitely needs a permanent pacemaker

- Symptomatic bradycardia due to sinus node dysfunction (sick sinus syndrome)
- Third-degree heart block
- **second-degree (AV) block** associated with any of the following:
  - symptomatic bradycardia
  - documented periods of asystole of 3 s or more
  - **any escape rate less than 40 bpm in awake, asymptomatic patients**
  - **type II second-degree AV block and a ventricular rate of 45 bpm when awake and asymptomatic**
  - asymptomatic sinus rhythm resulting in **periods of asystole longer than 3.0 seconds**
    - **asystolic pause causing syncope.**
    - **dual chamber permanent pacemaker (DDDR).**
      - The R in this code stands for responsive, and in an otherwise fit and well 76-year-old, he should have a responsive element to his PPM (that is, increases his heart rate with exercise).
  - **Type II second-degree AV block has a high chance of progressing to asystole (35%) each year**
- Generally, permanent pacing can be justified for any degree of heart block associated with symptoms of bradycardia.

Indications for a temporary pacemaker

- symptomatic/haemodynamically unstable bradycardia, not responding to atropine
- post-ANTERIOR MI: type 2 or complete heart block
  - post-INFERIOR MI complete heart block is common and can be managed conservatively if asymptomatic and haemodynamically stable
- trifascicular block prior to surgery
- Other indications for transvenous pacing in setting of acute MI are:
  - asystole
  - new bundle branch block (BBB) with first-degree heart block
  - an old right BBB with first degree atrioventricular (AV) block and a new fascicular block

Notes

- All modern ICDs also function as pacemakers.
- Chest pain in **Ventricular pacing**
  - Pacemaker rhythm may prevent interpretation of ST-segment changes and may require **urgent angiography** to confirm diagnosis.
  - **Reprogramming the pacemaker**—allowing an evaluation of ECG changes during intrinsic heart rhythm—may be considered in patients who are not dependent on ventricular pacing, without delaying invasive investigation

Types of Pacemakers

- Pacemakers are classified by the nature of their pacing mode using a code of up to five letters.
- The NBG Pacemaker code was developed by the North American Society of Pacing and Electrophysiology (NASPE) and the British Pacing and Electrophysiology Group (BPEG):

I	II	III	IV	V
Chamber(s) Paced	Chamber(s) Sensed	Mode(s) of Response	Rate Modulation	Multisite Pacing
O = None	O = None	O = None	O = None	O = None
A = Atrium	A = Atrium	T = Triggered	R = Rate modulation	A = Atrium
V = Ventricle	V = Ventricle	I = Inhibited		V = Ventricle
D = Dual (A+V)	D = Dual (A+V)	D = Dual (T+I)		D = Dual (A+V)

Single-chamber pacemakers

- utilised **for patients in permanent atrial fibrillation.**
- VVI means there is **one lead in the ventricle** (pacing and sensing the ventricle, indicated by the 'VV').
- VVI pacemaker will pace and sense the right ventricle.
- **VVI pacemaker** is useful when we are not too concerned about atrial activity (e.g. in patients with atrial fibrillation).
- In the presence or organised atrial activity, a VVI pacemaker may pace the ventricles out of synch with the atria resulting in pacemaker syndrome.
  - Since organised atrial activity is present, a **DDI pacemaker** would be preferred, as this **senses and paces both atria and ventricle to preserve synchrony.**

Dual-chamber pacemakers

- Have pacing electrodes in both the right atrium and the right ventricle.
- They allow maintenance of the physiological relationship between atrial and ventricular contraction and also allow the paced heart to follow the increase in sinus rate that occurs during exercise.

Biventricular pacemakers

- Pacemaker leads are placed in the right atrium, right ventricle and left ventricle.
- Useful in the management of patients with heart failure who have evidence of abnormal intraventricular conduction (most often evident as left bundle branch block (LBBB) on ECG) which causes deranged ventricular contraction or dyssynchrony.
- **In a patient with severe ischaemic heart failure and is on optimal medical therapy. Despite this he is still symptomatic → ICD with biventricular pacing**
  - very prolonged QRS duration is indicating left dyssynchrony which is an indication for biventricular pacing according to NICE guidance.
  - Documented VT in the context of ischaemic LV impairment necessitates the need for and a secondary prevention ICD.

Pacemaker complications

- Pacemaker complications are more common in the period following insertion.
- can be divided into early complications (<6 weeks) or late (>6 weeks).
- Most frequent complications are those related to implantation procedure, such as lead dislodgement and pneumothorax.
- **pneumothorax can occur up to forty-eight hours following pacemaker insertion.**
  - It occurs in 1-2% of procedures and most patients will require chest drain insertion.
- The most common complication is **lead dislodgement** (higher rate atrial dislodgment than ventricular dislodgment).
- Lead dislodgement can occur following trauma or sporadically and can be either atrial or ventricular.
- Atrial dislodgment affects up to 3% of people whereas ventricular is less common affecting 1%.
- **If the ECG shows loss of sensing and capture around the QRS complex → ventricular lead displacement in a dual chamber pacemaker.**
  - **What would be the likely ECG findings in ventricular lead displacement?**
    - **Loss of sensing and capture of the QRS complex**
- Atrial lead displacement would show an ECG with loss of atrial sensing and capture.
  - **The ECG in atrial lead displacement would show an ECG with loss of atrial sensing and capture in a dual chamber or single chamber pacemaker.**
- On occasion lead displacement can be seen on chest X-Ray, however, **it may not be seen**, in this case →a lateral chest X-Ray may be of use in this scenario.
- **Pacemaker syndrome** would show AV dyssynchronisation.
- **Subclavian vein obstruction** is a fairly common complication over time but many patients may remain asymptomatic due to collateral vein formation. It can present with symptoms of superior vena cava (SVC) obstruction in severe cases.
- **Twiddler's syndrome** is when the patient intentionally or accidentally turns the pacemaker on its longitudinal axis which can cause lead dislodgement.
- **Reel's syndrome** is Twiddler's syndrome but on the horizontal axis.
- **Pacemaker lead fracture**
  - occurs in 1-4% of pacemakers
  - **usually following excessive exercise or direct trauma.**
  - patient will require lead extraction and replacement.
- **myocardial rupture:**
  - incidence is relatively small (<1%)
  - can be divided into early or late rupture with respect to the time it occurs following procedure.
  - Delayed perforations are less likely to cause such acute symptoms as well as a reduced incidence of tamponade and sudden cardiac death.
  - Risk factors for perforation include physician technique, patient independent factor (i.e obesity or difficult anatomy) and lead design.
  - presenting features :pericardial effusion, haemodynamically compromised following pacemaker insertion and is likely to develop cardiac tamponade and needs urgent intervention with pericardiocentesis.

Pacemaker syndrome

- pacemaker syndrome
  - Loss of AV synchrony.
  - Retrograde VA conduction.
  - Absence of rate response to physiological need.

pacemaker syndrome (breathlessness associated with ventricular pacing in the context of normal atrial activity).

VVI pacemaker will pace and sense the right ventricle. In the presence or organised atrial activity, a VVI pacemaker may pace the ventricles out of sync with the atria resulting in pacemaker syndrome.

- pacemaker syndrome is related to nonphysiologic timing of atrial and ventricular contractions, which may occur in a variety of pacing modes
  - also named as "AV dyssynchrony syndrome,"
  - **typically associated with a VVI pacemaker** that results in simultaneous atria and ventricle conduction.

- **Risk factors**
  - Sick sinus syndrome as have preserved AV conduction.
  - Single-chamber ventricular pacing.
- **Features**
  - hypotension, tachycardia, tachypnoea,
    - dizziness, palpitations, syncope
  - Ventricular contraction against closed tricuspid and mitral valves can result in:
    - raised JVP (pulsation and fullness in the neck)
    - cannon waves
  - Complications of AV dyssynchrony include:
    - atrial fibrillation,
    - thromboembolic events, and
    - heart failure.
  - **What are the characteristic ECG findings associated with this syndrome?**
    - **Small P waves with dissociation from QRS complex**
- **Management**
  - In patients with other pacing modes, upgrading the pacemaker to a **dual-chamber pacing** or **reprogramming the pacemaker parameters** - eg, AV delay, post-ventricular atrial refractory period, sensing level, and pacing threshold voltage.

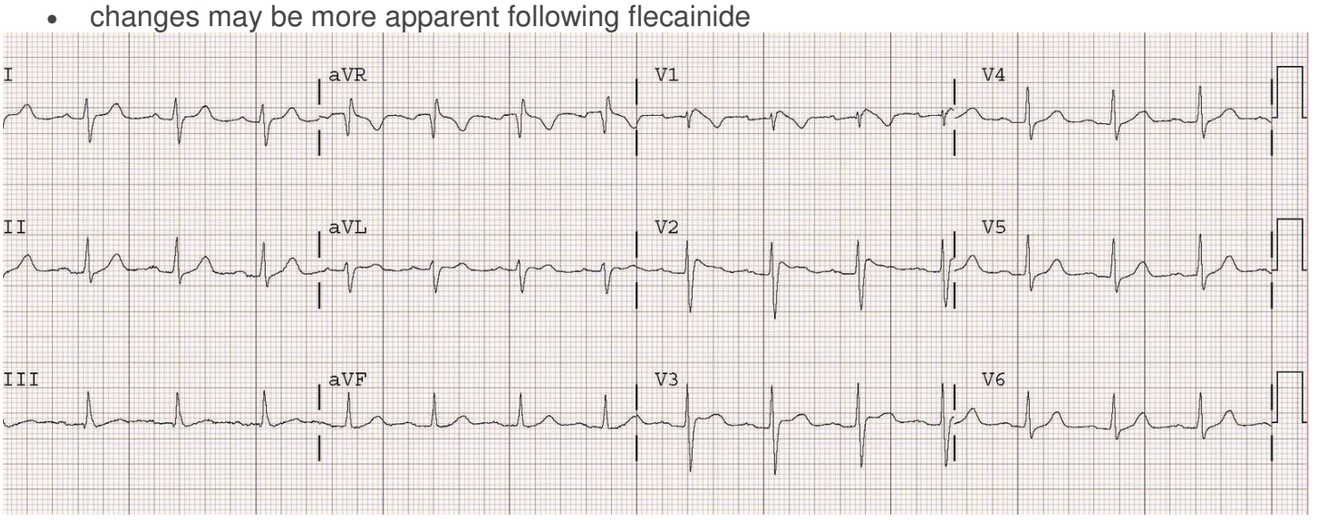
DC cardioversion in patients with pacemakers (eg : in AF)
- DC cardioversion is not contraindicated in patients with pacemakers
- **Pacemaker function should be checked after cardioversion and antiarrhythmic therapy added**

Brugada syndrome

- inherited cardiovascular disease with may present with sudden cardiac death.
- autosomal dominant
- prevalence → 1:5,000-10,000.
- more common in Asians.

Pathophysiology
- a large number of variants exist
- around 20-40% of cases are caused by a mutation in the SCN5A gene which encodes the myocardial sodium ion channel protein

ECG changes
- convex ST segment elevation > 2mm in > 1 of V1-V3 followed by a negative T wave
- partial right bundle branch block
- changes may be more apparent following flecainide



ECG showing Brugada pattern, most marked in V1, which has an incomplete RBBB, a downsloping ST segment and an inverted T wave

Management
- implantable cardioverter-defibrillator

Catecholaminergic polymorphic ventricular tachycardia (CPVT)

- (CPVT) is a form of inherited cardiac disease associated with sudden cardiac death.
- It is inherited in an autosomal dominant fashion
- has a prevalence of around 1:10,000.

Pathophysiology

- the most common cause is a defect in the ryanodine receptor (RYR2) which is found in the myocardial sarcoplasmic reticulum
- uncontrolled calcium release from the sarcoplasmic reticulum
- induced by adrenergic stress.

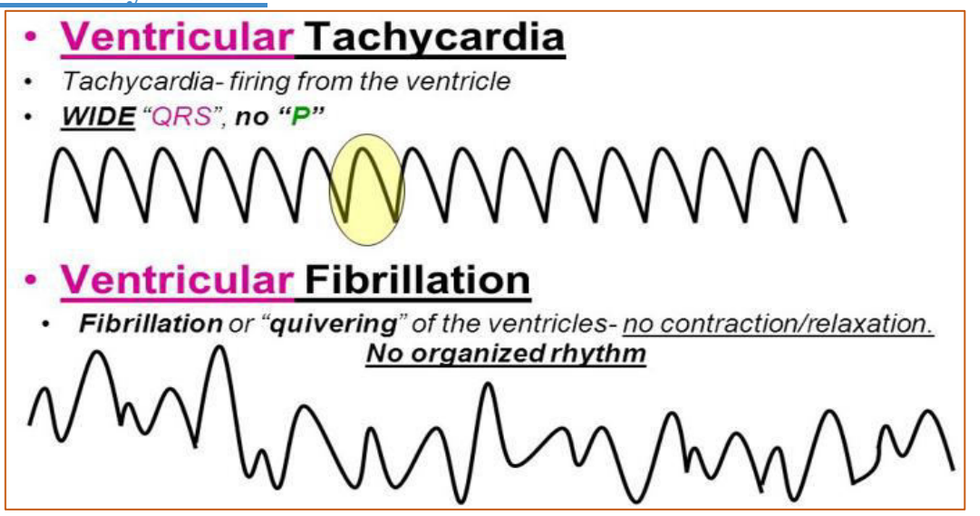
Features

- exercise or emotion induced polymorphic ventricular tachycardia resulting in syncope
- sudden cardiac death
- symptoms generally develop before the age of 20 years

Management

- beta-blockers
- There is strong evidence that flecainide is effective when prescribed in addition to beta blockers
- implantable cardioverter-defibrillator
- Left cervical sympathetic denervation
- All first-degree relatives should be evaluated with ECG, Holter monitoring and exercise stress testing.

Ventricular tachycardia



Definition

- wide QRS complex (duration >120 milliseconds) at a rate greater than 100 bpm, originating from a ventricular ectopic focus.
  - Whilst a broad complex tachycardia may result from a supraventricular rhythm with aberrant conduction, the European Resuscitation Council advise that in a peri-arrest situation it is assumed to be ventricular in origin.
- It has the potential to precipitate ventricular fibrillation and hence requires urgent treatment.

Pathophysiology

- Among patients with **prior MI** or non-ischaemic cardiomyopathy, VT is usually due to **re-entry involving regions of slowed conduction adjacent to scar.**
  - **Post MI ventricular tachycardia (VT) is most commonly due to scar tissue.**
    - **The definitive investigation would be → Electrophysiological study (EPS)**
      - due to the fact that if this were scar related VT, the site could be localised and even possibly ablated.
      - If not, then an implantable cardiac defibrillator (ICD) implantation may be warranted if left ventricular (LV) dysfunction exists.
        - ✓ MADIT-2 trial showed a 5.6% 20 month absolute survival benefit in patients with LV dysfunction (EF<30%), post MI, treated prophylactically with an ICD.
- (VT) may also arise from triggered activity due to **early after-depolarisations (EADs)** leading to torsades de pointes, a polymorphic ventricular tachycardia seen in the setting of a prolonged QT interval,

- **delayed after-depolarisations (DADs),** which are seen in:
  - idiopathic right ventricular outflow tract VT or
  - catecholaminergic polymorphic VT
    - cellular abnormalities of calcium handling → Increased intracellular calcium → predispose to VT. especially during periods of sympathetic stimulation.
- EADs occur during phase 2 or 3 of the action potential, whereas DADs occur during phase 4.
- When an EAD or DAD reaches a 'threshold' potential, it can result in triggering of another action potential.
- Ventricular tachycardia originates below the bundle of His.

Types

There are two main types of VT:

- monomorphic VT:
  - organised, single-morphology QRS arising from one of the ventricles.
  - most commonly caused by myocardial infarction
- polymorphic VT:
  - multiple different wide QRS morphologies arising from one of the ventricles.
  - results from abnormal myocardial repolarization.
  - A subtype of polymorphic VT is **torsades de pointes** which is precipitated by prolongation of the QT interval. The causes of a long QT interval are listed below.

Other classifications of VT

- Sustained VT
  - A ventricular rhythm faster than 100 bpm **lasting at least 30 seconds or requiring termination due to haemodynamic instability.**
  - almost always symptomatic.
- Non-sustained VT
  - A ventricular rhythm faster than 100 bpm lasting for at least 3 consecutive beats but **terminating spontaneously in less than 30 seconds,** and not resulting in significant haemodynamic instability.
  - If these do not cause any haemodynamic compromise, **treatment is not needed.**
  - **The most appropriate next step → Check potassium and magnesium levels**
    - During the GISSI-2 trial it was observed that a serum K^+ level of <3.6 mmol/l was associated with a twofold increased risk of VF. Therefore serum K^+ should be maintained >4 mmol/l by oral or intravenous (IV) supplementation in patients with acute MI.
    - Concomitant magnesium (Mg^{2+}) deficiency is present in many patients with hypokalaemia and also makes correction of hypokalaemia difficult. Hence serum Mg^{2+} levels should also be checked and maintained >1 mmol/l.
- Idiopathic VT
  - VT occurring in the **absence of apparent structural heart disease** (e.g., ischaemia, prior infarction, cardiomyopathy, valvular disease, arrhythmogenic right ventricular cardiomyopathy, left ventricular non-compaction, or other disorders of the myocardium), **known channelopathy** (e.g., long QT syndrome, Brugada syndrome, catecholaminergic polymorphic VT, short QT syndrome), **drug toxicity**, or **electrolyte imbalance**.
- Outflow tract VT
  - A form of 'idiopathic' VT
  - typically arises from the right ventricular outflow tract
  - results from cyclic AMP-mediated triggered activity;
  - uniquely sensitive to adenosine.
- Fascicular VT
  - A common form of idiopathic VT
  - arising from the left ventricle, with re-entrant circuit partially involving the Purkinje fibres,
  - characteristically sensitive to verapamil.

Feature

- Patients may have a normal cardiac output or may be haemodynamically compromised
- Sustained VT is usually observed in ischaemic cardiomyopathy, but idiopathic VT may also be observed in patients without structural heart disease.
- jugular veins may show **cannon A waves** due to atrioventricular dissociation.

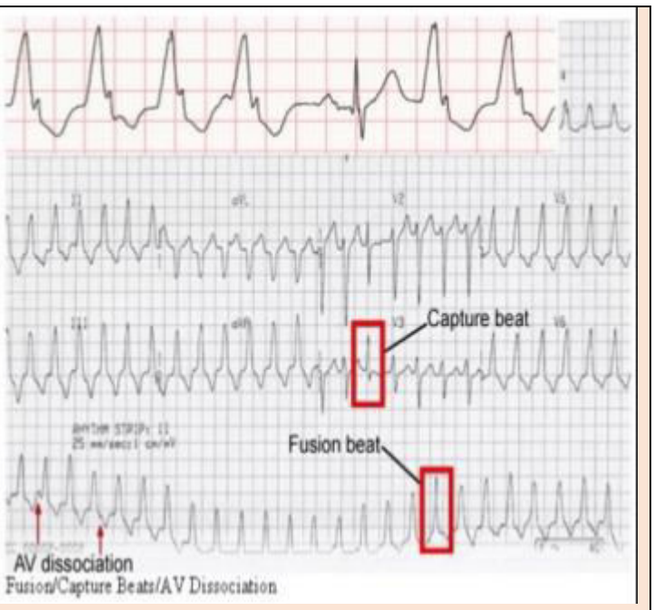
Differential diagnosis

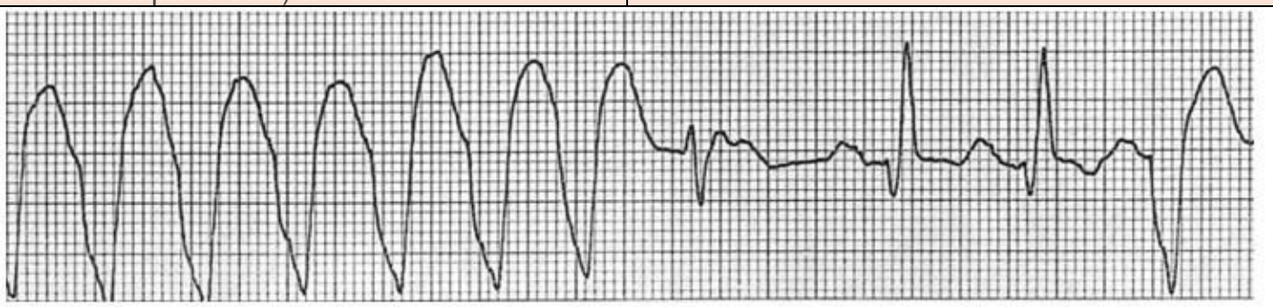
- Supraventricular tachycardia with bundle-branch block may resemble ventricular tachycardia on the ECG
- **Features suggesting VT rather than SVT with aberrant conduction**
  - AV dissociation
  - fusion or capture beats
  - positive QRS concordance in chest leads ((same polarity QRS direction in all chest leads V1 -V6)
  - marked left axis deviation
  - history of IHD
  - lack of response to adenosine or carotid sinus massage
  - very broad QRS > 160 ms
  - bifid upright QRS with a taller first peak in V1
  - deep S wave in V6

Capture beats

- intermittent narrow QRS complex owing to normal ventricular activation via the AV node
- occurs when a supraventricular and a ventricular impulse coincide to produce a hybrid complex.
- It indicates that there are two foci of pacemaker cells firing simultaneously: a supraventricular pacemaker (e.g. the sinus node) and a competing ventricular pacemaker (source of ventricular ectopics).
- Causes:
  - Ventricular tachycardia
  - Accelerated idioventricular rhythm (AIVR)

fusion beats
(intermediate between ventricular tachycardia beat and capture beat) are seen





Fusion beats due to VT - the first of the narrower complexes is a fusion beat (the next two are capture beats)

Management

- **VT with pulse** (not respond to medical treatment) → cardioversion (synchronized)
- **Pulseless VT or VF** → DC (asynchronized)

If the patient is unstable, and you can see a QRS-t complex use (LOW ENERGY) synchronized cardioversion.
If the patient is pulseless, or if the patient is unstable and the defibrillator will not synchronize, use (HIGH ENERGY) unsynchronized cardioversion (defibrillation).

Synchronization avoids the delivery of a LOW ENERGY shock during cardiac repolarization (t-wave). If the shock occurs on the t-wave (during repolarization), there is a high likelihood that the shock can precipitate VF (Ventricular Fibrillation).

- **If the patient has adverse signs** (systolic BP < 90 mmHg, chest pain, heart failure or **rate > 150** beats/min) then **immediate cardioversion** is indicated.
  - anaesthetist needs to be called to assist with direct current cardioversion (DCCV) which **should be 'synchronised' to limit the risk of conversion to VF.**
    - usually at a starting energy dose of 100 J (monophasic; comparable biphasic recommendations are not currently available).
  - If deteriorate in the meantime and become pulseless, then a precordial thump should be given, followed immediately by DCCV if not successful.
  - In cases of **pulseless VT**, the electrical cardioversion should be **unsynchronized.**
  - **Amiodarone is the drug of choice for acute VT refractory to cardioversion shock.**
  - Unstable polymorphic VT is treated with immediate defibrillation. The defibrillator may have difficulty recognizing the varying QRS complexes; therefore, synchronization of shocks may not occur.
- **In stable patients** (absence of adverse signs):
  - **stable patients stable patients with monomorphic VT and normal LV function,**
    - If LV function is impaired, amiodarone (or lidocaine) is preferred to procainamide for pharmacologic conversion because of the latter drug's potential for exacerbating heart failure.
    - restoration of sinus rhythm is typically achieved with IV pro**cainamide**, **amiodarone**, or **sotalol**.
  - **If LV function is impaired**, amiodarone (or lidocaine) is preferred to procainamide for pharmacologic conversion because of the latter drug's potential for exacerbating heart failure.
  - In the absence of such signs antiarrhythmics may be used. If these fail, then electrical cardioversion may be needed with **synchronised DC** shocks
  - If medical therapy is unsuccessful, synchronized cardioversion (50-200 J monophasic) following sedation is appropriate.
  - prophylactic implantable cardioverter defibrillator implantation is recommended in high-risk patients.
- **Polymorphic VT in stable patients**
  - **typically terminates on its own.**

	Unsynchronized	Synchronized
When to deliver electricity	At any point in cycle	Not during the T-wave
Indications	V-fib, pulseless VT	Everything except V-fib and pulseless VT

Drug therapy

Verapamil is contra-indicated in VT because it can cause a catastrophic fall in blood pressure.

- amiodarone: ideally administered through a central line
  - **(i.e. given after the third shock).** If amiodarone is not available lidocaine is a suitable alternative.
- lidocaine: use with caution in severe left ventricular impairment
- procainamide
- Adenosine is useful diagnostically when the diagnosis of regular wide complex tachycardia is in doubt.
- **Verapamil should NOT be used in VT**

Sotalol is recommended as the first-choice drug to prevent a recurrence of ventricular tachycardia (VT)

If drug therapy fails

- **electrophysiological study (EPS)**
- implant able cardioverter-defibrillator (ICD) - this is particularly indicated in patients with significantly impaired LV function

C.V Resuscitation:

- Guidelines from the Resuscitation Council (UK) state that if a patient has a monitored and witnessed VF/VT arrest in hospital, three quick successive (stacked) shocks should be given. Chest compressions should be started immediately after the third, with a compression to ventilation ratio of 30:2 for 2 minutes.

- **A precordial thump can be successful if given within seconds of the onset of a shockable rhythm.** Delivery should not delay calling for help, or accessing a defibrillator, but would be indicated here whilst awaiting the defibrillator. Chest compressions should start immediately if it is unsuccessful.
- Intravenous adrenaline would be given every 3-5 minutes once chest compressions had started.

P-wave asystole

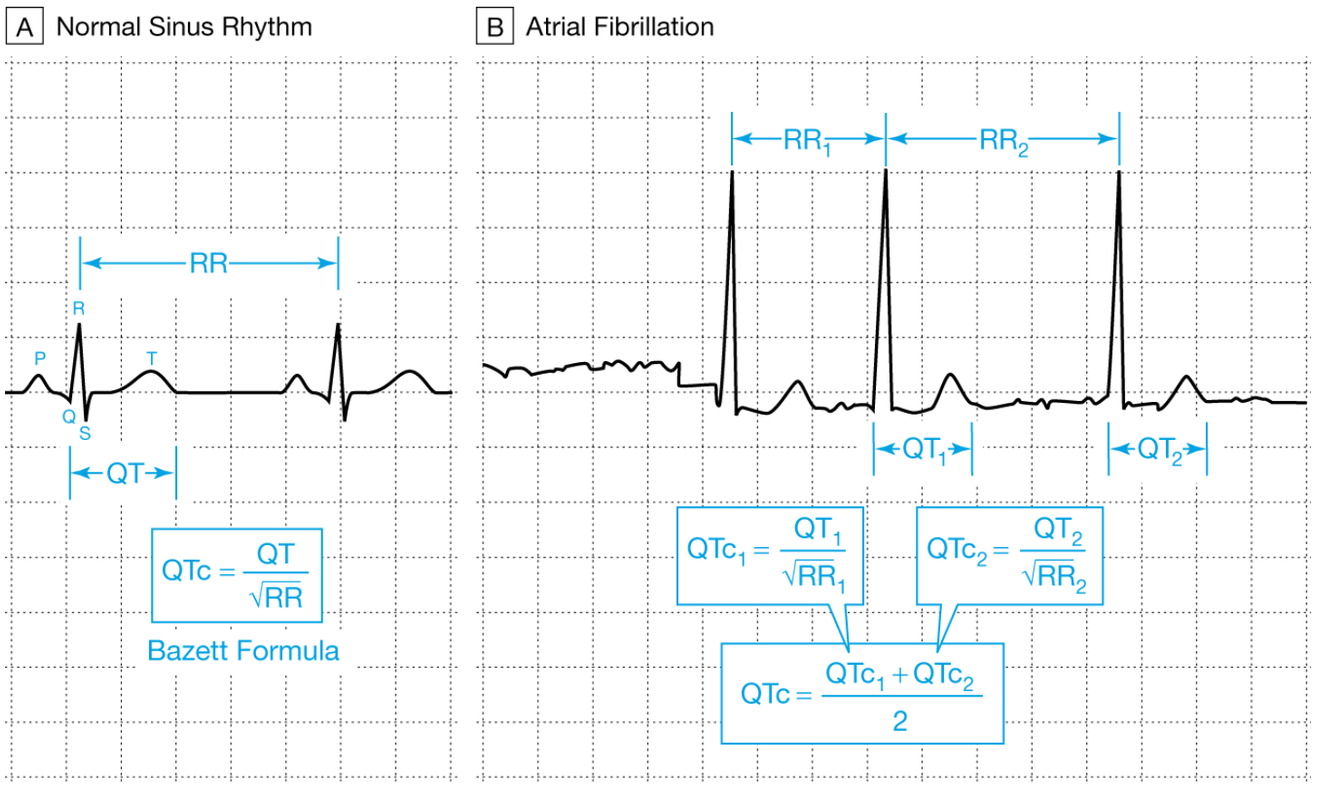
- Occasionally, atrial electrical activity continues in the absence of ventricular impulses.
- This is referred to as P-wave asystole and may respond to electrical pacing.
- initial treatment of choice → pacing (transvenous, transcutaneous or manual techniques).
  - Transvenous pacing takes longer to instigate, and **transcutaneous pacing is therefore the initial choice here.**
  - Manual pacing is an effective holding measure before more definitive pacing is instituted.

QT interval

QT interval: Time between the start of the Q wave and the end of the T wave

- **Definition**
  - **QT measured from the start of the QRS complex to the end of the T wave**
  - represents the duration of activation and recovery of the ventricular myocardium
- **Normal duration** → should be between 0.33 and 0.44 seconds
- **Corrected QT interval (QTc)** is calculated by dividing the QT interval by the square root of the preceding R - R interval. Normal = 0.42 s.

$$QTcB = \frac{QT}{\sqrt{RR}}$$



Long QT syndrome

Definition

- Long QT syndrome (LQTS) is an inherited condition associated with delayed repolarization of the ventricles.
- A normal corrected QT interval is less than 430 ms in males and 450 ms (0.45 s) in females.
  - One large box represents 200 ms , one small box represents 40 ms

Mechanism

Long QT syndrome - usually due to loss-of-function/blockage of K+ channels

- the usual mechanism by which drugs prolong the QT interval is blockage of potassium channels → **delayed repolarization of the ventricles.**
- **Most drugs that prolong the QT_c interval act by blocking *hERG*-encoded potassium channels, although some drugs modify sodium channels.**
- The most common variants of LQTS (LQT1 & LQT2) are caused by defects in the alpha subunit of the slow delayed rectifier potassium channel.

Epidemiology

- more common in females.

Classification

	LQT1	LQT2	LQT3
Gene	KCNQ1	KCNQH2/ hERG	SCN5A
Iron	**K**s (redifier potassium current, **s**low component)	**K**r (redifier potassium current, **r**apid component)	Na
Pathophysiology	Decreased potassium outward current	Decreased potassium outward current	excessive sodium inward current
Triger of arrhythmia	Exercise stress	Emotional stress	Rest
Occurrence	> 50%	34 – 40%	10 – 15%

Causes of a prolonged QT interval

Methadone is a common cause of QT prolongation

Anti-arrhythmics	*Antihistamines*	*Anti-infectives*	*Antimalarials*
Amiodarone **Disopyramide** **Dofetilide** **Ibutilide** **Procainamide** **Quinidine** **Sotalol**	**Astemizole** **Terfenadine**	**Clarithromycin** **Erythromycin** **Pentamidine** **Sparfloxacin**	**Chloroquine** **Halofantrine**
Antipsychotics	***Gastro-intestinal drugs***	***Opiate agonists***	***Other drugs***
Chlorpromazine **Haloperidol** **Mesoridazine** **Pimozide** **Thioridazone**	**Cisapride*** **Domperidone**	**Levomethadyl** **Methadone**	**tricyclic antidepressants, fluoxetine** **Arsenic trioxide** **Bepridil** **Droperidol** **Probuco**
Congenital	**Other conditions**		

Jervell-Lange-Nielsen syndrome (includes deafness and is due to an abnormal potassium channel) **Romano-Ward syndrome** (no deafness)	• **Electrolytes:** ➢ hypocalcaemia ➢ hypokalaemia ➢ hypomagnesaemia • acute myocardial infarction • myocarditis • hypothermia • subarachnoid haemorrhage

- *Cisapride have been withdrawn worldwide due to risk of QT prolongation
- **Jervell-Lange-Nielsen syndrome:**
  - ➢ **includes deafness** and is due to an abnormal potassium channel
  - ➢ **autosomal recessive**
  - ➢ **caused by Mutations in the KCNE1 and KCNQ1 genes**
    - Mutations in the KCNE1 and KCNQ1 genes → abnormal potassium channel → abnormal functions of **inner ear** structures and **cardiac muscle**.
- **Romano-Ward syndrome**:
  - ➢ congenital long QT syndrome
  - ➢ autosomal dominant
  - ➢ involves only cardiac (**no** deafness)
- The **human ether-à-go-go related gene (hERG)** is the gene affected by drugs that lengthen QT interval inadvertently; erythromycin, terfenadine, and ketoconazole.
- a non-sedating antihistamine are classic cause of prolonged QT in a patient, especially if also taking P450 enzyme inhibitor, e.g. Patient with a cold takes terfenadine and erythromycin at the same time

Features

A QT interval of greater than 0.44 seconds is associated with the development of ventricular arrhythmia, syncope and sudden cardiac death.

- asymptomatic
- may be picked up on routine ECG or following family screening
- Long QT1 - usually associated with exertional **syncope**, often swimming
- Long QT2 - often associated with syncope occurring following emotional stress, exercise or auditory stimuli
- Long QT3 - events often occur at night or at rest
- sudden cardiac death

Diagnosis

- corrected QT interval
  - ➢ Diagnosis is based upon the QTc (corrected QT interval),
  - ➢ QTc may be within the normal range at rest; hence **Holter ECG monitoring** is recommended.
- genetic testing of LQTS
  - ➢ Identification of an LQTS genetic mutation confirms the diagnosis.
  - ➢ However, a negative result on genetic testing is of limited diagnostic value because only approximately 50% of patients with LQTS have known mutations. The remaining half of patients with LQTS may have mutations of yet unknown gene. Therefore genetic testing of LQTS has high specificity but a low sensitivity.

Complications

- may lead to ventricular tachycardia → collapse/sudden death.

Management

Congenital long QT syndrome:

- **Beta-blockers**
  - ➢ **Beta-blockers are first-line** (commonly Propranolol) **(The most appropriate initial treatment)**

- Beta blockers alone are enough to abate collapses in up to 70% of patients.
- Beta blockers act by:
  1. decrease sympathetic activation from the left stellate ganglion,
  2. also decrease the maximal heart rate achieved during exertion and thereby prevent exercise-related arrhythmic events that occur in LQTS.
- should be avoided in those congenital cases in which bradycardia is a prominent feature.
- note sotalol may exacerbate long QT syndrome (due to blockage of K channel). This can be a particular risk in individuals with hypokalaemia. Therefore **Sotalol is better to be avoided in patients with thiazide diuretics.**

- patients who remain symptomatic despite receiving the maximally tolerated dose of beta-blockers → **Permanent pacing ,** and can be used in addition to beta-blockers.
- patients who remain refractory to beta-blockade and pacing → **High left thoracic sympathectomy**
- **Implantable cardioverter-defibrillators (ICDs)** are useful in rare instances when torsades still continues despite all of these treatments.
- Beta-blockers should be used along with ICDs because shock can further precipitate torsades by adrenergic stimulation.
- **Left stellate cardiac ganglionectomy** is an invasive procedure and results in Horner's syndrome. It is performed in patients who have symptoms despite βB and have frequent shocks with ICD.

Acquired long QT syndrome:

- **avoid drugs which prolong the QT interval** and other precipitants if appropriate (e.g. Strenuous exercise)
- Long-term treatment in acquired cases is usually not required because the QT interval returns to normal once the predisposing factor has been corrected.
- Correction of any electrolyte disturbance
  - Due to the **pseudo-obstruction** it is very likely that the patient is hypokalaemic and as such this is the **first reversible aetiology for the non-sustained VT** that needs to be investigated
    - **→ Check electrolytes**
    - Checking Magnesium would also be an appropriate step.
- **Beta-blockers are contra-indicated in acquired cases** because bradycardia produced by these agents can precipitate torsades. They should also be avoided in those congenital cases in which bradycardia is a prominent feature.
- Pacemaker implantation is effective in cases that are associated with heart block or bradycardia.
- ICDs are indicated in cases that cannot be managed by avoidance of any specific precipitating factor.

QT shortening: caused by:
- Hypercalcaemia
- Hypermagnesaemia
- Digoxin
- Thyrotoxicosis.

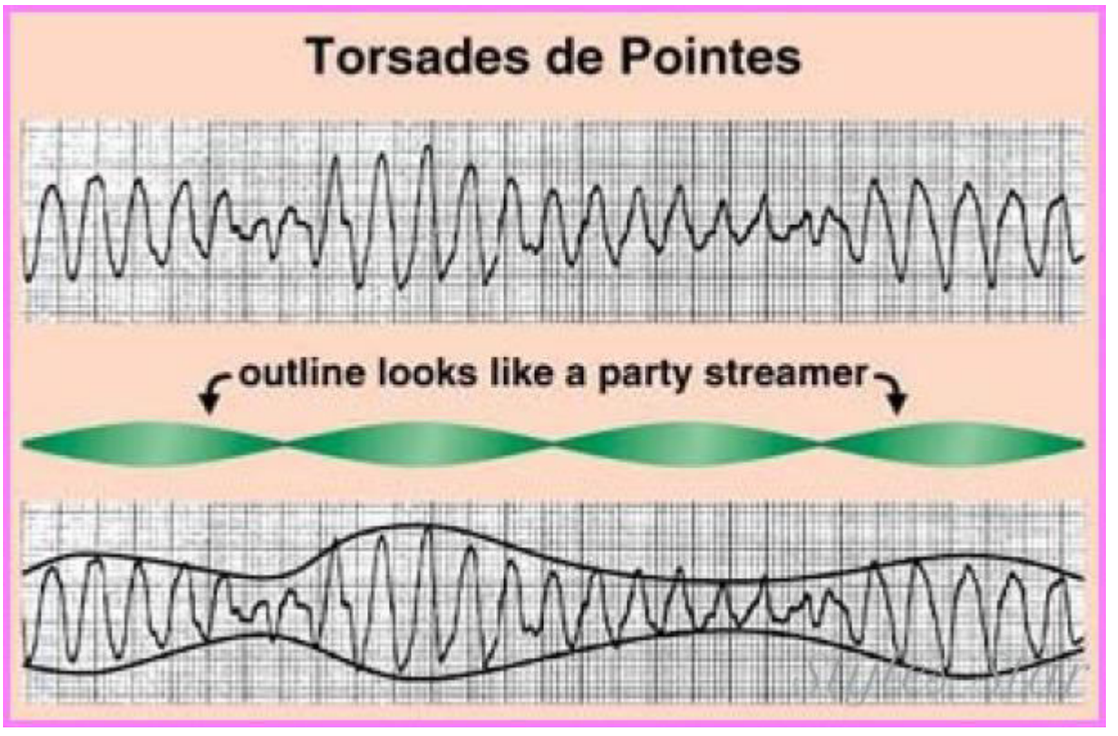
January 2013 exam: A patient develops torsades de pointes shortly after being started on sotalol. What effect does sotalol have on the cardiac cell membrane to make this more likely? Blockage of potassium channels → prolonged QT interval.

Torsades de pointes (TdP)

- Torsades de pointes ('twisting of the points') is a rare arrhythmia associated with a long QT interval.
- It may deteriorate into ventricular fibrillation and hence lead to sudden death
- In its most typical form, sudden slowing of heart rate (i.e., pauses) invariably precede each burst of TdP, and the recurrent arrhythmia is referred to as "pause-dependent TdP"
- **Risk factors**

- **Female sex**
- causes of QT prolongation,
- **R-on-T phenomenon**
  - the R-wave, representing ventricular depolarization, occurs during the relative refractory period at the end of repolarization (represented by the latter half of the T-wave).
    - Long QT intervals predispose the patient to an R-on-T phenomenon,
  - R-on-T can initiate torsades.
- bradycardia,
- congestive heart failure,
- digitalis therapy,
- severe alkalosis
- recent conversion from atrial fibrillation.

- **Management**
  - Stop all drugs which prolong QT
  - Correct any electrolyte abnormalities
  - IV magnesium sulphate (MgSo4)
    - **the best initial drug**
    - **Mode of action: MgSo4 → ↓ Ca influx →↓ amplitude of the VT and helping terminate runs of torsade's.**
    - Dose : 2 gm as bolus over 10 minutes, followed by another bolus in 15 minutes if required, or continuous infusion at a rate of 5-20 mg/min.
    - It is effective even when serum magnesium level is normal.
  - Temporary pacemaker/transvenous overdrive pacing (atrial or ventricular)
    - reserved for patients with long QT-related TdP who do not respond to intravenous magnesium.
  - Isoproterenol
    - usually used as a temporizing measure prior to pacing in patients **who have failed to respond to magnesium and are awaiting placement of a temporary pacemaker.**
    - Action → Strong beta-1 & beta-2 stimulation



Peri-arrest rhythms: tachycardia (The 2010 Resuscitation Council (UK) guidelines)

- **patients are classified as being stable or unstable** according to the presence of any adverse signs:
  - shock: hypotension (systolic blood pressure < 90 mmHg), pallor, sweating, cold, clammy extremities, confusion or impaired consciousness
  - syncope

- myocardial ischaemia
- heart failure

- **If a patient is unstable → synchronised cardioversion**
  - For a broad-complex tachycardia or atrial fibrillation, start with 120–150 J and increase in increments if this fails.
  - Atrial flutter and regular narrow-complex tachycardia will often be terminated by lower energies: start with 70–120 J.

- If cardioversion fails :
  - give amiodarone 300 mg IV over 10–20 min and re-attempt electrical cardioversion.
  - The loading dose of amiodarone may be followed by an infusion of 900 mg over 24 h.

- **If the patient is stable:**
  - **Regular broad-complex tachycardia** (QRS duration is 0.12 s or greater (3 small squares on standard ECG paper speed of 25 mm s^{-1})
    - ventricular tachycardia (VT) → amiodarone 300 mg IV over 20–60 min, followed by an infusion of 900 mg over 24 h
    - or a regular supraventricular rhythm with bundle branch block.
    - assume ventricular tachycardia (unless previously confirmed SVT with bundle branch block)

  - **Irregular broad-complex tachycardia**
    - (most likely due to atrial fibrillation (AF) with bundle branch block)
    - Other possible causes:
      - AF with ventricular pre-excitation (in patients with Wolff-Parkinson-White [WPW] syndrome),
      - or **polymorphic VT (e.g. torsade de pointes),** but sustained polymorphic VT is unlikely to be present without adverse features.
        - stop all drugs known to prolong the QT interval.
        - Correct electrolyte abnormalities, especially hypokalaemia.
        - Give magnesium sulfate 2 g IV over 10 min (= 8 mmol, 4 mL of 50% magnesium sulfate).
        - Do not give amiodarone for definite torsade de pointes.
        - If adverse features are present, which is common, arrange immediate synchronised cardioversion.
  - **Regular narrow-complex tachycardias include:**
    - sinus tachycardia
      - In a sick patient it may occur in response to many conditions including pain, infection, anaemia, blood loss, and heart failure.
      - Treatment is directed at the underlying cause.
      - Trying to slow sinus tachycardia that has occurred in response to most of these conditions will usually make the situation worse.
    - **AV nodal re-entry tachycardia (AVNRT) – the commonest type of regular narrow-complex tachyarrhythmia**
      - The usual cause is the presence of dual AV nodal pathways (slow and fast pathways within the AV node).
      - Vagal manoeuvres could be attempted to cardiovert the patient. If it fails, the use of IV adenosine in the presence of appropriate resuscitation facility would be appropriate.
      - Ensure that the patient is being monitored whilst adenosine is given so the underlying rhythm canbe captured. This cansometimes uncover underlying atrial flutter when the rate slows.
      - In cocaine overdose.
        - Calcium antagonists such as verapamil are the initial pharmacological therapy of choice if cardioversion does not work as beta blockade may lead to worsening of myocardial ischaemia in the context of cocaine overdose.
    - AV re-entry tachycardia (AVRT) – due to WPW syndrome
    - atrial flutter with regular AV conduction (usually 2:1).
      - Typical atrial flutter has an atrial rate of about 300 min^{-1}, so atrial flutter with 2:1 conduction produces a tachycardia of about 150 min^{-1}.

- Much faster rates (>160 min^{-1}) are unlikely to be caused by atrial flutter with 2:1 conduction.

- **If the patient is unstable→ synchronised electrical cardioversion.**
  - It is reasonable to apply vagal manoeuvres and/or give adenosine while preparations are being made urgently for synchronised cardioversion.
- **In the absence of adverse features:**
  - Start with vagal manoeuvres. Carotid sinus massage or the Valsalva manoeuvre will terminate up to a quarter of episodes of paroxysmal SVT.
  - If the arrhythmia persists, give adenosine 6 mg as a rapid IV bolus. Use a relatively large cannula and large (e.g. antecubital) vein.
  - If there is no response give a 12 mg IV bolus.
  - If there is no response give one further 12 mg IV bolus.
  - Apparent lack of response to adenosine will occur if the bolus is given too slowly or into a peripheral vein.
  - Termination of a regular narrow-complex tachycardia in these ways (Vagal manoeuvres or adenosine) identifies it as being AVNRT or AVRT.
  - Failure to terminate a regular narrow-complex tachycardia with adenosine suggests an atrial tachycardia such as atrial flutter (unless the adenosine has been injected too slowly or into a small peripheral vein).
  - If adenosine is contra-indicated, or fails to terminate a regular narrow-complex tachycardia without demonstrating that it is atrial flutter, consider giving verapamil 2.5–5 mg IV over 2 min.

- **Irregular narrow-complex tachycardia** is most likely to be AF or sometimes atrial flutter with variable AV conduction ('variable block').
  - most likely due to AF with an uncontrolled ventricular response
  - or, less commonly, atrial flutter with variable AV block.
  - If the patient is unstable → start antithrombotic therapy and attempt synchronised cardioversion.
  - patients who have been in AF for more than 48 h should not be treated by cardioversion (electrical or chemical) until they have been fully anticoagulated for at least three weeks, or unless trans-oesophageal echocardiography has shown the absence of atrial thrombus.
  - Continue anticoagulation after attempted cardioversion, whether or not it is successful, which should be a minimum of four weeks
  - If the aim is to control heart rate:
    - the usual drug of choice is a beta-blocker.
    - Diltiazem or verapamil may be used in patients in whom beta-blockade is contraindicated or not tolerated.
    - Digoxin or amiodarone may be used in patients with heart failure.
    - Amiodarone may be used to assist with rate control but is more useful in maintaining rhythm control.

management of tachyarrhythmia in pregnancy → Vagal manoeuvres followed by adenosine

- The most common tachyarrhythmias in pregnancy are AV nodal re-entrant tachycardia
- As in the non-pregnant population, vagal manoeuvres should be tried first.
- If these are unsuccessful, as in approximately 75% of cases, adenosine is the next step.
  - **Adenosine is safe in pregnancy**
- Verapamil should not be used in the first trimester.
- Some beta blockers can be used in pregnancy - there is small risk of fetal bradycardia and intrauterine growth retardation.
- Amiodarone should be avoided unless no alternative.

Peri-arrest rhythms: bradycardia

The 2010 Resuscitation Council (UK) guidelines emphasise that the management of bradycardia depends on:

- 1. identifying the presence of signs indicating haemodynamic compromise - 'adverse signs'
- 2. identifying the potential risk of asystole

Adverse signs

the following factors indicate haemodynamic compromise and hence the need for treatment:

- shock: hypotension (systolic blood pressure < 90 mmHg), pallor, sweating, cold, clammy extremities, confusion or impaired consciousness
- syncope

- myocardial ischaemia
- heart failure

Treatment

- Atropine is the first line treatment in this situation.
- If this fails to work, or there is the potential risk of asystole then transvenous pacing is indicated
  - **Emergency temporary transvenous pacing wire is the next most important treatment with the situation of inferior MI** until the MI fully resolved. Conduction block can recover in the next few days so a permanent pacemaker may not be required

Potential risk of asystole

the following indicate a potential risk of asystole and hence the need for treatment with transvenous pacing:

- complete heart block with broad complex QRS
- recent asystole
- Mobitz type II AV block
- ventricular pause > 3 seconds

If there is a delay in the provision of transvenous pacing the following interventions may be used:

- atropine, up to maximum of 3mg
- transcutaneous pacing
  - Transcutaneous is the same as external pacing (via pads); it is terrible for the patient and should only be used as a holding measure in emergency. transvenous is via the femoral or internal jugular vein.
- adrenaline infusion titrated to response

bradycardia-induced syncope in a cardiovascularly stable patient:

if the diagnosis is not certain in bradycardia-induced syncope and cardiovascularly stable What is the most appropriate next step in management? → observation as an inpatient with suitable heart rate monitoring is the best answer **(Admit and arrange monitored telemetry with printing)**

- Outpatient observation is not appropriate given the syncopal episode.
- Although this patient is likely to require a permanent pacemaker at some stage, emergency temporary wire is not indicated unless patient has recurrent syncope due to bradycardia or complete heart block.
- Because the patient is cardiovascularly stable a temporary wire, atropine or carotid sinus massage are not required.

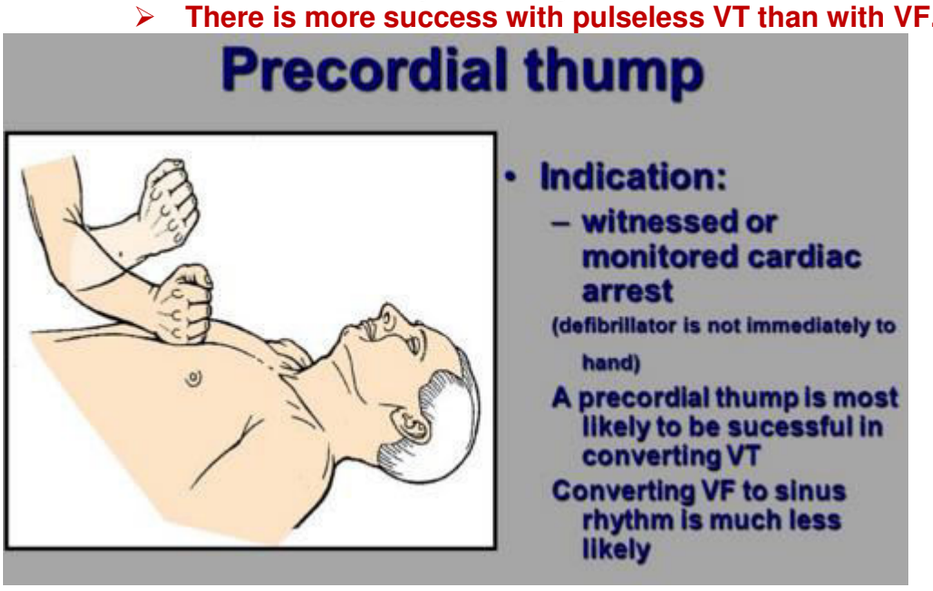
Adult advanced life support

The joint European Resuscitation Council and Resuscitation Council (UK) 2010 guidelines do not alter significantly from the 2005 guidelines.

Major points include:

- **Immediately after the first shock (and each subsequent shock) chest compressions should be restarted immediately and pulse and rhythm reassessed after two minutes.**
  - After each shock chest compressions should be restarted immediately before anything else is done.
- ratio of chest compressions to ventilation is 30:2
- chest compressions are now continued while a defibrillator is charged
- **during a VF/VT cardiac arrest, adrenaline 1 mg is given once chest compressions have restarted after the third shock** and then every 3-5 minutes (during alternate cycles of CPR). In the 2005 guidelines, adrenaline was given just before the third shock.
- Amiodarone 300 mg is also given **after the third shock**. it should be after adrenaline has been administered.
- A 1 mg dose of adrenaline (epinephrine) would be administered with:
  - 0.1 ml of 1 in 100,
  - 1 ml of 1 in 1000 and
  - 10 ml of 1 in 10,000.
- **10 ml of 1 in 10,000 is the recommended dose and concentration** by the UK Resuscitation Council.
  - **If not able to gain any venous access → Obtain intraosseous access**
    - Intraosseous access is a safe and effective method of administering drugs in cardiac arrest; it provides adequate plasma levels of drugs and allows equivalent flow rates to IV access.

  - Therefore if IV access cannot be gained within two minutes, IO access should be attempted (if trained). Tibial or humeral sites should be tried first.
- atropine is no longer recommended for routine use in asystole or pulseless
- **Refractory VF**
  - **Magnesium sulphate IV is recommended for the treatment of refractory VF, if there is anything to suggest the patient may be hypomagnesaemic (such as on medications which might cause this, that is, thiazides).**
  - There is no indication for increasing doses of adrenaline or amiodarone, or increasing shock energy.
  - Amiodarone can be given again but this should be at the reduced dose of 150 mg.
  - Lidocaine is only recommended if amiodarone is unavailable, and/or has not already been given.
- **Management of a patient post cardiac arrest**
  - **The first step in post-cardiac arrest care is to give aspirin and clopidogrel.** This can usually be achieved quickly and easily whilst other investigations and treatments are organised.
  - **Maintain glucose <10 mmol/L** (due to increased hypoglycaemia).
  - oxygen saturations should be kept at 94-98%, not 100%. (Hyperoxaemia (and hypoxia) is also associated with poor outcomes)
    - The oxygen dissociation curve is shifted to the right in acute acidosis, i.e. haemoglobin has a decreased affinity for oxygen.
    - **High pulmonary pressures** would be expected **after arrest** scenario, as the **pulmonary arterioles constrict in response to hypoxia.**
- The use of brief periods of echo (FAST scan) (10 seconds) is now supported in an arrest situation (but should be performed at the end of two minutes of compressions).
- **precordial thump**
  - A precordial thump can be successful if given within seconds of the onset of a shockable rhythm.
  - Delivery should not delay calling for help, or accessing a defibrillator, but would be indicated here whilst awaiting the defibrillator.
  - Chest compressions should start immediately if it is unsuccessful.
  - Only one thump should be delivered over the lower third of the sternum.
  - The ulnar edge of a tightly clenched fist is used to deliver a sharp impact from a height of about 20 cm, then retract immediately (thereby creating an impulse-like stimulus).
  - Repeating a precordial thump is not recommended.
  - It is important to remember that a precordial thump has a very low success rate for cardioversion.
  - In general it delivers approximately 7-10 joules of energy, but this is operator dependent and references vary to this regard.
  - **There is more success with pulseless VT than with VF.**



Electrical activity (PEA).

- a single shock for VF/pulseless VT followed by 2 minutes of CPR, rather than a series of 3 shocks followed by 1 minute of CPR

- asystole/pulseless-electrical activity should be treated with 2 minutes of CPR, rather than 3, prior to reassessment of the rhythm
  - **(PEA) → pulseless with no respiratory effort .ECG reveals small complexes with a normal morphology → CPR + Adrenalin 1mg repeated every 3-5 minutes**
  - In the presence of a non-shockable rhythm, the use of adrenaline (1mg) every alternate cycle of CPR is recommended. It should be given once IV or IO access is attained.
  - Adrenaline use is still recommended in **pulseless electrical activity (PEA)** and asystole, every 3-5 minutes (alternate cycles of cardiopulmonary resuscitation (CPR)), and in ventricular fibrillation (VF)/ventricular tachycardia (VT) which is non-responsive to shocking, also every 3-5 minutes.
- delivery of drugs via a tracheal tube is no longer recommended
- following successful resuscitation oxygen should be titrated to achieve saturations of 94-98%. This is to address the potential harm caused by hyperoxaemia

Defibrillation

- Defibrillation is used to convert ventricular fibrillation to sinus rhythm
- **The recommendation is initially a 360-joule shock**

Cardiac arrest in profound hypothermia

- Cardiac arrest in profound hypothermia has several differences from cardiac arrest in normothermic patients.
- **Prolonged cardiopulmonary resuscitation is likely to be required**
- At core temperatures of less than 30°C, treatment of ventricular arrhythmia with medical therapy is largely ineffective, and electrical cardioversion is less effective than in normotensive patients. For this reason, a prolonged period of CPR may be required until core temperature is above 30ºC.
- Between 30–35 °C, the intervals between drug doses should be doubled when compared with normothermia intervals.
  - In hypothermic arrest, drugs are less effective - metabolism is slowed and there is the possibility of accumulation to toxic levels - and prolonged resuscitation with re-warming is the management of choice.
- Recovery with intact neurology has been reported even after very prolonged arrests, therefore resuscitation should be continued for far longer than would normally be considered.
- Hypothermic patients do not respond well to shocks or drugs and **if there is no response to the first three shocks the patient should be rewarmed to at least 32°C before any drugs or shocks are administered.**
  - defibrillation can be tried up to three times but should then not be tried until the temperature reaches 30°C.
- Serious consideration should be given to cardiopulmonary bypass in a patient such as this.
- There is no place for 0.5 mg IV adrenaline in adult cardiac arrest.
- A half dose of amiodarone is indicated after the fifth, not the third shock.

Lance-Adams syndrome

- is a rare condition that can occur following a period of cerebral hypoxia.
- Onset **occurs within days to weeks of cardiac arrest**.
- It is characterised by **intention myoclonus**.
- Although no trials on effective treatment have been conducted, levetiracetam, clonazepam and valproate have been recommended as first-line treatments.

Management of cold water drowning

- The management of patients who nearly drown in cold water is quite different from that for routine cardiopulmonary arrests.
- Mechanism of circulatory collapse:
  - Head-out upright immersion in water at body temperature results in a 32–66% increase in cardiac output because of the pressure of the surrounding water

  - Resistance to circulation is suddenly removed as the person leaves the water, which when added to venous pooling, can cause circulatory collapse. This is believed to be the cause of death in many individuals
  - To counter this effect, **patients should be lifted out of the water in the prone position**
- **Re-warming** such patients should be undertaken in a hospital that has extracorporeal re-warming facilities
  - **Defibrillation is ineffective if the myocardium is cold.**
  - **Hypothermia may render the carotid pulse impalpable** so it is important to commence chest compression with firm evidence of cardiac arrest.
- Continuous chest compression should be applied throughout transportation, which is as effective as chest compression with expired air resuscitation
- Electrocardiographic monitoring should be available

Wolff-Parkinson White (WPW)

Definition

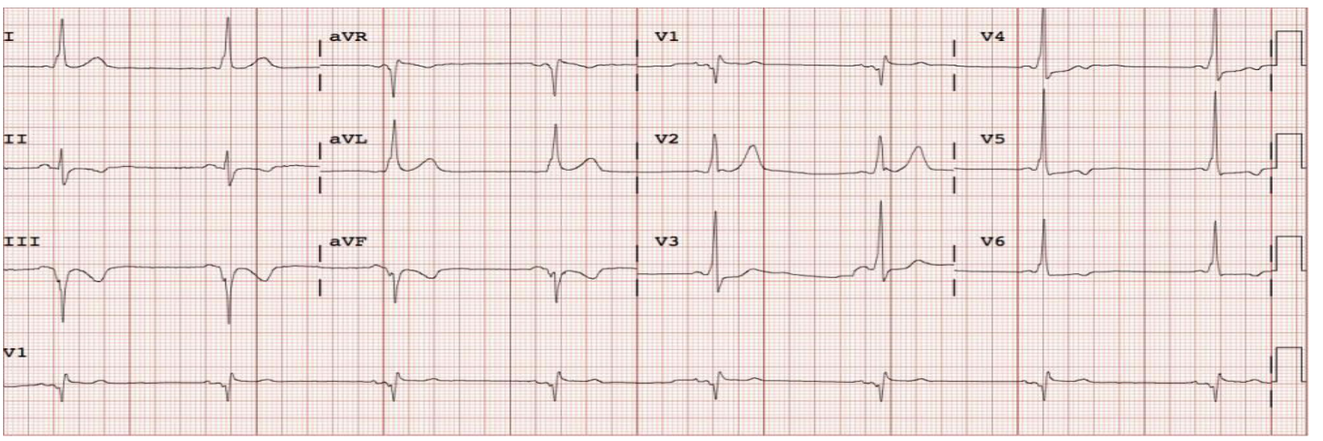
- congenital accessory conducting pathway between the atria and ventricles leading to a atrioventricular re-entry tachycardia (AVRT). → **Ventricular pre-excitation**
- due to a congenital accessory cardiac conduction pathway, called the **bundle of Kent**, that connects the atria to the ventricles, enabling electrical activity to bypass the atrioventricular node.
- As the accessory pathway does not slow conduction AF can degenerate rapidly to VF

Presentation

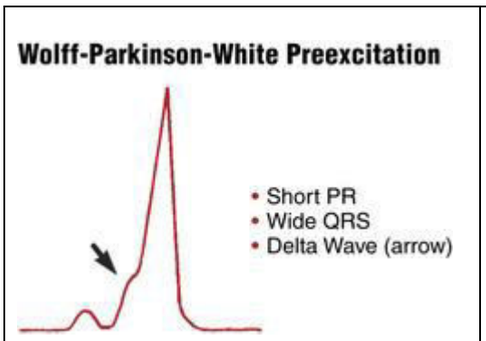
- Most patients are asymptomatic.
- **WPW presents as SVT that can alternate with ventricular tachycardia (VT).**
- SVT is the most common type of tachycardia seen in a patient with WPW.
- The other main clue to the diagnosis is **worsening of SVT after the use of calcium blockers or digoxin**

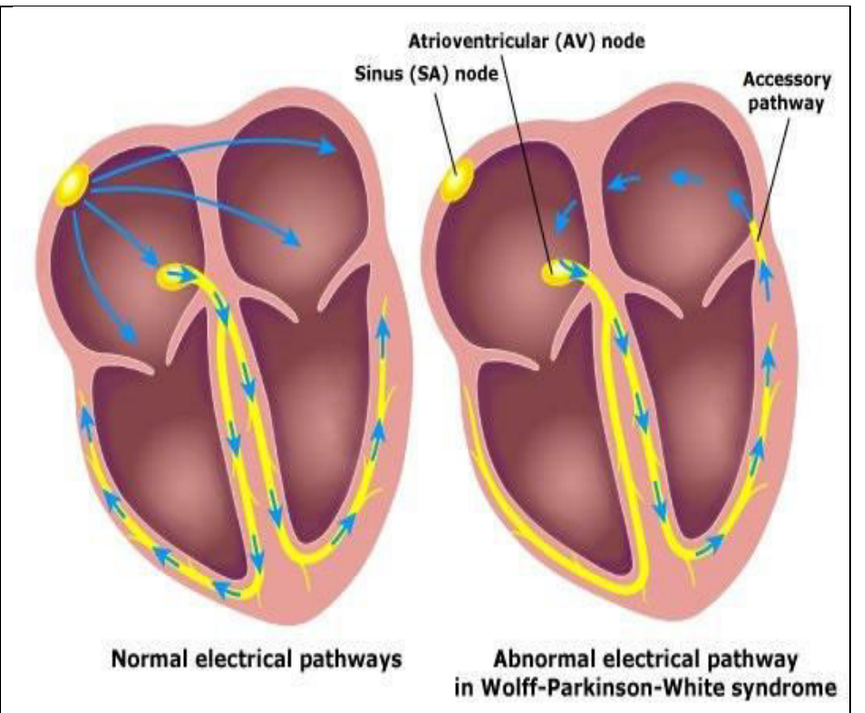
Possible ECG features include:

- short PR interval
- wide QRS complexes with a slurred upstroke - 'delta wave' (can be associated with negative delta waves in II, III and aVF)
- **ECG in sinus rhythm reveals right bundle-branch block**
- left axis deviation if right-sided accessory pathway*
  - *in the **majority** of cases or in a question without qualification, Wolff-Parkinson-White syndrome is associated with **left axis deviation**
- right axis deviation if left-sided accessory pathway
- non-specific ST-T changes which are common in WPW and may be mistaken for ischaemia.



ECG showing short PR interval associated with a slurred upstroke (delta wave). Note the non-specific ST-T changes which are common in WPW and may be mistaken for ischaemia. The left axis deviation means that this is type B WPW, implying a right-sided pathway





Differentiating between type A and type B**

- **type A** (left-sided pathway): dominant R wave in V1
- **type B** (right-sided pathway): no dominant R wave in V1
  - In type B pre-excitation, the accessory pathway connects the right atrium to the right ventricle
- **there is a rare type C WPW, WPW in which the delta waves are upright in leads V1-V4 but negative in leads V5-V6

Associations of WPW

- HOCM
- mitral valve prolapse
- **Ebstein's anomaly**
- thyrotoxicosis
- secundum ASD
- Leber's hereditary optic neuropathy (mitochondrial disease)

Investigations

- WPW is diagnosed with finding a delta wave on the EKG.
- **The most accurate test is electrophysiologic studies**

Management

- **asymptomatic : (incidentally found delta wave on ECG) → Reassurance**
- **Asymptomatic in high-risk professions (eg pilots) is best managed by catheter ablation of the accessory pathway**
- asymptomatic WPW in someone with a family history of sudden cardiac death is another indication for radiofrequency catheter ablation
- **definitive treatment: radiofrequency ablation of the accessory pathway**
  - **first-line therapy**
  - Risk of arrhythmia after ablation is 7% over five years.
- medical therapy: flecainide, amiodarone, sotalol***
  - **The most appropriate pharmacological management → Flecainide.**
    - is a sodium channel blocker (Class Ic anti-arrhythmic) which will reduce the excitability of the atrial and ventricular myocardium without AV nodal blockade.
  - ***sotalol should be avoided if there is coexistent atrial fibrillation as prolonging the refractory period at the AV node may increase the rate of transmission through the accessory pathway, increasing the ventricular rate and potentially deteriorating into ventricular fibrillation.
  - AV nodal blocking drugs should be avoided (**verapamil (the most contra-indicated)** , Adenosine, Beta-blockers)

- This is because blocking the AV node may enhance the rate of conduction through the accessory pathway, causing atrial fibrillation to degenerate into ventricular fibrillation (VF).

➢ **Digoxin and verapamil are contraindicated as they increase conduction in the bypass tract**

Lown–Ganong–Levine (LGL) syndrome:
LGL syndrome is like WPW in the sense that it is a pre-excitation syndrome. However, the ECG changes present is only short PR interval without delta waves or abnormal QRS complex.

Implantable cardiac defibrillators (ICD)

Indications

- Congenital long QT with family history of sudden cardiac death at young age.
- **hypertrophic obstructive cardiomyopathy (HOCM)**
- previous cardiac arrest due to VT/VF
- Sustained VT causing haemodynamic compromise
- previous myocardial infarction with non-sustained VT on 24 hr monitoring, inducible VT on electrophysiology testing and ejection fraction < 35%
- Brugada syndrome
- Arrhythmogenic right ventricular cardiomyopathy causing cardiac arrest.

Pericardial diseases

Acute pericarditis

- Pericarditis is one of the differentials of any patient presenting with chest pain.
- Between 15 and 30% of patients with idiopathic acute pericarditis may have recurrent attacks, and this is considered to be an autoimmune phenomenon.

Features

- Pleuritic chest pain
  - ➢ exacerbated by inspiration and lying flat,
  - ➢ **relieved by sitting up and leaning forwards**
- shoulder pain (referred pain)
  - ➢ pericarditis is innervated by phrenic nerve
- pericardial rub
  - ➢ the pathognomic feature
  - ➢ present in 50% of cases.
- tachypnoea
- tachycardia
- other symptoms include non-productive cough, dyspnoea and flu-like symptoms

Types and causes

- **Fibrinous pericarditis**
  - ➢ the most common type
  - ➢ Causes:
    - acute myocardial infarction (MI),
      - ❖ more common than dressler syndrome
      - ❖ friction rub is more common than pain
        - ⇨ may be heard within 24 hours and as late as 10 days.
      - ❖ Aspirin is the only NSAID that can be used in pericarditis complicating MI.
    - post MI (Dressler syndrome),
      - ❖ **rare**
      - ❖ autoimmune-mediated phenomenon to myocardial antigens
      - ❖ **occur 2 – 4 weeks post MI**
      - ❖ Because of the risk of hemorrhagic pericarditis, anticoagulant therapy should be stopped in patients with Dressler syndrome.
    - uremia,
    - radiation,

        - RA, SLE,
        - Trauma,
        - Severe infections
- **Serous pericarditis**
    - usually caused by noninfectious inflammation such as:
        - rheumatoid arthritis (RA)
        - systemic lupus erythematosus (SLE).
    - Fibrous adhesions rarely occur.
- **Purulent or suppurative pericarditis**
    - Most commonly caused by staphylococcal and gram-negative species,
    - high percentage of patients develop constrictive pericarditis.
- **Hemorrhagic pericarditis**
    - involves blood mixed with a fibrinous or suppurative effusion,
    - most commonly caused by:
        - **tuberculosis**
        - direct neoplastic invasion.
        - severe bacterial infections
        - bleeding diathesis,
        - cardiac surgery or trauma
            - (may cause tamponade).
- **Caseous pericarditis**
    - caseation within the pericardial sac is **tuberculous in origin, until proven otherwise**,
    - In tuberculous pericarditis, fever, night sweats, and weight loss are commonly noted (80%).
    - Untreated, caseous pericarditis is **the most common antecedent to chronic constrictive pericarditis** of a fibrocalcific nature.
        - Approximately **50%** of affected patients develop **constrictive pericarditis**.

- **Uremic pericarditis**
    - result from inflammation of the visceral and parietal layers of the pericardium by metabolic toxins
    - blood urea nitrogen (BUN) level is usually greater than 60 mg/dL (22 mmol/L).
    - **Hemorrhagic effusions are more common** and result in part from **uremia-induced platelet dysfunction.**
    - does not present with the classic diffuse ST-elevations seen on ECG as in other types of pericarditis.
    - Uremic pericarditis is an indication for urgent hemodialysis.
    - 2 types of pericarditis in patients with renal failure:
        - uremic pericarditis
            - occurs in patients with uremia who have never received dialysis.
        - dialysis-associated pericarditis,
            - occurs in patients who are already receiving dialysis.
            - The **usual cause** → inadequate dialysis, because aggressive dialysis often leads to resolution.
                - intensive dialysis is the most effective treatment for dialysis-associated pericarditis
            - Other causes:
                - volume overload
                - bacterial or viral infections

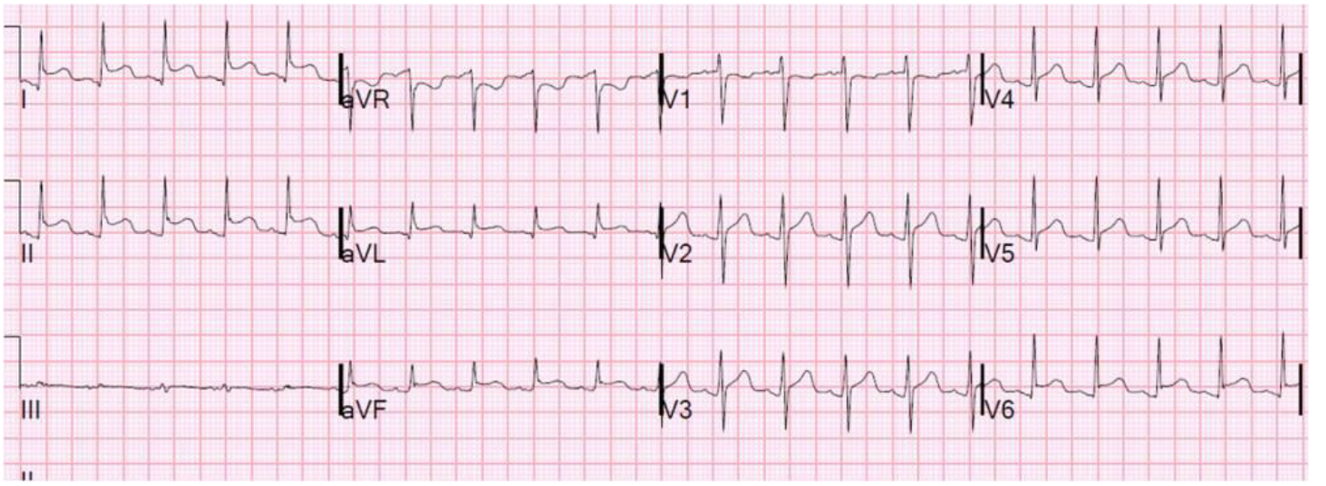
Other causes

- acute viral pericarditis
    - Viral infection is the most common cause of acute pericarditis
        - The most common viral cause is Coxsackie B virus
        - other causes include adenovirus, echovirus and influenza viruses.
- hypothyroidism

ECG changes

- wide spread 'saddle-shaped' ST elevation
- This is followed by the return of ST segments to baseline and flat T waves.
- **Which ECG changes would you expect to see in the next week or two?**
    - **T-wave inversion in all leads**

- **PR depression: most specific ECG marker for pericarditis**



ECG showing pericarditis. Note the widespread nature of the ST elevation and the PR depression

Diagnosis

ESC guidelines defined the **diagnosis** of acute pericarditis as **2 out of 4** of the following:

1) pericarditic chest pain;
2) pericardial rub;
3) new widespread ST-elevation or PR depression; and
4) pericardial effusion (new or worsening).

Treatment

- **Analgesia, observation** and attempts to ascertain a cause as well as ruling out any associated pericardial effusions would be appropriate.
  - high dose non-steroidal therapy (eg Aspirin 600mg QDS, ibuprofen 400-800mgs) is appropriate.
  - Increasingly oral **colchicine** is also used.
    - **Colchicine is useful both in acute episode and to prevent recurrence of pericarditis.**
    - If patients are unable to take NSAIDs, colchicine is the alternative.
- **Prednisolon**e can be considered in patients who fail to respond to non-steroidal anti-inflammatory drug and colchicine therapy.
- recurrent pericarditis post-transplant → **Cyclosporine**
- **Pericardectomy** is only indicated for recurrent pericarditis once medical interventions have failed.
- Treatment duration should be guided by symptoms and blood tests (CRP), but normally it is for 1-2 weeks' duration.
- Patients should be told to **reduce physical activity** for a minimum of **3 months** from initial onset.

Prognosis

- **Poor prognostic factors** include:
  - Temperature above 38ºC
  - Subacute disease course
  - Presence of a large effusion or tamponade
  - Unsuccessful therapy with nonsteroidal anti-inflammatory agents
- **Factors associated with complicated pericarditis** include:
  - Early administration of high-dose corticosteroids
  - Lack of colchicine treatment
  - Elevated levels of high-sensitivity C-reactive protein

Pericardial effusion

Cause of a pericardial effusion include:

- infectious pericarditis: viral, tuberculosis, pyogenic spread from septicaemia and pneumonia
- uraemia
- idiopathic

- post myocardial infarction (including Dressler's syndrome)
- malignancy
- heart failure
- nephrotic syndrome
- hypothyroidism
- **trauma**
  - **CT is the most appropriate investigation**
    - provide more information than Echo
    - quicker to obtain than (MRI).

Constrictive pericarditis

The right sided failure, ascites and pericardial calcification on x ray suggest a diagnosis of constrictive pericarditis.

Pathophysiology

- Inflammation of the pericardium → fibrosis and constriction

Risk factors

- **previous cardiac surgery**
- previous pericarditis,
- radiotherapy
- connective tissue disease

Causes

- **Mediastinal irradiation**
- TB :**Tuberculous pericarditis is the commonest cause of constrictive pericarditis worldwide.**
- any cause of purulent pericarditis

Features

- dyspnoea
- right heart failure: elevated JVP, ascites, oedema, hepatomegaly
- JVP shows prominent x and y descent
- pericardial knock - loud S3
- Kussmaul's sign is positive

Investigations

- **CXR**
  - pericardial calcification
  - can detect effusions only if larger than 250 mL.
- Echocardiography
  - Indication → to assess for pericardial effusion and cardiac tamponade
  - the best diagnostic tool for diagnosing pericardial effusion.
  - shows no increase in the venous return with inspiration.

The key differences between constrictive pericarditis and cardiac tamponade are summarized in the table below:

	Cardiac tamponade	Constrictive pericarditis
JVP	Absent Y descent	X + Y present
Pulsus paradoxus	Present	Absent
Kussmaul's sign*	Rare	Present
Characteristic features		Pericardial calcification on CXR

- **Kussmaul's sign* → a paradoxical rise in jugular venous pressure (JVP) on inspiration**
- In cardiac tamponade there is pulsus paradoxus (a greater than 10 mmHg fall in systolic BP on inspiration) but this is less commonly seen in constrictive pericarditis, though can still be present in both.

- Kussmaul's sign (a rise in the JVP on inspiration) is more likely to be seen in constrictive pericarditis than cardiac tamponade.

Hypotension is the best clinical features that distinguishes cardiac tamponade from constrictive pericarditis

- ➢ hypotension is a **late** feature in constrictive pericarditis.

Treatment

- The first line of treatment of symptomatic constrictive pericarditis is pericardiotomy.

Cardiac tamponade

Cardiac tamponade is characterised by **Beck's triad** of:

- **hypotension**
- raised JVP (with absent Y descent), and
- muffled heart sounds.

Features

- dyspnoea
- raised JVP, with an absent Y descent - this is due to the limited right ventricular filling
- tachycardia
- **Hypotension**
  - ➢ **the best clinical features that distinguishes cardiac tamponade from constrictive pericarditis**
    - hypotension is a **late** feature in constrictive pericarditis.
- muffled heart sounds
- pulsus paradoxus
- Kussmaul's sign (**rise in JVP on inspiration**)
- ECG: electrical alternans
- impalpable apex beat

MECHANISM OF PULSUS PARADOXUS

- Inhalation increases venous return. Increased venous return expands the right ventricle (RV). Expanded RV compresses the left ventricle (LV). Compressed LV decreases blood pressure. Tamponade compresses the whole heart.
- **Inhale = Big RV = Smaller LV = BP drop > 10 mm Hg**

Hypertension

Hypertension

Types

- Essential hypertension (95% of patients)
  - ➢ causes are multi-factorial with a combination of genetics and environmental factors.
- Secondary hypertension (5% of patients).

When a question says: 'What is the most likely diagnosis?' think about what is epidemiologically the most common cause of hypertension. Therefore the answer is essential hypertension. **The most likely cause of hypertension in an obese is still essential hypertension.**

Ref: www.mrcpuk.org/ Acute Medicine Specialty Certificate Examination/ sample questions

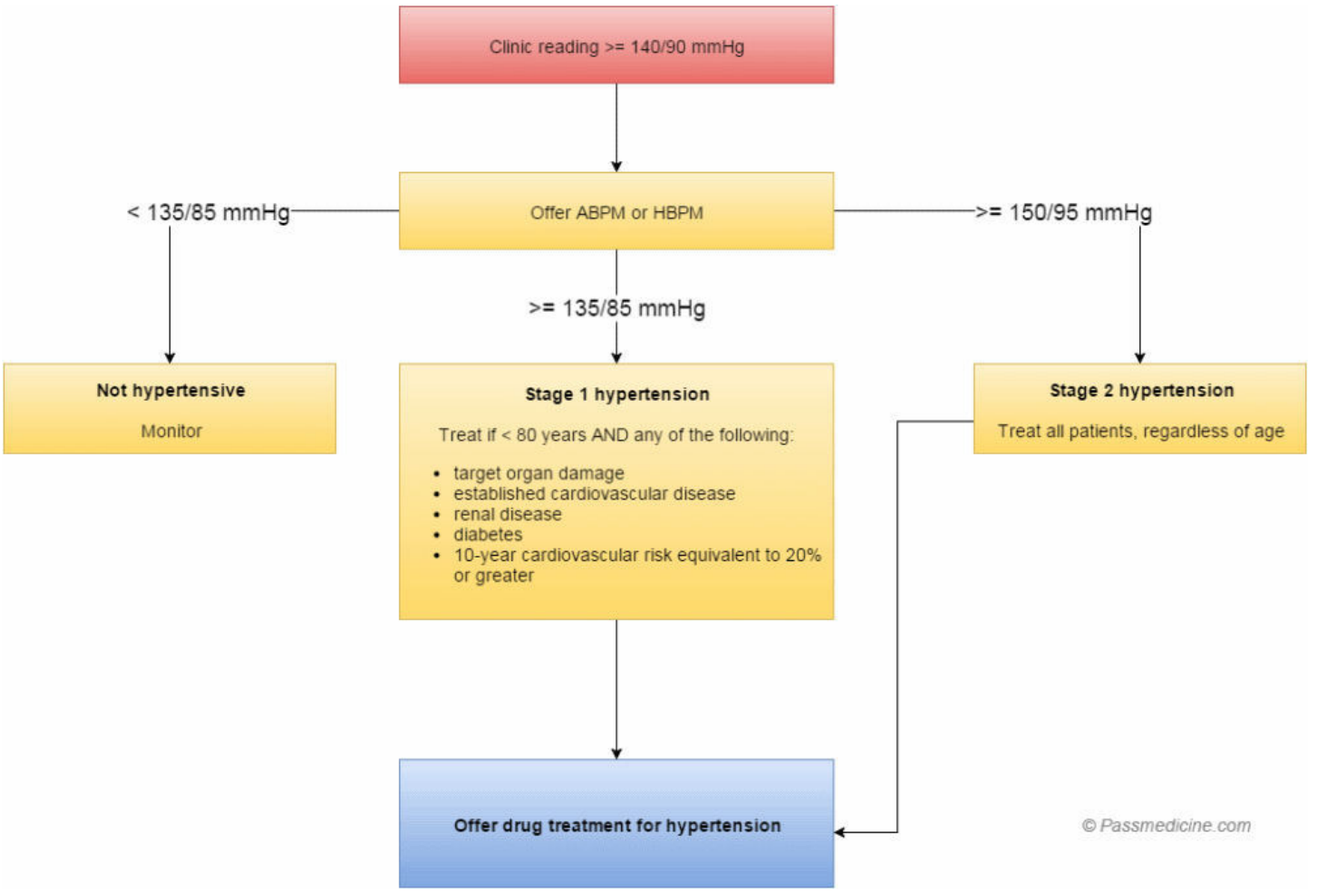
Diagnosis

Hypertension is defined as systolic blood pressure greater than the 95th centile for age.

Hypertension - NICE now recommend ambulatory blood pressure monitoring to aid diagnosis

NICE published updated guidelines for the management of hypertension in 2011. Some of the key changes include:

- classifying hypertension into stages
- recommending the use of ambulatory blood pressure monitoring (ABPM) and home blood pressure monitoring (HBPM)



Flow chart showing simplified schematic for diagnosis hypertension following NICE guidelines

The use of ambulatory blood pressure monitoring (ABPM) aims to:

- prevent diagnosing 'white coat hypertension' as having hypertension in patients whose blood pressure climbs 20 mmHg whenever they enter a clinical setting.
- ABPM has been shown to be a more accurate predictor of cardiovascular events than clinic readings.

Blood pressure classification

- This becomes relevant later in some of the management decisions that NICE advocate.

Stage	Criteria
Stage 1 hypertension	Clinic BP ≥ 140/90 mmHg and subsequent ABPM daytime average or HBPM average BP ≥ 135/85 mmHg
Stage 2 hypertension	Clinic BP ≥ 160/100 mmHg and subsequent ABPM daytime average or HBPM average BP ≥ 150/95 mmHg
Severe hypertension	Clinic systolic BP ≥ 180 mmHg, or clinic diastolic BP ≥ 110 mmHg

Diagnosing hypertension (NICE guidelines)

- Firstly, **measure BP in both arms** when considering a diagnosis of hypertension.
  - If the difference in readings between arms is **more than 20 mmHg** then the measurements should be **repeated**.

- If the difference **remains > 20 mmHg** then subsequent BP **should be recorded from the arm with the higher reading**.
- there are pathological causes of **unequal blood pressure readings from the arms**, such as:
  - supravalvular aortic stenosis.
    - listen to the heart sounds → further investigation if a very large difference is noted.

- **Take a second reading during the consultation**, if the first reading is > 140/90 mmHg.
  - The lower reading of the two should determine further management.
- Offer ABPM or HBPM to any patient with a blood pressure ≥ 140/90 mmHg.
- If the BP is ≥ 180/110 mmHg:
  - immediate treatment should be considered
  - NICE recommend same day assessment by a specialist if:
    - there are signs of papilloedema or retinal haemorrhages
    - phaeochromocytoma is suspected (labile or postural hypotension, headache, palpitations, pallor and diaphoresis)

Ambulatory blood pressure monitoring (ABPM)

- at least 2 measurements per hour during the person's usual waking hours (for example, between 08:00 and 22:00)
- use the average value of at least 14 measurements
- If ABPM is not tolerated or declined HBPM should be offered.

Home blood pressure monitoring (HBPM)

- for each BP recording, two consecutive measurements need to be taken, at least 1 minute apart and with the person seated
- BP should be recorded twice daily, ideally in the morning and evening
- BP should be recorded for at least 4 days, ideally for 7 days
- discard the measurements taken on the first day and use the average value of all the remaining measurements

Interpreting the results

- ABPM/HBPM ≥ 135/85 mmHg (i.e. stage 1 hypertension)
  - treat if < 80 years of age **AND** any of the following apply:
    - target organ damage,
    - established cardiovascular disease,
    - renal disease,
    - diabetes
    - 10-year cardiovascular risk equivalent to 20% or greater
- ABPM/HBPM ≥ 150/95 mmHg (i.e. stage 2 hypertension)
  - offer drug treatment regardless of age

Management (NICE guidelines 201)

Calcium channel blockers are now preferred to thiazides in the treatment of hypertension

Hypertension in diabetics - ACE-inhibitors are first-line regardless of age

ACE inhibitors have reduced efficacy in black patients and are therefore not used first-line

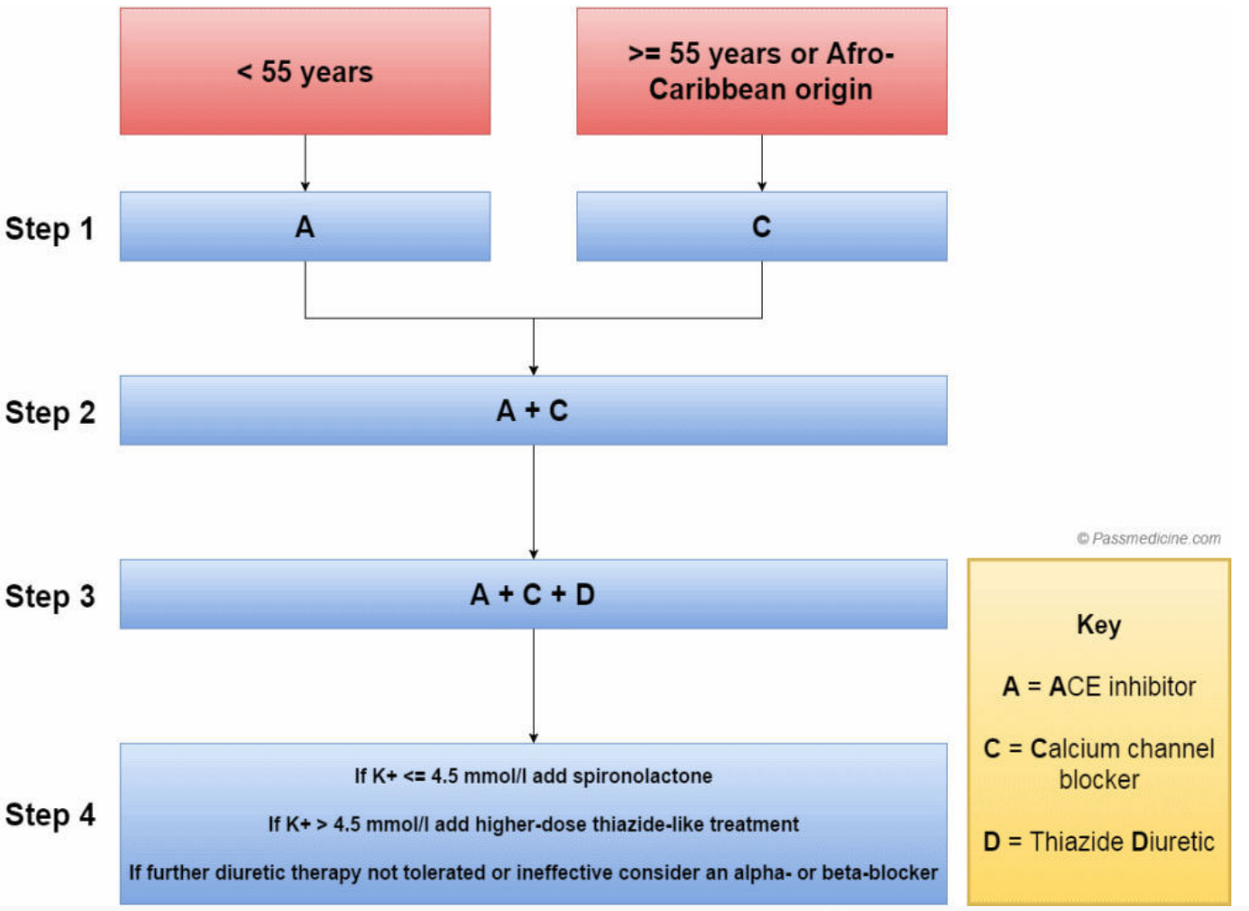
Hypertension - step 4
- K^+ < 4.5 then spironolactone
- K^+ > 4.5 then higher-dose thiazide-like diuretic

the key changes include:

- calcium channel blockers are now considered superior to thiazides
- bendroflumethiazide is no longer the thiazide of choice

Managing hypertension

- Lifestyle advice should not be forgotten and is frequently tested in exams:
  - **Of all the lifestyle modifications, weight reduction produces the greatest reduction in BP.**
    - A 10 kg weight loss is expected to decrease BP by 15–20 mmHg
  - a low salt diet is recommended,
    - aiming for less than 6g/day, ideally 3g/day.
    - The average adult in the UK consumes around 8-12g/day of salt.
    - A recent BMJ paper showed that lowering salt intake can have a significant effect on blood pressure. For example, reducing salt intake by 6g/day can lower systolic blood pressure by 10mmHg
  - caffeine intake should be reduced
  - the other general bits of advice remain: stop smoking, **drink less alcohol**, eat a balanced diet rich in fruit and vegetables, exercise more, lose weight
    - **If a patient on antihypertensive and drink alcohol → Reduction of alcohol intake is the next step in treatment.**
      - **Non-pharmacological** manoeuvres are paramount and **first line** in hypertension management
  - relaxation therapies have been shown to reduce blood pressure (**Meditation is currently advocated measures to reduce blood pressure**)
- For patients < 40 years → consider specialist referral to exclude secondary causes.



Flow chart showing the management of hypertension as per current NICE guideliness

Step 1 treatment

- patients < 55-years-old: ACE inhibitor (A)
- patients ≥ 55-years-old or of Afro-Caribbean origin: calcium channel blocker
  - If a Calcium channel blocker is not suitable, for example because of oedema or intolerance, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic.
  - **≥ 55 year old + HTN + history of MI → (ACE) inhibitor is the antihypertensive of choice**
    - ACE inhibitors and ARBs have beneficial effects on mortality after an acute MI.

Step 2 treatment
- ACE inhibitor + calcium channel blocker (A + C)

Step 3 treatment
- add a thiazide diuretic (D, i.e. A + C + D)
- NICE now advocate using either chlorthalidone (12.5-25.0 mg once daily) or indapamide (1.5 mg modified-release once daily or 2.5 mg once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide
- NICE define a clinic BP ≥ 140/90 mmHg after step 3 treatment with optimal or best tolerated doses as resistant hypertension. They suggest step 4 treatment or seeking expert advice

Step 4 treatment
- consider further diuretic treatment
  - if potassium < 4.5 mmol/l add spironolactone 25mg od
  - if potassium > 4.5 mmol/l add higher-dose thiazide-like diuretic treatment
- if further diuretic therapy is not tolerated, or is contraindicated or ineffective, consider an alpha- or beta-blocker
- Patients who fail to respond to step 4 measures should be referred to a specialist. NICE recommend: → ***seek expert advice.***

- *hypertensive with benign prostatic hyperplasia → alpha-blockers*
- *hypertensive with heart failure or angina → beta-blockers*
- *hypertensive post myocardial infarction either a beta blocker or ACE inhibitor would be the agent of choice.*

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Use of multiple anti-hypertensives at low doses is preferable to having fewer tablets at higher doses, in view of the synergistic effectiveness of targeting several mechanisms of hypertension.

Screening criteria for target end organ damage:

- Any patient with hypertension should prompt a search for markers of end organ damage and risk factors for cardiovascular disease:
  - From history-taking → (headache, epistaxis, visual disturbance)
  - Clinical examination → (fundoscopy, site and character of apex beat)
  - Investigations :
    - **Electrocardiogram screens for hypertensive left ventricular hypertrophy** (Sokolow-Lyon criteria: S1 +V5 or V6 >3.5 mV).
    - Renal function tests

Blood pressure targets

Blood pressure target (based on clinic readings) for patients < 80 years - 140/90 mmHg

	Clinic BP	ABPM / HBPM
Age < 80 years	140/90 mmHg	135/85 mmHg
Age > 80 years	150/90 mmHg	145/85 mmHg

Recommendations for BP target differ slightly among different guidelines.
- British Hypertension Society Guidelines for Hypertension Management (BHS-IV) recommend a goal BP of **less than 130/80** mmHg for patients with **diabetes**, **renal impairment** and established **cardiovascular disease**;
- while a Joint Negotiating Committee (JNC) 8 report and American College of Cardiology/American Heart Association Guidelines recommend a target **BP of less than 140/90** mmHg in **non-diabetic patients with cardiovascular disease.**

If a Patient Presents With Severe Headache and Markedly Elevated BP

- The first step is to lower the BP with an antihypertensive agent.
- The second step is to order a CT scan of the head to rule out intracranial bleeding (subarachnoid hemorrhage is in the differential diagnosis for severe headache).
- If the CT scan is negative, one may proceed to a lumbar puncture.

Hypertensive crisis

Hypertensive crisis:

- Hypertensive emergency → systolic BP ≥ 180 or diastolic BP ≥ 110 + end organ damage
- Hypertensive urgency → systolic BP ≥ 180 or diastolic BP ≥ 110 + **NO** end organ damage

- **The most common clinical presentations of hypertensive emergencies** are:
  - **cerebral infarction** (24.5%),
  - pulmonary edema (22.5%),
  - hypertensive encephalopathy (16.3%),
  - congestive heart failure (12%).
  - Other presentations include intracranial hemorrhage, aortic dissection, and eclampsia as well as acute myocardial infarction.
- (NICE) recommends **same day referral for:**
  1. **accelerated hypertension with papilloedema and/or retinal haemorrhages,** or
  2. for patients suspected of having a phaeochromocytoma (labile or postural hypotension, headache, palpitations, pallor and sweating).
- **Hypertensive emergency:**
  - **The initial target is to lower the mean arterial pressure (MAP) by no more than 25%, or reduce the diastolic blood pressure by one-third**
  - (MAP) = diastolic blood pressure + [(systolic blood pressure - diastolic blood pressure)/3]
    - Or MAP = (2x diastolic + systolic)/3
  - Even in the presence of heart failure or hypertensive encephalopathy, a controlled reduction, to a level of about 150/90 mmHg, over a period of 24-36 hours is ideal
  - In most patients, blood pressure can be brought down with bed rest and oral medication
  - Intravenous labetalol (2 mg/min to a maximum of 200 mg), intravenous glyceryl trinitrate (0.6-1.2 mg/h), intravenous sodium nitroprusside (0.3-1.0 mg/kg per min) and intramuscular hydralazine (5 or 10 mg repeated at half-hourly intervals) are all effective but require close monitoring
    - **Labetalol has both alpha- and beta-adrenoreceptor antagonistic activity and is the first choice for hypertensive crises where the aetiology is initially unclear.**

Malignant hypertension

A patient with malignant hypertension always has retinal papilledema

- The term **malignant hypertension** is usually reserved for cases where **papilloedema** is present
  - **The pathologic hallmark of malignant hypertension** is **fibrinoid necrosis of the arterioles**, which occurs systemically, but specifically in the kidneys.

Basics

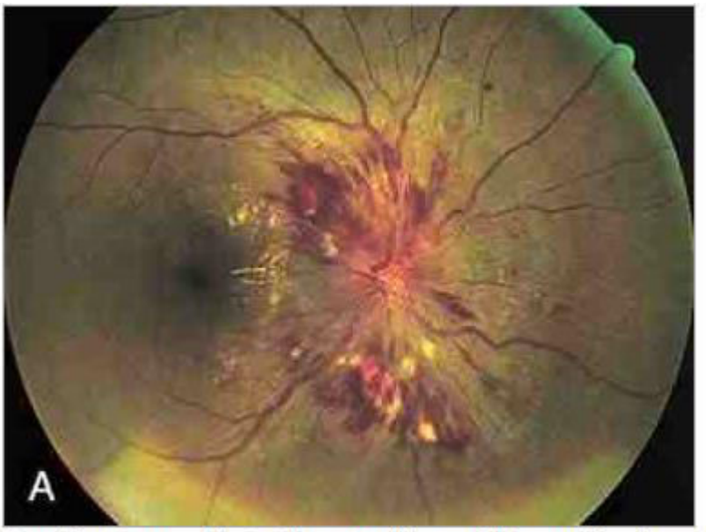
- severe hypertension (e.g. >200/130 mmHg)
- occurs in both essential and secondary types
- fibrinoid necrosis of blood vessels, leading to retinal haemorrhages, exudates, and proteinuria, haematuria due to renal damage (benign nephrosclerosis).
- can lead to cerebral oedema → encephalopathy

Features

- classically: severe headaches, nausea/vomiting, visual disturbance
- however chest pain and dyspnoea common presenting symptoms
- papilloedema
- severe: encephalopathy (e.g. seizures)

Management

- reduce diastolic no lower than 100mmHg within 12-24 hrs.
  - BP should not drop initially more than 25 per cent of presenting.
- bed rest
- most patients: oral therapy e.g. atenolol
- **if severe/encephalopathic: IV sodium nitroprusside/labetolol**
  - The major risk of any oral agent used for hypertensive emergencies is ischaemic symptoms (for example myocardial infarction, angina pectoris or stroke) due to an excessive and uncontrolled hypotensive response usually due to lowering of BP to below the autoregulatory threshold.
  - Therefore the use of oral agents should generally be avoided in the treatment of hypertensive emergencies if parenteral drugs are available.
  - Sublingual nifedipine is minimally and unpredictably absorbed. Therefore should be avoided



Papilledema. Note the swelling of the optic disc, with blurred margins

The diagnosis of **accelerated hypertension** requires the finding of fundal **haemorrhages and exudates**, **with or without papilloedema**, as manifestations of fibrinoid necrosis.

Prognosis

- These patients develop fatal complications if untreated, and more than 90% will not survive beyond 1-2 years.

Hypertension: secondary causes

- **Primary hyperaldosteronism**, including Conn's syndrome (5-10% of hypertensive patients)
  - **the single most common cause** of secondary hypertension
  - → **(↑BP + ↓ K^+ + ↑ Aldosterone)**
  - **CT or MRI of the abdomen identifies a secretory adrenal adenoma**
- **Renal diseases:** include
  - glomerulonephritis
  - pyelonephritis
  - **Reflux-associated scarring is the commonest renal disease.**
    - **This will cause abnormalities on dimercaptosuccinic acid (DMSA) scan.**
  - adult polycystic kidney disease
  - renal artery stenosis

- **Endocrine disorders** (other than primary hyperaldosteronism):
  - phaeochromocytoma
  - Cushing's syndrome
  - Liddle's syndrome → (↑BP + ↓ K^+ + ↑ Na^+)
    - hypokalaemic hypertension
    - metabolic alkalosis
    - low plasma renin and aldosterone (called pseudo-hyperaldosteronism).

  - congenital adrenal hyperplasia (11-beta hydroxylase deficiency)
  - acromegaly
- **Fibromuscular dysplasia,**
  - **a rare cause of hypertension and hypokalaemia,**
  - **more common in women.**
  - **It causes hyperreninaemic hyperaldosteronism.**
- **Liquorice ingestion**
  - causes a primary aldosterone type picture.
  - **It is caused by glycyrrhizic acid** contained in liquorice, blocking the enzyme 11b hydroxysteroid dehydrogenase. This prevents the inactivation of cortisol, which in turn activates mineralocorticoid receptors in the kidney. driving hypokalaemic metabolic alkalosis with hypertension.
- **Other causes** include:
  - NSAIDs
  - pregnancy
  - coarctation of the aorta (**the commonest non-renal cause**)
  - the combined oral contraceptive pill
  - steroids
  - MAOI

MRCPUK- part 2- March 2017 : A 28-year-old woman of Afro-Caribbean ethnic origin c/o difficult-to-manage hypertension, despite taking maximal-dose amlodipine and indapamide. The GP trialled an ACE inhibitor, but this was discontinued due to a rise in serum creatinine. Renin and aldosterone are both Elevated. K is 3.1 mmol. Which of the following is the most likely diagnosis?

➔ **Fibromuscular renal artery dysplasia**

- This patient's age and ethnicity suggest that her hypertension is related to fibromuscular dysplasia rather than to atherosclerotic renal artery stenosis.
- The renin and aldosterone elevation, coupled with hypokalaemia and deterioration in renal function on starting ACE inhibitors, are consistent with the diagnosis.

Hypokalaemia and hypertension

Liddle's syndrome: hypokalaemia + hypertension

- For exams it is useful to be able to classify the causes of hypokalaemia in to those associated with hypertension, and those which are not
- The first step in case of (↑ BP + ↓ K+) should be further simple investigations → **Plasma renin and aldosterone levels**
  - Cushing's & Conn's → high aldosterone and a low renin,
  - renal artery stenosis → high renin and aldosterone
  - Liddle's → low renin and aldosterone.

Hypokalaemia with hypertension

- Cushing's syndrome
- Conn's syndrome (primary hyperaldosteronism)
- Liddle's syndrome
  - autosomal dominant disorder that mimics hyperaldosteronism
- renal artery stenosis
- 11-beta hydroxylase deficiency*
  - *21-hydroxylase deficiency, which accounts for 90% of congenital adrenal hyperplasia cases, is not associated with hypertension
- Carbenoxolone, an anti-ulcer drug, and liquorice excess can potentially cause hypokalaemia associated with hypertension

Hypokalaemia without hypertension

- diuretics
- GI loss (e.g. Diarrhoea, vomiting)
- renal tubular acidosis (type 1 and 2**)
- Bartter's syndrome
- Gitelman syndrome

**type 4 renal tubular acidosis is associated with hyperkalaemia

Isolated systolic hypertension(ISH)

- isolated systolic hypertension (systolic greater than 160 and diastolic below 90 mmHg).
- (ISH) is common in the elderly, affecting around 50% of people older than 70 years old.
- treating ISH reduced both strokes and ischaemic heart disease.
- Evidence from studies such as Systolic Hypertension in the Elderly Program and Syst-Eur indicate that both thiazides and calcium antagonists are the drugs of choice in terms of reducing morbidity and mortality in this patient group.
- the 2011 NICE guidelines recommends treating ISH in the same stepwise fashion as standard hypertension.
- **The incontinence may be exacerbated by the diuretic therapy and a calcium antagonist may be more appropriate.**

Hypertension in pregnancy (NICE guidance 2010)

Labetalol is first-line for pregnancy-induced hypertension

- Women who are at high risk of developing pre-eclampsia should take aspirin 75mg od from 12 weeks until the birth of the baby.
- High risk groups include:
  - hypertensive disease during previous pregnancies
  - chronic kidney disease
  - autoimmune disorders such as SLE or antiphospholipid syndrome
  - type 1 or 2 diabetes mellitus
- The classification of hypertension in pregnancy is complicated and varies. Remember, in normal pregnancy:
  - blood pressure usually falls in the first trimester (particularly the diastolic), and continues to fall until 20-24 weeks
  - after this time the blood pressure usually increases to pre-pregnancy levels by term
- Hypertension in pregnancy in usually defined as:
  - systolic > 140 mmHg or diastolic > 90 mmHg
  - or an increase above booking readings of > 30 mmHg systolic or > 15 mmHg diastolic
- After establishing that the patient is hypertensive they should be categorised into one of the following groups

Pre-existing hypertension	**Pregnancy-induced hypertension (PIH, also known as gestational hypertension)**	**Pre-eclampsia**
A history of hypertension before pregnancy or an elevated blood pressure > 140/90 mmHg before 20 weeks gestation No proteinuria, no oedema Occurs in 3-5% of pregnancies and is more common in older women	Hypertension (as defined above) occurring in the second half of pregnancy (i.e. after 20 weeks) No proteinuria, no oedema Occurs in around 5-7% of pregnancies Resolves following birth (typically after one month). Women with PIH are at increased risk of future pre-eclampsia or hypertension later in life	Pregnancy-induced hypertension in association with proteinuria (> 0.3g / 24 hours) Oedema may occur but is now less commonly used as a criteria Occurs in around 5% of pregnancies

Hypertension risk factors in women

Hypertension has classically been described in a male population, though relevant risk factors have been more recently identified in women.
These include:

- Multiple previous pregnancies
- Menopause
- Hysterectomy, and
- Hormone replacement therapy.

Target blood pressure in patients with pre-existing hypertension

- **The target blood pressure in patients with pre-existing hypertension is under 150/100 mmHg,** or 140/90 mmHg in the presence of end organ failure.
- In patients with longstanding hypertension aggressive blood pressure control may compromise placental function, so diastolic blood pressure should be preserved above 80 mmHg.

Pre-eclampsia

Severe pre-eclampsia - restrict fluids

Definition

- Pre-eclampsia is a condition seen after 20 weeks gestation characterised by pregnancy-induced hypertension in association with proteinuria (> 0.3g / 24 hours).
- Oedema used to be third element of the classic triad but is now often not included in the definition as it is not specific

Pre-eclampsia is important as it **predisposes to the following problems**

- fetal: prematurity, intrauterine growth retardation
- eclampsia
- haemorrhage: placental abruption, intra-abdominal, intra-cerebral
- cardiac failure
- multi-organ failure

Risk factors

- > 40 years old
- nulliparity (or new partner)
- multiple pregnancy
- body mass index > 30 kg/m^2
- diabetes mellitus
- pregnancy interval of more than 10 years
- family history of pre-eclampsia
- previous history of pre-eclampsia
- **pre-existing vascular disease** such as **hypertension** or renal disease

There is some evidence to suggest that pre-eclampsia is actually less common in smokers

Features of severe pre-eclampsia

- hypertension: typically > 170/110 mmHg and proteinuria as above
- proteinuria: dipstick ++/+++
- headache
- visual disturbance
- papilloedema
- RUQ/epigastric pain
- hyperreflexia
- platelet count < 100 * 10^6/l, abnormal liver enzymes or HELLP syndrome

Management

- consensus guidelines recommend **treating blood pressure > 160/110** mmHg although many clinicians have a lower threshold
- **oral labetalol is now first-line** following the 2010 NICE guidelines. Nifedipine and hydralazine may also be used
- **Beta blockers may restrict foetal growth but are sometimes used.**
- delivery of the baby is the most important and definitive management step. The timing depends on the individual clinical scenario

Eclampsia

Eclampsia - give magnesium sulphate first-line

Eclampsia may be defined as the development of seizures in association pre-eclampsia. To recap, pre-eclampsia is defined as:

- condition seen after 20 weeks gestation
- pregnancy-induced hypertension
- proteinuria

Magnesium sulphate is used to both prevent seizures in patients with severe pre-eclampsia and treat seizures once they develop. Guidelines on its use suggest the following:

- should be given once a decision to deliver has been made

- in eclampsia an IV bolus of 4g over 5-10 minutes should be given followed by an infusion of 1g / hour
- urine output, reflexes, respiratory rate and oxygen saturations should be monitored during treatment
- treatment should continue for 24 hours after last seizure or delivery (around 40% of seizures occur post-partum)

Other important aspects of treating severe pre-eclampsia/eclampsia include fluid restriction to avoid the potentially serious consequences of fluid overload

Pulmonary arterial hypertension (PAH)

Definition

- sustained elevation in mean pulmonary arterial pressure of greater than 25 mmHg at rest or 30 mmHg after exercise.

Epidemiology

- more common in females,
- typically presents at 20-40 years old

Classification & causes

- PAH has recently been reclassified by the WHO:

1. Group 1: idiopathic pulmonary arterial hypertension (IPAH)
   - Idiopathic (previously termed primary pulmonary hypertension (PPH)
   - 10% are familial (autosomal dominant)
   - diagnosed when no underlying cause can be found
   - endothelin thought to play a key role in pathogenesis
2. Group 2: Pulmonary hypertension with left heart disease
   - congenital heart disease with systemic to pulmonary shunts,
   - left-sided atrial, ventricular or valvular disease such as left ventricular systolic and diastolic dysfunction, mitral stenosis and mitral regurgitation
3. Group 3: Pulmonary hypertension secondary to lung disease/hypoxia
   - COPD
   - interstitial lung disease
   - sleep apnoea
   - high altitude
4. Group 4: Pulmonary hypertension due to thromboembolic disease
5. Group 5: Miscellaneous conditions
   - lymphangiomatosis e.g. secondary to carcinomatosis or sarcoidosis
   - collagen vascular disease,
   - HIV (the mechanism by which HIV infection produces pulmonary hypertension remains unknown)
   - sickle cell disease
   - drugs and toxins,
     - cocaine and anorexigens (e.g. fenfluramine)

Pathophysiology

Increased pressure in pulmonary circuit → elevated right ventricular afterload → dilatation and/or hypertrophy of the right heart → right heart failure and arrhythmias

- Increased pulmonary vascular resistance
  - Occlusive vasculopathy
    - idiopathic pulmonary arterial hypertension (IPAH) ,
    - connective tissue diseases
    - pulmonary embolism
  - Perivascular parenchymal changes (e.g. interstitial lung disease)
  - Hypoxic pulmonary vasoconstriction (e.g., COPD)
- Increased pulmonary venous pressure

  - Volume or pressure overload from left-sided heart disease (e.g. mitral valve regurgitation)
- Increased pulmonary blood flow
  - Left-to-right shunt (e.g., Eisenmenger's syndrome)
- haemoglobinopathy-associated pulmonary hypertension
  - eg:
    - Sickle cell anemia
    - thalassemia
  - Release of hemoglobin and arginase from lysed red cells causes scavenging of nitric oxide (NO) and catabolism of L-arginine, the obligate substrate for NO synthase. The resulting impairment in NO bioavailability is associated with pulmonary vasoconstriction, endothelial dysfunction
  - The pathophysiology of PAH in haemoglobinopathies is multifactorial, but epidemiological and biochemical data support a **prominent role for intravascular hemolysis** inducing a state of vascular dysfunction.

Features

Women with pulmonary hypertension should avoid becoming pregnant due to very high mortality levels

Bosentan - endothelin-1 receptor antagonist

- Symptoms
  - exertional dyspnoea is the most frequent symptom
    - progressive SOB
  - chest pain and syncope may also occur
- On examination:
  - cyanosis
  - Nail clubbing
  - raised JVP with prominent 'a' waves,
  - left parasternal heave (due to right ventricular hypertrophy)
  - loud P2
  - tricuspid regurgitation

Investigation

- **Doppler echocardiography**
  - **the initial investigation of choice**
  - the jet associated with tricuspid regurgitation can be visualised adequately (**tricuspid regurgitant jet velocity**)
- **right heart catheterization**
  - confirmatory test
  - **the gold standard for the diagnosis**

Management

- Treatment of the underlying cause for example:
  - anticoagulants for PE
  - bronchodilators and inhalation corticosteroids for COPD,
  - CPAP for patients with obstructive sleep apnea
- **Acute vasodilator testing** is central to deciding on the appropriate management strategy.
  - Acute vasodilator testing aims to decide which patients show a significant fall in pulmonary arterial pressure following the administration of vasodilators such as intravenous epoprostenol or inhaled nitric oxide
    - **If there is a positive response → oral calcium channel blockers**
    - If there is a negative response:
      - prostacyclin analogues: treprostinil, iloprost
      - endothelin receptor antagonists: bosentan
      - phosphodiesterase inhibitors: sildenafil

- diuretics if right heart failure
- heart-lung transplant

Whilst only 10-15% of patients appear to have a pulmonary vascular tree responsive to calcium antagonism, these agents still constitute the initial therapy of choice according to guidelines, but only in those patients who show a response to vasodilator testing.

Complication

- Cor pulmonale:
  - altered structure (hypertrophy, dilation) or impaired function of the right ventricle caused by pulmonary hypertension resulting from a primary disorder of the respiratory or pulmonary artery system

Ischemic heart disease

Atherosclerosis

Atherosclerosis is a complex process which develops over a number of years. A number of changes can be seen:

- initial endothelial dysfunction is triggered by a number of factors such as smoking, hypertension and hyperglycaemia
- this results in a number of changes to the endothelium including pro-inflammatory, pro-oxidant, proliferative and reduced nitric oxide bioavailability
- fatty infiltration of the subendothelial space by low-density lipoprotein (LDL) particles
- monocytes migrate from the blood and differentiate into macrophages. These macrophages then phagocytose oxidized LDL, slowly turning into large 'foam cells'. As these macrophages die the result can further propagate the inflammatory process.
- **macrophages play a greater role in the initial development of the plaque.**
- smooth muscle proliferation and migration from the tunica media into the intima results in formation of a fibrous capsule covering the fatty plaque.

Complications of atherosclerosis

Taking the coronary arteries as an example, once a plaque has formed a number of complications can develop:

- the plaque forms a physical blockage in the lumen of the coronary artery. This may cause reduced blood flow and hence oxygen to the myocardium, particularly at times of increased demand, resulting clinically in angina
- the plaque may rupture, potentially causing a complete occlusion of the coronary artery. This may result in a myocardial infarction

January 2016 exam: Which cell type is most implicated in the development of coronary artery plaques?
Macrophages

Chest pain: assessment of patients with suspected cardiac chest pain

NICE issued guidelines in 2010 on the 'Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin'.

The NICE guideline update (2016) makes three key changes to the 2010 version.

1. clinical assessment of the likelihood of CAD, based on the typicality of the chest pain into typical, atypical or non-cardiac, instead of the previous PTP RS*.
2. zero calcium score is no longer used to rule out CAD in patients with low PTP.
3. all patients with new onset chest pain with atypical or typical anginal features, as well as those with non-cardiac chest pain and an abnormal resting ECG, should first be investigated with CTCA using a 64-slice (or above) CT scanner.
   - Functional imaging tests are now reserved for:

- ❖ the assessment of patients with chest pain symptoms who are known to have CAD and
- ❖ for patients where the CTCA has been non-diagnostic or has shown CAD of uncertain significance.

*the pre-test probability (PTP) risk score (RS), which – based on the Duke clinical score – was calculated using age, gender, typicality of chest pain and the presence of cardiovascular risk factors

What is the next investigation for a patient presenting with atypical chest pain against a background of known coronary artery disease?

- The next investigation would ideally be a low-risk procedure that can demonstrate continued patency of the previously stented coronary artery.
- Dobutamine-atropine **stress echocardiography**, thallium perfusion scanning and myocardial contrast perfusion echocardiography are all capable of localising areas of myocardial ischaemia.
- This is the ideal investigation in that it is non-invasive, providing information on myocardial ischaemia as well as functional information (dobutamine stress if needed).
- In this patient with atypical chest pain, we would ideally aim for an investigation with lower risk but with sufficient sensitivity to exclude ischaemia as a cause for his symptoms.

Angina pectoris:

Prinzmetal angina - treatment = dihydropyridine calcium channel blocker

Non-atherosclerotic angina would be associated with conditions such as

- Thyrotoxicosis
- **Aortic regurgitation**
- Aortic stenosis
- Hypertrophic cardiomyopathy
- Anaemia

Anginal pain is:

1. constricting discomfort in the front of the chest, or in the neck, shoulders, jaw, or arms
2. precipitated by physical exertion
3. relieved by rest or GTN within about 5 minutes.

- Three of the features above are defined as **typical angina.**
- Two of the three features above are defined as **atypical angina.**
- One or none of the features above are defined as **non-anginal chest pain.**

Features which make a diagnosis of stable angina unlikely are when the chest pain is:

- continuous or very prolonged **and/or**
- unrelated to activity **and/or**
- brought on by breathing in **and/or**
- associated with symptoms such as dizziness, palpitations, tingling or difficulty swallowing. Consider causes of chest pain other than angina (such as gastrointestinal or musculoskeletal pain).

Investigations

- **First-line**: 64-slice CT coronary angiography
- **Second-line**: non-invasive functional testing (if CTPA is non-diagnostic.)
  - ➢ MPS with SPECT or
  - ➢ stress echocardiography or
  - ➢ first-pass contrast-enhanced magnetic resonance perfusion or
  - ➢ MRI for stress-induced wall motion abnormalities.
- **Third-line**: invasive coronary angiography (when the results of non-invasive functional imaging are inconclusive)

In the context of risk factors for ischaemic heart disease (hypertension, hypercholesterolaemia, smoking), the clinical diagnosis should be confirmed with non-invasive functional scanning such as myocardial perfusion scanning with SPECT.

- **High-risk patients** with **classic angina symptoms** should proceed directly to coronary angiography.
- Offer 64‑slice (or above) CT coronary angiography if:
  1. clinical assessment indicates typical or atypical angina or
  2. clinical assessment indicates non-anginal chest pain but 12‑lead resting ECG has been done and indicates ST‑T changes or Q waves.
- **Low-risk patients** can be evaluated with **non-invasive stress imaging.**
- Offer non-invasive functional imaging for myocardial ischaemia if 64-slice (or above) CT coronary angiography has shown CAD of uncertain functional significance or is non-diagnostic.
  - **non-invasive functional testing for myocardial ischaemia**
    1. **myocardial perfusion scintigraphy** with single photon emission computed tomography (MPS with SPECT)
       - Use adenosine, dipyridamole or dobutamine as stress agents
    2. **stress echocardiography**
       - Use exercise or dobutamine for stress echocardiography or MR imaging for stress-induced wall motion abnormalities.
    3. first-pass contrast-enhanced magnetic resonance (MR) perfusion
       - use adenosine or dipyridamole as stress agents
    4. MR imaging for stress-induced wall motion abnormalities
  - Take account of locally available technology and any contraindications (for example, disabilities, frailty, limited ability to exercise) when deciding on the imaging method.
- Offer invasive coronary angiography as a third-line investigation when the results of non-invasive functional imaging are inconclusive.
- Treadmill exercise is no longer recommended in the work-up of new-onset chest pain.

Definition of significant coronary artery disease (CAD)

- CT coronary angiography is:
  - ≥ 70% diameter stenosis of at least one major epicardial artery segment **or**
  - ≥ 50% diameter stenosis in the left main coronary artery

Factors intensifying ischaemia

- Such factors allow less severe lesions (for example, ≥ 50%) to produce angina:
  - reduced oxygen delivery: anaemia, coronary spasm
  - increased oxygen demand: tachycardia, left ventricular hypertrophy
  - large mass of ischaemic myocardium: proximally located lesions
  - longer lesion length.

Factors reducing ischaemia which may render severe lesions (≥ 70%) asymptomatic:

- Well-developed collateral supply.
- Small mass of ischaemic myocardium: distally located lesions, old infarction in the territory of coronary supply.

ESC guidelines 2017

- A reduction in chest pain after nitroglycerin (glyceryl trinitrate) administration can be misleading and is not recommended as a diagnostic manoeuvre
- In cases of symptom relief after nitroglycerin administration, another 12-lead ECG must be obtained.
- **A complete normalization of the ST-segment elevation after nitroglycerin administration, along with complete relief of symptoms, is suggestive of coronary spasm, with or without associated MI. In these cases, an early coronary angiography (within 24 h) is recommended.**
- In cases of recurrent episodes of ST-segment elevation or chest pain, **immediate angiography** is required.

Drug management

The management of stable angina comprises lifestyle changes, medication, percutaneous coronary intervention and surgery. NICE produced guidelines in 2011 covering the management of stable angina

Medication

- all patients should receive aspirin and a statin in the absence of any contraindication
- sublingual glyceryl trinitrate to abort angina attacks
- NICE recommend using either a beta-blocker or a calicum channel blocker first-line based on 'comorbidities, contraindications and the person's preference'
- if a calcium channel blocker is used as monotherapy a rate-limiting one such as verapamil or diltiazem should be used. If used in combination with a beta-blocker then use a long-acting dihydropyridine calcium-channel blocker (e.g. modified-release nifedipine). Remember that beta-blockers should not be prescribed concurrently with verapamil (risk of complete heart block)
- if there is a poor response to initial treatment then medication should be increased to the maximum tolerated dose (e.g. for atenolol 100mg od)
- if a patient is still symptomatic after monotherapy with a beta-blocker add a calcium channel blocker and vice versa
- if a patient is on monotherapy and cannot tolerate the addition of a calcium channel blocker or a beta-blocker then consider one of the following drugs: a long-acting nitrate, ivabradine, nicorandil or ranolazine
- if a patient is taking both a beta-blocker and a calcium-channel blocker then only add a third drug whilst a patient is awaiting assessment for PCI or CABG
- The FREEDOM trial demonstrated that **in diabetic patients CABG was superior to PCI** in that it significantly reduced rates of death and myocardial infarction.

Nitrate tolerance

- many patients who take nitrates develop tolerance and experience reduced efficacy
- the BNF advises that patients who develop tolerance should take the second dose of isosorbide mononitrate after 8 hours, rather than after 12 hours. This allows blood-nitrate levels to fall for 4 hours and maintains effectiveness
- this effect is not seen in patients who take modified release isosorbide mononitrate
- **the explanation for nitrate tolerance → generation of reactive oxygen species**
  - chronic nitrate therapy → ↑vascular oxidative stress → ↑ degradation of nitric oxide (NO) → reduced bioavailability

Ivabradine

- a new class of anti-anginal drug which works by reducing the heart rate
- acts on the I_f ('funny') ion current which is highly expressed in the sinoatrial node, reducing cardiac pacemaker activity
- adverse effects: visual effects, particular luminous phenomena, are common. Bradycardia, due to the mechanism of action, may also be seen
- there is no evidence currently of superiority over existing treatments of stable angina

Ulceration of an atheromatous plaque of the abdominal aorta is the most common source of emboli in old man presented with acute pain, pallor and absent pulses in his leg.

Coronary artery bypass graft (CABG)

- There are two main approaches.
  1. In one, the left internal thoracic artery (internal mammary artery) is diverted to the left anterior descending branch of the left coronary artery.
  2. In the other, a great saphenous vein is removed from a leg; one end is attached to the aorta or one of its major branches, and the other end is attached to the obstructed artery.
- CABG is superior to PCI in multivessel coronary disease.
- indicated when coronary arteries have a 50% to 99% obstruction.
- CABG guidelines state CABG is the preferred treatment for:
  - Disease of the left main coronary artery (LMCA).
  - Disease of all three coronary arteries (LAD, LCX and RCA).
  - Diffuse disease not amenable to treatment with a PCI.
  - high-risk patients such as those with severe ventricular dysfunction (i.e. low ejection fraction), or diabetes mellitus.
- **Benefits**
  - relief of angina
  - no survival benefit with bypass surgery vs. medical therapy in stable angina
  - Bypass surgery does not prevent future myocardial infarctions.
- **Complications**

- **The incidence of acute coronary syndrome within 30 days of CABG is high, at around 17.5%.**
- Aneurysms are a rare and late complication of CABG.

Cardiac syndrome X

- consist of:
  - angina-like chest pain during exertion
  - characteristic ECG changes during exercise testing
  - normal coronary arteries on cardiac catheterisation
  - no inducible coronary artery spasm during catheterisation

Acute coronary syndrome: Prognostic factors

Poor prognostic factors

- age
- development (or history) of heart failure
- peripheral vascular disease
- reduced systolic blood pressure
- Killip class*
- initial serum creatinine concentration
- elevated initial cardiac markers
- cardiac arrest on admission
- ST segment deviation

*__Killip class__ - system used to stratify risk post myocardial infarction

Killip class	Features	30 day mortality
I	No clinical signs heart failure	6%
II	Lung crackles, S3	17%
III	Frank pulmonary oedema	38%
IV	Cardiogenic shock	81%

Clinical factors which are good indicators of ACS:

- **These include typical pain lasting at least 15 minutes, associated nausea, and sweating.**
- Response to GTN **should not** be used as indicator of ACS

ACS referral:

Refer people to hospital as an **emergency** if:

- they currently have chest pain **or**
- they are currently pain free, but had chest pain **in the last 12 hours**, and a resting 12-lead ECG is abnormal or not available.

Refer people for **urgent same-day assessment** if:

- they had chest pain in the last 12 hours, but are now pain free with a normal resting 12-lead ECG **or**
- the last episode of pain was **12–72 hours ago**.

Referral

- current chest pain or chest pain in the last 12 hours with an abnormal ECG: emergency admission
- chest pain 12-72 hours ago: refer to hospital the same-day for assessment
- chest pain > 72 hours ago: perform full assessment with ECG and troponin measurement before deciding upon further action

Myocardial infarction

DVLA advice post MI - cannot drive for 4 weeks

Inferior MI - right coronary artery lesion

- **The most specific feature, which suggests that the pain is myocardial ischaemia, is the radiation to the jaw, which is relatively specific for pain of myocardial ischaemia.**

- **The clinical classification of MI includes: (NICE 2010)**
  - **Type 1**: ischaemia due to a primary coronary event such as plaque, fissuring or dissection.
  - **Type 2**: ischaemia due to either increased oxygen demand or decreased supply, such as coronary spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension.

The diurnal variation of myocardial ischaemia

- There is a diurnal variation in presentation of myocardial ischaemia.
- **Which physiological process is responsible for this? → Vasospasm**
- The peak incidence of **STEMI** and the peak incidence of death due to ischaemic heart disease both coincide at **around 8-9 am.**
  - The early morning is associated with several physiological and haematological factors which predispose to vasospasm, infarction and death.
  - There is
    - ↑ adrenergic activity
    - ↑plasma fibrinogen levels
    - ↑ inhibition of fibrinolysis and
    - ↑ platelet adhesiveness.
- Interestingly, NSTEMIs are not associated with this degree of diurnal rhythm.
- Precipitating factors for an infarct include:
  - physical exertion
  - Rest , Sleep
  - Surgical procedure
  - Emotional stressors.

Perioperative Myocardial Infarction (PMI)

- most PMIs start within 24 to 48 hours of surgery during the greatest postoperative stress.
  - **The highest prevalence of myocardial infarction is 72 hours post operation** (onexamination).
- ST elevation occurred in <2% of postoperative ischemic events and was a rare cause of PMI. Hence, prolonged, ST-depression–type ischemia is the most common cause of PMI.
- Two distinct **mechanisms** may lead to PMI
  - **Acute Coronary Syndrome (Type 1 PMI)**
  - **Myocardial Oxygen Supply-Demand Imbalance (Type 2 PMI)** in the presence of stable coronary artery disease (CAD)
- Most common than type 1
- **Tachycardia is the most common cause of postoperative oxygen supply-demand imbalance**
- **Heart rates >80 or 90 bpm in patients with significant CAD whose preoperative resting heart rate is 50 to 60 bpm can lead to prolonged ischemia and PMI**
- **In meta-analyses, trials achieving the most effective heart rate control were associated with less PMI**

- **Prognosis**
- Early mortality after PMI ranges from 3.5% to 25% and is **higher among patients with marked troponin elevation** compared with patients with minor troponin elevation
- cardiac biomarkers (eg, troponin T improve prediction of adverse cardiac events in the immediate postoperative period after major noncardiac surgery

http://circ.ahajournals.org/content/119/22/2936 (2009)

Risk factors

The **worst** risk factor for CAD is diabetes mellitus, but the most **common** risk is hypertension.

The highest prevalence of myocardial infarction is 72 hours post operation. Patients with diabetes may not have chest pain due to autonomic dysfunction.

Features

Typical Electrocardiographic Evolution of a STEMI

EKG Abnormality	Onset	Disappearance
Hyperacute T waves (tall, peaked T waves in leads facing infarction)	Immediately	6–24 hours
ST-segment elevation	Immediately	1–6 weeks
Q waves longer than 0.04 seconds	One to several days	Years to never
T wave inversion	6–24 hours	Months to years

Myocardial infarction: management

Primary percutaneous coronary intervention is the gold-standard treatment for ST-elevation myocardial infarction

PCI: stent thrombosis - withdrawal of antiplatelets biggest risk factor

Clopidogrel inhibits ADP binding to platelet receptors

Ticagrelor has a similar mechanism of action to clopidogrel - inhibits ADP binding to platelet receptors

PCI - patients with drug-eluting stents require a longer duration of clopidogrel therapy

Management

Immediate management of suspected acute coronary syndrome (ACS)

- glyceryl trinitrate
  - Sublingual glyceryl trinitrate and intravenous morphine + metoclopramide should be given to help relieve the symptoms.
  - **ongoing pain despite the use of sublingual GTN is suggestive of continuing myocardial ischaemia/infarction → IV GTN**
- aspirin 300mg.
  - **the initial drug therapy**
  - Aspirin 300mg should be given to all patients (unless contraindicated).
  - **It is safe in the post-surgical patient with no signs of bleeding** at three days post operation.
  - A second antiplatelet is normally given, usually ticagrelor, clopidogrel or prasurgel (all are antagonists of the $P2Y_{12}$ adenosine diphosphate receptor).
  - NICE do not recommend giving other antiplatelet agents (i.e. Clopidogrel) outside of hospital
    - The dose of clopidogrel is 300 mg in ACS.
- Other treatments that may be given include bivalirudin (a direct thrombin inhibitor, usually given alongside aspirin + clopidogrel) and a form of heparin (either low-molecular weight or unfractionated).
  - Heparin in Non-STEMI (has no benefit in ST elevation MI).
- do not routinely give oxygen, only give if sats < 94%*
- *NICE suggest the following in terms of **oxygen therapy**:
  - do not routinely administer oxygen, but monitor oxygen saturation using pulse oximetry as soon as possible, ideally before hospital admission. Only offer supplemental oxygen to:
    - people with oxygen saturation (SpO2) of less than 94% who are not at risk of hypercapnic respiratory failure, aiming for SpO2 of 94-98%
    - people with chronic obstructive pulmonary disease who are at risk of hypercapnic respiratory failure, to achieve a target SpO2 of 88-92% until blood gas analysis is available.
  - ESC guidelines 2017 state that : routine oxygen is not recommended when **SaO_2** is ≥ 90%.
- perform an ECG as soon as possible but do not delay transfer to hospital. A normal ECG does not exclude ACS
- percutaneous coronary intervention (PCI)
  - is the first-line and **the gold-standard treatment** management to revascularise the myocardium.
  - but is not available in all centres. Thrombolysis should be performed in patients without access to primary PCI
  - offer primary PCI to patients who present within 12 hours of onset of symptoms, if it can be delivered within 120 minutes of the time when fibrinolysis could have been given.
    - A practical example may be a patient who presents with a STEMI to a small district general hospital (DGH) which does not have facilities for PCI. If they cannot be transferred to a larger hospital for PCI within 120 minutes then fibrinolysis should be given. If the patient's ECG taken 90 minutes after fibrinolysis failed to show resolution of the ST elevation then they would then require transfer for PCI.

Percutaneous coronary intervention (PCI)

- (PCI) is a technique used to restore myocardial perfusion in patients with ischaemic heart disease, both in patients with stable angina and acute coronary syndromes.
- Stents are implanted in around 95% of patients - it is now rare for just balloon angioplasty to be performed
- Following stent insertion migration and proliferation of smooth muscle cells and fibroblasts occur to the treated segment. The stent struts eventually become covered by endothelium. Until this happens there is an increased risk of platelet aggregation leading to thrombosis.
- Following insertion the most important factor in preventing stent thrombosis is antiplatelet therapy. Aspirin should be continued indefinitely. The length of clopidogrel treatment depends on the type of stent, reason for insertion and consultant preference
- **How long should he continue dual antiplatelet therapy following stent insertion?**
  - **12 months**

- When dual therapy is maintained for less than 12 months, early cessation of clopidogrel is associated with an increased risk of further ischaemic events.
- Thrombosis of a drug-eluting stent is associated with high morbidity (42%) and mortality (71%). For this reason, dual antiplatelet therapy (usually aspirin and clopidogrel) is continued for at least twelve months following the insertion of this type of stent.

- **elective surgery should be postponed for twelve months when it is considered safe to stop clopidogrel and continue with aspirin.**

Complications: Two main complications may occur

1. **Stent thrombosis**:
   - due to platelet aggregation as above.
   - Occurs in 1-2% of patients, most commonly in the first month.
   - Usually presents with acute myocardial infarction
   - Treated by **primary angioplasty.**
2. **Restenosis**:
   - due to excessive tissue proliferation around stent.
   - Occurs in around 5-20% of patients, most commonly in the first 3-6 months.
   - Usually presents with the recurrence of angina symptoms.
   - Risk factors include diabetes, renal impairment and stents in venous bypass grafts
     - **In patients with type-2 diabetes, uncoated coronary stents are liable to re-stenosis at a rate of 40–50% by the end of a 6-month**
   - Drug eluting stents have been shown to reduce the relative risk of re-stenosis by around 80%, but only where dual anti-platelet therapy with clopidogrel and aspirin is continued for at least 1 year.

Types of stent

- bare-metal stent (BMS)
- drug-eluting stents (DES): stent coated with paclitaxel or rapamycin which inhibit local tissue growth. Whilst this reduces restenosis rates the stent thrombosis rates are increased as the process of stent endothelisation is slowed

Thrombolysis

Thrombolysis is no longer indicated except in the context of **STEMI** where **PCI** is not available within 90 minutes of first medical contact.

- **ECG criteria for thrombolysis** within 24 hours of typical pain include:
  - ST elevation of more than 1 mm in in two adjacent limb leads.
  - ST elevation more than 2 mm in in two adjacent anterior chest leads.
  - new left bundle branch block.
- **Pre-hospital thrombolysis** is indicated if the time from the initial call to arrival at hospital is likely to be over 30 minutes.
  - When primary percutaneous coronary intervention cannot be provided within 120 minutes of ECG diagnosis, patients with **STEMI** should receive immediate (pre-hospital or admission) thrombolytic therapy
  - (NICE) recommends using **intravenous bolus** (**reteplase** or **tenecteplase**) rather than an infusion for pre-hospital thrombolysis
- **Thrombolics**
  - **tissue plasminogen activator (tPA)** has been shown to offer clear mortality benefits over streptokinase
  - **streptokinase**
    - **mechanism of action →Combining with plasminogen to form a complex**
    - Streptokinase forms a 1:1 complex with plasminogen that induces structural changes in the protein that activates it without direct cleavage of the Arg-Val bond. it is not specific for fibrin-bound plasminogen.
  - **alteplase**
    - Unlike streptokinase, alteplase activates plasminogen bound to fibrin without activating unbound plasminogen proteins.
    - it is not associated with hypotension or allergic reactions like streptokinase.
    - It has a much shorter half-life of only 3-4 minutes compared to 18 minutes for streptokinase.
  - **tenecteplase**
    - easier to administer

    - has been shown to have non-inferior efficacy to alteplase with a similar adverse effect profile
- ECG should be performed 90 minutes following thrombolysis to assess whether there has been a greater than 50% resolution in the ST elevation
    - if there has not been adequate resolution then rescue **PCI** is superior to repeat thrombolysis
    - for patients successfully treated with thrombolysis PCI has been shown to be beneficial. The optimal timing of this is still under investigation
- **Contraindications to thrombolysis** include:
    - Gastrointestinal (GI) bleeding in the preceding three weeks.
    - Heavy vaginal bleeding
    - Recent stroke or surgery (Ischaemic stroke in last six months)
    - Uncontrolled severe hypertension
    - **Previous history of hemorrhagic stroke**
    - Prolonged cardiopulmonary resuscitation (CPR) (more than half an hour).
    - Known or suspected aortic dissection
    - Known bleeding disorder
    - Major surgery or serious trauma within two weeks.
    - Lumbar puncture in the preceding week.

- **Relative contraindications**
    - Proliferative diabetic retinopathy,
    - allergy and
    - oral anticoagulants
- **Risk factors for bleeding**
    - Advancing age
    - Renal impairment
    - **Low body weight** and
    - Known bleeding problems.

Management of hyperglycaemia in acute coronary syndromes

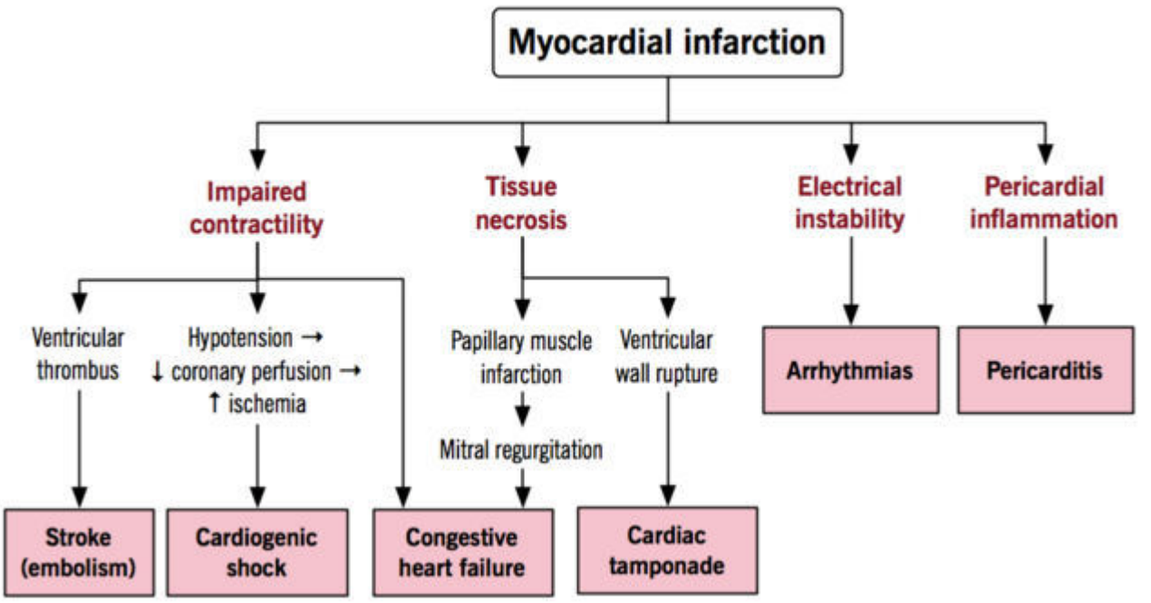
- **the most appropriate treatment for his glycaemic control → Commence intravenous insulin infusion and stop metformin**
    - metformin → increased risk of lactic acidosis.
- Nice in 2011 recommends using a dose-adjusted **insulin infusion** with regular monitoring of blood glucose levels to glucose below 11.0 mmol/l
- The Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction **(DIGAMI) study** demonstrated **significant reductions in mortality** in subjects with diabetes and myocardial infarction (MI) treated with IV insulin infusion (followed by three months of sc insulin) compared with conventional therapy with their oral hypoglycaemic agents.
    - intensive insulin therapy (an intravenous infusion of insulin and glucose with or without potassium, sometimes referred to as **'DIGAMI') regimes are not recommended routinely**

Myocardial infarction: complications

Complete heart block following a MI? - right coronary artery lesion

Complete heart block following an inferior MI is NOT an indication for pacing, unlike with an anterior MI

Complications of myocardial infarction



Patients are at risk of a number of immediate, early and late complications following a myocardial infarction (MI).

Cardiac arrest

- most commonly occurs due to ventricular fibrillation
- The most common cause of death following a MI.
- Patients are managed as per the ALS protocol with defibrillation.

Cardiogenic shock

- Infarction of a large part of the ventricular myocardium →↓↓ejection fraction →cardiogenic shock.
- Other causes of cardiogenic shock include the 'mechanical' complications such as left ventricular free wall rupture.
- **cardiac index would be below 2 l/min/m^2.**
  - Cardiac index relates cardiac output to body surface area and is calculated by CO/BSA.
  - Normal range is approximately 2.5-4.0 l/min/m^2.
- Management: inotropic support with an agent such as dobutamine, and ideally mechanical support with the insertion of an intra-aortic balloon pump (IABP).
- Patients may require inotropic support and/or an intra-aortic balloon pump.
  - **in case with hypotension and shock, the most appropriate intervention → Intra-aortic balloon counter pulsation (IABCP)** to support cardiac output.
    - An intra-aortic balloon pump is inserted under echocardiographic guidance. **At which point of the ECG should balloon inflation be timed?**
      - **Middle of the T wave**
        - Balloon inflation is timed with diastole once closure of the aortic valve has occurred; this corresponds to the middle of the T wave.
    - For blood to be ejected antegrade to perfuse the tissues and retrograde to perfuse the coronaries, the aortic valve must be closed and competent.
    - Aortic regurgitation is therefore a contraindication to placement of an intra-aortic balloon pump.
    - Inotropes such as adrenaline and noradrenaline can significantly increase myocardial ischaemia, as such they would only be adjunctive support after IABCP.

Chronic heart failure

- As described above, if the patient survives the acute phase their ventricular myocardium may be dysfunctional resulting in chronic heart failure.
- **The most important factor predicting outcomes post-STEMI is the presence of new systolic heart failure.**
- Loop diuretics such as furosemide will decrease fluid overload.
- Both ACE-inhibitors and beta-blockers have been shown to improve the long-term prognosis of patients with chronic heart failure.

Tachyarrhythmias

- **Ventricular fibrillation,** as mentioned above**, is the most common cause of death following a MI**. Other common arrhythmias including ventricular tachycardia.

Bradyarrhythmias

- Atrioventricular block is more common following inferior myocardial infarctions.
- Heart block post anterior MI is most likely to occur **within the first few days post MI** rather than months.
- **pacing wire induced RV perforation.**
  - **The time course in this situation is vital, as this often occurs through an infarcted RV wall which is more friable and thin walled.**

Pericarditis

- Pericarditis in the first 48 hours following a transmural MI is common (c. 10% of patients).
- The pain is typical for pericarditis (worse on lying flat etc), a pericardial rub may be heard and a pericardial effusion may be demonstrated with an echocardiogram.
- **Dressler's syndrome**
  - tends to occur around 1-6 weeks following a MI.
  - The underlying pathophysiology is thought to be an autoimmune reaction against antigenic proteins formed as the myocardium recovers.
  - It is characterised by a combination of fever, pleuritic pain, pericardial effusion, friction rub on auscultation and a raised ESR.
  - **the most appropriate way to treat this patient → Aspirin 650 mg QDS**
    - Other NSAIDs such as indomethacin if aspirin isn't tolerated.
  - corticosteroids are used in resistant cases, particularly those where pericardiocentesis has been required for drainage of pericardial effusion
    - in rare cases up to 1500 ml of fluid is recognised to accumulate in the pericardial sac.

Left ventricular aneurysm

- The ischaemic damage sustained may weaken the myocardium resulting in aneurysm formation.
- This is typically associated with **persistent ST elevation** and left ventricular failure.
- Thrombus may form within the aneurysm increasing the risk of stroke. Patients are therefore anticoagulated.
- **the most appropriate initial course of action → Observe in the coronary care unit → proceeding to echo to confirm the diagnosis.**

Left ventricular free wall rupture

- This is seen in around 3% of MIs
- and occurs around 1-2 weeks afterwards.
- Patients present with acute heart failure secondary to cardiac tamponade (raised JVP, pulsus paradoxus, diminished heart sounds).
- Urgent pericardiocentesis and thoracotomy are required.

Ventricular septal defect

- Rupture of the interventricular septum usually occurs in the first week and is seen in around 1-2% of patients.
- Features: acute heart failure associated with a pan-systolic murmur.
- An echocardiogram is diagnostic and will exclude acute mitral regurgitation which presents in a similar fashion.
- Urgent surgical correction is needed.

Acute mitral regurgitation

- More common with infero-posterior infarction and may be due to ischaemia or **rupture of the papillary muscle.**
- Papillary muscle rupture is rarer, with a reported incidence of <1%.
- The **posteromedial papillary muscle** is twice as likely to rupture as is the anterolateral papillary muscle.
  - This is because the anterolateral papillary muscle is more often supplied by two arterial systems (left anterior descending and left circumflex coronary arteries), whereas the **posteromedial papillary muscle** is frequently supplied by only one coronary artery (usually the right) system.

- Papillary muscle rupture leading to mitral regurgitation (MR) typically occurs 1-14 days after a myocardial infarction.
- Severe acute MR can cause abrupt haemodynamic compromise and cardiogenic shock with associated high mortality.

- suddenly develops pulmonary oedema and a loud systolic murmur at the apex which radiated into the axilla with associated pulmonary oedema..
  - early-to-mid systolic murmur is typically heard.
- **Right heart studies (Right heart catheterisation and oximetry) would provide information on left atrium (LA) pressures and suggestive information on MV prolapse.**
- Patients are treated with vasodilator therapy but often require emergency surgical repair.

Primary prevention

drugs which have evidence for the reduction of risk of developing a cardiac event ?

- Angiotensin converting enzyme inhibitor
  - **The most appropriate treatment to reduce cardiovascular risk should focus on adequate blood pressure control**
  - **↓ BP is most important than control of DM and lipids in CV risk reduction**
- Aspirin
- Metformin
  - treatment of overweight, diabetic patients with metformin, lowers the relative risk of (MI) by 40%, as opposed to treatment with sulphonylureas or insulin.
- Statins

Myocardial infarction: secondary prevention

Patients with established CVD should take atorvastatin 80mg on

Flash pulmonary oedema, U&Es worse on ACE inhibitor, asymmetrical kidneys → renal artery stenosis - do MR angiography

NICE produced guidelines on the management of patients following a myocardial infarction (MI) in 2013. Some key points are listed below

All patients should be offered the following drugs:

- dual antiplatelet therapy (aspirin plus a second antiplatelet agent)
- ACE inhibitor
- beta-blocker
- statin

Some selected lifestyle points:

- diet: advise a Mediterranean style diet, switch butter and cheese for plant oil based products. Do not recommend omega-3 supplements or eating oily fish
- exercise: advise 20-30 mins a day until patients are 'slightly breathless'
- sexual activity may resume 4 weeks after an uncomplicated MI. Reassure patients that sex does not increase their likelihood of a further MI. PDE5 inhibitors (e.g, sildenafil) may be used 6 months after a MI. They should however be avoided in patient prescribed either nitrates or nicorandil

Clopidogrel

- since clopidogrel came off patent it is now much more widely used post-MI
- STEMI: the European Society of Cardiology recommend dual antiplatelets for 12 months. In the UK this means aspirin + clopidogrel
- non-ST segment elevation myocardial infarction (NSTEMI): following the NICE *2013 Secondary prevention in primary and secondary care for patients following a myocardial infarction* guidelines clopidogrel should be given for the first 12 months

Aldosterone antagonists

- patients who have had an acute MI and who have symptoms and/or signs of heart failure and left ventricular systolic dysfunction, treatment with an aldosterone antagonist licensed for post-MI treatment (e.g. eplerenone) should be initiated within 3-14 days of the MI, preferably after ACE inhibitor therapy

Hyperlipidaemia: management

See endocrinology

Heart failure

Heart failure

Types

- **Systolic dysfunction**:
  - heart failure with reduced stroke volume and ejection fraction
  - the most common form of HF overall
  - Causes:
    - Decreased contractility (ischemia, MI, chronic mitral regurg),
    - Increased afterload (aortic stenosis, hypertensive crisis)
- **Diastolic dysfunction**:
  - heart failure with reduced stroke volume and **preserved ejection fraction**
  - Causes:
    - Chronic hypertension,
    - hypertrophic cardiomyopathy,
    - aortic stenosis,
    - coronary disease

Heart failure: NYHA classification

- The **New York Heart Association (NYHA)** classification is widely used to classify the severity of heart failure:
  - **NYHA Class I**
    - no symptoms
    - no limitation: ordinary physical exercise does not cause undue fatigue, dyspnoea or palpitations
  - **NYHA Class II**
    - mild symptoms
    - slight limitation of physical activity: comfortable at rest but **ordinary activity results in fatigue, palpitations or dyspnoea**
  - **NYHA Class III**
    - moderate symptoms
    - marked limitation of physical activity: comfortable at rest but **less than ordinary activity results in symptoms**
  - **NYHA Class IV**
    - severe symptoms
    - unable to carry out any physical activity without discomfort: **symptoms of heart failure are present even at rest with** increased discomfort with any physical activity

Heart failure: diagnosis (NICE 2010)

- The choice of investigation is determined by whether the patient has previously had a myocardial infarction or not.
  - **Previous myocardial infarction**
    - **arrange echocardiogram within 2 weeks**
      - if transthoracic doppler 2D echocardiography imaging is poor (eg: in obese) →consider other imaging methods, such as:
        - ⇨ **radionuclide angiography,**
        - ⇨ cardiac magnetic resonance imaging or
        - ⇨ transoesophageal Doppler 2D echocardiography.

- **No previous myocardial infarction**
  - measure serum natriuretic peptides (BNP)
    - if levels are '**high**' (> 400) arrange echocardiogram within 2 weeks
    - if levels are '**raised**' (100-400) arrange echocardiogram within 6 weeks
      - ⇨ 40% of patients with raised BNP will have left ventricular systolic dysfunction on echo. the remaining will have other cardiac abnormalities.
    - if levels are '**normal**' (< 100) hear failure is unlikely (investigate for other causes)

B-type natriuretic peptide (BNP)

- Source
  - produced mainly by the left ventricular myocardium in response to strain.
- Effect
  - The net effect of these peptides is:
    - ↓**BP** (due to the decrease in systemic vascular resistance) and, thus, afterload on the heart.
    - ↓cardiac output (due to an overall decrease in central venous pressure) and preload as a result of the reduction in blood volume that follows natriuresis and diuresis.
- Uses
  - normal level rules out acute heart failure in the emergency setting
  - Very high levels are associated with a poor prognosis.
- Excretion
  - Less than 5% of BNP is cleared renally whereas NT-proBNP is reliant solely on the kidney for excretion and hence it is unreliable in patients with coexistent renal dysfunction.

	BNP	**NTproBNP**
High levels	> 400 pg/ml (116 pmol/litre)	> 2000 pg/ml (236 pmol/litre)
Raised levels	100-400 pg/ml (29-116 pmol/litre)	400-2000 pg/ml (47-236 pmol/litre)
Normal levels	< 100 pg/ml (29 pmol/litre)	< 400 pg/ml (47 pmol/litre)

Diagnosis of acute heart failure (Nice guidelines 2014):

- **In people presenting with new suspected acute heart failure:**
  - rule out the diagnosis of heart failure if :
    - BNP less than 100 ng/litre
    - NT‑proBNP less than 300 ng/litre.
  - new suspected acute heart failure **with** raised natriuretic peptide levels → perform transthoracic Doppler 2D echocardiography (within 48 hours of admission)

Factors, which alter the BNP level:

Increase BNP levels	**Decrease BNP levels**
• Left ventricular hypertrophy • Aortic stenosis, • Hypertension • Ischaemia • Tachycardia • Right ventricular overload • Hypoxaemia (including pulmonary embolism) • GFR < 60 ml/min • Sepsis • COPD, Cor pulmonale	• Obesity • Diuretics • ACE inhibitors • Beta-blockers • Angiotensin 2 receptor blockers • Aldosterone antagonists

Increase BNP levels	Decrease BNP levels
• Diabetes • Age > 70 • Liver cirrhosis • Hyperaldosteronism • Cushing's syndrome • Stable angina, Acute coronary syndromes • Atrial fibrillation (AF)	

Mechanism of central sleep apnea (CSA) in HF:

- **Which mechanism is responsible for the patient's polysomnography findings in heart failure?**
  - **Increased sensitivity to carbon dioxide** and stimulation of the vagal receptors.
  - increased sensitivity to $PaCO_2$ is a protective mechanism from hypercapnia due to heart failure.
    - HF → ↑duration of circulation of blood gases from the lungs to the brain.
    - When these blood gases reach the brain, the increased sensitivity to $PaCO_2$ → higher-than-normal response of hyperventilation → ↓$PaCO_2$ lower than the apneic threshold.
    - As soon as the brain detects low $PaCO_2$ it will cease ventilation with apnea (central) so $PaCO_2$ can rise again.
    - As soon as the $PaCO_2$ rises again and reaches the brain (longer than normal due to heart failure), it will cause another episode of hyperventilation.
  - supine position → ↑ venous return → pulmonary congestion → **activate vagal receptors** → hyperventilation.

Hyponatraemia in patients with CHF

- **Water restriction is the first-line and mainstay of therapy**
- Stopping furosemide will not be possible for a patient who has decompensated heart failure.
- Similarly, administration of hypertonic saline is only indicated if there is neurological manifestation of hyponatremia.
- Moreover hypertonic or isotonic saline administration will be poorly tolerated in a volume-overloaded patient.
- **associated with the worst prognosis**

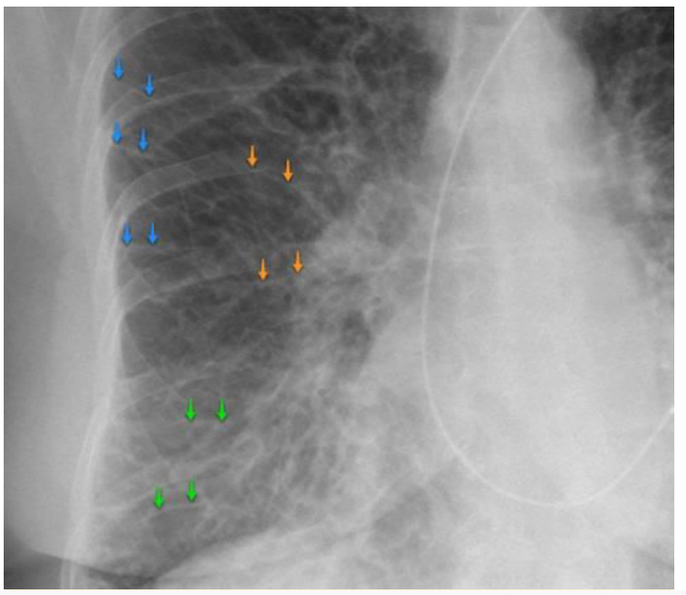
Prognostic markers → worse prognosis in heart failure include

- High BNP/NT-pro-BNP
- Anaemia
- **Hyponatraemia**
- Increased uric acid.

Chest x-ray: pulmonary oedema

Features of pulmonary oedema on a chest x-ray may include:

- interstitial oedema
- bat's wing appearance
- upper lobe diversion (increased blood flow to the superior parts of the lung)
- Kerley B lines
- pleural effusion
- cardiomegaly may be seen if there is cardiogenic cause



Kerley A lines (orange arrows), Kerley B lines (blue arrows) and Kerley C lines (green arrows) are all seen, and all represent essentially the same thing; expansion of the interstitial space by fluid.

The most common cause of flash pulmonary oedema is myocardial ischaemia.
Bilateral renal artery stenosis is a less common cause of flash pulmonary oedema.

Heart failure: drug management

Acute heart failure management (Nice guidelines 2014):

- **Initial pharmacological treatment**
  - intravenous diuretics
  - Do not routinely offer opiates
    - Morphine is an ungraded recommendation and is not actually included on guidelines as a drug to use in decompensated heart failure, though it is sometimes prescribed as a means of reducing anxiety and so the work of breathing.
  - Do not routinely offer nitrates
  - Do not offer sodium nitroprusside
  - Do not routinely offer inotropes or vasopressors
    - Consider inotropes or vasopressors in people with acute heart failure with potentially reversible cardiogenic shock.
- **Initial non-pharmacological treatment**
  - **cardiogenic pulmonary oedema with severe dyspnoea and acidaemia consider starting non-invasive ventilation**
    - in this case it is the most useful next step , before diuretics . The effect of the diuresis comes much later and has a modest overall contribution in managing the symptoms of shortness of breath.
  - Consider invasive ventilation in acute heart failure that, despite treatment, is leading to or is complicated by: respiratory failure or reduced consciousness or physical exhaustion.

In a person presenting with acute heart failure who is already taking beta-blockers:

- continue the beta-blocker treatment unless they have a heart rate less than 50 beats per minute, second or third degree atrioventricular block, or shock.
- restart beta-blockers once their condition has been stabilised – for example, when intravenous diuretics are no longer needed.

In a person presenting with acute heart failure who is already taking frusemide 80 mg:

- in a patient with evidence of decompensated heart failure and fluid overload. The most appropriate initial management is to **Increase furosemide** and relieve the symptoms of fluid overload – pulmonary and peripheral oedema.

Chronic management

- **4 drugs have been shown to improve mortality in patients with chronic heart failure:**
  1. ACE inhibitors
  2. spironolactone

3. beta-blockers
4. hydralazine with nitrates

- No long-term reduction in mortality has been demonstrated for loop diuretics such as furosemide.
- In patients with symptoms of heart failure not controlled on ACE inhibitors alone, switching to the combination of ARB and neprilysin inhibitor can further improve symptoms and quality of life.
  - e.g: **combination of sacubitril and valsartan reduced cardiovascular death and heart failure hospitalisations by 20%.**
- NICE issued updated guidelines on management in 2010, **key points** include:
  - first-line treatment for all patients is both an ACE-inhibitor and a beta-blocker
    - With the persisting symptoms despite 80 mg of furosemide, guidelines would **initially suggest the addition of an ACE inhibitor.**
    - **Although beta-blockers would be of further benefit in this patient, it is important first to establish him on ACEi and then introduce beta-blockers like carvedilol, metoprolol or bisoprolol in a small dose and gradually increase.**
  - second-line treatment is now either an aldosterone antagonist, angiotensin II receptor blocker or a hydralazine in combination with a nitrate
  - if symptoms persist cardiac resynchronisation therapy or digoxin should be considered
    - digoxin has also not been proven to reduce mortality in patients with heart failure.
    - It may however improve symptoms due to its inotropic properties.
    - Digoxin is strongly indicated if there is coexistent atrial fibrillation
    - There is no evidence that increasing a dose of digoxin above 62.5 µg in a patient in sinus rhythm would have any added benefit.
  - diuretics should be given for fluid overload
  - offer annual influenza vaccine
  - offer one-off pneumococcal vaccine
    - adults usually require just one dose but those with asplenia, splenic dysfunction or chronic kidney disease need a booster every 5 years

indications of anticoagulation in patients with heart failure
Anticoagulation should be considered for patients with heart failure and a low ejection fraction, particularly in those who have any of the following:

- A previous thromboembolic event
- Intracardiac thrombus
- Left ventricular aneurysm

In a patient with significant **heart failure on maximum medical therapy** (ramipril 10 mg OD, furosemide 80 mg OD, bisoprolol 10 mg OD and spironolactone 25 mg OD). Despite this, they have continued to deteriorate but **criteria for cardiac resynchronisation therapy (CRT) are not achieved**. **What is the most appropriate next step to improve mortality?**

➔ **Ivabradine**

- acts as an inhibitor of the I_f current within the myocardium. This current, particularly present in the sino-atrial and atrio-ventricular nodes, acts as the cardiac pacemaker.
- By inhibiting this current, ivabradine reduces the heart rate without impacting the force of cardiac contraction.
- This has been shown to reduce heart failure hospitalisation and mortality in patients already on maximum medical therapy.
- Due to its mechanism, ivabradine is only effective in patients in sinus rhythm.

What is the management of a patient with severe CHF who develops gynecomastia? Switch spironolactone to eplerenone.

If known case of heart failure – on β-blocker – presented with acute pulmonary oedema → Increase diuretics, **stop β-blockers and restart β-blockers when his lungs are dry**

A significant benefit from using IV iron in patients with heart failure and iron deficiency was demonstrated in a study
history of heart failure + iron deficiency. the first step → correcting iron deficiency

Heart failure: non-drug management

Cardiac resynchronisation therapy (CRT) (biventricular pacing)

- **criteria for resynchronisation therapy recommended by NICE guidance**
  1. They are in sinus rhythm +
     - either with a QRS duration of ≥ 150 ms estimated by ECG (LBBB)
     - or with a QRS duration of 120-149 ms estimated by ECG and mechanical dyssynchrony that is confirmed by echocardiography.
  2. They have a left ventricular ejection fraction of ≤ 35%.
  3. They are receiving optimal pharmacological therapy.
     - The echo will show asynchronous contraction of the LV and RV and subsequently reduced ejection fraction.
- improved symptoms and reduced hospitalisation in NYHA class III patients
- **Nice guidelines state that patients who are asymptomatic (NYHA class 1) with a LBBB and QRS of more 150 ms should be considered for a CRT.**
- **the most useful investigation in predicting symptomatic response to cardiac resynchronisation therapy is → transthoracic echocardiogram and ECG**
- When a CRT device is implanted the left ventricular lead is inserted in the coronary sinus. To obtain access to the coronary sinus a catheter with an aggressive tip is used. **There is a 1% risk of causing dissection/perforation to the coronary sinus which can lead to cardiac tamponade.**

Implantable cardioverter defibrillator (ICD)

- **Where there is no LBBB and QRS is between 120-149 ms, ICD is the recommended option according to NICE guidelines. This is because of the risk of VT on account of the low ejection fraction, (<35%), and symptomatic heart failure.**

Exercise training

- improves symptoms but not hospitalisation/mortality

Tocolysis-associated pulmonary oedema

- Tocolytics are medications administered for the suppression of premature contractions.
- **Acute pulmonary oedema can occur with administration of β_2 agonists for tocolysis in up to 5–15% of cases.**
- It usually occurs after 24 h of administration of these agents.
- The chest X-ray reveals pulmonary infiltrates and **normal heart size**.
- Concomitant use of corticosteroids that are often administered for lung maturation have also been implicated as risk factor for development of tocolysis-associated pulmonary oedema.
- Treatment involves stopping the tocolytics, oxygen and careful volume control.
- Deferential:
  - Peripartum cardiomyopathy:
    - typically presents in the last month of pregnancy and up-to 6 months postpartum.
    - cardiomegaly on chest X-ray.

Cardiac transplantation

- By five years following cardiac transplantation, **nearly all patients have some degree of small coronary vascular narrowing (Coronary arteriopathy).**

Cardiomyopathies

Hypertrophic obstructive cardiomyopathy (HOCM)

HOCM is the most common cause of sudden cardiac death in the young

- (HOCM) is an autosomal dominant disorder of muscle tissue caused by defects in the genes encoding contractile proteins.

- The most common defects involve a mutation in the gene encoding **β-myosin heavy chain** protein or myosin binding protein C.
- Mutations to various proteins including beta-myosin, alpha-tropomyosin and troponin T have been identified.
- **type of mutation → Frame-shift mutation**
- The estimated prevalence is 1 in 500.
- Septal hypertrophy causes left ventricular outflow obstruction.
- It is an important cause of sudden death in apparently healthy individuals.

Protein	Percentage
Beta-myosin heavy chain	35
Myosin-binding protein C	15
Troponin T	15
Alpha-tropomyosin	1
Myosin light chain	1

Mutations known to cause hypertrophic cardiomyopathy.

Features

Sudden death, unusual collapse in young person - ? HOCM

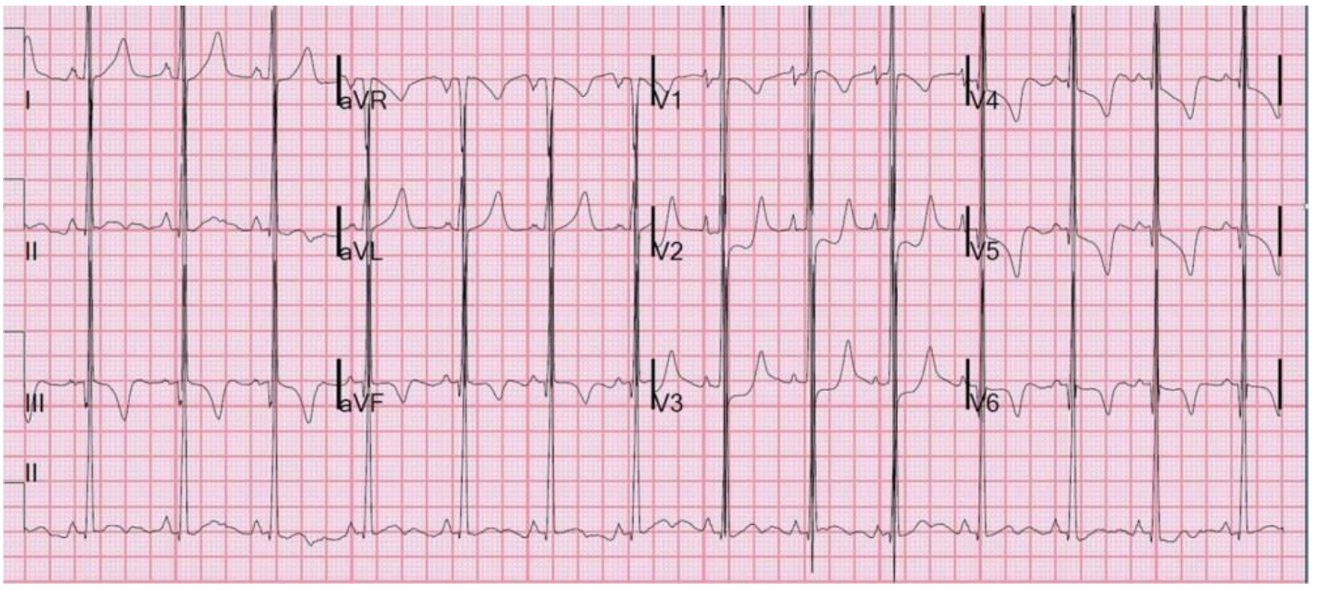
Symptoms and signs are similar to those of aortic stenosis, except that the character of the pulse in HOCM is jerky

- often asymptomatic
- dyspnea (the most common presenting symptom)
- angina,
- syncope
- sudden death (most commonly due to ventricular arrhythmias), arrhythmias, heart failure
- jerky pulse,
- large 'a' waves,
- double apex beat
- ejection systolic murmur: increases with Valsalva manoeuvre and decreases on squatting
  - Diastolic decrescendo murmur of aortic regurgitation (10% of patients)

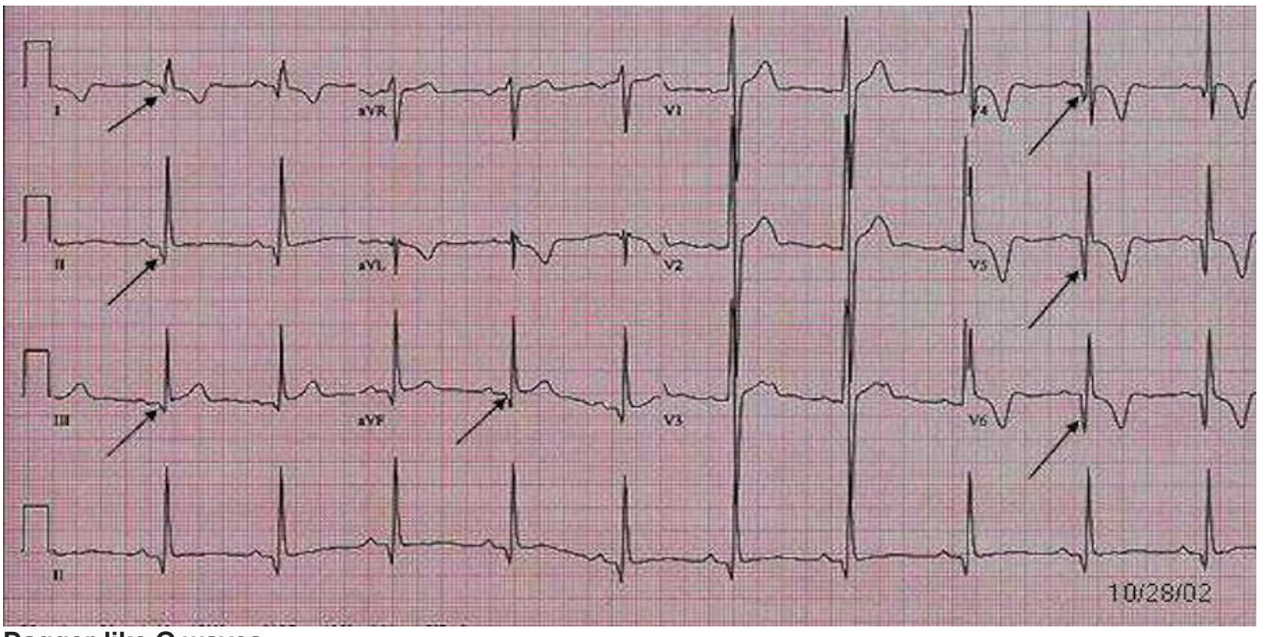
Associations
- Friedreich's ataxia
- Wolff-Parkinson White

Echo - mnemonic - MR SAM ASH
- mitral regurgitation (MR)
- systolic anterior motion (SAM) of the anterior mitral valve leaflet
- asymmetric hypertrophy (ASH)

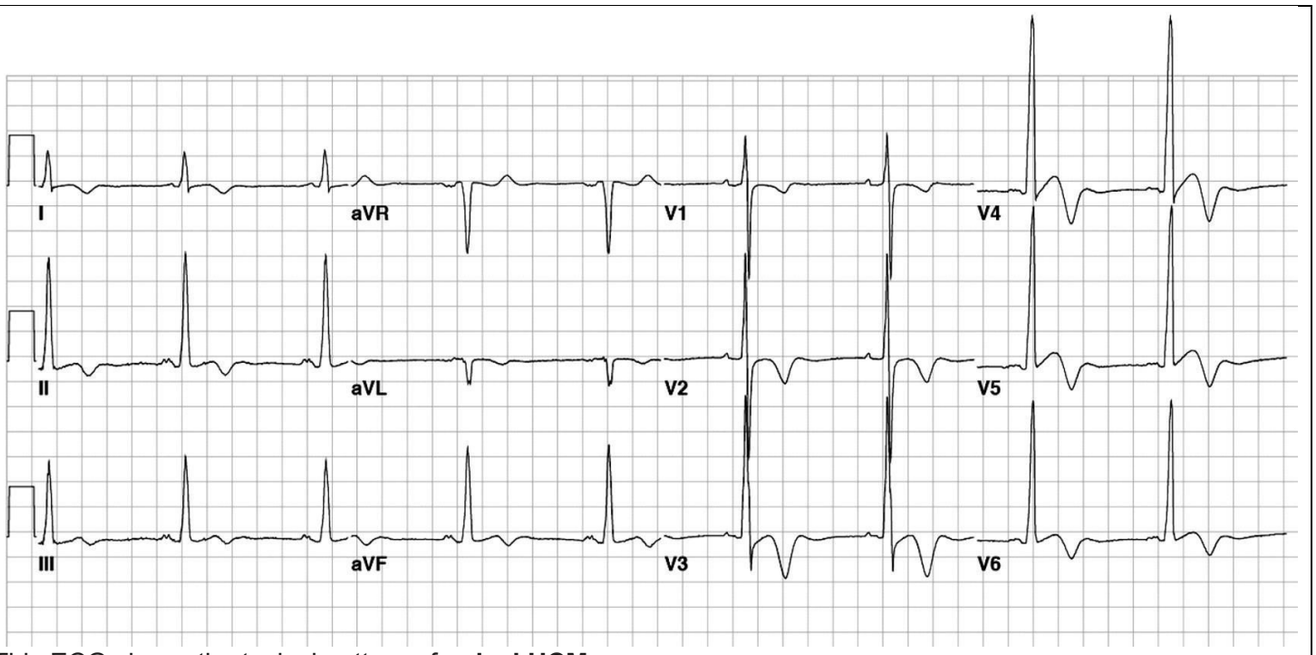
ECG
- left ventricular hypertrophy
- progressive T wave inversion
- deep Q waves
- right or left axis deviation
- PR prolongation
- atrial fibrillation may occasionally be seen
- **Right bundle branch block**
  - **the most ECG FINDING which support a diagnosis of HOCM**
  - RBBB is correlated with anterior, anteroseptal and mid-septal myocardial fibrosis in HOCM.



ECG showing typical changes of HOCM including LVH and T wave inversion



Dagger-like Q waves



This ECG shows the typical pattern of **apical HCM**:

- Large precordial voltages.

- Giant T wave inversions in the precordial leads
- Inverted T waves are also seen in the inferior and lateral leads.

Type of cardiomyopathy	Selected points
Hypertrophic obstructive cardiomyopathy	• Leading cause of sudden cardiac death in young athletes • Usually due to a mutation in the gene encoding **β-myosin heavy chain** protein • Common cause of sudden death • Echo findings include: ➢ MR, ➢ systolic anterior motion (SAM) of the anterior mitral valve ➢ asymmetric septal hypertrophy
Arrhythmogenic right ventricular dysplasia	• Right ventricular myocardium is replaced by fatty and fibrofatty tissue • Around 50% of patients have a mutation of one of the several genes which encode components of **desmosome** • ECG abnormalities in V1-3, ➢ typically T wave inversion. ➢ An epsilon wave is found in about 50% of those with ARV - this is best described as a terminal notch in the QRS complex

Management

- **A**miodarone
- **B**eta-blockers or verapamil for symptoms
- **C**ardioverter defibrillator
- **D**ual chamber pacemaker
- **E**ndocarditis prophylaxis

Beta-blockers

- Generally first-line agents
  - ➢ increase diastolic filling and decrease contractility
  - ➢ Reduces provocable gradient

disopyramide

- **If ß-blockers alone are ineffective, disopyramide, may be added** (Class IA anti-arrhythmic drug)
- anticholinergic side-effects include dryeyes and mouth, urinary hesitancy or retention, and constipation.
- QTc interval should be monitored during dose up-titration and the dose reduced if it exceeds 480 ms.
- Disopyramide should be avoided in patients with glaucoma, prostatism, and in patients taking other drugs that prolong the QT interval, such as amiodarone and sotalol.

Verapamil

- Verapamil (starting dose 40 mg three times daily to maximum 480 mg daily) can be used when ß-blockers are contraindicated or ineffective,
- close monitoring is required in patients with severe obstruction (≥100 mm Hg) or elevated pulmonary artery systolic pressures, as it can provoke pulmonary oedema.
- Verapamil should however be avoided in HOCM patients with coexistent Wolff Parkinson White as it may precipitate VT or VF.

Implantable cardioverter defibrillators (ICD) implantation → prevention of sudden cardiac death

- recommended in patients who have survived a cardiac arrest due to VT or VF or who have spontaneous sustained VT causing syncope or haemodynamic compromise

Invasive treatment (myomectomy or alcohol septal ablation) (ESC Guidelines 2014)

- Left ventricular outflow tract obstruction (LVOTO) is defined as a peak instantaneous Doppler LV outflow tract gradient of ≥30 mm Hg, but the threshold for invasive treatment is usually considered to be ≥50 mm Hg.
- **Septal reduction therapy** is recommended in patients with LVOT gradient of ≥ 50 mm Hg, who are in NYHA functional Class III–IV, despite maximum tolerated medical therapy.

- The most commonly performed surgical procedure used to treat LVOTO is ventricular septal myectomy (Morrow procedure).
- Pre-operative determinants of a good long-term outcome are age < 50 years, left atrial size < 46 mm, absence of atrial fibrillation and male gender.
- surgery VS septal alcohol ablation (SAA)
  - both procedures improve functional status with a similar procedural mortality.
  - Septal alcohol ablation is associated with a higher risk of AV block, requiring permanent pacemaker implantation and larger residual LV outflow tract gradients.
  - In contrast to myectomy, most patients develop right-, rather than left bundle branch block after SAA.

Drugs to avoid

- nitrates
- ACE-inhibitors
- Inotropes : Digoxin

Poor prognostic factors, which are predictive of sudden cardiac death

HOCM - poor prognostic factor on echo = septal wall thickness of > 3cm

- syncope
- family history of sudden death
- **Maximum left ventricular wall thickness greater than 3 cm**
- young age at presentation
- non-sustained ventricular tachycardia on 24 or 48-hour Holter monitoring
- Abnormal blood pressure changes on exercise (**Blood pressure drop during peak exercise on stress testing**).

Screening of HOCM

- Current guidelines suggest that a resting ECG and TTE (transthoracic ECHO) are the most effective screening strategies for relatives of patients with HOCM.
- Genetic testing is not recommended as a first line screening tool given varying rates of penetrance.

Dilated cardiomyopathy (DCM)

Overview

- Most common cardiomyopathy
- Sex: ♂ > ♀ (approx. 3:1)
- dilated heart leading to systolic (+/- diastolic) dysfunction
- all 4 chambers affected but LV more so than RV

Features

- arrhythmias,
- **emboli → cardio-embolic stroke,**
- mitral regurgitation
- absence of congenital, valvular or ischaemic heart disease

Causes

- Common causes
  - Idiopathic (approx. 50%)
  - alcohol: may improve with thiamine
  - postpartum
  - hypertension
- **Other causes**
  - genetic inherited dilated cardiomyopathy:
    - around third of DCM patients
    - **the majority** of defects are inherited in an **autosomal dominant** fashion although other patterns of inheritance are seen
  - infections e.g.
    - Coxsackie B,
    - HIV,
    - diphtheria,
    - parasitic
  - endocrine e.g.

        - Hyperthyroidism
    - neuromuscular e.g.
        - Duchenne muscular dystrophy
    - nutritional e.g.
        - Kwashiorkor,
        - pellagra,
        - thiamine/selenium deficiency
            - **Selenium deficiency is one of the reversible causes of dilated cardiomyopathy.**
    - drugs e.g.
        - Doxorubicin
    - Infiltrative (may also lead to **restrictive cardiomyopathy**) e.g.
        - Haemochromatosis,
        - Sarcoidosis

Diagnosis → Echocardiogram

- The echo may show:
    - Reduced left ventricular ejection fraction,
    - myocardial dyssynchrony (myocardial segments contract at different points in time),
    - thinning of the left ventricular wall
    - dilated left ventricle.

Type of cardiomyopathy	Selected causes/points
Dilated cardiomyopathy	Classic causes include • alcohol • Coxsackie B virus • wet beri beri • doxorubicin
Restrictive cardiomyopathy	Classic causes include • amyloidosis • post-radiotherapy • Loeffler's endocarditis

Becker's muscular dystrophy

- **X-linked recessive** disorder resulting from a mutation in the **dystrophin gene**.
- The clinical picture is similar to that of Duchenne's muscular dystrophy but it is much **milder**.
- Patients usually present between the ages of 5 and 15 years, though presentation may not be until the fourth or fifth decade.
- **Patients may present with heart failure secondary to dilated cardiomyopathy rather than the classic proximal muscle weakness.**

Restrictive cardiomyopathy

Restrictive cardiomyopathy: amyloid (most common), haemochromatosis, Loffler's syndrome, sarcoidosis, scleroderma

Causes

- amyloidosis (e.g. secondary to myeloma) - **most common cause in UK**
    - Cardiac involvement is the most common cause of death in patients with amyloidosis associated with an immunocyte dyscrasia - typically as restrictive cardiomyopathy
    - Transthyretin gene mutations can lead to restrictive cardiomyopathy from amyloid deposition in the heart.
    - Diagnosis is confirmed by **myocardial biopsy**, which shows **amyloid infiltration** when stained with **Congo Red**.

    - myocardial biopsy, which when stained with Congo Red will show "**apple green birefringence**" amyloid under polarized light.
- haemochromatosis
- Loffler's syndrome
- sarcoidosis
- scleroderma
- Radiotherapy
- Systemic sclerosis
- Carcinoid syndrome.

Pathophysiology:

- Proliferation of connective tissue → ↓ elasticity of myocardium → ↓ ventricular compliance → ↓ diastolic filling → atrial congestion → atrial enlargement and severe diastolic dysfunction

Features

- Physical examination reveals right heart failure with a raised JVP, characteristically showing a prominent deep Y descent
- Heart size is often normal.
- S 4 heart sound , due to ventricular noncompliance.
- Pericardial effusion is common, but rarely causes tamponade
- **The most characteristic ECG finding of restrictive cardiomyopathy is diffusely diminished voltages**
- **Echocardiography findings**
    - **small thick ventricles and a thick interatrial septum due to amyloid deposits, which have a 'granular sparkling' appearance**
        - Amyloid deposits in the heart produce generalized thickening of the myocardium (as opposed to asymmetrical septal hypertrophy commonly seen in hypertrophic cardiomyopathy) and diastolic dysfunction.
    - impaired relaxation in the diastolic phase.
    - **bright speckled appearance.**

Differential diagnosis

- **constrictive pericarditis**
    - Features are very similar in constrictive pericarditis, but in constrictive pericarditis:
        - **the apex is frequently non-palpable due to the thick pericardium**
        - chest X-ray may show pericardial calcifications

Features suggesting restrictive cardiomyopathy rather than constrictive pericarditis

- prominent apical pulse
- absence of pericardial calcification on CXR
- heart may be enlarged
- ECG abnormalities e.g. bundle branch block, Q waves

Clinical Features of Constrictive Pericarditis and Restrictive Cardiomyopathy

Clinical Features	Constrictive Pericarditis	Restrictive Cardiomyopathy
History	Prior history of pericarditis or condition that causes pericardial disease	History of systemic disease (eg, amyloidosis, hemochromatosis)
Systemic examination - Heart sounds	Pericardial knock, high-frequency sound	Presence of loud diastolic filling sound S_3, Low-frequency sound
Murmurs	No murmurs	Murmurs of mitral and tricuspid insufficiency
apical pulse	apex is frequently non-palpable due to the thick pericardium	prominent apical pulse
Prior chest radiograph	Pericardial calcification	Normal results of prior chest radiograph

Management

- Cardiac transplant

Peripartum cardiomyopathy (PCM)

- biventricular heart failure during the third trimester.
- the aetiology: unknown, although both myocarditis and low levels of dietary selenium have been postulated as causes.

Management

- similar to the management of heart failure in any other situation with vasodilators, diuretics and beta blockade. ACE inhibition is reserved for the post-partum period.
  - sodium restriction,
  - diuretics to optimise the volume status,
  - digoxin and afterload-reducing agents.
  - Hydralazine
- For patients presenting with PCM, defined as left ventricular systolic dysfunction 1 month prior to delivery or 5 months postpartum, volume status should first be managed with diuretics after liaison with obstetricians. **Beta-blockers should be added once the patient's volume status is optimised.**
- Anticoagulation
  - Patients with PCM are at risk of thromboembolism due to both hypercoagulable state of pregnancy and stasis of blood in the left ventricle. Therefore, anticoagulation with **heparin** is recommended.

Type of cardiomyopathy	Selected points
Peripartum cardiomyopathy	• Typical develops between last month of pregnancy and 5 months post-partum • More common in older women, greater parity and multiple gestations
Takotsubo cardiomyopathy	• 'Stress'-induced cardiomyopathy e.g. patient just found out family member dies then develops chest pain and features of heart failure • Transient, apical ballooning of the myocardium • Treatment is supportive

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Takotsubo cardiomyopathy

Definition:

- Takotsubo cardiomyopathy is a type of non-ischaemic cardiomyopathy associated with a transient, apical ballooning of the myocardium.
- acute, stress-induced, reversible dysfunction of the left ventricle

Epidemiology:

- especially postmenopausal women > 60 years

Pathophysiology:

- emotional/physical stress → massive catecholamine discharge → cardiotoxicity, multi-vessel spasms and dysfunction → myocardial stunning

Features

- chest pain
- features of heart failure
- ST elevation
- normal coronary angiogram

Treatment

- supportive

Prognosis:

- spontaneous recovery if stressors are avoided

Congenital heart diseases

Congenital heart disease: types

Paradoxical embolus - PFO most common cause - do TOE

Congenital heart disease
- **cyanotic: TGA most common at birth, Fallot's most common overall**
- **acyanotic: VSD most common cause**

Acyanotic - most common causes
- **ventricular septal defects (VSD) - most common**, accounts for 30%
- atrial septal defect (ASD) 10%.
- patent ductus arteriosus (PDA)
- coarctation of the aorta
- aortic valve stenosis

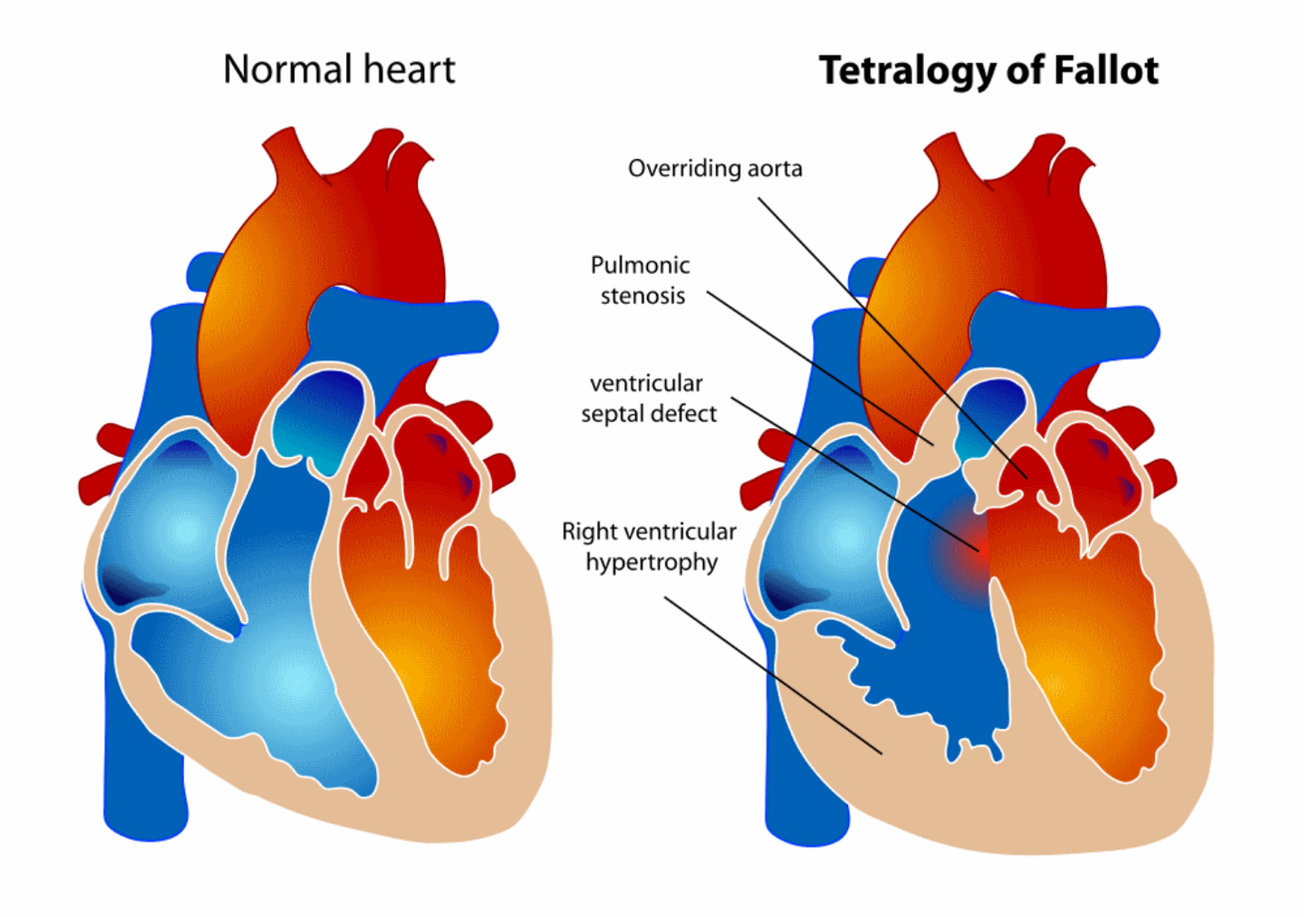
VSDs are more common than ASDs. However, in adult patients ASDs are the more common new diagnosis as they generally presents later

Cyanotic - most common causes
- tetralogy of Fallot
  - There is a single sound in Fallot's because of an absent P2.
  - A Blalock shunt (anastomosis of subclavian artery to pulmonary artery) used to be performed for Fallot's tetralogy and leads to a weak left radial pulse.
- transposition of the great arteries (TGA)
  - **Fallot's** is more common than TGA. However, at birth TGA is the more common lesion as patients with Fallot's generally presenting at around 1-2 months
  - TGA is usually treated by **prostaglandins in order to keep the ductus arteriosus patent** (from pulmonary artery to the descending aorta), so some oxygenated blood can reach systemic circulation.
- tricuspid atresia
- pulmonary valve stenosis
- **Total anomalous pulmonary venous connection (TAPVC)**
  - TAPVC consists of an abnormality of blood flow in which all four pulmonary veins drain into systemic veins or the right atrium with or without pulmonary venous obstruction.
  - Systemic and pulmonary venous blood mix in the right atrium.

Other notes
- Aortic regurgitation may be a feature of osteogenesis imperfecta.
- Ebstein's anomaly is associated with maternal $LiCO_3$ use if exposed in the first trimester.
- The majority of cases of neonates with complete heart block may be caused by autoimmune disease, particularly anti-ro antibodies in the mother.
- Left ventricle (LV) hypolasia occurs when the left sided chambers fail to develop and blood enters the systemic circulation from the right ventricle via the pulmonary artery and a patent ductus arteriosus.

Tetralogy of Fallot (TOF)
- TOF is the most common cause of cyanotic congenital heart disease*.
  - *however, at birth transposition of the great arteries is the more common lesion as patients with TOF generally present at around 1-2 months
- It typically presents at around 1-2 months, although may not be picked up until the baby is 6 months old
- TOF is a result of anterior malalignment of the aorticopulmonary septum. The four characteristic features are:
  1. ventricular septal defect (VSD)

2. right ventricular hypertrophy
3. right ventricular outflow tract obstruction, pulmonary stenosis
    - There is a single sound in Fallot's because of an absent P2.
4. overriding aorta



- The severity of the right ventricular outflow tract obstruction determines the degree of cyanosis and clinical severity

Other features

- cyanosis
- causes a right-to-left shunt
- ejection systolic murmur due to pulmonary stenosis (the VSD doesn't usually cause a murmur)
- a right-sided aortic arch is seen in 25% of patients
- chest x-ray shows a 'boot-shaped' heart, ECG shows right ventricular hypertrophy

Management

- surgical repair is often undertaken in two parts
- cyanotic episodes may be helped by beta-blockers to reduce infundibular spasm

The most common residual lesion in repaired tetralogy of Fallot is pulmonary regurgitation.

Ventricular septal defects (VSD)

Overview

- The second most common congenital heart defect
    - bicuspid aortic valve is the most common congenital heart defect
- They close spontaneously in around 50% of cases.
- **the most common site for a VSD → Perimembranous**
    - Perimembranous VSDs account for 70-80% of VSDs and are situated between the inlet and outlet portions of the septum.

Associations

- Congenital VSDs: associated with:
    - chromosomal disorders (e.g. Down's syndrome, Edward's syndrome, Patau syndrome)
- Non-congenital causes include:
    - Fetal alcohol syndrome

- Intrauterine infection (e.g., TORCH)
- post myocardial infarction

Features

- **Pan-systolic murmur** which is:
  - louder in smaller defects
  - **usually loudest at the left lower sternal edge (LSE)**
- Mid-diastolic murmur over cardiac apex
  - Due to increased flow through the mitral valve
- systolic thrill
- Loud pulmonic S2 (if pulmonary hypertension develops)

Investigations

- Chest x-ray
  - Enhanced pulmonary vascular markings
  - Left atrial and ventricular enlargement
- ECG
  - **The clue to diagnosis in the ECG finding → Biventricular hypertrophy**
    - Biventricular hypertrophy is classically described as having **biphasic QRS complexes in V2–5** – which is known as the **Katz Wachtel phenomenon** and is **classic for VSD**.
- Doppler echocardiography: confirms diagnosis

Complications

- Aortic regurgitation
  - due to a poorly supported right coronary cusp resulting in cusp prolapse
- Infective endocarditis
- Eisenmenger's complex
- Right heart failure
- Pulmonary hypertension
  - pregnancy is contraindicated in women with pulmonary hypertension as it carries a 30-50% risk of mortality.

Treatment

- small to moderate defects often heal spontaneously
- Symptomatic and large VSDs → Surgical (patch) repair
- Heart-lung transplant or lung transplant with concurrent VSD repair if Eisenmenger's reaction has occurred

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Atrial septal defect (ASD)

- common congenital heart lesion
  - VSD is more common

Types

- **Ostium secundum**
  - **70% of ASDs**
  - associated with Holt-Oram syndrome (tri-phalangeal thumbs)
  - ECG: **RBBB** with **RAD**
- **Ostium primum**
  - present earlier than ostium secundum defects
  - associated with abnormal AV valves
  - the AV node is displaced posteriorly and inferiorly and atrial and/or AV nodal conduction is often delayed.
  - ECG: RBBB with **LAD**, prolonged PR interval

wide, fixed, split-second sound + right-axis deviation → Ostium secundum
wide, fixed, split-second sound + left-axis deviation → Ostium primum

Features

- Symptoms
  - asymptomatic in youth
  - often discovered on routine school health exams
  - mild fatigue
  - frequent respiratory infections
  - Larger ones may lead to signs of right ventricular failure, such as shortness of breath and a parasternal heave.

- Physical exam
  - Mid-systolic ejection murmur (over the left second ICS)
    - Due to → Relative pulmonary stenosis due to an increase in stroke volume
  - Soft mid-diastolic murmur (over the lower left sternal border)
    - arises from increased flow across the tricuspid valve.
  - loud S1
  - **wide fixed-split S2**
    - The most frequently tested knowledge
    - splitting is fixed (does not vary with respiration)
  - heaving cardiac impulse (LLSB)

Predisposes patient to

- CHF
  - 2nd/3rd decades of life
- Eisenmenger's syndrome
  - pulmonary hypertension
  - right ventricular hypertrophy
  - reversal to a right-to-left shunt
- stroke
  - due to paroxysmal embolus

Associated condition

- Tricuspid atresia is the congenital cardiac disorder most commonly associated with an atrial septal defect.
- Down syndrome
- Fetal alchohol syndrome
- Holt-Oram syndrome
  - Autosomal dominant disorder, which is also called hand-heart syndrome because affected children present with an ASD, a first degree heart block, and abnormalities of the upper limbs (e.g., absent radial bones). It affects approx. 1 in 100,000 children.

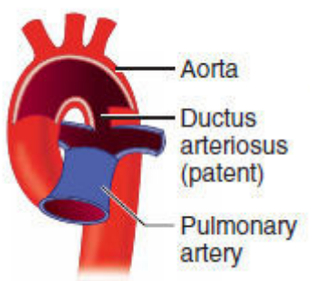
ECG

- **Right bundle branch block**
- ostium primum ASD →left axis deviation.
- ostium secundum ASD → right axis deviation.
- first degree heart block → **prolongation of the PR interval**
  - due to delayed conduction through the atria or through the AV node
- The QRS pattern typically is either an rSr' or an rsR' resulting from dilation and hypertrophy of the right ventricular outflow tract caused by volume overload of the right heart.

prominent left precordium in a young patient with an ejection murmur in the second left intercostal space indicat → **ASD with pulmonary hypertension**

- A prominent left precordium suggests that:
  - the right ventricle was dilated during childhood
  - RV working against a high pressure

Patent ductus arteriosus



"Endomethacin" (indomethacin) ends patency of PDA; PGE kEEps it open (may be necessary to sustain life in conditions such as transposition of the great vessels).
PDA is normal in utero and normally closes only after birth.

Overview

- acyanotic congenital heart defect
- connection between the pulmonary trunk and descending aorta

- more common in premature babies, born at high altitude or maternal rubella infection in the first trimester

Features

- left subclavicular thrill
- continuous 'machinery' murmur at the left upper sternal edge with late systolic accentuation
- large volume, bounding, collapsing pulse
- wide pulse pressure
- heaving apex beat

Management

- indomethacin closes the connection in the majority of cases
- if associated with another congenital heart defect amenable to surgery then prostaglandin E1 is useful to keep the duct open until after surgical repair

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Patent foramen ovale(PFO)

- **PFO** is **present in around 20% of the population**.
- It may allow embolus (e.g. from DVT) to pass from right side of the heart to the left side leading to a stroke - 'a paradoxical embolus'
- There also appears to be an association between migraine and PFO.
  - Some studies have reported improvement in migraine symptoms following closure of the PFO
- right heart catheter: left to right shunting of oxygenated blood at level of the atrium.
  - oxygen saturation data show a step-up in the saturations between the vena cava and the right atrium.

Paradoxical embolisation

For a right-sided thrombus (e.g. DVT) to cause a left-sided embolism (e.g. stroke) it must obviously pass from the right-to-left side of the heart

The following cardiac lesions may cause such events

- patent foramen ovale - present in around 20% of the population
- atrial septal defect - a much less common cause

Blue toe syndrome

- 80% of such digital ischaemias have an emboli originating from the heart and so an urgent echocardiogram is crucial to prevent further and more severe events occurring.
- **sudden onset of a cold, painful, and cyanotic big toe. the next steps → Therapeutic heparin and urgent echocardiogram**

Eisenmenger's syndrome

- Eisenmenger's syndrome describes the reversal of a left-to-right shunt in a congenital heart defect due to pulmonary hypertension.
- This occurs when an uncorrected left-to-right leads to remodeling of the pulmonary microvasculature, eventually causing obstruction to pulmonary blood and pulmonary hypertension.

Associated with

- ventricular septal defect
- atrial septal defect
- patent ductus arteriosus

Features

- original murmur may disappear
- cyanosis
- clubbing
- right ventricular failure
- haemoptysis, embolism

Management

- heart-lung transplantation is required

Ebstein's anomaly

- Ebstein's anomaly is a congenital heart defect characterised by low insertion of the tricuspid valve resulting in a large atrium and small ventricle. It is sometimes referred to as 'atrialisation' of the right ventricle.
- The most common findings are:
  - hypoplastic (atrialised) RV,
  - apical displacement of the septal and posterior tricuspid valve leaflets,
  - ASD.
- **Leads to right bundle branch block pattern on ECG.**
- Ebstein's anomaly may be caused by exposure to lithium in-utero

Associations

- tricuspid incompetence (pan-systolic murmur, giant V waves in JVP)
- Wolff-Parkinson White syndrome occurs in around 15% of the patients.

The presence of delta waves and short PR interval is indicative of WPW. When correlated with past surgical history (repair of atrial septal defect and tricuspid valve abnormalities as a child), Ebstein's anomaly is the most likely diagnosis.

Cardiac manifestations of genetic disorders

Genetic disorder	Associated cardiac manifestation
Marfan's syndrome	Aortic regurgitation (aortic dissection)
Down's syndrome	ASD, VSD
Turner's syndrome	Coarctation of the aorta
Spondyloarthritides, eg, ankylosing spondylitis	Aortic regurgitation

Vascular diseases

Peripheral vascular disease

- is a marker for increased risk of cardiovascular events even when it is asymptomatic.
- **the femoropopliteal artery, the most common site of peripheral arterial disease.**
  - paresthesia, intermittent claudication in calf and foot **and** palpable femoral pulses but absent pedal pulses

Risk factors

- age
  - about 20% of people aged over 60 years have some degree of peripheral arterial disease.
- male gender
- Smoking
- Diabetes
- hypertension
- coronary artery disease.

Feature

- intermittent claudication (leg pain while walking) (The most common initial symptom).
- Critical limb ischaemia : ischaemic pain, ulceration, tissue loss and/or gangrene.

Investigations

- measuring the ankle brachial pressure index
  - Calculate the index in each leg by dividing the highest ankle pressure by the highest arm pressure.

- Imaging before considering revascularization
  - duplex ultrasound (first-line imaging)
  - contrast-enhanced magnetic resonance angiography (after duplex ultrasound)
  - computed tomography angiography (if contrast-enhanced magnetic resonance angiography is contraindicated or not tolerated.)

Treatment

Mild symptoms:

- exercise programme
  - 2 hours of supervised exercise a week for a 3‑month period
  - encouraging people to exercise to the point of maximal pain.
- management of cardiovascular risk factors (for example, with aspirin or statins)
- vasoactive drug treatment (for example, with naftidrofuryl oxalate).
- **Which drug might help improve pain-free walking distance?**
  - ⇨ **Naftidrofuryl**
    - ❖ Indicated only when exercise has not led to satisfactory improvement and the person refuse angioplasty or bypass surgery.
    - ❖ discontinue naftidrofuryl oxalate if there has been no symptomatic benefit after 3–6 months.
- Vasoactive drugs have limited benefit in treating intermittent claudication.
- There is modest evidence for the use of drugs such as naftidrofuryl and pentoxifylline, but little benefit from cinnarizine or inositol nicotinate.
- Simvastatin may be prescribed for patients with peripheral vascular disease who have elevated cholesterol levels, but there is no data on improvements in walking distance.

severe symptoms:

- endovascular treatment (such as angioplasty or stenting), bypass surgery, pain management and/or amputation.

Venous ulceration

- venous ulcerations are the most common type of ulcer affecting the lower extremities.
- The probable underlying cause: venous insufficiency → venous congestion → ulceration
- Treatment of venous ulceration is control of oedema, treating any infection, and compression.
- **Compressive dressings or devices should not be applied if the arterial circulation is impaired, and ankle-brachial pressure index is needed before application of compression**

Monckeberg's calcific medial sclerosis,

- a benign condition involving muscular arteries of older persons.
- several prominent calcified vessels seen in the radiograph.
- **Management → Ignore it**

Other cardiac diseases

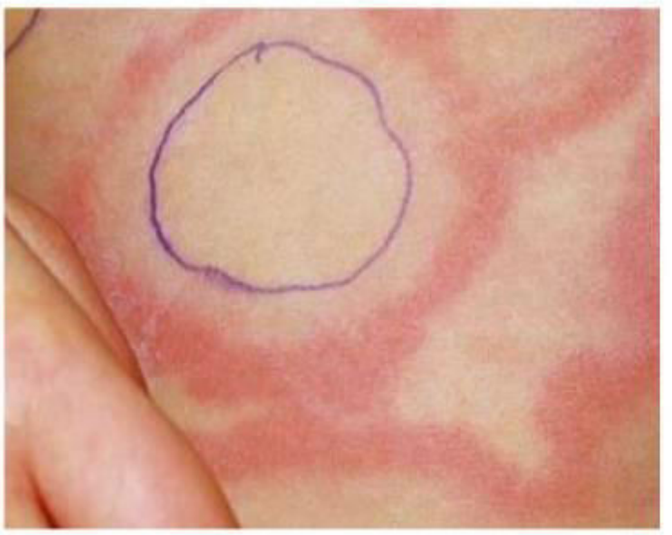
Rheumatic fever: criteria

- Rheumatic fever develops following an immunological reaction to recent (2-6 weeks ago) *Streptococcus pyogenes* infection.
- Diagnosis is based on **evidence of recent streptococcal infection** accompanied by:
  - 2 major criteria
  - 1 major with 2 minor criteria
- Evidence of recent streptococcal infection
  - ASOT > 200iu/mL
  - history of scarlet fever
  - positive throat swab
  - increase in DNase B titre

- **Major criteria**
  - erythema marginatum
  - Sydenham's chorea

- **polyarthritis**
- carditis (endo-, myo- or peri-)
- subcutaneous nodules
  - Pea-sized, firm and non-tender.
  - characteristically seen on the extensor surfaces of joints such as knees and elbows and also over the spine.

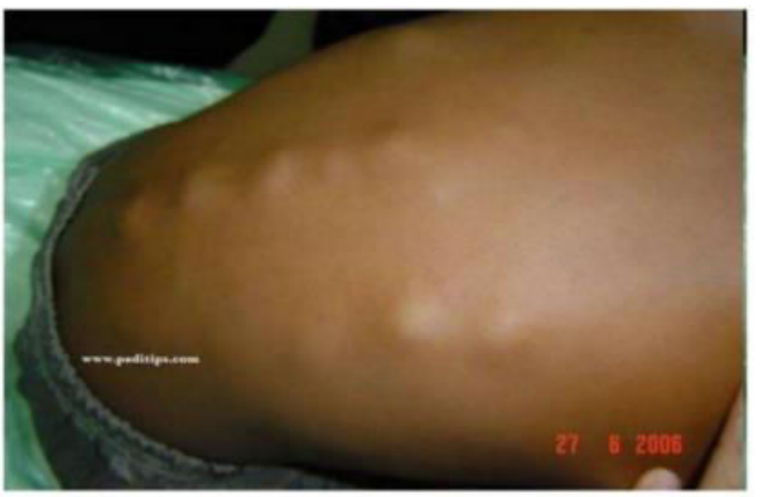
- **Minor criteria**
  - raised ESR or CRP
  - pyrexia
  - arthralgia (not if arthritis a major criteria)
  - prolonged PR interval



Erythematous patches with central clearing

Erythema marginatum

Erythema marginatum is seen in around 10% of children with rheumatic fever. It is rare in adults



Subcutaneous nodules
(nodules of rheumatoid arthritis are larger)

Infective endocarditis (IE)

Most common cause of endocarditis:
- Streptococcus viridans
- Staphylococcus epidermidis if < 2 months post valve surgery

Risk factors

- **previous episode of endocarditis**
  - **The strongest risk factor for developing infective endocarditis.**
- previously normal valves (50%, typically acute presentation)
- rheumatic valve disease (30%)
- prosthetic valves
- congenital heart defects
- intravenous drug users (IVDUs, e.g. Typically causing tricuspid lesion)
- Hypertrophic cardiomyopathy.

Frequency

- In terms of frequency, IE will most likely affect the mitral valve, then aortic valve, then both aortic and mitral valves, then tricuspid and finally (and rarely) the pulmonary valve.
- If the valve is already abnormal, then the likelihood of infection is greater and will be most likely on the aortic valve.
  - High-pressure systems create more blood turbulence and permit inoculation of the valve.
- **Which cardiac lesion is most likely to be prone to infection in patients with known heart disease?**
  - **Aortic regurgitation**

Causes

***Streptococcus bovis* endocarditis is associated with colorectal cancer**

- ***Streptococcus viridans* (most common cause - 40-50%).** Technically *Streptococcus viridans* is a pseudotaxonomic term, referring to viridans streptococci, rather than a particular organism.
  - The most common organisms causing **subacute bacterial endocarditis (SBE)** are the viridans streptococci.
    - Because viridans streptococci are relatively avirulent pathogens in normal hosts, they usually present as SBE.
  - The two most notable viridans streptococci are:
    1. *Streptococcus mitis* and
    2. *Streptococcus sanguinis*.
  - They are both commonly found in the mouth and in particular dental plaque so endocarditis caused by these organisms is linked with poor dental hygiene or following a dental procedure
- *Staphylococcus epidermidis* (especially prosthetic valves)
- *Staphylococcus aureus* (especially acute presentation, IVDUs)
  - ***Staphylococcus aureus* endocarditis is an aggressive disease frequently associated with valve destruction and abscess formation.**
- ***Streptococcus bovis* is associated with colorectal cancer → colonoscopy**
  - ***Streptococcus gallolyticus* is a subtype of *Streptococcus bovis***
- ***Bacteroides* is the most likely organism following bowel resection**, though *S. bovis* is also seen.
  - Passage of bacteria to the heart occurs via venous drainage, so valve lesions tend to be right-sided. Vegetations may also occur on the left side of the heart.
  - Management in → metronidazole.
- non-infective:
  - systemic lupus erythematosus (Libman-Sacks), (sterile vegetations)
    - commonly result in mitral **regurgitation**.
  - malignancy: marantic endocarditis
- **Culture negative causes**
  - prior antibiotic therapy
  - *Coxiella burnetii*
    - is the Q fever agent
    - typically associated with exposure to animals (sheep and cattle).
  - *Bartonella*
    - from cats
  - *Brucella*
  - Chlamydia psittaci
    - from birds.
  - **HACEK**: *(**H**aemophilus, **A**ctinobacillus, **C**ardiobacterium, **E**ikenella, **K**ingella*)
    - slow-growing, **Gram negative bacteria**

- These are normal flora of the upper respiratory tract
- constitute 5-10% cases of endocarditis;
- they require prolonged incubation in enriched media and increased carbon dioxide tension.
- **The human bite injury and gram-negative culture make *Eikenella corrodens* the most likely causative organism.**
- third-generation cephalosporin (**Ceftriaxone**) is effective against enteric gram-negative rods, including HACEK organisms

Following prosthetic valve surgery *Staphylococcus epidermidis* is the most common organism in the first 2 months and is usually the result of perioperative contamination. After 2 months the spectrum of organisms which cause endocarditis return to normal, except with a slight increase in *Staph. aureus* infections

Infective endocarditis: Modified Duke criteria

- **Infective endocarditis diagnosed if**
  - pathological criteria positive, or
  - 2 major criteria, or
  - 1 major and 3 minor criteria, or
  - 5 minor criteria
- **Pathological criteria**
  - Positive histology or microbiology of pathological material obtained at autopsy or cardiac surgery (valve tissue, vegetations, embolic fragments or intracardiac abscess content)
- **Major criteria**
  - **Positive blood cultures**
    - two positive blood cultures showing typical organisms consistent with infective endocarditis, such as *Streptococcus viridans* and the HACEK group, or
    - persistent bacteraemia from two blood cultures taken > 12 hours apart or three or more positive blood cultures where the pathogen is less specific such as *Staph aureus* and *Staph epidermidis*, or
    - positive serology for *Coxiella burnetii*, *Bartonella* species or *Chlamydia psittaci*, or
    - positive molecular assays for specific gene targets
  - **Evidence of endocardial involvement**
    - positive echocardiogram (oscillating structures, abscess formation, new valvular regurgitation or dehiscence of prosthetic valves), or
    - new valvular regurgitation

Minor criteria

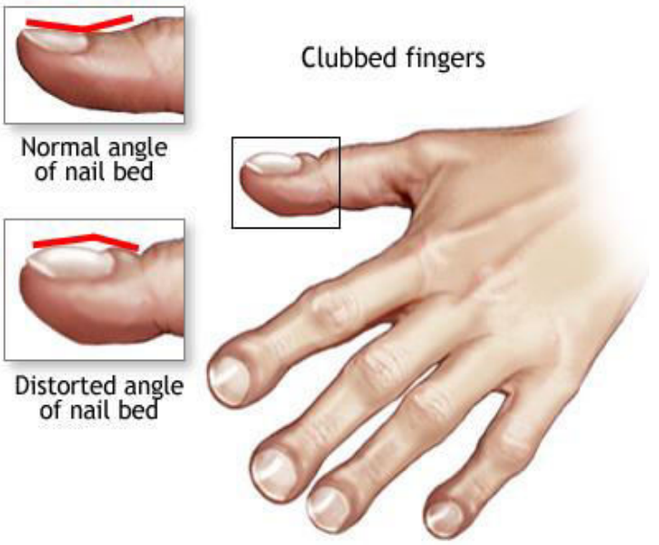
- predisposing heart condition or intravenous drug use
- microbiological evidence does not meet major criteria
- fever > 38 C
- vascular phenomena: major emboli, splenomegaly, clubbing, splinter haemorrhages, Janeway lesions, petechiae or purpura
- immunological phenomena: glomerulonephritis, Osler's nodes, Roth spots

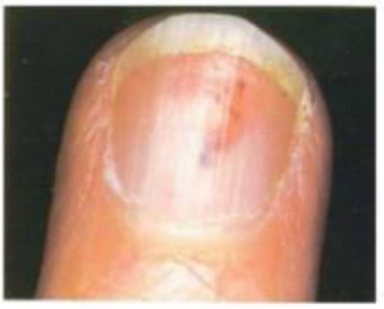
Aortic valve endocarditis can cause aortic root abscess which can cause damage to the AV node resulting in prolongation of the PR interval on ECG.

Conjunctival petechial haemorrhages are far more common than the classical skin signs of splinter haemorrhages, Osler's nodes and Janeway lesions.

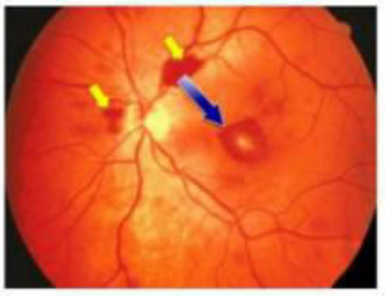
Most patients with endocarditis have evidence of vasculitis, strongly associated with microscopic haematuria. Other vasculitic features include splinter haemorrhages, Osler's nodes (finger/toe pulp infarcts) and Janeway lesions (palmar/plantar macules).

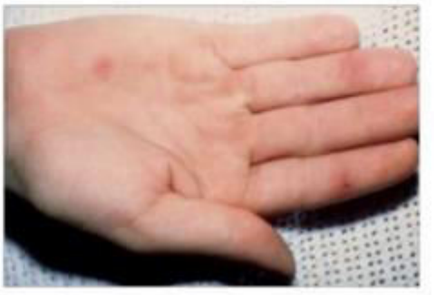
Peripheral signs associated with infective endocarditis




Splinter hemorrhage


Osler node


Roth's spot


Janeway lesion

Infective endocarditis: management

Current antibiotic guidelines (source: British National Formulary)

Scenario	Suggested antibiotic therapy
Initial blind therapy	Native valve • **amoxicillin**, consider adding low-dose gentamicin If penicillin allergic, **MRSA** or **severe sepsis** • vancomycin + low-dose gentamicin If prosthetic valve • vancomycin + rifampicin + low-dose gentamicin
Native valve endocarditis caused by staphylococci	Flucloxacillin If penicillin allergic or MRSA • vancomycin + rifampicin
Prosthetic valve endocarditis caused by staphylococci	Flucloxacillin + rifampicin + low-dose gentamicin If penicillin allergic or MRSA • vancomycin + rifampicin + low-dose gentamicin
Endocarditis caused by fully-sensitive streptococci (e.g. viridans)	Benzylpenicillin If penicillin allergic • vancomycin + low-dose gentamicin

Scenario	Suggested antibiotic therapy
Endocarditis caused by less sensitive streptococci	**Benzylpenicillin + low-dose gentamicin** If penicillin allergic • vancomycin + low-dose gentamicin

IV amoxicillin is the empirical treatment of choice in native valve endocarditis

The most useful laboratory test used to monitor the treatment of infective endocarditis is serial C reactive protein estimation.

- **length of treatment:**
  - 6 weeks of intravenous therapy is generally accepted as the length of treatment needed.

Indications for surgery

Infective endocarditis - indications for surgery:
- severe valvular incompetence
- aortic abscess (often indicated by a lengthening PR interval)
- infections resistant to antibiotics/fungal infections
- cardiac failure refractory to standard medical treatment
- recurrent emboli after antibiotic therapy

- severe valvular incompetence
- **aortic abscess (often indicated by a lengthening PR interval)**
- infections resistant to antibiotics/fungal infections
- **cardiac failure** refractory to standard medical treatment
- recurrent emboli after antibiotic therapy
- organisms that are difficult to eradicate by medical therapy as such **fungi**, brucella, coxiella, pseudomonas aeruginosa, vancomycin-resistant enterococci
- persistent bacteraemia despite appropriate antibiotic therapy
- extension of infection to a extravalvular site
- early prosthetic valve endocarditis (within 2 months)
- dehiscence or obstruction of a prosthetic valve.

Infective endocarditis related to cardiac devices

- The European Society of Cardiology recommends urgent extraction of the implanted device followed by prolonged antibiotic therapy in patients with cardiac device related infective endocarditis.
- Prolonged antibiotic therapy and device removal are recommended
- Percutaneous extraction is recommended in most patients with cardiac devices even those with large (>10 mm) vegetations
- After device extraction, reassessment of the need for re-implantation is recommended, and
- Routine antibiotic prophylaxis is recommended before device implantation.

Candida endocarditis
- Risk factors
  - Intravenous drug abuse,
  - immunodeficiency states and
  - indwelling catheters
- The aortic valve is the most common valve to be involved.
- **Treatment → Valve replacement followed by amphotericin B for 6 weeks**

Infective endocarditis: prophylaxis

- NICE recommends the following procedures **do not require prophylaxis**:
  - dental procedures
  - upper and lower gastrointestinal tract procedures
  - genitourinary tract; this includes urological, gynaecological and obstetric procedures and childbirth
  - upper and lower respiratory tract; this includes ear, nose and throat procedures and bronchoscopy

- **Prophylaxis is only recommended in** those patients who are at highest risk of adverse outcomes on the development of endocarditis. These patient groups include:
  - Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
  - Previous endocarditis
  - **Unrepaired cyanotic congenital heart disease** including palliative shunts and conduits
  - **Completely repaired congenital heart defect** with prosthetic material or device, whether placed by surgery or by catheter intervention, **during the first six months** after the procedure
  - **Repaired congenital heart disease with residual defects** (persisting leaks or abnormal flow) at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialisation)
  - Cardiac transplantation recipients who develop cardiac valve abnormalities.

Infective endocarditis: prognosis

Infective endocarditis - streptococcal infection carries a good prognosis

Infective endocarditis - strongest risk factor is previous episode of infective endocarditis

Poor prognostic factors

- Staph aureus infection (see below) (→Acute endocarditis)
  - **((*Streptococcus viridans*) → Subacute bacterial endocarditis has a better prognosis.)**
- prosthetic valve (especially 'early', acquired during surgery)
- culture negative endocarditis
- low complement levels
- Infection of the aortic rather than mitral valve
- Associated rhythm disturbance.
- Heart failure
- Intravenous drug abuse (often left and right sided disease)
- **Old age**
- Insulin dependent diabetes mellitus, and
- Severe co-morbidities.

Mortality according to organism

- staphylococci - 30%
- bowel organisms - 15%
- streptococci - 5%

Non-bacterial thrombotic endocarditis (marantic endocarditis)

- due to platelet-fibrin thrombi that are prone to embolising.
- This form of non-infective endocarditis can be seen in persons who are very debilitated or who have a hypercoagulable state.
- The deposition of fibrin on valve leaflets causes sterile vegetations that can embolise.

Myocarditis

The short prodromal illness coupled with the development of biventricular heart failure, tachycardia, T-wave inversion and elevated troponin is most consistent with viral myocarditis. The features, including the mild flu-like illness, are consistent with Coxsackie B.

Causes

- viral:
  - **Currently,** the **most common** in adults:
    - **Parvovirus B19**
    - **Human herpes virus 6**
  - Other Viral Causes
    - **Coxsackie B virus**
      - most common in children
      - results in **dilated** cardiomyopathy.
      - Previously, the enteroviruses (including coxsackie virus) were the most common identified viruses.
      - Currently, parvovirus B-19 and human herpes virus 6 are considered the most common causes of viral myocarditis.
    - Adenovirus
    - HIV
    - Hepatitis C
    - Cytomegalovirus
    - Echovirus
    - Influenza virus
    - Epstein-Barr virus

- bacteria: diphtheria, clostridia
- spirochaetes: Lyme disease → most commonly presents as heart block.
- protozoa:
  - Chagas' disease,
    - caused by Trypanosoma cruzi, a common pathogen in South America
    - Chagas disease myocarditis results in **dilated** cardiomyopathy.
  - Toxoplasmosis
- autoimmune
- drugs:
  - doxorubicin
  - clozapine.

Presentation

- usually young patient with acute history
- history of viral prodrome 2 to 3 weeks prior to the onset
- **fever**
- chest pain,
  - due to involvement of the pericardium.
- SOB
- Palpitations
  - typically **sinus** tachycardia.
- Myocarditis can have features similar to cardiomyopathy and the mild valvular disease is quite compatible.

Investigations

- **Markedly raised troponin.**
  - Troponin is more sensitive than creatine kinase-MB (CPK-MB) in detecting myocardial inflammation.
- On echocardiography, → **global systolic dysfunction**

Treatment

- Supportive
- usually managed similar to heart failure.

DVLA: cardiovascular disorders

ICD means loss of HGV licence, regardless of the circumstances

DVLA advice post MI:
- **if successfully treated by angioplasty → cannot drive for 1 weeks**
- **If does not undergo angioplasty → cannot drive for 4 weeks**

- The guidelines below relate to car/motorcycle use unless specifically stated.
- For obvious reasons, the rules relating to drivers of heavy goods vehicles tend to be much stricter

Specific rules

- Hypertension:
  - can drive unless treatment causes unacceptable side effects, no need to notify DVLA.
  - If Group 2 Entitlement the disqualifies from driving if resting BP consistently 180 mmHg systolic or more and/or 100 mm Hg diastolic or more
- angioplasty (elective) - 1 week off driving
- **Percutaneous coronary intervention (PCI) – elective angioplasty with or without stent**
  - Group 1 car → Must not drive for at least 1 week but need not notify the DVLA
  - **Group 2 bus and lorry → He has to stop driving, inform the DVLA and return for an exercise tolerance test in 6 weeks after he has stopped his β-blocker for 48 h**
    - the DVLA guidelines state that the patient has to complete stage 3 of a Bruce protocol exercise tolerance test. There should be no residual chest pain or significant ECG changes.
- **Coronary artery bypass graft (CABG)**
  - Group 1 car → 4 weeks off driving
  - Group 2 bus and lorry:
    - Must not drive and must notify the DVLA.
    - May be relicensed/licensed after 3 months if:
      1. LV ejection fraction is at least 40%
      2. the requirements for exercise or other functional tests can be met at least 3 months postoperatively
      3. there is no other disqualifying condition.
- **Acute coronary syndrome:**
  - **4 weeks off driving**,
  - 1 week if successfully treated by angioplasty
- angina - driving must cease if symptoms occur at rest/at the wheel
- pacemaker insertion - 1 week off driving
- **implantable cardioverter-defibrillator (ICD):**
  - if implanted **for sustained ventricular arrhythmia**: cease driving for **6 months**.
  - If implanted prophylactically then cease driving for 1 month.
  - **Having an ICD results in a permanent bar for Group 2 drivers**
- **successful catheter ablation for an arrhythmia- 2 days off driving**
- **aortic aneurysm:**
  - aortic aneurysm of 6cm or more:
    - notify DVLA.
    - Licensing will be permitted subject to annual review.
  - aortic diameter of 6.5 cm or more disqualifies patients from driving
- **Heart failure**
  - DVLA guidance for Group 2 entitlements (HGVs and buses) is much more strict than Group 1 entitlements (cars and vans).
  - Symptomatic heart failure will lead to revocation of a Group 2 licence, regardless of whether the symptoms lead to incapacity.
  - **a left ventricular ejection fraction (LVEF) of < 40% bars him from driving a lorry, even if he becomes asymptomatic with treatment**
    - If a patient on treatment becomes asymptomatic, then they may be relicensed only if their LVEF is ≥ 40%.
  - For Group 1 entitlements, the DVLA does not need to be informed of symptomatic heart failure if it does not lead to distracting or incapacitating symptoms.
  - Any form of defibrillator is a bar to a Group 2 entitlement.

- heart transplant: DVLA do not need to be notified

Lymphoedema

Definition

- Chronic, progressive swelling of tissue with protein-rich fluid as a consequence of developmental (primary lymphoedema) or acquired (secondary lymphoedema) disruption of the lymphatic system.
- Extremities are most commonly affected, followed by genitalia.

Causes of lymphoedema include:

- primary: inherited
- secondary
  - nematode infection (**filariasis**)
  - malignancy, or cancer-related treatment.
  - surgery, injury resulting in damage to the lymphatic system
  - radiation,

Features

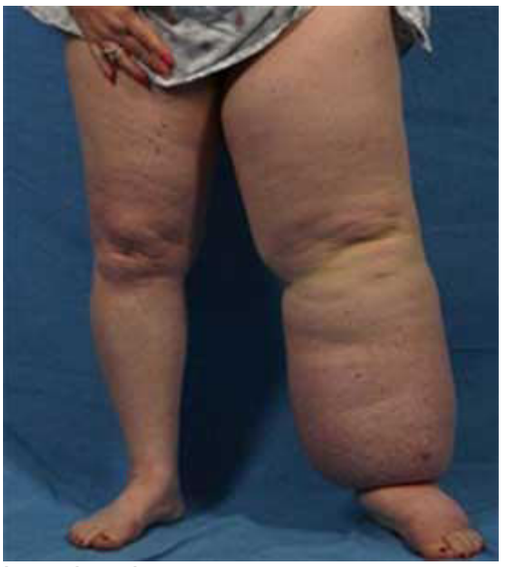
- **painless unilateral limb swelling;**
- pitting oedema is present in early disease, whereas non-pitting oedema is a sensitive but non-specific finding in advanced disease.

Diagnosis

- made on clinical grounds
- confirmed by **lymphoscintigraphy.**

Treatment

- First-line treatment involves **compression**, ranging from static garments to complex massage and pneumatic compression devices.
- Surgical procedures are reserved for patients refractory to conservative measures and/or with significant morbidity.
- There is no cure.



Lymphoedema

Notes & Notes

For MRCP part 1 & 11

By

Dr. Yousif Abdallah Hamad

Respiratory medicine

Updated

2017

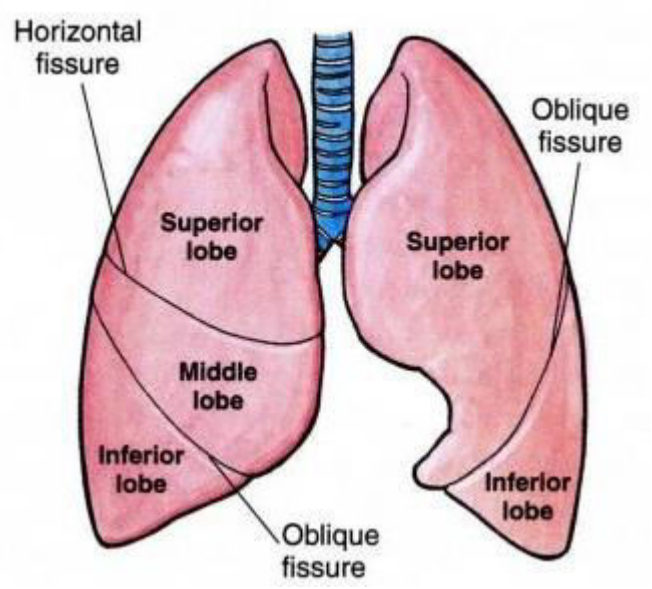
Contains:

1/ Passmedicine 2017
2/ On examination 2017
3/ Pastest 2017
4/ **Red fonts --> previous exams**
5/ Other updated UK sources

Lung development

- **Lamellar bodies in type II pneumocytes that produce surfactant** are seen by 22 weeks' gestation.
  - These contain 80% phosphatidylcholine.
- Absence of liquor, which is produced by the fetal kidneys, causes poor lung growth and a low phospholipid content. **Renal agenesis is therefore a cause of hypoplastic lungs**.
- Complete alveolisation does not occur until 28 weeks' gestation.
- **Complete development of the alveoli and the pores of Kohn only occurs around the age of 7 years.**

Anatomy



- The right lung is divided into three lobes: upper, middle and posterior. These are further divided into bronchopulmonary segments as follows:
  - Upper lobe – Three segments: apical, anterior and posterior
  - Middle lobe – Two segments: lateral and medial
  - Lower lobe – Five segments: apical, anterior basal, posterior basal, medial basal, lateral basal.
- The left lung has only nine segments. **The medial basal is absent in the left lower lobe.** Moreover, the middle lobe is replaced by the lingular lobe which has two segments called superior and inferior.
- On the right side the transverse fissure separates the upper lobe from the middle lobe.
- The oblique fissure runs posteriorly to anteriorly. As a result the upper lobe is represented anteriorly and the lower lobe is mainly posteriorly.
- The **oblique fissure** runs obliquely at 45 degrees from T4-5 to the anterior costo-phrenic angle, but is **only seen on the lateral chest radiograph**.

- The **horizontal fissure** runs from the hilum anteriorly to anterior chest wall, on the right side. The area above the horizontal fissure is the upper lobe, below the horizontal fissure is the middle lobe and below the **oblique fissure** is the lower lobe.
- Most of the resistance of the airway is due to the large central airways.
- The **Angle of Louis** (also known as the sternal angle or Angle of Ludwig) corresponds to **T4/T5 vertebral bodies**, which is the location at which the **trachea bifurcates to the main stem bronchi (carina).**

Azygos lobe of the lung

- azygos lobe is seen in about 0.5% of routine chest X-rays and is a normal variant.
- It is seen as a 'reverse comma sign' **behind the medial end of the right clavicle.**

Phrenic nerve palsy

- The diaphragm is innervated by the phrenic nerve (C3,4,5).
- **Causes of phrenic nerve palsy:**
  - thoracic surgery
  - infection
  - Guillain-Barré
  - invasion by an adjacent tumour
  - It may also be stretched by an aortic aneurysm.
- **supine FVC is significantly reduced**
- **Diagnosis** of unilateral paralysis:
  - In patients with normal lungs unilateral paralysis is usually asymptomatic and rarely requires treatment.
  - **suggested by** asymmetric elevation of the affected hemidiaphragm on X-ray,
  - **Confirmed by fluoroscopy**
    - **confirmed fluoroscopically by observing paradoxical diaphragmatic motion on sniff and cough**
    - **During a forced inspiratory manoeuvre (the 'sniff test),** the unaffected hemidiaphragm descends forcefully, increasing intra-abdominal pressure and pushing the **paralysed hemidiaphragm cephalad (paradoxical motion)**
    - Fluoroscopy is inaccurate for the diagnosis of bilateral paralysis.

The epithelium of respiratory tract

- The epithelium that lines the majority of the conducting portion of the respiratory tract is **pseudostratified** columnar epithelium with cilia and goblet cells.
- For trachea to primary bronchus to secondary bronchus, the epithelium in all regions is **pseudostratified.**
- **For Secondary bronchus to large bronchiole, the epithelium changes from pseudostratified to simple columnar**
- For large bronchiole to small bronchiole, the epithelium changes from **simple columnar** to **simple cuboidal.**
- For small bronchiole to terminal bronchiole, the epithelium in both these regions is **simple cuboidal.**

Lung physiology

Pulmonary surfactant

- Surfactant is a mixture of phospholipids, carbohydrates and proteins
- **Released by type 2 pneumocytes**
- **The main functioning component in surfactant is dipalmitoyl phosphatidylcholine (DPPC) or lecithin. which reduces alveolar surface tension.**
  - Lecithin makes up more than 75% of the phospholipids covering the air-liquid interface in pulmonary alveoli.
- The most abundant phospholipid in surfactant is dipalmitoylphosphatidylcholine, or lecithin. Lecithin makes up more than 75% of the phospholipids covering the air-liquid interface in pulmonary alveoli.

Basics

- first detectable around 28 weeks
- as alveoli decrease in size, surfactant concentration is increased, helping prevent the alveoli from collapsing
- reduces the muscular force needed to expand the lungs (i.e. decreases the work of breathing)
- lowers the elastic recoil at low lung volumes and thus helps to prevent the alveoli from collapsing at the end of each expiration
- Because of surfactant, the pressure difference across the pleura required to inflate the lungs, is usually no more than about 4 cmH_2O.

Other notes

- Resting pulmonary blood flow in an adult is around 5 L/min.
- The V: Q ratio is higher in the apical than the basal segments.
- While a single small airway provides more resistance than a single large airway, resistance to air flow depends on the number of parallel pathways present. For this reason, the large and particularly the medium-sized airways provide greater resistance to flow than do the more numerous small airways.
- Cartilage disappears in the terminal bronchioles.

Deference between pulmonary vascular system and systemic circulation:

- The normal **pulmonary circulation** is characterised by **low** pressures, **low** flow rates, **high** compliance vessels**.**

Control of respiration

- **central regulatory centres**
  - medullary respiratory centre
  - apneustic centre (lower pons)
  - pneumotaxic centre (upper pons)
- **central and peripheral chemoreceptors**
  - central: raised [H+] in ECF stimulates respiration
  - peripheral: carotid + aortic bodies, respond to raised pCO2 & [H+], lesser extent low pO2
- **pulmonary receptors**
  - stretch receptors, lung distension causes slowing of respiratory rate (Hering-Bruer reflex)

- irritant receptor, leading to bronchoconstriction
- juxtacapillary receptors, stimulated by stretching of the microvasculature

Peripheral chemoreceptors are known to transmit information via the glossopharyngeal and vagus nerves regarding changes of carbon dioxide in the blood. **Which will most likely receive information regarding these changes?**

➡ **Solitary nucleus** (in the medulla oblongata)

September 2015 exam: Which one is the most important stimulator of the central chemoreceptors? Decrease in pH

Chloride shift

- CO2 diffuses into RBCs
- CO2 + H2O → carbonic anhydrase → HCO3- + H+
- H+ combines with Hb
- **HCO3- diffuses out of cell, - Cl- replaces it**
- Therefore, **during exercise**, there is increased formation of CO_2 in the peripheral tissues that needs to be transported to the lungs. Since exercise increases CO_2 production which will enter the venous blood **the values of HHb, $HbCO_2$, RBC Cl^- content, and plasma HCO_3^- will all increase.**

Bohr Effect

- **Increasing acidity (or pCO2) means O2 binds less well to Hb**

Haldane effect

- ↑ pO2 means CO2 binds less well to Hb

Acclimatisation to life at high altitudes:

- Acclimatisation results in increased Hb with erythrocytosis.
- **Pulmonary artery pressure increases to oxygenate more blood.**
- **2,3-DPG increases.**
- Respiration is normal when subjects are acclimatised to altitude as is cardiac output. (Periodic respiration is a feature of non-acclimatisation).

Lung compliance is defined as change in lung volume per unit change in airway pressure

Causes of ↑ compliance	Causes of ↓ compliance
• Age • Emphysema	• Pulmonary edema • Pulmonary fibrosis • Pneumonectomy • Kyphosis

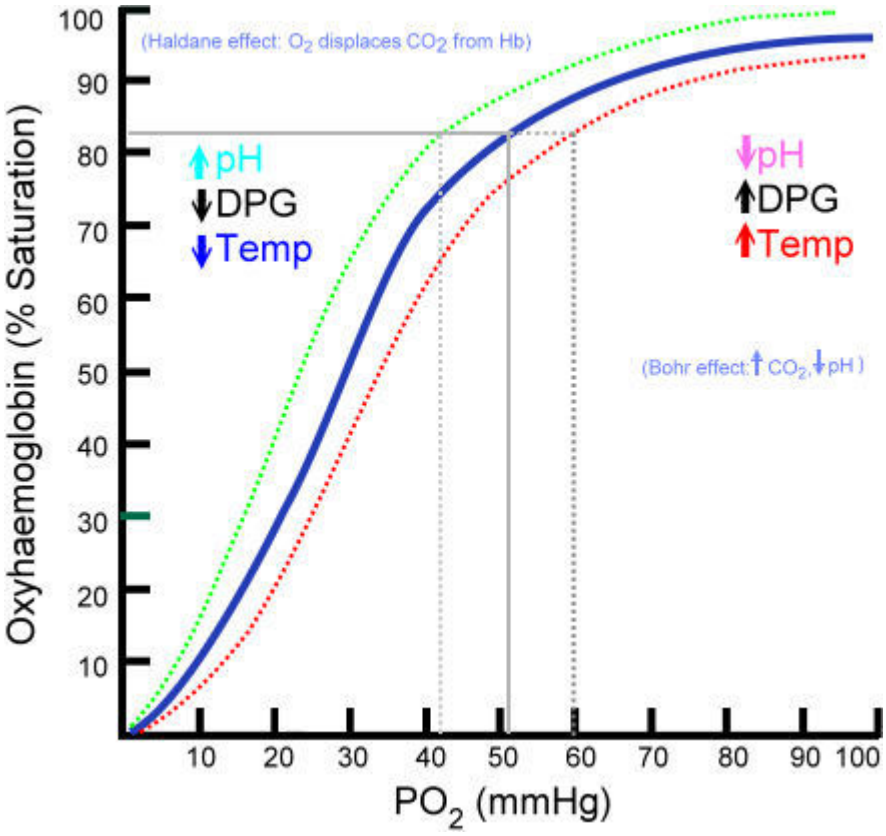
Gas exchange

- On average the bronchi divide 23 times.
- The initial 16 branches or so are known as the conducting zone and do not take part in gas exchange.
- Generation 17–23 contain alveoli and take part in gas exchange.

Gas exchange can occur in the final seven branches of the bronchoalveolar tree

Oxygen Dissociation Curve

Oxygen dissociation curve
- shifts Left - Lower oxygen delivery - Lower acidity, temp, 2-3 DPG - also HbF, carboxy/methaemoglobin
- shifts Right - Raised oxygen delivery - Raised acidity, temp, 2-3 DPG



The L rule

Shifts to L → Lower oxygen delivery, caused by
- Low [H+] (alkali)
- Low pCO2
- Low 2,3-DPG
- Low temperature

Another mnemonic is 'CADET, face Right!' for CO2, Acid, 2,3-DPG, Exercise and Temperature

- **Oxygen Dissociation Curve** describes the relationship between the percentage of saturated hemoglobin and partial pressure of oxygen in the blood.
- **It is not affected by hemoglobin concentration**, but affected by its quality (HbF, methemoglobin).
- Each hemoglobin molecule has the capacity to carry four oxygen molecules.

Basics

- Shifts to right = for given oxygen tension there is ↓ saturation of Hb with oxygen i.e. Enhanced oxygen delivery to tissues
- Shifts to left = for given oxygen tension there is ↑ saturation of Hb with oxygen i.e. ↓ oxygen delivery to tissues

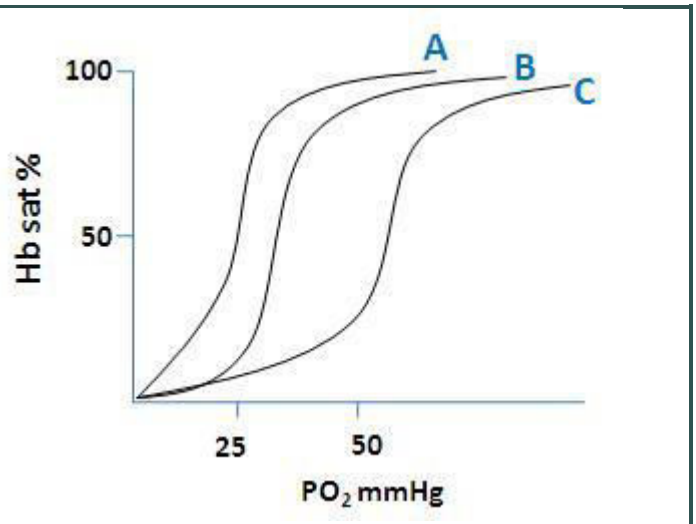
Shifts to **R**ight = **R**aised oxygen delivery	Shifts to **L**eft = **L**ower oxygen delivery
• **R**aised [H+] (acidity) • **R**aised PCO2 • **R**aised 2,3-DPG • **R**aised temperature	• **L**ow [H+] (alkali) • **L**ow PCO2 • **L**ow 2,3-DPG • **L**ow temperature • HbF, methemoglobin, carboxyhaemoglobin

- Left shift of the curve is a sign of hemoglobin's ↑ affinity for oxygen (eg. at the lungs).
- Similarly, right shift shows ↓ affinity, as would appear with an ↑ in body temperature, hydrogen ion, 2,3- **d**iphos**p**ho**g**lycerate (also known as bisphosphoglycerate) or carbon dioxide concentration (the Bohr effect)
- Carbon monoxide has a much higher affinity for hemoglobin than oxygen does. In carbon monoxide poisoning, oxygen cannot be transported and released to body tissues thus resulting in hypoxia.
- With fetal hemoglobin, the shift facilitates diffusion of oxygen across the placenta. The oxygen dissociation curve for myoglobin exists even further to the left.
- A fall in the partial pressure of oxygen (pO2) in the blood leads to vasoconstriction of the pulmonary arteries. This allows blood to be divered to better aerated areas of the lung and improves the efficiency of gaseous exchange.
- **The P_{50}**
  - **The P_{50}** is the oxygen tension at which hemoglobin is 50% saturated.
  - The normal P_{50} is 26.7 mm Hg.

- With increasing oxygen affinity of hemoglobin, P50 is decreased and unloading of oxygen to tissues becomes more difficult.

Pulmonary arteries vasoconstrict in the presence of hypoxia

Question
A 24-year-old woman is evaluated before and after practice to assess oxygen delivery to her muscles. The hemoglobin-oxygen dissociation curve is shown.
Curve B is taken before practice.
Which characteristics will most probably describe curve A?
Answer:
If curve B is taken before practice, it will be used as reference point. Curve A shows shifts to the left.
Increased pH with decreased 2,3-diphosphoglycerate concentration



Pulmonary function tests

Pulmonary function tests can be used to determine whether a respiratory disease is obstructive or restrictive.

Tidal Volume (TV)
- Volume inspired or expired with each breath at rest
- 500ml in ♂s, 350ml in ♀s

Inspiratory Reserve Volume (IRV) = 2-3 L
- Maximum volume of air that can be inspired after normal tidal inspiration
- Inspiratory capacity = TV + IRV

Expiratory Reserve Volume (ERV) = 750ml
- Maximum volume of air that can be expired after normal tidal expiration

Residual volume (RV) = 1.2L
- Volume of air remaining after maximal expiration
- ↑ with age
- Increased in obstructive lung disease due to air trapping
- RV = FRC – ERV (Functional Residual Capacity - Expiratory Reserve Volume)

The FEV1/FVC ratio:
- is < 70% in obstructive lung disease
- and > 70% in restrictive lung disease.

Vital Capacity (VC) = 5L
- Maximum volume of air that can be expired after a maximal inspiration
- 4,500ml in ♂s, 3,500 mls in ♀s
- ↓ with age
- VC = IC + ERV

- In the absence of equipment, having the patient count at a steady rate for one breath gives a rough estimate of how much air they can expel. This is a common bedside or outpatient procedure that is done with myasthenic patients.

Forced vital capacity

- is a measure of the force, volume, and speed with which air can be maximally expelled from the lungs.
- The maneuver would be to take a deep breath, and then blow it out as hard as you can for as long as you can to maximally expel air from the lungs.
- This is commonly done to assess patients with asthma and chronic obstructive pulmonary disease.

Total lung capacity (TLC) is the sum of the vital capacity + residual volume

Minute ventilation

- Minute ventilation is equal to tidal volume (volume of air moved in normal breathing) multiplied by the respiratory rate.
- In metabolic alkalosis, one could increase CO_2 content by decreasing the minute ventilation (volume of air moved per minute).
- **Reducing either one of these variables(↓tidal volume or ↓ respiratory rate) will decrease minute ventilation and lead to increased CO_2 retention.**

Pre-operative screen of pulmonary function

- **What is the best pre-operative screen of pulmonary function for a smoker patient evaluated for a coronary artery bypass graft (CABG).?**
  - **Ratio of the forced expiratory volume in 1 second to the forced vital capacity**
    - The arterial blood gas measurements reflect acid–base disorders, but they do not predict pulmonary complications in the post-operative period.

Anatomical dead space in the lung

- The anatomical dead space can be used to calculate **alveolar ventilation** by subtracting it from the tidal volume and multiplying the result by the respiratory rate.
  - **Alveolar ventilation = (tidal volume – anatomical dead space) X respiratory rate**
  - **The normal anatomical dead space is approximately 150 ml.**
  - **eg**: If we take the tidal volume to be about 500 ml and the respiratory rate to be about 15/min, this gives a normal alveolar ventilation of (500 - 150) X 15 = 5250 ml/min.
- The dead space can be increased in diseases that cause an additional physiological dead space, where parts of lung do not take part in gas exchange (eg **pneumonia**)

Forced vital capacity (FVC)

- Respiratory muscle function is best monitored by frequent assessment of the forced vital capacity (FVC).
- **FVC is also the best way to monitor respiratory function in any neurological disorders that can affect the respiratory muscles (e.g. GBS, myasthenia gravis)**
- Diaphragmatic weakness occurs in one-third of patients with Guillain-Barré syndrome (GBS) and involvement of the neck muscles, tongue and palate leads to further respiratory compromise

- **ITU admission** is recommended when **FVC is less than 20 mL/kg** and **intubation is recommended in most cases when FVC is less than 15 mL/kg.**

Obstructive vs. Restrictive lung diseases

	Obstructive	Restrictive
Spirometry	FEV1/FVC < 80% **(FEV1/FVC <0.7)**	FEV1/FVC > 80% **(FEV1/FVC >0.7)**
	FEV1 - significantly reduced (<80% predicted normal)	**FEV1** - reduced (<80% predicted normal)
	FVC - reduced or normal FEV1% (FEV1/FVC) - reduced	**FVC** - significantly reduced (<80% predicted normal) FEV1% (FEV1/FVC) - normal (>0.7) or increased
Examples	Chronic obstructive pulmonary disease • chronic bronchitis • emphysema Asthma Bronchiectasis	**Intrapulmonary** • idiopathic pulmonary fibrosis • extrinsic allergic alveolitis • coal worker's pneumoconiosis/progressive massive fibrosis • silicosis • sarcoidosis • histiocytosis • drug-induced fibrosis: amiodarone, bleomycin, methotrexate • asbestosis **Extrapulmonary** • neuromuscular disease: polio, myasthenia gravis • obesity • scoliosis

Explanation of high FEV-1/FVC ratio in lung fibrosis:

- In lung fibrosis both (FEV-1) and (FVC) are reduced below predicted values, but **because of high elastic recoil** most forced expiratory volume will be expelled in the first second compared to full forced expiration - this leading to a relatively high FEV-1/FVC ratio.

Pulmonary function in obesity

- **Obesity could show a significant restrictive defect**.
- It is associated with hypoventilation and thus can cause hypercapnia.

- **would not affect the transfer coefficient (Kco)** (ie after correcting for alveolar volumes). the gas exchange after correcting for the alveolar volume would in fact be high.
- FVC falls when measured in the supine position due to increased abdominal fat, leading to a functional reduction in FVC.

Peak expiratory flow rate (PEFR)

- PEFR readings are an objective measure of airway obstruction and advised for regular assessment of lung function.
- A mid-expiratory flow rate (**between 25% and 75%** of the expired vital capacity) is a good measure of **airways obstruction**.
- It is more sensitive than the forced expiratory volume in 1 second (FEV-1) for identifying early airway obstruction. It is effort-independent.
- In a restrictive pattern the flow-volume loop is reduced in size but looks similar in shape to normal.
- **The most accurate correlation of the peak expiratory flow rate (PEFR) is with height.**
- It is impaired in bronchiolitis obliterans, smokers , patients with rejection reactions following bone-marrow, lung and heart transplants.

Transfer factor (**D_{Lco}** or **T_{Lco}** (diffusing capacity or **t**ransfer factor of the lung for carbon monoxide (CO))

Transfer factor
- raised: asthma, haemorrhage, left-to-right shunts, polycythaemia
- low: everything else

- The transfer factor describes the rate at which a gas will diffuse from alveoli into blood.
- Carbon monoxide is used to test the rate of diffusion.
- Results may be given as the total gas transfer (TLCO) or that corrected for lung volume (transfer coefficient, KCO).
- Dlco is measured by looking at end-expiratory levels of carbon monoxide after inspiring a small amount and breath-holding.
- Diffusion capacity of carbon monoxide depends on the thickness of the alveolar wall. diffusion will be increased in healthy compared with unhealthy lungs, where the thickness is likely to increase and the surface area available for gas exchange to decrease.

Causes of raised and lower TLCO:

Where alveolar haemorrhage occurs, the TLCO tends to increase due to the enhanced uptake of carbon monoxide by intra-alveolar haemoglobin.

Causes of a raised TLCO	Causes of a lower TLCO
• asthma • pulmonary haemorrhage (Wegener's, Goodpasture's) • left-to-right cardiac shunts • polycythaemia • hyperkinetic states • early left heart failure • male gender, • exercise • obesity	• pulmonary fibrosis • pneumonia • pulmonary emboli • pulmonary oedema • emphysema • anaemia • low cardiac output

- convalescent asthma (ربو في طور النقاهة- مستقر) → ↑transfer factor - in contrast to **acute** asthma where it is decreased
- **Asthma is most likely associated with normal Tlco** , but sometimes increased during an attack, and the cause of this change is not known.
- **Pulmonary AV malformations cause right-to-left shunts, so reducing Tlco values and provoking hypoxaemia (↓ Pao2), with a normal lung volumes** (eg FEV1 & FVC).

Factors interfere with interpretation of the Diffusing capacity (DLCO) test:

- **Smoking on the morning of the test** (within around eight hours of the test**):**
  - **Carbon monoxide in cigarette smoke ==> raises ↑ carboxyhaemoglobin (COHb) (to as high as 10-15% (normal value 1-2%). ==> ↓ reduces DLCO.**
  - Increasing COHb reduces DLCO **because:**
    - carbon monoxide (CO) is substantially increased, leading to a reduced driving pressure for CO across the air-blood barrier.
    - some of the patient's haemoglobin (Hb) will already be tightly bound by CO and therefore the overall amount of Hb available for binding by the test CO is decreased.
- Significant amount of Alcohol vapours in the morning of the test (not small amount)
- Severe kyphosis (not mild)
- Sever scoliosis (not mild)

Transfer coefficient of carbon monoxide (KCO)

- .KCO is a measure of the efficiency of gas exchange into the blood stream.
- **It is reduced if the lungs are damaged**
  - **The transfer coefficient will be reduced in patients with interstitial lung disease**
  - normal KCO may rule out significant restrictive lung disease
  - **the best test - after CT- to confirm restrictive lung disease due to a parenchymal disorder**
  - **sarcoidosis would reduce the transfer coefficient as there is damage to the alveolar cells themselves**
- **Causes of an increased Kco**
  - increased if there is additional blood in the lungs to remove carbon monoxide.

- usually as results from an increase in red blood cells in the lungs due to greater blood flow, haemorrhage, or polycythaemia.
- If the density of pulmonary capillaries per unit alveolar volume is greater than normal.
  - This occurs most commonly in patients with **extrapulmonary volume restriction**, when the **density of pulmonary capillaries is unusually high in relation to the (restricted) lung volume** at which the measurement is made.
- increase with age.

- **Causes of an increased KCO with a normal or reduced TLCO**
  - (Low Tlco but normal/high Kco (ie the same cardiac output is going through a smaller alveolar volume) is **characteristic of extra-thoracic restriction:**
    - pneumonectomy/lobectomy
    - scoliosis/kyphosis
    - neuromuscular weakness
    - ankylosis of costovertebral joints e.g. ankylosing spondylitis
    - Severe thoracic skin thickening,
    - **Pleural disease**
    - **Obesity**
- In **intrapulmonary restriction**, both (Tlco & Kco) are usually decreased.
- Isolated decreases in gas transfer are typical of pulmonary vascular diseases such as vasculitis and recurrent pulmonary embolism.
- **Relation between Dlco, VA (alveolar volume) & KCO (transfer coefficient)**
  - Dlco is simply the product of Va and Kco,
  - **TLCO = KCO x Alveolar volume (VA)**
  - The transfer coefficient (Kco) represents the uptake of carbon monoxide per litre of effective alveolar volume (Va)
  - The Kco tending to be normal after lung resection, when both Tlco and Va are reduced to roughly the same degree
  - Dlco is used to monitor disease progression and response to treatment in fibrosing lung disease.
  - In lung fibrosis the Dlco is low, typically as a product of both low Va and Kco.
  - In lung haemorrhage, Dlco is high as a product of a low Va but a high Kco (in contrast to the pattern in pulmonary vasculitis, where there is a low Kco but often a normal Va).

Arterial Blood Gas (ABG)

Arterial blood gases should be used for assessing respiratory failure in Critically ill Patients or those with Shock or Hypotension (Systolic blood pressure < 90mmHg)
(British Thoracic Society, 2017)

The best site for sampling

- The **radial artery** is the one most often used in practice in the acute care setting because of easy access and the fact that the artery is superficial and easily palpated.

- **Prior to any attempt at arterial puncture the practitioner must perform the Modified Allen's Test** (WHO, 2010)

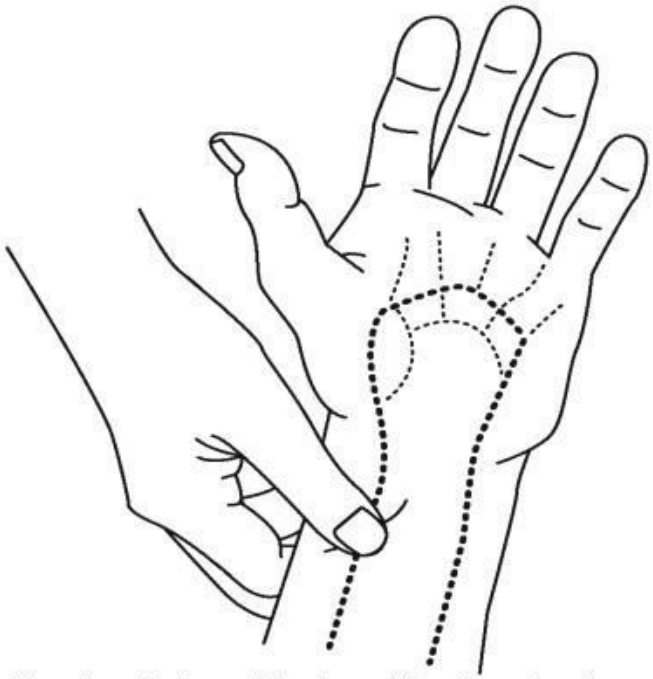
Contra-Indications of ABG sampling

- **Absent ulnar circulation – as demonstrated by Modified Allen's Test.**
- Impaired circulation e.g. **Raynaud's Disease**
- History of arterial spasms
- Arteriovenous fistula
- Distorted anatomy/ trauma/burns to the limb - at or proximal to the
- attempted arterial puncture site
- Medium or high dose anticoagulation therapy, or history of clotting disorder
- Severe coagulopathy
- Abnormal or infectious skin processes at/or near puncture site

Modified Allen's test

- modified Allen test measures arterial competency, and **should be performed before taking an arterial sample**.
- **Method**
  - Instruct the patient to clench his or her fist; if the patient is unable to do this, close the person's hand tightly.
  - Using your fingers, apply occlusive pressure to both the ulnar and radial arteries, to obstruct blood flow to the hand.
  - While applying occlusive pressure to both arteries, have the patient relax his or her hand, and check whether the palm and fingers have blanched. If this is not the case, you have not completely occluded the arteries with your fingers.
  - Release the occlusive pressure on the ulnar artery only to determine whether the modified Allen test is positive or negative.
- **Interpretation**
  - ***Positive modified Allen test***
    - If the hand **flushes within 5-15 seconds** it indicates that the ulnar artery has good blood flow; this normal flushing of the hand is considered to be a **positive test**.
  - ***Negative modified Allen test***
    - If the hand does not flush within 5-15 seconds, it indicates that ulnar circulation is inadequate or nonexistent;
    - in this situation, the **radial artery supplying arterial blood to that hand should not be punctured.**

Thumbs occlude radial and ulnar arteries. Pallor is produced by clenched fist.



Thumb occludes radial artery while ulnar artery is released and patent. Unclenched hand returns to baseline colour because of ulnar artery and connecting arches.

Interpretation of ABG

- **Mixed metabolic and respiratory acidosis**
  - pH → below 7.35
  - PCO_2 → elevated (> 6 kP_a) indicating a respiratory cause for acidosis
  - Bicarbonate → reduced (< 20 mmol/L) which is contributing to the acidosis.

Respiratory acidosis

- Respiratory acidosis may be caused by a number of conditions:
  - COPD
  - decompensation in other respiratory conditions e.g. life-threatening asthma / pulmonary oedema
  - sedative drugs: benzodiazepines, opiate overdose

Signs and symptoms of respiratory acidosis		
Central nervous system	**Respiratory system**	**Cardiovascular system**
Cerebral vasodilation	Breathlessness	Flushing, bounding pulse
Increased intracranial pressure	Cyanosis	Cor pulmonale
Headache, confusion, agitation	Pulmonary hypertension	Systemic hypotension
Hallucinations, transient pyschosis		Arrhythmias
Myolonic jerks, flapping tremor, extensor plantars, depressed reflexes		Initially good cardiac output, then decreases
Papilloedema, constricted pupils		
Seizures, coma		

- Pathophysiological changes in case of **acute acidosis**:
  - Occurred too quickly for metabolic compensation to occur via renal bicarbonate reabsorption, which takes 3-5 days to occur. **(bicarbonate will be normal in acute respiratory acidosis)**
  - The oxygen dissociation curve is shifted to the right in acute acidosis, i.e. haemoglobin has a decreased affinity for oxygen.
  - High pulmonary pressures would be expected after arrest scenario, as the **pulmonary arterioles constrict in response to hypoxia**.

- **Compensated respiratory acidosis ==> normal PH, high CO_2, low O_2 .**
  - The fact that the pH is normal means that there must be bicarbonate retention to compensate.

- In **bronchopulmonary dysplasia**, there is usually long-term CO_2 retention with compensatory increase in bicarbonate leading to a positive base excess and normal pH.

Respiratory alkalosis

Common causes

- Anxiety leading to hyperventilation (Hyperventilation will result in carbon dioxide being 'blown off', causing an alkalosis.) **=>** high PH , low PCO2 , normal PO2.
  - not associated with hypoxia.
- pulmonary embolism
- Acute severe asthma
  - associated with hypoxia and normal or rising CO_2
- salicylate poisoning
  - salicylate overdose leads to a mixed respiratory alkalosis and metabolic acidosis.
    - **Early stimulation of the respiratory centre** leads to a **respiratory alkalosis** whilst later the **direct acid effects of salicylates** (combined with acute renal failure) may lead to an **acidosis**.
- CNS disorders:
  - stroke,
  - subarachnoid haemorrhage,
  - encephalitis
- altitude
- pregnancy
- pain
- Excessive mechanical ventilation.

Differential diagnosis of respiratory alkalosis with type 1 respiratory failure (low pO_2 and low pCO_2.):

- Chronic venous thromboembolism (most likely).
- Pulmonary fibrosis (but basal crackles may be expected).

Acute vascular response to hypoxia

- acute vascular response to hypoxia is thought to be mediated by nitrous oxide (NO).
- Systemic reaction to hypoxia is an increase in sympathetic tone, which leads to vasoconstriction;
- however in the vital body organs (such as the brain, heart, kidneys and intestines) local mediators cause vasodilation in the vascular bed to maintain sufficient glucose and oxygen supply.
- **Within the pulmonary vasculature, hypoxia induces sustained vasoconstriction** which redirects blood flow to areas of the lungs that are relatively oxygen rich. This limits the amount of blood passing through the lungs that is not oxygenated; i.e. it improves the ventilation / perfusion ratio (V/Q).

Which vascular beds vasoconstrict in response to hypoxia?
➔ **Pulmonary**

Chest x-ray

Cavitating lung lesion

Differential

- abscess (Staph aureus, Klebsiella and *Pseudomonas*)
- squamous cell lung cancer
- tuberculosis
- Wegener's granulomatosis
- Progressive massive fibrosis: is a complicated coal worker's pneumoconiosis where pulmonary nodules coalesce and cavitate.
- pulmonary embolism
- Systemic embolisation: occurs in 20-50% of cases of infective endocarditis, and can involve the lungs, central nervous system, coronary arteries, spleen, bowel and extremities.
- rheumatoid arthritis
- aspergillosis, histoplasmosis, coccidioidomycosis
- Actinomycosis: is a chronic granulomatous disorder caused by a Gram-positive anaerobe.

Differential diagnosis of diffuse opacities on chest X-ray

The fluffy shadows on the chest X-ray could represent:

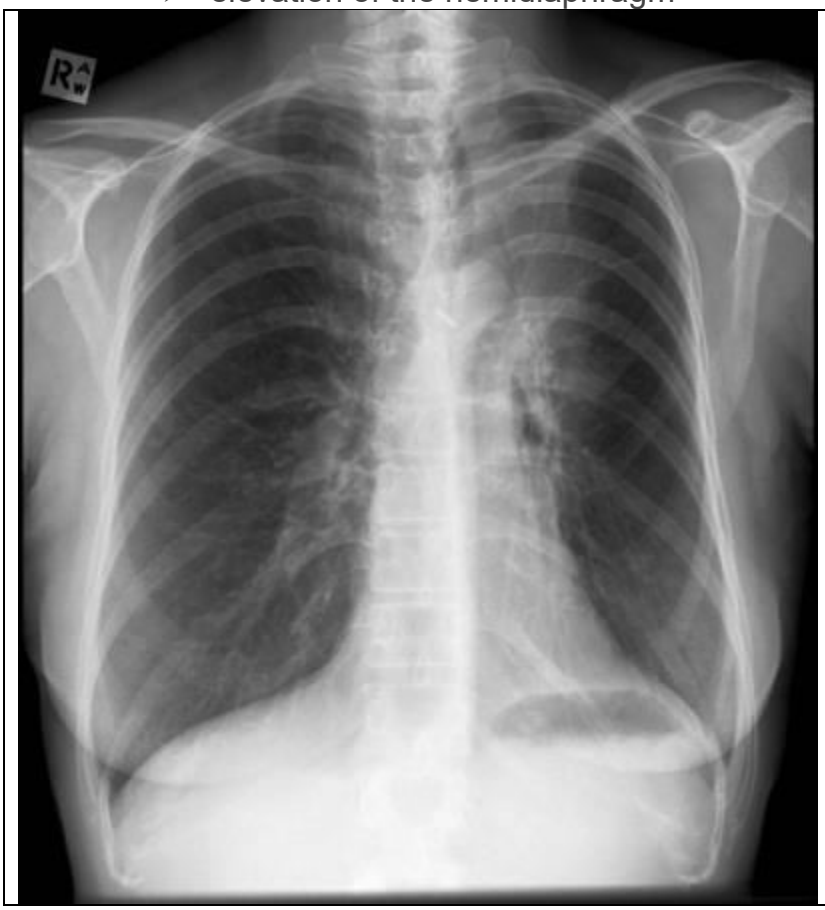
- Pulmonary oedema
- Interstitial lung disease
- Vasculitic lung disease
- Pulmonary haemorrhage

Coin lesions on chest x-ray

- **Coin lesions** (solitary pulmonary nodule)
  - malignant tumour: lung cancer or metastases
  - benign tumour: hamartoma
  - infection: pneumonia, abscess, TB, hydatid cyst
  - AV malformation
- Risk stratification of incidental pulmonary nodules
  - Risk stratification needs to take into account the risk factors for lung cancer or metastases, as well as size and character of the nodule.
  - surveillance according to British Thoracic Society Guidelines published in 2005.
    - Nodules **<** 5 mm require no further surveillance.
    - Nodules 5-6mm require CT at 1 year
    - **Nodules 6-8 mm require CT at 3 months**
    - Nodules **>** 8 mm require malignancy risk calculation using the Brock model and should then have CT or PET according to whether this risk is > 10%.
      - The Brock model takes into account age, gender, family history and features of the nodule

Lobar collapse on chest x-ray

- Common causes of lobar collapse include:
  - lung cancer (the most common cause in older adults)
  - asthma (due to mucous plugging)
    - Mucous plugging is not uncommon in asthmatic patients and can occasionally cause lobar collapse.
    - Treatment
      - adequate hydration and chest physiotherapy.
      - Bronchoscopy with lavage may be required if this is unsuccessful.
  - foreign body
- The general **signs of lobar collapse on a chest x-ray** are as follows:
  - tracheal deviation towards the side of the collapse
  - mediastinal shift towards the side of the collapse
  - elevation of the hemidiaphragm



This patient has a **left upper lobe collapse**. The following can be seen on the film to support this:

- hazy opacity projected over the left upper zone
- deviation of the trachea to the left
- elevation of the left hemidiaphragm
- loss of lung volume in the left hemithorax

White lung lesions on chest x-ray

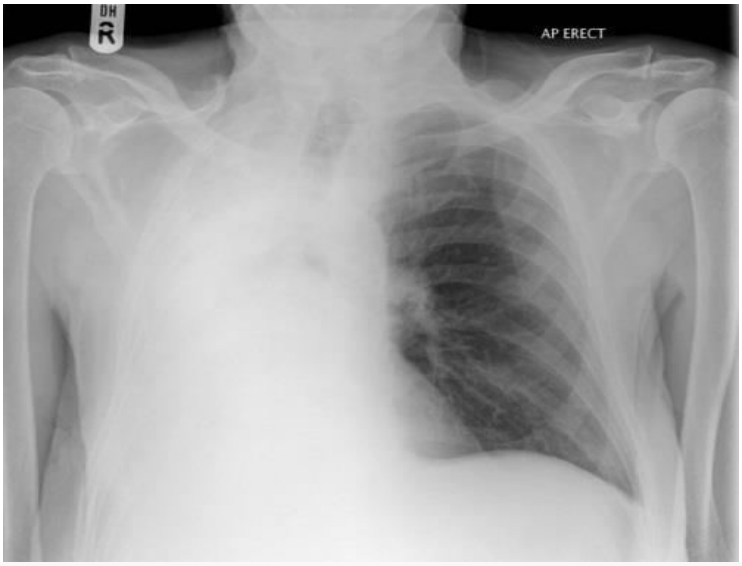
There are numerous causes of white shadowing in the lungs including:

- consolidation
- pleural effusion
- **collapse**
- pneumonectomy
- specific lesions e.g. tumours
- fluid e.g. pulmonary oedema

If there is a **'white-out' of a hemithorax** it is useful to assess the position of the trachea - is it central, pulled or pushed from the side of opacification.

Trachea pulled toward the white-out	Trachea central	Trachea pushed away from the white-out
Pneumonectomy Complete lung collapse (Atelectasis) e.g. endobronchial intubation **Pulmonary hypoplasia**	**Consolidation** Pulmonary oedema (usually bilateral) **Mesothelioma**	**Pleural effusion** Diaphragmatic hernia **Large thoracic mass**

- **In the context of an acute aspiration, the most likely process is atelectasis secondary to bronchial obstruction.**
- Obstruction of the mainstem bronchus will prevent gas from entering the affected lung and will lead to the collapse of that lung.
- The collapsed lung will cause complete whiteout of the hemithorax on chest X-ray and will cause ipsilateral tension on the mediastinum leading to shifting of the trachea toward the affected lung.



Lung collapse - note how the trachea is pulled towards the side of the white-out

Characteristics of consolidation on chest x-ray:

- **Consolidation in the left lower lobe** ➔obliterates the diaphragm.
- **Lingular consolidation** ➔will obliterate the left heart border. **The loss of the left heart border is a classic sign of left lingual consolidation.**
- **Consolidation of the right middle lobe** ➔ obscures the right heart border (right atrial edge). More extensive consolidation also involves the right and left peri-hilar regions. The superior extent is well demarcated, due to the horizontal fissure.
- **Right upper lobe collapse** results in ➔displacement of the horizontal fissure upwards. The right hilum can also appear enlarged.

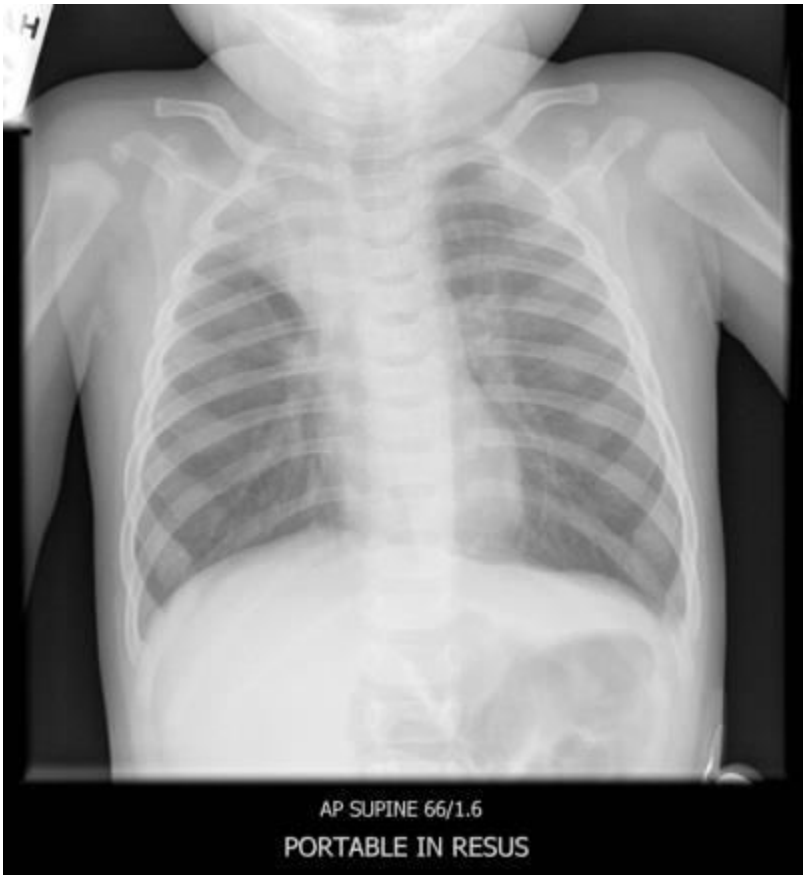
- **The classical signs of right upper lobe consolidation → abnormal opacity within the right upper lobe abutting the horizontal fissure.**

Atelectasis (lung collapse)

- Atelectasis is when part or all of one lung collapses, preventing normal oxygen absorption.
- Breath sounds are quietened over areas of atelectasis.
- During expiration normal breath sounds rapidly fade out, probably due to the decreasing airflow rate.

Causes of atelectasis

- Obstruction of an air passage by a thick mucus plug from an infection or other disease, such as cystic fibrosis
- Tumours in the air passages
- Tumours or blood vessels outside the air passages, causing pressure on the airways
- Inhaled objects, such as peanuts or small toys
- Prologoned chest or abdomincal surgery under general anaesthetic
  - **Atelectasis is a common post-operative complication**
- Chest injury or fractured ribs
- **Penetrating wounds**



There is increased opacity in the right upper zone, The lateral / inferior border of the shadowing actually represents the horizontal fissure which has been 'dragged' upwards.

Alveolar-arterial (A-a) oxygen gradient

- is a measure of the difference between the alveolar concentration (**A**) of oxygen and the arterial (**a**) concentration of oxygen.
- It is used in diagnosing the source of hypoxemia. For example,
  - in high altitude, the arterial oxygen PaO_2 is low but only because the alveolar oxygen (PAO_2) is also low.
  - in states of **ventilation perfusion mismatch,** such as pulmonary embolism or right-to-left shunt, oxygen is not effectively transferred from the alveoli to the blood which results in elevated A-a gradient
- the normal approximately 0.5-2.0 kPa (< 15 mmHg).
- Causes of widening A-a gradient
  - Ventilation/perfusion (V/Q) mismatch,
  - diffusion abnormalities and
  - right to-left shunting
- Hypoventilation causes hypoxaemia with a normal A-a gradient.
- This means that changes in alveolar-arterial gradient occur with ventilatory disorders such as pneumonia and disorders of the vasculature such as a pulmonary embolus.
- The alveolar arterial (a-a) gradient is calculated using the following equation (where PAO2 = alveolar oxygen and the Pao2 and PaCO2 are the arterial O2 and CO2 levels respectively):
- A–a gradient = **PA**O2 − PaO2
- A–a gradient is approximated: **$(150 - 5/4(pCO_2)) - Pa_{O2}$**

Flow volume loop → Assessing compression of the upper airway

Flow volume loop is the investigation of choice for upper airway compression

A normal flow volume loop is often described as a 'triangle on top of a semi circle'

Cough (www.brit-thoracic.org.uk)

- Acute cough is defined as one lasting less than 3 weeks
- Chronic cough is defined as one lasting more than 8 weeks.
- There is a grey area between 3 to 8 weeks and this includes post-viral coughs.
- Failure to consider GORD as a cause for cough is a common reason for treatment failure.
  - Reflux associated cough may occur in the absence of gastrointestinal symptoms.
  - proton pump inhibitors and alginates should be undertaken for a minimum of 3 months.
- the **cough center of the brain, located in** the **nucleus tractus solitarius of the medulla** of the brainstem

Dyspnoea

Medical Research Council dyspnoea scale:

Grade	Degree of breathlessness related to activities
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying or walking up a slight hill
3	Walks slower than contemporaries on level ground because of breathlessness, or has to stop for breath when walking at own pace
4	Stops for breath after walking about 100 m or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when dressing or undressing

Respiratory failure:

Type 1 ➔ hypoxaemia (P_aO_2 < 8.0 kPa) without hypercapnoea (P_aCO_2 normal or decreased (<6.0 kPa)

Causes:

- Low ambient oxygen (e.g. at high altitude)
- Ventilation-perfusion mismatch (parts of the lung receive oxygen but not enough blood to absorb it, e.g. pulmonary embolism)
- Alveolar hypoventilation (decreased minute volume due to reduced respiratory muscle activity, e.g. in acute neuromuscular disease); this form can also cause type 2 respiratory failure if severe
- Diffusion problem (oxygen cannot enter the capillaries due to parenchymal disease, e.g. in pneumonia or ARDS)
- Shunt (oxygenated blood mixes with non-oxygenated blood from the venous system, e.g. right-to-left shunt)

Type 2 ➔ Hypoxemia (PaO2 <8kPa) with hypercapnia (PaCO2 >6.0kPa).

Causes:

- Increased airways resistance (COPD, asthma, suffocation)
  - ➢ The commonest cause is chronic obstructive airway disease,
- Reduced breathing effort → hypoventilation:
  - ➢ acutely due to drug overdose and brain stem lesion
  - ➢ chronically due to: gross obesity, kyphoscoliosis (and similar musculoskeletal disorders)

- **Hypoventilation, where inadequate alveolar ventilation results in low alveolar PO_2, is the only cause of hypoxia that inevitably causes raised $PaCO_2$.**

- A decrease in the area of the lung available for gas exchange (such as in chronic bronchitis)
- Neuromuscular problems (**respiratory muscle weakness**) (Guillain-Barre syndrome , motor neuron disease)
- Deformed (kyphoscoliosis), rigid (ankylosing spondylitis), or flial chest.

Bronchial Asthma

Basics

Immunomodulators involved in asthma:

Inhalation of allergens by individuals with atopic asthma initiates:

- **Immediate response:**
  - **type I hypersensitivity**
  - immunomodulators involved:
    - **mast cells**
    - histamine
    - prostaglandin D_2
    - Leukotriene C_4 (LTC_4) and D_4.
  - Result in immediate bronchoconstriction reaction
  - Usually subsides within two hours
  - Reversible with bronchodilators.
- **Late phase:**
  - **type IV hypersensitivity response**
  - immunomodulators involved:
    - Eosinophil cationic protein (ECP)
    - Major basic protein (MBP)
    - Platelet activating factor (PAF)
    - T_{H2} lymphocytes
  - Results in bronchoconstriction, airways inflammation, hyper-responsiveness and oedema.
  - This **typically occurs three to12 hours after the immediate response**
  - Less susceptible to bronchodilators.

Pathogenesis of asthma:

- **Asthma occurs due to a combination of airway hyper-responsiveness, airflow limitation and airway inflammation**
- **The alveolar functional structure is preserved in asthma.**

Genetics of bronchial asthma

- autosomal recessive pattern of inheritance is prominent in asthma;
- parental consanguinity (صلة قرابة) and **serum intracellular cell adhesion molecule-1** (ICAM-1) is significantly associated with asthma
- **There is a contribution from HLA alleles**

- There may be genetic linkage of atopic trait to chromosome 11, with association between response to antigen and HLA haplotype.
- IgE concentrations are influenced by genetic factors.

Classification of asthma severity

- **Mild, intermittent asthma** - symptoms occur less than weekly, with normal or near-normal lung function between episodes
- **Mild persistent asthma** - symptoms occur more than weekly but less than daily, with normal or near-normal lung function between episodes
- **Moderate persistent asthma** - symptoms occur daily, with mild to moderate variable airflow limitation
- **Severe persistent asthma** - symptoms occur daily and interfere with normal activities; there is frequent nocturnal waking and moderate to severe variable airflow limitation
- **Severe asthma** - severe distressing symptoms prevent sleep; severe airflow limitation responds poorly to inhaled bronchodilators and can be life-threatening

Near fatal asthma

- The British Thoracic Society defines **near fatal asthma as an attack with raised $PaCO_2$** and/or requiring mechanical ventilation with raised inflation pressures.
- A **raised $PaCO_2$** is an important sign that intubation may be required if the patient is not responding to maximum medical management.

Allergic and non-allergic forms of asthma

- Allergic asthma
  - results from excess immunoglobulin E (IgE) produced in response to environmental allergens such as house dust mites, pollen and moulds.
- Non-allergic asthma
  - can be triggered by factors such as anxiety, stress, exercise, cold air, smoke and infection.

Diagnosis of asthma in adults

Asthma - intermediate probability - do spirometry first-line

Asthma diagnosis - if high probability of asthma - start treatment

- If the FEV1/FVC < 0.7 then a trial of treatment is appropriate. Otherwise further investigations should be performed.
- If a patient has typical symptoms of asthma, a trial of treatment is recommended.
- we should classify patients as having either a high, intermediate or low probability of asthma based on the presence or absence of certain symptoms.
- For adults it is recommend that they have a **clinical assessment including spirometry** (or Peak Expiratory Flow measurement if spirometry is not available).
- The BTS produced a list of features, which are helpful when deciding this:

Features which make a diagnosis of asthma more likely	Features which make a diagnosis of asthma less likely
More than one of the following symptoms: wheeze, breathlessness, chest tightness and cough, **particularly if**: symptoms worse at night and in the early morning symptoms in response to exercise, allergen exposure and cold air symptoms after taking aspirin or beta blockers History of atopic disorder Family history of asthma and/or atopic disorder Widespread wheeze heard on auscultation of the chest Otherwise unexplained low FEV1 or PEF (historical or serial readings) Otherwise unexplained peripheral blood eosinophilia	Prominent dizziness, light-headedness, peripheral tingling Chronic productive cough in the absence of wheeze or breathlessness Repeatedly normal physical examination of chest when symptomatic Voice disturbance Symptoms with colds only Significant smoking history (ie > 20 pack-years) Cardiac disease Normal PEF or spirometry when symptomatic

- **High probability** of asthma
  - patient has many symptoms which make a diagnosis of asthma more likely
  - BTS recommend that we start a trial of treatment.
  - A good response is considered a positive 'test of reversibility'.
  - If a patient has a poor response to treatment then further investigations should be considered.
- **Low probability** of asthma
  - an alternative diagnosis should be sought.
  - Further investigations and referral to a respiratory specialist should be considered.
- **Intermediate probability** of asthma
  - BTS recommend *'to carry out further investigations, including an explicit trial of treatments for a specified period, before confirming a diagnosis and establishing maintenance treatment.*
  - Spirometry is the preferred initial test
  - Treatment should be partly guided by the **FEV_1/FVC ratio:**
    - **a ratio of < 0.7 is suggestive of asthma →** trial of treatment
    - **a ratio of > 0.7** → further investigation/consider referral

Spirometer vs peak flow meter

- **Spirometer** measures the total volume of air that can be exhaled or inhaled. It can also measure the rate at which a certain volume of air is expelled from the lungs.
  - Spirometry is the most accurate breathing test for asthma.

- spirometry may be normal in asymptomatic patients so it may be necessary to repeat spirometry or peak flow readings on a number of occasions in patients where the diagnosis is not clear.
- In adults with obstructive spirometry, an **improvement in FEV1 of 12% or more** in response to either β2 agonists or corticosteroid treatment trials, together with an **increase in volume of 200 ml or more**, is regarded as a positive test. (British guideline on the management of asthma 2016) **(this fact was tested in mrcp part 1 sep 2017)**

- **Peak flow meter**, on the other hand, only measures the rate at which air is forced out of the lungs. This is known as the peak expiratory flow.
  - It is now advised to interpret peak flow variability with caution due to the poor sensitivity of the test
    - diurnal variation % = [(Highest - Lowest PEFR) / Highest PEFR] x 100
    - assessment should be made over 2 weeks
    - **greater than 20% diurnal variation is considered significant**
    - A variation of **> 25%** on a peak flow chart (**pre- and post-bronchodilator**) would support a diagnosis of asthma.

NICE quality statement : **Adults with new onset asthma are assessed for occupational causes.**

- Are you better on days away from work?
- Are you better on holiday?

Asthma diagnosis (NICE guidelines 2017)

- **Patients ≥ 17 years**
  - patients should be asked if their symptoms are better on days away from work/during holidays. If so, patients should be referred to a specialist as possible occupational asthma
  - all patients should have spirometry with a bronchodilator reversibility (BDR) test
  - all patients should have a FeNO test
- **Patients 5-16 years**
  - all patients should have spirometry with a bronchodilator reversibility (BDR) test
  - a FeNO test should be requested if there is normal spirometry or obstructive spirometry with a negative bronchodilator reversibility (BDR) test
- **Patients < 5 years**
  - diagnosis should be made on clinical judgement Do not use symptoms alone without an objective test to diagnose asthma.

Objective tests for diagnosing asthma:

- Airway inflammation measures
  - Fractional exhaled nitric oxide (FeNO) test
    - FeNO level of 40 parts per billion (ppb) or more is a positive test.
    - current smoking status can lower FeNO levels

- **Lung function tests**

- Spirometry
  - (FEV1/FVC) ratio < 70% is a positive test for obstructive airway disease (obstructive spirometry).
- Bronchodilator reversibility (BDR)
  - Offered for patient with obstructive spirometry (FEV1/FVC ratio **<** 70%).
  - improvement in FEV1 **≥** 12%, together with an increase in volume **≥** 200 ml is a positive test.
- Peak expiratory flow variability
  - if there is diagnostic uncertainty after initial assessment and a FeNO test + either:
    - normal spirometry or
    - (positive BDR) **but** a FeNO **≤** 39 ppb.
  - if there is diagnostic uncertainty after initial assessment and they have:
    - obstructive spirometry **and** irreversible airways obstruction (negative BDR) **and** a FeNO level between 25 and 39 ppb.
  - monitoring peak flow variability for 2 to 4 weeks
  - **value ≥ 20% variability is a positive test.**

- **Airway hyperreactivity measures**
  - Direct bronchial challenge test with histamine or methacholine
    - if there is diagnostic uncertainty after a normal spirometry and either a:
      - FeNO ≥ 40 ppb + no variability in peak flow readings or
      - FeNO ≤ 39 ppb + variability in peak flow readings.
    - If there is obstructive spirometry without bronchodilator reversibility and a FeNO level between 25 and 39 ppb and no variability in peak flow readings
    - PC20 value ≤ 8 mg/ml is a positive test.

Order of tests

Measure FeNO first followed by spirometry in adults with symptoms of asthma · Carry out BDR test if spirometry shows an obstruction

If diagnostic uncertainty remains after FeNO, spirometry and BDR, monitor peak flow variability for 2 to 4 weeks

If diagnostic uncertainty remains after measuring peak flow variability, refer for a histamine or methacholine direct bronchial challenge test

If histamine or methacholine direct bronchial challenge test is unavailable: · suspect asthma and review diagnosis after treatment or · refer to a centre with access to histamine or methacholine challenge testing

Positive test thresholds:

- Obstructive spirometry: FEV1/FVC ratio less than 70% (or below the lower limit of normal if available)
- FeNO: 40 ppb or more
- BDR: improvement in FEV1 of 12% or more and increase in volume of 200 ml or more

- Peak flow variability: variability over 20%
- Direct bronchial challenge test with histamine or methacholine: PC20 of 8 mg/ml or less

forced expiratory flow 25–75% of vital capacity (FEF 25–75)

- One of parameters measured in spirometry
- the flow (or speed) of air coming out of the lung during the middle portion of a forced expiration.
- **It reflects the status of the small airways**
- **It is more sensitive than the forced expiratory volume in 1 second (FEV1) for identifying early airway obstruction.**
- This portion of the flow volume curve is the most **effort independent** portion.
- A normal FEF_{25-75} was defined as ≥ 60% predicted.

Lab findings

- **sputum**
  - **Curschmann's spirals**
    - microscopic finding in the sputum of asthmatics.
    - spiral-shaped mucus plugs from subepithelial mucous gland ducts or bronchioles.
  - **Charcot–Leyden crystals**
    - microscopic crystals found in allergic diseases such as asthma or parasitic infections
    - hallmark of eosinophil-associated allergic inflammatory diseases such as asthma, allergic rhinitis and also atopic dermatitis.
    - formed from the breakdown of eosinophils in sputum and crystallization of major basic protein.

Management of asthma (NICE guidance 2017).

One of the key changes is in 'step 3' - patients on a SABA + ICS whose asthma is not well controlled should be offered a leukotriene receptor antagonist, not a LABA

Step	Notes
1 Newly-diagnosed asthma	Short-acting beta agonist (SABA)
2 Not controlled on previous step OR Newly-diagnosed asthma with symptoms	SABA + low-dose inhaled corticosteroid (ICS)

Step	Notes
>= 3 / week or night-time waking	
3	SABA + low-dose ICS + leukotriene receptor antagonist (LTRA)
4	SABA + low-dose ICS + long-acting beta agonist (LABA) Continue LTRA depending on patient's response to LTRA
5	SABA +/- LTRA Switch ICS/LABA for a maintenance and reliever therapy (MART), that includes a low-dose ICS
6	SABA +/- LTRA + medium-dose ICS MART OR consider changing back to a fixed-dose of a moderate-dose ICS and a separate LABA
7	SABA +/- LTRA + one of the following options: • increase ICS to high-dose (only as part of a fixed-dose regime, not as a MART) • a trial of an additional drug (for example, a long-acting muscarinic receptor antagonist or theophylline) • seeking advice from a healthcare professional with expertise in asthma

- **Maintenance and reliever therapy (MART)**
  - a form of combined ICS and LABA treatment in which a single inhaler, containing both ICS and a fast-acting LABA, is used for both daily maintenance therapy and the relief of symptoms as required
  - MART is only available for ICS and LABA combinations in which the LABA has a fast-acting component (for example, formoterol)

- **Table showing examples of inhaled corticosteroid doses**

Dose	Example
low dose	≤ 400 micrograms budesonide or equivalent
moderate dose	400 micrograms - 800 micrograms budesonide or equivalent
high dose	**>** 800 micrograms budesonide or equivalent

B-blockers, including eye drops, are contraindicated in patients with asthma

Steroid inhalation

- Fluticasone is more lipophilic and has a longer duration of action than beclometasone
- Hydrofluoroalkane is now replacing chlorofluorocarbon as the propellant of choice.
  - Only half the usually dose is needed with hydrofluoroalkane due to the smaller size of the particles
- **Inhaled corticosteroids → ↓↓ skin collagen synthesis → skin fragility → ↑↑ tendency for bruising & vascular changes**

Long acting B2-agonists

- acts as bronchodilators but also inhibit mediator release from mast cells.
- **Salmeterol → may cause paradoxical bronchospasm**
  - Salmeterol has been reported to produce an acute exacerbation of asthma, possibly through an **acute hypersensitivity reaction**.
- The duration of action of salmetrol is around 12 hours, and has gone completely by 36 hours.

Leukotriene receptor antagonists

- Action
  - Montelukast, zafirlukast
    - Cys**LT**1 antagonist; it **blocks the action of leukotriene on** cysteinyl leukotriene **receptor** Cys**LT**1 by binding to it.
  - Zileuton → blocks leukotriene **synthesis** by **inhibiting 5-lipoxygenase**,
    - inhibits 5-lipoxygenase pathway, **blocking the conversion of arachidonic acid to leukotrienes.**
  - have both anti-inflammatory and bronchodilatory properties
- Inductions:
  - **should be used when patients are poorly controlled on high-dose inhaled corticosteroids and a long-acting b2-agonist**
  - have been shown to be as effective as doubling the dose of inhaled steroid.
  - asthma with allergic rhinitis
  - aspirin-induced asthma
  - **exercise-induced asthma**
- Side effects
  - associated with the development of Churg-Strauss syndrome

Asthma drugs: leukotriene inhibitor action:
- Zafirlukast → Inhibitor of LT receptor
- Zilueton → Antagonist of lipoxygenase

Omalizumab (NICE guidelines 2013)
- a monoclonal antibody that **binds to IgE**.
- given subcutaneously every 2 or 4 weeks.
- recommended for treating severe persistent confirmed **allergic IgE-mediated asthma**
- Common SE:
  - injection site pain, swelling, erythema and pruritus, and **headaches**

Drugs used in asthma

Drug	Mechanism of action	Notes
Salbutamol	Beta receptor agonist	• Short-acting inhaled bronchodilator. Relaxes bronchial smooth muscle through effects on beta 2 receptors • Used in asthma and chronic obstructive pulmonary disease (COPD). • Salmeterol has similar effects but is long-acting
Corticosteroids	Anti-inflammatory	• Inhaled corticosteroids are used as mainterance therapy • Oral or intravenous corticosteroids are used following an acute exacerbation of asthma or COPD
Ipratropium	Blocks the muscarinic acetylcholine receptors	• Short-acting inhaled bronchodilator. Relaxes bronchial smooth muscle • Used primarily in COPD • Tiotropium has similar effects but is long-acting
Methylxanthines (e.g. theophylline)	Non-specific inhibitor of phosphodiesterase resulting in an increase in cAMP	• Given orally or intravenously • Has a narrow therapeutic index
Monteleukast, zafirlukast	Blocks leukotriene receptors	• Usually taken orally • Useful in aspirin-induced asthma

NON-PHARMACOLOGICAL MANAGEMENT (British guideline on the management of asthma 2016)

- stop smoking.
- **Weight-loss** interventions (including dietary and exercise-based programmes) can be considered for overweight and obese with asthma to improve asthma control.
- **Breathing exercise** programmes (including physiotherapist-taught methods) can be offered to people with asthma as an adjuvant to pharmacological treatment to improve quality of life and reduce symptoms.

Teaching **diaphragmatic breathing**, (as opposed to thoracic breathing which is practised by many asthmatics), may significantly impact on symptoms. Reducing the likelihood of future attendance in the Emergency department

Buteyko technique → associated with improved symptoms.

- The Buteyko technique controls chronic hyperventilation, as such patients perceive less symptoms of shortness of breath, and their use of short acting bronchodilators is reduced.
- This does not however have any impact on lung function including FEV1 and FVC.
- It may be particularly valuable in patients who complain of symptoms of shortness of breath significantly in excess of those expected when you review their lung function.

Mepolizumab may be used for resistant asthma with high eosinophils

* Mepolizumab is an anti-IL5 monoclonal antibody
* IL5 is a cytokine which promotes growth in eosinophil numbers and activity.
* By blocking IL5 mepolizumab down-regulates eosinophil activity and has been shown to significantly improve symptoms in resistant asthma.

Omalizumab is an anti-IgE monoclonal antibody, it is effective in treating resistant asthma with evidence of raised IgE and allergic symptoms.

Acute severe asthma

Magnesium sulphate - monitor reflexes + respiratory rate

Patients with acute severe asthma are stratified into moderate, severe or life-threatening

Moderate	Severe	Life-threatening
• PEFR 50-75% best or predicted • Speech normal • RR < 25 / min • Pulse < 110 bpm	• **PEFR 33 - 50%** best or predicted • Can't complete sentences • **RR > 25/min** • Pulse > 110 bpm	• PEFR < 33% best or predicted • **Oxygen sats < 92%** • PaO_2 < 8 kPa • Normal $PaCO_2$ (4.6-6.0 kPa) • Silent chest, cyanosis or feeble (Poor) respiratory effort • Bradycardia, dysrhythmia or hypotension • Exhaustion, confusion or coma

- Note that a patient having any one of the life-threatening features should be treated as having a life-threatening attack.
- A pH less than 7.35 likely represents carbon dioxide retention in a tiring patient and is an ominous sign in acute asthma.
- **A normal or elevated pCO2 in an asthmatic indicates failing respiratory effort,** and although oxygen saturation may be not severely depressed, patient is in danger of decompensation and - aside from high flow oxygen, nebulised salbutamol and ipatropium, and steroids - it would be prudent to inform the ICU. Therefore, even though it is in the normal range, this is **the most worrying result for life-threatening**.
- **A normal PaCO2 in an asthmatic is a warning of impending respiratory failure as the patient becomes too tired to ventilate adequately.**
- If PCO2 is just outside the upper limit of normal, the patient will requires urgent admission to the Intensive Therapy Unit.

Lung function in an acute asthma attack

- The classic abnormalities are **reduced** (FEV-1) & (FVC) & FEV-1/FVC ratio.
- Because of gas trapping there is an **increase in residual volume** and an increase in total lung capacity, but the ratio of residual volume (RV) to total lung capacity (TLC) is increased (TLC = vital capacity [VC] + RV).
- Airway conductance (the reciprocal of airway resistance) is decreased in acute asthma.
- Gas transfer would be difficult to measure in acute asthma but can be elevated in stable asthma where there might be chronic hyperinflation giving rise to a greater surface area for blood/gas interfacing.
- **asthma is most likely associated with an obstructive spirometry and normal Tlco (transfer factor for carbon monoxide)**

Management

- In acute severe asthma, **β2-agonists should be administered as soon as possible, preferably nebulised driven with high flow oxygen.**
  - salbutamol administration can rapidly worsen the V/Q mismatch which is the cause of hypoxia in asthma. They can therefore cause reduction in arterial oxygen tension unless supplemental oxygen is given

Physiologic changes following a nebuliser in acute asthma :
initially , poor ventilation ➔ hypoperfusion to certain lung areas .
Following a nebuliser and subsequent improved ventilation, there is then a ventilation/perfusion mismatch which may lead to ➔ **a transient drop in oxygen saturation**.

- **Nebulised ipratropium bromide** should be added for patients with acute severe or life threatening asthma, or those with a poor initial response. It's addition produces significantly greater bronchodilation than a β2-agonist alone.
- **Oxygen:**
  - Targeted oxygen in asthma => SpO2 level of 94–98%.
  - Patients with saturations less than 92% on air should have an ABG to exclude hypercapnia. However, starting treatment should not be delayed to do the ABG.
  - Initially high-flow oxygen is used, and then weaned to maintain adequate saturations. Unless you suspect COPD there is no need to be cautious with oxygen therapy.
- **Steroids:**

Nice 2013➔ People aged 5 years or older presenting to a healthcare professional with a severe or life-threatening acute exacerbation of asthma receive oral **or** intravenous steroids **within 1 hour** of presentation.

  - steroids reduce mortality, relapses, subsequent hospital admission and requirement for β2-agonists1.
  - The earlier they are given in the attack, the better the outcome.
  - A dose of 40-50 mg should be given once oxygen and nebuliser therapy has been established. This should be continued for five days, and can then be stopped abruptly.
- **Magnesium sulphate** recommended as next step for patients who are not responding (e.g. 1.2 - 2g IV over 20 mins) .
  - Mechanism: low magnesium levels in bronchial smooth muscle favour bronchoconstriction.
  - reduce rates of admission to intensive therapy units
- little evidence to support use of IV aminophylline (although still mentioned in management plans)
- if no response consider IV salbutamol
- **Intensive care** is indicated for patients with severe acute or life threatening asthma who are failing to respond to therapy.
- **Strongest indicator of a need for intubation and ventilation?**
  - **PH 7.31**

Asthma in pregnancy

- In general, the medicines used for asthma are safe during pregnancy.
- The British Thoracic Society (BTS) guidelines make it clear that short-acting /long-acting beta 2-agonists, inhaled and oral corticosteroids should all be used as normal during pregnancy.
- The BNF advises that 'inhaled drugs, theophylline and prednisolone can be taken as normal during pregnancy and breast-feeding'.

Asthma during labour:

- Women receiving steroid tablets at a dose exceeding prednisolone 7.5 mg per day for more than two weeks prior to delivery should receive parenteral hydrocortisone 100 mg 6–8 hourly during labour.:
- prostaglandin F2α → inducing bronchoconstriction

Extra notes

Pulsus paradoxus:

- The right heart responds directly to changes in intrathoracic pressure, while the filling of the left heart depends on the pulmonary vascular volume.
- At high respiratory rates, with severe air flow limitation (for example, acute asthma) there is an increased and sudden negative intrathoracic pressure on inspiration and this will enhance the normal fall in blood pressure.

Exercise-induced asthma:

- The most likely diagnosis would be with **spirometry before and after exercise**, (NOT before and after administration of bronchodilators) where a typical obstructive pattern may be displayed following exercise.

Cough-variant asthma

- airway inflammation but minimal bronchoconstriction.
- **Response to steroids is helpful when making the diagnosis of asthma.**
- Bronchodilators often have little effect.
- No typical asthma history; the cough is typically worse in the mornings, in the cold air and after exercise.
- Treatment is with high-dose inhaled steroids for at least 2 months, or a short course of oral steroids.

Difficult asthma → persisting asthma, despite prescription of high-dose asthma therapy.

- Always consider poor adherence to maintenance therapy.
- Consider monitoring induced sputum eosinophil counts to guide steroid treatment.
- Dysfunctional breathing should be considered as part of a difficult asthma assessment.
- allergen testing to moulds should be performed.
- Commonly associated with co-existent psychological
- differential diagnosis in difficult asthma clinic:
  - **Subglottic stenosis**
    - defined as a narrowing of the airway below the vocal cords (subglottis) and above the trachea. It may be congenital or acquired.
    - can occur from birth, idiopathically and **in patients who have been intubated**.
    - predominance of **inspiratory** rather expiratory **wheeze**

Chronic Obstructive Pulmonary Disease(COPD)

Definition

- COPD is a long-term respiratory condition characterised by airflow obstruction that is not fully reversible.

Subtypes of COPD

1. **chronic bronchitis**
   - defined as chronic cough and sputum production for at least three months of two consecutive years in the absence of other disease which could explain these symptoms.
   - inflammatory changes leads to ciliary dysfunction and **increased goblet cell size and number**, which leads to the excessive mucus secretion.
2. **Emphysema**

Pathophysiology

- These changes are responsible for decreased airflow, hypersecretion, and chronic cough. In both conditions, changes are progressive and usually not reversible.
- **Increased airway resistance** is the physiological definition of COPD.
  - Decreased elastic recoil, fibrotic changes in lung parenchyma, and luminal obstruction of airways by secretions all contribute to increased airways resistance.
- Progressive hypoxia causes vascular smooth muscle thickening with subsequent pulmonary hypertension
- **Which mechanism is most likely responsible for the increased mean arterial pulmonary pressure in COPD?**
  - **Hypoxic induced pulmonary vasoconstriction**

Causes

- Smoking
- Alpha-1 antitrypsin deficiency

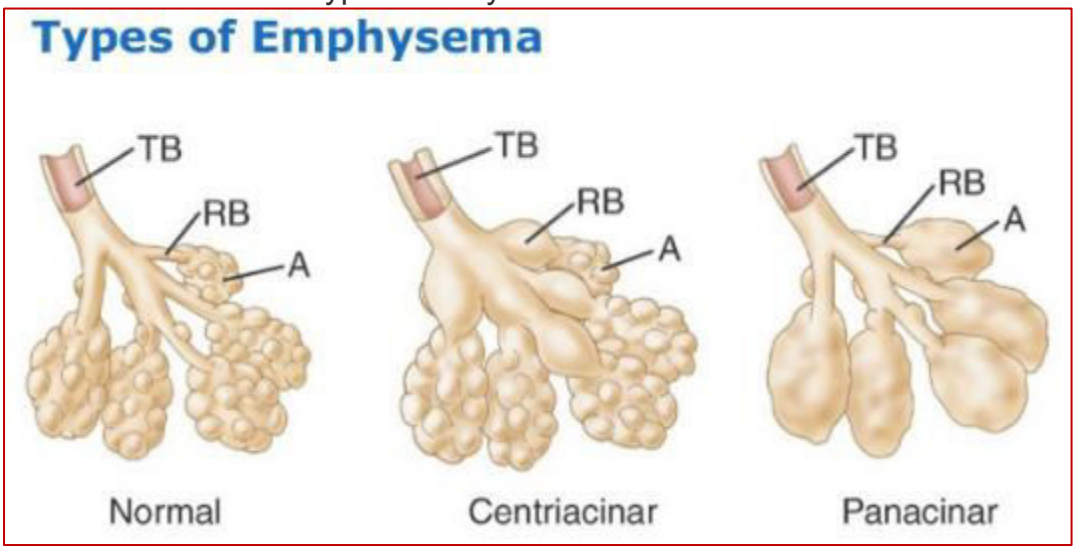
- patients from the developing world present with a COPD-like history from using open fires in their homes for cooking or heating (accounting for up to 1 million deaths worldwide as a result of COPD without smoking history)
- Other causes (particularly **occupational exposures**, such as harmful dust and chemicals)
  - **cadmium (used in smelting) (recognised cause of emphysema specifically)**
  - coal
  - cotton
  - cement
  - grain

Emphysema

- **Definition**
  - emphysema is a term that refers to the actual damage to the air sacs in the lung, called the alveoli. In other words, emphysema is a pathological term.
- **Pathophysiology**
  - destruction of alveolar air sacs due to an **imbalance between protease and anti-protease action.**
  - Emphysema is an irreversible degenerative condition;
  - **loss of elastic recoil, which drives airflow limitation.**
    - Although airflow limitation is virtually irreversible, the small inflammatory component can respond to high-dose inhaled corticosteroids.
  - Lung recoil decreases in emphysema.
  - the final outcome of the inflammatory responses is **elastin breakdown** and subsequent loss of alveolar integrity.
    - involves an **increase in elastase activity.**
- **Types**
  - **Panlobular (panacinar) pulmonary emphysema**
    - Rare
    - Associated with **α1-antitrypsin deficiency**
    - Characterized by destruction of the entire acinus
    - Usually affects the **lower lobe**
  - **Centrilobular or proximal acinar pulmonary emphysema**
    - Common
    - Classically seen in **smokers**
    - Characterized by destruction of the respiratory bronchiole (central portion of the acinus)
    - Usually affects the **upper lobe**
    - most severe at the apex of the lung.
- **Features**
  - Hyper-expanded lung fields on CXR, reduced transfer factor and an FEV1/FVC < 70 %.
  - MacLeod syndrome is unilateral **emphysema following childhood bronchiolitis**.
  - Loss of lung recoil causes a reduction of alveolar pressure (elastic recoil pressure of lung + pleural pressure) leading to collapse of peripheral airways on expiration.

Emphysematous patients purse their lips in expiration to increase airway pressure to prevent this collapse.

- CO transfer factor is reduced.
- ↑ Residual Volume (RV)
- ↑ Total Lung Capacity (TLC)
- Giving typical obstructive pathology
- Flattening of diaphragms: ↑ lung volumes
- Enlarged left pulmonary artery
- Attenuation of vessels
- Diffuse hyperlucency



Types of emphysema

Type	Centriacinar (centrilobula)	Panacinar
Prevalence	the **most common** type	**Less common**
destruction	focal destruction mainly localized to the proximal respiratory bronchioles	destroys the entire alveolus uniformly
Location	**upper lung** zones.	lower half of the lungs.
causes	**smoking** & dust	**alpha 1-antitrypsin (AAT) deficiency**

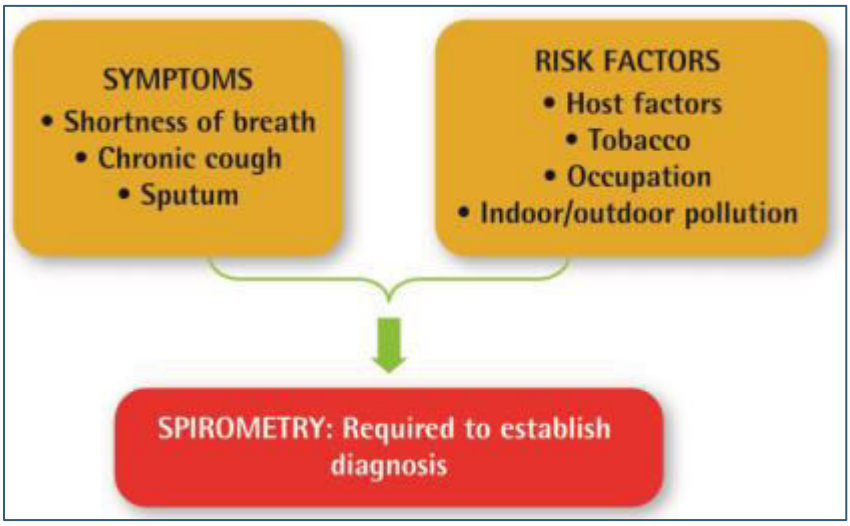
What is the most important factor in airflow limitation in severe emphysema?

- **Loss of elastic recoil**

Other features

- **extensor plantar response is common in (COPD) due to carbon dioxide retention, which results in carbon dioxide narcosis.**

Investigation and diagnosis



- NICE recommend considering a diagnosis of COPD in patients over 35 years of age who are smokers or ex-smokers and have symptoms such as exertional breathlessness, chronic cough or regular sputum production.
- The following investigations are recommended in patients with suspected COPD:
  - Post-bronchodilator spirometry to demonstrate airflow obstruction: FEV1/FVC ratio less than 70%
  - Chest x-ray: hyperinflation, bullae, flat hemidiaphragm. Also important to exclude lung cancer
  - Full blood count: exclude secondary polycythaemia
  - Body mass index (BMI) calculation
- Measuring peak expiratory flow is of limited value in COPD, as it may underestimate the degree of airflow obstruction.
- A methacholine challenge is useful in differentiating between asthma and chronic obstructive pulmonary disease (COPD).
  - methacholine utilizes the M3 receptor for bronchoconstriction.
- In long standing COPD the bicarbonate is likely to be normal, or raised if the patient has chronic hypercapnia. (a low pH, low pO_2, high pCO_2 and a high HCO_3)
- Peripheral oedema may be present as a dependent oedema, as patients with COPD may have limited mobility due to dyspnoea, and therefore does not necessarily indicate heart failure.

The severity of COPD is categorised using the FEV1:

Post-bronchodilator FEV1/FVC	FEV1 (of predicted)	Severity
< 0.7	> 80%	Stage 1 - Mild
< 0.7	**50-79%**	**Stage 2 - Moderate**
< 0.7	**30-49%**	**Stage 3 - Severe**
< 0.7	< 30%	Stage 4 - Very severe

Nocturnal oxygen desaturation in COPD

- COPD patients commonly suffer from **nocturnal oxygen desaturation** which is not usually caused by sleep apnoea. **Sleep-related hypoxaemia** can result in the patient reporting morning headaches and daytime somnolence. The diagnosis is made via **overnight home monitoring with a pulse oximeter** which shows dramatic falls in saturation levels that occur during REM sleep.

Acute exacerbations

Infective exacerbation of COPD

- **is the most common cause of haemoptysis in UK patients**

COPD: causes of acute exacerbations

- The most common bacterial organisms that cause infective exacerbations of COPD are:
  - *Haemophilus influenzae* **(most common cause)**
    - The patient should be treated with a course of amoxicillin or a tetracycline together with prednisolone.
  - *Streptococcus pneumoniae*
  - *Moraxella catarrhalis*
- If the patient had pneumonia then *Streptococcus pneumoniae* would be the most likely causative organism. But if the chest x-ray shows no evidence of consolidation this will make a diagnosis of pneumonia unlikely.
- Respiratory viruses account for around 30% of exacerbations, with the **human rhinovirus** being the most important pathogen.

COPD: management of acute exacerbations: NICE guidelines from 2010 recommend the following:

- increase frequency of bronchodilator use and consider giving via a nebuliser
- Give prednisolone 30 mg daily for 7-14 days. Prolonged courses offer no additional benefit
- It is common practice for all patients with an exacerbation of COPD to receive antibiotics. NICE do not support this approach. They recommend giving oral antibiotics 'if sputum is purulent or there are clinical signs of pneumonia'

Other notes

- **Doxapram** infusion can be useful in patients as a short-term treatment while other, more effective support is instituted or a decision is made not to proceed with mechanical support.

- Doxapram is a respiratory stimulant, which can be effective at improving ventilation.
- Its use has been superseded by non-invasive ventilation (NIV), but it might be useful in situations where NIV is unavailable.

COPD: stable management

COPD - reason for using inhaled corticosteroids - reduced exacerbations

COPD - still breathless despite using inhalers as required?
- FEV1 > 50%: LABA or LAMA
- FEV1 < 50%: LABA + ICS or LAMA

COPD - LTOT if 2 measurements of pO2 < 7.3 kPa

NICE guidance (2010)

General management
- smoking cessation advice
- annual influenza vaccination
- one-off pneumococcal vaccination

Bronchodilator therapy
- a short-acting beta2-agonist (SABA) or short-acting muscarinic antagonist (SAMA) is first-line treatment

for patients who remain breathless or have exacerbations despite using short-acting bronchodilators the next step is determined by the FEV1
- FEV1 > 50%
  - long-acting beta2-agonist (LABA), for example salmeterol, or:
  - long-acting muscarinic antagonist (LAMA), for example tiotropium
- FEV1 < 50%
  - LABA + inhaled corticosteroid (ICS) in a combination inhaler, or:
  - LAMA

For patients with persistent exacerbations or breathlessness
- if taking a LABA then switch to a LABA + ICS combination inhaler
- otherwise give a LAMA and a LABA + ICS combination inhaler

Oral theophylline
- NICE only recommends theophylline after trials of short and long-acting bronchodilators or to people who cannot used inhaled therapy
- the dose should be reduced if macrolide or fluoroquinolone antibiotics are co-prescribed

Mucolytics
- should be 'considered' in patients with a chronic productive cough and continued if symptoms improve

Cor pulmonale

- features include peripheral oedema, raised jugular venous pressure, systolic parasternal heave, loud P2
- use a loop diuretic for oedema, consider long-term oxygen therapy
- ACE-inhibitors, calcium channel blockers and alpha blockers are not recommended by NICE

Factors, which may improve survival in patients with stable COPD

- **smoking cessation - the single most important intervention in patients who are still smoking**
- **long term oxygen therapy** in patients who fit criteria
- lung volume reduction surgery in selected patients

LTOT should be offered to patients with a pO2 of < 7.3 kPa or to those with a pO2 of 7.3 - 8 kPa and one of the following:

- secondary polycythaemia
- nocturnal hypoxaemia
- peripheral oedema
- pulmonary hypertension

Inhaled steroids have been shown to improve quality of life and reduce hospitalisation rates by reducing the number of exacerbations, but they do not slow the rate of decline of FEV_1 (hence **do not affect prognosis**).

Roflumilast should be used in COPD for patients who are losing control on triple inhaled therapy

- Roflumilast is a selective long-acting phosphodiesterase-4 inhibitor.
- recommended by NICE for patients who have suffered two or more exacerbations in a year, despite triple inhaled therapy, where FEV1 is less than 50% of predicted.
- It is orally administered.

Management of side effect of steroid inhaler (oro-pharyngeal and oesophageal candidiasis):

- the patient should be taught adequate inhaler technique**. Advise him to rinse his mouth each time he uses his inhaler and use a spacer device and review him in a month**.
- Resistant symptoms can be managed with oral nystatin or a course of fluconazole.

Pulmonary rehabilitation

- This is a programme of aerobic lower-extremity training combined with education.
- Patients with very limited exercise tolerances may benefit from pulmonary rehabilitation and in the most severely limited patients chair-based exercises can be taught.
- **It leads to improvements in exercise capacity (walking distance should improve after the rehabilitation programme)**
- Pulmonary rehabilitation **does not improve lung function.**
- The improvement in walking distance would **not be a long-lasting improvement**
  - Decline in exercise tolerance and health status tends to occur 6–12 months after the completion of a course.

  - The effect of sustained improvement with ongoing rehabilitation has yet to be evaluated.
- Patients who have completed pulmonary rehabilitation experience **no fewer hospital admissions because of chest problems**, but their **hospital stays are likely to be shorter.**

Surgery

- The National Emphysema Treatment Trial was a prospective, randomised, multi-centre trial which compared the results of **lung volume reduction surgery** to medical therapy which showed that there were **3 groups of patients that tend to benefit**:
  - **Group 1**: **Upper lobe emphysema and low exercise capacity**.
    - These patients show **improvement in both functional outcomes and survival** after lung volume reduction surgery compared to medical therapy.
  - **Group 2**: **upper lobe emphysema and high exercise capacity**.
    - These patients have **improved functional outcomes but no difference in survival** compared to medical therapy.
  - **Group 3**: **non-upper lobe emphysema and low exercise capacity**.
    - These patients have **improved survival after surgery but there is no difference in survival compared to medical therapy.**
- The trial also identified **patients with emphysema that are unlikely to do well from lung volume reduction surgery** and have a high risk of death. This includes:
  1. Patients with **non-upper lobe emphysema and high exercise capacity**.
  2. Patients with **extremely poor pulmonary function** (forced expiratory volume in 1 second **(FEV1) 20% or less** than predicted) and either homogenous distribution of emphysema on computed tomography scan or extremely poor carbon monoxide diffusing capacity (20% or less than predicted).

Lung volume reduction surgery:

- Is a palliative treatment which can be used in advanced COPD to remove the least functional part of the lungs.
- Techniques used include median sternotomy, video-assisted thoracoscopy and thoracotomy.
- **Indications:**
  - CO_2 retention: **The upper cut off for referral for lung reduction surgery for pCO_2 is 7.3**
  - Severe limitation of exercise capacity despite maximal therapy
  - predominant upper lobe emphysema, and persistent symptoms despite a period of pulmonary rehabilitation.
- **selection criteria**: used when assessing suitability for treatment:
  - Age <75 years
  - Emphysema by clinical evaluation
  - Ex-smoker of more than 4 months
  - Clinically stable on no more than 20mg prednisolone daily
  - Significant functional limitation after 6-12 weeks of pulmonary rehabilitation on optimal medical therapy

- Demonstrated compliance with medical regimen
- FEV-1 >20% predicted
- Post-bronchodilator FEV-1 >45% predicted and >15% if >70 years
- Hyperinflation demonstrated by TLC >100% predicted and RV >150% predicted
- Carbon monoxide lung transfer factor greater than 20% predicted
- Post rehabilitation 6 minute walk distance >140 m
- Low post rehabilitation exercise capacity
- HRCT demonstrating bilateral severe emphysema, ideally with upper-lobe predominance

Symptomatic relief of breathlessness in end-stage COPD

- **If the patient has end-stage COPD** and has himself indicated that control of symptoms is his priority. As such, consideration of use of **opioid or benzodiazepine medications for symptomatic relief of breathlessness is appropriate.**
- A recent prospective study demonstrated that lower dose opioid use (< 30 mg daily oral morphine equivalent) does not increase risk of hospitalisation or increase mortality in patients with COPD on long-term oxygen therapy.

Oxygen therapy

- When managing patients with COPD, once the pCO2 is known to be normal the target oxygen saturations should be 94-98%.
- Patients with (COPD) should not in general receive more than 24-28% oxygen without arterial blood gas monitoring.
- **In patients who are critically ill (anaphylaxis, shock etc) oxygen should initially be given via a reservoir mask at 15 l/min. Hypoxia kills.**

Oxygen saturation targets

- acutely ill patients: 94-98%
- patients at risk of hypercapnia (e.g. COPD patients): 88-92% (see below)
- oxygen should be reduced in stable patients with satisfactory oxygen saturation

Management of COPD patients

- prior to availability of blood gases, use a 28% Venturi mask at 4 l/min and aim for an oxygen saturation of 88-92% for patients with risk factors for hypercapnia but no prior history of respiratory acidosis
- adjust target range to 94-98% if the pCO2 is normal
- Oxygen should be given to maintain SaO2 within the patient's individual target range, if available (COPD patients are being given cards with this information, so always ask). If the individual target is not known, saturations should be maintained at 88-92%.
- Hudson face masks are less precise than venturi masks, so do not use if hypercapnic or type II respiratory failure. Risk of CO_2 accumulation if flow rate <5 L/min due to rebreathing of CO_2.
  - Venturi mask
    - often utilized in the COPD patient
    - **often employed when the clinician has a concern about carbon dioxide retention** or when respiratory drive is inconsistent.
    - mixes oxygen with room air, creating **high-flow** oxygen

- addition of humidification is not necessary with this device,
- provides an accurate and constant FiO_2 despite varied respiratory rates and tidal volumes.

- The British Thoracic Society in conjunction with the Intensive Care Society has produced **oxygen alert cards** that can be downloaded and printed to give to patients.it **include** – in addition to patient's name:
  - that they are at risk of type II respiratory failure (with raised CO_2 levels),
  - **the concentration of oxygen to be delivered via venturi mask**
  - their target oxygen saturations.
  - advice regarding the use of air and oxygen driven nebuliser machines

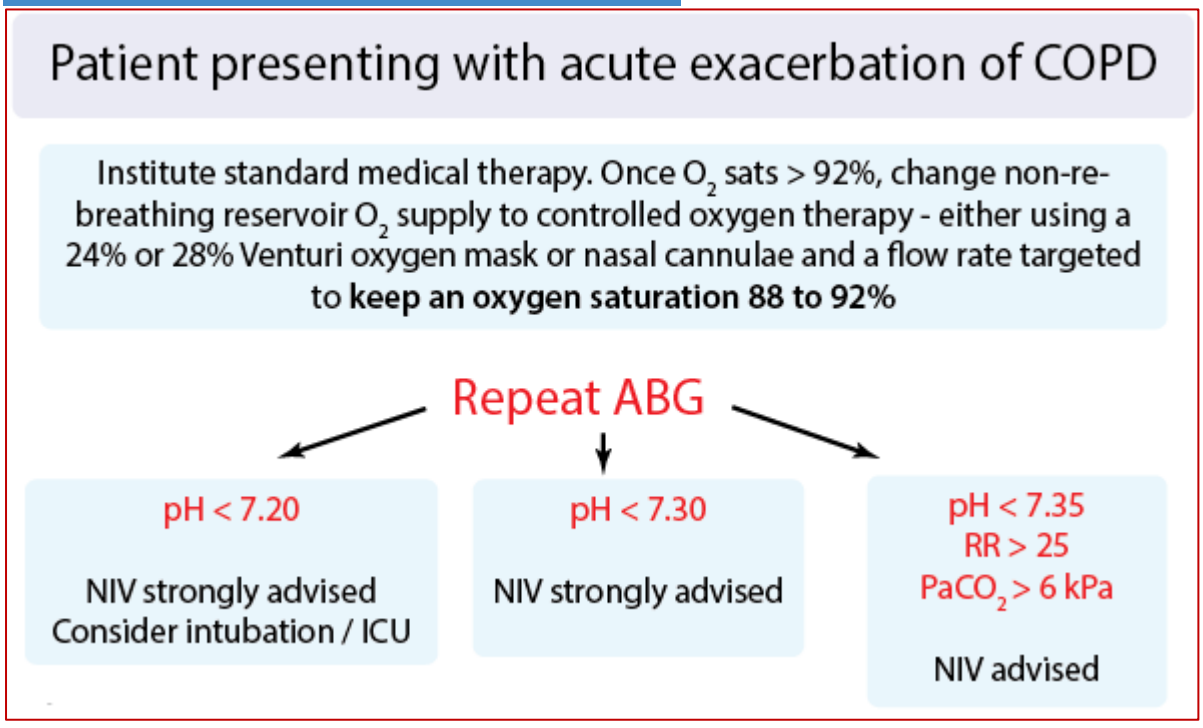
Situations where oxygen therapy should not be used routinely if there is no evidence of hypoxia:

- myocardial infarction and acute coronary syndromes
- stroke
- obstetric emergencies
- anxiety-related hyperventilation

There are three forms of domiciliary supplemental oxygen therapy:

1. Long-term controlled oxygen therapy for at least 15 hours per day in patients with chronic respiratory failure
2. Portable oxygen therapy for exercise-related hypoxaemia
3. Short-burst oxygen therapy, as a palliative treatment for the temporary relief of symptoms.

Non-invasive ventilation (NIV)



Non-invasive ventilation - key indications

- COPD with respiratory acidosis **pH 7.25-7.35** who have not improved on controlled oxygen and standard medical therapy.
  - (NIV) is the treatment of choice for persistent hypercapnic ventilation failure **despite optimal medical therapy.**
    - According to the guidelines, 'maximal medical therapy' is defined as:
      - Controlled oxygen to maintain SaO_2 88-92%
      - Nebulised salbutamol 2.5-5 mg
      - Nebulised ipratropium 500 µg
      - Prednisolone 30 mg
      - Antibiotic agent (when indicated).
  - The evidence surrounding the use of NIV in COPD shows that patients with a pH in the range of 7.25-7.35 achieve the most benefit.
  - The guidelines mention that NIV should be considered in patients with COPD exacerbation in whom a respiratory acidosis persists **despite immediate maximum standard medical treatment on controlled oxygen for no more than one hour.**
  - If the pH is < 7.25 then invasive ventilation should be considered if appropriate.
  - **pCO_2 >6.0** (fits the criterion for respiratory acidosis)
    - **Hypercapnia without profound hypoxia**
- type II respiratory failure secondary to chest wall deformity, neuromuscular disease or obstructive sleep apnoea
- cardiogenic pulmonary oedema unresponsive to CPAP
- weaning from tracheal intubation

Non-invasive, positive-pressure ventilation (NIPPV) has been shown to reduce intubation rates, lower hospital mortality rates and lead to shorter hospital stays.

Recommended initial settings for bi-level pressure support in COPD

- Expiratory Positive Airway Pressure (**EPAP**): 4-5 cm H2O
- Inspiratory Positive Airway Pressure (**IPAP**): RCP advocate 10 cm H20 whilst BTS suggest 12-15 cm H2O.
- back up rate: 15 breaths/min
- back up inspiration: expiration ratio: 1:3
- **ABGs**
  - ABGs should be repeated after 1 hour of NIV therapy, and 1 hour after subsequent change in settings or 4 hours in stable patients.
- **If gas exchange is not significantly improved:**
  - the **IPAP** can be gradually increased at a rate of approximately 5 cms (2-5cm) H2O every 10 minutes with a usual target of 20cm H2O or until a response has been achieved or patient tolerability has been reached.
  - Increases in **EPAP** are not recommended without specialist advice.

How to give nebulisation during NIV in patient with severe exacerbation of COPD ?

- **take off the mask to administer nebulisers**

- Giving nebulised medication into ongoing NIV is not recommended by the BTS as the pressures reduce the effective dose reaching the airways.

Important complication of NIV

- ventilation associated pneumothorax is (most important complication of NIV ==> present acutely)
- Ventilator associated pneumonia ==> present in patients who have been ventilated for long period of time and would not present so acutely).

Contraindications to NIV include:

- facial burns/trauma/recent facial or upper airway surgery
- vomiting
- fixed upper airway obstruction
- undrained pneumothorax
- upper gastrointestinal surgery
- inability to protect the airway
- copious respiratory secretions
- life threatening hypoxaemia
- **haemodynamically unstable** requiring inotropes/pressors (unless in a critical care unit)
- severe co-morbidity
- **confusion/agitation**
- bowel obstruction
- patient declines treatment

Invasive ventilation:

- Patients with a pH <7.26 should be managed with a low threshold for intubation.
- Mechanical ventilation might be necessary if the patient is unconscious or if the pH is below 7.25.
- give NIV whilst awaiting for intensive care.
- in Guillain Barre syndrome with respiratory involvement => the parameter used to assess whether a patient needs ventilator support is an FVC <15-20ml/kg.

Decision to ventilate in COPD

- If the patient had a written advanced directive, properly witnessed, **while he was well**, then it would not be possible to consider intervention if he wished for it not to happen.
- On the other hand**, if he has significant hypoxia, he might not be able to give a rational decision** with respect to his further treatment.
- The family should not have the final decision with respect to intubation - the decision on.
- so **if significantly hypoxic patient refused intubation during acute exacerbation => Intubate and act on the best interests of the patient, while informing the relatives**

Intermittent positive-pressure ventilation (IPPV)

Effects of increased lung volume

- Volumes are significantly increased when compared with spontaneous ventilation
- ↑↑tidal volume → pulmonary vascular resistance, which may lead to → pulmonary hypertension → right ventricular compromise.

- over-inflated alveoli → compression of the alveolar blood vessels → ↑↑ right ventricle volume →↓↓ left ventricle (LV) filling (ventricular interdependence)
- Hyperinflation also leads to prostaglandin release which may be a protective mechanism against lung injury

Effects of increased intrathoracic pressure

- Intrathoracic pressure is increased at all points in the respiratory cycle
- **Inspiration during IPPV → ↑↑ intrathoracic pressure → ↑↑ right atrial pressure → ↓↓ venous return → ↓↓ cardiac output**
- The increased intrathoracic pressure also decreases the gradient across the LV that it has to work against, which results in a decreased afterload. Both these effects reduce intrathoracic blood volume

Long-term oxygen therapy (LTOT)

COPD - LTOT if 2 measurements of pO2 < 7.3 kPa

Which patients should be assessed for and offered (LTOT)? (2010 NICE guidelines**)**

- **Assess patients if any of the following:**
  - Very severe airflow obstruction (FEV1 < 30% predicted).
    - Assessment should be 'considered' for patients with severe airflow obstruction (FEV1 30-49% predicted)
  - cyanosis
  - polycythaemia
  - peripheral oedema
  - raised jugular venous pressure
  - oxygen saturations less than or equal to 92% on room air

How to assess patient for LTOT?

- Assessment is done by measuring **arterial blood gases** on **2 occasions** at least **3 weeks apart** in patients with **stable COPD** on optimal management.
- Blood gases should be performed in a **stable state**, which should be at least **four weeks after an** exacerbation of the disease.

Indications (British Thoracic Society (BTS)

- **General Indications for LTOT:**
  - Chronic obstructive pulmonary disease (COPD)
  - Severe chronic asthma
  - Interstitial lung disease
  - Cystic fibrosis
  - Bronchiectasis
  - Pulmonary vascular disease
  - Primary pulmonary hypertension
  - Pulmonary malignancy
  - Chronic heart failure

- **Indications for LTOT in COPD:**
  - **patients with pO2 of < 7.3 kPa**
  - **patients with pO2 of 7.3 - 8 kPa and one of the following:**
    - secondary polycythaemia
    - nocturnal hypoxaemia
    - peripheral oedema
    - pulmonary hypertension
  - **Borderline results should be repeated in three months (eg PO2 = 7.3 or slightly above, without additional factors).**

Duration of LTOT:

- Patients who receive LTOT should breathe supplementary oxygen for at least **15 hours** a day including at night time.
- At least **15 hours** of oxygen therapy per day is required to **reduce the pulmonary hypertension** associated with (COPD) and to treat the underlying pathology of incipient right heart failure.
- **A reduction in mortality is only seen when oxygen therapy is used for more than 19 hours a day.**
  - **Improvements in pulmonary artery hypertension** were obtained in patients who used oxygen for more than **15 hours** per day,
  - reduction in **mortality** was only improved in patients who used oxygen for more than **18 hours** per day.

Contraindications

- Continued cigarette smoking should be a **relative** contraindication to long-term oxygen therapy.

In patients with chronic hypoxaemia, **LTOT** should be prescribed after assessment, when the **PaO_2 is** consistently at or **below 7.3 kPa** (55 mm Hg) when breathing air during a period of clinical stability. **Clinical stability** is defined as the absence of exacerbation of chronic lung disease for the previous five weeks. The level of $PaCO_2$(which may be normal or elevated) does not influence the need for LTOT prescription.
mrcpass.com

The only treatment that improves the long-term prognosis in patients with (COPD) is LTOT, given for at least 15 hours per day.

Effects of supplementary oxygen therapy:

- Improvement in survival,
- Improvement in exercise endurance, associated with a reduction in ventilation at a given submaximal work rate, and an improvement in walking distance and in the ability to perform daily activities.
- **After 6 months of oxygen therapy, 42% of patients showed evidence of an improvement in cognitive function**, but little change in mood or quality of life.
- Affect the polycythaemia that occurs in patients with chronic hypoxaemia, by **reducing both the haematocrit and the red cell mass**.

Ambulatory oxygen therapy (AOT):

Ambulatory oxygen therapy (AOT):
(New development with light portable cylinders lasting six hours).

- Offer (AOT) to people already on LTOT who want to use oxygen outside the home, following assessment by a specialist.
- Consider it in motivated individuals who have exercise desaturation and PaO_2 less than or equal to 7.3 kPa and whose exercise capacity and/or breathlessness improve with oxygen.

The British Thoracic Society (BTS) recommends:

- AOT should not be routinely offered to patients who are not eligible for LTOT.
- AOT should not be routinely offered to patients already on LTOT.
- AOT assessment should only be offered to patients already on LTOT if they are mobile outdoors.
- AOT should be offered to patients for use during exercise in a pulmonary rehabilitation programme or during an exercise programme following a formal assessment demonstrating improvement in exercise endurance.

Ref: Patient.info

*COPD Patients without chronic hypoxaemia (=paO2 ≤ 7.3 kPa on air **+** Clinical stability (=no exacerbation of COPD in last 5 weeks)) and not on LTOT ➔ perform Walking test with a trial of oxygen ➔ if they show evidence of exercise oxygen desaturation (a fall of SaO2 of at least 4% below 90%) **+** improvement in exercise capacity with **O2 ➔ambulatory oxygen therapy (AOT)** mrcpass.com

Clinical variants of COPD
Pink puffers
Pink puffers have a good respiratory drive.
Clinical features:

- Pursed-lip breathing with intense dyspnoea
- Often thin and elderly
- Sparce production of sputum
- Oedema and overt heart failure (rare complications)

Investigations:

- Blood gases are near-normal until pre-terminally there is very severe airways obstruction
- total lung capacity increased
- Reduction in transfer factor

Blue bloaters
Blue bloaters have a poor respiratory drive.
Clinical features:

- Quite mild dyspnoea
- Often obese
- Production of large volumes of sputum
- Infective exacerbations
- Often oedematous
- Can develop cor pulmonale

Investigations:

- Blood gases show hypercapnia, hypoxaemia, elevated plasma bicarbonate
- Severe nocturnal hypoxaemia
- Airways obstruction might only be moderate

Prognosis of COPD

- Once respiratory failure criteria have been met, the 5-year survival rate is only around 25%.
- **Prognostic indicators in COPD**
  - **The strongest predictors of survival in patients with (COPD) are:**
    - **FEV1**
    - Age
  - Fewer than 50% of patients whose FEV-1 has fallen to 30% of predicted are alive 5 years later.
  - There is a stronger relationship between survival and the post-bronchodilator FEV-1, rather than the pre-bronchodilator FEV-1.
  - Other unfavourable prognostic factors which become apparent in patients with severe disease include:
    - Severe hypoxaemia
    - Raised pulmonary arterial pressure
    - Low carbon monoxide transfer
  - Factors favouring improved survival are:
    - stopping smoking
    - marked bronchodilator response.
  - A reduced FEV-1 is also an important additional risk factor for lung cancer, independent of age or cigarette smoking.

- **MRC dyspnoea scale:**
  - One of the main symptoms of chronic obstructive pulmonary disease (COPD) is breathlessness and the MRC dyspnoea scale should be used to quantify this.

Grade	Degree of breathlessness related to activities
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying or walking up a slight hill
3	**Walks slower than contemporaries on level ground because of breathlessness, or has to stop for breath when walking at own pace**
4	Stops for breath after walking about 100 metres or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when dressing or undressing

- **BODE index**, an index of mortality in COPD developed by the Medical Research Council (**MRC**). This index also incorporates the body mass index, dyspnoea and exercise capacity (as
  - evidenced by a 6-minute walk test). The BODE index can also be used to estimate the risk of hospitalisation.

Air flight in COPD:

Assessment of severity of (COPD) and O_2 sat at sea level should be performed.

A summary is present in the table below:

assessment	advice
Sea level SpO_2 > 95%	**Oxygen not required**
Sea level SpO_2 92-95% and **NO** additional risk factor	Oxygen not required
Sea level SpO_2 92-95% and additional risk factor	Perform hypoxic challenge test with arterial or capillary measurements
Sea level SpO_2 < 92%	In-flight oxygen
Receiving supplemental oxygen at sea level	Increase the flow while at cruising altitude.

The additional risk factors
1/ hypercapnia
2/ FEV1 <50% predicted, lung cancer
3/ restrictive lung disease involving the parenchyma [fibrosis], chest wall [kyphoscoliosis] or respiratory muscles
4/ ventilator support
5/ within six weeks of discharge for an exacerbation of chronic lung or cardiac disease
6/ cerebrovascular or cardiac

disease

Hypoxic challenge test: (to assess flight fitness if SpO2= 92 – 95% **+** additional risk factor in COPD)

Give the patient FiO_2 15% for 15 minutes and measures PaO_2.

- **PaO2 > 7.4 kPa (> 55 mmHg) - Oxygen not required.**
- PaO2 6.6-7.4 kPa (50-55 mmHg) - Borderline. A walk test may be helpful.
- PaO2 < 6.6 kPa (< 50 mmHg) - In-flight oxygen (2L/min).

Pulmonary embolism (PE)

Basic

- PE can cause ventilation- perfusion mismatches.
- When blood flow to the lung is decreased to embolism, the perfusion (Q) is diminished, but ventilation remains unchanged. This results in increasing physiologic dead space.
  - **Decreased perfusion + normal ventilation**

Risk factors

major risk factors (relative risk 5-20) in the development of VTE	**minor risk factors** with a relative risk of (2-4)
• lower limb problems including a fracture or varicose veins • postoperative intensive care • hospitalisation • abdominal/pelvic or advanced malignancy • previous VTE, and • pregnancy.	• occult malignancy • long distance travel • hypertension • congestive cardiac failure, and • thrombotic disorder. • use of the oral contraceptive pill

Features

Sudden shortness of breath, pleuritic chest pain with haemoptysis and tachypnoea are the commonest features. (triad of pleuritic chest pain, dyspnoea and haemoptysis)

- Sudden shortness of breath, tachypnoea
- **Pleuritic chest pain**
  - **worse on deep breathing**
- haemoptysis
- PE can present with virtually any cardiorespiratory symptom/sign depending on its location and size.

Which features make pulmonary embolism *more* likely?

The relative frequency of common clinical signs is shown below:

- Tachypnea (respiratory rate >16/min) - 96%
- Crackles - 58%

- Tachycardia (heart rate >100/min) - 44%
- Fever (temperature >37.8 C) - 43%.
  - **Low-grade pyrexia is common in pulmonary embolism.**
- Atrial flutter, atrial fibrillation and premature beats can also occur

Diagnosis

- **If a patient presents with signs or symptoms of pulmonary embolism (PE)**
  - performed chest x-ray to exclude other pathology.
  - estimate the clinical probability of PE by two-level PE **Wells score**

Clinical feature	Points
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3
An alternative diagnosis is less likely than PE	3
Heart rate > 100 beats per minute	1.5
Immobilisation for more than 3 days or surgery in the previous 4 weeks	1.5
Previous DVT/PE	1.5
Haemoptysis	1
Malignancy (on treatment, treated in the last 6 months, or palliative)	1

Clinical probability simplified scores	
PE *likely*	More than 4 points
PE *unlikely*	4 points or less

- **PE likely (> 4 points):**
  - arrange an immediate computed tomography pulmonary angiogram (CTPA).
    - If there is a delay in getting the CTPA then give low-molecular weight heparin until the scan is performed.
    - If the patient has an allergy to contrast media or renal impairment a V/Q scan should be used instead of a CTPA.
      - ventilation/perfusion single photon emission computed tomography (V/Q SPECT) scan
      - if a V/Q SPECT scan is not available → V/Q planar
- **PE unlikely (≤ 4 points):**
  - arranged a D-dimer test:
    - If this is positive arrange an immediate (CTPA).
    - If there is a delay in getting the CTPA then give low-molecular weight heparin until the scan is performed.

It is interesting to note that the Well's criteria for diagnosing a PE use tachycardia rather than tachypnoea.

Question

The chest X-ray is normal. However, the patient's respiratory rate is high and his oxygen saturation is low. What is the most appropriate next step?

Answer ✔

➔ **assess clinical probability score for pulmonary thromboembolism**

Investigations

Pulmonary embolism - CTPA is first-line investigation

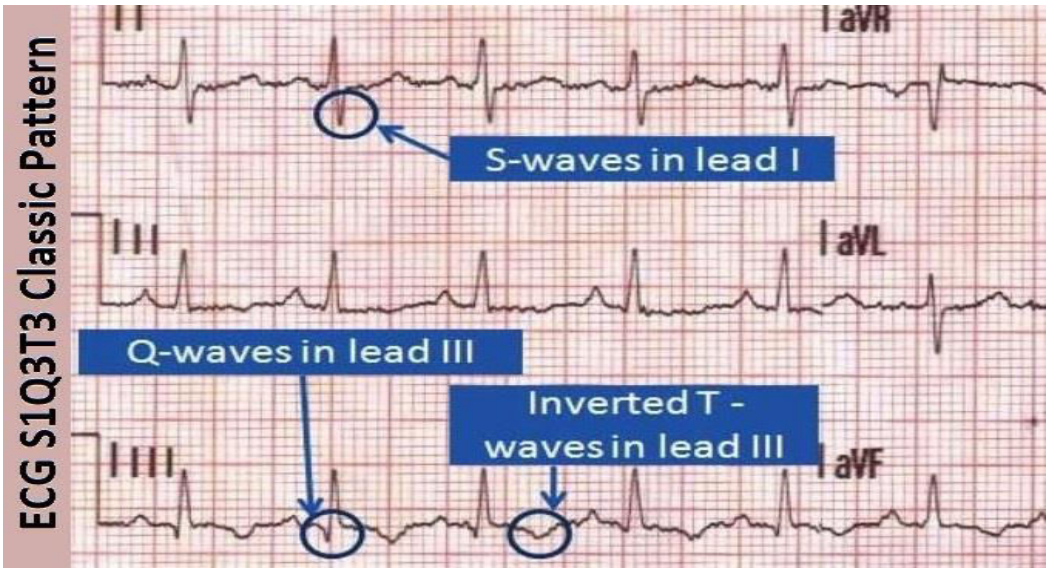
Pulmonary embolism - normal CXR

- **Chest x-ray**
  - Should be performed in all patients with symptoms or signs suggestive of PE
  - **to exclude other pathology**
  - **usually normal in PE**
- **Computed tomographic pulmonary angiography** (**CTPA**)
  - the first-line investigation
  - Advantages compared to V/Q scans?
    - speed, easier to perform out-of-hours,
    - reduced need for further imaging
      - ❖ if the CTPA is negative then patients do not need further investigations or treatment for PE
    - the possibility of providing an alternative diagnosis if PE is excluded
  - Disadvantages of CTPA
    - peripheral emboli affecting subsegmental arteries may be missed .
      → **Low sensitivity for detecting pulmonary emboli in sub-segmental pulmonary arteries**

- **Ventilation-perfusion (V/Q) scans**
  - Indication?
    - If CTPA is contra-indicated
      - ❖ renal impairment (as the contrast media used during CTPAs is nephrotoxic).
      - ❖ allergy to contrast media
      - ❖ high risk from irradiation
  - which type of (V/Q SPECT) scan?
    - If CTPA is contra-indicated → ventilation/perfusion single photon emission computed tomography (**V/Q SPECT**) scan
    - if a V/Q SPECT scan is not available → **V/Q planar**
  - Sensitivity & specificity?

        - sensitivity = 98%; specificity = 40%
    - predictive value of (V/Q) scans?
        - high negative predictive value, i.e. if normal virtually excludes PE
    - other causes of mismatch in V/Q ?
        - old pulmonary embolisms,
        - AV malformations,
        - vasculitis,
        - previous radiotherapy
        - COPD
        - Asthma
        - Increased pulmonary venous pressure, especially secondary to mitral valve disease, causes increased flow to the upper lobes.
    - (V/Q) scan in pregnancy
        - Ventilation quotient (VQ) scan is not contraindicated in pregnant women, although the perfusion only scan is adequate.
        - Radiation to the fetus is small.
    - Which materials are used in (V/Q) imaging?
        - **Xenon** is used for imaging **ventilation**, whilst technetium labelled macroaggregated human serum albumin (**MAA**) is used to image **perfusion**.
- **D-dimers**
    - Indication?
        - Measurement of D-dimer should only be performed when the probability of PE is low, when a normal value would be taken as reassuring and further investigation would not be pursued.
    - Sensitivity & specificity?
        - high sensitivity (95-98%), but poor specificity
        - A negative d-dimer is useful for excluding PE in patients who are clinically thought to be at low risk, but a 'positive' result does not establish the diagnosis.
    - The predictive value of d-dimer?
        - the negative predictive value is greater than the positive predictive value
            - only 30% of patients with positive d-Dimer have a confirmatory diagnosis of PE
    - d-dimers can be positive in:
        - hospitalised patients
        - obstetric patients
        - patients with peripheral vascular disease, cancer and inflammatory conditions
        - increasing age
    - D-Dimer measurements should not be performed if:
        - an alternative diagnosis is likely,
        - the clinical probability is high or
        - there is a probable massive PE.
- **ECG**
    - sinus tachycardia
        - **the most common abnormality**; seen in 44% of patients.

- **the classic ECG changes → S1Q3T3** (seen in no more than 20% of patients)
  - large S wave in lead I
  - large Q wave in lead III
  - inverted T wave in lead III
- Right bundle branch block
  - seen in 18% of patients.
  - associated with increased mortality;
- Right axis deviation (seen in 16% of patients).



- **Pulmonary angiography**
  - **the gold standard**
  - significant complication rate compared to other investigations
- **Elevated cardiac troponin levels also occur in patients with pulmonary embolism** because of right ventricular dilation and myocardial injury

Management

Start low molecular weight heparin and request CT pulmonary angiography **if the symptoms and findings clearly point towards pulmonary embolism (PE).**

Fluid resuscitation is the most appropriate immediate measure before further investigations confirm the presence of a pulmonary embolism (PE).

Massive PE + hypotension - thrombolyse

- anticoagulant
  - Heparin
    - When should be started?
      - For patients with a high or intermediate probability of a non-massive PE → **low molecular weight heparin should be given before imaging**

- ❖ For patient with low probability of non-massive PE → immediately after diagnosis.
- Which type?
  - ❖ For **non-massive PE** →Low molecular weight heparin (LMWH) or fondaparinux.
  - ❖ For patients with **severe renal impairment** ([eGFR] <30 ml/min/1.73 m^2) offer either:
    - unfractionated heparin (UFH) with dose adjustments based on the APTT **or**
    - LMWH with dose adjustments based on an anti-Xa assay.
  - ❖ For patients with an **increased risk of bleeding** consider UFH.
  - ❖ for **massive PE** where **thrombolysis** is being considered, → **unfractionated heparin** should be used
- For how long?
  - ❖ the LMWH or fondaparinux should be continued for at least 5 days or until the international normalised ratio (INR) is 2.0 or above for at least 24 hours, whichever is longer, i.e. LMWH or fondaparinux is given at the same time as warfarin until the INR is in the therapeutic range
  - ❖ for patients with active cancer NICE recommend using LMWH for 6 months
- Benefit of heparin?
  - ❖ Heparin reduces risk of further embolism (anticoagulant) and reduces pulmonary vasoconstriction.

➢ Warfarin
- a vitamin K antagonist (i.e. warfarin) should be given within 24 hours of the diagnosis
- for how long?
  - ❖ warfarin should be continued for at least 3 months.
  - ❖ NICE advise extending warfarin beyond 3 months for patients with *unprovoked* PE. This essentially means that if there was no obvious cause or provoking factor (surgery, trauma, significant immobility)

- **Thrombolysis**

➢ Indication?
- Thrombolysis is now recommended as the first-line treatment for **massive PE** where there is circulatory failure (e.g. hypotension).
  - ❖ Haemodynamic instability may be demonstrated by hypotension, right ventricular strain on an ECG or signs of right heart failure.
- Thrombolysis is indicated in the cardiac arrest situation for suspected PEs. However, it can take 90 minutes to be effective and therefore must only be used if it is appropriate to continue CPR for this duration.
  - ❖ **Cardiac arrest for suspected PEs → Intravenous thrombolysis followed by CPR for 90 minutes**

➢ Which drug? by which root?
- Give alteplase 100 mg over 1.5 hours peripherally.

  - **Thrombolysis administered through a peripheral vein is as effective as through a pulmonary artery catheter**
- percutaneous insertion of **Inferior vena cava (IVC) filter**
  - Indication?
    - If anticoagulation is a contraindicated (eg PE following a recent haemorrhagic stroke)
    - if anticoagulation alone fails
  - Benefit of **IVC** filter?
    - may be as effective as anticoagulation.

PE causing pneumothorax

- **serious rare complication of PE**
- It is important to treat the underlying pneumothorax if severe while still treating the PE with anticoagulation.
- **It may be favourable, therefore, to use unfractionated heparin where there is increased risk of bleeding from the drain site.**
  - Rivaroxaban and other NOACs, such as apixiban, are becoming more favourable in treating DVTs and PEs, however, the **inability to monitor the level accurately** poses an increased risk for this patient.

Ref:
NICE guidelines. published date: June 2012 Last updated: November **2015**

Recurrent pulmonary emboli

- Recurrent pulmonary emboli should always be considered in cases of progressive shortness of breath with no obvious cause.
- **Predisposing factors for recurrent pulmonary embolism include:**
  - Antithrombin III deficiency
  - Protein C deficiency
  - Factor V Leiden mutation
- **Possible clues** include pulmonary hypertension, right ventricular enlargement, hypoxia with a low PaCO2 and a low transfer factor.
- **Widening of the alveolar-arterial (A-a) gradient on exercise is likely to be found**.
- Mismatched defects are classic features of pulmonary embolus.
- Consider inferior vena caval filters for patients with recurrent proximal DVT or PE despite adequate anticoagulation treatment only after considering alternative treatments such as:
  - increasing target INR to 3–4 for long-term high-intensity oral anticoagulant therapy **or**
  - switching treatment to LMWH.

DVT/PE in pregnancy

Investigations

In suspected **PE** in pregnant patients the Royal College of Obstetricians and Gynaecologists recommend the following (updated in 2015):

- Chest x-ray and ECG to look for an alternative diagnosis such as pneumonia and pneumothorax.
- If the chest x-ray is normal:
  - In women with suspected PE who also have **symptoms and signs of DVT** → consider a compression duplex doppler of both legs to exclude a DVT.
    - this may provide indirect evidence of a pulmonary embolism and negate the need for further radiation exposure
    - If this is positive, the patient is treated with full dose low molecular weight heparin (LMWH) (warfarin is of course teratogenic).
  - In women with suspected PE **without symptoms and signs of DVT** → ventilation/perfusion (V/Q) lung scan **or** a computerised tomography pulmonary angiogram (CTPA) should be performed.
    - When the **chest X-ray is abnormal** and there is a **clinical suspicion of PE**, **CTPA** should be performed in preference to a **V/Q** scan. [New 2015]
    - **Current guidance however favours a perfusion scan as it has lower lung radiation doses than a CTPA.**
    - **Half dose VQ involves a lower dose of radiation and therefore preferred.**
- If V/Q scan or CTPA is normal but the clinical suspicion of PE remains:
  - Alternative or repeat testing should be carried out
  - Anticoagulant treatment should be continued until PE is definitively excluded.

Comparing CTPA to V/Q scanning in pregnancy

CTPA	V/Q scanning
CTPA slightly increases the lifetime risk of **maternal breast cancer** (increased by up to 13.6%, background risk of 1/200 for study population). Pregnancy makes breast tissue particularly sensitive to the effects of radiation	V/Q scanning carries a slightly increased risk of **childhood cancer** compared with CTPA (1/280,000 versus less than 1/1,000,000)

- D-dimer is of limited use in the investigation of thromboembolism as it often raised in pregnancy.

Treatment of PE in pregnancy

- In clinically suspected DVT or PE, treatment with low-molecular-weight heparin (LMWH) should be commenced immediately until the diagnosis is excluded by objective testing
- Obstetric patients who are postoperative and receiving unfractionated heparin should have platelet count monitoring performed every 2–3 days from days 4 to 14 or until heparin is stopped. [New 2015]

- Postpartum warfarin should be avoided until at least the fifth day and for longer in women at increased risk of postpartum haemorrhage. [New 2015]
- Intravenous unfractionated heparin is the preferred, initial treatment in massive PE with cardiovascular compromise.

Post-thrombotic syndrome (PTS)

- can develop in nearly half of all patients who experience a DVT
- symptoms include chronic leg pain, swelling, redness, and ulcers
- prevention of post-thrombotic syndrome
  - **prolonged use of LMWH (more than 12 weeks)** is associated with a significantly lower chance of developing post-thrombotic syndrome. [New 2015]
  - Following a DVT, elastic compression stockings should be worn on the affected leg **to reduce pain and swelling.**
    - the role of compression stockings in the prevention of post-thrombotic syndrome is **unclear**. [New 2015]

Fat embolism

The classic triad of presentation is:

- **Eosinophilia**
- **Acute renal failure and**
- **Livedo reticularis.**

The diagnosis of cholesterol embolism should be considered in any patient with atherosclerotic disease presenting with deteriorating renal function, multisystem disease or distal ischaemia developing after an invasive arterial procedure.

Overview

- Unlike emboli that arise from a thrombus, fat emboli are small and multiple producing widespread effects.
- They may occur one to three days following a fracture
- more common in closed fractures on the long bones or pelvis.

mechanism: suggested 2 mechanisms:

- release of lipid globules from damaged bone marrow fat cells.(eg fracture femor).
- increased mobilisation of fatty acids peripherally.

Features: depends on what part of the microvasculature is affected by the lipid globules.

- Pulmonary symptoms (shortness of breath, hypoxia) are caused by ventilation perfusion mismatch.
  - may progress to respiratory failure and ARDS requiring mechanical ventilation.
- Neurological (confusion and agitation)
  - Cerebral emboli produce neurological signs in up to 86% cases.

  - often occur after onset of respiratory symptoms
  - Usually there is an acute confusional state with or without focal signs.
  - Most neurological deficits are transient and reversible.
- Haematological (thrombocytopenia, anaemia).
- Dermatological: Petechial rash caused by capillary damage in the skin.
  - **Multiple petechiae in the distribution of the axilla or upper body is characteristic of a fat embolism.**
  - The petechial rash is pathognomonic of this syndrome, but occurs in only 30-50% of cases
  - Rash is seen in the conjunctiva, mucous membranes, skin folds of upper body particularly neck and axilla, appearing within the first 36 hours.
- Other features:
  - pyrexia
  - tachycardia
  - ECG changes (ST segment depression and right heart strain)
  - fluffy retinal exudates
  - coagulopathy, and
  - renal changes (oliguria, lipiduria, proteinuria or haematuria).

Treatment

- Initial resuscitation should involve
  - **high flow oxygen**
  - **intravenous (iv) fluids** to maintain high right ventricular filling pressures.
- Continuous positive airways pressure ventilation would help in the management of the pulmonary oedema and is the next consideration after IV fluids.
- Steroid therapy is normally introduced later in ARDS, used at early stage can worsen pulmonary oedema, and evidence is equivocal as to benefit.
- It should be noted that **diuretic treatment would be strongly contraindicated** in this case. This is because right ventricular output is dependent on elevated filling pressures. Reducing the preload is therefore not a good idea.

Pneumonia

Community-acquired pneumonia (CAP)

***Streptococcus pneumoniae* is associated with cold sores**

Preceding influenza predisposes to *Staphylococcus aureus* pneumonia

Both Klebsiella and Staphylococcus are associated with empyema formation and cavitating lung lesions.

Causes of Community acquired pneumonia (CAP) :

- ***Streptococcus pneumoniae***
  - **(accounts for around 80% of cases) the most common cause** of CAP & **single lobar** pneumonia.
  - **Streptococcus pneumoniae commonly causes reactivation of the herpes simplex virus resulting in 'cold sores'**
  - **S. pneumoniae is the most important cause of fulminant sepsis in patients with hyposplenism.**
  - **Streptococcus pneumoniae is the commonest cause of community-acquired pneumonia in the elderly and young children .**
    - Elderly patients may present atypically, complaining **less frequently of respiratory symptoms,** headache, and myalgias, and are **more likely to have absence of fever** and **altered mental status** on admission.
  - Bacteraemic Streptococcus pneumoniae pneumonia is the number one cause of mortality in community- acquired pneumonia, representing up to 70% of all deaths.
  - most common cause of a single lobar pneumonia.
  - Characteristic features of pneumococcal pneumonia
    - rapid onset
    - high fever
    - pleuritic chest pain
    - herpes labialis

- ***Haemophilus influenzae***
  - more likely to be associated with exacerbations of COPD
- ***Staphylococcus aureus*:**
  - commonly **after the 'flu** .
  - the BNF advises the co-prescription of flucloxacillin.
  - It's an organism often found on the skin. It is therefore commonly associated with systemic infections in **intravenous drug users** ,this is may hinted in questions by the presence of track marks.
  - It also causes a **bibasal pneumonia** as opposed to *Streptococcus pneumoniae* that is the most common cause of a single lobar pneumonia.
  - seen most frequently in the **elderly** and in **intravenous drug users** or **patients with underlying disease**.
  - It can result in a cavitating pneumonia.
  - S. aureus is the most common organism responsible for secondary **necrotizing pneumonia**
    - characteristics of necrotizing pneumonia include:
      - preceding influenza infection,
      - rapid onset and progressive symptom worsening,
      - decreased WBC count,

- airway hemorrhages,
- respiratory failure,
- necrotic destruction of lung parenchyma,
- high mortality rate.

  - **Carries a high mortality, and therefore if suspected treatment should initially be for a severe CAP.**
  - Capable of production of Panton-Valentine-Leucocidin toxin , associated with severe illness and high mortality.
  - Pneumothorax, pleural effusion and empyema are common in staphylococcal pneumonia.
- **atypical pneumonias** (e.g. Due to *Mycoplasma pneumoniae*)
  - Coxiella burnetii (Q fever) ==> relation to animal sources (usually sheep).
  - Chlamydophila psittaci ==> bird contact (eg, poultry or duck workers)
- **Viruses**
- ***Klebsiella pneumoniae* is classically in alcoholics**.
  - Klebsiella pneumonia (Friedlander's pneumonia) typically occurs in middle-aged alcoholic men.
  - can cause cavitating pneumonia
  - usually affects the upper lobes
  - occurs in immunosuppressed individuals or, classically, alcoholics.
  - Chest x-ray features may include abscess formation in the middle/upper lobes and empyema.
  - The mortality approaches 30-50%.

Organism	Characteristic chest x-ray
Streptococcus pneumoniae	**lobar** consolidation
Legionella	**bibasal** consolidation
Staphylococcus aureus	bilateral **cavitating** bronchopneumonia,

Management

Mild community acquired pneumonia (CURB 0-1) should be treated with oral penicillin therapy alone assuming no allergies and no other complicating factors

- **CURB-65 criteria of severe pneumonia**
  1) **C**onfusion (abbreviated mental test score <= 8/10)
  2) **U**rea > 7 mmol/L
  3) **R**espiratory rate >= 30 / min
  4) **BP**: systolic <= 90 or diastolic <= 60 mmHg
  5) age **≥ 65** years

  - Patients with **3 or more** (out of 5) of the above criteria are regarded as having a **severe pneumonia**

- **Low or moderate severity CAP**:
  - oral amoxicillin.
  - A macrolide should be added for patients admitted to hospital.

- There is a high incidence of *Staphylococcus aureus* pneumonia in patients following influenza. As a result the BNF advises the co-prescription of flucloxacillin in this situation.

- **High severity CAP**:
  - intravenous co-amoxiclav + clarithromycin OR cefuroxime + clarithromycin OR cefotaxime + clarithromycin
    - Intravenous clarithromycin is an extremely irritant drug and it should be avoided wherever possible if a patient can take it orally.
    - Where patients require intravenous administration this should be via a wide bore cannula and the site checked regularly for signs of **thrombophlebitis**.
  - the current BNF has slightly different recommendations for high severity CAP:
    - intravenous benzylpenicillin + clarithromycin OR benzylpenicillin + doxycycline.
    - For 'life-threatening' infections the BNF recommends the same as the BTS guidelines for high-severity CAP

- **Follow up**
  - NICE have provided guidance on what advice patients should be given in terms of **response to treatment and recovery**, by:
    - week 1: fever should resolve
    - week 4: chest pain and sputum should have significantly reduced
    - **week 6: cough and shortness of breath should have significantly reduced**
    - month 3: most symptoms should have resolved, except for tiredness
    - month 6: should be returned to normal

  - A repeat chest X-ray may be indicated to ensure resolution and that there is no underlying pathology, but **radiological changes can take up to 6 weeks to improve**.

A summary table of empirical antibiotics as suggested by the BTS is shown below.

Pneumonia Severity (based on clinical judgement and CURB score)	Treatment Site	First line	Second line
Low Severity (CURB65 = 0-1)	Home	Amoxicillin orally	Doxycycline or clarithromycin orally
Low Severity (CURB65 = 0-1)	Hospital(reason for admission other than pneumonia severity i.e. social reasons)	Amoxicillin orally	Doxycycline or clarithromycin orally
Moderate severity (CURB65 = 2)	Hospital	Amoxicillin **plus** clarithromycin orally (IV if oral administration not possible)	Doxycycline, Levofloxacin or moxifloxacin orally
High Severity (CURB65 = 3-5)	Hospital	Co-amoxiclav plus clarithromycin IV	Benzylpenicillin plus levofloxacin or ciprofloxacin IV **OR** **Cefuroxime plus clarithromycin IV**

- **Adding a fluoroquinolone is an option for those with high severity pneumonia not responding to a b-lactam/ macrolide combination antibiotic regimen** (BTS 2009).
  - The chance of cross reactivity of penicillin allergy with beta-lactams is only 10%. A rash is not a contraindication for this.

- **Panton-Valentine Leukocidin-producing Staphylococcus aureus (PVL-SA)**
  - a rare cause of high severity pneumonia , associated with rapid lung cavitation (necrotising pneumonia) and multiorgan failure**.**
  - empirical antibiotic combination of IV **linezolid** 600 mg twice daily, IV **clindamycin** 1.2 g four times a day and IV rifampicin 600 mg twice daily
- **For those patients referred to hospital with suspected life threatening CAP , general practitioners should administer I.V Penicillin G 1.2 g or amoxicillin 1 g orally.** (BTS 2009).
  - For high severity the BNF suggest benzylpenicillin with either clarithromycin or doxycycline as first line, however if the patient has life-threatening infection,

gram-negative organisms are suspected, co-morbidities are present or the patient is a nursing or residential home resident (probably the vast majority of hospital inpatients) then co-amoxiclav and clarithromycin should be used.

- If ***Staphylococcus aureus*** is identified, treatment should be altered:
  - **Non-MRSA** organisms should be treated with flucloxacillin and/or rifampicin; an alternative for penicillin-allergic patients is teicoplanin and rifampicin.
  - **MRSA** should be treated with vancomycin.

BNF antibiotic guidelines

The following is based on current BNF guidelines: **Respiratory system**

Condition	Recommended treatment
Exacerbations of chronic bronchitis	Amoxicillin or tetracycline or clarithromycin
Uncomplicated community-acquired pneumonia	Amoxicillin (Doxycycline or clarithromycin in penicillin allergic, add flucloxacillin if staphylococci suspected e.g. In influenza)
Pneumonia possibly caused by atypical pathogens	Clarithromycin
Hospital-acquired pneumonia	Within 5 days of admission: co-amoxiclav or cefuroxime More than 5 days after admission: piperacillin with tazobactam OR a broad-spectrum cephalosporin (e.g. ceftazidime) OR a quinolone (e.g. ciprofloxacin)

Pneumonia: Prognostic factors

- The British Thoracic Society recommends that patients should be assessed for the severity of their pneumonia using several core prognostic features (CURB-65 score).

- **The CURB-65 score** is as follows:

Criterion	Marker
C	Confusion (abbreviated mental test score ≤ 8/10)
U	Urea >7 mmol/L
R	Respiration rate >= 30/min
B	Blood pressure: systolic <= 90 mmHg and/or diastolic <= 60 mmHg
65	Aged ≥ 65 years

  - **Interpretation**
    - CURB-65 score of 0:
      - should be managed in the community.
    - CURB-65 score of 1:
      - should have their SaO_2 assessed which should be > 92% to be safely managed in the community and a CXR performed.
      - If the CXR shows bilateral/multi-lobar shadowing hospital admission is advised.
    - CURB-65 score of **2 or more:**
      - should be managed in hospital as this represents a severe community acquired pneumonia.
    - CURB-65 score of 4:
      - CURB-65 score correlates with an increased risk of mortality at 30 days with patients with a CURB-65 score of 4 approaching a **30% mortality rate at 30 days**.
- **Factors associated with a poor prognosis include:**
  - ↑ CURB-65 score
  - Co-morbidity such as renal disease
  - hypoxaemia (pO2 < 8 kPa) independent of FiO2
  - White cell count less than 4 ×109/L or greater than 20 ×109/L
  - Multi-lobar involvement on CXR
  - Temperature less than 35°C or more than 40°C.
  - **Thrombocytosis** is associated with increased mortality compared to thrombocytopaenia or normal platelet levels.

- **How to define mental confusion in the CURB65 severity score?**

  - **The Abbreviated Mental Test** (each question scores 1 mark, total 10 marks)

1. Age
2. Date of birth
3. Time (to nearest hour)
4. Year
5. Hospital name
6. Recognition of two persons (eg, doctor, nurse)
7. Recall address (eg, 42 West Street)
8. Date of First World War
9. Name of monarchs
10. Count backwards 20 R 1
    - Score of 8 or less has been used to define mental confusion in the CURB65 severity score. (2009 BTS guideline for CAP),

- **The risk of death at 30 days increases as the score increases**:

Score	Risk of death at 30 days
0	0.7%
1	3.2%
2	13.0%
3	17.0%
4	41.5%
5	57.0%

- Similarly, with any infection **the risk of mortality increases as the CURB score increases**

Score	Risk of death at 30 days
0 to 1	<5% mortality
2 to 3	**< 10% mortality**
4 to 5	15-30% mortality

- **Factors help guide the decision to admit**
  - age,
  - co-morbidities,
  - social factors
  - CURB score

- hypoxia
- bilateral chest consolidation which can also indicate a more severe pneumonia.

Score	Management
0-1	Treat as an outpatient
>2	Treat as an inpatient

- **Indicators of poor prognosis in pneumonia** include:
  - Age more than 65
  - **Co-existing morbidity including diabetes mellitus**, congestive cardiac failure, coronary artery disease, stroke, chronic lung disease
  - Respiratory rate more than 30
  - Low systolic (<90mmHg) or diastolic (<60mmHg) blood pressure
  - Bilateral involvement or involvement of more than two lobes on chest radiograph
  - Altered mental state.
  - Biochemical/haematological markers include:
    - White count less than 4 or more than 20
    - Hypoxaemiaia or patients requiring FiO2 greater than 60% to maintain saturations
    - Positive blood culture
    - Blood urea more than 7.
- **CRP test**
  - NICE also mention point-of-care CRP test.
  - This is currently not widely available but they make the following **recommendation with reference to the use of antibiotic therapy**:
    - CRP < 20 mg/L - do not routinely offer antibiotic therapy
    - CRP 20 - 100 mg/L - consider a delayed antibiotic prescription
    - CRP > 100 mg/L - offer antibiotic therapy

Discharge criteria and advice post-discharge

- NICE recommend that patients are **not routinely discharged if in the past 24 hours they have had 2 or more of the following findings:**
  - temperature higher than 37.5°C
  - respiratory rate 24 breaths per minute or more
  - heart rate over 100 beats per minute
  - systolic blood pressure 90 mmHg or less
  - oxygen saturation under 90% on room air
  - abnormal mental status
  - inability to eat without assistance.
- They also recommend delaying discharge if the temperature is higher than 37.5°C.

How quickly their symptoms should resolve?

- NICE recommend that the following information is given to patients with pneumonia in terms of how quickly their symptoms should resolve:

Time	Progress
1 week	Fever should have resolved
4 weeks	Chest pain and sputum production should have substantially reduced
6 weeks	Cough and breathlessness should have substantially reduced
3 months	Most symptoms should have resolved but fatigue may still be present
6 months	Most people will feel back to normal.

Follow up

- **What review policy should be adopted in patients managed in the community?**
  - Review is recommended after 48 h or earlier if clinically indicated for disease severity assessment
  - Those who fail to improve after 48 h of treatment should be considered for hospital admission or chest radiography.
- **C-reactive protein should be re-measured and a chest radiograph repeated in patients who are not progressing satisfactorily after 3 days of treatment.**
- **Chest x ray in six weeks to ensure complete resolution**.
  - This is to exclude any underlying cause especially malignancy.
  - those who have persistent shadowing on the lung need referral to a respiratory physician**.**
  - **What arrangements should be made for follow-up after hospital discharge?**
    - **Clinical review should be arranged for all patients at around 6 weeks.**

Complications of pneumonia

- **Acute complications**:
  - might be obvious at presentation or might appear after an interval (empyema, abscess, fistula and organising pneumonia).
- **Chronic complication:**
  - **Bronchiectasis**
    - only diagnosed after the illness because temporary or reversible bronchial dilatation is sometimes seen during the acute illness.

Prevention and vaccination

- All patients aged 65 years or at risk of invasive pneumococcal disease who are admitted with CAP and who have not previously received pneumococcal vaccine should receive 23-valent pneumococcal polysaccharide vaccine (23-PPV)

Ref:

- NICE 2014 Pneumonia in adults: diagnosis and management
- The British Thoracic Society published guidelines in 2009

Klebsiella

Pneumonia in an alcoholic - Klebsiella

Overview

- *Klebsiella* is a **Gram-negative rod** that is part of the **normal gut flora**.
- It can cause many infections in humans including:
  - pneumonia (typically following aspiration) and
  - urinary tract infections.

Pathophysiological mechanism

- colonization of the oropharynx followed by microaspiration of upper airway secretions in the setting of decreased consciousness (due to heavy drinking).

Features of *Klebsiella* pneumonia

- more common in alcoholic and diabetics
- may occur following aspiration
- 'red-currant jelly' sputum
- Cavitating lesions, often affects **upper lobes**.

Treatment:

- Third-generation cephalosporins or quinolones are used as standard therapy

Prognosis

- commonly causes lung abscess formation and empyema
- mortality is 30-50%

Legionella pneumonia

Legionella pneumophilia is best diagnosed by the urinary antigen test

Epidemiology:

- Cause 2-5% of community-acquired pneumonia admitted to hospital.
- Most patients require hospital admission within 5-7 days of the start of symptoms.
- Incubation period 2-10 days,
- Males are two to three times more frequently affected than females.
- Highest incidence in the 40- to 70-year-old age group.

features which strongly suggest Legionella:

- recent foreign travel
- flu-like symptoms
- hyponatraemia
- pleural effusion

Etiology

- *Legionella* are **gram-negative rod** bacteria
- Legionnaire's disease is caused by the **intracellular** bacterium *Legionella pneumophilia*.

Source infections

- It is typically **colonizes water tanks** and hence questions may hint at air-conditioning systems or foreign holidays.
- Factors that encourage colonisation and multiplication are:
  - temperature (20-45 °C) and
  - stagnation.
- **The most common sources in buildings in which Legionella organisms have been found** are:
  - Hot-water calorifiers
  - Storage tanks
  - Piped water, especially hot water from the calorifiers in large buildings and industrial complexes with long runs of pipework

- **Other well-recognised sources** include:
  - Recirculating water in air-conditioning and cooling systems
  - Whirlpool spas and other warm-water baths
  - Decorative fountains
  - Nebulisers and humidifier reservoirs of hospital ventilation machines if topped up with contaminated tap water

Transmission

- Dissemination of infection is by inhalation of contaminated water droplets (aerosol) aerosolised bacteria
  - To cause infection the droplets must be of a size that can reach the alveoli of the lungs (less than 5 mm in diameter).
  - Taps and shower-heads produce very localised aerosols, whereas the water droplets (drift) contained in the airstream released from a cooling tower can be carried a considerable distance and expose a greater number of people to risk.
- rarely, micro-aspiration of contaminated drinking water.
- **Person-to-person transmission is not seen**

Features

- flu-like symptoms including fever (**present in > 95% of patients**)
- dry cough
- **relative bradycardia**
- confusion
  - may represent toxic encephalopathy.
- **lymphopaenia**
  - A marked **neutrophil leukocytosis** may be associated with concomitant **lymphopenia**.
- hyponatraemia
  - Hyponatraemia **secondary to** syndrome of inappropriate antidiuretic hormone secretion **(SIADH)** is more common in *Legionella* infection than other pathogens.
  - **Hyponatraemia occurs more commonly than with other pneumonias.**
- deranged liver function tests
- pleural effusion:
  - seen in around 30% of ptients
  - may be accompanied by pleuritic chest pain

- Typically, starts with high fever, shivers, severe headache and muscle pains.
- **may start abruptly with a brief prodrome of malaise, myalgia and headache. High fever and non-productive cough are common and may be accompanied by pleuritic chest pain.**
- dyspnoea is common
- diarrhea
- renal
  - Up to 40% of patients may also have proteinuria.
  - microscopic haematuria
- Amnesia on recovery is common.

Two **classic signs** of Legionnaires' disease are **fever that does not coincide with** tachycardia and a **prominent headache**.

Diagnosis

- **urinary antigen (the most useful diagnostic test)**
  - Sensitivity 80%; specificity >99%.
  - a negative urinary antigen does not exclude the diagnosis of *Legionella* infection, because it only identifies **serogroup 1** (which is the most common serogroup).
  - Test may remain positive for weeks or months and it is, therefore, not a test for cure.
- It is important to remember that the organism does not show up on Gram-staining.
- Cultures
  - on buffered charcoal yeast extract (BCYE) agar.
  - Sensitivity 20% to 95%; specificity 100%

Management

- Legionnaires' disease is treated with antibiotics that achieve high intracellular concentration, particularly:
  - **First line**
    - macrolides
      - erythromycin (500-1000 mg every 6 hours) **or** clarithromycin (500 mg twice daily for clarithromycin)
      - if patient allergic or intolerant to macrolides → ciprofloxacin
    - **fluoroquinolones (such as levofloxacin).**
      - **favoured when the illness is severe enough to warrant admission.**
  - **Second line**
    - tetracyclines
      doxycycline open_in_new: 200 mg orally/intravenously as a loading dose, followed by 100 mg every 12 hours for 14-21 days
    - OR
    - tetracycline open_in_new: 500 mg orally every 6 hours for 14-21 days
  - **For severe infections**
    - **quinolone-macrolide combinations**

- ❖ Ciprofloxacin is also a useful drug in combination with clarithromycin.
- ❖ this combination has significant potential toxicity, such as prolongation of the QT interval and possible torsades de pointes arrhythmia

- Both doxycycline and ciprofloxacin are reasonable second line choices for the treatment of *Legionella*.
- Rifampicin is often recommended as additional therapy to erythromycin, in a dose of 600 mg once or twice daily in patients with severe infection or who are deteriorating.
  - ➢ *Legionella* resistance to rifampicin is noted, therefore this is not a first line option.
  - ➢ A small recent study also noted increased liver function abnormalities in patients with legionnaire's exposed to rifampicin.

Prevention

- **The most important** principle to follow is to avoid holding water at temperatures between 20 °C and 45 °C, which is the range in which Legionella multiplication occurs.

Prognosis

- The mortality rate may approach 100% in patients with underlying disease.
- In untreated patients, the mortality rate may be as high as 80%.

Pontiac fever

- **Non-pneumonic *Legionella* infection is known as Pontiac fever.**
- It causes a mild upper respiratory infection that resembles acute influenza.
- unlike Legionnaires' disease **Pontiac fever** does not cause pneumonia.

Mycoplasma pneumoniae

Mycoplasma pneumonia presents with **systemic upset**, **dry cough** and **fever**. **Myalgia** and **arthralgia** are common. The **WBC** is often within the **normal** range.

- *Mycoplasma pneumoniae* is a cause of atypical pneumonia which often affects younger patients
- most commonly causes disease in individuals aged 15-30 years.
- accounts for about 7% of all community-acquired pneumonias.
- **it occurs in epidemics every 4 years** , **more commonly among close-knit populations like those in schools and colleges.**
- It is important to recognise atypical pneumonias as they may **not respond to penicillins** or cephalosporins **due to it lacking a peptidoglycan cell wall**.,

Features

The longer duration of symptoms and unusual features of **abdominal pain**, **dry cough** and **hyponatraemia** should alert you to an atypical organism of which *Mycoplasma pneumoniae* is one of the commonest.

- the disease typically has a prolonged and gradual onset
- flu-like symptoms classically precede a dry cough
- It is characterised by Headaches, malaise and cough.
- bilateral consolidation on x-ray

- complications may occur as below

Extra-pulmonary manifestations occur in ~10% of cases:

- Rash
  - **erythema multiforme**
  - erythema nodosum
  - urticarial
- Neurological syndromes
  - aseptic meningitis
  - encephalitis,
  - neuropathies
  - Guillain-Barré syndrome
  - transverse myelitis
- cardiac:
  - Myocarditis
  - Pericarditis
- Renal failure
- **Hepatitis**
- Pancreatitis (rarely).
- Arthritis
- Cold agglutinins
- **Haemolytic anaemia.**
  - found in up to 50% of cases.
  - **Presence of spherocytes or fragmented red blood cells on the film is suggestive of haemolytic anaemia**.
  - In mycoplasma infection spherocytes are a result of cold agglutinin damage to the red cell membrane.
  - Nucleated red cells may also be seen.
  - Haemolysis is associated with the presence of IgM antibodies (cold agglutinins) directed against the I antigen of the erythrocyte membrane.
  - **Haemolysis would be confirmed on a blood film and a direct Coombs' test.**
  - Reticulocyte counts are increased
  - bilirubin is predominantly unconjugated.
  - Lactate dehydrogenase (LDH) is increased and haptoglobins are reduced.
  - Urinary urobilinogen is increased and haemosiderinuria may be seen.

Complications

- cold agglutins (IgM) may cause an haemolytic anaemia, thrombocytopenia
- erythema multiforme, erythema nodosum
- meningoencephalitis, Guillain-Barre syndrome
- bullous myringitis: painful vesicles on the tympanic membrane
- pericarditis/myocarditis
- gastrointestinal: hepatitis, pancreatitis , Vomiting , Diarrhoea
- renal: acute glomerulonephritis

Investigations

Mycoplasma? - Serology is diagnostic

- diagnosis is generally by Mycoplasma serology
- positive cold agglutination test (cold agglutinins occur in only half of patients)
- The chest X-ray findings might not correlate with the patient's condition.theX-ray appearances are usually much worse than would be suggested by the clinical examination of the respiratory system.
- The white blood count can be normal

Management

Mycoplasma pneumonia if allergic/intolerant to macrolides – doxycycline

- **First line → erythromycin/clarithromycin**
- alternative → tetracyclines such as doxycycline.
- The pathogen does not have a cell wall and so is not susceptible to penicillin, cephalosporins or other antibiotics that are active against the bacterial cell wall

Prognosis

- Most cases resolve **spontaneously** within a few weeks.

The golden notes

Mycoplasma pneumoniae

- more closely related to gram positive bacteria**.**
- **Basic**
  - **The absence of cell wall structure**
    - Distinguish them from other bacteria
    - makes them insensitive to beta-lactam anti-microbial
    - prevents them from staining by gram's stain
    - responsible for their polymorphism
- **Presentation**
  - **dry cough** (preceded by flu-like symptoms) **and fever**
  - **systemic upset** (arthralgia, haemolytic anaemia, erythema multiforme, Neurological, pericarditis/myocarditis, GIT, renal)
  - the most common non-pulmonary manifestation → neurological
  - occurs in epidemics every 4 years , commonly in close-knit populations (eg: schools and colleges)
  - **Haemolysis:**
    - **Caused by IgM antibodies (cold agglutinins) directed against the I antigen of the erythrocyte membrane.**
    - **confirmed by** blood film and a direct Coombs' test
- **Investigations**
  - Hyponatraemia
  - Normal WBC
  - **the cause of spherocytes in In mycoplasma?**

- **cold agglutinin damage to the red cell membrane**
- **CXR:** might not correlate with the patient's condition → much worse than would be suggested by the clinical examination
  - bilateral consolidation on x-ray
  - the commonest chest x-ray abnormality is interstitial infiltrate (90%)
  - the commonest chest CT abnormality is bronchial wall thickening.
    - *M. pneumoniae* attaches to cilia via **P1 protein** and multiplies in the respiratory epithelial layer.
    - Attachment to epithelial cilia is responsible for bronchial wall thickenings.

- **Diagnosis**
  - **the diagnostic test → serology is the "gold standard"**
    - Enzyme immunoassays (EIAs) are the most widely used and reliable commercial Mycoplasma serology tests.
      - 92% sensitivity and 95% specificity
      - It allows IgG and IgM titration
      - more sensitive than culture for detecting acute infection
  - **positive cold agglutination test**
  - **PCR**
    - sensitivity is very high
    - Faster than serology
    - Unlike serology, it requires only one specimen.
    - does not require viable organisms only. It can amplify the dead bacilli also.
    - Causes of Positive PCR but negative serology tests
      - asymptomatic carriage of M. pneumoniae (after disease, or during incubation period).
      - immuno compromised patients,→ no diagnostic antibody response.
      - Early successful antibiotics therapy.
  - **Culture**
    - rarely used for routine diagnosis
    - sensitivity may be no more than 60% , But when positive, its specificity is 100%,
- **Treatment**
  - **First line → erythromycin/clarithromycin**
  - alternative → tetracyclines such as doxycycline.

Aspiration pneumonia

- The typical patient with aspiration pneumonia has gingival crevice disease combined with a predisposition for aspiration that is usually due to a suppressed level of consciousness or dysphagia.
- Chest X-rays usually show infection in a dependent segment (usually the superior segments of the lower lobes or posterior segments of the upper lobes as these are dependent in the recumbent position),

- **Aspiration pneumonia** => typically affects in **right lower lobe** in persons with impaired swallowing.

Psittacosis (Chlamydia psittaci pneumonia)

Exposure to an ill bird and a rash (Horder's spots) are pathognomonic

- Chlamydia psittaci infection (psittacosis) is characterised by malaise, fever, myalgia and pneumonia.
- **Exposure to an ill bird and a rash (Horder's spots) are pathognomonic.**
- Pet owners, vets and zoo keepers are most at risk. It is rare in children.
- Person to person transmission occurs especially in a hospital environment.
- Sputum Gram stain reveals a few leucocytes and no predominant bacteria. There are few signs and few laboratory/x ray findings.
- The chest X-ray can show segmental or diffuse consolidation.
- Relative bradycardia with non-specific chest signs, coupled with diffuse chest x ray changes, a low white count and abnormal LFTs are consistent with the disease. Abnormal LFTs in up to 50%.
- Positive serology is with complement-fixing antibodies.
- Diagnosis is confirmed by enzyme immunoassay
- Erythromycin or tetracyclines are the drugs of choice.

Pseudomonas pneumonia

Risk factors

- bronchiectasis
- cystic fibrosis.
- hospital-acquired infections,
  - particularly in intensive care units or after surgery.
  - Nosocomial or **hospital-acquired infections** should be suspected in patients with an onset of symptoms at least 48 hours after admission to the hospital.

Treatment

- anti-pseudomonal penicillin, ceftazidime, meropenem or ciprofloxacin.

Hospital-acquired pneumonia

Prevalence

- The third most common hospital-acquired infection after urinary tract infections and wound infections.

Causes

- **Gram-negative organisms** are far more common, owing to:
  - Colonisation of the oropharynx by Gram-negative bacilli, which is very common in hospitalised patients, who have often been on broad-spectrum antibiotics already
  - Increased risk of micro-aspiration of nasopharyngeal secretions
  - Increased likelihood of immunodepression

Treatment

- most commonly as combination therapy. A third generation cephalosporin with an aminoglycoside is the current British Thoracic Society (BTS) recommendation.

Mendelson syndrome

Definition

- acute pneumonia caused by regurgitation of stomach contents and aspiration of chemical material, usually gastric juices.
- Often follows anaesthesia, when the gag reflex is depressed.

Features

- Symptoms develops rapidly, and within hours the patient can become tachypnoeic, hypoxic and febrile.
- **It can cause severe bronchospasm**.
- There is minimal sputum.

Chest auscultation signs

- **Whispering pectoriloquy** is a sign of consolidation. It can occur because of the tumour and the locally trapped secretions.
- **Polyphonic wheeze** can indicate obstructive lung disease,
- **inspiratory crackles** can be associated with:
  - pulmonary fibrosis
  - heart failure
  - consolidation.

Lung abscess

- **Predisposing factors** include:
  - dental disease,
  - **impaired consciousness**, for example, alcohol, **post-anaesthesia**,
  - bronchial carcinoma
  - immunosuppression.
- An **air-fluid level is characteristic of a lung abscess.**
- A contrast-enhanced computerised tomography (CT) scan would show the abscess more clearly.

Radiation pneumonitis

Prevalence

- Occur in 10-30% of patients following radiotherapy for lung cancer.

Symptoms

- cough (which can be severe and can produce thick sputum),
- breathlessness
- fever.

On examination

- tachypnoea,
- cyanosis in severe disease,
- local crepitations.

- Telangiectases, the result of cutaneous radiation damage, are often observed in the overlying skin.

Radiographic changes:

- X-ray
  - The most characteristic X-ray feature is an **area of hazy consolidation** demarcated by a sharp margin (crossing anatomical pulmonary planes) that corresponds to the limits of the irradiation field, though additional effects are usually detectable beyond these boundaries.
- **CT** provides the best means of early identification,
  - ground-glass attenuation and inter-alveolar septal thickening being the early characteristic features.
  - Dense local fibrosis can develop up to 1-2 years after radiation,
    - (MRI) might be required to differentiate this from tumour recurrence.

Management

- If symptoms are slight, no specific treatment is needed.
- **In more severe disease, corticosteroids produce symptomatic relief**
  - **Corticosteroids at high dose (prednisolone at least 60 mg/day) are the initial therapy of choice.**
  - Response to corticosteroids occurs within 3-4 days, with clinical and radiographic improvement,
  - treatment should be continued for 3-4 weeks before tapering and stopping.
  - Corticosteroids do not, however, influence the extent of subsequent pulmonary fibrosis.
- Symptomatic relief of cough and hypoxaemia by an opioid antitussive and oxygen supplementation may also be needed.
- In those who cannot tolerate corticosteroids, azathioprine is a reasonable alternative.

HIV: *Pneumocystis jiroveci* pneumonia

Pneumocystis jiroveci pneumonia - pneumothorax is a common complication

Overview

- Whilst the organism *Pneumocystis carinii* is now referred to as *Pneumocystis jiroveci*, the term *Pneumocystis carinii* pneumonia (PCP) is still in common use.
- *Pneumocystis jiroveci* is an **unicellular** eukaryote, generally classified as a **fungus** but some authorities consider it a protozoa.

Association

- PCP is the most common opportunistic infection in AIDS
  - **Pneumocystis jirovecii pneumonia is unlikely in a patient who has had a CD4 count above 200 cells/mm3** in the preceding 2 months in the absence of other HIV-associated symptoms.
- immunosuppressed patients, particularly after organ transplantation

Pathophysiology

- The organism is **confined to the alveolar space** of the lung and produces debris and cysts in the alveolar space with interstitial infiltration of lymphocytes and plasma cells.

As a result, it can **cause profound disturbance of oxygen exchange** and fatal hypoxaemia if left untreated.

- **The morphological appearance of *Pneumocystis jirovecii* infection in the lung => An interstitial pneumonitis with foamy intra-alveolar exudate**

Features

- dyspnoea
- dry cough
- fever
- **very few chest signs**
  - **Auscultation of the lungs usually reveals no abnormality**
- **Pneumothorax is a common complication of PCP.**
- Extra-pulmonary manifestations are rare (1-2% of cases), may cause
  - hepatosplenomegaly
  - lymphadenopathy
  - choroid lesions can result in
    - pancytopenia, retinal cotton wool spots and thyroid masses.
- **The lungs are commonly clear on auscultation**

Investigation

Pneumocystis carinii pneumonia → **Definitive diagnosis is by bronchial alveolar lavage with silver staining**

- CXR:
  - typically shows **bilateral interstitial pulmonary infiltrates** (usually diffuse ground-glass opacities)
  - can present with other x-ray findings e.g. lobar consolidation.
  - May be normal
- exercise-induced desaturation
- **bronchoalveolar lavage (BAL)** often needed to demonstrate PCP (**silver stain shows characteristic cysts**).
  - The organism may be identified on microscopy after:
    - methenamine **silver staining** for the cyst phase of the organism
    - giemsa staining that demonstrates the small, punctate nuclei of the trophozoites and intracystic sporozoites, or
    - fluorescence-tagged monoclonal antibody.
  - sputum often fails to show PCP,
- Lactate dehydrogenase
  - raised in 90% of patients with PCP (but this can occur with other pulmonary diseases).
- **lymphopenia is very suggestive of PCP with AIDS** (and therefore low CD4 lymphocyte count),
  - although patients may have low lymphocyte counts with other acute viral infections
  - indeed may be normal in HIV/AIDS due to a compensatory increase in the CD8 lymphocyte subset.

Management

- co-trimoxazole (120 mg/kg daily in divided doses) for 3 weeks (should be given for 21 days in HIV, but can be shorter in other causes of immunosuppression)
- IV pentamidine in severe cases (or In patients who are intolerant of co-trimoxazole)
  - **allergic to co-trimoxazole alternative therapy would be IV pentamidine or clindamycin with primaquine.**
- Steroids have been shown to reduce mortality and prevent lung damage in people with moderate-to-severe PCP. (The severity is determined on the basis of arterial blood gas results).
  - **severe PCP is defined by a room air arterial oxygen pressure (pO2) of less than 9 kPa** (70 mmHg) or an arterial-alveolar O2 gradient that exceeds 4.5 kPa (35 mmHg).
  - if pO2 < 9.3kPa then steroids reduce risk of respiratory failure by 50% and death by a third
  - While it is true that long term steroid use is immunosuppressive a **21 day** tapering course has been shown to be safe and effective.
- **co-trimoxazole is the preferred initial therapy during pregnancy** according to consensus guidelines.
  - The BNF states that **there is a teratogenic risk in the first trimester** (as trimethoprim is a folate antagonist), and neonatal haemolysis and methaemoglobinaemia in the third trimester. However, there is also considerable risk of harm to the foetus if the mother is unwell. **The benefits in this situation therefore outweigh the risks**, and it should be used.
- Glucose 6-phosphate dehydrogenase deficiency (G6PD) levels should be checked prior to TMP-SMX, dapsone or primaquine use
  - If allergic to co-trimoxazole, IV pentamidine or clindamycin are appropriate.
- For the treatment of infections that are resistant to TMP-SMX, the combination of clindamycin and primaquine is likely to be more effective than intravenous pentamidine.

Prophylaxis

- all patients with a CD4 count < 200/mm should receive PCP prophylaxis (Co-trimoxazole is the preferred agent. Dapsone and inhaled pentamidine are also used.)
- **Discontinuing Primary Prophylaxis**
  - Primary *Pneumocystis* prophylaxis should be discontinued if the patient responded to ART with an increase in CD4 counts ≥200 cells/mm^3 for ≥3 months.

January 2016 exam:
HIV positive but poorly compliant with his antiretroviral therapy (ART). CD4 : 180 cells/ml. oxygen saturations 97% on room air with a temperature of 38.1ºC. He has coarse crackles on the right side of his chest. A chest x-ray shows consolidation of the right mid zone. What is the most likely causative organism? *Streptococcus pneumoniae* (Whilst *Pneumocystis jirovecii* is of course associated with HIV, patients who are immunocompromised are more likely to develop infections due to the common pathogens which affect immunocompetent individuals. *Streptococcus pneumoniae* is therefore the most likely cause of community-acquired pneumonia in this patient. *Pneumocystis jirovecii* tends to present with very few chest signs and bilateral interstitial pulmonary infiltrates on chest x-ray)

Allergic bronchopulmonary aspergillosis (ABPA)

In the exam questions often give a history of bronchiectasis and eosinophilia.

Definition

- **ABPA** results from an allergy to Aspergillus spores (**Type I hypersensitivity to Aspergillus fumigatus**).

Risk factors

- asthma,
- cystic fibrosis
- bronchiectasis.

Features

- bronchoconstriction: wheeze, cough, dyspnoea
  - Clinical deterioration in asthma symptoms
- bronchiectasis (**proximal**)

Investigations

- serum **eosinophilia**
- Raised IgE
  - helpful test, but in isolation is **not specific** enough to establish the diagnosis.
- **Aspergillus skin-prick test (the most specific investigation)**
  - Positive radioallergosorbent (RAST) test to Aspergillus.
  - Immediate (type I) reactions occur in virtually all patients with ABPA following intradermal injections of *Aspergillus fumigatus* extracts, with only 16% developing delayed (type IV) reactions.
  - **An early positive skin-prick test for Aspergillus fumigatus is the most specific to (ABPA)**.
    - Positive skin-prick tests reflect antigen-specific IgE.
- **Positive IgG precipitins** (not as positive as in aspergilloma) in 70% of patients.
  - **Precipitins (IgG) are more usual with an aspergilloma**, but may be positive in ABPA or in up to 10% of patients with asthma.
- Pulmonary infiltrates on CXR. Lobar collapse can also occur, due to mucus plugging.

Management

- First line → steroids
- **Second line → add itraconazole**

Aspergilloma

the clue can be a lack of improvement with broad spectrum intravenous antibiotics, haemoptysis and chest X-Ray findings.

Definition

- An aspergilloma is a mycetoma (**mass-like fungus ball**) which often colonises an existing lung cavity (e.g. secondary to tuberculosis, lung cancer, cystic fibrosis or emphysema)

Feature:

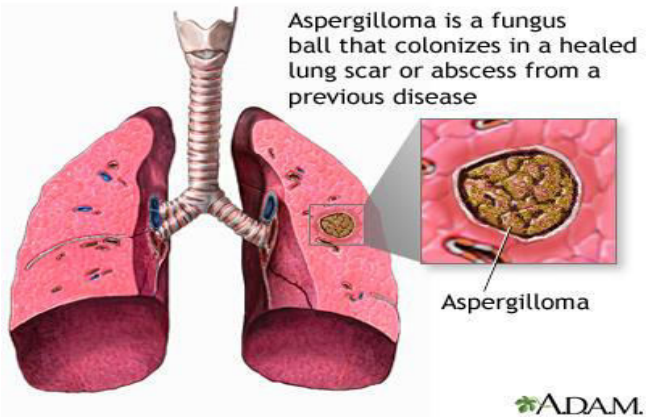
- often asymptomatic
- cough
- **haemoptysis** in up to three quarters of patients **(**may be severe and fatal **)**
- Systemic symptoms of weight loss, lethargy and fever are less common.

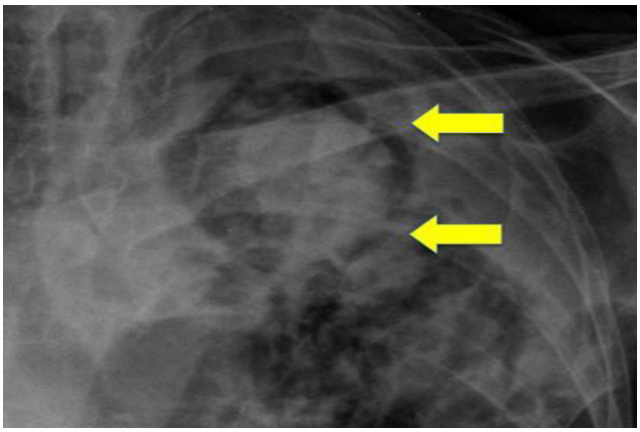
Investigations

- chest x-ray containing a rounded opacity within a cavity often associated with a rim of air.
  - These features are seen more clearly on **CT**.
- high titres Aspergillus precipitins (IgG antibodies)
  - present in 95% of cases.

Treatment:

- Up to 10% of aspergillomas resolve spontaneously but, if treatment is required, possibilities are:
  - surgical excision or
  - long-term treatment with oral itraconazole.
- **Surgery should be considered as a first-line** option where erosion into a major vessel and massive haemoptysis is a possibility
- **In case of massive haemoptysis the next appropriate management – after transfusion and resuscitation- is → Angiography and embolisation, after that → lobar resection as the intervention of next resort**





Invasive aspergillosis

Risk factors of fungal infections:

- **patients undergoing chemotherapy**,
- stem cell transplant,
  - It is a leading cause of death in acute leukaemia and haemopoietic stem cell transplantation.
- patients on immunosuppressive medications for autoimmune conditions
- HIV positive.

Features:

- Symptoms of active infection & haemoptysis.
  - include cough, haemoptysis, chest wall pain, fever and shock.

Investigations:

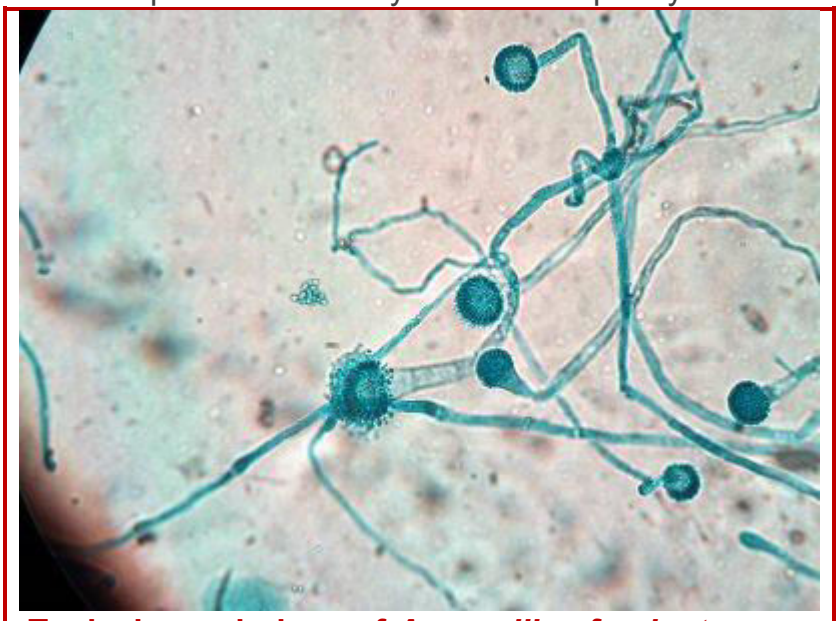
- the classical signs on CT scanning the '**halo sign**' **air crescent sign**
- Silver staining shows → hyphae.
  - **Haematoxylin and eosin (H&E) stain** does not stain most of the fungi, except the **Aspergillus** species.
- galactomannan test:
  - Galactomannan is a component of the cell wall of the *Aspergillus* and is released during growth.
  - Detection of galactomannan in blood by ELISA is used to diagnose invasive aspergillosis

Treatment:

- The first line treatment is **voriconazole**
  - should be started intravenously before oral dosing is considered. This is due to oral voriconazole taking at least 10 days to get to therapeutic levels.
- If voriconazole is not tolerated, then lipsomal **amphotericin B** should be used.

Prognosis

- Mortality for invasive aspergillosis vary from 40-90% in the literature. As such it is important to identify it and treat quickly.



Typical morphology of *Aspergillus fumigatus*.

Alpha-1 antitrypsin (A1AT) deficiency

Alpha-1 antitrypsin deficiency - autosomal recessive / co-dominant

- Alpha-1 antitrypsin (A1AT) deficiency is a common inherited condition
- Caused by a **lack of a protease inhibitor (Pi)** normally produced by the liver.
  - **the main role of alpha-1 antitrypsin in the body → Protease inhibitor**
  - The role of A1AT is to protect cells from enzymes such as neutrophil elastase.

- AAT neutralises neutrophil elastase, thereby preventing lung destruction.

Genetics

- located on the long arm of **chromosome 14**
- inherited in an autosomal recessive / **co-dominant fashion**
  - **the likely mode of inheritance → Autosomal codominant**
- caused by a mutation in the **SERPINA-1 gene** on chromosome 14 (14q32),
- alleles classified by their electrophoretic mobility - M for normal, S for slow, and Z for very slow

The serum levels of some of the common genotypes are:

- PiMM: 100% (normal)
- PiMS: 80% of normal serum level of A1AT
- PiSS: 60% of normal serum level of A1AT
- PiMZ: 60% of normal serum level of A1AT
- PiSZ: 40% of normal serum level of A1AT
- PiZZ: 10-15% (severe alpha 1-antitrypsin deficiency).

Features

- patients who manifest disease usually have **PiZZ** genotype
- lungs:
  - **panacinar emphysema**, most marked in **lower lobes** (2% of cases of emphysema)
  - 75% of patients develop chest pathology
    - **Which form of lung disease develops typically in people with α1-antitrypsin deficiency?**
      - **Emphysema**
        - ⇨ results from an imbalance between proteases and antiproteases within the lung.
        - ⇨ The **elastase and α1-antitrypsin balance** clearly illustrates the processes involved in the development of emphysema
        - ⇨ the interplay between the **environmental and genetic factors** determine its onset.
        - ⇨ Patients usually present with increasing dyspnoea and weight loss, with cor pulmonale and polycythaemia occurring late in the course of the disease.
        - ⇨ Chest X-rays typically show bilateral **basal emphysema** with **paucity** and pruning of the basal pulmonary vessels.
- liver:
  - cirrhosis and hepatocellular carcinoma in adults,
    - (15% of patients have associated cirrhosis)
  - cholestasis in children .

Investigations

- A1AT concentrations
- All patients under the age of 35 years presenting with COPD should have their α1-antitrypsin tested.

Management

- no smoking
  - smoking is harmful to those with A1AT deficiency and can accelerate the progression of emphysema by 10 years.
- supportive:
  - bronchodilators,
  - physiotherapy
- intravenous alpha1-antitrypsin protein concentrates
- surgery:
  - volume reduction surgery, lung transplantation

Associated conditions:

- malignancies including:
  - hepatocellular cancer,
  - lung cancer,
  - bladder cancer and
  - lymphoma.
- Cirrhosis
- Pancreatitis
- Gall stones
- COPD
- Bronchiectasis
- Primary sclerosing cholangitis
- Wegener's granulomatosis and
- Pelvic prolapse.

Acute respiratory distress syndrome (ARDS)

Basics

- Pathophysiology
  - ↑ permeability of alveolar capillaries →↑fluid accumulation in alveoli i.e. non-cardiogenic pulmonary oedema
  - deficiency in surfactant which reduces lung compliance and predisposes to collapse (especially in dependent zones)
- there tends to be a type 1 respiratory failure, rather than type 2.
- ARDS is characterised by diffuse injury to the pulmonary capillary endothelium and alveolar epithelium that ultimately leads to alveolar collapse and impaired pulmonary gas exchange.

Diagnostic Criteria (American-European Consensus Conference)

1. Acute onset
2. Bilateral infiltrates (on chest x ray or CT scan)
3. PaO_2:FiO_2 ratio < 26.7 kPa (200 mmHg)
4. Lack of evidence of left atrial hypertension

- (pulmonary artery wedge pressure (PAWP) <18 mmHg if available).
- Patients with acute respiratory distress syndrome have **normal pulmonary capillary wedge pressure.**

Deferential diagnosis

- The following are helpful in differentiating ARDS from other conditions, such as LVF:
  - normal heart size
  - absent septal lines
  - air bronchograms, and
  - a peripheral distribution.

Causes

- infection: sepsis, pneumonia
  - the most common CAUSE is systemic inflammation.
- massive blood transfusion
- trauma
- smoke inhalation
- **pancreatitis**
- cardio-pulmonary bypass

Direct and indirect causes:

- **Direct** pulmonary causes include:
  - Inhalation of gastric contents (pH <2)
  - Infective (pneumonia, tuberculosis)
  - Pulmonary trauma
  - Near drowning
  - Toxic gas inhalation and
  - Oxygen toxicity.
- **Indirect** causes include:
  - Sepsis
  - Non-thoracic trauma
  - Uraemia
  - Bowel infraction
  - Anaphylaxis and
  - Burns.

Investigation

ARDS causes restrictive lung disease.

- The CXR classically shows **bilateral peripheral interstitial and alveolar infiltrates** that become progressively more confluent **but spare the costophrenic angles**.
- A **lecithin: sphingomyelin ratio** of less than 1.5 is predictive of infant respiratory distress syndrome.
- **ARDS is associated with increased elastic recoil.**
- **ARDS is associated with low pulmonary artery wedge pressure.**

- **ARDS is associated with low compliance.**

Treatment:

- **Which therapies has been shown to most likely decrease overall mortality of ARDS?**
  - **Implementing a low tidal volume ventilation protocol**
    - ARDS with respiratory acidosis is best managed with invasive ventilation using **low tidal volumes (6 mL/kg based upon ideal body weight).**
    - mechanical ventilation itself can injure the damaged lungs causing ventilation-induced lung injury.
    - The main goal of treatment is to minimise any additional damage while maintaining adequate gas exchange. This has been effectively done by maintaining low tidal volume ventilation.
    - low tidal volume ventilation reduces the absolute mortality by about 7-9% as compared to using higher tidal volumes.
- **Mechanical ventilation**
  - **if the patient's blood gases reflect hypoxaemia and a slight respiratory alkalosis, (despite high FiO_2 settings and sufficient ventilation, his arterial oxygenation remains inadequate):**
    - **the best next step is → adding positive end-expiratory pressure (PEEP)**
    - **The ventilator strategy should employ a relatively high level of positive end-expiratory pressure (PEEP)**
      - Generally speaking, oxygenation may be improved by further increasing the FiO_2 or by adding positive end-expiratory pressure (PEEP).
      - High FiO_2 is contraindicated due to the risk of pulmonary oxygen toxicity. Thus, the goal in managing mechanically ventilated patients should be to keep the FiO_2 below 40% at all times.
      - The patients FiO_2 may need to be reduced soon- if more than 40% - in order to avoid pulmonary oxygen toxicity, **but this should be accomplished by first increasing oxygenation by another means, such as by increasing PEEP.**
      - Adding PEEP is the next best step here.
      - PEEP prevents alveolar collapse, directly counteracting the means by which ARDS causes hypoxaemia. It may also reopen some alveoli that have already collapsed.

- **Extracorporeal membrane oxygenation (ECMO):**
  - **If the patient is on maximal ventilatory therapy but is still hypoxic & hypercapnic? → (ECMO)**

  - trial demonstrated a significant increase in survival without significant disability
  - ECMO involves connecting a patient's circulation to an external oxygenator and pump, via a catheter placed in the right side of the heart.
  - It requires the continuous infusion of anticoagulant, and as such bleeding is the most commonly associated complication.
  - Infection and haemolysis are also a risk.
- Since the infiltrate of ARDS is primarily inflammatory, **diuretics** are **NOT** particularly effective. Over-diuresis also runs the risk of hemodynamic compromise, further decreasing the patient's already insufficient oxygen delivery to tissues.
- **glucocorticoids** have **NOT** been shown to help patients in the acute phase of ARDS.
  - There is some evidence that they may help in the fibroproliferative stage but not acutely.

Acute Respiratory Distress Syndrome (ARDS) & Acute Lung Injury (ALI):

- **ARDS is a severe form of Acute Lung Injury (ALI)**
- **ARDS has the same definition except that the PaO_2/FiO_2 ratio is less than 200.**
- **ALI** has a specific definition:
  - PaO_2/FiO_2 ratio of less than 300
  - Bilateral infiltrates on a chest radiograph
  - Pulmonary capillary wedge pressure of less than 18 mmHg

Prognosis:

- ARDS mortality is generally high (40%), but is determined by the cause with aspiration pneumonia having a mortality rate of almost 80% when associated with ARDS.

Altitude related disorders

Acetazolamide can be used to prevent acute mountain sickness. It causes a primary metabolic acidosis and compensatory respiratory alkalosis which increases respiratory rate and improves oxygenation

- There are three main types of altitude related disorders:
  1. **acute mountain sickness (AMS),** which may progress to
  2. **high altitude pulmonary edema** (HAPE) or
  3. **high altitude cerebral edema** (HACE).
- All three conditions are due to the chronic hypobaric hypoxia which develops at high altitudes

Acute mountain sickness

- Acute mountain sickness is generally a self-limiting condition.

- Features of AMS start to occur above 2,500 - 3,000m, developing gradually over 6-12 hours and potentially last a number of days:
  - headache
  - nausea
  - fatigue
- Altitude sickness is characterized by **no change in the A-a gradient.**
- Prevention and treatment of AMS
  - the risk of AMS may actually be positively correlated to physical fitness
  - gain altitude at no more than 500 m per day
  - acetazolamide (a carbonic anhydrase inhibitor) is widely used to prevent AMS and has a supporting evidence base
- treatment: descent

High altitude pulmonary oedema (HAPE) or high altitude cerebral oedema (HACE)

- A minority of people above 4,000m go onto develop high altitude pulmonary oedema (HAPE) or high altitude cerebral oedema (HACE), potentially fatal conditions
  - HAPE presents with classical pulmonary oedema features
  - HACE presents with headache, ataxia, papilloedema

Management of HACE

- descent
- dexamethasone

Management of HAPE

- descent
- **High concentration O_2**
  - oxygen should be initiated first
  - **Is the next most appropriate intervention**
- nifedipine, dexamethasone, acetazolamide, phosphodiesterase type V inhibitors*
  - If high-flow oxygen is not available, then nifedipine can be used as second line.
  - * All seem to work by reducing systolic pulmonary artery pressure

Other features of Altitude sickness:

- acid-base abnormality → respiratory alkalosis as an.
- hematological manifestation → Increase in erythropoietin.

Bronchiectasis

Bronchiectasis should be suspected in a patient with chronic cough producing large amounts of sputum

Definition

- permanent dilatation of the airways secondary to chronic infection or inflammation.

Causes

- Post-infective: (i.e., bacterial, viral, fungal)
  - tuberculosis, measles, pertussis, pneumonia
  - **A history of previous whooping cough suggests bronchiectasis.**
- Disorders of secretion clearance or mucous plugging
  - Cystic fibrosis

  - Primary ciliary dyskinesia
    - Kartagener's syndrome (situs inversus and sinusitis associated with non-motile cilia),
    - Young's syndrome (a combination of bronchiectasis, rhinosinusitis and infertility)
  - **Allergic bronchopulmonary aspergillosis (ABPA)**
    - proximal bronchiectasis (centrally dilated thickened airways with 'signet rings')
    - **raised IgE is most useful for confirming the diagnosis**
- Bronchial obstruction e.g.
  - lung cancer/foreign body
  - Patients with longstanding chronic obstructive pulmonary disease (COPD)
    - **Patients with longstanding COPD often develop localised areas of bronchiectasis because of progressive damage to the lung tissue**
      - **HRCT is the most useful investigation in establishing the diagnosis.**
- Immune deficiency
  - selective IgA,
  - hypogammaglobulinaemia
    - **Hypogammaglobulinaemia in ataxia telangiectasia**
  - common variable immunodeficiency,
  - HIV
- Chronic inflammatory diseases
  - Inflammatory bowel disease
  - Rheumatoid arthritis (3-4% of RA developed bronchiectasis).
- yellow nail syndrome

Features: The most common findings on examination are crackles (75%) and wheeze (22%). Clubbing is only found in 2%.

- chronic productive cough, with **copious amounts of sputum** (expectorating phlegm on most days)
- Dyspnea
- frequent chest infections
- haemoptysis
- Post nasal drip - common (chronic sinusitis in around 30%)
- tiredness - many patients find this more troublesome than the productive cough
- Low Ventilation perfusion ratio leading to hypercapnia → Respiratory acidosis, and the body compensate by increasing heart rate and vasodilatation.

Diagnosis

- Chest X-ray
  - the best **initial** test
  - can be normal in 50% of patients
    - **Bronchiectasis cannot be ruled out with a chest x-ray**

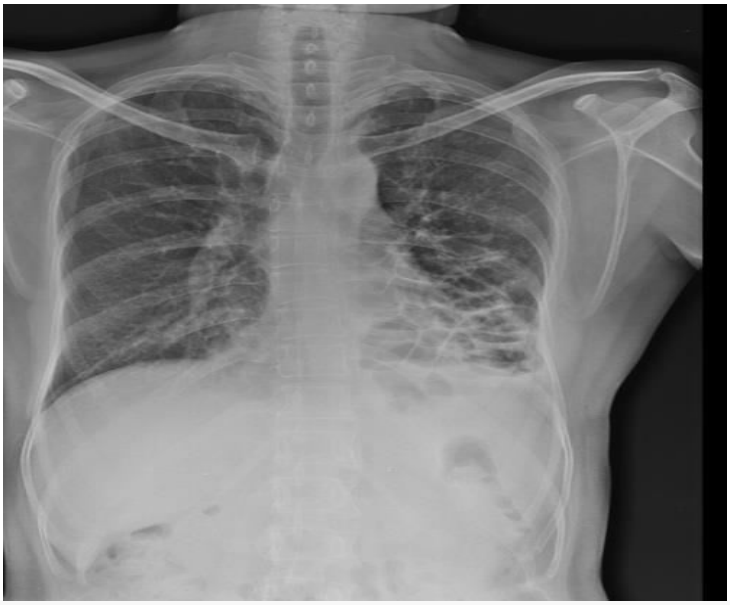
- the findings:
  - thickened and dilated bronchi, which produce **tramline opacities** and **ring shadows**.
  - **"tram track" lines**
    - Due to Inflammation and fibrosis of bronchial walls
  - Retained mucus might be seen as tubular opacities,
  - volume loss of the affected lobe.
  - Thin-walled cysts (i.e., dilated bronchi forming sacs), possibly with air-fluid levels
  - Late-stage bronchiectasis: honeycombing

- **High-resolution computed tomography scan of the lungs (HRCT) is the gold standard for the diagnosis of bronchiectasis.**

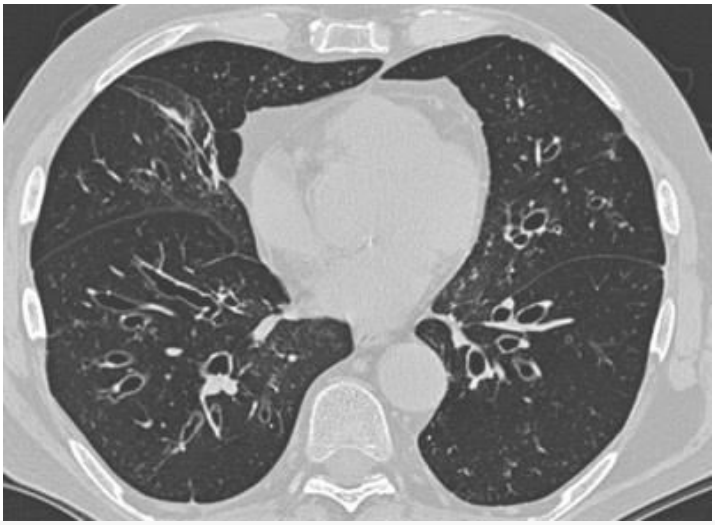
- **The diagnostic criteria for bronchiectasis on HRCT** depend on finding both dilatation and thickening of the affected bronchi.
  - **tram track lines and honeycombing**
  - **'signet ring' sign**
    - The classic appearance of a cross-section of a **thick-walled dilated** bronchus next to the accompanying pulmonary artery.
  - **Bronchial dilatation**
    - Dilatation being present if the internal diameter of the bronchus is greater than the diameter of its accompanying pulmonary artery.
      - ⇨ **increased broncho-arterial ratio** (bronchus larger than neighboring pulmonary artery)

Differential diagnosis

- Carcinoma of the lung:
  - Lung cancer can present with non-resolving respiratory infection with productive cough due to endobronchial obstruction by tumour, **but there would be a much shorter duration of symptoms**. Without treatment **most patients would be dead within a year of the onset of lung cancer**.



Chest x-ray showing tramlines, most prominent in the left lower zone



CT chest showing widespread **tram-track and signet ring signS**

Management

Symptom control in non-CF bronchiectasis → inspiratory muscle training + postural drainage

The mainstay of therapy for bronchiectasis is antibiotics and chest physiotherapy.

After assessing for treatable causes (e.g. immune deficiency) management is as follows:

- physical training (e.g. inspiratory muscle training) - has a good evidence base for patients with non-cystic fibrosis bronchiectasis
- postural drainage
- antibiotics for exacerbations + long-term rotating antibiotics in severe cases
- bronchodilators in selected cases
- Immunisations: Influenza and pneumococcal vaccinations are strongly recommended.
- surgery in selected cases (e.g. Localised disease that fails to resolve after I.V antibiotic)

Most common organisms isolated from patients with bronchiectasis:

Bronchiectasis: most common organism → *Haemophilus influenzae*

- ***Haemophilus influenzae* (most common)**
- *Pseudomonas aeruginosa*
- Klebsiella spp.
- *Streptococcus pneumoniae*

Prevention

- Primary prevention:
  - antibiotic control of bronchial and pulmonary infections in predisposed individuals
- Secondary prevention:
  - long-term low-dose macrolide treatment (e.g., azithromycin) in patients with two or more bronchiectasis exacerbations within one year.

Cystic fibrosis

Genetics

- autosomal recessive
- Due to mutation of CFTR gene on chromosome 7.
- The most common mutations is delta-F508.
- If both parents are **carriers** of the CF gene:
  - The chance of another child being affected (homozygote) is 1 in 4 (25%).
  - The chance of their child being free from the CF gene is also 1 in 4 (25%)
  - And the chance of a child being a carrier (heterozygote) is 1 in 2 (50%).
- the sibling of an **affected** person has a 3 in 4 chance of being a CF carrier **or** having the disease. if one sibling is not affected , the chance of being a carrier for the CF gene is 2 in 3.

Epidemiology

- Occurs in 1 in 2500 live births.
- **The carrier frequency in white populations is 1 in 25.**
- the most common genetically inherited diseases in Caucasian individuals.
- Rare in patients of Afro-Caribbean and Asian origin.
- 10% of people with cystic fibrosis are not diagnosed until adult life.

The most common features

- failure to thrive and delayed puberty (100%)
- **infertility**
  - **male infertility** occurs in 98% **due to failure of development of the vas deferens**
  - Female subfertility secondary to viscid cervical secretions. (only a 20% will be infertile)
- **Pancreatic insufficiency** (**the most common, 85%**)
  - **almost always present in adult patients**
- diabetes mellitus : occurs in > 65% of patients by age 25
  - main manifestations => weight loss, repeated respiratory infections and decline in lung function.
  - treatment of choice is subcutaneous insulin
  - Calorie intake should not be restricted in CF patients, who are prone to malnutrition due to their pancreatic insufficiency.
- Recurrent chest infections (40%)
- malabsorption (30%): steatorrhoea, **It is associated with pancreatic insufficiency, which is almost always present in adult patients**
  Constipation is common
- hepatobiliary dysfunction (cholestasis)
  - **due to Defective cystic fibrosis transmembrane regulator (CFTR) protein on bile duct epithelial cells**
- neonatal period (around 20%): meconium ileus, less commonly prolonged jaundice
- other features (10%): liver disease

Other features of cystic fibrosis

- short stature
- rectal prolapse (due to bulky stools)
- nasal polyps
  - While nasal polyps occur in adults secondary to recurrent episodes of rhinitis, **nasal polyps in children should always raise the suspicion for cystic fibrosis.**
- Depletion of sodium, chloride and potassium due to excessive sweating, and secondary renal chloride retention, can result in presentation with dehydration and heat exhaustion in an otherwise apparently completely fit adult.
- Pneumothorax is seen in up to 5% of patients over 10 years of age and approximately 50% recur.
- **Allergic bronchopulmonary aspergillosis (ABPA) is a recognised complication, occurring in 15% of adult CF patients**
  - Affect 1 in 6 adult CF patients.
  - Manifestations => asthma symptoms, flitting opacities on chest X-ray, ↑↑eosinophil count, hyper-reactivity to skin prick test and ↑↑ plasma IgE.
  - Main treatment => high-dose corticosteroids initially, with a smaller maintenance dose. Antifungal agents may be used to allow a reduction in corticosteroid dose.
- **Distal intestinal obstruction syndrome :**
  - Occurs in 10-20% of patients with cystic fibrosis and incidence increases with age. About 80% of cases present for the first time in adults.
  - The **pathogenesis** is partially due to loss of CFTR function in the intestine which results in deregulation of chloride secretion from the crypts, bicarbonate secretion from Brunner's glands and sodium transport. This leads to the accumulation of viscous mucus and faecal material in the terminal ileum, caecum and ascending colon.

Diagnosis

- **Sweat test**
  - patient's with CF have abnormally high sweat chloride
  - normal value < 40 mEq/l, **CF indicated by > 60 mEq/l**
  - 99% of children with CF have sweat chloride **>** 70 and sodium levels **>** 60.
  - In normal children, sweat sodium is higher than chloride. The reversed ratio is another pointer to CF.
  - Two sweat tests should be performed spontaneously on both arms with pilocarpine iontophoresis.
  - A negative sweat test is sufficient evidence to exclude cystic fibrosis.
  - If the sweat chloride test is abnormal, the patient should undergo **CFTR gene mutation testing.**
- **Method of sweat test**
  - sweat test is conducted using **pilocarpine** iontophoresis.(**a direct acting muscarinic agonist)**
  - A 3 mA current carries pilocarpine into the skin of the forearm stimulating local sweating.

- The arm is washed with distilled water and sweat collected on a filter paper or gauze.
- The duration of collection is usually 30-60 minutes.
- The filter paper is removed, weighed and eluted in distilled water.
- At least 50 mg and preferably 100 mg of sweat should be collected for reliable results. It may not be possible to collect this amount in young infants.
- More than 60 mmol/L of chloride is diagnostic of CF when one or more other criteria are present.

- **Causes of false negative sweat test**
  - nephrotic syndromes.

- **Causes of false positive sweat test**
  - malnutrition
  - adrenal insufficiency
  - glycogen storage diseases
  - nephrogenic diabetes insipidus
  - hypothyroidism, hypoparathyroidism
  - G6PD
  - ectodermal dysplasia

Management

Management of cystic fibrosis involves a multidisciplinary approach

Key points

- chest physiotherapy and postural drainage
  - regular (at least twice daily).
  - Parents are usually taught to do this.
- Deep breathing exercises are also useful
- **high calorie** diet, including **high fat** intake,
  - Patients with cystic fibrosis suffer significant difficulties in maintaining their weight.
  - Weight loss in cystic fibrosis is closely allied to both risk of exacerbations of the disease and an increase in overall mortality.
  - For this reasons:
    - it's important to maintain a high calorie diet
    - **the best way to manage diabetes in CF is insulin and high calorie diet** to allow them to convert those calories into stored energy.
- vitamin supplementation
- pancreatic enzyme supplements taken with meals
- antibiotics
- heart and lung transplant

Chest infections in cystic fibrosis:

The culture plate shows a growth of *Pseudomonas aeruginosa*, characterised by the green colouration of the colonies due to production of the pigment pyocyanin.

bronchiectasis associated with CF frequently results in recurrent infections with *Pseudomonas*.

- Mechanism:
  - In cystic fibrosis → defective chloride secretion and increased sodium resorption → thick mucus → airways obstruction →bacterial colonisation early in life.
- Organisms:
  - infants and young children become colonised by *Staphylococcus aureus* and then *Haemophilus influenzae*.
    - (70–80% of children aged 6–18 years with CF have chronic S. aureus infection).
  - In teenagers, **Pseudomonas aeruginosa** colonisation occurs.
    - **Pseudomonas aeruginosa is the commonest colonising organism in patients with cystic fibrosis** after the age of 10 years, with a reported prevalence of 40-80%.
    - (70% of adults with CF have chronic P. aeruginosa infection)
  - ***Aspergillus***
    - One Australian study suggested that colonisation rates for *Aspergillus* in patients with cystic fibrosis approach 19%. **(CF is most likely to be associated with *Aspergillus* colonisation)**
  - Burkholderia cepacia
    - Gram-negative, aerobic, rod bacteria, part of Proteobacterial genus (previously part of *Pseudomonas*)
    - occurs in 5–10% of patients,
    - **associated with the worst prognosis**
    - **Burkholderia cepacia is seen in severe lung disease and is often associated with a rapid deterioration.**
    - Burkholderia and Pseudomonas are two pathogens which are very difficult to eradicate. Of those, Burkholderia has the worst prognosis.
  - Other organisms

- pneumoniae,
- *Mycobacterium tuberculosis*, other mycobacteria, Aspergillus fumigatus and viruses.

- Treatment:
  - Indications of antibiotics: In the UK, antibiotics are usually given when:
    - the sputum becomes purulent,
    - pulmonary function deteriorates,
    - or the patient is unwell (e.g. weight loss).
  - **Drugs**
    - **Anti- Pseudomonal**
      - **In teenagers groups, Pseudomonal cover is needed and a combination of intravenous antibiotics is used to reduce the risk of resistance developing. The usual combination is ceftazidime and tobramycin, for a period of two weeks.**
      - The combination of **ceftazidime and tobramycin** is **the antibiotic regimen of choice** for the treatment of cystic fibrosis exacerbations in patients with *Pseudomonas aeruginosa*.
        - Treatment should be continued for 10-14 days.
        - **ceftazidime** is a **third-generation cephalosporin**, and works by interfering with bacterial cell wall.
        - **Tobramycin** is an aminoglycoside antibiotic , works by **binding to a site on the bacterial 30S and 50S ribosome**, **preventing formation of the 70S complex.** As a result, mRNA cannot be translated into protein → cell death
          - SE:
            - Nephrotoxicity
            - ototoxicity (generally irreversible).
      - Most colonising types of P. aeruginosa are sensitive to antibiotics at first, but over the years and in association with antibiotic treatment, multiple resistance to most antibiotics (except colistin) develops.

    - **The combination of piperacillin and tazobactam (Tazocin®) is indicated for the treatment of cystic fibrosis exacerbations.**
      - Tazobactam is not an antibiotic rather a beta-lactamase inhibitor, so Tazocin, which is a mixture of piperacillin (an antibiotic) and tazobactam (a drug which prevents bacteria from inactivating piperacillin) **does not count as combination antibiotic therapy.**
      - Tazocin® is active against *Pseudomonas aeruginosa*. However, a combination of antibiotics is preferable to minimise the risk of antibiotic resistance which is why **the correct choice here is ceftazidime and tobramycin.**
      - SE: **Rash and fever** are more common in patients with cystic fibrosis than in patients without cystic fibrosis.

- **Nebulised tobramycin for *Pseudomonas* colonisation of the lower respiratory tract**
  - Nebulised tobramycin or gentamicin may be given when airway pathogens are resistant to oral antibiotics, or where infection is difficult to control at home.
  - Gentamicin can be used in place of tobramycin, but has poorer pseudomonal cover and is associated with significant side effects (nephrotoxicity and ototoxicity).
  - **Nebulised treatments** such as aminoglycosides and colistin can be used for prevention of a flare-up of a patient colonised with Pseudomonas aeroginosa and their use as **prophylactic therapy** has been shown to imporove lung funtion in patients with cystic fibrosis, but this **not adequate as a treatment of acute infection**.

- **Lung transplantation in cystic fibrosis**
  - Heart-lung transplantation is offered to patients who exhibit a rapid decline in lung function despite optimal treatment, and to patients with respiratory failure.
  - **Indications**
    - Age under 60 years
    - Life expectancy of less than 18 months
    - No underlying cancer or serious systemic disease
  - severe reduction in BMI is a **relative** contraindication to transplantation because it is associated with reduced survival but it is not an absolute contraindication.
  - **Donor characteristics**
    - The donor is matched for ABO grouping.
    - Rhesus blood group compatibility is not essential.
    - The donor should have had good cardiac and lung function
    - The donor should have been under the age of 40.
    - The chest of the donor should be slightly smaller than that of the recipient.
    - A double lung transplant is usually performed because of the risk of chronic infection in the remaining lung.

Prognosis

- The median survival is now predicted to be at least 40 years for children born in the 1990s.
- Median survival has increased significantly over the past 10 years, and is now around 37 years.

Occupational lung diseases

Occupational asthma

Isocyanates are the most common cause of occupational asthma

Serial peak flow measurements at work and at home are used to detect occupational asthma

- **Occupational asthma occurs more frequently in atopic persons** and smokers.

Causes: Exposure to the following chemicals is associated with occupational asthma:

- **Isocyanates - the most common cause**. Example occupations include spray painting and foam moulding using adhesives (used in the manufacture of foams/plastics)
- **platinum salts**
- other metals: Aluminium, Chrome, Manganese, Nickel, Zinc
- soldering flux resin
- glutaraldehyde (and other disinfectant and preservatives: Chlorhexidine , Formaldehyde)
- flour
- epoxy resins
- proteolytic enzymes

Diagnosis

- Patients may either present with concerns that chemicals at work are worsening their asthma or you may notice in the history that symptoms **seem better at weekends / when away from work.**
- **Serial PEFR measurement is the diagnositic test of choice**
  - Serial measurements of peak expiratory flow are recommended at work and away from work.
  - Recordings should be performed two hourly for four weeks or if this is not possible methacholine/histamine challenges can be undertaken after days at work and away from work.
- bronchial provocation tests and specific IgE radioallergosorbent tests (RAST) are required **to identify the specific agent at work causing the asthma.**

Management

- Referral should be made to a respiratory specialist for patients with suspected occupational asthma.
- Reduction of further exposure to the allergen.
- Affected individuals who continue to work in the occupation responsible for their disease can often reduce their exposure substantially by **changing the pattern of their particular duties**. An alternative is to use **industrial respirators**, which filter out 98-99% of respirable dust from the ambient air.
- Corticosteroid

Extrinsic allergic alveolitis (EAA)

Saccharopolyspora rectivirgula causes farmer's lung, a type of EAA

Aspergillus clavatus causes malt workers' lung, a type of EAA

- Extrinsic allergic alveolitis (EAA, also known as hypersensitivity pneumonitis) is a condition caused by hypersensitivity induced lung damage due to a variety of inhaled organic particles.
- It is thought to be largely caused by immune-complex mediated tissue damage (type III hypersensitivity) although delayed hypersensitivity (type IV) is also thought to play a role in EAA, especially in the chronic phase.
- Despite its name, EAA is not allergic and therefore features associated with allergy and type I reactions do not tend to occur in EAA (ie wheeze, immediate symptoms, raised IgE, positive skin-prick test, eosinophilia of blood or sputum).
- Extrinsic allergic alveolitis is characterised **histologically** by:
  - **alveolar destruction** and **interstitial inflammation**.
  - **Non-caseating granulomas** are also present
  - **asteroid bodies** may be found in or adjacent to the granulomas.

Examples

- **bird fanciers' lung**: avian proteins
- **farmer's lung**: spores of *Saccharopolyspora rectivirgula* (formerly *Micropolyspora faeni*)
  - **the commonest occupational hypersensitivity pneumonitis**
  - **Contaminated hay is the most common source of *Saccharopolyspora rectivirgula***
  - caused by dust from mouldy hay contaminated with thermophilic *Actinomyces* bacteria
  - Basal crackles are the **typical** feature.
  - **Serum precipitating antibodies to *Saccharopolyspora rectivirgula* is the most useful diagnostic test**
  - precipitins to *Saccharopolyspora rectivirgula* or *Thermoactinomyces vulgaris* are found in 75-100% of cases during an acute episode.
- **malt workers' lung**: *Aspergillus clavatus*
- mushroom workers' lung: thermophilic actinomycetes
- maple bark stripper's lung : caused by Cryptostroma corticale
- *Penicillium* species are responsible for respiratory disease in cheese and cork workers and are due to fungal contaminants of materials.

Presentation

- acute: occur 4-8 hrs after exposure, SOB, dry cough, fever
- chronic: exertional shortness of breath and pulmonary fibrosis **(typically upper-lobe).**

Investigation

- Chest x-ray: upper/mid-zone fibrosis. nodular shadowing or ground glass appearances. Classically show diffuse air-space consolidation
- Broncho alveolar lavage: lymphocytosis , eosinophilia
- **Blood: Circulating IgG precipitins. NO eosinophilia**
  - confirmed by demonstration of precipitating antibodies (precipitins) in the patient's serum to the causal antigen.

Treatment:

- Prednisolone
- Symptoms may settle within 12 hours of removal of the antigen.
- Optimal management is removal of exposure to the antigen, change of job plan

A 65-year-old **farmer** presents with **SOB** and **wheeze** progressively worsening over the past 6 months. He is a **smoker**, and **has two daughters with asthma**. There was obvious wheeze and coarse end-inspiratory crackles on examination of the chest. A chest X- ray shows diffuse non-specific changes consistent with lung disease.

Which would be the next most appropriate investigation?

➔ **Spirometry and reversibility**

- This man either has asthma, chronic obstructive pulmonary disease or farmer's lung
- Spirometry and reversibility would be the investigation of choice.
  - A **restrictive defect** would support a diagnosis of **farmer's lung**;
  - an **obstructive defect with reversibility** would support a diagnosis of **asthma**,
  - **respiratory obstruction without reversibility** would support a diagnosis of **COPD**.

Byssinosis

- Rare in UK, occurs in areas of **cotton** production, such as India.
- Characteristic symptoms: shortness of breath, cough and chest tightness that begin on the first day of the working week and ease during the remainder of the working week.
- It is thought to be due to endotoxin released by bacteria that are found in cotton dust.
- Usually no chest X-ray changes.
- The more severe changes noted in some patients might be related to associated asthma or cigarette smoking.

Pneumoconioses

Definition

- A group of chronic lung diseases caused by exposure to a mineral dust or a metal.

Type

- The major pneumoconioses include:
  - asbestosis,
  - silicosis,
  - coal workers' pneumoconiosis (black lung disease), and
  - chronic beryllium disease.

Risk factor

- In **silicosis** and **coal** workers' pneumoconiosis, exposure should be (at least 10 and usually 20 or more years prior to radiographic changes).
  - The best predictor for the development of silicosis or coal workers' pneumoconiosis is the total amount of silica or coal inhaled (the **cumulative dose** inhaled).
- **Beryllium** is immunologically mediated with a **strong genetic component**, so that the typical dose response demonstrated with the other pneumoconioses is not seen.
  - NO need for cumulative dose

Features

- dyspnoea on exertion
  - Typically the first sign of pneumoconiosis
- Dry, non-productive cough
  - productive cough if developed COPD as a complication
- Chest auscultation will be normal early in these diseases.

Diagnosis

- usually by typical chest x-ray appearance.
  - The presence of non-calcified, multiple (in the hundreds), **rounded opacities** in the **upper zones** is highly suggestive of **silicosis** or **coal workers'** pneumoconiosis.
- **high-resolution CT (HRCT) scan chest**
  - more sensitive than CXR in identifying interstitial fibrosis.
- Individuals with silicosis should be tested for TB.

Treatment

- smoking cessation + removal of occupational exposure
- advice regarding compensation
- Patients with end-stage respiratory failure (PaO2 <60 mmHg despite oxygen therapy)
  - Referral for lung transplant
  - Absolute contraindications include:
    - other incurable advanced disease,
    - addictions including tobacco,
    - lack of social support,
    - untreatable psychiatric condition, or
    - documented non-adherence to medical therapy.
  - Relative contraindications include:
    - age >65 and
    - obesity.
  - Major complications include:
    - graft failure and
    - development of bronchiolitis obliterans.
    - ↑ risk of hypertension, diabetes, dyslipidaemia, renal dysfunction, and infection from the immunosuppressive medication.

Asbestos and the lung

Risk of asbestos exposure

- **Ship building**,
- car manufacture,
- boiler making and
- plumbing industries

Asbestos can cause a variety of lung disease from benign pleural plaques to mesothelioma.

Pleural plaques

- **the most common form of asbestos related lung disease**
- occur after a latent period of 20-40 years.
- rarely cause symptoms
- benign and do not undergo malignant change.

- **CXR may shows calcification on both hemidiaphragms** which are most likely to be pleural plaques from previous asbestos exposure.
- Do not require long term follow up

Pleural thickening

- Asbestos exposure may cause diffuse pleural thickening in a similar pattern to that seen following an empyema or haemothorax.

Asbestosis (asbestos-related pulmonary fibrosis)

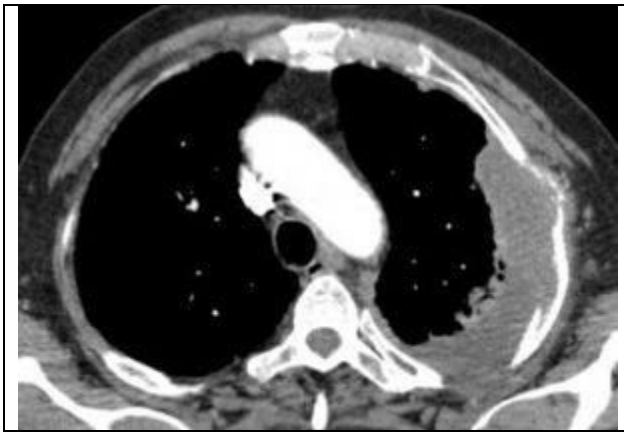
- Definition
  - Asbestosis, defined as **diffuse interstitial fibrosis** secondary to asbestos inhalation
- Overview
  - The latent period is typically 15-30 years.
  - **The condition is slowly progressive**
  - The severity of asbestosis is related to the length of exposure.
    - This is in contrast to mesothelioma where even very limited exposure can cause disease.
- Feature
  - Asbestosis **typically causes lower lobe fibrosis.**
  - As with other forms of lung fibrosis the most common symptoms are shortness-of-breath and reduced exercise tolerance.
  - Clubbing occurs in 43% of people with asbestosis.
- Diagnosis
  - Biopsy is not mandatory as the diagnosis can be made on clinical and radiological grounds.
  - In an alveolar sputum sample obtained by bronchoalveolar lavage, asbestos bodies are visualized using **Prussian blue stain.**
- Treatment
  - avoid further exposure to asbestos
  - stop smoking.
  - resistant to treatment with immunosuppressive therapy.
- Prognosis
  - The risk of lung cancer is raised more than 50-fold in smokers with asbestos.

Mesothelioma

- Definition
  - Mesothelioma is a malignant disease of the pleura.
- Pathophysiology
  - **Loss of material from chromosome 22 is commonly seen in mesothelioma cell lines**
- Risk factor
  - **asbestos** is the primary risk factor associated with the development of mesothelioma.
    - Crocidolite (blue) asbestos is the most dangerous form.
    - it takes 40 years for the disease to begin
  - Smoking is not a risk factor for mesothelioma.
- Features
  - progressive shortness-of-breath

  - chest pain
  - pleural effusion (exudative and hemorrhagic)
  - pleural thickening
- Diagnosis
  - made with patient's history, imaging (chest x- ray or computed tomography), and is confirmed with biopsy.
  - The appearance on CT is of nodular thickening which spreads along the pleural surfaces.
  - **Psammoma bodies** are seen on histology in mesotheliomas.
  - **Cytokeratin** and **calretinin** are two markers that are positive in almost all mesotheliomas.

- Treatment
  - palliative chemotherapy
  - there is also a limited role for surgery and radiotherapy.
    - **Surgical cure is usually not possible**, although pleurectomy or pneumonectomy can provide symptomatic relief.
  - **Drainage of pleural effusion may cause tumour seeding along the track.**
- **Prognosis**
  - very poor, with a median survival from diagnosis of 8-14 months.



CT scan showing mesothelioma

- There is a large rind of soft tissue related to the left chest wall.
- This is a malignant process as there is destruction of the associated rib.

Lung cancer

- Asbestos exposure is a risk factor for lung cancer and also has a synergistic effect with cigarette smoke.
- **Bronchogenic carcinoma** is the most common malignant pulmonary tumor in patients with asbestosis
  - **Bronchogenic carcinoma is more common than mesothelioma**
  - **The lack of smoking history along with previous asbestos exposure and signs of a pleural effusion make malignant mesothelioma more likely than bronchial carcinoma.**

Disease	Agent	Effects
Aluminosis	Alum, and al. oxide	Fibrosis, bullae, pneumothorax
Asbestosis	Asbestos	Pleural plaques, lung cancer, mesothelioma
Byssinosis	Cotton, flax, hemp	Airway obstruction, loss of elasticity
Metal fume fever	Cadmium, cobalt, nickel, zinc and others	Chemical pneumonitis
Occupational asthma	Western Red SCedar and others	Reversible airway obstruction
Siderosis	Iron oxide	Dust deposits
Silicosis	Silica	Dust deposits and fibrosis
Talcosis	Talc, hydrated Mg. silicates	Perivascular fibrosis

Silicosis

Overview

- Is a form of occupational lung disease caused by inhalation of crystalline silica dust, usually in the form of quartz.
- It is a type of pneumoconiosis
- **affects upper lobes**
- **Risky jobs:**
  - Silicosis can affect anyone involved in quarrying(المحاجر), carving, mining (تعدين), tunneling (حفر الانفاق), grinding(طحن) or sand-blasting (نسف) , if the dust generated contains quartz.
  - manufacture of toilet bowls, sinks(مغاسل), and ceramics;
  - hydraulic fracking while drilling for gas and oil.

Pathology

- macrophages activated by silica (quartz)
  - release fibrogenic cytokines
  - It causes inflammation and scarring in the form of nodular lesions in the upper lobes of the lungs.
- Silicosis features pathologic changes of **both restrictive and obstructive lung disease**

Classifications

- **Acute silicosis**:
  - **The most severe form**

- develops a few weeks to 5 years after exposure
- acquired after very heavy exposure over just a few months, patients become intensely breathless and die within months.
- The X-ray shows appearances resembling pulmonary oedema.

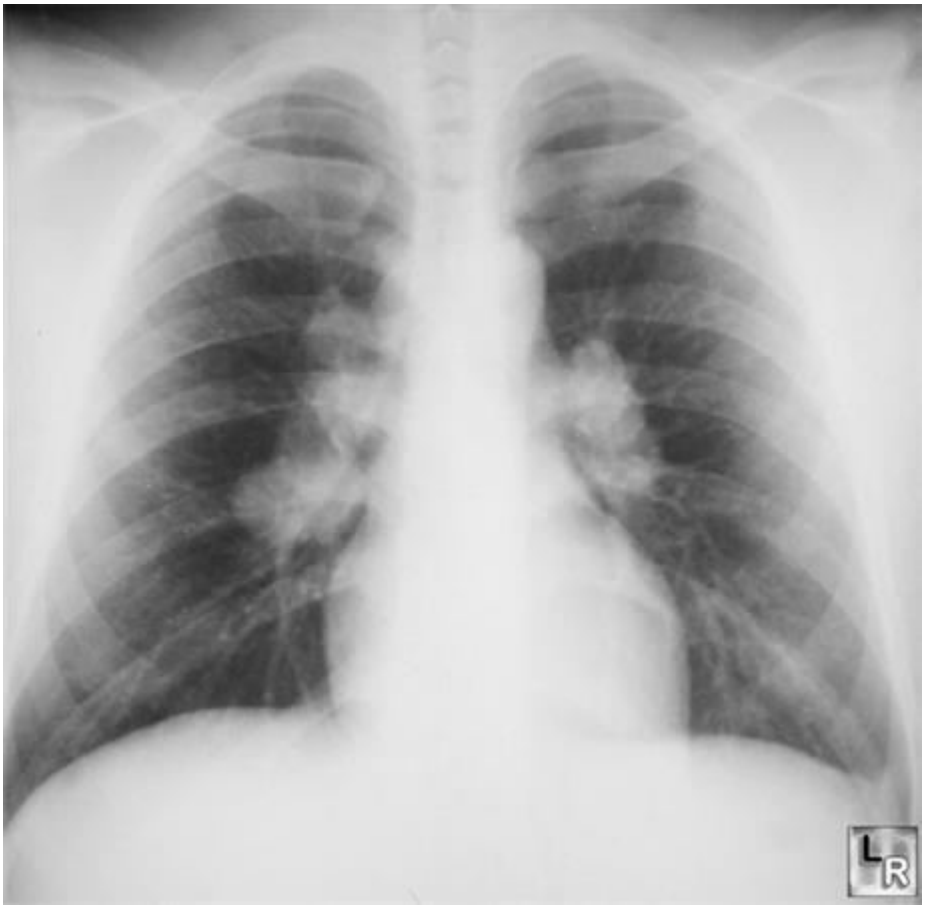
- **Accelerated silicosis:**
  - develops 5–10 years after first exposure
  - Less heavy exposure causes progressively less dramatic symptoms, a progressive upper lobe fibrosis with slowly increasing exertional dyspnoea over several years
- **Simple nodular silicosis:**
  - **the most common type**
  - resulting from long-term exposure (10 years or more) to relatively low concentrations of silica dust
  - Usually appearing 10–30 years after first exposure
  - radiographic nodular changes similar to coal-worker's pneumoconiosis ,
  - usually associated with exposure to dust containing 10-30% silica over a prolonged period.
  - In early disease no signs or symptoms , but abnormalities may be detected by x-ray. Chronic cough and exertional dyspnoea are common findings
  - Radiographically, chronic simple silicosis reveals a profusion of small (<10 mm in diameter) opacities, typically rounded, and predominating in the upper lung zones.
  - **Differential diagnosis**
    - **Simple nodular silicosis differs from coal-worker's pneumoconiosis in that** :
      - the lesions tend to be larger (3-5 mm)
      - and it is progressive even after dust exposure ceases

Features

- fibrosing lung disease
- pulmonary function usually reveal mixed obstructive / restrictive picture
- **'egg-shell' calcification of the hilar lymph nodes is pathognomonic for silicosis;**
- biopsy shows silica particles (birefringent) surrounded by collagen

Sequelae

- may impair macrophage function
  - ↑ **susceptibility to TB**
    - Patients with silicosis should be considered for treatment of latent TB if their tuberculin skin test result is 10 mm or greater, or if the blood assay for *M tuberculosis* **interferon gamma-release assay (IGRA)** result is positive.
  - **silica is toxic to macrophages**
- ↑ incidence of primary **lung cancer**
- ↑ risk of connective-tissue disease, vasculitides, (COPD), and chronic renal failure.



The chest radiograph shows **"eggshell" calcification** of the hilar lymph nodes, as seen with **silicosis.**

Treatment

- **acute secondary alveolar proteinosis (acute silicosis)**
  - occur within weeks to months of extremely high exposure.
  - Symptoms same as chronic silicosis, but develop at a faster rate.
  - **1st line → whole lung lavage.**

Berylliosis

- Epidemiology
  - aerospace or nuclear industry workers
- Pathology
  - **noncaseating granulomas**, nodular infiltrates, and enlarged lymph nodes
    - resembles sarcoidosis
- Risk factor
  - manufacture of electronics, manufacture of heat-resistant ceramics, dental prostheses, and metal products
  - The presence of glutamic acid at position 69 of the HLA-DP1 beta chain is strongly associated with chronic beryllium disease.
- Features
  - acute form of berylliosis may present as pneumonitis, with acute wheezing, chest tightness, and shortness of breath.

- the usual radiographic changes with chronic beryllium disease are **linear opacities.**
  - silicosis and coal workers' are rounded opacities
- **beryllium lymphocyte proliferation test (BeLPT)**
  - Essential component of the diagnosis of chronic beryllium disease.
  - Sensitive test that identifies individuals sensitised to beryllium.
  - if sensitised to beryllium: positive response
  - performed on a blood sample first, and confirmed with a repeat test.
  - Bronchoscopic lavage fluid may be positive when the blood test is negative.
  - The occurrence of a **positive BeLPT without granulomas on histology** is an indication of **sensitisation to beryllium and absence of chronic beryllium disease.**
- Bronchoscopic biopsy
  - granulomas present

- Sequelae
  - ↑ risk for primary lung cancer
- Treatment
  - Acute and chronic berylliosis → Oral corticosteroid therapy.

Coal workers' pneumoconiosis (CWP)

- Pathology
  - affects **upper lobes** (high ventilation)
  - macrophages phagocytose particles ("dust cells")
- Types
  - simple CWP
    - like smoking, can produce centrilobular emphysema
    - 1 cm fibrotic centers
    - **Simple coal-worker's pneumoconiosis** causes no symptoms or physical signs, but it **predisposes to progressive massive fibrosis**
  - complicated CWP
    - 1-2 cm fibrotic centers
- Sequelae
  - ↑ risk of connective-tissue disease and COPD
  - **NO** association with lung cancer or TB

Categories: depends on chest x-ray appearance

- Category 1 disease
  - the least severe, with fewer opacities and normal lung markings clearly visible.
  - progression to massive fibrosis → never
- Category 2 pneumoconiosis
  - less severe, with a number of opacities but normal lung markings still visible;
  - progression to massive fibrosis → 7%
- **Category 3 pneumoconiosis**

- chest X-ray reveals a large number of small round opacities within the lung fields, with almost complete obscuration of normal lung markings.
- progression to massive fibrosis → 30%

Progressive massive fibrosis (PMF)

Causes

- **exposure to dust of high silicon content** and hence PMF is more likely with higher silicon exposure than in simple coal worker's lung.
- Coal worker's pneumoconiosis
  - The rate of progression of category 3 pneumoconiosis is much higher, at around 30%.
  - Category 2 pneumoconiosis progresses to PMF in around 7% of cases.

Feature

- There is usually a history of dust inhalation (eg coal dust).
- An unusual, but **pathognomonic symptom** is **melanoptysis** -the expectoration of the black contents of a cavitated lesion.
- There are also emphysematous changes.
- there is a mixed obstructive and restrictive lung defect with reduced transfer factor.
- Rheumatoid factor and antinuclear antibody are often positive.
- PMF can progress rapidly, even in the absence of further dust exposure, leading to respiratory failure and eventually death.

Diagnosis

- Is diagnosed by **chest x ray**:
  - as round masses, several centimetres in diameter, sometimes up to 10 cm
  - usually in the upper lobes.
  - They may have necrotic centres.
    - In silicosis a more accurate term is 'conglomerate nodules'
- CT
  - Mass-like areas of lung opacification associated with radiating strands are seen; the "sausage-shaped" mass is characteristic.
- MRI
  - can be helpful for distinguishing between progressive massive fibrosis and lung cancer.
    - lung cancer typically appears as T2-**bright**,
    - whereas progressive massive fibrosis appears as T2-**dark** (compared to skeletal muscle)

Caplan's syndrome

- Is the combination of rheumatoid arthritis with pneumoconiosis related to coal dust.
- There is a rapid development of basal peripheral nodules, which can progress to severe pulmonary fibrosis.

Other occupational risks and cancer

- **Exposure to isocyanates most likely associated with squamous-cell carcinoma of the bronchus.**
- Aromatic amines are associated with bladder carcinoma,
- exposure to vinyl chloride is associated with angiosarcoma of the liver.

hard metal lung disease (Cobalt exposure)

- Persons **working in the hard metal industry** are prone to develop a condition called hard metal lung disease.
- A worker in the hard metal industry, comes with progressive dyspnea. Chest X-ray shows diffuse interstitial fibrosis bilaterally. **what is the typical cellular component found in a bronchoalveolar lavage (BAL) of this patient?**
  - **Giant cells**
- Pathological findings in lung biopsy include bronchiolitis and bizarre multinucleated giant cells in the alveoli. The pathological diagnosis is giant cell interstitial pneumonia (GIP).

Churg-Strauss syndrome

- Churg-Strauss syndrome is an ANCA associated small-medium vessel vasculitis.
- also known as Eosinophilic granulomatosis with polyangiitis

Features

- asthma
- paranasal sinusitis
- mononeuritis multiplex
- blood eosinophilia (e.g. > 10%)
- Serum IgE is very commonly elevated and correlates with disease severity.
- pANCA positive in 60%
- Commonly associated with antimyeloperoxidase antibodies.
- Non-fixed pulmonary infiltrates visible on chest radiographs
- Rarely, it can cause ischaemic optic neuropathy, which presents with visual loss.

Leukotriene receptor antagonists may precipitate the disease

Diagnosis

- It is diagnosed **clinically**, although a biopsy should be sought for pathological confirmation.
- **Skin biopsy** reveals small-vessel arteriopathy with **granuloma** formation and is the diagnostic investigation of choice.
  - Blood vessels with **extravascular eosinophils** on biopsy.

Treatment:

- High-dose methylprednisolone, with or without cyclophosphamide is the treatment of choice

Prognosis:

- Without treatment, the 5-year survival rate for Churg-Strauss syndrome is around 25%; with appropriate therapy this rises to over 60%.

Primary ciliary dyskinesia (PCD)

- autosomal recessive disorder
- deficiency of **dynein** arms of cilia causing slow and poorly co-ordinated ciliary beating throughout the body.
  - characterised by abnormal ciliary motion and impaired mucociliary clearance.
- incidence → 1:15 000 in the Caucasian population
- **Features**
  - Recurrent or persistent respiratory infections (which may lead to bronchiectasis),
  - sinusitis,
  - otitis media,
  - male infertility.
  - ↑ risk of ectopic pregnancy due to defective movement of the cilia in the fallopian tube
  - In 50% of the patients, PCD is associated with situs inversus (**Kartagener's syndrome).**
- **Differential diagnoses**
  - **cystic fibrosis**
    - The diagnosis of CF is based on typical pulmonary and/or gastrointestinal tract manifestations and positive results on sweat test (pilocarpine iontophoresis).
    - A negative sweat test is sufficient evidence to exclude CF as a diagnostic possibility.

Diagnosis

- Nasal nitric oxide (NNO) levels,
  - **the most sensitive and specific screening test for PCD**
    - Sensitivity of 97% and specificity of 90% for PCD.
  - A low NNO (<100 parts per billion) should be followed up with confirmatory testing (**nasal or bronchial brush biopsy** for ciliary examination) because other conditions such as cystic fibrosis may present with low NNO.
  - A high NNO virtually excludes PCD
- **Ciliary function tests:**
  - This would confirm a diagnosis of primary ciliary dyskinesia.
  - Ciliary function is commonly tested by the use of saccharin.
  - Saccharin is placed 1cm behind the inferior turbinate and the test is positive if the patient does not taste sweetness within 20min.
  - This is because if cilia work normally they will sweep the sweet saccharin inwards, allowing the patient to taste it.

- light microscopy of biopsies for ciliary beat pattern and frequency
- electron microscopic examination of dynein arms.
- Genetic test is difficult due to multiple phenotypes

Kartagener's syndrome

PCD + situs inversus → Kartagener's syndrome

- most frequently occurs in examinations due to its association with dextrocardia (e.g. 'quiet heart sounds', 'small volume complexes in lateral leads')

Pathogenesis

- autosomal recessive mutation.
- **dynein** arm defect results in **immotile cilia**
  - **dynein** is a protein found in Cilia and flagella of microtubule

Features

Kartagener syndrome: triad of

1. **situs inversus,**
2. **chronic sinusitis, and**
3. **bronchiectasis.**

- Dextrocardia or complete situs inversus
  - Situs inversus occurs in about half of people with Kartagener syndrome
- bronchiectasis
- recurrent sinusitis
- male infertility and female subfertility (secondary to diminished sperm motility and defective ciliary action in the fallopian tubes)
- Deafness
- Hydrocephalus.

H/O recurrent chest infections , situs inversus, and sperm sample shows nonmotile spermatozoa. The cause of this condition is most likely a mutation in the genes for which protein? → Dynein

Lung cancer

Risk factors

- **Smoking**
  - increases risk of lung ca by a factor of 10
  - **Smoking and asbestos are synergistic**, i.e. a smoker with asbestos exposure has a 10 X 5 = **50 times increased risk**
  - Whilst many chemicals have been implicated in the development of lung cancer **passive smoking** is the most likely cause.

- Up to 15% of lung cancers in patients who do not smoke are thought to be caused by passive smoking

- **Other factors:** (**coal dust is not a risk factor**)
  - asbestos - increases risk of lung ca by a factor of 5
  - **Isocyanates are a recognised risk factor for the development of non-small-cell lung cancer.**
    - Exposure to isocyanate fumes occurs in chemical workers, particularly those who work in the rubber industry,
    - most likely to be associated with **squamous-cell carcinoma** of the bronchus.
  - arsenic
  - radon
  - nickel
  - chromate
  - aromatic hydrocarbon
  - cryptogenic fibrosing alveolitis
  - TTF-1 (thyroid transcription factor 1) is a protein which regulates the transcription of genes specific for the thyroid and lung.
    - **Lung adenocarcinomas and small cell carcinomas are usually TTF-1 positive.**
- **Factors that are NOT related**
  - coal dust

Lung cancer: types

- **The most common type of lung cancer**
  - In the UK → squamous cell cancer
  - in the USA → Adenocarcinoma

Lung cancer

- squamous: c. 35%
- adenocarcinoma: c. 30%
- small (oat) cell: c. 15%
- large cell: c. 10%
- other c. 5%

Other tumours

- alveolar cell carcinoma:
  - not related to smoking,
  - ++ sputum (production of large amounts of sputum (**bronchorrhoea**).
  - account for up to 1% of all bronchial carcinomas.
  - alveoli are often filled with mucin.
- bronchial adenoma: mostly carcinoid

What is the most common malignant tumour found in the lung?

- **Metastatic carcinoma**
  - Solitary metastasis represents some 10% of round lesions in general, but some 70% of round lesions in patients with a known malignancy.
    - **Colorectal cancer** is the most common tumour of **origin**.
  - **Lymphangitis carcinomatosa** is most commonly due to breast and primary lung tumours (usually adenocarcinomas).
    - Patients can be asymptomatic when the disease is first suspected on the basis of an X-ray showing diffusely increased interstitial markings accompanied by Kerley B lines, hilar lymphadenopathy or pleural effusion.

Lung cancer: non-small cell

- There are three main subtypes of non-small cell lung cancer:
  1. Squamous cell cancer:
  2. Adenocarcinoma:
  3. Large cell lung carcinoma:

Squamous cell cancer

- Typically central **(**Squamous**=** Sentral**)**
- associated with:
  - parathyroid hormone-related protein (PTHrP) secretion → **hypercalcaemia**
  - strongly associated with finger **clubbing**
  - hypertrophic pulmonary osteoarthropathy (**HPOA**)
    - **The presence of clubbing and tender wrists without synovitis makes pulmonary osteoarthropathy the most likely diagnosis.**
    - **It is usually associated with underlying carcinoma of the lung.**
    - **associated with bronchogenic carcinoma in 90% of cases**.
    - The most sensitive diagnostic investigation is **isotope bone scan**:
      - increase in the uptake in long bones, around periarticular surfaces, and also mandible and scapulae.
    - **Regression of the pain has been reported with successful resection of the tumour and after vagotomy.**
  - Hyperthyroidism due to ectopic TSH
- Cavitate (In 10% of cases)
- Most squamous-cell carcinomas present as obstructive lesions, which can manifest as infection.
- **Life threatening haemoptysis** is a medical emergency that requires prompt action.
  - **Pulmonary angiography** will identify the blood supply to the tumour and **embolisation of this vessel(s)** will immediately stem the bleeding.
- Histology will show clusters of lightly stained cells, often associated with groups of partially **keratinized**, acidophilic cell clusters.
  - Pleomorphic cells in cluster with **keratin** pearls and intercellular bridges

Adenocarcinoma

Lung adenocarcinoma
- most common type in non-smokers
- peripheral lesion

- most common type of lung cancer in non-smokers, although the majority of patients who develop lung adenocarcinoma are smokers
- Typically located on the lung periphery → Normal bronchoscopy.
- May associate with Gynaecomastia.
- PET/CT scan offers the best imaging modality to determine **LN** involvement in bronchial adenocarcinoma
- Histology will show:
  - malignant cells more often arranged in small clusters with an **obvious lumen and duct-like structures.**
  - **Mucin-containing tumor cells with glandular differentiation**

Bronchioloalveolar cell carcinoma
- It is an adenocarcinoma.
- accounts for around 5% of all primary lung carcinomas.
- 1% of all bronchial carcinomas.
- Its name arises from its pattern of growth along the alveolar walls without actually destroying them.
- **The classic massive clear frothy sputum (bronchorrhoea) can be up to one litre a day.**
- Other symptoms are dyspnoea, weight loss and chest pain.
- Almost a half of patients are diagnosed on routine CXR, usually demonstrating a peripheral lesion.
- The tumour spreads using the alveolar walls as a frame and the alveoli are often filled with mucin.
- In those whose tumour is not resectable, prognosis is poor.

Management of non-small cell lung cancer

Contraindications to lung cancer surgery include SVC obstruction, FEV < 1.5, MALIGNANT pleural effusion, and vocal cord paralysis

Surgery
- only 20% suitable for surgery
  - Stage I (cT1N0 and cT2N0) and stage II (cT1N1, cT2N1 and cT3N0) tumours should be considered operable.
  - Stage IIIA (cT3N1 and cT1-3N2) tumours have a low chance of being cured by surgery alone, but it can be used in combination with chemotherapy.
  - Stage IIIB and IV tumours considered inoperable.

- mediastinoscopy performed prior to surgery as CT does not always show mediastinal lymph node involvement
- The functional criteria for pneumonectomy are:
  - Forced expiratory volume in 1 second (FEV-1) of >1.5 litres
  - **FEV-1 > 50% of the observed forced vital capacity,** and
  - Normal partial pressure of arterial CO2 (Paco2) with the patient at rest
- Prognosis after surgery is about 50-67% at 5 years with stage 1disease

Absolute contraindications for surgery include:

- Patient refusal
- **FEV1 < 1.5 litres** is considered a general cut-off point
  - If the tumour necessitates a pneumonectomy, the post-bronchodilator FEV should be more than 2 litres.
- **Reduction** in the **gas transfer** test of **more than 50%** is a contraindication to surgery.
- Metastases.
  - stage IIIb or IV (i.e. metastases present)
  - tumour near hilum
  - vocal cord paralysis (implies extracapsular spread to mediastinal L.N)
  - SVC obstruction
  - **malignant pleural effusion (not just 'pleural effusion' (which may be reactive))**
    - Most pleural effusions associated with lung carcinoma are due to the tumour (and results in classification as a T4 tumour).
  - **Spread to involve the C8, T1 and T2 nerve roots** occurs by rib erosion by tumour to involve the lower roots of the brachial plexus and is known as a ***Pancoast tumour***.
    - This causes severe pain in the shoulder and down the inner aspect of the arm on the affected side and is a contraindication to surgery.

Relative contraindications include:

- Cell type: small cell carcinoma are usually inoperable
- Poor respiratory reserve - FEV1 > 1.2l is necessary for lobectomy, and > 1.8l for pneumonectomy
- Raised PaCO2 is a contraindication for surgery
- Other disease - especially myocardial
  - surgery should be delayed until 6 weeks following myocardial infarct if possible.
- Mediastinal involvement
- Age - in patients over 70, surgery is usually inadvisable because the benefits are outweighed by operative morbidity and mortality.
  - Age over 80 alone is not a contraindication to lobectomy or wedge resection for stage I disease, but may be a contraindication to pneumonectomy.

Radiotherapy → Curative or palliative

- Radical radiotherapy is indicated for patients with stage I, II or III NSCLC who have good performance status (WHO 0, 1)
- **Sequential chemo-radiotherapy should be offered to patients with stage III NSCLC who are not suitable for surgery but are eligible for radical radiotherapy**.
- **Chemotherapy and radical radiotherapy is the first choice treatment in eligible patients with stage IIIa non-small cell lung cancer (NSCLC).**

Radical radiotherapy

- Definition =>That is, radiotherapy with intention to cure using doses of at least 60 Gy.
- Indication =>Patients with potentially operable tumours that are either too unfit for surgery or refuse surgery may be suitable for radical radiotherapy,
- Benefit => using continuous hyperfractionated accelerated radiotherapy (CHART) can improve two year survival significantly from 20% to 29% compared with conventional radiotherapy.
- **Contraindications =>**
  - tumours larger than 4 cm
  - and poor pulmonary function (generally taken as FEV1 less than 50% predicted).
  - Malignant pleural effusion

Chemotherapy → poor response

Prognosis

Overall lung cancer survival is less than 15% at five years

Performance status

- Assessing a patient's performance status is important when evaluating the most appropriate treatment options.
- It is commonly used by cancer MDTs, but has a role in assessing patients with chronic illnesses including COPD.

WHO (Zubrod) Scale	Description
0	Asymptomatic
1	**Symptomatic but ambulatory (can carry out light work)**
2	In bed less than 50% of the day. Unable to work but can live at home with some assistance
3	In bed more than 50% of the day (unable to care for self)
4	Bedridden

As taken from NICE guidance on Lung cancer (CG121).

Staging lung carcinoma

- It is important to remember the criteria for staging carcinoma of the lung. TNM staging takes into account;
  - The size and position of the tumour (T)
  - Whether the cancer cells have spread into the lymph nodes (N)

  - Whether the tumour has spread anywhere else in the body - secondary cancer or metastases (M)
- Computed tomographic (CT) scanning is recommended as a staging procedure. Where available, PET scanning may be superior, but there are a limited number of scanners in the UK.
- CT can be performed with or without contrast enhancement, but Contrast enhancement makes it easier for inexperienced observers to interpret the CT.
- Overall, preoperative CT staging has been shown to overstage or understage when compared with operative findings in 40% of patients. So biopsy is also needed.

Chest computed tomography is the best method for staging squamous-cell carcinoma of the lung.

SEVENTH EDITION OF THE TNM SYSTEM

The International Association for the Study of Lung Cancer (IASLC) developed a **SEVENTH EDITION OF THE TNM SYSTEM** in 2010 replaced earlier editions: as fellow

Primary tumor — (T)

- T0 – No evidence of primary tumor.
- Tis – Carcinoma in situ.
- T1 – Tumor that is ≤3 cm
  - T1a: Tumor is ≤2 cm
  - T1b: Tumor is >2 cm, but ≤3 cm
- **T2 – Tumor that is >3 cm but ≤7 cm**
  - T2a: Tumor is >3 cm, but ≤5 cm
  - T2b: Tumor is >5 cm, but ≤7 cm
- T3 – Tumor that is >7 cm ; invades the chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium
- T4 – Tumor of any size that invades the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; or separate tumor nodule(s) located in a different lobe of the ipsilateral lung.

Regional lymph nodes — (N)

- N0 – No regional lymph node involvement.
- **N1 – Involvement of ipsilateral intrapulmonary, peribronchial, or hilar lymph nodes.**
- N2 – Involvement of ipsilateral mediastinal or subcarinal lymph nodes.
- N3 – Involvement of contralateral mediastinal or hilar lymph nodes.

Metastasis — (M)

- **M0 – No distant metastasis**
- M1a – Malignant pleural effusion, pericardial effusion, pleural nodules, or metastatic nodules in the contralateral lung
- M1b – Distant (extra-thoracic) metastasis

Carcinoid lung cancer:

- The vast majority of bronchial adenomas are carcinoid tumours, arising from the amine precursor uptake and decarboxylation (APUD) system, like small cell tumours.

- The term bronchial adenoma is being phased out.

Carcinoid tumour as general (see gastroenterology section)
- neuroendocrine tumours of predominantly enterochromaffin cell origin.
- can occur in the small intestine, bronchi, rectum appendix or stomach.
- in the lung are most often located in the main bronchi, and occur most frequency in the right middle lobe.

Carcinoid lung

Overview
- Carcinoid tumours (so called argentafinomas as they take up silver) are neuroendocrine cells
- **originate from Kulchitsky (K) cells in the lung**
- **slow growing**
- smoking is **NOT** a risk factor

Incidence: Lung carcinoid accounts
- 1% of lung tumours
- 10% of carcinoid tumours.
- typical age = 40-50 years
- The incidence is equal between men and women.

Feature

Recurrent haemoptysis with segmental collapse on x-ray is a typical presentation of bronchial carcinoid.

- Often asymptomatic
- long history of cough,
- Recurrent haemoptysis
- Recurrent infections
  - carcinoid tumours → (80-90%) develops in a bronchus → bronchial obstruction → lower respiratory tract infection.
- Carcinoid syndrome (rare)
- **Associated conditions with carcinoid tumour in the lung**
  - carcinoid syndrome (**rare**)
    - depends on associated liver metastases
    - occurs in less than 10% of patients with carcinoid tumours, but occurs most commonly in GIT tumours.
    - can secrete a number of vasoactive compounds (including serotonin and bradykinin), which result in:
      - bronchospasm
      - diarrhoea,
      - skin flushing and
      - right-sided valvular heart lesions.
  - **ACTH secretion and subsequent Cushing's syndrome.**
  - ectopic growth hormone-releasing hormone [GHRH] and subsequent acromegaly

- multiple endocrine neoplasia (MEN) type 1 where pancreatic neuroendocrine tumours predominate.

Investigations:

The 'cherry-red' lesion is a typical finding of lung carcinoid.

- CXR
  - often **centrally** located and not seen on CXR.
  - Usually occur in the major bronchi, 85% can be seen bronchoscopically.
  - most often located in the main bronchi, and occur most frequency in the right middle lobe.
  - A carcinoid tumour in the left lower lobe bronchus could cause distal collapse of the left lower lobe.
- **Bronchoscopy:**
  - **identifies up to 80% of carcinoid tumours in the main bronchi**.
  - seen as a highly vascular **'cherry-like' tumour** (**'cherry red ball'**)
  - Biopsy is usually followed with brisk bleeding and should be done via **rigid bronchoscopy**.
  - The histological picture of **granular eosinophilic staining of the cytoplasm**, is highly suggestive of a carcinoid tumour.
  - Histologically, these tumors consist of compact nests of epithelial cells surrounded by neat, delicate connective tissue capsules.
  - **histology might not be necessary prior to surgery if the clinical picture is typical**.
- **Plasma chromogaffin A** is an effective **screening test** for carcinoid as it is **very sensitive**, but it is not specific.
- **24 hour urinary excretion of 5-hydroxyindoleacetic acid** is **more specific** for the **diagnosis**, but false positives and negatives are present.
- Scintigraphic imaging with labelled somatostatin increases the ability to diagnose a carcinoid tumour, but biopsy is required to confirm.

Management

- surgical resection
  - **A person with an isolated pulmonary carcinoid should be referred for tumour resection,**
  - **histology might not be necessary prior to surgery if the clinical picture is typical**.

Prognosis

- if no metastases then 90% survival at 5 years

Small cell lung cancer

The presence of hyponatraemia strongly points towards a diagnosis of small cell lung cancer.

- Also known as "oat-cell carcinoma"
- usually central
- arise from APUD* cells
  - *an acronym for
    - **A**mine - high amine content
    - **P**recursor **U**ptake - high uptake of amine precursors
    - **D**ecarboxylase - high content of the enzyme decarboxylase
- Most aggressive cancer which typically presents with a short history and 80–90% will have metastases at the time of presentation.

Features

- ectopic ADH → hyponatraemia (SIADH)
  - SIADH occurs in 5–10% of cases.
- ectopic ACTH → Cushing's syndrome
  - Due to the short natural history of this type of cancer, Cushing syndrome in small-cell carcinoma **does not manifest classically** by buffalo hump, striae or central obesity.
  - Its presence is suspected by arterial hypertension, hyperglycaemia, hypokalaemia, alkalosis and muscle weakness.
  - ACTH secretion can cause bilateral adrenal hyperplasia,
  - the high levels of cortisol can lead to **hypokalaemic alkalosis**
  - in case of chronic heavy smoker with chest infection + hyperglycaemia + ↓ K + ↑ HCO3**?**
    - Suspect SCLC with ectopic ACTH secretion.
    - But if with ↓Na and ↑K → think of Adrenal metastasis → MRI adrenals
- Lambert-Eaton syndrome: antibodies to voltage gated calcium channels causing myasthenic like syndrome
- **Neuron-specific enolase (NSE)** is a tumor marker indicative of small cell carcinoma
- **associated with L-myc amplification.**
- Histologically, Small cell carcinoma has clusters of small, **basophilic cells** and surrounding areas of tissue necrosis.

H/O Rapid progression (cough, lung mass and weight loss within 2 months) + paraneoplastic peripheral neuropathy. What is the most likely diagnosis?

- **small-cell carcinoma.**
  - Squamous cell carcinoma and adenocarcinoma are usually very slow growing.

Management

Stage	Treatment
Early stage (T1-2a,N0,M0)	Surgery
Early stage (T1-2a,N0,M0)- Limited disease (T1-4,N0-3,M0)	4-6 cycles **cisplatin** based chemotherapy, carboplatin if poor renal function/poor performance status +/- radiotherapy
Extensive disease (T1-4, N0-3, M1a/b)	6 cycles platinum based combination chemotherapy + thoracic radiotherapy if good response

- **Surgery**
  - patients with very early stage disease (T1-2a, N0, M0) are now considered for surgery.
  - usually metastatic disease by time of diagnosis. **Surgery is therefore not recommended as first-line treatment in the UK.**
- **Chemotherapy and radiotherapy**
  - most patients with limited disease receive a combination of chemotherapy and radiotherapy. they are very sensitive to combination chemo-radiation. It is the **standard treatment in the UK.**
  - Because of the frequent presence of occult metastatic disease**, chemotherapy is the cornerstone of treatment for patients with limited-stage small cell lung cancer**.
    - Cytotoxic chemotherapy with a **platinum-based regimen** would be the treatment of choice.
  - **The chemotherapy should be initiated immediately, whilst the radiotherapy is being planned,**
  - radiotherapy should be started during either the first or second cycle of chemotherapy.
  - Current programmes yield overall objective response rates of 65% to 90% and complete response rates of 45% to 75%.
  - Patients who are not fit enough for concurrent chemoradiotherapy should be offered sequential chemo-radiation: 4 to 6 cycles of platinum-etoposide chemotherapy with consolidative radiotherapy for those who respond to chemotherapy.
  - patients with more extensive disease are offered palliative chemotherapy

Prognosis

- very poor and survival beyond two 2 years is exceptional
  - median survival is 6–12 months.
- **Adverse prognostic factors in small cell lung cancer**:
  - Serum Na < 132 mmol/l
  - Weight loss > 10%
  - WHO performance status > 2
  - Alkaline phosphatase > 1.5 times upper limit of normal
  - LDH > 1.5 times upper limit of normal

- Extensive disease (occurring outside one hemi-thorax and ipsilateral supraclavicular fossa nodes).

Bronchial Carcinoma

- 20-30% of cases with bronchial carcinoma are of small (oat) cell type from endocrine K-cells (Kulchitsky) cells.
- Primary bronchial cancer → the **tumour edge may have a fluffy or spiked appearance**.
- Paraneoplastic manifestations:
  - SIADH (5 - 10%)
  - ACTH (5 %)
  - ANP
- **The most appropriate tool to confirm the diagnosis of bronchial carcinoma is → Bronchoscopy ± Trans bronchial biopsy (NOT CT-guided FNA biopsy).**
  - CT-guided FNA would be useful; however, there is a **high risk of pneumothorax** in patients with FEV1 < 1.

Superior vena cava obstruction (SVCO)

- (SVCO) an oncological emergency caused by compression of the SVC.
- most commonly associated with lung cancer.
- Up to 4% of patients with lung cancer will develop SVCO at some point during their disease.
- SVCO is much **more likely to be associated with right sided lung lesion** 4 times than with left sided lesions

Features

- **dyspnoea is the most common symptom**
- swelling of the face, neck and arms - conjunctival and periorbital oedema may be seen
- headache
- visual disturbance
- pulseless jugular venous distension
- **may be associated with voice hoarseness**
- CXR is abnormal in around 85% of cases, mediastinal widening is common.

Causes

- **the most common cause → Non-small cell lung cancer**
- common malignancies: small cell lung cancer, lymphoma
- other malignancies: metastatic seminoma, Kaposi's sarcoma, breast cancer
- aortic aneurysm
- mediastinal fibrosis
- Mediastinal goitre
- SVC thrombosis

Below are the rates of SVC obstruction with different malignancies (UpToDate,2016)

Malignancy	Percent
Non-small cell lung cancer	**50%**
Small cell lung cancer	25%
Non-Hodgkin lymphoma	10%
Other malignancies	15%

Association:

- **Recurrent laryngeal nerve palsy (voice hoarseness):** usually occurs with malignant tumour but can occur with aneurysm of aortic arch.
- Horner's syndrome due to involvement of sympathetic chain.
- elevated non-pulsatile jugular venous pressure (JVP)
- Compression of vital structures can result in stridor and dysphagia.

Management

- general: dexamethasone, balloon venoplasty, stenting
  - Corticosteroids are most useful where the cause of compression is an underlying **haematological malignancy**.
    - **SVCO: immediate management → Dexamethasone IV + LMWH.**
  - **Stenting**
    - In 2004 NICE recommended considering **stenting** in the majority of cases of SVCO. This is a minimally invasive procedure which **relieves symptoms quicker than chemotherapy or radiotherapy.**
    - **Stenting is better than radiotherapy in terms of relief of symptoms.**
  - **Radiotherapy**
    - may be an option **later**. If radiotherapy is used initially then stenting becomes significantly more difficult due to local fibrosis.
    - Mediastinal radiotherapy leads to symptomatic relief in 80% of patients,

- small cell: chemotherapy + radiotherapy
  - Chemotherapy may be a first-line option in cases of histologically proven small-cell cancer.
- non-small cell: radiotherapy

Prognosis:

- Median survival of lung cancer presenting with SVCO, even with treatment is five months.
- Lymphoma has a better prognosis and will require specific chemotherapy ± radiotherapy.

Lung cancer: paraneoplastic features

Paraneoplastic features of lung cancer

- **Squamous cell:** PTHrp, TSH, Clubbing, HPOA
- **Adenocarcinoma:** Gynaecomastia
- **Small cell:** ADH, ACTH, Lambert-Eaton syndrome
- **Bronchial carcinoma:** SIADH, ACTH, ANP

- Paraneoplastic syndromes are a result of antibody generation from or against malignant cells attacking normal tissue.
- Both non-small cell and small cell lung cancers are associated with Paraneoplastic syndromes, although they are more common with the small cell due to its neuroendocrine cell origin.

Squamous cell

- Parathyroid hormone-related protein **(PTH-rp)** secretion causing hypercalcaemia
  - occurs in about 15%
  - best treated with intravenous fluids and bisphosphonates
- **clubbing**
- hypertrophic pulmonary osteoarthropathy **(HPOA)**
  - (HPOA) is a proliferative peri-ostisis typically involves the long bones.
  - It is often painful.
- hyperthyroidism due to ectopic **TSH**

Adenocarcinoma

- Gynaecomastia
  - **Bronchial carcinoma can presents with ataxia and bilateral Gynaecomastia** .
  - It can be painful and may be associated with testicular atrophy.
- **Ataxia** can occur as a result of a paraneoplastic cerebellar degeneration associated with the malignancy.

Small cell

- **ADH**
  - Symptomatic hyponatraemia due to SIADH is treated with demeclocycline which induces nephrogenic diabetes insipidus leading to excretion of excess water.
- **ACTH**
  - not typical, hypertension, hyperglycaemia, hypokalaemia, alkalosis and muscle weakness are more common than buffalo hump etc.
  - May manifest by Cushingoid facies and hyperpigmentation of the skin
- **Lambert-Eaton syndrome**
  - 70% occur in small cell carcinoma
  - is a pre-synaptic disorder of auto-antibody IgG directed against the pre-synaptic voltage gated calcium channel (VGCC) leading to impaired acetylcholine release.

- characterised by:
  - Proximal muscle weakness (the cranial nerves and respiratory muscles are usually spared)
  - Depressed or absent tendon reflexes and
  - Autonomic features (for example, dry mouth, impotence, etc).
- Weakness and fatiguability can be improved with guanidine hydrochloride
- Unlike myasthenia gravis exercise is associated with increasing muscle strength and there is a negative response to Tensilon.
- Electromyography is useful in confirming the diagnosis where repeated nerve stimulations cause a progressive increase in the size of the muscle action potential.

- **Cerebellar ataxia**:
  - Paraneoplastic syndromes are a result of antibody generation from or against malignant cells attacking normal tissue.
  - Examples include antineuronal antibodies (anti-Hu, anti-Yo, anti-Ri) directed against the Purkinje cells of the cerebellum leading to the cerebellar syndrome (truncal ataxia).
  - To diagnose this → Anti-Purkinje cell antibody levels.

Lung cancer: referral

Consider immediate referral for patients with:

- signs of superior vena caval obstruction (swelling of the face/neck with fixed elevation of jugular venous pressure)
- stridor

Refer urgently (for an appointment within 2 weeks) patients with:

- persistent haemoptysis (in smokers or ex-smokers aged 40 years and older)
- a chest X-ray suggestive of lung cancer (including pleural effusion and slowly resolving consolidation)
- a normal chest X-ray where there is a high suspicion of lung cancer
- a history of asbestos exposure and recent onset of chest pain, shortness of breath or unexplained systemic symptoms where a chest x-ray indicates pleural effusion, pleural mass or any suspicious lung pathology

Refer urgently for chest x-ray for patients with any of the following:

- haemoptysis
- unexplained or persistent (longer than 3 weeks): chest and/or shoulder pain, dyspnoea, weight loss, chest signs, hoarseness, finger clubbing, cervical or supraclavicular lymphadenopathy, cough, features suggestive of metastasis from a lung cancer (for example, secondaries in the brain, bone, liver, skin)
- underlying chronic respiratory problems with unexplained changes in existing symptoms
- **Under NICE guidelines a hoarse voice for three weeks or more is an indication for investigation to exclude malignancy.**

Lung cancer: stepwise investigations

1. **x-ray** :NICE guidelines recommend urgent chest radiograph in patients with haemoptysis or unexplained, persistent (>3 weeks) cough, chest or shoulder pain, dyspnoea, weight loss, chest signs, hoarseness, finger clubbing, cervical or supraclavicular lymphadenopathy. If this suggests lung carcinoma, patients should be referred urgently to the lung cancer multidisciplinary team (MDT).
2. **CT**: **Patients should then be offered a contrast-enhanced CT chest (including the liver and adrenals). before bronchoscopy or any other biopsy procedure.**
3. **Biopsy: If the CT demonstrates a peripheral lung lesion, CT or ultrasound-guided transthoracic needle biopsy should be offered.**
   - Endobronchial ultrasound guided biopsy is recommended for paratracheal and peri-bronchial intra-parenchymal lung lesions.
   - Enlarged mediastinal lymph nodes (>10 mm maximum short axis on CT) or other lesions should be biopsied in preference to the primary lesion if determination of stage affects treatment.
4. **Sputum cytology** is rarely indicated and should be reserved for the investigation of patients who have centrally placed masses and are unable to tolerate, or unwilling to undergo, bronchoscopy or other invasive tests.

Radiographical features of pulmonary tumours

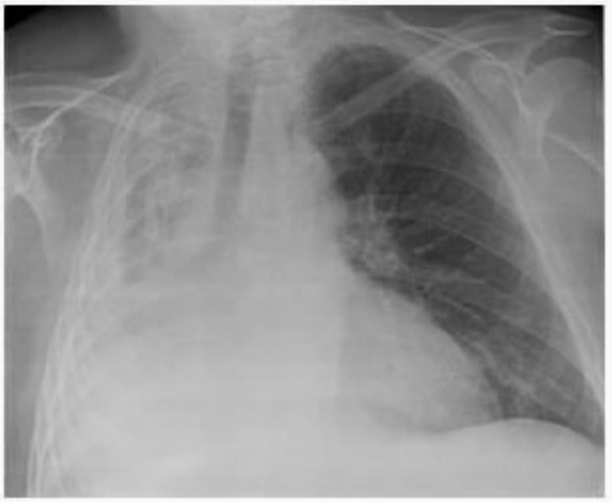
- No initial examination is complete without a **lateral film**.
- **normal X-ray of the chest does not exclude bronchial carcinoma** as patients presenting with haemoptysis and a normal chest X-ray are sometimes found to have a central tumour on bronchoscopy.
- **The common appearance** of a tumour arising from the main central airways (70% of all cases) is **enlargement of one or other hilum**.
- Consolidation and collapse distal to the tumour might have occurred.
- Collapse of the left lower lobe is often hard to identify, as is a tumour situated behind the heart.
- Apically located masses or superior sulcus tumours (Pancoast tumours) can be misdiagnosed as pleural caps, and patients often have a long history of pain in the distribution of the brachial nerve roots.
- Loss of the head of the first, second or third rib is not unusual.
- The mediastinum might be widened by enlarged nodes.
- Involvement of the phrenic nerve can lead to paralysis and elevation of the hemidiaphragm, which then moves paradoxically on sniffing.
- Spread of tumour from mediastinal nodes peripherally along the lymphatics gives the characteristic appearance of lymphangitis carcinomatosa - bilateral hilar enlargement with streaky shadows fanning out into the lung fields on either side.
- Pleural effusion: either by Tumour spread to the pleura **or** secondary to infection beyond obstruction caused by a central tumour.

- Rarely, localised obstructive emphysema is observed.

PET in lung cancer assessment

- **Positron-emission tomography (PET) would determine whether there are distant metastases and is performed after the CT.**
- Routine imaging to screen for distant metastases is not required for every case of suspected NSCLC. Imaging for metastatic disease should be symptom-focused or CT-directed
- For example in a patient with operable non-small-cell lung cancer, if CT has shown enlarged mediastinal nodes , he needs further assessment of his mediastinal nodes prior to surgery, because CT is not particularly good for assessing whether enlarged nodes are inflammatory or malignant. and this can be done with mediastinoscopy or a positron-emission tomography (PET) scan.
- **What is the usual tracer used for PET imaging in lung cancer?**
  - **Fluorodeoxyglucose**
- In a PET scan radiolabeled glucose is injected peripherally and is taken up by metabolically active tissues, such as the brain and any cancer. It would show metastases from the primary cancer.

Radiological signs:



Atelectasis of a person's right lung

- An endobronchial lesion commonly leads to partial or complete **atelectasis** and this is **the commonest sign of bronchogenic carcinoma.**
- Bronchial stenosis and post-stenotic changes are commonly seen because most non-small-cell carcinomas demonstrate intraluminal growth. Narrowing of the main bronchi or a complete cut-off can be identified on chest Xrays.
- Complete endobronchial obstruction can sometimes produce distal mucoid impaction, which can be visible on plain chest X-rays as a tubular or branching opacity.
- The opacity can contain air bronchograms and air alveolograms. This presentation is often seen with adenocarcinoma and bronchoalveolar carcinoma.

Mediastinal masses

- **anterior/superior** mediastinum may relate to the thymus, thyroid.
- **Inferior** or middle mediastinal masses relate to the aorta, lungs, hilar lymph nodes, oesophagus and heart.

- **Posterior** mediastinal masses may relate to the nerves and vertebrae.

Lung metastases

- **Metastatic carcinoma is the most common malignant tumour found in the lung**
- Malignant metastases to the lung can present as a solitary enlarging nodule, as multiple nodules or with diffuse lymphatic involvement.
- **Solitary metastases**
  - represents some 10% of round lesions in general, but some 70% of round lesions in patients with a known malignancy.
  - **Colorectal cancer is reported to be the commonest tumour of origin.**
  - A diagnosis can usually be secured by percutaneous computed tomography-(CT-) guided biopsy.
- **Multiple metastases**
  - Range in size and number, from cannon balls to miliary shadowing, and can be accompanied by hilar lymphadenopathy or pleural effusion.
  - Breast, colon, renal and lung primaries are the commonest underlying tumours.
  - A diagnosis might be made on the basis of cytology or histology (from pleura, lung or sputum).
- **Solitary or multiple Kaposi's sarcoma**:
  - Is a feature of AIDS, and can involve the bronchi and pleura as well as lung tissue.
- **Lymphangitis carcinomatosa:**
  - Most commonly due to breast and primary lung tumours (usually adenocarcinomas).
  - Patients can be asymptomatic when the disease is first suspected on the basis of an X-ray showing diffusely increased interstitial markings accompanied by Kerley B lines, hilar lymphadenopathy or pleural effusion.
  - Although the diagnosis can be established by cytology from sputum or pleural fluid, it often requires a bronchoscopic or transbronchial lung biopsy.
  - Later, progressive and severe breathlessness with hypoxaemia often develops, and patients require vigorous palliative relief with opiates and oxygen.
- **Bronchial metastases**
  - Not visible on a plain chest X-ray - diagnosis requires bronchoscopy.
  - Present with haemoptysis, effectively controlled by radiotherapy.
  - Renal carcinoma and malignant melanoma are recorded cause

Pancoast tumour

- a neoplasm of the apex of the lung that typically invades the chest wall and brachial plexus and is causing a Horner's syndrome (ptosis and constriction of the pupil).
  - compresses the sympathetic fibres (from T1 and T2) as they travel upwards to superior cervical ganglion and then to the **dilator pupillae as** the **long ciliary nerve**.
- The tumour causes pain in the **C8 and T1 distribution** and **Horner's syndrome**.
  - pain in the shoulder and the medial surface of the arm.
  - Patients may initially present to rheumatologists or orthopaedic surgeons.
- It may cause **small muscle wasting of the hands** and **erosion of the first rib**.

- **the investigation of choice → CT of chest**
  - CT is essential to locate the tumour and the extent of rib, vertebral and muscle involvement.
  - Chest x-ray may be normal
- Tumours are most commonly squamous cell and are usually inoperable on presentation.

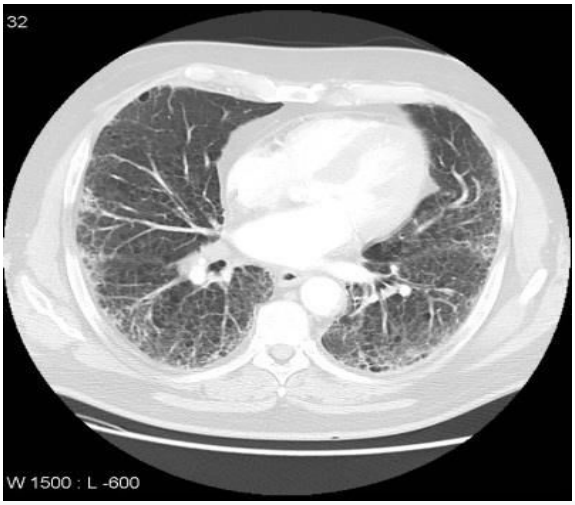
Lung fibrosis

Fibrosis predominately affecting the upper zones

- extrinsic allergic alveolitis
- coal worker's pneumoconiosis/progressive massive fibrosis
- silicosis (Silica is found in coal dust)
- **sarcoidosis**
- ankylosing spondylitis (rare)
- histiocytosis:
  - (Pentalaminar X bodies (Birbeck granules) found on bronchoalveolar lavage (BAL) are diagnostic)
- tuberculosis
- Allergic bronchopulmonary aspergillosis and farmers lung
- **R**adiation

Fibrosis predominately affecting the lower zones

- cryptogenic fibrosing alveolitis (the more common cause)
- most connective tissue disorders (except ankylosing spondylitis)
- drug-induced: amiodarone, bleomycin, methotrexate
- asbestosis



CT scan showing advanced pulmonary fibrosis including 'honeycombing'

Idiopathic pulmonary fibrosis (IPF) (previously termed cryptogenic fibrosing alveolitis)

Definition

- progressive fibrosis of the interstitium of the lungs, when **no underlying cause exists**.

Epidemiology

- IPF is typically seen in patients aged 50-70 years
- twice as common in men.

Pathophysiology

- **Transforming growth factor-beta** is a cytokine released from injured pneumocytes, **inducing fibrosis** in patients with IPF.

Features

- progressive exertional dyspnoea :
- **bibasal** crackles on auscultation
- dry cough
- Clubbing occurs in two-thirds of cases.
- Bilateral **lower-zone** reticulonodular shadows are seen on chest X-ray.

Diagnosis

- spirometry:
  - classically a restrictive picture (FEV1 normal/decreased, FVC decreased, FEV1/FVC increased)
- impaired gas exchange: reduced transfer factor (TLCO)
- imaging:
  - bilateral interstitial shadowing (typically small, irregular, peripheral opacities - 'ground-glass' - later progressing to 'honeycombing') may be seen on a chest x-ray but **high-resolution CT scanning is the investigation of choice** and required to make a diagnosis of IPF.
  - **The first chest x-ray findings develops➔small, peripheral opacities in the lower zones** (The classic finding **=>** reticular opacities predominantly in the bases)
  - The late chest x-ray findings develops➔ Honeycombing
- ANA positive in 30%, rheumatoid factor positive in 10% but this does not necessarily mean that the fibrosis is secondary to a connective tissue disease. Titres are usually low.
- Arterial oxygen desaturation on exercise is an early feature and this is reflected in widening of the alveolar-arterial (a-a) gradient on exercise.
- IPF lungs are stiff, ie poorly compliant, and therefore if compliance is low then **elastic recoil will be high** as the two are inversely related.

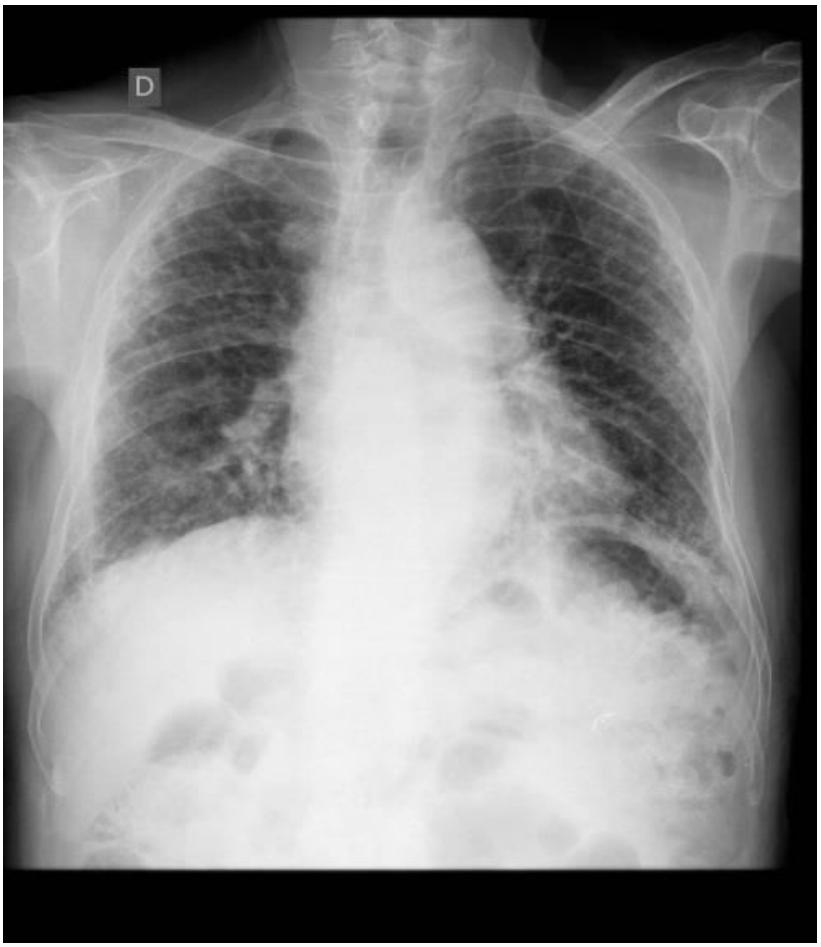
Management

- pulmonary rehabilitation
- **pirfenidone**
  - (anti-fibrotic agent) may be useful in selected patients .

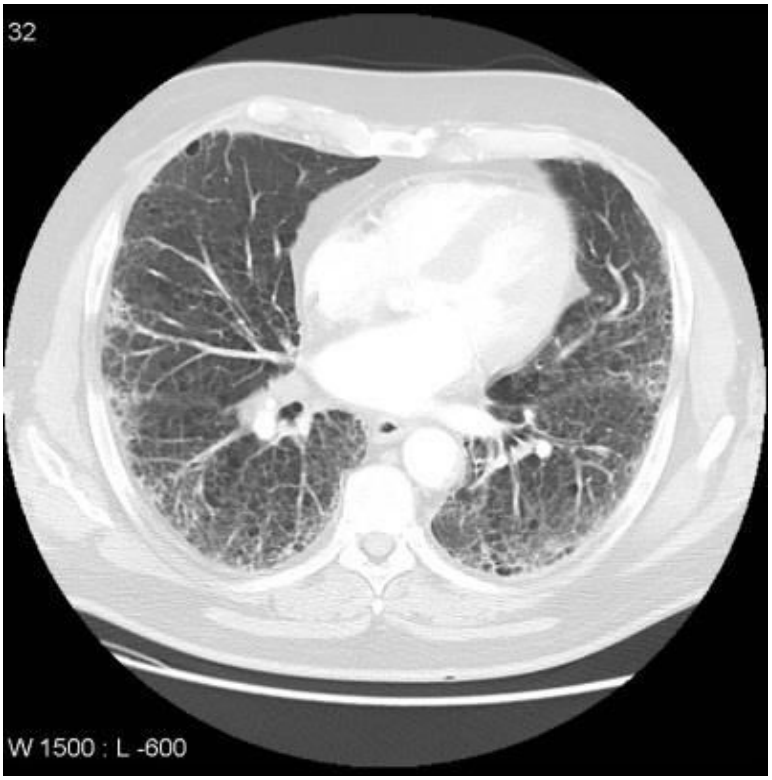
  - Pirfenidone reduces risk of disease progression by 30 % and has been approved by NICE for use in mild-moderate disease (FVC 50-80 % predicted).
  - mechanism of action includes anti-fibrotic, anti-inflammatory and antioxidant effects.
- many patients will require supplementary **oxygen** and eventually a lung transplant
- Treatment of idiopathic pulmonary fibrosis with immunosuppression have been shown by meta-analysis to have no benefit.
- N-acetyl cysteine, Nintedanib and Co-trimoxazole have all shown possible benefit in preliminary trials with further investigation on-going.
- **only 20% of patients may be steroid responsive (**1 in 5 **)**

Prognosis

- poor, average life expectancy is around 3-4 years
- increased risk of developing lung cancer (by 7- to 14-fold).



Chest X-ray shows sub-pleural reticular opacities that increase from the apex to the bases of the lungs



CT scan showing advanced pulmonary fibrosis including 'honeycombing'

Idiopathic interstitial pneumonitis (IIP)

IIP is further subdivided into:

- Usual interstitial pneumonia and
- Non-usual interstitial pneumonitis.

Usual interstitial pneumonia (**UIP)**

- ((**previously known as idiopathic pulmonary fibrosis, or cryptogenic fibrosing alveolitis**)
- causes 70% of IIP
- typically found in an older population
- characterised by a gradual onset with acute exacerbations.
- It is worse in smokers.
- **Diagnosis**: typical HRCT findings =>Reticular abnormalities, honeycombing and traction bronchiectasis.
- **Treatment**: UIP have a poor response to steroids and immunosuppressants.
- **Prognosis**: the median survival is 2 - 3 years post-diagnosis.

Non-usual interstitial pneumonitis (non-UIP):

- Contains :
  - Non-specific interstitial pneumonia (NSIP): is the most common non-UIP
  - Cryptogenic organising pneumonia (COP) :is subacute and tends to cause patchy consolidation and/or nodules on CT scan.

- Desquamative interstitial pneumonia (DIP) ;is a form of severe RB-ILD.
- Respiratory bronchiolitis - interstitial lung disease (RB-ILD

- On CT there is typically ground glass appearance and there is better steroid responsiveness when compared to UIP, with an improved survival.

Respiratory manifestations of rheumatoid arthritis

A variety of respiratory problems may be seen in patients with rheumatoid arthritis:

- pulmonary fibrosis
  - found in up to 60% of patients with rheumatoid arthritis, but chest X-ray changes are seen in only 5%.
  - Interstitial fibrosis - occurs in up to 20% of patients with rheumatoid arthritis
- pleural effusion
- pulmonary nodules
- bronchiolitis obliterans → (spirometry reveals an obstructive picture)
- complications of drug therapy e.g. methotrexate pneumonitis (**Acute interstitial pneumonitis is associated with methotrexate).**
  - Methotrexate is a recognised cause of pulmonary fibrosis. However, it is sometimes used in the treatment of idiopathic pulmonary fibrosis as a steroid sparing agent.
  - **Methotrexate-induced pneumonitis** usually occurs within 4 months of starting the drug a CT scan would show pulmonary infiltrates.
- pleurisy
- Caplan's syndrome - massive fibrotic nodules with occupational coal dust exposure
- infection (possibly atypical) secondary to immunosuppression
- **Organising pneumonia: can occur in rheumatoid arthritis, with fever, dyspnoea and multifocal consolidation.** This responds dramatically to steroids.

Rheumatoid respiratory nodules:

- Commonly associated with the disease.
- Associated with increased risk of respiratory tract infection.
- CXR - Nodular changes
- **If the appearance on chest X- ray has not changed over long times**(from previous CXR)**, no intervention is required , only observation**
- They are typically benign but can lead to pleural effusion, pneumothorax, haemoptysis, secondary infection, and bronchopulmonary fistula.

Bronchiolitis obliterans (BO)

Definition

- 'Bronchiolitis obliterans' is the term used to describe fibrous scarring of the small airways, characterized by fixed airway obstruction.

Mechanism

- inflammation that results in scar tissue formation.
- submucosal and peribronchiolar inflammation and fibrosis **without any intraluminal granulation tissue**

- BO should not be confused with bronchiolitis obliterans organising pneumonia (BOOP), a completely different disease.

Causes

- Inhalation of toxic fumes
- Exposure to mineral dust
- Respiratory infections: Viral, Mycoplasma, Legionella
- post-transplantation: Bone marrow, heart-lung or lung transplantation
  - BO seen as early as 3 months post-transplant, and responsible for over 50% of deaths after the first year.
- Connective tissue disorder: **Rheumatoid arthritis** or **SLE**
  - rheumatoid arthritis considered the commonest connective tissue disease to be associated with obliterative bronchiolitis
- **Penicillamine treatment**
- inflammatory bowel disease
- Idiopathic obliterative bronchiolitis disorder is **rare**

Feature

- dry cough and dyspnoea.
- wheeze might be audible.

Investigations

- HRCT
  - there are often sharply defined, areas of decreased lung attenuation associated with vessels of decreased calibre. These changes represent a combination of air trapping and oligaemia. This combination can give a mosaic attenuation pattern.
  - air trapping
  - thickening in the airway and haziness in the lungs.
- spirometry
  - a mixed obstructive/restrictive picture would be seen.
  - Inflammation in the small distal airways leads to obstructive spirometry .
  - Air trapping can occur, which leads to increased lung volumes.
- The chest X-ray findings can vary from normal to a reticular or reticulonodular pattern.
- **transfer factor may be low but the transfer coefficient (Kco) is often normal.**
- Rheumatoid serology often worsens with the onset of bronchiolitis obliterans.
- lung biopsy
  - The diagnosis can be confirmed by lung biopsy.
  - Histologically there is a mural concentric narrowing of the lumina of the bronchioles.
  - Transthoracic lung biopsies are preferable for diagnosis of constrictive BO compared to transbronchial biopsies

Differential Diagnosis

- Bronchiolitis obliterans is often misdiagnosed as asthma, chronic bronchitis, emphysema or pneumonia.

Treatment

- Patients rarely respond to steroids and the prognosis is poor.
- This disease is irreversible and severe cases often require a lung transplant

Drugs causing lung fibrosis

Causes

- Cardiac drugs: amiodarone, hydralazine , tocainide
- cytotoxic agents: busulphan, bleomycin , cyclophosphamide, carmustine , leflunomide
- anti-rheumatoid drugs: methotrexate, sulfasalazine, gold
- antibiotics: nitrofurantoin
- ergot-derived dopamine receptor agonists (bromocriptine, cabergoline, pergolide).
- Opiates: e.g. heroin abuse

Sulphasalazine pulmonary toxicity

- Is rare, but is increasingly recognised.
- Typically presents with new-onset dyspnoea and pulmonary infiltrates visible on chest radiograph.
- There may be peripheral blood eosinophilia.
- Histology most commonly demonstrates an eosinophilic pneumonia with interstitial inflammation and fibrosis.
- Drug withdrawal is standard treatment, with or without the addition of corticosteroids.

Penicillamine

- is associated with pulmonary toxicity in the form of diffuse alveolar damage, hypersensitivity pneumonitis and obliterative bronchitis.
- It does not cause pulmonary fibrosis however, and D-penicillamine has actually been shown to stabilse pulmonary fibrosis in the setting of systemic sclerosis.

Cyclophosphamide-induced lung fibrosis:

- is rare
- most likely occur in patients who have had concomitant pulmonary radiation therapy or have taken other drugs associated with pulmonary toxicity.
- The disorder usually occurs in patients who have been taking low doses for relatively prolonged periods (over six months) and presents several years after cessation of the drug and
- hence the deterioration of symptoms with time.
- The diagnosis is clinical. Chest X-ray reveals reticulonodular shadowing of the **upper zones**. Lung function tests demonstrate a restrictive lung defect. Lung biopsy is not helpful.
- Cyclophosphamide *per se* is not toxic to the lungs; however, it is metabolized in the liver to toxic metabolites such as hydroxycyclophosphamide, acrolein and phosphoramide mustard, which are responsible for pulmonary damage.
- Genetic factors may play a role in determining which individuals develop pulmonary fibrosis after exposure to the drug.

- Cyclophosphamide therapy can also result in an acute pneumonitis during treatment with the drug that causes cough, dyspnoea, hypoxia and bilateral nodular opacities **in the upper zones** of the lung.
- Acute cyclophosphamideinduced pneumonitis responds to cessation of the drug and corticosteroid therapy.

Pulmonary disorder associated with inflammatory bowel disease

- **Alveolitis**:
  - Restrictive defect.
  - A clinical picture similar to cryptogenic fibrosing alveolitis,
  - responsive to steroids,
  - **Seen more often in patients with Crohn's**, rather than ulcerative colitis.
- **Bronchiectasis**: lower zone signs would be more prevalent.
- **Bronchiolitis obliterans**: mixed obstructive/restrictive picture would be seen.

Lung disease in systemic sclerosis => Fibrosing alveolitis

History

- Lung disease is sometimes the first manifestation of systemic sclerosis,
- dyspnoea occurs in around 55% of patients.
- Cough is a less frequently reported symptom, but when it occurs it is dry and non productive.
- There is often a history of Raynaud's phenomenon.

Clinical findings

- Digital clubbing is rare because of the poor vasculature of the digits.
- Fine crackles are heard at the bases and are of a 'Velcro' character.
- Lung fibrosis occurs more commonly in patients with the Scl 70, anti-DNA topoisomerase autoantibody.
- Chest X-ray series have identified diffuse lung disease in up to 67% of patients.
- Oesophageal dilatation may be seen on chest X-ray and is almost universally present on high-resolution computed tomography.

Stridor

- Stridor is an abnormal sound produced by turbulent airflow through a partially obstructed airway at the level of the supraglottis, glottis, subglottis, or trachea.
- It can be inspiratory, expiratory or biphasic, although it is usually heard during inspiration.
- **Inspiratory stridor**
  - often occurs in children with croup.
  - It may be indicative of serious airway obstruction from severe conditions such as epiglottitis, a foreign body lodged in the airway, or a laryngeal tumor.
- **Expiratory stridor**
  - implies tracheobronchial obstruction.
  - Causes
    - can be congenital
    - tracheomalacia,

- previous surgery,
- reflux (particularly in paediatric cases).

Cricoarytenoid arthritis and stridor

- This is seen in up to 75% of patients **with rheumatoid arthritis.**
- **It can cause** sore throat, hoarse voice and **stridor**, but is often asymptomatic.
- symptoms can rapidly worsen in the postoperative period.
- The **flow-volume loop** can be abnormal, as can direct laryngoscopy and high-resolution CT of the larynx.
- Patients can need urgent tracheostomy and steroids, both orally and via joint injection.

Post-extubation stridor (PES)

- PES is a frequent complication of intubation, occurring in 2-16% of cases.
- It is caused by laryngeal oedema that results from damage to the mucosa of the larynx.
  - Mucosal damage is caused by pressure and ischaemia resulting in an inflammatory response.
  - Laryngeal oedema, in severe cases, can lead to acute respiratory compromise necessitating emergency reintubation.
- **Risk factors**
  - **Female gender**
    - **Female gender is a risk factor for both laryngeal oedema and PES**.
    - due to the female mucous membrane being less resistant to trauma and thinner than that in men.
  - Intubation >36 hours
  - Excessive cuff pressure
  - Large tube size, and
  - Tracheal infection.

Obstructive sleep apnoea (OSA)

Sleep apnoea causes include obesity and macroglossia

Overview

Definition

- Cessation of breathing during sleep because of upper airway obstruction.
- Apnea: respiratory arrests of ≥ 10 seconds
- Hypopnea: reduction of airflow by ≥ 50% for ≥ 10 seconds in combination with reduction of blood oxygenation by ≥ 3%

Epidemiology

- Sex: ♂ **>** ♀ (2:1)
- Prevalence: ~ 20–30% in men and 10–15% in women

Pathophysiology

- Obstruction of the upper airways → apnea → ↓ (PaO2), ↑ (PaCO2, hypercapnia)
  - → ↑ Hypoxic pulmonary vasoconstriction → ↑ pulmonary hypertension → Cor pulmonale
  - → ↑ Sympathetic activity → secondary hypertension
  - → Respiratory acidosis → renal compensation → increased HCO3 retention and decreased chloride reabsorption

Associations and Predisposing factors

- **Obesity**
  - **the most important risk factor**
- macroglossia:
  - acromegaly, hypothyroidism, amyloidosis
- large tonsils
- Marfan's syndrome
- Small pharyngeal opening
- Coexisting COPD
- Myxedema
- micrognathia/ retrognathia.
- Sedatives such as alcohol.
- **small or set-back mandible**
- Collar size greater than (17 inches) 43 cm is strongly associated.
  - **Neck size is the best predictor of obstructive sleep apnoea (OSA).**

Features

- Excessive daytime somnolence as a result of repeated arousals.
  - The dominant symptom is hypersomnolence (sleepiness).
- Repetative apnoeas (cessation of airflow for more than 10 seconds) and hypopnoeas (50% reduction in airflow for greater than 10 seconds)
- Loud snoring,
- Other more common symptoms include:
- Apparent personality changes ,
- True nocturnal polyuria, irritability
- hypertension
- less common
  - Reduced libido and erectile dysfunction
  - **erectile dysfunction**
    - Possibly related to hypoxaemia.
    - May respond to continuous positive airway pressure (CPAP) treatment.

Complications

- **Sleep apnoea is an independent risk factor for stroke** , **Sudden death** (and death from all causes),
- hypertension,
- Pulmonary hypertension and cor pulmonale

- Hypoxia-induced cardiac arrhythmia
- hyperglycaemia
  - obesity → insulin resistance → impaired glucose tolerance (IGT) → ↑ risk of type 2 diabetes.
- Risk of accidents (e.g., car crashes, occupational accidents) due to microsleep
- Increased risk of developing vascular dementia
- Poor sleep leads to increased appetite and obesity.

Assessment of sleepiness to diagnose (**excessive daytime sleepiness**)

- **Epworth Sleepiness Scale** - questionnaire completed by patient +/- partner
  - The Epworth sleepiness score can be between 0 and 24 (the higher the score, the more sleepy the patient is) and 6/24 is low.
  - A score of 11 or more is suggestive of OSA.
- Multiple Sleep Latency Test (MSLT) - measures the time to fall asleep in a dark room (using EEG criteria)

Diagnostic tests

- Sleep studies
  - Polysomnography: first-line method
    - **The gold standard diagnostic test is overnight polysomnography.**
    - Classic findings
      - Apnea and hypopnea events
        - Diagnose **OSA** if the **Apnoea-Hypopnoea Index (AHI):**
          - **≥**15 episodes/hour.
          - **≥** 5 episodes/hour + **additional symptoms** (eg: excessive daytime sleepiness, insomnia, mood disorder, or cognitive dysfunction) or **comorbidities** (eg: HTN, IHD, stroke)
        - To assess severity of obstructive sleep apnoea → Apnoea-Hypopnoea Index (AHI):
          - mild → 4-14 episodes,
          - moderate → 15-30 episodes,
          - severe → **>**30 episodes,
      - Oxygen desaturation
      - Arousal events on EEG
      - Bradycardia
      - Fragmentation of sleep

Management

- Weight loss.
  - **the definitive management**
  - takes time
- **CPAP** (continuous positive pressure airways ventilation),
  - **the most appropriate initial and quickest management** which acts as a splint to keep the airway open, leading to a normal night's sleep.
  - **the treatment of choice** for severe sleep apnoea.
- **In patients who do not want CPAP or who do not tolerate CPAP, Oral appliance or Upper airway surgery would be the next best option.**

  - Intra-oral devices (e.g. mandibular advancement)
  - may be used if CPAP is not tolerated
  - for patients with mild OSA where there is no daytime sleepiness.
- pharmacological agents
  - limited evidence to support use of pharmacological agents
  - **Modafanil** is a drug that is licensed for excessive daytime sleepiness in people with OSA treated with CPAP, as well as for narcolepsy.
- BiPAP (bilevel positive airways pressure ventilation)
  - is used if people are in respiratory failure: although this is rare with OSA alone, it can occur if they have an associated problem, such as obesity hypoventilation or COPD.
- avoid sedatives drugs/excess alcohol

Ref:

- **bestpractice.bmj.com 2018**
- **www.amboss.com 2018**

Obesity hypoventilation syndrome (OHS) (Pickwick syndrome)

Obesity + feature of OSA + abnormal ABG (↑ PCO2) → (OHS)

- Only affects **morbidly obese individuals**;
  - frequently accompanied by OSA,
- characterized by **diurnal hypercapnia**
- **Pathophysiology**:
  - ↑ production of CO_2 + sleep disordered breathing (e.g., OSA) + failure of ventilatory compensatory mechanisms → alveolar hypoventilation
- Clinical features → Same symptoms as those of OSA
- **Diagnostic criteria**
  - BMI ≥ 30 kg/m^2
  - Arterial blood gasses showing diurnal hypercapnia ($PaCO_2$ > 45 mm Hg) that cannot not be explained by another condition
  - Polysomnography shows hypoventilation during sleep with or without obstructive apnea events.
- **Treatment**
  - Weight loss
  - Nasal intermittent positive pressure ventilation

Pneumothorax (British Thoracic Society (BTS) guidelines 2010)

Classification

- **primary** pneumothorax : if there is no underlying lung disease,
- **secondary** pneumothorax : if there is.

Clinical features include:

- Sudden onset of chest pain, sometimes radiating to the shoulder

- Dyspnoea (may not be a dominant feature)
- Dry cough.
- **Left-sided pneumothoraces may be associated with a clicking sound** synchronous with the heart-beat and may occasionally be audible to the patient.
  - **Hamman's sign** (or 'crunch') is a crunching systolic sound heard over the sternal edge in mediastinal emphysema or **left apical pneumothoraces**.
  - It appears to be commoner in patients with small left-sided pneumothoraces.
- Young adult males, **often tall and slim**, are frequently affected by **spontaneous pneumothorax.**
- Patients with **Marfan** syndrome are prone to **recurrent pneumothoraces**.

Investigations

If the history and examination are suggestive of a pneumothorax and the patient being relatively stable, not in extremis (tension pneumothorax not suggested), the most appropriate first step would be → confirmation with chest x ray.

- Questions sometimes discuss the size of the pneumothorax in percentage terms rather than giving the interpleural distance.
  - A 50% pneumothorax is likely to have a rim of **>** 3cm.
  - A pneumothorax of 20% is therefore within the 2 cm limit
- As a very general rule of thumb:

Average interpleural distance	Approximate size of pneumothorax
0.5 cm	10%
1 cm	15 %
2 cm	**30%**
3 cm	45%
4 cm	60%

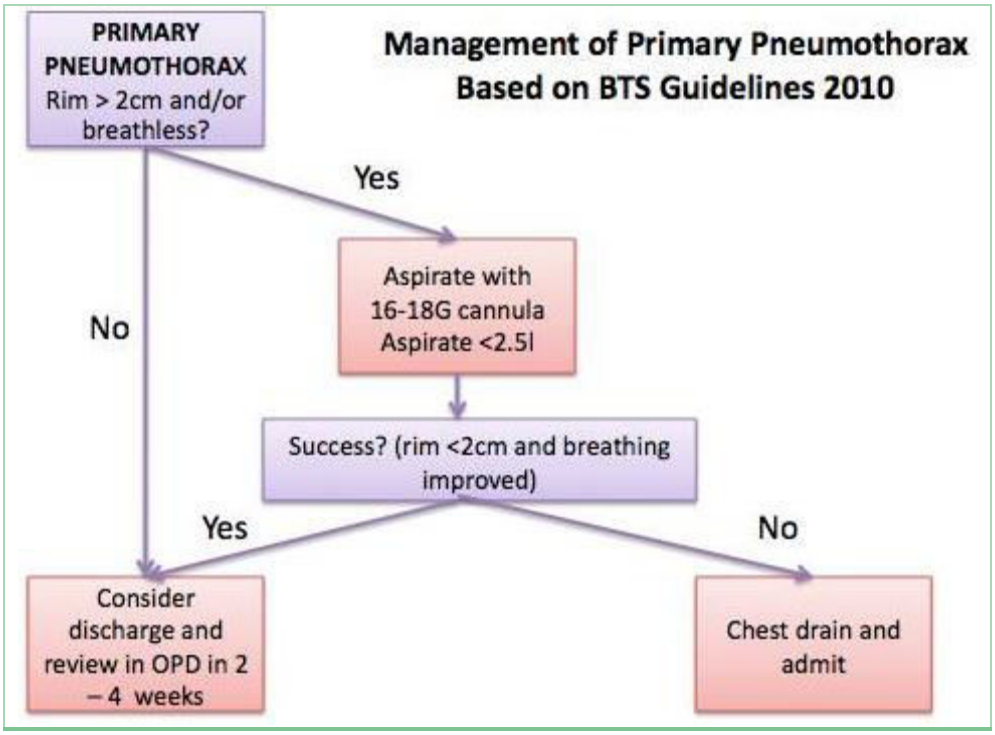
- **The next investigation to investigate the underlying cause of recurrent pneumothorax:**
  - **A CT scan is non-invasive and would therefore be a logical next step** in elucidating any abnormality which may predispose to pneumothorax.
  - If CT not help in pointing to a structural abnormality, and a further episode was to occur, then **video assisted thoracoscopy** would be considered.
  - Ultrasound scanning is mainly used in the diagnosis and management of pneumothorax in the trauma setting.

Primary pneumothorax

- **Definition:** Spontaneous primary pneumothorax is defined as:
  - age less than 50-years-old

- no significant smoking history,
  - minimal smoking history would be considered a primary pneumothorax
- no evidence of underlying lung disease.

- **Caused by the rupture of apical pleural blebs**.
- **Management**
  - if the rim of air is **<** 2cm and the patient is not short of breath then **discharge** should be considered
  - otherwise **aspiration** should be attempted
    - **If size is > 2 cm or the patient is breathless → chest aspiration**
  - if this fails (defined as **>** 2 cm or still short of breath) then a **chest drain** should be inserted
  - patients should be advised to avoid smoking to reduce the risk of further episodes - the lifetime risk of developing a pneumothorax in healthy smoking men is around 10% compared with around 0.1% in non-smoking men
  - if **following aspiration** the rim of air is **<** 2cm and the breathing has improved then discharge should be considered with outpatient review.
  - If a patient with a pneumothorax requires oxygen, this should be given at 10 L/min.



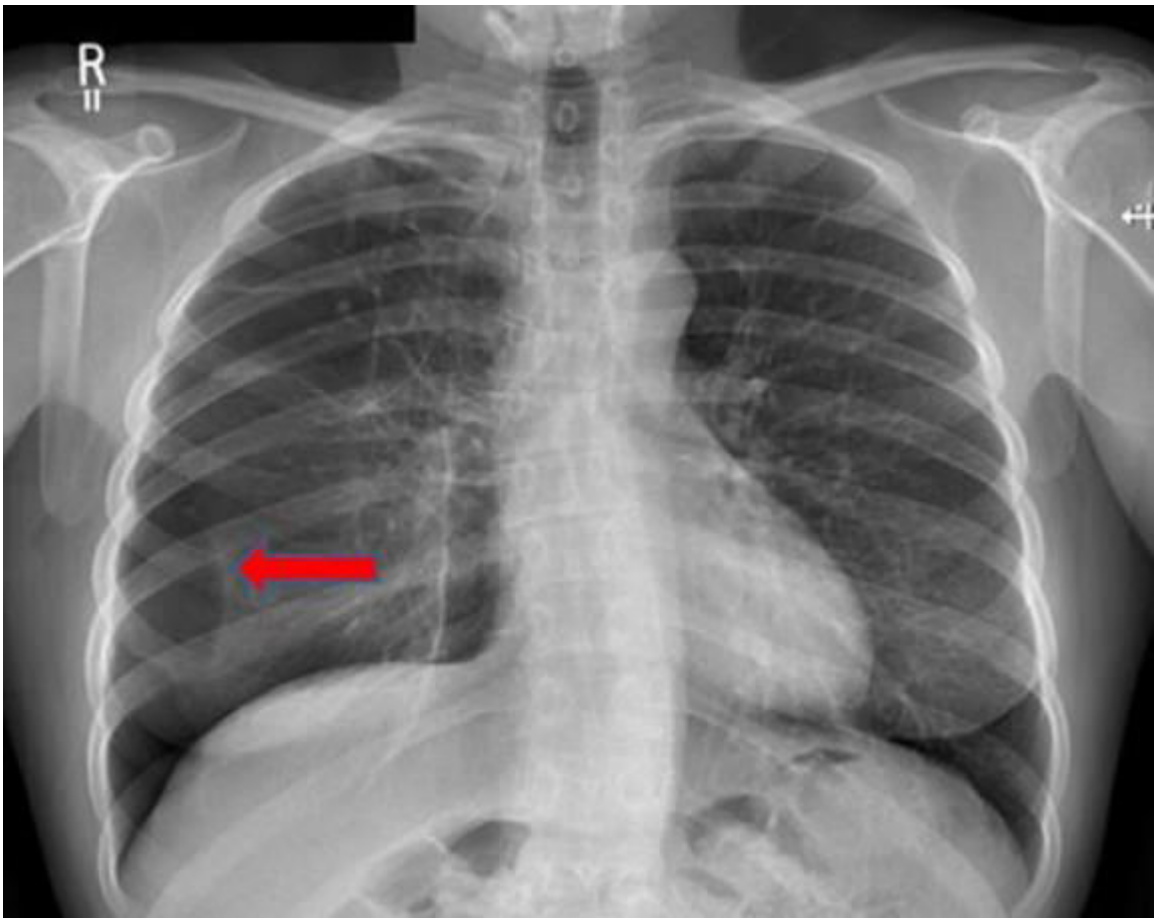
Asthmatics should be treated as a secondary pneumothorax

Secondary pneumothorax: Recommendations include:

- if the patient is **> 50 years** old and the rim of air is **>** 2cm **and/or** the **patient is short of breath** then a **chest drain** should be inserted.

- **Insert a small bore chest drain (8-14 FG) and attach to an underwater seal drain**

- otherwise aspiration should be attempted if the rim of air is between 1-2cm. If aspiration fails (i.e. pneumothorax is still greater than 1cm) a chest drain should be inserted.
- All patients should be admitted for at least 24 hours
- High flow oxygen should be given in all cases of pneumothorax, as it facilitates re-absorption of the pleural air, which is predominantly composed of nitrogen.
- if the pneumothorax is less than 1cm then the BTS guidelines suggest giving oxygen and admitting for 24 hours. Supplemental oxygen accelerates reabsorption of air by a factor of four
- **if the patient is very dyspneoic a drain should be inserted even though the pneumothorax is small (< 2cm).**
- All patients should be advised to avoid smoking to reduce the risk of further episodes



Chest x ray reveals a 3.2 cm rim of air around the lung.

Iatrogenic pneumothorax:

- less likelihood of recurrence than spontaneous pneumothorax
- majority will resolve with observation, if treatment is required then aspiration should be used
- ventilated patients need chest drains, as may some patients with COPD

Tension pneumothorax

- should be suspected in people on mechanical ventilators or nasal non-invasive ventilation who suddenly deteriorate or develop EMD arrest, and is frequently missed in the intensive care unit setting.
- Treatment:
  - needle thoracocentesis
    - Advanced Trauma Life Support (ATLS) guidelines recommend the use of a 3-6-cm-long cannula to perform needle thoracocentesis.
    - However, in 57% of patients with tension pneumothorax the thickness of the chest wall has been found to be greater than 3 cm.
    - It is therefore recommended that a cannula length of at least 4.5 cm should be used.
    - The cannula should be left in place until bubbling is confirmed in the underwater-seal system to confirm proper function of the intercostal tube.

Chest drains for pneumothorax

- **Insertion of a small bore chest drain using a Seldinger technique in the mid-axillary line**
  - The most appropriate point for chest drain insertion is in the 'safe triangle', in the mid-axillary line.
  - Scarring from insertion is less obvious than in the second intercostal space and mid-clavicular line, particularly important in women.
- **insert 14F drain immediately above a rib margin**
- **When the patient coughs, nothing happens. When he breathes in and out, the fluid in the tube moves up and down that means → Air is no longer draining from the pleural space, but the drain is still working.**
  - The fluid level rising and falling in the drain (swinging) shows that it is still in contact with the pleural space and the fluid level is moving with respiration.
- Air is not bubbling out of the drain when the patient coughs because the air has stopped draining from the pleural space and the lung has re-inflated.
- **If a drain does not bubble or swing, then it is blocked or kinked and is not working**.
- With a simple pneumothorax, there would be minimal fluid drainage from the chest.
- **Suction** is necessary **if the drain is still bubbling but the lung has not fully re-inflated on the chest X-ray.**
  - **After chest drain** if pneumothorax fails to re-expand or if there is a persistent air leak (bubbling present) **after 48 hours**, then you should → refer the patient to a respiratory specialist because **negative suction** might be required.
  - The normal intrapleural pressure is -3.4 cm H2O during expiration, rising to -8 cmH2O during inspiration**. Negative suction should be started at -10 to -20 cmH2O (-1 to -2 kPa = -7.5 to -15 mmHg) using a high-volume/low-pressure suction system**.
    - If high-volume/high-pressure suction is used, then high-airflow suction might be generated, which can lead to air stealing, hypoxaemia and/or the persistence of air leaks.
- If appropriate suction fails to result in adequate re-expansion by 5-7 days in patients without pre-existing lung disease (earlier if there is lung disease), then → **referral to a thoracic surgeon is indicated.**

- If a repeat chest X-ray reveals a persistent pneumothorax despite low-pressure, large-volume suction, you confirm on examination that the chest drain appears to have remained in position and is bubbling → **Cardiothoracic surgical referral**
- This patient appears to have developed a **bronchopleural fistula**, as evidenced by failure of the lung to re-inflate despite the drain remaining in place for 48 h and low-pressure suction being deployed.

Video assisted thoracoscopic surgery is indicated in:

- **Second ipsilateral pneumothorax**
  - The management of choice for a second unilateral pneumothorax in a fit individual is **referral for bullectomy and pleurectomy.** known as video assisted thoracoscopic surgery (VATS).
- Bilateral spontaneous pneumothorax
- Spontaneous haemothorax
- Persistent air leak (more than five to seven days of drainage)
- Certain occupations, for example, pilots or divers.

Chemical pleurodesis through the chest drain:

- used in **older** patients or frail individuals with **recurrent** pneumothorax, where surgery would be high risk.
- Failure rates can be 10-20%.

Open pneumothorax (stab wound to the chest)

- the most appropriate **next best step** in management → **Partially occlusive dressing** (gauze taped on three sides over the wound)
  - dressings taped at 3 out of 4 sides of the lesion
  - is temporary treatment to prevent further expansion of the pneumothorax until the diagnosis has been confirmed and definitive treatment (i.e., tube thoracostomy, surgery) is available.
  - The dressing works by occluding the wound during inspiration (e.g., "plugging" the wound). The open side allows air to pass out of the wound on expiration.

Fitness to fly

- Air travel is acceptable once the pneumothorax has fully resolved.
- Pneumothorax is an absolute contraindication,
- CAA suggest patients may travel 2 weeks after successful drainage if there is no residual air.
- The British Thoracic Society now recommend **1 week post check x-ray**.
- However, the British Thoracic Society emphasises that the recurrence risk only significantly falls after 1 year, and therefore in the absence of a definitive surgical procedure patients might wish to defer travel until then.

Diving

- The British Thoracic Society (BTS) guidelines state: *'Diving should be permanently avoided unless the patient has undergone bilateral surgical pleurectomy and has normal lung function and chest CT scan postoperatively.'*

Pleural effusion (British Thoracic Society (BTS) produced guidelines in 2010)

Exudate (> 30g/L protein)	Transudate (< 30g/L protein)
• infection: pneumonia, TB, sub-phrenic abscess • connective tissue disease: RA, SLE • neoplasia: lung cancer, mesothelioma, metastases • pancreatitis • pulmonary embolism • Dressler's syndrome • yellow nail syndrome	• heart failure • hypoalbuminaemia ➢ liver disease, ➢ nephrotic syndrome, ➢ malabsorption • hypothyroidism • Meigs' syndrome

Investigation

Imaging

- Posterior-anterior (PA) chest x-rays should be performed in all patients
- **Ultrasound** is recommended: it increases the likelihood of successful pleural aspiration and is sensitive for detecting pleural fluid septations
  - **Ultrasound thorax is the next most appropriate step after chest x-ray**
  - Ultrasound, followed by drainage of any large pockets of fluid, is much more effective, and will yield fluid samples for culture, pH, glucose and lactate dehydrogenase (LDH) testing.
  - **Ultrasound is better for pleural imaging than CT.**

Patients with cytology negative exudative effusions

- **Local anaesthetic thoracoscopy has a high yield and is now the investigation of choice in patients with cytology negative exudative effusions.**

Pleural aspiration

- ultrasound is recommended to reduce the complication rate
- a 21G needle and 50ml syringe should be used
- fluid should be sent for pH, protein, lactate dehydrogenase (LDH), cytology and microbiology

Light's criteria

- developed to distinguish between a transudate and an exudate.
- The BTS recommend using the criteria for borderline cases:
  - exudates have a protein level of >30 g/L, transudates have a protein level of <30 g/L
  - **if the protein level is between 25-35 g/L, Light's criteria should be applied.**
- An exudate is likely if at least one of the following criteria are met:
  - **pleural** fluid **protein** divided by **serum** protein >0.5

- **pleural** fluid **LDH** divided by **serum** LDH >0.6
- **pleural** fluid **LDH** more than two-thirds the upper limits of normal **serum** LDH

Pleural infection

- all patients with a pleural effusion in association with sepsis or a pneumonic illness require diagnostic pleural fluid sampling
- if the fluid is purulent or turbid/cloudy a **chest tube** should be placed to allow drainage
- if the fluid is clear but the pH is less than 7.2 in patients with suspected pleural infection a **test tube** should be placed

Rheumatoid pleural effusion

- Around 5% of patients with RA develop pleural effusions.
- mainly occur in older male patients who have subcutaneous nodules.
- About a quarter of patients experience bilateral effusions.
- Characterized by:
  - **Low glucose (< 1.6 mmol/l)**
  - High lactate dehydrogenase (> 700 IU/l)
  - Low pH (< 7.2)
  - high rheumatoid factor titre (> 1:320)
  - High cholesterol levels
- Treatment
  - The majority of these effusions resolve spontaneously within 3 months and require no intervention.
  - Management is with treatment of RA in general.
  - Occasionally they persist and massive pleural thickening develops. These patients might need decortication if they are symptomatic.

Other characteristic pleural fluid findings:

- Low glucose (less than 3.3 mmol/L):
  - rheumatoid arthritis,
    - **The lowest levels are found in rheumatoid effusions and empyema** with pleural glucose in rheumatoid effusions rarely being above 1.6 mmol/L.
  - empyema
  - tuberculosis,
  - malignancy.
  - Oesophageal rupture
  - Lupus
- raised amylase:
  - pancreatitis,
  - oesophageal perforation
- Heavy blood-staining:
  - mesothelioma,
  - pulmonary embolism,
  - tuberculosis, or
  - malignancy.
- Rheumatoid effusion is unlikely when peripheral joint disease is so well controlled.

- **Pleural fluid eosinophilia (> 10%) makes malignancy and TB less likely, and suggests air in the pleural cavity.**
- The presence of antinuclear factor is virtually diagnostic of systemic lupus erythematosus (SLE).

Video-assisted thoracoscopic surgery (VATS) :

- An underlying pleural pathology should be strongly suspected in the case of thickened pleura, restrictive lung function and non-specific constitutional symptoms.
- VATS is appropriate to differentiate pleural thickening between organised empyema or mesothelioma, and also to obtain tissue to differentiate mesothelioma from other primary or metastatic cancers.
- VATS is optimally performed with a small amount of pleural fluid in situ.
- Indications
  - It should be considered after other non-invasive tests have proven negative.
- Advantages of **VATS**
  - Ensure adequate pleural biopsies are obtained
  - Drain pleural fluid
  - Allow pleurodesis to prevent recurrence.
- pleural procedures **should not take place out-of-hours** except in an emergency due to increased risk

Indications for chest tube insertion in patients with an infected pleural effusion are:

- Presence of organisms on a Gram stain of the pleural fluid
- Frankly purulent pleural fluid
- **Pleural pH < 7.2** in the setting of an infected pleural effusion
- Loculated pleural effusions
- Poor clinical progress despite antibiotic treatment

Management of recurrent pleural effusion

- Options for managing patients with recurrent pleural effusions include:
  - recurrent aspiration
  - pleurodesis
  - indwelling pleural catheter
  - drug management to alleviate symptoms e.g. opioids to relieve dyspnoea

Complications of plural fluid drainage

- **Re-expansion pulmonary oedema**
  - This is a potentially life-threatening condition which can **occur when a large volume of fluid or air is rapidly drained**,
  - It is suggested by sudden onset of shortness of breath, cough and hypoxaemia following chest drain insertion.

Meigs syndrome

- **Characterised by the presence of a benign ovarian fibroma, associated with ascites and a right-sided pleural effusion.**
- The average age at presentation is 48 years.
- Meigs syndrome is associated in 0.004% of ovarian tumours.
- The aetiology of the pleural effusion is thought to be related to the size of fibroma, leading to accumulated peritoneal ascites that flows into the pleural cavity via the lymphatics or via abdominal-pleural communications (via the foramen of Bochdalek).
- Removal of the ovarian mass is associated with resolution of the ascites and pleural effusion and patients have an excellent prognosis.

Pleural effusion in rheumatoid arthritis

- Around 5% of patients with rheumatoid arthritis develop pleural effusions. These mainly occur in older male patients
- who have subcutaneous nodules. About a quarter of patients experience bilateral effusions.
- These effusions are characterised by some or all of the following:
- Low glucose (< 1.6 mmol/l)
- High lactate dehydrogenase (> 700 IU/l)
- Low pH (< 7.2)
- A high rheumatoid factor titre (> 1:320)
- High cholesterol levels
- The majority of these effusions resolve spontaneously within 3 months. Occasionally they persist and massive pleural
- thickening develops. These patients might need decortication if they are symptomatic.

Contraindications for Thoracentesis

absolute contraindications:

- uncooperative patient
- coagulation disorders that cannot be corrected

Relative contraindications:

- cases in which the site of insertion has known bullous disease (e.g. emphysema),
- use of positive end-expiratory pressure (PEEP, in mechanical ventilation)
- only one functioning lung (due to diminished reserve).

The aspiration should not exceed 1L as there is a risk of development of pulmonary edema.

Chylothorax

- A chylothorax occurs when lymph fluid from the thoracic duct or its tributaries accumulates in the pleural space. Chylous ascitic fluid can also flow into the pleural space.

- The etiologies of chylothorax can be categorized as nontraumatic or traumatic .Malignancy is the leading cause of nontraumatic chylothorax.
- Chyle (lymphatic fluid of intestinal origin) has a high content of triglycerides in the form of chylomicrons, which produce the milky, opalescent appearance of lymphatic fluid.
- The diagnosis of chylothorax is based on the pleural fluid triglyceride level .A triglyceride concentration greater than 110 mg/dL (1.24 mmol/L) strongly supports the diagnosis.
- lymphatic imaging typically performed when the diagnosis of thoracic duct tear is uncertain after pleural fluid analysis and chest computed tomography, when a chylothorax recurs after thoracic duct ligation, or when anomalous thoracic duct anatomy is suspected.

- It is differentiated from **empyema** because the latter yields a clear supernatant on centrifugation.
- **Pseudochyle** is differentiated from chylothorax by :
  - high cholesterol pleural effusion, **(** cholesterol greater than 200 mg/dL (5.18 mmol/L) and a triglyceride below 110 mg/dL (1.24 mmol/L).
  - Cholesterol crystals are diagnostic if present. chylomicrons, which are associated with chylothoraces, are absent.
  - and is typically seen in patients with tuberculosis.

Causes of chylothorax

Common causes

- Trauma (eg surgery)
- Malignancy, usually a lymphoma (metastatic lung deposits can cause chylothorax, but less commonly)

Less common causes:

- congenital :absence of thoracic ducts , Down syndrome, Noonan syndrome)
- filariasis
- tuberculous mediastinal lymphadenitis
- lymphangioleiomyomatosis (occurring much more commonly in
- females of child bearing age)
- yellow nail syndrome
- CVD :left subclavian venous thrombosis , thoracic aortic aneurysm, , venous thrombosis, mitral stenosis, heart failure,
- others : pleuritis, cirrhosis , lupus, tuberculosis, sarcoidosis, amyloidosis, nephrosis, thyroid goiter, tuberous sclerosis,

Haemothorax

- A bleeding into the pleural space,
- **Diagnosed** on the basis of having a haematocrit that is more than half that of peripheral blood. This distinguishes it from a blood-stained effusion.
- **Management**
  - The treatment of choice is to **insert a large intercostal drain (28-32 F)**
  - If this reveals continued bleeding, a thoracotomy might be required.
  - Surgery is not indicated simply to remove any residual blood clots because there is spontaneous lysis with no residual damage in the majority of patients.

Pleural calcification

Unilateral pleural calcification

- most commonly occurs as a chronic change secondary to:
  - pleural infection (particularly tuberculous empyema),
  - pyogenic empyema, or
  - **haemothorax.**

Bilateral pleural calcification

- Common
  - calcified pleural plaques are usually considered asbestos-related.
- Other rarer causes
  - radiation exposure,
  - hyperparathyroidism,
  - pulmonary infarction, and
  - pancreatitis.

Mesothelioma

Basics

- Malignancy of mesothelial cells of pleura
- Metastases to contralateral lung and peritoneum
- Right lung affected more often than left

Risk factors and pathophysiology

- Exposure to asbestos is the primary risk factor
- The role of cigarette smoking has not been proved
- **Loss of material from chromosome 22 is an abnormality commonly seen in mesothelioma**, and may contain code for tumour suppressor genes

Features

- Dyspnoea, weight loss, chest wall pain
- Clubbing
- 30% present as painless pleural effusion
- Only 20% have pre-existing asbestosis
- History of asbestos exposure in 85-90%, latent period of 30-40 years

Investigation/diagnosis

- suspicion is normally raised by a chest x-ray showing either a pleural effusion or pleural thickening
  - (Be aware that only 20% of mesothelioma patients present with radiographic changes consistent with asbestosis, although the majority present with pleural abnormalities).
- the next step is normally a **pleural CT**.
- if a pleural effusion is present fluid should be sent for MC&S, biochemistry and cytology (but **cytology is only helpful in 20-30% of cases**)
- **Thoracoscopy**

- local anaesthetic thoracoscopy is increasingly used to investigate cytology negative exudative effusions as it has a high diagnostic yield (around 95%).
- Tissue can be obtained from **thoracoscopy with biopsy** from abnormal looking areas
- **the most appropriate investigation to deliver the diagnosis.**
- if an area of pleural nodularity is seen on CT then an image-guided pleural biopsy may be used
  - CT might show pleural thickening and nodularity, which would be amenable to either CT-guided biopsy or thoracoscopy.
  - CT pleural biopsy has been shown to have a diagnostic advantage over a blind Abrams' biopsy in cytologically negative malignant pleural effusions with pleural thickening, with a sensitivity of 87% vs 47%.

Management

- Symptomatic
- Industrial compensation
- Chemotherapy
  - Patients with good performance status could be considered for palliative chemotherapy, which can result in tumour shrinkage.
- Radiotherapy
  - Radiotherapy to the thoracoscopy tract site is effective for preventing tumour seeding and growth and is recommended after pleural procedures. This is routine practice, along with providing symptomatic treatment.
  - Palliative radiotherapy
    - can be useful to reduce chest pain, shortness of breath and to relieve superior vena cava obstruction.
    - There is no evidence of benefit for radiology at the surgical port sites and surgical resection remains controversial.
- Surgery if operable
- Chest drains are usually reserved for recurrent pleural effusions and those that fail talc pleurodesis.

Prognosis

- poor
- The median survival after diagnosis is 2 years

Pulmonary eosinophilia

The defining characteristics of pulmonary eosinophilia include:

- peripheral blood eosinophilia
- radiographic evidence of pulmonary parenchymal disease;
- histopathologic evidence of lung tissue eosinophilia in a transbronchial or open lung biopsy specimen;
- increased eosinophils in bronchoalveolar lavage fluid (eg, >10 %). As peripheral blood eosinophils are not always increased in eosinophilic lung diseases, the other methods

(bronchoalveolar lavage [BAL], biopsy) are sometimes needed to document lung eosinophilia.

Causes of pulmonary eosinophilia

- Churg-Strauss syndrome
- allergic bronchopulmonary aspergillosis (ABPA)
- Loffler's syndrome
- eosinophilic pneumonia
- hypereosinophilic syndrome
- tropical pulmonary eosinophilia
- drugs: nitrofurantoin, sulphonamides
- less common: Wegener's granulomatosis

Cryptogenic pulmonary eosinophilia

- In this condition pulmonary eosinophilia occurs with **no identifiable cause**
- patients usually non-atopic (but 10% have had previous asthma)
- **When the disease is self-limiting and lasts less than 1 month it is known as Loeffler syndrome.**

Feature

- Systemic features: Malaise, fever, weight loss
- asthma (in around 50%)

Investigations

- widespread, mainly peripheral pulmonary infiltrates
- blood eosinophilia
- Raised ESR

Treatment

- The disease responds to steroid treatment, which needs to be continued for about 1 year.

Chronic eosinophilic pneumonia (CEP)

Definition

- CEP is an idiopathic disorder characterized by an abnormal accumulation of eosinophils in the interstitial and alveolar spaces

Feature

- dyspnea, cough, fever, and wheezing over three weeks to several months.

Diagnosis

- Chest imaging
  - showing predominantly peripheral or pleural-based opacities described as the "photographic negative" of pulmonary edema, are virtually pathognomonic for CEP
  - Peripheral alveolar filling infiltrate **predominantly in the upper lobes** on a chest radiograph is typical of chronic eosinophilic pneumonia.

- Bronchoalveolar lavage (BAL):

- To look for eosinophilia → cell count showing eosinophilia (≥25 %).
- To exclude infection.

Treatment: prednisolone

Tropical pulmonary eosinophilia

- associated with ***Wuchereria bancrofti*** infection (a condition associated with microfilaria).
- seen in the Asian subcontinent
- Presents with cough, wheeze, fever, lassitude and weight loss.
- The treatment of choice is a 10-14-day course of **diethylcarbamazine** to eradicate the infection.

Loffler's syndrome

- transient CXR shadowing and blood eosinophilia
- thought to be due to parasites such as *Ascaris lumbricoides* causing an alveolar reaction
- presents with a fever, cough and night sweats which often last for less than 2 weeks.
- generally a self-limiting disease

Organising pneumonia

- Organising pneumonia (formerly called bronchiolitis obliterans organizing pneumonia or BOOP), classified in to :
  1- Cryptogenic organizing pneumonia (COP): idiopathic
  2- secondary organizing pneumonia: can be seen in association with connective tissue diseases, a variety of drugs, malignancy, and other interstitial pneumonias

- is a type of diffuse interstitial lung disease that affects the distal bronchioles, respiratory bronchioles, alveolar ducts, and alveolar walls.
- The primary area of injury is within the alveolar wall.
- Onset is typically in the fifth or sixth decades of life,
- men and women affected equally

Causes of organizing pneumonia

- Cryptogenic organizing pneumonia (previously called bronchiolitis obliterans organizing pneumonia)
- Organizing diffuse alveolar damage
- Diffuse alveolar hemorrhage
- Drugs
  - Amiodarone
  - Cocaine
- Infections (organizing)
  - Mycoplasma
  - Viral
  - Pneumocystis jirovecii (carinii)
  - Bacterial
- Connective tissue diseases

- Hypersensitivity pneumonitis
- Idiopathic pulmonary fibrosis (minor scattered foci)
- Aspiration

Feature

- Persistent nonproductive cough (72%)
- Dyspnea (66 %)
- Fever (51 %)
- Malaise (48 %)
- Weight loss of greater than 10 pounds (57%)
- Hemoptysis is rarely reported as a presenting manifestation of COP

Cryptogenic organising pneumonia (COP)

Definition

- non-specific inflammatory pulmonary process, with buds of **granulation tissue forming in the distal air spaces**.
- Organising pneumonia can have a number of causes, including connective tissue disease, infection and drugs, but **if there is no obvious cause it is called 'cryptogenic'.**

Feature

- dry cough
- non-specific symptoms of fever, malaise, anorexia and weight loss.

Investigations

- ↑WBC and C-reactive protein (CRP) levels.
- chest X-ray
  - can show consolidation, nodules or thickened septal lines.
  - The consolidation typically occurs in different places at different times.
  - The most common chest imaging features are **multiple ground-glass or consolidative opacities.**
- **Pulmonary function tests** usually show a **restrictive** pattern with an associated gas transfer defect.
- **CT** findings are characteristic, with multiple patchy alveolar opacities, which often spontaneously migrate.
  - **Reversed halo sign**, better known as an **atoll sign**.
    - a region of ground-glass opacity surrounded by crescentic or annular denser tissue .
    - Cryptogenic organising pneumonia is the most common condition described in immunocompetent patients with this sign (found in 20% of the cases of COP)

Diagnosis

- The diagnosis might be made on the basis of CT alone, or on transbronchial or open lung biopsy.
- **Histopathologic characteristic lesions** include excessive proliferation or “plugs” of granulation tissue within alveolar ducts and alveoli, associated with chronic inflammation in the surrounding alveoli.
- The diagnosis requires histopathologic identification of a predominant pattern of organizing pneumonia and the exclusion of any possible cause

Differential diagnosis

- Recurrent lobar bacterial infection is unusual in an immunocompetent adult.
- Eosinophilic pneumonia leads to flitting peripheral chest X-ray shadows.
- **Lymphangioleiomyomatosis**
  - rare idiopathic disease, affecting women of reproductive years.
  - characterised by infiltration of immature muscle cells into the bronchiolar and alveolar walls. This results in destruction of the airways, cyst formation and progressive decline in lung function.
  - Typical radiological findings are of interstitial lung disease,
  - **recurrent pneumothoraces and chylous effusions.**
    - If this occurs in men then tuberous sclerosis
  - CT shows multiple small cysts.
  - Treatment is lung transplantation.
  - Patients are asked to avoid taking the oral contraceptive pill, pregnancy and long-haul flights.
  - Conservative management includes progesterone supplements but the response is variable.
- Pulmonary alveolar proteinosis
  - a rare defect in which the alveoli become filled with proteinaceous material that cannot be cleared. CT shows air-space shadowing.

Treatment

- Mild stable disease:
  - monitor without therapy & reassessed at 8 to 12 week intervals
- For symptomatic patients with moderate or severe disease:
  - oral prednisolone
  - COP usually responds to corticosteroid.
    - Initial doses of 0.75–1 mg/kg, weaning over 6–12 months, are reasonable.
- Persistent or gradually worsening disease:
  - methylprednisolone 500 to 1000 mg intravenously each day for three to five days rather than a lower oral dose
- Failure to respond to systemic glucocorticoids:
  - cyclophosphamide or azathioprine

Prognosis

- Relapse is common

Bronchiolitis obliterans organizing pneumonia (BOOP)

Definition

- BOOP is differentiated from organizing pneumonia, which is defined by the presence of granulation tissue in the distal air spaces; but when **associated with granulation tissue in the bronchiolar lumen**, organizing pneumonia is qualified by the term bronchiolitis obliterans (BO). Hence the term ‘bronchiolitis obliterans organizing pneumonia’ is used.
- BOOP is characterized by the presence of **granulation tissue** in the **bronchiolar** lumen, **alveolar ducts** and some **alveoli**, associated with a variable degree of interstitial and airspace infiltration by mononuclear cells and foamy macrophages.

Feature

- Approximately 50% of patients present with influenza-like illness followed by a short illness of few months′ duration characterized by a persistent nonproductive cough, effort dyspnea, low-grade pyrexia, malaise and weight loss.
- Less common symptoms include pleuritic chest pain and hemoptysis.
- fine, dry lung crepitations is common.

Causes

- most cases are idiopathic.
- Association
  - Associated collagen vascular disorder is found in 16%
  - inhalation exposure to toxins in 17%
  - organ transplantation, especially with bone marrow transplant
  - post infection: bacterial , viral, CMV pneumonia
  - Radiotherapy
  - Drugs: phenytoin , carbamazepine

Investigations

- chest radiographs revealed that bilateral patchy infiltrates and reticulonodular opacities
- **HRCT**
  - Patchy ground-glass opacities in a subpleural and/or peribronchovascular distribution (80%).
  - Bilateral basal airspace consolidation (70%)
  - Bronchial wall thickening and cylindrical bronchial dilatation in areas of air bronchogram (70%)
  - the consolidation in BOOP commonly involves the lower zones
- **Cytological profile of bronchoalveolar lavage**
  - reveals a mixed cell pattern with an increase in lymphocytes (20-40%),
  - ↑lymphocytes differentiate the condition from parenchymal pulmonary disease.
    - Neutrophils (10%), eosinophils (5%), mast cells, foamy macrophages and occasional plasma cells increase in patients with **Idiopathic pulmonary fibrosis** (**IPF**).
- **Lung biopsy is the preferred method for establishing the diagnosis.**
  - Most patients with BOOP require open-lung biopsy for diagnosis.
- ESR is usually elevated,
- pulmonary function tests show a **restrictive** pattern.

Treatment

- BOOP responds well to corticosteroid therapy, while **Usual interstitial pneumonia** (**UIP**) and **IPF** usually does not.
  - The dosage is generally 0.75 mg/kg/day for 1 to 3 months, then 0.50 mg/kg mg/day for 3 months, then 10 to 20 mg/day or every other day **for a total of 1 year.**
- Approximately 30% of the patients experience relapse upon withdrawal of treatment.

Pulmonary arterial hypertension (PAH)

Definition

- sustained elevation in mean **pulmonary arterial pressure of greater than 25 mmHg at rest or 30 mmHg after exercise**.
- pulmonary artery wedge pressure ≤15 mmHg and pulmonary vascular resistance > 3 Wood units.

Pathophysiology

- Endothelin-1 is a potent pulmonary vasoconstrictor produced in increased amounts in pulmonary hypertension, which also induces the proliferation of pulmonary vascular smooth muscle.
  - Bosentan is used to treat pulmonary hypertension by competitively antagonizing endothelin, thereby decreasing pulmonary vascular resistance.

WHO Classification

- Group 1: Pulmonary arterial hypertension (PAH)
  - Idiopathic
    - previously termed primary pulmonary hypertension (PPH)
  - familial
    - account for 15-20% of cases,
    - due to an inherited mutation in the **BMPR2 gene** which codes for a receptor in the TGF beta family.
    - The gene **BMPR2** normally inhibits vascular smooth muscle proliferation, and a mutation in this gene can lead to increased **proliferation of smooth muscle.**
    - The gene for primary pulmonary hypertension has now been mapped to chromosome 2,
  - associated conditions:
    - collagen vascular disease,
    - congenital heart disease with systemic to pulmonary shunts,
    - HIV,
    - drugs and toxins,
      - appetite suppressants
      - **amphetamines**
      - cocaine
    - sickle cell disease
  - persistent pulmonary hypertension of the newborn

- Group 2: Pulmonary hypertension with left heart disease
  - left-sided atrial, ventricular or valvular disease such as left ventricular systolic and diastolic dysfunction, mitral stenosis and mitral regurgitation
- Group 3: Pulmonary hypertension secondary to lung disease/hypoxia
  - COPD
  - interstitial lung disease
  - sleep apnoea
  - high altitude

- Group 4: Pulmonary hypertension due to thromboembolic disease
- Group 5: Miscellaneous conditions
  - lymphangiomatosis e.g. secondary to carcinomatosis or sarcoidosis

Features

- exertional dyspnoea is the most frequent symptom
- chest pain and syncope may also occur
- physical signs:
  - left parasternal heave, (due to right ventricular hypertrophy)
  - loud second pulmonary sound (P2),
  - pansystolic murmur of tricuspid regurgitation
  - early diastolic murmur of pulmonary insufficiency.

Mechanisms and causes:

- Pulmonary venous hypertension
  - Increased left atrial pressure: most commonly caused by left ventricular dysfunction as in congestive cardiac failure, which causes an elevation in PA pressure by increased back-pressure through the lungs.
  - mitral stenosis or insufficient,
  - fibrosing mediastinitis
  - veno-occulsive disease.
- mechanical obstruction of the pulmonary arteries
  - Acute or chronic thromboembolism.
- hypoxia leads to constriction of the pulmonary arteries
  - Interstitial lung disease (ILD)
  - Chronic obstructive airways disease (COAD)
  - Acute respiratory distress syndrome (ARDS)

Pulmonary hypertension in pregnancy:

- **Pregnant with pulmonary hypertension have a high mortality of at least 30%** - some authors put it at 50% - seemingly **highest immediately after delivery**.
- **Gold standard for diagnosis is right-heart catheterisation**, but echocardiogram can also give useful information.
- The mainstay of treatment is with pulmonary vasodilators, but use in pregnancy needs to be discussed with the cardiology and obstetric team, and a decision made regarding early delivery of the baby.
- **Drugs**:
  - anorectic (fenfluramine, dexfenfluramine),
  - **amphetamine**
  - Cocaine (but not heroin).

Investigations

- **Right heart catheterization** is the best investigation for diagnosing pulmonary hypertension,

- **Pulmonary angiography is the definitive diagnostic test**. It shows:
  - narrowed segmental pulmonary arteries,
  - sometimes accompanied by post-stenotic dilatation,
  - irregularity of the intima,
  - luminal narrowing of the central arteries
  - oddly shaped vessels.
- Pulmonary fibreoptic angioscopy is useful to define surgical accessibility.
- Ventilation/perfusion lung scans typically show:
  - one or more mismatched segmental or larger perfusion defects,
  - most patients have several bilateral mismatched perfusion defects.

Management

- First step: Treat any underlying conditions, for example with anticoagulants or oxygen.
- Second step: perform **acute vasodilator testing** to decide on the appropriate management strategy.
  - Acute vasodilator testing aims to decide which patients show a significant fall in pulmonary arterial pressure following the administration of vasodilators such as intravenous epoprostenol or inhaled nitric oxide
  - If there is a positive response to acute vasodilator testing:
    - oral calcium channel blockers
  - If there is a negative response to acute vasodilator testing:
    - endothelin receptor antagonists: bosentan
    - phosphodiesterase inhibitors: sildenafil
    - prostacyclin analogues: treprostinil, iloprost
- **Sequence of treatment:**
  - 10-15% of patients benefit from calcium channel antagonists.
  - If symptoms going on the ideal next step would be an endothelin A receptor antagonist, such as Bosentan.
  - following Bosentan, another oral therapy such as Sildenafil could be a logical next step,
  - followed by Prostacyclin.
  - Prostacyclin is currently delivered by infusion, oral prostaglandin receptor agonists are currently under development.

Complication

- Cor pulmonale (right ventricular failure),
  - presenting as jugular venous distension and hepatomegaly.

Prognosis:

- Several studies report a mean survival of only 2.5 years from diagnosis,
- Patients with mean pulmonary artery pressures over 30 mmHg have a 5-year survival rate of 30%, but this rate falls to 10% if the mean pulmonary artery pressure is over 50 mmHg.

Respiratory tract infections: NICE guidelines (2008)

No antibiotic prescribing or delayed antibiotic prescribing approach

- recommended for patients with:
  - acute otitis media,
  - acute sore throat/acute pharyngitis/acute tonsillitis,
  - common cold,
  - acute rhinosinusitis
  - acute cough/acute bronchitis.

Immediate antibiotic prescribing approach

- may be considered for:
  - children younger than 2 years with bilateral acute otitis media
  - children with otorrhoea who have acute otitis media
  - patients with acute sore throat/acute pharyngitis/acute tonsillitis when 3 or more Centor criteria are present
    - The Centor criteria are as follows:
      1. presence of tonsillar exudate
      2. tender anterior cervical lymphadenopathy or lymphadenitis
      3. history of fever
      4. absence of cough
    - if 3 or more of the criteria are present there is a 40-60% chance the sore throat is caused by Group A beta-haemolytic Streptococcus
  - If the patient is at risk of developing complications:
    - systemically very unwell patient
    - symptoms and signs suggestive of serious illness and/or complications (particularly pneumonia, mastoiditis, peritonsillar abscess, peri-tonsillar cellulitis, intra-orbital or intracranial complications)
    - pre-existing comorbidity
      - significant heart, lung, renal, liver or neuromuscular disease,
      - immunosuppression,
      - cystic fibrosis,
      - young children who were born prematurely
    - older than 65 years with acute cough and two or more of the following, or older than 80 years with acute cough and one or more of the following:
      1) hospitalisation in previous year
      2) type 1 or type 2 diabetes
      3) history of congestive heart failure
      4) current use of oral glucocorticoids

How long respiratory tract infections may last?

- acute otitis media: 4 days
- acute sore throat/acute pharyngitis/acute tonsillitis: 1 week
- common cold: 1 1/2 weeks
- acute rhinosinusitis: 2 1/2 weeks

- acute cough/acute bronchitis: 3 weeks

Sarcoidosis

Sarcoidosis CXR
- 1 = BHL
- 2 = BHL + infiltrates
- 3 = infiltrates
- 4 = fibrosis

Definition
- Sarcoidosis is a multisystem disorder of unknown aetiology characterised by non-caseating granulomas.

Epidemiology
- More common in black people (African descent) and subjects of Caribbean origin
  - in Europe, sarcoid is commonest amongst Caucasians and has a significantly higher incidence in the **Irish**.
- most common in black women
- More common in young adults.
- Has a bimodal age distribution with 2 peaks in the third and fifth decades.

Pathology
- **noncaseating granulomas** in the organ involved.
  - **the characteristic pathological feature of sarcoidosis.**
  - may occur anywhere
  - The centre of the granuloma includes macrophages and giant cells, which are of the **Langerhans** type and **can contain over ten nuclei**. This core of cells is surrounded by two rings of lymphocytes:
    - the larger, inner component of **CD4** helper cells and
    - the outer ring, which can comprise **CD8** suppressor cells.
  - The central area of the granuloma will occasionally contain a **Schaumann body**, formed of crystallised material (**calcium phosphate**).
  - These granulomas have the capacity to produce 1,25 vitamin D explaining the associated hypercalcaemia.

Presentation
- initially presents with one or more of the following **Abnormalities:**
  - Bilateral hilar lymphadenopathy
  - Pulmonary reticular opacities
    - Lungs and lymph nodes affected in >90% of patients.
  - Skin, joint and/or eye lesions

Features:
- Dry cough
- Dyspnoea (Pulmonary fibrosis)
- Arthralgia
  - Inflammatory arthritis in sarcoidosis typically targets the **ankle joint**.
- **Uveitis** (25% of cases)

- Skin lesions:
  - Erythema nodosum (10% of cases)
  - lupus pernio
- Systemic symptoms:
  - Fever
  - weight loss

Investigations :

- There is no one diagnostic test for sarcoidosis and hence diagnosis is still largely clinical.
- **Chest x ray**
  - Chest x ray is abnormal in 85% of lung sarcoid, but 30-60% are asymptomatic (that is, incidental chest x ray finding).
  - All patients should have a chest x-ray, which may show bilateral hilar lymphadenopathy.
  - **The differential of bilateral hilar lymphadenopathy includes:**
    - Sarcoidosis. **A positive tuberculin test in a patient with chronic sarcoidosis is suggestive of active tuberculosis**
    - Tuberculosis
    - Malignancy including lymphoma
    - Cystic fibrosis
    - Churg Strauss disease
    - HIV
    - Extrinsic allergic alveolitis
    - Phenytoin
    - Pneumoconiosis, especially **berylliosis.**
      - (**Exposure to beryllium is seen in the nuclear power, telecommunications, semi-conductor and electronics industries**).

Stage	Finding	Likehood of spontaneous resolution
0	Normal chest radiograph	>90%
I	Bilateral hilar lymphadenopathy (BHL)	60-90%
II	**BHL plus pulmonary infiltrates**	40-60%
III	Pulmonary infiltrates (no BHL)	10-20%
IV	Pulmonary fibrosis (+/- bullae)	<20%

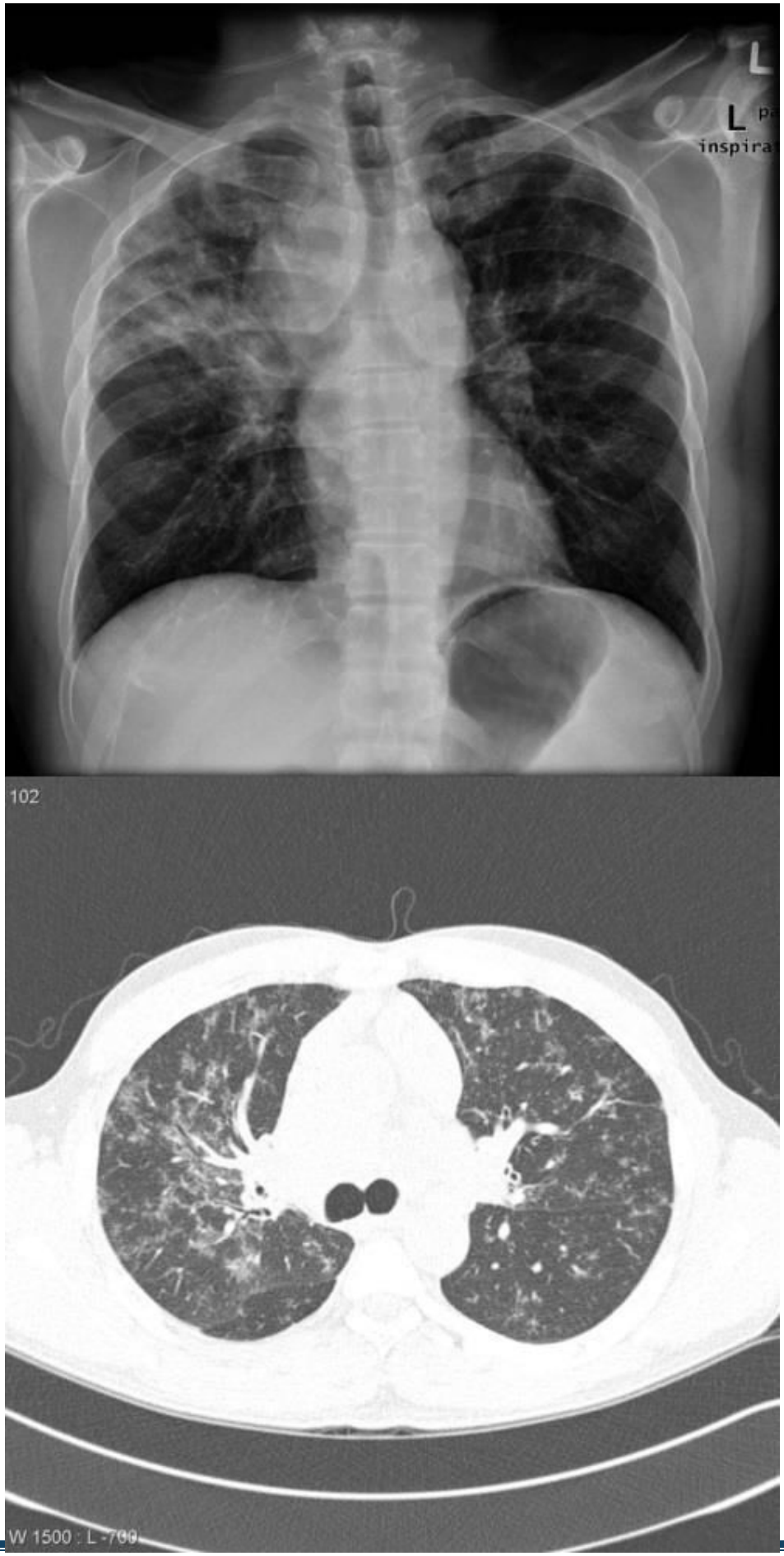
Other investigations

- **CT scan:**
  - It can demonstrate the degree of fibrosis, micronodules in a subpleural or bronchoalveolar distribution, fissural nodularity and bronchial distortion.
  - Irregular linear opacities and ground-glass shadowing may also be seen.
  - If the CT scan is diagnostic, then mediastinoscopy, bronchoscopy or biopsies can often be avoided.
- **Tissue biopsy**: non-caseating granulomas
  - If the history and radiology is typical, the diagnosis of sarcoidosis can be confidently made and there may not be a need to proceed to tissue biopsy.
  - The presentation of erythema nodosum, arthropathy, bilateral hilar lymphadenopathy is so characteristic that histological diagnosis is not necessary.
  - If there were atypical features and tissue biopsy was required, either transbronchial or open lung biopsy is preferable.
  - **With less characteristic presentations, positive biopsies are needed.**
  - Mediastinoscopy is the method of choice for anterior mediastinal nodes.
  - **If you are asked to specify the investigation most likely to confirm the diagnosis, only transbronchial biopsy will determine whether non-caseating granulomas are present or not.**
    - **Transbronchial lung biopsy** will provide positive histology in about 80% of patients, is safe and can be done under sedation with local anaesthesia and is therefore **the diagnostic investigation of choice.**
  - **Skin biopsy**

- **ACE levels**
  - It is elevated in about 70% of patients with active sarcoidosis.
  - have a sensitivity of 60% and specificity of 70% and are therefore **not reliable in the diagnosis of sarcoidosis although they may have a role in monitoring disease activity**.
- hypercalcaemia (seen in 10% if patients)
  - **Hypercalcaemia**, a potentially important complication of sarcoidosis, occurs in fewer than 10% of patients and is thought to be owing to elevated levels of 1,25-dihydroxyvitamin D (calcitriol), which is produced by macrophages within the granulomas.
  - hypercalciuria (up to 50%) are well recognised in sarcoidosis.
  - The pattern resembles hypervitaminosis D, with:
    - Elevated serum calcium
    - Normal serum phosphate and
    - Normal/slightly raised alkaline phosphotase.
  - Calculation of corrected calcium:
    - **Add 0.1 mmol/L of calcium for every 4 g/dL that the albumin level is below 40 g/dL.**
    - Example: (if Total protein = 55 g/L. Globulin= 31 g/L)

Albumin + globulin	= **Total protein**
Albumin	= Total protein − globulin
	= 55 − 31
	= 24
Corrected calcium	= 2.6 + (((40-24)/4) × 0.1)
	= 2.6 + ((16/4) × 0.1)
	= 2.6 + (4 × 0.1)
	= 2.6 + 0.4
	= 3.0 mmol/L

- Raised ESR.
- Hypergammaglobulinaemia (↑ Immunoglobulins) in 30-80%.
- Leukopenia in 5-10% of patients
- **Spirometry usually shows a restrictive defect (Decreased gas-transfer factor (Tlco) with decreased gas-transfer coefficient (Kco)**
- Broncho-alveolar lavage typically shows a lymphocytosis
- TB should be excluded by sending sputum or BAL washings for AFB
  - tuberculin test is negative in approximately 80-90 % of sarcoidosis cases
- gallium-67 scan - not used routinely
- **the Kveim test** (where part of the spleen from a patient with known sarcoidosis is injected under the skin) is no longer performed due to concerns about cross-infection
- **A positive tuberculin test in a patient with chronic sarcoidosis is suggestive of active tuberculosis**
  - tuberculin test is usually negative in chronic sarcoidosis,
  - most patients with sarcoidosis who develop tuberculosis become tuberculin-positive.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Chest x-ray and CT scan showing stage 2 sarcoidosis with both bilateral hilar lymphadenopathy + interstitial infiltrates. The reticulonodular opacities are particularly noted in the upper zones. Remember that pulmonary fibrosis (which this case has not yet progressed to) may be divided into conditions which predominately affect the upper zones and those which predominately affect the lower zones - sarcoidosis is one of the former. The CT of the chest demonstrates diffuse areas of nodularity predominantly in a peribronchial distribution with patchy areas of consolidation particularly in the upper lobes. There is some surrounding ground glass opacities. No gross reticular changes to suggest fibrosis.

Management

The majority of patients with sarcoidosis get better without treatment

- the fate of acute sarcoidosis
  - Spontaneous remission → occurs in two-thirds of patients
  - progress to chronic course → in 10-30%.
  - Spontaneous remissions occur in 55% to 90% of patients with stage I, 40% to 70% of patients with stage II, and about 20% of patients with stage III disease, but no remissions are expected in stage IV.
- Duration of remission
  - Remissions often occur within the **first 6 months** after diagnosis.
  - 50% of patients with **stage 2 sarcoidosis** (ie hilar lymphadenopathy and parenchymal infiltrate) recover spontaneously in **2 years**.
- Treated with topical corticosteroids for mild local cutaneous disease.
- Systemic corticosteroids are the mainstay of treatment for severe disease.
- **Prednisolone is the mainstay of initial treatment for sarcoidosis**, continued for 12 months or more in those patients who respond, but tapered to the minimal effective dose to stop within 2 years maximum.
- Methotrexate and hydroxychloroquine may be added as steroid sparing agents.

Indications for steroids

- patients with chest x-ray stage 2 or 3 disease who have moderate to severe or progressive symptoms. Patients with asymptomatic and stable stage 2 or 3 disease who have only mildly abnormal lung function do not require treatment
- hypercalcaemia (10% of cases)
- eye, heart or neuro involvement

Prognosis

Erythema nodosum is associated with a good prognosis in sarcoidosis.

- Sarcoidosis remits without treatment in approximately two-thirds of people
- The prognosis is excellent with less than 10% having persistent disease.
- Mortality in the UK from sarcoidosis is less than 5%.

Factors associated with a good prognosis include

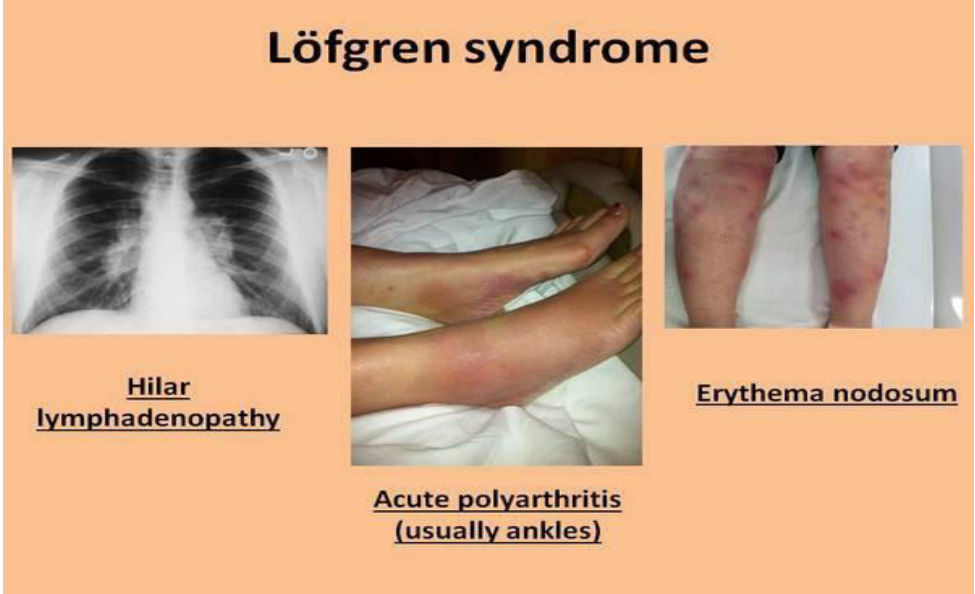
- HLA B8

- Lofgren's syndrome (bilateral hilar lymphadenopathy, erythema nodosum, polyarthritis and fever).

Factors associated with poor prognosis

- insidious onset, symptoms > 6 months (chronic pulmonary involvement)
- absence of erythema nodosum
- extrapulmonary manifestations: e.g.
  - lupus pernio
    - Lupus pernio: is a chronic raised indurated (hardened) lesion of the skin, often purplish in colour, and is associated with sarcoid.
  - splenomegaly
  - Cardiac involvement
    - Cardiac sarcoidosis is rare but can manifest as a prolonged PR interval.
  - Chronic hypercalcaemia
  - Nasal mucosal involvement
  - Neurosarcoidosis
- CXR: stage III-IV features
- black people (Afro-Caribbean or Afro-American race)
- Age of onset >40 years

Lofgren's syndrome



- Lofgren's syndrome is an acute form sarcoidosis characterised by:
  - bilateral hilar lymphadenopathy (BHL)
  - erythema nodosum,
  - fever
  - and polyarthralgia.
- it typically occurs in young females and carries an excellent prognosis.
- It is typically more common in Scandanavian patients and less common in Afro-Caribbean patients and typically has amuch better prognosis.
- **Treatment:**

- For less symptomatic patients then supportive measures and NSAIDs for arthralgia are the preferred treatment options.
- For patients who are not responsive to steroids or steroid intolerant then immunosuppressant agents such as methotreaxtae can be tried.

Loffler's syndrome is a cause of pulmonary eosinophilia thought to be caused by parasites such as Ascaris lumbricoides

Mikulicz syndrome:

- It is a chronic condition associated with sarcoidosis
- characterized by the abnormal enlargement of parotids, lacrimal, salivary glands, tonsils and other glands in the soft tissue of the face and neck.

Heerfordt's syndrome

- is an acute presentation of sarcoidosis, which presents with **fever**, **uveitis** (red, painful eyes), **bilateral swelling of the parotid** and other salivary and lacrimal glands. Facial nerve palsy (LMNL) may be a feature, and other features of sarcoidosis may co-exist (e.g. skin lesions, pulmonary involvement).
- As it represents a form of neuro-sarcoidosis, other neurological features may be present (e.g. meningism, ophthalmoplegia and pupillary reflex dysfunction).

Cough

- **Acute cough** is defined as one lasting less than three weeks.
- **Chronic cough** is defined as one lasting **over eight weeks**.
- There is a grey area between three to eight weeks and this includes **post-viral coughs**.
- drugs that can cause cough
  - The most common drugs:
    - Angiotensin converting enzyme inhibitors
      - (occurs in up to 15% of patients)
    - smoking.
  - Other drugs that can cause cough are:
    - statins,
    - amiodarone,
    - angiotensin II receptor blockers
    - interferon alpha and beta.
- The British Thoracic Society recommend the following for the initial evaluation of **chronic cough:**
  - History (including occupational) and physical examination
  - Chest x-ray and spirometry are mandatory
  - Bronchial provocation if no obvious aetiology and normal spirometry
  - Bronchoscopy if inhalation of a foreign body is suspected
  - High resolution CT scan if all targeted investigations are normal

Pulmonary side effects of drugs

Cardiac drugs

- Aspirin → nasal polyps, asthma
- Atenolol → bronchoconstriction
- Lisinopril → cough
- Amiodarone → pulmonary fibrosis
- Furosemide → bronchoconstriction (very rarely)

Pulmonary complications of cytotoxic and immunosuppressive drugs

- Methotrexate(disease-modifying anti-rheumatoid drug (DMARD)➔ may cause Pulmonary pneumonitis (inflammation of the lung).
- Penicillamine (DMARD)➔may cause bronchiolitis obliterans.

Other drugs:

- Non-steroidal anti-inflammatory drugs can cause asthma or pulmonary eosinophilia.
- Phenytoin characteristically causes pulmonary eosinophilia.

Idiopathic pulmonary haemosiderosis

- Idiopathic pulmonary haemosiderosis tends to occur in younger people
- characterised by pallor, weakness, lethargy, dry cough and occasional haemoptysis
- There are no extrapulmonary features.
- There are no abnormal immunological features, which differentiates it from Goodpasture syndrome and wegener's
- Gas transfer is elevated as blood is already in the alveolar space.

Finger clubbing

Definition

- Loss of the natural angle between the nail and the nail bed.
- increased curvature of the nail

Causes

- Suppurative diseases:
  - long-standing bronchiectasis
  - acute lung abscesses
  - empyema
- Malignant disease - especially carcinoma of the bronchus and pleural malignancy
- Fibrosing alveolitis
- Asbestosis
- hypertrophic pulmonary osteoarthropathy,
  - painful osteitis of the distal ends of the long bones of the lower arms and legs.
  - Malignancy is associated in 95% of these cases.

Finger clubbing is not seen in uncomplicated bronchitis.

Hyper-eosinophilic syndrome:

Definition

- **peripheral blood eosinophil count of >1.5 for more than 6 months.**

Features

- fatigue, myalgia,
- fever, night sweats,
- diarrhoea
- pruritus.
- Other symptoms depend on the organ involved:
  - cardiac disease causes chest pain and dyspnoea,
  - respiratory disease presents with a dry cough.

Cyanosis without hypoxia

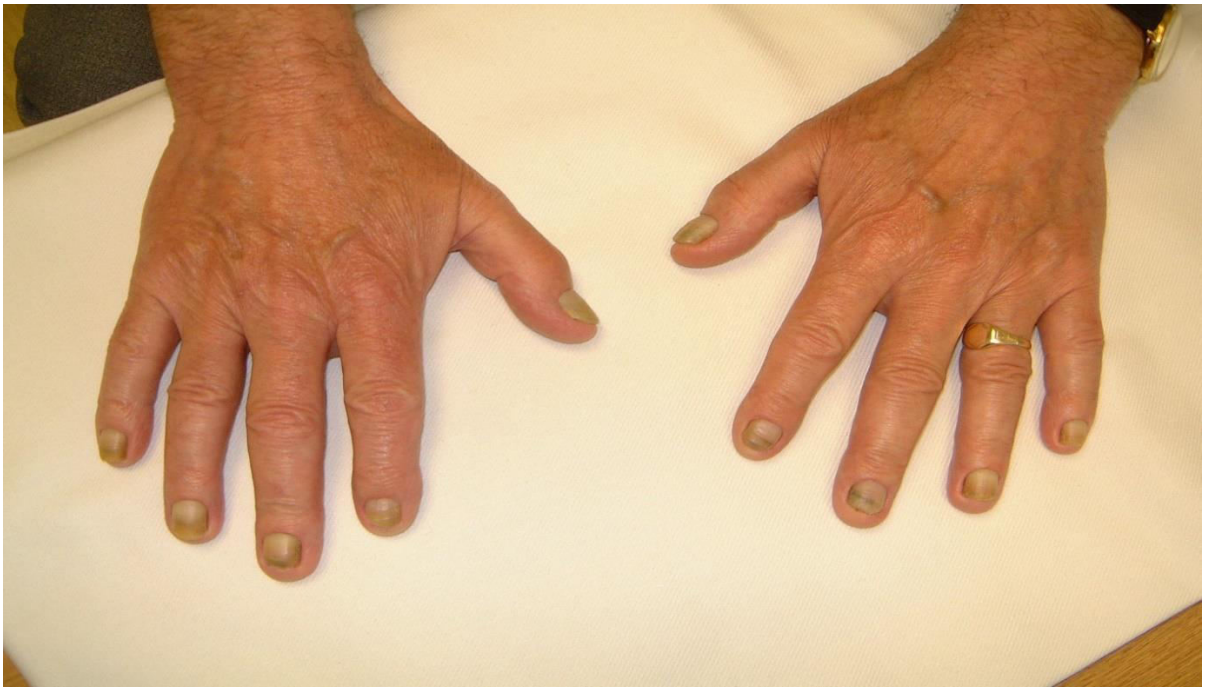
- **Persistent cyanosis without hypoxia (a normal Pao2) suggests a diagnosis of methaemoglobinaemia** or sulfhaemoglobinaemia.
- In a cyanosed patient the amount of reduced haemoglobin in the blood is at least 5 g/dl
- The blue colour of the skin and mucous membranes is due to hypoxia and not hypercapnia. Hypoxia should be corrected by oxygen therapy
- **What is the possible cause of Desaturation on SaO_2 (using an oximeter) in spite of normal PaO_2?**
  - Methaemoglobinaemia
    - accumulation of reversibly oxidised methaemoglobin causing reduced oxygen affinity of the Hb molecule with consequent cyanosis.
    - It can occur due to:
      - an inherited condition or
      - as a consequence of drugs such as **nitrites**.

Yellow nail syndrome

- It is an abnormality of lymphatic drainage.
- the nails are yellow, thickened, curved, stop growing and may become detached from the nail bed.

Associations

- congenital lymphoedema
- pleural effusions
- **bronchiectasis (40%)**
- chronic sinus infections
- Yellow discolouration of the nails.



Hepatopulmonary syndrome:

Definition

- oxygenation defect induced by **pulmonary vascular dilatation** in patients with liver cirrhosis or portal hypertension,→ (wide alveolar-arterial gradient (**>**15mmHg)).

Mechanism

- The vascular dilatation is thought to be induced by increased pulmonary levels of nitric oxide.

Prevalence

- It is seen in 15-30% of patients with cirrhosis.

Features:

- Most patients are asymptomatic
- Dyspnoea
  - dyspnoea with an insidious onset.
  - Dyspnoea whilst standing (platypnoea) and hypoxaemia exacerbated by being upright (orthodeoxia) are characteristic, and are thought to be due to the predominance of vascular dilatation in the lung bases. Blood flow to these areas is increased in the upright position.
  - 'orthodeoxia':
    - Hepatic disease → intrapulmonary vasodilatation mainly in the lower Lobes → right-to-left shunting (similar to pulmonary arteriovenous malformations (PAVMs) → increased blood flow through the lower lobes when the patient moves from the supine to the erect position → blood from the lower lobes,

which is more poorly oxygenated, entering the left side of the heart, → oxygen desaturation in the erect position.

- ➢ Desaturation during sleep

- clubbing
- cyanosis.

Investigations:

- **Contrast-enhanced transthoracic echocardiography is the best test to demonstrate intrapulmonary vascular dilatation. It can also exclude intracardiac shunting which may result in similar signs and symptoms to hepatopulmonary syndrome**.
  - ➢ Method
    - performed by injecting agitated saline intravenously during transthoracic echocardiography.
  - ➢ Interpretation
    - In a **normal** subject microbubbles are visualised in the right ventricle within seconds, which are then absorbed in the alveoli.
    - Immediate visualization in the left ventricle (within three cardiac cycles) indicates **intracardiac shunting**.
    - Delayed visualisation in the left ventricle (3-6 cardiac cycles) is diagnostic of **intrapulmonary shunting**.
- Radionuclide lung perfusion scanning can also be used.
- Chest radiographs can be normal or show non-specific interstitial changes.
- ABGs should be taken in the sitting position to grade the severity of the condition based on the degree of hypoxaemia.

Treatment:

- Liver transplantation is the only proven beneficial available treatment, with 85% of patients showing resolution or significant improvement in gas exchange postoperatively.

Prognosis

- It is a poor prognostic indicator.

Inhalation of hot smoke

- Inhalation of hot smoke can burn the upper airways and contributes significantly to deaths due to fires.
- Timing of obstruction development:
  - ➢ Upper airway obstruction due to heat injury and mucosal swelling usually develops within 24 hours of exposure,
  - ➢ stenosis due to scarring can develop later.
- Factors suggesting significant upper airway damage
  - ➢ hoarse voice, stridor, severe conjunctivitis, burnt nasal hairs and falling peak flow values.

- **The definitive investigation in assessing this condition:**
  - **Bronchoscopy is the best tool to establish whether there is significant oedema or mucosal ulceration obstructing the airways.**

Pulmonary alveolar microlithiasis (PAM)

Definition

- rare autosomal recessive disease in which calcium **phosphate** accumulate in the alveoli causes widespread damage to the alveoli and surrounding lung tissue

Pathophysiology

- *SLC34A2* gene mutations → ↓ activity of the type IIb sodium-phosphate cotransporter (which located mainly in alveolar type II cells) → accumulation of phosphate in the alveoli → formation of microliths
- *SLC34A2* gene is responsible for the uptake of phosphate released from phospholipids in outdated surfactant.

Feature

- usually diagnosed before age 40.
- Commonly asymptomatic, Often discovered, when medical imaging is done for other reasons. worsens slowly over many years.
  - Often patients may have no symptoms despite striking radiological abnormalities.
- persistent cough
- dyspnea, especially during physical exertion.
- PFT shows restrictive pattern
- chest pain that worsens when coughing, sneezing, or taking deep breaths.
- People with pulmonary alveolar microlithiasis can also develop calcium phosphate deposits in kidneys, gallbladder, testes, and aortic valve.

Diagnosis

- the best diagnostic schedule for PAM is the association of **BAL** and chest **HRCT**,
- as the BAL can document the diagnosis while the HRCT provides further information about the degree of inflammation and/or fibrosis or calcification of the interstitium.
- **A 'sandstorm-appearing' chest radiograph is a typical diagnostic finding**.
  - In the initial stages, the radiological finding may mimic miliary tuberculosis.
  - Calcified nodules are found in later stages.
  - An interesting radiological sign in PAM is a **black pleura sign**. Here, the calcification of alveoli and the adjacent rib make the pleura resemble a black line in between two white signals.
- BAL and **biopsy show the characteristic calciospherocitis (microliths) in the alveoli** (deposition of calcium and phosphate crystals).
- Biopsy also shows variable degrees of fibrosis in the lung interstitium

Treatment

- lung transplantation is the only effective therapy.
- No medical intervention has proved successful
- Bronchial lavage is not useful, unlike in pulmonary alveolar proteinosis.

Pulmonary Alveolar Proteinosis (PAP)

Definition

- It is a rare diffuse lung disease in which the alveolar sacs become filled with proteins that characteristically stain for periodic acid-Schiff (PAS) , a protein derived from surfactant .

Epidemiology

- prevalence of 1 case per 100,000
- Common in males (M: F = 4:1)
- It usually affects people aged between 20-60 years who have no previous lung disease,

Causes

- primarily
  - pneumocystis Jirovecii or
  - atypical mycobacteria,
- Secondary
  - immunosuppressants, HIV
  - organic dusts
  - haematological malignancy .

Feature

- Pulmonary symptoms: Persistent **dry cough**, progressive **dyspnea** and pleuritic chest **pain**
- General symptoms: Fatigue, malaise, weight loss and low-grade fever
- Clubbing (25%)

Diagnosis

- Flexible bronchoscopy with broncho-alveolar lavage (BAL)
  - The standard diagnostic test
  - PAS-positive stains
  - increased presence of surfactant proteins A and D .
- HRCT chest
  - shows a classical picture of dense infiltrates, often referred to as '**crazy paving'** Pattern.
- Spirometry
  - shows a restrictive pattern with reduced lung capacity and reduced CO diffusion .
- Autoantibodies
  - ↑ autoantibody against GM-CSF (immunoglobulin G [IgG] isotype) in serum and BAL fluid

Treatment

- Most patients do not require treatment unless their SOB is disabling .
- washing the alveoli out with salt solution.

  - This can be done with bronchoscopy or under general anaesthesia through the trachea.
  - If both lungs need washing then they are done about 5 days apart.
  - The number of washing depends on symptoms .
- **Prognosis** is good.

Parotitis

- **Bacterial parotitis**
  - Commonly unilateral
  - more common in older patients.
  - The risk is increased by agents that have an atropine-like action, including medications prescribed to reduce excess respiratory secretions.
  - A ductal stone, with consequent pooling of infected secretions, should be excluded, and ultrasound is an appropriate investigation to perform for this.
  - Antibiotics should be selected that cover typical mouth flora.
- **Viral parotitis**
  - Mumps parotitis is usually bilateral

Carbon monoxide poisoning

Confusion, pyrexia and pink mucosae are typical features of carbon monoxide poisoning

Carbon monoxide poisoning - most common feature = headache

Epidemiology

- Carbon monoxide is the **commonest** cause of poisoning-associated death in the United Kingdom
- There are approximately 50 per year deaths from accidental carbon monoxide poisoning in the UK.
- Patients with pre-existing vascular disease are at an increased risk of morbidity and mortality from carbon monoxide poisoning

Causes

- Fumes from cleaning fluids and paint removers that contain methylene chloride (dichloromethane) can also cause carbon monoxide poisoning. When breathed in, methylene chloride is converted into CO gas.

Pathophysiology

- Carbon monoxide binds with haemoglobin with a greater affinity than oxygen displacing it from the blood causing tissue hypoxia.
- carbon monoxide shifts the oxygen dissociation curve to the left reducing tissue delivery even more.
- the fetal haemoglobin of the unborn child in pregnant women preferentially bound to the poisonous carbon monoxide gas which may survived her.

Questions may hint at badly maintained housing e.g. student houses

Features of carbon monoxide toxicity

- headache: 90% of cases
- nausea and vomiting: 50%
- vertigo: 50%
- confusion: 30%
- subjective weakness: 20%
- hypertension, tachycardia and flushing.
- severe toxicity: (carboxyhaemoglobin levels more than 50%)
  - 'pink' skin and mucosae,
  - hyperpyrexia,
  - arrhythmias,
  - extrapyramidal features, convulsions, coma, death
- **Cerebellar signs are the most reliable indicator of significant neurological toxicity**

Typical carboxyhaemoglobin levels

- < 3% non-smokers
- < 10% smokers
- 10 - 30% symptomatic: headache, vomiting
- > 30% severe toxicity

Diagnosis

- **Arterial blood-gas analysis**
  - **Direct spectrophotometric measurement of HbCO in a blood-gas analyser is the gold standard.**
  - **Pulse oximeters cannot distinguish between COHb and HbO2, hence it is essential to take arterial blood gases** and – to make the specific diagnosis – measure the level of CO.
    - Pulse oximetry appears normal because carboxyhaemoglobin has similar absorption spectra to oxyhaemoglobin.

Management

- 100% oxygen (Give high-flow oxygen (12 l/min) via a tight-fitting mask without a re-breathing circuit)
- hyperbaric oxygen
- In severe cases intubation and mechanical ventilation may be required

Indications for hyperbaric oxygen

- loss of consciousness at any point
- neurological signs other than headache
- carboxyhaemoglobin concentrations over 40% at any time
- myocardial ischaemia or arrhythmia
- pregnancy

Smoking cessation

Bupropion: contraindicated in epilepsy

Action of smoking

- Nicotine is a stimulant and releases dopamine in the brain that leads to addictive effects of smoking.
- Its effects can be replaced in other ways using nicotine replacement therapy and this reduces the addiction to cigarette smoking.

Management of smoking cessation - General points (NICE guidance 2008)

- patients should be offered nicotine replacement therapy (NRT), varenicline or bupropion - NICE state that clinicians should not favour one medication over another
- NRT, varenicline or bupropion should normally be prescribed as part of a commitment to stop smoking on or before a particular date (target stop date)
- prescription of NRT, varenicline or bupropion should be sufficient to last only until 2 weeks after the target stop date. Normally, this will be after 2 weeks of NRT therapy, and 3-4 weeks for varenicline and bupropion, to allow for the different methods of administration and mode of action. Further prescriptions should be given only to people who have demonstrated that their quit attempt is continuing
- if unsuccessful using NRT, varenicline or bupropion, do not offer a repeat prescription within 6 months unless special circumstances have intervened
- do not offer NRT, varenicline or bupropion in any combination

NRT	Varenicline	Bupropion
Nicotine replacement therapy	**Nicotinic receptor partial agonist**	**Norepinephrine and dopamine reuptake inhibitor, and nicotinic antagonist**
• Adverse effects: nausea & vomiting, headaches and flu-like symptoms • Nice recommend offering a combination of nicotine patches and another form of NRT (such as gum, inhalator, lozenge or nasal spray) to people who show a high level of dependence on nicotine or who have found single forms of NRT inadequate in the past	• Should be started 1 week before the patient target date to stop • The recommended course is 12 weeks (but patients should be monitored regularly and treatment only continued if not smoking) • more effective than bupropion **Adverse effect:** • **the most common SE** is Nausea. • **Other SE**: headache, insomnia, abnormal dreams **used with caution in** • patients with a history of depression or self-harm → ↑risk of suicidal behaviour **Contraindicated in** • pregnancy and breast feeding	• Should be started 1 to 2 weeks before target date. • Small risk of seizures (1: 1,000) **Contraindicated in:** • **epilepsy** • other conditions that lower the seizure threshold, such as alcohol or benzodiazepine withdrawal, anorexia nervosa, bulimia, or active brain tumors. • patients taking **corticosteroids**, antimalarials, tramadol and antidepressants, as these lower seizure threshold. • individuals who are also taking MAOIs. When switching from MAOIs to bupropion, it is important to include a washout period of 2 weeks. • pregnancy and breastfeeding. **relative contraindication** • eating disorder

Pregnant women

- NICE recommended in 2010 that all pregnant women should be tested for smoking using carbon monoxide detectors, partly because *'some women find it difficult to say that they smoke because the pressure not to smoke during pregnancy is so intense.'*
- All women who smoke, or have stopped smoking within the last 2 weeks, or those with a CO reading of 7 ppm or above should be referred to NHS Stop Smoking Services.

Adverse effects of smoking in pregnancy

- **Reduces birth weight**
  - (the reduction in birth weight is related to the number of cigarettes smoked per day).
- increases risk of miscarriage and still birth.

- The infant has a greater risk of sudden infant death syndrome.
- affect ovarian function in female children.
- **increases lung maturity**, possibily by enhancing the production or secretion of cortisol. This makes neonates less likely to develop respiratory distress syndrome, but as lung maturation is often abnormal babies may have reduced lung function and increased rates of other respiratory illnesses.

Interventions in pregnant smoker:

- the first-line interventions in pregnancy should be cognitive behaviour therapy, motivational interviewing or structured self-help and support from NHS Stop Smoking Services
- if the above measures failed → NRT is often used.
  - There is no evidence that it affects the child's birthweight.
  - Pregnant women should remove the patches before going to bed
- varenicline and bupropion are contraindicated

Notes & Notes

For MRCP part 1 & 11

By

Dr. Yousif Abdallah Hamad

Gastroenterology

Updated

2017

Contains:

1/ Passmedicine 2017
2/ On examination 2017
3/ Pastest 2017
4/ **Red fonts --> previous exams**
5/ Other updated UK sources

Basic GIT

Anatomy

The golden notes

Relations to peritoneum

- **Primary retroperitoneal organs include: (from the start of their development)**
  - adrenal gland, kidneys, ureter,
  - aorta, IVC,
  - esophagus and rectum.
- **Secondary retroperitoneal**
  - Pancreas (except the tail which is intraperitoneal)
  - Duodenum (except the 1st part)
  - Ascending colon
  - Descending colon
- **Intraperitoneal organs include:**
  - stomach, duodenum, liver, spleen, appendix, cecum and transverse colon.

Gastrointestinal physiology

Acid secretion

Principle mediators of acid secretion are 3:

1. **Gastrin**
   - presence of breakdown products of protein (small peptides and amino acids) → stimulate **gastric G cells** to secrete gastrin
   - phenylalanine and tryptophan are most potent stimuli for gastric secretion
2. **Vagal stimulation**
   - direct pathway
     - vagus nerve innervates gastric parietal cells
       - smelling, tasting of food **and** distension of stomach → vagal stimulation
     - at synapse, **acetylcholine** (Ach) is released and binds **muscarinic M3 receptors** coupled to Gq proteins
     - ↑ ACh → (+) M3 receptors → (+) Gq proteins → (+)Phospholipase C (**PLC**) → ↑ diacyl glycerol (**DAG**) and inositol 1,4,5-trisphosphate (**IP3**)
     - IP3 releases Ca2+ from intracellular stores
     - DAG and Ca2+ → (+)protein kinase C (**PKC**) → (+) H+-K+ ATPase → ↑ HCl secretion via gastric parietal cells
   - indirect pathway
     - vagus nerve innervates gastric G cells
     - at synapse, gastrin-releasing peptide (GRP) is released
     - GRP → ↑ gastrin secretion via gastric G cells
3. **histamine**
   - the **primary** modulator of acid secretion
   - Released from: enterochromaffin-like (ECL) cells in gastric mucosa
   - diffused to nearby gastric parietal cells (paracrine mechanism of delivery)
   - action
     - histamine binds H2 receptors coupled to Gs proteins on gastric parietal cells
     - histamine → (+) H2 receptors → (+) Gs proteins → (+) adenylyl cyclase → ↑ cAMP → (+) protein kinase A (PKA) → (+) H+-K+ ATPase → ↑ HCl secretion via gastric parietal cells

Factors increasing acid secretion

- gastrinoma
- small bowel resection (removal of inhibition)
- **systemic mastocytosis (elevated histamine levels)**
- basophilia

Factors decreasing acid secretion

- drugs: H2-antagonists, PPIs
- hormones: secretin, VIP, GIP, CCK, glucagon
- **Prostaglandins**.
- atropine

- a cholinergic muscarinic antagonist
  - blocks muscarinic M3 receptors on gastric parietal cells
    - ☒ blocks ACh-mediated, direct pathway of HCl secretion
    - ☒ but does not block GRP-mediated, indirect pathway of HCl secretion
    - ☒ so atropine does not inhibit HCl secretion via gastric parietal cells completely

Gastrointestinal Hormones

	Source	Regulation	Actions
Gastrin	**G** cells in antrum of the stomach	**↑ by** • Stomach Distension • vagal stimulation **↓ by**: • low antral pH • somatostatin	• ↑ HCL, ↑acidity, pepsinogen and IF secretion, • ↑ gastric motility, • ↑ gastric mucosa breakdown (trophic effect)
CCK	**I cells** in upper small intestine (duodenum, jejunum)	**↑ by** Partially digested Proteins and Triglycerides	• ↑ secretion of enzyme-rich fluid from pancreas, **contraction of gallbladder** and relaxation of sphincter of Oddi, ↓ gastric emptying, trophic effect on pancreatic acinar cells, induces satiety
Secretin	**S** cells in upper small intestine (duodenum)	**↑ by** Acidic chyme, fatty acids **↓ by**: somatostatin	• **↑ secretion of bicarbonate**-rich fluid from pancreas and hepatic duct cells, • **↑ bile flow,** • ↓ gastric acid secretion
VIP	Small intestine pancreas	Neural	• ↑lipolysis, glycolysis • ↑ intestinal water and electrolyte secretion • ↑ relaxation of intestinal smooth muscle and sphincters • ↓acid and pepsinogen secretion. • vasodilator
Somatostatin	D cells in the pancreas & stomach	**↑ by** Fat, bile salts and glucose in the intestinal lumen	• ↓ acid and pepsin secretion, ↓ gastrin secretion, ↓ pancreatic enzyme secretion, ↓ insulin and glucagon secretion • inhibits trophic effects of gastrin, stimulates gastric mucous production

Brunner's glands which secrete alkaline mucus are found in the duodenum

Clinical relations

- Gastrin ↑↑ in Zollinger-Ellison syndrome
- A patient with cholelithiasis (**gallstones**) experiences **worsened pain after fatty food ingestion** due to ↑ release of **CCK → contraction of gallbladder**
- **Secretin** → ↑ pancreatic HCO_3^- secretion → neutralizes gastric H+ in duodenum, essential for fat digestion (pancreatic lipases have pH optimums between 6 and 8)
- Somatostatin
  - Inhibitory hormone
  - Antigrowth hormone effects (digestion and absorption of substances needed for growth)
  - Somatostatin is treatment for **VIPoma** and **carcinoid tumors**
- VIPoma is a non-α, non-β islet cell pancreatic tumor that secretes VIP and causes copious diarrhea

January 2015 exam: Which hormone is most responsible for the secretion of bicarbonate in the upper gastrointestinal tract? Secretin

Intrinsic factor

- Intrinsic factor is a glucoprotein secreted from the **parietal cells** which are **found in the fundus of the stomach** in response to gastrin, food or histamine.
- intrinsic factor transport vitamin B12 across the mucosal wall.
- When the vitamin B12 bound to intrinsic factor reaches the **terminal ileum**, it binds to receptors on the surface of the mucosal cells and is able to cross the membrane and enter the cytoplasm. **The intrinsic factor is then replaced by transcobalamin II which transports the B12 out of the cell and into the bloodstream.**

The golden notes

Intrinsic factor

- Secreted from → parietal cells of the stomach
- Function → transport vitamin B12 across the mucosal wall of terminal ileum
  - The intrinsic factor is then replaced by transcobalamin II which transports the B12 out of the cell and into the bloodstream.

B12 :

- Transported **in** to the cells by → **in**trinsic factor
- Transported out of the cells (into bloodstream) by → transcobalamin II

Gastrin

- Produced from the **G** cells of the gastric antrum into systemic circulation
  - not released into pyloric ducts that empty into lumen of stomach
  - delivered back to stomach via systemic circulation
  - endocrine mechanism of delivery
- Action →
  - stimulates the parietal cells to produce hydrochloric acid
  - stimulates gastric motility
  - Promotes release of secretin
  - **Gastrin promotes the synthesis of intrinsic factor** and pepsinogen
  - stimulates exocrine pancreatic secretions.
  - Promotes mucosal growth
  - Stimulates increased blood flow to stomach.
- gastrin stimulates HCl secretion via gastric parietal cells by 2 mechanisms
  - gastrin binds CCK_B receptors coupled to Gq proteins on gastric parietal cells
    - gastrin → (+) CCKB receptors → (+) Gq proteins → (+)Phospholipase C (**PLC**) → ↑ diacyl glycerol (DAG) and Inositol trisphosphate receptor (IP3)
    - IP3 releases Ca2+ from intracellular stores
    - DAG and Ca2+ → (+)Protein kinase C (PKC) → (+) H+-K+ ATPase → ↑ HCl secretion via gastric parietal cells
  - gastrin binds CCK_B receptors on **enterochromaffin-like** (ECL) cells
    - gastrin → (+) CCK_B receptors → ↑ histamine secretion → ↑ HCl secretion via gastric parietal cells
    - **gastrin stimulates HCl secretion primarily by acting on (ECL) cells**
- its production is stimulated by :
  - neural reflex pathways (parasympathetic nerves) (Vagal stimulation due to the smell and taste of food)
  - direct effect of digested peptides on the G cells (presence of **amino acids** in the stomach)
  - High gastric pH
  - Hypercalcaemia
  - Caffeine, alcohol, hypoglycaemia, calcium
- Inhibited by:
  - acid in stomach
  - somatostatin.
- **Gastrinoma**
  - **Gastrin levels above 1,000 are strongly indicative of a gastrinoma.**

- **Secretin stimulation test is the first choice**, and a rise of greater than 200 is a pointer towards a gastrinoma
- **Treatment**
  - **localised disease → Surgical resection is the treatment of choice**
    - possibility of cure is up to 25% of patients.
  - less advanced, smaller tumours → Whipple's procedure
    - A Whipple's procedure offers the best chance of effecting cure but excellent long term survival in those with less extensive procedures means that these may be considered for less advanced, smaller tumours.
  - metastatic disease → Chemotherapy

Enzymes

Brush border enzymes:
- maltase: glucose + glucose
- sucrase: glucose + fructose
- lactase: glucose + galactose

- Amylase is present in saliva and pancreatic secretions.
  - It breaks starch down into sugar
- The following brush border enzymes are involved in the breakdown of carbohydrates:
  - maltase: cleaves disaccharide maltose to glucose + glucose
  - sucrase: cleaves sucrose to fructose and glucose
  - lactase: cleaves disaccharide lactose to glucose + galactose

Biochemical abnormalities in persistent vomiting

- persistent vomiting → ↓↓ gastric hydrochloric acid → **hypochloraemia and metabolic Alkalosis**
- In the early stages the urine has low chloride and high bicarbonate levels in order to compensate for the loss of gastric hydrochloric acid and is appropriately alkaline.
- With the continued dehydration, sodium is preferentially reabsorbed over the potassium and hydrogen ions which are excreted by the kidneys.
- The urine becomes paradoxically acidic, hypokalaemia develops, and alkalosis leads to lower circulating levels of ionised calcium.

To quickly remember the PH changes associated with GI losses, think:
- With vomiting, both the PH and food come up.
- With diarrhoea, both the PH and food go down.

Clupping in GIT diseases

- Coeliac disease
- Crohn's disease
- Ulcerative colitis
- Whipple's disease

Ilio-caecal TB → no clupping

Oesophageal diseases

Achalasia

Dysphagia affecting both solids and liquids from the start - think achalasia

- Failure of oesophageal peristalsis and of relaxation of lower oesophageal sphincter (LOS) due to degenerative loss of ganglia from Auerbach's plexus i.e. LOS contracted, oesophagus above dilated.

Epidemiology

- prevalence of around 10.8/100,000 persons.
- typically presents in middle-age
- equally common in men and women.

Features

- Symptoms usually develop years before the patient presents
- dysphagia of BOTH liquids and solids **(but dysphagia to solids is most common than liquids)**
- typically variation in severity of symptoms
- heartburn
- regurgitation of food - may lead to cough, aspiration pneumonia etc
- Vague chest discomfort is common and results from oesophagal spasm.
- nocturnal cough (30%) due to aspiration of oesophageal contents.

Complications

- Increased risk of esophageal cancer.

Investigations

The gold standard test for achalasia is oesophageal manometry

- barium swallow
  - **initial investigation**
  - will show:
    - dilated oesophagus
    - fluid level,
    - 'bird's beak' appearance
- manometry:
  - considered **most important diagnostic test**
  - indicated to establish the diagnosis (**confirmatory test of choice**), irrespective of the initial imaging findings.
  - can detect achalasia **in the early stage** before oesophagal dilatation has occurred.
  - Will show:
    - excessive LOS tone which doesn't relax on swallowing
    - Lack of peristalsis in the lower two-thirds of the esophagus
- Upper endoscopy
  - to rule out pseudoachalsia
  - Usually normal
  - May show retained food in esophagus or increased resistance of LES during passage with endoscope
- CXR:
  - Will show:
    - wide mediastinum,
      - Widened mediastinum is where the mediastinum has a width greater than **6 cm** on an upright **PA** chest X-ray or **8 cm** on supine **AP** chest film.
    - fluid level

The most appropriate initial investigation of a high dysphagia is a barium swallow, which identifies the site of pathology and forewarns of pitfalls such as a pharyngeal pouch, which if unidentified can increase the risk of perforation at endoscopy.

Treatment

- Heller cardiomyotomy (Laparoscopic myotomy)
  - **The best initial treatment** for most patients with achalasia.
- balloon dilation (Pneumatic dilatation)
  - the most cost-effective **alternative**
  - long-term efficacy is less than that of surgical myotomy.
  - the preferred option for **older unfit patients**
  - Pneumatic dilation is currently the most effective nonsurgical option for treatment of achalasia

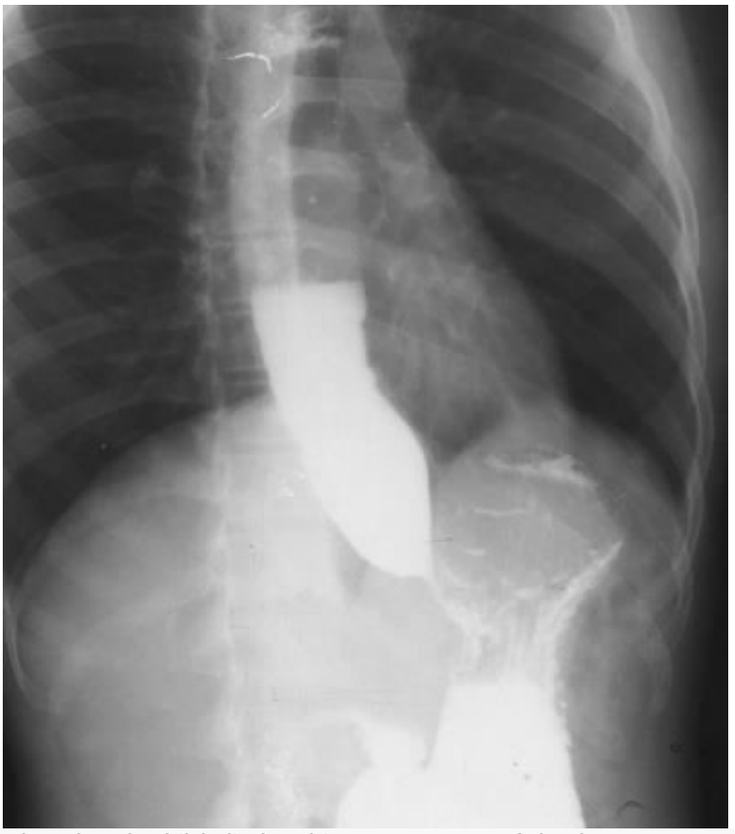
- Current guidelines recommend obtaining **gastrograffin study followed by barium esophagram in all patients after** pneumatic dilation **to exclude esophageal perforation**
- 25% of patients treated with pneumatic dilation required re-dilation.

- **intra-sphincteric injection of botulinum toxin**
  - Botulinum toxin injected into the lower oesophageal sphincter reduces the pressure and **provides symptomatic relief better than other drug therapy**
  - However, the effects are temporary and patients need to undergo repeat injections every six to twelve months.

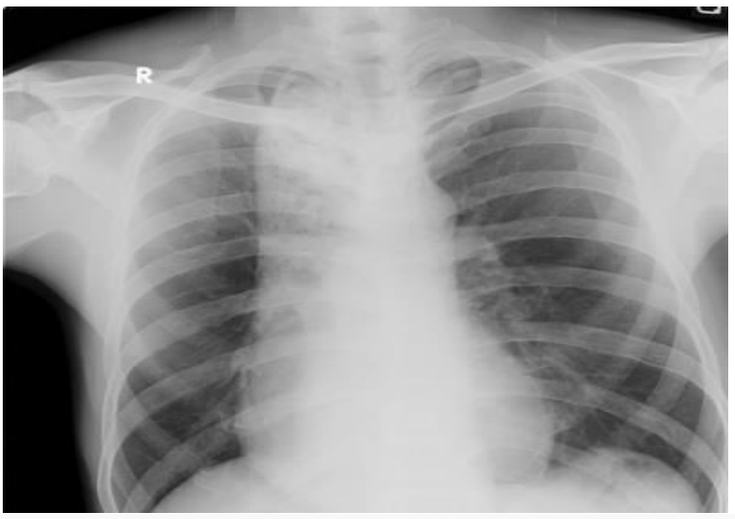
  - Endoscopic botulinum toxin injection can be considered when other forms of treatment are contraindicated. reserved for the elderly and who cannot tolerate dilatation or surgery.
- drug therapy has a role but is limited by side-effects
  - Short-term improvement in clinical symptoms may occur with isosorbide mononitrate, a long-acting nitrate or with nifedipine, a calcium-channel blocker.

Contraindications

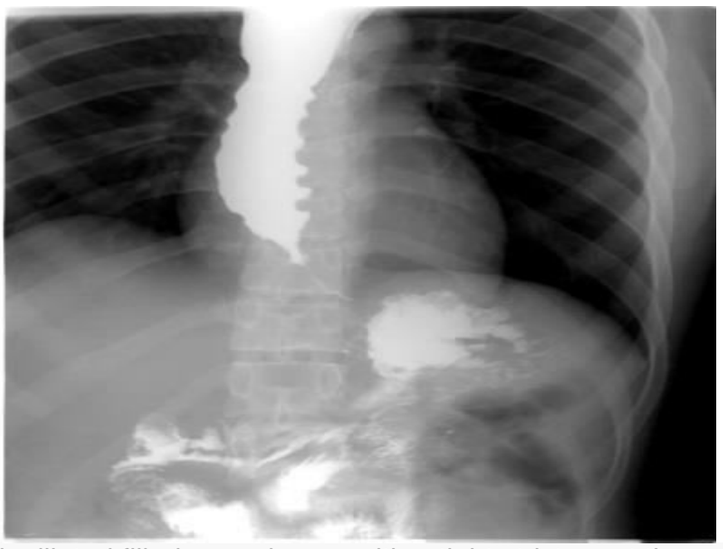
- **Promotility agents like metoclopramide** increase the lower oesophageal sphincter pressure and so are contraindicated in achalasia.



This film demonstrates the classical 'bird's beak' appearance of the lower oesophagus that is seen in achalasia. An air-fluid level is also seen due to a lack of peristalsis



Mediastinal widening secondary to achalasia. An air-fluid level can sometimes be seen on CXR but it is not visible on this film



Barium swallow - grossly dilated filled oesophagus with a tight stricture at the gastroesophageal junction resulting in a 'bird's beak' appearance. Tertiary contractions give rise to a corkscrew appearance of the oesophagus

Dysphagia

The table below gives characteristic exam question features for conditions causing dysphagia:

Oesophageal cancer	**Dysphagia may be associated with weight loss, anorexia or vomiting during eating Past history may include Barrett's oesophagus, GORD, excessive smoking or alcohol use**
Oesophagitis	May be history of heartburn Odynophagia but no weight loss and systemically well
Oesophageal candidiasis	There may be a history of HIV or other risk factors such as steroid inhaler use
Achalasia	Dysphagia of both liquids and solids from the start Heartburn Regurgitation of food - may lead to cough, aspiration pneumonia etc
Pharyngeal pouch	More common in older men Represents a posteromedial herniation between thyropharyngeus and cricopharyngeus muscles Usually not seen but if large then a midline lump in the neck that gurgles on palpation

Oesophageal cancer	**Dysphagia may be associated with weight loss, anorexia or vomiting during eating Past history may include Barrett's oesophagus, GORD, excessive smoking or alcohol use**
	Typical symptoms are dysphagia, regurgitation, aspiration and chronic cough. Halitosis may occasionally be seen
Systemic sclerosis	Other features of CREST syndrome may be present, namely Calcinosis, Raynaud's phenomenon, oEsophageal dysmotility, Sclerodactyly, Telangiectasia As well as oesophageal dysmotility the lower oesophageal sphincter (LES) pressure is decreased. This contrasts to achalasia where the LES pressure is increased
Myasthenia gravis	Other symptoms may include extraocular muscle weakness or ptosis Dysphagia with liquids as well as solids
Globus hystericus	May be history of anxiety Symptoms are often intermittent and relieved by swallowing Usually painless - the presence of pain should warrant further investigation for organic causes

Oesophageal disorders

The table below lists a small group of oesophageal disorders that are not covered elsewhere in the notes.

Disorder	Notes
Plummer-Vinson syndrome	Triad of: • dysphagia (secondary to oesophageal webs) • glossitis • iron-deficiency anaemia Treatment includes iron supplementation and dilation of the webs
Mallory-Weiss syndrome	Severe vomiting → painful mucousal lacerations at the gastroesophageal junction resulting in haematemesis. Common in alcoholics
Boerhaave syndrome	Severe vomiting → oesophageal rupture

Diffuse oesophageal spasm

Features

- dysphagia
- chest pain

Diagnosis

- barium swallow demonstrates a 'corkscrew appearance'
- Manometry reveals:
  - prolonged, repetitive and **high amplitude contractions**.
  - The lower oesophageal sphincter pressure is increased and there is incomplete relaxation of the sphincter.

Differential diagnosis manometry findings:

- **absence** of peristalsis in the body of the oesophagus + high lower oesophageal sphincter → **Achalasia**
- **normal** contractions in the body of the oesophagus + high lower oesophageal sphincter pressure → **hypertensive lower oesophageal sphincter**
- **high** amplitude contractions in the body of the oesophagus + high lower oesophageal sphincter pressure → **Diffuse oesophageal spasm**

Gastro-oesophageal reflux disease (GORD)

In a patient aged below 55 years the symptoms of heartburn which is exacerbated by fatty foods and the recumbent position in the absence of alarm features such as vomiting, bleeding, anaemia, unexplained weight loss, abdominal mass, or dysphagia makes the diagnosis of gastro-oesophageal reflux disease (GORD) the most likely.

Pathophysiology

- decreased tone of the lower esophageal sphincter.
  - **the most important physiological mechanism that prevents reflux → Parasympathetic stimulation of the lower circular smooth-muscle fibres of the oesophagus**

Cause

- **Transient lower esophageal sphincter relaxation is the most common cause**
- Other causes include
  - pregnancy
    - decreased motility secondary to progesterone
  - gastric acidity
  - gastric outlet obstruction
  - decreased esophageal motility
  - hiatal hernia
    - ≥ 90% of patients with **severe** GORD
  - Obesity
    - Transient relaxations of the lower esophageal sphincter (TRLES) have been observed to be more common in patients with obesity.
    - The main stimulus for TRLES is **gastric distension,** particularly in the fundus.
- Associated with:
  - Lifestyle habits such as **smoking, caffeine and alcohol consumption**
  - Scleroderma
  - Angle of His enlargement (> 60°)

Features

- heartburn and regurgitation when lying down.
- (GORD) is the most common non-cardiac cause of **chest pain**.
  - may occur in a supine position, after meals, and along with a sour, acidic taste in the mouth.
- Chronic GORD can present with chronic cough, new adult-onset of asthma, hoarseness, regurgitation, and dysphagia.
  - The three most common causes of a persistent cough are postnasal drip, asthma, and **GORD**.
- Acid reflux in chronic GORD can lead to damage of the enamel layer of teeth.
- **May present with over-the-counter antacids side effects** which may include magnesium hydroxide.
  - **Magnesium hydroxide** can act as an **osmotic laxative**, resulting in the adverse effect of **diarrhea**.
- **Symptoms do not correlate with mucosal status at endoscopy appearance**

Investigations

- **endoscopy**
  - **Indications for upper GI endoscopy:**
    - age > 55 years
    - symptoms > 4 weeks or persistent symptoms despite treatment
    - dysphagia
    - relapsing symptoms
    - weight loss
  - The most common endoscopic finding associated with esophageal mucosal injury is reflux esophagitis.
  - If endoscopy is negative consider **24-hr oesophageal pH monitoring (the gold standard test for diagnosis)**

Treatment

- **lifestyle changes**
  - Small portions;
  - avoid eating (< 3 hours) before bedtime.
  - Avoid foods with high fat content
  - **Avoid**: nicotine, alcohol, coffee[12][7], and certain drugs (e.g., calcium channel blockers, diazepam)
- Proton pump inhibition
  - **if lifestyle changes are ineffective, one month course of a proton pump inhibitor (PPI)**
  - **full dose (PPI)** for **one month** will typically result in healing in **76%, continuation for a further** month increases this by a further **14%.**
  - **In those failing to respond to two months of full dose therapy doubling the dose of proton pump inhibitor for one month increases response rate.**
    - increase the dose to (twice daily therapy)
  - In those failing to respond to a double dose of proton pump inhibition an **H2 receptor** antagonist may be added **or substituted** in treatment **or a prokinetic agent added** to treatment.
    - Offer H_2RA therapy if there is an inadequate response to a PPI.
    - Simply extending the duration of proton pump inhibitor therapy beyond two months without any additional change is not recommended.
  - A **regular maintenance low dose** of most PPIs will **prevent recurrent GORD** symptoms in 70-80% of patients and should be used in preference to the higher healing dose.
  - People who have had **dilatation of an oesophageal stricture** should remain on **long-term full-dose PPI** therapy
  - Offer a **full-dose PPI long-term as maintenance** treatment for people with **severe oesophagitis**
- **Laparoscopic fundoplication**
  - **the treatment of choice for patients with GORD refractory to or intolerant of proton pump inhibitor therapy.**
  - The patient should have had an endoscopy within the six months prior to surgery to exclude any unsuspected pathology such as Barrett's oesophagus or adenocarcinoma.
  - **the most useful in assessing the role of surgery → Oesophageal motility and pH study**

GORD management

- **1st line** - lifestyle changes
  - don't lie down after eating
  - avoid spicy foods
  - eat small servings
- **2nd line** → proton pump inhibitors (omeprazole, lansoprazole)
- **3rd line** → H2 receptor antagonists(cimetidine, ranitidine) or
- **4th line** → Surgical Nissen fundoplication or hiatal hernia repair

Treatment of choice: Standard-dose of PPI for at least 8 weeks (once daily therapy)

- No response: → further diagnostic evaluation
- Partial response: → increase the dose to (twice daily therapy)
- Good response: → discontinue PPI after 8 weeks
  - if symptoms recur after discontinuation of PPIs → Maintenance therapy
    - After 8 weeks of initial treatment, reduce PPI to lowest effective dose

Complications

- metaplasia of the lower esophagus, which is the first stage of Barrett esophagus.
- **Esophageal strictures** occur in 10%
  - Two types of rings (**Schatzki rings**):
    - muscular ring, or A ring:
      - located approximately 2 cm above the gastroesophageal junction.
      - rare
    - mucosal ring, or B ring,
      - **most common**
      - located at the squamo-columnar junction.
  - mechanical cause of dysphagia

        - characterized by **progressive symptoms**. Patients often first notice difficulty swallowing solid foods, and this then progresses to softer foods, and then fluids.
    - most patients respond well to dilatation therapy.
- adenocarcinoma of the lower esophagus.

Barrett's oesophagus

Definition

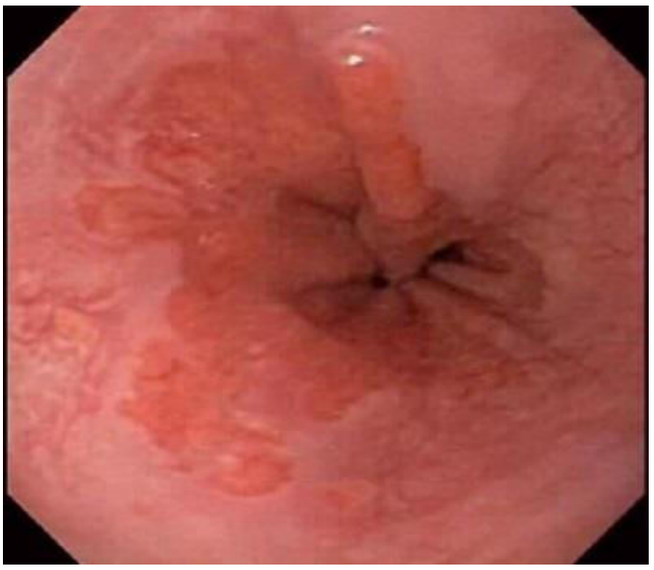
- metaplasia of the lower oesophageal mucosa (squamous epithelium replaced by → columnar epithelium).
- The physiological transformation zone ("Z-line") between squamous and columnar epithelium is shifted upwards

Risk factors

- long duration or frequency of GORD symptoms,
- previous oesophagitis,
- previous hiatus hernia,
- oesophageal stricture or ulcer
- male gender

Histological features

- the columnar epithelium may resemble that of either the cardiac region of the stomach or that of the small intestine (e.g. with goblet cells, brush border)



Barrett's oesophagus

Management

- endoscopic surveillance with biopsies
    - the merits of surveillance need to be assessed on a patient to patient basis:
        - **NO** dysplasia and **<3 cm** segment of Barrett's
            - **endoscopy every three to five years with biopsies**
        - **NO** dysplasia and segment Barrett's **>3 cm**
            - Endoscopy every **two to three** years
                - **Start a proton pump inhibitor and repeat the endoscopy and biopsy in two years**
        - Low grade dysplasia
            - six monthly biopsy
        - high grade dysplasia
            - needs therapy; oesophagectomy, photodynamic therapy, ablative therapy.
- **high-dose proton pump inhibitor**:
    - the best next line of management
    - whilst this is commonly used in patients with Barrett's the evidence base that this reduces the change of progression to dysplasia or induces regression of the lesion is limited
- moderate to severe grade dysplasia or recurrent disease
    - Endoscopic ablation therapy

- Endoscopic mucosal resection
- Lower esophageal resection

Prognosis

- ↑↑ risk of oesophageal adenocarcinoma (50-100 fold).
  - The risks of adenocarcinoma are relatively high but absolute risk is low 1% per year develop adeno-carcinoma.

Oesophagitis

- esophagitis in the immunocompromised that presents with **punched-out ulcers** → Herpes simplex virus-1
- esophagitis in the immunocompromised that presents with a **white pseudomembrane** → *Candida spp.*
- esophagitis in the immunocompromised that presents with **linear ulcers** → Cytomegalovirus

Candida oesophagitis

Although oropharyngeal candidiasis may be treated with topical antifungal agents (such as nystatin, clotrimazole, and amphotericin B oral suspension/lozenges) ***Candida* oesophagitis requires oral or IV therapy (usually with fluconazole or itraconazole for at least 14-21 days).**

Eosinophilic oesophagitis (EOE)

Causes

- unknown,
- **allergies**
  - At least **50% of children with EoE have allergies**, including food allergies, allergic rhinitis (hay fever) and asthma.

Features

- **episodic oesophageal spasm and intermittent dysphagia**

Diagnosis

- by endoscopy and **biopsy** → presence of **eosinophils**

Treatment

- **Responds to "swallowed" steroid**

Oesophageal cancer

Oesophageal adenocarcinoma is associated with GORD or Barrett's

Epidemiology

- **Sex: ♂ > ♀ (3:1)**
- **Adenocarcinoma is now the most common type** of oesophageal cancer and is more likely to develop in patients with a history of gastro-oesophageal reflux disease (GORD) or Barrett's.
- **The majority of tumours are in the middle third of the oesophagus**.

Types

- **Adenocarcinoma**
  - the most common form of esophageal cancer in the United States,
  - affects primarily white men.
  - begins in the cells of mucus-secreting glands in the esophagus.
    - develops in the **glandular cells of the submucosa**.
  - occurs most often in the **lower** portion of the esophagus.
    - Most cancers in the lower oesophagus, including the junction where the oesophagus joins the stomach, are adenocarcinomas.
    - 45% of oesophageal carcinomas occur in the lower third and are usually adenocarcinomas.
- **Squamous cell carcinoma**

- the most prevalent esophageal cancer worldwide.
- develops in the **thin, flat cells** of the **mucosa** , which line the oesophagus.
- occurs most often in the upper and **middle** portions (upper two-thirds) of the esophagus.
  - Cancers in the upper oesophagus are nearly always squamous cell cancers.
  - Most cancers in the middle of the oesophagus are squamous cell cancers.
  - 40% of oesophageal carcinomas occur in the middle third of the oesophagus and are usually squamous-cell carcinomas.

Risk factors (emedicine.medscape.com 2017)

- **Risk factors for SCC**
  - Smoking and alcohol use
    - No associations were found between alcohol consumption and esophageal adenocarcinoma.
  - Diet
    - Red meat consumption
    - Low selenium levels
      - selenium supplementation reduces the risk
    - Zinc deficiency
      - mediates carcinogenesis by
        - ⇨ **enhancing the carcinogenic effects of nitrosamines** and
        - ⇨ also leads to **overexpression of cyclooxygenase (COX)-2.**
    - Low dietary folate intake
    - low intake of fruits and vegetables
    - Foods products containing N-nitroso compounds
    - Toxin-producing fungi (eg, aflatoxin) induce carcinogenesis by reducing nitrates to nitroso compounds.
  - hot liquids
  - Certain infections
  - Tylosis
  - Caustic stricture
  - Achalasia cardia
  - Prior gastrectomy
  - Use of oral bisphosphonates
  - Drinking scalding-hot liquids
  - Poor oral hygiene
  - Plummer-Vinson syndrome
- **Risk factors for adenocarcinoma**
  - GORD
    - (the most common predisposing factor)
  - Barrett's oesophagus
  - Obesity and metabolic syndrome
- rare: coeliac disease, scleroderma

Risk factors for oesophageal cancer:

Squamous	Adenocarcinoma
Alcohol	-
Smoking	Smoking
Achalasia	Barrett's oesophagus
Plummer vinson	GORD

Although the mechanism of action is unclear population studies have shown a lower incidence of oesophageal cancer in patients infected with *H. pylori*.

Features

- Dysphagia is a **late** symptom.
  - **Presented with progressive dysphagia, initially worse on solids and then later to include liquids and weight loss**

- **dermatological conditions associated with oesophageal carcinoma → Tylosis**

Diagnosis

- **Upper GI endoscopy is the first line test**
  - **Esophagogastroduodenoscopy** (best initial and confirmatory test)
- **Staging**
  - **CT**
    - initially undertaken with **CT** scanning of the chest, abdomen and pelvis.
    - If overt metastatic disease is identified using this modality then further complex imaging is unnecessary
  - If CT does not show metastatic disease, then local stage may be more accurately assessed by use of **endoscopic ultrasound**.
  - **Staging laparoscopy** is performed to detect occult peritoneal disease.
  - **PET CT** is performed in those with negative laparoscopy.

Treatment

- **Most oesophageal cancers are not resectable at presentation**
  - Most patients present with stage 3 disease (late stage) and survival at 5 years is only 9%.
- Operable disease is best managed by **surgical resection**.
  - **chemoradiotherapy then surgery is preferred to surgery alone.**
    - A study of 1085 patients who underwent oesophagectomy surgery showed a 4% operative mortality rate and a 23% survival rate. For patients who had **preoperative chemoradiotherapy**, the **prognosis improved to 48%**
  - **The most standard procedure is an Ivor- Lewis type oesophagectomy**.
    - This procedure involves the mobilisation of the stomach and division of the oesophageal hiatus.
    - The abdomen is closed and a right sided thoracotomy performed.
    - The stomach is brought into the chest and the oesophagus mobilised further.
    - An intrathoracic oesophagogastric anastomosis is constructed.
  - Alternative surgical strategies include a transhiatal resection (for distal lesions),
  - left thoraco-abdominal resection (difficult access due to thoracic aorta)
  - total oesophagectomy (McKeown) with a cervical oesophagogastric anastomosis.

- The biggest surgical challenge is that of anastomotic leak, with an intrathoracic anastomosis this will result in mediastinitis. With high mortality. The McKeown technique has an intrinsically lower systemic insult in the event of anastomotic leakage.
- In addition to surgical resection many patients will be treated with adjuvant chemotherapy.
- **Nifedipine helps relieve painful oesophageal spasm and tenesmus associated with gastrointestinal tumours and could be used to relieve his odynophagia.**

What is the most common type of Oesophageal cancer?

- patient.info (https://patient.info/health/oesophageal-cancer-leaflet) (04 Dec 2017)
  - **Adenocarcinoma** of the oesophagus occurs in about **6 out of 10** cases in the UK.
  - **Squamous cell carcinoma** of the oesophagus occurs in about **4 out of 10** cases in the UK.
- mayoclinic.org (https://www.mayoclinic.org/diseases-conditions/esophageal-cancer/symptoms-causes/syc-20356084)
  - Squamous cell carcinoma is the most prevalent esophageal cancer worldwide.
  - Adenocarcinoma is the most common form of esophageal cancer in the United States
- emedicine.medscape.com (https://emedicine.medscape.com/article/277930-overview#a6) (Updated: Jun 20, 2017)
  - esophageal adenocarcinoma is the most common in the United States.
  - Unlike in the United States, squamous cell carcinoma is responsible for 95% of all esophageal cancers worldwide.

Pharyngeal pouch (or Zenker's diverticulum).

Definition

- A pharyngeal pouch is a **posteromedial** diverticulum through **Killian's dehiscence**.
  - Killian's dehiscence is a triangular area in the wall of the pharynx **between the thyropharyngeus and cricopharyngeus muscles.**

- Upper esophageal diverticulum (Common site)
- Most common type of esophageal diverticula

Epidemiology

- more common in **older** patients
- 5 times more common in **men**

Associations

- they may be related to poor relaxation of the **upper** oesophageal sphincter.
- association with gastro-oesophageal reflux disease has been noted.

Features

- dysphagia
- regurgitation
- aspiration
- neck swelling which gurgles on palpation (Boyce's sign).
- **halitosis** (a bad breath)

Diagnosis

- by barium studies
  - detected best by using **lateral X-ray** shows a contrast-filled pouch **protruding dorsally from the hypopharynx at the level of C5/C6**
  - Upper gastrointestinal endoscopy is risky, since the pouches are thin-walled and easy to perforate; this is the reason why a **barium swallow may be the preferable first-line investigation in elderly patients with dysphagia.**

Treatment

- surgical, with either an open or endoscopic approach.
- Diverticula of the **middle and distal** esophagus (traction diverticula and epiphrenic diverticula) usually do not require treatment

---

Acute upper gastrointestinal bleeding (UGIB) (NICE 2012)

Definition

- bleeding derived from a source proximal to the ligament of Treitz.

Causes: Most commonly due to either:

- peptic ulcer disease or
- oesophageal varices.

Risk assessment

- use the Blatchford score at first assessment, and
- the full Rockall score after endoscopy

Blatchford score

- The **Blatchford score** is based on clinical parameters alone:
  - Elevated blood urea nitrogen
  - Reduced haemoglobin
  - A drop in systolic blood pressure
  - Raised pulse rate
  - The presence of melaena or syncope, and
  - Evidence of hepatic or cardiac disease.

Admission risk marker	Score
Urea (mmol/l)	6.5 - 8 = 2 8 - 10 = 3 10 - 25 = 4 > 25 = 6
Haemoglobin (g/l)	Men • 12 - 13 = 1 • 10 - 12 = 3 • < 10 = 6 Women

Admission risk marker	Score
	• 10 - 12 = 1 • < 10 = 6
Systolic blood pressure (mmHg)	100 - 109 = 1 90 - 99 = 2 < 90 = 3
Other markers	Pulse >=100/min = 1 Presentation with melaena = 1 Presentation with syncope = 2 Hepatic disease = 2 Cardiac failure = 2

Patients with a Blatchford score of 0 may be considered for early discharge

Rockall score

- Used to:
  - determine the prognosis of upper GIT bleeds.
  - assess severity of GIT bleeds and / or to triage patients for emergency endoscopy.
- Consists of **5** categories:
  1. age
  2. shock
  3. **co-morbidity e.g. ischaemic heart disease (IHD)**
  4. diagnosis and
  5. evidence of bleeding (the latter two can only be categorised after endoscopy).
- Each category is scored between 0 and 2 points, with the exception of **co-morbidities which has a maximum score of 3.**
  - **Renal failure, liver failure and metastatic cancer carry the highest points, and thus confer the highest risk of death**, of any of the other parameters included in the scoring system.
- The full Rockall scoring system is shown in the table below:

	Score 0	Score 1	Score 2	Score 3
Age	<60	60-79	>80	-
Shock	No shock	Pulse >100	Systolic blood pressure <100 mmHg	-
Co-morbidity	Nil major		CCF, IHD, major morbidity	**Renal or liver failure, metastatic cancer**
Diagnosis	Mallory-Weiss tear	All other diagnoses	GI malignancy	-
Evidence of bleeding	None	-	Blood, adherent clot, spurting vessel	-

- **Interpretation:**
  - Increasing scores are strongly correlated with **increasing risk of mortality**,
    - The total score predicts mortality as follows:
      - Score 0, → 0.2%;
      - score 2, → 5%;
      - score 4, → 24%;

- ❖ score 6, → 49%.

➢ correlation with **risk of re-bleeding** is also present but not as strong.

Grades of hypovolaemic shock

The table below outlines the signs and symptoms of the different grades of hypovolaemic shock:

Grade 1	• Up to about **15% loss** of effective blood volume (**~750ml** in an average adult who is assumed to have a blood volume of 5 litres). • This leads to **a mild resting tachycardia** and can be well tolerated in otherwise healthy individuals. • In the elderly or those with underlying conditions such as ischaemic heart disease the additional myocardial oxygen demands may not be tolerated so well.
Grade 2	• Between **15-30% loss** of blood volume (**750-1500ml**) • will provoke a **moderate tachycardia and begin to narrow the pulse pressure**. • **The capillary refill time will be extended**.
Grade 3	• At **30 - 40% loss** of effective blood volume (**1500 - 2000 ml**) • the **compensatory mechanisms begin to fail** and **hypotension**, tachycardia and **low urine output** (<0.5ml/kg/hr in adults) are seen.
Grade 4	• At **40-50% loss** of blood volume (**2000-2500 ml**) • **profound hypotension** will develop and if prolonged will cause **end-organ damage and death**.

Classification of haemorrhage:

Parameter	I	II	III	IV
Blood loss (ml)	<750	750-1500	1500-2000	>2000
Blood loss (%)	<15%	15-30%	30-40%	>40%
Pulse rate (beats/min)	<100	>100	>120	>140
Blood pressure	Normal	Decreased	Decreased	Decreased
Respiratory rate (breaths/min)	14-20	20-30	30-40	>35
Urine output (ml/hour)	>30	20-30	5-15	Negligible
CNS symptoms	Normal	Anxious	Confused	Lethargic

Blood test evidence of upper gastrointestinal haemorrhage
- **Reactive thrombocytosis**
- Urea elevated in excess of creatinine

Treatment

- **Resuscitation**
  - ➢ ABC, wide-bore intravenous access
  - ➢ platelet transfusion if actively bleeding platelet count of **less than 50** x 10*9/litre
  - ➢ fresh frozen plasma to patients who have either a fibrinogen level of **less than 1 g/litre**, or a prothrombin time (international normalised ratio) or activated partial thromboplastin time greater than 1.5 times normal
  - ➢ prothrombin complex concentrate to patients who are taking warfarin and actively bleeding
- **Endoscopy**
  - ➢ should be offered immediately after resuscitation in patients with a severe bleed
  - ➢ all patients should have endoscopy within 24 hours

- Recent NICE guidelines do not recommend proton pump inhibition (PPIs) before endoscopy.
- **He may have alcohol dependency and therefore should be prescribed Pabrinex whilst waiting for endoscopy.**

- **Management of non-variceal bleeding**
  - NICE do not recommend the use of proton pump inhibitors (PPIs) before endoscopy to patients with suspected non-variceal upper gastrointestinal bleeding although PPIs should be given to patients with non-variceal **upper gastrointestinal bleeding and stigmata of recent haemorrhage shown at endoscopy**
  - The best evidence for pharmacological intervention post-stabilisation of bleeding peptic ulcer disease is for proton pump inhibitors.
    - **the most appropriate intervention to prevent further bleeding → IV omeprazole**
      - reduction in risk of recurrent bleeding of over 50%,
      - reduction in need for surgical intervention of approximately 40%.
  - if further bleeding then options include repeat endoscopy, interventional radiology and surgery
- **Management of variceal bleeding**
  - **terlipressin** and prophylactic antibiotics should be given to patients at presentation (i.e. before endoscopy)
  - band ligation should be used for oesophageal varices and injections of N-butyl-2-cyanoacrylate for patients with gastric varices
  - transjugular intrahepatic portosystemic shunts (TIPS) should be offered if bleeding from varices is not controlled with the above measures

Oesophageal varices

Antibiotic prophylaxis reduces mortality in cirrhotic patients with gastrointestinal bleeding

Oesophageal varices drain into azygous vein and thence into superior vena cava

- Esophageal varices are the most common cause of death in cirrhosis.

Acute treatment of variceal haemorrhage

Terlipressin - method of action = constriction of the splanchnic vessels

- ABC: patients should ideally be resuscitated prior to endoscopy
- correct clotting: FFP, vitamin K
- vasoactive agents:
  - **terlipressin is currently the only licensed vasoactive agent** and is supported by NICE guidelines.
    - powerful splanchnic vasoconstrictor
    - It has been shown to be of benefit in **initial haemostasis** and preventing **rebleeding**.
    - **the most appropriate treatment whilst awaiting urgent endoscopy**
    - As a vasoconstrictor its administration is **contraindicated in those with a history of ischaemic heart disease** as it may precipitate myocardial ischaemia.
  - Octreotide may also be used although there is some evidence that terlipressin has a greater effect on reducing mortality
- prophylactic antibiotics
  - have been shown in multiple meta-analyses to reduce mortality in patients with liver cirrhosis.
  - Quinolones are typically used.
- endoscopy:
  - endoscopic variceal band ligation is superior to endoscopic sclerotherapy. NICE recommend band ligation

- Sengstaken-Blakemore tube if uncontrolled haemorrhage
  - Balloon tamponade (for example, using a Sengstaken-Blakemore tube) may be used as a holding measure **in situations where, for whatever reason, a definitive procedure cannot be performed to control bleeding** (for example, endoscopy or transjugular intrahepatic portosystemic shunting).
  - It is generally very effective in achieving control of variceal bleeding.
- Transjugular Intrahepatic Portosystemic Shunt (TIPSS) if above measures fail

Prophylaxis of variceal haemorrhage

- propranolol:
  - reduced rebleeding and mortality compared to placebo
- endoscopic variceal band ligation (EVL)
  - is superior to endoscopic sclerotherapy.
  - It should be performed at two-weekly intervals until all varices have been eradicated.
  - Proton pump inhibitor cover is given to prevent EVL-induced ulceration

Esophageal Rupture

- **Causes**
  - Iatrogenic esophageal perforation:
    - most common cause of esophageal perforation
    - Generally injury during upper endoscopy
      - Symptoms usually within 24 hours of endoscopy
  - Foreign body ingestion
  - Trauma
  - Malignancy
  - Boerhaave syndrome
    - Severe vomiting/increased intrathoracic pressure → rupture of all layers of the esophageal wall
    - In > 90% of cases, the rupture occurs in the **distal third** of the esophagus on the **left dorsolateral** wall surface.
    - Sex: ♂ > ♀ (3:1)
    - Associations
      - Excessive intake of alcohol or food in the recent past
      - Repeated episodes of vomiting
      - Childbirth
      - Seizures
      - Prolonged coughing
      - Weightlifting
    -
- **Feature:**
  - Mackler's triad (vomiting, chest pain and surgical emphysema) is classical but absent in almost half the cases.
    - surgical emphysema
      - Subcutaneous emphysema → crepitus in the suprasternal notch
      - mediastinal emphysema → "crunching" or "crackling" sound on chest auscultation (**Hamman's sign**)
        - ⇨ **The most relevant finding on examination is the crepitus over the chest**
  - Dyspnea, cyanosis
- **investigations**:
  - **Gastrografin swallow** will confirm the site of perforation in approximately 65-75% of cases, and is the **recommended first line investigation.**
  - **chest x ray**
    - useful in the initial diagnosis
    - The most common finding is a **unilateral effusion**, usually on the left.
      - Because the most perforations occur in the left posterior aspect of the esophagus.
    - Other findings may include
      - pneumothorax, hydropneumothorax, pneumomediastinum,
      - surgical emphysema.
      - mediastinal widening.
  - **Lateral neck x rays**

- may be useful in the early stages where the diagnosis is uncertain and surgical emphysema is not seen on a plain CXR.

➢ **CT scan**:
- indicated in unstable/uncooperative patients, pneumoperitoneum on x-ray, or ifx-rays and contrast esophagram are inconclusive

➢ Barium swallow
- more sensitive at 90% for detecting small perforations but carries the risk of a severe inflammatory response (**mediastinaitis**).

- **Prognosis**
  - ➢ A reported mortality estimate is approximately 35%, making it the most lethal perforation of the GI tract.
  - ➢ If intervention is delayed longer than 24 hours, the mortality rate (even with surgical intervention) rises to higher than 50% and to nearly 90% after 48 hours. Left untreated, the mortality rate is close to 100%.

Hiccup

- caused by frequent or rhythmic clonic contraction of the diaphragm.
- When prolonged, other causes should be considered including:
  - ➢ CNS disease - posterior fossa tumour, brain injury, encephalitis
  - ➢ Phrenic nerve or diaphragm irritation - tumour, pleurisy, pneumonia, intrathoracic adenopathy, pericarditis, gastro-oesophageal reflux, oesophagitis
  - ➢ Systemic causes include alcohol intoxication and uraemia.
  - ➢ Other causes include foreign body or insect in the ear.
  - ➢ In infants it may be associated with apnoea or hyperventilation.
- Treatment
  - ➢ Folk remedies include aerophagia, breath holding, pharyngeal stimulation, distraction.
  - ➢ Haloperidol, metaclopramide and several anaesthetic agents are also said to work.

Gastric conditions

Helicobacter pylori

H. pylori eradication:
- PPI + amoxicillin + clarithromycin, or
- PPI + metronidazole + clarithromycin

- *Helicobacter pylori* is a **Gram negative bacteria** associated with a variety of gastrointestinal problems, principally peptic ulcer disease

Associations
- peptic ulcer disease (95% of duodenal ulcers, 75% of gastric ulcers)
- gastric cancer
- B cell lymphoma of MALT tissue (eradication of H pylori results causes regression in 80% of patients)
- atrophic gastritis

NOT associated with GORD
- The role of H pylori in Gastro-oesophageal reflux disease (GORD) is unclear - there is currently no role in GORD for the eradication of H pylori

Helicobacter pylori: tests

Urea breath test - no antibiotics in past 4 weeks, no antisecretory drugs (e.g. PPI) in past 2 weeks

Urea breath test
- patients consume a drink containing carbon isotope 13 (13C) enriched urea
- urea is broken down by *H. pylori* urease
- after 30 mins patient exhale into a glass tube
- mass spectrometry analysis calculates the amount of 13C CO2

- should not be performed within 4 weeks of treatment with an antibacterial or within 2 weeks of an antisecretory drug (e.g. a proton pump inhibitor)
- sensitivity 95-98%, specificity 97-98%
- **the preferred method for testing eradication.**

Rapid urease test (e.g. CLO test)

- biopsy sample is mixed with urea and pH indicator
- colour change if H pylori urease activity
- sensitivity 90-95%, specificity 95-98%
- Although rapid urease testing has a sensitivity of 93-97% the false negative rate increases significantly in the context of :
  - **recent gastrointestinal haemorrhage**,
  - acid suppression therapy and
  - recent antibiotic treatment.
    - **In this case a blood test for *Helicobacter pylori* infection is required**
      - Serological markers would indicate the likelihood of *Helicobacter pylori* infection and are **unaffected by the factors mentioned above.**

Serum antibody

- remains positive after eradication
- sensitivity 85%, specificity 80%

Culture of gastric biopsy

- provide information on antibiotic sensitivity
- sensitivity 70%, **specificity 100%**
- *H. pylori* colonized on the surface of regenerative epithelium (silver stain)

Gastric biopsy

- histological evaluation alone, no culture
- sensitivity 95-99%, specificity 95-99%

Stool antigen test

- sensitivity 90%, specificity 95%
- Whilst stool antigen testing is appropriate in the setting of initial diagnosis the NICE guidelines on dyspepsia **do not recommend its use to confirm eradication** due to a lack of evidence.
  - **it is important to be aware that testing may need to be delayed for three months after treatment to confirm eradication.**

Test to confirm eradication :

- **When to test for complete eradication?**
  - Re-testing for *Helicobacter pylori* is **indicated only in the setting of peptic ulcer** disease to confirm eradication where an initial test is positive.
- **Which test?**
  - **Carbon-13 urea breath testing is the only well validated method for confirming the successful eradication of *Helicobacter pylori.***

Management

- **First-line treatment**
  - eradication may be achieved with a 7 day course of
    - not allergic to penicillin → PPI + amoxicillin + clarithromycin, or
    - allergic to penicillin → PPI + metronidazole + clarithromycin
    - allergic to penicillin + previous exposure to clarithromycin → PPI + bismuth + metronidazole + tetracycline

- **Second-line treatment**
  - If still symptomatic after first-line → give a 7-day, twice-daily course of:
    - PPI + amoxicillin + either clarithromycin or metronidazole (whichever was not used first-line)
    - If there is a previous exposure to clarithromycin and metronidazole → PPI + amoxicillin + quinolone or tetracycline (whichever has the lowest acquisition cost).
    - allergic to penicillin + NO previous exposure to a quinolone → PPI + metronidazole + levofloxacin
    - allergic to penicillin + previous exposure to a quinolone → PPI + bismuth + metronidazole + tetracycline.
- If there is inadequate response with initial *H. pylori* eradication regime. Expert opinion recommends:

- **Re-testing for *H. pylori* before second-line treatment** is considered to confirm eradication as there are serious side effects associated with antibiotics, e.g. *Clostridium difficile* infection, and antibiotic resistance is increasing.
- According to the British Infection Association, **the carbon-13 urea breath test is the most accurate method of re-testing for *H. pylori*.**
  - This should be performed 4 weeks after the eradication therapy since antibiotics and proton pump inhibitors (PPIs) can suppress the bacteria causing a false negative result.
- Eradication therapy is effective in 80-85% of cases and should not be repeated without evidence of treatment failure.

Peptic ulcer

Basic

Bleeding from Posterior duodenal ulcers are due to erosion of the gastroduodenal artery

- **The right and left gastroepiploic arteries (gastro-omental arteries) supply the greater curvature of the stomach.**
  - **The source of ulcer bleeding in the greater curvature of the stomach → Left gastroepiploic artery**
- The **right gastric artery** arises from the hepatic artery or the left hepatic artery, supplies the pylorus and travels along the **lesser curvature of the stomach**, supplying it, and anastomosing with the left gastric artery.
  - **the cause of ulcer bleeding in the lesser curvature of the stomach → right gastric artery**
- The **pancreaticoduodenal artery** (a branch of the gastroduodenal artery) supplies mainly the upper and lower duodenum and the head of the pancreas.
- The **right hepatic artery** supplies the right lobe of the liver and part of the caudate lobe.

The golden notes

Sources of bleeding in peptic ulcers:

- greater curvature of the stomach → Left gastroepiploic artery
- lesser curvature of the stomach → right gastric artery
- Posterior duodenal ulcers → gastroduodenal artery
  - pancreaticoduodenal artery (a branch of the gastroduodenal artery) supplies mainly the upper and lower duodenum.

The golden notes

Sites of peptic ulcers:

- 80% are duodenal.
- The most common site → near the pylorus, on the duodenal side
- The less frequent site → lesser curvature of stomach or at the point at which the esophagus enters the stomach.

Risk factors for peptic ulceration include

- *Helicobacter pylori* (*H. pylori*) infection,
- non-steroidal anti-inflammatory drug (NSAID) use,
- cigarette smoking and
- genetic factors - Lewis blood group antigens facilitate *H. pylori* attachment to the mucosa.

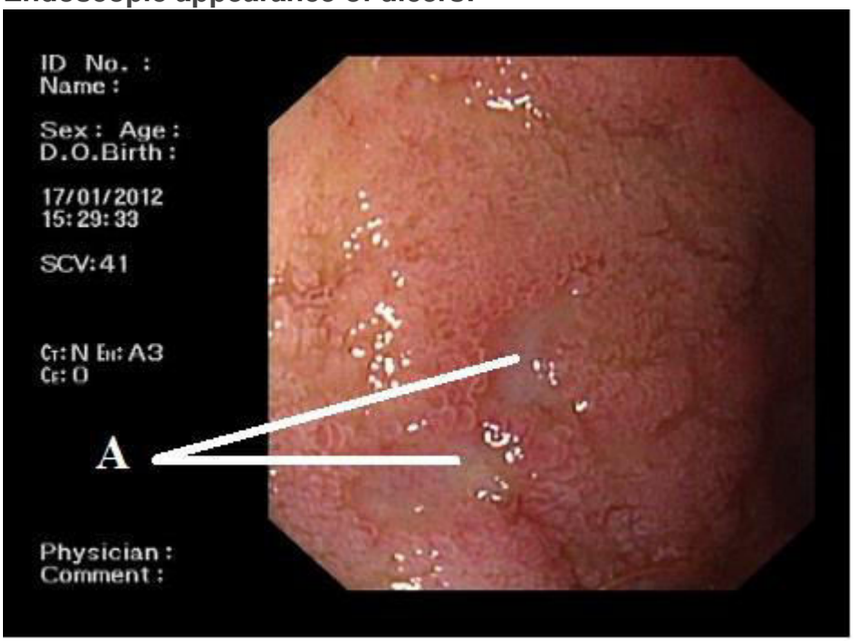
Interventions for peptic ulcer disease (NICE 2012)

- peptic ulcer + *H pylori* → *H pylori* eradication therapy
- peptic ulcer + *H pylori* → retesting for *H pylori* 6 to 8 weeks after beginning treatment,
- gastric ulcer + *H pylori* → repeat endoscopy 6 to 8 weeks after beginning treatment
- In people at high risk (previous ulceration) and for whom NSAID continuation is necessary, consider a COX-2 selective NSAID instead of a standard NSAID with a PPI.
  - The Two highly selective or specific in their ability to inhibit COX-2 while having little or no COX-1 affinity are rofe**coxib** and cele**coxib**.
- Offer H_2RA therapy if there is an inadequate response to a PPI.

The effect *of Helicobacter* eradication on healing and recurrence of peptic ulcer:

- The effects is dependent upon whether ulceration is gastric or duodenal and whether the patient is taking non-steroidal anti-inflammatory drugs or not.
  - **For duodenal ulcers** eradication slightly **increases healing** (additional 5.4% over acid suppression alone) but dramatically **decreases recurrence** (increases the number of patients ulcer free at 12 months by 52%).
  - **For gastric ulcers** eradication therapy **has no effect on healing but does decrease recurrence** (an additional 32% of patients are ulcer free at 12 months compared to acid suppression alone).
  - **In patients taking non-steroidal anti-inflammatory drugs** eradication therapy has **no effect on peptic ulcer healing** (gastric or duodenal), **but will decrease ulcer recurrence**
    - continued non-steroidal anti-inflammatory drug use markedly reduces the size of effect that eradication therapy has on reducing ulcer recurrence.

Endoscopic appearance of ulcers:



- The endoscopic appearances are of two small duodenal ulcers (**A**) without evidence of recent haemorrhage. There is some co-existent duodenitis.
- **The presence of villi identifies this as the duodenum.**
- The mucosal appearances are not consistent with that of the stomach (absence of rugae, paler squamous epithelium rather than redder columnar epithelium) or the oesophagus (pale pink non-villous squamous epithelium).

Following endoscopic intervention

- **immediately post-endoscopy, patients should be commenced on a high dose oral or intravenous proton pump inhibitor**, this reduces the risk of rebleeding.
- Amoxicillin and clarithromycin may be indicated if there is evidence of Helicobacter pylori infection. This need not be started immediately post-endoscopy but treatment should not be unnecessarily delayed.

Zollinger-Ellison syndrome

Zollinger-Ellison syndrome: epigastric pain and diarrhoea

Definition

- gastrinoma (Zollinger-Ellison syndrome) is a gastrin-secreting neuroendocrine tumor that is most often localized to the duodenum and pancreas.
  - Gastrin is released by G cells in the antrum under normal physiological conditions.

Tumor location

- Duodenum (~ 70% of cases)
  - Most ulcers are located in the first part of the duodenum.
- Pancreas (~ 25% of cases): typically the head
- Ectopic locations (5–15% of cases)

Causes

- Most gastrinomas occur sporadically.
- **Around 30% occur as part of MEN type I syndrome**

Epidemiology

- Sex: ♂ > ♀ (2:1)
- Age of onset: 30–50 years

Pathophysiology

- Hypergastrinemia → stimulation of parietal cells → gastric acid hypersecretion, which leads to:
  - Peptic ulcer disease
  - Inactivation of pancreatic enzymes → diarrhea, steatorrhea → malabsorption

Features

- multiple gastroduodenal ulcers
- diarrhoea
- malabsorption

Diagnosis

- Best initial test: esophagogastroduodenoscopy
  - Important to rule out *H. pylori* infection and malignant ulcers
  - Typically reveals multiple ulcers and thick gastric folds
  - ↓ Gastric pH

- **Fasting gastrin levels: the single best screen test**
  - fasting gastrin test **>** 1000 with low PH < 2 is **diagnostic**
  - if level **<** 1000 and the diagnosis is suspected, then **secretin stimulation testing** or calcium stimulation testing
    - secretin stimulation test
      - rise **>** 200 after 15 minute of dosing is considered positive
    - calcium stimulation test
      - rise **>** 395 is considered positive
- **Secretin stimulation test** (if fasting serum gastrin test is inconclusive)

The presence of multiple, large (> 2 cm) ulcers in atypical locations (e.g., the jejunum) should raise suspicion of gastrinoma.

Treatment

- Reduce acid production
  - **PPIs** (e.g., omeprazole), H2 antagonists (e.g., ranitidine)
  - Octreotide (a somatostatin analog) may be used in refractory cases.
- Non-metastatic disease:
  - surgical resection of the gastrinoma
- Metastatic disease:
  - chemotherapy
  - In approximately 50% of cases, the tumor has already metastasized at the time of diagnosis

Gastric MALT lymphoma

Gastric MALT lymphoma - eradicate H. pylori

Overview

- lymphoma of **M**ucosa-**A**ssociated **L**ymphoid **T**issue (MALT)
- (MALT) is typically a low-grade, B-cell neoplasia originating from mucosa-associated lymphoid tissue
- associated with *H. pylori* infection in 95% of cases
- good prognosis
- Within the stomach **the antrum is most commonly involved**

Epidemiology

- **MALT lymphoma**
  - 7% to 8% of all B-cell lymphomas
  - the third most common type of non-Hodgkin's lymphoma
  - the most common type of primary **extra-nodal** lymphoma and represents up to 50% of primary gastric lymphomas.
- **Gastric MALT lymphomas**
  - account for about 30% of all MALT lymphomas,
  - median age of 57 years
  - no sex predilection.

Features

- paraproteinaemia may be present
- infiltrate of small-size lymphocytes that destroy gastric glands, configuring the so-called '**lymphoepithelial lesion'** which is **pathognomonic of lymphoma**
- The common cytogenetic abnormalities demonstrated in MALT lymphomas is **t(11;18)**,
  - seen in 30% to 40% of gastric and lung MALT lymphomas
  - This is clinically important, as **t(11;18)-positive cases are less likely to respond to *H pylori*-eradication therapy**
  - there is a high incidence of t(11;18) in ***H pylori*-negative gastric MALT lymphoma,**
  - t(11;18)-positive cases are **more likely to present with advanced-stage disease** associated with aberrant expression of nuclear BCL10
  - t(11;18)-positive cases are **less likely to transform to aggressive lymphomas**, as they are unlikely to develop secondary chromosomal abnormalities.

Treatment

- if low grade then 80% respond to *H. pylori* eradication
- low grade localised gastric helicobacter pylori positive :
  - first line → antibiotics plus a proton-pump inhibitor (PPI)
  - second line → radiotherapy
    - Patients are considered to have failed *H pylori* eradication when:
      - there is no regression at repeat endoscopy 2 months after treatment,
      - or when there is lack of complete regression at approximately 18 months after treatment.
- low grade localised gastric helicobacter pylori negative:
  - first line → radiotherapy
- low grade advance gastric (Disease not confined to the stomach)
  - first line → chemotherapy
    - If *H pylori* -positive,→ add eradication therapy.
- High grade histological transformation:
  - First line → chemotherapy
  - MALT lymphoma is defined as a low-grade neoplasm. However, gastric MALT lymphoma can show a component of high-grade transformation.
  - This is characterised by an **increase in the number of transformed blasts**, which can eventually lead to **complete effacement of the original MALT lymphoma**.

Ref: bestpractice.bmj.com.2017

Gastric cancer

Gastric adenocarcinoma - signet ring cells

Epidemiology

- Sex: ♂ > ♀ (2:1)
- Peak incidence: 70 years
- Geographical distribution:
  - strong regional differences
    - High incidence in South Korea, china and Japan
    - Declining incidence in the United States and Europe
- overall incidence is decreasing, but **incidence of tumours arising from the cardia is increasing**
- **adenocarcinoma** is the most common gastric cancer (90% of cases)

Features

- often presents late, with weight loss, early satiety,

- postprandial vomiting
- in some cases acanthosis nigricans
- or Leser-Trélat sign.
  - multiple seborrheic keratoses, often with an inflammatory base (see below).
  - Associated with gastrointestinal adenocarcinomas as part of a paraneoplastic syndrome.
- **Sister Mary Joseph nodule** is a feature of gastric carcinoma and involves **metastasis to the periumbilical region.**
- metastasis
  - The liver is the most common site of metastasis of gastric carcinoma.
  - When first diagnosed with gastric cancer, ~ 70% of patients already show metastatic spread to the lymph nodes
  - The lymph node most commonly involved in the spread of gastric carcinoma is the left supraclavicular node (Virchow node).

Types of gastric adenocarcinoma

- **diffuse gastric adenocarcinoma**
  - characterized by thickening and rigidity of the gastric wall.
  - It often remains asymptomatic until an advanced stage.
  - Unlike the intestinal type of gastric adenocarcinoma, it is more common in women and individuals less than 50 years old.
  - associated with signet ring cells and linitis plastica.
  - **Linitis plastica** is a particularly aggressive form of diffuse adenocarcinoma.
    - It is also known as "leather bottle stomach" because the stomach is diffusely thickened, with a small lumen that cannot expand, leading to the symptom of early satiety. This thickening can be seen on the CT image.
  - These tumors infiltrate the **submucosa**, so that mucosal sampling may not show neoplastic cells.
  - The lesions are described as scirrhous, referring to the desmoplastic reaction that results in indurated, abundant fibrous tissue in the dense stroma.
    - **Scirrhous infiltration of the submucosa**
  - Histologically, **signet ring** cells are seen (named this way because mucin vacuoles displace the nucleus to the periphery).
- **Intestinal type of gastric adenocarcinoma**
  - the **most common** type of gastric adenocarcinoma.
  - presents as a large, irregular ulcer with heaped up margins,
  - typically at the lesser curvature of the antrum.

Histology

- **signet ring cells** may be seen in gastric cancer.
  - They contain a large vacuole of mucin which displaces the nucleus to one side.
  - **Higher numbers of signet ring cells are associated with a worse prognosis**

Associations

- *H. pylori* infection
  - The most common cause (> 60%)
- **blood group A: gAstric cAncer**
- gastric adenomatous polyps
- pernicious anaemia → Chronic atrophic gastritis → become gastric adenocarcinoma.
- smoking
- achlorhydria (decrease in gastric acid production)
- diet: salty, spicy, nitrates (dietary nitrosamines (smoked foods))
- **Associations with decreased risk of gastric tumours**
  - may be negatively associated with **duodenal ulcer**
  - **NSAID** use is associated with decreased risk of certain gastric tumours.

Investigation

- diagnosis: endoscopy with biopsy
- staging: CT or endoscopic ultrasound - **endoscopic ultrasound has recently been shown to be superior to CT**

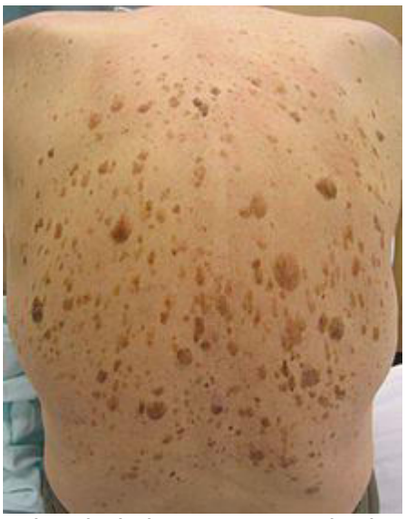
Treatment

- **gastrectomy**
  - **Iron deficiency is a possible complication of gastrectomy.**
    - The **body of the stomach** is the primary location for **parietal cells**,
    - Parietal cells produce gastric acid and intrinsic factor
      - Intrinsic factor is necessary for the absorption of vitamin B12.

- ❖ Gastric acid → aid the absorption of iron → low pH environment is necessary for the reduction of Fe^{3+} (ferric iron) to Fe^{2+} (ferrous iron) the absorbable form of iron.

Prognosis

- Early diagnosis of gastric carcinoma results in a five year survival rate of 90%
- At diagnosis, 60% of cancers have already reached an advanced stage that does not allow for curative treatment.
- **5-year survival**
  - confined to the mucosa and submucosa **(**> 90%)
  - extended beyond the submucosa (< 10%).



seborrheic keratoses on the back of a person with Leser–Trélat sign

Gastrointestinal stromal tumour (GIST)

- common type of sarcoma; it develops in the gastrointestinal (GI) tract
- occur most often in adults over the age of 50 years
- Location of GISTs:
  - **most commonly involve the stomach (60%),**
  - jejunum and ileum (30%),
  - duodenum (4%–5%), and
  - colorectal (< 5%).
- Tumours in the small bowel and rectum appear to be more aggressive than those occurring in the stomach.
- **the cell of origin of gastric GISTs → Interstitial cells of Cajal** within Auerbach's plexus
  - the interstitial cells of Cajal act as pacemaker cells of the GIT, with regulation of peristalsis in the adult intestine
- Approximately 80%–95% of GISTs harbor an activating mutation in the **KIT gene**
  - about 80% of KIT-negative GISTs have an activating mutation in the PDGFRA gene.
    - a mutation in PDGFRA may make the tumour resistant to the standard drugs to treat GIST.
    - tumours with a PDGFRA mutation are usually less aggressive than the more common ones with KIT mutation.
- 50% are present with metastatic disease, (commonly liver metastases),
- Features
  - Mostly asymptomatic.
  - Tumor induce GI bleed and anemia
  - Other symptoms secondry to mass effects:
  - Abdominal discomfort, early satiety, palpable abdominal mass
  - Bowel obstruction or perforation
  - Dysphagia
- Diagnosis:
  - Gold standard test is endoscopy with biopsy
    - Histopathology: **Spindle cell** in 70 to 80%, epitheliods cells in 20 to 30
    - **CT and endoscopic ultrasound allow tumour staging to plan further management.**

- Immunohistochemical Stainning
  - Up to 95% of GISTs are positive for KIT expression (CD117)
  - 60%–70% are positive for CD34 expression.

- Management
  - all GISTs ≥ 2 cm → surgery
    - Surgery is usually the first treatment method used for GIST.
    - If the tumour is too large to be removed at the time of diagnosis, it may be treated initially with imatinib. If sufficient shrinkage has occurred after 6-12 months, it may be operated .
  - incidentally encountered GISTs < 2 cm → watchful waiting and surveillance for such very small GISTs might be reasonable.
  - for patients with KIT-positive unresectable and/or metastatic GIST → ***Medical Management:***
    - **first line → Imatinib** mesylate is an oral adenosine triphosphate (ATP)–competitive TKI that selectively inhibits the activity of KIT, PDGFRA.
      - It is effective in 80% of patients and on average will control the disease for about two years.
      - imatinib may be used as an adjuvant therapy after surgery to reduces the risk of the cancer returning
    - ***second-line → In case of imitanib resistance:*** patients can be switched directly from low-dose imatinib (400 mg/day) to another TKI, such as the only approved **second-line** therapy, s**unitinib**.
    - **3rd line** → Regorafenib (if imatinib and sunitinib are not effective or not tolerated)

Menetrier's disease

- A rare condition associated with **giant gastric folds**, predominantly in the fundus and body of the stomach.
- **Histologically there is hyperplasia of the gastric pits, gland atrophy and an increase in overall mucosal thickness.**
- Hypochlorhydria is usually present.
- Patients often complain of epigastric pain
- protein loss from the gastric mucosa can result in mild hypoalbuminaemia.
- some patients improve spontaneously,whereas in others this can be a premalignant state.
- Antisecretory drugs such as proton-pump inhibitors can be tried for symptom relief.

Bowel conditions

Dyspepsia

Causes of dyspepsia

- Gastro-oesophageal reflux disease (GORD) (15 - 25%)
- Gastric and duodenal ulcers (15 - 25%) and
- Stomach cancer (2%).
- The remaining 60% are classified as non-ulcer dyspepsia (NUD).
- **Drugs causing dyspepsia**
  - NSAIDs (**ibuprofen is associated with the lowest risk of peptic ulcer disease**)
  - bisphosphonates
  - steroids
  - The following **drugs may cause reflux by reducing lower oesophageal sphincter (LOS)** pressure
    - calcium channel blockers*
    - nitrates*
      - *calcium channel blockers and nitrates are occasionally used in the management of achalasia, itself a cause of dyspepsia, because of their effect on the LOS.
    - **theophyllines**

Indications of **Urgent** referral for an endoscopy (i.e. within 2 weeks). (NICE 2015)

- **dysphagia**
- **upper abdominal mass** consistent with stomach cancer
- Any sign of chronic gastrointestinal bleeding

- Persistent vomiting
- Iron deficiency anaemia,
- Suspicious barium meal.
- Progressive unintentional weight loss
- Patients aged **≥** 55 years who've got **weight loss**, AND any of the following:
  - upper abdominal pain
  - reflux
  - dyspepsia

Non-urgent

- Patients with **haematemesis**
- Patients aged >= 55 years who've got:
  - **treatment-resistant dyspepsia** or
  - upper abdominal pain with low haemoglobin levels or
  - **raised platelet count** with any of the following: nausea, vomiting, weight loss, reflux, dyspepsia, upper abdominal pain
  - nausea or vomiting with any of the following: weight loss, reflux, dyspepsia, upper abdominal pain

Managing patients who do not meet referral criteria ('undiagnosed dyspepsia')

- This can be summarised at a step-wise approach
  1. Review medications for possible causes of dyspepsia
  2. Lifestyle advice
  3. Trial of full-dose proton pump inhibitor for one month OR a 'test and treat' approach for *H. pylori*
- lifestyle advice
  - avoid known precipitants: eg: smoking, alcohol, coffee, chocolate, fatty foods and being overweight
  - Raising the head of the bed and having a main meal well before going to bed may help some people.
- Testing for *H. pylori* infection
  - initial diagnosis: NICE recommend using a carbon-13 urea breath test or a stool antigen test, or laboratory-based serology 'where its performance has been locally validated'
  - test of cure: carbon-13 urea breath test
- cognitive behavioural therapy and psychotherapy, may reduce dyspeptic symptoms in the short term in individual people.
- If *H pylori* has been excluded and symptoms persist, offer either a **low-dose PPI** or an H_2RA for 4 weeks.

Malabsorption

Malabsorption is characterised by diarrhoea, steatorrhoea and weight loss.

Causes may be broadly divided into:

1. intestinal (e.g. villous atrophy),
2. pancreatic (deficiency of pancreatic enzyme production or secretion)
3. biliary (deficiency of bile-salts needed for emulsification of fats)

Intestinal causes of malabsorption

- coeliac disease
- Crohn's disease
- tropical sprue
- Whipple's disease
- Giardiasis
- brush border enzyme deficiencies (e.g. lactase insufficiency)

Pancreatic causes of malabsorption

- chronic pancreatitis
- cystic fibrosis
- pancreatic cancer

Biliary causes of malabsorption

- biliary obstruction
- primary biliary cirrhosis

Other causes

- bacterial overgrowth (e.g. systemic sclerosis, diverticulae, blind loop)
- lymphoma

- **short bowel syndrome**
  - Does not develop unless more than **two thirds of the small intestine** have been removed.
  - features include:
    - Abdominal pain
    - Diarrhea and steatorrhea
    - Fluid depletion
    - Weight loss and malnutrition
    - Fatigue
    - complications caused by malabsorption of vitamins and minerals

D-xylose test

- D-xylose is a monosaccharide which is absorbed through the small intestines and excreted through the kidneys.
- **D-xylose test** is helpful in differentiating between structural and functional causes of malabsorption.
  - structural (e.g. Celiac disease, Crohn disease) or functional (e.g. pancreatic insufficiency)
- An abnormally low excretion of D-xylose is indicative of a structural pathology.
- This test distinguishes between malabsorption due to small-intestinal diseases and malabsorption due to pancreatic exocrine insufficiency.
- A 5-hour urinary excretion of 5 g or greater is normal following the oral administration of 25 g of D-xylose to a well-hydrated subject.
- Decreased xylose absorption and excretion are found:
  - In patients with damage to the proximal small intestine
  - When there is bacterial overgrowth in the small intestine (the bacteria catabolise the xylose)
- **Patients with pancreatic steatorrhoea (chronic pancreatitis) usually have normal xylose absorption.**
- Abnormal results might be encountered in renal failure, in the elderly and in patients with ascites due to an excretion defect rather than malabsorption.

Diarrhoea (NICE 2012)

- Diarrhoea is defined as the abnormal passage of loose or liquid stools **more than 3 times** daily **or a volume of stool greater than 200 g/day**.
- Diarrhoea is considered to be chronic if it persists for **more than 4 weeks**.

Jejunal villous atrophy

Causes of villous atrophy (other than coeliacs): tropical sprue, Whipple's, lymphoma, hypogammaglobulinaemia

Causes

- coeliac disease
- tropical sprue
- hypogammaglobulinaemia
- gastrointestinal lymphoma
- Whipple's disease
- cow's milk intolerance

Coeliac disease

Coeliac disease - tissue transglutaminase antibodies first-line test

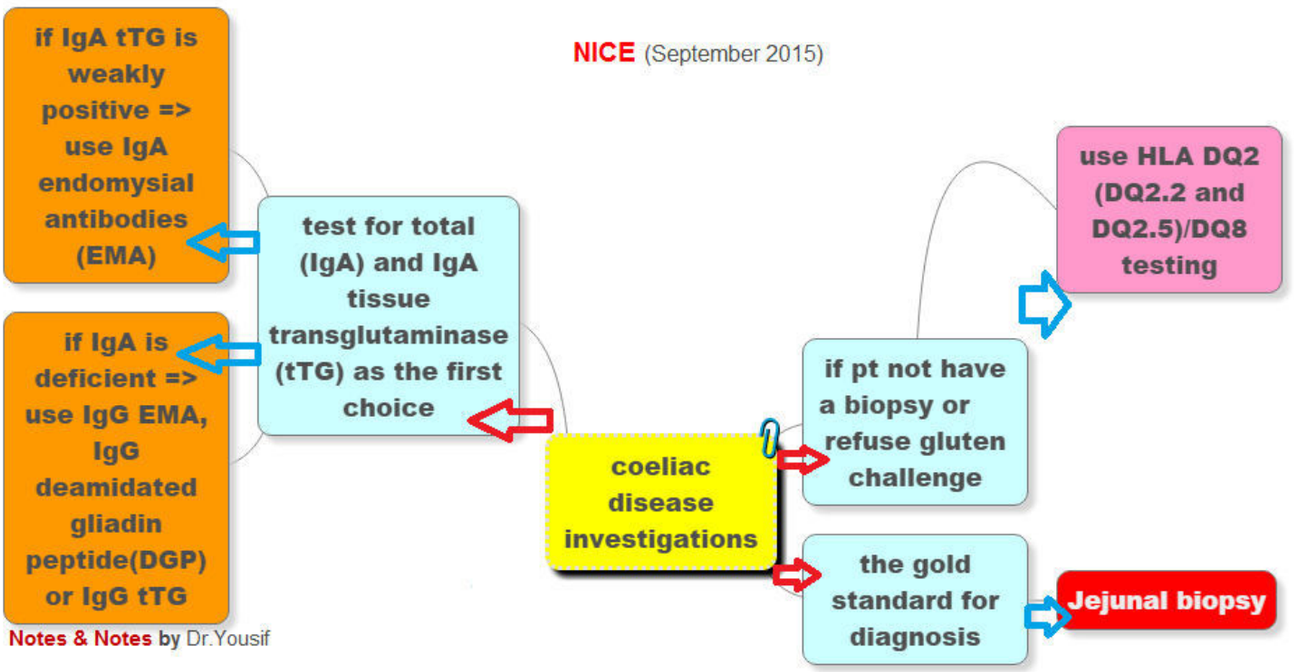
- Caused by sensitivity to the protein gluten.
- **due to T cell mediated hypersensitivity reaction**
- Mechanism: repeated protein gluten exposure → villous atrophy → malabsorption.

- Conditions associated with coeliac disease include dermatitis herpetiformis (a vesicular, pruritic skin eruption) and autoimmune disorders (type 1 diabetes mellitus and autoimmune hepatitis).
- It is strongly associated with HLA-DQ2 (95% of patients) and HLA-B8 (80%) as well as HLA-DR3 and HLA-DR7
- **The prevalence of coeliac disease in Europe between 1:100 and 1:300.**
- It presents at any age but in adults the commonest age of presentation is 20s and 30s.
- Women are slightly more commonly affected.
- The action of tissue transglutaminase on alpha-gliadin generates epitopes to CD4+ T-lymphocytes, which provoke an inflammatory response in the intestinal wall.

In 2009 NICE suggest that the **following patients should be screened for coeliac disease**:

Signs and symptoms	Conditions
• Chronic or intermittent diarrhoea • Failure to thrive or faltering growth (in children) • Persistent or unexplained gastrointestinal symptoms including nausea and vomiting • Prolonged fatigue ('tired all the time') • Recurrent abdominal pain, cramping or distension • Sudden or unexpected weight loss • Unexplained iron-deficiency anaemia, or other unspecified anaemia	• Autoimmune thyroid disease • Dermatitis herpetiformis • Irritable bowel syndrome • Type 1 diabetes • First-degree relatives (parents, siblings or children) with coeliac disease

Investigations



Diagnosis

- Diagnosis is made by a combination of immunology and jejunal biopsy. Villous atrophy and immunology normally reverses on a gluten-free diet.
- If patients are already taking a gluten-free diet they should be asked, if possible, to reintroduce gluten for at least 6 weeks prior to testing.

Immunology

- tissue transglutaminase (TTG) antibodies (IgA) are the **first-choice**
  - Selective IgA deficiency is more common in patients with coeliac disease.
  - For this reason IgA levels should be checked when serological tests are ordered.
  - If the patient has **selective IgA deficiency** → tissue transglutaminase **IgG** can be measured.
  - Patients normally need to be following a gluten-free diet for **at least 6 months before the serology becomes negatives**.

- endomyseal antibody (IgA) → 90% sensitive and almost 100% specific.
  - **Anti-endomysial antibodies are sensitive and specific, but miss the disease in about 5% of the population who are IgA deficient.**
- anti-gliadin antibody (IgA or IgG) tests are not recommended by NICE
- anti-casein antibodies are also found in some patients

Jejunal biopsy

- **duodenal biopsies are the gold standard for diagnosis:**
  - villous atrophy
  - **crypt hyperplasia**
  - increase in intraepithelial lymphocytes
  - lamina propria infiltration with lymphocytes
  - **Appearances may resemble severe tropical sprue**

Rectal gluten challenge has been described but is not widely used

Subtotal villous atrophy is seen in a number of conditions other than coeliac disease such as:

- Severe tropical sprue
- Cow's milk/soya sensitivity in children
- Gastroenteritis
- **Whipple's disease**
- Hypogammaglobulinaemia
- Neomycin therapy
- Laxative abuse
- Norwalk agent.

Other investigations

- **Imaging**
  - Which would most likely seen on abdominal radiograph with barium contrast?
    - **Decreased jejunal folds, increased ileal folds**
      - imaging and biopsy of the GI mucosa show a characteristic blunting of jejunal villi. This is often associated with a compensatory" jejunization" of the ileum to enhance nutrient absorption.
- **Screen for other related autoimmunities**
  - In a patient with newly diagnosed **celiac disease**, it is important to screen for other related autoimmunities as well, e.g. type 1 diabetes mellitus and autoimmune thyroiditis.

Management

- gluten-free diet.
  - **Gluten containing cereals include:**
    - wheat: bread, pasta, pastry
    - barley: beer
      - whisky is made using malted barley. Proteins such as gluten are however removed during the distillation process making it safe to drink for patients with coeliac disease
    - rye
    - oats (some patients with coeliac disease appear able to tolerate oats)
  - **Some notable foods which are gluten-free include:**
    - Rice
    - Potatoes
    - corn (maize)

follow-up

- Tissue transglutaminase antibodies may be checked to check compliance with a gluten free diet.

Associations and Complications

If the patient still symptomatic despite being compliant with a gluten free diet → think of T Cell lymphoma

- Enteropathy associated **T Cell lymphoma** (EATL)
  - is a form of Non-Hodgkins lymphoma
  - coeliac disease increase the risk of developing EATL within the 1st year of diagnosis, however with a strict gluten free diet, the risk returns to that of the general population after this point.

- **Recurrent mouth ulcers**
- **Hyposplenism (**Splenic atrophy**)**: seen in 50% of cases and responds poorly to gluten withdrawal.
- selective Ig A deficiency
- Small-bowel ulceration is associated with ulcerating jejunitis, but not colonic or gastric ulcers.

January 2016 exam: Why do patients with coeliac disease require regular immunisations? Functional hyposplenism

Whipple's disease

Whipple's disease: jejunal biopsy shows deposition of macrophages containing Periodic acid-Schiff (PAS) granules

- Whipple's disease is a rare **multi-system** disorder
- Caused by ***Tropheryma whippelii*,** a **Gram positive** bacterium

Epidemiology

- more common in those who are HLA-B27 positive
- most common in white males aged 40-50 years
- rarely is described in women (M:F ratio 9:1).

Pathophysiology

- Malabsorption in Whipple disease is caused by macrophages in the small bowel lamina propria compressing the lacteals.

Features

- malabsorption: diarrhoea, weight loss
- large-joint arthralgia
- lymphadenopathy
- skin: hyperpigmentation and photosensitivity
- pleurisy, pericarditis
- neurological symptoms (rare): ophthalmoplegia, dementia, seizures, ataxia, myoclonus, **characteristic oculo-masticatory movements**

Investigation

- **jejunal biopsy** shows deposition of macrophages containing **Periodic acid-Schiff (PAS)** granules
- presence of *T. whippelei* DNA in tissue by PCR.

Management

- oral co-trimoxazole for a year is thought to have the lowest relapse rate, sometimes preceded by a course of IV penicillin
- other option:
  - **initial two week course of parenteral penicillin** and streptomycin; followed by a prolonged course (one year) of tetracycline.

Tropical Sprue

- most common in the Carribbean and the Far-East.
  - occurs in tropical regions, predominantly central America and South-Eastern Asia.
- characterized by a picture of small intestinal malabsorption and the cause is thought to be infectious in origin.
  - It is thought that an initial GI infection results in small bowel stasis, opportunistic colonisation by organisms such as coliforms, and then a degree of villous atrophy leading to malabsorption and B12, folate deficiency.
    - deficiency in folate contributes to greater **mucosal injury**.

Features

- Patients classically have a history of recent travel to a tropical area
- present with indigestion, cramps within 2 or 3 weeks after an acute enteric infection.
- Megaloblastic anemia due to folate or B12 deficiency is a common finding.

Diagnosis:

- Jejunal biopsy reveals:

- Mild villous atrophy
- ↑↑ villous crypts
- Mononuclear cellular infiltrates
- Enlarged epithelial cells
- Large nuclei caused by folate and/or vitamin B12 deficiency.

- barium swallow may show thickening of mucosal folds

Treatment:

- The main treatment for tropical sprue is broad-spectrum antibiotics (i.e., tetracycline) and vitamin supplementation (i.e., folic acid, vitamin B12).
  - Tetracyclines 250mg qds up to 6 months
  - Ampicillin may be used as an alternative in patients who are intolerant of tetracyclines.
  - Folate and B12 deficiencies should also be corrected
- Complete recovery is possible with appropriate therapy.

Irritable bowel syndrome (IBS)

Insoluble sources of fibre such as bran and wholemeal should be avoided in IBS

Feature

- **features supporting a diagnosis of IBS** include:
  - A long history with a relapsing and remitting course
  - Exacerbations triggered by life events
  - Symptoms aggravated by eating, and
  - Coexistence of anxiety and depression.
- **features which suggest organic disease rather than IBS** include:
  - Fever
  - Onset of symptoms in old age
  - Progressive deterioration
  - Weight loss
  - Rectal bleeding (not due to fissures or haemorrhoids)
  - Steatorrhoea, and
  - Dehydration.

Diagnosis (NICE 2008)

- The diagnosis of IBS should be **considered** if the patient has had the following for at least 6 months:
  1. abdominal pain, and/or
  2. bloating, and/or
  3. change in bowel habit
- **A positive diagnosis of IBS should be made** if the patient has abdominal pain relieved by defecation or associated with altered bowel frequency stool form, in addition to 2 of the following 4 symptoms:
  1. altered stool passage (straining, urgency, incomplete evacuation)
  2. abdominal bloating (more common in women than men), distension, tension or hardness
  3. symptoms made worse by eating
  4. passage of mucus

- Features such as lethargy, nausea, backache and bladder symptoms may also support the diagnosis
- **Red flag features** should be enquired about:
  1. rectal bleeding
  2. unexplained/unintentional weight loss
  3. family history of bowel or ovarian cancer
  4. onset after 60 years of age
- Also on clinical examination the other '**red flag**' indicators are:
  - Anaemia
  - Abdominal mass

  - Rectal mass, and
  - Inflammatory markers for inflammatory bowel disease.
- Suggested primary care **investigations** are:
  - full blood count
  - ESR/CRP
  - coeliac disease screen (tissue transglutaminase antibodies)

Management (NICE 2015).

NICE recommend avoiding lactulose in the management of IBS

First-line pharmacological treatment - according to predominant symptom

- pain: antispasmodic agents
  - Pinaverium is used to reduce the pain duration associated with (IBS).
- diarrhoea: loperamide is first-line
- constipation: laxatives but avoid lactulose
- For patients with constipation who are not responding to conventional laxatives linaclotide may be considered, **if:**
  - optimal or maximum tolerated doses of previous laxatives from different classes have not helped and
  - they have had constipation for at least 12 months

Second-line pharmacological treatment

- low-dose tricyclic antidepressants (e.g. amitriptyline 5-10 mg) are used in preference to selective serotonin reuptake inhibitors

Other management options

- psychological interventions - if symptoms do not respond to pharmacological treatments after 12 months and who develop a continuing symptom profile (refractory IBS), consider referring for cognitive behavioural therapy, hypnotherapy or psychological therapy
- complementary and alternative medicines: 'do not encourage use of acupuncture or reflexology for the treatment of IBS'

General dietary advice

- have regular meals and take time to eat
- avoid missing meals or leaving long gaps between eating
- drink at least 8 cups of fluid per day, especially water or other non-caffeinated drinks such as herbal teas
- restrict tea and coffee to 3 cups per day
- reduce intake of alcohol and fizzy drinks
- consider limiting intake of high-fibre food (for example, whole meal or high-fibre flour and breads, cereals high in bran, and whole grains such as brown rice)
- reduce intake of 'resistant starch' often found in processed foods
- limit fresh fruit to 3 portions per day
- for diarrhoea, avoid sorbitol
- for wind and bloating consider increasing intake of oats (for example, oat-based breakfast cereal or porridge) and linseeds (up to one tablespoon per day).

Fibre

- There are two main types of fibre - soluble fibre (which dissolves in water) and insoluble fibre.
- It is **soluble fibre** rather than insoluble fibre that seems to help ease symptoms in some cases.
  - **A diet high in soluble fibre is often prescribed for the treatment of IBS**
  - Dietary sources of soluble fibre include **oats**, ispaghula (psyllium), nuts and seeds, some fruit and vegetables and pectins.
  - A fibre supplement called ispaghula powder is also available from pharmacies and health food shops. This seems to be the most beneficial type of supplement.
- **Insoluble fibre** is chiefly found in corn (maize) bran, wheat bran and some fruit and vegetables. In particular, avoid bran as a fibre supplement.

Malnutrition

- **Pathophysiology**
  - **Food intolerance (**in 30-60% of patients with (IBS).**)**

  - increased intestinal contractile and electrical activity with increased sensitivity to visceral stimulation.
  - Proliferation of intestinal mast cells is a proposed mechanism by which food and stress may trigger symptoms.
- **definition**: NICE define malnutrition as the following:
  1. a Body Mass Index (BMI) of less than 18.5; or
  2. unintentional weight loss greater than 10% within the last 3-6 months; or
  3. a BMI of less than 20 and unintentional weight loss greater than 5% within the last 3-6 months
- Around 10% of patients aged over 65 years are malnourished, the vast majority of those living independently, i.e. not in hospital or care/nursing homes.
- **Screening for malnutrition if mostly done using MUST (Malnutrition Universal Screen Tool).**
  - it should be done on admission to care/nursing homes and hospital, or if there is concern. For example an elderly, thin patient with pressure sores **(**The Waterlow score is used to estimate the risk of a patient developing a pressure sore**)**
  - it takes into account BMI, recent weight change and the presence of acute disease
  - categorises patients into low, medium and high risk
- **Management** of malnutrition is difficult. NICE recommend the following points:
  - dietician support if the patient is high-risk
  - a 'food-first' approach with clear instructions (e.g. 'add full-fat cream to mashed potato'), rather than just prescribing oral nutritional supplements (ONS) such as Ensure
  - if ONS are used they should be taken between meals, rather than instead of meals

Waterlow score is used to estimate the **risk of a patient developing a pressure sore**, this includes an assessment of malnutrition as one of it's components

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Lactose intolerance

- Lactase acts on lactose to generate glucose and galactose.
- **more common in Asian, and East Asian races.**
  - **South-east Asian** people, like the Vietnamese, Thais, and Chinese, have a very high prevalence of lactase deficiency.
- **Any GI infection may precipitate the diagnosis of lactose intolerance,** as gut flora may be altered by large bowel bacterial or viral load, as well as the treatment of infection.
- A change from an Eastern to a Western high lactose diet may also reveal lactose intolerance.
- Many patients labelled as having IBS may suffer from undiagnosed lactose intolerance
- many medications use lactose as a binding and stabilising agent.
- **Diagnosed with** a DNA assay of the lactase gene along with a hydrogen breath test.
- **Treatment** of lactose intolerance is with careful replacement of lactase.

Functional constipation

- The Rome III criteria for functional constipation is as follows (it must include two or more of the following):
  - straining during at least 25% of defecations
  - lumpy or hard stools in at least 25% of defecations
  - sensation of incomplete evacuation for at least 25% of defecations
  - sensation of anorectal obstruction/blockage for at least 25% of defecations
  - manual manoeuvres to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
  - fewer than three defecations per week
  - loose stools are rarely present without the use of laxatives, and
  - insufficient criteria for irritable bowel syndrome.
- These criteria must be fulfilled for the last three months with symptom onset at least six months prior to diagnosis.

Energy from food

- The amount of energy that may be derived from 1 gram of food is as follows:
  - carbohydrates: 4 kcal
  - protein: 4 kcal
  - **fat: 9 kcal**
- The amount of energy a food product contains is expressed in calories (kcal). In simple terms, per unit weight, fats contain twice as many calories as protein or carbohydrates.

Enteral feeding

Key points

- Identify patients as malnourished or at risk (see below)
- Identify unsafe or inadequate oral intake with functional GI tract
- Consider for enteral feeding
- Gastric feeding unless upper GI dysfunction (then for duodenal or jejunal tube)
- Check NG placement using aspiration and pH (check post pyloric tubes with AXR)
  - the most important first line investigation that will establish correct positioning of the tube in the stomach?
  - **The first line investigation to confirm correct placement of a nasogastric tube is → pH testing of gastric aspirate using indicator paper**
    - If the pH is between 1 and 5.5 then this is confirmatory evidence of correct placement.
    - If the pH reading is between 5.5 and 6 it is recommended that a second independent reading is made to confirm.
    - if aspirate pH ≥6 → nasogastric feeding tubes feeding cannot be commenced
  - If there is any doubt, then an appropriately interpreted **chest x ray is a second line investigation.**
- Gastric feeding > 4 weeks consider long-term gastrostomy
- Consider bolus or continuous feeding into the stomach
- ITU patients should have continuous feeding for 16-24h (24h if on insulin)
- Consider motility agent in ITU or acute patients for delayed gastric emptying. If this doesn't work then try post pyloric feeding or parenteral feeding.
- PEG can be used 4 hours after insertion, but should not be removed until >2 weeks after insertion.

Surgical patients due to have major abdominal surgery: if malnourished, unsafe swallow/inadequate oral intake and functional GI tract then consider pre operative enteral feeding.

Patients identified as being malnourished

- BMI < 18.5 kg/m^2
- unintentional weight loss of > 10% over 3-6/12
- BMI < 20 kg/m^2 and unintentional weight loss of > 5% over 3-6/12

AT RISK of malnutrition

- Eaten nothing or little > 5 days, who are likely to eat little for a further 5 days
- Poor absorptive capacity
- High nutrient losses
- High metabolism

Refeeding syndrome

Refeeding syndrome → hypophosphataemia

Give 50% of normal energy intake in starved patients (> 5 days) to avoid refeeding syndrome

Definition:

- Refeeding syndrome describes the metabolic abnormalities which occur on feeding a person following a period of starvation (≥ 5 days).

Pathophysiology:

- When malnourished, the body uses endogenous fuel stores for energy and maintains serum electrolytes by redistribution from intracellular spaces.
- **Exogenously administered glucose results in insulin release. This results in rapid uptake of glucose, potassium, phosphate and magnesium into cells, with dramatic falls in the extracellular concentrations.**

Features

- Hypophosphataemia (symptoms are **due predominantly to hypophosphataemia,**)
- hypokalaemia
- hypomagnesaemia
- abnormal fluid balance
- Due to understood reasons, the body retain fluid → ↑ extracellular space → ↑cardiac work → acute heart failure.
- neurological problems resulting in:
  - Oedema
  - Lethargy
  - Confusion
  - Coma
  - Convulsions, and
  - Death.
- Nausea and diarrhoea is also common due to gut intolerance.

Prevention (NICE 2006)

- Identify patients at a high-risk of developing refeeding syndrome
  - Patients are considered **high-risk:**
    - **if one or more of the following**:
      1. BMI < 16 kg/m^2
      2. unintentional weight loss >15% over 3-6 months
      3. little nutritional intake > 10 days
      4. hypokalaemia, hypophosphataemia or hypomagnesaemia prior to feeding (unless high)
    - **If two or more of the following:**
      1. BMI < 18.5 kg/m^2
      2. unintentional weight loss > 10% over 3-6 months
      3. little nutritional intake > 5 days
      4. history of: alcohol abuse, drug therapy including insulin, chemotherapy, diuretics and antacids
- Decrease oral calorific intake to less than 50% of the recommended amount.
  - **NICE recommend that if a patient hasn't eaten for > 5 days, aim to re-feed at no more than 50% of requirements for the first 2 days.**
    - limit initial dietary intake to 1000–1500 kcal/day

Management

- Correcting electrolyte abnormalities aggressively
  - it may be preferable to provide electrolyte replenishment prior to commencing calorific intake

A patient with a history of **alcoholism** is admitted for **re-feeding**. Which component of the feed may need to be reduced **to avoid encephalopathy**?

➔ **Protein**

- protein content of feeds should be strictly managed in patients with alcoholism.
- Protein rich feeds → ↑ total ammonia burden→ ↑ **risk of encephalopathy**.

Melanosis coli

Diarrhoea - biospy shows pigment laden macrophages = laxative abuse

- Melanosis coli is a disorder of pigmentation of the bowel wall.
- Causes
  - It is associated with laxative abuse, especially anthraquinone compounds such as senna

- This phenomenon is seen in over 70% of persons who use anthraquinone laxatives (for example, cascara sagrada, senna, and frangula) within several months of use.
- Also alternative "medicine" drugs contain ingredients like cascara which contain anthraquinones.
- The modern laxatives such as liquid paraffin and polyethylene glycol do not cause these changes.

- Pathophysiology
  - Chronic use of anthraquinone laxatives cause injury to the colonic epithelium, with generation of **lipofuscin pigment.** This pigment is subsequently engulfed by the macrophages to give rise to the histological picture.
- Diagnosis
  - Melanosis coli is a histological diagnosis made from rectal biopsy material which shows numerous macrophages filled with brown pigment within the lamina propria.
    - Histology demonstrates **pigment-laden macrophages**
    - The macroscopic appearance varies from deep black pigmentation to reticulated brown discolouration.
- Treatment
  - The condition is benign and reversible on stopping the laxatives.

Mesenteric ischaemia (ischaemic colitis)

The two most common symptoms of ischemic colitis are severe abdominal pain and hematochezia (passage of fresh blood through the anus).

- Mesenteric ischaemia is primarily caused by arterial embolism resulting in infarction of the colon.
- **More likely occur in areas such as the splenic flexure** that are located at the borders of the territory supplied by the superior and inferior mesenteric arteries.
  - especially the **superior mesenteric artery**.

Predisposing factors

- increasing age
- **atrial fibrillation**
- other causes of emboli: endocarditis
- cardiovascular disease risk factors: smoking, hypertension, diabetes

Features

- **abdominal pain**
- **rectal bleeding**
- diarrhoea
- fever
- bloods typically show an elevated WBC associated with acidosis
- Acute mesenteric ischaemia is a cause of elevated amylase that is unrelated to pancreatitis.
- **Elevated serum lactate also suggests ischaemic aetiology.**

Diagnosis

- **CT scanning**: **the imaging modality of choice**, with a sensitivity and specificity over 90%.
- Angiography: if the diagnosis is in doubt.
- Mucosal edema can be seen as the **thumbprinting sign** on plain **abdominal radiograph and barium enema.**

Management

- supportive care
- **balloon angioplasty and stenting**
  - the preferred treatment for hemodynamically stable patients with acute mesenteric ischemia who do not present with signs or symptoms of advanced intestinal ischemia (peritonitis, sepsis) because this procedure is minimally invasive and studies suggest similar efficacy to open surgical treatment.
- laparotomy and bowel resection
  - laparotomy is reserved for acutely ill patients who are hemodynamically unstable or have evidence of peritonitis (rebound tenderness and involuntary guarding).

Small bowel bacterial overgrowth syndrome (SBBOS)

Definition

- (SBBOS) is a disorder characterised by excessive amounts of bacteria in the small bowel resulting in gastrointestinal symptoms of **bloating, abdominal distension and diarrhoea**

.Risk factors for SBBOS

- neonates with congenital gastrointestinal abnormalities
- scleroderma
- absent gastric acid secretion
- **small bowel diverticulae**
- fistulae between the small and large bowel
- small bowel strictures
- diabetes mellitus (diabetic neuropathy)
- adhesions.

Features: It should be noted that many of the features overlap with irritable bowel syndrome:

- chronic diarrhoea
- bloating, flatulence
- abdominal pain
- **Biochemically there is classically a low vitamin B_{12} level and normal or elevated folate level as a result of bacterial metabolism of B_{12} to folate.**

Steatorrhoea and flatulence are classic presenting features of small bowel bacterial overgrowth.

Investigation

- **The gold standard investigation of bacterial overgrowth is small bowel aspiration and culture**
- Other possible investigations include:
  - **hydrogen breath test**
  - 14C-xylose breath test
  - 14C-glycocholate breath test: used increasingly less due to low specificity
- In practice many clinicians give an empirical course of antibiotics as a trial

Management

- correction of underlying disorder
- antibiotic therapy: **rifaximin is now the treatment of choice** due to relatively low resistance.
- Co-amoxiclav or metronidazole are also effective in the majority of patients.

Spontaneous bacterial peritonitis (SBP)

Spontaneous bacterial peritonitis - intravenous cefotaxime

- (SBP) is a form of peritonitis usually seen in patients with ascites secondary to liver cirrhosis. most commonly seen in alcoholic cirrhosis
- **typically caused by aerobic gram negative bacteria.** (usually *Escherichia coli, Klebsiella)*
  - ***sponteanous bacterial peritonitis is almost without exception caused by a single organism.***
- **Diagnosis**
  - paracentesis: **neutrophil count > 250 cells/ul**
    - Sending some ascitic fluid in blood culture bottles increases the yield.
  - high serum ascites albumin gradient (SAAG) (>11 g/L) ascitic fluid and the white cells will be **predominantly neutrophils (>500 WBCs/$mm^3$and >50% neutrophils).**
- **Management**:
  - **intravenous cefotaxime** is usually given
  - other option: **IV piperacillin-tazobactam**
    - It is important to start antibiotics promptly pending the results of an ascitic analysis.
  - Antibiotic prophylaxis should be given if:

- patients who have had an episode of SBP
- patients with fluid protein <15 g/l and either Child-Pugh score of at least 9 or hepatorenal syndrome
- **Norfloxacin** is recommended for short term **prophylaxis**.

- **Prognosis**
  - Alcoholic liver disease is a marker of poor prognosis in SBP.
  - Has poor prognostic significance with a one year survival after a diagnosis of between 30-50%.
- **Differential diagnosis**
  - pancreatic ascites (eg. Acute pancreatitis)
    - elevated fluid amylase helps confirm this (particularly the characteristic way in which it is in excess of the serum value).
    - The low lactate dehydrogenase (<225 IU/L) helps exclude a polymicrobial ascitic fluid infection which has similar findings
    - no mention of finding any organisms on the Gram stain.
      - Bacterial growth occurs in about 80% of specimens with polymorphonuclear (PMN) count of >250 cells/mm3.
    - Ascitic fluid analysis demonstrates a low serum albumin ascites gradient (SAAG) (<11 g/L).
      - Cirrhosis and spontaneous bacterial peritonitis are both characterised by a high SAAG (>11 g/L) and are differentiated from each other on the basis of white cell count, Gram stain and culture results.
  - secondary bacterial peritonitis (ruptured viscus or loculated abscess).
    - Lactate dehydrogenase >225mU/L, glucose <50mg/dL, total protein >1g/dL and **multiple organisms on gram stain suggest secondary bacterial peritonitis** (ruptured viscus or loculated abscess).
  - Chylous ascites
    - A high level of triglycerides confirms chylous ascites.
  - elevated amylase level suggest pancreatitis or gut perforation.
  - elevated bilirubin level suggest biliary or gut perforation.

Tubercular peritonitis

Features

- risk of tuberculosis
- extensive lymphadenopathy.

Diagnosis

- **The most sensitive test to establish the diagnosis is visually directed (laparoscopic) peritoneal biopsy with histology and culture for TB.**
- An alternative in this setting might be to perform fine needle aspiration or excision biopsy of one of the palpable lymph nodes.

VIPoma

VIP (vasoactive intestinal peptide)

- source: small intestine, pancreas
- stimulation: neural
- actions:
  - stimulates water and electrolytes secretion by pancreas and intestines,
  - inhibits gastric acid and pepsinogen secretion
  - peripheral vasodilation ,
  - potentiates acetylcholine action on salivary glands.

VIPoma

- **90% arise from pancreas**
- large volume diarrhoea,secretory diarrhoea ('pancreatic cholera')
  A stool volume of <700 mL/d excludes the diagnosis of VIPoma.
- weight loss
- dehydration
- hypokalaemia, **hypochlorhydia. Achlorhydria**

- hypokalaemic acidosis (loss of alkaline secretions)
- mildly raised glucose.
- raised plasma pancreatic polypeptide
- abdominal colic
- cutaneous flushing
- raised plasma VIP

Volvulus

- Volvulus defined as torsion of the colon around it's mesenteric axis resulting in compromised blood flow and closed loop obstruction.
- **Sigmoid volvulus (around 80% of cases**) describes large bowel obstruction caused by the sigmoid colon twisting on the sigmoid mesocolon. A similar problem may also occur at the caecum (20% of cases).
- In most people (around 80%) the caecum is a retroperitoneal structure so not at risk of twisting. In the remaining minority there is however developmental failure of peritoneal fixation of the proximal bowel putting these patients at risk of caecal volvulus.

Sigmoid volvulus associations	Caecal volvulus associations
• older patients • chronic constipation • Chagas disease • neurological conditions e.g. Parkinson's disease, Duchenne muscular dystrophy • psychiatric conditions e.g. schizophrenia	• all ages • adhesions • pregnancy

Features

- constipation
- abdominal bloating
- abdominal pain
- nausea/vomiting

Diagnosis

- usually diagnosed on the abdominal film
  - **The most helpful early diagnostic tool of intestinal obstruction is the plain abdominal X-ray.**
- sigmoid volvulus: large bowel obstruction (large, dilated loop of colon, often with air-fluid levels) + coffee bean sign
- caecal volvulus: small bowel obstruction may be seen

Management

- sigmoid volvulus: rigid sigmoidoscopy with rectal tube insertion
- caecal volvulus: management is usually operative. Right hemicolectomy is often needed

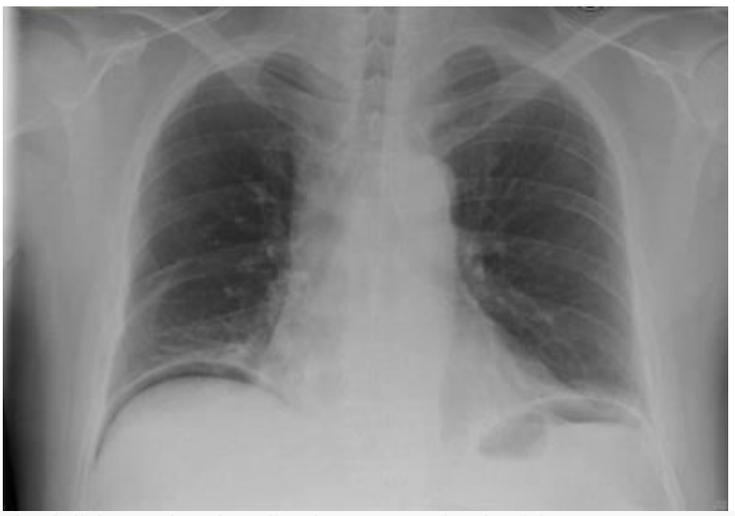
Imaging in bowel obstruction

Looking for small and large bowel obstruction is one of the key indications for performing an abdominal film.

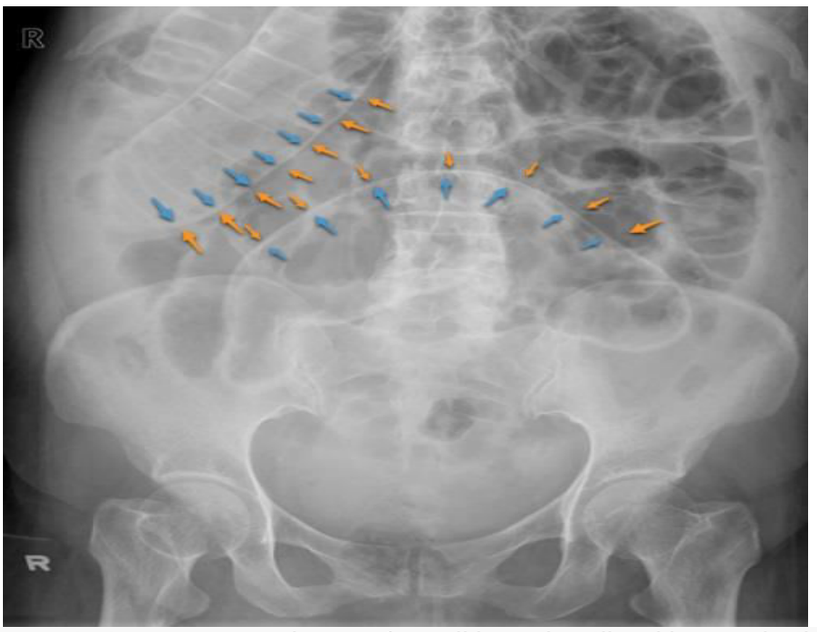
Small bowel	Large bowel
Maximum normal diameter = 35 mm Valvulae conniventes extend all the way across	Maximum normal diameter = 55 mm Haustra extend about a third of the way across

Radiology: pneumoperitoneum

- An erect chest x-ray is a useful investigation in patients with an acute abdomen as it may demonstrate free air in the abdomen (pneumoperitoneum) - an abnormal finding suggestive of a perforated abdominal viscus (e.g. a perforated duodenal ulcer).
- Rigler's sign (double wall sign) may be seen on an abdominal film.
- CT is now the preferred method for detecting free air in the abdomen.



Erect chest x-ray with air visible under the diaphragm on both sides.



Abdominal x-ray demonstrates numerous loops of small bowel outlined by gas both within the lumen and free within the peritoneal cavity. Ascites is also seen, with mottled gas densities over bilateral paracolic gutters. In a normal x-ray only the luminal surface (blue arrows) should be visible outlined by gas. The serosal surface (orange) should not be visible as it is normally in contact with other intra-abdominal content of similar density (other loops of bowel, omentum, fluid). In this case gas abuts the serosal surface rendering it visible. As this film has been obtained supine (note absence of air-fluid levels), ascites pools in the paracolic gutters, with fluid mixed in with gas bubbles (green arrows).

Dumping syndrome

- occur in up to 50% of patients who have undergone gastric bypass when high levels of simple carbohydrates are ingested.
- **early dumping syndrome**
  - rapid onset , usually **within 15 minutes of eating**
  - **results from rapid emptying of food into the small bowel.**

- Due to the hyperosmolality of the food there are rapid fluid shifts from the plasma into the bowel leading to hypotension and a sympathetic nervous system response.
- The presenting symptoms are often colicky abdominal pain, diarrhoea, nausea, and tachycardia.
- Treatment:
  - **usually self-limiting and resolves within 7 to 12 weeks.**
  - Patients should avoid foods high in simple sugar and replace them with high fibre, complex carbohydrates and protein-rich foods.
  - Small, frequent meals
  - leaving a 30 minute gap between solids and liquids

- **Late dumping syndrome**
  - **occurs as a result of the hyperglycaemia and subsequent insulin response leading to hypoglycaemia** which takes place **two to three hours after a meal.**
  - Symptoms include dizziness, fatigue, sweating, and weakness.
  - Management is similar to early dumping syndrome.

Small bowel lymphoma

Pain is the most common presenting feature of small bowel lymphoma

- Lymphoma comprises 15-20% of all small bowel tumours with the ileum most commonly affected.
- Primary lymphomas of the small bowel include
  - mucosa-associated lymphoid tissue (MALT) lymphoma
  - diffuse large B cell lymphoma
  - immunoproliferative small intestinal disease (IPSID), and
  - enteropathy-associated T cell lymphoma (EATL).
- Patients with coeliac disease are at higher risk of T cell lymphoma.
- There is a male predominance
- the median age at presentation of 25 years.
- Patients may present with:
  - anorexia
  - weight loss
  - nausea and vomiting
  - chronic pain
  - abdominal fullness
  - early satiety, and
  - constipation.
  - Findings on CT vary and may include multiple tumours, narrowing of the bowel lumen and mesenteric nodal masses.

Pancreatic conditions

Acute pancreatitis

Hypertriglyceridaemia (with levels > 10 mmol/l) is a risk factor for acute pancreatitis

- acute inflammation of the pancreas, results in release of exocrine enzymes that cause **auto-**digestion.

Pathophysiology

- **Sequence of events leading to pancreatitis:**
  - **Intrapancreatic activation of pancreatic enzymes**: secondary to pancreatic ductal outflow obstruction (e.g., gallstones, cystic fibrosis) or direct injury to pancreatic acinar cells (e.g., alcohol, drugs)
  - **Enzymatic autodigestion of pancreatic parenchyma**
  - Attraction of inflammatory cells (neutrophils, macrophages) → release of inflammatory cytokines → pancreatic inflammation (pancreatitis)
- **Sequelae of pancreatitis** (depending on the severity of pancreatitis)

- **Capillary leakage**: Release of inflammatory cytokines and vascular injury by pancreatic enzymes → vasodilation and increased vascular permeability → shift of fluid from the intravascular space into the interstitial space (third space loss)
  → hypotension, tachycardia→ **distributive shock**
- **Pancreatic necrosis**: Uncorrected hypotension and third space loss → decreased organ perfusion → multiorgan dysfunction (mainly renal) and pancreatic necrosis
- **Hypocalcemia**: Lipase breaks down peripancreatic and mesenteric fat → **release of free fatty acids that bind calcium → hypocalcemia**

Causes

The vast majority of cases in the UK are caused by gallstones and alcohol

Popular mnemonic is **GET SMASHED**

- **G**allstones
  - account for 50% of cases, with the majority of the rest being associated with alcohol.
  - For prediction of a biliary etiology, an **ALT level has the highest positive predictive value of any biochemical test.**
- **E**thanol
  - Amylase/lipase levels are **markedly** elevated in **gallstone** pancreatitis **(thousands),** whereas less increased in **alcoholic** (**hundreds**)
  - raised mean corpuscular volume (MCV) suggests chronic high alcohol use
- **T**rauma
- **S**teroids
- **M**umps (other viruses include Coxsackie B)
- **A**utoimmune (e.g. polyarteritis nodosa), **A**scaris infection
- **S**corpion venom
- **H**ypertriglyceridaemia, **H**yperchylomicronaemia, **H**ypercalcaemia,**H**ypothermia
- **E**RCP **(acute pancreatitis following ERCP should be treated with I.V fluids + analgesia)** ERCP is the third commonest cause of pancreatitis after alcohol and biliary tract disease.
- **D**rugs (azathioprine, mesalazine, didanosine, bendroflumethiazide, furosemide, pentamidine, steroids, sodium valproate)
  - pancreatitis is 7 times more common in patients taking mesalazine than sulfasalazine

Hypertriglyceridaemia

- **Considered a risk factor for pancreatitis when triglyceride levels are above 11.2 mmol/L.**
- **In a patient with hypertriglyceridaemia and acute abdominal pain, an amylase should be checked to exclude acute pancreatitis.**
- The third commonest cause of acute pancreatitis after alcohol and gallstones.
- The definition of hypertriglyceridaemia is a level greater than 1.7 mmol/L. Severe hypertriglyceridaemia is defined as 11.2-22.4 mmoL/L and very severe as above 22.4 mmol/L.
- pancreatitis secondary to hypertriglyceridaemia has greater severity and is associated with a higher complication rate.

Features

- Patients typically present with severe epigastric pain which radiates to the back, and vomiting.
- there is often a systemic inflammatory response (SIRS)
- Serum amylase is classically raised three or more times normal,
- hypocalcaemia is relatively common.
- Raised bilirubin and/or serum aminotransferase suggest underlying gallstones.
- Cirrhosis results in a small shrunken liver, and raised ALT and ALP (and gamma-GT if the cause is alcohol).
- Rare features associated with pancreatitis include:
  - ischaemic (Purtscher) retinopathy - may cause temporary or permanent blindness
- Skin changes (rare)
  - Cullen's sign: periumbilical ecchymosis and discoloration (bluish-red)
  - Grey Turner's sign: flank ecchymosis with discoloration
  - Fox's sign: ecchymosis over the inguinal ligament

Marker of severity

- **CRP is now a widely used marker of severity in acute pancreatitis.**
- Other methods which have to correlate with prognosis include the Ranson criteria and APACHE II score

Prognosis

- **Criteria of poor prognosis**
  - There are a number of scoring systems which can be used to guide prognosis, but they are **unreliable within the first 48 hours of the illness.**
  - Ranson's scoring system reflect prognosis associated with acute pancreatitis.
- **Ranson's criteria** on admission that signify a **worse prognosis** include:
  - **Criteria present at 0 hours:**
    - Age >55 years old - 1 point
    - WBC >16 $\times 10^9$ - 1 point
    - **Glucose >11.1 mmol/L** - 1 point
    - LDH >350 U/L - 1 point
    - AST >250 U/L - 1 point
  - **Criteria present at 48 hours:**
    - Hematocrit fall of 10% or greater - 1 point
    - Urea rise of 1.8 mmol/L or more despite fluids - 1 point
    - Serum Calcium <2 mmol/L - 1 point
    - pO2 <60 mmHg - 1 point **(PaO2 of < 8.0 kPa)**
    - Base deficit >4 meq/L - 1 point
    - Fluid sequestration >6000 mL - 1 point
- **The mortality associated with severe acute pancreatitis → 20%**
  - often due to sepsis or multiorgan failure.
- Hematocrit (Hct)
  - Should be conducted at presentation as well as 12 and 24 hours after admissions
  - ↑ Hct (due to hemoconcentration) indicates third space fluid loss and inadequate fluid resuscitation
  - ↓ Hct indicates the rarer acute hemorrhagic pancreatitis
- The following portend a **poor prognosis** in patients with acute pancreatitis:

WCC	**>15**
Urea	**>16**
Calcium	**<2.0**
Glucose	**>10**
CRP	**>150**

Complications

- ARDS (adult respiratory distress syndrome),
- acute kidney injury
- disseminated intravascular coagulation (DIC).
  - due to pancreatic enzymes entering the blood and acting on coagulation factors, thereby activating them.
- Pancreatic pseudocyst

Investigations

- **lab**
  - **Tests to confirm clinical diagnosis**
    - **Amylase is markedly raised**, often in excess of four times the normal value.
      - nonspecific
    - **Lipase**: if **≥ 3 x** the upper reference range → highly indicative of acute pancreatitis
    - The enzyme levels are not directly proportional to severity or prognosis
  - **Tests to assess severity**
    - **Hematocrit (Hct)**
      - Should be conducted at presentation as well as 12 and 24 hours after admissions

- ❖ ↑ **Hct** (due to hemoconcentration) indicates third space fluid loss and **inadequate fluid resuscitation**
- ❖ ↓ Hct indicates the rarer acute hemorrhagic pancreatitis

- WBC count
- Blood urea nitrogen
- ↑ CRP and procalcitonin levels
- ↑ ALT

- **Images**
  - Ultrasound
    - **the most useful initial test**
    - Main purpose: detection of gallstones and/or dilatation of the biliary tract (indicating biliary origin)
    - Signs of pancreatitis
      - ❖ Indistinct pancreatic margins (edematous swelling)
      - ❖ Peripancreatic build-up of fluid ; evidence of ascites in some cases
      - ❖ Evidence of necrosis, abscesses, pancreatic pseudocysts
  - **CT**
    - not routinely indicated
    - only when the diagnosis is in doubt
    - would be preferable to ultrasound in establishing the presence of inflammation (acute or chronic) of the pancreas and severity of disease
  - Abdominal x ray
    - has NO role in acute pancreatitis
    - Sentinel loop sign:
      - ❖ dilatation of a loop of small intestine in the upper abdomen (duodenum/jejunum)
    - Colon cut off sign:
      - ❖ gaseous distention of the ascending and transverse colon that abruptly terminates at the splenic flexure
    - Evidence of possible complications:
      - ❖ pleural effusions,
      - ❖ pancreatic calcium stones;
      - ❖ helps rule out intestinal perforation with free air
    - may demonstrate calcification in **chronic** pancreatitis.

Treatment

- supportive, and monitoring (often in the intensive care unit).
  - Fluid resuscitation: aggressive hydration with crystalloids (e.g., normal saline)
  - Analgesia: IV opioids (e.g., fentanyl)
  - Bowel rest (NPO)and IV fluids are recommended until the pain subsides
  - Nasogastric tube insertion:
    - not routinely recommended;
    - indicated in patients with vomiting and/or significant abdominal distention
  - Nutrition
    - Begin **enteral feeding** (oral/nasogastric/naso-jejunal) **as soon as the pain subsides**
    - Total parenteral nutrition:
      - ❖ **only in patients who cannot tolerate enteral feeds** (e.g., those with persistent ileus and abdominal pain)
- if there is **gallstones**:
  - urgent **ERCP** when stable.
  - **All should have a cholecystectomy** either **during the same admission** or within four weeks depending on their clinical progress.

Systemic inflammatory response syndrome (SIRS)

Causes

- sepsis
- **pancreatitis**

Criteria

- SIRS is defined as **two or more** of the following:
  1. Temperature more than 38°C or less than 36°C
  2. Heart rate more than 90 beats/min
  3. Respiratory rate more than 20 breaths/min or PaCO2 less than 4.3 kPa
  4. WBC count 12,000/mm^3, less than 4000/mm^3 , or more than 10% immature (bands) form.

Management

- **resuscitation of the sick patient still follows the ABC algorithm:**
  1. Airway
  2. Breathing
  3. Circulation.
  - **Airway control and oxygen to maintain normal saturations is the first part of that algorithm.**
  - Subsequent fluid resuscitation and treatment of the underlying cause can then be initiated.
  - The need for invasive monitoring and intensive care is then assessed, depending on the response to initial treatment.
- **Early goal-directed therapy (EGDT**) in cases of SIRS or septic shock is becoming increasingly recognised as potentially beneficial.
  - **EGDT** aims to:
    - increase organ perfusion through restoration of mean arterial pressure using inotropes if necessary,
    - maintaining central venous pressure (CVP),
    - maintaining oxygenation
      - using SjVO2 (jugular venous oxygen saturation) as a guide to oxygen utilisation at the tissue level.
  - If fluids are not achieving haemodynamic stability, and there is hypoperfusion (indicated by oliguria or lactataemia) → the most appropriate course of action → **central line** → vigorous resuscitation is indicated.
  - **Insertion of a central line allows measurement of CVP, SjVO2 and the use of inotropes.**
  - SjVO2 higher than 70% is indicative of organ hypoperfusion, as oxygen is not being extracted.
- **Obtain blood cultures prior to antibiotic administration**

Pancreatic pseudocysts

Definition

- encapsulated collection of pancreatic fluid which **develops 4 weeks after an acute attack of pancreatitis**; can occur in both acute and chronic pancreatitis

Pathophysiology

- pancreatic secretions leak from damaged ducts → inflammatory reaction of surrounding tissue → encapsulation of secretions by fibrous tissue

Clinical features

- Often asymptomatic
- Painless abdominal mass
- Pressure effects
- Gastric outlet obstruction (early satiety, non-bilious vomiting, abdominal pain)
- Bile duct obstruction with jaundice

Diagnostics

- abdominal ultrasound/CT/MRI → extrapancreatic fluid collection withinwell-defined wall/capsule, no solid cyst components detectable

Treatment

- Surgical/endoscopic; ultrasound/CT-guided **percutaneous drainage**

Chronic pancreatitis

Definition

- Chronic pancreatitis is an inflammatory condition, which can ultimately affect both the exocrine and endocrine functions of the pancreas.

Causes

- alcohol excess (80%)
  - what is the general mechanism by which alcohol induces the likely condition?
    - **Alcohol increases acinar cell sensitivity to CCK (cholecystokinin), stimulating trypsinogen production in the cell**
- Unexplained (20%)
- **PRSS-1 mutation** can cause a hereditary form of the disease.
  - It does this by allowing trypsin to be activated in the pancreas, thus causing enzymatic damage.
- **SPINK-1 mutation** can cause a hereditary form of the disease.
  - It does this by allowing trypsin to be activated in the pancreas, thus causing enzymatic damage.

Features

- pain is typically worse 15 to 30 minutes following a meal
- steatorrhoea:
  - symptoms of pancreatic insufficiency usually develop between 5 and 25 years after the onset of pain
  - **Late manifestation** (after **90%** of the pancreatic parenchyma is destroyed)
- diabetes mellitus develops in the majority of patients. It typically occurs more than 20 years after symptom begin

Investigation

- abdominal x-ray shows pancreatic calcification in 30% of cases.
- **CT is more sensitive at detecting pancreatic calcification.**
  - Sensitivity is 80%, specificity is 85%
  - More sensitive in **moderate to advanced chronic pancreatitis**
    - Malabsorption is only present in moderate to advanced chronic pancreatitis
  - abnormalities include:
    - pancreatic calcification,
    - pseudocyst formation and
    - ductal distortion.
  - CT scanning is much less effective in the diagnosis of **early chronic pancreatitis** and a normal scan does not exclude the diagnosis.
- functional tests: **faecal elastase** may be used to assess exocrine function if imaging inconclusive
- Both 72-hour faecal fat estimation and D-xylose absorption testing are used for their ability to indicate the presence, or absence, of malabsorption, neither is diagnostic of an underlying condition.

Management

- pancreatic enzyme supplements
  - **Pancrelipase (Creon)**
- Analgesia
  - In a patient with chronic liver disease presented with features of decompensation associated with chronic pancreatitis → **Naloxone**
    - Patients with alcoholic liver disease are often surprisingly sensitive to opiate analgesia which should only be used with caution.
- antioxidants: limited evidence base - one study suggests benefit in early disease

Complications

- **Pancreatic pseudocysts**
- **Splenic vein thrombosis**
  - Can occur in **10%** of patients with chronic pancreatitis
  - Pathophysiology: inflammation of the splenic vein → thrombus formation → left-sided portal hypertension → **gastric varices**

  - Clinical features: can present with upper GI bleeding, ascites, and splenomegaly
  - Diagnosis: ultrasound with doppler, CT/MR angiography
  - Treatment
    - Acute: anticoagulation and/or thrombectomy
    - Chronic and symptomatic: splenectomy

- **Pancreatic ascites**
- Pancreatic diabetes
- Pancreatic cancer (especially in patients with hereditary pancreatitis)

Pancreatic cancer

- Pancreatic cancer is often diagnosed late as it tends to present in a non-specific way.
- Over 80% of pancreatic tumours are **adenocarcinomas**
- typically occur at the **head** of the pancreas.
  - most often found in the **ductal cells in the head of the pancreas**.

Associations

- increasing age
- smoking
- **diabetes**
- chronic pancreatitis (alcohol does not appear an independent risk factor though)
- hereditary non-polyposis colorectal carcinoma
- multiple endocrine neoplasia
- BRCA2 gene
- Jewish or African descent.

Features

- classically painless jaundice
- however, patients typically present in a non-specific way with anorexia, weight loss, epigastric pain
- loss of exocrine function (e.g. steatorrhoea)
- **atypical back pain is often seen**
  - **the first symptom is often pain that radiates to the back.**
    - because it is found very late when it has already impinged on other structures.
- migratory thrombophlebitis (Trousseau sign) is more common than with other cancers
  - Migratory thrombophlebitis causes recurrent tender, palpable small blood clots that come and go in various locations on the body,

Investigation

- ultrasound has a sensitivity of around 60-90%
- **high resolution CT scanning is the investigation of choice** if the diagnosis is suspected
- **C**arbohydrate **A**ntigen 19-9 **(CA-19-9)** is a tumour marker is usually **used to monitor response to treatment** and **possible recurrance,** rather than for diagnosis.

Management

- less than 20% are suitable for surgery at diagnosis
- a Whipple's resection (pancreaticoduodenectomy) is performed for resectable lesions in the head of pancreas.
  - Side-effects of a Whipple's include dumping syndrome and peptic ulcer disease
- adjuvant chemotherapy is usually given following surgery
- **ERCP with stenting is often used for palliation**
  - relief of symptoms as soon as possible is the main objective of therapy.
  - Stenting relieves symptoms of itching and reverses jaundice in about 85% of patients.
  - Stents can be inserted during an ERCP or percutaneously in those with extensive disease or in those otherwise unsuitable for surgery.

Prognosis

- It has a very high mortality rate (approximately 1 year from diagnosis), usually because it is found very late when it has already impinged on other structures.

Biliary conditions

Ascending cholangitis

- Ascending cholangitis is a bacterial infection of the biliary tree.
- The most common predisposing factor is gallstones.

Features

- **Charcot's triad** (occurs in about 20-50% of patients)
  1. right upper quadrant (RUQ) pain, (70%)
  2. fever (the most common feature, seen in 90%)
  3. jaundice (60%)
- **hypotension** and **confusion** are also common
  - Combining these two additional symptoms to Charcot's triad results in **Reynold's pentad.**
- elevated alkaline phosphatase and elevated direct bilirubin suggest obstruction of the biliary tree

Investigation

- The initial imaging study is ultrasonography.
- The gold standard for diagnosis is **(ERCP)** endoscopic retrograde cholangiopancreatography.

Management

- intravenous antibiotics
- endoscopic retrograde cholangiopancreatography **(ERCP) after 24-48 hours** to relieve any obstruction

Gallstones (Cholelithiasis)

Risk factors for biliary stones

- Cholesterol gallstones are thought to arise as a result of a triple defect:
  1. Super saturation of gallbladder bile (high in cholesterol, low in bile salts)
  2. Increased rate of cholesterol nucleation in the gallbladder
  3. Reduction in gallbladder contractility
- **Predisposing factors to gallstone formation:**
  - Older age
  - Female sex (oestrogens)
  - Oral contraceptive use
  - Cirrhosis (bile pigment stones)
  - **ileal resection** (by reducing entero-hepatic circulation and increasing bile salt loss)
  - Clofibrate (by increasing biliary supersaturation)
  - rapid weight loss
  - Cholestyramine (by binding bile salts)
  - **Crohn's disease**

Features

- most will be asymptomatic
- Classic symptoms include biliary colic, nausea, and/or vomiting
  - biliary colic: sharp, colicky pain made worse with fatty food

Investigation

- liver function tests : obstructive jaundice
- Ultrasound
  - abdominal/right upper quadrant ultrasound is the test of choice for gallstone disease
  - ultrasound finding of a common bile duct dilatation is suggestive of an obstructing stone
  - Whilst ultrasound is a good preliminary investigation for common bile duct stones it lacks sensitivity.
  - The sensitivity of ultrasound for detecting stones is significantly reduced during an episode of acute pancreatitis (around 70%) so repeating an ultrasound is a reasonable suggestion as it would perform better in the current clinical context than it had done previously. However, its ability to detect CBD stones remains poor.
    - MRI is highly effective in confirming the presence of common bile duct stones,

- ❖ endoscopic ultrasound (EUS) is a suitable alternative.
- ❖ CT does not perform well when compared to MRI.

- Radiographs
  - ➢ cannot rule out stone with negative radiograph because cholesterol stones are radiolucent
  - ➢ pigment stones are radiopaque so may show up on radiograph
- Endoscopic retrograde cholangiopancreatography **(ERCP),** along with intra-operative cholangiography, is considered **the gold standard for diagnosis of common bile duct stones**.
  - ➢ However it is an invasive procedure associated with significant morbidity; thus it should ideally be performed as a **therapeutic rather than diagnostic** procedure.
  - ➢ The indication for ERCP is for the removal of ductal stones (predominantly CBD stones).
- Magnetic resonance cholangiopancreatography (MRCP)
  - ➢ The presence of a CBD calculus should be confirmed prior to subjecting the patient to a potentially dangerous procedure such as an ERCP - **MRCP would be the most appropriate test to do this.**
  - ➢ **the most sensitive for a diagnosis of gallstones**
    - In terms of sensitivity for determining the presence of stones anywhere within the biliary tract, MRCP and EUS would be the most sensitive investigations with little to choose between them (ERCP may well miss small stones in the gallbladder).

Management

- **In patients with severe gallstone pancreatitis → ERCP and endoscopic stone extraction should be performed within 72 hours of the onset of pain.**
- In patients with **mild gallstone pancreatitis**, in the absence of cholangitis, there is no evidence to support ERCP and stone extraction in the acute setting; however arrangements must be made for definitive management of common bile duct stones on the same admission or **within two weeks of recovery**.
- **Asymptomatic gallstones** which are located in the gallbladder are common and **do not require treatment.**
- However, if stones are present in the common bile duct there is an increased risk of complications such as cholangitis or pancreatitis and surgical management should be considered.
- endoscopic retrograde cholangiopancreatography (**ERCP**) for biliary sphincterotomy and stone extraction.
  - ➢ **the most common procedure-related complication is → Pancreatitis**
    - risks of developing this complication:
      - ❖ Female sex,
      - ❖ age less than 60 and
      - ❖ a low probability of structural disease (suggested by a normal bilirubin, non-dilated ducts or suspected sphincter of Oddi dysfunction)
- Percutaneous transhepatic cholangiography is an interventional radiological procedure which is generally reserved for therapeutic decompression of an obstructed biliary system where ERCP is unsuccessful or not possible.

Complications

- Cholecystitis
- Acute pancreatitis
- Gallbladder cancer
- Choledocolithiasis
  - ➢ calculi in the common bile duct
- Fistula between gallbladder and small intestine
  - ➢ passed gallstone can obstruct the ileocecal valve

Glasgow score for Pancreatitis:

1. PaO_2 <7.29 kPa
2. Glucose >10 mmol/L
3. Age >55 years
4. WBC >15
5. Calcium <2.0 mmol/L
6. Urea >16 mmol/L

7. LDH >600 IU/L
8. Albumin <32 g/L

Interpretation of glasgow score for pancreatitis:

- The presence of **three or more** of these criteria within the first 48 hours is indicative of **severe pancreatitis.**
- If the score ≥3, severe pancreatitis is likely Referral to the HDU/ICU is suggested in this case. If the score <3, severe pancreatitis is unlikely.

Functional gall bladder pain

- The Rome III criteria for functional gall bladder pain are as follows:
  - episodes lasting 30 minutes or longer
  - recurrent symptoms occurring at different intervals (not daily)
  - the pain builds up to a steady level
  - the pain is moderate to severe enough to interrupt the patient's daily activities or lead to an Emergency Department visit
  - the pain is not relieved by bowel movements
  - the pain is not relieved by postural change
  - the pain is not relieved by antacids, and
  - exclusion of other structural disease that would explain the symptoms.
- The pain may present with one or more of the following supportive criteria:
  - associated with nausea and vomiting
  - radiates to the back and/or right infra subscapular region, and
  - awakens from sleep in the middle of the night.

Choledochal cysts

- Choledochal cysts are congenital bile duct anomalies, cystic dilatations of the biliary tree
- The classic triad in adults with choledochal cysts is:
  1. abdominal pain, (Most common symptom)
  2. jaundice, and
  3. palpable right upper quadrant abdominal mass.
  - However, this triad is found in only 10-20% of patients.
- Adults may present with complications (eg, hepatic abscesses, cirrhosis, portal hypertension, recurrent pancreatitis, cholelithiasis)
- Abdominal ultrasonography is the investigation of choice
- Choledochal cysts are usually diagnosed in the neonatal period but a few are delayed until adulthood. The Todani classification is used to define these:
  - **Type 1 - a fusiform dilation of the common hepatic duct (CHD) - the most common**
  - Type 2 - a diverticulum of the CHD
  - Type 3 - a choledochcele
  - Type 4 - describes extension into the intrahepatic ducts (the second most common)
  - Type 5 - intrahepatic cystic disease only.
- Treatment
  - Resection and reconstruction is advised to prevent recurrent cholangitis, pancreatitis, and malignant change.

Sphincter of Oddi dysfunction

- Type 1 Sphincter of Oddi dysfunction (SOD) is characterised by:
  - abdominal pain,
  - deranged liver function tests,
  - a dilated biliary tree without strictures, and
  - delayed emptying of contrast at ERCP.

  - Delayed excretion of contrast is definitive and Sphincter of Oddi manometry need not be carried out with this finding.
- Type 2 SOD
  - pain with only one or two other criteria from the type 1 definition
- type 3 SOD
  - biliary type pain only.
  - Diagnosis in type 3 is supported by abnormal manometry although this will only be present in 12-28% of these patients so the diagnosis is most often one of exclusion.

Post-cholecystectomy syndrome

- Post-cholecystectomy syndrome is a recognised complication of cholecystectomies.
- Typically symptoms of dyspepsia, vomiting, pain, flatulence and diarrhoea occur in up to 40% patients post surgery.
- The pathology behind the syndrome isn't completely clear, however there is some association with remnant stones and biliary injury.
- Pain is often due to sphincter of Oddi dysfunction and the development of surgical adhesions.
- Management:
  - low-fat diet
  - bile acid sequestrants, such as Cholestyramine, to bind the excess bile acids and thus preventing lower gastrointestinal signs.
  - Proton-pump inhibitors like Lansoprazole do play a role, if the patient is complaining of dyspeptic like symptoms.

Bile-acid malabsorption

SeHCAT is the investigation of choice for bile acid malabsorption

- Although a small proportion of bile acids (3%) are excreted in the faeces, about 97% of bile acids are recycled.
- Bile-acid malabsorption is a cause of chronic diarrhoea.
  - the bile, with no gall bladder to store it, is excreted directly into the gut → diarrhoea
- In people with bile acid malabsorption, excess bile in the colon stimulates electrolyte and water secretion, which results in chronic watery diarrhoea.
- **May affect 10% of patients following cholecystectomy.**
- **Typically it is post-prandial**
- There is evidence suggesting that up to **one-third** of people with a diagnosis of IBS with diarrhoea (IBS-D) have bile acid malabsorption

mechanisms

- Bile acid malabsorption causes diarrhoea by 1 of the following mechanisms:
  - inducing secretion of sodium and water increasing colonic motility
  - stimulating defecation
  - inducing mucus secretion
  - damaging the mucosa, thereby increasing mucosal permeability.

Types: divided into 3 types depending on aetiology:

- type 1: following ileal resection, disease or bypass of the terminal ileum
- type 2: primary idiopathic malabsorption
- type 3: associated with cholecystectomy, peptic ulcer surgery, chronic pancreatitis, coeliac disease or diabetes mellitus.

Causes:

1. **Primary**: due to an excessive production of bile acid,

2. **Secondary:** Due to an underlying gastrointestinal disorder, causing reduced bile acid absorption
   - often seen in patients with ileal disease, such as with **Crohn's**.
   - cholecystectomy
   - coeliac disease
   - small intestinal bacterial overgrowth

- Ileal resection
- drugs:
  - Biguanides (metformin) ,
  - Colchicine, used for treating gout in patients where (NSAIDs) are contraindicated

Investigation

- **the test of choice is SeHCAT**
  - nuclear medicine test using a gamma-emitting selenium molecule in **se**lenium **h**omocholic **a**cid **t**aurine or tauroselcholic acid (SeHCAT) (^{75}Selenium HomotauroCholic Acid Test)
  - scans are done 7 days apart to assess the retention/loss of radiolabelled ^{75}SeHCAT
    - Retention values of less than 15% have been considered abnormal and indicative of bile acid malabsorption.
      - retention values of 10–15% (mild bile acid malabsorption)
      - retention values of 5–10% (moderate bile acid malabsorption)
      - retention values of 0–5% (severe bile acid malabsorption).

Management

- bile acid sequestrants e.g. cholestyramine

Primary biliary cirrhosis

Primary biliary cirrhosis - the **M** rule

- Ig**M**
- anti-**M**itochondrial antibodies, **M**2 subtype
- **M**iddle aged females

- Aetiology: not fully understood although it is thought to be an autoimmune condition.
- Mechanism: chronic inflammatory process → damage to interlobular bile ducts → cholestasis & cirrhosis.
- female: male ratio → 9:1
- classic presentation → itching in a middle-aged woman

Associations

- **Sjogren's syndrome (seen in up to 80% of patients)**
- rheumatoid arthritis
- systemic sclerosis
- thyroid disease

Clinical features

The two main conditions causing **pigmentation** and **chronic liver disease** are:
1. primary biliary cirrhosis (PBC) and
2. Haemochromatosis.

- early: may be asymptomatic (e.g. raised ALP on routine LFTs) or fatigue, pruritus
- cholestatic jaundice
- **hyperpigmentation**, especially over pressure points
- xanthelasmas, xanthomata
- also: clubbing, hepatosplenomegaly
- Fat malabsorption leading to deficiency of the vitamins A, D, E, K (hence osteomalacia and also bruising).
- **Back pain due to osteomalacia resulting from malabsorption or osteoporosis - hepatic osteodystrophy.**
- late: may progress to liver failure

Diagnosis

- anti-mitochondrial antibodies (AMA) M2 subtype are present in 98% of patients and are highly specific
  - **(AMAs) targeted against pyruvate dehydrogenase.**
  - **Pyruvate dehydrogenase (PD) is found in the mitochondria. required for the generation of acetyl-CoA from pyruvate for entry into the tricarboxylic acid (TCA) cycle.**
- smooth muscle antibodies in 30% of patients

- raised serum IgM

Liver functon tests correlate poorly with histology in PBC – the disease may progress insidiously with normal or near-normal LFTs.

Complications

- malabsorption: osteomalacia, coagulopathy
- **Osteoporosis** is a common complication, possibly due to vitamin D malabsorption and/or premature ovarian failure. All patients with PBC should be screened for the condition → **The patient should undergo bone mineral densitometry.**
- sicca syndrome occurs in 70% of cases
- portal hypertension: ascites, variceal haemorrhage
- **hepatocellular cancer (20-fold increased risk)**

Management

- pruritus: cholestyramine
- fat-soluble vitamin supplementation
- ursodeoxycholic acid (**UDCA**)
  - UDCA delays the need for liver transplantation
  - improves liver biochemistry and may slow disease progression.
  - **The effectiveness of UDCA is monitored by improvements in ALP and GGT, but ALP is more widely used than GGT.**
- liver transplantation
  - e.g. if bilirubin > 100 (PBC is a major indication)
  - **Liver transplantation has a good prognosis (90–95% survival)**
  - recurrence in graft can occur but is not usually a problem
    - occur in 10% to 40% of patients
    - but recurrent PBC does not affect either graft or patient survival rates.
  - **contraindication to liver transplantation:**
    - **Psychological factors that may impair compliance with immunosuppression**

Primary sclerosing cholangitis (PSC)

4% of patients with UC have PSC, 80% of patients with PSC have UC

Primary sclerosing cholangitis is a biliary disease of unknown aetiology characterised by inflammation and fibrosis of intra and extra-hepatic bile ducts

Associations

- ulcerative colitis: 4% of patients with UC have PSC, 80% of patients with PSC have UC
- Crohn's (much less common association than UC)
- HIV

Features

- **50 % of patients with primary sclerosing cholangitis (PSC) will have a normal physical examination at the time of diagnosis**
- cholestasis: (alkaline phosphatase greater than transaminases) → jaundice and pruritus
- right upper quadrant pain
- fatigue
- **intermittent diarrhoea.**

Investigation

- **ERCP** is the **standard diagnostic tool**, showing multiple biliary strictures giving a 'beaded' appearance
- Non-invasive magnetic resonance cholangiopancreatography (**MRCP**) is often performed **initially**.
  - MRCP would be the initial diagnostic investigation of choice particularly given a lower complication rate and its ability to image ducts proximal to obstructing strictures.
- Antibodies: ANCA may be positive (pANCA 84%, aCL 66%, , and ANA 53%)
- increase in IgM
- there is a limited role for liver biopsy, which may show fibrous, obliterative cholangitis often described as 'onion skin'

Complications

- **cholangiocarcinoma** (in 10%)
- increased risk of colorectal cancer

Prognosis

- The median time to liver failure around 12 years.

Cholangiocarcinoma

- The vast majority of cholangiocarcinomas (70%) are sporadic.
- Risk factors:
  - **Primary sclerosing cholangitis (PSC) is the most common risk factor**
  - Others
    - diabetes
    - fatty liver disease, and
    - inflammatory bowel disease without PSC.
    - Alcohol
    - Smoking
    - Chronic hepatitis B
    - obesity
- **The imaging characteristics of a cholangiocarcinoma are hypovascularity with scarring and calcification.**
  - CT contrast is delivered in early (hepatic arterial) phase and delayed (portal venous) phase.
  - 80% of normal liver tissue derives its blood supply from the portal vein, but tumours generally derive their blood supply from the hepatic artery and are therefore hypervascular.
  - Cholangiocarcinomas are an exception as **hypovascular lesions**.
- The Bismuth-Corlette classification is as follows:
  - Type I - below confluence of left and right hepatic ducts
  - Type II - reaching confluence but not involving left or right hepatic ducts
  - Type III - occluding common hepatic duct and either right (IIIa) or left (IIIb) hepatic duct
  - Type IV - multicentric or bilateral intrahepatic segmental involvement; or involving confluence and both right and left hepatic ducts.
  - It is commonly used but does not take into account factors such as distant metastases or vessel involvement.

hypervascular lesions on CT scan (most prominent on arterial phase imaging):

- Breast cancer metastasis
- Focal nodular hyperplasia
- Hepatic adenoma
- HCC

Liver conditions

Hepatomegaly

Common causes of hepatomegaly

- Cirrhosis: if early disease, later liver decreases in size. Associated with a non-tender, firm liver
- Malignancy: metastatic spread or primary hepatoma. Associated with a hard, irregular. liver edge
- Right heart failure: firm, smooth, tender liver edge. May be pulsatile

Other causes

- viral hepatitis
- glandular fever
- malaria
- abscess: pyogenic, amoebic
- hydatid disease
- haematological malignancies
- haemochromatosis
- primary biliary cirrhosis
- sarcoidosis, amyloidosis

Hepatosplenomegaly

Causes of hepatosplenomegaly

- chronic liver disease* with portal hypertension
- infections: glandular fever, malaria, hepatitis
- lymphoproliferative disorders
- myeloproliferative disorders e.g. CML
- amyloidosis

*the latter stages of cirrhosis are associated with a small liver

Gaucher's disease is a lysosomal storage disease, **due to deficiency of the lysosomal hydrolase beta-glucosidase**. most commonly seen in Ashkenazi Jews. Its features include hepatosplenomegaly, haematological abnormalities and skeletal involvement.

Liver function test

- **Gamma-glutamyl-transferase (GGT)**
  - ↑↑ by drugs such as phenytoin and alcohol.
  - Mild raises in GGT can occur with any alcohol intake, and a rise does not always indicate liver pathology.
  - **↑↑ in fatty liver**
- **Alkaline phosphatase (ALP)** typically ↑↑ in pregnancy.
- Only ischaemic hepatitis and paracetamol overdose tend to produce transaminase levels that are raised to very high degree (250 times the upper limit of normal).
- Remember that the level to which transaminases are elevated cannot be used to judge the degree of liver damage and impairment of hepatic function.

Alkaline phosphatase

Causes of raised alkaline phosphatase (ALP)

- liver: cholestasis, hepatitis, fatty liver, neoplasia
- Paget's
- osteomalacia
- bone metastases
- hyperparathyroidism
- renal failure
- physiological: **pregnancy**, growing children, healing fractures

The table below splits the causes according to the calcium level

Raised ALP and raised calcium	Raised ALP and low calcium
• Bone metastases • Hyperparathyroidism	• Osteomalacia • Renal failure

Liver biopsy

Contraindications to percutaneous liver biopsy

- deranged clotting (e.g. INR > 1.4)
  - Percutaneous liver biopsy should be avoided if the INR is greater than 1.3 (prothrombin time greater than three seconds above normal).
  - If the INR is >1.4, **fresh frozen plasma** (FFP) may be administered and liver biopsy then carried out if the INR is less than 1.4.
- low platelets (e.g. < 60 * 10^9/l)
  - The minimum safe lower limit of platelets is 60.
  - Where the platelet count is 40-60 biopsy can be performed immediately after **platelet transfusion** provided there has been an increment to the recommended level.
- Anti-platelet medication
  - should be stopped for at least one week prior to liver biopsy.
- anaemia

- **extrahepatic biliary obstruction**
- hydatid cyst
- haemoangioma
- **uncooperative patient**
- ascites
  - Significant volume ascites is a contraindication to percutaneous liver biopsy but a **transjugular biopsy can be performed as an alternative.**

Acute liver failure

Acute liver failure describes the rapid onset of hepatocellular dysfunction leading to a variety of systemic complications.

Causes

- paracetamol overdose
- alcohol
- viral hepatitis (usually A or B)
- acute fatty liver of pregnancy

Features*

- jaundice
- coagulopathy: raised prothrombin time
- hypoalbuminaemia
- hepatic encephalopathy
- renal failure is common ('hepatorenal syndrome')

*remember that 'liver function tests' do not always accurately reflect the synthetic function of the **liver. This is best assessed by looking at the prothrombin time and albumin level.**

Ascites

Causes

- **The serum ascites albumin gradient (SAAG) is the most sensitive and specific method of categorising ascites.**
  - To calculate the ascitic fluid albumin should be subtracted from the serum albumin.
    - A value that is ≥11 g/L (high SAAG) indicates a transudate (e.g. cirrhosis, cardiac failure),
    - <11 g/L (low SAAG) indicates an exudate (e.g. malignancy, pancreatitis).

- The causes of ascites can be grouped into those with a serum-ascites albumin gradient (SAAG) <11 g/L or a gradient >11g/L as per the table below:

SAAG > 11g/L	SAAG <11g/L
Cirrhosis Alcoholic hepatitis Cardiac ascites Mixed ascites Massive liver metastases Fulminant hepatic failure Budd-Chiari syndrome Portal vein thrombosis Veno-occlusive disease Myxoedema Fatty liver of pregnancy	Peritoneal carcinomatosis Tuberculous peritonitis **Pancreatic ascites** Bowel obstruction Biliary ascites Post operative lymphatic leak Serositis in connective tissue diseases

Characteristics of ascitic fluid

- **Causes of a transudate (protein < 30 g/l, assuming a normal albumin level):**
  - Hepatic cirrhosis
  - Right-sided cardiac failure
  - Hypoalbuminaemia (nephrotic syndrome)
  - Acute nephritis
  - Budd-Chiari syndrome
- **Causes of an exudate (protein > 30 g/l):**
  - Infection (tuberculosis, peritonitis)

- Inflammation (vasculitis)
- Malignancy
- **inhaler.**

Treatment

- **Large, symptomatic ascites → therapeutic paracentesis.**
  - Several large randomised, controlled trials have shown that repeated large volume paracentesis (4-6 L) is safer and more effective for the treatment of tense ascites compared with larger than usual doses of diuretics.
  - Paracentesis is relatively contraindicated if the patient is encephalopathic,
  - **Paracentesis is less likely to be successful if the patient has peripheral oedema**
  - Whilst therapeutic paracentesis will be necessary in light of the large volume tense ascites it would be advisable to consider doing this with FFP cover.
- Not large, asymptomatic ascites → dietary salt restriction (to no more than 90 mmol/day) + spironolactone.
  - **The initial management would be spironolactone**
  - Initial dose of spironolactone is 100 mg/day and may be titrated up to 400 mg/day.
  - Once the maximum dose of spironolactone has been reached furosemide can be added if there is still significant ascites accumulation and the renal function and electrolytes will tolerate further diuresis.
  - Doses of furosemide are advised start at 40 mg/day titrating up to 160 mg/day as tolerated or needed.
  - Furosemide alone has poor efficacy in cirrhosis.
  - A major reason for so-called diuretic-resistant ascites is an excess sodium intake
  - Spironolactone is more effective than furosemide **because** the site of sodium retention in cirrhosis is the distal nephron
  - The ideal weight loss is 0.5 kg/day
- transcutaneous liver biopsy is contraindicated with ascites (use transjugular biopsy if absolutely necessary).
- **Management of hyponatraemia in patients with chronic liver disease and ascites:**
  - serum sodium is 126-135 mmol/L → No specific intervention other than monitoring
  - serum sodium is 121-125 mmol/L + normal creatinine → Reduce diuretics
  - serum sodium is 121-125 mmol/L + high creatinine → Stop diuretics + give volume expansion
  - **serum sodium is ≤120 mmol/L → Stop diuretics + give volume expansion with colloid or normal saline.**
- **Management of hypoproteinemia in patients with chronic liver disease**
  - Cirrhotic ascites has significantly lower protein and complement levels than non-cirrhotic ascites.
    - This can result in less opsonic activity of the peritoneal fluid predisposing to spontaneous bacterial peritonitis.
  - indications for the use of albumin in cirrhosis:
    - post-paracentesis circulatory dysfunction,
    - spontaneous bacterial peritonitis, and
    - hepatorenal syndrome.
  - Albumin replacement treatment is warranted in this diagnosis and can also decrease the development of the hepatorenal syndrome.
  - **20% salt poor albumin (human albumin solution)**
    - The salt-poor preparation of albumin is particularly important in this scenario as high salt load will encourage fluid to shift into the extravascular compartment resulting in fluid overload.

Complications of cirrhosis	Albumin use	
PPCD	8 g/l of ascites removed (above 5 l)	According to guidelines
SBP	1.5 g/kg on day 1 and 1g/kg on day 3 (in association with antibiotics)	
HRS	Loading and maintenance dose + terlipressin untill HRS resolution	
Non-SBP Infections	Improvement in renal and circulatory function (no effect on survival, only one study available)	Controversial indications (more studies needed)
HE	Only two discordant studies available (effect on oxidative stress)	
Ascites	Not yet enough evidence for the utility of chronic use *(ANSWER Study currently ongoing)*	
ACLF	Albumin dialysis (MARS and Prometheus systems)	

Summary table of the current uses of albumin in hepatology, according to the main international guidelines and looking at future perspectives (**PPCD**: post-paracentesis circulatory dysfunction; **SBP**: spontaneous bacterial peritonitis; **HRS**: hepatorenal syndrome; **HE**: hepatic encephalopathy; **ACLF**: acute-on-chronic liver failure).

Meig's syndrome → ovarian fibroma associated with a pleural effusion and ascites

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Liver cirrhosis

Pathophysiology

- which hepatic cells are central to the process of fibrosis?
  - The hepatic **stellate cells are central to the process of fibrosis within the liver.**
- What is the pro-inflammatory factor in fibrotic liver injury which activate the stellate cells?
  - **Tumour necrosis factor-a** is a pro-inflammatory effector in fibrotic liver injury, through activation of the **stellate cells**. These cells then secrete the fibrillar collagen constituting the defining features of hepatic fibrosis.
  - Interleukin-10 is thought to exert anti-inflammatory effects on the stellate cell.
- Which mediator is released by stellate cells that causes fibrosis seen in cirrhosis?.
  - **Transforming growth factor-beta** is the mediator **released by stellate cells** that causes fibrosis
- Which factor that causing contraction of the hepatic stellate cells?
  - **Endothelin** is a **vasoconstrictor in the hepatic sinusoids** (similarly in the endothelium of the systemic circulation) and functions by causing **contraction of the hepatic stellate cells** thus increasing **intrahepatic sinusoidal resistance** and promoting **portal hypertension**.
  - Nitric oxide antagonises the effects of endothelin in the liver.
- Pathogenesis includes the replacement of type IV collagen in the perisinusoidal space (space of Disse) with type I and III collagen.

Features

- **Cardiac**
  - Cardiac output is often elevated
  - The cardiomyopathy of **alcoholism** is a dilated or congestive form.
    - **Dilated cardiomyopathy**
  - hyperdynamic circulation

- systemic vasodilatation
- ↓↓ vascular resistance,
- increased plasma volume → low serum sodium.
  - Most patients have **sodium and water retention**.
  - Secondary hyperaldosteronism will result in total body sodium overload but not necessarily hypernatraemia.
  - Remember that the sodium level is a concentration, therefore if the amount of solvent (water) is increased then it will not necessarily rise.

- **Abdominal symptoms**
  - Hepatomegaly (possibly causing RUQ pain)
  - Splenomegaly
  - Ascites
- **Portal hypertension**
  - Hepatic intrasinusoidal pressure is elevated
  - **Which features is most indicative of decompensated portal hypertension?**
    - ⇨ **Caput medusae**
- Which sign is a direct result of **decreased hepatic oncotic** function in cirrhotic patients?
  - **Lower limb swelling**
- **Hormone disorders**
  - Hyperestrogenism
    - Gynecomastia, decreased body hair (e.g., chest hair)
      - Gynaecomastia
        - ⇨ **What is the cause of gynaecomastia in cirrhosis?**
          - **Altered oestrogen metabolism**
            - ↓↓ metabolism of sex steroids → ↑↑ oestrogen level.
            - there is associated testicular atrophy and loss of body hair.
            - May occur as a result of spironolactone therapy (an aldosterone antagonist).
    - Hypogonadism (testicular atrophy)
    - Reduced libido, erectile dysfunction, infertility
  - Amenorrhea

Classifications

- **Child-Pugh classification of liver cirrhosis**
  - The Child-Pugh classification is a scoring system to **assess the severity** of liver cirrhosis

Score	1	2	3
Bilirubin (m mol/l)	<34	34-50	>50
Albumin (g/l)	>35	28-35	<28
Prothrombin time, prolonged by (s)	<4	4-6	>6
Encephalopathy	None	mild	marked
Ascites	None	mild	marked

    - Summation of the scores allows the severity to be graded either A, B or C:
      - **< 7 = A**
      - **7- 9 = B**
      - **9 = C**
- Cirrhosis can be micro- or macronodular in type.
  1. **micronodular** form: the nodules are less than 3 mm across with uniform liver involvement - seen in **alcohol** or **biliary disease**.
  2. **macronodular** form: there are larger nodules, classically seen in **chronic viral hepatitis**.

Investigations

- **ALT is more specific than other liver enzymes in diagnosing hepatic injury.**

- **the most important immediate investigation for patient with hepatic cirrhosis presented in a confused and drowsy state → Blood glucose (**hepatic gluconeogenesis can be significantly down-regulated)
- ↑↑ plasma volume
- ↓↓ **serum sodium**
  - **Patients with cirrhosis are frequently hyponatraemic.**
    - This is a function of an inability to excrete free water (increased ADH levels and systemic vasodilation contribute, but the underlying mechanism is complex and not entirely understood).
- Urinary sodium concentration is usually less than 10 mmol/l
  - **Reduced urinary sodium excretion**
    - Patients with cirrhosis are frequently hyponatraemic. This is a function of an inability to excrete free water (increased ADH levels and systemic vasodilation contribute, but the underlying mechanism is complex and not entirely understood).

Thrombocytobenia is a common finding in chronic liver disease.

Sex hormones in liver cirrhosis

- Clinical features of male cirrhotic subjects are feminization(gynecomastia etc) and hypogonadism(testicular atrophy, reduced fertility, loss of libido, impotence etc).
- sex hormones
  - decrease in serum testosterone levels
  - increase in serum estrogen levels
  - increase in ratio of estrogen to testosterone
  - Hyperestrogenization may be related with feminization of male cirrhotic subjects, whereas hypogonadism is the result of alcohol abuse per se, rather than the indirect consequence of liver cirrhosis.

Prognosis

- Five year survival after liver transplantation is now 75%.

liver transplant

Guidelines for referral to a liver unit following paracetamol overdose include

- Metabolic acidosis (**pH <7.3** or bicarbonate <18 mmol/L).
- INR >3 (or prothrombin time >50 seconds)
  - **INR >2.0 at or before 48 hours or >3.5 at or before 72 hours should prompt referral to a specialist unit.**
  - Peak elevation occurs around 72-96 hours.
- Oliguria
- Creatinine >200 µmol/L,
  - (use haemodialysis if >400 µmol/L)
- Hypoglycaemia.
- Systolic BP <80 mm Hg despite adequate fluid resuscitation
- Any degree of encephalopathy 48 hours after ingestion.
- raised intracranial pressure (ICP)
  - signs of CNS oedema include:
    - BP >160/90 mmHg (sustained) or brief rises (systolic >200 mmHg),
    - bradycardia,
    - decerebrate posture,
    - extensor spasms, and
    - poor pupil responses

Criteria for liver transplant in fulminant failure in cases of paracetamol overdose include:

- arterial pH lower than 7.3 or
- all of the following:
  - Prothrombin time greater than 100 seconds
  - Creatinine greater than 300 µmol/L, and
  - Grade 3-4 encephalopathy.

Criteria for liver transplant in fulminant failure in non-paracetamol cases include:

- INR greater than 6.7 or
- prothrombin time greater than 100 seconds, or
- any three of the following:
  - Aetiology that is not due to hepatitis A, hepatitis B or a drug reaction
  - Age less than 10 years or more than 40 years
  - Jaundice more than seven days before encephalopathy
  - INR greater than 4 or prothrombin time greater than 50 seconds, and
  - Bilirubin greater than 300 µmol/L.

Portal hypertension

Basics

- The liver receives approximately 1500 ml of blood each minute, **two-thirds of which is provided by the portal vein**.

Definition:

- abnormally high pressure in the hepatic portal vein (hepatic venous pressure gradient of 10 mm Hg or more).
- Portal hypertension is present when the wedged hepatic vein pressure is more than 5 mmHg higher than the inferior vena cava pressure.

Mechanism of porto-systemic collaterals

- Because the **veins in the portal system lack valves**, increased resistance to flow at any point between the splanchnic venules and the heart will increase the pressure in all vessels on the intestine site of the obstruction.
- This is manifest clinically by the development of porto-systemic collaterals (oesophageal varices), splenomegaly and/or ascites.

Causes : (Vascular resistance and blood flow are 2 important factors in its development).

Pre-hepatic - (pre-sinusoidal) **blockage of the portal vein before the liver**

- Congenital atresia or stenosis.
- **Portal vein thrombosis** (idiopathic, **umbilical and portal sepsis**, malignancy, hypercoagulable states, pancreatitis).
  - **Longstanding portal vein thrombosis is a well recognised complication in premature neonates due to cannulation of the umbilical vein during neonatal intensive care.**
    - **the best initial investigation is → Ultrasound with Doppler**
- Splenic vein thrombosis.
- Extrinsic compression - eg, tumours.

Hepatic (sinusoidal)

- Cirrhosis. **(the most common cause)**
- Chronic hepatitis.
- Schistosomiasis.
- Myeloproliferative diseases.
- Idiopathic portal hypertension.
- Granulomata - eg, sarcoid.
- Nodular (nodular regenerative hyperplasia, partial nodular transformation).
- Toxins (arsenic, vinyl chloride).
- Fibropolycystic disease (including congenital hepatic fibrosis).

Post-hepatic - (post-sinusoidal) **blockage of hepatic veins or venules**

- Budd-Chiari syndrome (hepatic vein obstruction).
- Constrictive pericarditis.
- Right heart failure.

- Veno-occlusive disease of the smaller hepatic veins/venules (due to ingestion of pyrrolizidine alkaloids; antileukaemic drugs, radiation).
- Sclerosing hyaline necrosis.

Portal hypertension measurement:

- Portal pressure is indirectly measured in clinical practice by the hepatic venous pressure gradient (HVPG).
- The HVPG is calculated by subtracting the free hepatic venous pressure (which reflects intra-abdominal pressure) from the wedged hepatic venous pressure (which reflects portal venous pressure). These values are obtained by hepatic venous catheterization.
- Normal HVPG values are <5 mm Hg.
- HVPG >10 mm Hg predicts the development of oesophageal varices.
- However, HVPG is moderately invasive and its clinical role is uncertain.
- The normal hepatic venous pressure gradient (normal HVPG = 1-5 mmHg) means that the portal hypertension is not related to post-sinusoidal intrinsic liver disease such as cirrhosis (caused in children by metabolic disorders such as A1ATD) or post-hepatic venous obstruction (HV thrombosis).
- The haemodynamic goal of treatment is reduce the HVPG by 20% or to less than 12 mmHg, using a non-selective beta blocker. If this is not achievable despite titrating the beta-blocker dose, then endoscopic variceal ligation must be considered.
- **Wedged hepatic venous pressure**
  - the pressure recorded by a catheter wedged in a hepatic vein. It reflects the portal venous pressure in the hepatic sinusoids.
  - **↑↑ in sinusoidal and post-sinusoidal portal hypertension,**
  - remains normal in pre-sinusoidal portal hypertension.

Complications of portal hypertension:

- Haematemesis or melaena - suggest bleeding varices.
- Lethargy, irritability and changes in sleep pattern - suggest encephalopathy.
- Increased abdominal girth, weight gain - suggest ascites.
- Abdominal pain and fever - suggest spontaneous bacterial peritonitis.
- Pulmonary involvement is common in patients with portal hypertension

Trans-jugular intrahepatic porto-systemic shunt (TIPSS)

- Indications are:
  - Diuretic resistant ascites (**Intractable ascites**)
  - Intractable portal hypertensive bleeding and
  - Hepato-renal failure.
- contraindications to shunting:
  - Severe hepatic encephalopathy
  - Severe heart failure
  - Septicaemia

Hepatic encephalopathy

- Hepatic encephalopathy may be seen in liver disease of any cause.
- The aetiology is not fully understood but is thought to include excess absorption of ammonia from bacterial breakdown of proteins in the gut

Features

- confusion, altered GCS (see below)
- hepatic flap

  - Asterixis (also called the flapping tremor, or liver flap) is a tremor of the hand when the wrist is extended, sometimes said to resemble a bird flapping its wings.
  - **hepatic encephalopathy is unlikely to be present if a liver flap (asterixis) cannot be detected.**
- constructional apraxia: inability to draw a 5-pointed star
- triphasic slow waves on EEG
- raised ammonia level (not commonly measured anymore)

Grading of hepatic encephalopathy

- Grade I: mood changes like depression or irritability, and sleep abnormalities (typically sleep inversion)
- Grade II: Confusion, inappropriate behaviour
- Grade III: Incoherent, restless
- Grade IV: Coma

Precipitating factors

- infection e.g. spontaneous bacterial peritonitis
- GI bleed
- constipation
- drugs: sedatives, diuretics
- hypokalaemia
- renal failure
- increased dietary protein (uncommon)

Treatment

- Treat precipitating cause (*e.g.,* give K+ if hypokalemic)
- Lactulose
  - metabolized to lactic acid by colonic flora, converts NH_3 to NH_4+ which can be absorbed
- Neomycin
  - replaced with rifamixin, neomycin no longer routinely used
  - antibiotics kill colonic flora leading to decreased NH_3 production

Hepatorenal syndrome:

Hepatorenal syndrome is primarily caused by splanchnic vasodilation

Pathophysiology

- vasoactive mediators cause → **splanchnic vasodilation** → ↓↓ systemic vascular resistance → 'underfilling' of the kidneys → activation of the renin-angiotensin-aldosterone system by the juxtaglomerular apparatus → renal vasoconstriction which is not enough to counterbalance the effects of the splanchnic vasodilation.

Types

- Hepatorenal syndrome has been categorized into two types:

Type 1 HRS	Type 2 HRS
Rapidly progressive Doubling of serum creatinine to > 221 mmol/L or a halving of the creatinine clearance to less than 20 ml/min over a period of less than 2 weeks Very poor prognosis	Slowly progressive Prognosis poor, but patients may live for longer **characterised by a moderate and stable reduction in renal function, hypotension and diuretic resistance.**

Management

- The **ideal treatment** is liver transplantation but patients are often too unwell to have surgery and there is a shortage of donors
- Other Management options
  - agonists of vasopressin V1 receptors such as **terlipressin** → vasoconstriction of the splanchnic circulation
  - volume expansion with 20% albumin
  - transjugular intrahepatic portosystemic shunt

Wilson's disease

Wilson's disease - serum caeruloplasmin is **decreased**

Wilson's disease - autosomal recessive

Definition

- Wilson's disease is an autosomal recessive disorder characterised by impaired copper transport via caeruloplasmin results in excessive copper deposition in the tissues.
- **Wilson disease** is a disorder resulting from **impaired copper excretion into bile**. Copper overload and deposition in tissues leads to predominantly hepatic and neuropsychiatric symptoms.
- Metabolic abnormalities include increased copper absorption from the small intestine and decreased hepatic copper excretion.

Aetiology and pathophysiology

- autosomal recessive
- caused by a defect in the ATP7B gene located on chromosome 13.
- Mutations within the ATP7B gene result in disruption of an ATPase within hepatocytes which is responsible for the movement of copper across intracellular membranes. This results in **hepatic retention of copper, and low serum levels.**
- The mechanism of tissue damage in Wilson disease is copper-mediated hydroxyl free radical tissue damage.

Features

- The onset of symptoms is usually between 10 - 25 years.
- Children usually present with liver disease whereas **the first sign of disease in young adults is often neurological disease**
- liver: hepatitis, cirrhosis
- neurological:
  - **basal ganglia degeneration, speech and behavioural problems are often the first manifestations**.
  - **The most common early neurological sign is an asymmetrical tremor**,
  - Also: the initial sign is usually increased clumsiness.
  - parkinsonism,
  - dystonia.
  - asterixis,
  - chorea,
  - dementia
- Kayser-Fleischer rings
  - Golden corneal rings
  - **in the posterior surface of the retina, within its Descemet's membrane.**
  - Detected by **Slit lamp examination**
  - Present in up to 90% of symptomatic patients, but is not pathognomonic.
- renal tubular acidosis (esp. Fanconi syndrome)
- haemolysis
- blue nails

Diagnosis

- **Reduced serum caeruloplasmin**
- ↓ Total serum copper
- increased 24hr urinary copper excretion
  - greater than 1.6 µmol/day
- **Liver biopsy**
  - **The most reliable investigation to confirm the diagnosis**
  - Shows:
    - increased hepatic parenchymal copper concentration

- steatosis, glycogenated nuclei, focal hepatocellular necrosis, fibrosis and cirrhosis.

- MRI of the brain
  - commonly shows increased density in the basal ganglia.
- Genetic testing for ATP7B mutation
  - usually reserved for patients where the diagnosis is in doubt, or for screening of siblings.

Complications

- higher risk of hepatocellular carcinoma.

Management

- **General management**
  - Low-copper diet: avoid foods such as **organs, shellfish, nuts, and chocolate**
  - Hepatotoxic drugs, alcohol and foods high in copper (liver, chocolate, shellfish etc.) should be avoided.
  - Regular check-ups: liver biochemical tests every 6 months if disease is stable[9]
  - Liver transplantation in cases of fulminant liver failure
- **Medical therapy**
  - **Initial therapy**: **chelating agents**
    - **Penicillamine**:
      - first-line treatment
      - side effects in ~ 30% of cases
        - (e.g., sensitivity reactions)
        - bone marrow suppression
    - Alternatives: trientine or zinc salts
      - **Trientine**
        - may become first-line treatment in the future
        - better tolerated than penicillamine, and is therefore used as an alternative where side effects are seen when penicillamine is initiated.
  - **Maintenance therapy**: **zinc salts** or low dose chelating agents

- **Zinc acetate is the intervention of choice for patients with asymptomatic Wilson's disease (i.e. those who present with elevated transaminases without evidence of cirrhosis or neurological dysfunction).**

- screening of first degree relatives
  - Once a diagnosis of Wilson's disease is made, screening of first degree relatives (with genetic testing) should be done.

Treatment with a chelating agent should be administered gradually over the course of 3 to 6 months, as mobilizing the copper stored in tissues too rapidly may exacerbate neurological symptoms

Prognosis

- Early treatment allows a normal length of life,
- however without treatment Wilson's disease is usually fatal by the age of 40 years.

September 2014 exam: A 23-year-old woman developed unilateral hand tremor at rest, behaviour & mood changes, speech problems & bradykinesia. Dark circular marks noted around the iris. her uncle died of liver cirrhosis at the age of 40 years. Given the likely diagnosis, what is the mode of inheritance? Autosomal recessive

Hyponatraemia in Patients with chronic liver disease

- Patients with chronic liver disease and ascites often develop hyponatraemia, the management of which can be difficult.
- Diuretic therapy for the management of ascites often contributes to the hyponatraemia.
- **The British Society of Gastroenterology guidelines** suggest that:
  - **serum sodium is ≤120 mmol/L→ normal saline + stop diuretic**
  - serum sodium is 126-135 mmol/L → No intervention other than careful monitoring.

- serum sodium is 121-125 mmol/L + normal serum creatinine → reduce diuretics or stop it if necessary
- serum sodium is 121-125 mmol/L +↑↑ serum creatinine → volume expansion + stop diuretics
- fluid restriction should only be used in patients who are clinically euvolaemic, not on diuretics and have severe hyponatraemia with a normal serum creatinine.

Alcohol

After drinking excessive amounts alcohol

- **Mechanism of polyuria → Ethanol inhibits ADH secretion**
- Mechanism of nausea → vagal stimulation to the vomiting centre.
- Mechanism of tremors → increase glutamate production by neurones to compensate for the previous inhibition by ethanol.
- **Mechanism of hypoglycemia → hepatic sequestration of Reduced nicotinamide adenine dinucleotide (NADH)**
  - In the liver alcohol dehydrogenase converts ethanol to acetaldehyde but to do so requires the reduction of oxidized nicotinamide adenine dinucleotide (NAD^+) to reduced nicotinamide adenine dinucleotide (NADH).
  - Acetaldehyde is then further oxidized to acetate to aldehyde dehydrogenase, which requires the reduction of another NAD^+ to NADH.
  - When excess alcohol is consumed then the system becomes overwhelmed and NADH accumulates in hepatocytes.
  - This **sequestration of NADH reduces the amount of NAD^+ available to oxidize gluconeogenic precursors → hypoglycemia**

Alcohol - drinking problems: management

Nutritional support

- SIGN recommends alcoholic patients should receive oral thiamine if their 'diet may be deficient'

Drugs used

- benzodiazepines for acute withdrawal
- disulfram: promotes abstinence - alcohol intake causes severe reaction due to inhibition of acetaldehyde dehydrogenase. Patients should be aware that even small amounts of alcohol (e.g. In perfumes, foods, mouthwashes) can produce severe symptoms. Contraindications include ischaemic heart disease and psychosis
- acamprosate: reduces craving, known to be a weak antagonist of NMDA receptors, improves abstinence in placebo controlled trials

Alcoholic liver disease

The recommended maximum alcohol intake per week is 21 units for men and 14 units for women.

Governmental guidelines suggest that women should not have more than 2-3 units per day and men should not have more than 3-4 units per day

Alcoholic liver disease includes fatty liver, alcoholic hepatitis and cirrhosis.

- **fatty liver** (hepatic steatosis)
  - accumulation of fat within the hepatocytes.
  - asymptomatic and detected incidentally.
  - Elevated transaminases and a background of alcoholism are clues to the diagnosis.
  - **macro**vesicular fatty changes.
    - Microvesicular fatty changes are not found in hepatic steatosis.
  - An ultrasound demonstrates hyperechogenicity and a bright liver.
  - This is **reversible with abstention from alcohol.**
- **Alcoholic hepatitis** presents as:
  - acute right upper quadrant (RUQ) pain
  - Tender hepatosplenomegaly
  - jaundice
  - fever
  - frequently occurs on a background of cirrhosis
  - marked derangement of LFTs
    - **LFT typically show an AST elevated greater than the ALT with at least a 2:1 ratio**

- AST:ALT ratio can be useful in diagnosing alcoholic liver disease, because more than two-thirds of patients will have a ratio greater than 2.
- transaminases are typically only slightly elevated rarely over 300 and virtually never over 500.
- The alkaline phosphatase may well be significantly elevated giving the liver profile an 'obstructive' appearance.
- High IgA levels are seen in alcoholic liver disease.

  - At a microscopic level there is inflammation of the liver.
- In **liver cirrhosis**, the hepatocytes are damaged so much that they are replaced by scar tissue which is permanent. **The cardiomyopathy of alcoholism is a dilated or congestive form.**
- Alcoholic hepatitis and cirrhosis may co-exist.
- Alcoholic hepatitis and cirrhosis may lead to encephalopathy, portal vein hypertension and hepato-renal syndrome, increase risk of infections and they are usually malnourished.
- **Treatmen**t involves:
  - good nutrition and abstinence from alcohol.
  - There is no specific therapy for alcohol-related hepatitis and cirrhosis.
  - treat the complications which include:
    - ascites → high doses of diuretics
    - spontaneous bacterial peritonitis,
    - hepatic encephalopathy
    - and oesophageal varices.

Chronic alcohol abuse is typically associated with → Increased carbohydrate deficient transferrin (CDT)

Which feature would suggest a diagnosis of hepatic steatosis rather than non-alcoholic fatty liver disease?
→ **Reversible hepatic damage after discontinuing alcohol consumption**

The common abnormalities in chronic alcohol dependence:

- Macrocytosis
- Elevated GGT - this is due to enzyme induction but does not necessarily indicate that there is liver damage
- Hypertriglyceridaemia - can contribute to pancreatitis
- Hyperuricaemia - can cause gout
- Hypoglycaemia - can contribute to seizures and coma
- Hypomagnesaemia
- Hypogonadism
- Thiamine deficiency
- Increased carbohydrate deficient transferrin - considered a marker of chronic abuse and sometimes checked to ensure abstinence, for example, while awaiting liver transplantation
- Iron levels are variable in alcohol dependence: hepatitis causes increased serum iron while poor diet can result in iron deficiency
- Ferritin can be elevated in the acute phase response, but reduced in advanced liver disease due to possible reduced synthesis rates
- Hyponatraemia and hypokalaemia are often seen in established liver disease
- ALT is elevated in liver disease and hepatocellular damage
- AST is elevated (but can also be increased in cardiac or muscular damage).
- AST:ALT ratio can be elevated due to the mitochondrial effects of alcohol causing a disproportionate increase in AST. However, this is not specific.

Alcoholic ketoacidosis

- Alcoholic ketoacidosis is a non-diabetic euglycaemic form of ketoacidosis.
- It typically presents with a pattern of:
  - Metabolic acidosis
  - Elevated anion gap
  - Elevated serum ketone levels
  - Normal or low glucose concentration

- **The most appropriate treatment is an infusion of saline & thiamine.** Thiamine is required to avoid Wernicke encephalopathy or Korsakoff psychosis.

Disulfiram

- **Indication**: used as an aid to stopping alcohol abuse.
- **Mode of action**: irreversible inhibitor of aldehyde dehydrogenase, therefore if alcohol is ingested, aldehyde accumulates causing unpleasant reactions including vomiting, palpitations and breathlessness.
- The reaction with alcohol only occurs at least **12 hours after the start of disulfiram** therapy and may occur **up to 10 days after stopping disulfiram** therapy.
- **Disulfiram is active against scabies,** although other treatments are usually preferred.

Ref : medical-masterclass.2017 part 2

Non-alcoholic fatty liver disease

Obese T2DM with abnormal LFTs - ? non-alcoholic fatty liver disease

- Non-alcoholic fatty liver disease (NAFLD) is now the most common cause of liver disease in the developed world.
- It is largely caused by obesity and describes a spectrum of disease ranging from:
  - steatosis - fat in the liver
  - steatohepatitis - fat with inflammation, non-alcoholic steatohepatitis (NASH), see below
  - progressive disease may cause fibrosis and liver cirrhosis
- NAFLD is thought to represent the hepatic manifestation of the metabolic syndrome and hence insulin resistance is thought to be the key mechanism leading to steatosis
- **Non-alcoholic steatohepatitis (NASH)**
  - liver changes similar to those seen in alcoholic hepatitis in the absence of a history of alcohol abuse.
  - **the diagnosis is made only by histology of liver biopsy which shows lesions suggestive of ethanol intake in a patient known to consume less than 40 g of alcohol per week.**
  - The diagnosis is supported by the presence of obesity, hyperglycaemia and hyperechogenic hepatic parenchyma on US.
  - relatively common and though to affect around 3-4% of the general population.
  - The progression of disease in patients with NASH may be responsible for a proportion of patients previously labelled as cryptogenic cirrhosis

Associated factors

- obesity
- hyperlipidaemia
- **type 2 diabetes mellitus**
- jejunoileal bypass
- sudden weight loss/starvation

Features

- usually asymptomatic
- hepatomegaly
- **ALT is typically greater than AST**
- increased echogenicity on ultrasound
- The hallmark of the condition on liver biopsy is the association of inflammation with fatty infiltration of the liver. This can progress to fibrotic change and eventually to cirrhosis.

Management

- the mainstay of treatment is lifestyle changes (particularly weight loss) and monitoring
- there is ongoing research into the role of gastric banding and insulin-sensitising drugs (e.g. Metformin)

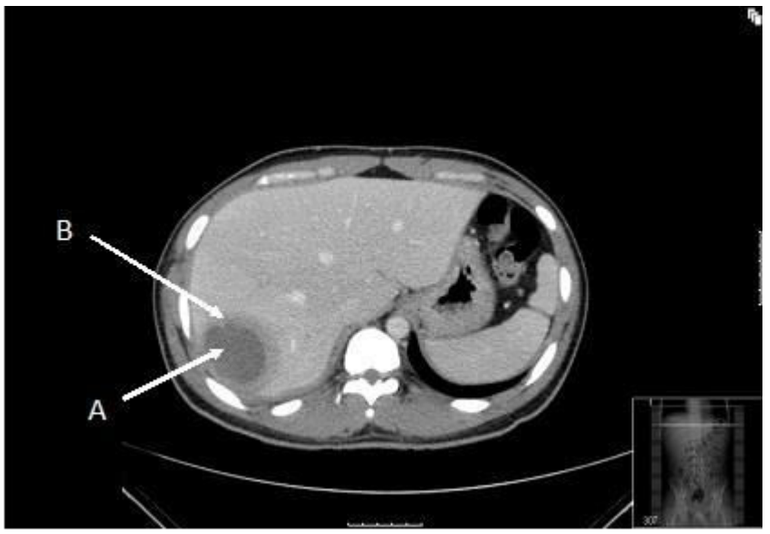
Prognosis

- Approximately 20% develop cirrhosis

Liver abscess

Pyogenic liver abscess

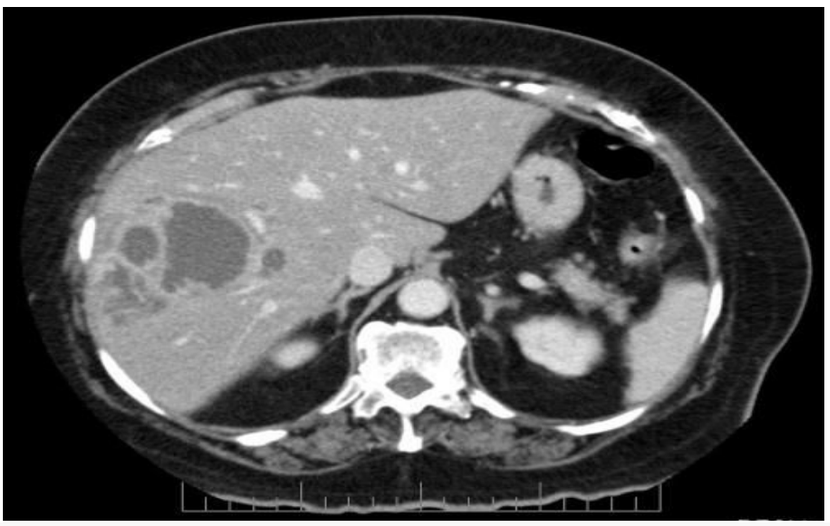
- The most common organisms found in pyogenic liver abscesses are *Staphylococcus aureus* in children and *Escherichia coli* in adults.
- usually complicates pre-existing biliary and gastrointestinal tract infections.
- **Management**
  - **Ideally, a penicillin-based β-lactamase antibiotic combined with metronidazole to provide anaerobic cover would be the treatment of choice.**
  - amoxicillin + ciprofloxacin + metronidazole
  - if penicillin allergic: ciprofloxacin + clindamycin



The CT demonstrates a hypodense lesion (A) with surrounding oedema (B).

Amoebic liver abscess

- A solitary abscess in the right lobe of the liver is typical of amoebic liver abscess.
- A history of chronic diarrhoea might be elicited in patients with amoebic liver abscess.



CT showing a pyogenic liver abscess in the right lobe of the liver.

Hydatid cysts

Asymptomatic, calcified cystic lesions in the liver are typical of hydatid cysts.

- Hydatid cysts are endemic in Mediterranean and Middle Eastern countries.
- Hydatid infection was endemic in sheep farming regions (such as Wales or New Zealand) in the past and sheep dogs were infected by eating infected offal. Humans contract hydatids via faecal/oral spread from dogs.

- most commonly seen in farming and rural communities

- They are caused by the tapeworm parasite ***Echinococcus granulosus***.
- Up to 90% cysts occur in the liver and lungs
- An outer fibrous capsule is formed containing multiple small daughter cysts.
- These cysts are allergens which precipitate a **type 1 hypersensitivity reaction**.

Clinical features:

- Can be asymtomatic, or symptomatic if cysts > 5cm in diameter
  - The liver cysts are usually asymptomatic and calcification usually denotes a non-viable cyst.
- Morbidity caused by cyst bursting, infection and organ dysfunction (biliary, bronchial, renal and cerebrospinal fluid outflow obstruction)
- In biliary ruputure there may be the classical triad of; biliary colic, jaundice, and urticaria

Investigations

- Ultrasonography is the most helpful **initial test** since it can usually differentiate a simple cyst from other cystic lesions. It should also be used for follow up studies.
- CT scan shows characteristic daughter cysts.
- **Hydatid serology has a sensitivity of 80-90%.**
- **If hydatid serology is negative then further imaging (CT/MRI) +/-** aspiration may be required to make a diagnosis.
- **CT is the best investigation to differentiate hydatid cysts from amoebic and pyogenic cysts.**

Treatment

- Surgery is the mainstay of treatment (the cyst walls must not be ruptured during removal and the contents sterilised first).
- benzimidazoles

Drug-induced liver disease

Flucloxacillin + co-amoxiclav are well recognised causes of cholestasis

Drug-induced liver disease is generally divided into hepatocellular, cholestatic or mixed. There is however considerable overlap, with some drugs causing a range of changes to the liver
The following drugs tend to cause a **hepatocellular** (hepatocellular pattern of injury with transaminases elevated in excess of alkaline phosphatase.) picture:

- paracetamol
- sodium valproate, phenytoin
- MAOIs
- halothane
- anti-tuberculosis: isoniazid, rifampicin, pyrazinamide
- statins
- alcohol
- amiodarone
- methyldopa
- **Statins**
- nitrofurantoin → **cause chronic active hepatitis.**

The following drugs tend to cause **cholestasis** (+/- hepatitis):

- oral contraceptive pill
- antibiotics: flucloxacillin, co-amoxiclav, erythromycin (risk may be reduced with erythromycin stearate)
- anabolic steroids, testosterones
- phenothiazines: chlorpromazine, prochlorperazine
- sulphonylureas
- fibrates
- rare reported causes: nifedipine

Liver cirrhosis

- methotrexate
- methyldopa

- amiodarone

Budd-Chiari syndrome

Triad of abdominal pain, ascites and liver enlargement.

Definition

- obstruction of the main hepatic veins by thrombus.
- Budd-Chiari syndrome, or hepatic vein thrombosis, is usually seen in the context of underlying haematological disease or another procoagulant condition

Causes

- polycythaemia rubra vera
- thrombophilia: activated protein C resistance, antithrombin III deficiency, protein C & S deficiencies
- **pregnancy**
- **oral contraceptive pill**

Features

- abdominal pain: sudden onset, severe
- ascites
- **tender hepatomegaly**
- Signs of portal hypertension are present and patients may develop acute variceal haemorrhage as a complication.

Diagnosis

- Ultrasound Doppler or contrast CT scan is often used to make the diagnosis.
  - Hypertrophy of the caudate lobe on imaging is a characteristic sign but is seen in only 50% of cases.
- Ascitic tap usually demonstrates a high SAAG (>11 g/L).

Management

- Thrombolysis and subsequent anticoagulation

Prognosis

- **Three year survival in patients with chronic Budd-Chiari syndrome has been reported as 50%.**

Gilbert's syndrome

- Gilbert's syndrome is an autosomal recessive* condition of defective bilirubin conjugation due to a **deficiency of UDP glucuronyl transferase**.
- The prevalence is approximately 1-2% in the general population

Features

- unconjugated hyperbilinaemia (i.e. not in urine)
- normal dipstix urinalysis excludes Dubin-Johnson and Rotor syndrome as these both produce a conjugated bilirubinaemia.
- jaundice may only be seen during an intercurrent illness

Investigation

- rise in bilirubin following prolonged fasting or **IV nicotinic acid**

Management

- no treatment required

*the exact mode of inheritance is still a matter of debate

Crigler-Najjar syndrome

- Crigler-Najjar syndrome refers to a condition of **absent** UDP-glucuronyl transferase.
- This condition presents early in life with jaundice, increased unconjugated bilirubin and kernicterus.
- This disease is life threatening and the only cure is liver transplant.

Dubin-Johnson syndrome

- benign autosomal recessive disorder
- Resulting in hyperbilirubinaemia (conjugated, therefore present in urine).
- It is due to a defect in the canillicular multispecific organic anion transporter (cMOAT) protein. This causes **defective hepatic bilirubin excretion**
- patients have a **black liver on gross examination** of the tissue.

- On microscopic examination, patients have **epinephrine metabolite accumulations in their hepatocytes.**
- No treatment is necessary.

Autoimmune hepatitis

The combination of **deranged LFTs** combined with **secondary amenorrhoea** in a **young female** strongly suggest → **autoimmune hepatitis**

- Autoimmune hepatitis is condition of unknown aetiology which is most commonly seen in young females.
- more common in females.

Pathophysiology

- T-cell mediated progressive necro-inflammatory process resulting in fibrosis and cirrhosis.

Associations

- Other autoimmune disorders including:
  - coeliac disease,
  - pernicious anaemia,
  - thyroiditis
  - type 1 diabetes mellitus.
- **IgG hypergammaglobulinaemia**
- sicca syndrome (xerostomia/dry eyes, **keratoconjunctivitis sicca) may occur.**
- HLA B8, DR3 and Dw3.

Disease	Associated raised immunoglobulin subtype
Alcoholic liver disease	IgA
Primary biliary cirrhosis	IgM
Autoimmune hepatitis	IgG

Types

- Three types of autoimmune hepatitis have been characterised according to the types of circulating antibodies present

Type I	Type II	Type III
Anti-nuclear antibodies (ANA) and/or **anti-smooth muscle antibodies** (**SMA**). **Affects both adults and children**	Anti-liver/kidney microsomal type 1 antibodies (LKM1) **Affects children only**	Soluble liver-kidney antigen **Affects adults** in middle-age

Features

- may present with signs of chronic liver disease
- acute hepatitis: fever, jaundice etc (only 25% present in this way)
- **amenorrhoea (common)**

Investigations

- ANA/SMA/LKM1 antibodies,
- raised **IgG** levels
- liver biopsy:
  - **The gold standard for diagnosis**
  - inflammation extending beyond limiting plate **'piecemeal necrosis'**, **bridging necrosis**

Management

- steroids, other immunosuppressants e.g. azathioprine
  - **Prednisolone (with or without azathioprine) is better than azathioprine alone.**
  - Steroid therapy produce symptomatic, biochemical and histological improvement, with improvement in survival.
  - It does not, however, prevent progression to frank cirrhosis.
- liver transplantation

Prognosis

- The prognosis with long-term immunosuppression is excellent even in the presence of cirrhosis and few patients subsequently develop liver failure.

Ischaemic hepatitis

- Ischaemic hepatitis is a diffuse hepatic injury resulting from acute hypoperfusion (sometimes known as 'shock liver').
- **It is diagnosed in the presence of an inciting event (eg: cardiac arrest) and marked increases in aminotransferase levels (exceeding 1000 international unit/L or 50 times the upper limit of normal).**
- Often, it will occur in conjunction with acute kidney injury (tubular necrosis) or other end organ dysfunction.

Pregnancy: jaundice

Physiological liver changes during pregnancy;

- albumin level decreases earlier in 1st trimester due to hemodilution
- **ALT& AST aminotransferase remains normal.** Thus, serum aminotransferase levels is the most useful test for the routine diagnosis of liver diseases during pregnancy.
- total and free **bilirubin decreases during all three trimesters**. Conjugated bilirubin ↓↓in 2nd & 3rd trimesters.
- **ALP ↑↑ in late pregnancy,** due both to the production of the placental isoenzyme and to the increase in bone isoenzyme. (Thus ALP levels is not a suitable test for the diagnosis of cholestasis during pregnancy).
- Serum gamma-glutamyl transferase ↓↓ in 2nd & 3rd trimesters,
- serum 5'nucleotidase slightly ↑↑ in 2nd & 3rd trimesters.
- Serum total bile acid concentrations not changed during pregnancy. Measurement of serum bile acids may be useful for the diagnosis of cholestasis, especially when serum aminotransferase levels are within normal limits.
- Intrahepatic cholestasis of pregnancy would not occur in the first trimester.

Gilbert's & Dubin-Johnson syndrome,

- may be exacerbated during pregnancy

HELLP syndrome

- HELLP syndrome is a mnemonic that stands for **H**emolysis, **E**levated Liver enzymes, and **L**ow **P**latelets in a patient with severe preeclampsia.
- HELLP syndrome is a manifestation of severe preeclampsia that can lead to hepatic subcapsular hematoma formation.
- Schistocytes are an erythrocyte variant that may be seen in HELLP syndrome.
- Immediate delivery is the only definitive treatment

Obstetric cholestasis

Epidemiology

- Obstetric cholestasis affects around 0.7% of pregnancies in the UK
- most common in the third trimester

Pathophysiology

- Caused by a bile acid transporter defect

Features

- pruritus - may be intense - typical worse palms, soles and abdomen
- Jaundice occurs in less than 10% of patients.

Diagnosis (cholestatic picture of (LFTs) with a high ALP and, with a lesser rise in ALT.)

- ↑ **Total Serum bile acid levels** (cholic acid and chenodeoxycholic acid) >10 micromol/L
- ↑↑ **GGT**
- ↑ ALT, AST
- ↑ direct bilirubin
  - bilirubin < 100
  - only slightly elevated in about 10%
- ↑ ALP

  - ALP is not useful as it is normally raised in late pregnancy anyway.
- prothrombin time may be prolonged in any cholestatic process due to vit k deficiency

Complications
- increased risk of prematurity and still birth.

Differential diagnosis:
- Viral hepatitis is the commonest cause of jaundice in pregnancy but the **elevated bile acids** make this unlikely

Management
- ursodeoxycholic acid
  - First-line medication
  - widely used but evidence base not clear
  - early therapy with ursodeoxycholic acid reduces the risk of preterm birth and stillbirth.
- Cholestyramine
  - SE: may cause a deficiency in fat-soluble vitamins
    - Rarely, there are cases of cerebral hemorrhage associated with vitamin K shortage under cholestyramine therapy.
- induction of labour at 37 weeks is common practice but may not be evidence based
- vitamin K supplementation
- phenobarbital

Prognosis
- fully reversible postpartum
- Recurrence in following pregnancies (40–60%)

Cardiac output and blood volume increase in pregnancy but hepatic blood flow does not.

Acute fatty liver of pregnancy (AFLP)

Definition
- a rare disease most common in the third trimester characterized by extensive fatty infiltration of the liver, which can result in acute liver failure

Risk factors
- older maternal age,
- primiparity,
- multiple pregnancies,
- pre-eclampsia,
- male foetus
- previous AFLP.

Pathophysiology
- dysfunction of fatty acid β-oxidation → microvesicular fat deposition.

Features
- abdominal pain
- nausea & vomiting
- headache
- jaundice
- hypoglycaemia
- severe disease may result in pre-eclampsia
- Coagulopathy with an increased risk of disseminated intravascular coagulation (DIC)
- Hypoalbuminemia → ascites
- encephalopathy later.

Investigations
- ALT is typically elevated e.g. 500 u/l
- ↑ WBC, ↓ platelets

Management
- support care
- once stabilised delivery is the definitive management

Haemochromatosis

Haemochromatosis is autosomal recessive

- Haemochromatosis is an **autosomal recessive** disorder of iron absorption and metabolism resulting in iron accumulation.

Aetiology

- It is caused by inheritance of **mutations in the HFE gene** on both copies of **chromosome 6***.
  - *there are rare cases of families with classic features of genetic haemochromatosis but no mutation in the HFE gene
- 90 % of cases are caused by the **substitution of tyrosine for cysteine at position 282** of the HFE gene found on chromosome 6.
- **HLA-A3 is associated with haemochromatosis**

Epidemiology

- 1 in 10 people of European descent carry a mutation genes affecting iron metabolism, mainly HFE
- prevalence in people of European descent = 1 in 200
- Haemochromatosis is the most prevalent genetic condition in Caucasian population, with a carrier rate of 1 in 10 and is present in about 1 in 200-400 people
- Males and females are affected equally but females are often 'protected' from the clinical features by menstrual blood loss.

Pathophysiology

- Iron absorption is regulated in the duodenal crypts.
- **HFE** is a protein that **regulates iron absorption**,
- HFE → forms a complex at the basolateral membrane that if bound to transferrin + iron at the basolateral membrane of the duodenal crypt cells prevents maturation and consequently absorption of iron in the bowel.
- mutation in the HFE gene → failure of complex formation and constant maturation of duodenal crypt cells → subsequent unregulated uptake of iron.

Presenting features

- often asymptomatic in early disease
- early symptoms include
  - fatigue,
  - erectile dysfunction
  - arthralgia (often of the hands)
    - Joint x-rays characteristically show chondrocalcinosis
- 'bronze' skin pigmentation
- diabetes mellitus
- liver: stigmata of chronic liver disease, hepatomegaly, cirrhosis, hepatocellular deposition)
- cardiac failure (2nd to dilated cardiomyopathy)
- hypogonadism (2nd to cirrhosis and pituitary dysfunction - hypogonadotrophic hypogonadism)
- arthritis (especially of the hands). Joint x-rays characteristically show chondrocalcinosis

Questions have previously been asked regarding **which features are reversible with treatment:**

Reversible complications	**Irreversible complications**
• Cardiomyopathy • Skin pigmentation	• Liver cirrhosis** • Diabetes mellitus • Hypogonadotrophic hypogonadism • Arthropathy

****whilst elevated liver function tests and hepatomegaly may be reversible, cirrhosis is not**

Investigation

Screening for haemochromatosis
- general population: transferrin saturation > ferritin
- family members: HFE genetic testing

The best investigation to screen for haemochromatosis

- **General population**: transferrin saturation is considered the most useful marker.

  - Ferritin should also be measured but is not usually abnormal in the early stages of iron accumulation.
- **testing family members: genetic testing for HFE mutation**

These guidelines may change as HFE gene analysis become less expensive

Diagnostic tests

- **liver biopsy:** Perl's stain
  - **the gold standard investigation** (as it quantifies iron deposition and also stages the amount of fibrosis)
- molecular genetic testing for the C282Y and H63D mutations
  - found in 90%
  - there is substitution of tyrosine for cysteine at position 282 of the HFE gene on chromosome 6.
  - However there is low penetrance of clinical disease and haemochromatosis also occurs in patients who are negative for this mutation.
- MRI has high specificity but low sensitivity for demonstrating iron overload in the liver - it has not replaced the need for biopsy in the majority of cases.

Typical iron study profile in patient with haemochromatosis

- transferrin saturation > 55% in men or > 50% in women
- raised ferritin (e.g. > 500 ug/l) and iron. Ferritin is measured to help guide further investigation and treatment: if more than 1000 a liver biopsy should be performed and treatment initiated.
- low TIBC

Treatment:

- Early diagnosis and treatment is critical in haemochromatosis as survival and morbidity are improved if phlebotomy is initiated prior to the development of cirrhosis.
- weekly or twice weekly (if tolerated) **venesections** of 500 cm^3 until the serum ferritin is less than 50 ng/mL & Transferritin saturation less than 50%
- When iron overload and anaemia are present concomitantly **chelation with desferoxamine** may be required.
- Patients should be told to **avoid vitamin C supplementation** as this can enhance iron toxicity.
- End stage liver disease, portal hypertension and hepatocellular carcinoma (which is increased up to 200-fold) may necessitate **liver transplantation**.

Monitoring adequacy of venesection

- BSCH recommend 'transferrin saturation should be kept below 50% and the serum ferritin concentration below 50 ug/l'

May 2005 exam: **Which feature of haemochromatosis may be reversible with treatment?** **Cardiomyopathy**

May 2014 exam: H/O fatigue and arthralgia. The joint pain is worse around his metacarpophalangeal joints and knees. polyuria and polydipsia. An x-ray of his knees reveals chondrocalcinosis. What is the mode of inheritance of the likely underlying diagnosis? Autosomal recessive (This patient has typical symptoms of haemochromatosis: 1/ Lethargy. 2/arthralgia, with evidence of chrondrocalcinosis. 3/diabetes mellitus (polyuria and polydipsia)

Hepatocellular carcinoma (HCC)

Hepatocellular carcinoma
- hepatitis B most common cause worldwide
- hepatitis C most common cause in Europe

- Hepatocellular carcinoma (HCC) is the third most common cause of cancer worldwide.
- Chronic hepatitis B is the most common cause of HCC worldwide with chronic hepatitis C being the most common cause in Europe.

Risk factors

- **The main risk factor** for developing HCC is
  - Liver cirrhosis, for example secondary* to hepatitis B & C, alcohol, haemochromatosis and primary biliary cirrhosis.
    - *Wilson's disease is an exception
    - 75% to 90% of patients with HCC have cirrhosis.

- HCC develops in 4% of cirrhotics per year.
- Patients with chronic hepatitis B have 100-fold higher risk of developing HCC.

- **Other risk factors** include:
  - alpha-1 antitrypsin deficiency
  - hereditary tyrosinosis
  - glycogen storage disease
  - aflatoxin
  - drugs: oral contraceptive pill, anabolic steroids
  - porphyria cutanea tarda
  - male sex
  - diabetes mellitus, metabolic syndrome

Features

- tends to present late
- features of liver cirrhosis or failure may be seen: jaundice, ascites, RUQ pain, hepatomegaly, pruritus, splenomegaly
- possible presentation is decompensation in a patient with chronic liver disease

Screening with ultrasound (+/- alpha-fetoprotein) should be considered for high risk groups such as:

- patients liver cirrhosis secondary to hepatitis B & C or haemochromatosis
- men with liver cirrhosis secondary to alcohol

Management options

- early disease: surgical resection
- liver transplantation
- radiofrequency ablation
- transarterial chemoembolisation
- sorafenib: a multikinase inhibitor

Management of liver capsule pain

- Stretching of the liver capsule by a primary hepatoma or metastases within the liver can cause chronic cancer pain.
- This commonly presents as dull, right-sided subcostal pain.
- Referred pain at the top of the ipsilateral shoulder occurs due to diaphragmatic irritation if the superior aspect of the capsule is involved.
- Corticosteroids can be used in the management of liver capsule pain and dexamethasone is usually the choice of steroid.
- **Which analgesics would be most suitable for the management of liver capsule pain?**
  - ➔ **Dexamethasone**

Carcinoid syndrome

Flushing, diarrhoea, bronchospasm, tricuspid stenosis, pellagra → carcinoid with liver mets - diagnosis: urinary 5-HIAA

Which biochemical markers is most likely depleted in carcinoid syndrome?

- ➔ Biosynthesis of serotonin begins with tryptophan, so **tryptophan depletion** is most likely.

- usually occurs when metastases are present in the liver and release serotonin into the systemic circulation
- may also occur with lung carcinoid as mediators are not 'cleared' by the liver

Features

- **flushing (often earliest symptom)**
- diarrhoea
- bronchospasm
- hypotension
- right heart valvular stenosis (left heart can be affected in bronchial carcinoid)
  - (mostly tricuspid insufficiency) and pulmonary stenosis,
  - **Endocardial fibrosis is due to constant exposure of the right heart to serotonin.**
- other molecules such as ACTH and GHRH may also be secreted resulting in, for example, Cushing's syndrome
- pellagra can rarely develop as dietary tryptophan is diverted to serotonin by the tumour

Investigation

- urinary 5-hydroxy-indole-acetic acid (5-HIAA) (**specificity 100% ,** sensitivity 70%)
- plasma chromogranin A y (**The most sensitive marker 100%**)

Management

- somatostatin analogues e.g. Octreotide (Side effects of octreotide therapy include increased risk of gallstones)
  - **The best treatment for symptoms of carcinoid is the somatostatin analogue, octreotide, which improves symptoms and prognosis**
- Other potential treatments following resistance or failure of octreotide include **hepatic artery embolisation.**
- diarrhoea: cyproheptadine may help
  - **the treatment for the diarrhoea will be through treating the underlying diagnosis, which is carcinoid → octreotide**
  - Cyproheptadine is not a first line treatment for diarrhoea and in fact may cause diarrnoea as a side effect.
  - Telotristat →inhibits tryptophan hydroxylase, which mediates serotonin biosynthesis. It is indicated for carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy.
    - Telostristat approved by (FDA) in 2017 for carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by an SSA.

Which vitamin deficiency may be associated with carcinoid syndrome?

→ **Vitamin B_3**

- Vitamin B_3, niacin, is used to make NAD and is derived from tryptophan.
- In carcinoid syndrome, the increased synthesis of serotonin would deplete the supply of tryptophan needed to make niacin.
- A deficiency of niacin would result in pellagra, which is characterized by diarrhea, dermatitis, and dementia

May 2007 exam: If the patient develops carcinoid syndrome, which one of the following symptoms is most likely to occur first? Facial flushing

Viral hepatitis

Hepatitis A

Diagnosis

- **Anti-hepatitis A IgM antibody will confirm the diagnosis**
- IgG antibody would suggest:
  - a previous hepatitis A infection **or**
  - another underlying cause such as cytomegalovirus.

Indicator of poor prognosis

- **Hepatitis A infection on a background of hepatitis C (but not B) has very poor prognosis.**

Hepatitis B

Deterioration in patient with hepatitis B - ? hepatocellular carcinoma

- Hepatitis B is a double-stranded DNA hepadnavirus

Spread through

- vertical transmission from mother to child.
  - **Perinatal transmission is the most common route of hepatitis B infection worldwide**
  - the infection rate is **90%** in infants born to HBeAg (hepatitis B envelope antigen) positive mothers.
- exposure to infected blood or body fluids,
  - Sexual transmission comprises **30%** of hepatitis B infections in developed countries.

Incubation period

- 6-20 weeks.

Features:

- fever,
- jaundice
- elevated liver transaminases.

- **Symptoms of decompensated liver disease include:**
  - ascites,
  - encephalopathy and
  - gastrointestinal haemorrhage.

Complications

- chronic hepatitis (5-10%)
- fulminant liver failure (1%)
- hepatocellular carcinoma
- glomerulonephritis
- polyarteritis nodosa
- cryoglobulinaemia

Immunisation against hepatitis B

- contains what?:
  - HBsAg adsorbed onto aluminium hydroxide adjuvant
- prepared from what?
  - prepared from yeast cells using recombinant DNA technology
- schedule?
  - give 3 doses of the vaccine **+** one-off booster 5 years following the initial primary vaccination
- **At risk groups who should be vaccinated** include:
  - healthcare workers,
  - intravenous drug users,
  - sex workers,
  - close family contacts of an individual with hepatitis B,
  - individuals receiving blood transfusions regularly,
  - chronic kidney disease patients who may soon require renal replacement therapy,
  - prisoners,
  - chronic liver disease patients
- **failure to respond or respond poorly to 3 doses of the vaccine**
  - occur in 10-15% of adults.
  - Risk factors include:
    - age over 40 years,
    - obesity,
    - smoking,
    - alcohol excess and
    - immunosuppression
  - how to check response?
    - testing for anti-HBs levels
      - testing for anti-HBs is **only recommended for**:
        - those at risk of occupational exposure (i.e. Healthcare workers) and
        - patients with chronic kidney disease.
      - In these patients anti-HBs **should be checked 1-4 months after primary immunisation**
      - how to interpret anti-HBs levels? the table below shows

Anti-HBs level (mIU/ml)	Response
> 100	Indicates **adequate response**, no further testing required. Should still receive booster at 5 years
10 - 100	**Suboptimal response** - one additional vaccine dose should be given. If immunocompetent no further testing is required
< 10	**Non-responder**. Test for current or past infection. Give further vaccine course (i.e. 3 doses again) with testing following. If still fails to respond then HBIG would be required for protection if exposed to the virus

Hepatitis B serology

HBsAg = ongoing infection, either acute or chronic if present > 6 months

anti-HBc = caught, i.e. negative if immunized

Interpreting hepatitis B serology: It is important to remember a few key facts:

- **surface antigen (HBsAg)**
  - is the first marker to appear and causes the production of anti-HBs
    - **appears in the serum 1 to 10 weeks following acute exposure, even** before symptoms or (ALT) rise.
  - normally implies acute disease (present for 1-6 months)
  - if present for > 6 months then this implies chronic disease (i.e. Infective)
  - In those who **recover** HBsAg will usually become undetectable **after 4 to 6 months**.
  -
- **Anti-HBs**
  - implies immunity (either exposure or immunisation).
  - It is negative in chronic disease
- **Anti-HBc**
  - implies previous (or current) infection.
    - IgM anti-HBc appears during acute or recent hepatitis B infection and is present for about 6 months.
      - Anti-HBc IgM is detectable between 6 and 32 weeks after exposure
    - IgG anti-HBc persists
- **HbeAg**
  - results from breakdown of core antigen from infected liver cells as is therefore a **marker of infectivity**
  - HBeAg is a marker of infectivity in all patients except those who have Hepatitis B virus (HBV) **pre-core mutant** or the core promoter mutant, because they do not synthesise HbeAg,
    - this is most commonly due to a stop-codon mutation at nucleotide 1896.
  - So the learning here is that **although the e antigen is negative, the patient may still be infective.**

- **previous immunisation:** anti-HBs positive, all others negative
- **previous hepatitis B (> 6 months ago), not a carrier:** anti-HBc positive, HBsAg negative
- **previous hepatitis B, now a carrier:** anti-HBc positive, HBsAg positive

IgM anti-HBc jointing HBV-DNA is most effective and most practicable in distinguishing Acute Hepatitis B from Chronic Hepatitis B With Acute Flare.

	Acute Infection	Chronic Carrier	Window Period	Complete Recovery	Immunized
HBs	+	+	-	-	-
Anti-HBs	-	-	-	+	+
Anti-HBc	+ (IgM)	+ (IgG)	+	+ (IgG)	-

Distinguish between acute HBV and a flare of chronic disease

- **originates from** an area of the world with a high prevalence of HBV infection
  - In areas of low HBV prevalence, such as the United Kingdom, a combination of HBsAg positivity and features of acute hepatitis usually indicates acute self-limiting hepatitis B infection.
  - In countries with high prevalence of hepatitis B the majority of infection is acquired vertically during childhood and leads to chronicity rather than acute infection.
- **Anti-HBc-IgM** is typically found in **acute HBV** infection, however it can be found in10-15% of patients with chronic HBV. This is especially true when considering acute flares of chronic hepatitis.
  - The sensitivity and specificity for HBc-IgM to distinguish between acute HBV and a chronic flare has been reported as low as 77% and 70% respectively.
  - Using high titres to determine cut-offs (1:10,000 or greater) does improve this significantly however.
- **Flares of chronic HBV** are typically associated with **higher levels of HBV DNA and AFP** than acute self-limiting disease.
  - The alpha-fetoprotein is commonly elevated during acute hepatitis due to hepatic regeneration.
- **flares of chronic HBV** tend to be associated with less necroinflammation, and thus ALT tends to be as raised as in acute HBV, but **hepatic synthetic dysfunction is more** common.

Assessment of liver disease in secondary specialist care for adults with chronic hepatitis B

- **The initial test** for liver disease in adults newly referred for assessment is → **transient elastography**
  - Transient elastography (FibroScan) is a new, non-invasive, rapid method allowing evaluation of liver fibrosis by measurement of liver stiffness.
  - Interpretation of transient elastography score
    - **≥ 11** kPa → antiviral treatment without a liver biopsy
    - between **6** and **10** kPa → liver biopsy to confirm the level of fibrosis
    - < 6 kPa → liver biopsy, **if the**:
      - **Age < 30** years and **HBV DNA > 2000 IU**/ml and **abnormal ALT** (≥30 IU/L for males and ≥ 19 IU/L for females) on 2 consecutive tests conducted 3 months apart.
    - < 6 kPa → NO liver biopsy, **if the**:
      - HBV DNA < 2000 IU/ml **and** normal ALT.
  - Offer annual reassessment of liver disease using transient elastography to adults who are not taking antiviral treatment.

Management

- **Acute** HBV
  - the majority of patients will resolve spontaneously,
  - treatment with an oral anti-HBV agent is not necessary.

Patients who are positive for HBsAg for more than six months but are HBeAg negative, HBV DNA negative and have normal ALT do not require liver biopsy nor do they require antiviral therapy, but hepatitis B serology and ALT should be monitored annually.

- **Chronic HBV**
  - **Indications of antiviral treatment in adults with chronic hepatitis** B (NICE 2013)
    - age ≥ 30 years + HBV DNA > 2000 IU/ml + abnormal ALT (≥30 IU/L in males ≥19 IU/L in females) on 2 consecutive tests conducted 3 months apart.
    - Age < 30 years + HBV DNA > 2000 IU/ml + abnormal ALT **if there is**:
      - evidence of necro-inflammation or fibrosis on liver **biopsy**

- ❖ **or** a transient **elastography** score > 6 kPa.
- HBV DNA > 20,000 IU/ml + abnormal ALT regardless of age or the extent of liver disease. (on 2 consecutive tests conducted 3 months apart)
- cirrhosis + detectable HBV DNA, regardless of HBeAg status, HBV DNA and ALT levels.
- HBV DNA greater than 2000 IU/ml + evidence of necro-inflammation or fibrosis on liver biopsy.

- **First-line** → pegylated **interferon-alpha**
  - →↓↓ viral replication in up to 30% of chronic carriers.
  - **better response** is predicted by being female, < 50 years old, low HBV DNA levels, non-Asian, HIV negative, high degree of inflammation on liver biopsy
  - Interferon alfa is **usually given short term and is not very effective in patients without an elevated ALT.**
- **other antiviral medications** (examples include tenofovir, **Adefovir** and entecavir)
  - are increasingly used with an aim to suppress viral replication (not in a dissimilar way to treating HIV patients)
  - **would be of most value for long-term treatment of his HBV**
  - Lamivudine would be an alternative, although resistance develops commonly.
- **adults with HBeAg-positive chronic hepatitis B and compensated liver disease**
  - **first-line** → 48-week course of peg-interferon alfa-2a
    - stopping peginterferon alfa-2a 24 weeks after starting treatment if HBV DNA level has decreased by less than 2 $\log_{10}$ IU/ml and/or if HBsAg is greater than 20,000 IU/ml → 2nd line
  - **second-line** → **tenofovir** disoproxil (**nucleotide** analogue, reverse transcriptase inhibitor (NRTI)
    - to people who do not undergo HBeAg seroconversion or who relapse (revert to being HBeAg positive following seroconversion) after first-line treatment with peginterferon alfa-2a.
    - Offer **entecavir** (**nucleoside analogue, reverse transcriptase inhibitor**) as an alternative second-line treatment to people who cannot tolerate tenofovir disoproxil or if it is contraindicated.
      - ❖ Entecavir is a pro-drug and requires phosphorylation to the triphosphate form before it becomes active.

Nucleoside = Sugar + Base
Nucleotide = Sugar + Base + Phosphate

  - If HBV DNA remains detectable at 96 weeks:
    - If No history of lamivudine resistance → add lamivudine to tenofovir disoproxil.
    - With a history of lamivudine resistance → add entecavir to tenofovir disoproxil.
- **When to consider stopping nucleoside or nucleotide analogue treatment?**
  - **without cirrhosis → 12 months after HBeAg seroconversion**
  - **with cirrhosis → do not stop**
- **Adults with decompensated liver disease** (portal hypertension, bleeding varices, ascites and encephalopathy)
  - Do not offer peginterferon alfa-2a → **worsen hepatic decompensation**
  - **First-line → entecavir** (if there is no history of lamivudine resistance).
  - people with a history of lamivudine resistance → **tenofovir** disoproxil
- **Co-infection with chronic hepatitis B and C** → peginterferon alfa + ribavirin

Hepatitis B and pregnancy

Basics

- all pregnant women are offered screening for hepatitis B
- Without intervention the vertical transmission rate is around 20%, which increases to 90% if the woman is positive for HBeAg.

- babies born to mothers who are chronically infected with hepatitis B or to mothers who've had acute hepatitis B during pregnancy should receive a **complete course of vaccination + hepatitis B immunoglobulin**
- (nice 2013) → Offer **tenofovir disoproxil** to women with HBV DNA greater than 10^7 IU/ml in the third trimester **to reduce the risk of transmission of HBV to the baby**. stopped at 4 to 12 weeks after the birth
- there is little evidence to suggest caesarean section reduces vertical transmission rates
- hepatitis B cannot be transmitted via breastfeeding (in contrast to HIV)

Hepatitis C

Hepatitis C - 80-85% become chronically infected

- Hepatitis C is likely to become a significant public health problem in the UK in the next decade.
- It is thought around 200,000 people are chronically infected with the virus.
- The most common route of transmission of hepatitis C in the United States is **intravenous drug use.**
- **Hepatitis C virus genotypes**
  - There are 6 genotypes and more than 50 subtypes.
  - In England and Wales genotypes 1 and 3 account for more than 90% of all diagnosed infections.
  - In Japan, North America, and western Europe, the majority of infections are with genotypes **1, 2, and 3.**
    - Subtype **1a** is the most predominant genotype in the US,
    - subtype **1b** predominates in Asia and Europe.
  - Genotype 4 is more prevalent in the middle east and in northern and central Africa.
  - Genotypes 5 and 6 have been identified in South Africa and southeast Asia, respectively.
  - Differences in subtype can result in subtle differences in response to antiviral therapies.
  - **Hepatitis C genotype 3 is associated with insulin resistance and hepatic steatosis**
  - **Genotype 3a is most strongly associated with a positive response to therapy**
  - Genotypes 2 and 3 respond reasonably well to polyethylene glycol (PEG) interferon and ribavirin; genotypes 1and 4 less well.
- At risk groups include:
  - **intravenous drug users**
  - and patients who received a blood transfusion prior to 1991 (e.g. haemophiliacs).

Pathophysiology

- hepatitis C is a RNA flavivirus
- incubation period: 6-9 weeks

The risk of Transmission:

- vertical transmission rate from mother to child is about **6%.**
- sexual intercourse is probably less than **5% (in contrast to hepatitis B, sexual transmission is uncommon).**
- needle stick injury is about **2%**
  - The risk is higher if there is coexistent HIV
- breast feeding is not contraindicated in mothers with hepatitis C

Features

- after exposure to the hepatitis C virus less than 20% of patients develop an acute hepatitis
- **Chronic hepatitis C is a very common cause of minor elevations in serum transaminases. Other liver function tests can be entirely normal**

Diagnosis

- first → **Arrange an anti-HCV antibody test**
- HCV RNA tests are normally only ordered following a positive antibody test.

Associations

- **chronic hepatitis C associated with insulin resistance**
- insulin sensitising drugs may improve response to anti-viral therapy

Extrahepatic association of hepatitis C

- **Sjögren's syndrome**
- Porphyria cutanea tarda
- Lichen planus

- Cryoglobulinaemia (mixed essential type)
- myeloma and monoclonal gammopathies
- Lymphoma

Complications

- chronic infection (80-85%) - only 15-20% of patients will clear the virus after an acute infection and hence the majority will develop chronic hepatitis C
- cirrhosis (20-30% of those with chronic disease)
- hepatocellular cancer
- **cryoglobulinaemia**
- porphyria cutanea tarda (PCT): it is increasingly recognised that PCT may develop in patients with hepatitis C, especially if there are other factors such as alcohol abuse

Management of chronic infection

- chronic hepatitis C is defined as infection that lasts for more than 6 months.
- The effectiveness of antiviral treatment depends on the viral genotype; the response is generally better in people infected with genotypes 2 or 3 than in those infected with genotypes 1, 4, 5 or 6.
  - The recommended treatment duration is 24 weeks (genotypes 2 or 3) or 48 weeks (all other genotypes)
- Combination therapy with interferon-alfa and ribavirin is generally recommended for those with moderate-sever disease (histological diagnosis of significant scarring and/or significant necrotic inflammation).
- In cases where a liver biopsy carries a high risk (e.g. haemophilia), treatment can be initiated without histological confirmation.
- Both treatment-naïve (new) patients and those who have relapsed following initial response to interferon-alfa should be considered for 6 months of combination therapy.
- currently a combination of pegylated interferon-alpha, ribavirin and a protease inhibitor (e.g. boceprevir, simprevir and telaprevir) is used
- cure rates are now approaching 90%, including for some strains which have been previously difficult to treat
- Genotype 1 hepatitis C have low rates of viral clearance with dual interferon and ribavirin therapy alone. **the recommended duration of therapy is 48 weeks**
- the aim of treatment is sustained virological response (SVR), defined as undetectable serum HCV RNA six months after the end of therapy
- **treatment is not generally recommended in those patients who consume large quantities of alcohol**, given the increased risk of liver damage.
- **the best way to assess response to treatment → Viral load**
- relapse occurs in approximately 5% of people after 5 years.

Complications of treatment

- ribavirin - side-effects: haemolytic anaemia, cough. Women should not become pregnant within 6 months of stopping ribavirin as it is teratogenic
- interferon alpha - side-effects: flu-like symptoms, depression, fatigue, leukopenia, thrombocytopenia.
  - For this reason close monitoring of FBC is recommended, with initial review after 4 weeks of therapy.
  - Peginterferon alfa 2a and 2b are contraindicated in severe psychiatric conditions.

Factors Associated With Accelerated Fibrosis Progression	
Host	**Viral**
Nonmodifiable • Fibrosis stage • Inflammation grade • Older age at time of infection • Male sex • Organ transplant **Modifiable** • Alcohol consumption • Nonalcoholic fatty liver disease • Obesity • Insulin resistance	• Genotype 3 infection • Coinfection with hepatitis B virus or HIV

Hepatitis D

- Hepatitis D is a single stranded RNA delta virus
- It is an incomplete RNA virus that requires hepatitis B surface antigen to complete its replication and transmission cycle.
- It is transmitted in a similar fashion to hepatitis B (exchange of bodily fluids)
- and patients may be infected with hepatitis B and hepatitis D at the same time.
- Hepatitis D terminology:
  - Co-infection: Hepatitis B and Hepatitis D infection at the same time.
  - **Superinfection: A hepatitis B surface antigen positive patient subsequently develops a hepatitis D infection.**
- Superinfection is associated with high risk of fulminant hepatitis, chronic hepatitis status and cirrhosis.
- Diagnosis is made via reverse polymerase chain reaction of hepatitis D RNA.
- Interferon is currently used as treatment, but with a poor evidence base.

Hepatitis E

Severe hepatitis in a pregnant woman - think hepatitis E

- RNA hepevirus
- spread by the faecal-oral route
- incubation period: 3-8 weeks
- common in Central and South-East Asia, North and West Africa, and in Mexico
- causes a similar disease to hepatitis A,
- **does not result in a carrier state**
- **carries a significant mortality (about 20%) during pregnancy**
- does not cause chronic disease or an increased risk of hepatocellular cancer
- In general, hepatitis E is a self-limiting viral infection followed by recovery. **Prolonged viraemia or faecal shedding are unusual**
- a vaccine is currently in development*, but is not yet in widespread use

Hepatitis histology

- **hepatitis E → Marked cholestasis**
- chronic hepatitis → Ground-glass hepatocytes (large hepatocytes containing surface antigen).

- hepatitis C → Lymphoid aggregates and a marked increase in the activation of sinusoidal lining cells
- hepatitis D → Microvesicular steatosis

Colorectal conditions

Colorectal cancer

Endometrial cancer is the second most common association of HNPCC after colorectal cancer

- Colorectal cancer is the third most common type of cancer in the UK and the second most cause of cancer deaths
- **Adenocarcinomas** comprise the vast majority (98%) of colon and rectal cancers
- **Location of cancer** (averages)
  - **rectal: 40%**
  - **sigmoid: 30%**
  - descending colon: 5%
  - transverse colon: 10%
  - ascending colon and caecum: 15%

Colorectal cancer: genetics

There are three types of colon cancer:

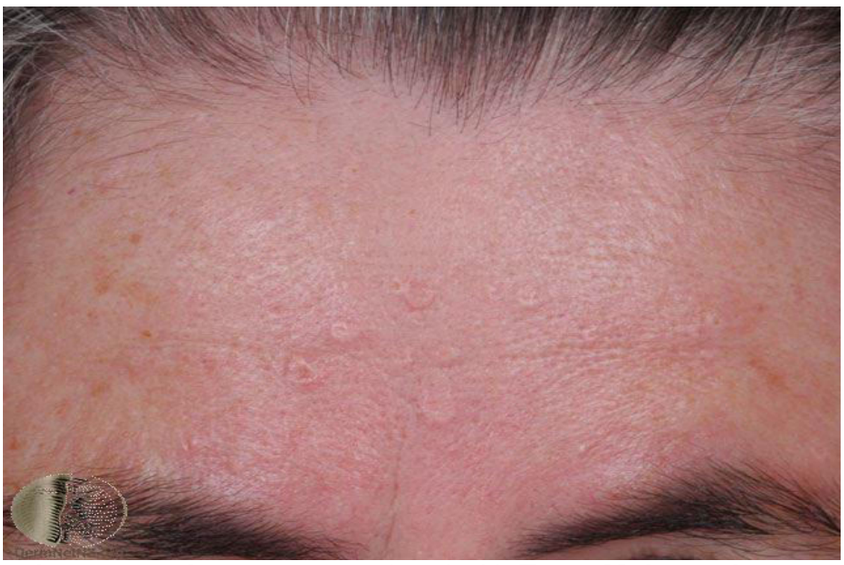
- Sporadic (95%)
- Hereditary non-polyposis colorectal carcinoma (HNPCC, 5%)
- Familial adenomatous polyposis (FAP, <1%)

Sporadic colon cancer

- may be due to a series of genetic mutations. For example:
  - allelic loss of the **APC** gene → more than half of colon cancers
  - further gene abnormalities e.g.
    - activation of the **K-ras** oncogene,
      - *RAS* is an intracellular signaling molecular that acts downstream of the epidermal growth factor receptor (EGFR) to stimulate cell division and growth
      - present in 30-50% of colorectal cancers
      - associated with failure to respond to EGFR based therapies such as the monoclonal antibodies **Cetuximab** and Panitumumab.
        - **The presence of a *KRAS* mutation is a contraindication to treatment with these agents.**
    - deletion of **p53** and **DCC** tumour suppressor genes lead to invasive carcinoma

Hereditary non-polyposis colorectal carcinoma (HNPCC)

- also known as (Lynch syndrome)
- autosomal dominant mutation of **DNA mismatch repair** genes with **microsatellite instability**.
- most common form of inherited colon cancer.
- Around 90% of patients develop cancers, often of the proximal colon, which are usually poorly differentiated and highly aggressive.
- The most common genes involved are:
  - **MSH2** (60% of cases) **the function of this gene → DNA mismatch repair**
  - MLH1 (30%)
- Patients with HNPCC are also at a higher risk of other cancers, with **endometrial cancer** being the next most common association, after colon cancer.
- The **Amsterdam criteria** are sometimes used to aid diagnosis:
  - at least **3** family members with colon cancer
  - the cases span at least **two** generations
  - at least **one** case diagnosed before the age of 50 years
- **Torre-Muir syndrome**, a type of hereditary nonpolyposis colorectal cancer (HNPCC), is **characterized by sebaceous adenomas.**
  - These lesions are usually present on the face, near the eyes and forehead and appear as yellow papules/nodules.



sebaceous adenomas associated with **Torre-Muir syndrome** a type of HNPCC

- Polyp cancers represent T1 disease and have been sub-classified.
- **The Haggitt system is used for pedunculated polyps and describes the deepest invasion of carcinoma cells within the polyp**:
  - Level 1 is limited to the head of the polyp
  - Level 2 is extension into the neck
  - Level 3 is invasion of the stalk, and
  - Level 4 is invasion beyond the stalk but above the muscularis propria.
- The Kicuchi system describes the depth of invasion in sessile polyp cancers.

Familial adenomatous polyposis (FAP)

- FAP is a rare autosomal dominant condition which leads to the formation of hundreds of polyps by the age of 30-40 years.
- Patients inevitably develop carcinoma.
- It is due to a mutation in a tumour suppressor gene called adenomatous polyposis coli gene (**APC**), located on chromosome 5.
- Genetic testing can be done by analysing DNA from a patients white blood cells.
- Patients generally have a total colectomy with ileo-anal pouch formation in their twenties.
- Patients with FAP are also at risk from duodenal tumours.
  - Oesophagogastroduodenoscopy (OGD) surveillance is recommended.
- A variant of FAP called **Gardner's syndrome** can also feature:
  - osteomas of the skull and mandible,
  - retinal pigmentation,
  - thyroid carcinoma
  - and epidermoid cysts on the skin

Carcinoembryonic antigen may be used to monitor for recurrence in patients post-operatively or to assess response to treatment in patients with metastatic disease

Colorectal cancer: screening

Colorectal cancer screening - PPV of FOB = 5 - 15%

Overview

- most cancers develop from adenomatous polyps. Screening for colorectal cancer has been shown to reduce mortality by 16%
- the NHS now has a national screening programme offering screening every 2 years to all men and women aged 60 to 74 years. Patients aged over 74 years may request screening
- eligible patients are sent faecal occult blood (FOB) tests through the post
- patients with a single positive results are offered a colonoscopy
- An uncertain or unclear result will result in a request to repeat up to a maximum of two further tests. Persistent unclear results require further investigation with consideration of colonoscopy.
- A negative faecal occult blood does not exclude an underlying diagnosis of colorectal cancer.

- Any patient with symptoms, irrespective of a negative faecal occult blood test, should be investigated for the possibility of underlying bowel cancer as appropriate.

At colonoscopy, approximately:

- 5 out of 10 patients will have a normal exam
- 4 out of 10 patients will be found to have polyps which may be removed due to their premalignant potential
- 1 out of 10 patients will be found to have cancer

Streptococcus bovis bacteraemia and endocarditis is associated with **colon cancer** (in around half of cases). All patients should, therefore, undergo **colonoscopy**

Colorectal cancer: referral guidelines

NICE updated their referral guidelines in 2015. The following patients should be **referred urgently** (i.e. within 2 weeks) to colorectal services for investigation:

- patients >= 40 years with unexplained weight loss **AND** abdominal pain
- patients >= 50 years with unexplained rectal bleeding
- patients >= 60 years with iron deficiency anaemia **OR** change in bowel habit
- tests show occult blood in their faeces (see below)

An urgent referral (within 2 weeks) should be 'considered' if:

- there is a rectal or abdominal mass
- there is an unexplained anal mass or anal ulceration
- patients < 50 years with rectal bleeding **AND** any of the following unexplained symptoms/findings:
- -⟶ abdominal pain
- -⟶ change in bowel habit
- -⟶ weight loss
- -⟶ iron deficiency anaemia

Faecal Occult Blood Testing (FOBT)

This was one of the main changes in 2015. Remember that the NHS now has a national screening programme offering screening every 2 years to all men and women aged 60 to 74 years. Patients aged over 74 years may request screening.

In addition FOBT should be offered to:

- patients >= 50 years with unexplained abdominal pain **OR** weight loss
- patients < 60 years with changes in their bowel habit **OR** iron deficiency anaemia
- patients >= 60 years who have anaemia even in the absence of iron deficiency

Risks for colorectal carcinoma

Population risk	1 in 40
One first-degree relative more than 45 years old	1 in 17
One first-degree plus one second-degree relative	**1 in 12**
Two first-degree relatives	1 in 6
Familial polyposis	1 in 2

Which drugs may reduce the risk of colon cancer?

- ⇨ **Vitamin D**
- ⇨ **Aspirin and NSAID**

The Dukes' System

- The Dukes' staging system has now largely been replaced with the TNM system, however it is still used.
- The Dukes' staging system has been proven to correlate well with a patient's chance of survival.
- It is classified as following:
  - Dukes' A:
    - Invasion into but not through the bowel wall,
    - 80%+ 5 year survival
    - **Follow-up of a Dukes' A colon cancer**

- **Colonoscopy - indicated on an annual basis for the first 2 years, then this should be done 3-yearly**
- Faecal occult blood - should be tested 6-monthly for the first 4 years and then once yearly
- Carcinoembryonic antigen (CEA) - can be used to monitor for recurrence if it is elevated initially

- Dukes' B:
  - Invasion through the bowel wall but not involving lymph nodes,
  - 60-70% 5 year survival
- **Dukes' C:**
  - Involvement of lymph nodes,
  - **30-40% 5 year survival**
- Dukes' D:
  - Widespread metastases,
  - 0% 5 year survival

AJCCC (American Joint Committee) Staging of Colorectal Cancer

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4a	Tumor penetrates to the surface of the visceral peritoneum
T4b	Tumor directly invades or is adherent to other organs or structures

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-3 regional lymph nodes
N1a	Metastasis in one regional lymph node
N1b	Metastasis in 2-3 regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in 4 or more regional lymph nodes
N2a	Metastasis in 4-6 regional lymph nodes
N2b	Metastasis in 7 or more regional lymph nodes

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ or site (for example, liver, lung, ovary, nonregional node)
M1b	Metastases in more than one organ/site or the peritoneum

Residual tumour (R) classification exists in addition to the TNM classification and the histological grade (G):

- RX presence of residual tumour cannot be assessed
- R0 no residual tumour
- **R1 microscopic residual tumour**
- R2 macroscopic residual tumour.

Management

Management of metastatic lesions

- **Metastatic lesion resection:**
  - Colorectal carcinoma is one of the only oncological diseases where the presence of a metastatic deposit can be treated with curative intent.
  - A solitary liver lesion should be surgically resected.
  - In fact, the purpose of following patients with CEA is to identify patients with solitary metastatic lesions amenable to surgical resection.
- Transarterial chemoembolization & Radiofrequency ablation are used as palliative procedures when the lesions are too numerous or large to resect.

January 2015 exam: A man has hereditary non-polyposis colorectal cancer secondary to a mutation in the MSH2 gene. which other cancers his daughter will most be at risk from? Endometrial cancer

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Dysplastic colonic polyps

The British Society of Gastroenterology (BSG) published guidelines on the follow-up period for dysplastic colonic polyps in 2002:

- 5-year interval is indicated for low-risk patients (one to two adenomas that are both small, ie <1 cm)
- **3-year follow up is recommended for medium-risk patients (three to four adenomas or one or two adenomas where one adenoma bigger than or equal to 1 cm)**
- 1-year follow-up is recommended for high-risk patients (five or more small adenomas or more than three with at least one at or above 1 cm in size).

Polyp characteristics: associated with a **higher risk of malignant change:**

- **polyps greater than 1.5 cm, which are sessile or flat**
- Histology demonstrating severe dysplasia, predominantly villous architecture or squamous metaplasia

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Peutz-Jeghers syndrome

- Peutz-Jeghers syndrome is an **autosomal dominant** condition
- Characterised by:
  - numerous hamartomatous polyps in the gastrointestinal tract.
  - pigmented freckles on the lips, face, palms and soles.
- Around 50% of patients will have died from a gastrointestinal tract cancer by the age of 60 years.
- incidence of 1:50,000 live births.

Genetics

- autosomal dominant
- **responsible gene encodes serine threonine kinase LKB1 or STK11**

Features

- hamartomatous polyps in GI tract (mainly small bowel)
- pigmented lesions on lips, oral mucosa, face, palms and soles
- intestinal obstruction e.g. intussusception
- gastrointestinal bleeding

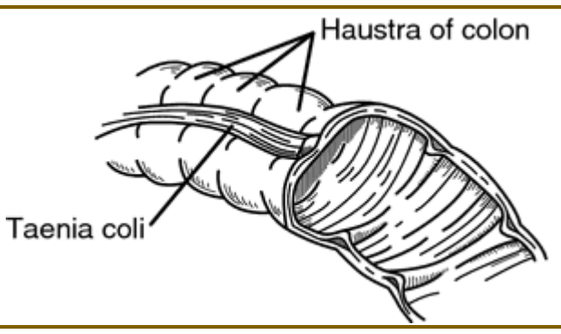
Management

- conservative unless complications develop
- **colonoscopy every two years** after the age of 25 for evaluation of the presence of polyps and polypectomy.

Cowden's syndrome is an inherited condition resulting from a defect in the PTEN tumour suppressor gene. Hamartomatous polyps of the GI tract are often the first manifestation along with characteristic muco-cuteneous lesions such as oral mucosal papillomas, palmoplantar keratoses and trichilemmomas (benign tumours of hair follicles). The syndrome is important to diagnose early because of the high risk of malignancy, particularly of the breast and thyroid. Thyroid dysfunction is common even in the absence of cancer.

Familial juvenile polyposis also results in multiple polyps in the colon identical to those found in Cowden's syndrome but the associated oral lesions are absent.

Sigmoid volvulus
The most important feature of a sigmoid volvulus rather than a large redundant distended loop of sigmoid colon is the absence of haustra.



Capsule endoscopy

- Capsule endoscopy is currently used in UK to identify the source of occult gastrointestinal bleeding when an OGD and colonoscopy and failed to show a cause.
- It is particularly useful for identifying pathology in the ileum.

Pseudomyxoma peritonei

- Pseudomyxoma peritonei is a rare mucinous tumour most commonly arising from the appendix.
- The disease is characterised by the accumulation of large amounts of mucinous material in the abdominal cavity.
- It is rare, with an incidence of 1-2/1,000,000 per year

Treatment

- usually surgical and consists of cytoreductive surgery (and often peritonectomy) combined with intra-peritoneal chemotherapy with mitomycin C.

Villous adenoma

Diarrhoea + hypokalaemia → villous adenoma

Villous adenomas are colonic polyps with the potential for malignant transformation. They **characteristically secrete large amounts of mucous**, potentially resulting in electrolyte disturbances.

Features: The vast majority are asymptomatic. Possible features:

- non-specific lower gastrointestinal symptoms
- secretory diarrhoea may occur
- microcytic anaemia
- hypokalaemia

Carcinoid tumours

Carcinoid syndrome

Left-sided valvular lesions are not observed in carcinoid syndrome because the lung metabolizes serotonin (5-HT). Remember the symptoms of carcinoid syndrome as **"Be FDR" :** **B**ronchospasm**, F**lushing**, D**iarrhoea, and **R**ight-sided valvular lesions.

- Carcinoid syndrome occurs in only 5% of patients with carcinoid tumour
- usually occurs when metastases are present in the liver and release serotonin into the systemic circulation
- **The most common originating sites of carcinoid is the small bowel, particularly the ileum;**
  - Around 55% of all carcinoid tumours arise from the GI tract,
  - the most common site of origin is the small bowel (45% of those arising within the GI tract).
  - Within the small bowel, the most common site of origin is the distal ileum.
- **carcinoid tumors** are the **most common** malignancy of the appendix.
- 5-HT, kinins, prostaglandins and other vasoactive substances are secreted.
- may also occur with lung carcinoid as mediators are not 'cleared' by the liver
- the caecal-appendiceal region is the commonest location for a carcinoid primary.
- These tumours are slow growing

Features

- flushing (often earliest symptom) **the most common feature (**occurring in 85% of patients**)** .often provoked by alcohol.
- diarrhoea (75%)and abdominal cramps in the majority of patients.
- bronchospasm
- hypotension
- right heart valvular stenosis (left heart can be affected in bronchial carcinoid)
  Cardiac abnormalities develop in 50% of patients and consist of tricuspid regurgitation or pulmonary stenosis.
  Fibrosis of the heart valves is a recognised feature
- **other molecules such as ACTH and GHRH may also be secreted resulting in, for example, Cushing's syndrome**
- pellagra can rarely develop as dietary tryptophan is diverted to serotonin by the tumour

Investigation

- **urinary 5-HIAA**
  - 24-hour urine collection for 5-hydroxy-indole-acetic acid (5-HIAA) - excretion is greater than 0.3 mmol.
- plasma chromogranin A y
- Biopsy of the lesion show cells staining for chromogranin A on histology → consistent with a neuroendocrine tumour
- **Octreotide scanning** is positive in up to 85% of cases, however a negative scan does not rule out liver metastases.
- **The liver should be imaged by high resolution CT with fine cuts or by USS**.
  - The sensitivity of USS may be increased by the use of microbubble contrast medium (levovist), which is available at some centres.
- **Fasting gut hormones** should be measured as neuroendocrine tumours may co-secrete other hormones such as VIP, which may contribute to the diarrhoea.

Management

- somatostatin analogues e.g. octreotide
  - Octreotide is less likely to be effective **if octreotide scan negative**, but other analogues such as **lanreotide** have different affinities for different somatostatin receptor subtypes, which may be present on the tumour.
- diarrhoea: cyproheptadine may help
- Other Symptomatic management may include hepatic embolisation, hepatic chemo-embolisation and chemotherapy.
- echocardiography to screen for carcinoid heart disease (right-sided valvular lesions).

Prognosis

- generally good.

Ref:

- Ref → www.medical-masterclass.com (mrcp part 2)

Gorlin syndrome causes:
1. gastric hamartomas,
2. basal cell carcinomas,
3. mandibular bone cysts,
4. intracranial calcification,
5. pits on the palms and soles.

Diverticular disease

- Diverticulosis → presence of diverticula which are asymptomatic.
- Diverticular disease → diverticula associated with symptoms → **typically painless bleeding**
- Diverticulitis → diverticular inflammation (fever, tachycardia) with or without localised symptoms and signs → **painful , No bleeding**

Overview

- Diverticula are bulging sacs that push outward on the colon wall.can occur anywhere in the colon, but **most commonly form near the end of the colon on the left side (sigmoid colon).**
- A diverticulum consists of a herniation of mucosa through the thickened colonic muscle.
- most common in industrialized countries where diets are lower in fiber and higher in processed carbohydrates.
- **Diverticular disease is by far the commonest cause of severe fresh bleeding per rectum.**

Causes: It is believed diverticula form when there is increased pressure in the colon

- Diets low in fiber cause hard stool and slower "transit time" through the colon, increasing pressure.
- repeated straining during bowel movements also increases pressure.
- Drugs: diuretics, and narcotic pain relievers, can increase constipation and increase pressure in the colon.

Epidemiology

- Approximately 50% of all people have diverticula by the time they are 50 years of age, and nearly 70% of all people have diverticula by the time they are 80 years of age
- **Diverticular disease is rare in people younger than 40 years**
- **Disease is more virulent in young patients, with a high risk of recurrences or complications.**
- **The most common fistula is colovesicular and then colovaginal fistulas.**

Risk factors

- The main risk factors are age over 50 years and low dietary fibre.
- Obesity is an important risk factor in young people.
- Complicated diverticular disease has an increased frequency in:
  - patients who smoke,
  - use non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol,
  - and those who are obese and have low-fibre diets

Features

- Approximately 75% of people with diverticula have asymptomatic diverticulosis
- Pain is generally exacerbated by eating and diminished with defecation or flatus.
- Other symptoms, such as bloating, constipation or rectal bleeding, may also occur.
- **Diverticulitis**
  - may occur if some faeces get trapped and stagnate in a diverticulum bacteria then multiply and cause infection.
  - Generally presents with left lower quadrant pain. Asian patients have predominantly right-sided diverticula and will usually present with right lower quadrant pain.
  - Pain may be intermittent or constant and may be associated with a change in bowel habits.
  - Fever and tachycardia are present in most patients
  - One third of patients who develop diverticulitis will develop further complications (perforation, abscess, fistula, stricture/obstruction)

Diagnosis: → colonoscopy

- sensitivities and specificities for CT are significantly better than for contrast enemas.

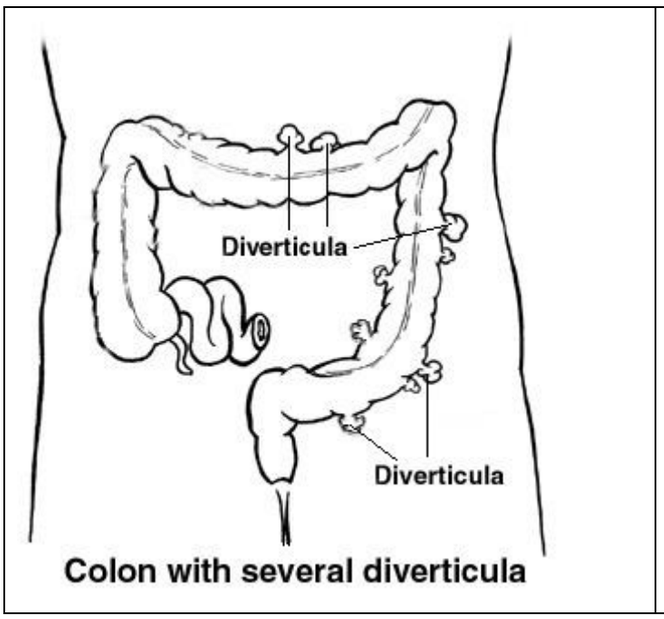
- When an abscess is suspected, CT scanning is the best modality for making the diagnosis and following its course.
- Because of risk of perforation, endoscopy is generally avoided in initial assessment of the patient with acute diverticulitis.
- **Haemorrhage**:
  - Flexible sigmoidoscopy is an appropriate initial approach to rule out an obvious rectosigmoid lesion.
  - If no cause is identified, further assessment with non-invasive (nuclear scintigraphy) or invasive (angiography, colonoscopy) techniques can be undertaken in an attempt to localise and treat the bleeding source.

Management

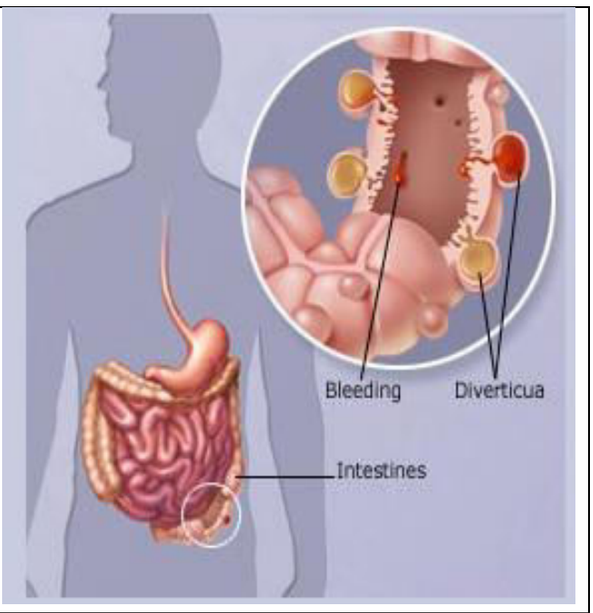
- **asymptomatic**
  - No treatment or follow-up needs
  - there may be a prophylactic benefit of a high-fibre diet.
  - The risk of perforation may be increased by the use of NSAIDs and long-term use of opioids.
  - Calcium-channel blockers are associated with a reduction in diverticular perforation but there is insufficient evidence to recommend their use.
- **Diverticulitis**
  - Broad-spectrum antibiotics to cover anaerobes and Gram-negative rods - eg, co-amoxiclav or a combination of ciprofloxacin and metronidazole (if allergic to penicillin).
  - Paracetamol should be used for pain.
  - Recommend clear liquids only; gradually reintroduce solid food as symptoms improve over 2-3 days.
  - Review within 48 hours, or sooner if symptoms deteriorate. Hospital admission should be arranged if symptoms persist or deteriorate.
  - Mesalazine has been shown to be more effective in improving the severity of symptoms, bowel habit, and in preventing symptomatic recurrence of diverticulitis, than antibiotics alone
  - Most patients admitted with acute diverticulitis will respond to conservative treatment, but 15-30% will need surgery.
  - The indications for surgery are:
    - Purulent or faecal peritonitis.
    - Uncontrolled sepsis.
    - Fistula.
    - Obstruction.
    - Inability to exclude carcinoma.
  - CT-guided percutaneous drainage of abdominal abscesses is now used in preference to surgery when feasible.
  - Risk of recurrent symptoms after an attack of acute diverticulitis is about one in three.
  - Recurrent attacks are less likely to respond to medical treatment and they have a high mortality rate.
- **Haemorrhage**
  - Haemorrhage ceases spontaneously in 70-80% of patients.. Subsequent colonoscopy should be performed to establish the source of the bleeding and to exclude neoplasia.
  - Intra-arterial vasopressin at angiography can control haemorrhage in more than 90% of patients. The benefit is usually only temporary but may allow time to prepare the patient adequately for surgery.
  - Angiographic embolisation of very distal bleeding branches is also effective and safe.
  - Surgery in lower gastrointestinal bleeding is usually reserved until endoscopic or angiographic treatments fail.
  - Segmental resection is most usually done if the bleeding site is clearly identified from a therapeutically unsuccessful angiographic or endoscopic procedure. In patients with persistent bleeding and no angiographic or endoscopic identification of a definite bleeding site, subtotal colectomy may be required.
  - The chance of a third bleeding episode can be as high as 50%, so many authorities recommend surgical resection after a second bleeding episode.
- **Prognosis**
  - Approximately three quarters of patients with anatomical diverticulosis remain asymptomatic.
  - Most complications of diverticulitis are associated with the initial attack, after which the disease tends to run a benign course.

- Mortality and morbidity are related to complications of diverticulosis, which are mainly diverticulitis and lower gastrointestinal bleeding. These occur in 10-20% of patients with diverticulosis during their lifetime.

- **Prevention**
  - Dietary fibre may prevent development of diverticular disease but, once symptoms develop, the benefit from fibre supplementation is unclear.
  - Physical exercise has also been shown to help prevent the development of diverticular disease.



Colon with several diverticula



Meckel's diverticulum

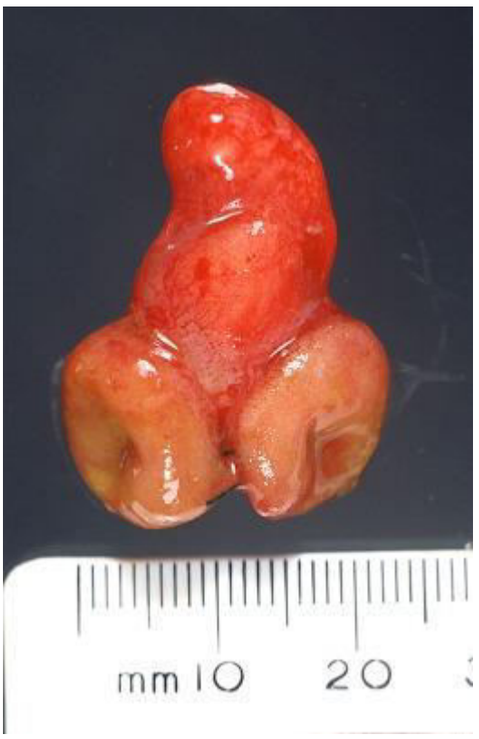
- Meckel's diverticulum is the vestigial remnant of the omphalomesenteric duct.
- It is normally located in the terminal ileum within ~60 cm of the ileocaecal valve and it averages 6 cm in length.
- the diverticulum is frequently located near the ileocecal valve in the small bowel.
- In Meckel diverticulum, there is persistence of the vitelline duct, an embryologic structure necessary for receiving nutrients. When this structure persists, the Meckel diverticulum may contain ectopic tissue, such as the acid-secreting gastric mucosa
- Although it occurs much more commonly in children it is an important differential consideration for gastrointestinal bleed in adults.
- also quite common in Down's syndrome.

Features

- About 50% of these contain ectopic gastric mucosa, commonly leading to clinical presentations of peptic ulceration and haemorrhage.
- Other complications of Meckel's diverticulum include
  - Diverticulitis
  - Intussusception
  - Perforation
  - Obstruction.

Diagnosis

- **Technetium^{99m} pertechnetate scintigraphy**
  - Tc-99m pertechnetate accumulates in gastric mucosa and is the study of choice for identifying ectopic gastric mucosa in a Meckel's diverticulum.



The picture shows an excised Meckel's diverticulum.

Meckel diverticula: rule of 2's

- **occurs in 2% of the population,**
- **commonly located within 2-feet of the ileocecal valve,**
- **2-inches in length,**
- **commonly occurs before the age of two.**

Intussusception

- Hirschsprung disease is aganglionosis of colon, causing obstruction. It usually presents in neonatal period.
- common cause of intestinal obstruction in children in general and in Down's syndrome in particular.
- There is a classic triad in intussusception of:
  1. acute abdominal pain,
  2. currant jelly stool and
  3. palpable abdominal mass, usually in right iliac fossa.

Aorto-enteric fistulae (AEF)

- known to occur following endovascular repair of abdominal aortic aneurysms (AAA) and secondary to aortic grafting of any kind, presumably because of mechanical forces of dislodged or migrating devices.
- May occur after aorto-bifemoral graft as treatment for peripheral vascular disease.
- **Strongly positive faecal occult blood (FOB) suggests significant GI haemorrhage in spite of normal upper GI endoscopy.**

Anal fistula

- Goodsall's rule describes the likely location of the internal opening of a fistula-in-ano based on its external opening.
  - **If the external opening is anterior to the 9-3 o'clock** plane then the fistula forms a direct radial tract and opens **internally at the same clock face point**.
  - If the external opening is posterior to this line then it will generally follow a more circuitous route opening at 6 o'clock.

Angiodysplasia

Angiodysplasia is associated with aortic stenosis

- Angiodysplasia is a vascular deformity of the gastrointestinal tract which predisposes to bleeding and iron deficiency anaemia.
- generally seen in elderly patients
- Second most common cause of lower GI bleeding in patients >60 years of age.
- There is thought to be an association with aortic stenosis, although this is debated.
- predominantly located in the proximal colon (77%) **(located most commonly in the ascending colon and caecum)** but is also found in the jejunum and ileum (15%) and transverse colon.
- In Heyde's syndrome, a syndrome of aortic valve stenosis and colonic angiodysplasia, a possible mechanism is the induction of von Willebrand's disease type IIA by the valvular stenosis.
- Bleeding stops spontaneously in >90% of cases.

Diagnosis

- colonoscopy
- mesenteric angiography if acutely bleeding
- The repeated negative upper and lower GI endoscopies suggest that **small bowel angiodysplasia** may be the cause, in an area which is difficult to image via conventional endoscopy. **In this situation capsule endoscopy has a higher yield and would be the appropriate next step.**
  - The pathophysiology of angiodysplasia in this situation isn't known, although it may be due to changes in pressure within the mesenteric venous plexus, as the condition often resolves once the valve is treated.

Management

- endoscopic cautery or argon plasma coagulation
- antifibrinolytics e.g. Tranexamic acid
- oestrogens may also be used

Heyde's syndrome → gastrointestinal bleeding from angiodysplasia in the presence of aortic stenosis.

Anal fissure

Anal fissure - topical glyceryl trinitrate

Anal fissures are longitudinal or elliptical tears of the squamous lining of the distal anal canal. If present for less than 6 weeks they are defined as acute, and chronic if present for more than 6 weeks. Around 90% of anal fissures occur on the posterior midline

Management of an acute anal fissure (< 6 weeks)

- dietary advice: high-fibre diet with high fluid intake
- bulk-forming laxatives are first line - if not tolerated then lactulose should be tried
- lubricants such as petroleum jelly may be tried before defecation
- topical anaesthetics
- analgesia topical steroids do not provide significant relief

Management of a chronic anal fissure (> 6 weeks)

- the above techniques should be continued
- topical glyceryl trinitrate (GTN) is first line treatment for a chronic anal fissure
- if topical GTN is not effective after 8 weeks then secondary referral should be considered for surgery or botulinum toxin

Inflammatory bowel disease

Crohn's disease

Definition

- Crohn's disease is a form of inflammatory bowel disease.
- Commonly affects the terminal ileum and colon but may be seen anywhere from the mouth to anus.

Epidemiology

- IBD is more common in white people than in African-Caribbean people or those of Asian origin.
- has a lower incidence in non-white races; people of Jewish origin are more prone to inflammatory bowel disease than non-Jews; and **Ashkenazi Jews are at higher risk than Sephardic Jews.**
- slightly more common in females (male to female ratio is 1:1.2)
- typically presents in late adolescence or early adulthood. The highest incidence of Crohn's disease in the 15–30 year age
- The ratio of Crohn's disease to ulcerative colitis varies between adults and children. In adults, the ratio of Crohn's disease to ulcerative colitis is 2:3, while the ratio in children is much higher (2.3:1).

Pathology

- cause is unknown but there is a strong genetic susceptibility
- inflammation occurs in all layers, down to the serosa. This is why patients with Crohn's are prone to strictures, fistulas and adhesions

Features

- presentation may be non-specific symptoms such as weight loss and lethargy
- diarrhoea:
  - the most prominent symptom in adults.
  - Crohn's colitis may cause bloody diarrhea.
  - Nocturnal diarrhoea is indicative of organic disease and is typical of a Crohn's disease flare.
- abdominal pain: the most prominent symptom in children. often in the lower right quadrant
- perianal disease: e.g. Skin tags or ulcers
- **An abdominal mass is often palpable in the presence of small bowel disease which can lead to Vitamin K malabsorption.**
- extra-intestinal features are more common in patients with colitis or perianal disease

Extra-intestinal manifestations of **IBD** → **A PIE SAC**:

- **A**phthous ulcers
- **P**yoderma gangrenosum
- **I**ritis
- **E**rythema nodosum
- **S**clerosing cholangitis
- **A**rthritis
- **C**lubbing of fingertips

Questions regarding **the 'extra-intestinal' features of inflammatory bowel disease** are common:

	Common to both Crohn's disease (CD) and Ulcerative colitis (UC)	Notes
Related to disease activity	Aphthous oral ulcers Arthritis: pauciarticular, asymmetric Erythema nodosum Episcleritis Osteoporosis	Arthritis is the most common extra-intestinal feature in both CD and UC **Episcleritis is more common in CD** **Interstitial lung disease is more common in CD**
Unrelated to disease activity	Arthritis: polyarticular, symmetric Uveitis Pyoderma gangrenosum Clubbing Primary sclerosing cholangitis	**Primary sclerosing cholangitis is much more common in UC** **Uveitis is more common in UC**

Smoking in IBD

- Smoking associated with earlier age of onset of disease and more frequent need for immunosuppression **among women** with Crohn's disease **but not men**.
- Smoking cessation is associated with an increased risk of ulcerative colitis.

Investigation

Bloods

- **C-reactive protein correlates well with disease activity**

Faecal calprotectin

- **Calprotectin** is a protein belonging to the S100 family and occurring in large amounts in neutrophil granulocytes
- Increased faecal calprotectin indicates increased migration of neutrophils to intestinal mucosa
- ↑↑ Calprotectin in stool is the direct consequence of neutrophil degranulation due to mucosal damage**.**
- **The logical next step in excluding inflammatory bowel disease**
- Recommended by NICE to distinguish between inflammatory bowel diseases and non-inflammatory bowel diseases, such as irritable bowel syndrome in people presenting with any of the following lower gastrointestinal symptoms for at least 6 weeks: abdominal pain or discomfort, bloating, or change in bowel habit.
- ↑↑ when there is any intestinal inflammation → Crohn's disease or ulcerative colitis.
- normal value is approximately 25 mg/kg.
- in IBS values may be slightly higher than those of healthy subjects , but in IBD significantly ↑↑
- **Calprotectin** exceeding 50 mg/kg should be considered positive → do endoscopy to confirm IBD
- Non-invasive screen for IBD
- Normal faecal calprotectin → makes IBD unlikely
- ↑↑ faecal calprotectin → drive further imaging

Stool culture

- **should be performed first**
- Even if the presentation is highly suggestive of inflammatory bowel disease. However, it is unforgivable not to do a stool culture in a case of diarrhoea and that should be the starting point before considering the other investigations

Endoscopy

- colonoscopy is the investigation of choice
  - Crohn's disease most typically affects the terminal ileum and proximal colon, therefore **the investigation of choice would be ileo-colonoscopy. A flexible sigmoidoscopy may not identify any areas of disease.**
- features suggest of Crohn's include deep ulcers, skip lesions

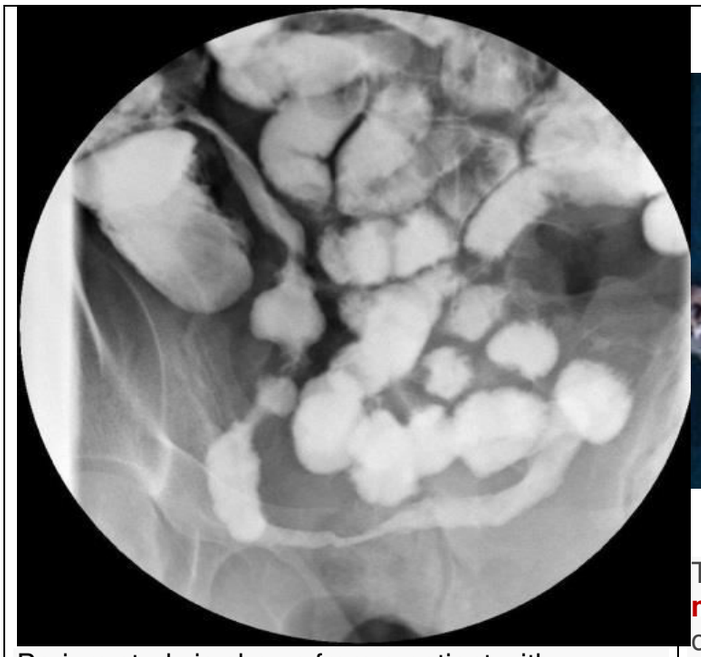
Histology

- inflammation in all layers from mucosa to serosa
- goblet cells
- granulomas

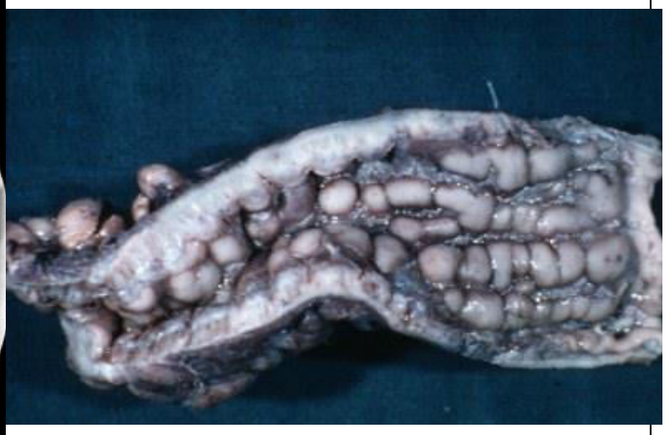
- **Patchy inflammation**

Small bowel enema

- high sensitivity and specificity for examination of the terminal ileum
- strictures: 'Kantor's string sign'
- proximal bowel dilation
- 'rose thorn' ulcers
- fistulae



Barium study is shown from a patient with worsening Crohn's disease. Long segment of narrowed terminal ileum in a 'string like' configuration in keeping with a long stricture segment. Termed **'Kantor's string sign'**.



The picture shows the typical '**cobblestone mucosa'** of Crohn's disease with isolated areas of normal mucosa surrounded by deep ulceration (ulcerative colitis does not result in such deep ulceration).

Thumb printing

- thumb printing is a predominantly radiological finding due to inflamed, oedematous folds of bowel as a result of mucosal oedema caused by inflammation. Thumb printing may be seen in either Crohn's disease or ulcerative colitis.

Management (NICE 2012)

	CD	UC
Inducing remission	**1st line** → **glucocorticoids** (oral, topical or I.V) , OR Budesonide. Fear of steroid S.E (e.g in children) → enteral feeding (in addition to or instead of)	**Mild & moderate UC** **1st line**: • Rectal & distal colitis → rectal (topical) Aminosalicylates is superior to rectal steroids • Proximal colitis → oral Aminosalicylates **Sever UC** → hospital → 1st line (I.V steroid)
	2nd line → 5-ASA drugs (e.g. mesalazine	**2nd line** → oral prednisolone
Maintaining remission	Stop smoking **1st line** → **azathioprine** or mercaptopurine **2nd line** → methotrexate previous surgery → 5-ASA drugs (e.g. mesalazine)	• oral 5-ASA e.g. mesalazine • azathioprine and mercaptopurine (methotrexate is NOT recommended for UC)

General points

- **patients should be strongly advised to stop smoking**
- some studies suggest an increased risk of relapse secondary to NSAIDs and the combined oral contraceptive pill but the evidence is patchy
- **dietary advice**
  - **Short-term use of TPN may be helpful in severe cases**
  - There is a significant portion of Crohn's patients who are lactose intolerant, and hence a **dairy free diet may reduce the frequency of diarrhoea**.

Inducing remission

- glucocorticoids (oral, topical or intravenous) are generally used to induce remission. Budesonide is an alternative in a subgroup of patients
- enteral feeding with an elemental diet may be used in addition to or instead of other measures to induce remission, particularly if there is concern regarding the side-effects of steroids (for example in young children)
- 5-ASA drugs (e.g. mesalazine) are used **second-line** to glucocorticoids but are not as effective
- azathioprine or mercaptopurine* may be used as an **add-on** medication to induce remission but is not used as monotherapy. Methotrexate is an alternative to azathioprine
- infliximab is useful in **refractory disease and fistulating Crohn's**. Patients typically continue on azathioprine or methotrexate
- metronidazole is often used for **isolated peri-anal** disease

Maintaining remission

- stopping smoking is a priority
  - **(remember: smoking makes Crohn's worse, but may help ulcerative colitis)**
- **first-line** → azathioprine or mercaptopurine
- **second-line** → methotrexate
- if a patient has had **previous surgery** → 5-ASA drugs (e.g. mesalazine) should be considered

Surgery

- around 80% of patients with Crohn's disease will eventually have surgery
- **Loss of the terminal ileum frequently leads to → bile salt malabsorption and treatment with the bile salt chelator cholestyramine quickly relieves the problem.**

Treatment during pregnancy

- For relapse during pregnancy
  - 1st line → **Prednisolone is the most appropriate initial treatment**
  - 2nd line (in patients who not responds to corticosteroids) → Infliximab
    - Infliximab is thought to be low risk in pregnancy although it does cross the placenta.
    - Patients on maintenance infliximab therapy should stop treatment by week 26 gestation.
    - In patients who require treatment in the last trimester, live vaccines should be avoided in the newborn for the first 6 months.
- For maintenance therapy → azathioprine or 6MP

Complications: There are 3 main serious intestinal complications in Crohn's disease:

1. Stricture (narrowing) of the bowel → intestinal obstruction
2. Fistulas, which are abnormal connections between sections of the bowel, or between the bowel and bladder.
3. colorectal cancer

Prognosis :(Nice 2013)

Prognostic feature	Crohn's disease	ulcerative colitis
prolonged remission	Only 10%	50%
surgery within 10 years of diagnosis	50%	20–30%
risk of mortality compared with the general population	slightly increased	Not increased
General outlook	worse than ulcerative colitis	Better than Crohn's

*assess thiopurine methyltransferase (TPMT) activity before offering azathioprine or mercaptopurine

Renal calculi are increased in Crohn's due to a mixture of dehydration and increased oxalate due to small bowel pathology and previous surgery. (Non-contrast helical CT abdomen is the investigation of choice for suspected renal calculi.)

Crohn's-like enterocolitis with mycophenolate mofetil

- Reported in renal transplant patients who have received mycophenolate mofetil.
- Investigations will reveal mucosal ulceration and skip lesions ordinarily seen in Crohn's.
- Treatment → Withdrawal of mycophenolate → resolution of symptoms

Ulcerative colitis (Nice guidelines 2013)

Ulcerative colitis - the rectum is the most common site affected

- Ulcerative colitis (UC) is a form of inflammatory bowel disease.
- Inflammation always starts at rectum (hence it is the most common site for UC),
- never spreads beyond ileocaecal valve and is continuous.
- The peak incidence of ulcerative colitis is in people aged 15-25 years and in those aged 55-65 years.

Features

The initial presentation is usually following insidious and intermittent symptoms:

- bloody diarrhoea
- urgency
- tenesmus
- abdominal pain, particularly in the left lower quadrant
- extra-intestinal features (see below)

Severity of ulcerative colitis (Mild, moderate and severe)

- In adults the severity criteria are based on the Truelove and Witts' severity index
- In children (≤ 11 years) and young people (12 to 17 years) these categories are based on the Paediatric Ulcerative Colitis Activity Index (PUCAI)

Truelove and Witts' severity index

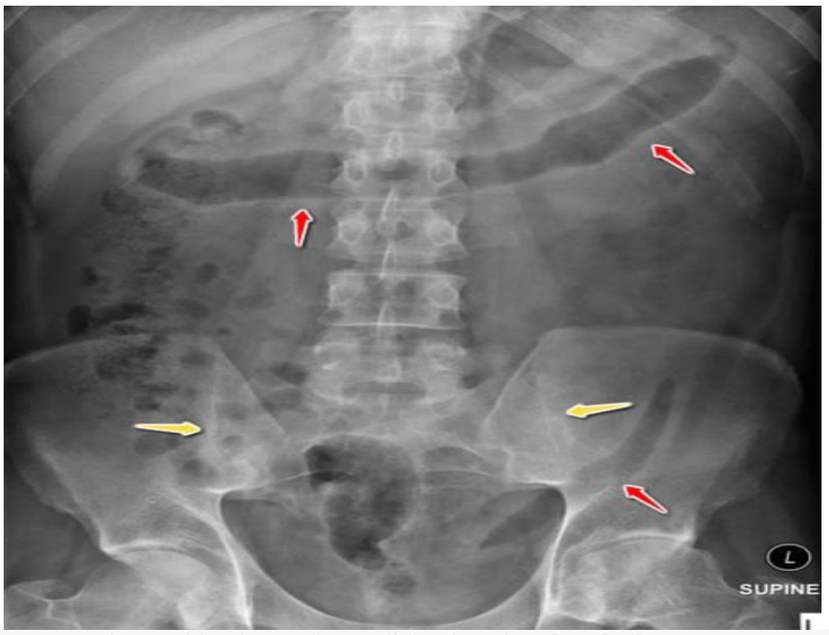
	Mild	Moderate	Severe
Bowel movements (no. per day)	< 4	4–6	≥ 6 + at least one of the features of systemic upset (Pyrexia, Pulse > 90, anaemia, ↑ESR)
Blood in stools	small amounts	Between mild and severe	Visible blood
Pyrexia (> 37.8°C)	No	No	Yes
Pulse > 90 bpm	No	No	Yes
Anaemia Haemoglobin <105 g/L	No	No	Yes
ESR	≤ 30	≤ 30	> 30
C reactive protein	≤ 30	**≤ 30**	**>30**

Pathology

- red, raw mucosa, bleeds easily
- no inflammation beyond submucosa (unless fulminant disease)
- widespread ulceration with preservation of adjacent mucosa which has the appearance of polyps ('pseudopolyps')
- inflammatory cell infiltrate in lamina propria
- neutrophils migrate through the walls of glands to form crypt abscesses
- depletion of goblet cells and mucin from gland epithelium
- granulomas are infrequent

Barium enema

- loss of haustrations
- superficial ulceration, 'pseudopolyps'
- long standing disease: colon is narrow and short -'drainpipe colon'



Abdominal x-ray from a patient with ulcerative colitis showing **lead pipe appearance** of the colon (red arrows). Ankylosis of the left sacroiliac joint and partial ankylosis on the right (yellow arrow), reinforcing the link with sacroilitis.

Ulcerative colitis: flares

- Non-steroidal anti-inflammatory drugs (NSAIDs) cause flares of inflammatory bowel disease.
- Cytomegalovirus is an uncommon cause of non-responsive colitis.

Flares of ulcerative colitis are usually classified as either mild, moderate or severe:

Mild	Moderate	Severe
Fewer than four stools daily, with or without blood No systemic disturbance Normal erythrocyte sedimentation rate and C-reactive protein values	Four to six stools a day, with minimal systemic disturbance	More than six stools a day, containing blood Evidence of systemic disturbance, e.g. • fever • tachycardia • abdominal tenderness, distension or reduced bowel sounds • anaemia • hypoalbuminaemia

Patients with evidence of severe disease should be admitted to hospital.

Risk factors for the precipitation of toxic colonic dilatation

ulcerative colitis identify the following as risk factors for the precipitation of toxic colonic dilatation:

- Hypokalaemia
- **Hypomagnesaemia**
- Under-treatment
- Purgative bowel preparations for colonoscopy
- Non-steroidals
- Opioids
- Anti-cholinergics, and
- Anti-diarrhoeal agents.
- inappropriately delayed

Ulcerative colitis: management

Treatment can be divided into inducing and maintaining remission. NICE released guidelines on the management of ulcerative colitis in 2013.

The severity of UC is usually classified as being mild, moderate or severe:

- mild: < 4 stools/day, only a small amount of blood
- moderate: 4-6 stools/day, varying amounts of blood, no systemic upset
- severe: >6 bloody stools per day + features of systemic upset (pyrexia, tachycardia, anaemia, raised inflammatory markers)

Inducing remission

- treatment depends on the extent and severity of disease
- rectal (topical) aminosalicylates or steroids: for distal colitis rectal mesalazine has been shown to be superior to rectal steroids and oral aminosalicylates
- oral aminosalicylates
- oral prednisolone is usually used **second-line** for patients who fail to respond to aminosalicylates. NICE recommend waiting around 4 weeks before deciding if first-line treatment has failed
- **severe colitis should be treated in hospital. Intravenous steroids are usually given first-line**

Maintaining remission

- oral aminosalicylates e.g. mesalazine
- azathioprine and mercaptopurine
- methotrexate is not recommended for the management of UC (in contrast to Crohn's disease)
- there is some evidence that probiotics may prevent relapse in patients with mild to moderate disease

Inactive (quiescent) colitis:

- **(ESR) is not raised in quiescent UC**
- **If the ESR, CRP and platelet counts are not raised, indicating that the patient's symptoms are not due to active disease.**
- **Neutrophilic infiltrate is present if disease is active**
  - **Involves epithelium of surface and crypts**
  - **Frequently forms crypt abscesses**

Ulcerative colitis: colorectal cancer

Overview

- risk of colorectal cancer is significantly higher than that of the general population although studies report widely varying rates
- the increased risk is mainly related to chronic inflammation
- worse prognosis than patients without ulcerative colitis (partly due to delayed diagnosis)
- lesions may be multifocal

Factors increasing risk of cancer

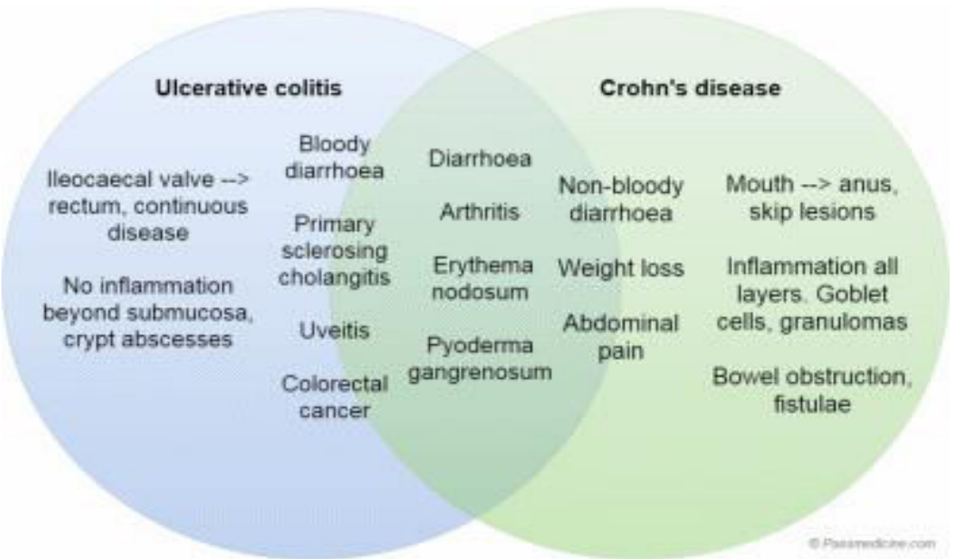
- disease duration > 10 years
- patients with pancolitis
- onset before 15 years old
- unremitting disease
- poor compliance to treatment

Colonoscopy surveillance & Risk stratification of IBD

- All patients with a diagnosis of colitis should have a screening colonoscopy 10 years after index presentation, preferably when they are in remission.
- patients should be decided following risk stratification.
  - **Lower risk** → 5 year follow up colonoscopy
    - Extensive colitis with no active endoscopic/histological inflammation
    - left sided colitis
    - Crohn's colitis of <50% colon
  - **Intermediate risk** → 3 year colonoscopy
    - Extensive colitis with mild active endoscopy/histological inflammation
    - post-inflammatory polyps
    - OR family history of colorectal cancer in a first degree relative aged 50 or over
  - **Higher risk → 1 year follow up colonoscopy**
    - Extensive colitis with moderate/severe active endoscopic/histological inflammation
    - stricture in past 5 years
    - dysplasia in past 5 years declining surgery
    - **primary sclerosing cholangitis** / transplant for primary sclerosing cholangitis
    - family history of colorectal cancer in first degree relatives aged <50 years

Inflammatory bowel disease: key differences

- The two main types of inflammatory bowel disease are Crohn's disease and Ulcerative colitis.
- They have many similarities in terms of presenting symptoms, investigation findings and management options.
- There are however some key differences which are highlighted in table below:



Venn diagram showing shared features and differences between ulcerative colitis and Crohn's disease. Note that whilst some features are present in both, some are much more common in one of the conditions, for example colorectal cancer in ulcerative colitis

	Crohn's disease (CD)	Ulcerative colitis (UC)
Features	Diarrhoea usually non-bloody Weight loss more prominent Upper gastrointestinal symptoms, mouth ulcers, perianal disease Abdominal mass palpable in the right iliac fossa	Bloody diarrhoea more common Abdominal pain in the left lower quadrant Tenesmus
Extra-intestinal	Gallstones are more common secondary to reduced bile acid reabsorption Oxalate renal stones*	Primary sclerosing cholangitis more common
Complications	Obstruction, fistula, colorectal cancer	Risk of colorectal cancer high in UC than CD
Pathology	Lesions may be seen anywhere from the mouth to anus Skip lesions may be present	Inflammation always starts at rectum and never spreads beyond ileocaecal valve Continuous disease
Histology	Inflammation in all layers from mucosa to serosa • increased goblet cells • granulomas	No inflammation beyond submucosa (unless fulminant disease) - inflammatory cell infiltrate in lamina propria • neutrophils migrate through the walls of glands to form crypt abscesses • depletion of goblet cells and mucin from gland epithelium • granulomas are infrequent
Endoscopy	Deep ulcers, skip lesions - 'cobble-stone' appearance	Widespread ulceration with preservation of adjacent mucosa which has the appearance of polyps ('pseudopolyps')
Radiology	Small bowel enema • high sensitivity and specificity for examination of the terminal ileum • strictures: 'Kantor's string sign' • proximal bowel dilation	Barium enema • loss of haustrations • superficial ulceration, 'pseudopolyps' • long standing disease: colon is narrow and short -'drainpipe colon'

	Crohn's disease (CD)	Ulcerative colitis (UC)
	• 'rose thorn' ulcers • fistulae	

*impaired bile acid rebsorption increases the loss calcium in the bile. Calcium normally binds oxalate.

IBD: histology

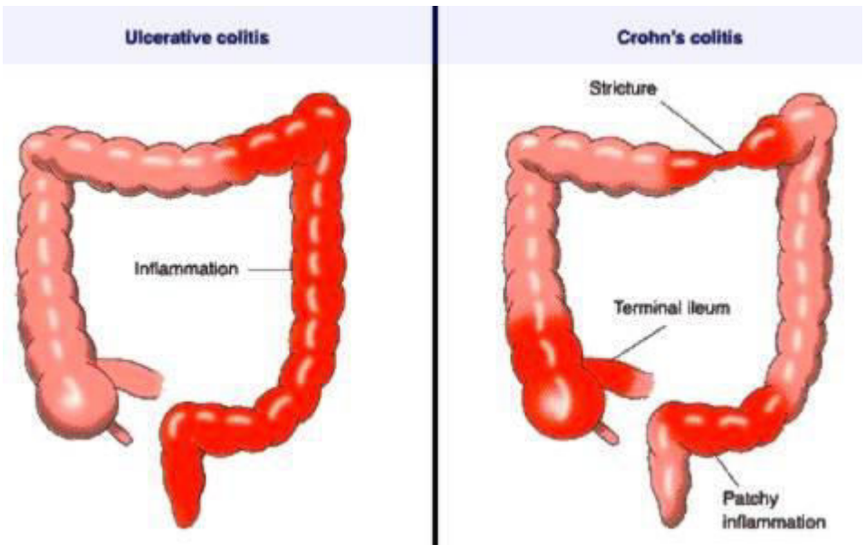
This histological differences between Crohn's and ulcerative colitis are summarised below:

Crohn's

- inflammation occurs in all layers, down to the serosa. This predisposes to strictures, fistulas and adhesions
- oedema of mucosa and submucosa, combined with deep fissured ulcers ('rose-thorn') leads to a 'cobblestone' pattern
- lymphoid aggregates
- non-caseating granulomas

Ulcerative colitis

- inflammation in mucosa and submucosa only (unless fulminant disease)
- widespread ulceration with preservation of adjacent mucosa which has the appearance of polyps ('pseudopolyps')
- inflammatory cell infiltrate in lamina propria
- crypt abscesses
- depletion of goblet cells and mucin from gland epithelium
- granulomas are infrequent



feature	Ulcerative colitis	Crohn's
Most common site	Rectum	Terminal ileum
Distribution	Rectum to colon "backwash" ileitis	Mouth to anus
Spread	Continuous	Discontinuity "skip" lesions
Gross features	▪ Extensive ulceration ▪ Pseudo-polyps	• Focal aphthous ulcers with intervening normal mucosa • Linear fissures • Cobblestone appearance • Thickened bowel wall "linitis plastic" • Creeping fat
Micro	▪ Crypt abscess	Noncaseating granulomas
Inflammation	▪ Limited to mucosa and submucosa	Transmural
Complication	▪ Toxic megacolon	• Strictures • String sign on barium study • Obstruction • Abscess • Fistula • Sinus tract
Genetic Association	HLA-B27	
Extraintestinal manifestation	Common	Uncommon
Cancer risk	5-25%	Slight 1-3%
Presentation	Bloody diarrhea	Variable : Pain, diarrhea, weight loss

Pseudopolyps are seen in both ulcerative colitis and Crohn's disease.

history of previously well-controlled ulcerative colitis, treated with mesalazine 1.2 g daily. presented with a 5-day history of increasing bowel frequency. A diagnosis of active proctitis was made. What is the most appropriate treatment?

⇨ **increase mesalazine dosage**

Microscopic colitis (Collagenous colitis and Lymphocytic colitis)

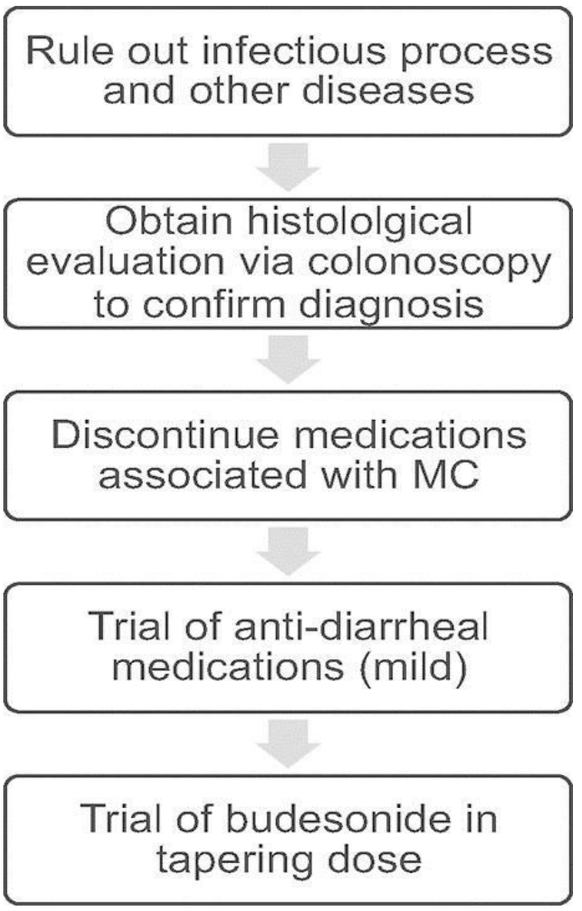
- Microscopic colitis (MC) is an inflammatory condition of the colon that presents with two subtypes: collagenous (CC) and lymphocytic colitis (LC).
- Both types of MC present with watery diarrhea, and normal endoscopic findings. Differentiation is made by histological examination but treatment is the same.
- **Risk factors** for MC are female gender, higher age, concomitant autoimmune disease, past and current diagnosis of malignancy of organ transplant
  - Among all autoimmune disorders, celiac disease appears to have the strongest association.
  - The use of proton pump inhibitors (PPIs) (lansoprazole), low dose aspirin, β-blockers, angiotensin II receptor antagonists, nonsteroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRI), statins, and bisphosphonates have all been associated with MC
- **Diagnosis**
  - histological evaluation through lower endoscopy.
    - The histology found in MC (both CC and LC) demonstrates **lymphocytic infiltration of the lamina propria and the epithelium**.
    - **CC** differs from LC in that there is marked **thickening of the subepithelial layer**.
    - **Intraepithelial lymphocytosis (IEL)** can be found in both CC and LC, but is **more pronounced in LC**: ≥ 20 intraepithelial lymphocyte per 100 surface epithelial cells are needed to make the diagnosis

- Both MC respond well to oral budesonide.
- Prognosis is good with resolution of symptoms after medical therapy.
- 38% of the patients achieve spontaneous remission with either no treatment or with simple anti-diarrheals.

Histological features of collagenous colitis and lymphocytic colitis

	Collagenous colitis	Lymphocytic colitis
Lamina propria	Lymphocytic infiltration of the lamina propria with little or no damage in mucosal architecture	
Subepithelial layer	Thickening of subepithelial layer > 10 µm	Subepithelial collagen layer not present or < 10 µm
Intraepithelial	Intraepithelial lymphocytosis could be present, but necessary for the diagnosis	Intraepithelial lymphocytosis (≥ 20 IEL per 100 surface epithelial cells)

- **Management**
  - discontinue any potentially offending drug.
  - mild and intermittent symptoms can be treated with anti-diarrheal medication (loperamide).
  - moderate to severe symptoms: only budesonide has strong supporting evidence and should be the first-line treatment in inducing and maintaining clinical remission in both CC and LC
    - Prednisone is an alternative corticosteroid that has shown some efficacy in treating MC. however it is less effective than budesonide.



Collagenous colitis

- **Collagenous colitis is one of the forms of microscopic colitis, i.e. a condition in which the colon appears normal on colonoscopy, but where the diagnosis is made based on the abnormal histology of colonic biopsies.**
- predominantly affects women (male: female of 1: 4) in the fifth and sixth decades of life.
- aetiology is unknown,
- although associated with
  - several medications – in particular, non-steroidal anti-inflammatory drugs

  - coeliac disease and other autoimmune disorders.
- chronic watery diarrhoea (which tends to be worse during the day than at night), and is also often accompanied by crampy, diffuse abdominal pain.
- normal blood tests, radiological and macroscopic appearances.
- The diagnosis is made based on the typical histological appearances of a thickened subepithelial collagen band, a moderate inflammatory cell infiltrate, and an increase in intraepithelial lymphocytes.
- Treatments include antidiarrhoeal agents (such as Loperamide), 5-aminosalicyclate drugs, corticosteroids, and bile acid sequestrants, all of which are variably effective.

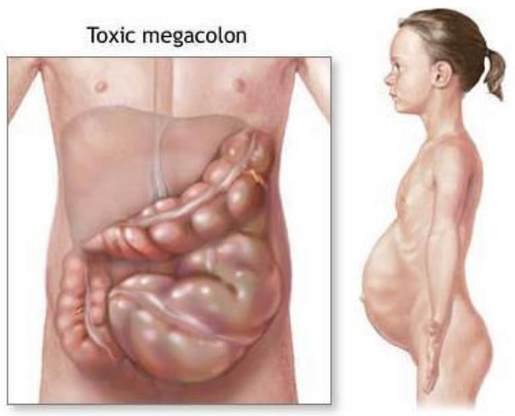
Lymphocytic colitis

- Associations
  - occur in patients with other forms of GI pathology, including Crohn's and Coeliac.
  - **Sertraline also appears to be associated with the development of lymphocytic colitis.**
- Management
  - Withdrawal of the offending agent is preferable,
  - loperamide is often used as a first line therapy to reduce the severity of diarrhoea, with cholestyramine an alternative if there is bile salt malabsorption.
  - Other alternatives include immune modulating agents such as azathioprine, although a response to therapy may take many months to appear.

Toxic megacolon (Toxic dilatation of the colon)

DON'T GIVE ANTI-DIARRHEAL Rx FOR ACUTE COLLITIS → TOXIC MEGACOLON

Flexible sigmoidoscopy is the best investigation - safer than colonoscopy (relative contraindication in active colitis), allowing biopsies to be taken and the viewing of a possible pseudomembrane. Occasionally the mucosa has a characteristic appearance.



Toxic megacolon is characterized by extreme inflammation and distention of the colon. Common symptoms are pain, distention of the abdomen, fever, rapid heart rate, and dehydration. This is a life-threatening complication that requires immediate medical treatment.

- Usually associated with severe colitis.
  - usually due to severe UC but also with Crohn's colitis and rarely ischaemic or infective colitis
- The transverse or right colon is usually the most dilated part in toxic megacolon, often greater than 6 cm and occasionally up to 15 cm on supine films.

Diagnostic criteria

toxic megacolon → transverse colon dilatation ≥ 6 cm + signs of systemic toxicity.

- Radiographic evidence of colonic distension
- **plus** at least three of the following:
  - Fever >38.6°C
  - Heart rate >120 beats per minute (The most reliable sign is the pulse rate)

- Neutrophilic leucocytosis >10.5 × 10^9/L, or
- Anaemia.

- **Plus,** at least one of the following:
  - Dehydration
  - Altered mental status
  - Electrolyte disturbances, or
  - Hypotension.

Investigation

- **The most helpful investigation is a plain abdominal X-ray.**
  - **Radiological colonic dilatation - widest diameter ≥ 6 cm in the transverse colon.**
  - Other radiological findings include:
    - loss of haustral pattern,
    - mucosal oedema and
    - thumbprinting.

Treatment

The treatment of choice for established dilatation is colectomy.

- Treatment includes 3 main goals:
  1. reduce colonic distention to prevent perforation (5-fold increase in mortality after free perforation)
     - Rolling techniques (knee-elbow and prone) may be performed to assist in redistribution of colonic gas and decompression
     - Medical treatment:
       - antibiotics to cover the colonic bacterial flora, gram-negative and anaerobic bacteria
       - steroids: either hydrocortisone 100 mg IV every 6 hours or methylprednisolone 60 mg IV every 24 hours is acceptable. The latter has greater relative anti-inflammatory potency and less relative mineralocorticoid potency.
       - cyclosporine may be effective
     - colectomy: Most authors recommend colectomy if persistent dilatation is present or if no improvement is observed on maximal medical therapy after 24-72 hours.
  2. correct fluid and electrolyte disturbances
     - fluid replacement, electrolyte repletion, and transfusion should be aggressive.
  3. treat toxemia and precipitating factors.
     - Broad-spectrum (IV) antibiotics with coverage equivalent to ampicillin, gentamicin, and metronidazole should be initiated.
     - Possible **triggers for TM** should be stopped, including:
       - **narcotics**
       - **antidiarrheals**
       - **anticholinergics**

Prognosis

- The mortality rate for non-perforated, acute toxic colitis is about 4%; if perforation occurs, the mortality is approximately 20%.

Gastroenteritis and food poisoning

Diarrhoea

- **Osmotic diarrhoea** occurs in patients with diabetes who ingest too much sorbitol (a common substitute for glucose in so-called 'diabetic foods'.
- **Secretory diarrhoea** commonly occurs in response to endotoxin-producing bacteria, (eg cholera or Escherichia coli).

- **Chronic radiation enteritis** is diagnosed if diarrhoea and abdominal pain persist for 3 or more months following irradiation.

Gastroenteritis

E. coli is the most common cause of travellers' diarrhoea

Travellers' diarrhoea

- defined as at least 3 loose to watery stools in 24 hours with or without one of more of abdominal cramps, fever, nausea, vomiting or blood in the stool.
- The most common cause is *Escherichia coli*
- **Ciprofloxacin is recommended for first line antibiotic therapy (when needed) before stool culture results are available.**

Acute food poisoning

- Sudden onset of nausea, vomiting and diarrhoea after the ingestion of a toxin.
- typically caused by *Staphylococcus aureus*, *Bacillus cereus* or *Clostridium perfringens*.
- *Clostridium perfringens*:
  - a Gram-positive, rod shaped, anaerobic, spore-forming bacterium.
  - The spores can withstand (يقاوم) cooking temperatures, so if food (meat and poultry) is left to stand for a long time, germination of spores can occur, causing food poisoning.
  - The CPE (clostridium perfringens enterotoxin) can be detected in food that has been improperly prepared.
  - ***Clostridium perfringens* can also cause gas gangrene, a necrosis of tissues with gas production. The toxin responsible for gas gangrene is called alpha-toxin.**
- ***reservoir for this pathogen***
  - ***Vibrio* species are most commonly found in seafood (Fish), are comma-shaped, and prefer alkaline media.**
  - Improperly **canned foods** are reservoirs for ***Clostridium botulinum***. This is an anaerobic gram-positive organism that creates spores. If the can is bulging, it is probably contaminated and should not be eaten.
  - **Honey** can be a reservoir for ***Clostridium botulinum***. Newborn babies are at risk for contracting spores from eating honey since their immune systems are poorly developed. This can lead to “floppy baby” syndrome.
  - **Mayonnaise and other cream-based dishes** are often reservoirs for ***Staphylococcus aureus*.**

Stereotypical histories

Infection	Typical presentation
Escherichia coli	Common amongst travellers Watery stools Abdominal cramps and nausea
Giardiasis	Prolonged, non-bloody diarrhoea
Cholera	Profuse, watery diarrhoea Severe dehydration resulting in weight loss Not common amongst travellers
Shigella	Bloody diarrhoea Vomiting and abdominal pain
Staphylococcus aureus	Severe vomiting Short incubation period
Campylobacter	**commonest cause of bacterial gastroenteritis in the UK** A flu-like prodrome is usually followed by crampy abdominal pains (often a prominent feature), 'pseudoappendicitis' (RIF pain), fever and diarrhoea which may be bloody. **Treatment:** • **the most appropriate therapy → IV fluids** • most units advocate no antibiotic treatment. • Antibiotic of choice in this infection is erythromycin, though ciprofloxacin and tetracycline may also be appropriate. **Complications** include Guillain-Barre syndrome
Salmonella	• After *Campylobacter, Salmonella* is the most commonly isolated bacterial pathogen when laboratory diagnosis of diarrhea is sought. • acute onset of fever, diarrhea, and cramping • antibiotic treatment of patients with nontyphoidal salmonellosis may actually prolong, rather than limit, fecal shedding of these organisms. • **the likely sources are poultry (دواجن) and eggs.**
Bacillus cereus	Two types of illness are seen • vomiting within 6 hours, stereotypically due to rice • diarrhoeal illness occurring after 6 hours
Amoebiasis	Gradual onset bloody diarrhoea, abdominal pain and tenderness which may last for several weeks

Incubation period

- 1-6 hrs: *Staphylococcus aureus*, *Bacillus cereus**
- 12-48 hrs: *Salmonella*, *Escherichia coli*
- 48-72 hrs: *Shigella*, *Campylobacter*
- > 7 days: Giardiasis, Amoebiasis

Amoebic dysentery

- Acute amoebic dysentery is managed with:
  1. a course of **oral metronidazole** or tinidazole,
  2. followed by a ten day course of diloxanide to eradicate colonisation of the gut.
- Amoebic liver abscess may appear at any time from eight weeks after infection, and presents with night sweats, anorexia and right upper quadrant pain.
- mortality from amoebiasis is less than 1%.

Giardiasis

- Giardiasis is caused by the flagellate protozoan *Giardia lamblia*.
- It is spread by the faeco-oral route
-

Features

- often asymptomatic (carriers)
- lethargy, bloating, abdominal pain
- non-bloody diarrhoea
- chronic diarrhoea, malabsorption and lactose intolerance can occur
- **steatorrhoea**

Diagnosis

- stool microscopy for trophozoite and cysts are classically negative, therefore duodenal fluid aspirates or 'string tests' (fluid absorbed onto swallowed string) are sometimes needed
- initial investigation for *Giardia* is microscopy → three stool samples
- if repeated stool samples are negative and symptoms continue, current NHS guidelines suggest that **endoscopy is the best way to confirm the diagnosis.**
- It is diagnosed by stool microscopy; **if negative → duodenal aspirates or biopsy.**
- Testing of serum antibodies against *G. lamblia* trophozoites is not useful in diagnosing current infection.
- immunoassays using antibodies against cyst or trophozoite antigen have greater sensitivity and faster than conventional stool microscopy methods.
- **the specificity of a number of different immunoassays (eg: ELISA) was ≥98%.**

Treatment

- Metronidazole
- *Alternatives* (quinacrine, tinidazole, ornidazole, furazolidone, paromomycin).

Clostridium perfringens

The food poisoning with Colicky abdominal pain and diarrhoea **without vomiting** after incubation period between 9-13 hours is typical of ***Clostridium perfringens*.**

Bacillus cereus

typical case of Bacillus cereus, profuse vomiting occurs one to five hours after eating (rice).

B.cereus can cause two patterns of disease:

1. classic emetic form:
   - caused by the **ingestion of toxin**
   - Characterised by nausea and vomiting, similar to *Staphylococcus aureus*.
   - Rice products are generally the cause of this form.
2. diarrhoeal form:
   - less common
   - Caused by the **ingestion of the organism**, which releases toxin within the stomach.
   - Produce an illness similar to *C. perfringens (but the incubation period is classically shorter (1-6 hours)* with watery diarrhoea and abdominal cramps.
   - Meats, milk, vegetables and fish have been associated with this form.

*vomiting subtype, the diarrhoeal illness has an incubation period of 6-14 hours

Shigella

- causes bloody diarrhoea, abdominal pain
- severity depends on type: S sonnei (e.g. from UK) may be mild, S flexneri or S dysenteriae from abroad may cause severe disease
- treat with ciprofloxacin
- Reactive arthritis and Reiter's syndrome can develop following infection with a number of enteric pathogens including *Shigella*, *Salmonella*, *Campylobacter* and *Yersinia*.

Yersinia enterocolitica

- gram-negative bacillus
- *the second most common cause of bacterial gastrointestinal infection in children.*
- most frequently associated with enterocolitis, acute diarrhea, terminal ileitis, mesenteric lymphadenitis and **pseudoappendicitis**
- *Pseudoappendicitis syndrome is more common in older children and young adults.*
- *Enterocolitis, the most common presentation of Y enterocolitica, occurs primarily in young children,* Most cases are self-limited.
- *Y enterocolitica* is potentially transmitted by contaminated unpasteurized milk and milk products, raw pork, tofu, meats, oysters, and fish.
- The usual presentation of *Y enterocolitica* infection includes diarrhea (the most common clinical manifestation of this infection), low-grade fever, and abdominal pain lasting 1-3 weeks. Diarrhea may be bloody in severe cases. Vomiting is present in approximately 15-40% of cases
- Stool culture is the best way to confirm the diagnosis
- Ultrasonography or computed tomography (CT) scanning may be useful in delineating true appendicitis from pseudoappendicitis
- **Complications**
  - After an incubation period of 4-7 days, infection may result in mucosal ulceration (usually in the terminal ileum and rarely in the ascending colon), necrotic lesions in Peyer patches, and mesenteric lymph node enlargement.
  - In persons with human leukocyte antigen (HLA)–B27, reactive arthritis is not uncommon, possibly because of the molecular similarity between HLA-B27 antigen and *Yersinia* antigens.
- First-line drugs used against the bacterium include aminoglycosides and trimethoprim-sulfamethoxazole (TMP-SMZ). Other effective drugs include third-generation cephalosporins, tetracyclines (not recommended in children < 8 y), and fluoroquinolones (not approved for use in children < 18 y).

- *Yersinia pestis* is the causative agent of the plague.
- *Yersinia* bacteria has an ability to survive, and actively proliferate at temperatures as low as 1–4°C (e.g., on food products in a refrigerator).
- *Yersinia is one of the causes of reactive arthritis*
- ***Yersinia* may be associated with Crohn's disease**
  - Iranian sufferers of Crohn's disease were more likely to have had earlier exposure to refrigerators at home, consistent with its unusual ability to thrive at low temperatures.
- **Which bacteria can multiply and produce endotoxin even in refrigerated blood?**
  - ***Yersinia***
  - it is a prominent cause of life-threatening post-transfusion infection.
  - Endotoxins can result in septic shock

Gastrointestinal parasitic infections

Common infections

Organism	Notes
Enterobiasis	• Due to organism *Enterobius vermicularis* • Common cause of pruritus ani • Diagnosis usually made by placing scotch tape at the anus, this will trap eggs that can then be viewed microscopically • Treatment is with mebendazole
Ancylostoma duodenale	• Hookworms that anchor in proximal small bowel • Most infections are asymptomatic although may cause iron deficiency anaemia • Larvae may be found in stools left at ambient temperature, otherwise infection is difficult to diagnose • Infection occurs as a result of cutaneous penetration, migrates to lungs, coughed up and then swallowed • Treatment is with mebendazole
Ascariasis	• Due to infection with roundworm *Ascaris lumbricoides* • Infections begin in gut following ingestion, then penetrate duodenal wall to migrate to lungs, coughed up and swallowed, cycle begins again • Diagnosis is made by identification of worm or eggs within faeces • Treatment is with mebendazole
Strongyloidiasis	• Due to infection with *Strongyloides stercoralis* • Rare in west • Organism is a nematode living in duodenum of host • Initial infection is via skin penetration. They then migrate to lungs and are coughed up and swallowed. Then mature in small bowel are excreted and cycle begins again • An auto infective cycle is also recognised where larvae will penetrate colonic wall • Individuals may be asymptomatic, although they may also have respiratory disease and skin lesions • Diagnosis is usually made by stool microscopy • In the UK mebendazole is used for treatment
Cryptosporidium	• Protozoal infection • Organisms produce cysts which are excreted and thereby cause new infections • Symptoms consist of diarrhoea and cramping abdominal pains. Symptoms are worse in immunosuppressed people • Cysts may be identified in stools • Treatment is with metronidazole
Giardiasis	• Diarrhoeal infection caused by *Giardia lamblia*(protozoan) • Infections occur as a result of ingestion of cysts • Symptoms are usually gastrointestinal with abdominal pain, bloating and passage of soft or loose stools • Diagnosis is by serology or stool microscopy • First line treatment is with metronidazole

Exotoxins and endotoxins

Exotoxins are secreted by bacteria where as endotoxins are only released following lysis of the cell. **Exotoxins are generally released by Gram positive bacteria** with the notable exceptions of *Vibrio cholerae* and some strains of *E. coli*

It is possible to classify exotoxins by their primary effects:

- pyrogenic toxins
- enterotoxins
- neurotoxins
- tissue invasive toxins

- miscellaneous toxins

Pyrogenic toxins

Pyrogenic toxins stimulate the release of endogenous cytokines resulting in fever, rash etc. They are super-antigens which bridge the MHC class II protein on antigen-presenting cells with the T cell receptor on the surface of T cells resulting in massive cytokine release.

Organism	Toxin	Notes
Staphylococcus aureus	Toxic shock syndrome (TSST-1 superantigen) toxin	Results in high fever, hypotension, exfoliative rash
Streptococcus pyogenes	Streptococcal pyrogenic exotoxin A & C	Results in scarlet fever

Enterotoxins

Enterotoxins act on the gastrointestinal tract causing one of two patterns of illness:

- diarrhoeal illness
- vomiting illness ('food poisoning')

Organism	Toxin	Notes
Vibrio cholerae	Cholera toxin	Causes activation of adenylate cyclase (via G_s) leading to increases in cAMP levels, which in turn leads to increased chloride secretion and reduced sodium absorption
Shigella dysenteriae	Shiga toxin	Inactivates 60S ribosome → epithelial cell death
Escherichia coli	1. Heat labile toxin 2. Heat stabile toxin	1. Activates adenylate cyclase (via G_s), increasing cAMP → watery diarrhoea 2. Activates guanylate cyclase, increasing cGMP → watery diarrhoea
Staphylococcus aureus	*Staphylococcus aureus* enterotoxin	Vomiting and diarrhoeal illness lasting < 24 hours
Bacillus cereus	Cereulide	Potent cytotoxin that destroys mitochondria. Causes a vomiting illness which may present within 4 hours of ingestion

Neurotoxins

Neurotoxins act on the nerves (tetanus) or the neuromuscular junction (botulism) causing paralysis.

Organism	Toxin	Notes
Clostridium tetani	Tetanospasmin	Blocks the release of the inhibitory neurotransmitters GABA and glycine resulting in continuous motor neuron activity → continuous muscle contraction → lockjaw and respiratory paralysis
Clostridium botulinum	Botulinum toxin	Blocks acetylcholine (ACh) release leading to flaccid paralysis

Tissue invasive toxins

Organism	Toxin	Notes
Clostridium perfringens	α-toxin, a lecithinase	Causes gas gangrene (myonecrosis) and haemolysis
Staphylococcus aureus	Exfoliatin	Staphylococcal scalded skin syndrome

Miscellaneous toxins

Organism	Toxin	Notes
Corynebacterium diphtheriae	Diphtheria toxin	ADP ribosylates elogation factor (EF-2), resulting in inhibition, causing a 'diphtheric membrane' on tonsils caused by necrotic mucosal cells. Systemic distribution may produce necrosis of myocardial, neural and renal tissue
Pseudomonas aeruginosa	Exotoxin A	Also inhibits EF-2 by the same mechanism as above
Bacillus anthracis	Oedema factor (EF)	Forms a calmodulin-dependent adenylate cyclase which increases cAMP, impairing the function of neutrophils/macrophages → reduced phagocytosis
Bordetella pertussis	Pertussis exotoxin	Inhibits G_i leading to increases in cAMP levels, impairing the function of neutrophils/macrophages → reduced phagocytosis

Endotoxins

Endotoxins are lipopolysaccharides that are released from Gram-negative bacteria such as *Neisseria meningitidis*.

Pseudomembranous colitis (Clostridium difficile)

- *Clostridium difficile* is a **Gram positive** rod
- often encountered in hospital practice.
- It produces an exotoxin which causes intestinal damage leading to a syndrome called pseudomembranous colitis.
- *Clostridium difficile* develops when the normal gut flora are suppressed by broad-spectrum antibiotics.
- Clindamycin is historically associated with causing *Clostridium difficile* but the aetiology has evolved significantly over the past 10 years.
- **Second and third generation cephalosporins are now the leading cause of *Clostridium difficile*.**
- symptoms can occur **up to 10 weeks** following antibiotic therapy.

Features

- diarrhoea
- abdominal pain
- a **raised white blood cell count** is characteristic
- if severe toxic megacolon may develop

Diagnosis

- is made by detecting ***Clostridium difficile* toxin (CDT) in the stool**
  - **the most widely used diagnostic tool.**
- ELISA tests are specific but not as sensitive.
- Culture is sensitive but often does not differentiate between toxigenic and non-toxigenic strains.
- **sigmoidoscopy may show → multiple white plaques adhered to the gastrointestinal mucosa**
  - **The classic sigmoidoscopic appearance of 2 to 10 mm raised yellow nodules are pathognomonic.**
  - **90% of cases can be detected macroscopically by flexible sigmoidoscopy**
  - **mild cases may not be evident macroscopically → microscopic examination of a biopsy sample**
- **Plain AXR is useful for diagnosing toxic dilatation**
  - would be the investigation of choice if there is abdominal distension.
  - **Toxic dilatation should be excluded prior to sigmoidoscopy**.
  - However it does not establish the diagnosis.

Management

- first-line therapy is oral metronidazole for 10-14 days
- if **severe** or not responding to metronidazole then oral vancomycin may be used

- The major advantage of vancomycin over metronidazole is that vancomycin is not absorbed, so maximal concentrations of the drug can act intracolonically at the site of infection.
- **indicators for severe disease** include:
  - An age greater than 60
  - Albumin <25 g/L
  - Temperature >38.3°C
  - White cell count >15 ×109/L
  - Endoscopic evidence of pseudomembranous colitis and
  - Intensive care admission.

- Intravenous metronidazole can be used where oral administration is impossible; intravenous vancomycin is not effective.
- for life-threatening infections a combination of oral vancomycin and intravenous metronidazole should be used

Amoebiasis

- caused by *Entamoeba histolytica* (an amoeboid protozoan)
- spread by the faecal-oral route.
- 10% of the world's population is chronically infected.
- **Features**
  - can be asymptomatic,
  - May cause mild diarrhoea
  - **Amoebic dysentery**
    - profuse, bloody diarrhoea
    - stool microscopy may show trophozoites
    - treatment is with metronidazole
- **Complication**
  - **Amoebic liver abscess**
    - usually a single mass in the right lobe (may be multiple)
    - features: fever, RUQ pain
    - serology positive in > 90%

Viral gastroenteritis

- Most cases of acute infectious gastroenteritis are viral,
- **Causes**
  - **most common:**
    - **norovirus is the most common cause of acute gastroenteritis** and the second most common cause of hospitalisation for acute gastroenteritis.
      - large outbreaks from consumption of contaminated food and water,
      - spread person-to-person.
  - other common
    - rotavirus,
    - enteric adenovirus and
    - astrovirus.
- **Features**
  - Characteristics of the history that suggest a viral aetiology of acute gastroenteritis include:
    - intermediate incubation period (24–60 h),
    - short infection duration (12–60 h) and
    - high frequency of vomiting.

Scombrotoxin food poisoning

- Caused by the ingestion of foods that contain **high levels of histamine** and possibly other vasoactive amines and compounds.
- Histamine and other amines are formed by the growth of certain bacteria and the subsequent action of their decarboxylase enzymes on histidine and other amino acids in food, by spoilage of foods such as;
  - **fishery products, particularly tuna or mahi mahi**.

- **dark meat fish such as tuna, mackerel and marlin.**
- The most common cause of scombroid poisoning is due to ingestion of spoiled fish following inadequate refrigeration or prolonged time at room temperature. Cooking does not inactivate the toxin/histamines.

- **Incubation period**
  - **10-60 minutes**.
- **Feature**
  - The symptoms are due to ingestions of amines, **predominantly histamines**, produced by bacterial decarboxylation of histidine in fish meat.
  - Onset is usually 10-30 minutes post-ingestion of the implicated fish but a delayed onset may occur up to two hours.
  - Patients with pre-existing conditions such as bronchial asthma, and those taking isoniazid (a histaminase inhibitor) may be more symptomatic.
  - **Presented with diarrhoea, flushing, sweating and a hot mouth, minutes after eating**
  - Urticarial rash, Bronchospasm

Treatment

- usually self-limiting
- In severe cases, symptoms respond rapidly to antihistamines, for example, chlorpheniramine and intravenous cimetidine by slow intravenous injection over at least five minutes.

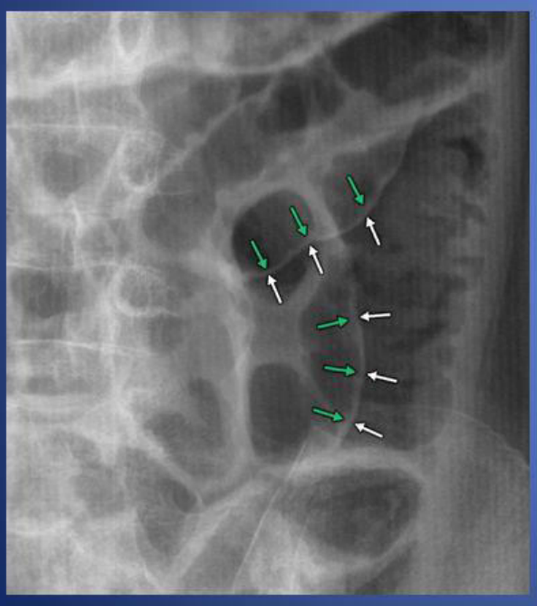
Perforated viscus

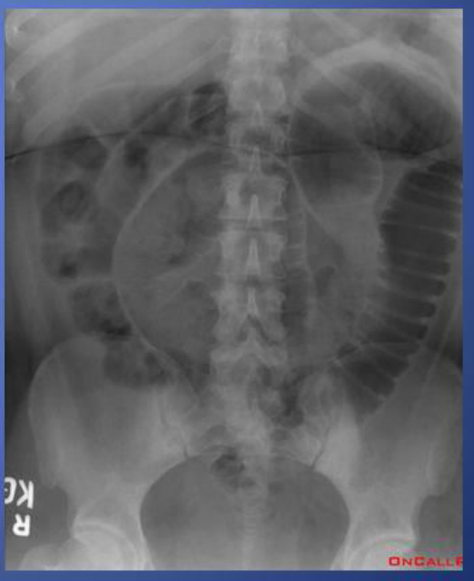
the most appropriate next step in making the diagnosis → abdominal CT scan

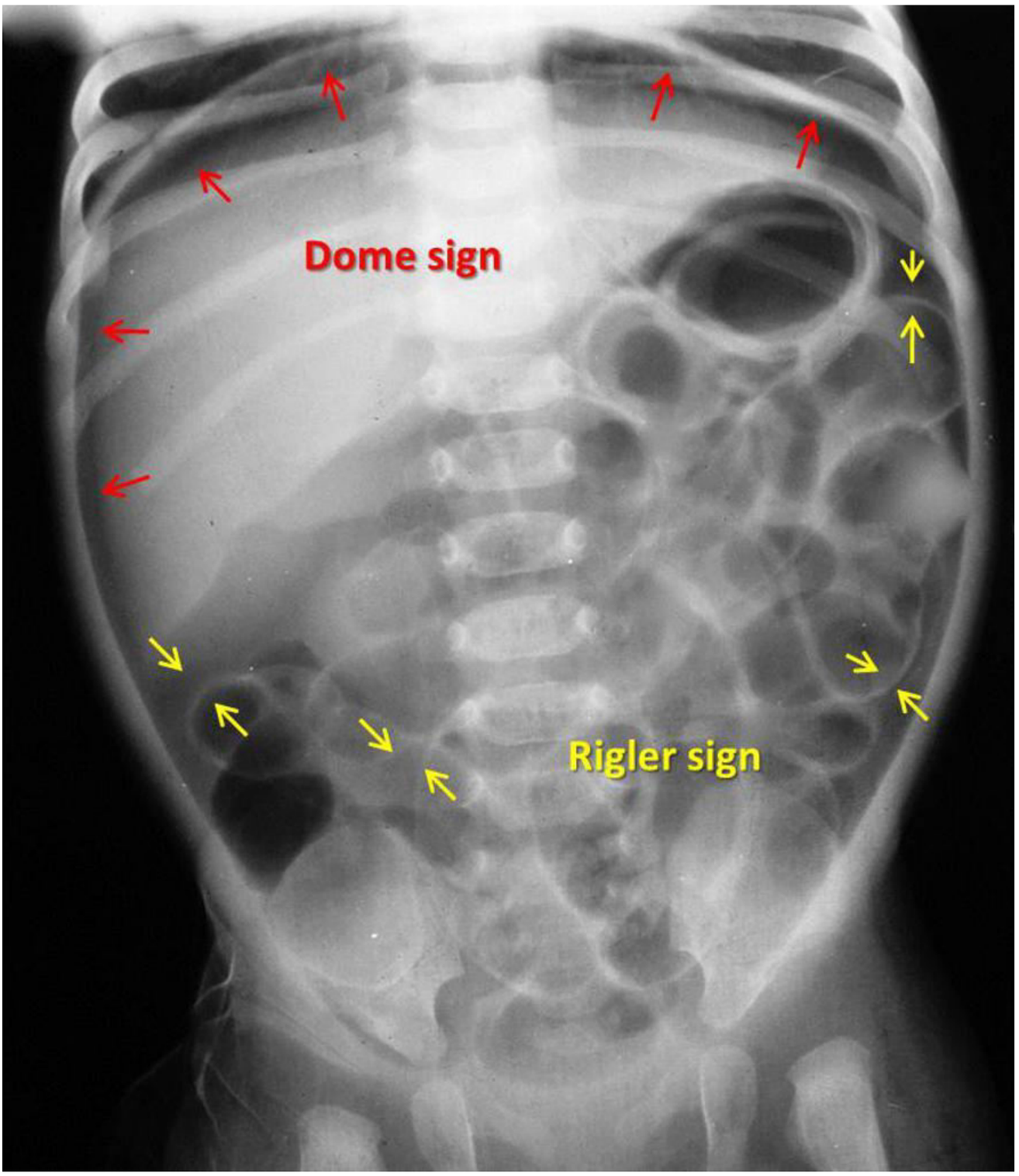
- Ascitic fluid analysis:
  - very bloody ascites
  - secondary bacterial peritonitis
    - very inflammatory (very high neutrophil count)
    - exudate (low serum albumin ascites gradient - <11 g/L).
    - **Gram stain demonstrates multiple bacteria.**
- X-ray
  - distended bowel loops (dilated, oedematous)
  - **Rigler's sign**, which indicates a perforated viscus.
    - also known as the double wall sign, is seen on an X-ray of the abdomen when
    - the air is present on both sides of the intestine, (luminal and peritoneal side of the bowel wall).
  - **Dome sign**
    - Air on the top of the liquid (fluid level)
  - pneumatosis coli which are suggestive of ischaemic bowel but not diagnostic of this or perforation.

Rigler's Sign

Bowel wall visualised on both sides due to intra and extraluminal air
Usually large amounts of free air
May be confused with overlapping loops of bowel, confirm with upright view





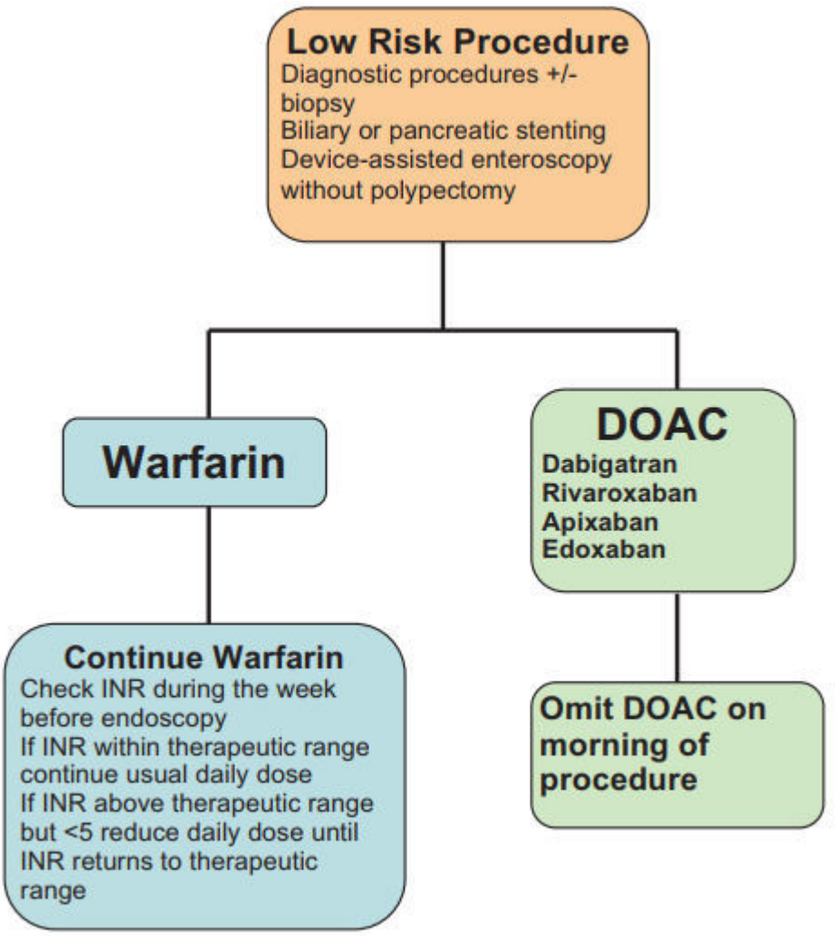


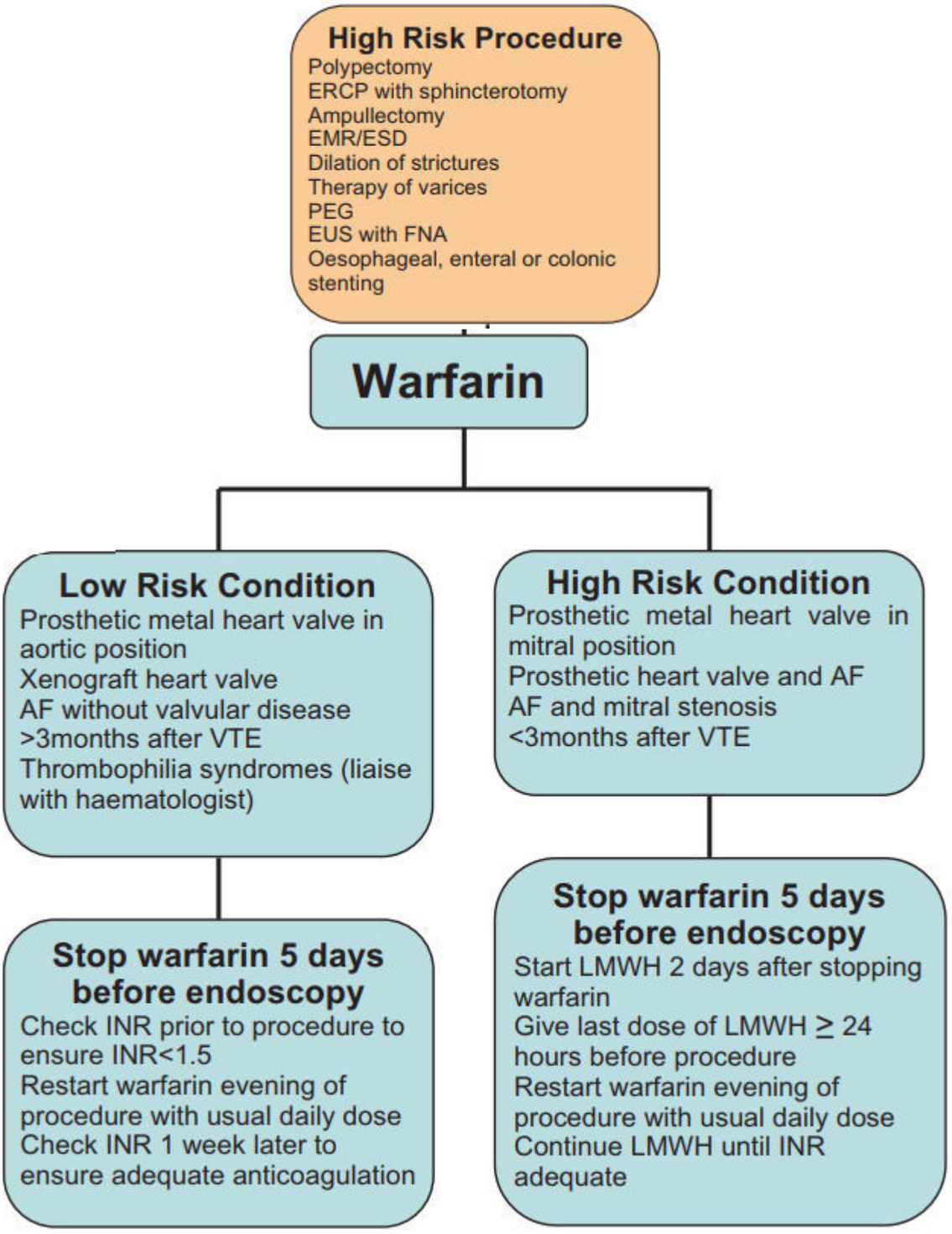
Endoscopy in patients on antiplatelet or anticoagulant therapy

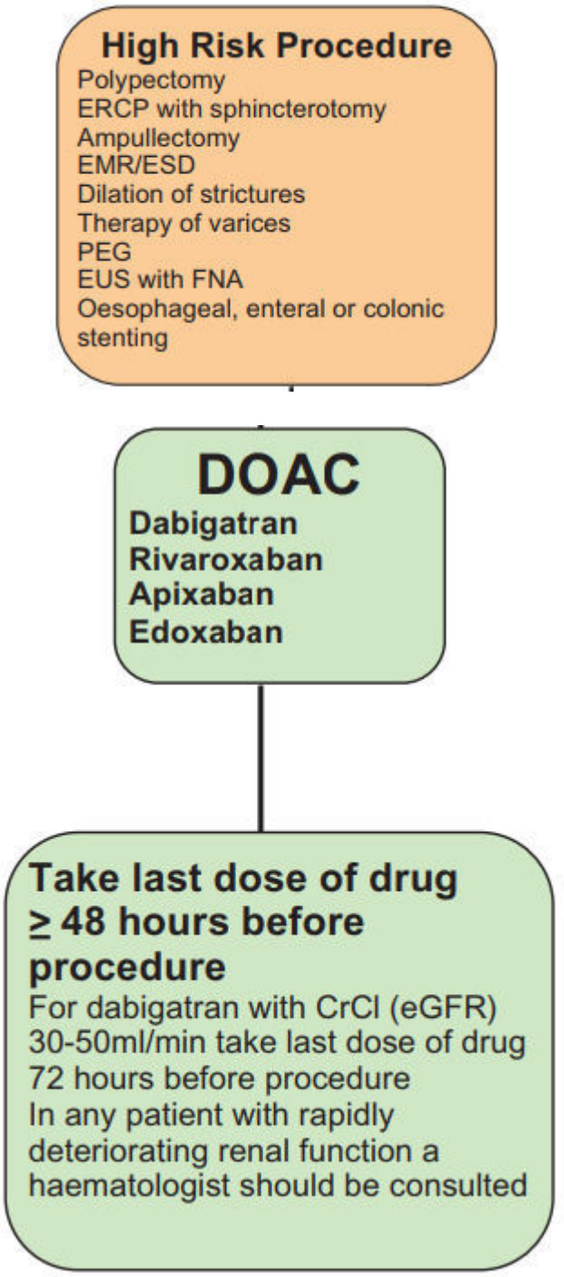
British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines (2016)

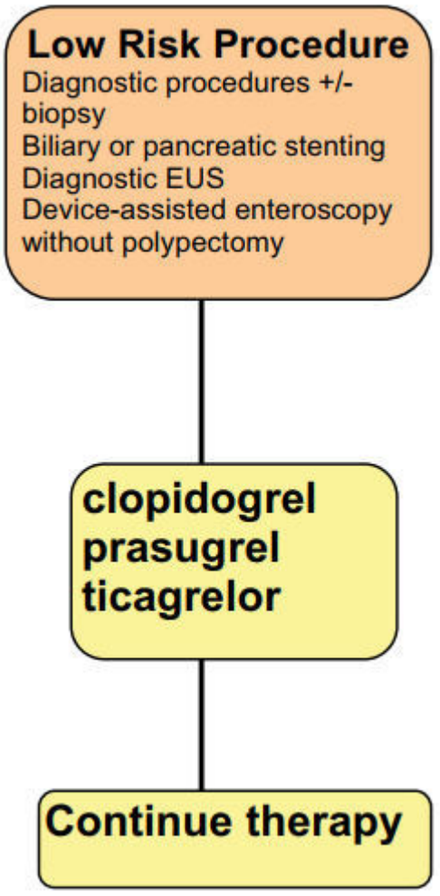
- The risk of endoscopy in patients on antithrombotics depends on the risks of procedural haemorrhage versus thrombosis due to discontinuation of therapy.
- Where the endoscopic procedure carries a **high risk of bleeding** and the indication for **anticoagulation is low risk** for discontinuation then anticoagulation should be discontinued until the INR is <1.5 and restarted post-procedure. Bridging with heparin is not required.
  - Bridging is only recommended if the **indication for anticoagulation is high risk** - for example, mechanical mitral valve, atrial fibrillation (AF) and prosthetic valve, recent venous thromboembolism (VTE) (less than three months), thrombophilia.
  - Low molecular weight heparin **(LMWH) is relatively contraindicated in patients with an estimated glomerular filtration rate (eGFR) less than 30 mls/min**, these patients may require admission for unfractioned heparin (UFH) infusion.

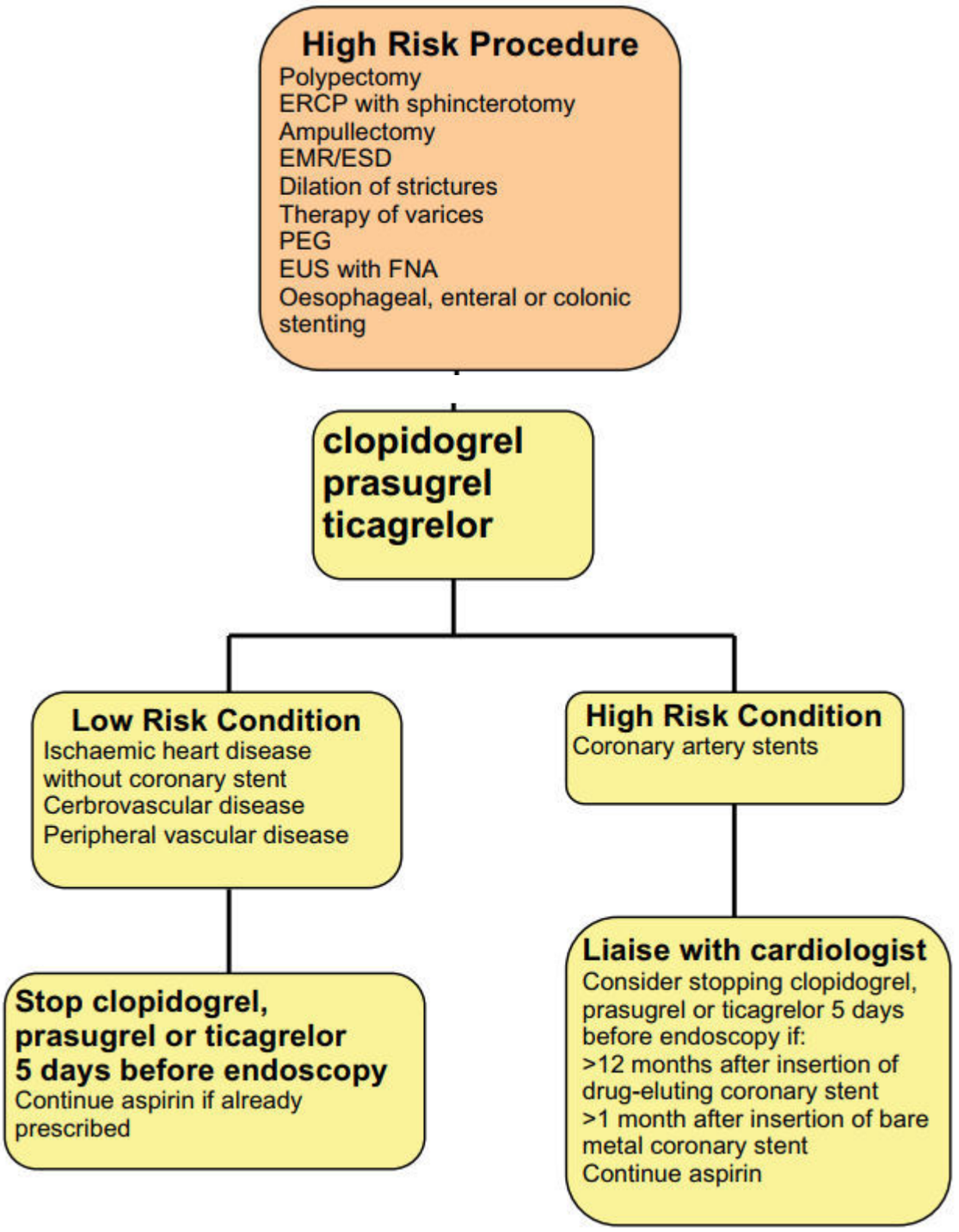
- Where an endoscopic procedure is associated with a **low risk of haemorrhage** then the BSG recommends **continuation of anticoagulation at the current dosage** providing an INR within the last seven days is within the therapeutic range.




High Risk Procedure
Polypectomy
ERCP with sphincterotomy
Ampullectomy
EMR/ESD
Dilation of strictures
Therapy of varices
PEG
EUS with FNA
Oesophageal, enteral or colonic stenting
Warfarin
Low Risk Condition
Prosthetic metal heart valve in aortic position
Xenograft heart valve
AF without valvular disease
>3months after VTE
Thrombophilia syndromes (liaise with haematologist)
High Risk Condition
Prosthetic metal heart valve in mitral position
Prosthetic heart valve and AF
AF and mitral stenosis
<3months after VTE
Stop warfarin 5 days before endoscopy
Check INR prior to procedure to ensure INR<1.5
Restart warfarin evening of procedure with usual daily dose
Check INR 1 week later to ensure adequate anticoagulation
Stop warfarin 5 days before endoscopy
Start LMWH 2 days after stopping warfarin
Give last dose of LMWH ≥ 24 hours before procedure
Restart warfarin evening of procedure with usual daily dose
Continue LMWH until INR adequate


High Risk Procedure
Polypectomy
ERCP with sphincterotomy
Ampullectomy
EMR/ESD
Dilation of strictures
Therapy of varices
PEG
EUS with FNA
Oesophageal, enteral or colonic stenting
DOAC
Dabigatran
Rivaroxaban
Apixaban
Edoxaban
Take last dose of drug ≥ 48 hours before procedure
For dabigatran with CrCl (eGFR) 30-50ml/min take last dose of drug 72 hours before procedure
In any patient with rapidly deteriorating renal function a haematologist should be consulted


Low Risk Procedure
Diagnostic procedures +/- biopsy
Biliary or pancreatic stenting
Diagnostic EUS
Device-assisted enteroscopy without polypectomy
clopidogrel
prasugrel
ticagrelor
Continue therapy



Proctitis

- **Definition**
  - Proctitis is inflammation of the lining of the rectal mucosa
- **Causes**
  - radiation therapy or antibiotics
    - usually within 6 months of treatment with a total dose of greater than 50 Gy.
    - can occur any time up to 30 years post irradiation.
  - sexually transmitted diseases (STDs) : anal intercourse
    - **most commonly due to gonorrhea and chlamydia,**
    - less commonly lymphogranuloma venereum or herpes virus
      - **HSV types 1 and 2 infections**: Symptoms may include: tenesmus, rectal pain, discharge, hematochezia and tender inguinal lymph nodes.
  - autoimmune disease of the colon, such as Crohn disease and ulcerative colitis

Notes & Notes

For MRCP part 1 & 11

By

Dr. Yousif Abdallah Hamad

Nephrology

Updated

2017

Contains:

1/ Passmedicine 2017

2/ On examination 2017

3/ Pastest 2017

4/ **Red fonts --> previous exams**

5/ Other updated UK sources

Renal anatomy The tables below show the anatomical relations of the kidneys:

Right kidney

Direct contact	Layer of peritoneum in-between
Right suprarenal gland Duodenum Colon	Liver Distal part of small intestine

Left kidney

Direct contact	Layer of peritoneum in-between
Left suprarenal gland **Pancreas** Colon	Stomach Spleen Distal part of small intestine

Renal physiology

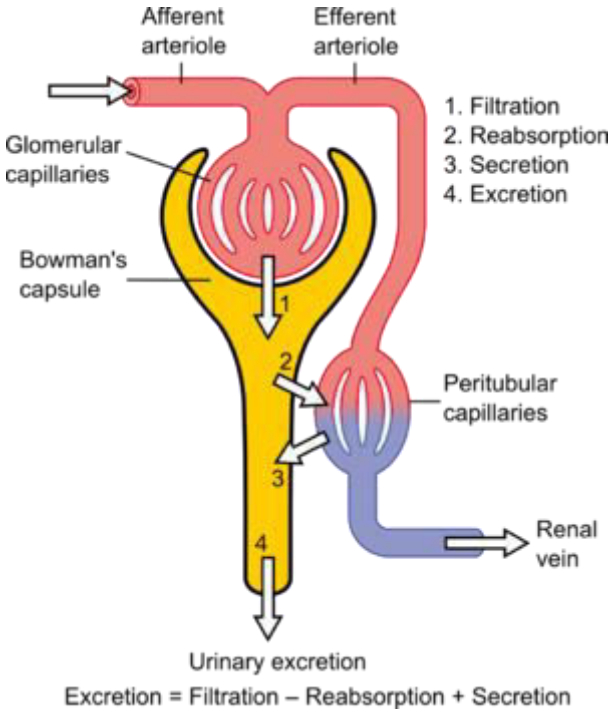


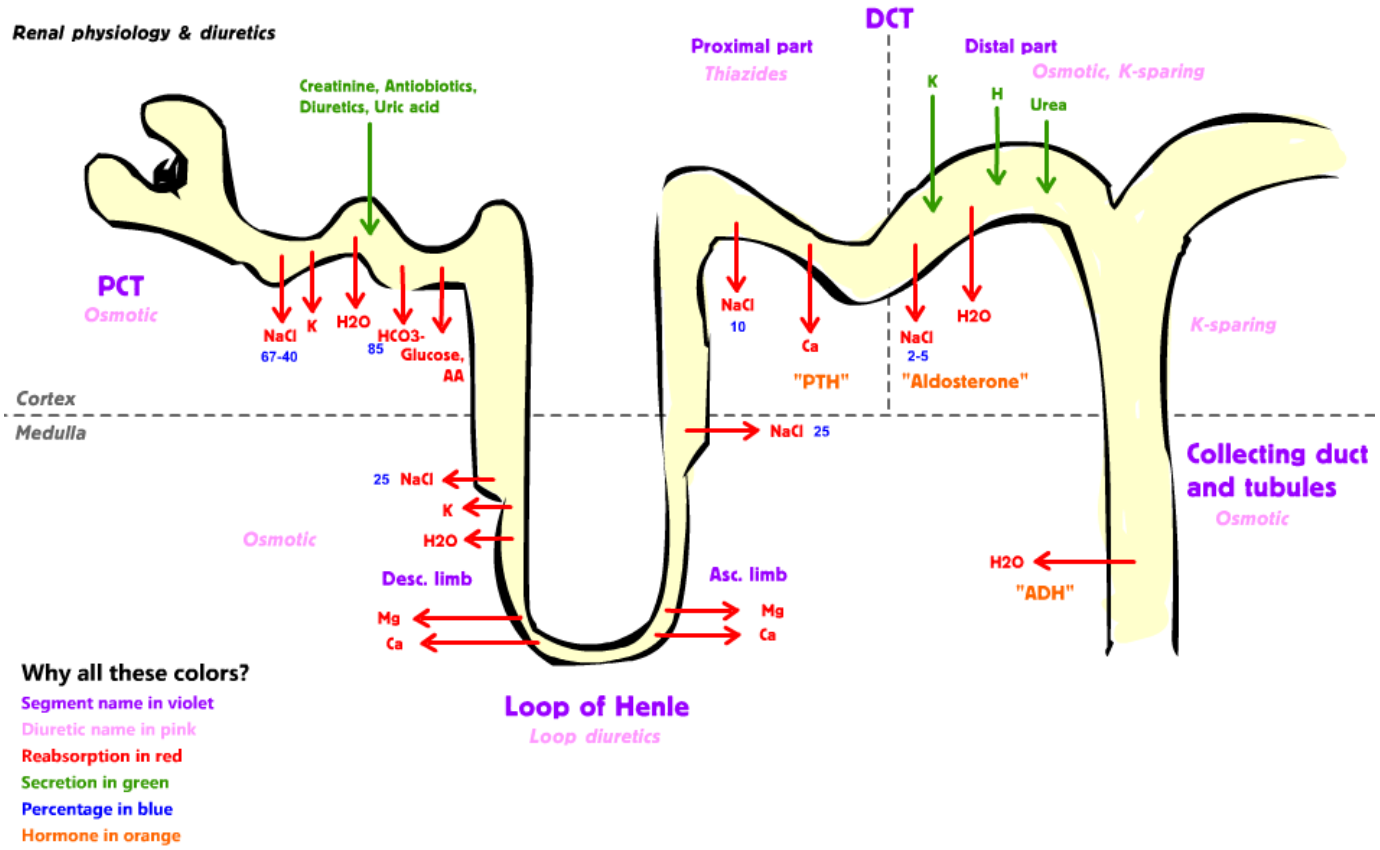
Diagram showing the basic physiologic mechanisms of the kidney

Renal blood flow (RBF)

- **Renal blood flow is 20-25% of cardiac output**
- **The 'Fick principle' can be used to estimate RBF** through clearance.
- Sympathetic stimuli produce vasoconstriction and RBF should be increased in response to hypoxia.
- Renal cortical blood flow > medullary blood flow (i.e. tubular cells more prone to ischaemia)
- **Glomerular filtration rate and renal blood flow increase by about 50% in pregnancy** leading to **decreased BUN and creatinine** on laboratory examination.

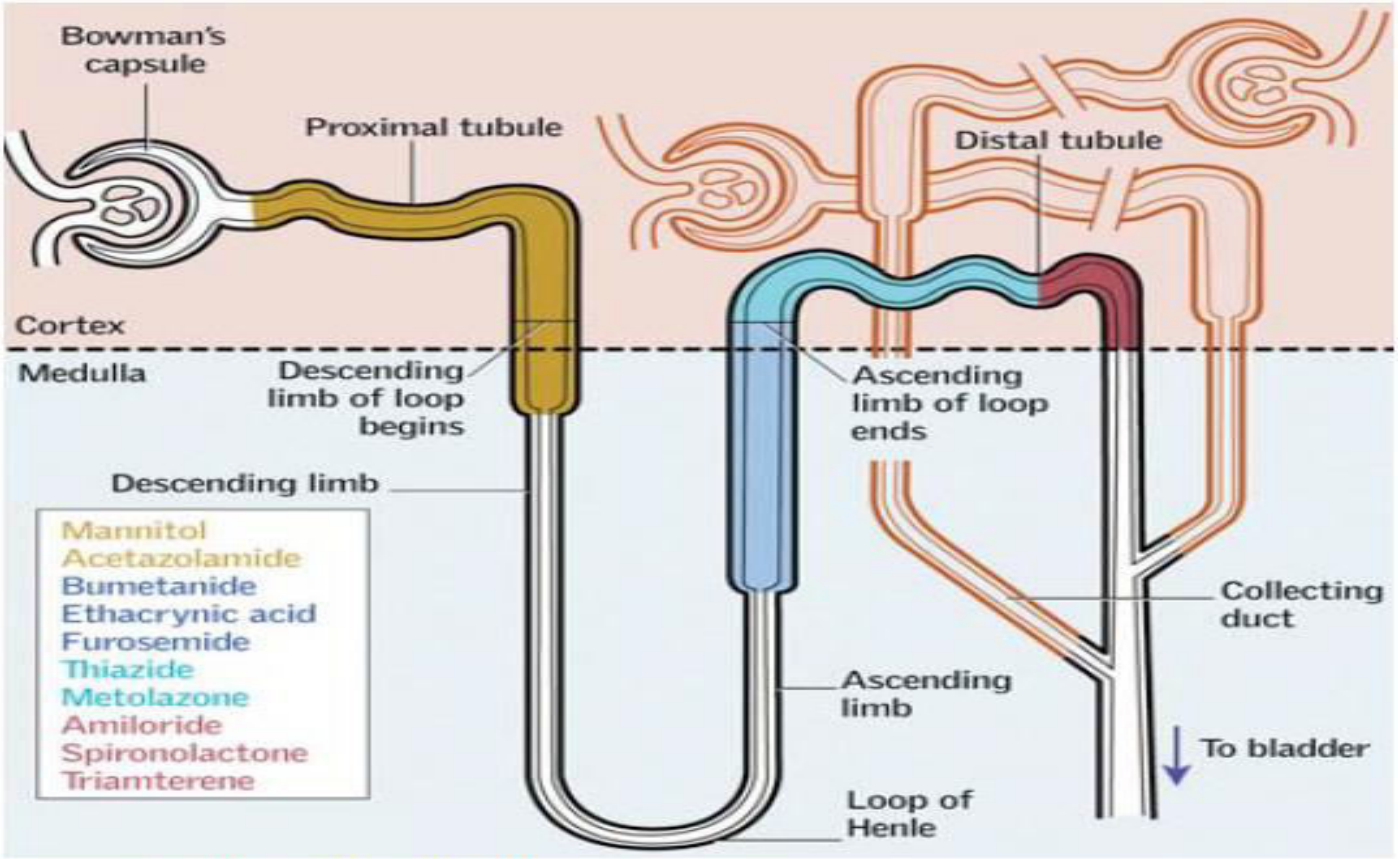
- **What is the effect of decrease in hematocrit on renal function?**
  - **Decreased Renal Blood Flow**
    - the relationships between Renal Blood Flow (RBF), Renal Plasma Flow (RPF), Hematocrit (Hct), and Glomerular Filtration Rate (GFR):
      - RBF = RPF / (1 - Hct).
      - Assuming that the GFR is stable, this equation suggests that a **decrease in Hct would lead to an decrease in RBF**.

Renal tubular functions



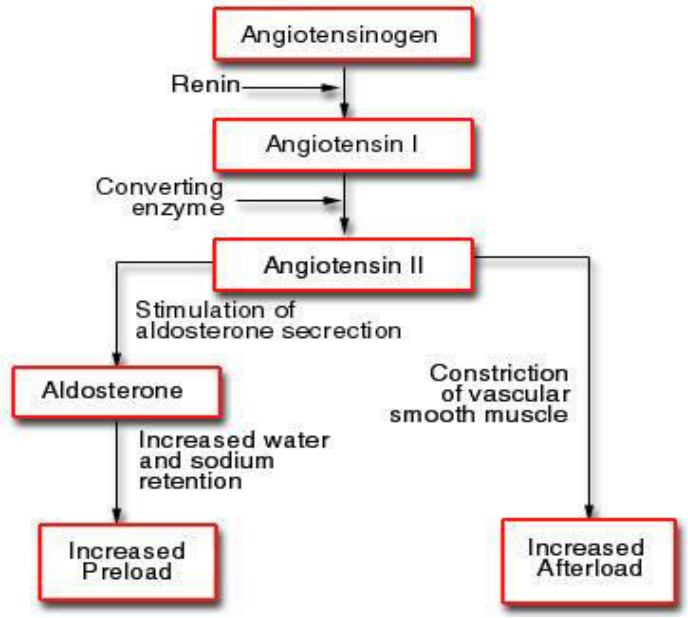
- **Sodium, glucose, bicarbonate and amino acids are absorbed at the proximal tubule level**
- Sodium reabsorption is mostly through active transport in the loop of Henle with only a modest reabsorption facilitated by aldosterone.
- Ammonia is secreted by the distal tubule
- **Regulation of water secretion is by the distal tubule and the collecting ducts under the influence of vasopressin** ➔ increase permeability to water.
- The relative hyperosmolality of the medulla is maintained by a counter-current mechanism and is responsible for the flux of water across the renal tubule
- **descending loop of Henle** is permeable to water but impermeable to solutes, due to the presence of aquaporin 1 in its tubular wall → water moves to medullary space → hypertonic filtrate
- **ascending loop of Henle** is impermeable to water (because of a lack of aquaporin, a common transporter protein for water channels in all cells except the walls of the ascending loop of Henle) but permeable to solutes, but here Na^+, Cl^-, and K^+ are actively transported into the medullary space, making the filtrate hypotonic

- **What is the renal cellular mechanism that prevents a sodium load intake from drastically increasing plasma osmolality?**
  - **Movement of aquaporin channels to the apical surface of collecting duct cells**
    - An increase in sodium intake will cause an increase in plasma osmolality, triggering the release of antidiuretic hormone (ADH), a.k.a. vasopressin.
      - **The immediate effect of ADH** (occurs over minutes) → movement of aquaporin channels to the apical surface of collecting duct cells.
      - **the long-term effect of ADH** (occurs over days) →Increase in aquaporin gene expression by collecting duct cells.



The nephron and sites of action of diuretics.

Renin-angiotensin –aldosterone system



Renin

- Released by juxtaglomerular cells in kidney in response to ↓ renal perfusion, low sodium
- Hydrolyses angiotensinogen to form angiotensin I
- when decreased cardiac output occurs, stimulation of **renin release is the primary event which leads to peripheral oedema**
- renin ↓ in primary hyperaldosteronism due to negative feedback (↑ Aldosterone → ↑ BP → ↑renal perfusion → ↓ renin)

Which renal cells would respond first to this acute event of hypotension to increase blood pressure?

➡ Juxtaglomerular cells

Factors stimulating renin secretion

- **↓ BP → ↓ renal perfusion**
- Hyponatremia
- renal artery stenosis
- Sympathetic nerve stimulation
- Catecholamines
- Erect posture

Factors reducing renin secretion

- β-blockers
- NSAIDS

Angiotensin

- ACE in lung converts angiotensin I → angiotensin II
- Vasoconstriction leads to raised BP
- Stimulates thirst
- Stimulates aldosterone and ADH

Aldosterone

- Released by the zona glomerulosa (the outer layer of adrenal cortex) in response to

raised angiotensin II, potassium, and ACTH levels

- Act in distal tubule → retention of Na+ in exchange for K+/H+ :
  - ↑ resorption of Na+ → ↓Na+ loss in urine
  - ↑ resorption of water (osmotic effect due to ↑ Na+)
  - ↑ excretion of K+

The counter-current concentrating mechanism in the kidney

Urine is concentrated by a complex interaction between the loops of Henle, the medullary interstitium, vasa recta and the collecting tubules, collectively termed **'the counter-current mechanism'**:

- Vasa recta possess fenestrated walls that facilitate the movement of diffusible substances **(free movement of water and electrolytes across the walls of the vasa recta)**
- Fine-tuning of the salt and water balance is achieved in the distal and collecting tubules under the influence of aldosterone and antidiuretic hormone
- The ascending limb of the loop of Henle is impermeable to water but permeable to sodium
- All nephrons are involved in this process
- The glomerular filtration rate ensures that the elimination of compounds such as urea from plasma can take place without losing large amounts of water as well

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Renal Investigations

Urinalysis

Significance of presence of casts in urine

- **Hyaline casts** → may be seen in normal urine, particularly after exercise
- **Coarse granular casts** → occur in glomerular and tubular disease
- **Tubular cell casts** → may be seen in patients with acute tubular necrosis
- **The presence of 10 or more white blood cells/mm3** → infection
- **The presence of red-cell casts** → characteristic of glomerulonephritis

Red cell casts: Present in:

- Acute glomerulonephritis
- Renal vasculitis
- Accelerated hypertension
- Interstitial nephritis.

Oliguria

- Oliguria is defined as <400 ml urine/day.
- a urine output of <0.5mL/kg/h.

urinalysis	Normal limits	comment
(WBCs) / leukocytes / (pus cells)	< 10	"Significant pyuria " ≥ 10 leucocytes per microlitre (µl) or cubic millimeter (mm^3)
dysmorphic RBCs	0 - 3	characteristic of glomerular origin
hemoglobinuria	0	Suggestive of *in vivo* hemolysis, but must be distinguished from hematuria. In case of hemoglobinuria, a urine dipstick shows presence of blood, but no RBCs are seen on microscopic examination.
nitrites	0	a positive test suggests presence of bacteria in significant numbers (ie more than 10,000 per ml) , A negative result does not rule out a UTI

Sterile pyuria

Pyuria in the absence of bacteriuria

Causes

- adult polycystic kidney disease
- Chemical cystitis (eg cyclophosphamide)
- analgesic nephropathy
- Acute glomerulonephritis
- Tubulo-interstitial diseases
- partially treated UTI
- urethritis and sexually transmitted diseases e.g. *Chlamydia*
- **renal tuberculosis**
- renal stones
- foreign body eg: urinary catheter,
- appendicitis
- bladder/renal cell cancer

Glycosuria in pregnancy

- **The most likely mechanism of glycosuria in pregnant woman➔ Reduced renal reabsorption**
- patients with persistent glycosuria should be investigated with a glucose tolerance test at around 24 weeks

Ketonuria in pregnancy

- Ketonuria may also be seen in normal pregnancy, as a result of the increased metabolic requirements

Urine pH

- The range is 4.5 to 8. urine is commonly acidic (ie 5.5-6.5)
- **Acidic urine** (low pH) may be caused by:
  - diet (eg, acidic fruits such as cranberries)
  - uric acid calculi.

- Urine pH generally reflects the blood pH but in renal tubular acidosis (RTA) this is not the case. In type 1 RTA (distal) the urine is acidic but the blood alkaline. In type 2 (proximal) the urine is initially alkaline but becomes more acidic as the disease progresses.
- **Alkaline urine** (high pH) is seen in:
  - the initial stages of type 2 RTA
  - Infection with urease-splitting organisms,
  - and may be associated with the formation of stag-horn calculi.
  - Diet, with **vegetarians having more alkaline** urine when compared with omnivores.

- Animal proteins contained in meat, eggs and cheese are often converted into acidic products (for example, amino acids) during digestion, absorption or metabolism. This provides a daily increase in the body's acid content, which has to be excreted by the kidneys.
- For people eating a vegetarian diet, consumption of foods rich in citrate or carbonated drinks raise the urine pH.
- Other situations can interfere with this balance, such as tubular function or bacterial infection, which often promotes an alkaline urine pH due to the presence of bacterial enzymes converting urea to ammonia.
- Effects of urine pH on stone formation:
  - Acidic urine➔ uric acid stones are more likely to form.
  - Alkaline urine ➔ phosphate stones are more likely to form (calcium phosphate becomes less soluble at pH>6;).
- Excretion of ammonium occurs when an acid urine is produced but the pH of urine is of course determined by the concentration of H+ ions.
- **Unable to lower the pH to less than 5.5 ➔ in type 1 RTA.**
- A pH of above 7.0 after prolonged and severe vomiting would be expected in an attempt to compensate for the loss of acid; however when there is extracellular fluid depletion the retention of sodium takes priority.Instead of bicarbonate being excreted it is reabsorbed in the proximal and distal nephron and this perpetuates the metabolic alkalosis until the fluid balance is restored with intravenous (IV) fluids.

Disproportionately raised creatinine compared with the urea level leads to suspicion of rhabdomyolysis. Additional clue is raised PO4 and K+ & renal failure.
Disproportionately raised urea compared with creatinine level leads to suspicion of dehydration.

Renal investigations:

- **The most appropriate an urgent scan to exclude obstruction of the kidneys is Ultrasound renal tract**
- **Retrograde urethro-graphy is the mainstay of investigation for urethral stricture disease**
- **Renal scintigraphy with DMSA**
  - Involves administration of radioactive isotope (dimercaptosuccinic acid) which is taken up by the renal parenchyma.
  - **This identify regions of decreased uptake due to acute inflammation (such as pyelonephritis) or renal scarring.**
  - The technique of dimercaptosuccinic acid DMSA scan also allows detection of congenital renal disorder.
  - A small kidney with uniform uptake of DMSA is likely to represent congenital hypodysplasia, whereas a focal area of reduced cortical uptake associated with loss of contours is more likely to represent an infection-related scar.

Renal Biopsy

- The hila of the kidneys lie at the L1 and L2 vertebral levels.
- For a routine biopsy there is no preferable side to biopsy, but **commonly it is the Lt Kidney**.
- Coagulation studies should always be performed prior to renal biopsy due to the risk of bleeding (e.g. in a case of alcohol excess, clotting studies may be deranged).

Complications

- **Macroscopic haematuria** can occur in up to 10% of renal biopsies.
- Nephrectomy is a rare but serious complication of renal biopsy required to control bleeding. It **should be consented for that.**

Haematuria

- Haematuria is defined as >3 RBC/high power field (hpf) of centrifuged sediment under the microscope.
- Non-visible (Microscopic) haematuria is found in around 2.5% of the population.

Causes of transient or spurious non-visible haematuria

- urinary tract infection
- menstruation
- vigorous exercise (this normally settles after around 3 days)
- sexual intercourse

Causes of persistent non-visible haematuria

- cancer (bladder, renal, prostate)
- stones
- benign prostatic hyperplasia
- prostatitis
- urethritis e.g. *Chlamydia*
- renal causes: IgA nephropathy, thin basement membrane disease

Spurious causes - red/orange urine, where blood is not present on dipstick

- foods: beetroot, rhubarb
- drugs: rifampicin, doxorubicin

what is the pathophysiology of Exercise-induced hematuria?

➔ **Extracorpuscular mechanical trauma causing hemolysis**

- patients present after the event with rust-colored urine.

Management

- Current evidence does not support screening for haematuria.
- The incidence of non-visible haematuria is similar in patients taking aspirin/warfarin to the general population hence these patients should also be investigated.

Testing

- urine dipstick is the test of choice for detecting haematuria
- persistent non-visible haematuria is often defined as blood being present in 2 out of 3 samples tested 2-3 weeks apart
- **The incidence of non-visible haematuria is similar in patients taking aspirin/warfarin to the general population hence these patients should also be investigated as normal.**
- renal function, albumin: creatinine (ACR) or protein: creatinine ratio (PCR) and blood pressure should also be checked
- urine microscopy may be used but time to analysis significantly affects the number of red blood cells detected
- **in an elderly presented with painless macroscopic haematuria**. the most important thing to exclude after infection would be a bladder tumour initially **before embarking upon a renal biopsy.** Therefore **cystoscopy is the best initial investigation.**

NICE urgent cancer referral guidelines (updated in 2015).

- **Urgent referral (i.e. within 2 weeks)**
  - Aged ≥ 45 years AND:
    - unexplained visible haematuria without UTI, or
    - visible haematuria that persists or recurs after successful treatment of UTI.
  - Aged ≥ 60 years AND have unexplained nonvisible haematuria and either dysuria or a raised white cell count on a blood test.
- **Non-urgent referral**
  - Aged ≥ 60 years with recurrent or persistent unexplained UTI.
- patients under the age of 40 years with normal renal function, no proteinuria and who are normotensive do not need to be referred and may be managed in primary care.

May 2009 exam: A 62-year-old man with H/O hypertension & AF, on warfarin. A urine dipstick showed blood + with no protein or leucocytes. This result repeated twice. What is the most appropriate action? Cystoscopy (The incidence of non-visible haematuria is similar in patients taking warfarin to the general population therefore these patients should be investigated as normal)

Acute interstitial nephritis (AIN)

The rapid onset of renal failure, coupled with a rash and eosinophilia is highly suspicious of a diagnosis of interstitial nephritis

Overview

- Acute interstitial nephritis is inflammation of the renal tubulo-interstitium, secondary to a hypersensitivity reaction to drugs.
- accounts for 25% of drug-induced acute renal failure
- An acute allergic reaction with infiltration of immune cells occurs in response to the causative drug, causing direct cytotoxicity.
- The onset of AIN occurs approximately 10-14 days after the initiation of the inciting agent and resolves with removal of the offending drug.
- It is **typically** characterized by **eosinophilia and eosinophiluria** with elevated levels of **IgE** in the serum suggesting a **type I hypersensitivity**.
- AIN may also be caused by type IV hypersensitivity with mononuclear interstitial infiltrate on renal biopsy.

Features

- fever, rash, arthralgia
- Eosinophilia and **Eosinophiluria.**
  - in blood (50%),
  - in **urine (70%)** and in renal biopsy.
  - **eosinophilia is common, and eosinophiluria is pathognomonic**
  - **Typically, eosinophilia is absent in AIN-induced by NSAIDs**
- mild renal impairment
- Many patients are not oliguric despite moderately severe acute renal failure. Patients with non-oliguric acute renal failure should always be investigated for AIN
- hypertension
- Proteinuria is dominant,

Causes

The drugs that most commonly cause acute interstitial nephritis are **proton pump inhibitors**, **penicillins**, **NSAIDs** and **thiazide** diuretics.

- idiopathic
- drugs: (40-60% of cases of interstitial nephritis are due to drug hypersensitivity).
  - penicillin, **rifampicin**, cephalosporins, vancomycin, Co-trimoxazole, Sulphonamides
  - NSAIDs, (The most common causative drug)
  - allopurinol,

- thiazides and furosemide
- Phenytoin.
- Ranitidine. Cimetidine . **Omeprazole**

- infection: Hanta virus , staphylococci

Diagnosis

- A definite diagnosis can only be made with **renal biopsy**, which usually shows mononuclear cell infiltrate throughout the interstitium with associated oedema.

Treatment

- untreated AIN results in interstitial fibrosis.
- The mainstay of treatment is to withdraw any drug which may be causative. **The majority of patients recover following withdrawal of the offending drug**
- High-dose prednisolone is indicated in some cases to hasten recovery. There is no proof that corticosteroids are effective in drug-induced AIN
- Dialysis may be required in severe cases.

Acute kidney injury (AKI) (previously termed acute renal failure or ARF)

Nice guideline tells **what increases the risk of AKI**:

1. Emergency surgery, ie, risk of sepsis or hypovolaemia
2. Intraperitoneal surgery
3. CKD, ie if eGFR < 60
4. Diabetes
5. Heart failure
6. Age >65 years
7. Liver disease
8. Use of nephrotoxic drugs

It also defines **the criteria for diagnosing AKI**

- 1. Rise in creatinine of 26 micromol/L or more in 48 hours OR
- 2. 50% + rise in creatinine over 7 days OR
- 3. Fall in urine output to less than 0.5ml/kg/hour for more than 6 hours in adults (8 hours in children) OR
- 4. 25% + fall in eGFR in children / young adults in 7 days.

Refer to a nephrologist if any of the following apply:

- 1. Renal transplant
- 2. ITU patient with unknown cause of AKI
- 3. Vasculitis/ glomerulonephritis/ tubulointerstitial nephritis/ myeloma
- 4. AKI with no known cause
- 5. Inadequate response to treatment
- 6. Complications of AKI
- 7. Stage 3 AKI
- 8. CKD stage 4 or 5
- 9. Qualify for renal replacement hyperkalaemia / metabolic acidosis/ complications of uraemia/ fluid overload (pulmonary oedema)

Acute tubular necrosis vs. prerenal uraemia

ATN or prerenal uraemia? In prerenal uraemia think of the kidneys holding on to sodium to preserve volume

	Pre-renal uraemia	Acute tubular necrosis
Pathology	due to hypoperfusion	due to circulatory compromise and/or nephrotoxins
Urine sodium	**< 20 mmol/L**	**> 30 mmol/L**
Urine osmolality	**>500**	**<350**
Fractional sodium excretion*	< 1%	> 1%
Fractional urea excretion**	< 35%	>35%
Urine: plasma osmolality	> 1.5	< 1.1
Urine: plasma urea	> 10:1	< 8:1
urine/plasma creatinine	>40	<20
Specific gravity	> 1020	< 1010
Urine	'bland' sediment **A urine free of red blood cells or casts**	brown granular casts
Response to fluid challenge	Yes	No

- *fractional sodium excretion = (urine sodium/plasma sodium) / (urine creatinine/plasma creatinine) x 100
- **fractional urea excretion = (urine urea /blood urea) / (urine creatinine/plasma creatinine) x 100
- **80-90% Of the acute renal failure seen by physicians will fall into the category of prerenal failure or ATN.**
- **Normal plasma osmolality = 278 – 305 mOsmol/Kg**
- **Normal urinary osmolality = 350 – 1000 mOsmol/Kg**

September 2009 exam: Which test is most useful when determining whether there is prerenal uraemia or acute tubular necrosis? Urinary sodium

Acute tubular necrosis (ATN)

Pathological mechanism

- **ATN** usually arises following an acute ischaemic or nephrotoxic event
  - in ischemic causes of ATN → the thick ascending limb of the Loop of Henle is injured
  - in nephrotoxic event → the proximal convoluted tubule is affected.
- the injured tubular cells fail to reabsorb sodium, tubular concentrating ability is lost, and urea clearance is low

Causes of ATN include

- Hypotension
- Hypertension: Accelerated hypertension can cause small vessel obstruction with proliferative endarteritis of intralobular arteries and fibrinoid necrosis of afferent arterioles and glomerular capillary tuft.
- Rhabdomyolysis
- Hepatic failure: Renal failure from ATN occurs in 25% of patients with severe hepatic damage.
- Eclampsia
- Drugs such as :
  - **aminoglycosides**,
    - Aminoglycoside undergoes glomerular filtration and then reabsorption **in the proximal tubule where tubular cell injury/death occurs**.
  - cephalosporins,
  - cisplatin,
  - amphotericin.
  - Heavy metal poisoning, carbon tetrachloride,
  - **Heroin addicts**. Associated furosemide is likely to increase the plasma concentration of toxic drugs and leads to (ATN).
  - **Corticosteroid therapy has not been associated with ATN.**

Phases: (ATN) is characterised by 3 phases:

1. **Initiation phase**, with acute decrease in GFR with sudden rise in serum creatinine ± oliguria
2. **Maintenance phase**, with a sustained marked reduction in GFR and rising Cr (1-2 weeks)
3. **Recovery phase**, in which tubular function is gradually restored and urine volume gradually rises, with concomitant decrease in Cr to pre-injury levels

Features

- Oliguria is common in the early stages of acute tubular necrosis (ATN)
- **ATN after aminoglycoside → impairment in the concentrating ability, and most patients are non-oliguric**

- acute renal failure expected to begin **more than five days after** the initiation of gentamicin
- Small amounts of 'tubular' proteinuria (<1 g/day) may be seen, but >3 g suggests a glomerular leak
- Urinalysis often reveals **brown granular casts**, which are tubular epithelial cells.

Precautions in management

- After inappropriate attempts to initiate a diuresis by infusion of normal saline without adequate monitoring of the patient's volume status, pulmonary oedema due to salt and water retention is not uncommon

- **Aminoglycoside nephrotoxicity correlates with➔ Frequency of aminoglycoside dosing**

- Multiple human clinical trials (including meta-analysis) studies report less nephrotoxicity and equal efficacy when aminoglycosides are given once daily (supratherapeutic doses) rather than in conventional divided doses.

Prognosis

- Oliguria during the initial stages of ATN is followed by polyuria, and even after a relatively minor insult, recovery may take up to 6 weeks
- Creatinine clearance would be expected to be normal **in only 40% of cases** one year after the initial insult.
- The mortality rate associated with ATN may be up to 50%, but this is largely dependent on the precipitating illness
- **the chance of recovery of renal function to the level where dialysis is not required ➔ 95 %**

Complication

- **Sepsis, particularly Gram-negative septicaemia, is the most frequent complication and cause of death in acute renal tubular necrosis** while awaiting spontaneous recovery of renal function

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Papillary necrosis

Causes

- chronic analgesia use (concomitant diuretic use may exacerbate renal hypotension)
- **sickle cell disease**
- TB
- acute pyelonephritis
- **diabetes mellitus**

Features

- fever, loin pain, haematuria
- IVU - papillary necrosis with renal scarring - 'cup & spill'

Consequences of renal papillary necrosis

- Ureteric obstruction may result if the papillae have sloughed off

Management

- Where there is obstruction, ➔ review by a urologist is advised as ureteric stent placement may be required
- If there is no obstruction ➔ withdrawal of the offending agent **+** adequate hydration

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Acute Pyelonephritis

Epidemiology

- The two peaks of incidence in adults occur in young sexually active women and in men > 50 years of age

Aetiology

- **Gram-negative bacilli such as Escherichia coli or Klebsiella** species are responsible in more than **95% of cases**
- Unusual organisms may be responsible if there has been a history of urethral instrumentation
- Staphylococcal urinary sepsis is usually indicative of haematological seeding of infection

Symptoms

- include fever, rigors, flank pain, dysuria, polyuria, haematuria, nausea and vomiting, headache and diarrhea. **The absence of fever rules out acute pyelonephritis**

Investigations

- In young women with a first infection, urine culture may be all that is required
- Otherwise, work-up includes urea and electrolytes measurement, a full blood count and blood cultures, and renal ultrasound in compromised patients

Treatment

- trimethoprim or ciprofloxacin
- Surgical opinion may be required for:
  - recurrent infections
  - evidence of vesicoureteric reflux on scanning

Acute vs. chronic renal failure

Best way to differentiate is renal ultrasound - most patients with CRF have bilateral small kidneys.

(normal range for both kidneys 10-12 cm)

Renal size

Renal size asymmetry in the presence of hypertension and renal impairment suggest renovascular disease.

Small kidneys suggest chronic renal failure

The usual range of kidney size measured longitudinally is between 9-12 cm.

Causes of Large kidneys → (chronic renal failure with normal/enlarged kidneys)

- amyloidosis
- Stage 1 diabetic nephropathy
- Hydronephrosis
- Rapidly progressive glomerulonephritis
- HIV-associated nephropathy
- Acromegaly
- Renal vein thrombosis
- Adult polycystic kidney disease
- Scleroderma

Causes of one small kidney

- Renal arterial disease
- or chronic renal scarring due to vesico-ureteric reflux (associated with recurrent UTI) → **Voiding cysto-urethrogram (VCUG) is the investigation of choice to demonstrate potential reflux disease**

Other features suggesting CRF rather than ARF

- hypocalcaemia (due to lack of vitamin D)
- **evidence of renal osteodystrophy on plain X-ray**
- skin pigmentation and peripheral neuropathy are the result of long-standing metabolic abnormality such as chronic renal failure

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Cholesterol embolization

Overview

- cholesterol emboli may break off causing renal disease
- seen more commonly in arteriopaths, abdominal aortic aneurysms

Features

- eosinophilia
- purpura
- renal failure
- livedo reticularis

May 2014 exam: H /O impaired RFT + purpuric rash on feet after coronary angiogram is performed for acute MI. What is the most likely diagnosis? Cholesterol embolization (Cholesterol embolisation is a well-documented complication of coronary angiography)

Chronic kidney disease (CKD)

Definition

- **Impaired renal function for >3 months** based on abnormal structure or function,
- **OR** GFR <60mL/min/1.73m2 for >3 months with or without evidence of kidney damage.

Common causes

- diabetic nephropathy (Type II > type I)
- chronic glomerulonephritis (commonly IgA nephropathy)
- chronic pyelonephritis
- hypertension
- adult polycystic kidney disease

Risk factors

- NICE recommend that screening for chronic kidney disease should be offered to patients with:
  - Diabetes
  - Hypertension
  - **Cardiovascular disease**
  - Structural renal tract pathology
  - Multisystem disease with potential renal involvement
  - Opportunistically detected haematuria or proteinuria
  - **family history** of stage 5 chronic kidney disease, or
  - Hereditary kidney disease.
- In the absence of other risk factors the guidelines recommend that age, gender and ethnicity should not be used as risk markers to test people for chronic kidney disease.
- Obesity alone should not be used as a risk factor (features of the metabolic syndrome should also be present).

eGFR and classification of CKD

CKD: only diagnose stages 1 & 2 if supporting evidence to accompany eGFR

eGFR variables => CAGE => **C**reatinine, **A**ge, **G**ender, **E**thnicity

Serum creatinine may not provide an accurate estimate of renal function due to differences in muscle. For this reason formulas were develop to help estimate the glomerular filtration rate (estimated GFR or eGFR). The most commonly used formula is the **Modification of Diet in Renal Disease (MDRD)** equation, which uses the following variables:

1. serum creatinine
2. age **(GFR ↓↓ with age)**
3. gender
4. ethnicity

Factors, which may affect the result

- **muscle mass (e.g. amputees**, body-builders)
  (↓muscle mass → overestimation.
  ↑ muscle mass → underestimation of the GFR.)
- eating red meat 12 hours prior to the sample being taken
- pregnancy

- **Which advice should be delivered to the patient before the test?** → avoid eat any meat in the 12 hours before

CKD may be classified according to GFR:

Classifying renal impairment in chronic kidney disease (CKD)[2] NICE		
This is based on presence of kidney damage and GFR, irrespective of diagnosis.		
Stage	**GFR (mL/min)**	**Notes**
1	>90	Normal or ↑GFR with other evidence of renal damage*
2	60–89	Slight ↓GFR with other evidence of renal damage*
3 A 3 B	45–59 30–44	Moderate ↓GFR with or without evidence of other renal damage*
4	15–29	Severe ↓GFR with or without evidence of renal damage*
5	<15	Established renal failure

*Proteinuria, haematuria, or evidence of abnormal anatomy or systemic disease.

- One reason to classify renal impairment is to motivate secondary prevention, eg to 'mandate' ACE-i or ARB if BP >140/85 especially if proteinuria is present or stage ≥3.
- Symptoms usually only occur once stage 4 is reached (GFR <30).
- End-stage renal failure (ESRF) is defined as GFR <15 mL/min/1.73m2 or need for renal replacement therapy (RRT—dialysis or transplant).
- **A falling GFR is an *independent risk* factor for cardiovascular disease → *this is the chief cause of death from renal failure.***
- *In CKD stages 1 and 2, risk from cardiovascular death is higher than the risk of reaching ESRF.*
- **Cystatin c represents a novel marker of estimating GFR**
- Estimating GFR is difficult and notoriously inaccurate. If in doubt, calculate using 24 hour creatinine clearance or radioisotope clearance.
- If GFR is greater than 90 ml/min/1.73 m^2 , Which test will indicate ↓ kidney function? ↑ creatinine more than 20%
- **If eGFR result is less than 60 ml/min/1.73 m^2 in a person not previously tested, what is the next step? → Repeat the test within 2 weeks.**
- (GFR) can be estimated from serum creatinine using the modification of diet in renal disease (MDRD). Cystatin C is less influenced by age, gender and muscle mass than serum creatinine, and it has been proposed as an alternative marker for (eGFR).
- estimates of GFR become less accurate as the true GFR increases (eGFR values of 60 ml/min/1.73 m^2 or more)
- The CKD-EPI equation is more accurate than the MDRD Study equation
  - Less bias at eGFR >60
  - performs better in people aged 75 years and over.
  - use of the MDRD Study equation may over-diagnose CKD.

Measuring kidney function (Nice guidelines 2014)

Creatinine-based estimate of GFR	Cystatin C-based estimate of GFR
• avoid meat in the 12 hours before the test • Avoid delaying the blood sample (used within 12 hours of venipuncture). • use the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) • Apply a correction factor to GFR values for African-Caribbean (multiply eGFR by 1.159). • less reliable in: ➢ acute kidney injury ➢ pregnancy ➢ oedematous states ➢ muscle wasting disorders ➢ malnourished ➢ amputation ➢ certain ethnic groups (eg: Asian family origin).	• have a higher specificity for significant disease outcomes than those based on serum creatinine. • When an improved assessment of risk is needed, the CKD-EPI cystatin C equation should be used to estimate GFR cystatin C • eGFR cystatin C → ↑ in hypothyroidism & ↓ in hyperthyroidism

When to use a cystatin C-based estimate of GFR for diagnosis of CKD (Nice 2014)

- If eGFR creatinine is 45–59 ml/min/1.73 m^2, sustained for at least 90 days + no proteinuria (albumin: creatinine ratio [ACR] less than 3 mg/mmol) or othere marker of CKD → **do eGFR cystatin C**, if it is more than 60 ml/min/1.73 m^2 → rule out CKD

GFR vs creatinine level:

- normal creatinine in an elderly patient is not indicative of normal renal function because serum creatinine does not increase due to age related muscle loss
  - **this may explain same creatinine levels with deferent GFR in some patients**
- (eGFR) is more accurate.

January 2010 exam: Which factor is most likely to invalidate the use of the Modification of Diet in Renal Disease (MDRD) equation to calculate a patients eGFR? Pregnancy

May 2012 exam: Which factor is most likely to explain unexpectedly low result of eGFR? Large muscle mass secondary to body building

Consequences of CKD

- **Hypocalcaemia: secondary to reduced levels of 1,25$(OH)_2$ vitamin D**
  - CKD → failure of the 1α-hydroxylation of vitamin D to form 1,25 dihydroxycholecalciferol (a step that usually occurs in renal tubular cells)

→↓↓**1,25(OH)$_2$ vitamin D** → ↓↓calcium absorption from the gut, which is often exacerbated by poor oral intake of calcium in patients with CKD.

- The kidneys are responsible for converting inactive vitamin D (25-hydroxycholecalciferol) to its active form 1,25-dihydroxycholecalciferol **via the enzyme 1-alpha-hydroxylase.**

- **Serum alkaline phosphatase is raised** when renal osteodystrophy develops, specifically the bone isoenzyme rather than the liver form.
- **Hyperphosphataemia PO(4)** ↑↑ :Reduced glomerular filtration rate results in reduced phosphate excretion.
  - **Dialysis is able to remove only about half of the phosphate that the healthy kidney would be able to do.**
    - The healthy adult kidney excretes **5400 mg per week** of phosphate.
    - the maximum amount of phosphate that can be removed by dialysis in a patient with anuric renal failure who is dialysis dependent is **2700 mg / week.**
  - calcium containing **phosphate binder** such as **calcium acetate is the most appropriate initial treatment**. In conjunction with dietary phosphate restriction this will help reduce the plasma phosphate.
    - calcium acetate should be taken with meals
    - the additional calcium in calcium acetate may be sufficient to increase the plasma calcium into the normal range.
  - Aluminium hydroxide and sevelamer are both phosphate binders - whilst they would help correct the elevated phosphate they would not have any impact on the low calcium.
- **Secondary hyperparathyroidism**: hyperphosphataemia and hypocalcaemia → ↑↑ parathyroid hormone (secondary hyperparathyroidism) → renal osteodystrophy.
  - Secondary hyperparathyroidism arises in established renal failure due lack of vitamin D production and reduced ability to absorb and retain calcium.
  - Causes of ↑↑ (PTH) in CKD include:
    1. hypocalcaemia
    2. impaired 1,25-dihydroxyvitamin D production by the diseased kidneys
    3. hyperphosphataemia
  - **In most patients on dialysis**, the primary bone disease is **osteitis fibrosa cystica**, a disease of **increased bone resorption caused by elevated PTH levels related to low levels of vitamin D and hyperphosphataemia.**
  - Slightly elevated parathyroid hormone level is actually desirable in the management of renal bone disease. Suppression is not generally necessary until levels exceed 300 ng/L.
- **Reduced tubular secretion of urate**
- **Hyperkalaemia** is a classical finding due to metabolic acidosis and decreased glomerular filtration rate.

- **Metabolic acidosis** is a result of bicarbonate wasting and reduced ammonia and acid excretion.
- **Hypertension** is seen due to sodium and water overload and direct renal effects secondary to the underlying renal disease.
- **Anaemia:** decreased erythropoietin production, low grade haemolysis, inadequate intake
- **Hypertriglyceridaemia:** decreased plasma lipoprotein lipase activity
- **Pericarditis and cardiomyopathy**: **uraemia leads to exudation of fibrin onto the epicardial and pericardial surfaces**.
- **Glucose intolerance**: tissue insulin resistance.
- **Increased skin pigmentation**
- **Extra-skeletal calcification:** Prolonged treatment with vitamin D (hence hypercalcaemia and hyperphosphataemia) increases

chronic renal failure and hypocalcaemia with a raised parathyroid hormone (PTH) → secondary hyperparathyroidism.

Chronic renal failure leads to hyperphosphataemia, which triggers release of parathyroid hormone.

Studies such as UKPDS reveal that:

- improving **glycaemic control** would reduce microvascular complications but this has no significant impact upon cardiovascular morbidity and mortality.
- lowering **blood pressure** significantly reduced morbidity from both microvascular and macrovascular disease.

Chronic kidney disease: hypertension

- Hypertension is both a cause and consequence of chronic kidney disease.
- Pathogenesis of hypertension caused by CKD is multifactorial. **It is caused by:**
  - Increased intravascular volume (due to reduced glomerular filtration)
  - Excessive activity of the renin angiotensin system
  - Increased activity of the sympathetic nervous system
  - Endothelial dysfunction, and
  - Other neural and humoral factors.
- The majority of patients with (CKD) will require more than two drugs to treat hypertension.
- **ACE inhibitors** are first line and are particularly helpful in proteinuric renal disease (e.g. diabetic nephropathy).

- As these drugs tend to reduce filtration pressure a small fall in glomerular filtration pressure (GFR) and rise in creatinine can be expected.
- NICE suggest that **a decrease in eGFR of up to 25% or a rise in creatinine of up to 30% is acceptable**, although any rise should prompt careful monitoring and exclusion of other causes (e.g. NSAIDs). **A rise greater than this may indicate underlying renovascular disease.**

- **Furosemide is useful as a anti-hypertensive in patients with CKD, particularly when the GFR falls to below 45 ml/min*.(***the NKF K/DOQI guidelines suggest a lower cut-off of less than 30 ml/min**)**
  - It has the added benefit of lowering serum potassium.
  - High doses are usually required.
  - If the patient becomes at risk of dehydration (e.g. Gastroenteritis) then consideration should be given to temporarily stopping the drug

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Chronic kidney disease: proteinuria

- **Microalbuminuria is defined as a urine albumin excretion of between 30-300 mg per 24 hours.**
- A concentration above 300 mg/24 hours signifies albuminuria and a concentration above 3.5 g/24 hours signifies overt proteinuria.
- Proteinuria is an important marker of chronic kidney disease, especially for diabetic nephropathy.
- NICE recommend using the albumin: creatinine ratio (ACR) in preference to the protein: creatinine ratio (PCR) when identifying patients with proteinuria as it has greater sensitivity.
- For quantification and monitoring of proteinuria, PCR can be used as an alternative, although ACR is recommended in diabetics.
- Urine reagent strips are not recommended unless they express the result as an ACR
- In the presence of mild to moderate hypertension, proteinuria indicates either underlying renal disease or renovascular disease.
- NICE guidelines recommend BP target range:
  - CKD patient who have proteinuria equivalent to ACR ≥70 mg/mmol → **120-129/<80** mmHg. The same target range should be used in patients with diabetes.
  - Non-diabetic patients with CKD and an ACR <70 mg/mmol → **120-139/<90** mmHg

Approximate equivalent values

Conversion factors		
ACR mg/mmol	PCR mg/mmol	Protein excretion g/24h
30	50	0.5
70	100	1

- Average individuals pass around 10mmol urinary creatinine each day. Therefore:
  - U PCR 50 = 500mg protein/day
  - U PCR 100 = 1000mg protein/day

- a 24 hour urinary protein collection of 1g is therefore approximately equivalent to urinary PCR of 100 mg/mmol.

Collecting an ACR sample

- by collecting a 'spot' sample it avoids the need to collect urine over a 24 hour period in order to detect or quantify proteinuria
- should be a first-pass morning urine specimen
- if the initial ACR is greater than 30 mg/mmol and less than 70 mg/mmol, confirm by a subsequent early morning sample. If the initial ACR is greater than 70 mg/mmol a repeat sample need not be tested

Interpreting the ACR results

- in **non-diabetics** an ACR greater than 30 mg/mmol is considered clinically significant proteinuria
- in **diabetics** microalbuminuria (ACR greater than 2.5 mg/mmol in men and ACR greater than 3.5 mg/mmol in women) is considered clinically significant.
- An elevated albumin-to-creatinine ratio should be confirmed with at least two additional tests performed over the subsequent 3 to 6 months, with confirmation of the diagnosis requiring at least 2 of 3 positive samples.

Management

- Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockres (ARBs)
  - ACEi and ARBs **reduce intra-glomerular pressure** by inhibiting angiotensin II–mediated **efferent** arteriolar vasoconstriction.
  - Also have a proteinuria-reducing effect, which is independent of their antihypertensive effect.
  - reduce the breakdown of bradykinin (an efferent arteriolar vasodilator);
  - restore the size and charge selectivity to the glomerular cell wall (GCW);
  - reduce the production of cytokines, such as transforming growth factor–beta (TGF-beta), that promote glomerulosclerosis and fibrosis.
- **Spironolactone**
  - **The most likely therapy to reduce proteinuria after ACEi**
    - **Even if serum K is 5.2 mmol**
  - Addition of aldosterone antagonist therapy to ACE inhibition further impacts to reduce proteinuria in diabetic renal disease.
  - It may however worsen hyperkalaemia, and for this reason close monitoring of urea and electrolytes is required after commencing therapy.
  - A small reduction in glomerular filtration rate (GFR) is also seen during the first 12 weeks after commencement of therapy.

Diabetic nephropathy (See Endocrinology system)

Chronic kidney disease: anaemia

- normochromic normocytic anaemia
- becomes apparent when the GFR is less than 35 ml/min (other causes of anaemia should be considered if the GFR is > 60 ml/min).
- Anaemia in CKD predisposes to the development of left ventricular hypertrophy - associated with a three fold increase in mortality in renal patients

Causes of anaemia in renal failure

- reduced erythropoietin levels - the most significant factor
- reduced erythropoiesis due to toxic effects of uraemia on bone marrow
- reduced absorption of iron
- anorexia/nausea due to uraemia
- reduced red cell survival (especially in haemodialysis)
- blood loss due to capillary fragility and poor platelet function
- stress ulceration leading to chronic blood loss
- The tubing of dialysis equipment causes continued low level blood loss

NICE guidelines 2015 : Diagnostic tests to determine iron status and predict response to iron therapy in anaemia with CKD

- Do it **every 3 months** (1–3 months for people receiving haemodialysis).
- Use percentage of hypochromic red blood cells (% **HRC**; more than 6%), but only if processing of blood sample is possible within 6 hours.
- If using % **HRC** is not possible, use reticulocyte Hb content (**CHr**; less than 29 pg)
- If these tests are not available or the person has thalassaemia or thalassaemia trait, use a **combination** of transferrin saturation (less than 20%) and serum ferritin measurement (less than 100 micrograms/litre). **[new 2015]**
- **Do not request transferrin saturation or serum ferritin measurement alone** to assess iron deficiency status in people with anaemia of CKD. **[new 2015]**

Management

- It is important to correct anaemia, as it leads to ventricular hypertrophy, which increases the cardiovascular morbidity and mortality.
- NICE guidelines suggest a target haemoglobin of 10 - 12 g/dl
- determination and optimisation of iron status should be carried out prior to the administration of erythropoiesis-stimulating agents (ESA). Many patients, especially those on haemodialysis, will require IV iron
- **If there is iron depletion, I.V iron transfusion will be the most appropriate next step**
- Once iron stores are restored and ferritin is in the normal range, if the patient is still anaemic then erythropoietin would be the next appropriate option
- It is imperative that renal patients avoid repeated blood transfusion, unless in extremis, so that future renal transplantation will not be precluded by allo-sensitisation.

- **If patient is exhibiting symptoms and signs of severe anaemia, i.e. angina, the treatment of choice is an urgent blood transfusion.** If the patient did not have **symptoms** the correct answer would be subcutaneous erythropoietin and intravenous iron.
- ESAs such as erythropoietin and darbepoetin should be used in those 'who are likely to benefit in terms of quality of life and physical function'
- When receiving erythropoetin therapy, it is important to note that over-correction of a low haemoglobin can have harmful effects such as cardiovascular problems and thrombophlebitis.

Targets for treatment

- **Hb** : maintain Hb range between 100 and 120 g/litre (**10 - 12 g/dl**) (NICE 2015)
- **Ferritin**:
  - in pre-dialysis and peritoneal dialysis patients **>**100 µg/L,
  - in haemodialysis patients >200 µg/L
    - ferritin level maintained at **200-500** µg/L
    - NICE 2015 → should not rise above 800 micrograms/litre (review the dose of iron when serum ferritin levels reach 500 micrograms/litre)
- **Transferrin saturation >20%**
- **haematocrit <33%.**
- **percentage hypochromic red cells <6%.**

Chronic kidney disease: bone disease

Renal osteodystrophy (ROD)

- consists of a mixture of osteomalacia, hyperparathyroid bone disease (osteitis fibrosa), osteoporosis and osteosclerosis
- **Pathogenesis of osteomalacia in renal osteodystrophy**
  - **Diminished activity of renal 1-α-hydroxylase** → failure of converting cholecalciferol to its active metabolite 1,25-dihydroxy-cholecalciferol → ↓ intestinal absorption of calcium → hypocalcaemia, hyperphosphataemia and stimulation of the parathyroid glands
- The gold standard for the diagnosis and classification of ROD is **bone biopsy**
  - The preferred site of biopsy is 2 cm posterior and 2 cm inferior to the anterior iliac crest.

Metastatic calcification in CRF

- mainly due to calcium phosphate deposition,
- **Increased prevalence with time on haemodialysis**
- CRF managed with dialysis is the commonest cause of secondary **oxalosis** (acute arthritis of small joints with digital calcific deposits).

Management

- **Aims**
  - reduce hyperphosphataemia
  - reduce PTH level

- **medications**
  - phosphate binders
  - vitamin D
- **Phosphate binders**
  - aluminium containing binders are no longer used
  - calcium based binders much more common
  - problem is vascular calcification
  - non-calcium based agents currently being developed

Calciphylaxis

- Calciphylaxis is a rare complication of end-stage renal failure. The underlying mechanism is not clear
- Results in deposition of calcium within arterioles causing microvascular occlusion and necrosis of the supplied tissue.
- most commonly affects the skin and presents with painful necrotic skin lesions.
- The risk of developing calciphylaxis is linked with hypercalcaemia, hyperphophataemia and hyperparathyroidism.
- Warfarin is widely reported as causing/exacerbating calciphylaxis in high risk patients, however the underlying mechanism is not known.
- Treatment focuses on:
  - reducing calcium and phosphate levels
  - controlling hyperparathyroidism
  - avoiding contributing drugs such as warfarin and calcium containing compounds.

CKD - Referral criteria

(Nice 2014) : People with CKD in the following groups should be referred for specialist assessment:

- GFR less than 30 ml/min/1.73 m^2 (GFR category G4 or G5), with or without diabetes
- ACR 70 mg/mmol or more, unless known to be caused by diabetes and already appropriately treated
- ACR 30 mg/mmol or more (ACR category A3), together with haematuria
- sustained decrease in GFR of 25% or more, and a change in GFR category or sustained decrease in GFR of 15 ml/min/1.73 m^2 or more within 12 months
- hypertension that remains poorly controlled despite the use of at least 4 antihypertensive drugs at therapeutic doses.
- known or suspected rare or genetic causes of CKD
- suspected renal artery stenosis.

CKD –management (Nice 2014)

- **BP control:**
  - aim for
    - Patient with CKD < 140/90
    - Patient with CKD + DM or ACR ≥ 70 mg/mmol < 130/80
  - Do not offer a combination of renin–angiotensin system antagonists to people with CKD.
  - measure serum potassium & GFR before starting renin–angiotensin system antagonists. Repeat these measurements between 1 and 2 weeks after starting renin–angiotensin system antagonists and after each dose increase.
  - If pretreatment serum potassium **>** 5.0 mmol/litre → Do not offer renin–angiotensin system antagonist
  - Stop renin–angiotensin system antagonists if the serum potassium ≥ 6.0 mmol/litre
  - If there is ↓eGFR or ↑creatinine after starting or increasing the dose of renin–angiotensin system antagonists, but it is less than 25% (eGFR) or 30% (serum creatinine) of baseline:
    - repeat the test in 1–2 weeks.
    - Do not modify the renin–angiotensin system antagonist dose if the change is less than 25% (eGFR) or 30% (serum creatinine) of baseline
    - If the eGFR change is 25% or more, or the change in serum creatinine is 30% or more:
      i. Check other cause for the deterioration in renal function such as volume depletion or concurrent medication (for example, NSAIDs)
      ii. if no other cause for the deterioration in renal function is found, stop the renin–angiotensin system antagonist or reduce the dose
      iii. add an alternative antihypertensive if required.

- Consider apixaban in preference to warfarin in people with a confirmed eGFR of 30–50 ml/min/1.73 m^2 and non-valvular atrial fibrillation who have 1 or more of the following risk factors:
  - prior stroke or transient ischaemic attack
  - age 75 years or older
  - hypertension
  - diabetes mellitus
  - symptomatic heart failure.
- **Bone metabolism and osteoporosis**
  - Measure serum calcium, phosphate and PTH concentrations in people with a GFR of less than 30 ml/min/1.73 m^2
    - vitamin D deficiency → colecalciferol or ergocalciferol

        - If vitamin D deficiency has been corrected and symptoms of CKD–mineral and bone disorders persist, offer alfacalcidol (1-alpha-hydroxycholecalciferol) or calcitriol (1-25-dihydroxycholecalciferol)
    - raised serum phosphate → **Sevalamer**
        - Sevalamer is a **non-aluminium containing phosphate binder**
            - Aluminium hydroxide was previously the drug of choice, but due to concern about accumulation of aluminium, leading to possible aluminium related dementia, it has now fallen out of favour.
- **management of metabolic acidosis**
    - Consider oral sodium bicarbonate supplementation for people with both:
        - a GFR less than 30 ml/min/1.73 m2 (GFR category G4 or G5) **and**
        - a serum bicarbonate concentration of less than 20 mmol/litre.

Prescribing in patients with renal failure

Questions regarding which drugs to avoid in renal failure are common

Drugs to avoid in renal failure

- antibiotics: tetracycline, nitrofurantoin
- **NSAIDs**
    - NSAIDs reduce glomerular perfusion by inhibiting production of prostaglandins which dilate the afferent arteriole of the glomerulus. The reduction in blood supply to the kidney results in impairment of kidney function.
    - **Thus, the most likely cause of renal decline is prostaglandin related.**
    - NSAIDs can also cause an interstitial nephritis but this is often accompanied by a nephrotic syndrome-like picture.
- lithium
- metformin

Drugs likely to accumulate in chronic kidney disease - need dose adjustment

- most antibiotics including penicillins, cephalosporins, vancomycin, gentamicin, streptomycin
- digoxin, atenolol
- methotrexate
- sulphonylureas
- furosemide
- opioids
    - **Alfentanil, buprenorphine and fentanyl are the preferred opioids in patients with chronic kidney disease.**

Drugs relatively safe - can sometimes use normal dose depending on the degree of chronic kidney disease

- antibiotics: erythromycin, rifampicin
- diazepam
- warfarin
- **Omeprazole is principally dependent upon hepatic clearance and safe even with marked renal impairment.**

Erythropoietin

- Erythropoietin is a haematopoietic growth factor that stimulates the production of erythrocytes.

Sources of Erythropoietin

- **interstitial fibroblasts in the kidney** (predominant during adulthood)
- perisinusoidal cells in the liver (predominates in the fetal period)
- Exogenous erythropoietin, or recombinant human erythropoietin (rhEPO), is produced by recombinant DNA technology .

The main uses of erythropoietin are

- to treat the anaemia associated with chronic kidney disease
  - **The best option to relieve fatigue in patient with end stage renal failure is Treatment of anaemia with erythropoietin**
  - **Improvement in haemoglobin level results in the increased well-being and better appetite.**
- Anaemia associated with cytotoxic therapy.
- Prevention of anaemia in premature babies with low birth weight.

Side effects of erythropoietin

- accelerated hypertension → headache, encephalopathy & seizures (BP ↑↑ in 25%)
- ischaemic stroke
- bone aches
- flu-like symptoms
- skin rashes, urticaria
- pure red cell aplasia (PRCA)
- raised PCV thrombocythaemia → ↑ risk of thrombosis (e.g. Fistula)
- iron deficiency 2nd to increased erythropoiesis
- anaphylaxis
- Hyperkalaemia in uraemic patients
- **↑mortality of patients with malignancy (e.g. renal cell carcinoma)**

Causes of response failure to erythropoietin therapy:

- iron deficiency
- inadequate dose
- concurrent infection/inflammation
- hyperparathyroid bone disease
- **aluminium toxicity** : if suspected, perform a desferrioxamine test
- folate deficiency
- marrow fibrosis
- development of antibodies against the treatment
- **ESA-induced PRCA**
- testosterone deficiency in males
- poor compliance

ESA induced pure red cell aplasia (PRCA)

- due to antibodies against erythropoietin
- Indicated by a low reticulocyte count, together with anaemia and the presence of neutralising antibodies.
- Confirmed by presence of anti-erythropoietin antibodies together with a lack of pro erythroid progenitor cells in the bone marrow

- the risk is greatly reduced with **darbepoetin**

Treatment protocol

- Ideally, before starting EPO in renal patients you should get their haematinics (iron, B12, folate) to ensure they are replete of all. If any are found to be low they should be replaced.
- Parameters commonly measured to assess iron status are: serum ferritin and transferrin saturation.
  - Both are indirect measures of iron and frequently do not permit an assessment of the adequacy of iron supply to the erythron.
  - direct measures by flow cytometry, cell volume and hemoglobin concentration can be measured in individual red blood cells and reticulocytes, using two parameters (particularly useful in identifying iron-deficient erythropoiesis).
    - **The percentage of hypochromic erythrocytes** (defined as red blood cells with a hemoglobin concentration of less than 28 g/dl)
    - the content of hemoglobin in reticulocytes (CHr)
- If there is Iron deficiency (NICE 2015)
  - For patient on haemodialysis or ESA → I.V iron therapy.
  - For patient not on haemodialysis → trial of oral iron
  - **If they are intolerant of oral iron or target Hb levels are not reached within 3 months → intravenous iron therapy.** (part 2 Exam July 2002)
  - offer maintenance iron to people with anaemia of CKD who are receiving ESAs
  - haemodialysis patients will need the equivalent of 50–60 mg intravenous iron per week (1 mg/kg/week). [NICE 2015]
- **If Ferritin is below the recommended level of 200 for patients receiving erythropoietin treatment → iron supplementation is recommended.**
  - GI absorption of iron is suboptimal in patients with renal failure, and IV replacement is therefore the preferred intervention.
- Erythropoietin is given subcutaneously at a dose of 25-50 U/kg three times per week
- The blood pressure, haemoglobin and reticulocyte count should be monitored every 2 weeks
- **erythropoiesis-stimulating agent (ESAs): dose and frequency**
  - adjusted to keep the rate of Hb increase between 10 and 20 g/litre/month.
- **Adjusting ESA treatment**
  - if ACEi & ARB are used, an increase in ESA therapy should be considered.

ferritin should be >200g/l in patients treated with EPO.

Significance of erythropoietin levels (EPO test)

- Low serum erythropoietin levels suggest → polycythaemia vera
- raised serum erythropoietin level suggests→
  - hypoxic cause
  - autonomous production of erythropoietin (as in renal carcinoma).
  - erythropoietin abuse (Erythropoietin has been misused as a performance-enhancing drug by some athletes)

May 2010 exam: H/O CKD patient started on erythropoietin. What is the main benefit of this treatment? Improved exercise tolerance

Erythropoietin can be detected in urine for few weeks after the latest dose

Renal replacement therapy

CKD on haemodialysis - most likely cause of death is IHD

- Patients usually begin dialysis when their glomerular filtration rate (GFR) reaches 10 ml/minute or 15 mL/minute if they are diabetic.

Indications for dialysis

- Refractory pulmonary oedema
- Persistent hyperkalaemia (K+ >7mmol/L)
- Severe metabolic acidosis (pH<7.2 or base excess <10)
- Uraemic complications such as
  - encephalopathy or
  - Uraemic pericarditis (pericardial rub)
  - **Uraemic peripheral neuropathy**
- Drug overdose—BLAST: Barbituates, Lithium, Alcohol (and ethylene glycol), Salicylates, Theophyline,

Arterio-venous fistula is the first choice of vascular access for dialysis.

Haemodialysis (HD)

Assessment of haemodialysis adequacy:

The adequacy of haemodialysis session is best measured by :

- 'Clearance' is used to indicate dialysis adequacy, and most commonly the clearance of urea is used.
  - Clearance is the ratio of removal rate to blood concentration.
  - Removal rate can be measured by sampling blood on either side of the dialyser and multiplying the difference by the inflow rate.
  - Clearance is the removal rate divided by the inflow concentration.
  - However, this only provides a measure of **dialysis at one point in time**.
- The adequacy of an **entire haemodialysis session** is best measured by the fall in solute concentration from before dialysis to after.
  - This is calculated using complex equations and is expressed as Kt/V.
  - The current recommendation for adequate dialysis for three treatments per week are a Kt/V of 1.2.
- (the 'urea reduction ratio').A more crude assessment of the adequacy of dialysis obtained by noting the magnitude of the decrease in blood urea concentration

- It is standard practice in the UK to take biochemical and haematological measurements before and after haemodialysis sessions at regular intervals (monthly in hospital HD patients and at least 3 monthly in home HD patients). Adequate HD is indicated by:
  - pre-dialysis serum bicarbonate levels of 18-24 mmol/L,
  - potassium 4.0-6.0 mmol/L,
  - phosphate 1.1-1.7 mmol/L,
  - calcium and albumin within normal range.

Pre and post- dialysis values:

- . A high pre-dialysis or inter-dialysis blood pressure may be related to:
  - excessive sodium and water ingestion during the inter-dialysis period
  - or a high dialysate sodium level,
- A high post-dialysis blood pressure may reflect inadequate achievement of dry weight.
  - Volume and blood pressure are linked and it is therefore important to optimise ultrafiltration and dry weight to control blood pressure.
  - A patient's dry weight is their normal weight when they are not fluid overloaded, also called euvolemia
  - The rate of **ultrafiltration** depends upon the porosity of the membrane and the hydrostatic pressure of the blood, which depends upon blood flow. This is very effective in removal of fluid and middle-sized molecules, which are thought to cause uremia.
- Weight gain between dialyses of more than 4.8% is associated with increased mortality.
- **The combination of high pre- and post-dialysis blood pressure, and high pre-dialysis potassium, indicate that the patient is receiving inadequate dialysis.**
  - Both procedural issues (insufficient blood flow rate, **dialysis time and frequency** and needle size) and access issues should be addressed.
  - If these fail to improve the situation a different dialysis modality should be considered, such as more frequent or sustained haemodialysis.
- It is recommended that pre-dialysis haemoglobin concentration should be maintained between 100-120 g/L.
  - If his haemoglobin below the recommended level for a dialysis patient, you need to measure haematinics initially prior rather than jumping in with EPO treatment.
  - Many haemodialysis patients are iron deplete, and in these cases intravenous iron is indicated rather than EPO in the first instance.

Adverse effects of dialysis

- Modem techniques of dialysis preclude chances of vitamin D or calcium deficiency, fluid and electrolyte imbalance or risk of viral hepatitis
- **protein-calorie malnutrition is seen in up to 50% of patients**

- Dietary restriction of foods with high phosphate content (milk, eggs and cheese), decreased protein intake,anorexia, nausea and vomiting, may all contribute to this condition

Complications of rapid haemodialysis

- **Disequilibrium syndrome:**
  - Caused by cerebral oedema, resulting from the rapid shifts of uraemic toxins associated with too-rapid haemodialysis in a severely uraemic patient
  - characterized by weakness, dizziness, headache, and in severe cases, mental status changes.
  - The diagnosis is one of exclusion;
  - a prime characteristic of this syndrome is that it is nonfocal.

Long-term haemodialysis

- **associated with carpal tunnel syndrome this is due to beta-2 microglobulin deposition**
- **Cardio-vascular disease is the commonest cause of death (50%) in dialysis patients**
- **Carnitine deficiency**
  - Patients on chronic hemodialysis may have carnitine deficiency.
  - Carnitine is essential for the transport of long-chain fatty acids from the cytosol into the mitochondria.
  - **chronic hemodialysis → carnitine deficiency → Impaired mitochondrial transport of long-chain fatty acids**
  - Cardiomyocytes and skeletal muscle cells extensively use fatty acids as a fuel.
  - Carnitine deficiency leads to:
    - accumulation of long-chain fatty acids in the cytosol of cardiomyocytes (resulting in cardiac fatty change and **cardiomegaly**)
    - accumulation of long-chain fatty acids in the cytosol of skeletal muscle cells (resulting in **muscle cramps**).
  - **Treatment** is via L-carnitine administration.

Indications of Catheter removal :

- ***Staphylococcus aureus* bloodstream infection**
  - ***Methicillin-resistant Staphylococcus aureus (MRSA) infection***
    - **vancomycin is the drug of choice**
- non-staphylococcus aureus catheter-related bloodstream infection in the following circumstances:
  - Severe sepsis
  - Haemodynamic instability
  - Endocarditis
  - Evidence of metastatic infection, or
  - Persistence of bacteraemia after 48-72 hours of effective antibiotics.

Dialysis amyloidosis

Aetio-pathogenesis

- Occurs due to the failure of clearance of **B2-microglobulin**
  - This protein, the light chain of class-1 HLA antigens, is usually freely filtered at the glomerulus but is not cleared by cellulose-based dialysis membranes
- There is resulting amyloid deposition within the synovium

Clinical features: Amyloid deposition within the synovium results in:

- **clinical syndrome of median nerve compression**
- **pain and stiffness in multiple joints**

Treatment & Prognosis

- The syndrome resolves slowly after renal transplantation,
- some benefit is seen in switching patients to dialysis with a biosynthetic dialysis membrane

Complications:

- gastrointestinal haemorrhage caused by amyloid deposition around submucosal blood vessels

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Peritoneal dialysis

- Peritoneal dialysis (PD) is a form of renal replacement therapy. It is sometimes used as a stop-gap to haemodialysis or for younger patients who do not want to have to visit hospital three times a week.
- The majority of patients do Continuous Ambulatory Peritoneal Dialysis (CAPD), which involves four 2-litre exchanges/day.

Complications:

- Peritoneal dialysis-associated peritonitis
- sclerosing peritonitis
- Adynamic bone disease (ABD)

Peritoneal dialysis-associated peritonitis

- **Causes:**
  - **The most common cause → coagulase-negative staphylococci** such as ***Staphylococcus epidermidis* (40-50% of cases).**
  - **another common cause →** *Staphylococcus aureus*
- **Diagnosis**
  - is made by peritoneal fluid cell count (**neutrophils above 100/ml**).**(White cell count > 100/mm^3 in PD fluid sample)**
  - PD fluid neutrophil percentage of greater than 50% is in keeping with PD peritonitis.
- **Treatment**
  - **intraperitoneal antibiotics** (vancomycin) And oral quinolone (Before culture results are received).
    - **the initial treatment of choice would be intraperitoneal antibiotics.**
    - initial antibiotic regimes should cover Gram positive (including MRSA) and Gram negative organisms.
      - **Give intra-peritoneal vancomycin and gentamicin**
  - **Intravenous antibiotics** would be preferable if the clinical condition **worsened despite intraperitoneal antibiotics,**
  - **Recurrent** Staph, epidermidis peritonitis may necessitate **removal and replacement of the peritoneal dialysis catheter** due to chronic colonisation

Adynamic bone disease (ABD) → (low bone turnover)

- **Definition**: (ABD) is a variety of renal osteodystrophy characterized by reduced osteblasts and osteoclasts, no accumulation of osteoid and markedly low bone turnover (↓bone formation and resorption).
- **Distinguish ABD from the second low-turnover form, i.e. osteomalacia:**
  - **In ABD**: Both the rate of collagen synthesis by osteoblasts and the subsequent mineralization of bone collagen are subnormal. there are few or no osteoblasts
  - **In osteomalacia**: mineralization defect exceeds the defects in bone formation, resulting in a relative osteoid excess.
  - Bone alkaline phosphatase (BAP) is the single most useful biochemical parameter for the assessment of bone formation.
    - ↑↑ BAP exclude ABD
    - elevations of BAP along with total AP may be seen in severe osteomalacia.
- **Risk factors & Causes**: overtreatment of secondary hyperparathyroidism associated with CKD

  (ABD is, at least in part, often iatrogenic)
  - commonly CKD patients on dialysis, either peritoneal or hemodialysis
    - ↑ in CAPD compared to haemodialysis
    - **Especially prevalent in diabetic patients on peritoneal dialysis**
    - ↑ in Increasing age of dialysis patients
  - Aluminum overload
    - Serum aluminium levels do not correctly reflect body aluminium stores and do not correlate well with signs of aluminium toxicity.
    - desferrioxamine (DFO) test increases the diagnostic accuracy
  - High calcium load
  - Low PTH levels
  - Vitamin D over-treatment (eg : alfacalcidol)
  - High prevalence of diabetes mellitus

- **Pathophysiology:**
  - basically in CKD:
    - PTH serum levels are higher than normal
    - bone tissue is resistant to PTH
  - PTH serum levels decrease beyond relatively low levels, which would be considered normal in the general population.
  - So that a relative reduction of PTH → low turnover state.
- **Complications:** (pain, fracture,↑ Ca+)
  - bone pain
  - increased incidence of hip fracture
  - hypercalcaemia as the bone loses its capacity to buffer serum calcium

- **Treatment:** currently follows two principles:
  1. reduce calcium and vitamin D load
     - Stop calcium-containing phosphate binders and replace with non-calcium-, non-aluminium-containing phosphate binders

- Assess oral dietary calcium intake and reduce to <2000 mg/day
- Reduce or stop active vitamin D compounds
- Lower dialysate calcium to 1.25 mmol/L or below
- Avoid bisphosphonates, strontium and fluoride administration

2. restore PTH activity

- **Follow- up**
  - Changes of bone markers, such as bone-specific alkaline phosphatase, over time, may be suitable indicators for the assessment of therapeutic effects.

Other complications of peritoneal dialysis

- **Worsening of diabetic control**:
  - dialysis fluid contains a high glucose
  - **patients with diabetes may require significantly more diabetes treatment to reduce their blood glucose once dialysis is commenced**
- **Worsening of abdominal hernias**: due to the large fluid volume expansion and should be surgically repaired
- **Stomas adhesions:**
  - **Stomas may be associated with significant adhesions and changes within the abdominal cavity making catheter placement impossible**

Contraindication of continuous ambulatory peritoneal dialysis (CAPD):

- Colostomy.
  - increase the risk of peritonitis
- Recent or prospective abdominal surgery
  - **Complex abdominal surgery** and resultant extensive adhesion damage the peritoneal membrane (peritoneal fibrosis) and lead to compartments within the peritoneum.
  - Simple abdominal surgery, however, does not preclude peritoneal dialysis; examples include cholecystectomy, appendectomy or caesarian section.

May 2013 exam: A patient on Ambulatory Peritoneal Dialysis (CAPD). Feels generally unwell with abdominal pain and fever. Which organism is most likely to be responsible for this presentation?
Staphylococcus epidermidis

Renal transplant

Cytomegalovirus is the most common and important viral infection in solid organ transplant recipients

Hyperacute graft rejection is due to pre-existent antibodies to HLA antigens and is therefore IgG mediated

Renal transplant HLA matching ➔ DR is the most important

Some basic points on the HLA system

- class 1 antigens include A, B and C. Class 2 antigens include DP,DQ and DR
- when HLA matching for a renal transplant the relative importance of the HLA antigens are as follows **DR** > B > A
- **Which HLA subtypes is usually implicated with respect to matching for avoiding hyperacute rejection?**
  - **HLA-C**
    - Anti-HLA-C IgG antibodies are usually implicated in hyperacute rejection;
    - specifically, HLA-CW5 subtype antibodies have been implicated most in hyperacute rejection of renal transplant.

Types of Transplants :

- **Autografts**:
  - same individual acts as both donor and recipient.
- **Isografts**:
  - donor and recipient are genetically identical (twins).
- **Allografts**:
  - donor and recipient are genetically dissimilar but belong to the same species (the commonest).
- **Xenografts**:
  - donor and recipient belong to different species (between animal and human).
- **Orthotopic transplants**:
  - the transplanted part is placed in its normal anatomical location.
- **Heterotopic transplants**:
  - the transplanted part is placed in different anatomical location.

Graft survival	1 year	10 years
Cadaveric transplants	90%	60%
Living-donor transplants	95%	70%

Post-operative problems

- ATN of graft
- vascular thrombosis
- urine leakage
- UTI

Hyper acute rejection (minutes to hours)

- due to pre-existent antibodies against donor HLA type 1 antigens (a type II hypersensitivity reaction) and is therefore IgG mediated
- rarely seen due to HLA matching
- antigen-antibody complexes → activate the complement system → causing massive thrombosis in the capillaries → avascularization of the graft.
- the kidney is most susceptible to hyperacute rejection; the liver is relatively resistant, possibly because of its dual blood supply, but more likely because of incompletely understood immunologic properties.

Reasons for deterioration in renal function soon after a renal transplant:

- Hyperacute rejection (which usually occurs in hours)

- Acute tubular necrosis, and
- Surgical complications (renal arterial or venous thrombosis and ureteric stenosis).

In the presence of a dropping urine output and rising creatinine, an urgent ultrasound scan should be obtained to exclude any mechanical obstruction of the renal tract before considering other options.

Acute graft failure (< 6 months)

- Approximately 25% of transplant patients will have at least one episode of rejection mostly between days 7 and 21, and less commonly up to three months post-operation.
- usually due to mismatched HLA. Cell-mediated (cytotoxic T cells)
- other causes include cytomegalovirus infection
  - Although CMV infection **would not cause a sudden deterioration in renal function**
- Doppler ultrasound studies may show a sharp deterioration in graft perfusion, and kidney biopsy will show invading lymphocytes penetrating the tubular basement membrane, causing tubulitis.
- It is often clinically silent, with only a sharp rise in serum creatinine pointing towards the diagnosis.
- may be reversible with steroids and immunosuppressants

Chronic graft failure (> 6 months)

- both antibody and cell mediated mechanisms cause fibrosis to the transplanted kidney (chronic allograft nephropathy)
- caused by recurrence of original renal disease (MCGN > IgA > FSGS)
  - Recurrence of renal pathologies post-renal transplantation:
    1. Membranoproliferative GN: 40-90% recurrence rate, type 2 much greater than type 1).
    2. FSGS: 40%.
    3. Membranous GN: 30%.

Differentiate between acute cellular rejection and CMV

	Onset	Feature	Renal function
Acute cellular rejection	Commonly between days 7 and 21	often clinically silent	Sudden sharp rise in serum creatinine
CMV	Usually seen after four weeks	Systemic feature (pulmonary, GIT and Retinitis).	Gradual rise in serum creatinine

Risk factors of chronic rejection include:

- number of previous acute rejection episodes
- **presence of anti-HLA antibodies**
- anti-endothelial antibodies
- CMV infection
- dyslipidaemia
- hypertension

- functional mass of the donor kidney, and
- delayed graft function (a clinical manifestation of ischaemia/reperfusion injury).

Type of transplant rejection	Hyperacute rejection	Acute rejection	Chronic rejection
Frequency	• < 1%	• 50%	• 50%
Onset after transplantation	• **< 48** (usually within minutes to hours)	• **< 6 months** (usually within days to weeks)	• > 6 months (usually after a few years)
Pathophysiology	• **Preformed antibodies against class I HLA** → activation of complement system and adhesion to granulocytes → thrombosis of vessels → graft ischemia	• T-lymphocyte induced cell-mediated and/or humoral immunity	• Irreversible intimal fibrosis and obstruction of vessels
Clinical findings	• **Intraoperative assessment**: swelling of the organ as soon as perfusion is restored	• Pain in the graft region • Graft edema • Fever and deterioration of general condition • In kidney transplants: ↑ BP and RFT; ↓urine output	• Slow, progressive loss of organ function
Diagnosis	• Biopsy: small vessel thrombosis and graft infarction	• Biopsy (confirmatory test) ➢ Heterogenous mononuclear aggregates± antibody deposition ➢ **C4d** staining indicates **humoral** graft rejection	• Biopsy ➢ Kidney: Glomerular sclerosis ➢ Heart: accelerated coronary artery disease ➢ Liver: vanishing bile duct syndrome

Type of transplant rejection	Hyperacute rejection	Acute rejection	Chronic rejection
		➢ Negative **C4d** staining indicates **cellular** rejection	
Prevention	• Preoperative cross- matching, ABO grouping and HLA matching	• Post-transplant immunosuppressive therapy	• Irreversible process with no known prevention
Treatment	• Graft removal	• Change or **increase dosage of immunosuppressive therapy**	• Graft removal, and retransplantation

Graft versus host disease (GVHD)

presents with liver abnormalities, significant diarrhoea and skin changes.

Definition

- damage to the host as a result of a systemic inflammatory reaction induced by T lymphocytes present in the graft

Etiology

- Allogenous hematopoietic stem-cell transplantation
- Small bowel transplantation
- Transfusion of non-irradiated blood products
  - ➢ **Products implicated in cases of transfusion associated GVHD include:**
    - Non-irradiated whole blood
    - **Packed red blood cells**
    - Platelets
    - Fresh **non**-frozen plasma
    - Granulocytes
  - ➢ **The following have not been implicated:**
    - Frozen deglycerolised red blood cells
    - FFP and
    - Cryoprecipitate

Types of graft-versus-host disease

	Acute graft-versus-host disease	Chronic graft-versus-host disease
Onset	• **< 100 days** after transplantation	• **> 100 days** after transplantation
Pathophysiology	• Donor T lymphocytes react with the recipient's organs	• Mostly unknown
Clinical presentation	• **Pruritic or painful maculopapular rash** • **Nausea, vomiting, diarrhea, and/or cramping abdominal pain** • Hepatic dysfunction: jaundice	• **Scleroderma-like and lichenoid skin changes** • **Sicca syndrome: xerophthalmia, xerostomia, dry pruritic skin** • Chronic enteritis (similar to inflammatory bowel disease): bloody diarrhea, abdominal pain, weight loss • Hepatic dysfunction: jaundice • **Bronchiolitis obliterans**: chronic cough, wheezing, and dyspnea that is not responsive to bronchodilator therapy • Myasthenic symptoms • polymyositis: weakness, muscle pain
Diagnostics	• CBC: anemia, thrombocytopenia, leukopenia • ↑ **ALP** • Confirmatory test: biopsy of skin, rectum, or liver	• Spirometry: obstructive lung disease • Confirmatory test: biopsy of the skin, oral cavity, liver, or lung
Prevention	• **Antithymocyte globulin** • **Cyclosporine** and one of the following: ➢ Methotrexate ➢ Mycophenolate mofetil	
Treatment	• Optimize GvHD prophylaxis (e.g., cyclosporine levels) • Corticosteroids ➢ < 50% skin involvement: **topical steroids** ➢ Involvement of the GI tract, liver, or > 50% of skin: **systemic steroids** ± topical steroids	• First-line: **corticosteroids** • Second-line : cyclosporine and increased corticosteroid dose

Post-transplant problems

Cytomegalovirus (CMV) infection

Renal transplant + infection → CMV

- Over 50% of renal transplant patients have a significant infection within the first 12 months of having a renal transplant.
- (CMV) infection occur as a result of immunosuppression
- **Usually seen after four weeks as before this time the immune system has not been fully affected by the immunosuppressants.**
- At the time of transplant the CMV-serological status of the donor and recipient are noted. The highest risk is seen in CMV-seronegative recipients who receive a kidney from a CMV-seropositive donor. These patients are usually given antiviral prophylaxis.
- associated with increased graft rejection and renal artery stenosis in renal transplant recipients.
- Typical manifestations of infection would include
  - Interstitial pneumonitis
  - Oesophagitis
  - Peptic ulceration
  - Colitis and
  - Retinitis.
- **Management**
  - **Ganciclovir (synthetic guanine derivative) is the most appropriate treatment for CMV**
    - concomitant use with ciclosporin leads to elevated creatinine
    - Pancytopenia may occur as a result of ganciclovir toxicity
  - **Foscarnet** is the drug of choice for **ganciclovir-resistant cytomegalovirus retinitis**.

the two most common causes of declining renal function post renal transplant are:

- **graft rejection and**
- **ciclosporin toxicity.**

Acute pyelonephritis:

- **high risk of acute episode of pyelonephritis in the transplanted kidney, due to the immunosuppression, the neuropathic bladder and self-catheterisation.**
- present like an acute rejection episode, with a tender swollen graft, low-grade pyrexia, and deteriorating graft function.
- Especially in the intermediate stage of the post-transplantation immunosuppression, when the patient is most immunocompromised (three to six months post-transplant).

Interstitial pneumonia

- **Cytomegalovirus is the predominant cause of infection in patients within a period of 1-4 months after renal transplantation**

- A chest X-ray will show a bilateral interstitial or reticulonodular infiltrate that begins in the periphery of the lower lobes and spreads centrally and peripherally

BK virus:

- C4d staining is used for detection of BK virus after renal transplantation

Epstein-Barr virus (EBV)

- **Epstein-Barr virus (EBV)-associated lymphoproliferative disease** (e.g: non-Hodgkin's lymphoma) may occur in individuals with inherited or acquired immunodeficiency syndromes.
- **Approximately 1% of renal transplant recipients develop post-transplant lymphoproliferative disease (PTLD) in the first year following their transplant.**

skin cancer

- Kidney transplant recipients have a high risk of developing **non-melanoma skin cancer**, therefore, cancer surveillance is an important consideration in kidney transplant recipients .
- The patient may has a **malignant melanoma with liver metastases**, hence the deranged liver function tests and liver capsule pain.
- The patient is often unaware of the melanoma lesion, and the primary lesion may in fact disappear as the disease progresses. Patient may present with RUQ pain and high LFT.
- Post-transplant patients are much more prone to develop malignancy compared to normal population.
  - **Cyclosporine is one of the main reasons for development of post-transplant malignancy.**
- Non-melanoma skin cancers (NMSC) are the commonest malignancies in post-transplant state. Of these, **squamous cell Ca is the commonest.**

Kidney donation

- Providing there is a sibling who is proven not to have polycystic kidney disease, living related donation should be considered as this would ensure a better match and better graft survival.
- Siblings are close genetically, and therefore usually are a better match than spouses. **The husband should not be accepted for kidney donation until all siblings have been considered**
- The age difference is not, however, a contraindication to kidney donation.
- Living unrelated kidney donation could also be considered, and is increasing in use in the UK.
- Adults should be considered as doner prior to children because renal cysts usually develop during teenage years, so one cannot be confident a child has not been affected until they are at least 20.

Autosomal dominant polycystic kidney disease (ADPKD)

ADPKD type 1 = chromosome 16 = 85% of cases

ADPKD type 2 = chromosome 4 = 15% of cases

Ultrasound is the screening test for adult polycystic kidney disease

- (ADPKD) is the most common inherited cause of kidney disease,
- affecting 1 in 1,000 Caucasians.
- Accounting for approximately 8% of cases of end-stage renal disease (ESRD).
- Two disease loci have been identified, PKD1 and PKD2, which code for polycystin-1 and polycystin-2 respectively
- Typically presents between the ages of 30-50.
- **As it is an autosomal dominant, the chance of passing this condition from affected patient to his son is 50%.**

ADPKD type 1	ADPKD type 2
85% of cases	15% of cases
Chromosome **16**	Chromosome **4**
Presents with renal failure earlier, reach ESRF by 50s.	Have a slower course, reaching ESRF by 70s.

ADPKD: features

- Hypertension (the **earliest** manifestation of ADPKD)
- recurrent UTIs
- abdominal pain (**loin pain due to a cyst haemorrhage** or infection)
- renal stones
- haematuria (**rupture cysts** presents with **visible haematuria**) (Gross haematuria in ADPKD carries a poor prognosis however microscopic haematuria may be a complication)
- chronic kidney disease

Renal Complications

- CKD
  - ADPKD is like a CKD with high phosphate, low calcium but with normal/high Hb due to excess erythropoietin secretion.
- Excessive erythropoietin production → polycythaemia.
- Renal cell carcinoma with lung metastasis: it is very rare but recognized complication of ADPCKD >>> CT Thorax & Abdomen.

Extra-renal manifestations

- Liver cysts (70%)
- Berry aneurysms (8%)
  - Subarachnoid haemorrhage may be a cause of mortality in 9% of patients with ADPKD,
  - 8% of patients have an asymptomatic intracranial aneurysm

- screening for cerebral aneurysms should only be carried out in high risk patients. These include factors such as:
  1. Previous rupture of aneurysm
  2. Concerning neurological symptoms (for example, severe headache)
  3. Positive family history of haemorrhagic stroke or aneurysm.
- Even if aneurysms are found, the rupture risk can still be low and the morbidity implications of curative surgery may outweigh conservative management.

- **Cardiovascular system: mitral valve prolapse (25%)** → (needs echo screening), mitral/tricuspid incompetence, aortic root dilation, aortic dissection
- Colonic diverticula (with any related symptoms, screen by barium enema)
- cysts in other organs: pancreas, spleen; very rarely: thyroid, oesophagus, ovary

Investigations

- **Ultrasound** (Sensitivity for ADPKD1 is 99% for at-risk patients older than 20 years)
  - **Sonographic diagnostic criteria** (in patients with positive family history):
    - age < 30 years → 2 unilateral or bilateral cysts
    - age 30-59 years → 2 cysts in each kidney
    - age > 60 years → 4 cysts in each kidney
  - **Sensitivity of these criteria**
    - nearly 100% for patients 30 years of age or older and for younger patients with PKD1 mutations,
    - 67% for patients with PKD2 mutations younger than 30 years of age.
    - CT scan or MRI should therefore be used in the latter group.
    - one cannot be confident a child has not been affected until they are at least 20:
      - a normal ultrasound scan at 20 years of age means you can be 90% confident they are not affected,
      - a normal scan at 30 increases the confidence level to 98%.
  - Screening is not usually recommended in children because the presence or absence of cysts does not affect management (tight blood pressure control), and the absence of cysts in children does not exclude the disease.
  - All children of affected patients should have their blood pressure monitored at least annually, from early childhood (around age 3) onwards.
  - If cysts are not seen in a younger with a positive family history, the ultrasound should be repeated every five years until the age of 30.
- **Contrast-enhanced CT scan or MRI**
  - Abdominal CT is sensitive for the detection of cysts however the high radiation dose, particularly in young patients, means it is not widely used as a screening test.
  - should be used if ultrasound is equivocal, especially in patients with PKD2 mutations younger than 30 years of age.
  - ***CT***: More sensitive than USS and may aid in diagnosis in younger patients.
  - ***MR angiography***: In patients with a family history of intracranial aneurysm - to screen for cerebral aneurysms.
- **Genetic testing**
  - **The most appropriate strategy to investigate younger with a family history of ADPK is genetic counselling (referral)**

- **The major indication for genetic screening in (ADPKD) is for subjects who are considering donating a kidney to a relative affected by the disease**
- **sequence analysis** can identify only around 70% of known mutations and **linkage analysis** requires the availability of sufficient family members.
- can be used in the following cases:
  - The imaging results are equivocal or inconclusive.
  - To confirm a presumed diagnosis in the absence of family history of the disease (conclusive proof of the diagnosis in these patients relies on mutation analysis).
  - When a definite diagnosis is required in a younger patient, such as a potential living related kidney donor.

- **Renal biopsy is contraindicated** due to a high risk of haemorrhage into a cyst

Treatment

- high fluid intake (to prevent the formation of renal stones or blood clots)
- non-NSAID-based analgesia are the cornerstones of management
  - **IV fluids, paracetamol and codeine**
- Hypertension → ACE inhibitors or angiotensin receptor antagonists
  - ACE inhibitors reduce proteinuria and may reduce cyst formation in ADPKD,
  - aliskiren, the direct renin inhibitor, also has early data which show promise with respect to reducing new cysts.
- A new therapy (**tolvaptan**) to delay disease progression (recommended by NICE in 2015)
  - **Action:** selective vasopressin antagonist → inhibit the binding of vasopressin to the V2 receptors → reduces cell proliferation, cyst formation and fluid excretion.
  - **adverse reactions:** thirst, polyuria, nocturia, pollakiuria (frequent urination),↑ liver enzyme.
- Urinary tract infections should be treated with lipophillic drugs (for example, ciprofloxacin, trimethoprim-sulphamethoxazole) as they have the best penetration into cyst fluid.
- End-stage renal disease → Transplantation

Prognosis

- the renal function usually deteriorates in a gradual fashion, **usually with a drop in creatinine clearance of 5/6 ml/min/year**
- **Approximately half of patients require dialysis by the age of 60**

January 2016 exam: You are reviewing a patient with adult polycystic kidney disease. Which cardiovascular feature are you most likely to find on examination? Mitral valve prolapse

Autosomal recessive polycystic kidney disease (ARPKD)

- Autosomal recessive polycystic kidney disease (ARPKD) is much less common than autosomal dominant disease (ADPKD).
- **It is due to a defect in a gene located on chromosome 6**
- Diagnosis may be made on prenatal ultrasound or in early infancy with abdominal masses and renal failure. Newborns may also have features consistent with Potter's syndrome secondary to oligohydramnios.
- **End-stage renal failure develops in childhood.**
- Patients also typically have liver involvement, for example portal and interlobular fibrosis.
- Renal biopsy typically shows multiple cylindrical lesions at right angles to the cortical surface.

Medullary sponge kidney

- is a disorder characterised by dilatation of the collecting ducts in the papillae, with accompanying cystic changes
- It is often associated with **calculi**, which can result in pyelonephritis and renal tract obstruction.
- **Typically not inherited but is a congenital condition.** The aetiology is uncertain, but it is thought to be a developmental abnormality, possibly resulting from tubular or collecting duct obstruction at any early age.
- The kidneys size are normal or increased.
- The age of presentation is usually in the third or fourth decade
- The majority of cases are sporadic, although a rare autosomal dominant familial form exists with onset in adulthood, and a juvenile autosomal recessive form is also recognised. Recent research has identified a possible defect in the development of the proton pump mechanism in the kidney.
- **Diagnosis**
  - Diagnosis is made via excretion urography, showing small calculi in the papillary zones with surrounding increase density; this is because the dilated collecting ducts are filled with contrast medium
  - About 20% of patients have associated hypercalciuria or renal tubular acidosis
  - Skeletal hemihypertrophy may be associated
  - Renal failure is highly unusual

Alport's syndrome

Alport's syndrome - X-linked dominant (in the majority)

Alport's syndrome - type IV collagen defect

- Alport syndrome is the second most common inherited cause of renal failure (after polycystic kidney disease)
- usually inherited in an **X-linked dominant** pattern.
  - Inheritance is variable, but the majority are X linked dominant (85%) ;
    - Therefore, as only the Y chromosome is passed from father to son there is no chance of the son having the disease.
  - 15% are autosomal recessive with rare autosomal dominant variants
- Most cases arise from the COL4A**5** gene on the X chromosome .
- It is due to a defect in **the gene which codes for type IV collagen** resulting in an abnormal glomerular-basement membrane (GBM).
  - Patients with Alport syndrome are **at risk of** developing antiglomerular basement membrane disease (**Goodpasture's** disease) **following transplantation**, as their immune systems have never been exposed to type IV collagen and hence lack tolerance.
  - **What is the most likely reason for the decline in graft function?**
    - **Anti-glomerular-basement membrane antibodies (Goodpasture's syndrome)**
- There is a high spontaneous mutation rate, which means 20% of patients have no family history.
- Prevalence is around **1 in 5000**
- The disease is more severe in males with females rarely developing renal failure
- usually presents in childhood.
- more severe in males
  - females do not develop progressive renal failure with this condition.
- **A favourite question is an Alport's patient with a failing renal transplant. This may be caused by the presence of anti-GBM antibodies leading to a Goodpasture's syndrome like picture**

Features

"Can't see, can't pee, can't hear a bee."

- microscopic haematuria
  - Most common and earliest manifestation
- progressive **renal failure**
- bilateral **sensorineural deafness (**usually occurs before the onset of renal failure**)**
- ocular
  - Anterior lenticonus
    - protrusion of the lens surface into the anterior chamber
    - Occurs in 25% of patients
    - is the **pathognomonic** feature of Alport syndrome
  - Dot-and-fleck retinopathy
    - **Most common ocular manifestation** of patients with Alport syndrome, (occurring in 85%)
  - retinitis pigmentosa

Investigations

- renal biopsy:

- **Light microscopy**
  - **usually unremarkable and electron microscopy is usually required.**
- **Electron microscopy**
  - **splitting of lamina densa**
    - basket weave pattern of glomerular basement membrane
  - foam cells
    - produced by lipid accumulation in visceral epithelial cells

- slit lamp examination:
  - bilateral thin lens capsules
  - conical protrusions on the anterior aspect of the lens,
  - subcapsular cataracts.

Treatment

- Rigorous control of hypertension may delay the onset of end stage renal failure,
- angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers if they have proteinuria
- Renal transplant

Prognosis

- ESRF seen in 90% of patients with Alport's by the age of 40 years.

September 2009 exam: What is the mode of inheritance of Alport's syndrome in the majority of cases? X-linked dominant

January 2008 exam: Alport's syndrome is due to a defect in:? Type IV collagen

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Haemolytic uraemic syndrome

The presence of **thrombocytopenia** and evidence of **haemolysis** in association with **bloody diarrhoea** should make you think of haemolytic uraemic syndrome (HUS).

Haemolytic uraemic syndrome - classically caused by E coli 0157:H7

Haemolytic uraemic syndrome is generally seen in young children and produces a **triad of:**

- acute renal failure
- microangiopathic haemolytic anaemia
- thrombocytopenia with normal clotting.

Causes

- **post-dysentery - classically E coli 0157:H7** ('verotoxigenic', 'enterohaemorrhagic') .Toxins produced in the intestine enter the blood and bind to endothelial cells in target organs. Endothelial cell damage leads to platelet and fibrin deposition with resultant fragmentation of circulating red blood cells and microvascular occlusion.
  The syndrome has also been reported after infections with coxsackie, echovirus and *Shigella*.
- tumours

- pregnancy
- ciclosporin, the Pill
- systemic lupus erythematosus
- HIV
- Inherited recurrent HUS has been described with both dominant and recessive patterns of inheritance

Investigations

- full blood count: anaemia, ↓↓Serum haptoglobins (which bind haemoglobin), thrombocytopaenia, **fragmented blood film**
  - ➢ The hallmark of HUS is the appearance of **schistocytes** (fragmented, deformed, irregular, or helmet shaped red cells) on the blood film.
- There is normal coagulation and fibrinogen.
- U&E: acute renal failure
- stool culture

Major differential diagnosis is:

1. Sepsis with DIC - **presents with abnormalities of clotting parameters.**
2. TTP - thrombotic thrombocytopenic purpura presents with microangiopathic haemolytic anaemia, thrombocytopenic purpura, neurologic abnormalities, fever, and renal disease.
   - ➢ Patients with TTP lack a plasma protease that is responsible for the breakdown of von Willebrand factor (vWF) multimers and these accumulate in the plasma. The activity of this protease is normal in patients with HUS.
   - ➢ Until the test for vWF protease activity becomes available, differentiation between HUS and TTP is based on the presence of central nervous system involvement in TTP and the more severe renal involvement in HUS.
   - ➢ In HUS 90% of patients are children and a history of prodromal diarrhoeal illness is more common.

feature	HUS	TTP
Acute kidney injury	more severe	Less severe
Neurological symptoms	less common	More common

Complications include:

- Stroke, seizure and coma occur in 25% of patients
- Rarely pancreatitis, and
- Pleural and pericardial effusions.
- Approximately 5% of patients will develop end stage renal failure.

Management

- treatment is supportive e.g. Fluids, blood transfusion and dialysis if required
- there is no role for antibiotics, despite the preceding diarrhoeal illness in many patients
- the indications for plasma exchange in HUS are complicated. As a general rule plasma exchange is reserved for severe cases of HUS not associated with diarrhoea

- Non-steroidal anti-inflammatory drugs and anti-diarrhoeals should be avoided

Prognosis

- Most children recover spontaneously from the illness, but mortality may be high in the elderly.
- Unfortunately fatality rates from HUS remain high, at between 5 and 10%.

MRCPUK- part-1- September 2012 exam: H/O bloody diarrhea and dehydration + ↓Platelet , ↑WBC, ↑urea & creatinine. Given the likely diagnosis, which organism is the most likely cause?

➔ ***E. coli***

MRCPUK- part-1- May 2010 exam: Feature of diarrhoea , lethargy & acute renal failure. There is a known local outbreak of E coli 0157:H7. Given the likely diagnosis, which one of the following investigation results would be expected?

➔ **Fragmented red blood cells** (∆ haemolytic uraemic syndrome)

Renal tubular defects

- **thick ascending limb of Henle's loop**: Bartter syndromes are renal tubular salt-wasting disorders in which the kidneys cannot reabsorb chloride in the thick ascending limb of Henle's loop
- **distal convoluted tubule**: Gitelman syndrome are renal tubular salt-wasting disorders in which the kidneys cannot reabsorb chloride due to defect of thiazide-sensitive Na-Cl cotransporter in the distal convoluted tubule
- **proximal tubule**: Carbonic anhydrase is expressed in the proximal tubule and is inhibited by acetazolamide; this is manifested biochemically by normal anion-gap metabolic acidosis Fanconi syndrome refers to a proximal tubular defect that results in wasting of phosphate, calcium and amino acids .It is an important feature of cystinosis and is also seen in myeloma kidney and Wilson's disease
- **collecting ducts** :Aquaporin channels are expressed in the cortical collecting ducts and are involved in water handling; defects result in diabetes insipidus

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Fanconi syndrome

- Fanconi's syndrome characterised by **generalised dysfunction of the proximal tubule**, with the resultant urinary loss of bicarbonate, calcium, phosphate, urate, amino acids, glucose, and other organic acids and bases.
- Most diseases associated with Fanconi syndrome are inherited in an **autosomal recessive** pattern. Consequently:
  - the child of 2 heterozygous parents, whether male or female, has a 25% chance of being homozygous.
  - The children of an affected individual (homozygous) are all heterozygous and can be affected only if the other parent is heterozygous, a very rare event.
- Fanconi's syndrome is marked by the **appearance in the urine of all amino acids**. Specific amino aciduria as seen in isolated cystinuria, glucose loss in isolated glycosuria, and isolated phosphaturia do not constitute Fanconi's syndrome.

Causes

- cystinosis (most common cause in children)
- Sjogren's syndrome
- multiple myeloma
- nephrotic syndrome
- Wilson's disease

Feature

- type 2 (proximal) renal tubular acidosis (RTA)
- polyuria
- aminoaciduria
- glycosuria
- phosphaturia
- osteomalacia

Complications

- **In children**, Fanconi's syndrome results in growth retardation, renal rickets, and severe metabolic acidosis.
- **Adult** cases exhibit similar urinary losses, but the clinical impact is largely restricted to **metabolic acidosis.**

Gitelman's syndrome

Gitelman's syndrome: normotension with hypokalaemia

- Gitelman's syndrome is due to a **defect in the thiazide-sensitive Na^+ Cl- transporter in the distal convoluted tubule.**
- Caused by loss-of-function mutations in the SLC12A3 gene
- It is the **most common congenital renal tubular disorder** in Caucasians, with a prevalence of 1 in 40,000
- autosomal recessive

Features

- patients may be highly symptomatic (eg salt craving, dizziness, fatigue, muscle weakness and cramps, paraesthesiae, non-specific aches and pains) or may have minimal symptomatology
- hypokalaemia
- **hypomagnesaemia** (**which is pathognomic**)
- hypocalciuria
- metabolic alkalosis
- normotension
- salt wasting leads to activation of the renin-angiotensin system also leading to raised aldosterone levels.
    - **The most useful investigation in pointing to the diagnosis is → Renin and aldosterone levels**

Bartter syndrome and Gitelman syndrome

- Clinical diagnosis of Bartter or Gitelman syndrome:
  1. Unexplained hypokalemia and metabolic alkalosis
  2. Normal or low blood pressure,
  3. Other, more common, etiologies are ruled out (ie, surreptitious vomiting and diuretic use).
- Laboratory diagnosis
  - Urine chloride concentration, (typically greater than 25 meq/L)
    - In contrast, patients with hypokalemia and metabolic alkalosis caused by vomiting have a urine chloride concentration that is usually less than 25 meq/L
  - Urine diuretic screen.
  - The practicality of genetic testing is limited.
- Patients who secretively take diuretics have a variable urine chloride concentration; it is high when the diuretic effect is present and low when it dissipates. A urine diuretic screen should be sent.
- Treatment of patients with Bartter and Gitelman syndromes:
  - life-long administration of a drug that blocks distal tubule sodium-potassium exchange (eg,spironolactone)
  - supplementation with potassium chloride and magnesium.
  - NSAIDs.

	Gitelman syndrome	**Bartter syndrome**
Gene affected	SLC12A**3**	SLC12A**1** (Bartter syndrome type I)
prevalence	1 in 40,000	1 in a million.
Site of defect	thiazide-sensitive Na-CI cotransporter in the distal convoluted tubule	sodium chloride reabsorption in the thick ascending limb of Henle's loop (NKCC2)
presentation	present in adolescence and early adulthood (milder symptoms)	Most cases are discovered in **infancy or early adolescence** (more severe symptoms)
Concentrating and diluting abilities	Concentrating capacity normal/near normal and diluting capacity reduced	Concentrating capacity reduced and diluting capacity reduced
Urinary calcium	reduced	increased
serum magnesium	severe hypomagnesemia is common	either normal or mildly reduced

Bartter syndrome

Bartter's syndrome is associated with normotension

Loop diuretics work by inhibiting NKCC2 - think of Bartter's syndrome as like taking large doses of furosemide

Basics

- Bartter syndrome is a childhood disease inherited as an autosomal recessive trait
- Leads to tubular **defects in Na-K-Cl cotransporter** and increased intrarenal production of ProstaglandinE2 (PGE2)
- The defect located **in the thick ascending limb of the loop of Henle**
- usually diagnosed at school age or later.

Aetio-pathogenesis

- ↓Chloride reabsorption →↓loop (NaCl) reabsorption → ↑renin & aldosterone secretion with **juxtaglomerular (JGA) hyperplasia**
- ↑ (NaCl) in collecting duct → ↑K+ & H+ secretion → hypokalaemia & metabolic alkalosis
- High levels of aldosterone also enhance potassium and hydrogen exchange for sodium.
- ↑ kinin & prostaglandins secretion → vascular unresponsiveness to presser effect
- K+ → ↑PGE2 → afferent arteriole dilation →↓Renal Perfusion Pressure (RPP) → chronic renin secretion with no effect on GFR, RPP, Na, Cl, K reabsorption (because PGE2 overcome this reaction) →**JGA hypertrophy due to excess of work.**

Features

- usually presents in children, polyuria, Polydipsia ,dehydration, **mimics loop diuretic use**
  - nocturnal enuresis,
- Hypokalaemia → muscle weakness
- Alkalosis
- Hypercalci**uria**
- normal to low BP:
  - ↑renin and aldosterone **NOT** ↑ BP because of **vascular unresponsiveness to presser effect**
- growth retardation.
- rarely sensorineural defects
- Other symptoms, which appear during late childhood, include fatigue, muscle weakness, cramps, and recurrent carpopedal spasms.

Investigations (Exclude diuretic abuse**)**

- urinary chloride: high (>20 mmol/L or 20 mEq/L)
- urinary calcium**:** high (normal range 100 – 300 mg/day)
- Urinary sodium: high
- serum potassium: low (hypokalaemic alkalosis)
- increased plasma renin and aldosterone levels.
- Hyponatraemia and hypochloraemia may also be present.
- Renal biopsy → **Hyperplasia of the juxtaglomerular apparatus is characteristic**

Differential diagnosis

- Gitelman

  - Gitelman → hypocalciuria
  - Bartter → hypercalciuria + high renin, high aldosterone
  - While Bartter may or may not have hypomagnesemia, it is pathognomonic for Gitelman.
- Chronic vomiting
  - Chronic vomiting: → low urine chloride levels
  - Bartter's → higher urine chloride levels.
- Abuse of diuretic medications (water pills):
  - The physician must screen urine for multiple diuretics before diagnosis is made.

Treatment

- K^+-sparring diuretic (eg: spironolactone)
  - Treatment is aimed at preventing potassium wasting
- NSAID (eg: Indomethacin) →↓ production of prostaglandins → restores the normal physiological vascular response.

Liddle's syndrome

Liddle's syndrome: hypokalaemia + hypertension

hypokalaemic alkalosis + suppressed renin and aldosterone + hypertension → Liddle's syndrome

Overview

- **autosomal dominant**
- mutation in genes mapped to chromosome 16.
- Caused by increased sodium reabsorption due to **increased activity of epithelial sodium channels in the distal tubules** from gain-of-function mutations. This leads to activation of sodium/potassium exchange independent of circulating mineralocorticoid.

Features

- hypertension
  - caused by increased sodium reabsorption.
- hypokalaemia
- metabolic alkalosis.

Treatment

- potassium-sparing diuretics
  - either **amiloride** or triamterene (epithelial sodium channel (ENaC) antagonists)
  - Hypertension and hypokalaemia respond well to amiloride but not spironolactone, because **amiloride acts directly on the sodium channel**, whereas spironolactone acts on the mineralocorticoid receptor.
    - Amiloride specifically inhibits overactive sodium channels and effectively controls blood pressure in Liddle's syndrome, in which hypertension is caused by separate epithelial sodium channel mutations.

- **Spironolactone is not an effective treatment** as the increased activity of the ENaC is not mediated by aldosterone (as reflected by the low plasma and urinary aldosterone levels).

HIV: renal involvement

Renal involvement in HIV patients may occur as a consequence of treatment or the virus itself. Protease inhibitors such as indinavir can precipitate intratubular crystal obstruction

HIV-associated nephropathy (HIVAN) accounts for up to 10% of end-stage renal failure cases in the United States. Antiretroviral therapy has been shown to alter the course of the disease. There are five key **features of HIVAN:**

- massive proteinuria
- normal or large kidneys
- focal segmental glomerulosclerosis with focal or global capillary collapse on renal biopsy. (collapsed appearance of glomeruli on light microscopy) is typical
- elevated urea and creatinine
- normotension

Glomerulonephritides

Knowing a few key facts is the best way to approach the difficult subject of glomerulonephritis:

Membranous glomerulonephritis

- presentation: proteinuria / nephrotic syndrome / chronic kidney disease
- cause: infections, rheumatoid drugs, malignancy
- 1/3 resolve, 1/3 respond to cytotoxics, 1/3 develop chronic kidney disease

IgA nephropathy - aka Berger's disease, mesangioproliferative GN

- typically young adult with haematuria following an URTI

Diffuse proliferative glomerulonephritis (DPGN)

Diffuse proliferative glomerulonephritis, causes:

- post-streptococcal
- SLE

Diffuse proliferative glomerulonephritis is the most common and severe form of renal disease in SLE patients

- classical post-streptococcal glomerulonephritis in child
- presents as nephritic syndrome / acute kidney injury
- The following features are supportive of diagnosis:
  - haematuria
  - proteinuria
  - oedema
  - hypertension

- **most common form of renal disease in SLE**
- In DPGN, **more than 50% of the glomeruli** (diffuse) show an increase in mesangial, epithelial, endothelial (proliferative), and inflammatory cells (ie, glomerulonephritis). (Increased cellularity)
- when **<** 50% of the glomeruli are involved, the condition is termed focal proliferative glomerulonephritis. However, this entity has the potential to progress to DPGN.

Minimal change disease

- typically a child with nephrotic syndrome (accounts for 80%)
- causes: Hodgkin's, NSAIDs
- good response to steroids

Focal segmental glomerulosclerosis

- may be idiopathic or secondary to HIV, heroin
- presentation: proteinuria / nephrotic syndrome / chronic kidney disease

Rapidly progressive glomerulonephritis - aka crescentic glomerulonephritis

- rapid onset, often presenting as acute kidney injury
- causes include Goodpasture's, ANCA positive vasculitis

Mesangiocapillary glomerulonephritis (membranoproliferative)

- type 1: cryoglobulinaemia, hepatitis C ➔ **associated with low C4**
- type 2: partial lipodystrophy ➔ **associated with low C3**
- C3 nephritic factor is an autoantibody specific for alternative pathway C3 convertase (C3NeF), found in mesangiocapillary GN type II and partial lipodystrophy.

Diagnosis

- **Renal biopsy is the best investigation to diagnose Glomerulonephritis**
- **RBC casts in urinary sediment suggest a diagnosis of acute glomerulonephritis (Acute nephritic syndrome)**

- Immune complex glomerulonephritides can be classified based on normal or decreased C^3.
  - ➢ **Associated with reduced C^3 and C^4**
    - Cryoglobolinaemia
    - Infective endocarditis
    - lupus nephritis
  - ➢ **Associated with reduced C^3.**
    - membranoproliferative GN
    - post-streptococcal GN

Glomerulonephritis and low complement

Disorders associated with glomerulonephritis and low serum complement levels:

1. post-streptococcal glomerulonephritis
2. subacute bacterial endocarditis
3. systemic lupus erythematosus
4. mesangiocapillary glomerulonephritis

May 2014 exam: A patient of SLE present with pedal oedema , ↑ BP. Dipstick urine shows protein ++, blood+++.What is the renal biopsy most likely to show? Diffuse proliferative glomerulonephritis
(Diffuse proliferative glomerulonephritis is the most common and severe form of renal disease in SLE patients.)

Minimal change disease

Minimal change glomerulonephritis - prednisolone

Nephrotic syndrome in children / young adults - minimal change glomerulonephritis

- Minimal change disease nearly always presents as nephrotic syndrome,
- accounting for 75% of cases in childrenand 25% in adults.
- peak incidence 2-3 years of age

Causes

- The majority of cases are idiopathic, but in around 10-20% a cause is found:
- drugs: NSAIDs, rifampicin **gold** and lithium
- **Hodgkin's lymphoma**, thymoma
- infectious mononucleosis

Pathophysiology

- **The glomerular basement membrane is normal on electron microscopy**
- T-cell and cytokine mediated damage to the glomerular basement membrane → polyanion loss
- the resultant reduction of electrostatic charge → increased glomerular permeability to serum albumin

Features

- nephrotic syndrome
- normotension
  - hypertension is rare (only 10%)
- highly selective proteinuria* (*only intermediate-sized proteins such as albumin and transferrin leak through the glomerulus)
  - A protein selectivity index of less than 10% is highly selective and is a ratio of serum and urine IgG and albumin.
  - High selectivity suggests minimal change disease but is less reliable in adults.
- **Renal biopsy:**
  - **light microscopy** are normal or small looking glomeruli
  - **electron microscopy** shows fusion of podocytes
    (Effacement of the epithelial cell foot processes over the outer surface of the GBM)
  - renal biopsy is not indicated unless no response to steroids is seen within one month, there is hypertension, haematuria or renal impairment.

- renal biopsy is usually only attempted when three or more episodes of oedema have occurred.

Podocytes fusion is seen in minimal change glomerulonephritis but may occasionally be a feature of focal segmental glomerulosclerosis as well. Minimal change however is far more common

Management

- majority of cases (80%) are steroid responsive
- cyclophosphamide is the next step for steroid resistant cases
  - Immunosuppression treatment (cyclophosphamide) should be considered in patients who are **frequent relapsers** (**two or more episodes in six months** of the initial response, or **four relapses in any one year**, children who are steroid dependent or steroid toxic).

Prognosis is overall good

- **Remission: Full renal recovery is the most likely outcome.**
  - **In Children**:
    - 30 – 40% of children achieve spontaneous remission
    - and 90% achieve remission following eight weeks treatment with high dose steroids.
  - **In adults** only around 50% achieve remission.

- **Relapse** is common. Roughly:
  - 1/3 have just one episode
  - 1/3 have infrequent relapses
  - 1/3 have frequent relapses which stop before adulthood

Membranous glomerulonephritis

Nephrotic syndrome - malignancies cause membranous glomerulonephritis

- **Membranous glomerulonephritis is the commonest type of glomerulonephritis in adults** and is the third most common cause of end-stage renal failure (ESRF).
- It usually presents with nephrotic syndrome or proteinuria.
- It is an antibody mediated disease in which the immune complexes localise to the subepithelial aspect of the capillary loop. That is, between the outer aspect of the basement membrane and the podocyte (epithelial cell).
- **Males are twice as commonly affected as females**
- Typically seen in the over 40 age group (Elderly patients)

Causes

- idiopathic
- infections: **hepatitis B**, hepatitis C , **malaria**, syphilis , leprosy, HIV, schistosomiasis,
- **malignancy**: lung cancer, **non-Hodgkin's lymphomas lymphoma**, leukaemia, **colon** and gastric cancer
  - (30% of membranous nephropathy cases are secondary, of those around a third (10% of the total cases of membranous nephropathy) are diagnosed with an underlying malignancy)
  - (NOTE: In the case of **Hodgkin's lymphoma,** the most common histological type of renal involvement is **minimal change** glomerulonephritis followed by focal segmental glomerulosclerosis).
- drugs: gold, **penicillamine**, NSAIDs , captopril, and heavy metals: mercury and cadmium
- autoimmune diseases: systemic lupus erythematosus (class V disease), thyroiditis, rheumatoid
- Sickle cell disease.
- Diabetes mellitus.

Renal biopsy demonstrates:

- electron microscopy: the basement membrane is thickened with subepithelial electron dense deposits (**Thickened capillary loops**). This creates a 'spike and dome' appearance
- Immune complex **deposition with IgG and C3**

Complications

- **Renal vein thrombosis is particularly likely to complicate membranous glomerulonephritis**
  - As the left testicular vein drains into the left renal vein, a left-sided varicocele may develop in this condition.

Prognosis

- Rule of thirds
  - one-third: spontaneous remission
  - one-third: remain proteinuric
  - one-third: develop ESRF
- Good prognostic features include:
  - female sex
  - young age at presentation and
  - asymptomatic proteinuria of a modest degree at the time of presentation.

Management: aims are:

1. induce a remission of the nephrotic syndrome, and
2. prevent the development of end stage renal failure.

- Immunosuppression: corticosteroids alone have not been shown to be effective. A combination of corticosteroid + another agent such as chlorambucil is often used
  - **Cyclophosphamide plus methylprednisolone is the most appropriate management**

- blood pressure control: ACE inhibitors have been shown to reduce proteinuria
  - **Ramipril is proven to affect both proteinuria and hypertension in patients with a diagnosis of membranous nephropathy, and is therefore the most likely treatment to affect the patient's prognosis**
- consider anticoagulation
- Approximately 30% of cases are secondary to other conditions, and in those cases treatment of the underlying cause may be curative.

September 2011 exam: H/O colorectal cancer developed 'frothy' urine. The results suggest nephrotic range proteinuria. Assuming the proteinuria is related to his colorectal cancer what is the renal histology most likely to show? Membranous glomerulonephritis

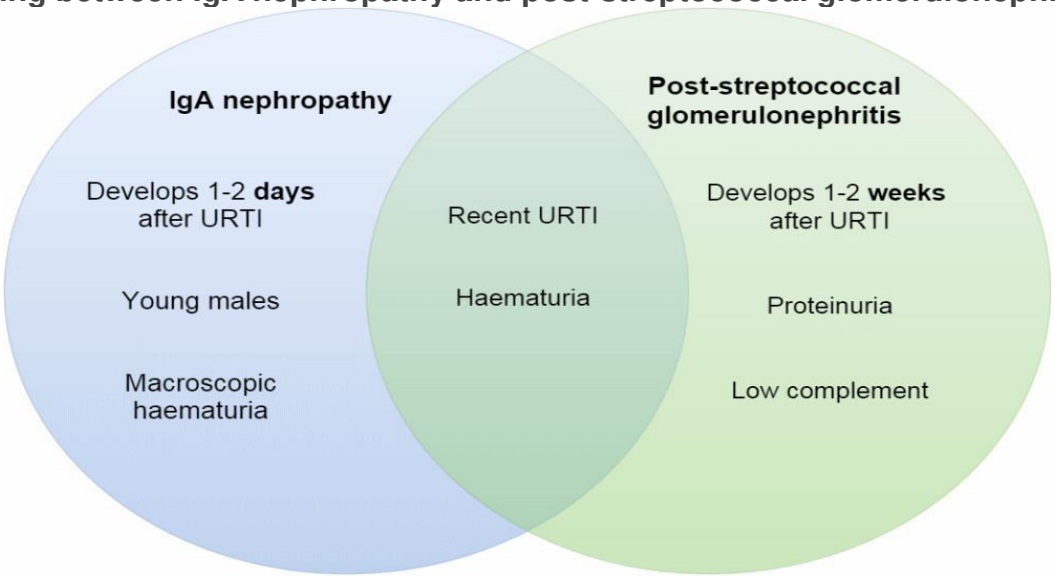
May 2012 exam: H/O peripheral oedema with no past medical history of note. His urinary protein is 4.2g/24 hours. BP is 160/92 mmHg. A renal biopsy shows: thickened capillary walls& Subepithelial deposits.Given the likely diagnosis, which one of the following drugs is most likely to be beneficial? ACE inhibitor (∆ membranous glomerulonephritis)

IgA nephropathy

Basics

- also called Berger's disease or mesangioproliferative glomerulonephritis
- **commonest cause of glomerulonephritis worldwide**
- thought to be caused by mesangial deposition of IgA immune complexes
- there is considerable pathological overlap with Henoch-Schonlein purpura (HSP)
- Has a male preponderance
- **commonly diagnosed in the age range of 20-40**.

Differentiating between IgA nephropathy and post-streptococcal glomerulonephritis



- post-streptococcal glomerulonephritis is associated with low complement levels
- main symptom in post-streptococcal glomerulonephritis is proteinuria (although haematuria can occur)

- there is typically an interval between URTI and the onset of renal problems in post-streptococcal glomerulonephritis

Presentations

- young male, recurrent episodes of macroscopic haematuria
- Haematuria occurs within 12-24 hours of pharyngitis,
- typically associated with mucosal infections e.g., URTI , or less commonly infection of other mucous membranes (e.g. GI, bladder, breast).
- accompanied also by loin pain, muscle pain and fever.
- nephrotic range proteinuria is rare
- The majority of patients have normal renal function.
- renal failure

Associated conditions

- **Alcoholic** cirrhosis (**Alcohol excess) (haematuria + alcohol excess ➔ IgA nephropathy).**
- coeliac disease/dermatitis herpetiformis
- Henoch-Schonlein purpura

Diagnosis

- **Renal biopsy is the investigation of choice to confirm the diagnosis**
  - **histology: Mesangial hypercellularity,**
  - positive immunofluorescence for IgA & C3

Management

- No specific treatment is available. **Observation is the most appropriate management**
- steroids/immunosuppressants not be shown to be useful**.**
  - Treatment with corticosteroids is usually reserved for those patients with hypertension and a rising creatinine.
- When there is nephrotic range proteinuria (>3 g/day) an 8-12 week course of prednisolone should be prescribed.
- If the proteinuria is <3 g/day an ACE inhibitor can be used.

Prognosis

- 30% of children will have a spontaneous remission within 10 years
- 25% of patients develop ESRF within 20 years
- markers of good prognosis: frank haematuria
- **markers of poor prognosis:**
  - male gender,
  - proteinuria (especially > 2 g/day),
  - **hypertension**
  - smoking,
  - hyperlipidaemia,
  - ACE genotype DD

September 2011 exam: A 17-year-old man with several episodes of visible haematuria. occurs within a day or two of URTI . Urine dipstick is normal. What is the most likely diagnosis? IgA nephropathy

January 2006 exam: A 10-year-old boy with past two days H/O sore throat associated with blood in his urine. glomerulonephritis is suspected. What would a renal biopsy most likely show? Mesangial hypercellularity (Δ IgA nephropathy)

September 2007 exam: A 12-year-old boy with purpuric rash on the extensor surfaces of his lower legs + abdominal pain and an urticarial rash. Urine dipstick reveals blood ++.What would be the likely finding on renal biopsy? Mesangial hypercellularity (Henoch-Schonlein purpura is associated with IgA nephropathy)

January 2014 exam: A 19-year-old woman C/O painless visible haematuria, occur within a day or two of developing tonsillitis. BP is 148/90 mmHg. Given the likely diagnosis, which marker indicate poor prognosis? Hypertension (Δ IgA nephropathy)

September 2007 exam: Which one of the following is associated with a better prognosis in patients with IgA nephropathy? Frank haematuria

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Post-streptococcal glomerulonephritis

- typically occurs 7-14 days following a group A beta-haemolytic *Streptococcus* infection (usually *Streptococcus pyogenes*).
- caused by immune complex (IgG, IgM and C3) deposition in the glomeruli.
- Young children most commonly affected.

Features

- general: headache, malaise
- haematuria
- nephritic syndrome
- hypertension
- low C3
- normal C4 level or only slightly reduced, indicating activation of the alternate complement pathway
- **Depressed CH 50 level**
- raised ASO titer

Renal biopsy features

- post-streptococcal glomerulonephritis causes acute, diffuse proliferative glomerulonephritis
- endothelial proliferation with neutrophils
- electron microscopy: subepithelial 'humps' caused by lumpy immune complex deposits. **The hump-like appearance in subepithelial space is characteristic of post-streptococcal glomerulonephritis**.
  - **'Lumpy-bumpy' appearance on immunofluorescence is characteristic.**
- immunofluorescence: granular or 'starry sky' appearance
- **'wire-loop' lesions on light microscopy.**
- There is antibody and compliment deposition on immunostaining.

Prognosis

- **Carries a good prognosis**

- **Age is the most important prognostic factor** in post-streptococcal glomerulonephritis. 95% of affected children recover completely, compared with 25% of adults over 60 years old.

Membrano-proliferative glomerulonephritis (MPGN).

Membranoproliferative glomerulonephritis (mesangiocapillary)
- type 1: cryoglobulinaemia, hepatitis C
- type 2: partial lipodystrophy

Overview
- also known as **mesangio-capillary** glomerulonephritis(MCGN),
- may present as nephrotic syndrome, haematuria or proteinuria
- It is associated with SLE, cryoglobulinaemia with or without **hepatitis C**, chronic infections (SBE) , neoplasms. hepatitis B, schistosomiasis, malaria and leprosy,may also be associated
- **Circulating immune complexes are seen**
- Classically associated with decreased serum C3 (and a normal C4, indicating activation of the alternative pathway of complement).
- poor prognosis
- Hypocomplementemia (Low C3 levels) is a characteristic finding with all types of (MPGN).

Type 1
- accounts for 90% of cases
- **histology: sub-endothelial immune deposits** of electron dense material, **Thickening and splitting of the capillary basement membrane**, resulting in a 'tram-track' appearance
- causes: cryoglobulinaemia (➔ **low C3**), **hepatitis C** (hepatitis C is endemic among the iv drug-users). Hepatitis C is now considered the principal cause of 'idiopathic' mesangiocapillary glomerulonephritis (MCGN),

Type 2 - **'dense deposit** disease'
- causes: partial lipodystrophy, factor H deficiency , may be idiopathic or **may occur after measles**
- reduced serum complement
- C3b nephritic factor (an antibody against C3bBb) found in 70% ➔ **low C3**
- characterised by mesangial cell proliferation with electron-dense, linear intramembranous deposits that stain positive for C3
- may be associated with:
  - Partial lipodystrophy
  - reduced plasma levels of C3, C4
  - hepatitis B or C

Type 3
- Subepithelial and subendothelial deposits
- causes: hepatitis B and C

Management

- steroids may be effective

September 2009 exam: patient of nephrotic syndrome is noted to have marked loss of subcutaneous tissue from the face. What is the most likely underlying cause of her renal disease? Membranoproliferative glomerulonephritis type II (Δ partial lipodystrophy)

September 2009 exam: A patient develops membranoproliferative glomerulonephritis secondary to partial lipodystrophy. Which type of complement is likely to be low? C3

Rapidly progressive glomerulonephritis (RPGN)

Rapidly progressive glomerulonephritis, causes:
- Goodpasture's
- ANCA positive vasculitis

- is a rapid loss of renal function associated with the formation of epithelial **crescents** in the majority of glomeruli.
- results in a rapid decrease in GFR of at least 50% over a short period (a few days to 3 months).
- The most aggressive GN, with potential to cause ESRF over days.

Causes

- Goodpasture's syndrome
- Wegener's granulomatosis
- others: SLE, microscopic Polyarthritis
- **secondary syphilis**

Types

Rapidly progressive glomerulonephritis (RPGN) is classified into three major groups:

- **Type I RPGN** (~3%): Serum anti-glomerular basement membrane (Anti-GBM) antibody is positive. Antibody deposits along the glomerular basement membrane in a linear fashion. Example: Goodpasture syndrome.
- **Type II RPGN**: Immune complex disease (~45% of cases): (Anti-GBM) antibody is negative, but irregular immune complex (antibody-antigen) deposits are found within the glomeruli. Example: lupus nephritis and post-streptococcal glomerulonephritis.
- **Type III RPGN**: (**Pauci-immune** disease (~50% of cases, 80–90% ANCA +ve): Serum anti-neutrophil cytoplasmic (ANCA) antibodies are positive. Example: **Wegener** granulomatosis and microscopic polyangiitis.

Features

- nephritic syndrome: haematuria with red cell casts, proteinuria, hypertension, oliguria
- features specific to underlying cause (e.g. haemoptysis with Goodpasture's, vasculitic rash or sinusitis with Wegener's

Investigations

- Immunofluorescence detects deposits of IgG and C3 in the glomerular BM

- The main pathological finding is **fibrinoid necrosis** > 90% of biopsy specimens with extensive **crescent formation** in at least 50% of the glomeruli. These crescents are collections of epithelial cells and macrophages proliferation within the Bowman's space.

Treatment

- Aggressive immunosup pres sion with high-dose IV steroids and cyclophosphamide
- +/- plasma exchange.

Prognosis: 5-year survival 80%.

January 2012 exam: H/O chronic sinusitis, haemoptysis and microscopic haematuria. cANCA (PR3)= Positive. Given the likely diagnosis, what findings would be expected on renal biopsy? Crescentic glomerulonephritis

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Focal segmental glomerulosclerosis (FSGS)

- cause nephrotic syndrome and chronic kidney disease.
- generally presents in young adults.
- Incidence: 40% in adults. 20% in children of cases of nephrotic syndrome
- **have a high recurrence rate in renal transplants**

Causes

- idiopathic (in 80%)
- secondary to other renal pathology e.g. IgA nephropathy, reflux nephropathy
- **HIV➔ 'collapsing glomerulopathy'**
- **heroin**
- Alport's syndrome
- sickle-cell
- **associated with severe obesity**

Histology

- **histology may appear normal and may be confused with minimal change nephropathy**
- deep glomeruli at the corticomedullary junction are affected first, these may be missed on transcutaneous biopsy, leading to a mistaken diagnosis of a minimal change glomerular lesion
- hyaline deposits consist of IgM, C3, IgA
- fibrinogen are deposited in juxtamedullary capillaries

Treatment

- 50% of (FSGS) do not respond to steroid
- (ACE) inhibitors are a recognised strategy to slow the progression of renal disease.

Prognosis

- It leads to chronic renal failure in 50% of cases.
- FSGS recurs in 40% of renal transplants

January 2011 exam: A patient with H/O heroin abuse, his creatinine = 156, urine show = ++ protein. What is the most likely cause of his deteriorating renal function? Focal segmental glomerulosclerosis (Heroin is a known cause of focal segmental glomerulosclerosis)

Goodpasture's syndrome

Goodpasture's syndrome
- IgG deposits on renal biopsy
- anti-GBM antibodies

Goodpasture's syndrome is characterised by pulmonary haemorrhage and crescentic glomerulonephritis.

Definition
- Goodpasture's syndrome is rare condition associated with both pulmonary haemorrhage and rapidly progressive glomerulonephritis.

Epidemiology
- more common in men (sex ratio 2:1)
- has a bimodal age distribution (peaks in 20-30 and 60-70 age bracket).

Genetics
- associated with **HLA DR2**
- p-ANCA positive in 30% and is directed against myeloperoxidase.

Pathophysiology
- It is a type II cytotoxic reaction caused by anti-glomerular basement membrane (anti-GBM) **antibodies against the α 3 chain of type IV collagen** (basement membrane of both the kidneys and lungs).
- Goodpasture syndrome is due to **IgG antibodies produced against the basement membrane causing damage via a type II hypersensitivity reaction**.

Features
- pulmonary haemorrhage
  - respiratory symptoms can vary from minimal **hemoptysis** to massive **alveolar hemorrhage**, leading to respiratory failure. In lungs, this is a **type 2 hypersensitivity** reaction.
    - Hemoptysis is a clinical feature of Goodpasture's syndrome **due to cross reaction of anti-glomerular basement membrane antibodies** at the lungs.
  - cough
  - Fever
- followed by rapidly progressive glomerulonephritis (RPGN) (Renal impairment is caused by a **crescentic glomerulonephritis**)
  - haematuria
  - proteinuria, and
  - red cell casts.

Factors which increase likelihood of pulmonary haemorrhage

- normally, the alveolar epithelium prevents contact of antibody with basement membrane collagen, thus any **condition that increases permeability of alveoli** can cause triggering of this syndrome. Such susceptibility factors include:
  - smoking
  - lower respiratory tract infection
  - pulmonary oedema
  - inhalation of hydrocarbons and toxic gases
- young males

Investigations

- **serological testing** (for anti-GBM antibodies)
- **biopsy** from kidney rather than lung.
  - Renal biopsy: **linear IgG deposits along basement membrane** (the most likely finding on renal biopsy → **Linear immunofluorescence)**
- raised transfer factor secondary to pulmonary haemorrhages.
- Serial measurement of carbon monoxide (CO) diffusing capacity or transfer factor (Tlco) can be used to monitor progression,

Management

- General management
  - **ABC**
    - **If the patient is hypoxic → intubate and mechanically ventilate the patient.**
  - Patients should not smoke and should avoid hydrocarbon exposure.
- **The most appropriate initial management → IV methylprednisolone and cyclophosphamide**
- plasma exchange (plasmapheresis)
  - Where there is severe haemoptysis, rapid removal of anti-GBM antibody is indicated, and the best way to do this is by plasmapheresis **at a specialist centre.**
  - This is usually accompanied by pulsed therapy with IV methylprednisolone and cyclophosphamide.
- steroids
- cyclophosphamide
  - Response is assessed by monitoring symptoms and anti-GBM antibody titres.
  - Cyclophosphamide and prednisolone continued, typically for 6 - 9 months following remission.

In the acute setting, treatment is focused on:

1. managing life threatening complications of renal failure, such as hyperkalaemia → haemodialysis.
2. Removing the circulating auto-antibody responsible for disease → **plasmapharesis** (therapeutic plasma exchange),
   - **the most important management step in the next few days after haemodialysis**

Prognosis:

- Despite treatment, the **mortality** of Goodpasture's is 11% and it has a high **morbidity** with 60% of patients becoming dependent on dialysis.

- In practice, glomerulonephritis proves to be a much commoner threat to survival than lung haemorrhage,

Other causes of raised anti-GBM antibody levels:

- Some healthy individuals exposed to inhaled oils,hydrocarbons or solvents can have borderline raised anti-GBM antibody levels.
- Anti-GBM antibodies have also been detected in HIV-negative patients with Pneumocystis pneumonia.

Nephrotic syndrome

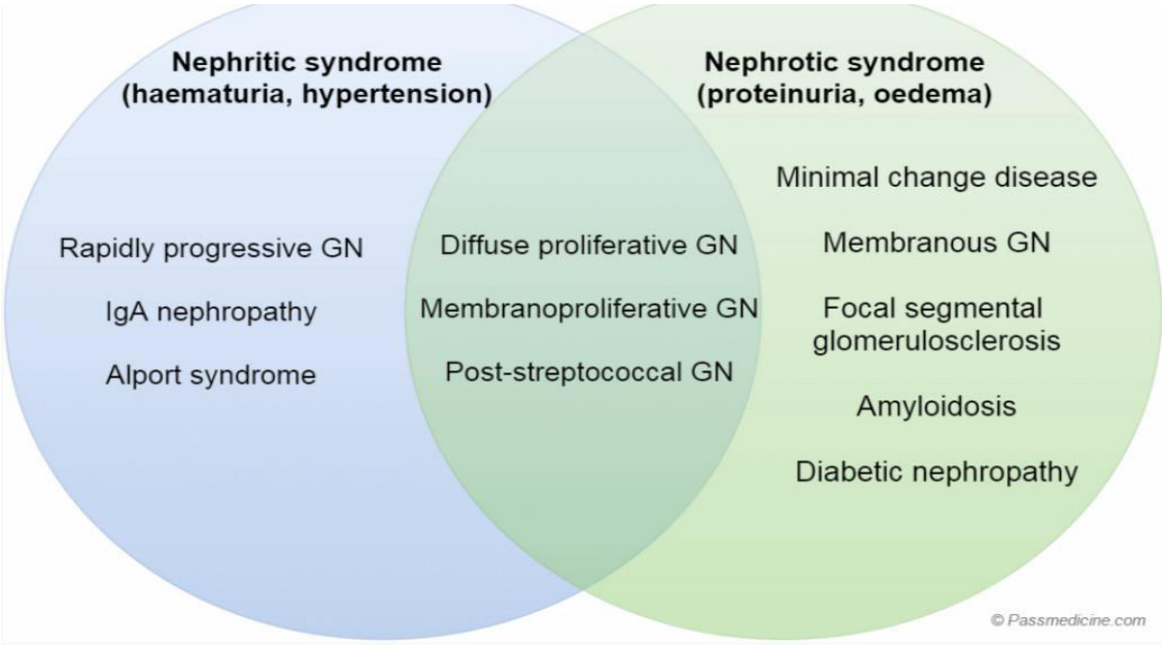
Triad of:

- 1. Proteinuria (> 3g/24hr) **(The minimum proteinuria which is defined as 'nephrotic' is 300 mg/mmol)** causing →
- 2. Hypoalbuminaemia (< 30g/L) and
- 3. Oedema

Other features:

- **Loss of antithrombin-III, proteins C and S and an associated rise in fibrinogen levels predispose to thrombosis.**
- Loss of thyroxine-binding globulin lowers the total, but not free, thyroxine levels.
- **Increased serum cholesterol**
  - **↑(LDL)**
    - LDL and VLDL are removed from serum by lipoprotein signals. If the lipoprotein is lost in the urine with nephrotic syndrome, then the lipid levels in the blood rise.
  - **HDL is usually normal**
- ↓↓ Ca & vit D (loss of 25-hydroxyvitamin D3 (25OHD3) in the urine ➔ hypocalcaemia)
- Serum C3 levels are decreased in immune complex-mediated glomerulonephritis

	Nephrotic	**Nephritic**
Common primary causes	Membranous Minimal change FSGS Mesangiocapillary GN	IgA nephropathy Mesangiocapillary GN
Common secondary causes	Diabetes SLE (class V nephritis) Amyloid Hepatitis B/C	Post streptococcal Vasculitis SLE (other classes of nephritis) Anti-GBM disease (Figs 1 & 2) Cryoglobulinaemia
BP	Normal–mild ↑	Moderate–severe ↑
Urine	Proteinuria >3.5g/day	Haematuria (mild–macro)
GFR	Normal–mild ↑	Moderate–severe ↓



Causes

Nephrotic syndrome - malignancies cause membranous glomerulonephritis

- glomerulonephritis accounts for around 80% of cases
  - minimal change glomerulonephritis (causes 80% in children, 30% in adults)
  - membranous glomerulonephritis
  - focal segmental glomerulosclerosis (FSGS).
    - Patients presenting with **isolated heavy proteinuria without the other components of nephrotic syndrome** is more likely due to **(FSGS).**
  - membranoproliferative glomerulonephritis
- Systemic disease (about 20%)
  - diabetes mellitus
    - (Diabetic nephropathy often presents as nephrotic syndrome but typically develops at least 15 years after onset).
  - systemic lupus erythematosus
  - amyloidosis **(in patient with chronic inflammatory state , amyloidosis is the likely cause of NS)**
- Drugs
  - gold (sodium aurothiomalate), penicillamine
- Others
  - congenital
  - neoplasia: carcinoma, lymphoma, leukaemia, myeloma
    - Chronic lymphocytic leukemia (CLL) and Non-Hodgkin's lymphoma (NHL) are the most common hematologic malignancies associated with glomerular diseases.
    - Membranoproliferative glomerulonephritis (MPGN) are most common glomerular disease associated with CLL and NHL
    - the most common renal lesion associated with Hodgkin's disease is minimal change disease
  - infection: bacterial endocarditis, hepatitis B, malaria **(commonly plasmodium malariae)**

Investigations

- **Renal biopsy**
- *Contraindications for renal biopsy:*
  - Abnormal clotting
  - Hypertension >160/>90mmHg
  - **Single kidney** (except for renal transplants)
  - Chronic kidney disease with small kidneys (<9cm)
  - Uncooperative patient
  - Horseshoe kidney
  - Renal neoplasms.

Serum electrophoresis in nephrotic syndrome

- ↑ serum α- and β-**globulin** fractions. (The increase in globulin fractions is thought to occur due to increased synthesis in patients with urinary protein loss)
- A monoclonal paraprotein band will be present where myeloma is the underlying cause,
- there may be associated immune paresis with reduced concentrations of one or more of the immunoglobulins IgG, IgA or IgM

Complications

- increased risk of infection in particular pneumococcal infections **due to** urinary immunoglobulin loss and decreased splanchnic blood flow.
- **Increased risk of thromboembolism related to loss of antithrombin III** and plasminogen in the urine , increased fibrinogen and increased factor VIIIc. Renal vein thrombosis occurs in 15-20% of patients with nephrotic syndrome
  - **Renal vein thrombosis**
    - Occurs in 10-20%
    - Feature → (loin pain + haematuria) and acute renal injury
    - Initial investigation → US (swollen oedematous kidney)
    - Diagnosis →Duplex US renal veins, CT or MRV
    - Treatment → long term anticoagulation.
- hyperlipidaemia
- hypocalcaemia (vitamin D and binding protein lost in urine)
- acute renal failure
- **Intravascular volume depletion :**Hypoalbuminaemia results in decreased intravascular oncotic pressure, leading to leakage of extracellular fluid from blood to the interstitium

Treatment

- In general, steroids are tried first and then second line agents such as cyclosporin and cyclophosphamide are introduced if needed.
- **Cyclophosphamide is the best treatment for steroid-dependent nephrotic syndrome**
  - No more than two courses of cyclophosphamide should be prescribed in children because of the risk of side effects, which include azoospermia
  - An alternative to cyclophosphamide is ciclosporin, which is effective but must be continued long-term to prevent relapse on stopping treatment. Ciclosporin is also potentially nephrotoxic

January 2006 exam: What changes in patients with nephrotic syndrome predispose to the development of venous thromboembolism? Loss of antithrombin III

Contrast-induced nephropathy

- Contrast media nephrotoxicity may be defined as a 25% increase in creatinine occurring within 3 days of the intravascular administration of contrast media.
  - **Most likely to occur 48 to 72 hours after the administration of intravenous contrast**
- **eg: intravascular contrast agent during angiography**
- A continued **enhancement of the kidneys** days after contrast injection suggests contrast-induced nephropathy.

Risk factors include

- known renal impairment (especially diabetic nephropathy) ➔ **25%**
  - In those patients with pre-existing renal disease & (creatinine > 400 mmol/l) **without** diabetes➔ 60%
  - In those patients with pre-existing renal disease & (creatinine > 400 mmol/l) **with** diabetes➔ 100%
  - In an unselected population the incidence ➔ 2% to 7%
- age > 70 years
- dehydration
- cardiac failure
- the use of nephrotoxic drugs such as NSAIDs
- **Metformin**
  - Metformin is usually withheld for 48 hours after the use of contrast

Prevention

- **Adequate hydration is the most important step to prevent contrast media nephropathy**
  - the evidence base currently supports the use of **intravenous 0.9% sodium chloride at a rate of 1 mL/kg/hour for 12 hours pre- and post- procedure.**
  - There is also evidence to support the use of isotonic sodium bicarbonate.
  - When patients are dialysis-dependent it would be potentially dangerous to "pre-hydrate" the patient and potentially fluid overload them.
- N-acetylcysteine (usually given orally) has been shown to reduce the incidence of contrast-nephropathy in some studies but the evidence base is not as strong as for fluid therapy
- **The magnetic resonance angiography with gadolinium**
  - According to the latest guidelines, the need for a gadolinium-based contrast study should be avoided in any patient with chronic kidney disease stage 3 or greater.
  - **The magnetic resonance angiography with gadolinium is not recommended because it carries a risk of nephrogenic systemic fibrosis**
  - This toxicity of gadolinium cannot be circumvented by hydration or N-acetylcysteine
- Dialysis-dependent patients who receive **contrast for a CT** scan may need haemodialysis to remove the contrast.
- **MR contrast** tends not to be nephrotoxic and therefore haemodialysis is not usually necessary to remove MR contrast.

January 2014 exam: Which one is the most important step in reducing the risk of contrast-induced nephropathy? Intravenous 0.9% sodium chloride pre- and post-procedure

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Analgesic nephropathy

- common in women , F : M = 2: 1 , and presents most often in middle age
- caused by non-steroidal anti-inflammatory drugs (NSAIDs) for **chronic pain or headache,**
- Characteristically, associated with phenacetin use, particularly in Australia and New Zealand
- features may include **anaemia**, chronic renal failure, **symptoms of urinary tract infection**, haematuria or hypertension.
- **Complications**
  - **Urinary tract malignancy** (8-10% of patients with analgesic nephropathy),
  - For example, in women under the age of 50 analgesic abuse is the most common cause of bladder cancer.

Renal stones

Renal stones on x-ray
- cystine stones: semi-opaque
- urate + xanthine stones: radio-lucent

Stag-horn calculi
- composed of Struvite (ammonium magnesium phosphate, triple phosphate)
- form in alkaline urine (ammonia producing bacteria such as Ureaplasma urealyticum and Proteus therefore predispose)

- The most common stones are **calcium oxalate** stones **followed by calcium phosphate.**
- Calcium phosphate stones are seen in renal tubular acidosis (RTA).

Risk factors

- dehydration
- hypercalciuria, hyperparathyroidism, hypercalcaemia
- cystinuria (AR defect in dibasic amino acid transporter)
- high dietary oxalate. hyperoxaluria (for example, XS intake, ileal disease and bypass)
- renal tubular acidosis => (Calcium phosphate stones)
- medullary sponge kidney, polycystic kidney disease
- beryllium or cadmium exposure

- Chronic infection with urea splitting organisms: causes stones made of magnesium ammonium phosphate and calcium phosphate (infection stones (5%)
- Familial : Idiopathic hypercalciuria inherited as autosomal dominant whereas cystinuria, cystinosis, urate uropathy and hyperoxaluria are autosomal recessive conditions.
  - the most common cause being increased gastrointestinal (GI) absorption of calcium.
  - The most common stones are calcium oxalate stones.
- there appears to be a male predominance with a 2:1 ratio.

Risk factors for oxalate stones (Calcium oxalate)

- foods high in oxalate, (such as spinach, rhubarb and tea)
  - In patients who have oxalate kidney stones, dietary restrictions are necessary. Foods that should be avoided include: spinach, nuts, chocolate, dry beans, rhubarb and strawberries.
- calcium-restricted diet
- **gastrointestinal disease such as Crohn's which increase colonic oxalate absorption**
  - in malabsorption, the calcium in the small bowel is bound by the unabsorbed excess fatty acids. Oxalates are left free and are excessively absorbed. Subsequently, they can deposit in the kidney to form stones.
- enteric oxaluria may occur in a number of disorders in which **malabsorption results in excessive colonic absorption of oxalate**. These include:
  - Coeliac disease
  - **Crohn's disease**
  - Chronic pancreatitis, and
  - **Short bowel syndrome.**
    - Bile salts in the colon increase oxalate absorption.
- **Excess vitamin C can be converted to oxalic acid in the body. Subsequent hyperoxaluria can lead to the formation of a kidney stone.**

Risk factors for urate stones

- gout
- ileostomy:
  - loss of bicarbonate and fluid results in acidic urine, causing the precipitation of uric acid
- high purine intake,
- High cell turnover. (for example, haematological malignancy).
  - Primary polycythaemia would predispose to uric acid stone formation, whereas secondary polycythaemia does not.
- Dehydration
- **Thiazide diuretics ➔ cause hyperuricaemia and can predispose to hyperuricosuria and uric acid stone formation**.

Stag-horn calculi (**Triple phosphate stones:** magnesium ammonium phosphate):

- involve the renal pelvis and extend into at least 2 calyces.
- They develop in alkaline urine and are composed of struvite (ammonium magnesium phosphate, triple phosphate).
- Urea plasma urea lyticum and Proteus infections predispose to their formation

- Proteus produces urease, which leads to hydrolysis of urea to produce ammonia, this leads to precipitation of organic and inorganic salts, one of which is known as struvite, or magnesium ammonium phosphate

- **classically produced by urea splitting organisms such as *Klebsiella* or *Proteus*.**

Drug causes

- drugs that promote calcium stones: loop diuretics, steroids, acetazolamide, theophylline
- **topiramate (anti-epileptic) increase the propensity to form calcium phosphate stones.**
- thiazides can prevent calcium stones (increase distal tubular calcium resorption)

Renal conditions associated with recurrent urinary tract infections:

- **Reflux nephropathy**.
- Renal stone (but is less likely than reflux nephropathy)

Hypercalcuria

Thiazide diuretics reduce renal tubular calcium excretion, and therefore can prevent calcium stone formation.

- high urine calcium that is not due to hypercalcemia (idiopathic hypercalciuria)
- Idiopathic hypercalciuria is often familial, the most common cause being increased gastrointestinal absorption of calcium.
- predisposes to stone formation.
- The 24-hour urine is an essential component of the initial evaluation and guides recommendations for prevention
- **Treatment** including dietary calcium restriction and pharmacological management.
- Both thiazide diuretics and potassium citrate can be used to reduce urinary excretion of calcium. **Potassium citrate is generally preferred as it has fewer side effects,** and is therefore better tolerated.
- **Thiazide diuretics are the drug treatment of choice as they act directly on the renal tubule to reduce urinary calcium excretion** (there is a disagreement between onexamination and pastest in which drug is better for hypercalcuria? But after thorough review of sources and uptodate, **thiazide is a better choice than potassium citrate**)
- Dietary calcium restriction alone has minimal effect on calciuria, given the large amount of calcium that can be mobilised from bone..
- Loop diuretics increase urinary excretion of calcium, and therefore would exacerbate calcium renal stone formation.
- Pencillamine is used in the management of hypercalcuria associated with Wilson's disease
- **Idiopathic hypercalciuria** has a familial or sporadic pattern. In the familial pattern an autosomal dominant inheritance is present. The type of the disease is identical in affected members of the same family and **the typical presentation is of recurrent urinary calculi.**

Imaging

The table below summarises the appearance of different types of renal stone on x-ray

Type	Frequency	Radiograph appearance
Calcium oxalate **(the most common)**	40%	Opaque
Mixed calcium oxalate/phosphate stones	25%	Opaque
Triple phosphate stones	10%	Opaque
Calcium phosphate	10%	Opaque
Urate stones	5-10%	Radio-lucent
Cystine stones	1%	Semi-opaque, 'ground-glass' appearance
Xanthine stones	<1%	Radio-lucent

- patients presenting to the Emergency Department usually have a KUB x-ray (shows 60% of stones)
- the imaging of choice is a non-contrast CT (NCCT). 99% of stones are identifiable on NCCT.

Imaging (European Association of Urology guidelines 2016)

- Ultrasound (US) should be used as the primary diagnostic imaging tool.
  - US is safe (no risk of radiation), reproducible and inexpensive.
  - US has a sensitivity of 45% and specificity of 94% for ureteric stones and a sensitivity of 45% and specificity of 88% for renal stones.
  - the preferred method of imaging in pregnant women.
- KUB (kidney-ureter-bladder radiography) x-ray
  - The sensitivity: 44-77% and specificity: 80-87%.
  - should not be performed if NCCT is considered.
  - KUB is helpful in differentiating between radiolucent and radiopaque stones and be used for comparison during follow-up.
- Non-contrast CT (NCCT)
  - **The imaging of choice** is a non-contrast CT (NCCT).
  - become **the standard** for diagnosing acute flank pain
  - 99% of stones are identifiable on NCCT.
  - Following initial ultrasound assessment, use non-contrast-CT to confirm stone
  - more accurate than intravenous urography (IVU), so has replaced it.

- **Imaging in pregnant women**

- first-line → ultrasound as the preferred method of imaging
- second-line → magnetic resonance imaging (MRI)
- last-line option → low-dose computed tomography (CT)

Management
Acute management of renal colic

Medication

- the British Association of Urological Surgeons (BAUS) recommend diclofenac (intramuscular/oral) as the analgesia of choice for renal colic*
  - *Diclofenac use is now less common following the MHRA warnings about cardiovascular risk.
  - It is therefore likely the guidelines will change soon to an alternative NSAID such as naproxen
- BAUS also endorse the widespread use of alpha-adrenergic blockers to aid ureteric stone passage
- Stones < 5 mm will usually pass spontaneously.
- Lithotripsy and nephrolithotomy may be for severe cases.

Prevention of renal stones
Calcium stones may be due to hypercalciuria, which is found in up to 5-10% of the general population.

- high fluid intake
  - **the main initial treatment**
  - should aim for a daily urinary output in excess of 2000 ml.
- low animal protein, low salt diet (a low calcium diet has not been shown to be superior to a normocalcaemic diet)
- **thiazides diuretics (increase distal tubular calcium resorption)** and hence lower calcium concentration in the urine.

Oxalate stones

- cholestyramine reduces urinary oxalate secretion
- pyridoxine reduces urinary oxalate secretion
- **High fluid intake and calcium carbonate are mainstay of prevention.**
- Avoid foods high in oxalate such as chocolate, rhubarb and nuts .
- Increasing dietary calcium intake decreases urinary oxalate excretion by reducing absorption (as free oxalate is bound).
- **Other treatments which can help enteric hyperoxaluria include**:
  - Calcium, cholestyramine and magnesium - bind strongly to free intestinal oxalate, preventing absorption.
  - Iron and aluminium - act as intestinal oxalate binding agents.
  - Potassium citrate - alkalinises the urine, which reduces urinary oxalate excretion.
    - propensity to form stones is reduced when citrate intake is increased.

Uric acid stones

- allopurinol
- urinary alkalinization e.g. oral bicarbonate
- Reducing intake of offal is most helpful at reducing urate excretion

Contraindications to lithotripsy

- **absolute contraindication → uncorrected bleeding disorder**
- relative contraindications → Ureteric stricture, UTI and cardiac pacemaker

September 2008 exam: What is the most likely composition of a stag-horn calculus? Struvite

September 2012 exam: What are stag-horn calculi normally composed of? Magnesium ammonium phosphate

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Cystinuria

- The commonest inborn error of amino acid transport.
- **Amino acids excreted in urine are cystine, ornithine, arginine and lysine (mnemonic - COAL).**
- The glomerulus is unable to resorb these amino acids, and they are therefore excreted into the urine.

Genetics

- **autosomal recessive** condition.
- The rBAT gene is responsible,
- There are two genes identified:
  - SLC3A1 (Chromosome 2)and
  - SLC7A9(Chromosome 19)

Features:

- Cystinuria usually presents with **recurrent nephrolithiasis** in the form of cystine stones (which are often bilateral, multiple, and can form staghorns).
- The renal stones are semi radio-opaque due to the presence of sulphur. (Semi-opaque, 'ground-glass' appearance)
  - On plain film, which is not used as much in the UK any more, they are radio-lucent.
  - On CT, as with almost all stones, cysteine stones are radio-opaque.

Diagnosis

- Diagnosis of cystinuria can be made by **stone analysis**; such stones are pale yellow and analysis reveals high cystine levels. It can then be confirmed by an amino acid chromatogram and quantification of cystine excretion.
- cystine may precipitate out as **pathognomonic hexagonally-shaped crystals**

Management includes:

- conservative

- high fluid intake (>4 L/day);
- alkalinisation
- Urine pH should be regularly monitored (aiming for 7.5-8), with sodium bicarbonate being used if necessary (not in hypertensive patients or those with renal failure).
- The aim of such treatment is to reduce the urinary cystine concentration to below 300 mg/L.

- If this fails, d-penicillamine, alpha-mercaptopropionylglycine or captopril can be used.
- Cystine stones are not easily broken by lithotripsy, and therefore percutaneous removal is most often used.

Cystinosis

- autosomal recessive
- caused by mutations in the CTNS gene, which encodes a lysosomal transporter of the amino acid cystine. Without this transporter, cystine accumulates in the lysosomes of proximal tubule cells, eventually leading to cell toxicity.
- the most common form of Fanconi syndrome in children.
- occurs almost exclusively in whites.

Feature

- presents in the first year of life with
- failure to thrive, and rickets
- progressive renal damage (Renal failure develops before the age of 10 years)
- polyuria, polydipsia
- Visual impairment (occurs as a result of cystine deposits in the retina and cornea)
- hypothyroidism

Renal tubular acidosis (RTA)

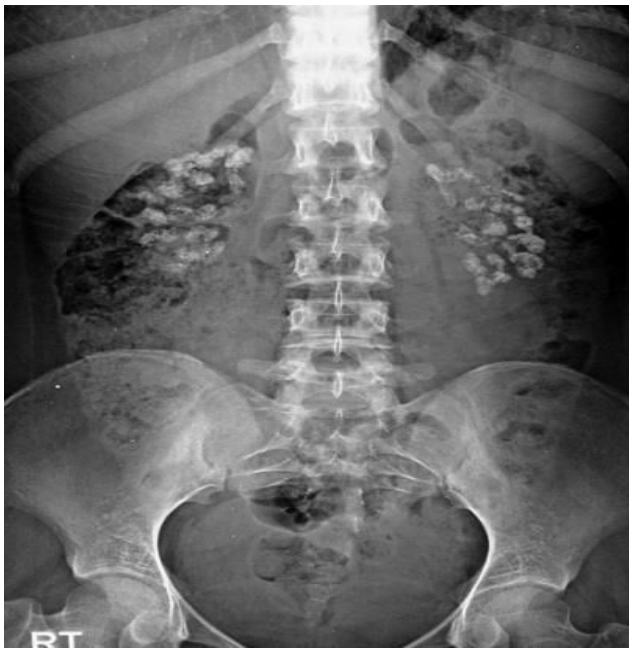
- All three types of renal tubular acidosis (RTA) are associated with hyperchloraemic metabolic acidosis (normal anion gap)

Type 1 RTA (distal) (acid retention)

- **Inability to generate acid urine (secrete H+)** by a failure of the alpha intercalated cells of the **distal tubule** to excrete hydrogen ions.
- **Causes**
  - Idiopathic, gene defects,
  - Autoimmune disease such as primary biliary cirrhosis, thyroiditis RA, SLE, Sjogren's,
  - Drugs: **amphotericin B toxicity**, analgesic nephropathy ,
  - hypergammaglobulinaemic states,
- **Features**
  - hypokalaemia, (as K^+ reabsorption is linked to H^+ excretion).
  - acidosis
  - low urinary ammonium production

- **inability to lower the urinary pH below 5.3** after ammonium chloride administration despite systemic acidosis
- **low urinary citrate**
- **Hypercalciuria:** These predispose to renal stones, rickets or osteomalacia and nephrocalcinosis

- **Complications**
  - nephrocalcinosis and renal stones (Alkaline urine increases the risk of calcium deposition)
  - Osteomalacia develops because of calcium loss and buffering of retained H+ in bone
- **Management**
  - Bicarbonate and potassium supplements should be given to maintain adequate plasma levels.



Abdominal x-ray showing nephrocalcinosis - a classical finding in type 1 RTA

Type 2 RTA (proximal) (bicarbonate loss)

- decreased HCO3- reabsorption in proximal tubule
- very rare in adult practice
- As the distal tubule functions normally, the acidosis is less severe than type 1 RTA, and they urine has a pH of less than 5.3.
- **Causes** include
  - idiopathic,
  - as part of Fanconi syndrome,
  - **Wilson's disease**,
  - cystinosis,
  - outdated tetracyclines
  - carbonic anhydrase inhibitors
- **Features**
  - The cardinal features are acidosis, hypokalaemia and **hypophosphataemia**
  - increased risk for hypophosphatemic rickets.

- **Complications**
  - osteomalacia (Phosphate wasting results in marked bone demineralisation)

Type 4 RTA (hyperkalaemic)(hypoaldosteronism)

- the most common renal tubular disorders
- **Causes** include:
  - **hypoaldosteronism** ,
  - **diabetes**
    - Diabetic nephropathy is associated with decreased renin production.
    - Patients with diabetes may have impaired extrarenal potassium homeostasis, caused by a lack of insulin, and autonomic neuropathy with resulting impaired beta2 -mediated influx of potassium into cells.
  - chronic reflux nephropathy
  - decreased aldosterone production, secondary to:
  - diabetic hyporeninism,
  - angiotensin-converting enzyme inhibitors, angiotensin receptor blockers,
  - non-steroidal anti-inflammatory drugs,
  - heparin,
  - cyclosporine, or
  - adrenal insufficiency.
- **Features:**
  - **hyperkalaemia**
    - usually mild but may be exacerbated by drugs such as beta-blockers and ACE inhibitors.
  - **low sodium**
  - metabolic acidosis
  - reduction in renin and aldosterone leads in turn to a reduction in proximal tubular ammonium excretion
- **Treatment:**
  - Treatment is usually successful with **conservative measures** such as:
    - stopping provocatory agents,
    - low potassium diet.
  - Small doses of **fludrocortisone** could be considered for refractory cases.

Type 3 RTA (Juvenile RTA) is combined proximal & distal RTA.

- autosomal recessive
- Results from inherited carbonic anhydrase II deficiency.
- 70% of the reported cases are from the Magreb region of North Africa
- rarely discussed
- described as a failure to generate NH3 in the setting of a decreased glomerular filtration rate,
- **Features:**
  - normokalaemic hyperchloraemic metabolic acidosis.
  - Asyndrome of osteopetrosis
  - Renal tubular acidosis

- Cerebral calcification
- Mental retardation.

Type	Type 1	Type 2	Type 4
Location	Distal tubules	Proximal tubules	Adrenal
Acidosis?	Yes (severe)	Yes	Mild when present
Potassium	Hypokalemia	Hypokalemia	Hyperkalemia
Pathophysiology	H+ secretion	Bicarb reabsorption	hypoaldosteronism/ pseudohypoaldosteronism

January 2010 exam: Which feature is most likely to be seen as a consequence of type 1 renal tubular acidosis? Nephrocalcinosis

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Renal vascular disease (RAS)

Flash pulmonary oedema, U&Es worse on ACE inhibitor, asymmetrical kidneys → renal artery stenosis - do MR angiography

The presence of difficult to treat hypertension, renal impairment, evidence of other atherosclerotic disease (carotid bruit) and discrepent renal size makes renovascular disease a distinct possibility.

- Renovascular disease is due to disease affecting the arterial supply of the kidney(s).
- The resulting renal hypoperfusion leads to hyperactivation of the renin-angiotensin-aldosterone axis, causing hypertension.
- In one third of cases the disease is bilateral; 40% may have peripheral vascular disease and there may be proteinuria.

Suspicion for renal artery stenosis:

Current UK guidelines with regard to chronic kidney disease recommend **referral for further investigation of atherosclerotic renal artery stenosis** when there is:

- Refractory hypertension (BP >150/90 mmHg despite 3 antihypertensives);
- Recurrent episodes of pulmonary oedema despite normal left ventricular function;
- Rise of >20% serum creatinine or **fall of GFR >15% over 12 months** with high clinical suspicion of widespread atherosclerosis, or during the first 2 months after initiation with an ACE inhibitor or angiotensin receptor blocker.

A rise in serum creatinine **more than 20% above the baseline** after starting an angiotensin-converting enzyme inhibitor (ACEI) should prompt the clinician to hold the drug, monitor renal function and investigate for renal artery stenosis.

Causes

- Atherosclerosis is most common cause (> 95% of patients).
- Arteriosclerosis (renal artery sclerosis) is a more common cause of RAS than fibromuscular dysplasia.
  - 40% may have peripheral vascular disease (PVD) with intermittent claudication
  - there may be proteinuria.
- In younger patients however fibromuscular dysplasia (FMD) needs to be considered.
  - FMD is more common in **young women**
  - and characteristically has a **'string of beads' appearance on angiography**.
  - Patients respond well to **balloon angioplasty**
  - **renal artery narrowing is unlikely to progress**
- Takayasu's arteritis
- Congenital RAS is extremely rare and may be associated with coarctation of the aorta

Associated risk factors

- Smoking and hypertension that cause atheroma elsewhere in the body.

Presentation It may present as:

- Hypertension, which can be resistant to standard treatment.
- chronic renal failure
- 'flash' pulmonary oedema.
- It can also lead to renal impairment when patients are started on ACE inhibitors or angiotensin-II receptor antagonists, hypokalaemia or flash pulmonary oedema**.** A rise in creatinine of 15% from baseline is expected with commencement of an ACE-inhibitor.

Investigation

- **MR angiography is now the investigation of choice** and can be performed safely in patients with CKD stage 3 and 4
- CT angiography. Commonly used, but can be complicated by radio-contrast nepropathy in patients with CKD.
- conventional renal angiography is less commonly performed used nowadays, but may still have a role when planning surgery
- Atherosclerotic renal artery stenosis (RAS) is suggested by the asymmetric reduction in renal size on U/S, with mild proteinuria quite common in the condition.
- ↑↑ Aldosterone
- ↑↑ Renin
  - **Serum renin can differentiate renal artery stenosis (↑↑ Renin +↑↑ Aldosterone) from primary hyperaldosteronism (↓↓ Renin +↑↑ Aldosterone)**
  - ↑↑ Renin work as a mechanism to improve renal perfusion.
  - ↓↓ Renin in primary hyperaldosteronism is due to the resulting hypertension causing excessive renal perfusion, which results in decreased renin production (negative feedback mechanism).

Flash pulmonary edema, U&Es worse on ACE inhibitor, asymmetrical kidneys

↓

Renal Artery Stenosis

↓

do MR angiography

Treatment:

- Optimize vascular risk factors,
- cautious use of ACE inhibitors and angiotensin-II receptor antagonists and avoiding other nephrotoxics.
- **The current evidence favours medical therapy in these patients, that is, an antiplatelet agent (aspirin), lipid lowering therapy (simvastatin) and tight blood pressure control (amlodipine).**
- **No benefit of vascular intervention such as stenting.**
  - The ASTRAL trial showed no significant difference between stenting and medical therapy, it is often decided on an individual level.
- Although patients with unilateral renal artery stenosis who have recurrent pulmonary oedema may benefit from stenting, **the optimal first step is control of hypertension.** *Per se*, better targeting of blood pressure is likely to reduce the number of episodes of heart failure.
- Renal artery **stenting to reduce further risk of pulmonary oedema is the next step following medical therapy to control blood pressure.** The subsequent reduction in renin production will reduce the incidence of heart failure.
- Although surgical renal artery bypass is successful, it is invasive and associated with significant operative morbidity versus percutaneous stent insertion.

Indication for stenting in renal artery stenosis:(mrcpass.com)

- hemodynamically significant renal artery stenosis
  - **Flash pulmonary oedema**
  - episodic pulmonary edema,
  - congestive cardiac failure,
  - unstable angina.

Prognosis

- poor prognosis (**80% mortality at five years**) is related to concurrent coronary disease.

SLE: renal complications

Epidemiology

- Lupus nephritis affects a **third of patients** early in the disease it is frequently unrecognised until nephritic and/or nephrotic syndrome with renal failure occur.

WHO classification

- class I: normal kidney
- class II: mesangial glomerulonephritis
- class III: focal (and segmental) proliferative glomerulonephritis

- class IV: diffuse proliferative glomerulonephritis
- class V: diffuse membranous glomerulonephritis
- **class VI**: **sclerosing** glomerulonephritis
  - **end stage renal disease**
  - **irreversible**
  - **not respond to any immunosuppression**

Class IV (diffuse proliferative glomerulonephritis)

- is the most common
- **the most severe form**, affecting > 50% of glomeruli,
- **Renal biopsy** characteristically shows the following findings:
  - glomeruli shows endothelial and mesangial proliferation, **'wire-loop'** appearance
  - the capillary wall may be thickened secondary to immune complex deposition
    - electron microscopy shows subendothelial immune complex deposits
  - granular appearance on immunofluorescence

Class V (Membranous nephropathy in SLE)

- **Nephrotic syndrome without haematuria in a patient with (SLE) suggests membranous nephropathy (class V)**
- **The lesion is differentiated from idiopathic (non-lupus) membranous nephropathy by**:
  - The presence of tubuloreticular structures on electron microscopy, immune deposits along the tubular basement membrane (in addition to the glomerular basement membrane)
  - and the presence of concurrent subendothelial and mesangial immune deposits (in addition to the subepithelial deposits typical of membranous)
  - Class V lupus nephritis is the only form of renal disease in SLE where serological and clinical manifestations of the underlying disease may be absent. Complement levels may be normal and dsDNA antibodies may be absent

Clinical features

- Hypertension is found at presentation in 20-50%
- 20-30% present with acute renal failure
- **Lupus nephritis typically occurs in SLE patients with extrarenal symptoms such as a rash, arthralgia, Raynaud's phenomenon, and pleuro-pericarditis**

Laboratory features

- Proteinuria is found in all patients with lupus nephritis and in 50-60% of cases is heavy enough to lead to a nephrotic syndrome
- Microscopic haematuria (80% of patients)
- **In lupus nephritis a biopsy is indicated in those patients with abnormal urinalysis and/or reduced renal function , for histological classification ,disease activity, chronicity and prognosis.**

Immunological features

- the pathognomonic feature of lupus on renal biopsy is 'full house' immunology on immunostaining, ie **mesangial deposition of IgA, IgG, IgM, C3 and C4**

  - This differentiates the necrotising glomerulonephritis with crescent formation seen in lupus from a similar pattern which is seen in systemic vasculitis, as the latter condition is 'pauci immune', ie no immunoglobulin deposition
- Lupus nephritis is associated with **activation of the classical pathway**, and often associated with **suppression of both C3 and C4.**

Prognosis

- **Features associated with a poorer prognosis**, and increased risk of progression to end stage renal failure include:
  - young age (<23)
  - Increased serum creatinine
  - Diffuse proliferative lesions (WHO classification class IV) and
  - high chronicity index on renal histologic analysis.

Management

- treat hypertension
- corticosteroids if clinical evidence of disease
- immunosuppressants e.g. azathiopine/cyclophosphamide
- patients with type IV (and sometimes type III, where < 50% of glomeruli are involved) should be treated with a combination of cyclophosphamide and steroids,

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Urinary incontinence

Epidemiology

- Urinary incontinence (UI) is a common problem, affecting around 4-5% of the population.
- It is more common in elderly females.

Causes

- overactive bladder (OAB)/**urge incontinence**: due to detrusor over activity
  - The most common cause of post-prostatectomy incontinence in the patient with Parkinson's disease is detrusor hyperreflexia
  - associated with hereditary spastic paraplegia (HSP)
- **stress incontinence**: leaking small amounts when coughing or laughing
  - Urethral hypermobility is one of the most common causes of stress incontinence, which is common in postmenopausal women.
- **mixed incontinence**: both urge and stress
- **overflow incontinence**: due to bladder outlet obstruction, e.g. due to prostate enlargement
  - Impaired detrusor contractility is the underlying mechanism of overflow incontinence,
- **loss of sphincter function** → Total incontinence
  - is likely to occur in patients with a history of spinal dysfunction (due to previous surgery, trauma, nerve damage, metastasis)

Initial investigation

- bladder diaries should be completed for a minimum of 3 days
- vaginal examination to exclude cystocele
- urine dipstick and culture

Management depends on whether urge or stress UI is the predominant picture.

If urge incontinence is predominant:

- bladder retraining (lasts for a minimum of 6 weeks, the idea is to gradually increase the intervals between voiding)
- bladder stabilising drugs: (antimuscarinic) is first-line
  - **Oxybutynin** is an effective treatment for detrusor instability and is a parasympathetic muscarinic antagonist.
    - Consequently **dry mouth is a problem in up to 70% of cases.**
- surgical management: e.g. sacral nerve stimulation

If stress incontinence is predominant:

- pelvic floor muscle training (for a minimum of 3 months)
- surgical procedures: e.g. retropubic mid-urethral tape procedures

March 2017 part 2: A 72-year-old woman with urinary incontinence. Urodynamic studies confirm detrusor overactivity and significant post-voiding residual volume. She is unable to tolerate oxybutynin for bladder control due to postural hypotension and GI symptoms. Which of the following is the most appropriate intervention for control of her bladder symptoms?

➔ **Sacral nerve stimulator**

Type of incontinence	Pathophysiological mechanism	Key features	Treatment
Stress incontinence	Increase in intra-abdominal pressure (e.g., from laughing, sneezing, coughing, exercising) → ↑ pressure within the bladder → bladder pressure > urethral sphincter resistance to urinary flow	Urinary leakage on activities that **increase intra-abdominal pressure**	General principles of treatment of urinary incontinence Duloxetine, surgery (see "Treatment" in stress incontinence)
Urge incontinence	Inflammatory conditions or neurogenic disorders → sphincter dysfunction, detrusor overactivity or overactive bladder → autonomous contractions of the detrusor muscle and premature initiation of a normal micturition	Strong, sudden sense of **urgency**, followed by involuntary leakage	General principles of treatment of urinary incontinence Anticholinergic medication, surgery (see "Treatment" in urge incontinence)

Type of incontinence	Pathophysiological mechanism	Key features	Treatment
	reflex		
Mixed incontinence	Combination of mechanisms of stress and urge incontinence	May have any of the clinical features above	General principles of treatment of urinary incontinence Anticholinergics to treat aspects of urge incontinence
Total incontinence	Complete loss of sphincter function (due to previous surgery, nerve damage, metastasis) or abnormal anatomy (fistula between urinary tract and skin)	Urinary leakage occurs at all times, with no associated preceding symptoms or specific trigger activity	General principles of treatment of urinary incontinence Usually requires surgery
Overflow incontinence(overflow bladder)	**Impaired detrusor contractility** and/or bladder outlet obstruction → chronically distended bladder with ↑ bladder pressure → dribbling of urine when intravesical pressure > outlet resistance	Frequent, involuntary intermittent/continuous dribbling of urine in the **absence of an urge** to urinate Occurs only when the bladder is full Often occurs with changes in position	Acute settings: **intermittent catheterization** Timed voiding for day to day management Treatment of underlying condition (see also "Treatment" in urinary retention)
Further causes of urinary incontinence	Commonly seen in multiple sclerosis or spinal cord injury **Detrusor sphincter dyssynergia** → simultaneous contractions of the detrusor muscleand involuntary activation of the internal urethral sphincter → blockage of bladder outlet → small	Voiding and/or storage dysfunction, **intermittent voiding, urinary retention** Irregular, small volume **incontinence without an associated urge to void**(sometimes referred to as reflex incontinence)	General principles of treatment of urinary incontinence Injection of botulinum toxininto the detrusor muscle Transurethral resection of external urinary sphincter (TURS) Alpha-blockers and/or anticholinergics

Type of incontinence	Pathophysiological mechanism	Key features	Treatment
	amounts of urine are pressed through the contracted sphincter muscle → high intravesical pressure along with inappropriate contraction of the urethral sphincter		

Urinary retention

Causes: Drugs

- **Amitriptyline has anticholinergic effects being associated with tachycardia, dry mouth and urinary retention.**
- These features are not typical of selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine or seratonin and noradrenaline reuptake inhibitors (SNRIs) such as venlafaxine with urinary retention and dry mouth rarely reported.
- Diazepam, a benzodiazepine does not have anticholinergic effects. It has been associated with urinary retention, but this is much less common than with anticholinergics.

Recovery from obstructive uropathy

- Amelioration of urinary obstruction and subsequent recovery initially results in a large electrolyte and water loss.
- **Osmotic cerebral changes precipitated by urinary sodium loss, the major intravascular cation, is the cause of drowsiness.**
- Hypocalcaemia and hypomagnesaemia may occur as tubular reabsorption is suboptimal in the early stages of recovery, but is unlikely to affect conscious level. Acid-base status should improve after relief of the obstruction.
- Hyperglycaemia is not a common complication of recovery from obstructive uropathy.

Benign prostatic hypertrophy (BPH)

Risk factors

- Age: around 50% of 50-year-old men will have evidence of BPH and 30% will have symptoms. Around 80% of 80-year-old men have evidence of BPH
- Ethnicity: Black > White > Asian

Features

BPH typically presents with lower urinary tract symptoms (LUTS), which may be categorized into:

- Voiding symptoms (obstructive): weak or intermittent urinary flow, straining, hesitancy, terminal dribbling and incomplete emptying
- Storage symptoms (irritative) urgency, frequency, urgency incontinence and nocturia
- Post-micturition: dribbling
- Complications: urinary tract infection, retention, obstructive uropathy

Investigations

- If the suspicion is of prostatic hypertrophy, then **post-void residual volume is the best way to estimate the degree of bladder obstruction.**

Management options

- Watchful waiting
- Medication:
  - **α-blocker (e.g. tamsulosin, alfuzosin) → for rapid symptom relief**
    - Considered first-line, improve symptoms in around 70% of men
    - **α-Blockers relax the smooth muscle of the bladder neck and can improve urinary flow rates**
    - ↓ smooth muscle tone (prostate and bladder)
    - Adverse effects: dizziness, postural hypotension, dry mouth, depression
  - **5 α-reductase inhibitors (e.g. finasteride and dutasteride) → to reduce prostate volume**
    - Block the conversion of testosterone to dihydrotestosterone (DHT), which induces BPH
    - Unlike α-1 antagonists causes a reduction in prostate volume and hence may slow disease progression. This however takes time and symptoms may not improve for 6 months.
    - They may also ↓ PSA concentrations by up to 50%
    - Adverse effects: erectile dysfunction, ↓ libido, ejaculation problems, gynecomastia
  - The use of **combination** (α-1 antagonists, 5 α-reductase inhibitors) therapy was supported by the medical therapy of prostatic symptoms (MTOPS) trial
- Surgery: transurethral resection of prostate (TURP)

Medications for BPH

	α_1-Blockers	5α-Reductase Inhibitors
Drugs	Prazosin, doxazosin, terazosin, tamsulosin.	Finasteride.
Mechanism	↓ contractility of the prostate and bladder neck.	Block testosterone conversion to the more potent dihydrotestosterone.
Results	Improve symptoms and urinary flow rates; more effective than 5α-reductase inhibitors for symptom relief.	Improve symptoms; ↓ prostate size and PSA, especially in men with larger prostates.
Side effects	**Orthostatic hypotension,** nasal congestion, dizziness, fatigue.	↓ libido, ejaculatory dysfunction, impotence.

Prostatic carcinoma

A man of advanced age presenting with bony metastases is most likely to have metastatic prostate cancer.

- These are **adenocarcinomas** and hormonal factors are thought to play a part in the aetiology
- As a rule, prostate cancer is more aggressive in younger men.
- Prostate cancer begins in the outer peripheral zone of the prostate, and grows *outward*, invading surrounding tissue. BPH begins in an area of the inner prostate called the transition zone, a ring of tissue that makes a natural circle around the urethra. In BPH, the growth is *inward* toward the prostate's core.

Epidemiology

- Prostate cancer is now the most common cancer in adult males in the UK and is the second most common cause of death due to cancer in men after lung cancer.
- **By 80 years of age some 80% of men appear to have malignant foci within the prostate gland**
- Prostatic carcinoma is found in 10-30% of patients with BPH.

Risk factors (BPH is not a risk factor)

- ↑ age (the strongest risk)
- obesity
- High intake of animal fats
- low intake of selenium
- Afro-Caribbean ethnicity
- family history: 5-10% of cases have a strong family history

Features

- Localised prostate cancer is often asymptomatic. This is partly because cancers tend to develop in the periphery of the prostate and hence don't cause obstructive symptoms early on.
- bladder outlet obstruction: hesitancy, urinary retention
- haematuria, haematospermia
- pain: back, perineal or testicular
- digital rectal examination: asymmetrical, hard, nodular enlargement with loss of median sulcus

Investigation (NICE 2015)

- lower urinary tract symptoms **or**
- erectile dysfunction **or**
- visible haematuria

} **assess for prostate cancer** → **(PSA)** test and **digital rectal examination**

↑ **PSA**

Refer for P. cancer → **(within 2 weeks)**

- Prostate-specific antigen (PSA)
  - (PSA) may be elevated in:
    - Prostatitis
    - Benign prostatic hyperplasia, and
    - Prostate cancer.
  - Some prostatic carcinomas may not be associated with an elevated PSA.
  - **False positives PSA associated with:**

- **UTI & catheterisation thus should be measured at least two weeks after a treated UTI**.
- prostatic needle biopsy
- PR examination

➢ **False negatives PSA: Finasteride is the only factor likely to decrease the level of serum PSA.**

- **Trans-rectal prostatic biopsy**
  - ➢ The most commonly used pathological grading system is the **Gleason score**
  - ➢ The most well differentiated tumours have a Gleason score of 2, and the most poorly differentiated a Gleason score of 10.
- Bone scan, CT abdomen and pelvis also indicated to assess both extent of bony metastases and local spread. (metastases may mimic the appearance of Paget's)

Management: depends on histological grading of the tumour

prostate cancer stage	Treatment options
Localised (T1/T2) T1 - clinically unapparent disease T2 - palpable disease confined to prostate	• conservative: active monitoring & watchful waiting • radical prostatectomy • radiotherapy: external beam and brachytherapy
Localised advanced (T3/T4) T3 = beyond prostatic capsule T4 = involves bladder neck or rectum Most men will have occult mets	• hormonal therapy: see below • radical prostatectomy • radiotherapy: external beam and brachytherapy
Metastatic	**hormonal therapy** • Synthetic GnRH agonist ➢ e.g. Goserelin (Zoladex) ➢ cover initially with anti-androgen to prevent rise in testosterone • Anti-androgen ➢ cyproterone acetate prevents DHT binding from intracytoplasmic protein complexes **Orchidectomy**

- **Buserelin** (Synthetic GnRH agonist)
  - ➢ **Decreased androgen production**
  - ➢ gonadotrophin releasing hormone agonist that exerts its actions at the level of the pituitary gland.
  - ➢ Initially treatment causes increased gonadotrophin release; however, after a few weeks of continued therapy, gonadotrophin production is inhibited, and testosterone levels fall.
  - ➢ The initial increase in testosterone levels may be accompanied by a 'flare' in disease symptoms in some patients.

What histological grading system is used to grade prostate cancer?

➢ **Gleason grading**

- Gleason grading takes account of the most prevalent tumour pattern in the pathological system (1-5) and the second most prevalent tumour pattern (1-5).

- It is presented as, for example, Gleason 3+4 = 7. This is important as a Gleason 4+3 = 7 obviously has a worse prognosis than a Gleason 3+4 = 7 even though they both have the same total score.

Neurogenic bladder

- Although BPH is the commonest cause of **obstructive renal failure** in older men, the need to consider neurogenic bladder when risk factors for this are present is very important
- Neurogenic bladder is seen in :
  - diabetes mellitus,
  - multiple sclerosis,
  - cerebrovascular disease,
  - **advanced Parkinson's disease,**
  - spinal injuries

Renal cell cancer (also known as hypernephroma)

- accounts for 85% of primary renal neoplasms.
- It arises from proximal renal tubular epithelium

Associations*

- more common in middle-aged men
- smoking
- von Hippel-Lindau syndrome (**the most likely inherited condition)**
  is an inherited syndrome in which cysts or tumours in the kidney, pancreas, adrenal gland, epididymis, cerebellum, and spinal cord may form.(30 - 50% develops renal cell tumors)
- tuberous sclerosis
- *incidence of renal cell cancer is only slightly increased in patients with autosomal dominant polycystic kidney disease

Features

classical triad: haematuria, loin pain, abdominal mass

- only a minority being diagnosed with the classical triad of:Haematuria,Loin pain, A palpable mass.
- Haematuria is the presenting feature in 50-60% of cases
- pyrexia of unknown origin
- Anaemia → Fatigue
- Hypertension
- left varicocele (due to occlusion of left testicular vein)
- endocrine effects:
  - may secrete erythropoietin (polycythaemia) →Increased plasma viscosity.
  - may secrete parathyroid hormone (hypercalcaemia), renin, ACTH
- 25% have metastases at presentation
  - **Commonest sites of metastases are lung (50-60%) and bone (30-40%)**
- Urinalysis may show sterile pyuria
- Liver dysfunction
- Myopathy.

Investigations

- **Ultrasound scan of the renal tract would be the first investigation of choice**, as it is able to pick up 95% of renal cell carcinomas greater than 1 cm in diameter. It would also exclude infective or inflammatory collections within the renal tract.
- If required a computerised tomography (CT) +/- guided biopsy could be obtained to prove the diagnosis.

Management

- for confined disease a partial or total nephrectomy depending on the tumour size
- alpha-interferon and interleukin-2 have been used to reduce tumour size and also treat patients with metatases
- receptor tyrosine kinase inhibitors (e.g. sorafenib, **sunitinib**) have been shown to have superior efficacy compared to interferon-alpha
  - **recommended by NICE as a treatment for advanced renal cell carcinoma.**

Prognosis

- Prognosis is related to tumour staging:
  - the 5-year survival rate is around 80-100% in those with TNM stage-1 lesions, but this falls to 5-10% in those with stage-4 lesions

Wilms' tumour

- Wilms' nephroblastoma is one of the most common childhood malignancies.
- typically presents in children under 5 years of age, with a median age of 3 years old.
- primarily **composed of blastema,** which is primitive kidney mesenchyme.

Features

- abdominal mass (most common presenting feature)
- painless haematuria
- flank pain
- hypertension
- other features: anorexia, fever
- unilateral in 95% of cases
- metastases are found in 20% of patients (most commonly lung)
- Histologic examination is characterized by blastemal, stromal, and epithelial cells (triphasic tumor).

Associations

- Beckwith-Wiedemann syndrome
- as part of **WAGR** syndrome with **A**niridia, **G**enitourinary malformations, mental **R**etardation
- hemihypertrophy
- **around one-third of cases are associated with a mutation in the WT1 gene on short arm of chromosome 11**

Management

- nephrectomy
- chemotherapy
- radiotherapy if advanced disease

prognosis:

- good, 80% cure rate

Angiomyolipoma

- the most common benign tumour of the kidney
- is a benign hamartomatous tumor composed of blood vessels, smooth muscle cells and fat cells.
- caused by mutations in either the TSC1 or TSC2 genes, which govern cell growth and proliferation.
- **Association**
  - commonly seen among patients with tuberous sclerosis.
  - also commonly found in women with the rare lung disease lymphangioleiomyomatosis.
- **Presentation:**
  - retroperitoneal hemorrhage (most frequent)
  - unilateral flank mass.
- **Diagnosis**
  - There are three methods of scanning that detect angiomyolipoma: ultrasound, CT and MRI.
  - Ultrasound is standard and is particularly sensitive to the fat in angiomyolipoma but less so to the solid components. However it is hard to make accurate measurements with ultrasound.
  - Computed tomography (CT) is very detailed and fast and allows accurate measurement. However, it exposes the patient to radiation and the dangers that a contrast dye used to aid the scanning may itself harm the kidneys.
  - Magnetic resonance imaging (MRI) is safer than CT but many patients (particularly those with the learning difficulties or behavioural problems found in tuberous sclerosis) require sedation or general anaesthesia and the scan cannot be performed quickly.
  - Some other kidney tumours contain fat, so the presence of fat isn't diagnostic. It can be difficult to distinguish a fat-poor angiomyolipoma from a renal cell carcinoma and a lesion growing at greater than 5 mm per year may warrant a biopsy in order to distinguish it from this form of cancer.
- **Treatment**
  - Large angiomyolipoma can be treated with embolisation.
  - do not normally require surgery unless there is life-threatening bleeding

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Bladder cancer

Epidemiology

- In the Western world
  - **transitional-cell (TCC) => 93% of bladder cancers**
  - squamous-cell carcinomas (SCCs) ➔ 6%
  - adenocarcinomas ➔ less than 1%
- male: female ratio 3:1
- women generally have a worse prognosis than men.

- At the time of diagnosis around 70% of carcinomas are still localised to the bladder, 20% extend to involve regional lymph nodes and 3% present with distant metastases

Risk factors

- **Risk factors for transitional cell carcinoma of the bladder include:**
  - Smoking
  - Exposure to aniline dyes in the printing and textile industry
  - Rubber manufacture →(exposure to nitrosamines (used in the manufacture of some cosmetics, pesticides, and in most rubber products))
  - Cyclophosphamide
- **Risk factors for squamous cell carcinoma of the bladder include:**
  - Schistosomiasis
  - Calmette-Gurin (BCG) treatment
  - Smoking

Diagnosis

- **Cystoscopy is the gold standard for diagnosing bladder cancer.**

Treatment

- Treatment of choice for localised tumours is transurethral tumour resection, with the use of intravesical chemotherapy.

Orthotopic bladder reconstruction for carcinoma of the bladder:

- **Hyperchloraemic metabolic acidosis is a documented complication of neobladder formation.**
  - Neobladder formation following radical cystectomy or cystoprostatectomy is becoming increasingly more common
  - Severe and persistent metabolic acidosis may manifest when patients undergo further surgery for other reasons.
  - Associated electrolyte abnormalities may include hypokalemia, hypocalcaemia, and hypomagnesaemia.
  - it's usually improves with time and is mild.
  - treat metabolic acidosis with intravenous fluids and bicarbonate.
    - **Intravenous infusion of 1.26% sodium bicarbonate and potassium replacement**

Rhabdomyolysis

Collapse + ARF → rhabdomyolysis - treat with IV fluids

- Rhabdomyolysis will typically feature in the exam as a patient who has had a fall or prolonged epileptic seizure and is found to have acute renal failure on admission
- muscle trauma or necrosis → **myoglobin (**a muscle protein**), which may cause tubular damage** or blockage, intense renovascular constriction, and local inflammation → Acute renal failure
- Rhabdomyolysis is strongly suggested by the fact that urinalysis is strongly positive for blood, whereas urine microscopy is negative for red blood cells. The positive urinalysis is caused by **myoglobin**, a muscle protein released during muscle damage; this appears in the urine and can cause acute renal failure.

Causes

- seizure
- collapse/coma (e.g. elderly patients collapses at home, found 8 hours later)
- ecstasy
- Crush injury: electrical injury, compartment syndrome, prolonged limb or tourniquet anaesthesia, extensive surgical dissection and infectious or inflammatory myopathies.
- McArdle's syndrome
- **Metabolic myopathy**
  - should be suspected when myoglobinuria is recurrent, associated with exercise or fasting and occurring with muscle cramps or weakness
  - **Carnitine palmitoyltransferase (CPT) deficiency is the commonest cause of inherited metabolic myopathy resulting in recurrent myoglobinuria**
  - The enzyme defect is diagnosed using ischaemic forearm testing and muscle biopsy, which demonstrates abnormal lipid or glycogen deposits
- Drugs: statins (**should be stopped in any patient presenting with the syndrome.)**

Features

The biochemical features of rhabdomyolysis are raised creatine kinase, hypocalcaemia (especially early after injury), hyperkalaemia and acute kidney injury.

- acute renal failure with disproportionately raised creatinine
- elevated CK , detectable a few hours after injury and peaks at the 48-h stage
- myoglobinuria, on urine dipstick (shows as haematuria),
  - Urine is dark due to myoglobin.
  - Dipstick will be positive for blood (a false positive). On microscopy no red cells are seen although there may be pigmented granular casts.
- **hypocalcaemia** (myoglobin binds calcium)
- elevated phosphate (released from myocytes)
- hyperuricaemia
- **hyperkalaemia**

Management

- **IV fluids to maintain good urine output**
- urinary alkalinization is sometimes used

Loin pain-haematuria syndrome

- **characterised by severe, unrelenting loin or flank pain and haematuria with dysmorphic features suggesting a glomerular origin**
- A recent report suggested an important **psychological component** (unexplained somatic symptoms, an adverse psychological event preceding the onset of pain and a history of greater analgesic ingestion)
- One possible explanation for the haematuria in some patients is coexistent thin basement membrane disease.

- It was proposed that bleeding into and obstruction of the renal tubules was responsible for the loin pain
- Management
  - difficult to treat
  - Dependency on narcotic analgesia is common
  - Some patients undergo autotransplantation of the affected kidney in an attempt to relieve the pain

Renal tuberculosis

- **The combination of sterile pyuria, haematuria, dysuria and renal tract calcification is highly suggestive of renal tuberculosis**
- Many patients have refractory hypertension, which is renin-mediated and presumably due to segmental renal ischaemia
- **Excretion urography is the most helpful diagnostic investigation**, may show cavitating lesions in the renal papillary areas, commonly with calcification. There may also be evidence of ureteral obstruction with hydronephrosis

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Xantho-granulomatous pyelonephritis (XGP)

Pathogenesis

- It develops as an abnormal macrophage response to infection, particularly in the presence of urinary tract obstruction, and is pathologically related to malacoplakia

Clinical features

- A flank mass is usually palpable, thereby distinguishing it from simple acute pyelonephritis or renal abscess, and occasionally mimicking renal cancer
- The disease is almost invariably unilateral
- Patients with XGP often appear chronically ill
- Symptoms include anorexia, fevers, weight loss and flank pain

Diagnosis

- The relatively rapid history, leukocytosis, renal impairment and positive urine culture make XPN much more probable than cancer
- **Computed tomography is the investigation of choice to confirm the diagnosis**, and it will show the replacement of renal parenchyma by rounded, low-density areas surrounded by a ring of enhancement; it will also establish the extent of the lesion (which may involve surrounding structures)

Prognosis and complications

- The course may extending over months or years
- AA amyloid may develop, resulting in the onset of nephrotic syndrome

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Vesico-ureteric reflux

Vesico-ureteric reflux management:

- in childhood: surgical intervention would be beneficial.
- When picked up in adulthood, the mainstay of management would be
  - blood pressure control
  - **Strict glycaemic control (reduce the frequency of recurrent infections and reduce the risk of progression to diabetic nephropathy.)**
  - prompt treatment of UTI and careful surveillance during pregnancy.

- Vesicoureteric reflux refers to the retrograde flow of urine from the bladder to the upper urinary tract
- **It is the most common cause of recurrent urinary tract infections in children.**
- This may occur due to incompetence of the valve at the vesicoureteric junction
- **It is most commonly detected the earliest in newborn girls**
- Present with recurrent UTI
- **Micturating cystourethrography is the most useful investigation** to check for vesicoureteric reflux during voiding in children. It is identified in approximately 40% of patients. (not useful in adult women because by this time the reflux tends to disappear)
- **the single most appropriate management for grade-V vesicoureteric reflux in child less than 1 year ➔ Antibiotic prophylaxis**

grade	Age(year)	scaring	Initial treatment	Follow up
V	**< 1**	**No**	**Antibiotic prophylaxis**	Surgery
V	1-5	No	If unilateral: antibiotic prophylaxis	Surgery
V	1-5	No	If bilateral: surgery	
V	1-5	Yes	Surgery	
V	> 5		Surgery	

Grading of vesicoureteric reflux

grade	Description
I	Reflux into a non-dilated ureter
II	Reflux into the upper collecting system without dilatation
III	Reflux into a dilated ureter and/or blunting of calyceal fornices
IV	Reflux into a grossly dilated ureter
V	Gross dilatation of the ureter, renal pelvis and calyces; calyces show loss of papillary impression

Chronic reflux nephropathy (Chronic pyelonephritis)

- **Chronic pyelonephritis** is also known as **'reflux nephropathy':**
- starts in infancy or early childhood,
- predisposes to recurrent infections and progressive renal fibrosis and loss of function
- the kidneys are small, shrunken and scarred

Renal scarring

- is a serious complication of chronic pyelonephritis that occurs due to vesicoureteric reflux.
- It is mediated by cytokines, chemokines and their receptors, complement, adhesion molecules and extracellular matrix proteins.
- **The cytokines which seem to play the largest role are:**
  - interleukin (IL)-1beta,
  - IL-3
  - **Transforming growth factor (TGF)-beta.**

- TGF-beta in particular seems to be **pro-fibrotic** by **recruiting fibroblasts**,
- In a genotype where its production is limited has been shown to be less likely to develop renal scarring.

- Chronic reflux nephropathy should be suspected in the presence of multiple urinary tract infections, including during childhood
- may present with difficult-to-treat hypertension in young age
- **The investigation of choice is excretion urography (Micturating cystourethrogram)**, which may show :
  - an irregular renal outline,
  - calyceal clubbing
  - and cortical scarring on the affected side
- The best course of action is to recognise this condition in childhood and consider surgical management where demonstrable ureteric reflux exists, or early intervention with antibiotics where repeat infection exists
- Chronic reflux nephropathy is a relatively common cause of end-stage renal failure in late childhood or early adult life if it goes unrecognized

Recommendations *for the diagnostic evaluation of uncomplicated pyelonephritis*
• Perform urinalysis (e.g. using a dipstick method), including the assessment of white and red blood cells and nitrite, for routine diagnosis.
• Perform urine culture and antimicrobial susceptibility testing in patients with pyelonephritis.
• Perform ultrasound of the upper urinary tract to exclude obstructive pyelonephritis.
• Additional imaging investigations, such as an unenhanced helical computed tomography should be done if the patient remains febrile after 72 hours of treatment or in patients with suspected complications e.g. sepsis.

(European association of urology)

Phimosis

- Phimosis is common in 2 year olds
- **Prognosis and management**
  - **Most will slowly dilate, thus Wait and watch is the most appropriate treatment**
  - In those who have persistent problems into teenage years, around 85% will respond to topical steroids, reducing the need for circumcision
  - Where there is obvious infection, a dorsal slit may be considered

Urethral syndrome

- The condition is common in elderly postmenopausal women due to dryness and atrophy of the urethral tissue
- Presented with dysuria , increased frequency of micturition and sterile urine.
- **Treatment**: **Topical oestrogen cream often results in a dramatic response**

Urinary tract infection (UTI) in adults

***Staphylococcus saprophyticus* is the second leading cause of UTI in sexually active women (*E. coli* is the first).**

Classification of UTI (European association of urology guidelines)	
Uncomplicated UTIs	Acute, sporadic or recurrent lower (uncomplicated cystitis) and/or upper (uncomplicated pyelonephritis) UTI, limited to non-pregnant, pre-menopausal women with no known anatomical and functional abnormalities within the urinary tract or comorbidities.
Complicated UTIs	All UTIs which are not defined as uncomplicated. Meaning in a narrower sense UTIs in a patient with an increased chance of a complicated course: i.e. all men, pregnant women, patients with anatomical or functional abnormalities of the urinary tract, indwelling urinary catheters, renal diseases, and/or with other concomitant immunocompromising diseases for example, diabetes.
Recurrent UTIs	Recurrences of uncomplicated and/or complicated UTIs, with a frequency of at least three UTIs/year or two UTIs in the last six months.
Catheter-associated UTIs	UTIs in a person **currently** catheterised or has been catheterised **within the past 48 hours**.
Urosepsis	A systemic, deleterious host response to infection originating from the urinary tract and/or male genital organs. Urosepsis is accompanied by signs of systemic inflammation, presence of symptoms of organ dysfunction and persistent hypotension associated with tissue anoxia.

Features

- **classic symptoms of (UTI):**dysuria, frequency of urination, suprapubic tenderness, urgency, polyuria, haematuria
- **upper urinary tract infection (UUTI):** evidence of UTI with symptoms suggestive of pyelonephritis (loin pain, flank tenderness, fever, rigors or other manifestations of systemic inflammatory response).
- **lower urinary tract infection (LUTI):** evidence of UTI with symptoms suggestive of cystitis (dysuria or frequency without fever, chills or back pain).

Diagnosis

- Diagnosis of UTI is primarily based on symptoms and signs. Bacteriuria or pyuria do not establish the diagnosis of UTI.
- **The gold standard test** for diagnosis of bacteriuria is culture of bladder **urine obtained by needle aspiration of the bladder** as it minimises the risk of contamination of the urine specimen.
  - All other techniques (urethral catheter and midstream specimens of urine) carry a higher risk of contamination and therefore produce some false positive results
- **nitrite test:**

- Gram negative organisms test positive on the nitrite test as they convert nitrates to nitrites for energy.

- **Gram positive organisms are unable to reduce nitrate to nitrite and therefore, test negative.**

- UTI is **usually diagnosed by** a bacterial count of >100 000/ml at mid-stream urine (MSU)
- **Presentation with a first urinary tract infection associated with haematuria in elderly patient ➔ Re-testing of urine with cytological examination after antibiotics**
- Persistent haematuria should be investigated with excretion urography and cystoscopy

Recommendations for the diagnostic evaluation of uncomplicated cystitis (European association of urology)
Diagnose uncomplicated cystitis based on: • a focused history of lower urinary tract symptoms (dysuria, frequency and urgency); • the absence of vaginal discharge or irritation, in women who have no other risk factors for complicated urinary tract infections.
Use urine dipstick testing, as an alternative to culture for diagnosis of acute uncomplicated cystitis.
Urine cultures should be done in the following situations: • suspected acute pyelonephritis; • symptoms that do not resolve or recur within two-four weeks after the completion of treatment; • women who present with atypical symptoms; • pregnant women.

Management (Sign.uk recommendations for UTI 2012)

- **Men**
  - urine sample should be taken for culture.
  - empirical antibiotics with a quinolone in men with symptoms suggestive of prostatitis.
- **Non-pregnant women**
  - **LUTI**
    - Symptomatic bacteriuria ➔ **three-day course of trimethoprim or nitrofurantoin.**
    - Amoxicillin, ampicillin, nitrofurantoin and oral cephalosporins may be considered as alternatives
    - **Routine urine culture is not required to manage**
    - If not respond to trimethoprim or nitrofurantoin ➔ urine for culture to guide change of antibiotic
    - asymptomatic bacteriuria ➔ Do not treat with an antibiotic.
    - Recurrent UTI ➔ consider using cranberry products to reduce the frequency of recurrence.
  - UUTI
    - ciprofloxacin (7 days) or co-amoxiclav (14 days).
    - Acute pyelonephritis
      - hospital admission should be considered
      - the BNF currently recommends a broad-spectrum cephalosporin or a quinolone (for non-pregnant women) for 10-14 days

- **Pregnant women:**
  - **Treat symptomatic and asymptomatic UTI**
  - Urine culture before starting empiric antibiotic and 7 days after completion empiric antibiotic treatment.
  - **First line agent → Nitrofurantoin**
    - A dose of 50 mg QDS or 100 mg BD of modified release for 7 days is recommended.
    - Care for nitrofurantoin
      - elderly patients may be at increased risk of toxicity.
      - contraindicated in significant renal impairment. The BNF advises against its use in patients with GFR<60.
      - Advise women with LUTI, who are prescribed nitrofurantoin, not to take alkalinising agents (such as potassium citrate).
  - Second line →Trimethoprim
    - contra indicated in established folate deficiency, low dietary folate intake, or women taking other folate antagonists.
  - Third line →cephalosporins
    - There is 20% cross-over with respect to allergy to penicillin and cephalosporins.
  - **Complications**
    - **asymptomatic bacteriuria** is associated with **premature delivery** and **low birthweight**.
      - routine screening for asymptomatic bacteriuria at antenatal appointments is therefore recommended.
    - Infections in pregnancy should be treated, as 25% of patients will develop acute **pyelonephritis**

UTI in diabetes

- Data from the American Diabetes Association have shown that **9.4% of people diagnosed with type 2 diabetes had a UTI** compared to only 5.7% of those without.
- **The most common pathogens isolated from the urine of diabetic patients with UTI were *E. coli*** and other Enterobacteriaceae such as *Klebsiella* spp., *Proteus* spp., *Enterobacter* spp. and Enterococci.
- **Infection with Extended spectrum beta-lactamase-producing *coli* (ESBL-producing *E. coli*) is an increasingly recognised cause of infection in diabetes** patients and is associated with poor outcomes.
  - **Carbapenems are generally considered the drug of choice for the treatment of ESBL/*E. coli* (ESBL–EC) infections**
    - With a half-life of 4 h, **ertapenem** is commonly used as it is administered only once daily.
  - Fosfomycin is an oral antibiotic agent that has broad activity against multi-drug-resistant pathogen, including ESBL–EC.
  - Another oral antimicrobial agent that can be considered for the treatment of ESBL-EC cystitis is nitrofurantoin.

Extended spectrum beta lactamase (ESBL) urine infection → Intravenous meropenem

Antibiotic guidelines for urinary tract:

The following is based on current BNF guidelines:

Condition	Recommended treatment
Lower urinary tract infection	Trimethoprim or nitrofurantoin. Alternative: amoxicillin or cephalosporin
Acute pyelonephritis	Broad-spectrum cephalosporin or quinolone
Acute prostatitis	Quinolone or trimethoprim

Asymtomatic bacteriuria (ABU)

Risk factors for asymptomatic bacteriuria

- Female sex
- Sexual activity
- Comorbid diabetes
- Age
- Institutionalisation
- Presence of catheter

Recommendations for the management of ABU (European association of urology)
• Do not screen or treat asymtomatic bacteriuria in the following conditions: • women without risk factors; • patients with well-regulated diabetes mellitus; • post-menopausal women; • elderly institutionalised patients; • patients with dysfunctional and/or reconstructed lower urinary tracts; • patients with catheters in the urinary tract; • patients with renal transplants; • patients prior to arthoplasty surgeries; • patients with recurrent urinary tract infections.
• Screen for and treat asymptomatic bacteriuria prior to urological procedures breaching the mucosa.
• Screen for and treat asymptomatic bacteriuria in pregnant women with standard short course treatment.
• Take a urine culture following treatment of asymptomatic bacteriuria to secure treatment effect.

UTI in childhood

- In up to 75% cases of single infection, no abnormality can be found
- Escherichia coli is the most common organism isolated (> 70% of cases)
- **Chronic diarrhoea or even acute diarrhoea can be a presenting feature** of childhood urinary tract infection
- Trimethoprim is often the best initial antibiotic of choice
- In children (particularly neonates and infants), UTI can be haematogenous and may be part of a septicaemic process, therefore, blood cultures and iv antibiotics are necessary

Recurrent urinary tract infection (rUTI)

Definition

- two episodes of infection in six months, or three episodes in one year

Incidence

- annual incidence of a single UTI is 30 per 1000 women, with 44% experiencing recurrence within 12 months

Risk factor

Age-related risk factors for rUTI in women

Young and pre-menopausal women	Post-menopausal and elderly women
• Sexual intercourse • Use of spermicide • A new sexual partner • A mother with a history of UTI • History of UTI during childhood • Blood group antigen secretory status	• History of UTI before menopause • Urinary incontinence • Atrophic vaginitis due to oestrogen deficiency • Cystocoele • Increased post-void urine volume • Blood group antigen secretory status • Urine catheterisation and functional status deterioration in elderly institutionalised women

Diagnosis of rUTI

- should be confirmed by urine culture.

Recommendations *for the diagnostic evaluation and treatment of rUTIs*
• Do not perform an extensive routine workup in women with recurrent UTI without risk factors.
• Advise patients on behavioural modifications which might reduce the risk of recurrent UTI.
• Use vaginal oestrogen replacement in post-menopausal women to prevent recurrent UTI.
• Use immunoactive prophylaxis to reduce recurrent UTI in all age groups.
• When non-antimicrobial interventions have failed, continuous or post-coital antimicrobial prophylaxis should be used to prevent recurrent UTI, but patients should be counselled regarding possible side effects.
• For patients with good compliance, self-administrated short term antimicrobial therapy

should be considered.

(European association of urology)

Treatment

- After treating the acute infection, **low dose antibiotics for 6-12 months** are the most evidence based **preventive measure** for recurrent (UTI) in women, and are recommended by Scottish Intercollegiate Guidelines Network and the European Association of Urology guidelines as the standard of care.

Ref:

- http://www.bmj.com/content/359/bmj.j5193
  Non-antibiotic options for recurrent urinary tract infections in women (Published 23 November 2017)
- European association of urology http://uroweb.org/guideline/urological-infections/#3

Recurrent lower urinary tract infection

- **Sexual activity in young females**
  - **Recurrent cystitis may often accompany the onset of sexual activity in young females**
  - The appropriate **first-line management is to advise strict attention to personal hygiene, and an increase in fluid intake** and subsequent urine flow around times of sexual activity
- **Vesicoureteric reflux**
- **Chronic reflux nephropathy:**
  - **the best diagnostic investigation is → Micturating cystourethrogram**
- **Posterior urethral valves**
  - the chief complaint of children with this disorder is a poor urinary stream
- **Urinary tract obstruction in BPH:**
  - post-void residual volume is the best way to estimate the degree of bladder obstruction

Catheter-Associated UTI

- Once catheter is in place, the
- risk of bacteriuria Once catheter is in place:
  - short-term catheterization (ie, 2-4 days) → 10% - 30%
  - long-term catheterization→ 90% -100%
- the most common source of gram-negative bacteremia in hospitalized patients
- **Causes**
  - Enteric pathogens (eg, **Escherichiacoli**) are most commonly responsible
  - ***Proteus* and *Pseudomonas*** species are the organisms most commonly associated with **biofilm growth on catheters**.
  - *Candida*, especially ***Candida albicans*,** is the **second-most-common organism** that can cause catheter-associated urinary tract infection or asymptomatic colonization
- **diagnosis** of catheter-associated urinary tract infection can be made when the **urine culture** shows **100 or more** CFU per mL of urine from a catheterized patient.
- **Treatment**

- **Symptomatic bacteriuria**
  - **mild to moderate infections** :oral quinolones, usually for 10 to 14 days.
  - The recommended duration of therapy for **severe infections** is **14 to 21 days**.
- **asymptomatic bacteriuria**
  - **not recommended**, with the following **exceptions**:
    - patients who are immunosuppressed after organ transplantation,
    - patients at risk for bacterial endocarditis and
    - patients who are about to undergo urinary tract instrumentation

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Urinary tract obstruction in children (posterior urethral valves)

- A poor urinary stream suggests a urinary tract obstruction (usually infravesical)
- **The most common cause in a male child is posterior urethral valves**
- **posterior urethral valves:** symmetrical folds of urothelium extending distally from the prostatic urethra to the external urinary sphincter
- **Renal dysplasia is usually associated with posterior urethral valves**
- **Diagnosis**
  - **The best diagnostic method is a micturating cystourethrography**
  - The other option is endoscopy .
- **Complications**
  - 30% of patients experience end-stage renal disease
  - Vesicoureteric reflux occurs in half the patients

Urinary incontinence (UI)

- (UI) is a common problem, affecting around 4-5% of the population.
- more common in elderly females.

Mechanisms

- **urge** incontinence /overactive bladder (OAB): due to detrusor over activity
- **stress** incontinence: leaking small amounts when coughing or laughing
  - coughing, sneezing, and laughing → ↑ intra-abdominal pressure and overwhelm the strength of bladder sphincter muscles in those with weak pelvic floors.
- **mixed** incontinence: both urge and stress
- **overflow** incontinence: due to bladder outlet obstruction, e.g. due to prostate enlargement
- **Autonomous neurogenic bladder** (detrusor areflexia)
  - caused by damage to the conus, cauda equina, and sometimes S2-4 nerve roots.
  - characterized by absent bladder sensation, decreased tone, increased capacity, hesitancy, and significant residual urine.

Initial investigation

- bladder diaries should be completed for a minimum of 3 days
- vaginal examination to exclude cystocele
- urine dipstick and culture

Management depends on whether urge or stress UI is the predominant picture.

- **If urge incontinence is predominant:**
  - bladder retraining (lasts for a minimum of 6 weeks, the idea is to gradually increase the intervals between voiding)
  - bladder stabilising drugs: antimuscarinic is first-line

        - In older men, **tolterodine** is preferred to oxybutynin as the latter has a greater risk of causing confusion.
        - If anticholinergics fail or are contraindicated, mirabegron may be trialled.
            - Its mechanism of action is via beta-adrenoreceptor-mediated relaxation of the bladder wall.
    - surgical management: e.g. sacral nerve stimulation
- **If <u>stress incontinence</u> is predominant:**
    - pelvic floor muscle training:
        - NICE recommend at least 8 contractions performed 3 times per day for a minimum of 3 months
    - surgical procedures: e.g. retropubic mid-urethral tape procedures

Which pharmacotherapies represents the most appropriate initial management step for overactive bladder? Tolterodine

Notes & Notes

For MRCP part 1 & 11

By

Dr. Yousif Abdallah Hamad

Rheumatology

Updated

2017

Contains:

1/ Passmedicine 2017

2/ On examination 2017

3/ Pastest 2017

4/ **Red fonts --> previous exams**

5/ Other updated UK sources

Hyaline cartilage

- Hyaline cartilage forms the articular surface
- **It is avascular,** relying on diffusion from synovial fluid for nutrients
- It is rich in **type II collagen** and forms a meshwork containing **proteoglycan** molecules that retain water
- Intermittent pressure from joint loading is essential to maintain normal cartilage function
- **Chondrocytes secrete proteoglycans and collagen and are embedded in the cartilage**
- Chondrocytes migrate to the joint surface along with the matrix that they produce

---

Bone markers

- Markers are useful for:
  - prediction of prognosis,
  - prediction of fracture risk,
  - assessing suitability for therapy and
  - monitoring the success of therapy.

Markers of bone formation (measured in serum)	**Markers of bone resorption** (measurable in serum or urine)
• Bone-derived alkaline phosphatase (**ALP**). • Osteocalcin • Procollagen type 1 propeptides.	• Telopeptides • Pyridinium cross-linking molecules • Tartrate-resistant acid phosphatase (TRAP) • Hydroxyproline.

Markers of bone formation

- **Alkaline phosphatase** is useful but not specific to bone.
- **Osteocalcin**
  - is the main non-collagenous protein in bone.
  - During bone formation, osteoblasts make osteocalcin and release some of it into the circulation.
  - Resorption may cause a smaller increase in serum osteocalcin.
- Collagen is made from **procollagen**, with cleavage of N- and C-terminal peptides. These peptides can be measured but are not as sensitive or specific as bone alkaline phosphatase**.**

Markers of bone resorption

- Telopeptides and the pyridinium cross-linking molecules are formed during the hydrolysis of type 1 collagen.
- TRAP is released by osteoclasts directly but the serum also contains TRAP from other sources, making interpretation difficult.
- Hydroxyproline is mainly found in collagens and is excreted in the urine when collagen is broken down: this is also non-specific.

Rheumatoid factor

Rheumatoid factor is an IgM antibody against IgG

- Rheumatoid factor (RF) is a circulating antibody (usually IgM) which reacts with the Fc portion of the patients own IgG.
- **Rheumatoid factor is an antibody with reactivity to the heavy chain of IgG.**
- The rheumatoid factor may be of IgM, IgG or IgA class.
- The conventional (agglutination) test, detects only IgM RF.

- high titre levels are associated with severe progressive disease (but NOT a marker of disease activity).

RF can be detected by either:

- Rose-Waaler test: sheep red cell agglutination
- Latex agglutination test (less specific)

A positive rheumatoid factor is associated with:

- **More severe erosive disease**
- Extra-articular manifestations including subcutaneous nodules and
- Increased mortality.

Conditions associated with a positive RF include:

- Sjogren's syndrome (around 100%)
- Felty's syndrome (around 100%)
- Mixed cryoglobulinemia (types II and III) - 40 to 100%
- rheumatoid arthritis (70-80%)
- Mixed connective tissue disease - 50 to 60%
- infective endocarditis (= 50%)
- SLE (= 20-30%)
- systemic sclerosis (= 30%)
- Polymyositis/dermatomyositis - 5 to 10%
- general population (= 5%)

Rheumatoid arthritis

Rheumatoid arthritis - HLA DR4

Rheumatoid arthritis - TNF is key in pathophysiology

Around 70% of patients with rheumatoid arthritis are HLA-DR4. Patients with Felty's syndrome (a triad of rheumatoid arthritis, splenomegaly and neutropaenia) are even more strongly associated with 90% being HLA-DR4

Epidemiology

- **Prevalence = 1%**
- F:M ratio = 3:1
- there is a slight female preponderance. In younger patients, females have a 2:1 predominance but as age increases this becomes closer to 1:1.
- It appears to be milder in less developed countries, raising the possibility of some new environmental agent that may be more common in industrialised nations.
- peak onset = 30-50 years, although occurs in all age groups
- some ethnic differences e.g. high in Native Americans

Aetiology

- unknown.
- Genetics: (HLA), DRw4, is more common in patients with RA.
- A number of studies have suggested a link between **Proteus mirabilis** infection and the development of RA, and this may contribute to the increased incidence of RA in women, who are more susceptible to **UTI**.
  - *Proteus mirabilis* is a bacterium in fecal flora.
  - ***Proteus mirabilis*** is a Gram-negative, anaerobic, rod
  - molecular structure of Proteus mirabilis is very similar to cells in joints.

- When the immune system develops antibodies to combat the bacteria, the antibodies inadvertently attack the similarly structured joint tissues.

Pathophysiology

Rheumatoid arthritis - TNF is key in pathophysiology

- Cytokines affect all phases of the inflammatory process and tumour necrosis factor (TNF), **interleukin 1**, and interleukin 6 seem to be the most abundant in the joint.
- **TNF is an important in the pathogenesis of rheumatoid arthritis.**
  - TNF is secreted mainly by macrophages
  - TNF blockers (e.g. infliximab, etanercept) are now licensed for treatment of severe RA.
  - See topic about TNF in immunology part
- Rheumatoid arthritis involves **pannus formation**, which leads to cartilage destruction and joint ankylosis.
  - **Pannus** is an abnormal layer of fibrovascular tissue or granulation tissue.
    - Common sites for pannus formation include over the cornea, over a joint surface (as seen in rheumatoid arthritis), or on a prosthetic heart valve.
    - Pannus may grow in a tumor-like fashion, as in joints where it may erode articular cartilage and bone.

Diagnosis

Anti-cyclic citrullinated peptide antibodies are associated with rheumatoid arthritis

NICE have stated that clinical diagnosis is more important than criteria such as those defined by the American College of Rheumatology.

2010 American College of Rheumatology criteria

Target population. Patients who

- 1) have at least 1 joint with definite clinical synovitis
- 2) with the synovitis not better explained by another disease

Classification criteria for rheumatoid arthritis (add score of categories A-D;
a score of 6/10 is needed definite rheumatoid arthritis)

Factor	Scoring	
A. Joint involvement		
	1 large joint	0
	2 - 10 large joints	1
	1 - 3 small joints (with or without involvement of large joints)	2
	4 - 10 small joints (with or without involvement of large joints)	3
	10 joints (at least 1 small joint)	5
B. Serology (at least 1 test result is needed for classification)		
	Negative RF and negative ACPA	0
	Low-positive RF or low-positive ACPA	2

Factor	Scoring	
	High-positive RF or high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)		
	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
D. Duration of symptoms		
	< 6 weeks	0
	> 6 weeks	1

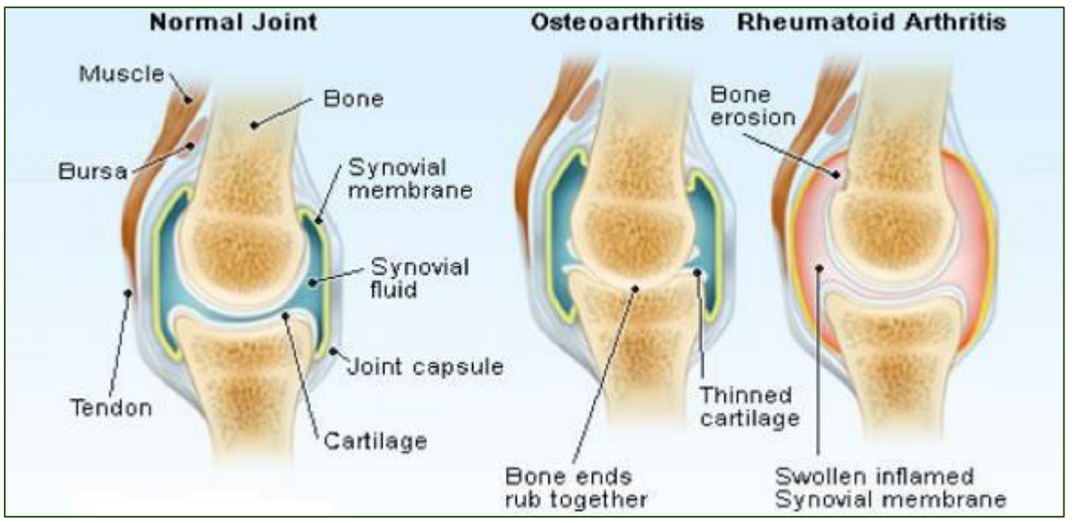
Key

- RF = rheumatoid factor
- ACPA = anti-cyclic citrullinated peptide antibody

Differential diagnosis:

- **Rheumatoid arthritis typically affects the metacarpophalangeal and proximal interphalangeal joints symmetrically. Psoriatic arthritis affects the distal interphalangeal joints and tends to be asymmetrical.**
- **Rheumatoid arthritis vs osteoarthritis**

	Rheumatoid arthritis	Osteoarthritis
pathophysiology	autoimmune (inflammatory)	degenerative due to ↑ wear and tear on joints → loss of cartilage (non-inflammatory)
Age of starting	At any age	Usually later in life
Speed of onset	Rapid, over weeks to months	Slow, over yeas
Pain	**improves with movement**	worse with movement and better with rest
Primary joint affected	**Proximal** interphalangeal	**Distal** interphalangeal
	Metacarpophalangeal	Carpometacarpal
Heberdens nodes	Absent	Present
Joint characteristics	Soft, warm and tender	Hard and bony (little or no swelling)
Stiffness	Worse after resting (morning stiffness)	If present, worse after effort, may be described as evening stiffness
	Usually **>** 1 hour	Usually **<** 1 hour
Systemic symptoms	Present (eg: fatigue)	Absent
RF and anti-CCP	Positive	Negative
ESR and C-reactive protein	Elevated	Normal
x-ray	Osteophytes absent	Osteophytes may be present

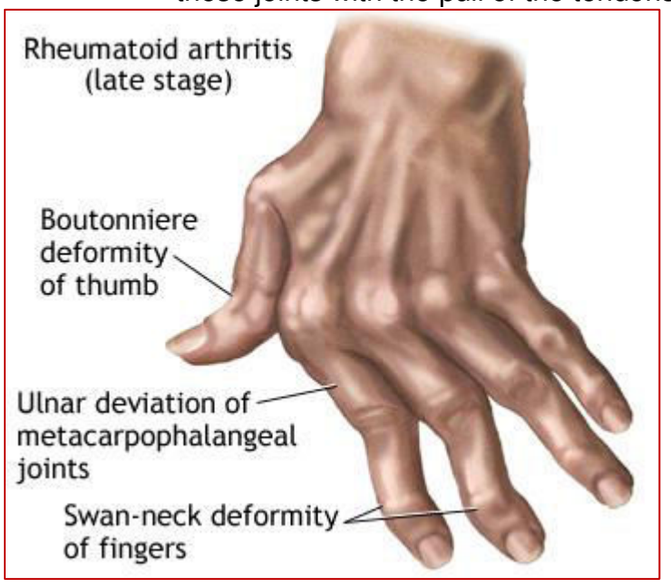


What is the earliest manifestation of rheumatoid arthritis in the feet?

Swelling of the metatarsophalangeal joints

Features

- The most common form, inflammatory arthritis, is characterised by symmetric arthritis of the small joints of the hands and feet that has lasted for >6 weeks.
  - typically affects the proximal interphalangeal, metacarpophalangeal and wrists joints.
  - The sacroiliac joint is spared in rheumatoid arthritis.
- Morning stiffness lasting >1hour
- Extra-articular features, such as:
  - rheumatoid nodules over the extensor surfaces of tendons
  - vasculitic skin involvement
- **Joint deformity:** (in advanced RA with damage to the ligaments and joints).
  - **Swan neck deformity**: DIP hyperflexion with PIP hyperextension.
  - **Boutonniere's deformity**: PIP flexion with DIP hyperextension.
  - **Ulnar deviation**: due to inflammation of the MCP joints, which leads to dislocation of these joints with the pull of the tendons on the dislocated joints.



Lab

- Analysis of synovial fluid
  - **abundant neutrophils**.
  - High protein levels.

Referral

Indications for urgent referral for specialist opinion:

any person with suspected persistent synovitis of undetermined cause. **Refer urgently** if any of the following apply:

- the small joints of the hands or feet are affected

- more than one joint is affected
- there has been a delay of 3 months or longer between onset of symptoms and seeking medical advice.

Investigations

Anti-cyclic citrullinated peptide antibodies are associated with rheumatoid arthritis

- Erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)
  - up to 40% of patients with RA may have normal levels
  - In the early stages of an insidious onset of the RA disease, the acute phase markers CRP and ESR are often normal, particularly when small joints are involved.
  - A normal C-reactive protein can help to exclude the diagnosis of an inflammatory arthritis, but an elevated value is never a specific finding.
- Rheumatoid factor (RF) is positive in about 60% to 70%
- **anti-cyclic citrullinated peptide (CCP) antibodies**
  - Anti-CCP positivity is a prognostic marker.
  - Anti-cyclic citrullinated peptide antibody may be detectable up to 10 years before the development of rheumatoid arthritis.
  - It may therefore play a key role in the future of rheumatoid arthritis, allowing early detection of patients suitable for aggressive anti-TNF therapy.
  - It has sensitivity similar to rheumatoid factor (70-80%) with a much higher specificity of 90-95%.
  - NICE recommends that patients with suspected RA with RF negative should be tested for Anti-CCP Abs.
  - NICE state that: Consider measuring anti-cyclic citrullinated peptide (CCP) antibodies in people with suspected RA if:
    - they are negative for rheumatoid factor, and
    - there is a need to inform decision-making about starting combination therapy
- ANA: present in 20-30% of patients with rheumatoid arthritis.
- **x-ray**
  - **at the early stage, the most likely investigation that will help with a diagnosis are → the X-rays.**
  - **At the stage of early RA → the diagnostically most informative test is hand and feet X-ray → periarticular osteopenia and marginal erosions at affected joints.**
  - Foot joints are often radiologically affected before hand joints.
  - **Periarticular osteopenia and osteoporosis would point towards a diagnosis of (RA).**
    - Loss of joint space is common in both RA and OA also in Pseudogout.

The radiographic features of rheumatoid arthritis can be remembered by the mnemonic LESS: Loss of joint space, Erosions, Soft tissue swelling, and Soft bones (osteopenia)

Early x-ray findings	Late x-ray findings
• loss of joint space • **juxta-articular osteoporosis** • soft-tissue swelling	• periarticular erosions • subluxation

Prognostic features

Poor prognostic features:

- **Anti-CCP antibodies (The poorest prognostic factor)**
- Rheumatoid factor positive
- HLA DR4
- Insidious onset
  - Acute or Sudden onset is not a poor prognosis.
- Poor functional status at presentation
- X-ray: early articular erosions (e.g. within the first 6 months of presentation and in less than < 2 years).
- Extra articular features e.g. nodules
- Female sex.

Complications

Rheumatoid arthritis: patients have an increased risk of IHD

Popliteal cysts ('Baker's cysts') may occur in rheumatoid arthritis following persistent effusion into the knee joint.

Extra-articular complications

- **Ocular:** common, with 25% of patients having eye problems
  - **keratoconjunctivitis sicca (most common)**
    - characterised by **dry**, burning and gritty eyes caused by decreased tear production
    - Other associated symptoms include irritation, redness, discharge, and easily fatigued eyes. Blurred vision may also occur. Scarring of the cornea may occur in some cases without treatment
    - do Tear-film integrity
    - A reflex response to irritation of the corneal surface is epiphora, or watering.
    - Symptoms will be worse when tear-film evaporation is greater,
  - episcleritis (erythema)
  - scleritis (erythema and pain)
  - corneal ulceration,
  - keratitis,
  - Iatrogenic
    - steroid-induced cataracts,
      - 'steroid cataract' is typically **posterior subcapsular**, and causes constant and gradually progressive blur.
      - (Steroids → raised intraocular pressure)
      - Steroids can cause raised blood glucose levels. Fluctuating blood sugar levels can cause osmotic swelling of the lens in the eye, resulting in fluctuations in vision. However, diabetic retinopathy will not affect vision unless maculopathy occurs or vitreous haemorrhage occurs.
    - chloroquine retinopathy

- **Cardiac:**
  - **Constrictive pericarditis is the commonest cardiac complication of rheumatoid arthritis**
  - ischaemic heart disease: RA carries a similar risk to type 2 diabetes mellitus.
- **Respiratory:**
  - pulmonary fibrosis,
  - pleural effusion (**rheumatoid pleural effusion: characterised by → low glucose level)**
  - pulmonary nodules,
  - bronchiolitis obliterans,
  - methotrexate pneumonitis,
  - pleurisy
  - cricoarytenoid arthritis:
    - seen in up to 75% of patients with rheumatoid arthritis.
    - It can cause sore throat, hoarse voice and **stridor**, but is often asymptomatic.
    - **symptoms can rapidly worsen in the post-operative period.**
    - It is unrelated to any lung fibrosis.
    - **the most helpful diagnostic test → Spirometry with flow–volume loop**
    - Also: direct laryngoscopy and high-resolution computed tomography of the larynx.
    - Patients can need urgent tracheostomy and steroids, both orally and via joint injection.
- Osteoporosis
- cord compression
  - The recent limb weakness and the presence of pyramidal signs in the legs in a patient with rheumatoid arthritis are highly suggestive of spinal cord lesion at the cervical or thoracic region.

  - Although plain radiography of the cervical spine is the initial imaging assessment tool for neck pain in patient with rheumatoid arthritis, those with symptoms or signs of cord compression should undergo **immediate MRI** and be sent for surgical consultation.
- Increased risk of infections
  - **Which micro-organisms may be associated with the development of rheumatoid arthritis in susceptible patients? → Proteus mirabilis**
- Depression

Less common

- Felty's syndrome (RA + splenomegaly + low white cell count)
- Amyloidosis
  - **Poorly controlled rheumatoid arthritis + proteinuria and hypoalbuminaemia raises the possibility of systemic amyloidosis → Rectal biopsy**
  - Secondary amyloid A (AA) amyloidosis is an important complication of rheumatoid arthritis (RA) → (~20%).
  - It is caused by extracellular accumulation of AA fibrils, derived from the acute-phase-reactant serum amyloid A protein, within various tissues and organs.
  - Any patient with longstanding RA who develops proteinuria, or intractable diarrhoea, should be investigated for AA amyloidosis.
- **Normocytic, normochromic anemia of chronic disease is very characteristic of RA.**

Atlanto-axial subluxation

Rheumatoid arthritis is the most common inflammatory disease involving the spine. It has a predilection for the craniocervical spine.
The three different patterns of instability which can result are:

- **Atlantoaxial subluxation**
- Atlantoaxial impaction, and
- Subaxial subluxation.

Atlantoaxial subluxation (distance between the arch of atlas and odontoid peg >2.5 mm)

- may occur due to erosion of the odontoid process or due to laxity of the transverse ligament from rheumatoid pannus resulting in posterior subluxation of the odontoid.
- **can lead to cervical cord compression**
- Although radiographic changes are seen in up to 86% of patients, the prevalence of neurological deficit is relatively low.
- Radiographs should be taken laterally with the neck held in flexion.
- Only a minority of patients require surgical management.
- Non-surgical treatment options include patient education, lifestyle modification and regular radiographic follow up.

Management (Nice guidelines 2015)

- Patients with evidence of joint inflammation should start a combination of disease-modifying drugs (DMARD) as soon as possible.
- Other important treatment options include analgesia, physiotherapy and surgery.

Pharmacological management
DMARDS

- **first-line for newly diagnosed active RA → combination of DMARDs (including methotrexate and at least one other DMARD, plus short-term glucocorticoids)** as soon as possible, ideally within 3 months of the onset of persistent symptoms.

- Consider offering short-term treatment with glucocorticoids (oral, intramuscular or intra-articular) to rapidly improve symptoms in newly diagnosed RA if they are not already receiving glucocorticoids as part of DMARD combination therapy.

- If DMARD therapy induce disease control → reduce drug doses to levels that still maintain disease control.

- DMARDs: (**Drug-specific Recommendations** (BSR guidelines February 2017)
  1. Methotrexate (**MTX**) (the most widely used DMARD).
     - All patients should be co-prescribed **folic acid** supplementation at a minimal dose of 5 mg once weekly.

        - Monitoring of FBC & LFTs is essential due to the risk of myelosuppression and liver cirrhosis.
        - Other important side-effects include pneumonitis
    2. Sulfasalazine
    3. Azathioprine (AZA)
        - Patients should have baseline thiopurine methyltransferase (TPMT) status assessed
    4. Leflunomide
    5. Hydroxychloroquine (**HCQ**)
        - Patients should have baseline formal **ophthalmic examination**, ideally including objective retinal assessment for example using optical coherence tomography, within 1 year of commencing an antimalarial drug

Recommended DMARD Blood Monitoring Schedule when Starting or Adding a New DMARD (BSR guidelines February 2017)

- Check FBC, creatinine/calculated GFR, ALT and/or AST and albumin
    - **every 2 weeks** until on stable dose for 6 weeks;
    - then once on stable dose, **monthly** for 3 months;
    - thereafter, at least **every 12 weeks**.
- Contact rheumatology team **urgently** and **consider interruption in treatment** if any of the following develop:
    - white cell count <3.5 × 10^9/l;
    - mean cell volume >105 fL;
    - neutrophils <1.6 × 10^9/l;
    - creatinine increase >30% over 12 months and/or calculated GFR <60 ml/min;
    - unexplained eosinophilia >0.5 × 10^9/l;
    - ALT and/or AST >100 U/l;
    - platelet count <140 × 10^9/l;
    - unexplained reduction in albumin <30 g/l
- **In the setting of acute infection, most DMARDs (except hydroxychloroquine) should be discontinued until the infectious process has resolved.**

Monitoring rheumatoid arthritis

- Measure CRP and key components of disease activity (using a composite score such as DAS28) regularly (**monthly until treatment has controlled the disease)** to inform decision-making about:
    - increasing treatment to control disease
    - cautiously decreasing treatment when disease is controlled.

- Offer people with RA an annual review to:
    - assess **disease activity** and damage, and measure functional ability (using, for example, the Health Assessment Questionnaire [HAQ])
    - check for the development of **comorbidities**, such as hypertension, ischaemic heart disease, osteoporosis and depression
    - assess symptoms that suggest **complications**, such as vasculitis and disease of the cervical spine, lung or eyes

TNF-inhibitor

- The current indication for a TNF-inhibitor is an inadequate response to at least two DMARDs including methotrexate
- Examples of anti-TNF alpha agents:
    - Etanercept
        - SC administration twice weekly
    - Infliximab
        - IV administration
    - Adalimumab
        - SC administration
- Adverse effects of TNF blockers include:
    - reactivation of latent tuberculosis and demyelination.
    - The risk of TB reactivation is most pronounced in the first 3 months of treatment.
    - BTS guidelines therefore recommend a clinical examination, and chest radiograph to check for TB.
    - In the UK, patients have a baseline CXR and assessment of risk of infection with Mycobacterium tuberculosis prior to starting treatment with anti-TNF α.

- Any **patient with active TB**,
  - should receive standard chemotherapy.
  - **They must complete two months full treatment before starting anti-TNF alpha treatment.**
- **Patients with past TB**,
  - who have received previous adequate therapy → can be started on anti-TNF alpha therapy but need to be monitored regularly.
  - TB not previously adequately treated, → chemoprophylaxis should be given before commencing anti-TNF alpha treatment.
  - **What is the optimal TB screening test in patient with previous TB?**
    - **Interferon gamma release assay**
      - The test is not altered by previous TB or previous BCG vaccination.
      - Positive testing indicates a need for anti-tuberculous treatment alongside golimumab, for example isoniazid.
      - Mantoux testing is less indicative of prior infection because it is likely to evoke a positive reaction in patients with previous TB or who have received BCG vaccination.
- **Patients with a normal chest radiograph who have not started immunosuppressive** threrapy, → a tuberculin test is helpful.
- **Patients with a normal chest radiograph + already on immunosuppressive treatment**,
  - the result of the tuberculin test is dampened and it is therefore not useful.
  - An individual risk assessment should be made: **if the annual risk of TB is greater than that of drug-induced hepatitis then chemoprophylaxis should be given**. If not, the patient should be monitored and investigated early if symptoms consistent with TB develop.
  - Chemoprophylaxis is generally with isoniazid for 6 months.

- Patients who test positive with either of Quantiferon Gold test and Elispot tests should be treated with chemoprophylaxis (either isoniazid for 6 months, or dual therapy Rifampicin + INH for 2 months) at the same time as being started on anti-TNF alpha treatment.
- **TNF-inhibitors should be stopped 2-4 wks before any major operation.**

Rituximab

- **Anti-CD20 monoclonal antibody, results in B-cell depletion.**
- Two doses of 1g intravenous infusions are given two weeks apart.
- **Nice guidelines of RA → Rituximab in combination with methotrexate** is recommended as an option for treatment of rheumatoid arthritis who have had an inadequate response to or intolerance of other disease-modifying anti-rheumatic drugs (DMARDs), including treatment with at least one tumour necrosis factor α (TNF-α) inhibitor therapy.

- Treatment with rituximab plus methotrexate should be continued only if:
  - There is an adequate response following initiation of therapy.
  - An adequate response is defined as an improvement in disease activity score (DAS28) of 1.2 points or more.
  - Repeat courses of treatment with rituximab plus methotrexate should be given no more frequently than every 6 months.

Tocilizumab

- **anti-IL 6 receptor monoclonal antibody.**
- It is licensed for the treatment of moderate to severe rheumatoid arthritis (RA) which has responded inadequately to DMARDs or TNF antagonists.

Rheumatoid arthritis: pregnancy

Key points

- patients with early or poorly controlled RA should be advised to defer conception until their disease is more stable
- RA symptoms tend to improve in pregnancy but only resolve in a small minority. Patients tend to have a flare following delivery
- patients should be referred to an obstetric anaesthetist due to the risk of atlanto-axial subluxation

Medications in pregnancy and breast feeding

- **Methotrexate (teratogenic) and NSAIDs (1st trimester, risk of abortion) so they are absolutely contraindicated.**
- methotrexate is not safe in pregnancy and needs to be stopped at least 3 months before conception
- NSAIDs may be used until 32 weeks but after this time should be withdrawn due to the risk of early close of the ductus arteriosus
- leflunomide is not safe in pregnancy
- Prednisolone, Sulfasalazine and hydroxychloroquine are safe in pregnancy
- **Corticosteroids**
  - relatively safe in pregnancy when used in low dose < 20 mg daily.
  - low-dose corticosteroids may be used in pregnancy to control symptoms
  - The routine use of oral calcium and Vit D is recommended.
  - Stress doses of steroids should be used during labour and delivery if the mother received steroids (even low dose) for more than 2-3 weeks during pregnancy, and the neonate should be monitored for evidence of adrenal insufficiency and infection.
- **Sulfasalazine** can be safely used during all stages of pregnancy, it is compatible with breast feeding, although should be advised with cautions because of the rare possibility that the mother is a slow acylator.
- **Azathioprine** can be used in pregnancy if Sulfasalazine and hydroxychloroquine are not controlling.
  - **During pregnancy → continue current dose of azathioprine and add folic acid**
  - Breast feeding is not recommended with azathioprine.
- Prednisolone and hydroxychloroquine may be taken whilst breast-feeding.
- Azathioprine, cyclophosphamide, methotrexate and cyclosporine are contraindicated in breast-feeding mothers.

A piano player in a local hotel c/o morning stiffness, and pain affecting his hips, knees and elbows. On examination he has nodules over his elbows and pain over the PIP joints of his fingers.

What is the most appropriate initial therapy in this man with respect to his long term ability to play the piano? → **Splinting of his fingers for a period**

September 2009 exam: A 25-year-old woman presents with a symmetrical arthropathy affecting her hands. On examination she has synovitis of the 2nd and 3rd metacarpophalangeal joints. What type of HLA allele is most associated with this condition? HLA DR4

A patient of RA on etanercept, scheduled for elective surgery. What advice regarding his medication should be given prior to surgery? → Stop etanercept 2–4 weeks prior to surgery

Updated British Society for Rheumatology (BSR) guidelines (January 2005) for prescribing tumour necrosis factor (TNF-α) blockers in adults with RA recommend:

- **withholding etanercept and other TNF- blockers (infliximab and adalimumab) for 2–4 weeks prior to a major surgical procedure.**
- restarted postoperatively if there is no evidence of infection and once wound healing is satisfactory.

Felty's syndrome:
SANTA

- **S**plenomegaly
- **A**nemia
- **N**eutropenia
- **T**hrombocytopenia
- **A**rthritis (*Rheumatoid*)

Felty's syndrome

- defined as the **triad of rheumatoid arthritis, splenomegaly and leukopenia**

- It is considered an extra-articular manifestation of rheumatoid arthritis,
- occurs more frequently in patients suffering from other extra-articular manifestations such as Sjogren syndrome
- occur in less than 1% of patients with rheumatoid arthritis.
  - ➢ usually occurs in patients with long-standing seropositive RA.
- There is a female preponderance (60-70%).Two-thirds of the patients are females.
- Cases are usually recognised from the fifth decade of life, patients having suffered from rheumatoid arthritis for around 10 years

Feature

- RA, leucopenia, lymphadenopathy and splenomegaly.
- Leg ulcers, recurrent infections and episcleritis may be present.
- **ANA is positive in more than 90% of patients**

Treatment

- **most appropriate initially → Pulsed corticosteroid therapy**
- Pulsed corticosteroid and/or cyclophosphamide therapy may be effective in raising neutrophil counts, as may appropriate switching / intensification of DMARD therapy for the rheumatoid.
- disease-modifying anti-rheumatic drugs (DMARDs) including in severe disease use of cyclophosphamide
- colony stimulating factor to stimulate production of granulocytes.
  - ➢ A few studies have suggested that the short-term use of lithium may be useful in stimulating granulopoiesis
- Splenectomy : usually reserved for patients with severe neutropenia and recurrent infections who fail to respond to medical intervention.

Torn rotator cuff

- torn rotator cuff can occur spontaneously in elderly patients with rheumatoid arthritis.
- The patient is able to abduct the arm, but **the pain worsens during the middle of the range of abduction.**
- Differential diagnosis
  - ➢ Rotator cuff tendonitis:
    - usually insidious in onset with **pain from 0-90 degrees.**

Seronegative spondyloarthropathies

Common features

- associated with HLA-B27
- rheumatoid factor negative - hence 'seronegative'
- peripheral arthritis, usually asymmetrical
- sacroiliitis
- enthesopathy: e.g. Achilles tendonitis, plantar fasciitis
- extra-articular manifestations: uveitis, pulmonary fibrosis (upper zone), amyloidosis, aortic regurgitation

Spondyloarthropathies

- ankylosing spondylitis
- psoriatic arthritis
- Reiter's syndrome (including reactive arthritis)
- enteropathic arthritis (associated with IBD)

Adhesive capsulitis

See endocrinology (diabetes)

Ankle injury: Ottawa rules

- The Ottawa Rules for ankle x-rays have a **sensitivity approaching 100%**
- An ankle x-ray is required only if there is any pain in the **malleolar zone** and any one of the following findings:
  1. bony tenderness at the lateral malleolar zone (from the tip of the lateral malleolus to include the lower 6 cm of posterior border of the fibular)
  2. **bony tenderness at the medial malleolar zone** (from the tip of the medial malleolus to the lower 6 cm of the posterior border of the tibia)

3. **inability to walk four weight bearing steps immediately after the injury and in the emergency department**

- There are also Ottawa rules available for both foot and knee injuries

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Ankylosing spondylitis

Ankylosing spondylitis features - the 'A's
- Apical fibrosis
- Anterior uveitis
- Aortic regurgitation
- Achilles tendonitis
- AV node block
- Amyloidosis

Ankylosing spondylitis - x-ray findings: subchondral erosions, sclerosis
and squaring of lumbar vertebrae

Definition
- seronegative spondyloarthropathy that involves chronic inflammatory disease of the spine and sacroiliac joints.

Pathophysiology
- autoimmune disorder;
- Ankylosing spondylitis is a HLA-B27 associated spondyloarthropathy.
- **It has a polygenic inheritance**.

Epidemiology
- Typically presents in males (sex ratio 3:1)
- Age: 20 – 40 years

Features

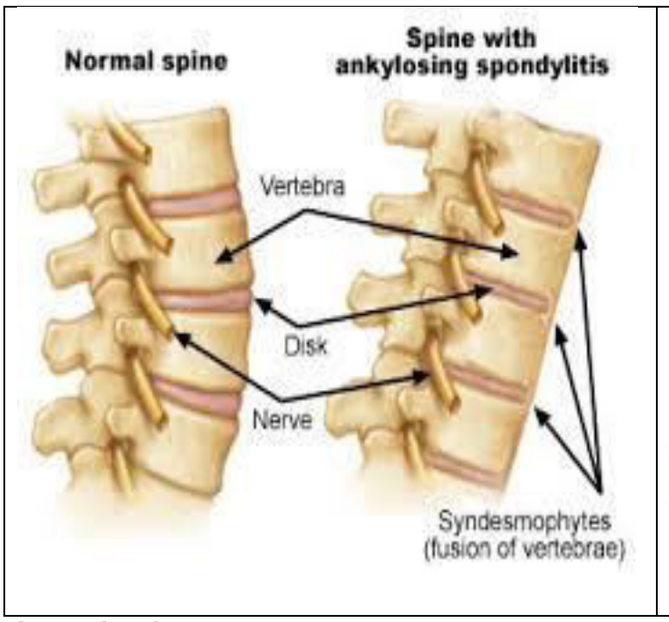
Typically a young man who presents with lower back pain and stiffness of insidious onset

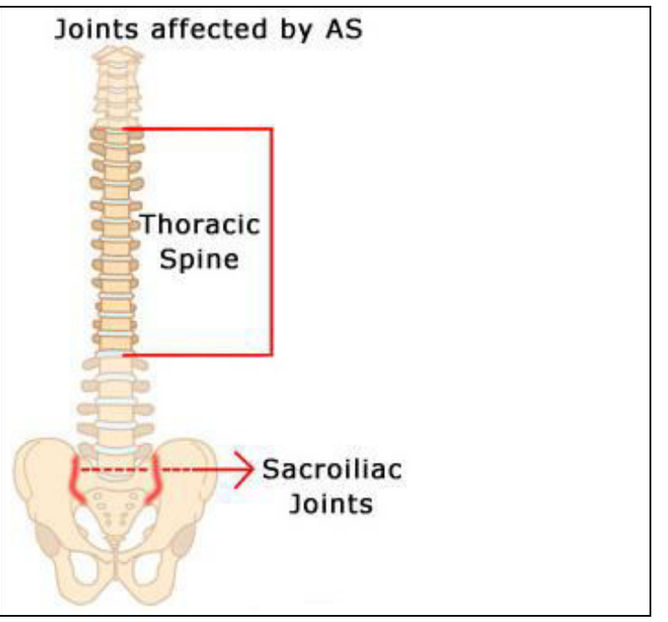
- Stiffness
  - Early morning stiffness of more than 30 minutes
  - usually worse in the morning and improves with exercise
- Back pain
  - the hallmark clinical feature
  - Key features of the pain include:
    - insidious onset
    - Alternating buttock pain
    - Waking in the second half of the night
    - Pain easing with non-steroidal anti-inflammatory drugs (NSAIDs)
    - Pain which is worse with rest and eases with exercise
    - Tenderness over the sacroiliac joints (positive Mennell's sign)

Clinical examination
- **reduced lateral flexion**
- reduced forward flexion (**Positive Schober's test**):
  - While the patient is in a standing position the examiner makes a mark approximately at the level of L5.
  - Two points are marked: 5 cm below and 10 cm above this point (for a total of 15 cm distance).
  - Then the patient is asked to touch his/her toes while keeping the knees straight.
  - If the distance of the two points do not increase by at least 5 cm (with the total distance greater than 20 cm), then this is a sign of restriction in the lumbar flexion.
- reduced chest expansion
- **accentuated** thoracic kyphosis
- **loss of** lumbar lordosis

Associations - the 'A's:

- Anterior **uveitis**
  - **The most common extra-articular manifestations** (in around 40% of patients)
  - Usually acute, unilateral anterior uveitis
  - more common in B27 positive than B27 negative patients.
- Apical fibrosis
- Aortic regurgitation
- Achilles tendonitis
- AV node block
- Amyloidosis
- cauda equina syndrome
- peripheral arthritis (25%, more common if female)
- features of inflammatory bowel disease (diarrhea with blood) (seen in around 5%)
- IgA-nephropathy
- Dactylitis
  - An inflammation of the fingers and/or toes
  - seen also in rheumatoid arthritis, sarcoidosis, and sickle-cell disease.



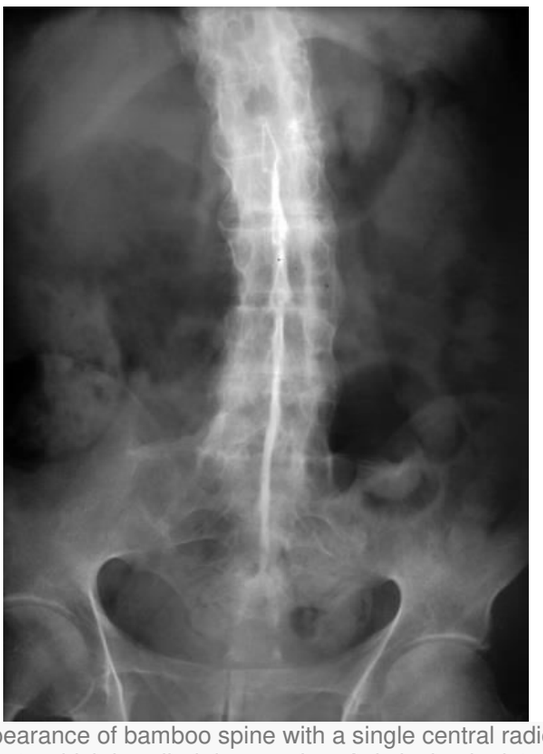


Investigations

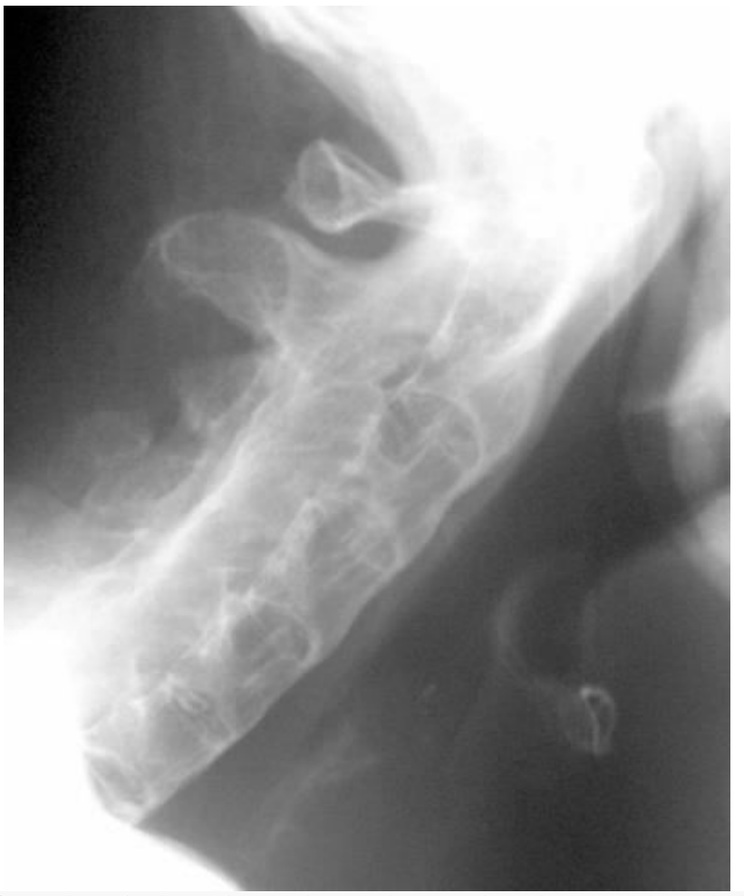
the best option to confirm a diagnosis of ankylosing spondylitis → Sacroiliac joints x ray

- Inflammatory markers (ESR, CRP) are typically **raised** although normal levels do not exclude ankylosing spondylitis.
- HLA-B27 is of little use in making the diagnosis because
  - it is positive in 90% of patients with ankylosing spondylitis and 10% of normal patients
  - **The likelihood of a positive test depends on the racial and ethnic background of the patient**
    - **The commonest subtype HLA associations** are
      - **HLA B*2705** (Caucasians),
      - **B*2704** (Chinese, Japanese) and
      - **B*2702** (Mediterranean).
      - The B*2706 subtype is weakly associated and commonly found in normal south east Asian individuals.
- Radiographs
  - **Plain x-ray of the sacroiliac joints is the most useful investigation in establishing the diagnosis**.
  - Radiographs may be normal early in disease, later changes include:
    - sacroilitis: subchondral erosions, sclerosis
    - squaring of lumbar vertebrae
    - 'bamboo spine' (vertebral fusion) (late & uncommon)

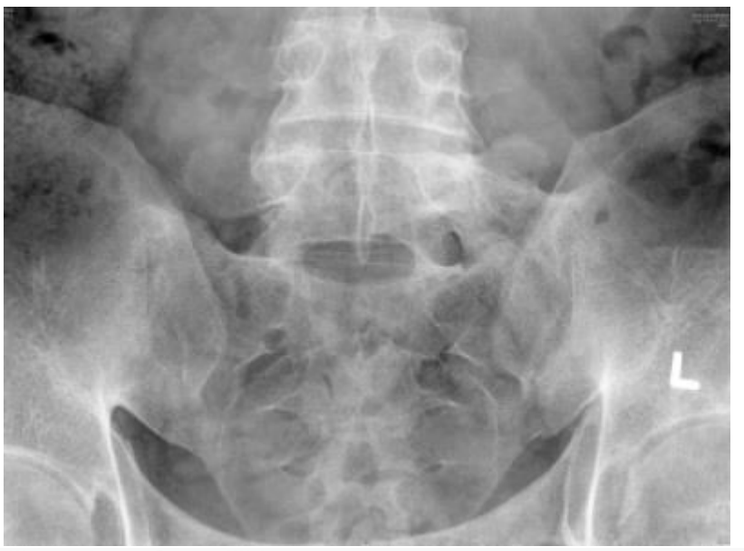
- syndesmophytes: due to ossification of outer fibers of annulus fibrosus (**The tramline appearance** is due to syndesmophyte growth between the margins of the vertebrae)
  - ❖ Syndesmophytes grow vertically, as opposed to spondylophytes, which grow horizontally
- chest x-ray: apical fibrosis



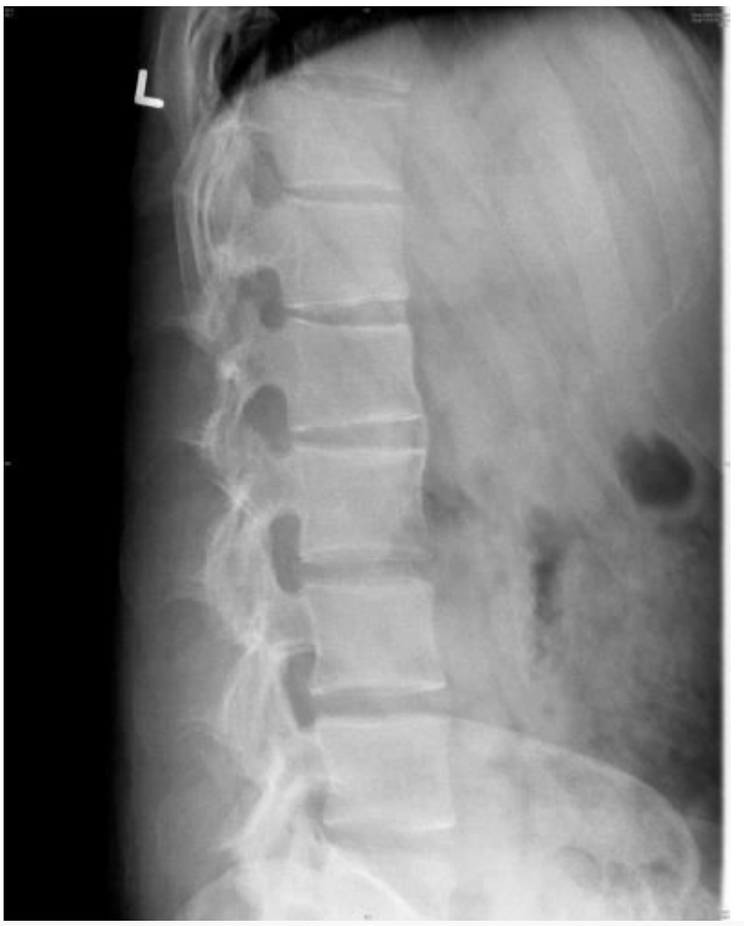
40-year-old male. There is typical appearance of bamboo spine with a single central radiodense line related to ossification of supraspinous and interspinous ligaments which is called dagger sign. Ankylosing is detectable in both sacroiliac joints



Lateral cervical spine. Complete fusion of anterior and posterior elements in ankylosing spondylitis, so called bamboo spine



Fusion of bilateral sacroiliac joints. Sacroiliitis may present as sclerosis of joint margins which can be asymmetrical at early stage of disease, but is bilateral and symmetrical in late disease



Syndesmophytes and squaring of vertebral bodies. Squaring of anterior vertebral margins is due to osteitis of anterior corners. Syndesmophytes are due to ossification of outer fibers of annulus fibrosus

- **MRI:**
  - **More sensitive than x-ray**
  - Best method for early detection
  - Shows:
    - **bone marrow edema** (The **earliest change** visible on MRI)
    - squaring of the vertebrae ,
    - erosion of apophyseal joint
    - obliteration of sacroiliac joint

- **Spirometry** may show a **restrictive defect** due to a combination of pulmonary fibrosis, kyphosis and ankylosis of the costovertebral joints.

New York criteria

- Current British Society for Rheumatology recommendations state that the modified New York criteria should be used to diagnose ankylosing spondylitis:
  - **Clinical criteria:**
    - Low back pain, present for more than three months, improved by exercise but not relieved by rest
    - Limitation of lumbar spine motion in both the sagittal and frontal planes
    - Limitation of chest expansion relative to normal values for age and sex.
  - **Radiological criteria**:
    - Sacroilitis on x ray.
  - **Diagnosis:**
    - Definite AS if the radiological criterion is present plus at least one clinical criterion
    - Probable AS if three clinical criteria are present alone or if the radiological criterion is present but no clinical criteria are present.

Management (2010 EULAR guidelines)

- Non-pharmacological:
  - encourage regular exercise such as swimming
  - physiotherapy
- Pharmacological
  - **NSAIDs**
    - **NSAIDs are the first-line treatment**
  - ***Anti-TNF therapy***
    - **The second line**
    - the 2010 EULAR guidelines suggest: *'**Anti-TNF therapy** should be given to patients with persistently high disease activity despite conventional treatments'*
    - The anti-TNF drugs are currently only used for patients with severe ankylosing spondylitis which has failed to respond to NSAIDs.
    - research is ongoing to see whether anti-TNF therapies such as etanercept and adalimumab should be used earlier in the course of the disease
  - Disease-modifying drugs
    - the disease-modifying drugs which are used to treat rheumatoid arthritis (such as sulphasalazine) are only really useful if there is **peripheral joint involvement**
    - where there is proved **inflammatory bowel disease**, many patients are started on sulfasalazine, as this may be a useful disease-modifying agent for both bowel and joint disease.

Avascular necrosis

Avascular necrosis (AVN) may be defined as death of bone tissue secondary to loss of the blood supply. This leads to bone destruction and loss of joint function. It most commonly affects the epiphysis of long bones such as the femur.

Causes

- long-term steroid use
- chemotherapy
- alcohol excess
- trauma

Features

- initially asymptomatic
- pain in the affected joint

Investigation

- plain x-ray findings may be normal initially
- **MRI is the investigation of choice.** It is more sensitive than radionuclide bone scanning
- treated with **lifelong warfarin with target INR 2-3**

Behcet's syndrome

Oral ulcers + genital ulcers + anterior uveitis = Behcet's

Overview

- Behcet's syndrome is a complex multisystem disorder associated with presumed autoimmune mediated inflammation of the arteries and veins.
- affects small and large vessels (venous and arterial).
- The pathogenesis of Behcet disease involves mainly the T helper cells.
- associated with HLA B5* (More than 60%)and MICA6 allele
  - *more specifically HLA B51, a split antigen of HLA B5
  - HLA B5 is associated with ocular disease;
  - **HLA B12 is associated with recurrent oral ulcers.**

Epidemiology

- more common in the eastern Mediterranean (e.g. Turkey)
- more common and more severe in men
- tends to affect young adults (e.g. 20 - 40 years old)
- around 30% of patients have a positive family history

Features

- **The classic triad of symptoms are: 1) oral ulcers 2) genital ulcers 3) anterior uveitis (iritis)**
- thrombophlebitis
- Seronegative arthritis
  - Usually asymmetric arthritis.
- neurological involvement (e.g. aseptic meningitis)
- GI: abdominal pain, diarrhoea, colitis
- erythema nodosum, DVT
- pathergy (development of pustules at venepuncture sites).
- Fever

Diagnosis

- no definitive test
- diagnosis based on clinical findings
- positive **pathergy test** is suggestive (puncture site following needle prick becomes inflamed with small pustule forming)
- **Pathergy** is the non-specific hyper-reactivity of the skin following minor trauma, and is **specific to Behcet's disease**. It involves intradermal injection of skin with a 20-gauge needle under sterile conditions. It is considered **positive if an erythematous sterile papule develops within 48 hours.**
- The International Study Group **criteria** for classification of Behcet's disease requires the presence of **recurrent oral ulceration** (minor aphthous, major aphthous or herpetiform ulceration observed by physician or patient, which have recurred at least three times in a 12 month period), **and two of the following:**
  - Recurrent genital ulceration: aphthous ulceration or scarring, observed by physician or patient
  - **Eye lesions**: anterior uveitis, posterior uveitis, or cells in vitreous on slit lamp examination; or retinal vasculitis observed by ophthalmologist
  - **Skin lesions**: erythema nodosum observed by physician or patient, pseudofolliculitis or papulopustular lesions; or acneiform nodules observed by the physician in post-adolescent patients not on corticosteroid treatment
  - **Positive pathergy test:** read by physician at 24-48 hours.

Treatment

- **Colchicine is the first line treatment.**
- Anterior uveitis associated with Behcet disease is treated with topical corticosteroids.

Charcot joint (Charcot's arthropathy) See endocrinology (diabetes)

Chronic fatigue syndrome

Definition

- Diagnosed after at least **4 months** of **disabling fatigue affecting mental and physical function more than 50% of the time** in the **absence of other disease** which may explain symptoms.

Epidemiology

- more common in females
- past psychiatric history has **NOT** been shown to be a risk factor

Fatigue is the central feature, other recognised features include

- sleep problems, such as insomnia, hypersomnia, unrefreshing sleep, a disturbed sleep-wake cycle
- muscle and/or joint pains
- headaches
- **painful lymph nodes without enlargement**
- Recurrent sore throat
- cognitive dysfunction, such as difficulty thinking, inability to concentrate, impairment of short-term memory, and difficulties with word-finding
- physical or mental exertion makes symptoms worse
- general malaise or 'flu-like' symptoms
- dizziness
- nausea
- palpitations

To confirm a diagnosis of fatigue the following main features need to be present:

- must be new in onset, persistent or recurrent and unexplained by other conditions.
- should be characterised by post-exertional malaise.
- should result in a substantial reduction in activity level.

Red flag symptoms which suggest another diagnosis include:

- Significant weight loss
- Inflammatory arthropathy or connective tissue disease
- Localising or focal neurological signs.

Investigation

- NICE guidelines suggest carrying out a large number of screening blood tests to exclude other pathology e.g. FBC, U&E, LFT, glucose, TFT, ESR, CRP, calcium, CK, ferritin* (*children and young people only), coeliac screening and also urinalysis

Management

- **treatment of choice: graded exercise therapy**
  - a formal supervised program,
  - not advice to go to the gym
  - 'pacing' - organising activities to avoid tiring
- cognitive behaviour therapy - very effective,
- low-dose amitriptyline may be useful for poor sleep
- referral to a pain management clinic if pain is a predominant feature

Prognosis

- Better prognosis in children

Compartment syndrome

Pain with passive stretching of the muscles, is the earliest clinical indicator of compartment syndrome.

- Patients with compartment syndrome typically present with **pain whose severity appears out of proportion to the injury**
- The pain of compartment syndrome is often:
  - described as burning, deep and aching in nature
  - **worsened by passive stretching of the involved muscles**.
  - The patient may describe a tense feeling in the extremity.
- The most important diagnostic physical finding is a firm, wooden feeling on deep palpation.

- **Decreased 2-point discrimination is the most consistent early finding**
- in acute anterior lower leg compartment syndrome, the first sign to develop may be numbness between the first 2 toes (superficial peroneal nerve).
- A **Creatine phosphokinase (CPK)** concentration of 1000-5000 U/mL or greater or the presence of **myoglobinuria** can suggest compartment syndrome.
- **Measurement of intracompartmental pressures** remains the **standard for diagnosis** of compartment syndrome.

Risk factors

- Trauma
- Anticoagulation therapy and bleeding disorders (eg, hemophilia) significantly increase the likelihood of compartment syndrome.
- Vigorous exertion may lead to compartment syndrome. Compartment syndrome has been found in soldiers and athletes without any trauma.
- If compartment syndrome is suspected, check intracompartmental pressure, even in the absence of any trauma history.

structures at risk

Forearm compartments and structures at risk:

- ventral compartment - median and ulnar nerves; radial and ulnar arteries
- dorsal compartment - posterior interosseous nerve; no major vessels

Lower limb and structures at risk:

- anterior tibial compartment - deep peroneal nerve; anterior tibial artery
- superfical posterior compartment - no major nerves or vessels
- deep posterior compartment - posterior tibial nerves and vessels; peroneal artery
- peroneal compartment - deep and superfical peroneal nerves
- Loss of peripheral pulses is a late sign indicating that the pressure within the compartment has exceeded arterial blood pressure.
- Compartment syndrome can occur in the absence of a fracture, for example, crush injuries.
- Pain is the earliest and most reliable symptom of the onset of compartment syndrome.
- **Passive stretch of the muscles traversing the compartment increases pain.**
- Treatment involves decompression of the affected compartment(s) including the skin.

Feature

High risk injuries are fractures of the forearm and lower leg, especially those that have been internally fixed or infected.

Early features of an evolving compartment syndrome are:

- increasing pain despite immobilisation
  - **Passive stretch of affected muscles exacerbates pain**
- sensory deficit in the distribution of the peripheral nerve(s) passing through that compartment
- swelling and tenderness of the muscle compartment
- pain on passive stretching of muscles within the compartment - for example, passive extension of the toes or fingers causing increased pain in the calf or the forearm

Late features are those of tissue ischaemia with additionally, pallor, pulselessness, paralysis, coolness and loss of capillary return

Treatment

- Early orthopaedic referral and continuous instrumented pressure monitoring is necessary.
- **Urgent decompression is required to prevent severe ischaemia.**
- All potentially constricting dressings, casts and splints must be removed
- The compartment pressure should be measured. **Open fasciotomy is indicated if it is above 40 mm Hg**. Otherwise, the limb should be closely observed until improvement is apparent clinically.
- If no improvement occurs, perform a fasciotomy, which in the leg, may mean opening all four compartments.

Complex regional pain syndrome (CRPS)

- **characterized by severe pain out of proportion to the original injury and is often accompanied by sensitivity, swelling, and changes in the skin**
- three times **more frequent in females** than males

- It may initially affect one limb and then spread throughout the body; 35% of affected people report symptoms throughout their whole body
- Precipitating factors
  - injury and
  - surgery
- CRPS type I caused by event, such as a crush or soft tissue injury; or by immobilization, such as a tight cast or frozen shoulder.
- CRPS type II caused defined nerve injury.
  - Type II, formerly known as causalgia
- Electromyography (EMG) and Nerve Conduction Studies (NCS) are the most reliable methods of detecting nerve injury. They can be used as one of the primary methods to distinguish between CRPS I & II, which differ based on whether there is evidence of actual nerve damage.
- The most common symptoms are pain sensations, including burning, stabbing, grinding, and throbbing. Moving or touching the limb is often intolerable.
- Both types demonstrate continuing pain, allodynia, or hyperalgesia that is usually disproportionate to the inciting event.
  - **allodynia** (pain resulting from a stimulus which would not normally provoke pain, such as a light touch of the skin) (perception of pain from a nonpainful stimulus)
  - **hyperalgesia** (an exaggerated sense of pain) disproportionate to the inciting event
- At some point during the syndrome's development, both show evidence of edema, changes in skin blood flow revealed by color changes and skin temperature changes greater than 1.1°C from the homologous body part, or abnormal sudomotor activity in the painful region.

A repeat X-ray is the most appropriate next investigation looking for patchy osteoporosis in patient developed clinical features consistent with complex regional pain syndrome type 1 (CRPS1)

Cryoglobulinaemia

consumption of C4 + strongly positive rheumatoid factor → cryoglobulinaemia.

- Cryoglobulins are abnormal immunoglobulins which precipitate when cooled below 37°C (maximum precipitate formation takes place at +4°C) and redissolve in plasma when warmed back to 37°C (**reversible precipitation at low temperatures**)
- The precipitated clump can block blood vessels and cause toes and fingers to become gangrenous.
- Cryoglobulins usually consist of IgM directed against the Fc region of IgG.
- Common causes:
  - hepatitis C,
  - multiple myeloma,
  - SLE, rheumatoid arthritis,
  - Idiopathic (one third of cases)

Pathophysiology

- **Immune deposition** on the wall of small vessels result in generalized **vasculitis**, which presents with a reticulated skin pattern of **micro-thrombosis** and areas of gangrene.
- cryoglobulins → form an immune complexes → activate the complement system, resulting in ↓complement levels (**Hypocomplementemia**)

Three types

- **Type I** (25%):
  - monoclonal (IgG or IgM)
  - associated with haematological diseases such as myeloma and Waldenstrom's.
- **Type II** (25%):
  - **mixed** monoclonal and polyclonal: usually with RF
  - composed of a **monoclonal IgM** rheumatoid factor plus **polyclonal IgG**
  - associations: **hepatitis C**, RA, Sjogren's, lymphoma
    - **most importantly, hepatitis C infection which should always be excluded.**
      - If serological testing is negative, then the cryoprecipitate should be checked for HCV RNA by PCR.

- ❖ For hepatitis C associated mixed cryoglobulinaemia, **interferon alpha is the treatment of choice**, although rapidly progressive disease may require immunosuppressive therapy.

- **Type III** (50%):
  - ➢ polyclonal: usually with RF
  - ➢ composed of a **polyclonal IgM** rheumatoid factor plus **polyclonal IgG**.
  - ➢ associations: RA, Sjogren's

Mixed cryoglobulinemia
- Types **II and III** cryoglobulinemia
- both type II and III cryoglobulinaemia have rheumatoid factor reactivity
- represent 80% of all cryoglobulins.
- contain rheumatoid factors (RFs) which are usually IgM
- closely associated with **hepatitis C** virus (HCV)

Symptoms (if present in high concentrations)

Meltzer's triad (seen in cryoglobulinaemia (types II/III)→palpable purpura, arthralgia and myalgia
- Raynaud's only seen in type I
- cutaneous: vascular purpura, distal ulceration
- arthralgia
- renal involvement (diffuse glomerulonephritis)
- **axonal peripheral neuropathy**
  - ➢ **cryoglobulins → small-vessel vasculitis → axonal peripheral neuropathy**
  - ➢ may be sensorimotor, or purely sensory.
- Pulmonary embolism, arterial and venous thrombosis are common.

A vasculitic rash and neuropathy in a patient with hepatitis C is suggestive of cryoglobulinaemia.

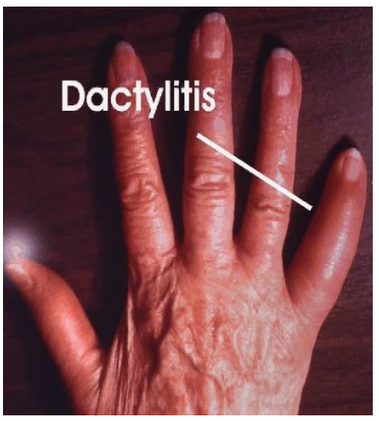
Tests
- **low complement (esp. C4)**
  - ➢ A markedly low C4 occurs in about 90% of patients with mixed cryoglobulinaemia (Type II) as a result of classic pathway activation.
- Since they precipitate at low temperatures, cryoglobulins should always be transported to the lab at 37°C. Failure to do this will result in a false negative result as the cryos will precipitate and be removed with the clot.
- high ESR

Treatment
- immunosuppression (high dose steroids and cyclophosphamide).
- Plasmapheresis

Hypocomplementemia is seen in many conditions, including:
- lupus,
- **mixed cryoglobulinemia**,
- membranoproliferative glomerulonephritis, and
- hereditary angioedema.

Dactylitis

- Dactylitis describes the inflammation of a digit (finger or toe).
- **A 'sausage-shaped' digit is a classical description of dactylitis**
- **Causes** include**:**
  - ➢ spondyloarthritis: e.g. **Psoriatic** and **reactive arthritis**
  - ➢ sickle-cell disease
  - ➢ other rare causes include tuberculosis, sarcoidosis and syphilis



De Quervain's tenosynovitis

- De Quervain's tenosynovitis is a common condition in which the sheath containing the extensor pollicis brevis and abductor pollicis longus tendons is inflamed.
- It typically affects females aged 30 - 50 years old

Causes

- commonly caused by **occupational** or avocational repetitive movement of the thumb
- also associated with RA, psoriatic arthritis, direct trauma, pregnancy, and the post-partum period.

Features

- pain on the radial side of the wrist
- tenderness over the radial styloid process
- abduction of the thumb against resistance is painful
- **Finkelstein's test:**
  - Used to confirm the diagnosis
  - the patient is asked to bring the thumb across the palm and clasp the fingers around it. The examiner then pulls it in the ulnar direction, which elicits a sharp pain.

Management

- analgesia
- steroid injection
- immobilisation with a thumb splint (spica) may be effective
- surgical treatment is sometimes required

Diffuse idiopathic skeletal hyperostosis

- Diffuse idiopathic skeletal hyperostosis (DISH) describes the relatively common finding of ossification at sites of tendinous and ligamentous insertion of the spine. It tends to be seen in elderly patients.
- DISH is generally asymptomatic.

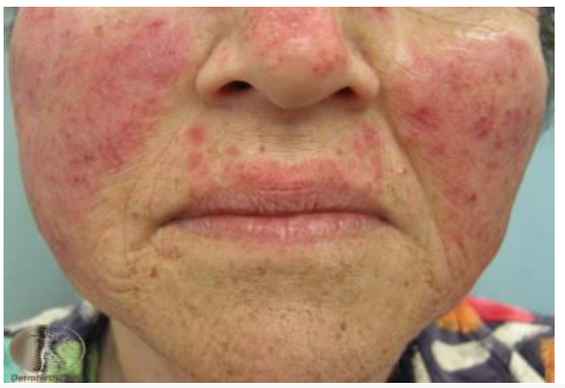
Drug-induced lupus

- In drug-induced lupus not all the typical features of systemic lupus erythematosus are seen, with renal and nervous system involvement being unusual.
- It usually resolves on stopping the drug.
- symptoms are said to appear some 3 weeks to 2 years after the onset of therapy
- affect the 50-70 year age group most commonly,
- has a male:female ratio of 1:1
- affects Caucasians more commonly than other populations.

Features

- joint pains, myalgia and malaise are more common
- skin (e.g. malar rash) (seen in 25%)
- pulmonary involvement (e.g. pleurisy) are common
- Raynaud's is seen in around 25%
- ANA positive in 100%, dsDNA negative
- **anti-histone antibodies are found in 80-90%**
- anti-Ro, anti-Smith positive in around 5%

- **C3/C4 levels are usually normal.**



A woman with drug-induced lupus

Most common causes
- procainamide
- hydralazine

Less common causes
- **simvastatin**
- captopril,
- isoniazid
- minocycline
- phenytoin
- valproate,
- penicillamine,
- methyldopa
- griseofulvin

Treatment:
- withdrawal of the offending medication, with rapid clinical resolution normally apparent.
- low-dose corticosteroids may speed recovery in patients who are slow to improve.

Extractable nuclear antigens

Overview
- specific nuclear antigens
- usually associated with being ANA positive

Examples
- anti-Ro: Sjogren's syndrome, SLE, congenital heart block
- anti-La: Sjogren's syndrome
- anti-Jo 1: polymyositis
- anti-scl-70: diffuse cutaneous systemic sclerosis
- anti-centromere: limited cutaneous systemic sclerosis

Gout

The vast majority of gout is due to decreased renal excretion of uric acid

Gout: start allopurinol if >= 2 attacks in 12 month period

- Gout is the most prevalent form of inflammatory arthropathy.
- **Primary gout has no obvious mode of inheritance**, **but** **familial juvenile gouty nephropathy** is an autosomal dominantly inherited disorder.
- Gout is a form of microcrystal synovitis caused by the deposition of **monosodium urate** monohydrate in the synovium.
- It is caused by chronic hyperuricaemia (uric acid > 0.45 mmol/l)
- Serum urate concentrations exceeding 7 mg/dl are associated with increased risk of gout.
- gout appears to be an independent risk factor for cardiovascular mortality and morbidity

- Hyperuricaemia may be associated with both hyperlipidaemia and hypertension. It may also be seen in conjunction with the metabolic syndrome
- Hyperuricaemia may be found in asymptomatic patients who have not experienced attacks of gout
- Gout attacks may occur when the serum uric acid is normal.
- The aetiology of gout can broadly be divided into:
    1. **Underexcretion of uric acid via the kidney (90%) or**
        - Uric acid is the end product of purine metabolism.
        - in normal circumstances, uric acid excretion is two thirds renal and one third via intestinal bacterial uricolysis.
        - Where renal elimination is impaired, the amount of extra-renal excretion can be increased.
    2. Endogenous overproduction of uric acid (10%)

Predisposing factors

Increased synthesis	Decreased excretion
• Lesch-Nyhan disease • myeloproliferative disorders **(eg: ALL)** • diet rich in purines • exercise • psoriasis • cytotoxics	• drugs: low-dose aspirin*, diuretics, pyrazinamide • pre-eclampsia • alcohol • renal failure • lead • Down's syndrome.

*aspirin in a dose of 75-150mg is not thought to have a significant effect on plasma urate levels. the British Society for Rheumatology recommend it should be continued if required for cardiovascular prophylaxis

Lesch-Nyhan syndrome

- **hypoxanthine-guanine phosphoribosyl transferase (HGPRTase) deficiency**
- x-linked recessive therefore only seen in boys
- features:
    - gout,
    - renal failure,
    - neurological deficits,
    - learning difficulties,
    - **aggressiveness**
    - self-mutilation (for example, biting of finger tips and/or lips).

Other rare causes

- Starvation leads to an increase in lactic acid, which impairs the kidneys' ability to excrete uric acid and therefore increases the risk of developing gout..

Gout: drug causes

Drug causes

- thiazides, furosemide
    - If diuretics are being used to treat hypertension an alternative antihypertensive should be considered, but they should not be stopped in the presence of heart failure
- alcohol
- cytotoxic agents
- pyrazinamide
- **Aspirin in a dose of 75-150mg is not thought to have a significant effect on plasma urate levels**

Investigations

- **joint aspiration → Presence of long needle-shaped Crystals** (uric acid crystal)
- Serum urate may reduce during an acute attack; (normal urate concentration does not rule out a diagnosis of gout).

Gout: management

Acute management

- **NSAIDs** are first line in conjunction with gastro-protective medication
    - NSAIDs should be avoided in elderly patients taking warfarin due to the risk of a life-threatening gastrointestinal haemorrhage.

- NSAIDs should be avoided in impaired renal function.
  - The first line treatment for acute gout is (NSAID) or colchicine. In renal impairment, a NSAID would be contraindicated. **Colchicine is safe to use in renal impairment.**
- NSAIDs are relatively contraindicated in congestive cardiac failure

- **Corticosteroids**
  Corticosteroids are highly effective, and can be used where NSAIDs are not tolerated, or in refractory disease (intra-articular, oral, intramuscular, intravenous).
  - **intra-articular steroid injection:** Potential local **side effects** of corticosteroid injections include:
    - increased pain for the first couple of days,
    - septic arthritis,
    - subcutaneous atrophy (causing skin dimpling),
    - skin depigmentation,
    - accidental nerve injury and tendon rupture.
  - **Oral steroids** may be considered **if NSAIDs and colchicine are contraindicated**. A dose of prednisolone 15mg/day is usually used
    - Avoided in diabetics because it would adversely affect diabetic control.
    - A recent trials found that oral prednisolone (30 mg/day for 5 days) had analgesic effectiveness equivalent to that of indomethacin and naproxen.
- **Colchicine:** has a slower onset of action.
  - **Colchicine may be given to patients with acute gout, even if there is renal failure**
  - effective when given within 12 hours of symptoms onset *at a loading dose of 1 mg followed 1 hour later by 0.5 mg on day 1*
  - inhibits microtubule polymerization by binding to tubulin, interfering with mitosis. Also inhibits neutrophil motility and activity
  - **useful in patients with renal impairment who develop gout as NSAIDs are relatively contraindicated. *should be avoided in patients with severe renal impairment.***
  - The BNF advises to reduce the dose by up to 50% if creatinine clearance is less than 50 ml/min and to avoid if creatinine clearance is less than 10 ml/min.
  - **the most appropriate management for patient on colchicine 600mcg daily presented with acute gout and mild renal impairment →Increase his colchicine to cope with the exacerbation**
  - may be increased up to a dose of 3mg, divided in 600mcg portions to cope with the acute attack.
  - **useful in patients taking warfarin as combined NSAID is harmful to GIT**
  - Until recently it was thought that colchicine had little or no interaction with warfarin therapy, but a case series was **recently published that suggested INR is increased in some patients prescribed colchicine**.
  - The main side-effect is diarrhea
  - increased risk of myopathy if co-prescribed a statin.
  - Colchicine should not be given to patients receiving strong P-glycoprotein and/or CYP3A4 inhibitors such as cyclosporin or clarithromycin. (2016 updated EULAR evidence-based recommendations for the management of gout. (http://ard.bmj.com.proxy1.athensams.net/content/76/1/29)
    - strong P-glycoprotein and/or CYP3A4 inhibitors such as cyclosporin, clarithromycin, verapamil and ketoconazole when prescribed with colchicine increased colchicine plasma concentration, thereby exposing patients to risk of serious side effects.
- ***IL-1 blockers:***
  - European Medicines Agency approved anti-IL-1β monoclonal antibody **canakinumab** (150 mg subcutaneously, one dose) **for patients with contraindication to colchicine, NSAIDs and steroids**
  - *Current infection is a contraindication to the use of IL-1 blockers.*

- **Rasburicase**
  - recombinant urate oxidase
  - **may be given during the acute attack of gout**, to allow allopurinol therapy to be commenced without the initial worsening of symptoms.
  - But it is **not currently licensed for the treatment of acute gout** associated with other conditions.
  - **the best choice for warfarinsed patient**
- if the patient is already taking allopurinol it should be continued

- Rest the affected joints

Acute gout pain with congestive cardiac failure and renal impairment, developed severe diarrhoea with colchicine. The treatment of choice → Prednisolone

Allopurinol prophylaxis

Allopurinol

Allopurinol inhibits xanthine oxidase

Allopurinol action

- Allopurinol is used in the prevention of gout. It works by inhibiting xanthine oxidase
  Allopurinol is an isomer of hypoxanthine and as such is a purine analogue. It acts by inhibiting xanthine oxidase thereby blocking the oxidation of hypoxathine and xanthine. This reduces the production of uric acid.
- In addition, the build up of hypoxanthine and xanthine results in their conversion to adenosine and guanosine. This causes feedback inhibition of amidophosphoribosyl transferase, which is the rate-limiting enzyme of purine biosynthesis.
- **Allopurinol therefore reduces both purine breakdown and synthesis.**

Allopurinol prescription

- allopurinol should not be started until 2 weeks after an acute attack has settled as it may precipitate a further attack if started too early
- initial dose of 100 mg od, with the dose titrated every few weeks to aim for a serum uric acid of < 300 µmol l/l
- can be used even in moderate–severe renal failure as long as dose reduction is employed
- NSAID or colchicine cover should be used when starting allopurinol
- allopurinol is recommended for first-line ULT, starting at a low dose (100 mg/day) and increasing by 100 mg increments every 2–4 weeks if required, to reach the uricaemic target.
- If the SUA target cannot be reached by an appropriate dose of allopurinol, or if allopurinol cannot be tolerated → switch to **febuxostat** or a **uricosuric**, or combined with a uricosuric.
  - **Febuxostat is a xanthine oxidase inhibitor that is recommended as second-line treatment to prevent gout when allopurinol has not been tolerated.**
- In refractory gout not responding to above → 3rd line drug (*pegloticase*)

Indications for allopurinol

- recurrent attacks - the British Society for Rheumatology recommend 'In uncomplicated gout uric acid lowering drug therapy should be started if a second attack, or further attacks occur within 1 year'
- tophi
- renal disease
- uric acid renal stones
  - The incidence of renal stones is increased in patients with gout; 80% of these are uric acid stones.
- prophylaxis if on cytotoxics or diuretics
- patients with Lesch-Nyhan syndrome often take allopurinol for life

Allopurinol interactions

- **Azathioprine**
  - metabolised to active compound 6-mercaptopurine
  - xanthine oxidase is responsible for the oxidation of 6-mercaptopurine to 6-thiouric acid
  - allopurinol can therefore lead to high levels of 6-mercaptopurine
  - a much reduced dose (e.g. 25%) must therefore be used if the combination cannot be avoided
  - **allopurinol Increases toxicity and effects of azathioprine and 6-mercaptopurine. So → Reduce dose of azathioprine and 6-mercaptopurine to one quarter of usual dose.**
- **Cyclophosphamide**
  - allopurinol reduces renal clearance, therefore may cause marrow toxicity
- **Warfarin**
  - Allopurinol can interact with warfarin to enhance the anticoagulant effect of warfarin.
  - **Allopurinol increase INR by inhibiting the metabolism of warfarin.**

Lifestyle modifications

- reduce alcohol intake and avoid during an acute attack
- lose weight if obese
- avoid food high in purines e.g. Liver, kidneys, **seafood, oily fish (mackerel, sardines)** and yeast products
- *avoid sugar-sweetened drinks*, foods rich in fructose and orange or apple juice
- ***foods negatively associated with gout (****should be encouraged)*
  - *Low-fat dairy products* (skimmed milk and low-calorie yoghurt. This likely results from the uricosuric property of milk)
  - Coffee
  - Cherries..الكرز

Prophylactic treatment

Prophylaxis against flares:

- Prophylaxis is recommended during the first 6 months of urate-lowering therapy (ULT).
- Recommended prophylactic treatment is **colchicine**, 0.5–1 mg/day, a dose that should be reduced in patients with renal impairment.
- In cases of renal impairment or statin treatment, patients and physicians should be aware of potential neurotoxicity and/or muscular toxicity with prophylactic colchicine.
- Co-prescription of colchicine with strong P-glycoprotein and/or CYP3A4 inhibitors should be avoided.
- If colchicine is not tolerated or is contraindicated, prophylaxis with **NSAIDs** at a low dosage, if not contraindicated, should be considered.

Target of serum uric acid (SUA) in long term

- *For patients on ULT, SUA level should be monitored and maintained to <6 mg/dL (360 µmol/L).*
- *A lower* ***SUA target (<5 mg/dL; 300 µmol/L) to facilitate faster dissolution of crystals is recommended for patients with severe gout*** *(tophi, chronic arthropathy, frequent attacks) until total crystal dissolution and resolution of gout.*
- *SUA level <3 mg/dL is not recommended in the long term.*
- *SUA <6 mg/dL (360 µmol/L) should be maintained lifelong.*

Other points

Antihypertensive drugs either increase serum **uric acid levels** (e.g., diuretics, β-**blockers**) or **decrease** serum **uric acid levels** (e.g., **calcium-channel blockers**, losartan).

- losartan has a specific uricosuric action (↑excretion of uric acid in the urine, thus reducing the serum uric acid) and may be particularly suitable for the many patients who have coexistant hypertension
- Uricosuric agents should be avoided in those with renal stones
- calcium channel blockers also decrease serum uric acid levels, possibly by a renal vasodilatory effect
- increased vitamin C intake (either supplements or through normal diet) may also decrease serum uric acid levels
- When gout occurs in a patient receiving loop or thiazide diuretics, substitute the diuretic if possible;
  - for hypertension, consider losartan or calcium channel blockers;
  - for hyperlipidaemia, consider a statin or fenofibrate. (have uricosuric property)

Management of Chronic Gout: Key facts	
First line treatment	**Second line treatment**
Allopurinol	Sulphinpyrazone Febuxostat Benzbromarone
Increase allopurinol by 100mg every 4 weeks until target reached	Uricosuric agents should be avoided in those with renal stones
Target uric acid 0.3 mmol/L. Monitor uric acid every 4 weeks until target reached	
Colchicine 0.5 mg twice daily is used for the first 6-12 months after initiating urate lowering therapy	

Recurrent arthritis

- Crystal arthritis (gout or Pseudo-gout) are the most common cause of recurrent arthritis.
- **Patient with recurrent arthritis but now is free → ask the patient to report to the clinic during the next attack → Crystal arthritis for aspiration during the attack**

Hip pain in adults

The table below provides a brief summary of the potential causes of hip pain in adults

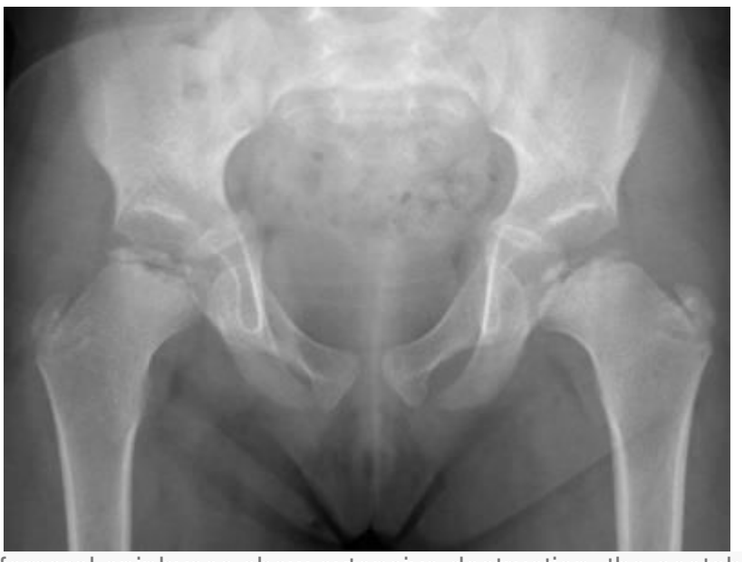
Condition	Features
Osteoarthritis	Pain exacerbated by exercise and relieved by rest Reduction in internal rotation is often the first sign Age, obesity and previous joint problems are risk factors
Inflammatory arthritis	Pain in the morning Systemic features Raised inflammatory markers
Referred lumbar spine pain	Femoral nerve compression may cause referred pain in the hip Femoral nerve stretch test may be positive - lie the patient prone. Extend the hip joint with a straight leg then bend the knee. This stretches the femoral nerve and will cause pain if it is trapped
Greater trochanteric pain syndrome (Trochanteric bursitis)	Due to repeated movement of the fibroelastic iliotibial band Pain and tenderness over the lateral side of thigh Most common in women aged 50-70 years
Meralgia paraesthetica	Caused by compression of lateral cutaneous nerve of thigh Typically burning sensation over antero-lateral aspect of thigh
Avascular necrosis	Symptoms may be of gradual or sudden onset May follow high dose steroid therapy or previous hip fracture of dislocation
Pubic symphysis dysfunction	Common in pregnancy Ligament laxity increases in response to hormonal changes of pregnancy Pain over the pubic symphysis with radiation to the groins and the medial aspects of the thighs. A waddling gait may be seen
Transient idiopathic osteoporosis	An uncommon condition sometimes seen in the third trimester of pregnancy Groin pain associated with a limited range of movement in the hip Patients may be unable to weight bear ESR may be elevated

Hip problems in children

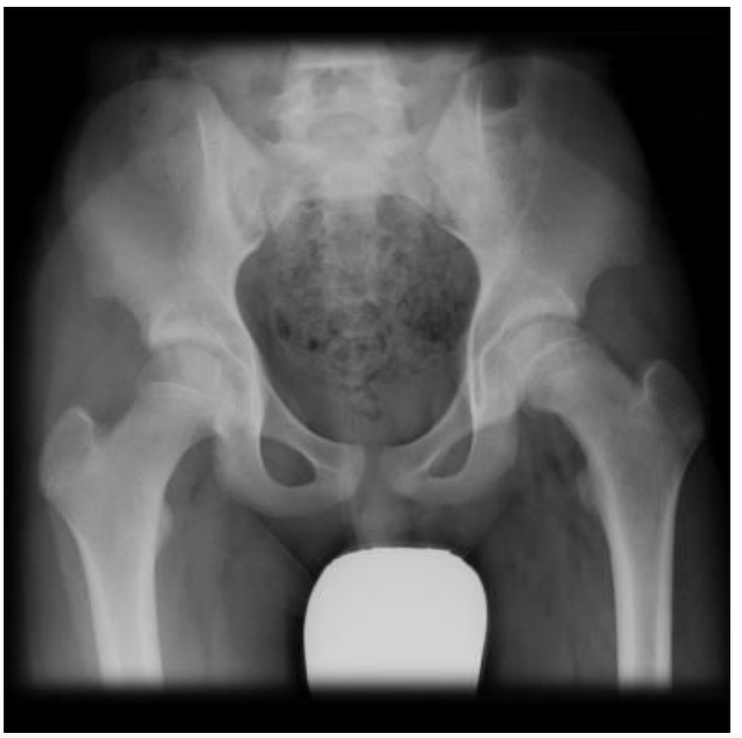
The table below provides a brief summary of the potential causes of hip problems in children

Condition	Notes
Development dysplasia of the hip	Often picked up on newborn examination Barlow's test, Ortolani's test are positive Unequal skin folds/leg length
Transient synovitis (irritable hip)	Typical age group = 2-10 years Acute hip pain associated with viral infection Commonest cause of hip pain in children
Perthes disease	Perthes disease is a degenerative condition affecting the hip joints of children, typically between the ages of 4-8 years. It is due to avascular necrosis of the femoral head Perthes disease is 5 times more common in boys. Around 10% of cases are bilateral Features • hip pain: develops progressively over a few weeks • limp • stiffness and reduced range of hip movement • x-ray: early changes include widening of joint space, later changes include decreased femoral head size/flattening
Slipped upper femoral epiphysis	Typical age group = 10-15 years More common in obese children and boys Displacement of the femoral head epiphysis postero-inferiorly Bilateral slip in 20% of cases May present acutely following trauma or more commonly with chronic, persistent symptoms Features • knee or distal thigh pain is common • loss of internal rotation of the leg in flexion
Juvenile idiopathic arthritis (JIA)	Preferred to the older term juvenile chronic arthritis, describes arthritis occurring in someone who is less than 16 years old that lasts for more than three months. Pauciarticular JIA refers to cases where 4 or less joints are affected. It accounts for around 60% of cases of JIA Features of pauciarticular JIA • joint pain and swelling: usually medium sized joints e.g. knees, ankles, elbows • limp • ANA may be positive in JIA - associated with **anterior uveitis**
Septic arthritis	Acute hip pain associated with systemic upset e.g. pyrexia. Inability/severe limitation of affected joint

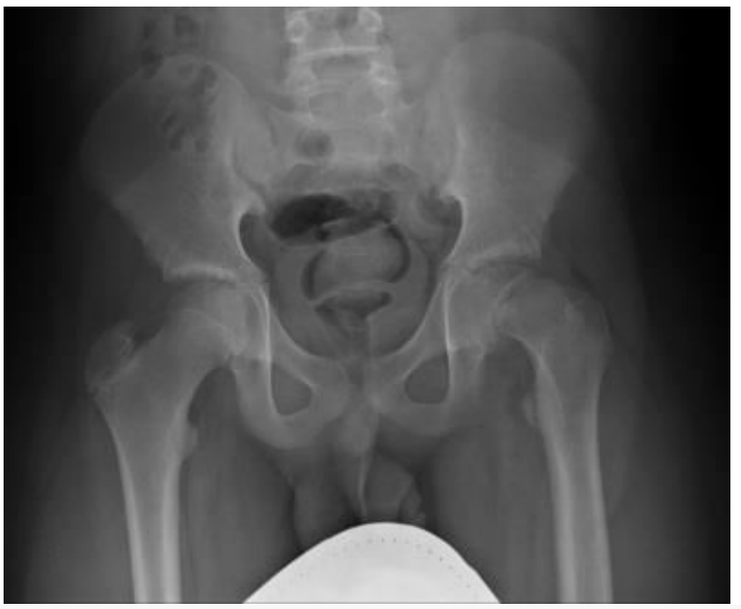
Image gallery



Perthes disease - both femoral epiphyses show extensive destruction, the acetabula are deformed
Perthes disease - bilateral disease



Slipped upper femoral epiphysis - left side



Slipped upper femoral epiphysis - left side

Lateral epicondylitis

Lateral epicondylitis: worse on resisted wrist extension/suppination whilst elbow extended

Lateral epicondylitis typically follows unaccustomed activity such as house painting or playing tennis ('tennis elbow'). It is most common in people aged 45-55 years and typically affects the dominant arm.

Features

- pain and tenderness localised to the lateral epicondyle
- pain worse on wrist extension against resistance with the elbow extended or supination of the forearm with the elbow extended
- episodes typically last between 6 months and 2 years. Patients tend to have acute pain for 6-12 weeks

Management options

- advice on avoiding muscle overload
- simple analgesia
- steroid injection
- physiotherapy

Lower back pain

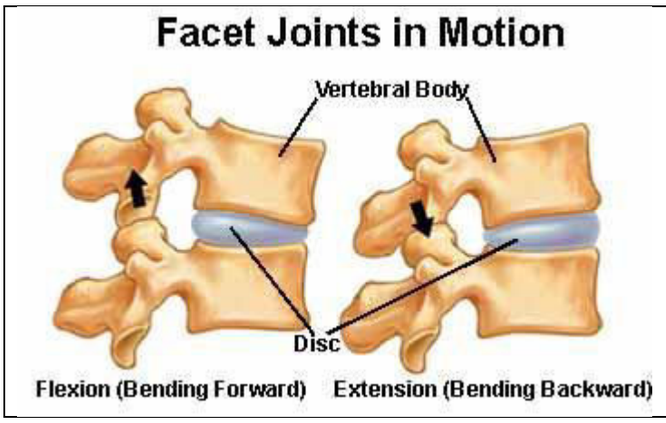
- Lower back pain (LBP) is one of the most common presentations seen in practice.
- Whilst **the majority of presentations will be of a non-specific muscular nature** it is worth keeping in mind possible causes which may need specific treatment.
  - musculogenic (strain) etiology is the most common cause of low back pain.

Red flags for lower back pain

- age < 20 years or > 50 years
- history of previous malignancy
- night pain
- history of trauma
- systemically unwell e.g. weight loss, fever

The table below indicates some specific causes of LBP:

Facet joint	• **May be acute or chronic** • **Pain worse in the morning and on standing** • **On examination there may be pain over the facets.** • **The pain is typically worse on extension of the back**
Spinal stenosis	• Usually gradual onset • Unilateral or bilateral leg pain (with or without back pain), numbness, and weakness which is worse on walking. Resolves when sits down. • Pain may be described as 'aching', 'crawling'. • Relieved by sitting down, leaning forwards and crouching down • Clinical examination is often normal • Requires MRI to confirm diagnosis
Ankylosing spondylitis	• Typically a young man who presents with lower back pain and stiffness • Stiffness is usually worse in morning and improves with activity • Peripheral arthritis (25%, more common if female)
Peripheral arterial disease	• Pain on walking, relieved by rest • Absent or weak foot pulses and other signs of limb ischaemia • Past history may include smoking and other vascular diseases



- (also known as zygapophyseal, apophyseal, or Z-joint)
- are synovial joints between the spinal vertebrae
- Function: guide and limit movement of the spinal motion segment.

Assessment

- Do risk stratification for new cases
  - such as the **STarT Back risk assessment tool**
- do not request imaging unless serious underlying pathology is suspected.

STarT Back Screening Tool

1. My back pain has spread down my leg(s) at some time in the last 2 weeks
2. I have had pain in the shoulder or neck at some time in the last 2 weeks
3. I have only walked short distances because of my back pain
4. In the last 2 weeks, I have dressed more slowly than usual because of back pain
5. It's not really safe for a person with a condition like mine to be physically active
6. Worrying thoughts have been going through my mind a lot of the time
7. I feel that my back pain is terrible and it's never going to get any better
8. In general I have not enjoyed all the things I used to enjoy
9. Overall, how bothersome has your back pain been in the last 2 weeks? Not at all (0), Slightly, (0), Moderately (0), Very much (1), Extremely (1)

- **STarT Back scoring:**
  - For questions 1-8, score 1 for agreement, 0 for disagreement
    - Low risk = total score 0-3;
    - high risk = score 4-5 of questions 5-9 only;
    - the rest are medium risk.

Management (NICE: November 2016)

- **Non-pharmacological**
  - Self-management
    - encouragement to continue with normal activities.
  - Exercise
  - Manual therapies (spinal manipulation, mobilisation or soft tissue techniques such as massage)
    - Traction is NOT recommended
  - Psychological therapy (cognitive behavioural)
  - Acupuncture and Electrotherapies are NOT recommended
- **Pharmacological**
  - NSAIDs
  - Do not offer paracetamol alone for managing low back pain.
  - Consider weak opioids (with or without paracetamol) for managing **acute** low back pain only if an NSAID is contraindicated, not tolerated or has been ineffective.
  - Do not offer opioids for managing **chronic** low back pain.
  - Antidepressants and anticonvulsants are not recommended
- **Invasive non-surgical treatments**
  - Spinal injections are not recommended for treatment.
    - except for 'radiofrequency denervation'.
      - To determine whether these people will benefit from this procedure, they may be offered a diagnostic block of the nerves that supply the joints between the vertebrae.
        - ⇨ If they experience significant pain relief they may then be offered radiofrequency denervation in an attempt to achieve longer-term relief.
  - **Radiofrequency denervation**
    - for chronic low back pain if**:**
      1) non-surgical treatment has not worked **and**
      2) the main source of pain is thought to come from structures supplied by the **medial branch nerve and**
      3) they have moderate or severe pain
    - Only performed after a positive response to a diagnostic medial branch block.
  - **epidural injections** of local anaesthetic and steroid in people with acute and severe **sciatica.**
- **Invasive surgical treatments:**
  - **spinal decompression**
    - for sciatica when non-surgical treatment has not improved pain
  - Spinal fusion and disc replacement are NOT recommended in treatment of low back pain.

(NICE - Low back pain and sciatica in over 16s Quality standard: July 2017)

Mixed connective tissue disease (MCTD)

Anti-ribonuclear protein (anti-RNP) = mixed connective tissue disease

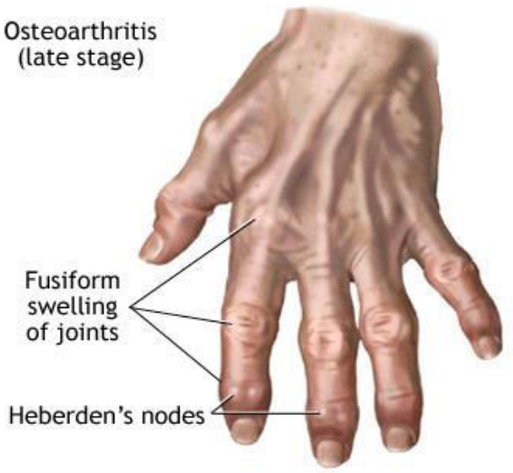
- MCTD is an overlap syndrome characterised by combinations of clinical features of SLE, systemic scleroderma and polymyositis **(e.g. arthralgia, myositis and Raynaud's**).
- **The presenting symptoms of MCTD are most often:**
  - Raynaud's phenomenon
  - puffy hands
  - arthralgias
  - myalgias
  - fatigue.
- **Diagnosis →Anti-RNP positive**
  - A defining feature of MCTD is the presence of antibodies against the U1 ribonucleoprotein (U1 RNP) complex, and hence the presence of high titre anti-U1 RNP will confirm the clinical diagnosis of MCTD.

Osteoarthritis

The trapezio-metacarpal joint (base of thumb) is the most common site of hand osteoarthritis

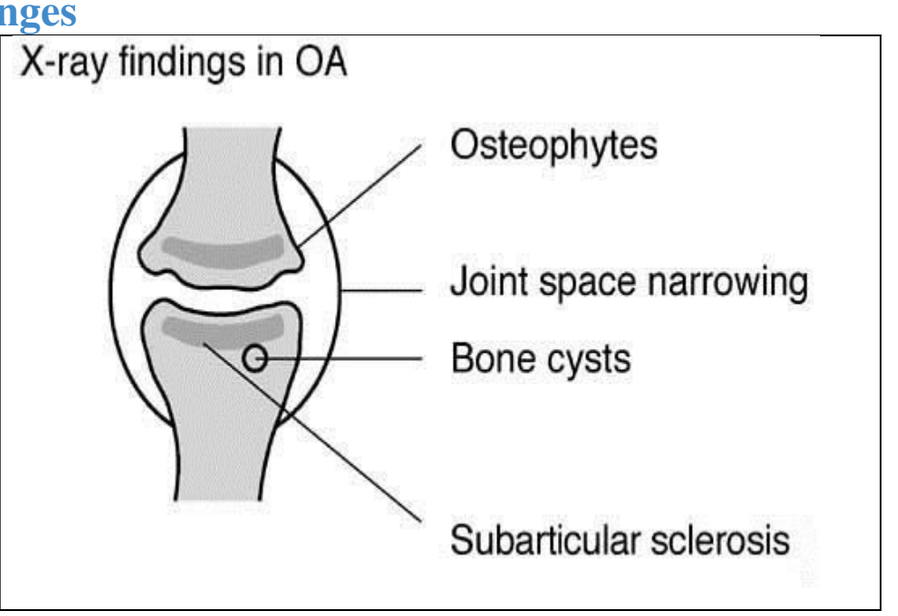
Osteoarthritis - paracetamol + topical NSAIDs (if knee/hand) first-line

- Pathogenesis involves the localised loss of cartilage, with remodelling of adjacent bone.
- Osteoarthritis characteristically affects the **distal interphalangeal** as well as the proximal interphalangeal and first metacarpophalangeal joints.
- The carpometacarpal (CMC) joint is classically involved
- **Joint swelling is bony in nature**, unlike the boggy swelling which occurs in inflammatory arthritis.
- Thenar wasting occurs in OA of the first CMC joint due to disuse.
- pain is exacerbated by exercise and relieved by rest, although in advanced disease rest and night pain can develop.
- **Obesity is one of the commonest causes for the early appearance of osteoarthritis**
- **Osteoarthritis may be secondary to haemochromatosis → do Ferritin**



Typical findings in the *hand* are bony enlargement of the proximal interphalangeal joints (Bouchard's nodes) and the distal interphalangeal joints (Heberden's nodes)

Osteoarthritis: x-ray changes



X-ray changes of osteoarthritis

- decrease of joint space
- subchondral sclerosis
- subchondral cysts

- osteophytes forming at joint margins

gull-wing or inverted-T pattern of erosions is typical of erosive inflammatory osteoarthritis.

Osteoarthritis: management

Osteoarthritis - paracetamol + topical NSAIDs (if knee/hand) first-line

NICE recommend co-prescribing a PPI with NSAIDs in all patients with osteoarthritis

NICE published guidelines on the management of osteoarthritis (OA) in 2014

- all patients should be offered help with weight loss, given advice about local muscle strengthening exercises and general aerobic fitness
- paracetamol and topical NSAIDs are first-line analgesics. **Topical NSAIDs are indicated only for OA of the knee or hand**
- second-line treatment is oral NSAIDs/COX-2 inhibitors, opioids, capsaicin cream and intra-articular corticosteroids. A proton pump inhibitor should be co-prescribed with NSAIDs and COX-2 inhibitors. These drugs should be avoided if the patient takes aspirin
- non-pharmacological treatment options include supports and braces, **Transcutaneous Electrical Nerve Stimulation (TENS)** and shock absorbing insoles or shoes
- if conservative methods fail then refer for consideration of joint replacement

What is the role of glucosamine?

- normal constituent of glycosaminoglycans in cartilage and synovial fluid
- a systematic review of several double blind RCTs of glucosamine in knee osteoarthritis reported significant short-term symptomatic benefits including significantly reduced joint space narrowing and improved pain scores
- more recent studies have however been mixed
- the 2008 NICE guidelines suggest it is not recommended
- a 2008 Drug and Therapeutics Bulletin review advised that whilst glucosamine provides modest pain relief in knee osteoarthritis it should not be prescribed on the NHS due to limited evidence of cost-effectiveness

Studies have shown that paracetamol 1 g combined with **codeine at dose of 60 mg** have the best analgesic outcomes.

The guiding principle in the management of osteoarthritis is to treat the symptoms and disability, not the clinical or radiological appearances. Educating the individual about the disease and its effects reduces pain, distress and disability and increases compliance with treatment. Psychological or social factors alter the impact of the disease.

The following table compares osteoarthritis with rheumatoid arthritis.

	OA	RA
Morning stiffness	< 30 minutes	> 1 hour
DIP	Yes	No
PIP	Yes	Yes
MCP	No	Yes
RF, anti-CCP	No	Yes
Joint fluid leukocyte count	< 2,000	5,000–50,000

Osteogenesis imperfecta

Osteogenesis imperfecta (more commonly known as brittle bone disease) is a group of disorders of collagen metabolism resulting in bone fragility and fractures. The most common, and milder, form of osteogenesis imperfecta is type 1

Overview
- autosomal dominant
- abnormality in type 1 collagen due to decreased synthesis of pro-alpha 1 or pro-alpha 2 collagen polypeptides

Features
- presents in childhood
- fractures following minor trauma
- blue sclera
- deafness secondary to otosclerosis
- dental imperfections are common

Osteomyelitis

Osteomyelitis: MRI is the imaging modality of choice

Patients with sickle cell disease have a predisposition to develop osteomyelitis due to *Salmonella* species.

Definition
- Osteomyelitis: infection of bone marrow and bone
- Acute form: develops within days or weeks
- Chronic form: develops slowly (over months or years) and is associated with avascular bone necrosis and sequestrum formation within the bone

Causes
- ***Staph. aureus* is the most common cause** followed by *Pseudomonas*
- *Pseudomonas aeruginosa* is more common in intravenous drug users.
- ***Salmonella* species is the commonest cause in patients with sickle-cell anaemia.**
- Pasteurella multocida
  - seen in cases caused by cat and dog bites
- **Haematogenous osteomyelitis:**
  - most commonly involves the vertebrae, but infection may also occur in the **metaphysis** of the long bones, pelvis, and clavicle.
    - The lumbar spine is most commonly affected, followed by the thoracic and cervical regions.
  - the location is usually **metaphyseal**
    - The metaphysis is commonest site of osteomyelitis, because:
      - Is highly vascular
      - Has a hair pin like arrangement of capillaries

- ❖ Has sluggish blood **flow**
- ❖ has relatively fewer phagocytic cells than the physis or diaphysis, allowing infection to occur more easily in this area
- ❖ thin cortex

- Posttraumatic osteomyelitis
  - ➢ typically found in the tibia.
- Contiguous-focus osteomyelitis
  - ➢ direct inoculation of bacteria via trauma
  - ➢ Infection usually results approximately one month after inoculation.

Predisposing conditions

- diabetes mellitus
- sickle cell anaemia
- intravenous drug user
- immunosuppression due to either medication or HIV
- alcohol excess

Investigations

- **MRI is the imaging modality of choice**, with a sensitivity of 90-100%
  - ➢ show → cortical destruction, bone marrow inflammation, soft tissue involvement
- Bone scintigraphy (Gallium bone scan) if MRI is contraindicated (metal foreign body implants) → detects sites of infection
- X-ray shows:
  - ➢ still provide the best initial **screening** test for acute and chronic osteomyelitis.
  - ➢ **Early stages (< 2 weeks of symptoms onset): typically no pathological findings**
  - ➢ Later stages: bone destruction, **sequestrum** formation, periosteal reactions
  - ➢ lytic lesion with sclerotic margins (**Brodie's abscess**)
    - a form of **chronic osteomyelitis**
    - thickened bone with irregular and patchy sclerosis that gives a honeycombed appearance.
    - Sequestra are seen as dense loose fragments lying within a cavity in the bone.
    - insidious onset (eg: 6-month history of gradually progressive swelling and pain)
    - often near the site of the metaphysis,
    - Deep 'boring' pain is often the predominant symptom.
  - ➢ Osteomyelitis can cause a raised periosteum which is part of the radiographic sign known as the Codman triangle.
- Bone biopsy
  - ➢ **confirmatory test**
  - ➢ Detects both osteonecrosis and the pathogen → confirms the diagnosis and helps guide more specific therapy

Differential diagnosis

- Septic arthritis
  - ➢ Infection of the joint; in contrast to osteomyelitis, **involvement of the metaphysis is rare**
- **Ewing sarcoma**
  - ➢ x-ray: lytic bone lesions, **onion skin appearance of the periosteum**

Management

- **flucloxacillin** for 6 weeks
- clindamycin if penicillin-allergic
- Beta-lactams and vancomycin are commonly used as initial empiric therapy.
- *Osteomyelitis from contiguous spread of infection*
  - ➢ *Piperacillin-tazobactam*
  - ➢ *Patients with penicillin allergy* → Clindamycin or metronidazole plus ciprofloxacin
  - ➢ If MRSA is suspected: → Add vancomycin (or linezolid if allergic to vancomycin)

Osteomalacia

The symptoms of proximal bone pain with hypocalcaemia and low phosphate suggest a diagnosis of osteomalacia

↓↓ Ca ↓↓ P ↓↓ vit D + ↑↑ ALP → osteomalacia

Basics

- normal bony tissue but decreased mineral content
- rickets if when growing
- osteomalacia if after epiphysis fusion
- occurs more commonly in patients of **South Asian origin**, particularly those who have a cultural tendency to spend more time inside.
- more common in ethnic groups who are dark-skinned, or cover themselves up so that cholesterol cannot be converted to vitamin D in the skin.
- Asians who eat chapattis are also at risk, as the phytic acid in the chapattis chelates vitamin D and calcium
- Europid ethnic origin is associated with a reduced risk of osteomalacia versus populations with increased skin pigmentation.

Causes

- vitamin D deficiency e.g. malabsorption, lack of sunlight, diet
- vitamin D resistant; inherited
- renal failure
- liver disease, e.g. cirrhosis
- drug induced e.g. anticonvulsants
- **Mercury poisoning** or any heavy metal poisoning causes an acquired Fanconi syndrome with proximal (type 2) renal tubular acidosis.

Features

- rickets: knock-knee, bow leg, features of hypocalcaemia
- osteomalacia:
  - bone pain, particularly around the hips and lower back,
  - fractures,
  - muscle tenderness,
  - proximal myopathy

Investigation

- low calcium, phosphate, 25(OH) vitamin D
- raised alkaline phosphatase as it is released from bone reflecting osteoblastic activity.
- Serum PTH is also usually elevated and normalises gradually on response to treatment.
- There is also acidosis which is caused by the inhibition of phosphate, bicarbonate, and sodium reabsorption by PTH.
- x-ray:
  - children - cupped, ragged metaphyseal surfaces;
  - adults - translucent bands (**Looser's zones (Linear areas of low density)** (pseudofractures)
    - Looser's zones characterised by **low-density bands extending from the** cortex inwards in the shafts of long bones.

Treatment

- calcium with vitamin D tablets

May 2013 exam: A 58-year-old woman C/O aches and pains in her bones. Generally weak and lethargic. low calcium, phosphate and vitamin D levels combined with a raised alkaline phosphatase and parathyroid hormone level .What is the most appropriate management? Start vitamin D3 supplementation (∆ → osteomalacia)

Oncogenic osteomalacia

- Certain tumours, including mesenchymal tumours, adenocarcinomas (e.g. prostatic carcinoma) and haematological malignancies such as myeloma and chronic lymphocytic leukaemia, appear to produce a phosphaturic substance.
- Features
  - bone pain and/or fracture, profound proximal myopathy and severe hypophosphataemia,
  - usually accompanied by a marked reduction in concentration of 1,25-OH vitamin D.
  - Other abnormalities of renal function such as glycosuria and aminoaciduria may also be present.
- Treatment
  - vitamin D metabolites and phosphate supplements may result in some resolution of skeletal symptoms.
  - In the case of solid tumours, removal of the primary tumour also results in improvement of symptoms.

Osteopetrosis

Overview

- also known as marble bone disease
- rare disorder of **defective osteoclast function** resulting in failure of normal bone resorption
- results in dense, thick bones that are prone to fracture
- bone pains and neuropathies are common.
- calcium, phosphate and ALP are normal
- stem cell transplant and interferon-gamma have been used for treatment

Osteoporosis

In osteoporosis, there is decreased bone mass, but mineralization is normal.

causes

- unknown (95%)
- **Advancing age and female sex**.
  - Prevalence increases from 2% at 50 years to more than 25% at 80 years in women.

Risk factors: the most 'important' ones are risk factors that are used by major risk assessment tools such as FRAX:

- history of glucocorticoid use
- rheumatoid arthritis
- alcohol excess
- history of parental hip fracture (**family history of osteoporotic fracture**)
- low body mass index
- current smoking

Other risk factors

- sedentary lifestyle
- premature menopause
  - Early menarche and late menopause are associated with reduced risk of fracture.
- Caucasians and Asians
- endocrine disorders: hyperthyroidism, hypogonadism (e.g. Turner's, testosterone deficiency), growth hormone deficiency, hyperparathyroidism, diabetes mellitus
- multiple myeloma, lymphoma
- gastrointestinal disorders: inflammatory bowel disease, malabsorption (e.g. Coeliac's), gastrectomy, liver disease
- chronic kidney disease
- osteogenesis imperfecta, homocystinuria

Risk factors for post-menopausal osteoporosis, include

- Early onset (<45 years) menopause
- Absence of hormone replacement therapy, calcium and vitamin D supplemention and
- Low body weight.

Medications that may worsen osteoporosis (other than glucocorticoids):

- SSRIs
- antiepileptics
- proton pump inhibitors
- glitazones
- long term heparin therapy
- aromatase inhibitors e.g. anastrozole (used for breast cancer in postmenopausal women and gynecomastia in men. aromatase, which converts androgens into estrogens by a process called aromatization.)

feature

- Classically, osteoporosis in the absence of fracture, **does not cause pain**. Many patients with osteoporosis have concomitant disorders such as osteomalacia and osteoarthritis which cause bone pain.
- Patients with osteoporosis may have no warning signs until the first **fracture** occurs.
- Gradual height loss and dorsal kyphosis may result from microfractures or complete fractures of vertebral bodies.

Investigations for secondary causes

If a patient is diagnosed with osteoporosis or has a fragility fracture further investigations may be warranted. NOGG recommend testing for the following reasons:

- exclude diseases that mimic osteoporosis (e.g. osteomalacia, myeloma);

- identify the cause of osteoporosis and contributory factors;
- assess the risk of subsequent fractures;
- select the most appropriate form of treatment

The following investigations are recommended by NOGG:

- History and physical examination
- Blood cell count, sedimentation rate or C-reactive protein, serum calcium,albumin, creatinine, phosphate, alkaline phosphatase and liver transaminases
- Thyroid function tests
- Bone densitometry (DXA)

Other procedures, if indicated

- Lateral radiographs of lumbar and thoracic spine/DXA-based vertebral imaging
- Protein immunoelectrophoresis and urinary Bence-Jones proteins
- 25OHD
- PTH
- Serum testosterone, SHBG, FSH, LH (in men),
- Serum prolactin
- 24 hour urinary cortisol/dexamethasone suppression test
- Endomysial and/or tissue transglutaminase antibodies (coeliac disease)
- Isotope bone scan
- Markers of bone turnover, when available
- Urinary calcium excretion

So from the first list we should order the following bloods as a minimum for all patients:

- full blood count
- urea and electrolytes
- liver function tests
- bone profile
- CRP
- thyroid function tests

DEXA scan

Basics

- T score: based on bone mass of young reference population (compare the patient's bone mineral density (BMD) with that of a healthy young adult)
- T score of -1.0 means bone mass of one standard deviation below that of young reference population
- Z score is adjusted for age, gender and ethnic factors (Z-scores compare the individual's BMD with that of a population of peers)
  - The Z-score is not routinely used in the diagnosis of osteoporosis
  - It can be used to investigate the possibility of osteoporosis in premenopausal women, men under the age of 50 and children.
  - It is most useful when the bone mineral density is less than 2 standard deviations below the normal.

T score

- > -1.0 = normal
- -1.0 to -2.5 = osteopaenia
- < -2.5 = osteoporosis

Osteoporosis diagnosis according to the WHO and International Osteoporosis Foundation criteria:

diagnosis	T score	definition
normal	**(≥ −1)**	hip BMD greater than the 1 SD below the young adult reference mean
osteopaenia	**(−1 to −2.5)**	hip BMD between 1 and 2.5 DS below the young adult reference mean
osteoporosis	**(≤ −2.5)**	hip BMD 2.5 SD or more below the young adult reference mean
Severe osteoporosis	**(≤ −2.5 PLUS fracture)**	hip BMD 2.5 SD or more below the young adult reference mean **+** one or more fragility fractures

May 2016	What percentage of young adults have a T score between -2.0 to +2.0?	95%

The T score is calculated based on the young adult mean bone density. Given bone density is normally distributed, a T score between -2.0 and +2.0 spans two standard deviations above and below the mean, which covers 95% of the population.

- 5% of young adults lie outside the boundaries of T score – 2.0 to +2.0
- 2.5% of young adults have a T score above + 2.0 **&** 2.5% of young adults have a T score below -2.0
- 99.7% of young adults have a T score between – 3.0 to +3.0
- 68% of young adults have a T score between – 1.0 to +1.0

Osteoporosis: glucocorticoid-induced

- Steroids cause a decrease in calcium absorption from the gut, increased urinary calcium excretion, and also causes bone resorption, resulting in osteoporosis.
- The risk ↑↑ with prednisolone 7.5mg a day for 3 or more months.
- patients should be managed in an anticipatory, i.e. if it likely that the patient will have to take steroids for at least 3 months then we should start bone protection straight away, rather than waiting until 3 months has elapsed.
- A good example is a patient with newly diagnosed polymyalgia rheumatica. As it is very likely they will be on a significant dose of prednisolone for greater than 3 months bone protection should be commenced immediately.

Management of patients at risk of corticosteroid-induced osteoporosis

The RCP guidelines divide patients into two groups.

1. age > 65 years **or** H/O previously fragility fracture → give bone protection.
   - Fragility fracture - defined by The WHO as resulting from a mechanical force equivalent to a fall from standing height or less which should not ordinarily cause a fracture.
2. age < 65 years → bone density scan

T score	Management
Greater than 0	Reassure
Between 0 and -1.5	Repeat bone density scan in 1-3 years
Less than -1.5	Offer bone protection

The first-line treatment is alendronate. Patients should also be calcium and vitamin D replete.

Osteoporosis: Assessing patients following a fragility fracture

- The management of patients following a fragility fracture depends on age.

Patients ≥ 75 years of age

- Patients ≥ 75 years + fragility fracture → start first-line therapy (an oral bisphosphonate), **without DEXA scan**.
- For example, a 79-year-old woman falls over on to an outstretched hand and sustains a Colles' fracture (fracture of the distal radius). Given her age she is presumed to have osteoporosis and therefore started on oral alendronate 70mg once weekly. No DEXA scan is arranged.
- the 2014 NOGG guidelines have a different threshold, suggesting treatment is started in all women > 50 years who've had a fragility fracture - *'although BMD measurement may sometimes be appropriate, particularly in younger postmenopausal women.'*

Patients < 75 years of age

- patient < 75 years + fragility fracture → DEXA scan should be arranged.
- These results can then be entered into a FRAX tool to assess ongoing fracture risk.

Osteoporosis: assessing risk NICE guidelines (2012)

Osteoporosis in a man - check testosterone

Who should be assessed for fragility fracture?

- all women aged ≥ 65 years and all men aged ≥ 75 years.
- Younger patients + presence of risk factors, such as:
  - previous fragility fracture
  - current use or frequent recent use of oral or systemic glucocorticoid
  - history of falls
  - family history of hip fracture
  - other causes of secondary osteoporosis
  - low body mass index (BMI) (< 18.5 kg/m)
  - smoking
  - alcohol (> 14 units/week for women and > 21 units/week for men).

Methods of risk assessment

- NICE recommend using a clinical prediction tool such as FRAX or Q Fracture to assess a patient's 10-year risk of developing a fracture. This is analogous to the cardiovascular risk tools such as QRISK.

FRAX

- estimates the 10-year risk of fragility fracture
- valid for patients aged 40-90 years
- based on international data so use not limited to UK patients
- assesses the following factors:
  1. age,
  2. sex,
  3. weight,
  4. height,
  5. previous fracture,
  6. parental fracture,
  7. current smoking,
  8. glucocorticoids,
  9. rheumatoid arthritis,
  10. secondary osteoporosis,
  11. alcohol intake
- bone mineral density (BMD) is optional, but clearly improves the accuracy of the results.
- NICE recommend arranging a DEXA scan if FRAX (without BMD) shows an intermediate result

Q Fracture

- estimates the 10-year risk of fragility fracture
- developed in 2009 based on UK primary care dataset
- can be used for patients aged 30-99 years (this is stated on the Q Fracture website, but other sources give a figure of 30-85 years)
- includes a larger group of risk factors e.g. cardiovascular disease, history of falls, chronic liver disease, rheumatoid arthritis, type 2 diabetes and tricyclic antidepressants

DEXA scan

- There are some situations where NICE recommend arranging BMD assessment (i.e. a DEXA scan) rather than using one of the clinical prediction tools:
  - before starting treatments that may have a rapid adverse effect on bone density (for example, sex hormone deprivation for treatment for breast or prostate cancer).
  - in people aged under 40 years who have a major risk factor, such as history of multiple fragility fracture, major osteoporotic fracture, or current or recent use of high-dose oral or high-dose systemic glucocorticoids (more than 7.5 mg prednisolone or equivalent per day for 3 months or longer).
- Indicators of low BMD are:
  - low body mass index (defined as less than 22 kg/m^2),
  - medical conditions such as ankylosing spondylitis, Crohn's disease,
  - conditions that result in prolonged immobility, and
  - untreated premature menopause

Interpreting the results of FRAX

- If the FRAX assessment was done **without a bone mineral density (BMD)** measurement the results (10-year risk of a fragility fracture) will be given and categorised automatically into one of the following:
  - low risk: reassure and give lifestyle advice
  - intermediate risk: offer BMD test
  - high risk: offer bone protection treatment
- If the FRAX assessment was done **with a bone mineral density (BMD)** measurement the results (10-year risk of a fragility fracture) will be given and categorised automatically into one of the following:
  - reassure
  - consider treatment
  - strongly recommend treatment
- If you use Q Fracture instead patients are not automatically categorised into low, intermediate or high risk. Instead the 'raw data' relating to the 10-year risk of any sustaining an osteoporotic fracture. This data then needs to be interpreted alongside either local or national guidelines, considering certain factors such as the patient's age.

When should we reassess a patient's risk (i.e. repeat the FRAX/Q Fracture)**?**

- *if the original calculated risk was in the region of the intervention threshold for a proposed treatment and only after a minimum of 2 years, or*
- *when there has been a change in the person's risk factors*

Osteoporosis: management

- **secondary prevention of osteoporotic fractures in postmenopausal women** (NICE guidelines 2008).**Key points include**
  - osteoporotic fragility fractures in postmenopausal women + confirmed osteoporosis (a T-score of - 2.5 SD or below) → treatment.
  - In women aged ≥ 75 years, a DEXA scan may not be required
  - vitamin D and calcium supplementation should be offered to all women unless the clinician is confident they have adequate calcium intake and are vitamin D replete
    - **If osteoporosis is established, the treatment includes 1500 mg/day of calcium and 400-800 pg /day of vitamin D**
    - Dietary intake of calcium should be:
      - 800-1000 mg/day in childhood through early adulthood
      - 1000-1200 mg/day in the middle years
      - 1500 mg/day in the elderly
  - **alendronate is first-line**
  - around 25% of patients cannot tolerate alendronate, usually due to upper gastrointestinal problems. These patients should be offered risedronate or etidronate (see treatment criteria below)
  - strontium ranelate and raloxifene are recommended if patients cannot tolerate bisphosphonates (see treatment criteria below)
- **Treatment criteria for patients not taking alendronate:** for patients who do not tolerate alendronate, the most important thing to remember is:
  - the T-score criteria for risedronate or etidronate are less than the others implying that these are the second line drugs
  - if alendronate, risedronate or etidronate cannot be taken then strontium ranelate or raloxifene may be given based on quite strict T-scores (e.g. a 60-year-old woman would need a T-score < -3.5)
  - the strictest criteria are for denosumab

Supplementary notes on treatment

- **Bisphosphonates**
  - **Oral bisphosphonates** (alendronic acid, ibandronic acid and risedronate sodium) are recommended for treating osteoporosis only if:
    - the 10‑year probability of osteoporotic fragility fracture is **at least 1%.**
  - **Intravenous bisphosphonates** (ibandronic acid and zoledronic acid) are recommended for treating osteoporosis only if:
    - the 10‑year probability of osteoporotic fragility fracture is at **least 10% or**
    - the 10‑year probability of osteoporotic fragility fracture is at least 1% **and** the person has difficulty taking oral bisphosphonates (alendronic acid, ibandronic acid or risedronate sodium) or these drugs are contraindicated or not tolerated.

- alendronate, risedronate and etidronate are all licensed for the prevention and treatment of post-menopausal and glucocorticoid-induced osteoporosis
- reduce the risk of both vertebral and non-vertebral fractures
- alendronate, risedronate may be superior to etidronate in preventing hip fractures
- Alendronic acid
  - tablets, 10 mg once a day
  - tablets, 70 mg once a week
- Risedronate sodium
  - tablets, 5 mg once a day
  - tablets, 35 mg once a week
- Etidronate is an oral bisphosphonate
  - administered in 90-day cycles, with each cycle consisting of etidronate (400 mg/day) for 14 days followed by calcium carbonate (1.25 g/day) for the remaining 76 days.
- Zoledronic acid
  - intravenous infusion, 50 micrograms/ml once a year
- ibandronate is a once-monthly oral bisphosphonate
- Ibandronic acid:
  - tablets, 150 mg once a month
  - injection, 3 mg/ml once every 3 months
- Instructions for administration
  - Alendronate and risedronate must be taken with 200 ml and 120 ml of water, respectively.
  - Before and immediately after administration patients should not eat or drink, and must remain upright for stipulated time periods.
  - Etidronate should be taken with water at the midpoint of a 4-hour fast (that is, 2 hours after and 2 hours before food, vitamins with mineral supplements such as iron, calcium supplements, laxatives containing magnesium, or antacids containing calcium or aluminium).
- **contraindicated in patients with a GFR less than 35 ml/min**
  - Data from randomised controlled trials supports use of bisphosphonates down to GFRs as low as 30-35 ml/min. Below this level RCT evidence is unavailable, and the risk of adynamic bone disease associated with renal impairment is significantly elevated.
- **Bisphosphonate induce osteonecrosis of the jaw** (associated with dental extraction surgery and increased with underlying malignancy, especially multiple myeloma)
  - Most cases have been associated with **zoledronic acid** and pamidronate given intravenously for metastatic bone disease.
  - The reported incidence in patients with malignancy treated with these drugs is between 1.3-4.0%.
  - Dental disease is a recognised predisposing factor.
  - The lesions usually heal with minimal surgical debridement, chlorhexidine mouthwashes, antibiotics and analgesia.

(Ref: NICE guidelines : Bisphosphonates for treating osteoporosis. Published date: 09 August 2017)

- **Vitamin D and calcium**
  - poor evidence base to suggest reduced fracture rates in the general population at risk of osteoporotic fractures - may reduce rates in frail, housebound patients
- **Raloxifene - selective oestrogen receptor modulator (SERM)**
  - (SERMs) are drugs with selective activity in various organ systems, acting as weak oestrogen-receptor agonists in some systems and as oestrogen antagonists in others.
  - prevent bone loss
  - reduce risk of vertebral fractures, but has not yet been shown to reduce the risk of non-vertebral fractures
  - increase bone density in the spine and proximal femur
  - less effective in preventing loss of bone mineral density versus bisphosphonates or denosumab.
  - disadvantages
    - may worsen menopausal symptoms
    - increased risk of thromboembolic events
  - contraindicated in:
    - history of venous thromboembolism (VTE),
    - hepatic impairment,

- cholestasis,
- severe renal impairment,
- unexplained uterine bleeding or endometrial cancer.
- Raloxifene should not be co-administered with systemic oestrogens,
- in patients with breast cancer it should not be used for osteoporosis treatment or prevention until treatment of the breast cancer, including adjuvant treatment, has been completed.

➢ advantage:
- may decrease risk of breast cancer

- **Strontium ranelate**
  - ➢ Action
    - 'dual action bone agent' - increases deposition of new bone by osteoblasts (promotes differentiation of pre-osteoblast to osteoblast) and reduces the resorption of bone by inhibiting osteoclasts
  - ➢ Indication
    - secondary prevention of osteoporotic fragility fractures in postmenopausal women who are:
      - ❖ unable to take alendronate and risedronate due to contraindication, intolerance or unable comply with the special instructions for the administration. **And**
      - ❖ have a combination of T-score, age and number of independent clinical risk factors for fracture (see denosumab indications below).
  - ➢ Dose and administration
    - The dose is 2 g once daily in water, preferably at bedtime.
    - **Advice is to avoid food for 2 hours before and after taking granules**, particularly calcium-containing products e.g. milk; also preferably avoid concomitant antacids containing aluminium and magnesium hydroxides for 2 hours after taking granules.
    - Treatment with strontium ranelate should be discontinued during treatment with oral tetracycline or quinolone antibiotics.
    - it is not recommended in patients with severe renal impairment
    - should be used with caution in patients at increased risk of VTE.
  - ➢ Disadvantages
    - concerns regarding the safety profile of strontium have been raised recently. It should only be prescribed by a specialist in secondary care
    - due to these concerns the European Medicines Agency in 2014 said it should only be used by people for whom there are no other treatments for osteoporosis
    - **increased risk of cardiovascular events**: any history of cardiovascular disease or significant risk of cardiovascular disease is a contraindication
    - **increased risk of thromboembolic events:** a Drug Safety Update in 2012 recommended it is not used in patients with a history of venous thromboembolism
    - may cause serious skin reactions such as Stevens Johnson syndrome
- **Denosumab**
  - ➢ human monoclonal antibody that **inhibits RANK ligand**, which in turn **inhibits the maturation of osteoclasts**
    - RANK occurs on the surface of osteoclast precursors and osteoclasts. Inhibiting it leads to reduced osteoclast formation, function and survival. This leads to reduced bone reabsorption in both cortical and trabecular bone.
  - ➢ given as a single subcutaneous injection **every 6 months**
  - ➢ initial trial data suggests that it is effective and well tolerated
  - ➢ (NICE guidelines 2010) state that : it is recommended only in postmenopausal women at increased risk of fractures:
    - who are unable to comply with alendronate and either risedronate or etidronate, or have an intolerance of, or a contraindication to, those treatments **and**
      - ❖ who have a combination of T-score, age and number of independent clinical risk factors for fracture
      - ❖ **independent clinical risk factors for fracture are**:
        - ⇨ parental history of hip fracture,
        - ⇨ alcohol intake of 4 or more units per day, and
        - ⇨ rheumatoid arthritis.

- The recommended dosage is 60 mg subcutaneous injection **once every 6 months**.
- Side effects:
  - Like bisphosphonates it is associated with **osteonecrosis of the jaw**, but not other adverse events such as reflux oesophagitis.
  - The risk of a dynamic bone disease may be less for denosumab versus bisphosphonates because it does not accumulate in bone.

- **Teriparatide**
  - is a recombinant fragment of human parathyroid hormone and, as an anabolic agent, it stimulates new formation of bone and increases resistance to fracture.
  - **Action**
    - **Increased osteoblast activity** (the main effect)
    - **increased calcium absorption from the gut and**
    - **reduced calcium excretion from the kidney.**
  - Indications
    - an alternative treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women who are:
      - unable to take alendronate and risedronate, or strontium ranelate due to contraindication, intolerance or unsatisfactory response **and**
      - age ≥ 65 years and have a T-score of ≤ –4.0 SD, **or** a T-score of **≤** –3.5 SD **plus** more than two fractures, **or**
      - age 55–64 years and have a T-score of **≤** –4 SD **plus** more than two fractures.
  - Dose
    - The recommended dose is 20 micrograms administered once daily by subcutaneous injection in the thigh or abdomen.
    - the maximum total duration of treatment was restricted, by the marketing authorisation, to 18 months.
  - Contraindications include:
    - pre-existing hypercalcaemia,
    - severe renal impairment,
    - metabolic bone diseases other than primary osteoporosis (including hyperparathyroidism and Paget's disease of bone),
    - unexplained elevations of alkaline phosphatase, and
    - previous radiation treatment to the skeleton.
- **Hormone replacement therapy**
  - has been shown to reduce the incidence of vertebral fracture and non-vertebral fractures
  - due to concerns about increased rates of cardiovascular disease and breast cancer it is no longer recommended for primary or secondary prevention of osteoporosis unless the woman is suffering from vasomotor symptoms
- **Hip protectors**
  - evidence to suggest significantly reduce hip fractures in nursing home patients
  - compliance is a problem
- **Falls risk assessment**
  - no evidence to suggest reduced fracture rates
  - however, do reduce rate of falls and should be considered in management of high risk patients

Raloxifene and teriparatide are second line treatments if bisphosphonates are not tolerated, ineffective or unsuitable for the patient.

(Ref: NICE guidelines . Last updated: 09 August 2017)

Pathophysiology of bone diseases

- **Osteoporosis → decreased bone mass, but mineralization is normal.**
- **Osteomalacia → Decreased bone mineralization (due to vitamin D deficiency)**
- **Paget's disease → Disorder of bone remodeling (excessive bone resorption, followed by disorganized bone formation occurs, producing thickened but weak bone.)**

Paget's disease of the bone

Paget's disease - old man, bone pain, raised ALP

The constellation of bony pain, unilateral hearing loss, and an isolated raised ALP should point you in the direction of Paget's disease of the bone.

Disease localization

- most commonly involves the axial skeleton, **the pelvis being the most common**, but it can affect any area.
- **In the majority of patients, the disease affects at least two bones**, but in one third of patients only one bone is affected.

Epidemiology

- Second most prevalent skeletal disease after osteoporosis
- (UK prevalence 5%) but symptomatic in only 1 in 20 patients
- more common in men (sex ratio 3:2 men: women).
- Age of onset: > 55 years

Pathophysiology

- increased but uncontrolled bone turnover
- **It is thought to be primarily a disorder of osteoclasts, with excessive osteoclastic resorption followed by increased osteoblastic activity.**
- it is a focal disorder of bone remodelling characterized by an increase in the number and size of osteoclasts in affected skeletal sites while the rest of the skeleton is spared.
- ↑↑osteoclasts → ↑↑bone resorption → subsequent increase in new bone formation and altered bone architecture.
- The structure of the new bone is disorganised and mechanically weaker and therefore liable to pathological fracture and deformity.

Predisposing factors

- increasing age
- male sex
- northern latitude
- family history

Clinical features - only 5% of patients are symptomatic

- **most commonly no symptoms**.
  - The diagnosis is typically found incidentally on radiographs and laboratory investigations.
  - Paget disease should be considered in an asymptomatic patient who presents with isolated ALP elevation that cannot be explained by any other means (e.g., cholestasis or bone metastases)
- bone pain (e.g. pelvis, lumbar spine, femur)
  - **Bone pain is typically increased with rest and on weight bearing.**
  - Unlike osteoarthritis, pagetic bone pain usually increases with rest, on weight bearing, when the limbs are warmed, and at night.
- classical, untreated features: bowing of tibia, bossing of skull

Complications

- deafness (cranial nerve entrapment)
  - In the skull, the 8th nerve can be compressed, resulting in hearing loss. This is one of the more common complaints, being present in 37% of respondents in a recent survey of 2000 patients with Paget's disease .
- **bone sarcoma** (1% if affected for > 10 years)
  - Although the risk of osteogenic sarcoma is 30 times that of patients without Paget's, the risk of sarcoma development is still small → **Less than 1%**
  - Symptoms of osteogenic sarcoma include increased pain localised to one particular area and pathological fracture.
  - tumor arising from mesenchymal stem cells (osteoblasts)
  - Most common primary bone malignancy
  - x-ray
    - **Sunburst appearance of lytic bone lesions** and/or codman triangles (a ridge of sub-periosteal new bone is raised by an underlying tumor)
  - Treatment

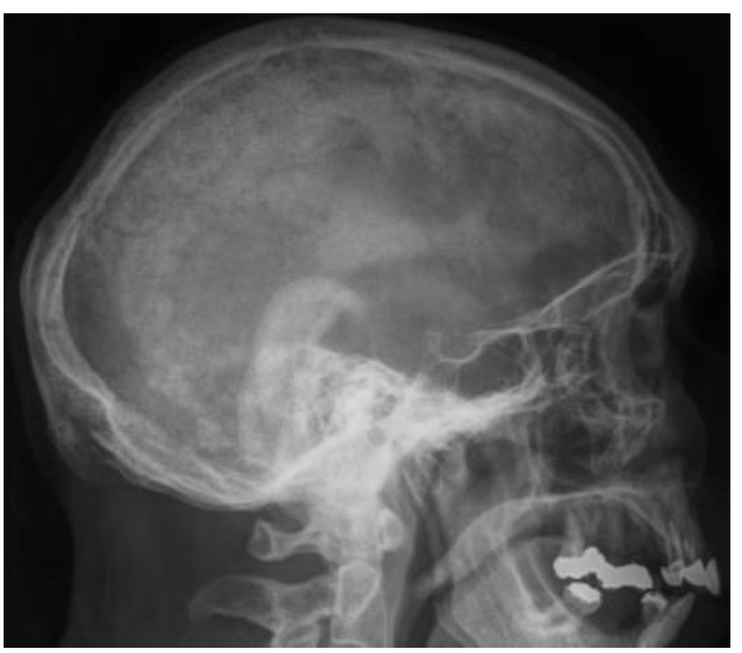
        - Surgery (definitive resection) with adjuvant polychemotherapy
        - usually resistant to radiation therapy
- Pathological fractures
- Spinal cord compression
- skull thickening
    - (A classic symptom: a hat which no longer fits)
- high-output cardiac failure
    - (due to AV shunts in bone)

Diagnosis

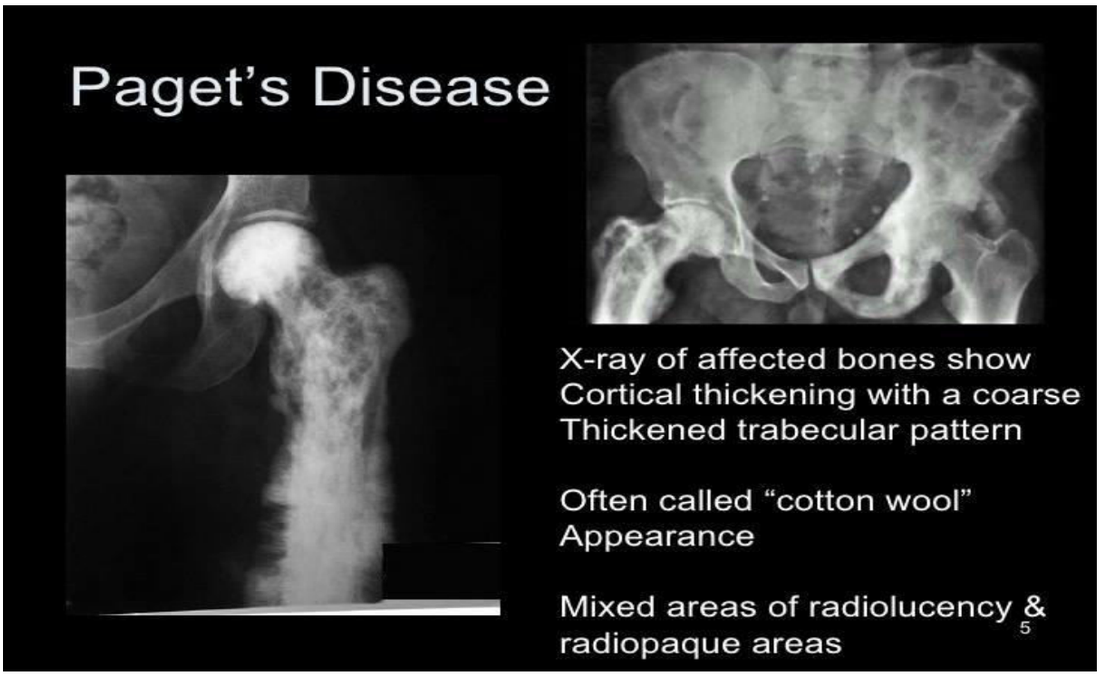
- Raised alkaline phosphatase (ALP) - **calcium* and phosphate are typically normal**
    - **the Best initial test**
    - * **calcium** is usually normal but hypercalcaemia may occur with prolonged immobilisation
- X-ray:
    - eg: (skull x-ray) thickened vault, osteoporosis circumscripta
    - Osteolysis and new bone formation typical of the disease.
    - **Radiographic features** in the mixed lytic and sclerotic phase of Paget's disease include:
        - bone expansion,
        - cortical thickening and
        - **trabecular bone thickening**.
- **the best investigation to confirm the diagnosis → Skeletal survey**
    - Recent evidence has suggested that limited **skeletal survey is superior to bone scan** for the assessment of the disease because, when there is significant osteoclastic resorption of bone, **bone scanning underestimates the extent of disease activity and still requires plain radiography for confirmation.**
- Bone biopsy
    - abnormal "**mosaic**" pattern in woven and lamellar bone.

Treatment

- **Indications for treatment include:**
    - **bone pain,**
    - **skull or long bone deformity,**
    - **fracture,**
    - **periarticular Paget's**
- **The mainstay of treatment for Paget's disease is bisphosphonate therapy,** which is proven to **relieve symptoms of pain** and has been shown to **reduce the risk of pathological fracture** in long bones **and complications of Paget's such as deafness**.
    - **bisphosphonate (either oral risedronate or IV zoledronate)**
        - Unless contraindicated, all patients on bisphosphonates should be given supplements of calcium and Vitamin D to avoid symptomatic hypocalcaemia.
    - In patients who cannot tolerate these, calcitonin is second-line therapy.
        - calcitonin is less commonly used now
- **the most appropriate way to monitor disease activity is → 6-monthly alkaline phosphatase levels**



The radiograph demonstrates marked thickening of the calvarium. There are also ill-defined sclerotic and lucent areas throughout. These features are consistent with Paget's disease.



Penicillamine

Mechanism of action

- largely unknown
- thought to reduce IL-1 synthesis and prevent the maturation of newly synthesized collagen

Uses

- rheumatoid arthritis

Adverse effects

- rashes
- disturbance of taste
- proteinuria

Perthes disease

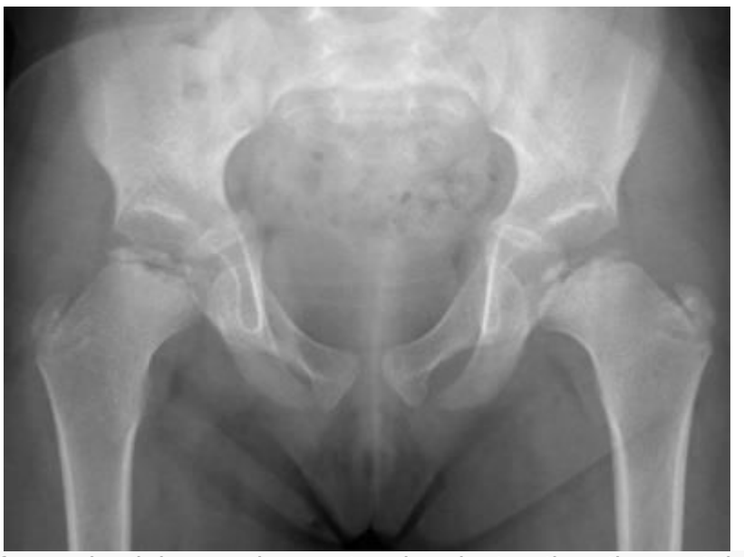
- Perthes disease is a degenerative condition affecting the hip joints of children, typically between the ages of 4-8 years.
- It is due to avascular necrosis of the femoral head
- Perthes disease is 5 times more common in boys.
- Around 10% of cases are bilateral

Features

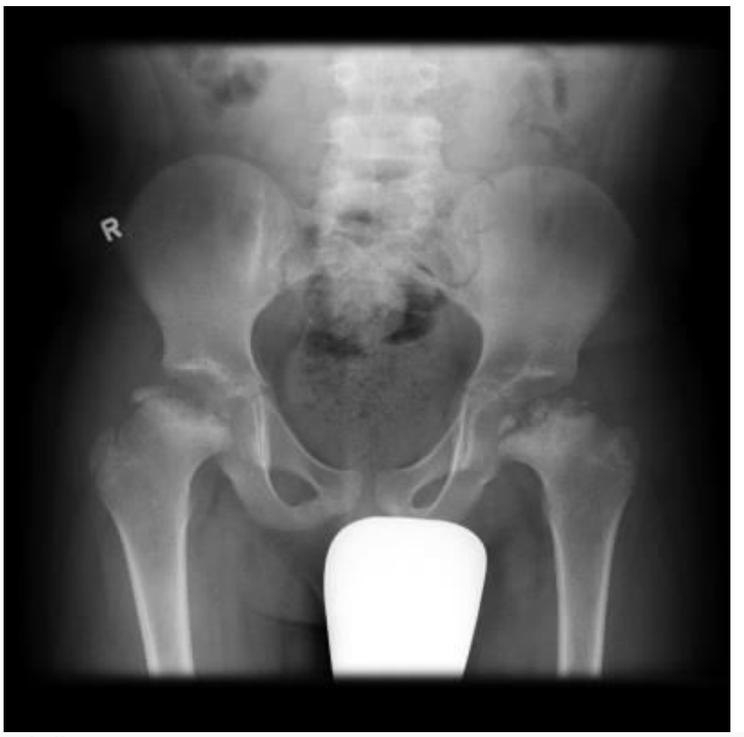
- hip pain: develops progressively over a few weeks
- limp
- stiffness and reduced range of hip movement
- x-ray: early changes include widening of joint space, later changes include decreased femoral head size/flattening

Complications

- osteoarthritis
- premature fusion of the growth plates



Perthes disease - both femoral epiphyses show extensive destruction, the acetabula are deformed



Perthes disease - bilateral disease

Pseudogout

Pseudogout - positively birefringent rhomboid shaped crystals

Chondrocalcinosis in a question is most likely to indicate → **Pseudogout**

Definition

- Pseudogout is a form of microcrystal synovitis **caused by the deposition of calcium pyrophosphate dihydrate in the synovium**

Risk factors

- hyperparathyroidism
- hypothyroidism
- haemochromatosis
- acromegaly
- low magnesium, low phosphate
- Wilson's disease

Features

- knee, wrist and shoulders most commonly affected

- joint aspiration:
  - Polar light microscopy:
    - weakly-positively birefringent **rhomboid shaped crystals**
  - Synovial fluid findings:
    - 10,000-50,000 WBCs/μL with > 90% neutrophils
- x-ray:
  - chondrocalcinosis
    - (cartilage called due to deposition of calcium pyrophosphate dihydrate crystals in the large joints, particularly the knees.)

Management

- aspiration of joint fluid, to exclude septic arthritis
- NSAIDs or intra-articular, intra-muscular or oral steroids as for gout

---

Psoriatic arthropathy

If first-degree relatives of patients with psoriasis have joint problems, psoriatic arthritis should be considered

- Chronic progressive seronegative inflammatory arthritis occurring in patients with underlying psoriasis.
- most commonly a seronegative **oligoarthritis** found in patients with psoriasis
  - **Oligoarthritis** (most common, accounting for 70% of cases)
- autoimmune disease , associated with an increased frequency of **HLA-B7 and HLA-B27.**

Epidemiology

- affects men and women equally
- the range of age of onset between 35–55 years.
- **Around 10-20% percent of patients with skin lesions develop an arthropathy**

Types

- Five subsets of psoriatic arthritis have been described based on the pattern of joint involvement, with an increased prevalence of the **spondylitic form in males** and the **rheumatoid form in females.**
  1. asymmetric oligoarthritis (most common) (43%).
  2. symmetric polyarthritis (33%)
     - proximal interphalyngeal joint involvement.
  3. sacroilitis
  4. DIP joint disease
     - associated with nail pitting, and onycholysis (separation of nail from nail bed)
  5. arthritis mutilans (severe deformity fingers/hand, 'telescoping fingers') (rare)

The relation between skin lesion and Psoariatic arthritis

- **Psoriatic arthropathy correlates poorly with cutaneous psoriasis and often precedes the development of skin lesions.**
  - Psoriasis precede psoriatic arthritis in 60-80% of patients (usually by less than 10 years)
  - **In 15-20% of patients, arthritis appears before the psoriasis**
    - Small plaques should be looked for on the elbows and scalp.

Feature

- Psoariatic arthritis tends to affect the **distal interphalangeal joints (DIP)**.
- can present with or without associated psoriatic skin lesions or only with nail malformations.
- If no obvious skin lesions are visible, the clinician must look for psoriasis in hidden sites such as the scalp, intergluteal cleft and umbilicus.
- Nail involvement includes onycholysis, transverse ridging and nail pitting.
- vertebrae may be asymmetrically affected and there may be involvement of the atlantoaxial joint with erosion of the odontoid and consequent subluxation.
- Dactylitis with sausage digits is seen in 35% of patients
- **Extra-articular features include:**
  - **Ocular involvement may occur in 30% of patients, including:**
    - conjunctivitis (in 20%)
    - acute anterior uveitis (in 7%);

- ❖ in patients with uveitis, 43% have sacroiliitis
- ➢ **Synovitis affecting flexor tendon sheaths,** (with sparing of the extensor tendon sheath)

Investigations

- ↑ (ESR) and C-reactive protein level
- Negative rheumatoid factor
- Low levels of circulating immune complexes (in 56% of patients)
- High Serum immunoglobulin A levels (in two thirds of patients)
- **Radiography**
  - ➢ asymmetric **"pencil-in-cup" deformity** in the distal interphalangeal joints of the fingers.

Diagnositic criteria

- established inflammatory articular disease with at least 3 points from the following features:
  1. Current psoriasis (assigned a score of 2)
  2. history of psoriasis (in the absence of current psoriasis; assigned a score of 1)
  3. **family history of psoriasis** (in the absence of current psoriasis and history of psoriasis; assigned a score of 1)
  4. Dactylitis (assigned a score of 1)
  5. Juxta-articular new-bone formation (assigned a score of 1)
  6. RF negativity (assigned a score of 1)
  7. Nail dystrophy (assigned a score of 1)

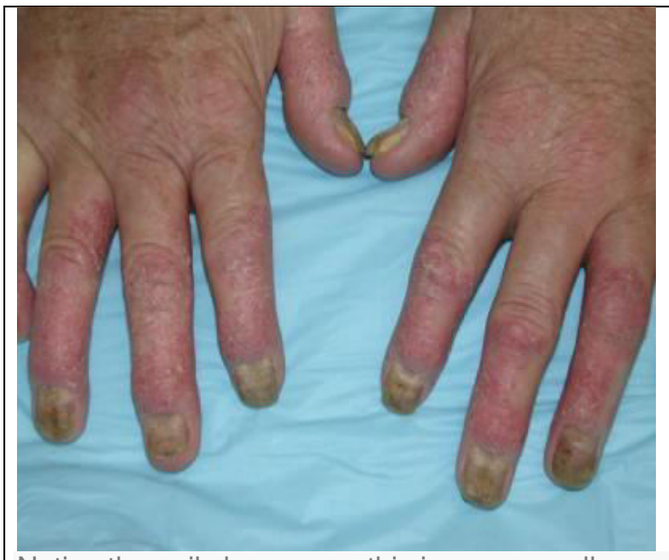
Differential diagnosis

- The condition can be distinguished from the sacroilitis seen in ankylosing spondylitis by the presence of the other clinical signs in the nails and the skin and by differences in the patterns of vertebral involvement.
- Polyarticular psoriatic arthritis distinguished from rheumatoid arthritis by:
  1. presence of dactylitis and
  2. absence of anticyclic citrullinated peptide antibodies.

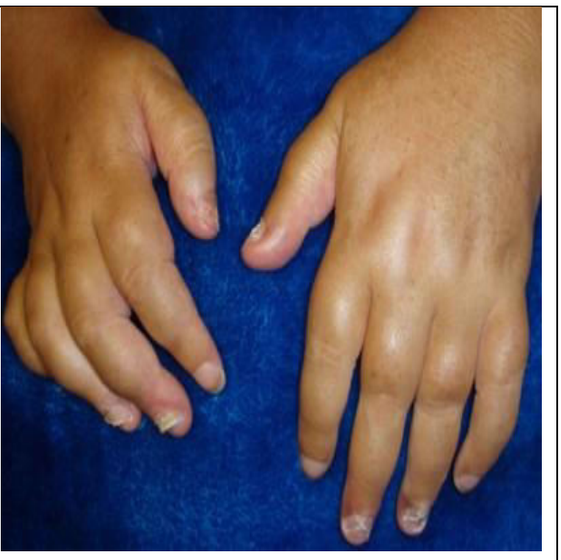
Management

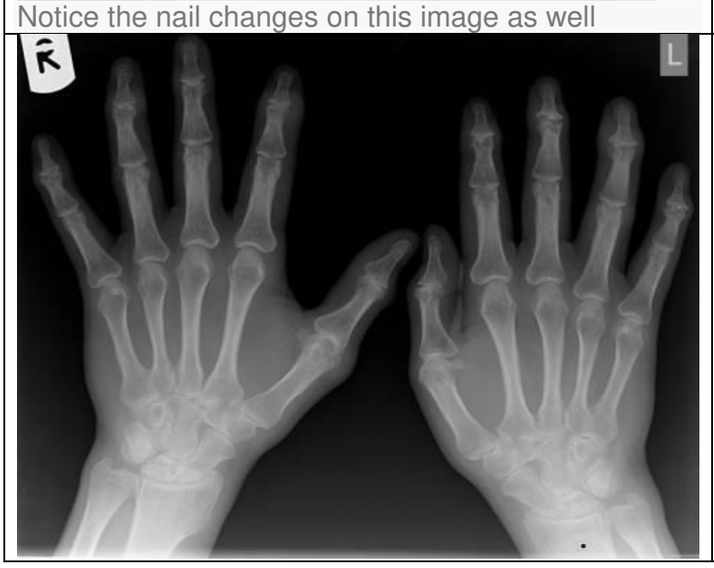
- treat as rheumatoid arthritis but better prognosis
- limited disease → NSAIDs usually sufficient
  - ➢ **do not prevent progressive joint damage**
- Patients with progressive peripheral arthritis (polyarthritis, joint erosions) or oligoarthritis refractory to NSAIDs and/or intra-articular corticosteroids require disease-modifying antirheumatic disease therapy (e.g., methotrexate) early in the disease course.
  - ➢ **methotrexate will improve both the joint and skin problems**
- **Sulfasalazine is safe to use in pregnancy and there is no need to stop it.**
  - ➢ **Sulphasalazine tends to only improve joint symptoms and not improve the psoriasis.**
- Tumour necrosis factor (TNF)-alpha inhibitors may be considered as **second-line** therapy for most disease manifestations.
  - ➢ If not respond to an adequate trial of two DMARDs (for example, leflunomide, methotrexate, sulfasalazine) → **anti-TNF agents**
- **Apremilast** (Nice guidelines February 2017)
  - ➢ phosphodiesterase 4 (PDE4) inhibitor.
  - ➢ ↓anti-inflammatory cytokines and mediators associated with psoriatic arthritis (including [TNF]-alpha and interleukin [IL]-23).
  - ➢ Apremilast, alone or in combination with (DMARDs), is recommended for psoriatic arthritis only if:
    - ▪ they have peripheral arthritis with 3 or more tender joints and 3 or more swollen joints and
    - ▪ not responded to adequate trials of at least 2 standard DMARDs.
  - ➢ Adverse effects
    - ▪ (GI) disorders (most commonly diarrhoea and nausea);
    - ▪ upper respiratory tract infections;
    - ▪ headache; and tension headache.
  - ➢ Stop apremilast at 16 weeks if the psoriatic arthritis has not shown an adequate response
- Hydroxychloroquine → exacerbate psoriatic skin lesions

- In patients with cutaneous psoriasis, systemic corticosteroids predispose to pustular psoriasis, and may result in a flare of skin psoriasis when they are stopped.

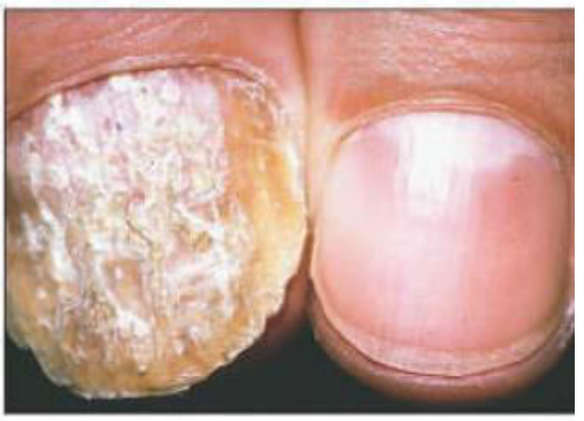


Notice the nail changes on this image as well

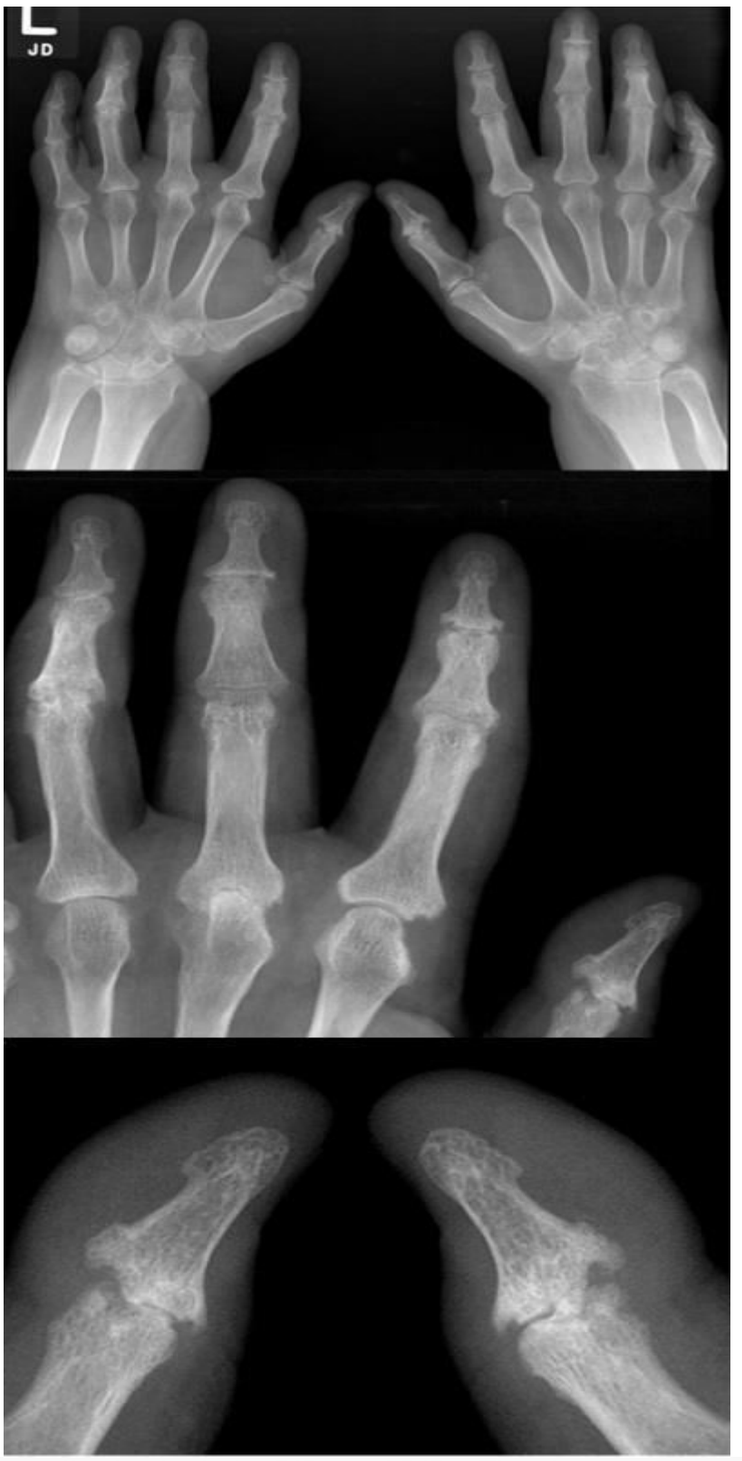




X-ray showing some of changes in seen in psoriatic arthropathy. Note that the DIPs are predominately affected, rather than the MCPs and PIPs as would be seen with rheumatoid. Extensive juxta-articular periostitis is seen in the DIPs but the changes have not yet progressed to the classic 'pencil-in-cup' changes that are often seen.



Psoriasis involvement of the nail produces pitting and yellowing, which can be mistaken for onychomycosis.



This x-ray shows changes affecting both the PIPs and DIPs. The close-up images show extensive changes including large eccentric erosions, tuft resorption and progresion towards a 'pencil-in-cup' changes.

Reactive arthritis (Reiter syndrome)

Reactive arthritis is defined as an arthritis that develops following an infection where the organism cannot be recovered from the joint.

'Can't see, pee or climb a tree'

Urethritis + arthritis + conjunctivitis = reactive arthritis

- Reactive arthritis is defined as an arthritis that develops following an infection where the organism cannot be recovered from the joint.
  - the presence of bacterial infection on joint aspiration would count **against it.**
- Reactive arthritis is one of the HLA-B27 associated seronegative spondyloarthropathies.
- It encompasses **Reiter's syndrome**, a term which described a classic triad of urethritis, **conjunctivitis** and arthritis following a dysenteric illness during the Second World War.
- Later studies identified patients who developed symptoms following a sexually transmitted infection (post-STI, now sometimes referred to as sexually acquired reactive arthritis, SARA).

Eye diseases in Reiter's syndrome:
- **Most common → conjunctivitis (50%)**
- **Less common → iritis (12%)**

Epidemiology
- post-STI form much more common in men (e.g. 10:1)
- post-dysenteric form equal sex incidence

The table below shows the **organisms that are most commonly associated with reactive arthritis**:

Post-dysenteric form	Post-STI form
Shigella flexneri *Salmonella typhi*murium *Salmonella* enteritidis *Yersinia enterocolitica* *Campylobacter*	*Chlamydia trachomatis*

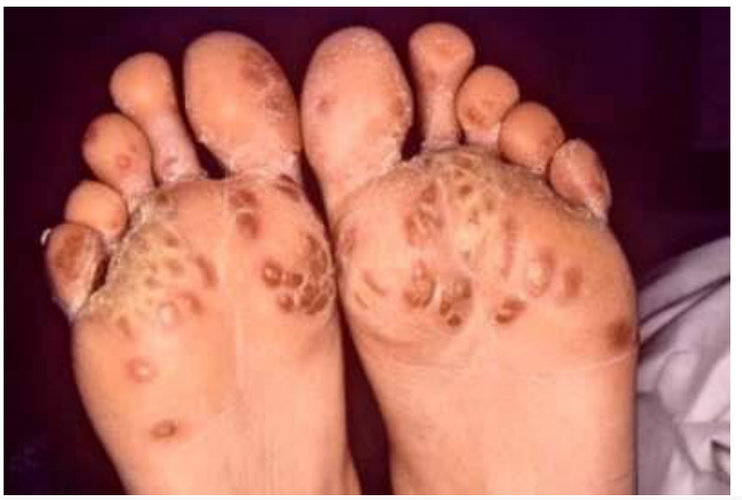
Features
- typically develops within 4 weeks of initial infection
  - symptoms generally last around 4-6 months
- arthritis is typically an **asymmetrical** oligoarthritis of lower limbs
  - mainly affecting the large weight-bearing joints (usually knee and ankle).
- dactylitis
- symptoms of urethritis
- eye:
  - **conjunctivitis (seen in 50%),**
  - anterior uveitis
- skin:
  - circinate balanitis (painless vesicles on the coronal margin of the prepuce),
  - **keratoderma blenorrhagica** (waxy **yellow**/**brown** papules on palms and soles)

Management
- usually self-limiting
- symptomatic: analgesia, NSAIDS, intra-articular steroids
- sulfasalazine and methotrexate are sometimes used for **persistent disease**

Prevention
- Antibiotics given at the time of the non-gonococcal venereal infection will **reduce the likelihood of that person developing reactive arthritis.**
  - Appropriate treatment during the acute stage would be **doxycycline 100 mg bd if Chlamydia infection is confirmed.**

Prognosis
- Prognosis with respect to long-term complications is better when **dysenteric** infection is the precipitant factor rather than **Chlamydial** infection.
- arthritis usually resolves in 3 months
- In general, symptoms last from a few weeks to around 6 months in total.
  - symptoms rarely last more than 12 months
- **Around 25% of patients have recurrent episodes**
- **10%** of patients develop **chronic disease**

- In **HLA-B27-positive** patients, **ankylosing spondylitis** may develop in up to **50%** of patients who have suffered an episode of **reactive arthritis**.
- HIV infection is associated with a higher risk of reactive arthritis
  - **HLA-B27** is found in 80–90 % of **Caucasians** with HIV-associated reactive arthritis,
  - while studies of **Africans** with HIV-associated reactive arthritis have found nearly all to be **HLA-B27-negative**
- Rarer **long-term complications** include:
  - urethral stricture,
  - cataracts, and
  - aortic root necrosis.



Keratoderma blenorrhagica

Amyloidosis

Amyloidosis should always be considered in a patient with a long-standing inflammatory and/or infectious disease who presents with kidney, liver, or GI involvement.

Overview

- amyloidosis is describes the extracellular deposition of an insoluble **fibrillar protein** termed amyloid
- amyloid also contains a **non-fibrillary protein** called:
  - amyloid-P component, derived from the acute phase protein serum amyloid P
  - apolipoprotein E
  - heparan sulphate proteoglycans
- the accumulation of amyloid fibrils leads to tissue/organ dysfunction

Causes

- Amyloidosis may be inherited or acquired; acquired form is associated with long standing chronic illnesses (DM, Rheumatoid Arthritis).

Feature

- unexplained weight loss,
- fatigue,
- oedema resistant to diuretic therapy.
- joint pains and stiffness, usually upper limbs more than lower limbs.

Types:

- **Light-chain amyloidosis (AL-amyloidosis)**
  - Most common form of amyloidosis in developed nations
  - Etiology:
    - primary disease caused by plasma cell dyscrasias e.g., :
      - multiple myeloma,
      - Waldenström's macroglobulinemia,
      - non-Hodgkin lymphoma
  - Pathophysiology:
    - increased production of the light chains of immunoglobulins → deposition of AL (amyloid light chain) protein in various organs
  - Features: rapidly progressive clinical course
    - Heart:

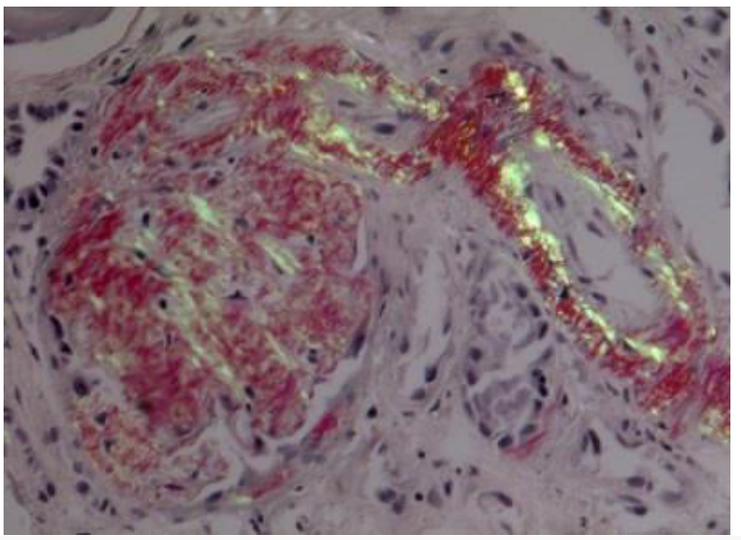
- restrictive cardiomyopathy,
- atrioventricular block
  - ⇨ An ECG is required in all patients to look for conduction abnormalities.

- Kidney:
  - nephrotic syndrome,
  - type II renal tubular acidosis,
  - nephrogenic diabetes insipidus
- Tongue:
  - **macroglossia** → obstructive sleep apnea
- Nervous system:
  - Amyloid peripheral neuropathy
    - ⇨ carpal tunnel syndrome
    - ⇨ only seen in AL, never seen in AA
  - autonomic neuropathy
- Gastrointestinal tract:
  - malabsorption
- **periorbital ecchymoses**
- **Enlargement of the submandibular salivary glands**
- shoulder pad sign due to periarticular infiltration with amyloid and pseudohypertrophy is specific for AL
- Bleeding disorders

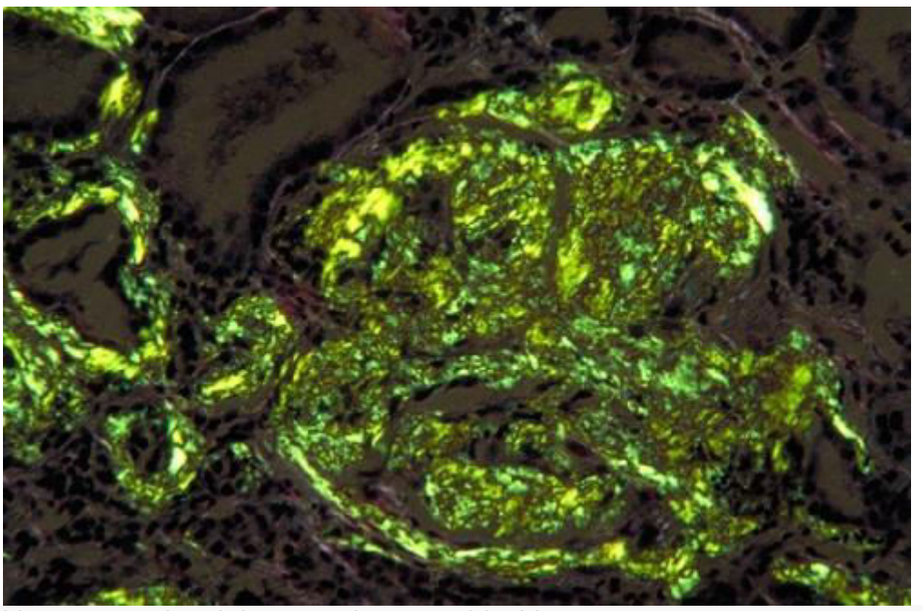
- **Reactive amyloidosis (AA-amyloidosis)**
  - Etiology: secondary disease
    - Chronic inflammatory conditions (e.g., IBD, **rheumatoid arthritis**, SLE, vasculitis)
    - Chronic infectious diseases (e.g., tuberculosis, bronchiectasis, leprosy, osteomyelitis)
    - Certain tumors (e.g., renal cell carcinoma, lymphomas)
  - Pathophysiology:
    - chronic inflammatory process → increased production of acute phase reactant SAA (serum amyloid-associated protein) → deposition of **AA** (**a**myloid-**a**ssociated) protein in various organs
  - Clinical features
    - Kidney: **most common feature → renal involvement**
      - nephrotic syndrome,
      - type II renal tubular acidosis,
      - nephrogenic diabetes insipidus
    - Adrenal glands:
      - primary adrenal insufficiency
    - Liver and spleen:
      - hepatomegaly, splenomegaly
    - Gastrointestinal tract:
      - malabsorption
- **β-2 microglobulin amyloidosis**
  - Precursor protein is β-2 microglobulin, part of the major histocompatibility complex
  - **Associated with patients on renal dialysis**
  - neurological impairment in patients on longstanding dialysis.

Diagnosis

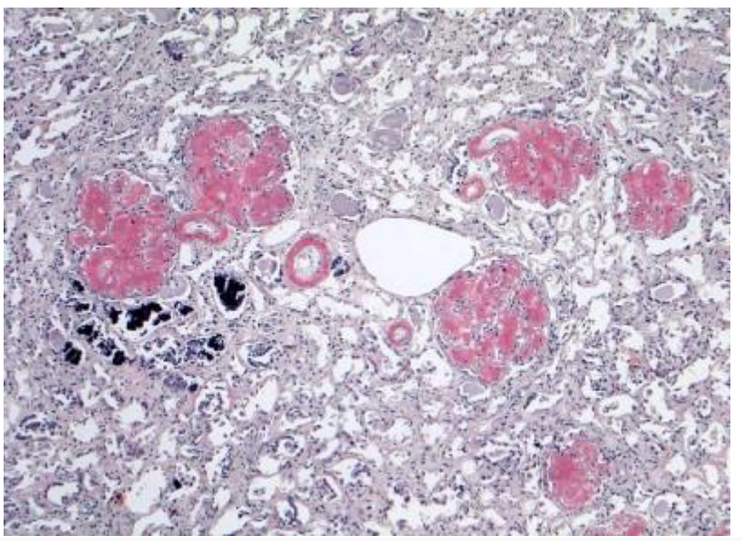
- **Biopsy**
  - Biopsy of abdominal wall fat, the **rectum** or a salivary gland can be examined
  - The tissue is treated with **Congo red stain** → the amyloid proteins appear **apple-green** birefringence on Light microscopy.
- Tests to diagnose the underlying disease
  - Light chain amyloidosis
    - Serum electrophoresis: → monoclonal gammopathy
    - Urine test for Bence-Jones proteins → multiple myeloma
  - Reactive amyloidosis: → ESR, CRP, chest x-ray



Renal amyloid with congo red staining - apple-green birefringence



Renal amyloid with congo red staining - apple-green birefringence



Congo red staining. Amyloid deposits are seen in both the arteries/arterioles and within the glomerulus. The deposit of amyloid within the mesangium is not dissimilar to the nodular lesions seen in diabetic nephropathy

Pathological feature of amyloidosis

1. **Electron micrography - fibrillar appearance**
2. x Ray diffraction pattern - beta pleated sheet structure
3. Haematoxylin and eosin staining - amorphous eosinophilic appearance

4. Congo red histological staining - apple-green birefringence
5. Solubility in water and buffers of low ionic strength.

Treatment

- The only treatment is renal transplantation.
- It can be reduced by using high flux dialysis membranes in patients who are likely to be on dialysis for a prolonged period.

Amyloidosis: cardiac

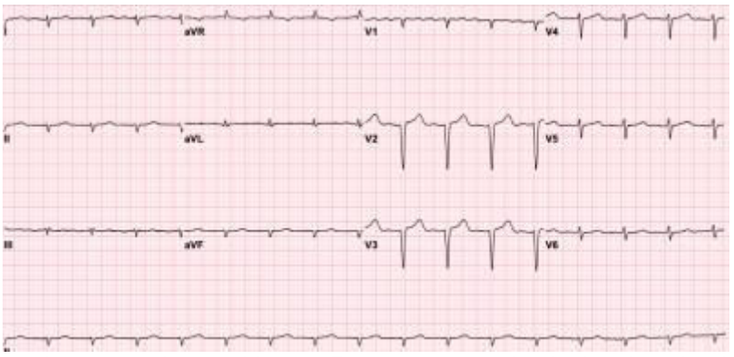
- Cardiac amyloidosis most commonly presents as restrictive cardiomyopathy, associated with AL Amyloidosis

Presentation: Typical presentation of right heart failure:

- Jugular venous distension
- Peripheral oedema
- Orthopnoea and paroxysmal nocturnal dyspnea are typically absent

Diagnosis

- Combination of low-voltage ECG and thickened ventricular walls is one of the characteristic features of cardiac amyloidosis.
- **Echocardiographic abnormalities** include:
  - dilatation of atria, thickened interatrial septum, diastolic dysfunction and small-volume ventricles.
  - The most distinctive feature of cardiac amyloidosis is a sparkling, granular appearance of myocardium, but this is a relatively insensitive feature occurring only in about 25% of cases.
  - Cardiac amyloidosis is associated with a 'global speckled' pattern on echo.



The ECG typically shows low-voltage complexes with poor R wave progression in the chest leads (a pseudoinfarction pattern).

Management of AL

- The most effective treatment is autologous bone marrow transplants with stem cell rescues. However many patients are too weak to tolerate this approach
- Other treatments can involve application of chemotherapy similar to that used in multiple myeloma. A combination of bortezomib and dexamethasone has been proposed, as has melphalan and dexamethasone.
- Digoxin is contraindicated in cardiac amyloidosis (restrictive cardiomyopathy)

Septic arthritis

Septic arthritis - most common organism: Staphylococcus aureus

Septic arthritis: IV flucloxacillin

Causes

- most common organism overall is *Staphylococcus aureus*
  - The most likely organisms are staphlococci (70%) and beta-haemolytic streptococci (20%).
- in young adults who are sexually active *Neisseria gonorrhoeae* should also be considered
- The most likely organism to have been aspirated from the **infected hip joint replacement** prosthesis → **Propionibacterium acnes** (PA):

- Gram positive bacilli,
- it is poorly virulent,
- symptoms of PA infection may occur many years after original arthropathy,
- it is sensitive to penicillins, clindamycin and carbapenems.

Feature

- Fifty percent of cases will have an associated bacteraemia.
- Early x-rays are almost always normal.
- **after original arthroplasty → Propionibacterium acnes**
  - gram positive bacterium which is poorly virulent.
  - Symptoms may occur many years after original arthroplasty and the bacteria are only identified at the time of joint revision.
  - Prolonged intravenous antibiotics given at the time of revision arthroplasty are said to resolve infection in around 90% of cases.
  - known to be sensitive to penicillins, clindamycin and carbapenems.

Management

- synovial fluid should be obtained before starting treatment
- intravenous antibiotics which cover Gram-positive cocci are indicated. The BNF currently recommends flucloxacillin or clindamycin if penicillin allergic
- antibiotic treatment is normally be given for several weeks (BNF states 6-12 weeks)
  - ideally these should be intravenous for 2 weeks and then oral for 4 weeks.
- needle aspiration should be used to decompress the joint
- surgical drainage may be needed if frequent needle aspiration is required
- if patient on warfarin, What is the most appropriate management of anticoagulation before joint aspiration and injection?
  - **If INR is within the therapeutic range → no need to stop the warfarin or change the dose.**
  - The risk of a thrombotic episode if anticoagulation is changed outweighs any risk associated with injecting joint while taking anticoagulation.

The following table compares synovial fluid cell count values.

Normal	Inflammatory (Gout/Pseudogout)	Infectious
< 2,000 WBCs	2,000–50,000 WBCs	> 50,000 WBCs

Sjogren's syndrome

- Sjogren's syndrome is an autoimmune disorder affecting exocrine glands resulting in dry mucosal surfaces.
- It may be primary (PSS) or secondary to rheumatoid arthritis or other connective tissue disorders, where it usually develops around 10 years after the initial onset.
- primary Sjögren's syndrome occurs alone and more likely to have positive anti Ro SSA antibodies than secondary Sjögren's).
- Hypergammaglobulinaemia is present in 80% of individuals.
- Typically secondary Sjögren's has pre-existent rheumatoid or systemic lupus erythematosus before the development of Sjögren's symptoms.
- more common in females (ratio 9:1).
- There is a marked increased risk of lymphoid malignancy (40-60 fold)

Features

- dry eyes: keratoconjunctivitis sicca
- dry mouth
- vaginal dryness
- arthralgia
- Raynaud's,
- myalgia
- sensory polyneuropathy
- renal tubular acidosis (usually subclinical)
- Plasma cell infiltration of salivary and lacrimal glands: Parotid swelling.

Complication

- **higher risk of developing lymphoma**
  - These lymphomas are primarily of B cell origin.
  - High risk factors for lymphoma development in Sjogren's syndrome patients include:
    - persistent unilateral or bilateral parotid gland enlargement,
    - splenomegaly and lymphadenopathy,
    - low C4 complement levels,
    - type 2 mixed cryoglobulinaemia

Investigation

- rheumatoid factor (RF) positive in nearly 100% of patients
- ANA positive in 70%
- anti-Ro (SSA) antibodies in 70% of patients with PSS
  - **Anti-Ro antibody is associated with:**
    - **congenital complete heart block**
    - **neonatal lupus**
      - The mother is usually positive for anti-Ro or anti-La antibodies but may not have overt lupus erythematosus.
- anti-La **(SSB)** antibodies in 30% of patients with PSS
- Hypergammaglobulinaemia (↑ IgG) in 80%
- low C4
- Schirmer's test: filter paper near conjunctival sac to measure tear formation
  - placement of a standard strip of filter paper on the inside of the lower eyelid.
  - **Wetting of less than 5 mm in 5 min indicates defective tear production.**
- **Rose Bengal staining of the eyes** commonly shows punctuate or filamentary **keratitis**.
- histology: focal lymphocytic infiltration
- **the most definitive test for Sjögren's syndrome → Labial gland biopsy**

Management

- artificial saliva and tears
- pilocarpine may stimulate saliva production

Other causes of dry eyes, and/or dry mouth include:

- past head and neck radiation
- hepatitis C infection
- acquired immunodeficiency disease
- pre-existing lymphoma
- sarcoidosis
- graft versus host disease, or
- the use of an anticholinergic drugs.

Systemic lupus erythematosus (SLE)

SLE - antibodies associated with congenital heart block = anti-Ro

SLE: C3 & C4 low

- Systemic lupus erythematosus (SLE) is a multisystem, autoimmune disorder.

Epidemiology

- much more common in females (F:M = 9:1)
- more common in Afro-Caribbeans* and Asian communities
  - *It is said the incidence in black Africans is much lower than in black Americans - the reasons for this are unclear
- onset is usually 20-40 years
- incidence has risen substantially during the past 50 years (3 fold using American College of Rheumatology criteria)

Pathophysiology

- autoimmune disease
- associated with HLA B8, DR2, DR3
- thought to be caused by immune system dysregulation leading to immune complex formation
- immune complex deposition can affect any organ including the skin, joints, kidneys and brain

Features

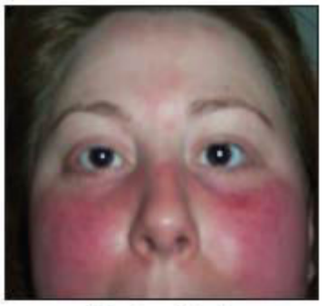
The triad of fever, arthralgia and rash in a woman of childbearing age should suggest the diagnosis of systemic lupus erythematosus (SLE).

General features

The multisystem presentation of fever, arthralgia, pericarditis and nephritis associated with the epidemiological clues (a young black female) suggest a diagnosis of (SLE).

- fatigue
- fever
- mouth ulcers
- lymphadenopathy

Skin



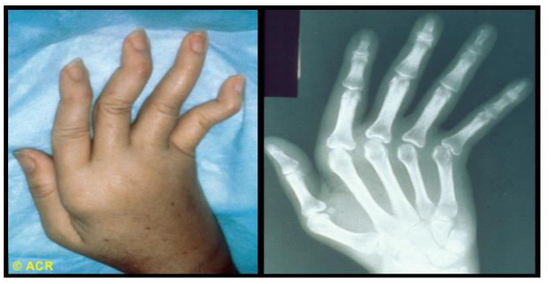
Malar Rash

- malar (butterfly) rash: spares nasolabial folds
- discoid rash: scaly, erythematous, well demarcated rash in sun-exposed areas. Lesions may progress to become pigmented and hyperkeratotic before becoming atrophic
- photosensitivity
- Raynaud's phenomenon
- livedo reticularis
- non-scarring alopecia

Musculoskeletal

- arthralgia typically affecting the small joints of the hands, wrists and knees.
- non-erosive arthritis

Jaccoud's Arthropathy



- **Jaccoud's arthropathy** → gross deformities of the hands without joint damage or erosions
- **caused by** recurrent episodes of synovitis that damage tendon sheaths and slings resulting in joint deformity
- **seen in:**
  - SLE
  - Rheumatic fever
  - Parkinson's disease, and
  - Hypocomplementaemic urticarial vasculitis.

Cardiovascular

- myocarditis

Respiratory

- pleurisy
- fibrosing alveolitis
- Direct pulmonary involvement in (SLE) occurs in 30% (pleuropericarditis, atelectasis, pneumonitis, raised hemidiaphragms and **pulmonary fibrosis**).

Renal

- proteinuria
- glomerulonephritis **(diffuse proliferative glomerulonephritis is the most common type)**

Neuropsychiatric

- anxiety and depression
- psychosis
- seizures

Investigations

Immunology

SLE: ANA is 99% sensitive - anti-Sm & anti-dsDNA are 99% specific

SLE - antibodies associated with congenital heart block = anti-Ro

- **99% are ANA positive (the best screening test for SLE)**
  - Almost all patients with SLE have a positive ANA test result.
  - ANA test is sensitive but not specific for SLE.
  - A negative result argues strongly against a diagnosis of active SLE, but does not exclude the possibility of other autoimmune diseases.
  - **Negative ANA has the highest negative predicted value** (The highest negative predicted value implies the test with the greatest sensitivity.)

- 20% are rheumatoid factor positive
- anti-dsDNA: highly **specific** (> 99%), but less sensitive (70%)
- anti-Smith: most specific (> 99%), sensitivity (30%)
  - Therefore, absence of anti-DNA or anti-Sm antibodies should not exclude SLE as a diagnosis
- also: anti-U1 RNP, SS-A (anti-Ro) and SS-B (anti-La)
  - Anti-Rho and -La antibodies are associated with the development of neonatal lupus.
  - Anti-Ro/SS-A antibodies are found in 30% of patients with SLE.
  - Anti-Ro antibodies can cross the placenta to cause transient cutaneous lupus in the neonate (5-25% of babies) or permanent congenital heart block (1-3% of babies).

Markers of SLE disease activity

- Early markers of SLE disease activity include:
  - **falling C_4 levels,**
    - although congenital C_4 deficiency is itself a predisposing factor for SLE development, so these tests must be interpreted with caution.
  - rising immunoglobulins,
  - falling haemoglobin (Hb), white cell count (WCC), platelets and albumin.

Monitoring

- ESR: during active disease the CRP is characteristically normal - a raised CRP may indicate underlying infection
- complement levels (C3, C4) are low during active disease (formation of complexes leads to consumption of complement)
- **anti-dsDNA titres can be used for disease monitoring** (but note not present in all patients)

Management

- **Basics**
  - NSAIDs
  - sun-block
- **Hydroxychloroquine**
  - useful for skin disease
- If internal organ involvement e.g. renal, neuro, eye then consider prednisolone, cyclophosphamide

Complication

- Lupus patients are **more prone to infection**.
  - Up to two-thirds of lupus patients will have some lung involvement during the course of their disease. The most common manifestations are pleuritis and pleural effusions.

SLE: pregnancy

Overview

- Unlike many autoimmune diseases **(SLE) often becomes worse during pregnancy and the puerperium**
- risk of maternal autoantibodies crossing placenta
- leads to condition termed neonatal lupus erythematous
- **neonatal complications include congenital heart block**

- **strongly associated with anti-Ro (SSA) antibodies**

treatment

- **azathioprine**
  - A large body of evidence from the use of azathioprine in pregnancy for the treatment of both rheumatological conditions and inflammatory bowel disease, supports it's use.
  - Although it is less effective in the management of SLE with renal disease versus other options, balance of benefit risk makes it the preferred intervention.
- **Ciclosporin**
  - appears to be associated with premature delivery and low birth weight,
  - although it does not seem to be associated with malformations, this drives it's use as an **alternative to azathioprine** in patients who fail to gain control of their disease.
- Cyclophosphamide, methotrexate and mycophenolate are all contraindicated for use in pregnancy.

Drug-induced lupus erythematosus

Pathogenesis

- The pathogenesis of drug-induced lupus is unclear.
- Factors that influence drug metabolism, such as acetylator status, have been implicated.
- In addition, lupus-inducing drugs have been shown to generate a variety of cytotoxic products on exposure to **MPO** released from activated neutrophils.

Causes

The most commonly associated drugs

- **procainamide**
- **hydralazine 2,**
- **quinidine.**
- Isoniazid (INH) - low risk
- Sulfasalazine - low risk.
- anti-TNF alpha agents,
- Statins
- **minocycline**.
  - Minocycline associated with the development of long term immunological memory, and therefore exacerbation of symptoms within 12-24 hours of rechallenge.

Risk factors

- strongly positive ANA
- HLA-DR4 phenotype (hydralazine-induced disease)
- **slow** acetylator status
  - Slow acetylators have increased risk of isoniazid-induced peripheral neuropathy, and hydralazine or procainamide-induced systemic lupus erythematosus (SLE).
- large total daily doses of precipitating drugs

Features

Classically, **drug-induced lupus erythematosus is characterised by**

- Systemic disease with a lower incidence of nephritis
- Lack of cutaneous involvement and
- The presence of **antihistone antibodies**.

Laboratory features

- Characteristically, the erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) are both markedly elevated,
- the ANA is strongly positive
- and there is a hypergammaglobulinaemia.
- Anti-dsDNA antibodies are usually negative;
- antihistone antibodies are positive in 95% of drug-induced lupus (but also 50-80% of idiopathic

SLE3).

There are several features which distinguish drug-induced lupus from idiopathic SLE:

- Males and females are equally affected in drug-induced lupus, whereas idiopathic SLE affects females nine times more frequently.
- **Caucasians are affected by drug-induced lupus more commonly than Afro-Caribbeans**, whereas the inverse is true of idiopathic SLE.
- the age of onset is typically older in drug-induced lupus, but this depends on the age at drug exposure.
- Fever, arthralgia, serositis and ANA occur at least as frequently in drug-induced lupus as idiopathic SLE.
- Haematological, renal and central nervous system (CNS) involvement, and double-stranded DNA autoantibodies are rare.

Treatment

- Typically, no further treatment is required after Withdrawal of the precipitating drug
- However, there are situations where corticosteroids or disease modifying antirheumatic drugs (DMARDs) are required to aid resolution.
- The time taken for symptoms to resolve after stopping minocycline is highly variable, from a few days to two years.

Prognosis

- Spontaneous recovery usually occurs promptly

Juvenile idiopathic arthritis (JIA) (Still's disease)

Definition

- The ACR criteria define juvenile rheumatoid arthritis (JRA) by **age limit (< 16 y)** and the duration of disease (**> 6 weeks**).

Epidemiology

- the most common form of arthritis in children and adolescents.
- Prevalence: 1/1000 children
- Sex: ♀ > ♂

Types

- **Oligoarticular JIA**
  - **Most common form** (accounts for 50% of all JIA cases)
  - affects **four joints or fewer** during the **first 6 months**,
  - has the highest risk of developing Chronic anterior uveitis (up to 25%)
    - Bilateral eye involvement is common
  - RF negative
  - ANA positive (~ 70% of cases)
  - Treatment
    - NSAIDs
    - Possibly intra-articular steroid injections
    - Possibly methotrexate
- **Polyarticular JIA**
  - 40% of cases
  - characterised by inflammatory arthritis affecting **five or more joints** during the first **6 months** of the disease.
  - RF negative
  - ANA positive (~ 40% of cases)
  - Treatment: Standard therapy with methotrexate and NSAID
- **Systemic-onset JIA** (**Still's disease**)
  - < 10% of cases
  - presents with **fever**, **arthritis and at least one of the following**:
    - erythematous rash,
    - generalised lymphadenopathy,
    - Hepatosplenomegaly
    - serositis (including pleural and pericardial effusions)

- RF negative
- ↑ Acute phase reactants (e.g., CRP, ferritin)
- Treatment: Poor response to methotrexate and TNF inhibitors (etanercept, adalimumab)

Risk factors

- **Exposure to antibiotics during childhood may increase the risk of JIA.**

Features

Joint pain, daily spiking fevers, and a 'salmon-pink' rash are classic symptoms.

- persistent non-tender joint swelling → (The cardinal feature)
  - The first manifestation of JIA is often **limping**, especially in young children.
  - The persistent swelling most often occurs in the large joints.
  - Damage to joints is associated with a T_H1 response.
- Up to 25% of patients have a **positive anti-nuclear antibody**.
- microcytic anaemia which tends to be resistant to iron replacement
- pericarditis is often found.
- hepatosplenomegaly,
- JIA can decrease bone mass and increase the risk of osteoporosis.
- ↑ ESR (usually seen with all forms of JIA).
- Rheumatoid nodules and rheumatoid factor are usually absent
  - Rheumatoid factor (RF) is absent in most cases of JIA except seropositive polyarticular JIA.
- **anterior uveitis**
  - **What eye condition is most commonly associated with this presentation? anterior uveitis.**
    - about 30–50% of children with JIA have uveitis at diagnosis, especially those who are antinuclear antibody (ANA) positive.
    - The uveitis is typically asymptomatic at onset and must be **screened** for with an ophthalmologic **slit lamp examination**.
    - Untreated uveitis can be associated with cataracts, glaucoma and macular oedema
    - about 50–70% of people with severe uveitis develop visual impairment.
    - **If a patient with (JIA) developed new-onset anterior uveitis despite treatment with subcutaneous methotrexate → adalimumab** (as adalimumab is more effective in treating uveitis than etanercept)

Treatment

- Options for pharmacotherapy include NSAIDs, corticosteroids, methotrexate, and anti-TNF biologicals.
- Treatment with a **IL-6 receptor antibody** has proved to be successful.
- As per NICE guidance, **if patient had not responded to methotrexate and should be considered for biologic therapy with either adalimumab, etanercept or tocilizumab.**

Prognosis

- Anti-CCP antibodies indicate a poor prognosis.
- Early disease onset is associated with a greater degree of growth impairment and deformity.

Adult onset Still's disease (AOSD) (Adult Still's disease)

Adult-onset Still's disease → triad of persistent **high spiking fevers**, **joint pain**, and a distinctive salmon-colored bumpy **rash**.

- typically affects 16-35 year olds

Features

- arthralgia
- rash: salmon-pink, maculopapular (most prominent with fever)
  - occurs in approximately 90% of patients
  - often seen only when the patient is febrile and is easily missed.
- pyrexia (> 39°C) especially in the afternoon and evening
  - described as quotidian or diquotidian returning to 37°C or below between episodes.

- lymphadenopathy
- Hepatosplenomegaly,
- There is often an accompanying sore throat and myalgia.

Rarely there may be:

- Aseptic meningitis
- Cranial nerve palsies
- **Iritis**, and
- Peripheral neuropathy.

Investigation

- neutrophilic leukocytosis, thrombocytosis,
- ↑ serum ferritin
  - High serum ferritin, with low glycosylated fraction, are characteristic and **can be used as disease activity markers.**
- ↑ ESR and C-reactive protein.
- Interleukin (IL)-1, IL-6, IL-18, macrophage colony stimulating factor, interferon gamma and TNF-alpha are all elevated.
- rheumatoid factor (RF) and anti-nuclear antibody (ANA) negative

Diagnosis

- Diagnosis is clinical, and should include exclusion of infectious disease, neoplasms and other autoimmune disease.

Treatment

- non-steroidal anti-inflammatory drugs (NSAIDs),
- corticosteroids,
- disease-modifying anti-rheumatic drugs
- biological agents.
- Intravenous immunoglobulin may have a role.

Prognosis

- tends to be better when systemic symptoms predominate.

Adult onset Still's disease is typically rheumatoid factor negative

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Raynaud's

Raynaud's disease (i.e. primary) presents in young women with bilateral symptoms

Definition

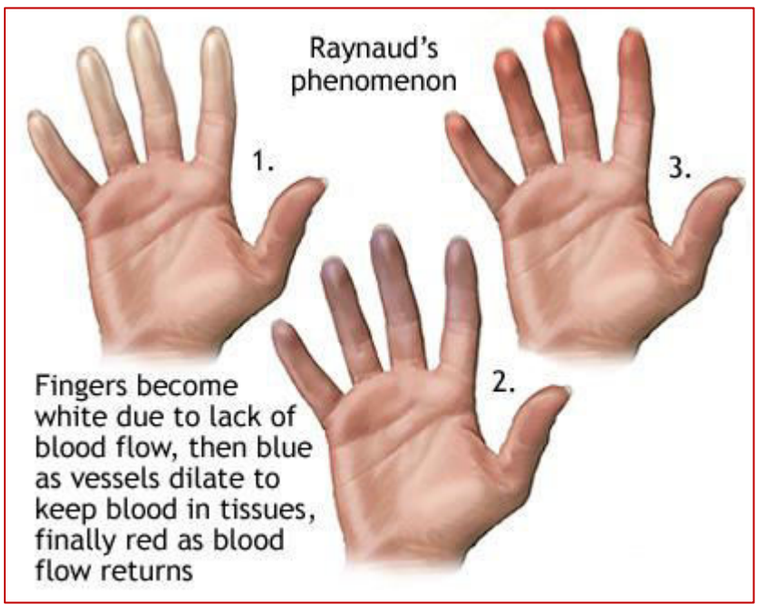
- Raynaud phenomenon manifests as recurrent vasospasm of the fingers and toes and usually occurs in response to stress or cold exposure.

Types

- **Primary Raynaud phenomenon (Raynaud disease).**
  - Raynaud disease is characterized by the occurrence of the vasospasm alone, with no association with another illness.
  - Raynaud's disease typically presents in **young women** (e.g. 30 years old) with **symmetrical attacks**
  - Around 2% of women and 6% of men with Raynaud's phenomenon develop systemic sclerosis.
  - **Diagnosis**: Primary Raynaud's can be diagnosed **if all the following are present**:
    - Attacks triggered by exposure to cold and/or stress
    - No suspicion of underlying disease
    - Symmetrical episodes affecting both hands, but not necessarily all fingers
    - No tissue necrosis, ulceration, gangrene or severe ischaemia
    - Normal nail-fold capillaries (Normal capillaroscopy findings)
    - Normal ESR and negative anti-nuclear antibodies.
- **Secondary Raynaud phenomenon**
  - Secondary **causes**
    - connective tissue disorders:
      - **scleroderma (most common)** (90%)
      - mixed connective-tissue disease (85%)

        - rheumatoid arthritis
        - SLE
    - leukaemia
    - Hyperviscosity: polycythemia, paraproteinemias (plasmacytoma, Waldenstrom's disease), cryoglobulinemia, cold agglutinin disease
    - use of vibrating tools
    - Vasculitides: e.g., Buerger's disease
    - cervical rib
    - drugs:
        - oral contraceptive pill,
        - ergot
        - methysergide (for intermittent migraine)
        - beta-blockers
        - vinblastine
        - bleomycin

- **Factors suggesting underlying connective tissue disease**
    - onset after 40 years
    - **Episodes lasting in excess of one hour**
        - episodes of secondary **Raynaud's** are longer
        - **Episodes of primary disease typically terminate within 15 minutes** following warming in, but can often be prolonged in secondary disease.
    - unilateral symptoms
    - rashes
    - presence of autoantibodies
    - features which may suggest rheumatoid arthritis or SLE, for example arthritis or recurrent miscarriages
    - digital ulcers,
    - calcinosis
    - very rarely: chilblains



Investigations

Which investigation would be most useful in determining whether the Raynaud's is related to vasculitis? → Nail fold capillaroscopy

- **The most useful initial assessment** must include **nail fold capillary loop examination**,
    - ideally by **capillaroscope** or, if not available, by **ophthalmoscope** using magnification.
        - method
            - Nailfold capillaroscopy is performed by applying a drop of oil onto the periungual region of the nail and using an ophthalmoscope set to 40 diopter to examine.
        - interpretation

- Patients with connective tissue disorder such as systemic sclerosis most often will show → dilated, distorted, paucity or missed nail fold capillary loops.

Management

- For primary Raynaud phenomenon:
  - First line → lifestyle measures.
    - **The best initial line**
    - **Advise on lifestyle changes to reduce the frequency of the attacks, such as heated gloves, stopping smoking and avoiding the cold environments**
  - Second line → pharmacologic treatment.
    - **First pharmacologic line: calcium channel blockers e.g. nifedipine**
    - **IV prostacyclin infusions:**
      - **effects may last several weeks/months**
      - indications
        - if the patient does not respond to nifedipine Retard or
        - has developed digital ulceration or ischaemia
    - **iloprost** is a synthetic analogue of prostacyclin
      - **The urgent treatment of severe Raynaud's with threatened or established gangrene is with intravenous iloprost.**
  - **Third line → non-**pharmacologic treatment.
    - **Digital sympathectomy** should be considered as a last resort when drug therapy has failed or has not been tolerated.
- For secondary Raynaud phenomenon:
  - Treatment of underlying disorder
  - **ACE inhibitors** also have the best evidence for **reno-protection** where **there is underlying autoimmune pathology**.
    - If there is NO underlying autoimmune pathology → ACEi has NO benefit
      - ACE inhibitors and anti-platelet agents have been trialled in small case series, although no definitive benefit has yet been shown.

Chilblains (pernio)

- Chilblains (pernio) are **itchy, painful purple swellings which occur on the fingers and toes after exposure to the cold.**
- They are occasionally associated with underlying connective tissue disease but this is **rare**

Systemic sclerosis (SSc)

- Systemic sclerosis is a chronic autoimmune disease characterised by increased **fibroblast** activity and fibrosis in a number of different organ systems.
- characterised by hardened, sclerotic skin and other connective tissues.

Epidemiology

- It is four times **more common in females (♀ > ♂)**
- Higher incidence in African Americans
- Peak incidence: 30–50 years

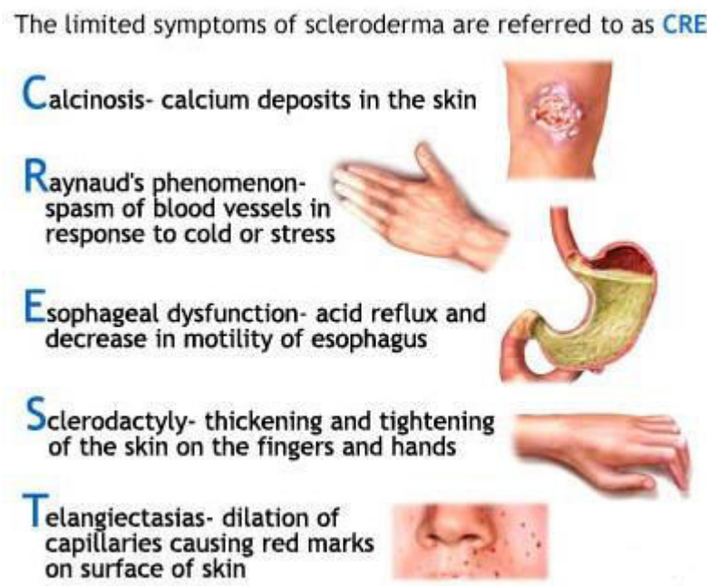
Types: There are three patterns of disease:

1. Limited cutaneous systemic sclerosis

Limited (central) systemic sclerosis = anti-centromere antibodies

- The more common type of SSc.
- **Raynaud's may be first sign**
  - seen in 90-95% of patients with systemic sclerosis.
- scleroderma **affects face** and distal limbs predominately
  - Areas of skin affected include only the face, forearms and lower legs up to the knee.
  - It does not affect the upper arms, upper legs, or trunk.
- **associated with anti-centromere antibodies**

- Previously known as CREST syndrome (**C**alcinosis, **R**aynaud's phenomenon, **E**sophageal dysmotility, **S**clerodactyly, **T**elangiectasia)
  - the most likely cause of this patient's dysphagia? → Esophageal smooth muscle **atrophy and fibrosis**
- **Pulmonary hypertension is one of the more common late complications seen in CREST syndrome**
  - **The most common cause of death**
- **Malabsorption is most likely to develop as a further complication**
  - Involvement of GIT can occur from mouth to anus
    - can present with both diffuse and limited cutaneous forms.
    - Most GIT manifestations result from **dysmotility secondary to infiltration of the intestinal wall with fibrous tissue**,
    - can cause life-threatening malabsorption and malnutrition.
    - **Gastric emptying is delayed in 10-75%** of patients and causes symptoms of early satiety, bloating and emesis.
      - Treatments include metoclopramide and erythromycin.
    - small bowel is also involved in 20-60% of patients, **due to reduced or absent migrating motor complexes** predisposing to bacterial overgrowth.
    - The contributes to malabsorption, as does associated pancreatic insufficiency.
    - In the colon there is often development of diverticuli involving all layers of the intestinal wall, or constipation due to reduced motility.

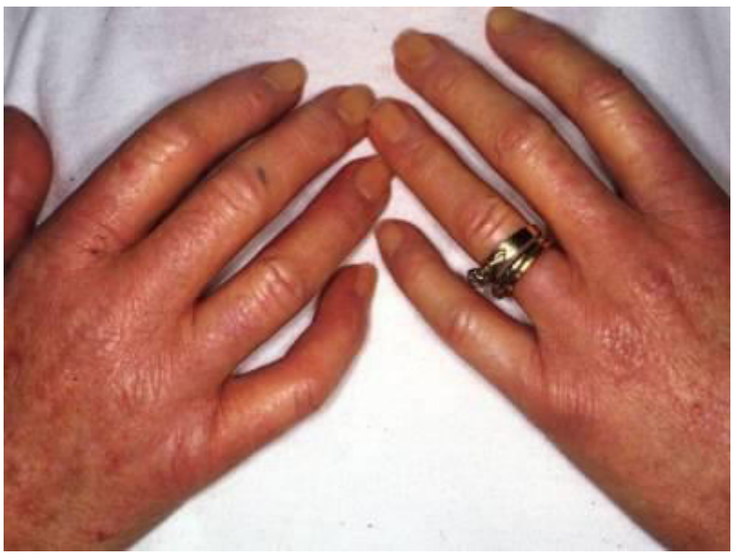


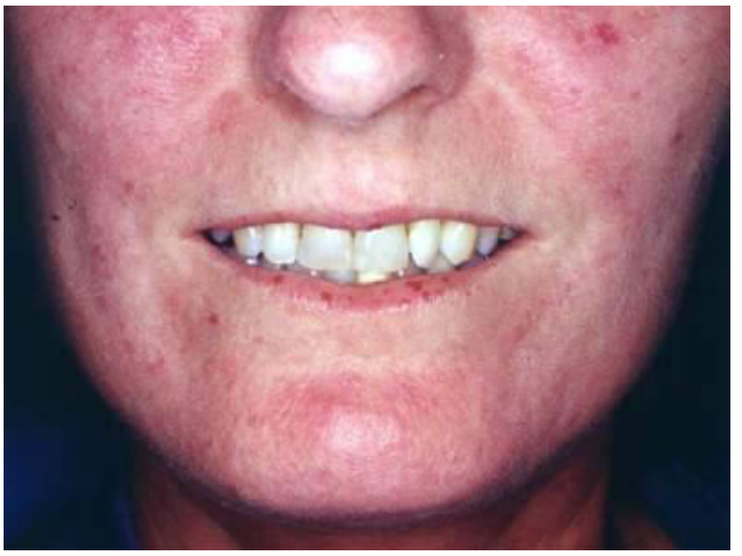
2. Diffuse cutaneous systemic sclerosis

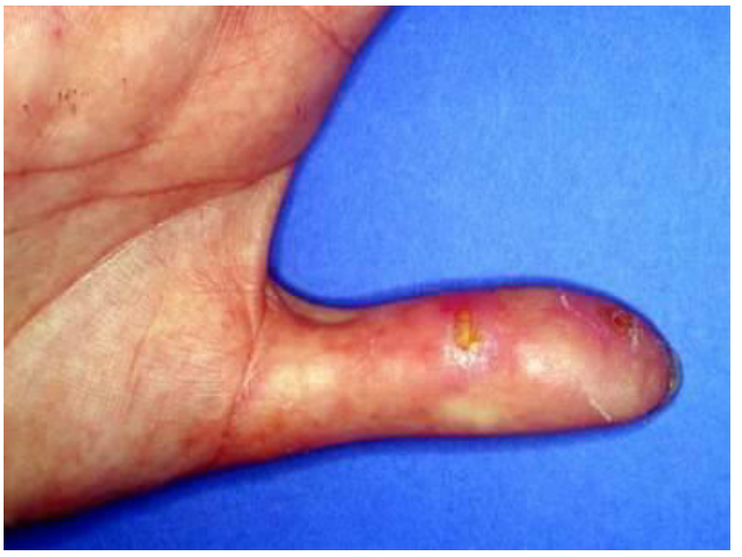
- less common.
- scleroderma **affects trunk and proximal limbs predominately** (although face may be involved in either type)
  - Skin areas involved include also the upper arms, thighs or trunk.
- **associated with scl-70 antibodies**
- hypertension, **lung fibrosis** and renal involvement seen
  - Pulmonary involvement is the second commonest organ involvement after oesophageal disease and is the leading cause of death.
  - **Pulmonary fibrosis is associated with anti-Scl-70 antibodies in up to 70% of cases.**
  - scl-70 antibodies associated with a higher risk of severe interstitial lung disease
  - **Reduced DLCO is the earliest sign of pulmonary disease in systemic sclerosis, often before fibrotic changes manifest clinically.**
- poor prognosis

3. Scleroderma (without internal organ involvement)

- tightening and fibrosis of skin
- may be manifest as plaques (morphoea) or linear







Antibodies

- **ANA positive in 90%**
  - therefore **in a negative test → consider an alternative diagnosis**
- RF positive in 30%
- **Anti-centromere** antibodies associated with **limited cutaneous** systemic sclerosis
- **Anti-scl-70** antibodies associated with **diffuse cutaneous** systemic sclerosis
  - (anti-Scl-70) also known as **Anti-topoisomerase I antibodies**
  - associated with a higher risk of severe interstitial lung disease

- **Anti-RNA polymerase III** antibodies
  - found in patients with **diffuse disease**
  - associated with:
    - rapidly progressive skin involvement
    - **increased risk for scleroderma renal crisis.**
    - increased risk for cancer

Other investigations

- Serum protein electrophoresis: ↑ γ-globulins

Treatment

- Immunosuppressive therapy: e.g., methotrexate
- **Organ-specific therapy:**
  - gastroesophageal reflux disease → PPIs
  - **Renal crisis → ACE inhibitors**
    - Renal crises result from an acute renal **vasculopathy** with associated hyper-reninaemia, not glomerulonephritis.
    - ACE inhibitors in the acute setting **improves long term survival**, end organ damage due to hypertension, and can lead to an improvement in renal function even up to 2 years after crisis.
  - **Interstitial lung disease** secondary to underlying diffuse systemic sclerosis:
    - **The most appropriate treatment is cyclophosphamide**
    - Azathioprine is normally used as maintenance therapy following cyclophosphamide.

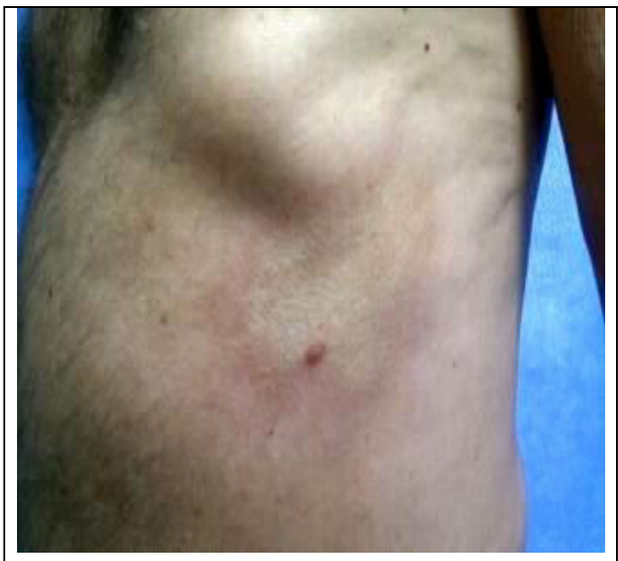
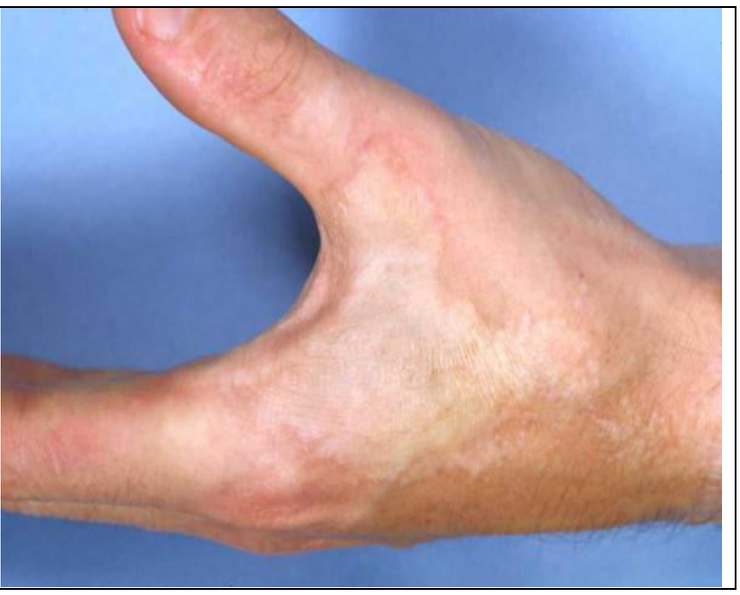
Prognosis

- **U&Es** have a crucial role with respect to determining prognosis and appropriate therapeutic intervention.
- **the most important initial investigation with respect to determining patient outlook ? → Urea and electrolytes**

Sclerodema renal crisis

- A major complication of systemic sclerosis
- Severe and life threatening renal disease develops in approximately 10-15% of patients.
- Features
  - severe hypertension, with diastolic BP over 100 mmHg, usually with grade III or IV hypertension retinopathy, together with rapid deterioration of renal function and heart failure;
  - symptoms of malignant hypertension, with headaches, blurred vision, fits and heart failure.
  - haematological tests often demonstrate a thrombocytopenia and/or **microangiopathic** haemolysis.
- Treatment
  - **Hypertension → ACE inhibitor** (calcium channel blockers can be added).
    - **While ACE inhibitors are generally avoided in most patients with acute renal failure, scleroderma renal crisis is an exception to the rule** as long as renal function is closely monitored.
  - Renal dialysis may be required.
  - An excessive reduction in BP or hypovolemia (should be avoided) →↓ renal perfusion → acute tubular necrosis. Thus, **parenteral antihypertensive agents (such as intravenous nitroprusside or labetalol) should be avoided.**

Morphea (localised scleroderma)

Definition

- idiopathic inflammatory skin condition which causes excessive collagen deposition and fibrosis.

Types

- Morphea is classified into subtypes according to the clinical presentation and depth of tissue involvement:
  - circumscribed morphea,
    - the commonest form, "circumscribed/plaque" morphea.
    - This is a well-defined oval to round plaque that fails to meet the criteria for generalised morphea.
  - generalized morphea,
  - linear morphea
  - pansclerotic morphea

Pathophysiology

- autoimmune component is suggested by enhanced **T helper 2** (Th2) dependent **interleukin 4** (IL-4) activity, which in turn upregulates transforming growth factor beta (**TGF -beta**).
- **TGF-beta** stimulates **fibroblast** production of collagen and other extracellular matrix proteins.

Features

- Unlike systemic sclerosis, morphea lacks features such as sclerodactyly, Raynaud phenomenon, nailfold capillary changes, telangiectasias, and progressive internal organ involvement.
- Morphea can present with extracutaneous manifestations, including fever, lymphadenopathy, arthralgias, fatigue, central nervous system involvement,

Investigations

- Hypergammaglobulinaemia (↑↑IgM , IgG)
- peripheral eosinophilia
- ↑↑ ESR and CRP
- **Anti-Cu/Zn superoxide dismutase** antibodies have been found in up to 90%

Treatment

- Superficial circumscribed morphea
  - Tacrolimus 0.1% **ointment** applied twice daily for 12 weeks may be a useful **first-line**
- Generalized, linear, or deep morphea
  - combination therapy with oral prednisone and methotrexate
  - To minimize the risk of relapse, the recommended treatment duration of MTX is at least 2 years.
  - Systemic corticosteroids can be helpful in the inflammatory phases of morphea, but they are not recommended for long-term monotherapy
  - Mycophenolate mofetil is a second-line

Prognosis

- generally resolves within 3–5 years, although sometimes a patch may persist for over 25 years.

Polymyalgia rheumatica (PMR)

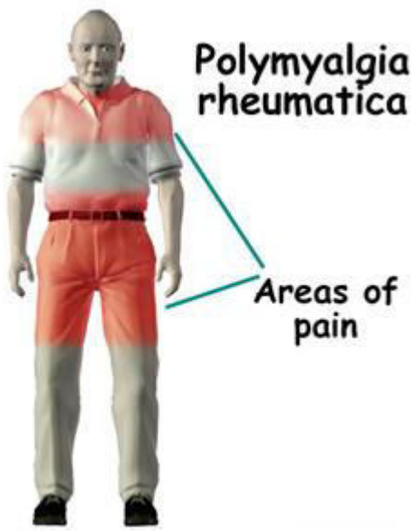
Pathophysiology

- overlaps with temporal arteritis 30% of patients also have giant cell arteritis.
- histology shows vasculitis with giant cells, characteristically 'skips' certain sections of affected artery whilst damaging others
- muscle bed arteries affected most in polymyalgia rheumatica

Epidemiology

- occurring in patients age 50 years or older.
- More common in women

Features



- typically patient > 60 years old
  - very rarely seen in the under 50s.
- usually rapid onset (e.g. < 1 month)
- **typically presents with pain and stiffness of the shoulder and pelvic girdle muscles.**
- aching, morning stiffness in proximal limb muscles (not weakness)
  - **Pain and muscle stiffness worst in the mornings**
- mild polyarthralgia, lethargy,
- depression,
- **low-grade fever**, anorexia, night sweats
- **Weight loss**

Investigations

- ESR > 40 mm/hr
  - **the next best investigation**
  - a high ESR would prompt immediate treatment with steroids.
- Raised C reactive protein (CRP)
- Alkaline phosphatase is an acute-phase reactant and is raised in approximately a third of patients with polymyalgia rheumatica.
- note CK and EMG normal
- reduced CD8+ T cells
- Normochromic / normocytic anaemia

Differential diagnosis

- **Giant cell arteritis (GCA)**
  - GCA and PMR frequently co-exist,
  - cranial symptoms including **headache**, **jaw claudication**, and **vision symptoms** are **typically absent in patients with PMR**.
  - PMR typically has less prominent symptoms than GCA.

Treatment

- prednisolone e.g. 15mg/od - dramatic response
  - Response to a moderate dose of steroids can be useful in confirming the diagnosis of PMR.

- The maximum dose of prednisolone should not exceed 20 mg once daily.
- Patients should report 70% improvement in symptoms within three to four weeks, and inflammatory markers should have normalised by this point.
- Calcium and vitamin D supplementation should be initiated for all patients with PMR who are starting corticosteroid therapy. Bisphosphonates should be added for long term steroid therapy.
- The usual starting dose is 15 mg prednisolone per day.
- Patients should expect relief of symptoms within 24-72 hours.
  - One of the best 'tests' for Polymyalgia Rheumatica (PMR) is how patients respond to corticosteroid therapy.
- Tapering
  - Tapering should be guided by clinical response.
  - The dose should be increased if symptoms are not well controlled within one week.
  - The effective starting dose should be maintained for two to four weeks after the patient becomes asymptomatic.
  - Generally, the daily dose can be lowered by 1.0-2.5 mg every two to four weeks to find the minimum dose needed to maintain symptom suppression. Once the patient is reduced to 10 mg per day, the daily dose can be tapered by 1 mg every four weeks.
  - Approximately 50-75% of patients can discontinue corticosteroid therapy after two years of treatment.
- **Methotrexate and azathioprine**
  - **If symptoms relapsed when the dose of prednisolone has been reduced below the current dose, → Continue the current dose of prednisolone and start methotrexate**
  - used in patients with corticosteroid intolerance or as corticosteroid-sparing agents.
  - These are generally reserved for patients in whom it has been difficult to reduce the prednisolone after prolonged high dosages (for example, 10 mg or more per day for more than a year).
  - These agents should be added to the prednisolone initially, but with a view to slowly reduce and withdraw prednisolone.
  - As with steroid therapy, azathioprine or methotrexate can be discontinued if there has been sufficient response.

Prognosis

- Rapid improvement often occurs within 24 to 72 hours with **low-dose** prednisolone.

Temporal arteritis (Giant cell arteritis (GCA).

Giant cell arteritis should always be considered in elderly patients with headaches, ocular symptoms, systemic symptoms and high ESR.

In elderly people giant cell arteritis is a common presentation of acute monocular visual loss.

Temporal artery biopsy is the definitive diagnostic test for giant-cell arteritis. A 2-cm segment of a tender artery will provide positive histology in 70% of cases. The diagnostic rate may be enhanced by taking longer segments or by the biopsy. While biopsy confirmation of the diagnosis is important, it should not be a reason for withholding steroids because the patient is at risk of irreversible blindness without treatment.

- also known as giant cell arteritis (GCA).
- Temporal arteritis is large vessel vasculitis
- overlaps with polymyalgia rheumatica (PMR).
- Histology shows changes which characteristically 'skips' certain sections of affected artery whilst damaging others.
- It is a clinical emergency.

Epidemiology

- Sex: ♀ > ♂
- Peak incidence: 70–79 years; rarely seen in patients < 50 years

Diagnosis

- The American College of Rheumatology 1990 criteria requires 3 of the following for GCA diagnosis:

    1. Age >50 y/o
    2. New onset localised headache
    3. Temporal artery tenderness or decreased pulsation
    4. ESR >50mm/hr
    5. Temporal artery biopsy positive

Features

- typically patient > 60 years old
- usually rapid onset (e.g. < 1 month)
- headache (found in 85%)
- **jaw claudication (65%) is a very specific sign for temporal arteritis.**
- visual disturbances secondary to anterior ischemic optic neuropathy
    - 15-20% of patients develop permanent visual loss.
- tender, palpable temporal artery
- features of PMR: aching, morning stiffness in proximal limb muscles (not weakness)
- also lethargy, depression, low-grade fever, anorexia, night sweats

Investigations

- raised inflammatory markers: ESR > 50 mm/hr (note ESR < 30 in 10% of patients). CRP may also be elevated
    - ESR can be within normal range in 5-10% of GCA cases.
- temporal artery biopsy: ***skip lesions*** may be present (certain sections of affected artery whilst damaging others)
    - An adequate length of temporal artery (3 to 5 cm) should be obtained because inflammatory lesions may be present in a segmental fashion.
    - A negative temporal artery biopsy can occur in up to 50 percent of patients, often because the sampled region was not involved in the pathologic process. Therefore, **it is not sensitive enough to rule out temporal arteritis**.
    - Treatment should not be delayed while waiting for the biopsy to be performed.
- note creatine kinase and EMG normal

Treatment

- **high-dose prednisolone** - there should be a dramatic response, if not the diagnosis should be reconsidered
- urgent ophthalmology review. Patients with visual symptoms should be seen the same-day by an ophthalmologist. Visual damage is often irreversible
- As GCA requires long-term steroid therapy bone sparing agents (a **bisphosphonate and vitamin D)** and a gastroprotective drug (e.g omeprazole) should be prescribed.
- Also, low dose **aspirin** should be considered as it has been shown to reduce the rate of visual loss and cerebrovascular accidents in GCA.

Current BSR guidelines recommend:

1. Uncomplicated GCA (no jaw or tongue claudication, or visual symptoms)
    - prednisolone 40-60 mg daily
2. **Complicated GCA: (with visual involvement and/or jaw/tongue claudication**)
    - **Evolving visual loss or history of amaurosis fugax: IV methylprednisolone 500 mg-1 g** daily for three days, followed by oral corticosteroids
    - Established visual loss: at least 60 mg prednisolone daily

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Polyarthritis

Differential diagnosis

- rheumatoid arthritis
- SLE
- seronegative spondyloarthropathies
- Henoch-Schonlein purpura
- sarcoidosis
- tuberculosis
- pseudogout
- viral infection: EBV, HIV, hepatitis, mumps, rubella

Polyarteritis nodosa (PAN)

Definition

- systemic vasculitis of the **medium**-sized vessels, with necrotizing inflammation leading to aneurysm formation and tissue ischemia;
- most commonly involving skin, peripheral nerves, muscles, joints, gastrointestinal tract, and kidneys .
- any organ with the **exception of the lung** can be affected,

Epidemiology

- Peak incidence: ~ 45–65 years
- Sex: ♂ > ♀
- more common in middle-aged men

Pathophysiology

- diffuse vascular inflammation and ischaemia of the affected organs.
- PAN is a medium-vessel vasculitis that is a type III hypersensitivity reaction.

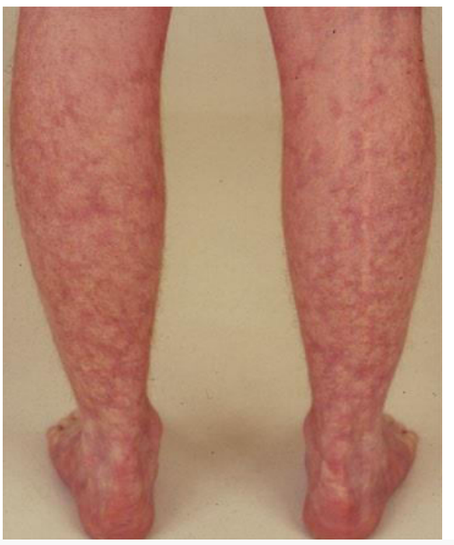
Association

- hepatitis B infection

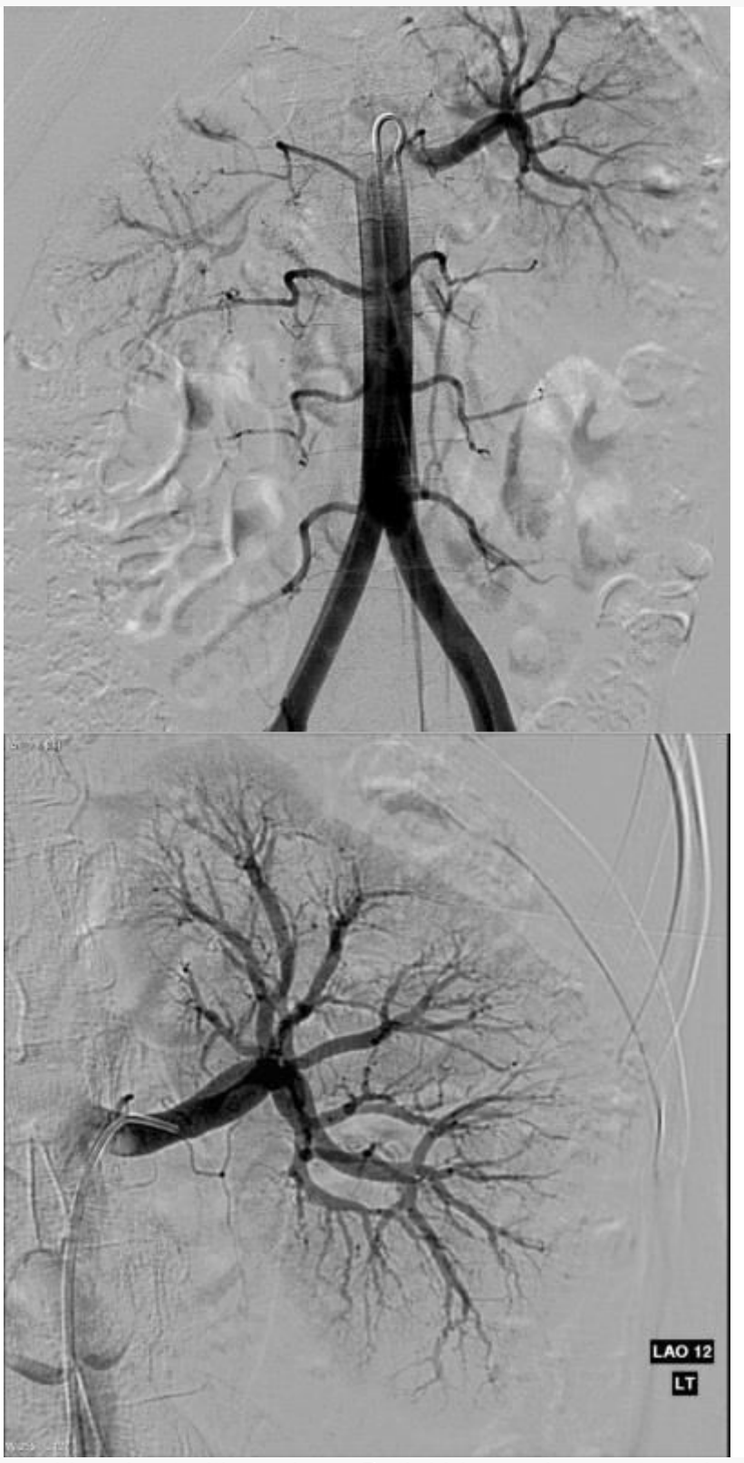
Features

- Nonspecific symptoms: (found in 65% to 80% of patients)
  - fever, malaise, arthralgia, weight loss
- Neurological involvement: (in 55% of patients)
  - polyneuropathy (**mononeuritis multiplex**),
  - cerebral ischemia (stroke)
- Skin involvement: (in 44%)
  - skin rash,
  - Skin ulcers, nodules
  - **livedo reticularis**
- Renal involvement : (in 11%)
  - hypertension,
    - Hypertension is a manifestation of renal ischaemia via activation of the renin-angiotensin system.
  - haematuria
    - but red cell casts are absent because glomerular inflammation is not a feature.
  - renal impairment
- Coronary artery involvement ;
  - increased risk of myocardial infarction
- GI involvement:
  - abdominal pain, nausea, vomiting
  - can present with abdominal pain and melena due to involvement of the mesenteric arteries.
- **Testicular pain**
  - **testicular pain from ischaemic orchitis is a characteristic feature**
  - uncommon presentation
- **Usually spares the lungs**

PAN should be considered in young adults presenting with stroke or myocardial infarction
The diagnosis may be confirmed with a biopsy of involved tissue



Livedo reticularis



Angiogram from a patient with polyarteritis nodosa. Both kidneys demonstrate beading and numerous microaneurysms affecting the intrarenal vessels. Similar changes are seen affecting the intrahepatic

vessels with a few small microaneurysms noted. The proximal branches of the SMA appears normal; however there are no normal straight arteries from the jejunal arteries and lack of normal anastomotic arcades and loops. This is associated with multiple microaneurysms.

Diagnosis

- **The American College of Rheumatology (ACR) 1990 criteria**
  - **Three of the following 10 criteria are required:**
    1. Weight loss ≥4 kg
    2. Livedo reticularis
    3. Testicular pain or tenderness
    4. Myalgias, weakness, or leg tenderness
    5. Mononeuropathy or polyneuropathy
    6. Diastolic blood pressure >90 mmHg
    7. Elevated urea or creatinine
    8. Positivity for hepatitis B virus (HBV) infection
    9. Arteriographic abnormality
    10. Biopsy of small- or medium-sized artery containing polymorphonuclear leukocytes.

Investigations

- Hepatitis B surface antigen is positive in 30%,
- p-ANCA is positive **only** in 20%.
  - **ANCA is classically negative in PAN.**
- Angiography:
  - Conventional angiography is **the imaging modality of choice**, and should be performed if there is a clinical suspicion of PAN.
  - typically demonstrates:
    - microaneurysms and
    - focal narrowing in medium-sized blood vessels.
- Biopsy
  - should be performed **if angiography is not available or does not conclusively show a medium-vessel vasculitis.**
  - Shows:
    - focal and segmental transmural necrotising inflammation with **fibrinoid necrosis** in medium-sized vessels.
    - **pleomorphic cellular infiltrate** of lymphocytes, neutrophils, macrophages, and eosinophils.
    - **granulomas are absent.**

Differential diagnosis

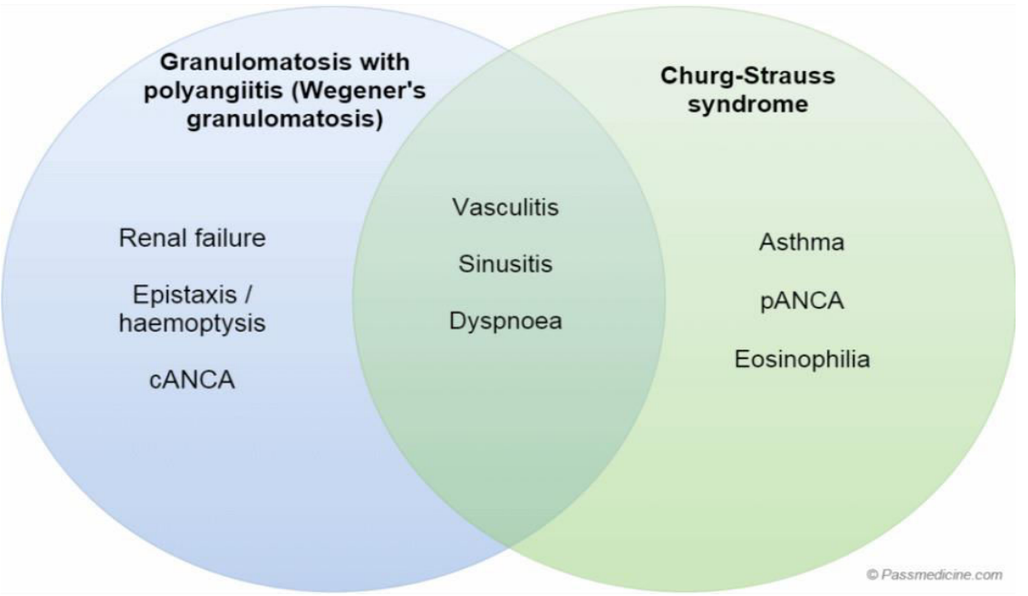
- PAN are differentiated from the other small- and medium-vessel vasculitides by:
  - absence of anti-neutrophil cytoplasmic antibodies,
  - **Glomerulonephritis is not a feature of PAN**, but it is common in anti-neutrophil cytoplasmic antibodies (ANCA) vasculitis. Making this distinction early by way of urinalysis for protein, blood, and **casts** is a **simple first-line test** that can guide further investigation and treatment.
    - **Red cell casts are absent in PAN**
    - If there is evidence of glomerular inflammation such as urinary casts, then an alternative diagnosis such as microscopic polyangiitis (MPA) or granulomatosis with polyangiitis (Wegener's) (GPA),must be considered.
  - lung involvement is not seen in PAN, and abnormal respiratory findings should suggest an alternative diagnosis
  - and by confirmation that small vessels (i.e., arterioles, capillaries, venules) are not involved.

Treatment

- idiopathic PAN → corticosteroids and cyclophosphamide
- hepatitis B related disease → plasmapheresis and antiviral agents.
- Azathioprine can be used as maintenance therapy, and typically has fewer side effects than cyclophosphamide.

Cyclophosphamide → causes premature ovarian failure and infertility in both men and women.

Granulomatosis with polyangiitis (Wegener's granulomatosis)



- Granulomatosis with polyangiitis is now the preferred term for Wegener's granulomatosis.
- It is an autoimmune condition associated with a necrotizing granulomatous vasculitis, affecting both the upper and lower respiratory tract as well as the kidneys.
- **the classical triad** consists of
  1. necrotising granulomatous inflammation of the respiratory tract,
  2. glomerulonephritis
  3. small-vessel vasculitis.

Features

- upper respiratory tract: epistaxis, sinusitis, nasal crusting
- saddle-shape nose deformity
- lower respiratory tract: dyspnoea, haemoptysis
  - **migrating alveolar shadowing**
- rapidly progressive glomerulonephritis ('pauci-immune', 80% of patients)
  - It usually presents with rapidly progressing renal failure (within three months), proteinuria and microscopic haematuria.
- also:
  - vasculitis (causing carotid artery tenderness)
  - vasculitic rash,
  - eye involvement (e.g. proptosis),
  - cranial nerve lesions

Investigations

- c-ANCA (PR3-ANCA (targeting peroxidise-3) positive in > 90%, p-ANCA (MPO-ANCA (targeting myeloperoxidase) positive in 25%
  - cANCA directed against proteinase-3
  - cANCA is highly specific, but is found in only 50% of patients with disease localised to the respiratory tract and 95% with generalised Wegener's.
- chest x-ray: wide variety of presentations, including cavitating lesions
- renal biopsy: epithelial crescents in Bowman's capsule

Management

- steroids
  - **Prednisolone** is given in doses of around 1 mg/kg per day initially, after which the dose is reduced rapidly, typically at weekly intervals.
  - **In case of renal failure with indications for dialysis, the initial management →Methylprednisolone**

  - **Methylprednisolone should be given immediately, followed by haemodialysis and then cyclophosphamide.**
- cyclophosphamide (90% response)
  - **The combination of prednisolone and cyclophosphamide is now established as the standard therapy and the treatment of choice for induction of remission in Wegener's granulomatosis**
  - **Cyclophosphamide**: Traditionally, oral dose (2 mg/kg per day), but latterly intravenous boluses have proved increasingly popular, given in doses of 0.5-0.75 g/m2 body surface area at intervals of 2 weeks (at least for short periods) to 2 months.
  - **If a patient had a vasculitic neuropathy. Current practice is to use cyclophosphamide for induction therapy.**
- Both rituximab and methotrexate have also been used for induction therapy in ANCA-associated vasculitis, although they would not be first-line treatment.
- Azathioprine is used as maintenance treatment following cyclophosphamide
- ciclosporin is rarely used in the management of ANCA-associated vasculitis.
- Evidence from controlled trials suggests that once remission is achieved azathioprine or methotrexate may be reasonable alternatives to cyclophosphamide.
- In refractory Wegener's, both infliximab and rituximab have shown some degree of promise.
- plasma exchange
- **in case of decreased conscious level with acute renal failure (with indication for dialysis) and respiratory function is failing. The first immediate step → Endotracheal intubation and positive pressure ventilation, transfer the patient to a critical care setting (especially to protect airway with a GCS 8/15).**

Prognosis

- median survival = 8-9 years

Extra notes:

- Alveolar proteinosis is a rare diffuse lung condition, characterised by alveolar and interstitial accumulation of phospholipid protein derived from surfactant. It can be congenital, secondary or acquired, and patients often present with recurrent respiratory infections. Transfer factor (KCO) is typically reduced.
- Microscopic polyangiitis is a small vessel vasculitis which classically spares the upper respiratory tract.

Microscopic Polyangiitis

Usually the PR3 antibody is associated with Wegener's granulomatosis, whereas the MPO antibody is associated with microscopic polyangiitis, which is closely linked.

- Microscopic polyangiitis is similar to wegener's granulomatosis except in 3 things:
  1. it only affects small blood vessels in the lungs or kidneys.
     - No nasopharyngeal damage like wegener's
  2. Associated with p-ANCA antibodies.
     - anti-MPO (pANCA, 45%) antibody is strongly positive than anti-PR3 (cANCA, 30%)
  3. No granuloma on biopsy

Henoch-Schonlein purpura

- Henoch-Schonlein purpura (HSP) is an **IgA mediated** small vessel vasculitis
- involving mainly the blood vessels of the skin, GI tract, the kidneys and the joints.
- 90% of cases of HSP occur in children aged 2-10 years but can occur in any age group.
- In children, (HSP) is the most common cause of vasculitis affecting the kidneys.
- typically commoner in males,
- may follow an infectious agent.
- It can present one to three days following infection of an IgA secreting mucous membrane (commonly following pharyngitis, but can occur following infection of the gastrointestinal tract, bladder or breast).

- An important risk factor in adults → chronic alcohol intake.
- associated with: *Helicobacter pylori*, hepatitis B and malignancy.

Features

HSP is characterised by the **tetrad of**:
- purpura
- abdominal pain
- arthritis, and
- renal involvement (haematuria and proteinuria).
  - Patients with proteinuria have a worse prognosis than patients with haematuria alone.

- palpable purpuric rash (with localized oedema) over buttocks and extensor surfaces of arms and legs (due to a cutaneous vasculitis)
- abdominal pain (due to gut vasculitis, which may be severe in some cases, leading to bloody diarrhoea)
- polyarthritis (common symptom)
- features of IgA nephropathy may occur e.g. haematuria, renal failure
  - HSP nephritis becomes clinically manifest in only 20-30%.
  - It usually presents as macroscopic haematuria and proteinuria
  - Of those patients with renal involvement, as many as 10% may develop chronic renal failure and end-stage renal disease. However, fewer than 1% of all patients with HSP suffer this poor prognosis.

Diagnosis:

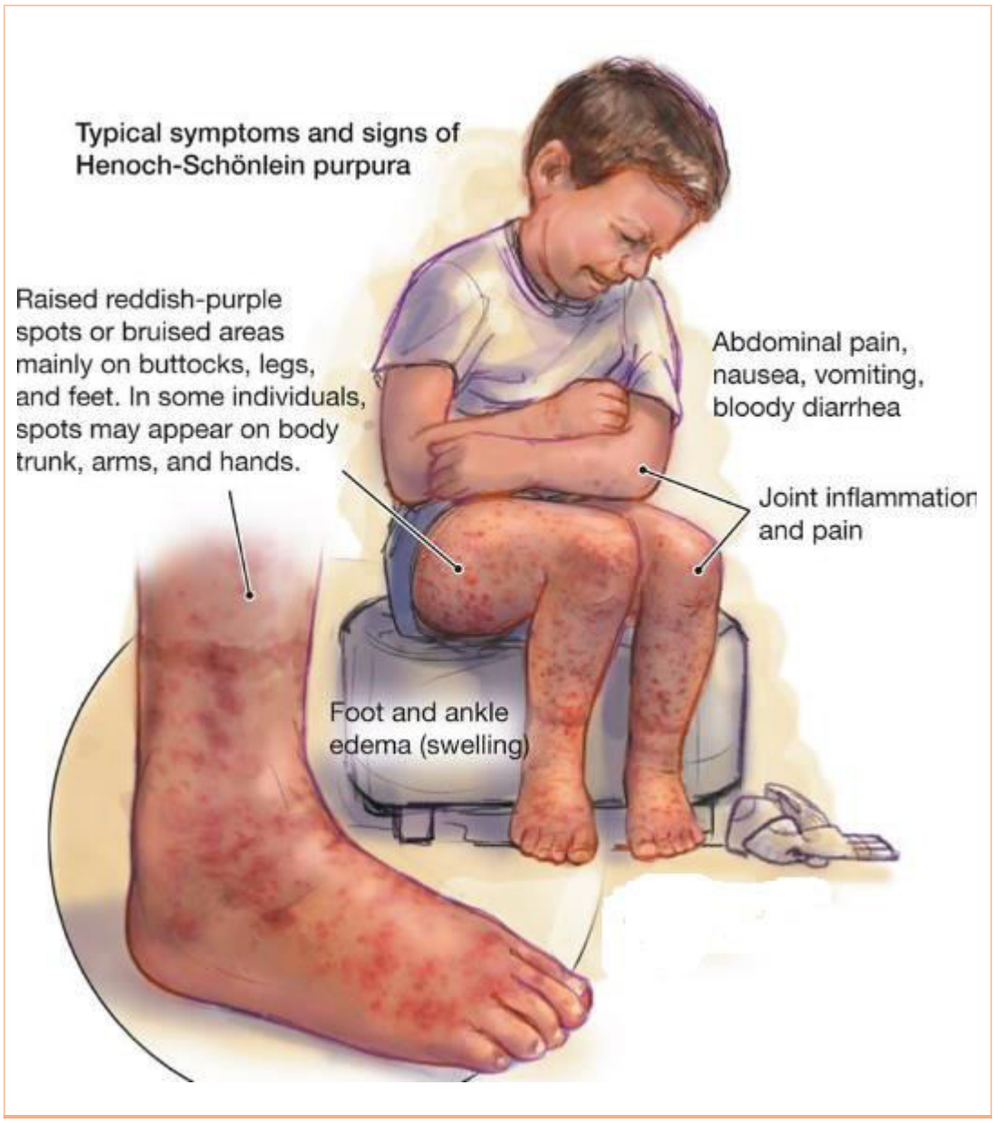
- Skin biopsy and immunofluorescence demonstrate **leukocytoclastic vasculitis with IgA deposition,**(meaning lots of white blood cells in the skin around small blood vessels) **which is pathognomonic for HSP.**
  - Immunofluorescence studies will reveal → **IgA deposits within blood vessel walls**

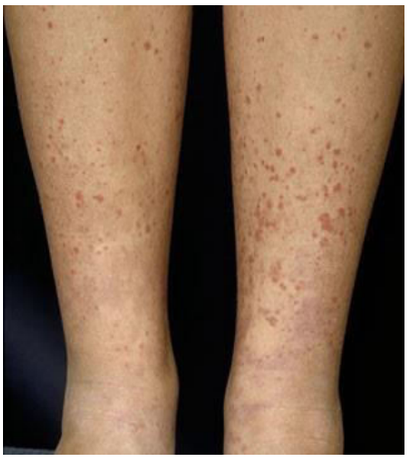
Treatment

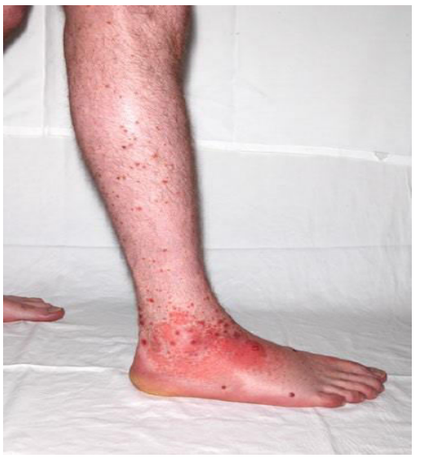
- analgesia for arthralgia
- treatment of nephropathy is generally supportive.
  - **All patients with hypertension and proteinuria (greater than 1 g/day) should be started on an angiotensin-converting enzyme (ACE) inhibitor**, which may control the BP and proteinuria.
  - Once the BP has been controlled, patient should have a renal biopsy, and if this showed changes of a crescentic glomerulonephritis (GN), then an immunosuppression regime similar to that used in renal vasculitis should be started (probably with high dose steroids in the first instance +/- cyclophosphamide).
  - There is inconsistent evidence for the use of steroids and immunosuppressants
  - Management of HSP in adults often involves the use of immunomodulatory or immune-suppressive regiments (in contrast to children where the majority of cases resolve spontaneously).

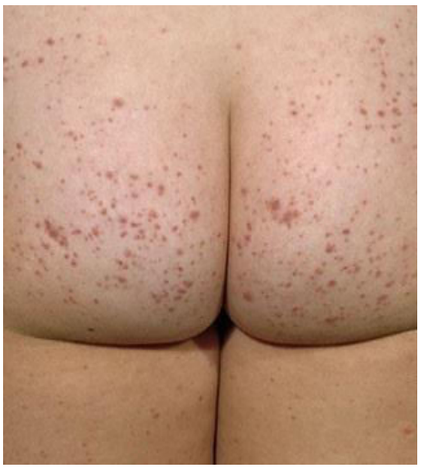
Prognosis

- usually excellent, HSP is a self-limiting condition, especially in children without renal involvement
- There is often a more complicated course in adults, and 50% of patients who present with renal involvement develop renal insufficiency.
- around 1/3rd of patients have a relapse









September 2011 exam: What is the most likely renal outcome in Henoch-Schonlein purpura? Full renal recovery

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Kawasaki disease

- Kawasaki disease is a type of **vasculitis** which is predominately seen in children.
- Whilst Kawasaki disease is uncommon it is important to recognise as it may cause potentially serious complications, including **coronary artery aneurysms**

Features

- high-grade fever which lasts for > 5 days. Fever is characteristically resistant to antipyretics

- conjunctival injection
- bright red, cracked lips
- **strawberry tongue**
- cervical lymphadenopathy
- red palms of the hands and the soles of the feet which later peel

Diagnosis

- Kawasaki disease is a clinical diagnosis as there is no specific diagnostic test

Management

- high-dose aspirin*
  - *Kawasaki disease is one of the few indications for the use of aspirin in children. Due to the risk of Reye's syndrome aspirin is normally contraindicated in children.
- intravenous immunoglobulin
  - **Combination therapy with intravenous immunoglobulin (IVIG) and aspirin during the acute phase of Kawasaki disease produces a more marked anti-inflammatory effect and reduction in coronary artery abnormalities than does aspirin alone.**
- echocardiogram (rather than angiography) is used as the initial screening test for coronary artery aneurysms

Complications

- coronary artery aneurysm (25% of cases)
- lakayasu1s arter1 t1s

Kawasaki Disease

- Lymphomucocutaneous Disease
- Five Characteristics of Disease (4/5 for diagnosis)
  - **Fever >5 days**
  - **Cervical lymphadenopathy (usually unilateral)**
  - **Erythema and edema of palms and soles with desquamation of skin**
  - **Nonpurulent Bilateral Conjunctivitis**
  - **Strawberry Tongue**
- Treatment
  - **IVIG and Aspirin**

Takayasu's disease (TD)

Definition

- Takayasu's arteritis is a large vessel vasculitis.
- chronic inflammatory granulomatous pan-arteritis of the **major arteries** Affected vessels
  - It typically causes occlusion of the aorta (the ascending arch of the aorta)
  - The subclavian artery is commonly affected, and subclavian steal syndrome may occur
  - The brachial, radial and ulnar arteries can also be involved.

Pathology

- continuous or patchy granulomatous inflammatory process involving macrophages, lymphocytes, and multinucleated giant cells which causes progressive occlusive disease of the aorta and its branches.

Epidemiology

- most commonly affects women (the ratio of women to men is 8:1).
- typical age onset of 25-30 years.
- most common in Asia.
- It is very rare in the Western world with an annual incidence of between 2 and 3 per million.

Features

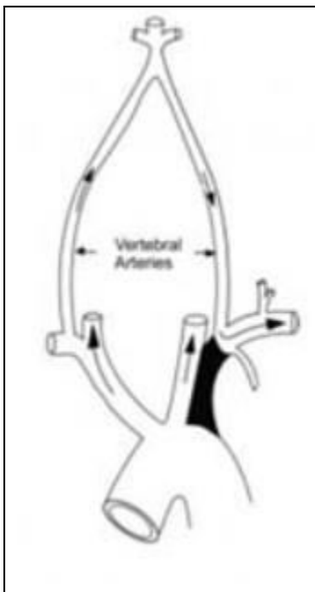
- questions commonly refer to an **absent limb pulse**.
- systemic features of a vasculitis e.g. malaise, headache
- unequal blood pressure in the upper limbs
- carotid bruit
- vascular symptoms such as **claudication.** (intermittent claudication)

- systemic symptoms of fever, arthralgia and weight loss.
- neurological symptoms such as transient ischaemic attacks.
- Cardiac features include angina, heart failure, and aortic regurgitation.
- Renal manifestations may include mesangial proliferative glomerulonephritis.
- aortic regurgitation (around 20%)
- ESR and CRP are usually elevated,
- levels of pentraxin 3 may be a useful marker of disease activity.

Associations
- renal artery stenosis

Treatment
- Corticosteroids with the addition of steroid sparing second agents such as methotrexate or azathioprine are the mainstay of therapy.

Prognosis
- With good care, 15-year survival rates approach 90%.



Subclavian steal syndrome (SSS)

The **proximal part of left subclavian is blocked on left side** so no flow in vertebral and to left arm. Blood from right vertebral enters left vertebral and flows back to supply left arm

Etiology
- Atherosclerosis
- Cervical rib
- **Takayasu's arteritis**

Features
- Presyncope (sensation that one is about to faint)
- Syncope (fainting)
- Neurologic deficits
- Blood pressure differential between the arms
- severe memory problems
- hands showing circulation problems (hands can have blotchy patches of red and white) (associated with other stigma to vascular disease (e.g. vascular insufficiency ulcers of the foot).

Buerger's disease

Overview
- Thromboangiitis obliterans (Buerger's disease) is a disease of **small and medium-sized arteries and veins** resulting in inflammation and ulceration, in which the distal vessels become blocked in the hands and feet.
- There is no excessive atheroma and it does not involve the coronary arteries like atherosclerosis.
- The disease **occurs mainly in cigarette smokers; it has not been documented in non-smokers**.
- Prevalence is higher in men and people of Far Eastern origin.

Feature
- symptoms of arterial ischaemia → resulting in **gangrene of the digits.**
  - claudication with diminished or absent pulses.
  - The feet or legs may be cyanosed or dusky; the skin is thin and without hair.
  - Ulcerations occur and necrosis follows
- **Migratory phlebitis in the superficial vein** is present in 40% of cases.

Diagnosis
- usually clinical.
- Arteriogram will show occlusion of distal arteries of the hands and feet.
- Histopathology
  - examination of affected arteries reveals fresh inflammatory thrombus within both small and medium-sized arteries and veins, with giant cells surrounding the thrombus.

Treatment
- Supportive

- **stop smoking.**

Prognosis

- can be excellent (i.e. complete resolution of symptoms) with smoking cessation
- in some cases, however, amputation is unavoidable

IBD-associated arthropathy

- The history of weight loss, diarrhoea and a mono/oligo-arthropathy suggests a diagnosis of inflammatory bowel disease (IBD).
- IBD-associated arthropathy is considered a subtype of seronegative spondyloarthropathy.
- A variety of joint involvement has been described, from large joint pauciarticular arthropathy to a rheumatoid pattern polyarthropathy.
- Peripheral arthritis is generally non-erosive and the oligoarticular variant particularly may correlate with intestinal disease activity.
- Axial arthritis may include inflammatory back pain, sacroilitis, or ankylosing spondylitis and is less likely to correlate with gastrointestinal symptoms.
- mechanisms remain unclear.
- Treatment of the gastrointestinal disease is not always sufficient for control of arthritis, and biologic agents may be indicated.

The description of weight loss, diarrhoea and a mono/oligo-arthropathy suggests a diagnosis of inflammatory bowel disease. (IBD).

Differential diagnoses of arthropathies associated with iron deposition in the joints: → brown-stained synovial fluid.

- Haemophilia
- Haemosiderosis from recurrent haemarthrosis
- Haemochromatosis, and
- **Pigmented villonodular synovitis (PVNS).**

SAPHO syndrome

SAPHO is an acronym for synovitis, acne, pustulosis, hyperostosis, and osteitis. It is characterised by osteosclerotic bone lesions, sterile osteomyelitis, and a variety of skin lesions.

- **Synovitis** - may be present rarely, and associates with erosions.
- **Acne -** may be severe (conglobate or fulminans) and recur with new bony involvement.
- **Pustulosis** - palmo-plantar pustulosis occurs in approximately 50% of patients, other skin lesions may include psoriasis, hidradenitis suppurativa, acne, and rarely Sweet's syndrome.
- **Hyperostosis** (increase in bone substance) and osteitis (inflammation of the bones) - the bony lesions typically involve the acromioclavicular, and sternoclavicular joints. Other sites include anterior chest wall, sternum, clavicle, pubic symphysis, spine, and mandible. These lesions are visualised on 99m technetium bone scan or MRI.

The cause of the SAPHO syndrome is unknown.

Investigation

- skin lesions are characterised by neutrophilic pseudoabscesses.
- Bone biopsy can reveal sterile osteomyelitis.

Diagnosis should be suspected when there is an association of rheumatic pain with a pustular skin disease.

treatment

- no specific treatment,
- some cases remit spontaneously
- Typical treatment can be used for the arthritic symptoms (i.e. non-steroidal anti-inflammatories and disease modifying anti-rheumatic agents).
- Isotretinoin and aciretin can be used to treat the skin disease.
- In the more severe cases corticosteroids, calcitonin, bisphosphonates and TNF-inhibitors can be used.

Elbow pain

The table below details some of the characteristic features of conditions causing elbow pain:

Lateral epicondylitis (tennis elbow)	**Features** • **pain and tenderness localised to the lateral epicondyle** • **pain worse on resisted wrist extension with the elbow extended or supination of the forearm with the elbow extended** • **episodes typically last between 6 months and 2 years. Patients tend to have acute pain for 6-12 weeks** • **most appropriate to gain short term relief for the patient? → Local steroid/anaesthetic injection**
Medial epicondylitis (golfer's elbow)	**Features** • pain and tenderness localised to the medial epicondyle • pain is aggravated by **wrist flexion** and pronation • symptoms may be accompanied by numbness / tingling in the 4th and 5th finger due to ulnar nerve involvement
Radial tunnel syndrome	• Most commonly due to compression of the posterior interosseous branch of the radial nerve. • It is thought to be a result of overuse. **Features** • symptoms are similar to lateral epicondylitis making it difficult to diagnose • however, the pain tends to be around 4-5 cm distal to the lateral epicondyle • symptoms may be worsened by extending the elbow and pronating the forearm
Cubital tunnel syndrome	Due to the compression of the **ulnar nerve.** **Features** • initially intermittent tingling in the **4th and 5th finger** • may be worse when the elbow is resting on a firm surface or flexed for extended periods • later numbness in the 4th and 5th finger with associated weakness
Olecranon bursitis	Swelling over the posterior aspect of the elbow. There may be associated pain, warmth and erythema. It typically affects middle-aged male patients.

Shoulder problems

The table below summarises the key features of common shoulder problems:

Condition	Notes
Adhesive capsulitis (frozen shoulder)	Common in middle-age and diabetics Characterised by painful, stiff movement Limited movement in all directions, with loss of external rotation and abduction in about 50% of patients
Supraspinatus tendonitis (Subacromial impingement, painful arc)	Rotator cuff injury Painful arc of abduction between 60 and 120 degrees Tenderness over anterior acromion

Prepatellar bursitis

- **The most useful in initial diagnosis of prepatellar bursitis → Crepitation of the knee**

Polymyositis

Polymyositis is the commonest cause of inflammatory muscle disease in people under 50-years-old (inclusion body myositis is the commonest in those over 50-years-old).

Anti-Jo-1 antibodies are more common in polymyositis than dermatomyositis

Overview

- inflammatory disorder causing **symmetrical**, **proximal**, **painless** muscle weakness
- thought to be a T-cell mediated cytotoxic process directed against muscle fibres
- dermatomyositis is a variant of the disease where skin manifestations are prominent, for example a purple (heliotrope) rash on the cheeks and eyelids
- typically affects middle-aged,
- female: male 3:1

Associations

- idiopathic
- connective tissue disorders
- malignancy
  - **Adenocarcinomas** of the cervix, lung, ovaries, pancreas, bladder, and stomach account for approximately **70%** of the cancers associated with inflammatory myopathies.

Features

- **proximal muscle weakness** +/- tenderness
- Raynaud's
- respiratory muscle weakness
- interstitial lung disease: e.g. fibrosing alveolitis or organising pneumonia
- **dysphagia**, dysphonia
  - Dysphagia is common but the ocular muscles are very rarely involved unlike myasthenia gravis where this is a predominant feature.

Investigations

- **elevated creatine kinase (the initial investigation)**
- Electromyography (EMG)
  - EMG are abnormal in almost all patients (90%).
  - Triad of:
    1. Short, small polyphasia motor units
    2. Fibrillation and sharp waves
    3. Bizarre, repetitive discharges
- muscle biopsy
  - **muscle biopsy is the definitive investigation to establish the diagnosis**
  - Histopathology → **endomysial** mononuclear **inflammatory infiltrate** and muscle fiber **necrosis**.
    - **endomysial inflammation with CD8 T cells (MHC class I)**.
- anti-Jo-1 antibodies are seen in pattern of disease associated with lung involvement, Raynaud's and fever
- Positive rheumatoid factor - Found in more than 50%
- Myoglobinuria
- CBC - May show leukocytosis (in more than 50%) or thrombocytosis.
- ESR or CRP: elevated in 50%
- **Antinuclear antibody -** Positive in one third

Treatment

- Prednisolone is the mainstay of treatment, at an initial dose of 1 mg/kg/d.
- In patients who fail to show improvement, disease-modifying steroid-sparing agents may be added.
- A high-protein diet and supervised exercise may further improve symptoms.

Prognosis

- Most patients have a favourable response to corticosteroid therapy, and 5-year survival rates approach 80%.

Dermatomyositis

proximal weakness with normal reflexes and sensation and absence of fasciculations :

➔ without skin lesion → polymyositis

➔ with skin lesion → dermatomyositis

Dermatomyositis antibodies: ANA most common, anti-Mi-2 most specific

Overview

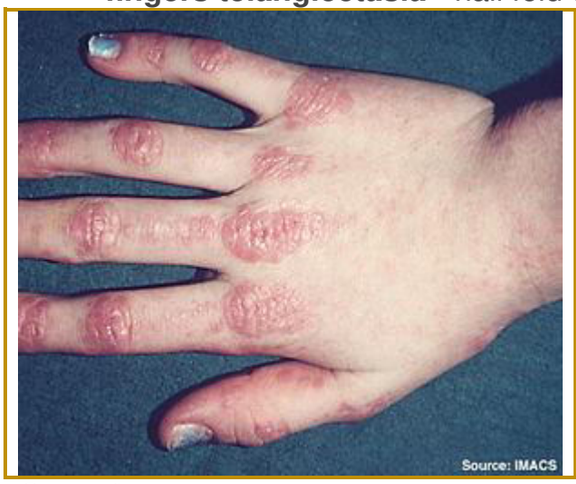
- inflammatory disorder causing symmetrical, proximal muscle weakness and characteristic skin lesions
- may be idiopathic or associated with connective tissue disorders or underlying malignancy (typically lung cancer, found in 20-25% - more if patient older)
- **polymyositis** is a variant of the disease where skin manifestations are not prominent

Pathophysiology

- **Autoantibodies binding to the vasculature**, muscle atrophy, and lymphocytic inflammation
- **caused by CD4 T cells that cause perimysial inflammation and atrophy.**

Skin features

- photosensitive
- Pruritus of skin lesions, sometimes intense enough to disturb sleep
- **'shawl sign'**: macular rash over back and shoulder
- **"V-neck sign":** Violaceous erythema or poikiloderma involving the anterior chest
- **heliotrope rash** in the periorbital region
  - The characteristic heliotrope rash consists of a violaceous or erythematous rash (sometimes with oedema) in a symmetrical distribution involving periorbital skin. This is frequently subtle and may involve only a mild discolouration along the eyelid margin.
  - Since a heliotrope rash is rarely observed in other disorders, its presence is highly suggestive of dermatomyositis .
- **Gottron's papules** - roughened red papules over extensor surfaces of fingers
- **"mechanic's hands" (rough, cracked skin),**
- **fingers telangiectasia** - nail fold capillary dilatation.



Gottron's papules (rough papules on extensor surfaces of the phalanges are pathognomonic if there is a history of weakness and elevated creatine kinase (CK)).

Gottron's papules are found over bony prominences, particularly the metacarpophalangeal joints, the proximal interphalangeal joints, and/or the distal interphalangeal joints. Papules may also be found overlying the elbows, knees, and/or feet.

Other features

- proximal muscle weakness +/- tenderness
- Raynaud's
- respiratory muscle weakness → ↓ Vital capacity (VC)
- Commonly, there is muscle wasting and reduced reflexes
- interstitial lung disease: e.g. Fibrosing alveolitis or organising pneumonia

- dysphagia, dysphonia
- Ocular symptoms are rare and if present should alert you to consider a different diagnosis

Investigations

- elevated creatine kinase
  - **the most helpful test in the diagnosis**
- EMG
- muscle biopsy
  - high levels of the complement component **C5b-9 around the capillary vessels**.
  - **Perimysial inflammation with lymphocytic infiltrate**
- ANA positive in 60%
- **anti-Mi-2 antibodies are highly specific** for dermatomyositis, but are only seen in around 25% of patients
- anti-Jo-1 antibodies are not commonly seen in dermatomyositis - they are more common in polymyositis where they are seen in a pattern of disease associated with lung involvement, Raynaud's and fever
- **Screen for malignancy**

Management

- prednisolone

Inclusion body myositis (IBM)

Painless weakness and wasting with selective involvement of long finger flexors and quadriceps is characteristic of inclusion body myositis.

Overview

- a syndrome of diffuse, progressive, **asymmetric**, proximal, and distal weakness that is generally **refractory to immunosuppressive treatment**.
- cause of myopathy associated with **cytoplasmic inclusions on muscle biopsy**

pathology

- the pathologic findings involve both inflammatory and degenerative characteristics
- Like in polymyositis, inclusion body myositis presents with and increased sarcolemmal expression of **MHC class I** antigens.

Epidemiology

- IBM occurs **more frequently in men than women**.
- More common in older Caucasian males.
- the most common acquired myopathy in **patients older than 50 years**
- and accounts for 16-28% of inflammatory myopathies in the United States and Canada.

Features

- muscle weakness can affect **both proximal and distal muscles**
  - **unlike polymyositis and dermatomyositis, asymmetry is common.**
  - characteristically affects quadriceps and finger/wrist flexors are usually more severely affected than extensor counterparts
  - The onset of muscle weakness in IBM is generally gradual (over months or years).
- Dysphagia is common, occurring in 40-66% of patients

Complications

- Dysphagia due to weakness of the cricopharyngeal musculature may predispose to aspiration pneumonia
- The most common cause of death is respiratory system disorders.

Diagnosis

- anti-**cN1A** autoantibodies
- Muscle biopsy shows **intranuclear or cytoplasmic tubofilaments** on electron microscopy.

Treatment:

- Poor response to immunosuppressive or immunomodulatory therapies
- Polymyositis and dermatomyositis show a much better response to steroids than IBM.

	Polymyositis	Dermatomyositis	IBM
Onset	Subacute	Subacute	**Slow**
age	Commonest < 50 years	Commonest < 50 years	**commonest > 50 years**
Affected muscles	Proximal	Proximal	**Proximal and distal**
symmetry	symmetrical	symmetrical	**Asymmetrical**
Common incidence	Female	Female	**Male**
Skin lesion	NO	**Characteristic rash**	NO
CK	Highly elevated (up to 50 fold)	Highly elevated (up to 50 fold)	**Mild elevated (up to 10 fold) or normal**
antibodies	anti-Jo-1 are more common	**anti-Mi-2 are highly specific**	anti-cN1A autoantibodies
Muscle biopsy	endomysial mononuclear **inflammatory infiltrate** and muscle fiber **necrosis**.	perivascular and interfascicular inflammatory infiltrates with adjoining groups of muscle fiber degeneration/regeneration	**intranuclear or cytoplasmic tubofilaments**
T cell	CD8 T cell	CD4 T cell	
Response to steroids	good	Good	**Poor**

Fibromyalgia (FM)

- Fibromyalgia is a syndrome characterised by widespread pain throughout the body with **tender points at specific anatomical sites**.
- The cause of fibromyalgia is unknown.but may involve hyperexcitability within the spinal cord or brainstem, altered pain perception and somatisation.

Epidemiology

- occur in between 1 and 2% of the general population
- **women are 10 times more** likely to be affected
- typically presents between 30-50 years old

Features

- chronic pain: at multiple site, sometimes 'pain all over'
- lethargy
- sleep disturbance, headaches, dizziness are common
- 50% of patients with fibromyalgia complain of **diarrhoea and constipation**, often associated with abdominal bloating.
- Morning fatigue
- patients often look unwell, and may appear depressed and anxious.
- Other features include tissue swelling, morning stiffness

Diagnosis

- is clinical → **pain in all four quadrants of the body**, as well as **tenderness** in 11 of 18 anatomically defined trigger areas.
- The **normal ESR** in patients with FM contrasts with the high ESR in elderly patients with polymyalgia rheumatica.
  - ESR and CRP can assist in identifying/excluding an underlying inflammatory disorder.

Management

- explanation
- **aerobic exercise: has the strongest evidence base**
- cognitive behavioural therapy

- medication: pregabalin, duloxetine, amitriptyline
  - **Tricyclic anti-depressants such as amitriptyline are first line agents used for treatment.** (medical-masterclass.com 2017 mrcp part 2)

Key facts:
- How to diagnose?
  - A female, presented with a feature of pain and **tenderness** over multiple area + **normal ESR** and CRP.
- What is the best management?
  - aerobic exercise

Cervical spondylosis

- Cervical spondylosis is the most common progressive disorder of the spine, associated with normal aging.

Pathophysiology
- degeneration of the intervertebral discus and facet joints in the cervical spine.

Risk factors
- rugby, horse-riding and flying, all of which increase loads on the head.

Symptoms
- **Asymptomatic** In the majority of cases
- **myelopathy and radiculopathy**
  - **Radiculopathy** is due to compression, stretching or angulation of the cervical nerve roots.
  - **Myelopathy** is due to compression, ischaemia or recurring minor trauma to the cord.
- Cervical spondylitic myelopathy is the most common cause of myelopathy in adults.
- There is a mixture of upper and lower motor neurone signs. These may or may not be accompanied by pain in the neck and/or upper limb, orbits or temporal regions. In addition there is often cervical stiffness, and poor balance. On examination there is limited range of movement of the cervical spine and poorly localised tenderness.
- Radiculopathy causes dermatomal pain, often with accompanying changes in sensation or weakness in related muscles. The most commonly affected nerve roots are C5-7, and sensory symptoms (shooting pain, numbness, hyperaesthesia) are more common than weakness. Dural irritation can be demonstrated with the Spurling test in which radicular pain is reproduced with lateral flexion and rotation of the neck, with pressure on top of the patient's head. Reflexes are usually reduced.
- **differential diagnosis** is broad, and includes acute neck strain, osteomyelitis, fibromyalgia, inflammatory arthritis and osteoporosis.
- MRI and electrophysiology.

investigation
- The investigation of choice is (MRI)
  - High signal-intensity lesions on MRI indicate a poor prognosis.
- **nerve conduction studies to assess the degree of nerve damage**.

Management
- Initially conservative measures such as regular activity, physiotherapy and addressing risk factors should be instigated.
- cervical collar should not be used.
- Analgesia, anti-inflammatories and tricyclic antidepressants can be helpful.
- Indications for surgery include progressive neurological defects, compression of the cervical nerve root and/or spinal cord and intractable pain.
- Decompression improves neurologic function in some patients and prevents worsening in others, but there are significant risks.
- Epidural injection can be considered where surgical intervention is not an option.
- Patients will usually improve with time, and surgical intervention is needed in less than 5% of patients.
- In general, progression of cervical spondylosis is slow, although 10% develop chronic neck pain.

Dupuytren's contracture.

Definition
- progressive painless contracture of the palmar facial bands, causing flexion deformities of the fingers.
- **autosomal-dominant** condition with variable penetrance.

Prevalence

- has a **male**: female predominance of 10:1.
- prevalence rates approaching 25% in elderly Scandinavians.
- most commonly observed in persons of Northern European descent and affects 4-6% of Caucasians worldwide.

Pathophysiology

- **fibroblast proliferation**, and collagen deposition leading to contractures of the palmar fascia.
- **Interleukin 1 (IL-1)** is the most abundant cytokine
- Normal palmar fascia is primarily composed of type I collagen; Dupuytren disease is associated with an **increase in type III collagen**.

Risk factor:

- **Alcoholism** (10%),
- diabetes mellitus (8%).
- previous myocardial infarction,
- hand trauma,
- HIV infection,
- cigarette smoking.

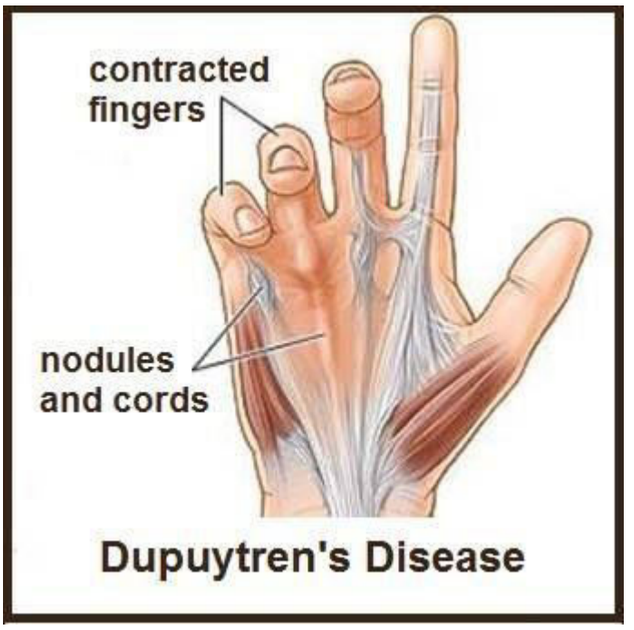
Features

- bilateral in 45%;
- in unilateral cases, the right side is more often affected.
- The ring finger is most commonly involved, followed by the fifth digit and then the middle finger. The index finger and the thumb are typically spared.
- Penile fibromatosis (Peyronie's disease) is seen in about 7-10% of patients.

Rheumatoid arthritis seems to protect against the development of Dupuytren disease.

Management

- Surgery followed by physiotherapy to improve finger function is the recommended course of action.
- Collagenase therapy may be an alternative to surgery in some cases.



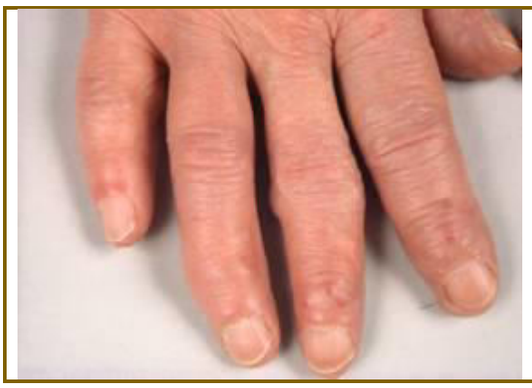
Ledderhose disease is involvement of the plantar fascia by a similar process of nodule and cord formation leading to **contraction of the toes**.

Costochondritis

- has a higher prevalence in women
- commoner over the age of 40 years.
- It is associated with **tenderness over the costochondral junctions and/or sternum**, pain on coughing and deep breathing, and equal involvement with both sides of the chest.
- Non-steroidals would be an appropriate first line intervention for pain relief.

Multicentric reticulohistiocytosis

- Multicentric reticulohistiocytosis is a rare non-Langherhan's cell histiocytosis with skin and joint involvement.
- Nearly all organs can be involved.
- Association with cancer occurs in about 25% of cases.
- Association with autoimmune diseases has also been recorded.
- The characteristic **nail fold nodules** of multicentric reticulohistiocytosis have the appearance of 'coral beads'. Nodules may be numerous, may grow to as large as 2 cm, and may involve mucosal surfaces.
- Hand radiograph shows **erosive changes in multiple joints**. Distal interphalangeal erosions are characteristic and may lead to pseudo-widening of the joint spaces.
- Microscopic examination shows a histiocytic nodular infiltrate made of giant cells with ground-glass appearance and periodic acid-schiff (PAS) positive cytoplasm.

	characteristic nail fold nodules of multicentric reticulohistiocytosis

Relapsing polychondritis (RP)

- inflammatory condition that involves cartilaginous structures, predominantly those of the pinna, nasal septum and larynx.
- most common in the fifth decade.

Feature

- General symptoms include: intermittent fever and weight loss
- other more specific symptoms include:
  - sudden onset of **ear pain** with an inability to sleep on the affected side, diminished hearing,
  - monoarthritis or polyarthritis, back pain, myalgias,
  - mild epistaxis, saddle-shaped nose,
  - redness of the eyes indicative of conjunctivitis, episcleritis and/or scleritis,
  - **hoarseness of the voice** and recurrent respiratory infections.
  - patient may presents with symptoms suggestive of tracheal involvement and is at risk of developing tracheomalacia.
    - **The most appropriate next investigation is a flow–volume loop,** which might show a truncated expiratory limb that is characteristic of tracheomalacia, as well as provide information on the severity of the disease.

Investigations

- no specific diagnostic laboratory findings
- the non-specific indicators of inflammation (ESR, CRP) are often elevated.
- It is important in these patients to investigate for the presence of other concurrent autoimmune diseases.

Treatment

- systemic corticosteroids.

Baker cyst

Look for a patient with osteoarthritis or rheumatoid arthritis with a swollen calf. A ruptured Baker's cyst is a "pseudophlebitis." Unruptured cysts can be palpated.

- A Baker's cyst (popliteal cyst) is a posterior herniation of the synovium of the knee.
- A Baker cyst is the most common mass in the popliteal fossa.
- Since the cyst is an extension from the knee joint, it is lined by synovium.

Causes

- **the most common cause → osteoarthritis**
- rheumatoid arthritis
- Gout
- Reiter's syndrome
- Psoriasis
- Systemic lupus erythematosus
- Internal derangement (meniscal tears, anterior cruciate ligamaent (ACL) tears, osteochondral fractures)
- Infection (septic arthritis, tuberculosis)
- Chronic dialysis
- Haemophilia
- Hypothryroidism
- Pigmented villonodular synovitis
- Sarcoidosis

Investigations

- **Ultrasonography** is the imaging technique of choice in the evaluation of a popliteal mass, but using this technique it may be difficult to show a true connection with the joint space to establish a definitive diagnosis of popliteal cyst.

complication

- The most common **complication** is rupture or dissection of fluid into the adjacent proximal gastrocnemius muscle belly which results in a syndrome mimicking the symptoms of a deep vein thrombosis.
  - Doppler ultrasonography will, however, show the vascular lumen to be compressible (the lumen is not compressible in deep vein thrombosis due to the presence of the thrombus).

Familial Mediterranean Fever (FMF) also known as recurrent polyserositis)

- autosomal recessive disorder
- FMF is an **autoinflammatory** disease
- **caused by mutations in** Mediterranean fever *(MEFV)* gene, which **encodes** a protein called **pyrin**.
- The ***MEFV* gene** is **located on** the **short arm of chromosome 16**

Epidemiology

- typically presents by the second decade.
- more common in people of Turkish, Armenian and Arabic descent

Features - attacks typically last 1-3 days

- pyrexia
- abdominal pain(95%) (due to peritonitis)
- pleurisy
- pericarditis
- arthritis
- erysipeloid rash on lower limbs

Diagnosis

- ↑acute phase response, ↑C-reactive protein, ↑WBCC and other markers of inflammation.
- In patients with a long history of attacks, monitoring the kidney function is of importance in predicting chronic kidney failure.
- genetic test to detect mutations in the MEFV gene.
- A specific and highly sensitive test for FMF is the "Metaraminol Provocative Test (MPT)," whereby a single 10 mg infusion of Metaraminol is administered to the patient. A positive diagnosis is made if the patient presents with a typical, albeit milder, FMF attack within 48 hours.

Management

- Attacks are self-limiting, and require analgesia (NSAIDs)

- **Colchicine is most effective in preventing attacks of and preventing the development of amyloidosis in FMF.**

- anakinra is indicated in those who do not respond to colchicine.
- **Anakinra** is a drug used to treat rheumatoid arthritis. It is an interleukin 1 (IL1) receptor antagonist.

Notes & Notes

For MRCP part 1 & 11

By

Dr. Yousif Abdallah Hamad

Haematology

&

Oncology

Updated

2017

Contains:

1/ Passmedicine 2017

2/ on examination 2017

3/ pastest 2017

4/Red fonts: previous exams

5/ Other updated UK sources

Haematological changes during pregnancy

- **Platelet**
  - **Isolated thrombocytopenia**
    - **occur in 8%**
    - Usually mild with platelet above 70
    - Occur due to presence **IgG antibodies**, which are reactive to platelet
    - **No intervention** , recover after delivery

Hyposplenism

Causes

- splenectomy
- sickle-cell
- coeliac disease, dermatitis herpetiformis
- Graves' disease
- systemic lupus erythematosus
- amyloid

Features

- Howell-Jolly bodies
- siderocytes

Eosinophilia

Causes of eosinophilia may be divided into pulmonary, infective and other

Pulmonary causes

- asthma
- allergic bronchopulmonary aspergillosis
- Churg-Strauss syndrome
- Loffler's syndrome
- tropical pulmonary eosinophilia
- eosinophilic pneumonia
- hypereosinophilic syndrome

Infective causes

- schistosomiasis
- nematodes: Toxocara, Ascaris, Strongyloides
- cestodes: Echinococcus

Other causes

- **drugs: sulfasalazine, nitrofurantoin**
- psoriasis/eczema
- eosinophilic leukaemia (very rare)

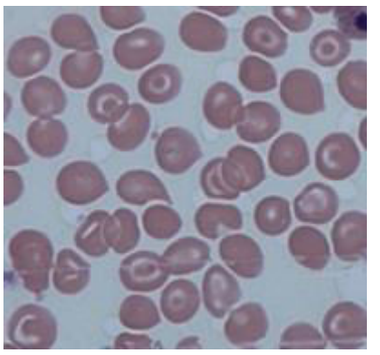
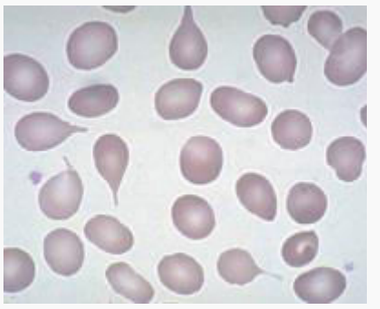
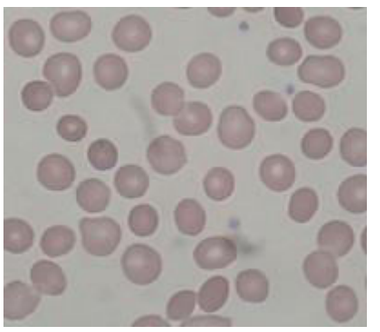
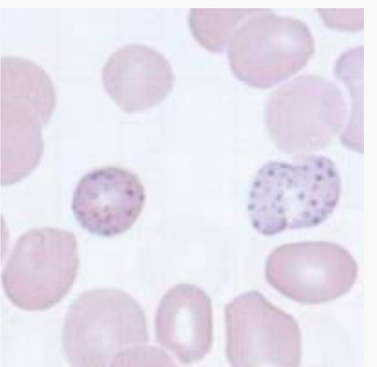
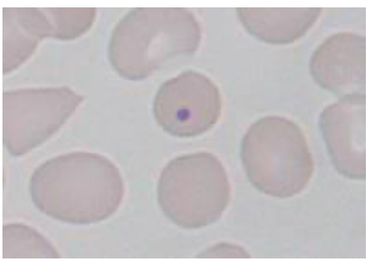
Lymphopenia

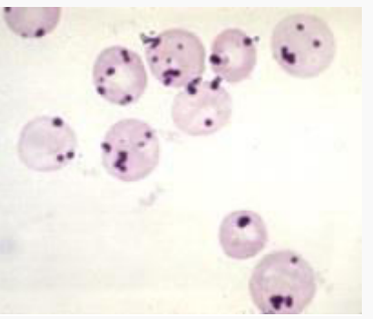
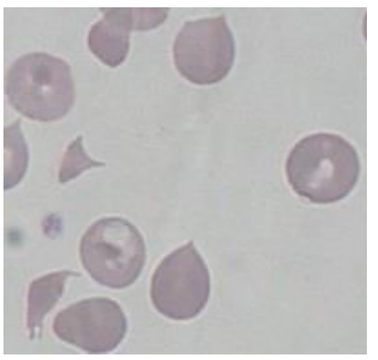
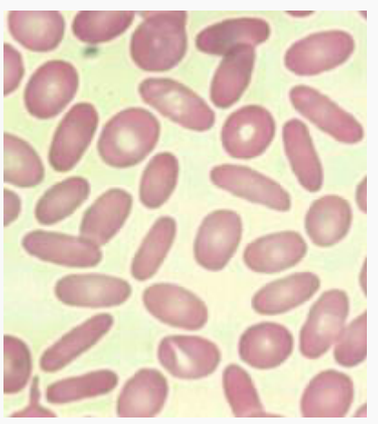
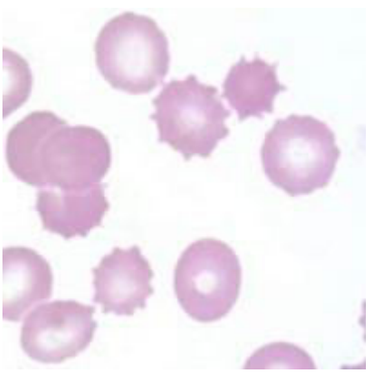
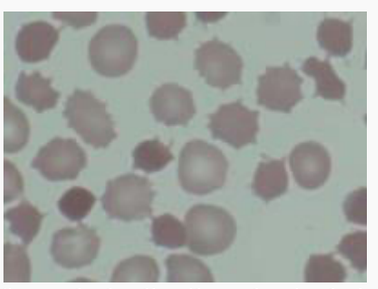
Causes

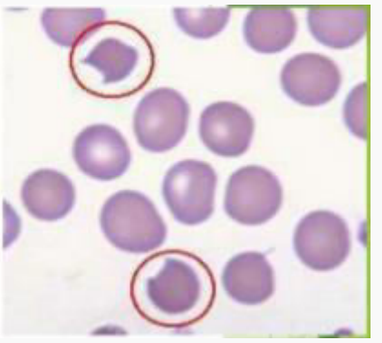
- **common finding in elderly patients.**
  - **If greater than 0.5 * 10^9/l no action is normally needed**
- immunosuppresive drugs e.g. methotrexate
- viral infections e.g. HIV
- non-viral infections e.g. tuberculosis, malaria
- autoimmune disorders e.g. rheumatoid
- lymphoproliferative disorders

Blood films: pathological cell forms

Pathological red cell forms

Abnormality	Associated condition(s)	Appearance
Target cells	Sickle-cell/thalassaemia Iron-deficiency anaemia **Hyposplenism** Liver disease	
'Tear-drop' (Dacrocyte) poikilocytes	**Myelofibrosis** (The morphology results because RBCs are **mechanically** squeezed out of the bone marrow.)	
Spherocytes	Hereditary spherocytosis Autoimmune hemolytic anaemia	
Basophilic stippling	**Lead poisoning** Thalassaemia Sideroblastic anemia Myelodysplasia	
Howell-Jolly bodies	Hyposplenism (Howell-Jolly bodies are the **basophilic remnants of the RBC nucleus**.)	

Abnormality	Associated condition(s)	Appearance
Heinz bodies	G6PD deficiency Alpha-thalassaemia	
Schistocytes ('helmet cells')	Intravascular haemolysis Mechanical heart valve Disseminated intravascular coagulation	
'Pencil' poikilocytes	Iron defiency anaemia	
Burr cells (echinocytes)	**Uraemia** Pyruvate kinase deficiency liver disease	
Acanthocytes	**Abetalipoproteinemia**	 (irregularly distributed spicule in

Abnormality	Associated condition(s)	Appearance
		red blood cells).
Bite cell (Degmacyte)	G6PD (**when spleen removes heinz bodies from RBCs**)	

Blood films: typical pictures

Hyposplenism e.g. post-splenectomy

- target cells
- **Howell-Jolly bodies**
  - These are spherical bluish inclusions within erythrocytes
  - They are nuclear fragments of condensed DNA which are normally removed by the spleen.
  - They are seen in severe haemolytic anaemias or in hyposplenic/asplenic patients.
- Pappenheimer bodies
- siderotic granules
- acanthocytes

Iron-deficiency anaemia

- target cells
- 'pencil' poikilocytes
- if combined with B12/folate deficiency a 'dimorphic' film occurs with mixed microcytic and macrocytic cells

Myelofibrosis

- 'tear-drop' poikilocytes

Intravascular haemolysis

- schistocytes

Megaloblastic anaemia

- hypersegmented neutrophils

Congenital Pelger–Huet anomaly

- is a laminopathy associated with mutations in the lamin B receptor.
- This leads to **bilobed nuclei in neutrophils** and in homozygotes,
- can also be associated with:
  - skeletal abnormalities which include shortened limbs.
  - Like this patient, heterozygotes usually suffer no symptoms and the neutrophil anomaly is picked up as an incidental finding.

MRCP part-1 – jan 2017
A 23-year-old man with tiredness and was noted to have a **neutrophil abnormality** on his blood film with **bilobed nuclei**. His father has a skeletal anomaly with a short right arm, Examination reveals no lymphadenopathy, and abdominal examination is entirely normal. What is the most likely diagnosis?

➔ **Congenital Pelger–Huet anomaly**

Leucocyte alkaline phosphatase

Raised in	Low in
• myelofibrosis • leukaemoid reactions • polycythaemia rubra vera • infections • steroids, Cushing's syndrome • pregnancy, oral contraceptive pill	• chronic myeloid leukaemia • pernicious anaemia • paroxysmal nocturnal haemoglobinuria • infectious mononucleosis

Leukaemoid reaction

- The leukaemoid reaction describes the presence of immature cells such as myeloblasts, promyelocytes and nucleated red cells in the peripheral blood. This may be due to infiltration of the bone marrow causing the immature cells to be 'pushed out' or sudden demand for new cells

Causes

- severe infection
- severe haemolysis
- massive haemorrhage
- metastatic cancer with bone marrow infiltration

Differentiating chronic myeloid leukaemia from a leukaemoid reaction:

Chronic myeloid leukaemia	Leukaemoid reaction
low leucocyte alkaline phosphatase score	• high leucocyte alkaline phosphatase score • toxic granulation (Dohle bodies) in the white cells • 'left shift' of neutrophils i.e. three or less segments of the nucleus

Coagulation study

Prothrombin time (PT)

- Prothrombin time (PT) is a measure of the time it takes for the extrinsic pathway to create a fibrin clot.
- tests function of factors (I, II, V, **VII**, X)
  - ➢ defect in any of these → ↑ PT
  - ➢ e.g. vitamin K deficiency
- **best test to follow warfarin therapy**
  - ➢ normalized as an INR (international normalized ratio)
  - ➢ note also increases PTT time
- also used to measure hepatic function as most of the factors are synthesized in the liver Used to monitor the extrinsic pathway
- Factors make up the extrinsic pathway:
  - ➢ Damaged endothelium → tissue factor release → Factor VII activation → common pathway activation
- **In patients with vitamin K deficiency, the PT is typically prolonged while the partial thromboplastin time (PTT) is usually normal.**
- **Long-term use of antibiotics → changes in the gut flora → vitamin K deficiency → ↑PT**
  - ➢ Long-term use of antibiotics (particularly cephalosporins like cefepime) would cause changes in the gut flora that result in vitamin K deficiency (due to decreased populations of the bacteria that synthesize it).
  - ➢ vitamin K deficiency would impair the gamma-carboxylation of factors II, VII, IX, and proteins C and S.
  - ➢ As a result, the **PT**, which **measures the clotting time of the extrinsic pathway** (starting with tissue factor and factor VII), would **increase**, just as it would in a patient on warfarin.

Partial Thromboplastin Time (PTT) (sometimes also called Activated Partial Thromboplastin Time)

- tests function of all factors EXCEPT (VII, XIII)

  - defect in any of these→ ↑ PTT
- when prolonged indicating hemophilia or (sometimes) von Willebrand's Disease.
- **best test to follow heparin therapy**
  - note also increases PT time
- Used to monitor the **intrinsic pathway**
- Factors make up the intrinsic pathway:
  - Factors XII, XI, IX, VIII.
- **elevated APTT could be due to:**
  - treatment with heparin
  - haemophilia
  - von Willebrand's disease, or
  - antiphospholipid syndrome.

The commonest cause of reduced APTT is → in-vitro clotting cascade activation, but tests should be repeated to exclude pathological causes of hypercoagulability.

DIC vs TTP

- DIC is distinguished from thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) based on coagulation studies.
- Although TTP and HUS are also microangiopathic hemolytic anemias, patients with these conditions do not have derangement or consumption of clotting factors.
  - **DIC → Increased PT, PTT, decreased platelets**
  - **TTP & HUS → normal PT, normal PTT, and decreased platelets.**

Isolated factor deficiency

- Normal PT, **increased PTT**, and normal platelets suggests an isolated factor deficiency such as hemophilia A and B, in which there is a deficiency of factors VIII and IX, respectively.
- An isolated elevated PTT may also suggest von Willebrand's disease.

Disease	PT	PTT	Platelet count	Bleeding time
Warfarin (or vitamin K deficiency)	Raised	Raised (in severe or prolonged cases)/nl	Raised	nl
DIC	Raised	Raised	Decreased	Raised
Thrombocytopenia	nl	nl	Decreased	Raised
Bernard-Soulier	nl	nl	Decreased	Raised
Hemophilia (A or B)	nl	Raised	nl	nl
von Willebrand	nl	nl/raised	nl	Raised
Glanzmann's	nl	nl	nl	Raised

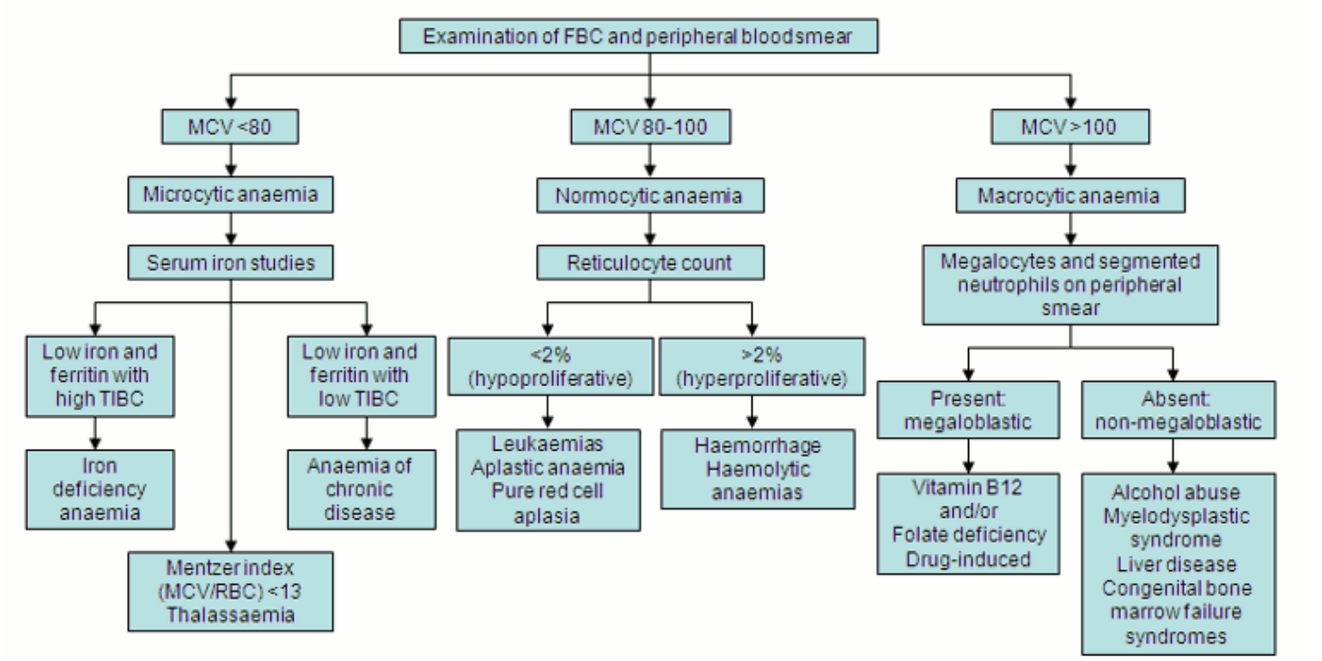
Giant platelet syndrome (Bernard-Soulier syndrome; BSS)

- is a defect in platelet adhesion.
- The genetic defect is in glycoprotein 1b (GP1b).
- characterized by increased megakaryocytes and abnormally large platelets on peripheral smear, hence its name.
- **thrombocytopenia and an elevated bleeding time but a normal prothrombin time (PT) and partial thromboplastin time (PTT).**
- BSS can be distinguished from a deficiency in von Willebrand factor (vWF) by a **ristocetin test**.
  - Ristocetin is an antibiotic that causes vWF to bind to GP1b, causing agglutination in normal blood.
  - In patients with either defective vWF or GP1b (BSS), platelets do not aggregate in the presence of ristocetin.
  - The addition of normal plasma corrects this defect in von Willebrand's disease, but not in BSS (because the platelet receptor remains defective).

Bone marrow sampling

- There are two types of sample that are typically taken: an aspirate and a trephine biopsy. The aspirate just looks at the cells whereas a trephine biopsy shows the structure of the bone marrow.
- It is typically performed to investigate the possiblity of bone marrow involvement in leukaemia, lymphoma and myeloma.

Assessment of anaemia



From BMJ best practice

Iron metabolism

Absorption:

- **Upper small intestine.**
- About 10% of dietary iron absorbed.
- Fe2+ (ferrous iron) much better absorbed than Fe3+ (ferric iron).
- Absorption is regulated according to body's need.
- **Increased by vitamin C (ascorbic acid)** and gastric acid.

- **vitamin C aids iron absorption** by reducing iron from the ferric to the ferrous form, and by chelating it into a complex which enhances absorption.

- Decreased by PPIs, tetracycline, gastric achlorhydia, tannin (in tea).
- From an intake of approximately 6 mg/1000 kcal of dietary iron **only 15% is bioavailable.**

Oral iron absorption.

A. Effectors of iron absorption.	
Inhibiting iron absorption	**Facilitating iron absorption**
• **Coffee, tea, milk, cereals, dietary fiber, phosphate-containing carbonated beverages** • **Multivitamin or dietary supplements containing calcium, zinc, manganese or copper** • **Antacids, H2 blockers and proton pump inhibitors.** • **Quinolones and tetracycline antibiotics**	• **Vitamin C** • **Acidic foods e.g. tomato sauce** • **Non enteric coated iron tablets** • **Fasting ingestion of iron supplements**
B. Oral iron absorption test.	
Step 1: Measure morning serum iron level (fasting).	
Step 2: Ingest approximately 60mg elemental iron (324 mg ferrous sulphate) with water.	
Step 3: After 1-2 hours, measure the serum iron level.	
Step 4: Compare the serum iron levels.	
Interpretation: An increase in serum iron of >100 µg/dL suggests gut absorption is generally adequate.	

Distribution in body

- Total body iron = 4g (2500 mg in the RBCs, 500 mg in liver, 500 mg in macrophages and about 500 mg in muscle).
- **Haemoglobin = 70%**
- Ferritin and hemosiderin = 25%
- Myoglobin = 4%
- Plasma iron = 0.1%
  - Approximately 4 mg of iron circulate within the plasma. So approximately 0.1% of body iron circulates in the plasma.

Transport

- Carried in plasma as Fe3+ bound to transferrin.

Storage

- Stored as ferritin in tissues.
  - It is the plasma protein responsible for binding iron,
  - is an acute phase reactant protein which is increased in inflammatory conditions.

Excretion

- The majority of iron contained within the RBCs is metabolised and re-utilised but 1 mg per day is lost through the gut.

Transferrin

- serum transferrin is the bus that carry absorbed iron to storage places & stored as ferritin.
- transferrin saturation is the % of people [iron] carried by that bus [transferrin].
- TIBC is the no. of empty chairs in that bus.

- Transferrin is a glycoprotein responsible for internal iron exchange
  - **Iron (Fe 3+)** is carried in the blood bound to **transferrin**.
  - **Fe2+ (ferrous iron) is oxidised to Fe3+ (ferric iron) by caeruloplasmin to bind to transferrin**
- Transferrin is the binding protein of iron. So when the levels of ferritin are low, the body signals the liver to synthesize more of Transferrin to maintain the levels of iron
- **Pregnancy and oral contraceptive pill (OCP) both increase transferrin.**
- **Transferrin saturation %**

  - The transferrin saturation % (plasma iron /TIBC x 100) is used as a measure of iron stores.
  - In absence of anaemia, transferrin is about 33% saturated with iron (about one third saturated with iron).
  - A value below 16% is indicative of iron deficiency.
- iron deficiency → low serum Fe, rise TIBC, rise the transferrin level.
- iron overload → fall in both TIBC and transferrin
- haemochromatosis → increased in Transferrin saturation%
  - the content within mucosal cells is naturally high in haemochromatosis with high iron store saturation.
  - in haemochromatosis TIBC is low because transferrin is FULL of iron and no more empty space, hence LOW TIBC and for the same reason transferrin saturation is high [FULL]

Iron studies

- **Serum iron**
- **Total iron binding capacity (TIBC)**
- **Transferrin**
  - raised in iron deficiency anaemia (IDA)
  - raised in pregnancy and by oestrogen
- **Transferrin saturation**
  - calculated by serum iron / TIBC
- **Ferritin**
  - raised in inflammatory disorders
  - low in IDA
- **Rarer tests**
  - transferrin receptors → increased in IDA
- **Anaemia of chronic disease**
  - normochromic/hypochromic, normocytic anaemia
  - reduced serum and TIBC
  - normal or raised ferritin

Iron deficiency anaemia (IDA)

- iron deficiency is the most common cause of anemia worldwide.

Causes

- the commonest cause of iron-deficiency anaemia worldwide being hookworm infection (***Necator americanus*** and *Ancylostoma duodenale*), which affects 25% of the global population.
- microcytic anaemia in a female should raise the possibility of either gastrointestinal blood loss or menorrhagia.

Features

- Koilonychia (spoon-shaped nails)
- atrophic glossitis
- post-cricoid webs
  - Plummer-Vinson syndrome (dysphagia, esophageal webs and iron deficiency)
- other cutaneous manifestations of iron deficiency include:
  - pruritus,
  - dry and brittle hair
    - the hair, skin, nail and mucous membrane changes are often visible before the patient is clinically anemic.
- angular stomatitis

Investigations

- **Blood film**
  - target cells
  - 'pencil' poikilocytes
  - if combined with B12/folate deficiency a 'dimorphic' film occurs with mixed microcytic and macrocytic cells
- Serum ferritin
  - Hypoferritinaemia confirms IDA and is **the preferred screening test**.
  - **the most sensitive marker for iron deficiency**

- Ferritin is an acute phase reactant and may be grossly elevated in the context of acute inflammation (when it does not accurately reflect iron stores) and to a lesser degree in chronic inflammation.
  - British Society Guidelines on the diagnosis and management or iron deficiency anaemia suggest that:
    - a cut-off of 12-15 mg/L reflects iron deficiency in the absence of inflammation.
    - Where inflammation is present a ferritin of 50 mg/L or more may still be compatible with iron deficiency.

Treatment of IDA

Iron tablet preparations

- Among the tablet preparations, there are:
  1. non-enteric coated pills
     - most commonly used as initial treatment due to their lower cost.
  2. enteric-coated
  3. prolonged-release formulations.
     - Delayed release and enteric-coated iron are better tolerated than the non-enteric coated tablets.
     - less effective since they may contain less iron and their iron may not be released in the duodenum, where iron is absorbed.
     - patients who have been treated unsuccessfully with enteric-coated and prolonged-release iron preparations may respond well to the administration of nonenteric-coated ferrous salts
- **Ferrous sulphate** has more elemental iron by mass than the same dose of ferrous gluconate
- **Sustained release preparations** may improve tolerance of oral iron but do not aid absorption.

Iron prescription

- Ideally, patients should not take iron supplements within 1-2 hours of **antacids** → alkaline environment reduces absorption (acidity required for iron solubility)
- Iron tablets are recommended **between meals or at bedtime** to avoid the alkalinizing effect of food and to take advantage of the peak gastric acid production late at night.
- calcium, phosphorus and magnesium salts contained in iron-containing multivitamin pills impair absorption of elemental iron. For this reason, **multivitamin preparations should never be recommended as a sole therapy for iron deficient anemia.**
- Iron absorption is also delayed with tetracyclines, milk, and phosphate-containing, carbonated beverages such as soft drinks.
- **Iron replacement in chronic renal failure**
  - In chronic renal failure, Erythropoeitin (EPO) therapy is only considered in pateints where the ferritin is >l00 mg/1.
  - If ferritin < 100 → iron replacement is the initial intervention of choice.

- **IV iron**
  - Parenteral iron acts no faster than oral iron. It is indicated when oral iron cannot be tolerated or is not absorbed.
  - **Indications for IV iron include:**
    - unable to tolerate orally,
    - Patients who fail to comply with prescriptions for oral iron supplementation.
    - **A history of exertional angina with anaemia → strongest indication for transfusion**
    - GIT disorders, such as IBD (ulcerative colitis and Crohn's disease), in which symptoms may be aggravated by oral iron therapy
    - **Iron is poorly absorbed from the GI tract in patients with renal failure, as such IV replacement is the modality of choice.**
  - It is considered best practice to administer 1000 mg of low molecular weight iron dextran in 250 mL of normal saline in 1 hour without premedication;
  - a test dose of 10 to 25 mg is infused over 3 to 5 minutes prior to the first infusion.
  - If no acute reaction is observed, the remaining solution is infused over the balance of 1 hour.
  - For those with a history of drug allergies or hypersensitivity, 125 mg of methylprednisolone is infused prior to the test dose.

British society of gastroenterology (BSG) guidelines 2011:

- correct anaemia and replenish body stores achieved most simply and cheaply with ferrous sulphate 200 mg twice daily.
- Lower doses may be as effective and better tolerated and should be considered in patients not tolerating traditional doses.
- Other iron compounds (eg, ferrous fumarate, ferrous gluconate) or formulations (iron suspensions) may also be tolerated better than ferrous sulphate.
- Oral iron should be continued for 3 months after the iron deficiency has been corrected so that stores are replenished.
- Ascorbic acid (250e500 mg twice daily with the iron preparation) may enhance iron absorption
- Iron treatment should follow transfusion to replenish stores.

Anemia of Chronic Disease

Definition

- decreased RBC production due to any longstanding inflammatory, infectious, or malignant disease (includes rheumatoid arthritis, severe trauma, heart disease, diabetes mellitus, and inflammatory bowel disease)

Mechanism of Anemia of Chronic Disease

- there is primarily a decreased availability of iron, relatively decreased levels of erythropoietin, and a mild decrease in the lifespan of RBCs to 70-80 days (normally 120 days)
  - in anemia of chronic kidney disease, ↓erythropoietin production by the interstitial fibroblasts, (also known as type I interstitial cells), → anemia.
    - The kidneys are responsible for approximately 90% of erythropoietin production.
- Increase in **hepcidin** level in the course of inflammatory disease →↓release of iron from macrophages +↓dietary iron absorption.
  - hepcidin is an acute-phase reactant that is increased in states of inflammation
- cytokines, such as interleukins (IL-1 and IL-6), and tumor necrosis factor (TNF-alpha), → destruction of RBC precursors and decrease the number of erythropoietin receptors on progenitor cells.

Investigations

- RBCs morphology
  - normochromic, normocytic anemia.
- Reticulocyte count
  - ↓reticulocyte count points to ↓RBC production as the primary mechanism responsible for anemia,
- ↑ ferritin
- ↓ serum iron
- ↓ TIBC, transferrin saturation, and MCV

Treatment

- treatment of the underlying disease.
- If underlying disease is unknown or treatment of underlying disease does not improve symptomatic anemia
  - measure EPO
    - if low, administer EPO or erythropoiesis-stimulating agents (ESAs)
      - make sure iron stores are sufficient
      - if insufficient, patients may be resistant to EPO
  - if normal, give packed RBCs

Hepcidin

- Hepcidin, a peptide hormone synthesized in the liver.
- reduces extracellular iron in the body by several mechanisms:
  1. lowers dietary iron absorption by reducing iron transport across gut mucosal cells (enterocytes);
  2. reduces iron exit from macrophages, the main site of iron storage;
  3. reduces iron exit from the liver. In all three instances this is accomplished by reducing the transmembrane iron transporter ferroportin.
- inflammation →↑hepcidin → ↓serum iron due to:
  - iron trapping within macrophages and liver cells

- decreased gut iron absorption.
- inadequate amount of serum iron being available for developing red cells →anemia

- hemochromatosis →↓hepcidin level → iron overload due to:
  - increased **ferroportin** mediated iron efflux from storage and increased gut iron absorption.
- Hepcidin inhibits iron transport by binding to the iron export channel **ferroportin** which is located on the basolateral surface of gut enterocytes and the plasma membrane of macrophages.
  - Inhibiting ferroportin leads to:
    - ↓ iron release from macrophages
    - ↓ dietary iron absorption.

Thalassaemias

Alpha is located on **16**, beta on **11**chromosome .

- The thalassaemias are a group of genetic disorders characterised by a reduced production rate of either alpha or beta chains.
- It is a haemoglobinopathy resulting from defective synthesis of globin chains required for Hb synthesis.
- Each copy of **chromosome 16** has two genes for the **alpha globin** subunit (**four in total**).
- And each copy of **chromosome 11** has one genes for the **beta globin** subunit (**two in total**).

Types of haemoglobin

Haemoglobin	Chains	% Hb in normal adult
Hb A	$\alpha_2\beta_2$ ((two alpha and two beta chains)	97%
Hb A_2	$\alpha_2\delta_2$ (two alpha and two delta chains)	< 3.5%
Hb F	$\alpha_2\gamma_2$ (two alpha and two gamma chains)	<1%

Alpha-thalassaemia

- Alpha-thalassaemia is due to a deficiency of alpha chains in haemoglobin
- Alpha-thalassaemia is found in malarial regions of the world (Mediterranean, South-east Asia, Indian sub-continent, Middle East, Sub-Saharan Africa) and should be suspected in patients with these ethnic backgrounds and with microcytosis and/or anaemia.
- Acquired Hb H disease is rare and occurs most commonly in male patients with myelodysplastic syndrome.

Overview

- 2 separate alpha-globulin genes (four in total) are located on each **chromosome 16**
- There are 4 different alpha-thalassaemias:
  1. **silent carrier** (1 affected alpha-globin gene),
  2. **alpha-thalassaemia trait** (2 affected alpha-globin genes),
  3. **Hb H disease** (typically 3 affected alpha-globin genes)
  4. **Hb Bart hydrops fetalis syndrome** (typically deletion of all 4 alpha-globin genes).
- Clinical severity depends on the number of alpha chains present
  - **If 1 or 2 alpha chains are absent** then the blood picture would be **hypochromic** and **microcytic**, **but the Hb level would be typically normal**
  - **Loss of 3 alpha chains results in a hypochromic microcytic anaemia with splenomegaly and HbH in red cells. This is known as Hb H disease**
  - If all 4 alpha chains absent (i.e. homozygote) then death in utero (hydrops fetalis, Bart's hydrops)
- **Persistence of HbF has survival advantages in severely affected subjects.**
- Co-inheritance of alpha-gene mutations, and persistence of fetal haemoglobin production, may restore the globin balance and result in a milder syndrome.
- **Features**
  - most are asymptomatic.
  - Many patients with Hb H are also clinically well, but are at risk for:
    - acute haemolytic episodes
    - aplastic crises
    - iron overload, even in the absence of chronic transfusions
    - hypersplenism; and
    - endocrine disease.

- Hemoglobin gel-electrophoresis
  - α-thalassemia trait → normal
  - 3 gene deletion α-thalassemia → HbH (β,β,β,β)
  - 4 gene deletion α-thalassemia → Hb Barts (γ,γ,γ,γ)

Beta-thalassaemia

Disproportionate microcytic anaemia - think beta-thalassaemia trait

If a person has **MCV > 80** and **MCH > 27**, in the **absence of symptoms**, **thalassemia can be reasonably excluded.**

- Beta-thalassaemias are due to mutations in the HbB gene on chromosome 11
- **autosomal recessive**
- **β thalassaemia minor / trait** → protects against malaria
  - ↑(Hb F) → inhibits the development of the malarial parasite.

Types

- **β thalassaemia major** (**β 0**):
  - prevent any formation of β chains,
  - the most severe form of β thalassemia.
  - 2 gene depletion (β0β0) (α,α,α,α hemoglobin present)
  - HbF tries to convert to HbA during first year of life,
  - extramedullary haemopoiesis with hepatosplenomegaly and bone marrow expansion, "hair on end" appearance of bone.
  - **Features**
    - anaemia
    - splenomegaly
      - occurs secondary to extramedullary hematopoiesis.
    - bone deformities
      - bone marrow expansion can cause "chipmunk facies" or "crew cut sign" on a skull X-ray.
    - early death if not treated appropriately.
  - **Treatment**:
    - *The recommended treatment for thalassaemia major involves lifelong regular blood transfusions, usually administered **every two to five weeks**, to maintain the pretransfusion haemoglobin level **above 9–10.5 g/dl**.*
    - transfusion programme with iron chelation is the best initial approach.
    - Indications for transfusion
      - Hb < 7g/dl on 2 occasions, > 2 weeks apart (excluding all other contributory causes such as infections) **or**
      - Hb > 7g/dl **with**: Facial changes, Poor growth, Fractures, and Extramedullary haematopoiesis
    - The transfusional iron overload can be managed with iron chelation, both IV/SC (desferrioxamine) and/or oral (deferasirox).
      - Desferrioxamine binds iron but needs to be given for 8-12 hours a day for 5-7 days per week, so is a major undertaking for the patient.
      - SE: high frequency deafness, retinopathy and Yersinia infection.
    - Stem cell transplantation options offer cure.
    - **parents and other siblings should be screened by genetic testing.**

- **β thalassaemia intermedia** (**β+**):
  - caused by a mutation in the Kozak consensus sequence of the Beta globin gene on chromosome 11.
  - they allow some β chain formation to occur.
  - In either case there is relative excess of α chains, but these don't form tetramers.
- **β thalassaemia minor / trait:**
  - 1 gene deletion
  - **Features**
    - usually asymptomatic

- **mild hypochromic, microcytic anaemia** - **microcytosis is characteristically disproportionate to the anaemia** (marked microcytosis (very low MCV) (i.e. the Microcytosis is disproportionately with very low MCV for the near normal Hb level >9).
- HbA2 raised (> 3.5%)
  - **HbA2 levels above 3.5% are screening criteria for the β-thalassemia carrier state.**
  - **Note that in cases of severe iron deficiency anaemia the HbA2 may be normal in thalassemia minor.**

- Thalassemia can co-exist with other haemoglobinopathies. The most common of these are:
  - **HbE/thalassaemia:**
    - common in Cambodia, Thailand, and parts of India
    - clinically similar to β thalassaemia major or thalassaemia intermedia.
  - **HbS/thalassaemia:**
    - common in African and Mediterranean populations
    - clinically similar to sickle cell anaemia with additional feature of splenomegaly.
  - **HbC/thalassaemia:** common in African and Mediterranean populations:
    - **HbC/β0 thalassaemia:** causes moderate to severe haemolytic anaemia with splenomegaly.
    - **HbC/β+ thalassaemia:** produce a milder disease.

Delta thalassaemia

- about 3% of adult Hb is made of alpha and delta chains.
- mutations can occur which affect the ability of this gene to produce delta chains.

Aplastic anaemia

- Characterised by pancytopaenia and a hypoplastic bone marrow
- Peak incidence of acquired = 30 years old

Features

- Assessment of bone marrow cellularity is best made on **trephine biopsy**, which often shows replacement of the normal cellular marrow by **fatty marrow.**
- normochromic, normocytic anaemia
- leukopenia, with lymphocytes relatively spared
- thrombocytopenia
- may be the presenting feature acute lymphoblastic or myeloid leukaemia
- a minority of patients later develop paroxysmal nocturnal haemoglobinuria or myelodysplasia
- In patients with aplastic anemia, the bone marrow is markedly **hypocellular**.

Causes

- idiopathic
- congenital: Fanconi anaemia, dyskeratosis congenita
- drugs: cytotoxics, chloramphenicol, sulphonamides, phenytoin, gold
- toxins: **benzene**
- infections: parvovirus, hepatitis
- radiation

management

Supportive

- blood products
- prevention and treatment of infection

Anti-thymocyte globulin (ATG) and anti-lymphocyte globulin (ALG)

- prepared in animals (e.g. rabbits or horses) by injecting human lymphocytes
- is highly allergenic and may cause serum sickness (fever, rash, arthralgia), therefore steroid cover usually given
- immunosuppression using agents such as ciclosporin may also be given

Stem cell transplantation

- allogeneic transplants have a success rate of up to 80%

Pure Red Cell Aplasia (PRCA)

Overview

- uncommon disorder
- maturation arrest occurs in the formation of erythrocytes. Erythroblasts are virtually absent in bone marrow; however, white blood cell and platelet production are normal.
- The anemia due to PRCA is usually normocytic but can be macrocytic.

Diagnosis

- characteristics of PRCA include
  1. Severe unexplained anemia
  2. ↓Reticulocyte count <1%
  3. The presence of less than 0.5% mature erythroblasts in the bone marrow
  4. Normocellular bone marrow in most cases

Causes

- most cases of chronic PRCA are idiopathic (acquired primary).
- Secondary PRCA associated with:
  - Autoimmune disorders (eg, type 1 diabetes, thyroiditis, rheumatoid arthritis, Sjögren syndrome)
  - Thymomas
  - Systemic lupus erythematosus
  - Hematologic malignancies
  - Solid tumors
  - **Erythropoietin-induced pure red cell aplasia in treatment of CKD anaemia**

Treatment

- can be transient and reversible (PRCA due to medications and infections are often reversible.)
- symptomatic anaemia → transfusion
- Treatment of underlying conditions
  - parvovirus B19 infections → High-dose intravenous immunoglobin
  - PRCA due to drugs → disappear when the drug is stopped.
  - thymoma → thymectomy or gamma irradiation of the thymus
- Immunosuppressive:
  - Corticosteroids are the mainstay of therapy (45% respond)→ the first choice
  - cyclosporine, azathioprine, Cyclophosphamide and rituximab are used

Fanconi's Anaemia

- Autosomal recessive
- Aplastic anaemia
- ↑ risk of AML
- Neurological manifestation
- Skeletal abnormalities
- Skin pigmentation (café; au lait spots)

Macrocytic anaemia

Macrocytic anaemia can be divided into causes associated with a megaloblastic bone marrow and those with a normoblastic bone marrow

Megaloblastic causes	Non-megaloblastic causes
• vitamin B12 deficiency • folate deficiency	• alcohol • liver disease • hypothyroidism • pregnancy • reticulocytosis • myelodysplasia • drugs: cytotoxics

- If serum folate levels are low, serum vitamin B12 and methylmalonic acid levels should be measured to exclude concurrent vitamin B12 deficiency before folate levels are corrected.
- Normal serum homocysteine levels make folate deficiency unlikely.
- RBC folate is a more accurate indicator of folate deficiency than serum folate level.

Vitamin B12 (cobalamin) deficiency

Function of vitamin B12 deficiency

- Red blood cell development
- Maintenance of the nervous system.
- B12 is necessary for normal folate metabolism, and therefore when there is a primary B12 deficiency, one can see a low red cell folate as a consequence.

Sources

- Vit B12 is only found in foods of animal origin e.g. meat, fish and eggs.

Metabolism

- It is absorbed after binding to intrinsic factor (IF) (secreted from parietal cells in the stomach) and is actively absorbed in the **terminal ileum.**
- A small amount of Vit. B12 is passively absorbed without being bound to IF.
- **Hepatic stores of vitamin B12 can last for up to 5 years**, so it is not uncommon for vegans to display vitamin B12 deficiency years after starting their diet

Causes

- Dietary deficiency of Vit B12: like vegetarians
  - An MCV of >115 fL is typically seen in nutritional deficiency.
  - very rare
    - Folate deficiency due to dietary problems is common, particularly in the elderly, but **it does take many years to become B12 deficient** as a result of dietary deficiency.
- Pernicious anaemia
- Post gastrectomy
  - **A patient with combined iron deficiency and B_{12} deficiency, Which operation is he most likely to have had?→ Partial gastrectomy**
- Disorders of terminal ileum (site of absorption): Crohn's, blind-loop, Malabsorption of vitamin B-12 secondary to small bowel bacterial overgrowth, tapeworm, etc.
- **Bacterial overgrowth syndrome**
  - characterized by diarrhea, steatorrhea, and macrocytic anemia.
  - The common feature is proliferation of colonic bacteria in the small bowel. In normal individuals, the small bowel is relatively sterile.
  - Common bacteria involved are E.coli or bacteroides.
  - Macrocytic anemia results from increased utilization of vitamin B12 by the colonized bacteria.
  - Steatorrhea is caused by reduced concentration of conjugated bile acids. Bacteroides can convert conjugated bile acids to unconjugated bile acids, which result in impaired micelle formation.
  - Diarrhea is due to steatorrhea.

Features of vitamin B12 deficiency

- Macrocytic anaemia
- **mild jaundice** is typical of megaloblastic anaemia (vitamin B_{12} or folate deficiency) because of increased destruction of red cell precursors in the bone marrow.
- Sore tongue and mouth
- Neuropsychiatric symptoms: e.g. Ataxia, Mood disturbances
  - Neurological involvement can be present in B12 deficiency even in the absence of anaemia, especially in patients over the age of 60.
  - The peripheral nerves are most commonly involved, followed by subacute degeneration of the spinal cord.
  - **Early signs are loss of peripheral vibration and joint position sense**, which is usually followed by loss of reflexes and weakness.
  - The legs and feet are usually more involved than the hands.
  - In the late stages there may be spasticity, upgoing plantars and ataxia but thankfully this is rare in the UK.
- Serum **methylmalonic acid** levels are **elevated** in vitamin B12 deficiency.
  - more sensitive Serum vitamin B12 levels, and should be used to definitively exclude vitamin B12 deficiency.
  - elevated **homocysteine** and **methylmalonic** acid levels.
- Blood smear will show hypersegmented neutrophils.

Treatment

- **even in case of profound anaemia, if the patient is not haemodynamically compromised → no need for blood transfusion.**

- **intramuscular vitamin B_{12} and oral folic acid.**
- Patient need to continue on treatment with ferrous sulphate as iron stores are likely to be depleted rapidly once the marrow starts functioning.
- Giving oral folic acid without vitamin B_{12} would be hazardous and could precipitate subacute combined degeneration of the spinal cord.

Pernicious anaemia

Epidemiology

- more common in females (F:M = 1.6:1)
- typically develops in middle to old age
- more common if blood group A

Pathophysiology

- autoimmune disease caused by antibodies to gastric parietal cells or intrinsic factor
- results in vitamin B12 deficiency
- associated with thyroid disease,
  - diabetes
  - Addison's
  - rheumatoid
  - vitiligo
- predisposes to gastric carcinoma

Features

- lethargy, weakness
- dyspnoea
- paraesthesia
- mild jaundice
- diarrhoea
- sore tongue
- possible signs:
  - retinal haemorrhages,
  - mild splenomegaly,
  - retrobulbar neuritis

Investigation

Normal serum gastrin excludes pernicious anaemia

- anti-gastric parietal cell antibodies in 90% (**most common**, but low specificity)
- anti-intrinsic factor antibodies in 50% (**specific** for pernicious anaemia)
- macrocytic anaemia
- **pancytopenia** (with low WCC and platelets)
- LDH may be raised due to ineffective erythropoiesis
- also low serum B12,
- hypersegmented polymorphs on film, megaloblasts in marrow
- **Schilling test**
  - radiolabelled B12 given on two occasions
    - first on its own
    - second with oral IF
  - urine B12 levels measured

macrocytic anaemia and isolated B12 deficiency (folate is normal) suggest an isolated problem with B12 absorption → pernicious anaemia

Management

- If no neurological involvement: **1 mg of IM Hydroxocobalamin 3 times each week for 2 weeks, then once every 3 months.**
- If a patient has deficient in both vitamin B12 and folic acid then it is important to **treat the B12 deficiency first** to avoid precipitating subacute combined degeneration (SCD) of the cord.

Sickle cell disease

Overview

- autosomal recessive
- Sickle cell disease is a haemoglobinopathy **caused by** the **substitution of glutamic acid by valine at position 6** (from the N-terminal) of the beta chain. (In sickle cell anaemia, valine replaces glutamic acid at the sixth amino acid of the beta globin)
- **HbS is caused by a single base mutation on the beta-chain**
- The β globin gene is found on the short arm of chromosome 11.

HbS has the following properties:

- contains two α-like globins and two β-like globins and four haem molecules.
- less negatively charged, due to the loss of glutamate for valine.
- has a life span of only 30 days compared to the normal 120 days.
- less soluble than HbA.
- has lower affinity for oxygen than HbA (right-shift of the oxygendissociation curve), which increases the risk of desaturation, but improves the yield of oxygen to the tissues.

Types

- Sickle cell trait: heterozygous (HbAS)
  - occurs when a child inherits a sickle gene from one parent and a normal gene from the other parent.
- Sickle cell disease: homozygous (HbSS)
  - occurs when a child inherits a sickle gene from each parent.
- Other, rarer forms of sickle cell disease in which the person has only one copy of the mutation that causes Hb S and one copy of another abnormal Hb allele. Examples:
  - "HbSC": (sickle –haemoglobin C disease).
  - "HbS/β+": (sickle-beta-plus-thalassemia).
  - "HbS/β0" : (sickle-beta-zero-thalassemia)

Sickling of the erythrocyte

- A low partial pressure of oxygen (PO_2) causes HbS to polymerise and precipitate resulting in sickling of the erythrocyte.
  - **HbSS patients sickle at PO_2 of 5-6 kPa**
  - **HbAS patients sickle at PO_2 of 2.5-4 kPa.**
  - **HbSC Sickling occurs at around 4 kPa.**

Sickle cell disease and malaria

- Sickle cell trait (HbAS) is known to protect against falciparum malaria. As a result, the frequencies of sickle cell carriers are high in malaria-endemic areas.
- Patients with HbSS are at higher risk of severe malaria with complications and have a higher mortality rate.

Feature

- **Black pigment gallstones occur in 50 % of patients with sickle cell disease**
  - due to an increase in bilirubin excretion.
  - Their small size allows migration into the common bile duct causing low-grade obstruction.
  - Typically leading to hyperbilirubinaemia rather than bile duct dilatation.
  - cholecystectomy is suggested for patients with sickle cell disease if abdominal surgery is being performed for other reasons.
  - Due to decreased life span of the erythrocyte, average 17 days (normal 120 days), there is also a chronic circulating unconjugated hyperbilirubinaemia.

- **There is often an inability to concentrate urine**
  - The inner medulla is hypoxic, hypertonic and acidotic and therefore predisposes to sickling of red blood cells, which results in vasoocclusion and reduction in renal medullary blood flow.
  - proximal tubule dysfunction → impairs urinary concentration
  - distal tubular dysfunction → impairs potassium excretion.
- Functional hyposplenism in SCD also renders sufferers susceptible to infection with encapsulated bacteria (pneumococci, meningococci).
  - Patients with sickle cell disease have a predisposition to develop osteomyelitis due to Salmonella species.

Sickle-cell crises: Four main types of crises are recognised:

- **thrombotic crises**, also known as painful crises or vaso-occlusive crises
  - precipitated by infection, dehydration, deoxygenation ,acidosis , cold temperatures, extreme exercise and stress.
  - infarcts occur in various organs including the bones (e.g. avascular necrosis of hip, hand-foot syndrome in children, lungs, spleen and brain
- **sequestration crises**
  - sickling within organs such as the spleen or lungs causes pooling of blood with worsening of the anaemia
  - acute chest syndrome: dyspnoea, chest pain, pulmonary infiltrates, low pO2 - the most common cause of death after childhood
  - stroke
    - 5-10% of sickle cell patients will suffer a stroke, usually during childhood.
    - The risk can be predicted by transcranial Doppler measurement of middle cerebral artery (MCA) flow rate,
    - prompt institution of a prophylactic transfusion program to reduce the HbS % can prevent further strokes.
    - treatment once occurred → **Exchange transfusion programme**
- **aplastic crises**
  - caused by infection with parvovirus
  - sudden fall in haemoglobin without an appropriate ↑ reticulocytosis.
  - The condition is self-limited, with bone marrow recovery occurring in 7-10 days, followed by brisk reticulocytosis.
- **haemolytic crises**
  - rare
  - fall in haemoglobin due an increased rate of haemolysis
  - The anaemia associated with sickle cell disease is usually only symptomatic below 70 g/L, as oxygen is released more readily from erythrocytes.
  - (remember, patients with sickle cell tend to run with a Hb between 70-90 g/L normally)
  - The anemia of SC is usually a chronic, reasonably well-compensated hemolytic anemia with an appropriate reticulocytosis. For example, the mean hemoglobin and hematocrit concentrations on average may be 79 g/L and 22.9% respectively, with a **reticulocyte count of between 3-15%.**

Diagnosis of sickle cell disease requires the detection of HbS.

- **Sickledex test**: addition of reagent to blood → turbidity confirming the presence of HbS, but it gives no information on other haemoglobins.
- **Haemoglobin electrophoresis** is the only investigation that determines the nature of the haemoglobinopathy

Treatment

- General management
  - analgesia e.g. opiates
  - rehydrate

- oxygen
- consider antibiotics if evidence of infection
- blood transfusion
- exchange transfusion: e.g. if neurological complications

- Avoid
  - iron therapy: There is a tendency to iron overload and therefore iron therapy is not usually indicated.
  - Intra-articular steroids have been associated with a sickle cell crisis, the mechanism of which is not fully understood, but they should be avoided.
- **pharmaceutical interventions to prevent sickle cell crisis and other acute complications**
  - Hydroxyurea
    - acts by **inhibiting ribonucleotide reductase**, which inhibits both purine and pyrimidine synthesis.
    - Action: ↑fetal haemoglobin (Hb F) which protects against sickling.
    - reduces the incidence of acute chest syndrome and the need for blood transfusion
    - The major side effect is severe myelosuppression.
  - Malaria chemoprophylaxis in endemic area

- **Acute chest syndrome**
  - defines as 'an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on chest X-ray'.
  - management:
    - Oxygen therapy to maintain saturations > 95%
    - Intravenous fluids to ensure euvolaemia
    - Adequate pain relief
    - Incentive spirometry in all patients presenting with rib or chest pain
    - Antibiotics with cover for atypical organisms
    - Early consultation with the critical care team and haematology
    - Blood transfusion:
      - A senior haematologist will make a decision as to whether a simple or exchange transfusion is necessary.
      - guidelines suggest Hb target of 100-110g/L in either instance.
- All adults who have hyposplenism, including patients with SCD, need:
  - Yearly influenza vaccine.
  - Pneumococcal C vaccine, (adults and children over 2 years) repeated every five years.
  - Haemophilus influenzae type b; if not already given as part of childhood immunisation.
  - Conjugated meningococcal C vaccine; if not already given as part of childhood immunisation.
  - Meningococcal ACWY vaccine; if travelling to areas with high risk of meningitis.
- Patients with sickle cell disease are prone to infections within **encapsulated organisms** because of their asplenic state.
  - These include:
    - *Streptococcus pneumoniae*,
    - *Haemophilus influenzae* and
    - *Neisseria meningitidis*.
  - To combat these infections, patients with homozygous sickle cell disease should be on **lifelong penicillin** and be **vaccinated against these organisms**.

***Salmonella* osteomyelitis is seen in patients with sickle cell anaemia**

screening for sickle cell disease in a pregnant women:

- She will first be screened for sickle cell carrier status.
- If that test is positive, her partner will be screened,
- If both are found to be carriers this is confirmed by genetic testing before offering chorionic villus sampling (CVS) (8-10 weeks) or amniocentesis (14-16 weeks).

Priapism

- Priapism is most often due to idiopathic thrombosis of the prostatic venous plexus.
- Other causes include:
  - leukaemia,
  - **sickle-cell anaemia** and
  - carcinomatosis.
- Priapism occurs fairly frequently which may lead to permanent impotence if it is not relieved.

Sideroblastic anaemia

- Sideroblastic anaemia is a condition where red cells fail to completely form haem, whose biosynthesis takes place partly in the mitochondrion. This leads to **deposits of iron in the mitochondria** that form a ring around the nucleus called a ring sideroblast.

Causes: It may be congenital or acquired

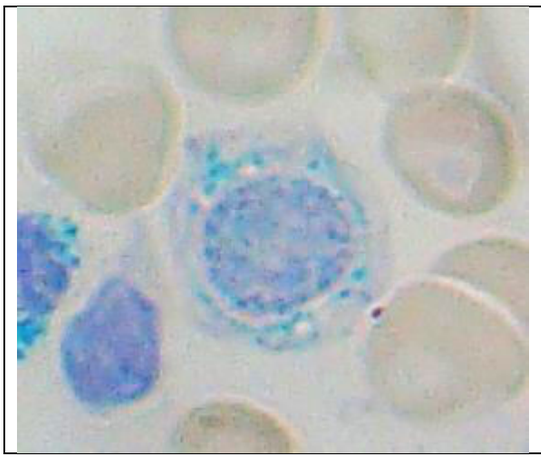
- Congenital cause: delta-aminolevulinate synthase-2 deficiency
  - The enzyme delta aminolevulinic acid (ALA) is essential in the biosynthesis of heme.
    - Delta ALA requires pyridoxine (vitamin B6) and copper as cofactors.
  - Hereditary sideroblastic anemia follows a **X-linked** genetic inheritance pattern.
- **Acquired causes**
  - myelodysplasia (seen in older age groups)
  - alcohol
    - the most common reversible cause
  - lead
  - drugs: anti-TB medications, chloramphenicol.
    - Pyridoxine (vitamin B6) deficiency, caused by isoniazid and oral contraceptives, is a reversible cause of sideroblastic anemia.

Investigations

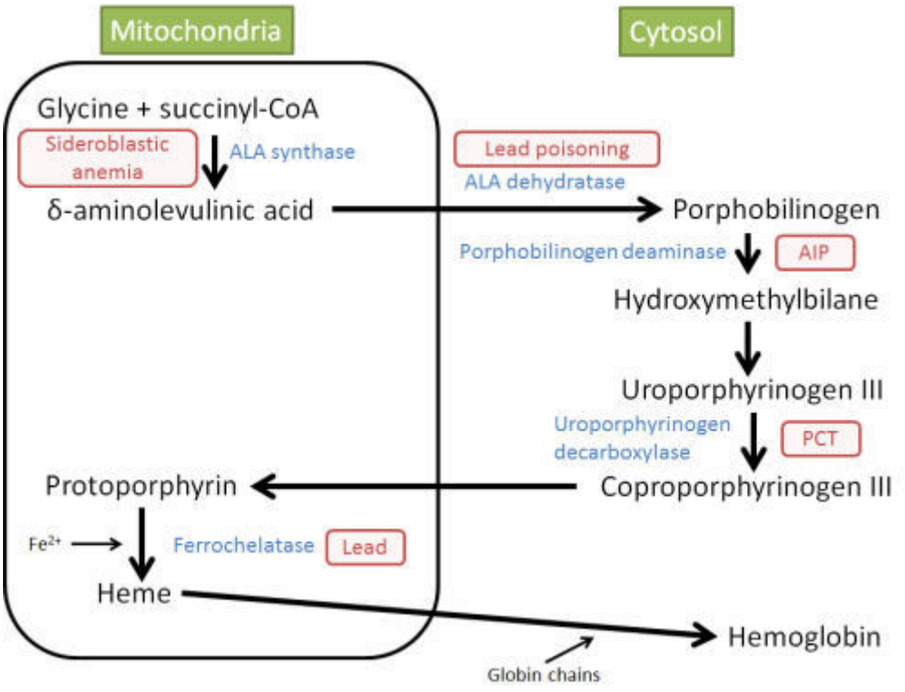
- hypochromic microcytic anaemia (more so in congenital)
- Basophilic stippling:
  - visualization of ribosomes on the surface of red blood cells
  - can be seen on a peripheral blood smear of patients with sideroblastic anemia.
- Ferritin levels are increased
- bone marrow:
  - sideroblasts and increased iron stores
  - Sideroblasts are red cell precursors with iron-laden mitochondria and are detected via **Prussian blue** staining.
  - Ringed sideroblasts are **pathognomonic** for sideroblastic anemia.

Management

- supportive
- treat any underlying cause
  - removal of toxic agents such as zinc and lead, and drugs such as penicillamine and isoniazid.
- **pyridoxine** may help



The figure illustrates sideroblasts, which are nucleated (immature) erythrocytes with granules of iron in their cytoplasm.



Haemolytic anaemias: by site

The combination of anaemia and jaundice should always suggest haemolytic anaemia until proved otherwise

- In intravascular haemolysis free haemoglobin is released which binds to haptoglobin.
  - The benefit of this process (**Haptoglobin binds with free plasma hemoglobin**):
    - permits degradative enzymes access to the hemoglobin,
    - preventing the loss of iron via the kidneys,
    - shielding the kidneys from damage by hemoglobin.
- As haptoglobin becomes saturated haemoglobin binds to albumin forming methaemalbumin (detected by Schumm's test).
- Free haemoglobin is excreted in the urine as haemoglobinuria, haemosiderinuria

Intravascular haemolysis	Extravascular haemolysis
• mismatched blood transfusion • G6PD deficiency* • red cell fragmentation: heart valves, TTP, DIC, HUS • paroxysmal nocturnal haemoglobinuria • cold autoimmune haemolytic anaemia	• haemoglobinopathies: sickle cell, thalassaemia • hereditary spherocytosis • haemolytic disease of newborn • warm autoimmune haemolytic anaemia

*strictly speaking there is an element of extravascular haemolysis in G6PD as well, although it is usually classified as a intravascular cause

Haemolytic anaemias: by cause

Hereditary causes

- can be subdivided into membrane, metabolism or haemoglobin defects
  - membrane: hereditary spherocytosis/elliptocytosis
  - metabolism: G6PD deficiency
  - haemoglobinopathies: sickle cell, thalassaemia

Acquired causes

- can be subdivided into immune and non-immune causes
  - Acquired: immune causes
    - autoimmune: warm/cold antibody type
    - alloimmune: transfusion reaction, haemolytic disease newborn
    - drug: methyldopa, penicillin
      - methyldopa → Anti-RBC antibodies
      - penicillin → reaction between penicillin-like drugs and their antibodies
  - Acquired: non-immune causes
    - microangiopathic haemolytic anaemia (MAHA): TTP/HUS, DIC, malignancy, pre-eclampsia
    - prosthetic cardiac valves
    - paroxysmal nocturnal haemoglobinuria
    - infections: malaria

laboratory tests

- Hemoglobin: decreased
- MCV: normocytic
- Reticulocyte count and reticulocyte production index: increased
- Unconjugated bilirubin: increased
- LDH: increased (esp. in intravascular hemolysis)
- **Haptoglobin: reduced**

Microangiopathic anemia

- **The patient's newly diagnosed heart murmur along with new anemia and schistocytes indicate aortic stenosis as the underlying cause.**
- **Aortic stenosis → mechanical destruction of RBCs (as they travel through the narrowed aortic opening) → microangiopathic anemia**
- **Schistocytes** are fragmented RBCs. Also called helmet cells, they are pathognomic of microagiopathic hemolytic anemias.

Zieve syndrome

- **triad of jaundice, hemolytic anemia, and hyperlipidemia.**
- Hepatic dysfunction is usually evident in all cases.
- Hemolytic anemia is reversible.
- Hyperlipidemia due to excess alcohol intake causes metabolic and osmotic abnormalities in (RBCs), making them very susceptible to hemolysis.
- Peripheral blood smear reveals:
  - normocytic normochromic anemia
  - **acanthocytes**
    - Acanthocytes are also called spur cells.
    - They have multiple projections on their surface caused by hyperlipidemia.
- Definitive treatment → alcohol cessation.

Zieve's syndrome should be suspected whenever there is anemia and elevation of unconjugated bilirubin in the setting of acute alcohol intake with no obvious sign of gastrointestinal bleeding.

Autoimmune haemolytic anaemia (AIHA)

- Autoimmune haemolytic anaemia (AIHA) may be divided in to 'warm' and 'cold' types, according to at what temperature the antibodies best cause haemolysis.
- It is most commonly idiopathic but may be secondary to a lymphoproliferative disorder, infection or drugs.
- **AIHA is characterised by a positive direct antiglobulin test (Coombs' test)**

Warm AIHA

- In warm AIHA the antibody (usually **IgG**) causes haemolysis best at body temperature and haemolysis tends to occur in **extravascular** sites, for example the spleen. Management options include steroids, immunosuppression and splenectomy.
- **Causes of warm AIHA**
  - **autoimmune disease**: e.g. systemic lupus erythematosus*
    - SLE can rarely be associated with a mixed-type AIHA
  - neoplasia: e.g. lymphoma, CLL
  - drugs: e.g. methyldopa, Penicillins, Cephalosporins, levodopa, NSAIDs and Quinidine
    - treated by → stopping the drug ± short course of oral prednisolone.
- The bone marrow respond by increasing RBCs production, which will be evident in peripheral blood by increase in the reticulocytes, immature RBCs, which will have high MCV.
- **Management** options include steroids, immunosuppression and splenectomy.
- Blood transfusion can be life-saving until immunosuppression can take effect.
- All patients with active haemolysis are at risk of acquiring folate deficiency due to increased metabolic demands and all should receive **folic acid** replacement therapy.

Cold AIHA

- The antibody in cold AIHA is usually **IgM** and causes haemolysis best at 4 deg C.
- Haemolysis is mediated by complement and is more commonly **intravascular**.
- **Causes of cold AIHA**
  - neoplasia: e.g. lymphoma
  - **infections:** e.g. mycoplasma, EBV
  - **Secondary cold agglutinin disease typically presents with anaemia and haemoglobinuria due to intravascular haemolysis two to three weeks following infection** such as with:
    - *Mycoplasma pneumoniae*
    - Viruses (EBV, CMV, etc)
    - Legionnaires' disease
    - Malaria → **The best diagnostic test** → **Cold agglutinin titre**
  - Cold agglutinins occur normally but at very low titres.
- Features may include symptoms of Raynaud's and acrocyanosis
- Patients respond less well to steroids

	Warm AIHA	Cold AIHA
Definition	haemolysis best at body temperature	haemolysis best at 4 deg C
antibody	**IgG**	**IgM**
Site of haemolysis	**extravascular** (e.g :spleen)	**intravascular**
Causes	• **autoimmune disease**: e.g. systemic lupus erythematosus • neoplasia: e.g. lymphoma, CLL • drugs: e.g. methyldopa	• neoplasia: e.g. lymphoma • **infections**: e.g. mycoplasma, EBV
treatment	steroids, immunosuppression and splenectomy.	respond less well to steroids

Paroxysmal cold haemoglobinuria (PCH)

- a rare type of autoimmune haemolytic anaemia (AIHA) occurring primarily in children/adolescent.
- The classic symptom is a sudden onset of haemoglobinuria following exposure to cold, even for a few minutes.
- Symptoms may occur minutes to hours following exposure to cold.
- Haemoglobinuria is not always present because in some persons with PCH the autoantibody level is not high enough to cause intravascular haemolysis.
- **The direct agglutination test (DAT) (Coomb's test) is usually negative.**

Cold agglutinin disease

- caused by autoantibodies that react at temperatures < 37 °C,
- typical causes are:
  - lymphoproliferative disorders,
  - infections such as mycoplasma or Epstein–Barr virus.
  - Around 50% of cases are idiopathic.
  - **Non-Hodgkin's lymphoma is more typically associated with cold agglutinins than Hodgkin's.**

Hook effect

- Also called or the **prozone effect**
- In agglutination test, a person's serum (which contains antibodies) is added to a test tube, which contains a particular antigen.
- If the antibodies agglutinate with the antigen to form immune complexes, then the test is interpreted as positive.
- However, if too many antibodies are present that can bind to the antigen, then the antigenic sites are coated by antibodies, and few or no antibodies directed toward the pathogen are able to bind more than one antigenic particle. Since the antibodies do not bridge between antigens, no agglutination occurs. Because no agglutination occurs, the test is interpreted as negative. In this case, the result is a false negative.
- The range of relatively high antibody concentrations within which no reaction occurs is called the prozone.
- The effect can also occur because of antigen excess, when both the capture and detection antibodies become saturated by the high analyte concentration. In this case, no sandwich can be formed by the capturing antibody, the antigen and the detection antibody. In this case, free antigen is in competition with captured antigen for detection antibody binding.
- Examples include:
- high levels of syphilis antibodies in HIV patients or high levels of cryptococcal antigen leading to false negative tests in undiluted samples.
- This phenomenon is also seen in serological tests for Brucellosis.
- when the serum is diluted, the blocking antibody is as well and its concentration decreases enough for the proper precipitation reaction to occur.

Hereditary spherocytosis

Epidemiology

- most common hereditary haemolytic anaemia in people of northern European descent

Aetiology

- **autosomal dominant** defect of red blood cell cytoskeleton
- the most frequent cause is a mutation in the spectrin gene;
  - spectrin is a component of the red cell membrane.
- **The most common mutation in a Northern European population is a combined spectrin and ankyrin mutation**, which is found in 40–65% of patients.
- the normal biconcave disc shape is replaced by a sphere-shaped red blood cell
- red blood cell survival reduced as destroyed by the spleen

Pathophysiology

- Genetic mutation → Defects in RBC membrane proteins (especially spectrin and/or ankyrin) responsible for tying the inner membrane skeleton with the outer lipid bilayer → Continuous loss of lipid bilayer components → Decreased surface area of RBCs in relation to volume → Sphere-shaped RBCs with decreased membrane stability → Inability to change form while going through narrowed vessels:
  → Entrapment within splenic vasculature → Splenomegaly
  → Destruction via splenic macrophages → Extravascular hemolysis

Features

Patient with hereditary spherocytosis + acute abdomen → think of: Biliary colic or rupture spleen.

normocytic anaemia, gallstones and family history → hereditary spherocytosis

- failure to thrive
- Congenital skeletal abnormalities (eg, tower-shaped skull, polydactylism) occasionally occur.
- Anemia and pallor
- jaundice (↑unconjugated bilirubin)
- gallstones (pigment stones)
  - **common and may be the presenting symptom**
  - (made of calcium bilirubinate)
  - may lead to cholecystitis
- Splenomegaly with left upper quadrant pain
- aplastic crisis precipitated by parvovirus infection

Complications

- Aplastic crisis
  - can be triggered by parvovirus B19 infection.

Investigations

- Normocytic anemia (normal MCV)
- increase in both RDW and MCHC
- Findings of hemolytic anemia
  - ↑ Unconjugated bilirubin
  - ↑ LDH
  - ↓ Haptoglobin
  - Reticulocytosis
- Direct antiglobulin (direct Coombs) test
  - to exclude autoimmune hemolytic anemia (positive Coombs test), since spherocytosis is seen in both clinical presentations
  - Direct Coombs' test is negative in Hereditary spherocytosis, as it is not an immune haemolysis
- **E**osin-5-**ma**leimide binding test (**EMA**): **test of choice**, as results are readily available (within two hours)
- Osmotic fragility test (Rupture of Spherocytes in mildly hypotonic solution),
  - unreliable and is no longer recommended in routine clinical practice.
  - this has now been replaced by the **eosin-5-maleimide binding to red cells** and then being detected by **flow cytometry.**
- Osmotic gradient ektacytometry
  - used to differentiate hereditary spherocytosis from hereditary stomatocytosis, but is only available in specialised laboratories.
- If the diagnosis is equivocal, the cryohaemolysis test and EMA binding can be used.
- In atypical cases, gel electrophoresis analysis of erythrocyte membranes is the test of choice.
- Blood smear
  - Characteristic spherocytes (absent central pallor)
  - Potentially anisocytosis
- Ultrasound:
  - to evaluate gallbladder complications

Diagnosis

1. **The first step in analysis of a spherocytic hemolytic anaemia is → direct antiglobulin test (to determine whether the process is hemolytic or not).**
2. **If negative → confirm HS with other tests.**
3. **The osmotic fragility test is unreliable and is no longer recommended in routine clinical practice.**
4. **Osmotic gradient ektacytometry is used to differentiate hereditary spherocytosis from hereditary stomatocytosis**

Management

- supportive for most patients: folate replacement
- splenectomy
  - best avoided until at least 6 years of age to reduce the risk of post-splenectomy sepsis.
  - It is important to rule out stomatocytosis where splenectomy is contraindicated because of the thrombotic risk.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency

Basics

- (G6PD) plays a vital role in the hexose monophosphate pathway
- It is involved in the oxidation of glucose 6-phosphate to 6-phosphoglycerate.This oxidation reaction is needed in RBCs as it provides the only source of **NADPH**
- NADPH → maintains the level of glutathione → protect the RBCs against oxidative damage from compounds like hydrogen peroxide

Prevalence

- G6PD deficiency is the commonest red blood cell enzyme defect.
- It is more common in people from the Mediterranean, Africa and Chinese

Aetiology

- inherited in a X-linked recessive fashion.
- Homozygotes and heterozygotes can be symptomatic, although the disease typically is more severe in persons who are homozygous for the deficiency.

Factors which Precipitates crisis:

- drugs
- infections (the most common cause)
- broad (fava) beans
  - Favism is most common in persons with G6PD class II variants, but rarely it can occur in patients with the G6PD A–variant (Class III → African descent).
- henna

Pathophysiology

- ↓ G6PD → ↓ glutathione → increased red cell susceptibility to oxidative stress
- The haemolytic anaemia is non-immune (direct antiglobulin test [DAT] negative).

Features

- usually asymptomatic
- neonatal jaundice is often seen
- intravascular haemolysis
  - **Decreased haptoglobin levels**, hematuria, and presence of **urinary hemosiderin** indicate severe intravascular hemolysis.
- acute hemolysis can cause back or abdominal pain and jaundice secondary to a rise in unconjugated bilirubin
  - Jaundice, in the setting of normal liver function, typically does not occur until **>** 50% of the erythrocytes have been hemolyzed.
- gallstones are common
- splenomegaly may be present
- **Heinz bodies** (denatured hemoglobin) on blood films

Diagnosis:

- made by using a G6PD enzyme assay
- usually done by **fluorescent spot test** detecting the generation of NADPH from NADP**.**
  - The test is positive if the blood spot fails to fluoresce under ultraviolet light.
- In patients with acute hemolysis, testing for G6PD deficiency may be falsely negative because older erythrocytes with a higher enzyme deficiency have been hemolyzed. Young erythrocytes and reticulocytes have normal or near-normal enzyme activity.

- Female heterozygotes may be hard to diagnose because of X-chromosome mosaicism leading to a partial deficiency that will not be detected reliably with screening tests.
- **Acute haemolytic reaction**
  - Blood count is normal between attacks of haemolysis
  - During an attack the blood film may show:
    - irregularly contracted cells
    - bite cells
    - blister cells
    - Heinz bodies
    - Reticulocytosis
- Peripheral blood smear → **Heinz bodies** (rarely seen in clinical practice)
- Reticulocyte count: Increases four to seven days after hemolysis
- Haptoglobin → Decreased

Treatment

- avoidance exposure to an oxidative stressor in the form of an infection, oxidative drug, or fava beans
- Acute hemolysis is self-limited, but in rare instances it can be severe enough to warrant a blood transfusion
  - Hemolysis typically occurs 24 to 72 hours after ingestion, with resolution within 4 to 7 days.

Some drugs causing haemolysis

- anti-malarials: primaquine
- Quinine/quinidine.
- Ciprofloxacin
- Nitrofurantoin
- chloramphenicol
- sulph- group drugs: sulphonamides, sulphasalazine, sulfonylureas
- vitamin K, probenecid
- aspirin and (NSAIDs)

Some drugs thought to be safe

- penicillins
- cephalosporins
- macrolides
- tetracyclines
- trimethoprim
  - In "Co-trimoxazole": the sulfamethoxazole causes haemolysis in G6PD, not the trimethoprim.

Comparing G6PD deficiency to hereditary spherocytosis:

	G6PD deficiency	Hereditary spherocytosis
Gender	Male (X-linked recessive)	Male + female (autosomal dominant)
Ethnicity	African + Mediterranean descent	Northern European descent
Typical history	• Neonatal jaundice • Infection/drugs precipitate haemolysis • Gallstones	• Neonatal jaundice • Chronic symptoms although haemolytic crises may be precipitated by infection • Gallstones • Splenomegaly is common
Blood film	Heinz bodies	Spherocytes (round, lack of central pallor)
Diagnostic test	Measure enzyme activity of G6PD	Osmotic fragility test

Other notes

- G6PD deficiency confers partial protection against malaria
- Hemolysis begins 24 to 72 hours after exposure to oxidant stress.
- Hemolysis due to oxidant stresses are usually self-limiting within 8 to 14 days due to the compensatory production of young red blood cells with high levels of G6PD.

- Young RBCs are not vulnerable to oxidative damage and hence limit the duration of hemolysis.
- G6PD deficiency is an X-linked inherited disease that primarily affects men.
- Women may be affected if:
  - they are **homozygous**, which occurs in populations in which the frequency of G6PD deficiency is quite high.
  - Heterozygous women (carriers) can experience clinical disease as a result of:
    1. X chromosome inactivation,
    2. gene mosaicism, or
    3. hemizygosity
- Severe hemolysis due to G6PD deficiency may manifest as **methemoglobinemia**
- **Methaemoglobinaemia in G6PD-deficient patients is best treated with exchange transfusion.**

Paroxysmal nocturnal haemoglobinuria (PNH)

The triad of hemolytic anemia, pancytopenia, and thrombosis → PNH

- (PNH) is an acquired disorder leading to haemolysis (mainly intravascular) of haematological cells.
- Caused by increased sensitivity of cell membranes to complement **due to a lack of glycoprotein glycosyl-phosphatidyl-inositol (GPI).**
- Patients are more prone to venous thrombosis
- **50% of PNH affected individuals are died due to thrombotic complications**

Pathophysiology

- GPI can be thought of as an anchor which attaches surface proteins to the cell membrane
- complement-regulating surface proteins, e.g. decay-accelerating factor CD 55 (DAF) and Membrane Inhibitor of Reactive Lysis CD 59 (MIRL)., are not properly bound to the cell membrane due a lack of GPI
- Hemolysis occurs when patients develop a mild acidosis at night, due to a relative hypoventilation, resulting in the passage of dark urine in the early morning.
- **thrombosis is thought to be caused by a lack of CD59 on platelet membranes** predisposing to platelet aggregation
- Intrinsic hemolytic anemia with intravascular hemolysis

Features

- symptoms of anemia (Pallor, fatigue, weakness)
- Intermittent jaundice
- haemoglobinuria
  - classically dark-coloured urine in the morning (although has been shown to occur throughout the day)
- Abdominal pain
  - may be due to small mesenteric vein thrombi.

Complications

- thrombosis e.g. Budd-Chiari syndrome
- Vasoconstriction: headache, pulmonary hypertension
- aplastic anaemia may develop in some patients
- ↑ Risk of acute leukemias

Investigations

- CBC
  - haemolytic anaemia
  - red blood cells, white blood cells, platelets or stem cells may be affected therefore pancytopaenia may be present
- dipstick analysis of the urine:
  - will be positive for 'blood', but the microscopy will show no red blood cells.
    - This because there is intravascular haemolysis, with intravascular release of haemoglobin. This then passes through the renal tubules, ending up in the urine, and turning the dipstick analysis positive. However, because there are no actual red blood cells in the urine, the microscopy will be negative.
- **flow cytometry (immunophenotyping) of blood**
  - **absence of CD55 and CD59 on the surface of RBCs**
  - **now replaced Ham's test as the gold standard investigation in PNH**
- Ham's test: acid-induced haemolysis (normal red cells would not)
- Coombs test: negative

Management

- blood product replacement
- anticoagulation
- **eculizumab**, a **monoclonal antibody directed against terminal protein C5**, is reducing intravascular haemolysis
- stem cell transplantation
  - The gold standard curative treatment

Splenectomy

- Following a splenectomy patients are particularly at risk of infections from:
  - pneumococcus,
  - Haemophilus,
  - meningococcus and
  - Capnocytophaga canimorsus*(*usually from dog bites)
- Vaccination
  - if elective, should be done 2 weeks prior to operation
  - Hib, meningitis A & C
  - annual influenza vaccination
  - pneumococcal vaccine every 5 years
- Antibiotic prophylaxis
  - penicillin V: unfortunately clear guidelines do not exist of how long antibiotic prophylaxis should be continued. It is generally accepted though that penicillin should be continued for at least 2 years and at least until the patient is 16 years of age, although the majority of patients are usually put on antibiotic prophylaxis for life

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Blood products

Whole blood fractions

Fraction	Key points
Packed red cells	• Used for transfusion in chronic anaemia and cases where infusion of large volumes of fluid may result in cardiovascular compromise. • Product obtained by centrifugation of whole blood. • **In a stable patient, red cell packs may be transfused over 90-120 minutes** ➢ Rapid infusion of red cells or fresh frozen plasma may be required in an acutely bleeding patient but not in patient who is stable.
Platelet rich plasma	• Usually administered to patients who are thrombocytopaenic and are bleeding or require surgery. • It is obtained by **low speed** centrifugation.

Platelet concentrate	• Prepared by **high speed** centrifugation
	• administered to patients with thrombocytopaenia.
	• **the life span of transfused platelets is only 3-7 days.**
	• **platelet transfusion should not take more than 20-30 minutes.**
	• **Patients who are refractory to platelet transfusions:**
	  ➢ **should be first investigated to check for adequate platelet rises. This is best done on a one or two-hour post platelet transfusion sample.**
	  ➢ **Further test would include checking for HLA antibodies**

Fresh frozen plasma	• Prepared from single units of blood. • Contains clotting factors, albumin and immunoglobulin. • Unit is usually 200 to 250ml. • Usually used in correcting clotting deficiencies in patients with hepatic synthetic failure who are due to undergo surgery. • Usual dose is 12-15ml/Kg^{-1}. • It should not be used as first line therapy for hypovolaemia.
Cryoprecipitate	• Formed from supernatant of FFP.

Fraction	Key points
	• Rich source of Factor VIII and fibrinogen. • Allows large concentration of factor VIII to be administered in small volume.
SAG-Mannitol Blood	Removal of all plasma from a blood unit and substitution with: • Sodium chloride • Adenine • Anhydrous glucose • Mannitol Up to 4 units of SAG M Blood may be administered. Thereafter whole blood is preferred. After 8 units, clotting factors and platelets should be considered.

Plasma derivatives

- plasma derivatives (such as factor VIII) are prepared from several thousand plasma donations, typically 20,000, or 5,000 kg of plasma at a time.
- **Pooled plasma** has been sourced from outside the UK since 1999 to avoid vCJD risks.
  - The process involves several chemical steps including:
    - ethanol extraction,
    - chromatography, and
    - **viral inactivation steps which results in a freeze-dried product.**
- These products have a long shelf life of several months to years.

Cell saver devices

These collect patients own blood lost during surgery and then re-infuse it. There are two main types:

- Those which wash the blood cells prior to re-infusion. These are more expensive to purchase and more complicated to operate. However, they reduce the risk of re-infusing contaminated blood back into the patient.
- Those which do not wash the blood prior to re-infusion.

Their main advantage is that they avoid the use of infusion of blood from donors into patients and this may reduce risk of blood borne infection. It may be acceptable to Jehovah's witnesses. It is contraindicated in malignant disease for risk of facilitating disease dissemination.

Blood products used in warfarin reversal

Immediate or urgent surgery in patients taking warfarin:

1. Stop warfarin
2. Vitamin K (reversal within 4-24 hours)
   - IV takes 4-6h to work (at least 5mg)
   - Oral can take 24 hours to be clinically effective
3. Fresh frozen plasma
   - *Used less commonly now as 1st line warfarin reversal*
   - $30ml/kg^{-1}$
   - Need to give at least 1L fluid in 70kg person (therefore not appropriate in fluid overload)
   - Need blood group
   - Only use if human prothrombin complex is not available
4. Human Prothrombin Complex (reversal within 1 hour)
   - Bereplex 50 u/kg
   - Rapid action but factor 6 short half life, therefore give with vitamin K

Neonatal exchange transfusion

- **An exchange transfusion requires blood which is plasma reduced whole blood in CPD (citrate phosphate dextrose/anticoagulant), irradiated and less than five days old.**
- The Rh group should either be Rh negative or identical to the neonate, to avoid haemolytic transfusion reaction in the neonate.

Blood product transfusion complications

Complications

- haemolytic: immediate or delayed
- febrile reactions
- transmission of viruses, bacteria, parasites, **vCJD**
- hyperkalaemia
- iron overload
- ARDS
- clotting abnormalities

Immediate haemolytic reaction

- occur during the transfusion.
- e.g. ABO mismatch
- massive intravascular haemolysis

Delayed haemolytic transfusion reaction

- occurs 24 hours after the transfusion.
- This happens in a patient who has been previously immunised by transfusions or pregnancy. The antibodies are not detectable initially but become obvious as a secondary immune response to the antigen exposure during the transfusion occurs.

Febrile reactions

- due to white blood cell HLA antibodies
- often the result of sensitization by previous pregnancies or transfusions
- Febrile non-haemolytic reactions are very common, and are **due to the presence of pyrogenic cytokines released from leucocytes during storage** of the blood units.
  - apart from a mild fever, the patient is very well.
    - rapid rise in temperature may be due to ABO incompatibility, but With ABO incompatibility patients become shocked very quickly.

Causes a degree of immunosuppression

- e.g. patients with colorectal cancer who have blood transfusions have a worse outcome than those who do not

The risk of viral transmission

- A broad knowledge of the risks may be required while consenting a patient for blood transfusion.
- in the United Kingdom, the risks;
  - **For hepatitis B are 1 per 1.3 million donations**
  - For HIV are 1 in 6.5 million and
  - For hepatitis C 1 in 28 million donations.

Transmission of vCJD

- although the absolute risk is very small, **vCJD may be transmitted via blood transfusion**
- a number of steps have been taken to minimise this risk, including:
- → from late 1999 onward, all donations have undergone removal of white cells (leucodepletion) in order to reduce any vCJD infectivity present
- →from 1999, plasma derivatives have been fractionated from imported plasma rather than being sourced from UK donors. Fresh Frozen Plasma (FFP) used for children and certain groups of adults needing frequent transfusions is also imported
- → from 2004 onward, recipients of blood components have been excluded from donating blood

iron overload

- secondary to chronic blood transfusion (eg : in myelodysplastic syndrome)
- early signs:
  - grey skin
  - early hear failure
  - diabetes
- treatment:
  - **iron chelation with desferrioxamine subcutaneously**
    - bind iron
    - needs to be given for 8 – 12 hours a day for 5 – 7 days per week
  - common side effects of desferrioxamine:
    - high frequency deafness
    - retinopathy
    - Yersinia infection

irradiated blood products

- **the advantage of irradiated red cells**

- **Inactivates donor lymphocytes**

- **Indications for irradiated blood products**
  - Those at risk of transfusion associated with graft versus host disease such as neonates
  - **Those receiving purine analogues based chemotherapy**
  - **Hodgkin's lymphoma**
  - Immunodeficiency states
  - Post bone marrow transplants

Pre-operative request for the blood bank for elective surgeries

- **Group and save only**
  - A 'group and save' is adequate for elective surgeries and is standard practice in most modern blood banks. This will involve blood grouping and its confirmation as well as an antibody screen.
  - Other options include cross match and a direct Coombs' test are not routinely done for elective surgery

Transfusion errors

- Mislabelling of samples, requests, or wrongly identifying recipients are the commonest transfusion errors.

January 2016 exam: What is the risk of variant Creutzfeldt-Jakob Disease (vCJD) transmission via blood transfusion?

➔ Measures are taken to reduce the risk of vCJD transmission but there remains a very small risk of transmission

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Transfusion Related Acute Lung Injury (TRALI)

Definition

- (TRALI) is a rare but serious syndrome characterized by sudden acute respiratory distress within six hours after blood product administration

Risk factors

- Caused by anti-HLA, Human Neutrophil Antigens (HNA) or anti-granulocytes antibody in donor blood.
- Donor's blood sensitization occurs in:
  - Multiparous ♀ develop these antibodies through exposure to fetal blood
  - Previous transfusion
  - Transplantation patient
- When blood is obtained from above mentioned donors, it carries higher risk for recipient to develop TRALI; those who have lung pathology are more susceptible. TRALI symptoms resemble ARDS.

Pathophysiology

- transfused human leukocyte or neutrophil antigen (HLA or HNA) antibodies → activation of donor neutrophils → Neutrophils adhere to pulmonary endothelium to increase permeability and cause pulmonary edema.
- Patients with certain clinical conditions (eg, infection, inflammation, surgery) have primed neutrophils that are susceptible to activation by transfused bioactive substances.

- TRALI has two proposed pathophysiologic mechanisms:
  1. the antibody hypothesis. (antigen-antibody interactions)
  - The human leukocyte antigen (HLA class I, HLA class II) or human neutrophil antigen (HNA) antibody in the transfused component reacts with neutrophil antigens in the recipient The recipient's neutrophils lodge in the pulmonary capillaries and release mediators that cause pulmonary capillary leakage.
  - As a consequence, many patients with TRALI will develop transient leukopenia.
  - However, transfusions of blood components containing neutrophil antibodies may cause leukopenia, that do not meet the definition of TRALI.

  2. The neutrophil priming hypothesis:
  - does not require antigen-antibody interactions

- occurs in patients with clinical conditions that predispose to neutrophil priming and endothelial activation such as infection, surgery, or inflammation.
- Bioactive substances in the transfused component activate the primed, sequestered neutrophils, and pulmonary endothelial damage occurs.

- Both mechanisms lead to pulmonary edema in the absence of circulatory overload.

Feature

- Occurring within 1 to 6 hours of transfusion of plasma-containing blood components.
- Patients present with the rapid onset of dyspnea and tachypnea.
- There may be associated fever, cyanosis, and hypotension.
- Clinical examination reveals hypoxic respiratory distress, and pulmonary crackles may be present without signs of congestive heart failure or volume overload.
- Chest x-ray (CXR) shows evidence of bilateral pulmonary edema unassociated with heart failure (non-cardiogenic pulmonary edema), with bilateral patchy infiltrates, which may rapidly progress to complete "white out" indistinguishable from acute respiratory distress syndrome (ARDS).
- Physiologic findings include acute hypoxemia with PaO2/FiO2 less than 300 mmHg and normal cardiac function on echocardiogram.

Diagnosis:

- confirmed by finding of anti-HLA or anti-Neutrophil antibody in donors' or recipient blood.

Treatment

- Early and intensive pulmonary support reduces the risk of a fatal outcome.
- Since the pulmonary edema in TRALI is not related to fluid overload or cardiac dysfunction, but to altered vascular permeability in the lungs with exudation of fluid and protein into the alveoli, it is logical that:
  - maintenance of adequate circulating volume is the most beneficial and appropriate therapy.
  - Corticosteroids,
  - epinephrine
  - and also ventilatory support are treatment options.

How to distinguish TRALI and ARDS from Pulmonary oedema?

- In the exam take into account the clinical findings and scenario to distinguish.
- The hallmark of ARDS is refractory hypoxia with non-cardiogenic pulmonary edema
- Normal **pulmonary capillary wedge pressure** is between 5 - 15 mmHg. A PCWP exceeding 15 mmHg suggests mitral stenosis, mitral insufficiency, severe aortic stenosis, aortic regurgitation, ventricular failure, or other cardiac defects or pathologies.
- When the PCWP exceeds 20 mmHg, the transmission of this pressure back into the pulmonary vasculature increases pulmonary capillary hydrostatic pressure which can lead to pulmonary oedema.

Graft versus host disease (GVHD)

See transplant topic in renal system

Plasma exchange

Indications for plasma exchange (also known as plasmapheresis)

- Guillain-Barre syndrome
- myasthenia gravis
- Goodpasture's syndrome
- ANCA positive vasculitis e.g. Wegener's, Churg-Strauss
- TTP/HUS
- cryoglobulinaemia
- hyperviscosity syndrome e.g. secondary to myeloma

Deep vein thrombosis (DVT)

Cancer patients with VTE - 6 months of LMWH

Venous thromboembolism - length of warfarin treatment

- provoked (e.g. recent surgery): 3 months
- unprovoked: 6 months

DVT Risk Factors:

- **Hematological**
  - Thrombophilia: e.g. Activated protein C resistance, protein C and S deficiency
  - Polycythemia
  - Paroxysmal nocturnal hemoglobinuria
  - Hyperviscosity syndrome

- **Autoimmune**
  - Antiphospholipid syndrome
  - Behcet's
- **Drugs**
  - Combined oral contraceptive pill: 3rd generation more than 2nd generation
  - Antipsychotics (especially olanzapine) have recently been shown to be a risk factor

- **Other conditions**
  - Homocystinuria

Diagnosis

If a patient is suspected of having a DVT a two-level DVT Wells score should be performed:

Two-level DVT Wells score

Clinical feature	Points
Active cancer (treatment ongoing, within 6 months, or palliative)	1
Paralysis, paresis or recent plaster immobilisation of the lower extremities	1
Recently bedridden for 3 days or more or major surgery within 12 weeks requiring general or regional anaesthesia	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than asymptomatic side	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
An alternative diagnosis is at least as likely as DVT	-2

Clinical probability simplified score

- DVT likely: 2 points or more
- DVT unlikely: 1 point or less

If a DVT is 'likely' (2 points or more)

- a proximal leg vein ultrasound scan should be carried out within 4 hours and, if the result is negative, a D-dimer test
- if a proximal leg vein ultrasound scan cannot be carried out within 4 hours a D-dimer test should be performed and low-molecular weight heparin administered whilst waiting for the proximal leg vein ultrasound scan (which should be performed within 24 hours)

If a DVT is 'unlikely' (1 point or less)

- perform a D-dimer test and if it is positive arrange:
- a proximal leg vein ultrasound scan within 4 hours
- if a proximal leg vein ultrasound scan cannot be carried out within 4 hours low-molecular weight heparin should be administered whilst waiting for the proximal leg vein ultrasound scan (which should be performed within 24 hours)

Management

Low molecular weight heparin (LMWH) or fondaparinux should be given initially after a DVT is diagnosed.

- a vitamin K antagonist (i.e. warfarin) should be given within 24 hours of the diagnosis
- the LMWH or fondaparinux should be continued for at least 5 days or until the international normalised ratio (INR) is 2.0 or above for at least 24 hours, whichever is longer, i.e. LMWH or fondaparinux is given at the same time as warfarin until the INR is in the therapeutic range

- warfarin should be continued for at least 3 months. At 3 months, NICE advise that clinicians should 'assess the risks and benefits of extending treatment'
- NICE add 'consider extending warfarin beyond 3 months for patients with *unprovoked* proximal DVT if their risk of VTE recurrence is high and there is no additional risk of major bleeding'. This essentially means that if there was no obvious cause or provoking factor (surgery, trauma, significant immobility) it may imply the patient has a tendency to thrombosis and should be given treatment longer than the norm of 3 months. In practice most clinicians give 6 months of warfarin for patients with an unprovoked DVT/PE
- for patients with active cancer NICE recommend using LMWH for 6 months
- **for patients with active ulcerative colitis who developed DVT** :
  - may require Emergency colectomy, as such warfarinisation would be inappropriate.
  - **should be heparinised** as this would be easily reversible if it needs to be discontinued prior to surgery or if severe worsening of bleeding occurs.

Time of starting prophylaxis in elective knee replacement surgery:
- LMWH or fondaparinux (s/c factor X inhibitor) → should be started 6 – 12 hours after surgery
- Dabigatran (oral factor X inhibitor) → 1 – 4 hours after surgery

Unprovoked VTE

➔ (**Malignancy investigations and thrombophilia screening)**
- As both malignancy and thrombophilia are obvious risk factors for deep vein thrombosis NICE make recommendations on **how to investigate patients with unprovoked clots**.

Malignancy investigations
- Offer all patients diagnosed with unprovoked DVT or PE who are not already known to have cancer the following investigations for cancer:
  - a physical examination (guided by the patient's full history) and
  - a **chest X-ray** and
  - blood tests (full blood count, serum calcium and liver function tests) and **urinalysis**.
- Consider further investigations for cancer with an abdomino-pelvic CT scan (and a mammogram for women) in all patients aged over 40 years with a first unprovoked DVT or PE

Thrombophilia screening
- not offered if patients will be on lifelong warfarin (i.e. won't alter management)
- consider testing for antiphospholipid antibodies if unprovoked DVT or PE
- consider testing for hereditary thrombophilia in patients who have had unprovoked DVT or PE and who have a first-degree relative who has had DVT or PE

The next most important investigation:
- Unprovoked VTE → chest X-ray, blood tests and urinalysis
- Unprovoked VTE + family history of VTE → Thrombophilia screening

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Pregnancy: DVT/PE

Coagulation elements in pregnancy:
- Increased → factors VII, VIII, IX, X, and XII ,fibrinogen, plasminogen, and D-dimer.
- **Decreased → factor XI and protein S.**
- Not changed → Factor II, protein C, and anti-thrombin III.

Overview
- pregnancy is a hypercoagulable state
- majority occur in last trimester

Pathophysiology
- increase in factors VII, VIII, X and fibrinogen
- **decrease in protein S**
- uterus presses on IVC causing venous stasis in legs

Management
- warfarin contraindicated
- S/C low-molecular weight heparin preferred to IV heparin (less bleeding and thrombocytopenia)

Post-thrombotic syndrome

- It is increasingly recognised that patients may develop complications following a DVT.
- Venous outflow obstruction and venous insufficiency result in chronic venous hypertension.

- The resulting clinical syndrome is known as post thrombotic syndrome.

Features

- painful, heavy calves
- pruritus
- swelling
- varicose veins
- venous ulceration

Management

- **Compression stockings** should be offered to all patients with deep vein thrombosis to help reduce the risk of post-thrombotic syndrome.
- NICE state the following:
  - *Offer below-knee graduated compression stockings with an ankle pressure greater than 23 mmHg to patients with proximal DVT a week after diagnosis or when swelling is reduced sufficiently and if there are no contraindications, and:*
    - *advise patients to continue wearing the stockings for at least 2 years*
    - *ensure that the stockings are replaced two or three times per year or according to the manufacturer's instructions*
    - *advise patients that the stockings need to be worn only on the affected leg or legs.*

Venous thromboembolism: prophylaxis in patients admitted to hospital

Venous thromboembolism (VTE) still accounts for a significant proportion of avoidable hospital deaths. In an effort to tackle this problem NICE produced guidelines in 2010.

Before admission

- advise women to consider stopping oestrogen-containing oral contraception or HRT 4 weeks before surgery.
- assess the risks and benefits of stopping antiplatelet therapy 1 week before surgery.

The following patients are deemed at risk of VTE

Medical patients

- if mobility significantly reduced for >= 3 days **or**
- if expected to have ongoing reduced mobility relative to normal state plus any VTE risk factor (see below)

Surgical patients and patients with trauma

- if total anaesthetic + surgical time > 90 minutes **or**
- if surgery involves pelvis or lower limb and total anaesthetic + surgical time > 60 minutes **or**
- if acute surgical admission with inflammatory or intra-abdominal condition **or**
- if expected to have significant reduction in mobility **or**
- if any VTE risk factor present (see below)

VTE risk factors

- active cancer or cancer treatment
- age > 60 years
- critical care admission
- dehydration
- known thrombophilias
- obesity (BMI > 30 kg/m^2)
- one or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)
- personal history or first-degree relative with a history of VTE
- use of HRT
- use of oestrogen-containing contraceptive therapy
- varicose veins with phlebitis

In-patient VTE prophylaxis

As a general rule pharmacological VTE prophylaxis is used for medical patients unless there is a contraindication.

For surgical patients mechanical VTE prophylaxis is offered for patients at risk. Pharmacological VTE prophylaxis is also given for if the risk of major bleeding is low.

Pharmacological VTE prophylaxis options:

- fondaparinux sodium
- low molecular weight heparin (LMWH)
- unfractionated heparin (UFH) (for patients with renal failure)

Mechanical VTE prophylaxis options:

- anti-embolism stockings (thigh or knee length)

- foot impulse devices
- intermittent pneumatic compression devices (thigh or knee length)

Post-procedure VTE prophylaxis

For certain procedures pharmacological VTE prophylaxis is recommended for all patients, using one of the following:

- dabigatran, started 14 hours after surgery
- fondaparinux, started 6 hours after surgery
- LMWH, started 6-12 hours after surgery
- rivaroxaban, started 6-10 hours after surgery.
- Apixaban

Procedure	Length of prophylaxis
Elective hip	28-35 days
Elective knee	10-14 days
Hip fracture	28-35 days

Superficial thrombophlebitis

- Superficial thrombophlebitis, as the name suggests describes the inflammation associated with thrombosis of one of the superficial veins, usually the long saphenous vein of the leg.
- This process is usually non-infective in nature but secondary bacterial infection may rarely occur resulting in septic thrombophlebitis.
- Around 20% with superficial thrombophlebitis will have an underlying deep vein thrombosis (DVT) at presentation and 3-4% of patients will progress to a DVT if untreated.
- The risk of DVT is partly linked to the length of vein affected - an inflammed vein > 5 cm is more likely to have an associated DVT.

Management

- Traditionally NSAIDs have been used, with topical NSAIDs for limited and mild disease and oral NSAIDs for more severe disease.
- Topical heparinoids have also be used in the management of superficial thrombophlebitis.
- A Cochrane review however found topical NSAIDs and heparinoids have no significant benefit in terms of reducing extension or progression to DVT.
- Oral NSAIDs were however shown to reduce the risk of extension by 67%.
- Compression stockings are also used.
- Remember that the ankle-brachial pressure index (ABPI) should be measured before prescribing compression stockings, particularly if using class 2 or above stockings.
- One of the major changes to the management of superficial thrombophlebitis is the increased use of low-molecular weight heparin. This has been shown to reduce extension and transformation to DVT.
- **SIGN produced guidelines in 2010:**
  - *Patients with clinical signs of superficial thrombophlebitis affecting the proximal long saphenous vein should have an ultrasound scan to exclude concurrent DVT.*
  - *Patients with superficial thrombophlebitis should have anti-embolism stockings and can be considered for treatment with prophylactic doses of LMWH for up to 30 days or fondaparinux for 45 days.*
  - *If LMWH is contraindicated, 8-12 days of oral NSAIDS should be offered.*
  - *Patients with superficial thrombophlebitis at, or extending towards, the sapheno-femoral junction can be considered for therapeutic anticoagulation for 6-12 weeks.*
- This may be a significant departure from our current practice - the majority of patients with superficial thrombophlebitis (i.e. those affecting the long saphenous vein) should be referred for an ultrasound scan.

Thrombophilia: causes

inherited thrombophilias:
- **the most common → Factor V Leiden**
- **the higher risk of VTE → Anti-thrombin III deficiency**

Inherited thrombophilias
- Gain of function polymorphisms
  - **factor V Leiden** (**activated protein C resistance**): most common cause of thrombophilia
  - prothrombin gene mutation: second most common cause
- Deficiencies of naturally occurring anticoagulants
  - antithrombin III deficiency
  - protein C deficiency → **Reduced degradation of factors Va and Villa**
  - protein S deficiency

The table below shows the prevalence and relative risk of venous thromboembolism (VTE) of the different inherited thrombophilias:

Condition	Prevalence	Relative risk of VTE
Factor V Leiden (heterozygous)	5%	4
Prothrombin gene mutation (heterozygous)	1.5%	3
Protein C deficiency	0.3%	10
Protein S deficiency	0.1%	5-10
Antithrombin III deficiency	0.02	10-20

Acquired thrombophilias:
- Antiphospholipid syndrome
- Drugs
  - the combined oral contraceptive pill

NICE recommend testing for thrombophilia in case of unprovoked venous thromboembolism and family history.

Factor V Leiden

Activated protein C resistance (Factor V Leiden) is the most common inherited thrombophilia

Factor V Leiden mutation results in activated protein C resistance

Epidemiology
- Factor V Leiden (activated protein C resistance) is **the most common inherited thrombophilia,** being present in around 5% of the UK population.
- present in 5-9% of the European population but is rare in people of Asian and African descent.

Aetiology
- It is due to a mutation in the Factor V Leiden mutation.
- mostly inherited in an autosomal dominant fashion
- caused by an amino acid substitution results in replacement of arginine with glutamine in the amino acid chain, that impairs the ability of activated protein C and S to inactivate factor Va.

Pathophysiology
- Normally, activated protein C inactivates factor V in the clotting cascade → decreases the activation of thrombin.

- However, in patients with these defects, factor V remains active → activates prothrombin → increases thrombotic events.

Features

- results in a 30% lifetime risk of VTE for homozygotes and 5-10% for heterozygotes.
- Heterozygotes have a 4-5 fold risk of venous thrombosis.

Diagnosis

- The gold standard for the diagnosis of factor V Leiden is **genetic testing** for the mutation.

Management

- prophylaxis against thromboembolism.
- Contraceptive medications and devices that contain the hormone estrogen should not be used
  - Non-hormonal and progesterone-only methods are safe for use in these patients
- patients with no history of VTE are not indicated for prolonged anticoagulation prophylaxis.

Protein C deficiency

- Protein C deficiency is an **autosomal codominant** condition which causes an increased risk of thrombosis
- Protein C is synthesized in the liver.

Function of protein C

- **inactivation of factors Va and VIIIa.**

Features

- venous thromboembolism
- skin necrosis following the commencement of warfarin:
  - when warfarin is first started biosynthesis of protein C is reduced. This results in a temporary procoagulant state after initially starting warfarin, normally avoided by concurrent heparin administration. Thrombosis may occur in venules leading to skin necrosis
  - The best initial step for the management of warfarin-induced skin necrosis is stopping warfarin.

Diagnosis

- **Copperhead snake venom assay**
  - **the best test to detect protein-C deficiency**

Management

- Patients with a history of a thrombotic event should receive prophylactic anticoagulation for life.

Antithrombin III deficiency

- Antithrombin III deficiency is an inherited cause of thrombophilia occurring in approximately 1:3,000 of the population.
- Inheritance is **autosomal dominant**

Function of Antithrombin III

- Antithrombin III inhibits several clotting factors, primarily thrombin, factors **II**, IX, and **X**.
  - the affinity of Antithrombin III for **Factor II and X is much greater**, and it thus has a much stronger inactivation effect on these factors.
- It mediates the effects of heparin

Features

- recurrent venous thromboses
- arterial thromboses do occur but are uncommon

Diagnosis

- The best initial test for diagnosing antithrombin III deficiency is **thrombin-heparin cofactor level.**

Management

- thromboembolic events are treated with lifelong warfarinisation
- heparinisation during pregnancy*
  - ***as patients with antithrombin III deficiency have a degree of resistance to heparin, anti-Xa levels should be monitored** carefully to ensure adequate anticoagulation
- antithrombin III concentrates (often using during surgery or childbirth)

Antiphospholipid syndrome

- Antiphospholipid syndrome is an acquired disorder characterised by a predisposition to both venous and arterial thromboses, recurrent fetal loss and thrombocytopenia.
- It may occur as a primary disorder or secondary to other conditions, most commonly systemic lupus erythematosus (SLE)
- A key point for the exam is to appreciate that antiphospholipid syndrome causes a paradoxical rise in the APTT. This is due to an ex-vivo reaction of the lupus anticoagulant autoantibodies with phospholipids involved in the coagulation cascade

Features

- venous/arterial thrombosis
- recurrent fetal loss
- livedo reticularis
- thrombocytopenia
- prolonged APTT
  - (raised aPTT which fails to correct after the addition of normal human plasma).
- other features: pre-eclampsia, pulmonary hypertension

Associations other than SLE

- other autoimmune disorders
- lymphoproliferative disorders
- phenothiazines (rare)

Risk factor for thrombosis

- **Lupus anticoagulant is the greatest predictor of future thrombosis in patients with anti-phospholipid syndrome**

Diagnosis

antiphospholipid antibody syndrome (APAS) can be diagnosed if:

- the patient has anticardiolipin antibodies, or lupus anticoagulant on two occasions, over a period of 12 weeks,

and either:

- has had a thrombus, or
- a history of recurrent < 10 week pregnancy loss, or one pregnancy loss > 10 weeks in gestation when other causes of pregnancy loss have been excluded.

Antibodies

the most clinically important autoantibodies directed against phospholipid binding plasma proteins are:

1. The lupus anticoagulant
2. Anti-beta-2 glycoproetin I antibodies, and
3. **The anticardiolipin antibodies.**

Management - based on BCSH guidelines

- initial venous thromboembolic events: evidence currently supports use of warfarin with a target INR of 2-3 for 6 months
  - **Other opinion**: The occurrence of even **a single thrombotic event in a patient with antiphospholipid syndrome warrants lifelong anticoagulation**, as the risk of recurrence is 20-70%.
- recurrent venous thromboembolic events: lifelong warfarin; if occurred whilst taking warfarin then increase target INR to 3-4
- arterial thrombosis should be treated with lifelong warfarin with target INR 2-3

Antiphospholipid syndrome: pregnancy

Antiphospholipid syndrome in pregnancy: aspirin + LMWH

Antiphospholipid syndrome: (paradoxically) prolonged APTT + low platelets

Antiphospholipid syndrome: arterial/venous thrombosis, miscarriage, livedo reticularis

- Antiphospholipid syndrome is an acquired disorder characterised by a predisposition to both venous and arterial thromboses, recurrent fetal loss and thrombocytopenia.
- It may occur as a primary disorder or secondary to other conditions, most commonly systemic lupus erythematosus (SLE)

In pregnancy the following complications may occur:

- recurrent miscarriage
- IUGR
- pre-eclampsia
- placental abruption
- pre-term delivery
- venous thromboembolism

Management

- low-dose aspirin should be commenced once the pregnancy is confirmed on urine testing
- low molecular weight heparin once a fetal heart is seen on ultrasound. This is usually discontinued at 34 weeks gestation
- these interventions increase the live birth rate seven-fold

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Hereditary haemorrhagic telangiectasia (HHT)

Hereditary haemorrhagic telangiectasia - autosomal dominant

- Also known as Osler-Weber-Rendu syndrome
- autosomal dominant
- characterised by (as the name suggests) multiple telangiectasia over the skin and mucous membranes.
- occurs in approximately 1 in 5000 of the population.
- 20 % of cases occur spontaneously without prior family history.
- commonly presents in teenagers. 62% are diagnosed by age 16.

Genetic

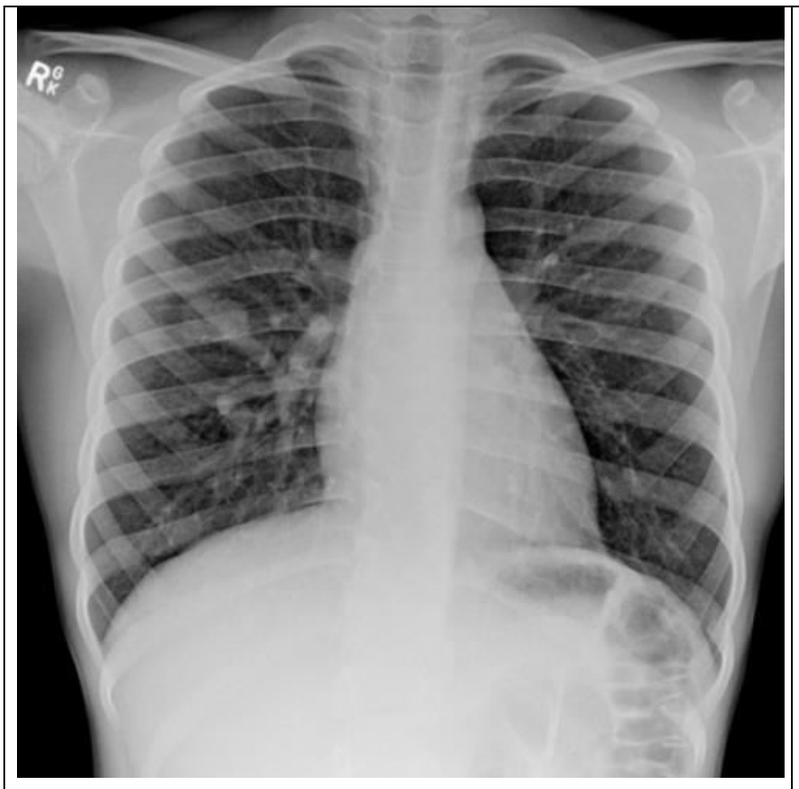
- Two genes: **ENG** (endoglin) and **ALK-1** (activin receptor like kinase-1) encode proteins expressed on vascular endothelial cells. Mutations in these genes cause an imbalance in angiogenesis.

Features and complications

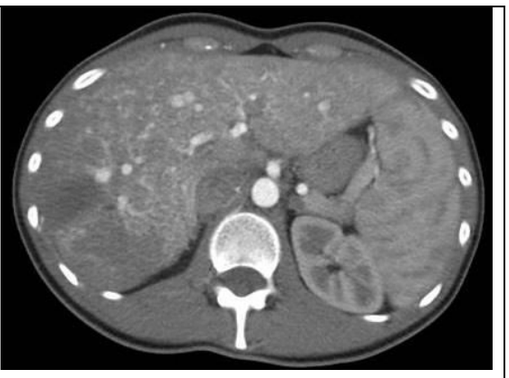
- **over 90% present with nosebleeds (the most common initial mode of presentation)**
- GI telangiectasias and arteriovenous malformations (AVMS) may cause chronic slow bleeding leading to iron deficiency **anemia**
- AVMS in the respiratory system may cause **dyspnoea and cyanosis and paradoxical cerebral emboli.**
- GI telangiectasias and arteriovenous malformations may cause **acute haemorrhage**
- In the brain AVMS, angiomas and aneurysms may lead to **stroke**

Diagnosis

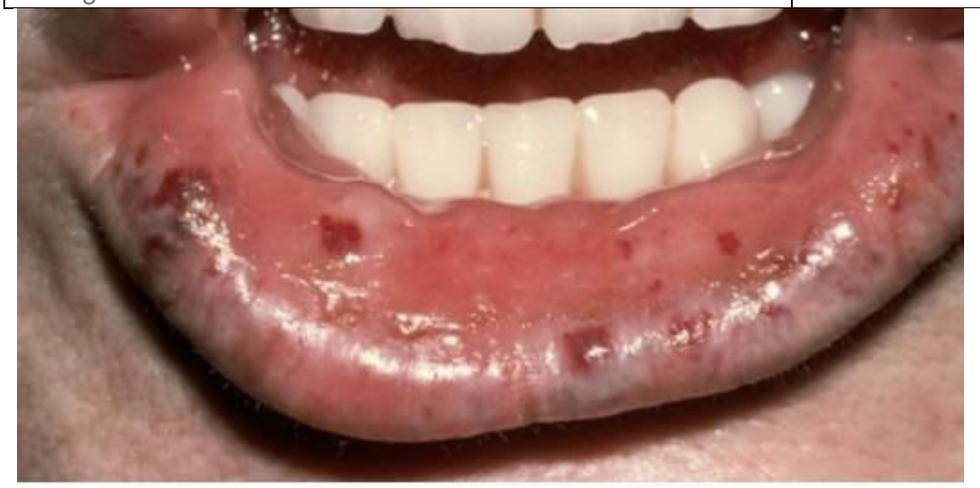
- There are 4 main **diagnostic criteria** (Curacao criteria).
    1. epistaxis : spontaneous, recurrent nosebleeds
    2. telangiectases: multiple at characteristic sites (lips, oral cavity, fingers, nose)
    3. visceral lesions: for example gastrointestinal telangiectasia (with or without bleeding), pulmonary arteriovenous malformations (AVM), hepatic AVM, cerebral AVM, spinal AVM
    4. family history: a first-degree relative with HHT
- The diagnosis is **definite** if 3 criteria are present, **suspected** with 2 criteria and **unlikely** if fewer than 2 criteria are present.



The chest x-ray shows **multiple pulmonary nodules** representing arteriovenous malformations, the largest in the right mid-zone.



The CT scan shows multiple hepatic arteriovenous malformations



Mucocutaneous telangiectasias involve the lips **(HHT)**

Idiopathic thrombocytopenic purpura (ITP)

ITP - give oral prednisolone

- **ITP** is an immune mediated reduction in the platelet count.
- Antibodies are directed against the glycoprotein IIb/IIIa or Ib-V-IX complex.
- Most often the stimulus is unknown, but it can be secondary to other autoimmune disorders (e.g. SLE), viral infections (e.g. CMV, VZV, hepatitis C, HIV), *Helicobacter pylori*, medication and lymphoproliferative disorders.
- It results in **isolated thrombocytopenia**, with the most common presenting sign being a purpuric rash.
- ITP can be divided into acute and chronic forms:

Acute ITP

- more commonly seen in children
- equal sex incidence
- may follow an infection or vaccination
- usually runs a self-limiting course over 1-2 weeks

Chronic ITP
- more common in young/middle-aged women
- tends to run a relapsing-remitting course

Evan's syndrome
- **ITP in association with autoimmune haemolytic anaemia (AIHA)**

Investigations
- antiplatelet autoantibodies (usually IgG)
- bone marrow aspiration shows megakaryocytes in the marrow. This should be carried out prior to the commencement of steroids in order to rule out leukaemia

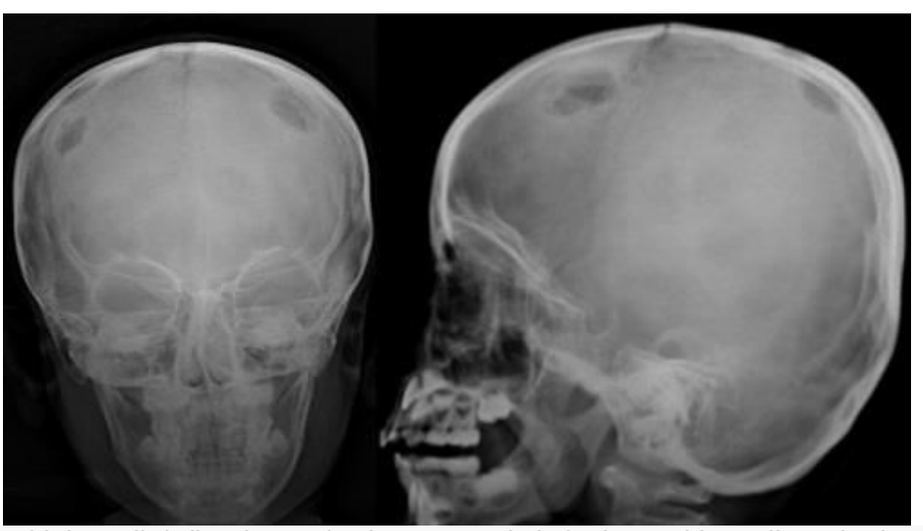
Management
- No treatment is an option if asymptomatic.
- **oral prednisolone (80% of patients respond)**
- splenectomy if platelets < 30 after 3 months of steroid therapy
- IV immunoglobulins
- immunosuppressive drugs e.g. cyclophosphamide

Prognosis
- The principal cause of death in patients with ITP is intracranial haemorrhage

Langerhans cell histiocytosis

- Langerhans cell histiocytosis is a rare condition associated with the abnormal proliferation of histiocytes.
- Also called (Eosinophilic granuloma, Histiocytosis X)
- It typically presents in childhood with bony lesions.

Features
- bone pain, typically in the skull or proximal femur
- cutaneous nodules
- **recurrent otitis media/mastoiditis**



Young girl with multiple well defined 'punched out' osteolytic lesions with scalloped edges (geographic skull) are seen in the bilateral parietal regions. The lesions have a characteristic bevelled edge.

Diagnostics
- X-ray: osteolytic lesions
- Biopsy (confirmatory test):
  - on electromicroscopy → tennis racket-shaped **Birbeck granules**
  - proliferation of Langerhans cells; polygonal cells with coffee-bean shaped nuclei, eosinophilic cytoplasm, and **Birbeck granules**

Myelofibrosis

Myelofibrosis - most common presenting symptom - lethargy

Tear-drop poikilocytes = myelofibrosis

Overview

- a myeloproliferative disorder
- thought to be caused by hyperplasia of abnormal megakaryocytes
- the resultant release of platelet derived growth factor is thought to stimulate fibroblasts
- haematopoiesis develops in the liver and spleen
- commonly **associated with the JAK2 kinase mutation.**

Features

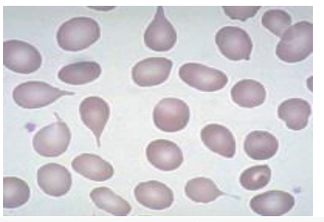
- e.g. elderly person with symptoms of anaemia e.g. **fatigue** (**the most common presenting symptom)**
- massive splenomegaly
  - (due to extramedullary hematopoiesis)
- hypermetabolic symptoms: weight loss, night sweats etc

Complications

- Myelofibrosis can change to acute myeloid leukaemia.

Laboratory findings

- anaemia
- high WBC and platelet count early in the disease
- 'tear-drop' poikilocytes on blood film
- unobtainable bone marrow biopsy - 'dry tap' therefore trephine biopsy needed
  - bone marrow biopsy is characterized by excessive proliferation of megakaryocytes.
- high urate and LDH (reflect increased cell turnover)



Blood film showing the typical 'tear-drop' poikilocytes of myelofibrosis

Treatment

- Bone marrow transplant is the only curative treatment

Myelodysplastic syndrome (MDS)

- premalignant condition.
- primarily affects elderly people (> 60).
- more common in males than in females

Pathophysiology

- clonal mutation predominates in the bone marrow, suppressing healthy stem cells.
- **the main cause of cytopenias**
  - **In the early stages of MDS → increased apoptosis (programmed cell death).**
  - As the disease progresses and converts into leukemia, → proliferation of leukemic cells overwhelms the healthy marrow.

Causes

- primary or idiopathic MDS (80%)
- genetic predisposition
- hematopoietic stem cell injury caused by exposure to any of the following:
  - Cytotoxic chemotherapy
  - Radiation
  - Viral infection

- Genotoxic chemicals (eg, benzene)

Features

macrocytic anaemia, thrombocytopenia and neutropenia with a small number of circulating blasts → suggests a diagnosis of myelodysplastic syndrome

- 80% of patients present because of symptoms of anaemia (fatigue and malaise)
- Petechiae, ecchymoses, and nose and gum bleeding are common manifestations of a low platelet count.
- neutropenia may leads to fever and infections
- **blood film:**
  - dimorphic picture (some red cells are hypochromic and microcytic, while others appear macrocytic)
  - neutrophils are hypogranular and hyposegmented (Pelger-Huet cells).
  - The peripheral blood count may show;
    - single cytopenia (anemia, thrombocytopenia, or neutropenia) in the early phase or
    - bicytopenia (2 deficient cell lines) or
    - pancytopenia (3 deficient cell lines) in later stages.
  - unexplained macrocytic anemia with no evidence of megaloblastic anemia
- **Bone marrow aspirate** stained with **Perls' stain** showed **ring sideroblasts**
  - Ring sideroblasts contain an abnormally high concentration of iron, usually stored in perinuclear mitochondria.
  - Perls' stain (which stains for iron) shows this iron deposition as a dark ring around the margin of the nucleus.
  - Cytogenetic studies of the bone marrow cells:
    - Chromosomal abnormalities are clonal and include 5q-, monosomy 7 (-7) or 7q-, trisomy 8 (+8),
      - Multiple combinations indicates a very poor prognosis.
      - A single abnormality, except those involving chromosome 7, indicates good prognosis.

Classification

- The (French-American-British (FAB) system classifies MDS into the following five subgroups :
  - Refractory anemia (RA)
  - RA with ringed sideroblasts (RARS)
    - RA and RARS are characterized by ≤ 5% myeloblasts in bone marrow.
    - RARS is defined morphologically as having 15% erythroid cells with abnormal ringed sideroblasts,
    - Both RA and RARS have a prolonged clinical course and a low prevalence of progression to acute leukemia.
      - progression to acute leukemia occurred in 5% of RARS cases, compared with 25% of RAEB cases
  - RA with excess blasts (RAEB; 6-20% myeloblasts)
  - RAEB in transition to AML (RAEB-T; 21-30% myeloblasts)
    - acute myeloid leukemia (AML; >30%).
  - Chronic myelomonocytic leukemia (CMML)
    - manifests as
      - monocytosis of ≥1000/μL,
      - total white blood cell (WBC) count of < 13,000/μL, and
      - trilineage dysplasia.
    - CMML must be differentiated from classic chronic myelocytic leukemia, which is characterized by a negative Ph chromosome.
- WHO classification 2008:
  - Refractory anaemia with unilineage dysplasia- ie anaemia, neutropaenia or thrombocytopaenia (<5% blasts)
  - Refractory anaemia with ring sideroblasts (<5% blasts; >15% sideroblasts)
  - Refractory anaemia with multilineage dysplasia (based on bone marrow dysplasia in 2 or more myeloid lineages)
  - Refractory anaemia with excess blasts-1(5-9% blasts) and refractory anaemia with excess blasts -2 (10-19%)
    - **Blasts > 20% is now classified as acute myeloid leukaemia.**
  - Myelodysplasia unclassified
  - Myelodysplasia with isolated 5qdel(cytogenetic abnormality with prognostic significance)

Prognosis

- Median survival is two years.
- **Patients are more likely to have serious infections or life-threatening bleeds than blastic transformation.**
- MDS who progress to acute leukemia have a poor prognosis than that of de novo acute myeloid leukemia (response to chemotherapy is worse)
- International Prognostic Scoring System (IPPS)
  - The revised I (IPSS-R) score is calculated on the basis of five variables:
    1. Hemoglobin level
    2. Absolute neutrophil count
    3. Platelet count
    4. Percentage of bone marrow blasts
    5. Cytogenetic category

Management

- Supportive therapy,
  - including transfusions of the cells that are deficient (ie, red blood cells [RBCs], platelets), and treatment of infections are the main components of care.
  - As the vast majority are elderly patients with other medical conditions, excessive intervention is unwarranted (لا مبرر له).
  - Granulocyte-colony stimulating factor (G-CSF) and recombinant erythropoietin (r-Epo) can improve blood counts.
    - National Comprehensive Cancer Network (NCCN) guidelines recommend the use of erythropoiesis-stimulating agents (ESAs) for treatment of symptomatic anemia in patients in the R-IPSS very low risk, low risk, or intermediate risk category whose tumor lacks the 5q31 deletion and whose level of endogenous EPO is ≤500 mU/mL.
    - In cases of the presence of ringed sideroblasts or an **absence of response**, the addition of **granulocyte colony-stimulating factor (G-CSF; filgrastim),** 1–2 µg/kg 1–3 times per week should be considered.
- hypomethylating agent azacytidine, which has been shown to improve survival compared with either supportive or aggressive therapy and is approved for use in MDS by (FDA).
- Aggressive cytotoxic chemotherapy is generally reserved for treatment of transformation to acute myelogenous leukaemia (AML) in younger patients.

Leuco-erythroblastic anaemia

- **leuco-erythroblastic anaemia (left-shifted granulocytic series and nucleated red blood cells)**
- This can be seen with:
  - high bone marrow turnover, e.g. in severe haemolytic anaemia
    - (the reticulocyte count will be high),
  - myelofibrosis and chronic myeloid leukaemia
    - (where there will be splenomegaly and the white cell and platelet count will usually be raised)
  - bone marrow invasion.
    - **Often in bone marrow invasion the invading malignancy will already have been diagnosed previously.**
    - The diagnosis requires a bone marrow trephine, which will usually show replacement of haematopoietic tissue with malignant cells.

Polycythaemia

Polycythaemia may be relative, primary (polycythaemia rubra vera) or secondary

Relative causes

- dehydration
- stress: Gaisbock syndrome

Primary

- polycythaemia rubra vera

Secondary causes

- COPD
- altitude
- obstructive sleep apnoea

- excessive erythropoietin: cerebellar haemangioma, hypernephroma, hepatoma, uterine fibroids*
  - *uterine fibroids may cause menorrhagia which in turn leads to blood loss - polycythaemia is rarely a clinical problem

To differentiate between true (primary or secondary) polycythaemia and relative polycythaemia:

- **red cell mass** studies are sometimes used. In true polycythaemia the total red cell mass in males > 35 ml/kg and in women > 32 ml/kg
- The discovery of the JAK2 mutation has made red cell mass a second-line investigation for patients with suspected JAK2-negative PRV.
- JAK2 is a crucial tyrosine kinase which transmits the EPO signal to increase red cells production.

Polycythaemia rubra vera (PRV)

Polycythaemia rubra vera is associated with a low ESR

Polycythaemia rubra vera - around 5-15% progress to myelofibrosis or AML

Polycythaemia rubra vera - JAK2 mutation

- Polycythaemia rubra vera (PRV) is a myeloproliferative disorder caused by clonal proliferation of a marrow stem cell leading to an increase in red cell volume, often accompanied by overproduction of neutrophils and platelets.
- a mutation in JAK2 is present in approximately 95% of patients with PRV and this has resulted in significant changes to the diagnostic criteria.
- peak incidence in the sixth decade

Features

- **hyperviscosity**
- **pruritus, typically after a hot bath**
- **splenomegaly**
- haemorrhage (secondary to abnormal platelet **function** NOT NUMBER)
- plethoric appearance
- hypertension in a third of patients
- low ESR
- **Low EPO levels**
  - **the strongest pointer towards primary polycythaemia**
  - myeloproliferative → increased red blood cell production by the marrow → turns off endogenous EPO production →low EPO level.
- raised leukocyte alkaline phosphatase (ALP)
- **Mild prolonged PT & PTT**: this is related to the ratio of plasma and citrate. In the blue tubes that are used for coagulation tests the ratio is normally 1 citrate to 9 of whole blood. If there is less plasma due to the polycythaemia there will be excess citrate and this will prolong coagulation tests such as the APTT and prothrombin time.
- Others: hyperuricaemia, peptic ulceration.

Investigations

Following history and examination, the British Committee for Standards in Haematology (BCSH) recommend the following tests are performed

- full blood count/film (raised haematocrit; neutrophils, basophils, platelets raised in half of patients)
- JAK2 mutation
- serum ferritin
- renal and liver function tests

If the JAK2 mutation is negative and there is no obvious secondary causes the BCSH suggest the following tests:

- red cell mass
- arterial oxygen saturation
- abdominal ultrasound
- serum erythropoietin level

- bone marrow aspirate and trephine
- cytogenetic analysis
- erythroid burst-forming unit (BFU-E) culture

Diagnostic criteria

JAK2-positive PRV - diagnosis requires both criteria to be present

Criteria	Notes
A1	High haematocrit (>0.52 in men, >0.48 in women) OR raised red cell mass (>25% above predicted)
A2	Mutation in JAK2

JAK2-negative PRV - diagnosis requires A1 + A2 + A3 + either another A or two B criteria

Criteria	Notes
A1	Raised red cell mass (>25% above predicted) OR haematocrit >0.60 in men, >0.56 in women
A2	Absence of mutation in JAK2
A3	No cause of secondary erythrocytosis
A4	Palpable splenomegaly
A5	Presence of an acquired genetic abnormality (excluding BCR-ABL) in the haematopoietic cells
B1	Thrombocytosis (platelet count >450 * 10^9/l)
B2	Neutrophil leucocytosis (neutrophil count > 10 * 10^9/l in non-smokers; > 12.5*10^9/l in smokers)
B3	Radiological evidence of splenomegaly
B4	Endogenous erythroid colonies or low serum erythropoietin

Management

- aspirin
- venesection - first line treatment
- hydroxyurea -slight increased risk of secondary leukaemia
- phosphorus-32 therapy

Prognosis

- thrombotic events are a significant cause of morbidity and mortality
- 5-15% of patients progress to myelofibrosis
  - **Pastest note → Transition from primary polycythaemia to myelofibrosis occurs in about 30%of patients,** therefore, **the probability of developing myelofibrosis is higher and thus more likely than acute leukaemia**
- 5-15% of patients progress to acute leukaemia (risk increased with chemotherapy treatment) particularly if patients have been exposed to radioactive phosphorous treatment or busulfan therapy.

Myelofibrosis

- Primary myelofibrosis is a disorder in which normal bone marrow tissue is gradually replaced with a fibrous scar-like material.
- Over time this leads to progressive bone marrow failure.
- Most commonly seen in older adults (5th/6th decade)
- It is almost always accompanied by significant splenomegaly and is JAK2 mutation-positive in about 50% of cases.
- fatigue, splenomegaly and teardrop cells

Complications

- Portal hypertension
  - occurs in 7% of patients with primary myelofibrosis
  - may be related to increased portal flow resulting from marked splenomegaly and to intrahepatic obstruction resulting from thrombotic obliteration of small portal veins.
  - This may result in variceal bleeding or ascites.
  - Hepatic or portal vein thrombosis may occur.
  - Symptomatic portal hypertension is managed by splenectomy, with or without the creation of a portosystemic shunt.
- Peripheral blood smear
  - **tear-drop** RBC
  - membrane is disrupted when RBC passed through fibrosis to leave bone marrow
  - nucleated RBCs
  - band granulocytes

Treatment

- It is generally incurable,
- although bone marrow transplantation and JAK2 inhibitors have a role in younger patients.

Disseminated intravascular coagulation (DIC)

- (DIC) is characterized by:
  - systemic activation of blood coagulation → deposition of fibrin →microvascular thrombi in various organs and contributing to multiple organ dysfunction syndrome (MODS).
  - Consumption of coagulation proteins and platelets (from ongoing activation of coagulation) may induce severe bleeding
- present in 1% of hospitalized patients.

Common Causes

- Sepsis and severe infection (most commonly)
- Trauma (neurotrauma)
- Organ destruction (eg, pancreatitis)
- Malignancy (solid and lymphoproliferative/myeloproliferative malignancies)
- Severe transfusion reactions
- Obstetric complications – Amniotic fluid embolism; abruptio placentae; hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome; eclampsia

Diagnosis

- The **platelet count and the fibrinogen level** are almost always decreased in the presence of DIC.Although these tests are not specific for DIC, **normal levels exclude the possibility of DIC**.
- The presence of schistocytes, or red cell fragments, is a frequent but non-specific finding in DIC.
- Increased levels of **fibrin degradation products (FDP)** occur in a variety of conditions in which clot formation and lysis occur. **D-dimers** are produced by the action of plasmin on cross-linked fibrin.These tests reflect the microangiopathy of DIC and have been found to be sensitive, specific, and efficient in the diagnosis of DIC.
- **the combination of the D-dimer and the FDP assay provides the most rapid and specific diagnosis of DIC.**

Treatment

- When bleeding is the major problem, the aim is to maintain the prothrombin and activated thromboplastin time at a ratio of 1.5 times of the control and the fibrinogen level above 1 g/L.
- **fibrinogen replacement infusion (cryoprecipitate) is the appropriate first choice**
- Platelet transfusion is recommended if the count is less than 50 $\times 10^9$/L.

Thrombocytopenia

Causes of thrombocytopenia:
- ❖ **↓production (bone marrow infiltration, suppression, or fibrosis),**
- ❖ **↑ destruction (DIC, ITP, and TTP/HUS),**
- ❖ **dilution**
- ❖ **sequestration due to splenomegaly.**

Causes of severe thrombocytopenia
- ITP
- DIC
- TTP
- haematological malignancy

Causes of moderate thrombocytopenia
- heparin induced thrombocytopenia (HIT)
- drug-induced (e.g. quinine, diuretics, sulphonamides, aspirin, thiazides)
- alcohol
- liver disease
- hypersplenism
- viral infection (EBV, HIV, hepatitis)
- **pregnancy**
- SLE/antiphospholipid syndrome
- vitamin B12 deficiency

Gestational thrombocytopaenia
- very common.
- Most importantly, the patient should be closely monitored from the present time until she delivers
- The platelet count is very mildly reduced
- **no specific intervention**
- Steroids may only need to be considered if the platelet count is persistently less than 30 within the last 2 weeks of pregnancy.
- Steroids may be considered in the last couple of weeks of pregnancy to raise the platelet count temporarily so that a caesarean section or epidural anaesthesia may be undertaken safely. This may well be combined with intravenous immunoglobulin

immune thrombocytopenia
- the patient is well.
- There is post viral illness with quite marked thrombocytopenia but other full blood count (FBC) parameters are normal.
- The diagnosis is one of exclusion,
- **The most important investigation is a blood film.** Although not diagnostic, this will confirm the FBC findings and also **exclude more sinister pathology such as leukaemia**.
- in the absence of major bleeding, management would be observation, as it can resolve spontaneously.

Thrombocytosis

- Thrombocytosis is an abnormally high platelet count, usually > 400 * 10^9/l.
- Thrombopoietin is the key hormone in the regulation of megakaryocyte differentiation.

Causes
- reactive: platelets are an acute phase reactant - platelet count can increase in response to stress such as a severe infection or surgery
  - **The most common cause of thrombocytosis is a reactive thrombocytosis.**
  - **May occur as a response to exercise**
  - Secondary thrombocytosis does not place the patient at risk for haemostatic or cardiovascular events.
- malignancy
- essential thrombocytosis (see below), or as part of another myeloproliferative disorder such as chronic myeloid leukaemia or polycythaemia rubra vera
- hyposplenism

Essential thrombocytosis (ET):

- Essential thrombocytosis is one of the myeloproliferative disorders which overlaps with chronic myeloid leukaemia, polycythaemia rubra vera and myelofibrosis.
- Megakaryocyte proliferation results in an overproduction of platelets, in the absence of any identifiable cause.
- usually affects older people between the ages of 50 and 70 years
- occurs equally in both males and females.

Features

- asymptomatic (25-33%)
- tingling or burning in the hands and feet, headache, visual problems, weakness and dizziness.
  - burning sensation in the hands is a characteristic symptom
  - Erythromelalgia
    - burning pain, warmth, and redness of the extremities
  - The pain increases with exposure to heat and improves with cold
  - These symptoms result from excessive numbers of platelets causing blockages in small or large blood vessels in different parts of the body.
- Other symptoms include sweating, low-grade fever, and pruritus.
- Splenomegaly (40-50%)
- Hepatomegaly (20%)
- both thrombosis and haemorrhage can be seen

Investigations

- Complete blood cell count (CBC)
  - platelet count > 600 * 10^9/l
  - Around 30% will also have a mildly raised RBC and / or WBC.
    - A red blood cell (RBC) mass study helps to exclude polycythemia vera. The RBC mass is elevated in polycythemia vera, but is normal in essential thrombocytosis.
- Genetic studies
  - The majority of patients have mutations in one of three genes:
    1. Janus kinase 2 (***JAK2***), **50-60%** of patients.
    2. calreticulin (*CALR*),
       - found in 25%
    3. myeloproliferative leukemia virus oncogene (*MPL*).
       - about 3-5% of cases.
       - *MPL* codes for the thrombopoietin receptor protein, which promotes the growth and proliferation of megakaryocytes.
       - The mutations result in constitutive activation of the thrombopoietin receptor protein.
  - Rare cases involve mutations in the thrombopoietin gene (*THPO*),
    - associated with autosomal dominant hereditary thrombocytosis
- Bone marrow examination
  - ↑ bone marrow cellularity (found in 90%)
  - Megakaryocytic hyperplasia is common
  - Bone marrow reticulin is usually increased, but collagen fibrosis is uncommon
- Elevation of C-reactive protein (CRP), fibrinogen, and interleukin 6 levels suggests secondary thrombocytosis, because those are acute-phase reactants
- Vitamin B-12 levels are increased in 25% of patients
- Uric acid levels are elevated in 25% of patients

Diagnosis

- British guidelines propose the following five criteria for diagnosis of essential thrombocytosis :
  1. Sustained platelet count ≥450 × 10^9/L
  2. Presence of an acquired pathogenetic mutation (eg, in the *JAK2, CALR* or *MPL* genes)
  3. No other myeloid malignancy, especially polycythemia vera, primary myelofibrosis, chronic myeloid leukemia, or myelodysplastic syndrome
  4. No reactive cause for thrombocytosis and normal iron stores
  5. Bone marrow aspirate and trephine biopsy showing increased megakaryocyte numbers displaying a spectrum of morphology with predominant large megakaryocytes with hyperlobated nuclei and abundant cytoplasm; reticulin is generally not increased (grades 0–2/4 or grade 0/3)
  - Diagnosis requires the presence of criteria 1–3 or criterion 1 plus criteria 3–5.

adverse prognostic markers for essential thrombocythaemia (ET):

- Age above 60
- Symptomatology - particularly thrombosis and
- Platelet count above 1500.
- Previous thrombosis
- Obesity
- Cardiovascular risk factors such as smoking, hypertension, and hypercholesterolemia
- Markers of hypercoagulability such as factor V Leiden and antiphospholipid antibodies [4]
- JAK2 mutation

Management

- **low risk → observation only**
- high-risk of thrombosis (eg, age >60, history of thrombosis, or platelet counts >1500).
  - hydroxyurea (hydroxycarbamide) is widely used to reduce the platelet count
    - first-line treatment
  - interferon-α is also used in younger patients
    - Interferon alfa is a biologic response modifier.
    - used as second line in older patient
    - Interferon alfa is not known to be teratogenic and does not cross the placenta, perhaps making it safe for use during pregnancy.
    - Italian guidelines recommend interferon alfa as a first-line platelet-lowering therapy for patients younger than 40 years
  - low-dose aspirin may be used to reduce the thrombotic risk
    - low-dose aspirin may be useful in treating patients with symptoms of microvascular occlusion (eg, erythromelalgia).
    - Patients with the JAK2 mutation or cardiovascular risk factors can be treated with daily low-dose aspirin
    - Extreme thrombocytosis may promote the abnormal adsorption of large von Willebrand factor (VWF) multimers.
      - These patients should be screened for the presence of acquired von Willebrand disease (VWD).
        - if **ristocetin cofactor level** (Functional von Willebrand Factor) is at least 30% in absence of other high risk factors; Low-dose aspirin therapy (eg, ≤100 mg/day) is acceptable
        - if it is less than 30%, all aspirin should be avoided.
- **Plateletpheresis**
  - If platelet is very high with symptoms of clotting or bleeding

Prognosis

- extremely good in ET with survival of over two decades expected.
- The risk of transforming to acute myeloid leukaemia is relatively low (<1%).

Thrombotic thrombocytopenic purpura (TTP)

(TTP) is classically characterised as a **pentad of**: thrombocytopenia, microvascular haemolysis, fluctuating neurological signs, renal impairment and fever.

HUS or TTP? Neuro signs and purpura point towards TTP

TTP - plasma exchange is first-line

Pathogenesis of thrombotic thrombocytopenic purpura (TTP)

- abnormally large and sticky multimers of von Willebrand's factor cause platelets to clump within vessels
- in TTP there is a deficiency of ADAMTS13 (a metalloprotease enzyme) which breakdowns large multimers of von Willebrand's factor
- The primary event that occurs appears to be endothelial damage, which then leads to → thrombus formation, → end organ damage (eg brain and kidneys) and platelet consumption
- overlaps with haemolytic uraemic syndrome (HUS)

Causes

- post-infection e.g. urinary, gastrointestinal (Escherichia coli 0157 subtype)
- pregnancy
- drugs:
  - ciclosporin,
  - oral contraceptive pill,
  - penicillin, metronidazole
  - antiplatelets**: clopidogrel** or ticlodipine (< 1%),
  - acyclovir,
  - FK506,
  - Penicillamine
  - sulphonamides
- tumours
- SLE
- HIV

Features

- rare, typically adult females
- fever
- fluctuating neuro signs (microemboli)
- microangiopathic haemolytic anaemia
- renal failure
- thrombocytopenia
- **Which investigation will be most useful to establish the diagnosis?**
  - **Peripheral blood film**
    - The peripheral blood film reveals fragmented RBCs (schistocytes, eg, spherocytes, segmented RBCs, burr cells, or helmet cells).

Management

- no antibiotics - may worsen outcome
- **plasma exchange is the treatment of choice**
  - **TTP has an untreated mortality of up to 90% and therefore rapid plasma exchange (PEX) may be a life saving intervention.**
- steroids, immunosuppressants
  - Intravenous methylprednisolone is indicated after treatment with PEX has been completed.
- Vincristine
- Platelet transfusion in TTP is only indicated if there is an on-going life-threatening bleed.
- There is no current role for intravenous immunoglobulin in the routine management of TTP, however there have been reports of its successful use in PEX- and steroid-refractory cases.

Prognosis

- In adults, the mortality rate 20-50%

January 2013 exam: H/O confusion + fever + ↓Platelets 65 , ↑Urea 23, ↑Creatinine 366.What is the most likely diagnosis? Thrombotic thrombocytopenic purpura

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Von Willebrand's disease

The combination of a petechial skin rash combined with a slightly elevated APTT and reduced factor VIII activity make Von Willebrand's disease the most likely diagnosis

Desmopressiin - induces release of von Willebrand's factor from endothelial cells

Overview

- Von Willebrand's disease is the most common inherited bleeding disorder.
- The majority of cases are inherited in an **autosomal dominant** fashion*
- characteristically behaves like a platelet disorder i.e. epistaxis and menorrhagia are common whilst haemoarthroses and muscle haematomas are rare
- Symptoms are exacerbated by medications that inhibit platelet function, such as aspirin and other NSAIDs.

Role of von Willebrand factor

- large glycoprotein which forms massive multimers
- Von Willebrand factor is a coagulation protein that **binds to collagen and to the GpIb platelet receptor during platelet adhesion.**
  - promotes platelet adhesion to damaged endothelium
- carrier molecule for factor VIII
- Factor VIII circulates bound to von Willebrand factor (vWF), which **protects factor VIII from degradation.**
  - Decreased vWF (in part) prolongs the PTT by leading to decreased factor VIII.
  - In people with hemophilia, strategies to increase circulating levels of factor VIII include maximizing vWF levels.
  - increases vWF secretion (leading to increased functional levels of factor VIII).
  - Even in hemophilia A, there is still a small amount of normal factor VIII (<5%).
- The **intrinsic** coagulation pathway is defective in von Willebrand disease.

Types

- **type 1**: partial reduction in vWF (80% of patients)
  - the most common form
  - patients have up to a 50% reduction in von Willebrand factor (vWF).
  - **Autosomal dominant with variable penetrance**
  - Many are asymptomatic and are only diagnosed following an episode of bleeding associated with a dental extraction or minor surgery.
- **type 2:** abnormal form of vWF
- **type 3**: total lack of vWF (autosomal recessive) (most severe form)

Investigation

- prolonged bleeding time (due to impaired platelet adhesion and aggregation)
  - The bleeding time would be a good screening test but it will not give a quantitative measurement of bleeding tendency in type I vWBD
  - neither sensitive nor specific
  - **platelet function analyser (PFA100), have better testing characteristics than the bleeding time**
- **APTT may be prolonged** (due to reduced circulating factor VIII).
- factor VIII levels may be moderately reduced
  - **the most useful test to assess bleeding tendency in Von Willebrand's disease ? → Plasma factor VIII activity**
- **vWB antigen and activity (Ristocetin cofactor assay) (RICOF)**
  - **The most useful test in practice is to do the vWB antigen and activity (RICOF),** but you would also do FVIIIc as this is also low in vWD.
- In type I vWD the prothrombin time (PT) and Platelet count **will be normal**.
- defective platelet aggregation with ristocetin

Management

- **tranexamic acid for mild bleeding**
- desmopressin (DDAVP):
  - raises levels of vWF by inducing release of vWF from Weibel-Palade bodies in endothelial cells
    - DDAVP is the initial treatment of choice for patients with VWD type 1.
      - Other therapies such as factor VIII concentrates containing VWF are not usually required.
- factor VIII concentrate
- In **minor trauma**,
  - desmopressin (DDAVP) can be used to increase the concentration of VWF.
  - The choice of treatment for a mild vWB facing a more invasive procedure would be DDAVP, providing there is no contraindication.
  - vWB factor concentrate would be reserved as second line treatment to DDAVP.
- for **major surgery**,
  - factor VIII concentrate is used to increase the concentration of vWF.
    - The most commonly used is Humate-P.
    - Purified or recombinant preparations are avoided since they contain only small concentrations of vWF.
- for Women with menorrhagia:
  - Oral contraceptives (the Pill) raise the level of von Willebrand factor in the blood for women with Type 1 VWD.

Haemophilia

Definitions

- Haemophilia A is due to a deficiency of factor VIII whilst in haemophilia B (Christmas disease) there is a lack of factor IX
  - Hemophilia A (factor VIII): ~ 80% of cases
  - Hemophilia B (factor IX): ~ 20% of cases

Etiology

- X-linked recessive disorder
  - Occurs almost exclusively in males due to an X-linked pattern of inheritance.
  - typically skips generations
  - A carrier mother has a 50% chance of passing down the disease to her sons and a 50% chance of passing down the carrier gene to her daughters.
- Up to 30% of patients have no family history of the condition.

Pathophysiology

- The pathological problem in both haemophilia A and haemophilia B is the inability to form a functional tenase complex to activate factor X to factor Xa
- The intrinsic coagulation pathway is defective in hemophilia.

Features

- typically present initially with easy bruising secondary to minimal trauma,
- haemoarthroses, haematomas
  - Musculoskeletal bleeding is the most common type of haemorrhage.
- prolonged bleeding after surgery or trauma,

Severity	Clinical signs	Factor VIII or IX activity
Physiologic condition	None	≥ 50%
Mild hemophilia	Hematomas following severe trauma	> 5% to < 50%
Moderate hemophilia	Hematomas following mild trauma	≥ 1% to 5%
Severe hemophilia	Spontaneous hematomas	< 1%

Petechial bleeding is a common sign of platelet disorders, NOT coagulation disorders such as hemophilia

Blood tests

- prolonged APTT
- mixing study
  - requested if the aPTT is prolonged.
  - The patient's plasma is mixed with normal plasma and the aPTT repeated.
  - Correction of aPTT with mixing study suggests coagulation factor deficiency.
- **plasma factor VIII and IX assay**
- bleeding time, thrombin time, prothrombin time normal

Although female carriers of the haemophilia gene do not normally suffer from increased bleeding risk, APTT may be prolonged.

Treatment

- factor VIII or IX replacement.
- Side effects:
  - Up to 10-15% of patients with haemophilia A develop **antibodies to factor VIII treatment**

Methemoglobinemia

Methemoglobin
- hemoglobin is oxidized to the ferric (Fe^{3+})
- ↓ affinity for O_2
- ↑ affinity for cyanide (CN^-)
  - ➢ CN^- poisoning treated with methemoglobin

- Methemoglobin (met-Hb) results from the presence of iron in the ferric form (Fe^{3+}) instead of the usual ferrous form (Fe^{2+}).
- met-Hb cannot carry oxygen
- met-Hb is a naturally occurring oxidized metabolite of hemoglobin, and physiologic levels (< 1%) are normal.
- Methemoglobinemia (congenital or acquired) occurs when (RBCs) contain methemoglobin at levels higher than 1%.
- Acquired methemoglobinemia is considerably more common than congenital forms.
- The low level of methemoglobin is maintained through 2 important mechanisms.
  1. the hexose-monophosphate shunt pathway within the erythrocyte. Through this pathway, oxidizing agents are reduced by glutathione.
  2. The second and more important mechanism involves two enzyme systems:
     - ❖ **diaphorase I:** requires nicotinamide adenine dinucleotide (NADH)
       - the major enzymatic system (This enzyme system is responsible for the removal of 95-99% of the methemoglobin that is produced under normal circumstances.)
       - Cytochrome b5 reductase plays a major role in this process by transferring electrons from NADH to methemoglobin, an action that results in the reduction of methemoglobin to hemoglobin.
     - ❖ diaphorase II: requires nicotinamide adenine dinucleotide phosphate (NADPH).
       - plays only a minor role in the removal of methemoglobin.
       - This enzyme system utilizes glutathione production and glucose-6-phosphate dehydrogenase (G6PD) to reduce methemoglobin to hemoglobin.
       - Play a more important role in methemoglobin regulation in patients with cytochrome b5 reductase deficiencies.
       - can be accelerated by exogenous cofactors such as methylene blue

Effect of Methemoglobin:
- does not bind oxygen, thus leading to a functional **anemia**.
- causes a **left shift of the oxygen-hemoglobin dissociation curve**, resulting in decreased release of oxygen to the tissues.
  - ➢ Normal people generate met-Hb but in very low levels in the range of 0.5% to 3%.
  - ➢ should be suspected when the oxygen saturation as measured by pulse oximetry is significantly different (lower) from the oxygen saturation calculated from arterial blood gas analysis (saturation gap). **(low SpO_2 with normal PaO_2 and SaO_2(on ABG)**
- presence of **anemia and cyanosis** despite oxygen treatment results from both of these effects.

Causes
- congenital (secondary to a deficiency in methemoglobinemia reductase)
- acquired
  - ➢ **Dapsone**
  - ➢ local anesthetics (topical and injectable)
  - ➢ nitrates
  - ➢ **amyl nitrite**
  - ➢ **aniline dyes**
  - ➢ The presence of methemoglobin may also be a marker and predictor of sepsis, resulting from release of excessive amounts of nitrous oxide (NO)
  - ➢ patients with low catalase activity (inherited or acquired) treated with rasburicase for tumor lysis syndrome → formation of hydrogen peroxide → methemoglobinemia
    - Some authors have suggested that catalase activity be measured before rasburicase therapy is initiated in this setting.

Drugs that cause methaemoglobinaemia include:
- Phenacetin
- Sulphonamides
- **Dapsone**
- **Primaquine**
- Lido**caine**
- Pro**caine**
- Benzo**caine**.

Congenital (hereditary) Methemoglobinemia
- autosomal recessive
- two forms of congenital **cytochrome b5 reductase (b5R) deficiency** exist:

type Ib5R deficiency	**type IIb5R**
more common cytochrome b5 reductase is absent only in RBCs Homozygotes appear cyanotic but usually are otherwise asymptomatic. Heterozygotes may develop acute, symptomatic methemoglobinemia after exposure to certain drugs or toxins. Methemoglobin levels typically range from 10% to 35%. Life expectancy is not influenced	less common cytochrome b5 reductase is deficient in all cells, not just RBCs. associated with several other medical problems, including mental retardation, microcephaly, and other neurologic complications. Life expectancy is severely compromised, and patients usually die at a very young age.

presence of abnormal hemoglobins (hemoglobin M [Hb M])
- autosomal dominant
- in most of these hemoglobins, tyrosine replaces the histidine residue, which binds heme to globin.
- This replacement displaces the heme moiety and permits oxidation of the iron to the ferric state.
- Hb M is more resistant to reduction by the methemoglobin reduction enzymes
- Patients with Hb M appear cyanotic but are otherwise generally asymptomatic.

Feature (are proportional to the methemoglobin level) :

Classical presentation includes cyanosis with chocolate-colored blood

- 3-15% - Slight discoloration (eg, pale, gray, blue) of the skin and blood color changes (brown or chocolate color).
  - Discoloration of the skin and blood is the most striking physical finding.
  - Fatigue, flu-like symptoms, and headaches may be the only manifestations in the initial phase.
- 15-20% - Cyanosis, though patients may be relatively asymptomatic
  - cyanosis is usually the first presenting symptom.
- 25-50% - Headache, dyspnea, lightheadedness (even syncope), weakness, confusion, palpitations, chest pain
- 50-70% - Abnormal cardiac rhythms; altered mental status, delirium, seizures, coma; profound **acidosis**
- >70% - Usually, death

Treatment:
- **Methylene blue :**
  - **the first line treatment**
  - contraindicated in G6PD deficiency and ineffective with hemoglobin M.
    - reduction of met-Hb by methylene blue is dependent upon NADPH generated by G6PD.
    - methylene blue has an oxidant potential → hemolysis in G6PD deficient.
- Second line treatment: when methylene blue therapy is ineffective or contraindicated
  - **Exchange transfusion**: for patients who do not respond to methylene blue or G6PD-deficient individuals who are severely symptomatic
  - Hyperbaric oxygen treatment: another option
- IV hydration and bicarbonate (for metabolic acidosis)

Anticoagulants

Heparin

- can be given as either:
  - unfractionated, intravenous heparin, or
  - low molecular weight heparin (LMWH), given subcutaneously.
- Heparins generally act by **activating antithrombin III**.
- **Unfractionated heparin** forms a complex which inhibits thrombin, **factors Xa, IXa, XIa and XIIa.**
- **LMWH however only ↑ the action of antithrombin III on factor Xa**

The table below shows the differences between standard heparin and LMWH:

	Standard Heparin	**(LMWH)**
administration	Intravenous	Subcutaneous
Action duration	short	long
Mechanism of action	Activates antithrombin III. Forms a complex that inhibits thrombin, factors Xa, IXa, XIa and XIIa	Activates antithrombin III. Forms a complex that inhibits factor Xa
Side-effects	Bleeding HIT **Osteoporosis**	Bleeding Lower risk of HIT and **osteoporosis**
Monitoring	Activated partial thromboplastin time (APTT)	Anti-Factor Xa (although routine monitoring is not required)
Notes	Useful in situations where there is a↑ risk of bleeding as anticoagulation can be terminated rapidly	Now standard in the management of venous thromboembolism treatment and prophylaxis and acute coronary syndromes

Heparin-induced thrombocytopaenia (HIT)

- **Types**
  1. **Type 1 HIT**
     - non-immune mediated reaction
     - occur soon after the initial administration of heparin (within two days)
     - due to a direct effect of the drug on platelets.
     - self-limiting condition and the platelet count will normalise with continued heparin administration.
  2. **Type 2 HIT**
     - immune mediated condition
     - **mechanism:**
       - IgG antibodies against heparin bound to platelet factor 4 (PF4).
       - Antibody-heparin-PF4 complex will be eliminated by the immune system (→ thrombocytopenia), and activates platelets → thrombosis
     - It is a prothrombotic condition despite being associated with low platelets.
     - typically arises 4 to 10 days after starting heparin therapy.
     - Patients may develop both venous and arterial thromboses,
     - low platelet counts and mild abnormalities of coagulation.
     - The D-dimer level is raised due to widespread thrombus formation.
- **Features** include a greater than 50% reduction in platelets, thrombosis and skin allergy

- Patients with (HIT), particularly those with associated thrombosis, often have evidence of **increased thrombin** generation that can **lead to consumption of protein C**.
  - If these patients are given warfarin without a concomitant parenteral anticoagulant to inhibit thrombin or thrombin generation, the further decrease in protein C levels induced by the vitamin K antagonist can trigger skin necrosis.
  - To avoid this problem, patients with HIT should be treated with a direct thrombin inhibitor, or fondaparinux, until the platelet count returns to normal levels.

- **Diagnosis**: HIT is confirmed by the presence of the HIT antibody and confirmed by the serotonin-release assay (SRA).
- **Treatment**
  - options include alternative anticoagulants such as lepirudin and danaparoid
  - Argatroban is not cleared via the kidneys; therefore, this drug is safer than lepirudin/fondaparinux for HIT patients with renal insufficiency.
  - Lepirudin is a direct thrombin inhibitor, which is cleared by kidneys exclusively, and is contraindicated in renal insufficiency.
  - Fondaparinux can be used in HIT as it does not bind to platelets, but it is contraindicated in renal insufficiency.

Heparin-induced hyperkalaemia

- Both unfractionated and low-molecular weight heparin can cause hyperkalaemia. This is thought to be caused by inhibition of aldosterone secretion.

Heparin overdose

- Heparin overdose may be reversed by protamine sulphate, although this only partially reverses the effect of LMWH.
- The dose of protamine sulphate given is dependent upon the dose of LMWH administered and the time of administration.
  - If protamine is given **within eight hours** of the LMWH then a maximum neutralising dose is **1 mg** protamine/100 units (or 1 mg) of LMWH given in the last dose.
  - If more **than eight hours** have passed since the dose of LMWH was given, administer **0.5 mg** protamine per 100 units (or 1 mg) of LMWH given.
- Protamine is administered by slow IV infusion (over 10 minutes) to avoid a **hypotensive reaction**.
- Protamine requires a high level of caution when being prescribed and administered.

Heparin resistance

- Heparin resistance is seen in up to 22% of patients undergoing cardiopulmonary bypass surgery.
- Several mechanisms resulting in heparin resistance have been identified, including:
  - **antithrombin deficiency,**
  - increased heparin clearance,
  - elevated heparin-binding proteins,
  - and elevated factor VIII and fibrinogen levels.
- For cardiopulmonary bypass in particular, rapid neutralisation of thrombin is required. In order for heparin to be successful in this, it requires antithrombin III which is an alpha2-globulin. It is therefore thought that **antitthrombin III deficiency** is the underlying problem which is seen in patients resistant to heparin during cardiopulmonary bypass.

- **Heparin and thyroid function test**
  - Heparin is having an "in vitro" effect on thyroxine (T4) levels.
  - IV heparin interferes with the thyroid function tests assay on occasions displacing bound thyroid hormone.
  - Normal TSH + high T3 and T4

Heparin and delivery

- Women who are anticoagulated with heparin until the onset of labor generally experience **vaginal delivery** with **no greater blood loss than non-anticoagulated** gravidas.
- However, Cesarean delivery in heparinized patients is **accompanied by a significantly greater blood loss** than would otherwise be anticipated.
- **If preterm labor develops in a patient receiving heparin, only the mother is anticoagulated, and protamine sulfate can be used** to reverse maternal heparinization.

Which of the following is the best way to monitor rivaroxaban compliance?

Prothrombin time

Prothrombin time(PT) is influenced by rivaroxaban in a dose-dependent way with a close correlation to plasma concentrations (r= 0.98). This makes it the optimal way to measure rivaroxaban compliance. International normalised ratiovalues are only relevant to coumarins.

Novel oral anticoagulants (NOACs)

The table below summaries the three NOACs: dabigatran, rivaroxaban and apixaban.

	Dabigatran	Rivaroxaban	Apixaban
UK brand name	Pradaxa	Xarelto	Eliquis
Mechanism of action	**Direct thrombin inhibitor**	**Direct factor Xa inhibitor**	Direct factor Xa inhibitor
Route	Oral	Oral	Oral
Excretion	Majority renal	Majority liver	Majority faecal
NICE indications	Prevention of VTE following hip/knee surgery Treatment of DVT and PE Prevention of stroke in non-valvular AF*	Prevention of VTE following hip/knee surgery Treatment of DVT and PE Prevention of stroke in non-valvular AF*	Prevention of VTE following hip/knee surgery Treatment of DVT and PE Prevention of stroke in non-valvular AF*

*NICE stipulate that certain other risk factors should be present. These are complicated and differ between the NOACs but generally require one of the following to be present:

- prior stroke or transient ischaemic attack
- age 75 years or older
- hypertension
- diabetes mellitus
- heart failure

Dabigatran

Stop dabigatran <u>two days</u> before polypectomy

- **Mode of action:** Dabigatran is a **direct thrombin inhibitor** with a rapid onset of action.
- **It is administered as a prodrug**
  - The prodrug dabigatran etexilate is rapidly converted by tissue esterases to dabigatran.
- it is predominately (80%) excreted by the kidneys.
- The anticoagulant effect starts within minutes of oral ingestion and peaks after 2-3 hours.
- **Advantage of dabigatran:**
  - due to its short half-life, a patient's coagulation status will normalize more rapidly than that of a patient treated with warfarin in almost all cases.
  - No need for routine monitoring
- **Disadvantage of dabigatran**
  - **Dabigatran is not recommended in patients with prosthetic heart valves** because their safety and efficacy have not established.
    - The rates of thromboembolism are higher for valves in the mitral compared with those in the aortic position.
    - **caged-ball valves are the most thrombogenic** followed by tilting-disk and bi-leaflet valves.
  - more thromboembolic events (e.g., valve thrombosis, stroke, TIA, and myocardial infarction) were observed with dabigatran than with warfarin;
  - excessive major bleeding (predominantly postoperative pericardial effusions requiring intervention for hemodynamic compromise) was observed with dabigatran, compared with warfarin.
- **Monitoring of the anticoagulant effects of dabigatran**
  - In general, "routine" monitoring is not required in most cases.
  - However, in some clinical situations a clinician may wish to determine the degree to which dabigatran is reducing the coagulant potential of the blood; e.g., if a patient taking dabigatran requires emergency surgery, has an intracranial or major systemic bleed, or is being considered for thrombolysis due to an ischemic stroke.
  - **The thrombin time (TT) and ecarin clotting time are considered the most accurate measures of dabigatran's anticoagulant effect.**
    - The aPTT and, if available, the thrombin time (TT) should be used to measure the anticoagulant effect of dabigatran,
  - INR and PT tests are unreliable
- **Effect of dabigatran on procedural bleeding risk**
  - **Dabigatran should be discontinued 1 to 2 days (creatinine clearance ≥ 50 mL/min)** or 3 to 5 days (creatinine clearance <50 mL/min) before invasive or surgical procedures.
  - Clinicians may want to consider "longer" periods of discontinuation for patients undergoing major surgery in which bleeding could have serious consequences (e.g., cardiac, neurosurgery, major abdominal or pelvic, spinal puncture, or placement of a spinal or epidural catheter or port).
  - If surgery is urgent and cannot be delayed, there is an increased risk of bleeding; **patients with a normal aPTT appear to have a low risk of serious bleeding.**
- **conversion from warfarin to dabigatran** (eg : patient had difficulty attending for regular INR)
  - **if a patient is taking warfarin with a therapeutic INR, it is recommended to : Stop warfarin, perform daily INR, start dabigatran when INR falls below 2.0**

- The anticoagulant effect of dabigatran starts minutes after its oral administration and peaks after 2-3 hours.

- **Contraindications**
  - **Dabigatran is contraindicated if eGFR <30ml/min.**
  - **Rivaroxaban, a direct inhibitor of activated factor X, is contraindicated if eGFR <15 and needs dose adjustment if eGFR 15–29 mL/minute**.

Ecarin clotting time is prolonged by direct thrombin inhibitors such as dabigatran.
Treatment with aspirin, warfarin or heparins does not affect Ecarin clotting time.

Idarucizumab reverses dabigatran

Ref → www.medical-masterclass.com 2017 -part 2

Warfarin

Warfarin - clotting factors affected mnemonic - 1972 (10, 9, 7, 2)

P450 inhibitors ↑ INR	**INR also ↑ by ABX that kill intestinal flora by ↓ Vit K absorption**

Dentistry in warfarinised patients - check INR 72 hours before procedure, proceed if INR < 4.0

Warfarin action → inhibition of vitamin K epoxide reductase

- Warfarin is an oral anticoagulant which inhibits the reduction of vitamin K to its active hydroquinone form, which in turn acts as a cofactor in the carboxylation of clotting factor II, VII, IX and X (mnemonic = 1972) **and protein C. (warfarin→reduces protein C levels in the blood)**
- Warfarin inhibits epoxide reductase (specifically the VKORC1 subunit), thereby diminishing available vitamin K and vitamin K hydroquinone in the tissues which inhibits the carboxylation activity of the glutamyl carboxylase.
- The half-life of warfarin is approximately 44 h

Indications

- venous thromboembolism: target INR = 2.5, if recurrent 3.5
- atrial fibrillation, target INR = 2.5
- mechanical heart valves, target INR depends on the valve type and location. Mitral valves generally require a higher INR than aortic valves.

Side-effects

- haemorrhage
- teratogenic, although can be used in breast-feeding mothers
  - **the most common teratogenic effect is →Nasal hypoplasia**
- skin necrosis: when warfarin is first started biosynthesis of protein C is reduced. This results in a temporary procoagulant state after initially starting warfarin, normally avoided by concurrent heparin administration. Thrombosis may occur in venules leading to skin necrosis
- purple toes

Contraindications

- **Warfarin is generally avoided in pregnancy.**

- **In the first trimester** it is associated with an increased risk of miscarriage, and teratogenic side effects which include chondrodysplasia patellae, asplenia and diaphragmatic herniae.
- **In the second and third trimester** it is associated with retroplacental and intracerebral foetal haemorrhage, as well as foetal microcephaly, optic atrophy and developmental delay.

Monitoring

- Patients on warfarin are monitored using the INR (international normalised ration), the ratio of the prothrombin time for the patient over the normal prothrombin time.
- Warfarin has a long half-life and achieving a stable INR may take several days.

Factors that may potentiate warfarin

- liver disease
- P450 enzyme inhibitors, e.g.: amiodarone, Clarithromycin, ciprofloxacin
  - **Clarithromycin increase INR more than ciprofloxacin**
    - Clarithromycin is metabolised by CYP3A4 and is an inhibitor, meaning that it does affect INR to a limited extent, leading to an increase.
    - Ciprofloxacin is a moderate inhibitor of CYP1A2; some effect is expected on INR, but **not as great as that for clarithromycin.**
- cranberry juice
- drugs which displace warfarin from plasma albumin, e.g. NSAIDs
- inhibit platelet function: NSAIDs

Interaction

- Lipid-lowering agents
  - Simvastatin, rosuvastatin and fibrate → potentiate the anticoagulant effects of warfarin
  - **Atorvastatin and pravastatinare least likely to interfere with warfarin**
  - **Cholestyramine** (a cholesterol-binding resin) is known to **reduce the anticoagulant action of warfarin**
    - Cholestyramine reduces absorption of a number of drugs including warfarin.
- **cranberry juice** →(↑↑warfarin effect → ↑↑ INR).The cause is thought to be bioflavonoids contained in the cranberry juice, which block cytochrome-P450-related warfarin metabolism (CYP2C9)
- **Paracetamol given in repeated doses may lead to an enhanced response to warfarin and therefore an increased INR**
- Commonly used drugs that may lead to an increased INR include cephalosporins, azathioprine, cimetidine, metronidazole and testosterone derivatives
- **Diazepam** is a p450 enzyme **inducer** and is therefore likely to reduce INR
- the concurrent use of clopidogrel with warfarin increases the bleeding risk.
- **Co-enzyme Q10 is similar to vitamin K and reduces warfarin's anticoagulant effect** (warfarin exerts its anticoagulant effect though inhibition of the synthesis of vitamin K dependent clotting factors).

Warfarin: management of high INR

A 2005 update of the BCSH guidelines emphasised the preference of prothrombin complex concentrate over FFP in major bleeding.

Situation	Management
Major bleeding	Stop warfarin Give intravenous vitamin K 5mg Prothrombin complex concentrate - if not available then FFP*
INR > 8.0 **Minor bleeding**	Stop warfarin Give intravenous vitamin K 1-3mg Repeat dose of vitamin K if INR still too high after 24 hours Restart warfarin when INR < 5.0
INR > 8.0 **No bleeding**	Stop warfarin Give vitamin K 1-5mg by mouth, using the intravenous preparation orally Repeat dose of vitamin K if INR still too high after 24 hours Restart when INR < 5.0
INR 5.0-8.0	Stop warfarin

Situation	Management
Minor bleeding	Give intravenous vitamin K 1-3mg Restart when INR < 5.0
INR 5.0-8.0 **No bleeding**	Withhold 1 or 2 doses of warfarin Reduce subsequent maintenance dose

*as FFP can take time to defrost prothrombin complex concentrate should be considered in cases of intracranial haemorrhage

Prothrombin concentrates are products of choice for warfarin reversal in the setting of active bleeding and a markedly raised INR.

management of mother and neonate if preterm labor develops in a patient on warfarin

(medical-masterclass.com 2017 part 2)

- The management is difficult if preterm labor develops in a patient on warfarin, because both the mother and the fetus are anticoagulated.
- **the best management to prevent fetal/neonatal hemorrhage → Give fresh frozen plasma to the neonate immediately after delivery**
- **Vitamin K administration does not achieve immediate reversal** of maternal anticoagulation (which may persist for 24 hours); more rapid reversal requires the transfusion of fresh frozen plasma.
- Fetal levels of coagulation factors do not correlate with maternal levels, and infusion of fresh frozen plasma into the mother does not reliably reverse fetal anticoagulation.
- A cesarean delivery may prevent hemorrhagic fetal death, and fresh frozen plasma should be administered to the neonate.

Oncology

Hodgkin's lymphoma (HL):

present at a younger age. Chest discomfort, including cough and shortness of breath, is common.

Hodgkin's lymphoma - most common type = nodular sclerosing

Hodgkin's lymphoma - best prognosis = lymphocyte predominant

Overview

- Hodgkin's lymphoma is a malignant proliferation of lymphocytes characterised by the presence of the Reed-Sternberg cell.
- haematological malignancy arising from mature B cells.
- Lymphadenopathy, typically painless and most commonly involving the cervical and/or supraclavicular nodal chain, is the most common presenting symptom of HL.

Epidemiology

- It has a bimodal age distributions being most common in the third and seventh decades

Risk factors

- history of EBV infection
- family history of Hodgkin's lymphoma
- young adults from higher socio-economic class
- Immunodeficiency: e.g., organ or cell transplantation, immunosuppressants, HIV infection , chemotherapy
- Autoimmune diseases (e.g., rheumatoid arthritis, sarcoidosis)

Features

- Painless lymphadenopathy
  - Most common is cervical lymph nodes (in ~ 60–70% of patients)
- Mediastinal mass → chest pain, dry cough, and shortness of breath
- Splenomegaly or hepatomegaly may occur if the spleen or liver are involved.
- B symptoms
  - Night sweats,
  - weight loss > 10% in the past 6 months,
  - fever > 38°C (100.4°F)
- Can occur in a variety of diseases, such as non-Hodgkin lymphoma, other malignancies, tuberculosis, and various inflammatory diseases
- Pel-Ebstein fever
  - Intermittent fever with periods of high temperature for 1–2 weeks, followed by afebrile periods for 1–2 weeks. Relatively rare but very specific for HL.
- Alcohol-induced pain
- Pruritus (focal or generalized)

Histological classification

Type	Frequency	Prognosis	Notes
Nodular sclerosing	**Most common** (around 70%)	Good prognosis	More common in women. **Associated with lacunar cells**
Mixed cellularity	Around 20%	Good prognosis	Associated with a large number of Reed-Sternberg cells
Lymphocyte predominant	Around 5%	**Best prognosis**	
Lymphocyte depleted	Rare	**Worst prognosis**	

Poor prognosis

- weight loss > 10% in last 6 months
- fever > 38 C
- night sweats
- **Other factors associated with a poor prognosis** identified in a 1998 NEJM paper included:
  - age > 45 years
  - stage IV disease
  - haemoglobin < 10.5 g/dl
  - lymphocyte count < 600/l or < 8%
  - male
  - albumin < 40 g/l
  - white blood count > 15,000/l
  - A mass of >10 cm in size

Fatigue, pruritus, EBV infection although they are common, BUT they have no prognostic significance.

staging

Ann-Arbor staging of Hodgkin's lymphoma

- I: single lymph node
- II: 2 or more lymph nodes/regions on same side of diaphragm
- III: nodes on both sides of diaphragm
  - Spleen is regarded as a Lymph Node region, So lymphoma with splenomegaly → Stage III
- IV: spread beyond lymph nodes

Each stage may be subdivided into A or B

- A = no systemic symptoms other than pruritus
- B = weight loss > 10% in last 6 months, fever > 38c, night sweats (**poor prognosis)**

Diagnosis

- **Lymph node biopsy** would be **more likely to be positive**, RSC is evident on microscopy.
- Bone marrow
  - Hodgkin results in **patchy** bone marrow infiltration, an isolated bone marrow biopsy may yield non-specific results.
  - Bone marrow biopsy is more useful for staging of advanced disease

Management:

- Early stage (IA or IIA): Radiotherapy and chemotherapy.
- Later stage (III, IVA or IVB): Chemotherapy alone.
- Large mass in chest regardless of stage: Radiotherapy and chemotherapy.
- Chemotherapy includes **ABVD**: **A**driamycin (also known as Doxorubicin), **B**leomycin, **V**incristine, **D**oxorubicin, cyclophosphamide, prednisolone, Rituximab & others
- **Relapsed Hodgkin lymphoma → salvage chemotherapy followed by BEAM conditioned autologous stem cell transplantation as the established gold standard.**

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Prognosis is good overall, but it depends on classification and staging.

Hodgkin's lymphoma (HL)	Non-Hodgkin's lymphoma (NHL)
Younger age	Older age
more often restricted to lymph nodes in the neck.	Peripheral lymphadenopathy is common
Reed-Sternberg cells are present.	Reed-Sternberg cells are NOT present.
Extra-nodal involvement un common	Extra-nodal involvement is common

Non-Hodgkin's lymphoma (NHL) (NICE guideline 2016)

- include any kind of lymphoma except Hodgkin's lymphomas.
- Most of NHL are of B cell phenotype, although T cell tumours are increasingly being recognized.
- subtypes of non-Hodgkin's lymphoma (NHL):
  - diffuse large B-cell lymphoma
  - Burkitt lymphoma.

Diagnosis

- Type of biopsy:
  - first line → excision biopsy
  - if not surgically feasible → needle core biopsy procedure
- in patient with histologically high-grade B-cell lymphoma:
  - use **FISH** (fluorescence in situ hybridisation) to identify a *MYC* rearrangement
  - If a *MYC* rearrangement is found, → use **FISH** to identify the immunoglobulin partner and the presence of *BCL2* and *BCL6* rearrangements.
- Indications of using FDG-PET-CT imaging (fluorodeoxyglucose-positron emission tomography-CT)
  - Staging
  - **to assess response** at completion of planned treatment for:
    - diffuse large B‑cell lymphoma
    - Burkitt lymphoma.
  - to assess response to treatment before autologous stem cell transplantation for high-grade (NHL).

Management

- **follicular lymphoma**
  - stage IIA → local radiotherapy as first-line
  - stage IIA + asymptomatic + single radiotherapy volume is not suitable →'watch and wait' (observation without therapy)
  - stage IIA + symptomatic + single radiotherapy volume is not suitable → treat as advanced-stage (stages III and IV) symptomatic
  - advanced-stage (stages III and IV) asymptomatic → rituximab
  - advanced-stage (stages III and IV) symptomatic → rituximab + combination with:
    - cyclophosphamide, vincristine and prednisolone (CVP)
    - cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)
    - mitoxantrone, chlorambucil and prednisolone (MCP)
    - cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon‑α (CHVPi) or
    - chlorambucil
  - **Relapsed or refractory** advanced-stage (stages III and IV) **:**
    - induction of remission → Rituximab + combination with chemotherapy
    - maintenance therapy → Rituximab monotherapy
    - **in second or subsequent remission → stem cell transplantation**
- **MALT lymphoma**
  - *H. pylori*-positive gastric MALT lymphoma → *Helicobacter pylori* eradication therapy
  - *H. pylori*-negative gastric MALT lymphoma → *Helicobacter pylori* eradication therapy
  - gastric MALT lymphoma that responds clinically and endoscopically to *H. pylori* eradication therapy but who have residual disease shown by surveillance biopsies of the stomach, + no high-risk features. → 'watch and wait' (observation without therapy)

- residual MALT lymphoma after H. pylori eradication therapy + high risk of progression [H. pylori- negative at initial presentation or t(11:18) translocation], →
  - chemotherapy (for example, chlorambucil or CVP) + rituximab **OR**
  - gastric radiotherapy.
- Non-gastric MALT lymphoma
  - localised disease sites → radiotherapy
  - if radiotherapy is not suitable **or** disseminated disease → chemotherapy (for example, chlorambucil or CVP) + rituximab
  - localised + asymptomatic + radiotherapy is not suitable → 'watch and wait' (observation without therapy)

- **mantle cell lymphoma**
  - advanced-stage , symptomatic → chemotherapy + rituximab
  - localised stage I or II → radiotherapy
  - non-progressive + asymptomatic + radiotherapy is not suitable → 'watch and wait' (observation without therapy)
  - chemosensitive mantle cell lymphoma → autologous stem cell transplantation
  - previously untreated + stem cell transplantation is unsuitable → Bortezomib

Non-Hodgkin's lymphoma

Painless, slowly progressive peripheral lymphadenopathy is the most common clinical presentation of non-Hodgkin's lymphoma. The presence of peripheral cyanosis implies the presence of cold agglutinins. Lymph node excision or core biopsy is the investigation of choice because the architecture of the node is important in determining the prognosis.

Which of the following receptors is commonly targeted in the therapy for B-cell non-Hodgkin's lymphoma?

$CD20^+$

The $CD20^+$ receptor is found on the surface of B lymphocytes and is a target for immune therapies such as rituximab. By targeting the $CD20^+$ receptor, cells that express it are depleted. Because there are greater numbers of lymphoma cells, these are depleted most.

Haematological malignancies: genetics

Below is a brief summary of the common translocations associated with haematological malignancies

t(9;22) - Philadelphia chromosome
- present in > 95% of patients with CML
- this results in part of the Abelson proto-oncogene being moved to the BCR gene on chromosome 22
- the resulting BCR-ABL gene codes for a fusion protein which has tyrosine kinase activity in excess of normal
- **poor prognostic indicator in ALL**

t(15;17)
- seen in acute promyelocytic leukaemia (M3)
- fusion of PML and RAR-alpha genes

t(1:14)
- This translocation is associated with MALT (mucosa-associated lymphoid tissue) lymphoma and deregulates BCL10

t(8;14)
- seen in **Burkitt's** lymphoma
- MYC oncogene is translocated to an immunoglobulin gene

t(11;14)
- **Mantle cell lymphoma**
- deregulation of the cyclin D1 (BCL-1) gene

t(11; 18)

- This translocation is associated with MALT (mucosa-associated lymphoid tissue) lymphoma and deregulates MALT1

t(14;18)

- This translocation is associated with follicular lymphoma
- results in a chimeric heavy-chain Ig (chromosome 14) and BCL2 (chromosome 18) gene.
- This disease presents with painless “waxing and waning” lymphadenopathy in additional to constitutional symptoms.

Haematological malignancies: infections

Viruses

- EBV: Hodgkin's and Burkitt's lymphoma, nasopharyngeal carcinoma
- **HTLV-1: Adult T-cell leukaemia/lymphoma**
- HIV-1: High-grade B-cell lymphoma

Bacteria

- *Helicobacter pylori*: gastric lymphoma (MALT)

Protozoa

- malaria: Burkitt's lymphoma

Burkitt's lymphoma

Burkitt's lymphoma - c-myc gene translocation

Burkitt's lymphoma is a common cause of tumour lysis syndrome

- Burkitt's lymphoma is a monoclonal proliferation of B lymphocytes, which results (in approximately 90% of the cases) from **chromosome translocations** that involve the Myc gene.
  - chromosome translocation means that a chromosome is broken, which allows it to associate with parts of other chromosomes.
- It is a high-grade B-cell neoplasm.
- There are two major forms:

  1. **endemic** (African) form: typically involves maxilla or mandible
  2. **sporadic** form:
     - abdominal (e.g. ileo-caecal) tumours are the most common form.
     - More common in patients with HIV
- Burkitt's lymphoma is **associated with the c-myc gene translocation, usually t(8:14).**
  - The classic chromosome translocation in Burkitt's lymphoma involves chromosome 8, the site of the MYC gene.
- The **Epstein-Barr virus (EBV)** is strongly implicated in the development of the African form of Burkitt's lymphoma and to a lesser extent the sporadic form.

Microscopy findings

- 'starry sky' appearance: lymphocyte sheets interspersed with macrophages containing dead apoptotic tumour cells

Management

- Management is with chemotherapy.
  - This tends to produce a rapid response which may cause **'tumour lysis syndrome'**.
    - Rasburicase (a recombinant version of urate oxidase, an enzyme which catalyses the conversion of uric acid to allantoin*) is often given before the chemotherapy to reduce the risk of this occurring.
      - *allantoin is 5-10 times more soluble than uric acid, so renal excretion is more effective
    - **Complications** of tumour lysis syndrome include:
      - Hyperkalaemia
      - Hyperphosphataemia
      - Hypocalcaemia
      - Hyperuricaemia
      - acute renal failure

Prognosis

- Localised Burkitt's is associated with around a 90% survival rate,
- although the prognosis is less good in adults.

Cancer in the UK

The most common causes of cancer in the UK are as follows*

• 1. Breast • 2. Lung • 3. Colorectal • 4. Prostate • 5. Bladder	• 6. Non-Hodgkin's lymphoma • 7. Melanoma • 8. Stomach • 9. Oesophagus • 10. Pancreas

The most common causes of death from cancer in the UK are as follows:

• **1. Lung** • 2. Colorectal • 3. Breast • 4. Prostate • 5. Pancreas	• 6. Oesophagus • 7. Stomach • 8. Bladder • 9. Non-Hodgkin's lymphoma • 10. Ovarian

- Cancer is the cause of 26% of deaths in the UK, and is a more common cause of death than cardiovascular disease.
- **Lung cancer is the biggest cancer killer in the UK** (in both male and female), although breast cancer has the highest incidence

*excludes non-melanoma skin cancer

Acute lymphoblastic leukaemia (ALL):

- (ALL) is a disease of children.
- Children with certain genetic and immunodeficiency syndromes are at **increased risk.** These **include:**
  - Down syndrome,
  - Neurofibromatosis type 1,
  - Bloom syndrome, and
  - ataxia telangiectasia.
- The most common presenting symptoms of ALL are nonspecific: fever, infection, bleeding, bone pain, or lymphadenopathy.

Prognostic features

Good prognostic factors	Poor prognostic factors
• French-American-British (FAB) L1 type • common ALL • pre-B phenotype • low initial WBC • del(9p) • **t(12;21)**	• FAB L3 type • T or B cell surface markers • Philadelphia translocation, t(9;22) • **t(8:14) the worst prognosis** • age < 2 years or > 10 years • male sex • CNS involvement • high initial WBC (e.g. > 100 * 10^9/l) • non-Caucasian

- **The 8:14 chromosomal translocation** is associated with a particularly **poor prognosis,** and is found in approximately 1% of adults with ALL. The incidence of CNS involvement is very high at the point of diagnosis, and median event free survival after chemotherapy is only two months.

Treatment

- Before ALL treatment with chemotherapy, if blast cells count is very high (> 100 * 109/l) → the patient needs **Leukapheresis** to prevent sludge in of capillary beds, this can be life-saving.
- Central nervous system (CNS) therapy (intrathecal) is indicated in all patients with ALL
- **Lumber puncture (LP) should be delayed until chemotherapy has begun**

Chronic lymphocytic leukaemia (CLL)

CLL - treatment: Fludarabine, Cyclophosphamide and Rituximab (FCR)

CLL - immunophenotyping is investigation of choice

- (CLL) is caused by a monoclonal proliferation of well-differentiated lymphocytes which are **almost always B-cells (99%)**

Prevalence

- CLL is the **most common form of leukemia found in adults** in Western countries.
- generally affects older populations (The median age at diagnosis is 72 years)

Features

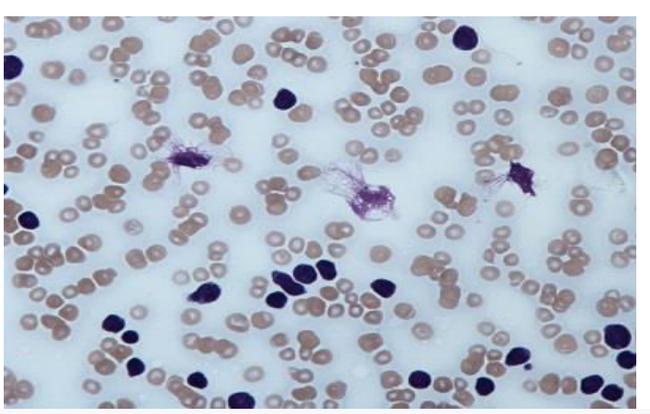
- often none
- constitutional: anorexia, weight loss
- bleeding, infections
- lymphadenopathy more marked than CML

Complications

- **hypogammaglobulinaemia** leading to recurrent infections
  - **Infections are the most frequent complication causing death in patients with CLL.**
  - Although intravenous immunoglobulin prevents recurrent infections it does not prolong survival.
- **warm autoimmune haemolytic anaemia** in 10-15% of patients
- transformation to high-grade lymphoma (Richter's transformation)

Investigations

- blood film:
  - smudge cells (also known as smear cells)
    - smudge cells are the artifacts produced by the lymphocytes damaged during the slide preparation.
  - ≥ 5000 monoclonal B lymphocytes/µl. The clonality of the circulating B lymphocytes needs to be confirmed by flow cytometry.
- **Immuno-phenotyping** → will demonstrate the cells to be B-cells (CD19 positive). CD5 and CD23 are also characteristically positive in CLL.
  - **Peripheral blood flow cytometry is the most valuable test to confirm a diagnosis of CLL.**
- Although a **bone marrow biopsy** is not required for diagnosis, it is recommended for the diagnostic evaluation of unclear cytopaenias, or FISH or molecular genetics if peripheral blood cell lymphocytosis does not allow adequate immunophenotyping
- An extended **FISH** analysis is recommended before the start of therapy because the detection of additional cytogenetic abnormalities [del(11q) or trisomy 12] may have therapeutic consequences



Peripheral blood film showing smudge B cells

Management

- **observation policy is usual during the early stages of the disease.**
- **Indications for treatment**
  - progressive marrow failure: the development or worsening of anaemia and/or thrombocytopenia
  - massive (>10 cm) or progressive lymphadenopathy
  - massive (>6 cm) or progressive splenomegaly
  - progressive lymphocytosis: > 50% increase over 2 months or lymphocyte doubling time < 6 months
  - systemic symptoms:
    - weight loss > 10% in previous 6 months,
    - fever >38 C for > 2 weeks,
    - extreme fatigue,
    - night sweats
  - autoimmune cytopaenias e.g. ITP
- **Drugs**
  - fludarabine, cyclophosphamide and rituximab **(FCR)** has now emerged as the **initial treatment of choice** for the majority of patients
  - monitoring by regular blood counts
  - **What antimicrobial prophylaxis should he receive before starting chemotherapy with fludarabine?**

    ➔ **Co-trimoxazole**
    - Fludarabine is a purine analogue that is phosphorylated intracellularly.
    - All of the purine analogues cause myelosuppression, but there is a significantly **higher risk of patients developing Pneumocystis jirovecii pneumonia** while on treatment.
    - Use of prophylactic co-trimoxazole (Septrin) has dramatically reduced the frequency of this severe opportunistic infection in these patients.
    - Co-trimoxazole should be **continued after chemotherapy until the CD4 counts exceeds 200** cells/mm3 (0.2 ×109/L).
- Regular infusions of **immunoglobulin** to prevent infections
  - Recurrent infections are recognised in CLL due to hypogammaglobulinaemia and immune paresis; but are not an indication for disease control.

CLL prognostic factors

Poor prognostic factors (median survival 3-5 years)

- male sex
- age > 70 years
- lymphocyte count > 50
- prolymphocytes comprising more than 10% of blood lymphocytes
- lymphocyte doubling time < 12 months
- raised LDH
- CD38 expression positive
- deletions of part of the short arm of chromosome 17 (del 17p)

Chromosomal changes

- deletion of the long arm of **chromosome 13** (del 13q) is the **most common** abnormality, being seen in **around 50%** of patients. It is associated with a **good prognosis**
- deletions of part of the short arm of **chromosome 17** (del 17p) are seen in around **5-10%** of patients and are associated with a **poor prognosis**

Differential diagnosis

- **mantle cell lymphoma (MCL)**
  - These tumour cells express B-cell surface antigens and also expresses CD5, **but usually not CD23.**
  - For cases that express CD23, staining for cyclin D1 or SOX11 and fluorescence *in situ* hybridisation **(FISH) for detecting a translocation (11;14)** are useful for establishing the diagnosis of MCL.
- **small lymphocytic lymphoma (SLL)**
  - In the World Health Organization classification, small lymphocytic lymphoma (SLL) and CLL are considered to be a single entity.

  - The diagnosis of SLL requires the presence of lymphadenopathy and/or splenomegaly with a number of B lymphocytes in the peripheral blood not exceeding 5 × 10^9/l.
  - SLL cells show the same immunophenotype as CLL.
  - The diagnosis of SLL should be confirmed by histopathological evaluation of a lymph node biopsy, whenever possible.
- **monoclonal B-lymphocytosis' (MBL)**
  - In absence of lymphadenopathy, organomegaly, cytopaenia and clinical symptoms, the presence of fewer than 5000 monoclonal B lymphocytes/µl defines 'monoclonal B-lymphocytosis' (MBL)
  - can be detected in 5% of subjects with normal blood count.
  - Progression to CLL occurs in 1%–2% of MBL cases per year.

Acute myeloid leukaemia (AML)

Acute myeloid leukaemia - poor prognosis: deletion of chromosome 5 or 7

Acute myeloid leukaemia - good prognosis: t(15;17)

- AML is the **most common form of acute leukaemia in adults**.
- It may occur as a primary disease or following a secondary transformation of a myeloproliferative disorder.
- **Acute leukemia is defined as an accumulation of more than 20 percent of immature blasts at the bone marrow.**
  - Chronic myeloid leukaemia often ends in acute blastic transformation after a mean duration of approximately four years.
- classically associated with **Down syndrome**.
- **Alkylating agents** is a chemotherapy drug class that increases the risk of developing AML.
- characterized by cells with positive cytoplasmic **staining for myeloperoxidase**.
- The median age of onset of AML is 65 years.

Presentation

- Vague and non-specific (flu-like symptoms)
- Due to pancytopenia (Infection, anaemia , bleeding)
- Splenomegaly may occur but typically mild and asymptomatic.
- LN swelling is rare.
- High total leucocyte count (TLC) leads to leucostasis and hyperviscosity → drowsiness and retinal vein dilatation.
- Blood film reveals white cells predominantly myeloblasts and promyelocytes.

Poor prognostic features

AML → Cytogenetics Karyotype is of most prognostic value.

- > 60 years
- > 20% blasts after first course of chemo
- cytogenetics: deletions of chromosome 5 or 7
  - bone marrow cytogenetics are the **most important** aspect in determining prognosis in AML

Good prognostic features

- Karyotype of bone marrow
  - patients with t(8:21) or chromosomes 16 inversion have a low risk of relapse

Classification - French-American-British (FAB)

- MO - undifferentiated
- M1 - without maturation
- **M2** - with granulocytic maturation
  - the **most common** (25% of adult AML)
  - associated with a t(8;21) translocation.
- **M3 - acute promyelocytic (APL)**

  - has the **best prognosis** of all the subtypes of AML.
  - Unlike the other AML subtypes, APL is treated with all-trans retinoic acid (ATRA).
  - t(15;17)
- M4 - granulocytic and monocytic maturation
  - associated with a t(16;16) translocation
- M5 - monocytic
- M6 - erythroleukaemia
- M7 – megakaryoblastic

AML (monocytic) **M5**: high count of circulating blasts → may lead to symptoms of cellular hyperviscosity (headache, confusion, fits, coma) and tissue deposits of leukaemia cells (gums hypertrophy) with cells stain positive with Sudan Black and myeloperoxidase plus NES.

ALL cells characteristically stain positive for **PAS** (Periodic acid-Schiff) and **NSE** (Non-specific Esterase).
AML cells characteristically stain positive for **Sudan Black** and **myeloperoxidase**, but **M4** and **M5** cells stain positive for **NSE**, while **M6** cells stain positive for **PAS**.

Differentiating between ALL and AML

	ALL	AML
Presence of auer rods in blood	None	Always present
Presence of lymphoblasts in blood	Always present	May or may not be present
Bone and joint pain	More common	Less common
Hepatosplenomegaly	More common	Less common
Organ infiltration	More common	Quite unusual

Management
- Combination chemotherapy including arabinosylcystosine after **apheresis**.
- Cytarabine and Anthracycline is considered the initial treatment of choice for patients with AML.

Bone marrow transplantation
- The aim would be to choose a fully matched sibling who was also CMV-negative.
- In general, **fully HLA matched, CMV matched, male donors are preferred over fully HLA matched, CMV matched female donors.** This is because of the **increased risk of graft versus host disease in stem cell donations from female donors to male recipients**.

Acute promyelocytic leukaemia (APML)

Acute promyelocytic leukaemia - t(15;17)

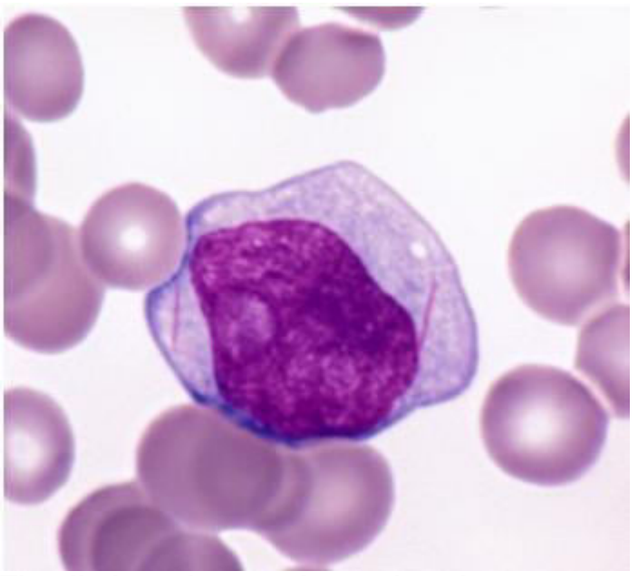
- APML, the M3 subtype of AML.
- The importance of identifying APML lies in both the presentation (classically disseminated intravascular coagulation) and management
- **APML is associated with the t(15;17) translocation**
  - causes fusion of the PML and RAR-alpha genes.
  - In 95% of cases, retinoic acid receptor-alpha (RARA) gene on chromosome 17 is involved in a reciprocal translocation with the promyelocytic leukaemia gene (PML) on chromosome 15.
  - The mechanism underlying leukaemogenesis is **aberrant fusion of 2 genes PML and RARA.**

Features
- presents younger than other types of AML (average = 25 years old)
- DIC or thrombocytopenia often at presentation
- **Auer rods** (seen with myeloperoxidase stain)
  - Auer rods are eosinophilic needle-like cytoplasmic inclusions found in blast cells

- good prognosis

management

- treatment of APML differs from that of all other AML forms
- **the most appropriate initial treatment regimen: All trans retinoic acid (ATRA) a derivative of vitamin A., plus Anthracycline based chemotherapy**



The distinct elongated cytoplasmic structures are Auer rods which are pathognomonic for AML.

Retinoic acid syndrome (or differentiation syndrome)

Pathophysiology

- thought to be the result of the release of cytokines and subsequent lung infiltration by the neutrophils created by the maturation of myelocytes in APML.
- The presence of CD13 expression on leukemic cells can be a predictor of the future development of this syndrome.

Causes

- after treatment of APML with all-trans retinoic acid (ATRA) (present within a week of treatment)
- after treatment of APML with arsenic trioxide.
- usually occurs during induction therapy

Incidence

- 14-16% of patients.

Features

- dyspnea, pulmonary edema and effusions, A chest X-ray shows interstitial infiltrates.
- fevers,
- hypotension,
- Other complications include pericardial effusion, renal insufficiency, and hypertension.

treatment

- Corticosteroids
- the drug is temporarily stopped, then started again at 50-75% of the earlier dose. Alternatively, arsenic therapy can be tried.

prognosis

- Without prompt treatment with glucocorticoids, patients with this disorder have a mortality rate as high as 30% due to brain edema or hypoxemic respiratory failure.
- Fortunately, most patients improve markedly within 12 hours and their symptoms resolved completely within 24 hours.

Chronic myeloid leukaemia (CML)

Chronic myeloid leukaemia - imatinib = tyrosine kinase inhibitor

CML - Philadelphia chromosome - t(9:22)

Philadelphia translocation, t(9;22) - good prognosis in CML, poor prognosis in AML + ALL

- The Philadelphia chromosome is present in more than 95% of patients with (CML).
- It is due to a translocation between the long arm of chromosome 9 and 22 - t(9:22)(q34; q11). This results in part of the ABL proto-oncogene from chromosome 9 being fused with the BCR gene from chromosome 22. The resulting BCR-ABL gene codes for a fusion protein which has tyrosine kinase activity in excess of normal

Presentation

- middle-age (40-50 years)
- anaemia,
- weight loss,
- splenomegaly may be marked → abdominal discomfort
- spectrum of myeloid cells seen in peripheral blood
  - The blood film shows both mature (neutrophils) and immature forms in various stages of differentiation (myelocytes and metamyelocytes)
    - In acute myelogenous leukemia (AML) one would expect only immature blasts.
- decreased leukocyte alkaline phosphatase
- may undergo blast transformation (AML in 80%, ALL in 20%)

Management

- Unlike (CLL), CML will progress to frank leukaemia quite rapidly, so treatment is needed.
- **imatinib** is now considered first-line treatment
  - inhibitor of the tyrosine kinase associated with the BCR-ABL defect
  - very high response rate in chronic phase CML
- If remission is not achieved with **imatinib**, then:
  - in a patient under 60-65 years, an allogeneic transplant would be considered if there was a matched sibling donor;
  - in a 50-year-old patient or younger a matched unrelated donor transplant would be considered too.
- If the patient had been in **blast crisis phase**, then AML-type chemotherapy as well as Glivec (**imatinib**) would be the choice.
- hydroxyurea
- interferon-alpha
- allogenic bone marrow transplant

Allogenic bone marrow transplant

Complication

Cytomegalovirus pneumonia

- The microscopy shows owl's eye inclusion bodies, characteristic of CMV, but diagnosis is usually made by PCR of blood/lavage fluid.
- It is the commonest life-threatening complication following allogenic bone marrow transplant,
- usually occurring within the first 4 months following surgery.
- **the treatment of choice → Ganciclovir**
- Onset is rapid and mortality in the context of BMT is around 80%, even with antiviral therapy (ganciclovir).

Ref → medical-masterclass.com 2017 part 2

Hairy cell leukaemia

- Hairy cell leukaemia is malignant proliferation disorder of **B cells**.
- Rare, about 2% of leukemias.
- more common in males (4:1)
- frequently occurs in **men in their fifth decade**.

Features

- pancytopenia

- splenomegaly
- skin vasculitis in 1/3 patients
- 'dry tap' despite bone marrow hypercellularity
- tartrate resistant acid phosphotase (TRAP) stain positive
- characteristic hairy leukocyte on blood smear with a “fried egg” appearance
  - medium-sized lymphocytes with numerous spiky, peripheral, cytoplasmic projections.

Management

- chemotherapy is **first-line**: **cladribine** (adenosine deaminase inhibitor), pentostatin
  - **Cladribine**
    - Cladribine is a purine analog → inhibit DNA polymerase and cause DNA strand breaks.
    - SE → myelosuppression, nephrotoxicity, and neurotoxicity.
- immunotherapy is second-line: rituximab, interferon-alpha

Paraproteinaemia

Causes of paraproteinaemia

- myeloma
- monoclonal gammopathy of uncertain significance (MGUS)
- benign monoclonal gammopathy
- Waldenstrom's macroglobulinaemia
- amyloidosis
- CLL, lymphoma
- heavy chain disease
- POEMS

Benign monoclonal gammopathy

- non-lymphoid malignancy (e.g. colon, breast)
- infections (CMV, hepatitis)
- autoimmune disorders (RA, SLE)

Multiple myeloma

classic symptoms of multiple myeloma: bone pain, pathological fracture, anaemia and hypercalcaemia (leading to thirst).

Multiple myeloma causes a **low anion gap**.

Definition

- Multiple myeloma is a **neoplasm of the bone marrow plasma cells**.

Epidemiology

- The peak incidence is patients aged 60-70 years.
- Multiple myeloma is the most common primary tumor of the bone in patients older than 50 years.
- equal sex ratio
- more common in Afro-Caribbean ethnic groups than in Caucasians

Monoclonal products produced

- IgG (50-60%)
- IgA (20-30%)
- light chain disease (20%)

Association

- **Type 2/Proximal renal tubular acidosis is a type of renal tubular acidosis associated with multiple myeloma.**

Pathophysiology

- Neoplastic proliferation of plasma cells
  - Bone marrow infiltration → suppression of hematopoiesis → leukopenia, thrombocytopenia, anemia
  - Cell proliferation → osteolysis → hypercalcemia
- Overproduction of monoclonal immunoglobulin and/or light chains
  - Non-functioning antibodies → functional antibody deficiency
  - ↑ Serum viscosity → hyperviscosity syndrome

Clinical features

- bone disease:
  - due to neoplastic plasma cells activating RANKL receptors on osteoclasts.

  - bone pain, (Bones commonly affected are the flat bones of the spine, and as such lower back pain is one of the most common presenting features)
  - osteoporosis + **pathological fractures (typically vertebral),** osteolytic lesions
  - weakness and paresthesias in the lower extremities due to vertebral compression fractures
- anaemia
  - fatigue and malaise
  - **The most common presenting manifestations of multiple myeloma are those related to anemia.**
- infection
- hypercalcaemia → nausea, fatigue, confusion, polyuria, constipation
- hyperphosphataemia
  - due to **reduced renal excretion** which may be directly **due to renal impairment** or interference with excessive protein load.
- Foamy urine,
  - caused by Bence Jones proteinuria
- renal failure
  - the most common cause is from **light chain deposition**.
  - **Usually**, the renal damage in MM is **tubular**. Occasionally there may be glomerular damage with consequent albumin loss.
- amyloidosis e.g. Macroglossia, carpal tunnel syndrome; neuropathy; hyperviscosity
  - carpal tunnel syndrome - the most common peripheral neuropathy associated with multiple myeloma

- **Multiple myeloma may present with roleaux formation on blood film and raised total protein (globulin component).**
  - The globulin level is markedly raised (albumin + globulin = total protein), suggesting the presence of a paraprotein.
  - (globulin level = total protein). A normal level should be below 36 g/L.
- **Hypercalcaemia in myeloma**
  - primary factor: due primarily to increased osteoclastic bone resorption caused by local cytokines (e.g. IL-1, tumour necrosis factor) released by the myeloma cells
  - much less common contributing factors: impaired renal function, increased renal tubular calcium reabsorption and elevated PTH-rP levels

Which acid-base disorders may be found in an IgG multiple myeloma?

- **Low anion-gap metabolic acidosis**
  - IgG tends to be cationic, whereas IgA tends to be anionic. As a consequence, patients with IgG myeloma will tend to have a lower than normal serum anion gap.

Diagnostic criteria for multiple myeloma requires one major and one minor criteria or three minor criteria in an individual who has signs or symptoms of multiple myeloma.

- **Major criteria**
  - Plasmacytoma (as demonstrated on evaluation of biopsy specimen)
  - 30% plasma cells in a bone marrow sample
  - Elevated levels of M protein in the blood or urine
    - monoclonal proteins:
      - in the serum → (usually IgG or IgA)
      - in the urine (Bence Jones proteins)
        - **there is Negative dipstick for protein and positive in biochemistry, because Bence jones proteins are not detected by dipstick**
- **Minor criteria**
  - 10% to 30% plasma cells in a bone marrow sample.
  - Minor elevations in the level of M protein in the blood or urine.
  - Osteolytic lesions (as demonstrated on imaging studies).
  - Low levels of antibodies (not produced by the cancer cells) in the blood.

Investigations: (NICE 2016)

1. **to confirm the presence of a paraprotein** indicating possible myeloma or (MGUS):

- serum protein electrophoresis **and** serum-free light-chain assay
  - (best initial test) → serum protein electrophoresis
- If serum protein electrophoresis is abnormal → use serum immunofixation
- Do not use serum protein electrophoresis, serum immunofixation, serum-free light-chain assay or urine electrophoresis (urine Bence–Jones protein assessment) **alone** to exclude a diagnosis of myeloma.

2. **to confirm a diagnosis of myeloma**:
   - **bone marrow aspirate** and trephine biopsy
   - **the bone marrow aspirate would confirm the diagnosis irrefutably.**
     - morphology to determine plasma cell percentage
       - Bone marrow examination would reveal increased plasma cells (greater than 4% and usually greater than 30%).
     - flow cytometry to determine plasma cell phenotype
     - **bone marrow aspirate → dark red jelly-like material in the syringe (Plasma cells)**

3. **in a patient presenting with spinal cord compression:**
   - **the most appropriate initial investigation is → Urgent MRI of her spine**
     - This should be done before investigation that used to confirm myeloma.
   - skeletal survey → bone lesions

Treatment : general view

- **The best initial treatment of multiple myeloma is chemotherapy induction.**
- **autologous bone marrow transplant in addition to chemotherapy has better results than chemotherapy alone.**

- Asymptomatic patients: → watch and wait, unless patients have:
  - ≥ 60% clonal cells,
  - excessive free light chains or
  - ≥ 1 bone lesion
- Symptomatic patients
  - HCT eligible : induction therapy followed by autologous HCT
  - HCT ineligible: chemotherapy alone (e.g., dexamethasone and lenalidomide)
- Supportive therapy
  - Osteolysis and bone pain
    - Bisphosphonates
    - Radiation therapy of osteolytic regions
  - Pancytopenia with anemia and increased risk of infection
    - Blood transfusions
    - Granulocyte-colony stimulating factor (G-CSF) and erythropoietin (EPO)

Treatment (NICE 2016)

- **previously untreated multiple myeloma (newly diagnosed)**
  - **Patients who are eligible for high-dose chemotherapy with stem cell transplantation**
    - bortezomib + dexamethasone,
    - **or** bortezomib + dexamethasone + thalidomide
  - **if high-dose chemotherapy with stem cell transplantation is considered inappropriate**
    - thalidomide + alkylating agent + corticosteroid
- **People who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation:**
  - bortezomib (a proteasome inhibitor) monotherapy
- **People who have received two or more prior therapies:**
  - lenalidomide + dexamethasone
    - lenalidomide → immunomodulatory derivatives (structural derivatives of thalidomide)
- **People with untreated, newly diagnosed, myeloma-induced acute renal disease:**
  - bortezomib + dexamethasone

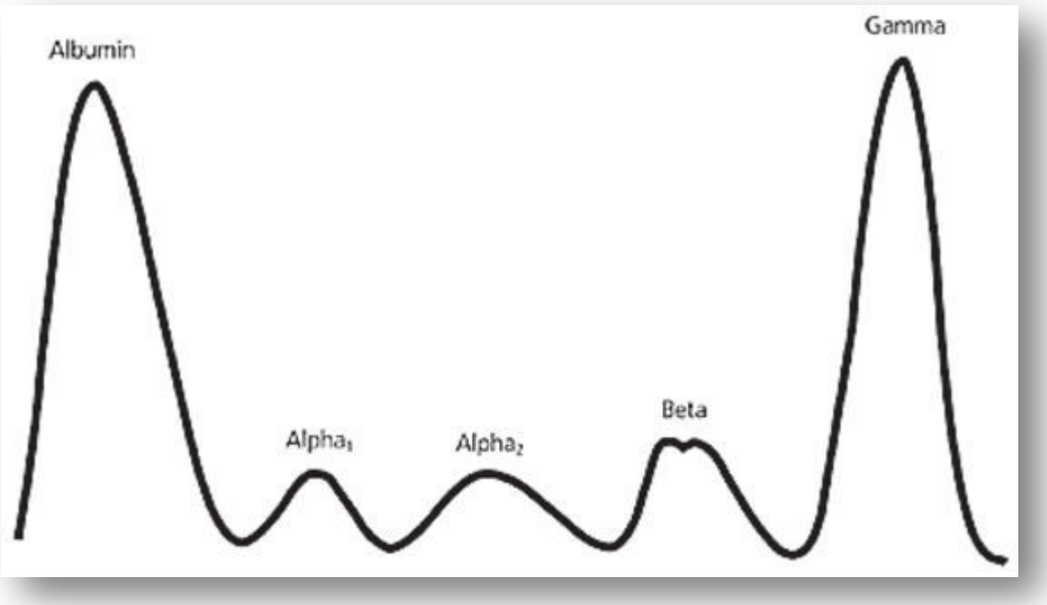
  - If a bortezomib is unsuitable → thalidomide + dexamethasone
  - Do not perform plasma exchange for myeloma-induced acute renal disease.
- **Preventing bone disease, managing non-spinal and spinal bone disease**
  - bisphosphonates should be given routinely, even in the absence of hypercalcaemia.
  - Bisphosphonates reduce bony disease in myeloma, lowering the frequency of pathological fractures, modulate the disease and have some antitumour activity.
    - zoledronic acid or
    - disodium pamidronate, if zoledronic acid is contraindicated or not tolerated or
    - sodium clodronate, if zoledronic acid and disodium pamidronate are contraindicated, not tolerated or not suitable
  - surgical stabilisation followed by radiotherapy for non-spinal bones that have fractured or are at high risk of fractures.
  - Consider radiotherapy for people who need additional **pain relief**
- **Managing peripheral neuropathy**
  - If patient on bortezomib
    - switch to subcutaneous injections and/or
    - reduce to weekly doses and/or
    - reduce the dose.
  - if patient on other than bortezomib
    - Temporarily stop neuropathy-inducing myeloma treatments if people develop either of the following:
      - grade 2 neuropathy with pain
      - grade 3 or 4 neuropathy
- **Managing fatigue**
  - Erythropoietin analogues (adjusted to maintain a steady state of haemoglobin at 110–120 g/litre) to improve fatigue in people with myeloma who have symptomatic anaemia.
- **Cord compression** secondary to bony involvement of multiple myeloma:
  - I.V Steroids should be commenced **immediately**
  - However, **the treatment of choice is local radiotherapy.** NICE suggest localised radiotherapy should be the first point of call for urgent treatment.
  - **Vertebroplasty** is typically considered in patients of whom have evidence of metastatic changes in the spine, but show no signs of spinal cord compression.
  - **Surgical decompression:** is also considered if imaging suggests any form of spinal instability or structural defects, but often after steroids and radiotherapy has been administered.
  - Other treatment options include analgesia, with non-steroidal anti-inflammatory drugs of particular use.

Myeloma: prognosis

- **B2-microglobulin is a useful marker of prognosis** - raised levels imply poor prognosis.
  - Beta-2-microglobulin has been shown to be predictive of risk of progression of disease in myeloma, myelodysplastic syndrome, and chronic myeloid leukaemia.
  - In myeloma it is an accurate estimate of total disease load, with guidelines suggesting that a beta-2-microglobulin level of >3.5 mg/L is strongly associated with increased mortality and morbidity.
- Low levels of albumin are also associated with a poor prognosis
- Increased **lactate dehydrogenase** levels more than **double** the normal is considered a bad prognostic sign in multiple myeloma.

International prognostic index

Stage	Criteria	Median survival (months)
I	B2 microglobulin < 3.5 mg/l Albumin > 35 g/l	62
II	Not I or III	45
III	B2 microglobulin > 5.5 mg/l	29



Abnormal serum protein electrophoresis pattern in a patient with multiple myeloma. Note the large spike in the gamma region.

- In the interpretation of serum protein electrophoresis, most attention focuses on the gamma region(gamma-globulin zone), which is composed predominantly of antibodies of the IgG type.

Monoclonal gammopathy of undetermined significance (MGUS)

- MGUS also known as benign paraproteinaemia and monoclonal gammopathy) is a common condition that causes a paraproteinaemia and is often mistaken for myeloma. Differentiating features are listed below.
- can be seen in >5% of people over 70 years of age.

Risk of transmission to malignancy:

- Around 10% of patients eventually develop myeloma at 5 years, with 50% at 15 years
- 1 percent per year develop multiple myeloma.

Features

- usually asymptomatic
- no bone pain or increased risk of infections
- around 10-30% of patients have a **demyelinating neuropathy**

Differentiating features from myeloma

- normal immune function
- normal beta-2 microglobulin levels
- lower level of paraproteinaemia than myeloma (e.g. < 30g/l IgG, or < 20g/l IgA)
- stable level of paraproteinaemia
- no clinical features of myeloma (e.g. lytic lesions on x-rays or renal disease)

feature	MGUS	myeloma
M protein concentration in serum	<30 g/l	>30 g/l
bone marrow plasma cells	<10 %	>10 %
organ and tissue impairment	no end organ damage including bone lesions	organ or tissue impairment (including bone lesions)

Treatment

- **Observation**
- **if there is neuropathy**
  - MGUS patients are associated with osteoporosis and osteopenia. They may benefit from treatment with **bisphosphonates**
    - Bisphosphonates
      - pyrophosphate analogue
      - act by binding to hydroxyapatite in bone which leads to low osteoclastic activity.

March 2017 part 2: A 72-year-old man C/O persistent tiredness over the past 3 months. No other abnormality. Investigations reveals Albumin: 38 g/l, IgG paraprotein band: 14 g/l, Bone marrow: 7% plasma cells. Which of the following is the most appropriate intervention?

➔ **Observation**

- MGUS is defined by paraprotein (<30 g/l), bone marrow plasma cells <10% and the absence of myeloma-related organ or tissue damage (predominantly renal, skeletal or bone marrow impairment).
- **Annual overall progression to myeloma is 1%** and, as such, no intervention is required.

Smoldering myeloma

- **Smoldering multiple myeloma** → multiple myeloma (M-protein >3g/dL or >10% plasma cells in bone marrow) + no end organ damage.
- **criteria for end-organ damage**, which are:
  - Serum calcium >11.5 mg/dL
  - Serum creatinine >2 mg/dL or estimated creatinine clearance <40 ml/min
  - Anemia with hemoglobin <10 g/dL
  - Bone lesions: osteolytic, pathological fracture; osteopenia
- **Treatment → Observe and monitor**

Non-secretory myeloma

- Bone marrow clonal plasma cells =10%, Myeloma-related end-organ damage, No M protein in blood or urine

---

Thymoma are the most common tumour of the anterior mediastinum and is usually detected between the sixth and seventh decades of life.

Associated with

- myasthenia gravis (30-40% of patients with thymoma)
- red cell aplasia
- dermatomyositis
- also : SLE, SIADH

Causes of death

- compression of airway
- cardiac tamponade

Tumour lysis syndrome (TLS)

Rasburicase - a recombinant version of urate oxidase, an enzyme that metabolizes uric acid to allantoin

- Tumour lysis syndrome (TLS) is a potentially deadly condition

causes:

- treatment of high grade lymphomas and leukaemias.
- It can occur in the absence of chemotherapy but is usually triggered by the introduction of combination chemotherapy.

Pathophysiology:

- breakdown of the tumour cells and the subsequent release of chemicals from the cell.

Features:

- **high** potassium
- **high** phosphate
- **low calcium**.
- It should be suspected in any patient presenting with an **acute kidney injury** in the presence of a high phosphate and **high** uric acid level.

Diagnosis:

- From 2004 TLS has been graded using the Cairo-Bishop scoring system - Laboratory tumor lysis syndrome: abnormality in **two or more of the following, occurring within three days before or seven days after chemotherapy.**
  - uric acid > 475umol/l or 25% increase

- potassium > 6 mmol/l or 25% increase
- phosphate > 1.125mmol/l or 25% increase
- calcium < 1.75mmol/l or 25% decrease

- Clinical tumor lysis syndrome: laboratory tumor lysis syndrome plus one or more of the following:
  - increased serum creatinine (1.5 times upper limit of normal)
  - cardiac arrhythmia or sudden death
  - seizure

Prevention:

- Patients at high risk of TLS should be given IV allopurinol or IV rasburicase immediately prior to and during the first days of chemotherapy.
  - Rasburicase is a recombinant version of urate oxidase, an enzyme that metabolizes uric acid to allantoin. Allantoin is much more water soluble than uric acid and is therefore more easily excreted by the kidneys.
    - The commonest reported side effect of rasburicase is fever.
    - rasburicase overdose may lead to accumulation of hydrogen peroxide.
- patients at low risk → oral allopurinol during chemotherapy
- Other options for the management of tumour lysis syndrome include
  - Acetazolamide to drive urine alkalinisation.

Waldenstrom's macroglobulinaemia

IgM paraproteinaemia - ?Waldenstrom's macroglobulinaemia

Overview

- It is a lymphoplasmacytoid malignancy seen in older men, characterised by the secretion of a monoclonal **IgM** paraprotein,
- indolent B-cell lymphoma
- Also known as **Lymphoplasmacytoid lymphoma**
- most common in older white men
-

Pathophysiology

- monoclonal IgM production by a malignant lymphoplasmacytic clone that can cause damage to multiple organs.
- The tumor cells in Waldenstrom macroglobulinemia are positive to CD20 markers.

Features

- monoclonal IgM paraproteinaemia
- systemic upset: weight loss, lethargy
- hyperviscosity syndrome e.g.:
  - visual disturbance,
  - neurological symptoms such as headache, dizziness, and vertigo
  - raynaud phenomenon
- Bleeding is a possible complication as viscous serum causes defective platelet aggregation.
- hepatosplenomegaly
- lymphadenopathy
- cryoglobulinaemia e.g. Raynaud's

Investigations

- protein electrophoresis → elevated IgM
- Bone marrow biopsy (the gold standard for the diagnosis)
  - Shows → abnormal plasma cells with **Dutcher bodies**(intranuclear inclusions of IgM deposits)

Differential diagnosis

- multiple myeloma
  - usually presents with IgG or IgA secretion and lytic bone lesions.

Treatment

- Treatment only indicated in symptomatic patients
  - asymptomatic → Follow-up
- Causative: CD20 antibodies (e.g., rituximab)
- Hyperviscosity syndrome: plasmapheresis

ECOG score

- The ECOG score (Eastern Cooperative Oncology Group (ECOG) score) is a 'performance status' scale, or a score that measures the functional status of a patient.
- It is **used to decide if a patient is a good or poor candidate for future oncological therapies.**
- Those with a poor functional status is a poor candidate for further chemotherapy.

0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Testicular seminoma

- **The triad of a testicular lump, a mass on chest X-ray and a raised (3-HCG (human chorionic gonadotrophin) are suggestive of testicular seminoma**
- A raised (3-HCG is found in around 15% of seminomas
- Orchidectomy with chemotherapy is curative in 90% of cases
- (3-HCG) levels may be a useful correlate with response to treatment

Tumour markers

Tumour markers may be divided into:

- monoclonal antibodies against carbohydrate or glycoprotein tumour antigens
- tumour antigens
- enzymes (alkaline phosphatase, neurone specific enolase)
- hormones (e.g. calcitonin, ADH)

It should be noted that tumour markers usually have a low specificity

Monoclonal antibodies

Tumour marker	Association
CA 125	Ovarian cancer **primary peritoneal cancer**
CA 19-9	**Pancreatic cancer**
CA 15-3	Breast cancer

Tumour antigens

Tumour marker	Association
Prostate specific antigen (PSA)	Prostatic carcinoma
Alpha-feto protein (AFP)	Hepatocellular carcinoma, **teratoma ,**

Tumour marker	Association
	non-seminomatous germ-cell tumours
Carcinoembryonic antigen (CEA)	Colorectal cancer
S-100	Melanoma, schwannomas
Bombesin	Small cell lung carcinoma, gastric cancer, neuroblastoma
β-human chorionic gonadotrophin	choriocarcinomas, germ-cell tumours and lung cancers

- Bence Jones protein → specific for myeloma. false positives are rare, and therefore it is **more specific than the other markers**. **The most specific tumour marker**
- **Alpha-fetoprotein** (AFP), **beta-hCG** and **PLAP** (placental like isoenzyme of alkaline phosphatase) are the major tumour markers in use for the monitoring of **testicular teratoma**.

Neutropenic sepsis (Febrile neutropenia)

- Neutropenic sepsis is a relatively common complication of cancer therapy (chemotherapy).
- It may be defined as a neutrophil count of < 0.5 * 10^9 in a patient who is having anticancer treatment and has one of the following:
  - a temperature higher than 38 C or
  - other signs or symptoms consistent with clinically significant sepsis
- **the most common pathogens are now gram-positive organisms.** such as **Staphylococcus epidermidis** or Streptococcus viridans (around 60% of cases)
- **Source of infection**
  - Indwelling lines → Staph.epidermidis infection
  - mucositis or previous quinolone treatment → viridans streptococci

Prophylaxis

- if it is anticipated that patients are likely to have a neutrophil count of < 0.5 * 10^9 as a consequence of their treatment they should be offered a fluoroquinolone

Management

- antibiotics must be started immediately, do not wait for the WBC,(N.B. after taking cultures).
- NICE recommend starting empirical antibiotic therapy with **piperacillin with tazobactam** (Tazocin) immediately

Piperacillin with tazobactam and gentamicin is the preferred first-line option according to the **Christie's guidelines** for the management of neutropenic sepsis, for patients who are not allergic to penicillin and have no significant renal impairment.

- many units add vancomycin if the patient has central venous access but NICE do not support this approach
- following this initial treatment patients are usually assessed by a specialist and risk-stratified to see if they may be able to have outpatient treatment
- if patients are still febrile and unwell after 48 hours an alternative antibiotic such as meropenem is often prescribed +/- vancomycin
- if patients are not responding after 4-6 days the Christie guidelines suggest ordering investigations for fungal infections (e.g. HRCT), rather than just starting antifungal therapy blindly
- there may be a role for G-CSF in selected patients

Guidelines suggest that in high-risk neutropenic patients with sepsis of unknown origin meropenem 1 g three times a day is an appropriate option where there is an underlying penicillin allergy. Dose adjustment may be needed where the glomerular filtration rate is less than 50 ml/min.

May 2016 exam: When is the risk of febrile neutropenia thought to be highest following chemotherapy? 10 days in to treatment

On average, initial chemotherapy regimens in haematological malignancy are associated with significant neutropaenia around 10 days after treatment initiation. Factors associated with greater risk of neutropaenia include age >65 years, albumin less than 35g/l at outset, planned relative dose intensity >80%, baseline neutrophil count less than 1.5 ×109/l, and significant hepatic dysfunction.

Systemic mastocytosis

Systemic mastocytosis results from a neoplastic proliferation of mast cells

Features

- urticaria pigmentosa - produces a wheal on rubbing (Darier's sign)
- flushing
- abdominal pain
- monocytosis on the blood film

Diagnosis

- raised serum tryptase levels
- urinary histamine

Cervical cancer

- Cervical cancer is the most common cancer worldwide
- The incidence of cervical cancer peaks around the 6th decade.
- It may be divided into
  - squamous cell cancer (80%)
  - adenocarcinoma (20%)

Features

- may be detected during routine cervical cancer screening
- abnormal vaginal bleeding: postcoital, intermenstrual or postmenopausal bleeding
- vaginal discharge

Risk factors

- **human papilloma virus (HPV) 16,18 & 33 → the most common**
  - associated with **HPV 16 and 18** in approximately 70% of cases.
  - New vaccines are currently available in the United Kingdom to help immunise against this virus and hopefully prevent future cases of cervical cancer.
- smoking
- human immunodeficiency virus
- early first intercourse, many sexual partners
- high parity
- lower socioeconomic status
- combined oral contraceptive pill*
  - *the strength of this association is sometimes debated but a large study published in the Lancet (2007 Nov confirmed the link

Mechanism of HPV causing cervical cancer

- HPV 16 & 18 produces the oncogenes E6 and E7 genes respectively
- E6 inhibits the p53 tumour suppressor gene
- E7 inhibits RB suppressor gene

Ovarian tumours

- germ cell tumours
  - Patients are usually young.
    - most commonly seen in adolescents due to embryologic remnants
  - early pulmonary metastases
    - **The fact that this lady is young, and has early pulmonary metastases, make a germ cell tumour much more likely**
- The diagnosis is usually made on biopsy in the case of ovarian tumours.
- treatment usually consists of surgery followed by chemotherapy (BEP).
- Epithelial cell tumours

- usually disseminate through the abdomen and peritoneum prior to metastasising to the lungs.

- Markers such as AFP, β-human chorionic gonadotropin (HCG) and lactate dehydrogenase (LDH) may be raised
  - **the most sensitive marker used for monitoring treatment efficacy and risk of relapse is AFP.**

- **A young man with a germ cell tumour (raised β-HCG) can expect a greater than 95% cure rate, especially with seminomas.**
- **β-HCG is the best tumour marker confers the best prognosis**

Breast cancer

The triple assessment of a breast lump is essential to diagnose a breast lump accurately. It involves physical examination, mammography and then ultrasound guided fine needle aspiration (FNA).

Risk factors

- **inherited BRCA-1 mutation (or BRCA-2)**
  - **the greatest risk**
  - family history of breast cancer at a young age makes this more likely.
  - **What is the DNA repair mechanism by which the BRCA1 and BRCA2 proteins act?**
    - **Double strand DNA break repair**
      - **BRCA** involved in repair of double strand DNA breaks by homologous recombination.
- Early menarche
- late menopause
  - due to increased hormone exposure throughout life.
- Nulliparity
- Oral contraceptive use is also associated with a slight increase in risk of developing breast and also endometrial cancer.

Screening

- Mammograms screening
  - sensitive in older (because of less dense breast tissue)
  - not sensitive in younger (because of denser breast tissue) → MRI and ultrasound are better in them.
  - **In young patients with a BRCA mutation, mammographic screening has a low sensitivity for detecting tumours**
- Mammographic screening of all women between the ages of 50 and 70 years can reduce mortality from breast cancer by 25%. There is no evidence for routine screening below this age.
- **mutation of BRCA1 or BRCA2 gene increases the risk of breast cancer** → should be screened at younger than 50 years.

Breast MRI is used for patients with invasive breast cancer in the following circumstances:

- if there is a discrepancy regarding the extent of disease from clinical examination, mammography and ultrasound assessment for planning treatment
- if breast density precludes accurate mammographic assessment
- to assess tumour size if breast conserving surgery is being considered for invasive lobular cancer
- Staging CT is not used routinely in primary breast cancer, only if there is suspicion of metastatic spread.

Tumour marker

- **CA15-3 tumour marker are used to assess disease activity in metastatic breast cancer**

Management

- **Adjuvant radiotherapy** is recommended by (NICE) given after wide local excision of a breast tumour to reduce the risk of local recurrence.
  - There is growing evidence that adjuvant radiotherapy also increases survival for those patients at high risk of relapse.
  - There is however a risk of increased cardiovascular mortality after 15-20 years, which may be reduced with the use of modern techniques such as conformal radiotherapy and intensity-modulated radiotherapy.
  - Wound healing can be reduced after radiotherapy, and a period of at least a few weeks is usually given between surgery and initiation of radiotherapy.

Drug therapy

- Hormonal treatment is used to remove the proliferative stimulus of oestrogen from tumour cells.
- **Tamoxifen** is used for adjuvant hormone treatment in **pre-menopausal** women **first line**.
  - Tamoxifen acts by blocking the binding of oestrogen to its receptor within the nucleus.
  - long-term use is associated with:
    - vaginal bleeding,
    - endometrial thickening and increased risk of endometrial cancer
    - **thromboembolism.**
  - The lack of oestrogen receptor staining suggests a poor response to hormonal therapy with tamoxifen.
- **Anastrozole** is used for adjuvant hormone treatment in **post-menopausal** women **first line**.
  - **aromatase inhibitor**
  - Three aromatase inhibitors are licensed for treatment of early oestrogen-receptor-positive breast cancer:
    1. anastrozole,
    2. exemestane,
    3. letrozole.
  - Aromatase inhibitors work by **preventing peripheral conversion of oestrogen** and therefore cause profound oestrogen deprivation in a post-menopausal woman.
  - This increases the risk of osteoporosis and fragility fractures.
  - **A DEXA scan must be done at the start of treatment** to identify those patients in whom a bisphosphonate must be considered for bone protection.
    - **Aromatase inhibitors can be continued** in a patient who has suffered **no fragility fractures** providing adequate measures are taken for bone protection, for example, **prescribing a bisphosphonate**.
    - **In patients who suffer a fragility fracture tamoxifen must be considered** as this does have a partial oestrogen agonist action on bone, reducing the risk of osteoporosis.
  - A common side-effect is **reduced bone mineral density**, and bone densitometry is therefore often carried out prior to and during treatment.
  - Anastrozole is currently indicated for early oestrogen-receptor-positive breast carcinoma at a dose of 1 mg daily for 5 years.
- Fulvestrant is a new pure anti-oestrogen agent which appears to be as effective as anastrozole. It is given by sub-cutaneous injection once every three weeks.
  - Fulvestrant is not currently given first line in post-menopausal women but this may change in the near future.
- The positive C-erb B2 (**HER2**/neu) staining suggests that **trast**uzumab (Herceptin) may be effective.

- **the best test for monitoring the patient while she is receiving Herceptin (trastuzumab)?**
  - **Three monthly echocardiogram**
    - Herceptin appears to be directly toxic to the cardiac muscle itself with relative sparing of the electrical conductivity of the heart.
    - As such regular echocardiograms are the best test to assess treatment safety, **a reduction of greater than 10% in ejection fraction indicating the need to stop treatment.**

What is **the best predictive factor for local recurrence of breast cancer after** surgery, chemotherapy and radiotherapy?

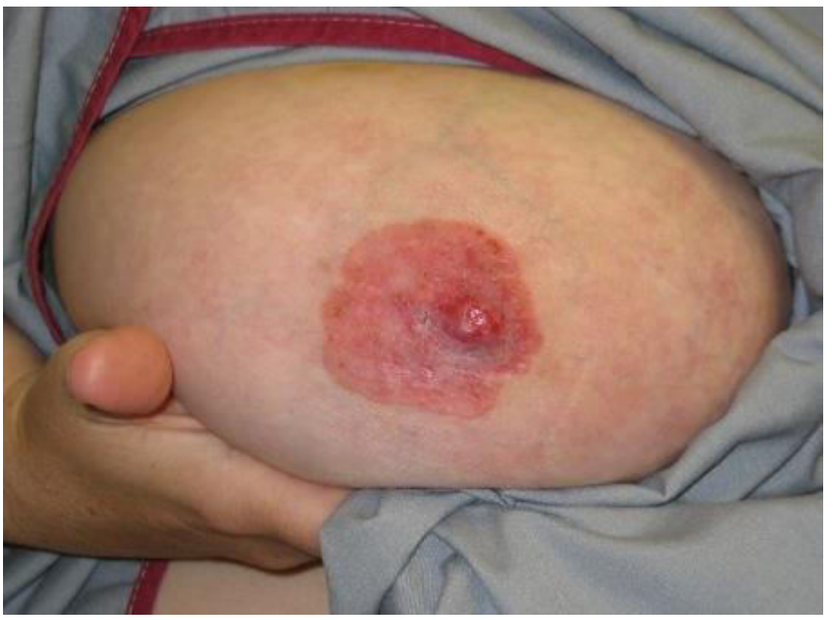
- **Age**
  - **Patients below the age of 40 are significantly more likely to develop local recurrence of a breast cancer than those aged 41+.**

Prognosis

- **Poor prognostic factors** include:
  - high-grade tumour,
  - positive lymph node status,
  - oestrogen-receptor-negative tumour,
  - progesterone-receptor-negative tumour,
  - **young age (< 40 years),**
  - premenopausal at diagnosis
  - increased tumour size.

Paget's disease of the breast

- **Overview**
  - Paget's disease of the breast is a rare (1-4% of breast cancers) form of breast cancer that affects the nipple and areola.
  - underlying invasive breast cancer, or ductal carcinoma in situ (DCIS) almost always present
    - unlike Paget's disease of the vulva
  - Malignant cells infiltrate into the epidermis via the mammary duct epithelium, leading to thickening of the affected skin.
- **Features**
  - Presents with dermatitis or macular rash over nipple or areola
  - It presents insidiously and is **similar in appearance to eczema**; as such it often goes undiagnosed for several months.
- **Diagnosis**
  - **Skin biopsy with immunohistochemistry is the first line investigation.**
  - Investigations should also be done for underlying malignancy:
    - biopsy if a lump is palpable,
    - imaging if no lump is palpable.
- **Management**
  - usually surgical with post-operative radiotherapy
- **Prognosis**
  - high chance of recurrence.



Paget's disease of the breast

Radiotherapy

- External beam radiotherapy or use of targeted intraoperative radiotherapy does not render the patient radioactive. **No radiation precautions need to be taken**
- Use of brachytherapy methods can involve insertion of radioactive seeds or beads which may require some radiation protection precautions depending on the site.
- Use of an unsealed source, for example radio-iodine treatment of thyroid cancer, has substantial need for precautions and patients need to be **isolated in a lead-lined side room, often for several days.**

Chemotherapy

- Adjuvant chemotherapy is commonly given in many cancers **to reduce** the risk of local or distant recurrence or **metastasis**.
- **multi-drug chemotherapy resistance**
  - **Upregulation of which protein is associated with multi-drug chemotherapy resistance? → P-glycoprotein**
    - P-glycoprotein, which is also known as multidrug resistance protein 1, is a member of the adenosine triphosphate (ATP)-binding cassette transporters which actively remove harmful substances from the cytoplasm.
    - If upregulated these proteins can pump chemotherapeutic agents out of tumour cells leading to drug resistance.

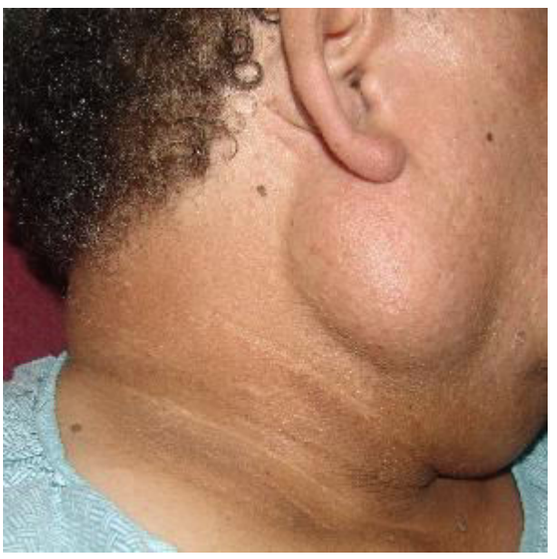
Chemotherapy complications

- **Oral mucositis**
  - **Severe mucositis** is common with head and neck cancer treatment due to the combination of chemotherapy and external beam radiotherapy.
    - **Admit the patient for IV fluids and nutritional support**
      - Often patients require a PEG or RIG to provide adequate nutritional support during their potentially curative treatment.
  - Oral hygiene is the mainstay of treatment in prevention of mucositis however it will not treat an existing mucositis.
  - Chlorhexidine mouthwash can improve a grade 1-2 mucositis.

Salivary Gland Tumors

- Most commonly occur in the **parotid gland**
  - generally **benign**
  - if the tumor involves a non-parotid gland it is more likely to be malignant
- Types
  - **pleomorphic adenoma**
    - **the most common benign salivary gland neoplasm.**
      - **70% to 80% of all benign salivary gland tumours.**
    - more common in **females** (middle-aged women **>** 40)
    - It is found mostly in the parotid gland (84%).
    - 90% of parotid gland pleomorphic adenomas arise lateral to the facial nerve.
    - benign with high rate of recurrence but may become malignant
    - Usually **they do not enhance** following intravenous contrast injection in CT.
    - The optimal treatment is superficial or total parotidectomy with facial nerve preservation
  - Warthin's tumor
    - benign
    - more common in **males**
    - **heterotopic salivary gland tissue located in a lymph node**
    - surrounded by lymphatic tissue
  - mucoepidermoid carcinoma
    - most common **malignant** tumor
      - note: muco = malignant
    - generally involves **parotid** gland
    - combination of neoplastic **mucus** and **squamous** cells

- Physical exam
  - **painless, moveable mass found at the angle of the jaw**
    - pleomorphic adenoma
  - **disturbance in CN VII function**
    - more likely to be malignant pleomorphic adenoma



Palliative care prescribing: pain

Metastatic bone pain may respond to NSAIDs, bisphosphonates or radiotherapy

The breakthrough dose of short acting morphine should be 1/6th of the total 24-hour dose.

NICE guidelines (2012**)** and **SIGN guidelines** (2008)

- metastatic bone pain may respond to NSAIDs, bisphosphonates or radiotherapy

Starting morphine

- Morphine is the opioid of choice for treating moderate to severe cancer pain.
- **Choices between morphine preparations**
  - when starting treatment, offer patients with advanced and progressive disease regular oral modified-release **(MR)** or oral immediate-release morphine**(IR)** (depending on patient preference), with oral immediate-release morphine for breakthrough pain
  - oral modified-release morphine should be used in preference to transdermal patches
  - **Immediate release preparations are used for titration** as they offer greatest flexibility. Most patients should be started on 5-10mg orally every 4-hours, with the same dose prescribed as a breakthrough (or 'rescue') dose wherever needed. **Once drug requirements are constant, the patient can be converted to modified-release morphine.**
  - Once a patient has been titrated on immediate release opioids these can be converted to the equivalent dose of a modified release preparation.
  - If a patient has good pain control on one drug, the modified release version of this drug should be used.
- **Morphine doses**
  - if no comorbidities use 20-30mg of MR a day with 5mg morphine for breakthrough pain. For example, 15mg modified-release morphine tablets twice a day with 5mg of oral morphine solution as required
  - When increasing the dose of opioids the next dose should be increased by 30-50%.
  - **An appropriate starting dose of morphine sulphate immediate release (IR) should not be more than 10mg every 4 hours.** Alternatively, morphine sulphate modified release (MR) 30mg 12 hourly could be used.
- **Opioids Side effects:**
  - Constipation: laxatives should be prescribed for all patients initiating strong opioids
    - **Morphine causes constipation by enhancing intestinal ring contractions**. This results in hypersegmentation which in turn impairs peristalsis.
    - 90% of patients taking morphine require a laxative and a stimulant is the best choice (such as senna). **Senna is the most commonly used laxative for this indication**
  - Nausea: patients should be advised that nausea is often transient. If it persists then an antiemetic should be offered
  - drowsiness is usually transient - if it does not settle then adjustment of the dose should be considered

Preferred opioids for patients with chronic kidney disease

Breakthrough dose = 1/6th of daily morphine dose

- **Opioids should be used with caution in patients with chronic kidney disease. Alfentanil, buprenorphine and fentanyl are preferred**
  - Fentanyl patches are difficult to titrate because they are used for 72 hours. therefore only used once a patient has a stable opiate usage.
  - Fentanyl is a selective μ receptor agonist.
  - It has extensive first-pass metabolism so is not especially effective orally.
  - However, buccal absorption is good so lozenges are an effective mode of administration and have a rapid onset of action (five minutes). This is therefore very useful for patients with "breakthrough pain".
  - It is very useful in renal failure as it is metabolised mainly in the liver and it has inactive metabolites.

What is the most appropriate opioid to prescribe for a syringe driver in renal failure?
➔ **Alfentanil**

Combination therapies antagonism

- Partial opioid agonists (for example, **buprenorphine),** when used in association with **morphine**, may **produce a reduction in the analgesic effect due to partial antagonism**.

- This is an aspect of pain management that needs to be considered when using combination therapies.

Oxycodone

- Oxycodone is often used as a second line opioid for patients who experience either inadequate analgesia or excessive side effects with morphine.
- It has similar analgesic properties to morphine but is twice as potent.
- It is available in immediate-release and modified- release oral preparations and can also be used parentally.
- **Parental oxycodone is twice as potent as oral oxycodone**.
- **The total daily dose of immediate and modified release oral oxycodone is the same.**
- Oxycodone generally causes less sedation, vomiting and pruritis than morphine but more constipation.

Opioid side-effects

Usually transient	Usually persistent
Nausea Drowsiness	Constipation

Conversion between opioids

From	To	Conversion factor
Oral codeine	Oral morphine	Divide by 10
Oral tramadol	Oral morphine	Divide by 10

From	To	Conversion factor
Oral morphine	Oral oxycodone	Divide by 1.5-2**

**historically a conversion factor of 2 has been used (i.e. oral oxycodone is twice as strong as oral morphine). The current BNF however uses a conversion rate of 1.5

Transdermal perparations:

The current BNF gives the following conversion factors for transdermal perparations

- **a transdermal fentanyl 12 microgram patch equates to approximately 30 mg oral morphine daily**
- a transdermal buprenorphine 10 microgram patch equates to approximately 24 mg oral morphine daily.

From	To	Conversion factor
Oral morphine	Subcutaneous morphine	Divide by 2
Oral morphine	**Subcutaneous diamorphine**	**Divide by 3**
Oral oxycodone	Subcutaneous diamorphine	Divide by 1.5

Diamorphine

Concerning diamorphine elixir for the relief of pain in terminal patients:

- Diamorphine has a rapid onset so could be used for breakthrough pain **if the renal function is normal.**
- **Constipation is a characteristic sequel to treatment**
- Hallucinations also tend to occur.
- An aperient (laxative) should always be added to the treatment regime.

- Addiction is not a problem.
- An intramuscular injection is three times more effective than the same oral dose.
- **the best option for controlling pain associated with vomiting in palliative care → Subcutaneous diamorphine by continuous infusion** (able to effectively titrate the dose to achieve adequate analgesia)

Other notes:

- **Nifedipine**
  - **Nifedipine helps relieve painful oesophageal spasm** and tenesmus associated with gastrointestinal tumours and could be used to relieve odynophagia.
- **Bisphosphonates**
  - Bisphosphonates are useful adjuncts for bone pain, especially in breast cancer and myeloma.
  - Clodronate inhibits osteoclastic bone resorption and is used to treat malignant bone pain and the associated hypercalcaemia.
  - **The risk of osteonecrosis of the jaw is much greater for patients receiving intravenous bisphosphonates in the treatment of cancer.**
    - All patients receiving bisphosphonates for cancer should have a dental check-up before bisphosphonate treatment.
    - other patients who are prescribed bisphosphonates should have a dental examination only if they have poor dental health.
  - The beneficial effect of bisphosphonates can be delayed for up to two weeks and can last for one month, and treatments are therefore usually given monthly (typically for 6 months).
  - increase analgesia while waiting for the bisphosphonates to work and review over the next few days to see whether you could reduce them again.
- **Corticosteroids**
  - Corticosteroids are used to treat pain from central nervous system tumours
- **Oxybutynin**
  - painful bladder spasm may be relieved by oxybutynin.
- **hyoscine**
  - **to reduce air way secretions in palliative care → Both hyoscine and atropine when given subcutaneously are thought to be equally appropriate for drying up secretions.**
  - hyoscine s/c can be given up to three times per day in boluses of 10-20 mg.
- **Haloperidol**
  - **Haloperidol is a first line antiemetic for opioid-induced nausea in the palliative care setting**.
  - Its action is predominantly via D2-receptor antagonism in the chemoreceptor trigger zone (CTZ) in the brain stem.
  - 90% of patients taking morphine require antiemetics (morphine stimulates D2 receptors in the CTZ). Cyclizine, although commonly used, is less effective.
  - **haloperidol → dopamine receptor antagonist (D2) activity → drug-induced parkinsonism (DIP).**
- **Cyclizine**
  - Cyclizine is a commonly used antihistamine antiemetic and its primary site of action is the vomiting centre (which is rich in histamine and muscarinic cholinergic receptors).
  - **Cyclizine has a strong affinity for muscarinic receptors and therefore anticholinergic side effects (dry mouth, drowsiness, blurred vision, constipation, etc) are common,** especially in the first few days.
- **Ondansetron**
  - Ondansetron is a $5HT_3$ antagonist and is mainly used in post-chemotherapy or radiotherapy induced nausea.
  - In the United Kingdom $5HT_3$ antagonists are licensed only for post-chemotherapy and post-operative nausea.
  - **Which antiemetics is most useful following treatment with a platinum based chemotherapy? → Ondansetron**
    - Examples of platinum based chemotherapies are cisplatin, carboplatin and oxaliplatin
- **Opioid toxicity**
  - **Reduced conscious level, hallucinations, vomiting, myoclonic jerks and pinpoint pupils are features of opioid toxicity.**

- **Pain management**
  - The pain may be due to metastatic deposits within the ribs, but may also have an element of neuropathic pain. Nerve pain often also has a nociceptive opioid responsive element and hence **opioids (with a combination of nonsteroidal anti-inflammatory drugs [NSAIDs]) should be tried first** (eg: ibuprofen and tramadol) and used as part of the WHO analgesic ladder. Morphine would be tried next, followed by the other agents.
- **Gabapentin**
  - **Gabapentin** is a commonly used adjunctive agent for neuropathic pain.
  - mechanism of action : **(Activation of GABA inhibitory system).**
  - Four to six weeks of treatment are often needed before the patient experiences benefit.
- **Hypercalcaemia**
  - Hypercalcaemia is a common problem in palliative care.
  - prostate cancer with bone metastasis is a frequent cause.
  - Hypercalcaemia can cause constipation **(a constipation in cancer → do blood tests, including bone profile)**
- **Codeine**
  - **The analgesic effect of codeine depends on its conversion to morphine by the CYP2D6 hepatic enzyme. Up to 10% of Caucasians are CYP2D6 poor metabolisers and are unlikely to derive any analgesia from it.**
  - If hepatic metabolise is impaired for any other reason (drugs or hepatic impairment) patients are also unlikely to benefit from codeine.

Acupuncture is playing an increasing role in pain management. **Which structures are involved in mediating the effects of acupuncture? Cerebral cortex and A beta nerve fibres.**

- The A beta nerve fibres are the path for fast transmission of sensation.
- Acupuncture also has a central effect.

Palliative care prescribing: agitation and confusion

- Underlying causes of confusion need to be looked for and treated as appropriate, for example hypercalcaemia, infection, urinary retention and medication.
- If specific treatments fail then the following may be tried:
  - first choice: haloperidol
  - other options: chlorpromazine, levomepromazine
  - In the terminal phase of the illness then agitation or restlessness is best treated with midazolam

Palliative care prescribing: hiccups

Hiccups in palliative care - chlorpromazine or haloperidol

Management of hiccups

- chlorpromazine is licensed for the treatment of intractable hiccups
- haloperidol, gabapentin are also used
- dexamethasone is also used, particularly if there are hepatic lesions

Palliative care: end of life care

Glucocorticoids are prominent in end of life care not only for control of pain, but also to relieve nausea and fatigue and improve general feelings of wellbeing. Randomised controlled trials have suggested only approximately a 15% improvement in pain, although other benefits including reduced nausea and improved energy are seen. Dexamethasone is the usual agent of choice.

Epstein-Barr virus: associated conditions

EBV: associated malignancies:
- Burkitt's lymphoma
- Hodgkin's lymphoma
- nasopharyngeal carcinoma

- **Epstein-Barr virus** infects B lymphocytes and squamous epithelial cells of the oropharynx. The virus can transform B cells and epithelial cells to produce tumors
- **Malignancies associated with EBV infection**
  - Burkitt's lymphoma (both African and sporadic Burkitt's)
  - Hodgkin's lymphoma
  - **nasopharyngeal carcinoma**
    - Epstein-Barr virus is detectable in over 90% of nasopharyngeal cancers
    - the most common type is the undifferentiated form.
  - HIV-associated central nervous system lymphomas
- The non-malignant condition hairy leukoplakia is also associated with EBV infection.

September 2009 exam: What type of virus family is associated with nasopharyngeal carcinoma? Herpesvirus (Epstein-Barr virus is one of the herpes viruses)

T cell lymphoma (Adult T-cell lymphoma (ATLL)

- makes up about 10-20% of non-Hodgkin's lymphomas
- has a worse prognosis than B cell lymphoma.
- Adult T-cell leukaemia/lymphoma (ATLL) is a potentially aggressive type of mature T-cell non-Hodgkin lymphoma.
- It is linked to the viral infection, HTLV-1 (human T-cell lymphotropic virus 1).
- It is more prevalent in countries where infection with HTLV-1 is common, such as Japan, China, the Caribbean, South and Central America and West Africa.
- ATLL occurs in 2%-5% of people who are infected with the HTLV-1 virus.
- The HTLV-1 virus is a retrovirus, and is in the same class of virus as the HIV/AIDS virus. It is believed that the HTLV-1 virus is a key factor in the development of this rare lymphoma which is transmitted through sexual contact, exposure to contaminated blood or breastfeeding.
- slightly more common in men than in women,
- In **acute ATLL**, symptoms develop rapidly and include:
  - fatigue,
  - skin rash
  - enlarged lymph nodes
  - hypercalcaemia may also be present which can cause confusion, bone pain and severe constipation.
- **lymphomatous form of ATLL** presents with:
  - enlarged lymph nodes.
- **Chronic ATLL** is slow growing and frequently characterised by:
  - enlarged lymph nodes
  - Skin rash and
  - fatigue.
- Smouldering ATLL develops slowly and presents with very mild symptoms such as a few lesions on the skin.
- Patients with the chronic or smouldering types of ATLL can progress to the acute form in about 25% of cases.
- for the acute and lymphomatous types: Therapies include antiviral drugs, such as acyclovir and interferon, together with chemotherapy regimens

Testicular cancer

Features

- fatigue, weight loss, and a testicular mass
- gynaecomastia
  - Rarely gynaecomastia can be the trigger by which a young man will seek medical attention; testicular examination should therefore be done in every case.
  - **What is the mechanism by which patients with testicular cancer develop gynaecomastia?**
  - ➔ **Raised oestrogen levels**
    - testicular cancers → ↑β-HCG → ↑oestrogen → stimulates hypertrophy of breast tissue.
- Raised oestrogen levels

Treatment

- **In testicular cancer** the BEP combination is used: Bleomycin, Etoposide and Cisplatin (Platinum).
- **Etoposide**
  - works by inhibiting topoisomerase II and causing DNA degradation.
  - Etoposide is also used in the treatment of small cell lung cancer, leukemias, and lymphomas.
  - adverse effects: myelosuppression and alopecia.

Tumor markers

Common tumor markers	
Tumor marker	**Associated conditions**
Alpha fetoprotein (AFP)	• Hepatocellular carcinoma (HCC) • Hepatoblastoma • Yolk sac tumor of the ovary (endodermal sinus tumor) • Mixed germ cell tumor
	• Transient elevation during pregnancy • ↑ AFP: abdominal wall defects, neural tube defects • ↓ AFP: associated with trisomy 21, 18, and 13 (See prenatal diagnostics for details)
β-HCG	• Testicular germ cell tumors (choriocarcinoma, embryonal cell carcinoma, mixed germ cell tumor, seminoma) • Ovarian cancer: choriocarcinoma (gestational trophoblastic disease)

	• If detectable in urine
	  • Pregnancy marker
	  • Molar pregnancy (hydatidiform mole)

Carcinoembryonic antigen (CEA)	• **Colorectal cancer** • **Pancreatic cancer** • Breast cancer • Lung cancer (especially in non-small cell cancers) • Gastric cancer • Endometrial cancer • Medullary thyroid cancer
	• Smokers
Prostate-specific antigen (PSA)	• Prostate cancer
	• Benign prostatic hyperplasia • Prostatitis
Calcitonin	• Medullary thyroid cancer

Common tumor markers	
Tumor marker	**Associated conditions**
Alkaline phosphatase	• Metastases to bone or liver
	• Paget disease of the bone
Lactate dehydrogenase	• Ovarian cancer (dysgerminoma) • Testicular germ cell tumors (both seminoma and nonseminoma) • Lymphomas • Ewing's sarcoma
	• Hepatitis • Hemolysis • Myocardial infarction
Neuron specific enolase (NSE)	• Small cell lung cancer • Neuroendocrine tumors • Neuroblastoma
	• NSE is released secondary to brain injury (e.g., stroke)
CA 19–9	• Pancreatic adenocarcinoma
CA 15–3/CA 27–29	• Breast cancer
CA 125	• **Ovarian carcinoma**(80–100%)
Chromogranin A	• Neuroendocrine tumors • Medullary thyroid cancer
S-100 protein (S100A) and (S100B)	• Malignant melanoma
β2 microglobulin (β2M)	• Multiple myeloma • Chronic lymphocytic leukemia • Renal disease
Thyroglobulin	• Papillary thyroid carcinoma • Follicular thyroid carcinoma
Monoclonal immunoglobulins	• Multiple myeloma • Waldenstroms macroglobulinemia
	• Monoclonal gammopathy • Infections • Certain autoimmune conditions (e.g., rheumatoid arthritis)

Von Hippel-Lindau syndrome

Definition

- Von Hippel-Lindau (VHL) syndrome is an **autosomal dominant** condition predisposing to neoplasia.

Aetiology

- due to an abnormality in the VHL gene located on short arm of **chromosome 3**
  - **v**on-**H**ippel-**L**indau= **3** words for chromosome **3.**
- VHL gene normally act as a tumor suppressor gene
  - VHL gene normally is responsible for regulating the **hypoxia-inducible factor (HIF),** a transcription factor.
  - In patients with VHL, there is constitutive expression of HIF resulting in angiogenesis and cancer development.

Epidemiology

- it has over 90% penetrance by the age of 65.
- prevalence is 1 in 39,000.
- Mean age at presentation of 27 years.

Types

- Type 1 VHL is associated with tumours in eye, brain, spinal cord, kidney and pancreas.
- Type 2 is associated with phaeochromocytoma:

Features

- haemangioblastomas of the CNS (The most common presentation)
  - retinal haemangiomas: vitreous haemorrhage
    - **Retinal haemangioblastomas** is the initial presentation in 40% of patients.
    - **Annual ophthalmological exam for haemangioblastoma is the most appropriate screening investigation**
  - cerebellar haemangiomas is another common initial presentation.
    - CNS haemangioblastomas tend to be infratentorial.
    - cerebellar haemangiomas secretes erythropoietin-like substance, leading to a **secondary polycythaemia.**
    - haemangioblastomas are typically not cancerous, but they can compress the brain and spinal cord resulting in headaches, vomiting, paralysis, and ataxia.
- cysts in various organs (e.g., kidney, pancreas, liver)
  - renal cysts (premalignant)
    - ↑ risk of developing **clear cell renal cell carcinoma.**
    - **Renal cell carcinoma** (Clear cell) **is the commonest cause of death** (70% of patients having renal cysts and carcinomas by age of 60 years).
  - extra-renal cysts: epididymal, pancreatic, hepatic
- phaeochromocytoma
  - occurs in 20% of patients, although the incidence is much higher in those with von Hippel Lindau type 2
- endolymphatic sac tumours

Diagnosis

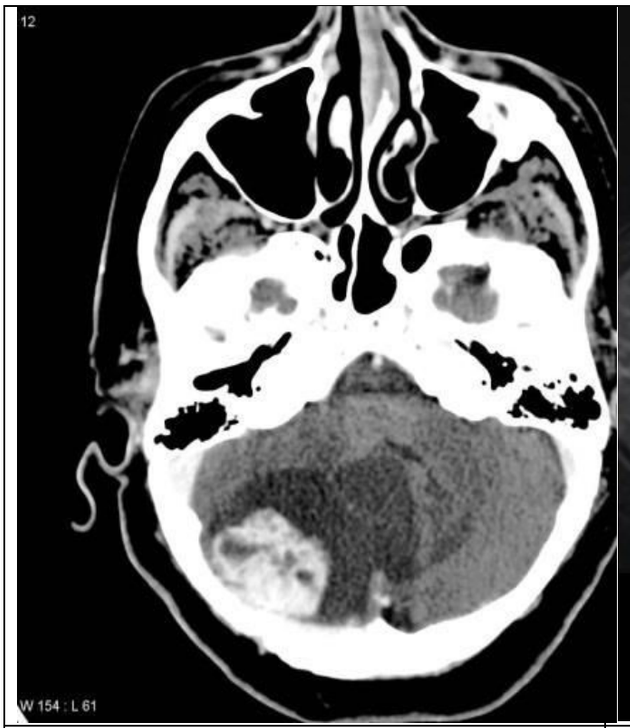
- genetic testing → mutations in the VHL gene.
  - Ideally, genetic testing in affected families should take place around the age of 5 years.

Treatment

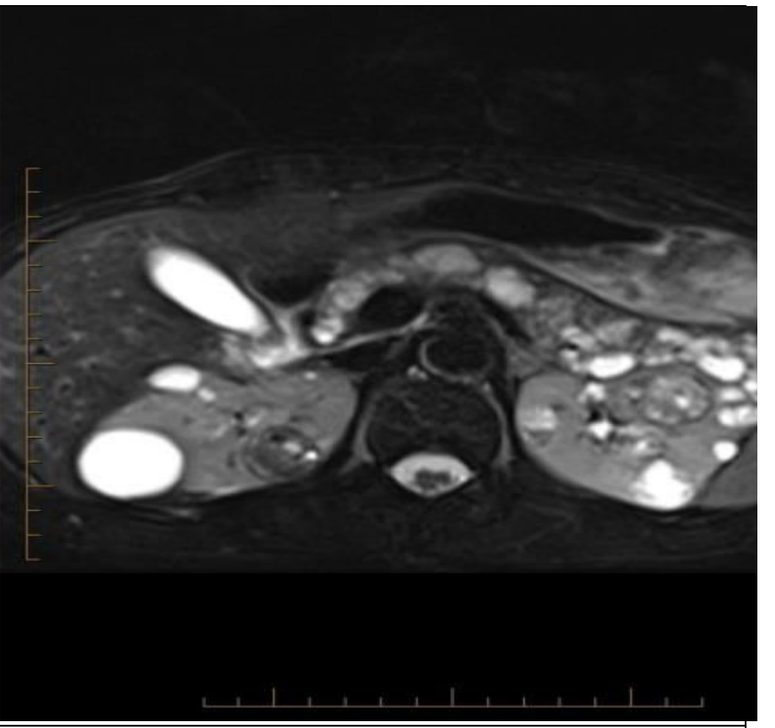
- Asymptomatic small haemangioblastomas→ observation.
- Renal cell carcinoma→ surgery.

Monitoring

- Affected individuals require:
  - yearly urinalysis, catecholamine screening, fluorescein angiography
  - 3-yearly brain magnetic resonance imaging.



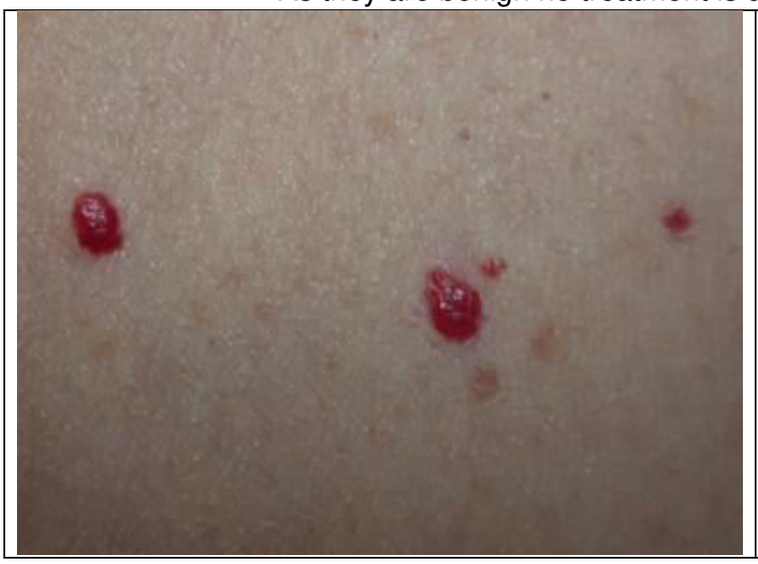
CT scan showing a cerebellar haemangioma in a patient with Von Hippel-Lindau syndrome.

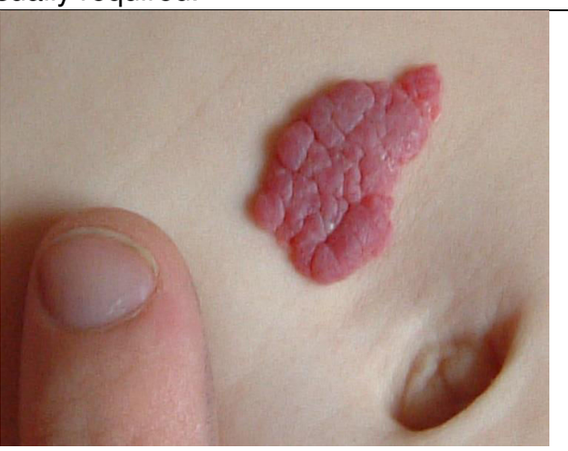


MRI showing renal cysts in patient with known Von Hippel-Lindau syndrome.

Haemangiomas

- Hemangiomas are benign vascular tumors that lead to a messy clump of dilated blood vessels.
- **Hepatic hemangioma**
  - a benign liver tumor composed of masses of blood vessels
  - the most common benign tumor affecting the liver.
  - The most common site of hemangiomas in internal organs is the liver.
  - mesenchymal in origin and usually, are solitary
  - oral contraceptives and steroids may accelerate the growth of a hemangioma.
  - Investigations
    - biopsies are contraindicated because of the risk of bleeding.
    - A good way to determine if a structure is hypervascular is to look for IV contrast enhancement.
- **Capillary hemangioma**
  - **cherry hemangioma:**
    - also known as (Campbell de Morgan spots)
    - benign **capillary** hemangioma of the elderly that does not regress
    - benign skin lesions which contain an abnormal proliferation of capillaries.
    - frequency increases with age.
    - The most common benign capillary skin tumor found in elderly
    - affect men and women equally.
    - Features
      - erythematous, papular lesions
      - typically 1-3 mm in size
      - non-blanching
      - not found on the mucous membranes
    - As they are benign no treatment is usually required.





- Infants with large hemangiomas should have **ultrasonography** of the abdomen to rule out the presence of other hemangiomas in the viscera.
- **Propranolol is the first line of treatment** of hemangiomas causing disfigurement.

Oncology drugs

Cytotoxic agents

The tables below summarises the mechanism of action and major adverse effects of commonly used cytotoxic agents.

Alkylating agents

Cytotoxic	Mechanism of action	Adverse effects
Cyclophosphamide	Alkylating agent - causes cross-linking in DNA	Haemorrhagic cystitis, myelosuppression, transitional cell carcinoma

Cytotoxic antibiotics

Cytotoxic	Mechanism of action	Adverse effects
Bleomycin	Degrades preformed DNA	**Lung fibrosis**
Doxorubicin	Stabilizes DNA-topoisomerase II complex inhibits DNA & RNA synthesis	Cardiomyopathy

Antimetabolites

Cytotoxic	Mechanism of action	Adverse effects
Methotrexate	Inhibits dihydrofolate reductase and thymidylate synthesis	Myelosuppression, mucositis, liver fibrosis, lung fibrosis
Fluorouracil (5-FU)	Pyrimidine analogue inducing cell cycle arrest and apoptosis by blocking thymidylate synthase (works during S phase)	Myelosuppression, mucositis, dermatitis
6-mercaptopurine	Purine analogue that is activated by HGPRTase, decreasing purine synthesis	Myelosuppression
Cytarabine	Pyrimidine antagonist. Interferes with DNA synthesis specifically at the S-phase of the cell cycle and inhibits DNA polymerase	Myelosuppression, ataxia

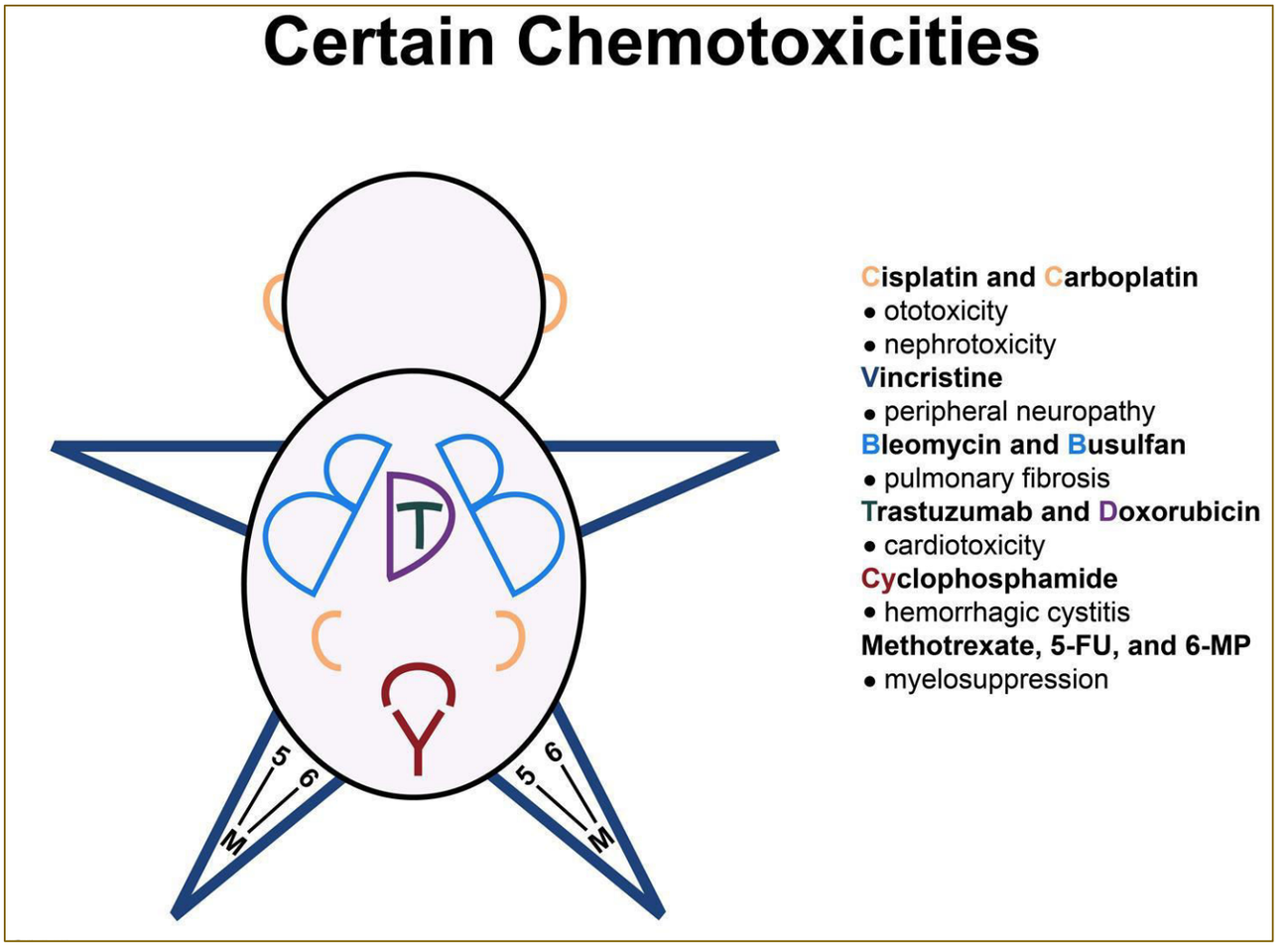
Acts on microtubules

Cytotoxic	Mechanism of action	Adverse effects
Vincristine, vinblastine	Inhibits formation of microtubules	**Vincristine: Peripheral neuropathy** (reversible) , paralytic ileus Vinblastine: myelosuppression
Docetaxel	Prevents microtubule depolymerisation & disassembly, decreasing free tubulin. has a further action in blocking bcl-2	Neutropaenia

Other cytotoxic drugs

Cytotoxic	Mechanism of action	Adverse effects
Cisplatin	Causes cross-linking in DNA	Ototoxicity, peripheral neuropathy, hypomagnesaemia
Hydroxyurea (hydroxycarbamide)	Inhibits ribonucleotide reductase, decreasing DNA synthesis	Myelosuppression

Vincristine - peripheral neuropathy



Busulfan

- alkylating antineoplastic agent,
- Busulfan was the mainstay of the chemotherapeutic treatment of chronic myeloid leukemia (CML) until it was displaced by the new gold standard, imatinib
- Busulfan is used in pediatrics and adults in combination with cyclophosphamide or fludarabine/clofarabine as a conditioning agent prior to bone marrow transplantation, especially in chronic myelogenous leukemia (CML) and other leukemias, lymphomas, and myeloproliferative disorders.
- **Busulfan lung**
  - **Busulfan lung is a form of drug-induced pulmonary toxicity with an idiopathic pulmonary fibrosis-like picture.**
  - It is clinically symptomatic in 5% of patients.
  - There are no predictors of toxicity and pulmonary function testing is not a useful "screening" test.
  - Withdrawal of busulfan is the key step in treatment.

Combinations of chemotherapeutic agents

- **what is the rationale behind using combinations of chemotherapeutic agents rather than single agents?**
  - ➔ **Combination therapy decreases the chances of drug resistance developing**
    - There are two main reasons for using combinations of different chemotherapy agents:
      1. **Different drugs will exert their effects through different mechanisms**, so combining them will increase the number of tumour cells killed in each cycle.
      2. It also reduces the chances therefore of drug resistance developing.

Vinblastine

- Vinblastine is an **M phase**-specific chemotherapeutic agent that works by **disrupting the assembly of microtubules via binding tubulin**.
- Cell death results because anaphase cannot commence without the formation of the mitotic spindle and kinetochore.
- **Which cellular event occurs in the same phase of the cell cycle at which vinblastine functions? → Breakdown of the nuclear membrane**
- **Breakdown of the nuclear membrane** occurs during the prometaphase portion of mitosis.

Taxanes (e.g. Docetaxel) prevent microtubule disassembly

Cyclophosphamide

Cyclophosphamide - haemorrhagic cystitis - prevent with mesna

- Cyclophosphamide is an **alkylating agent** used in the management of cancer and autoimmune conditions.
- It works by causing **cross-linking of DNA**
- Cyclophosphamide is **inactive unless metabolised by the liver to 4-hydroxyl cyclophosphamide**, which decomposes into alkylating species as well as to chloroacetaldehyde and acrolein

Adverse effects

- **haemorrhagic cystitis** (**Acrolein** causes **chemical cystitis**):
  - ➢ **incidence reduced by the use of hydration and mesna**
- myelosuppression
- transitional cell carcinoma
- premature ovarian failure ,
- **infertility** in both men and women.

Mesna

- 2-**me**rcaptoethane **s**ulfonate **Na**
- a metabolite of cyclophosphamide called **acrolein** is toxic to urothelium
- mesna binds to and inactivates acrolein helping to prevent haemorrhagic cystitis

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Cisplatin

Cisplatin may cause peripheral neuropathy

Cisplatin is associated with hypomagnesaemia

- **Platin**um-based antineoplastic (end with: -**platin**)

Mechanism of action

- **Causes crosslinking in DNA** → makes it impossible for rapidly dividing cells to duplicate their

DNA for mitosis.

Side effects

- Marrow toxicity
- **Ototoxicity**
  - Due to vestibulocochlear nerve damage (CNVIII)
  - Sodium Thiosulfate Prevents Cisplatin-Induced Hearing Loss in Children With Cancer
- Peripheral neuropathy
- Nephrotoxicity
  - The nephrotoxicity of platinum-class drugs seems to be related to reactive oxygen species
  - Hypocalcaemia, **hypomagnesaemia** and hypokalaemia may occur as a result of nephrotoxicity
  - Amifostine is an antidote for cisplatin treatment to counteract nephrotoxicity.
  - Adequate hydration and diuresis is used to prevent renal damage.
    - Chloride diuresis is a renal procedure that can be performed to prevent the nephrotoxicity caused by cisplatin.
- Alopecia,
- Changes in taste.
- Although optic neuritis is described it is not a typical side effect.

Trastuzumab

Trastuzumab (Herceptin) - cardiac toxicity is common

A baseline echocardiogram to assess heart function is recommended prior to starting trastuzumab.

- Trastuzumab (Herceptin) is a monoclonal antibody directed against the HER2/neu receptor.
- It is used mainly in metastatic breast cancer although some patients with early disease are now also given trastuzumab.

Adverse effects

- flu-like symptoms and diarrhoea are common
- **cardiotoxicity**: **associated with Dilated cardiomyopathy** in 2% to 7% of users
  - more common when anthracyclines have also been used(eg : **Doxorubicin)**.
  - Toxic to cardiac muscle itself with relative sparing of the electrical conductivity of the heart
  - Studies have shown that activation of **Erb-b2** (also known as HER-2), the receptor blocked by trastuzumab (Herceptin), is important in preventing the development of cardiomyopathy
  - Mechanism
    - Anthracyclines → activate stress signal pathways within the heart → cardiac damage
    - HER2 activation is protective against the damage that this stress signaling induces
    - HER2 inhibition removes this layer of protection, leading to → dilated cardiomyopathy.
  - An echo is usually performed before starting treatment
  - **Regular echocardiogram (three monthly) is the best test to assess treatment safety**
  - Reduction of greater than 10% in ejection fraction indicating the need to stop treatment.

In which chemotherapeutic agents is the cumulative dose limited due to cardiotoxicity?

- **anthracycline chemotherapeutic agents** (eg: Epi**rubicin**)
  - Epirubicin and the other anthracycline chemotherapeutic agents are extremely potent but are **limited by dose constraints**.
  - Cumulative doses of over 900 mg/m2 can lead to significant cardiac toxicity and heart failure.
  - Trastuzumab can cause direct myocardial damage and must be monitored with regular echocardiograms but it is not limited to a maximum lifetime dose.

Erlotinib

- Erlotinib specifically targets the epidermal growth factor receptor (EGFR) tyrosine kinase (which is required for the conformational change) and binds in a reversible fashion to the adenosine triphosphate binding site.
- For the signal to be transmitted, two members of the EGFR family need to come together to form a homodimer. These then use the molecule of adenosine triphosphate (ATP) to autophosphorylate each other, which causes a conformational change in their intracellular structure, exposing a further binding site for binding proteins that cause a signal cascade to the nucleus. By inhibiting the ATP, autophosphorylation is not possible and the signal is stopped.
- A key issue with EGFR-directed treatments is that **after a period of 8-12 months, the cancer cells become resistant to the treatment. This most commonly occurs due to a mutation in the ATP binding pocket of the EGFR kinase domain.** This prevents the binding of erlotinib (Tarceva).

Imatinib

- **Belong to the class of → Signal transduction inhibitor**
- Imatinib is a **tyrosine kinase inhibitor** which is fairly specific for the bcr/abl protein. It blocks the active site, which has a number of downstream effects.
  - The result is reduced cell proliferation, reduced cell motility, decreased adhesion and increased apoptosis.
- Indications
  - NICE recommend that imatinib should be used to treat people in the accelerated or blast crisis phase of CML.
  - It is also indicated in the treatment of gastrointestinal stromal tumours.

Tamoxifen

Tamoxifen is a selective estrogen receptor modulator (SERM) which acts as an oestrogen receptor antagonist and partial agonist. It is used in the management of oestrogen receptor positive breast cancer

Adverse effects

- menstrual disturbance: vaginal bleeding, amenorrhoea
- hot flushes
- venous thromboembolism
  Particularly during and immediately after major surgery or periods of immobility
- endometrial cancer

Tamoxifen is typically used for 5 years following removal of the tumour.
Raloxifene is a pure oestrogen receptor antagonist, and carries a lower risk of endometrial cancer

UK licensed monoclonal antibodies

Name	Type of antibody	Target	Licensed indication
Infliximab	Human–mouse chimaera IgG1	TNF-α	Refractory Crohn's, Crohn's fistulas, refractory rheumatoid arthritis
Palivizumab	Humanised IgG1	F protein on RSV	Prophylaxis, RSV in premature infants or brochopulmonary dysplasia
Abciximab	Human–mouse chimaera	Platelet glycoprotein IIb/IIIa	High risk coronary intervention
Rituximab	Human–mouse chimaera IgG1	CD20	Refractory low grade or follicular B cell lymphoma
Basiliximab	Human–mouse chimaera IgG1K	IL-2 receptor α chain	Prophylaxis of acute rejection in allogeneic renal transplantation
Daclizumab	Humanised IgG1	IL-2 receptor α	As Basiliximab
Trastuzumab	Humanised IgG1	HER 2 growth receptor	Relapsed HER2 (high) breast malignancy

IL-2, interleukin 2; TNF-α, tumour necrosis factor α; RSV, respiratory syncitial virus.

Rituximab

- **Rituximab binds to CD20,** an antigen located on pre-B and mature B-lymphocytes
- The receptor is thought to mediate B-cell lysis and apoptosis
- After rituximab therapy, levels of B-lymphocytes appear suppressed for around 6 months, with levels slowly increasing after this time
- As well as for rheumatoid arthritis, rituximab is **also used for the treatment of non-Hodgkin's lymphoma**
- Infusion reactions associated with cytokine release occur in up to 15% of patients receiving rituximab, and the medicine is administered in a specialist centre for this reason

Cetuximab

- Action → epidermal growth factor receptor (EGFR) inhibitor
  - Cetuximab works by blocking the extracellular domain of EGFR preventing ligand binding and therefore preventing downstream signal transduction.
- . Cetuximab is a monoclonal antibody given by intravenous infusion
- The patient's tumour must express k-ras wild-type as k-ras mutated is constitutively active regardless of whether a ligand is attached or not.
  - **Which histopathological subtypes is essential for successful treatment with cetuximab?**
    - **K-ras wild-type**
      - Cetuximab and other EGFR inhibitors only work on tumors in which K-ras is not mutated
      - it has no effect in colorectal tumors with a K-ras mutation (this also applied to the EGFR antibody panitumumab).
      - genetic testing to confirm the absence of K-ras mutations (and so the presence of the K-ras wild-type gene), is now clinically routine before the start of treatment with EGFR inhibitors.
- Cetuximab is licensed by NICE in metastatic colorectal cancer for k-ras wild-type proven patients who require downstaging prior to surgical resection of liver metastatic disease.
  - 75% of patients with metastatic colorectal cancer have an **EGFR-expressing tumor** and are therefore considered eligible for treatment with cetuximab or panitumumab
- **Side effect**
  - **acne type rash (the most important and serious SE).**

Alpha interferon at 2 million U/m^2 subcutaneously three times a week for 12-18 months can be **used to** salvage relapsed or refractory **hairy cell leukemia.**

Capecitabine versus 5-fluorouracil (5-FU)

- **Advantages of capecitabine versus 5-fluorouracil (5-FU) → Can be orally administered**
- The major difference between capecitabine and 5-FU is that capecitabine is an oral prodrug of 5-FU. The final step in metabolism to 5-FU is thymidine phosphorylase, higher activity of thymidine phosphorylase occurring in tumour tissues.
- Evidence suggests that efficacy of capecitabine versus 5-FU is broadly similar,

Chemotherapy side-effects: nausea and vomiting

- Nausea and vomiting are common side-effects of chemotherapy.
- Risk factors for the development of symptoms include:
  - anxiety
  - age less than 50 years old
  - concurrent use of opioids
  - the type of chemotherapy used
- For patients at low-risk of symptoms then drugs such as metoclopramide may be used first-line.
- For high-risk patients, then **5HT3 receptor antagonists such as ondansetron** are often effective, especially if combined with dexamethasone

Adverse effects of other cancer treatment

Purine analogue (eg: fludarabine) for CLL → Pneumocyscis jirovecii infection

- This cytotoxic agent affects T-cell function. Patients are therefore prone to opportunistic infections including pneumocystis infection.
- Patients therefore receiving purine analogues should also receive co-trimoxazole to reduce this risk.
- All patients who receive purine analogues are at risk of **transfusion-associated graft-versus-host disease** and therefore should receive irradiated blood products. The clinical features of transfusion associated graft-versus-host disease are:
  1. pancytopaenia,
  2. liver dysfunction,
  3. diarrhoea and
  4. rash

Etoposide → secondary haematological malignancy

- In patients who have received Etoposide, secondary haematological malignancy may develop in as little as 1-3 years.
- It is currently indicated for the treatment of small cell lung cancer and non-seminomatous testicular carcinoma.

Filgrastim

- Action
  - granulocyte colony-stimulating factor (G-CSF)
- Mechanism
  - Filgrastim is similar to naturally occurring granulocyte colony-stimulating factor (G-CSF).
  - produced by recombinant DNA technology using genetic material of *Escherichia coli*.
  - stimulating the bone marrow to increase production of neutrophils.
- Indications
  - used to treat neutropenia caused by:
    - chemotherapy,
    - radiation poisoning,
    - congenital neutropenia
    - aplastic anemia
    - also used to increase white blood cells for gathering during leukapheresis.
- It is given either by injection into a vein or under the skin.
- side effects
  - The most commonly observed adverse effect is mild bone pain after repeated administration and local skin reactions at the site of injection
  - Severe side effects include splenic rupture and allergic reactions.
  - Other side effects include

- serious allergic reactions (including a rash over the whole body, shortness of breath, wheezing, dizziness, swelling around the mouth or eyes, fast pulse, and sweating),
- alveolar hemorrhage, acute respiratory distress syndrome, and hemoptysis.
- Severe sickle cell crises, in patients with sickle cell disorders.

Sargramostim

- Action
  - granulocyte macrophage colony-stimulating factor (GM-CSF)
- It is produced in yeast
- stimulate other myeloid and megakaryocyte
- Indications
  - for myeloid reconstitution after bone marrow transplantation.
  - neutropenia induced by chemotherapy
- side effects
  - GM-CSF can cause more severe effects, including fever, arthralgias, and capillary damage with edema.
  - edema

Notes & Notes

For MRCP part 1 & 11

By
Dr. Yousif Abdallah Hamad

Infectious diseases

Updated
2017

Contains:
1/ Passmedicine 2017
2/ On examination 2017
3/ Pastest 2017
4/ **Red fonts --> previous exams**
5/ Other updated UK sources

Classification of bacteria

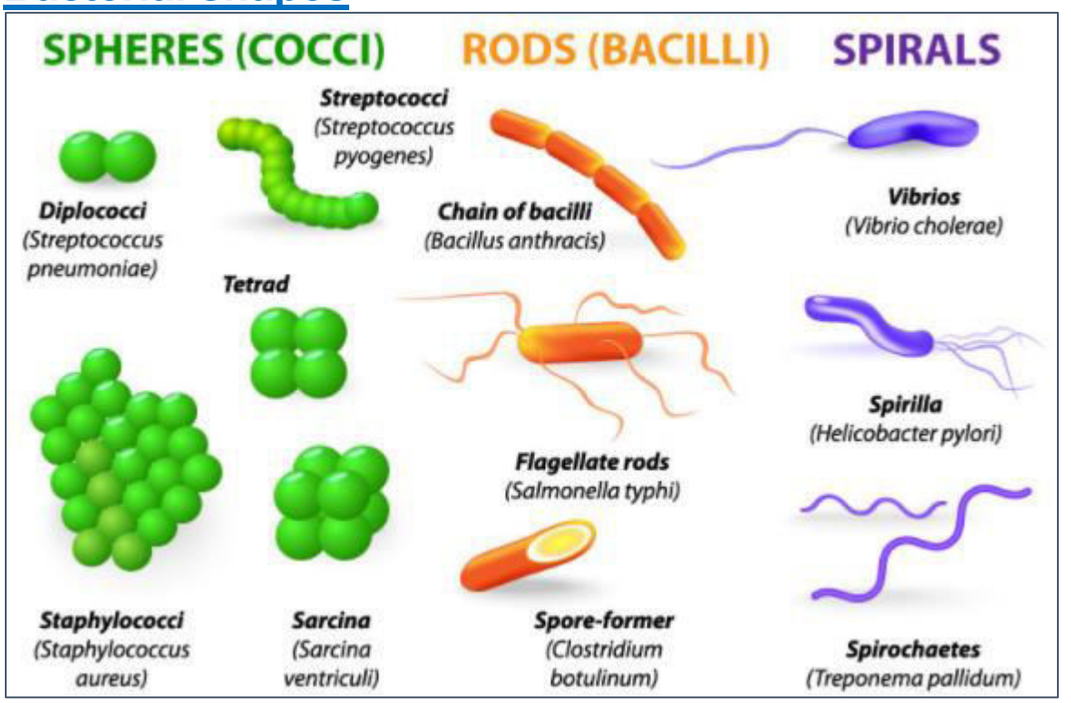
cocci

- **Remember:**
  - Gram positive cocci = staphylococci + streptococci (including **enterococci**)
  - **Gram negative cocci** = ***Neisseria*** *meningitidis* + ***Neisseria*** *gonorrhoeae*, also ***Moraxella***

Rods (bacilli)

- only a small list of **Gram positive rods** (bacilli) need to be memorised to categorise all bacteria - mnemonic = **ABCD L**
  - ***A****ctinomyces*
  - ***B****acillus anthracis* (anthrax)
  - ***C****lostridium*
  - **D**iphtheria: *Corynebacterium diphtheria*
  - ***L****isteria monocytogenes*
- Remaining organisms are Gram negative rods

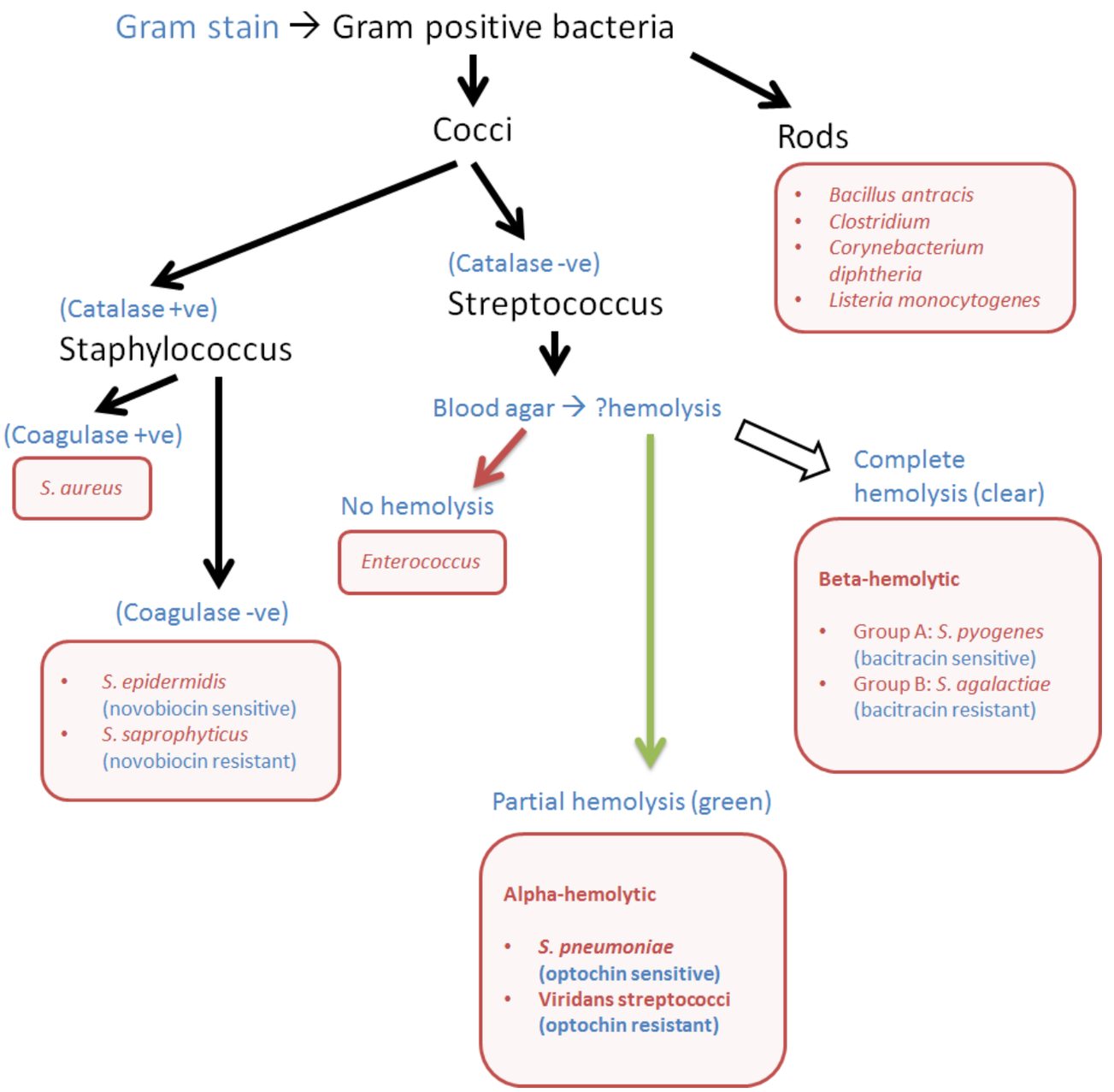
Bacterial shapes



- ***Staphylococcus aureus*** **appears as large Gram-positive cocci in clusters.**

Identifying gram-positive bacteria

Gram positive bacteria will turn purple/blue following the gram staining. Microscopy will then reveal the shape, either cocci or rods.



Rods (bacilli)

- *Actinomyces*
- *Bacillus antracis*
- *Clostridium*
- *Corynebacterium diphtheriae*
- *Listeria monocytogenes*

Cocci

- makes catalase: **Staphylococci**
- does not make catalase: **Streptococci**

Staphylococci

- makes coagulase: *S. aureus*
- does not make coagulase: *S. epidermidis* (novobiocin sensitive), *S. saprophyticus* (novobiocin resistant)

Streptococci

- partial haemolysis (green colour on blood agar): **α-haemolytic**
  - ➢ optochin sensitive: *S. pneumoniae*

  - optochin resistant: Viridans streptococci
- complete haemolysis (clear): **β-haemolytic**
  - bacitracin sensitive: Group A: *S. pyogenes*
  - bacitracin resistant: Group B: *S. agalactiae*
- no haemolysis: γ-haemolytic

Staphylococci

Most common organism found in central line infections - *Staphylococcus epidermidis*

- Staphylococci are a common type of bacteria which are often found normal commensal organisms but may also cause invasive disease.
- ***Staphylococci* are skin organisms most commonly introduced during pacemaker insertion and such a discitis would present with back pain.**

Basic facts :

- Gram-positive cocci
- facultative anaerobes
- produce catalase

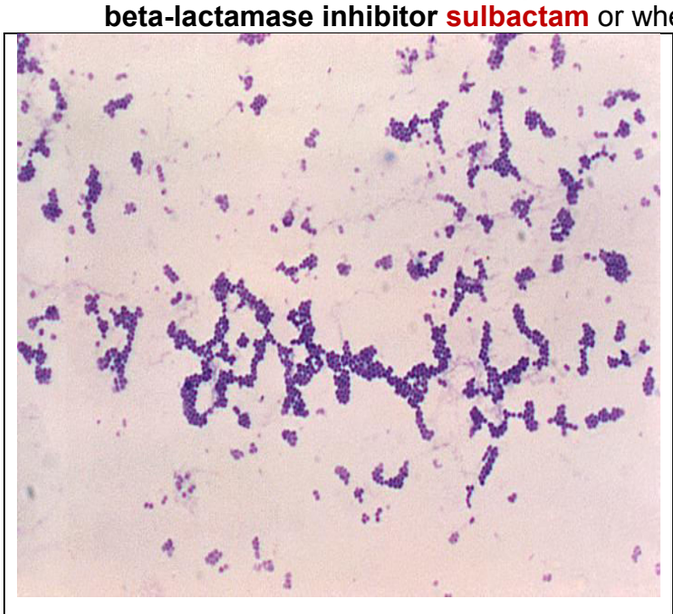
Types

- The two main types of Staphylococci you need to know about are *Staphylococcus aureus* and *Staphylococcus epidermidis*.

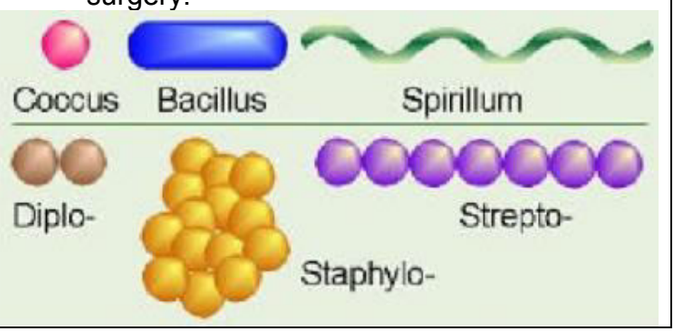
Staphylococcus aureus	***Staphylococcus epidermidis***
• Coagulase-positive • Causes skin infections (e.g. cellulitis), abscesses, osteomyelitis, toxic shock syndrome	• Coagulase-negative • Cause of central line infections and infective endocarditis

Effective antibiotics:

- Staphylococcal and streptococcal organisms are effectively treated by **semisynthetic penicillins**, including oxacillin, nafcillin, dicloxacillin, and **cloxacillin**. Also first- and second-generation cephalosporin
- Penicillin G, penicillin VK, **ampicillin**, and **amoxicillin** : These agents are effective against streptococci, such as S. pyogenes, viridans group streptococci, and S. pneumonia, **but not against staphylococci**
- Ampicillin and amoxicillin are only effective against staph when ampicillin is combined with the **beta-lactamase inhibitor sulbactam** or when amoxicillin is combined with **clavulanate**.



- The Gram stain shows Gram positive cocci **growing in clusters, typical of *Staphylococcus aureus*.**
- This is the most likely organism to cause post-operative infection of prosthetic joints within the first one to four weeks following surgery.



Streptococci

- Streptococci are gram-positive cocci.
- divided into alpha and beta haemolytic types

Alpha haemolytic streptococci (partial haemolysis)

- The most important alpha haemolytic *Streptococcus* is ***Streptococcus pneumoniae*** **(pneumococcus).**
  - carried asymptomatically in approximately 50% of people.
  - It can cause both non-invasive and invasive disease.
    - **Non-invasive**:
      - includes otitis media, sinusitis, pneumonia and bronchitis.
    - **Invasive pneumococcal disease (IPD)**
      - refers to disease in which the bacterium enters a sterile site such as blood, cerebrospinal fluid, pleural fluid or pericardial fluid.
        - **If grow in blood cultures → IPD by definition.**
      - **more common in HIV-infected patients** (20-30 times) compared to non-HIV infected patients.
        - offer HIV testing to all patients with IPD presenting to hospital.
      - Other immunodeficiency syndromes are associated with an increased risk of IPD, include:
        - X-linked (Bruton's) agammaglobulinaemia,
        - common variable immunodeficiency,
        - asplenia (anatomical or functional) and sickle cell disease.
  - **the mechanism of resistance for penicillin resistant *Streptococcus pneumoniae* → Alteration of penicillin binding proteins (PBPs)**
    - Penicillin is a bactericidal antibiotic which acts by inhibiting cell wall synthesis.
    - Mutations in PBPs (enzymes required for cell wall synthesis) result in penicillin resistance.
- Another clinical example is *Streptococcus viridans*

Beta haemolytic streptococci (complete haemolysis)

These can be subdivided into groups A-H. Only groups A, B & D are important in humans.

- **Group A**
  - most important organism is ***Streptococcus pyogenes***
  - responsible for erysipelas, impetigo, cellulitis, type 2 necrotizing fasciitis and pharyngitis/tonsillitis
  - immunological reactions can cause rheumatic fever or post-streptococcal glomerulonephritis
  - erythrogenic toxins cause scarlet fever
  - **Penicillin is the antibiotic of choice for group A streptococcal infections. The BNF suggests stopping flucloxacillin if streptococcal infection is confirmed in patients with cellulitis, due to the high sensitivity**.
- **Group B**
  - *Streptococcus* (*GBS) agalactiae*
    - Maternal vaginal colonization with GBS, primarily *Streptococcus agalactiae*, is associated with serious and highly fatal neonatal infections, such as sepsis and meningitis.
    - **Lipoteichoic acid is the primary virulence factor of this organism**
    - A prerequisite to mucosal colonization or infection is bacterial adherence to the epithelium. Lipoteichoic acid, a cell wall glycolipid polymer, mediates attachment of GBS to the vaginal epithelial cells. Lipoteichoic acid is also involved in host cell adherence of other Gram-positive bacteria as well. Without this adhesion, it would not be possible to have infection.
- **Group D**
  - *Enterococcus*

Bacteria and growing media

Bacteria	Type	Growth media
Staphylococci	Gram-positive cocci in clusters	LB broth agar
Streptococcal species (hemolytic Streptococcal species such as *Streptococcus pyogenes*).	Gram-positive cocci in chains	Trypticase Soy Agar (TSA) supplemented with 5% Sheep Blood
Streptococcus pneumoniae	Gram-positive bullet-shaped diplococci	Todd Hewitt Broth
E. coli, Klebsiella, or Enterobacter.	Gram-negative lactose fermenting bacilli	Super Optimal Broth (SOB)
Neisseria meningitidis	**gram-negative diplococcus**	**chocolate agar**

quellung test

- The quellung reaction is a test which uses antibodies to test for the presence of a bacterial capsule. The bacterial capsule helps the organism prevent phagocytosis and is therefore necessary for infection.
- S. pneumoniae displays a **positive quellung reaction**, owing to its capsule.
  - When incubated together with a specific anti-capsule antibody, the bacterial capsule (if present) swells and can be visualized under a microscope as a **positive quellung reaction**
  - the capsule is necessary for pathogenesis and an immune response to this bacteria generally contains antibodies against this target.
  - direct quellung testing on sputum smears was a 95% sensitive test for predicting pneumococcal isolation by sputum culture.
- **quellung test produce a difference in pathogenesis.**
  - Negative quellung test → NO capsule → bacteria is unable to cause disease

Vancomycin-resistant enterococci

- When they cause clinical problems they are usually urinary tract infections (UTI), bacteraemia, wound infections, neonatal infections, endocarditis, etc.
- **May be found in healthy community volunteers not recently hospitalised**
- Community reservoir in meat, poultry and perhaps cheese.
- Vancomycin-resistant enterococci alter peptidoglycan precursors used to build cell walls. Vancomycin binds to D-ala-D-ala but the resistant enterococci have D-ala-D-lac or D-ala terminating precursors.
- They acquire genes that produce enzymes to change the precursors.

Anthrax

- Anthrax is caused by *Bacillus anthracis*, **a Gram positive rod**. aerobic, non-motile
- It is spread by infected carcasses (جثث).
- It produces serious disease in the herbivore (عشبي) host and carnivores (لحمي) acquire the disease from either consuming the spores from the dead animal or by contact.
- It is also known as Wool-sorters' disease (مرض فارزي الصوف).
- Cutaneous disease is the commonest form of the infection in humans and is usually due to contact with infected animals or animal products.
- *Bacillus anthracis* produces a tripartite (composed of 3 parts) protein toxin
  1. protective antigen
  2. oedema factor: a bacterial adenylate cyclase which increases cAMP
  3. lethal factor: toxic to macrophages

Features

- **painless** non-tender **black eschar** (cutaneous 'malignant pustule', but no pus)
  - Following exposure, the skin lesion evolves over a period of ~2 weeks into a papule, pustule, vesicle and eventually forms an ulcer with a central black eschar.
  - The surrounding skin is usually boggy and oedematous.
  - Lesions are usually painless with tender regional lymph nodes.
- may cause marked oedema
- anthrax can cause gastrointestinal bleeding

Investigations

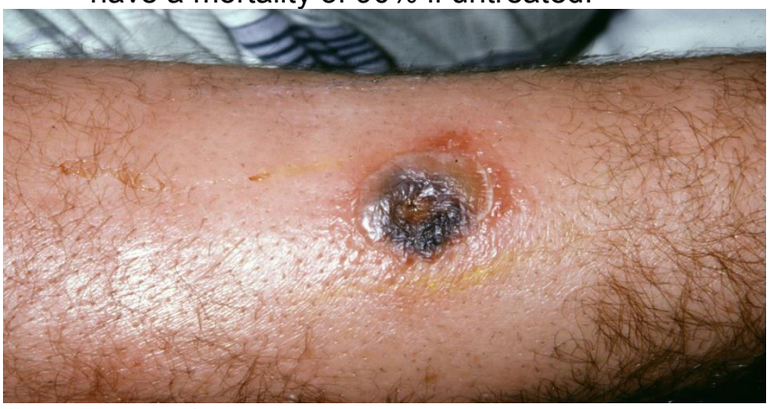
- Inhalational anthrax is associated with a poor yield from sputum culture with the greatest yield from **blood culture**.

Management

- Lesions heal spontaneously in 80-90% of cases;
- 10-20% of patients progress and become bacteraemic - associated with a high mortality.
- Penicillin is effective in treating the infection.
- the current Health Protection Agency advice for the **initial management** of **cutaneous anthrax** is **ciprofloxacin**
- further treatment is based on microbiological investigations and expert advice

Prognosis

- Mortality from cutaneous disease is 20% if untreated whereas inhalational anthrax may have a mortality of 90% if untreated.



Cutaneous anthrax

Clostridium difficile

Cephalosporins, not just clindamycin, are strongly linked to *Clostridium difficile*

- *Clostridium difficile* is a **Gram positive anaerobic rod** often encountered in hospital practice.
- It produces an exotoxin which causes intestinal damage leading to a syndrome called pseudomembranous colitis.
- *Clostridium difficile* develops when the normal gut flora are suppressed by broad-spectrum antibiotics.
- Symptoms are typically occur **5-10 days** after commencing antibiotic

Causes

- **C**lindamycin is historically associated with **c**ausing ***C****lostridium difficile*
- **Second and third generation cephalosporins** are now the leading cause of *Clostridium difficile*.
- penicillins and quinolones.

Features

- Diarrhea
  - The commonest symptoms are profuse watery diarrhoea (usually without blood or mucus)

  - Diarrhoea may not begin until several days after initial symptoms, especially in the elderly, in post-operative patients and in those who have received opiates for treatment of pain.
- abdominal pain
- fever
- **raised white blood cell count** is characteristic
- if severe, **toxic megacolon** may develop

Features suggestive of severe *Clostridium difficile* infection include

- Temperature greater than 38.5°C
- WCC >15
- Severe abdominal pain
- Hypovolaemia (low BP)
- Lactic acidosis.

Investigations

- **Diagnosis** is made by detecting ***Clostridium difficile* toxin (CDT) in the stool**
- **abdominal X-ray** is useful for diagnosing toxic dilatation and would be **the investigation of choice in patient with abdominal distension.** Toxic dilatation should be excluded prior to sigmoidoscopy. However it does not establish the diagnosis.
- **Sigmoidoscopy** is not used routinely, but can reveal distal ulceration and possible yellow slough or pseudo membrane in around half of patients (will shows multiple white plaques adhered to the gastrointestinal mucosa.).

Management

- first-line therapy is **oral metronidazole** for 10-14 days
- if severe or not responding to metronidazole then **oral vancomycin** may be used (it has no systemic absorption)
  - The major pharmacologic advantage of oral vancomycin over metronidazole is that **oral vancomycin is not absorbed,** so maximal concentrations of the drug can act intracolonically at the site of infection.
  - The instillation of **intracolonic vancomycin** (as a retention enema) is sometimes used as an adjunct to the treatment of severe disease.
  - IV Vancomycin is not effective.
- for life-threatening infections a combination of oral vancomycin and intravenous metronidazole should be used

Prognosis

- Mortality is high in elderly patients it may be as high as 10%

***The main Clostridium* species**

- ***Clostridium botulinum***: produce botulinum toxin in food or wounds and can cause botulism. This same toxin is known as Botox and is used in cosmetic surgery to paralyze facial muscles to reduce the signs of aging; it also has numerous other therapeutic uses.
- ***Clostridium difficile*** can flourish when other gut flora bacteria are killed during antibiotic therapy, leading to pseudomembranous colitis
- ***Clostridium perfringens*** causes food poisoning to cellulitis, fasciitis, and **gas gangrene.**
- ***Clostridium tetani*** causes tetanus.
- ***Clostridium sordellii*** can cause a fatal infection in exceptionally rare cases after medical abortions

Diphtheria

- caused by *Corynebacterium diphtheriae*,
- *Corynebacterium diphtheriae* is a **Gram positive**, non-spore-forming, pleomorphic bacteria that is also a facultative anaerobe.
- There are three recognised strains of *C.diphtheria*: gravis, intermedius, and mitis.

  - Intermedius is thought to be the one most associated with the exotoxin and is more virulent than the mitis strain.
- **Incubation period**: 2 - 5 days,
- patients may be infectious for 4 weeks.
- Diphtheria is spread by droplets, through contact with soiled articles (fomites), and, in areas of poor hygiene, from cutaneous spread.

Pathophysiology

- The inflammatory exudate forms a greyish membrane on the tonsils and respiratory tract which may cause respiratory obstruction.
- Diphtheria toxin inhibits elogation factor (EF-2)
- Diphtheria toxin commonly causes a 'diphtheric membrane' on tonsils caused by necrotic mucosal cells. Attempts to remove the pseudomembrane result in bleeding. Systemic distribution may produce necrosis of myocardial, neural and renal tissue.
- Exotoxins produced by the organism may cause myocarditis or neurological defects.
- secretion of an exotoxin that interferes with cellular protein synthesis, resulting in tissue necrosis.
- The exotoxin is composed of two chains:
  1. **chain B** is responsible for entry into host cells,
  2. **chain A** inhibits protein synthesis and causes cell death

Feature

history of severe exudative pharyngitis in a person who has recently travelled to eastern Europe is highly suggestive of diphtheria.

- Typically, diphtheria attacks the respiratory system, but **may also affect the skin**, conjunctiva, and external genitalia.
  - Cutaneous diphtheria presents with **non-healing ulcers covered with a grey membrane**, which can develop bacterial co-infection.
    - If isolated, the disease is indolent, but the ulcers can act as a reservoir which can subsequently lead to pharyngeal infection.
- **Pharyngeal diphtheria** presents with:
  - fever
  - sore throat
  - cervical lymphadenopathy,
    - 'bulls neck' which results from cervical lymphadenopathy and mucosal swelling.
  - adherent, grayish pharyngeal membrane.
- Neurological: cranial neuropathies, predominantly motor peripheral neuropathy (occasionally sensory neuropathy).
- Cardiac involvement is usually in the form of a cardiomyopathy and myositis, which is evident from the 10-14th day and may lead to arrhythmias. This accounts for 50% of deaths

Treatment

- isolation, securing a definitive airway, cardiac monitoring,
- antibiotic therapy and diphtheria antitoxin.
  - benzylpenicillin: children: 2.4 to 4.8 g/day intravenously/intramuscularly given in divided doses every 6 hours for 14 days
  - OR procaine benzylpenicillin 600,000 units intramuscularly once daily for 14 days
  - OR Erythromycin 250-500 mg orally four times daily for 14 days

- Early administration of antitoxin is necessary to enable it to bind to and de-activate the free toxin in serum. **Antitoxin cannot de-activate toxin once it has entered cells**, which is signalled by the presence of mucocutaneous symptoms.
- Patients with respiratory diphtheria are placed in respiratory isolation (masks and standard measures such as hand-washing), and those with cutaneous diphtheria are placed in contact isolation (gloves and gowns), until cultures taken after cessation of therapy are negative.
- **close contacts of respiratory and cutaneous cases:**
  - cultures taken immediately
  - prophylactic antibiotic (Erythromycin 250 mg orally four times daily for 7-10 days **Or** benzathine benzylpenicillin 1.2 million units intramuscularly as a single dose.
  - diphtheria toxoid immunisation

Complications

- **The toxin affects the myocardium, nervous and adrenal tissues.**

Listeria

***Listeria* meningitis should always be considered in patients with meningitis associated with brain stem involvement, in elderly and in immunosuppressed patients. The treatment of choice is gentamicin and ampicillin.**

- *Listeria monocytogenes* is a Gram positive bacillus
- has the unusual ability to multiply at low temperatures.
- It is typically spread via contaminated food, typically unpasteurised dairy products.
- infection is particularly dangerous to the unborn child where it can lead to miscarriage.
- Listeriosis is associated with the consumption of soft cheese.

Features - can present in a variety of ways

- diarrhoea,
- flu-like illness
- pneumonia ,
- meningoencephalitis
- ataxia and seizures

Investigations

- Suspected Listeria infection should be investigated by taking **blood cultures**.
- **CSF** may reveal a pleocytosis, with 'tumbling motility' on wet mounts

Management

- Listeria is sensitive to **amoxicillin/ampicillin** (cephalosporins usually inadequate)
- Listeria meningitis should be treated with IV amoxicillin/ampicillin and gentamicin

In pregnant women

- **pregnant women are almost 20 times more likely to develop listeriosis** compared with the rest of the population due to changes in the immune system
- fetal/neonatal infection can occur both transplacentally and vertically during child birth
- complications include miscarriage, premature labour, stillbirth and chorioamnionitis
- diagnosis can only be made from blood cultures
- treatment is with amoxicillin

Campylobacter

- Campylobacter is the commonest bacterial cause of infectious intestinal disease in the UK.
- The majority of cases are caused by the Gram-negative bacillus *Campylobacter jejuni*.
- It is spread by the faecal-oral route

- has an incubation period of 1-6 days.

Features
- prodrome: headache malaise
- diarrhoea: often bloody
- abdominal pain

Management
- usually self-limiting
- **the most appropriate therapy is IV fluids.** appropriate fluid replacement and anti-emetics are initially indicated - most units advocate no antibiotic treatment.
- the BNF advises treatment if **severe** or the patient is **immunocompromised**. Clinical Knowledge summaries also recommend antibiotics if severe symptoms (high fever, bloody diarrhoea, or more than eight stools per day) or symptoms have last more than one week
- the first-line antibiotic is **clarithromycin**

Complications
- Guillain-Barre syndrome may follow *Campylobacter jejuni* infections
- Reiter's syndrome
- septicaemia,
- endocarditis,
- arthritis

Escherichia coli

- *Escherichia coli* is a facultative anaerobic, lactose-fermenting, **Gram negative rod** which is a normal gut commensal.
- *E. coli* infections lead to a variety of diseases in humans including:
  - diarrhoeal illnesses
  - UTIs
  - neonatal meningitis

Serotypes

E. coli may be classified according to the antigens which may trigger an immune response:

Antigen	Origin	Notes
O	Lipopolysaccharide layer	
K	Capsule	Neonatal meningitis secondary to *E. coli* is usually caused by a serotype that contains the capsular antigen K-1
H	Flagellin	

***E. coli* O157:H7**
- is a particular strain associated with severe, haemorrhagic, watery diarrhoea.
- It has a high mortality rate and can be complicated by haemolytic uraemic syndrome.
- It is often spread by contaminated ground beef.

multiple drug resistant *Escherichia coli* :
- **mechanism of resistance → Extended spectrum beta-lactamase (ESBL) production**
  - Some *E. coli* isolates produce an Extended spectrum beta-lactamase (ESBL) that inactivates second and third generation cephalosporins.
- The class of drugs that will most reliably treat these infections are the carbapenems.
- Extended spectrum B-lactamase (ESBL) producing organisms are typically resistant to penicillins and cephalosporins and as such the **carbapenem class of antibiotics are typically first line** although nitrofurantoin or fosfomycin are also frequently effective.
- ESBL producers are most commonly *Escherichia coli* (E. coli) and *Klebsiella* species.

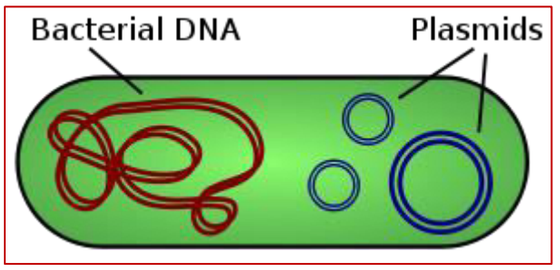
Incubation periods

Questions may either ask directly about incubation periods or they may be used to provide a clue in a differential diagnosis.

Less than 1 week	1 - 2 weeks	2 - 3 weeks	Longer than 3 weeks
• meningococcus • diphtheria • influenza • scarlet fever	• malaria • dengue fever • typhoid • measles	• mumps • rubella • chickenpox	• infectious mononucleosis • cytomegalovirus • viral hepatitis • HIV

Bacterial resistance

Plasmids



- **plasmid** is a small DNA molecule within a cell , separated from a chromosomal DNA and can replicate independently.
- plasmids carry genes that may benefit the survival of the organism, for example antibiotic resistance.
- Bacteria develop resistance to antibiotics by gaining genes that encode for particular proteins that offer protection to the organism.
- Sometimes this is by mutation and at other times the gene may be acquired from another bacterial species.
- The genes are usually found in **plasmids - circular segments of DNA separate from the bacterial chromosome.**
- They usually are
  - small
  - consist of a few thousand base pairs
  - carry one or a few genes, and
  - have a single origin of replication.
- Plasmids can be used to clone genes by splicing a particular gene into a plasmid and then allowing the bacteria to multiply - this is then called recombinant plasmid DNA.
- Plasmids can easily spread from one bacteria to another - a sort of resistance package that bacteria can share.
- **Which best explains the loss of antibiotic resistance in bacterial strain?**
  ➔ Loss of a plasmid containing the resistance gene

Antibiotic resistance mechanism

Antibiotic	Resistance mechanism
fluoroquinolones (eg: ciprofloxacin)	Change in the bacterial **DNA gyrase** due to genetic mutation
Macrolides (eg: Erythromycin)	Bacterial **ribosomal methylation**
Tetracycline	Bacterial **efflux of antibiotic**
chloramphenicol	**Antibiotic inactivation by acetyltransferase**
Penicillin	**Production of penicillinase** by the bacteria is the **most common** mechanism of bacterial resistance to penicillin.
	However, penicillin **resistance in streptococcus pneumonia** is due to **alteration in the penicillin-binding protein**, not production of penicillinase.
Vancomycin	**D-ala-D-ala mutates to D-ala-D-lac**

Vaginal discharge

Vaginal discharge is a common presenting symptom and is not always pathological

Common causes	Less common causes
• physiological • *Candida* • *Trichomonas vaginalis* • bacterial vaginosis	• *Gonorrhoea* • *Chlamydia* can cause a vaginal discharge although this is rarely the presenting symptoms • ectropion • foreign body • cervical cancer

- Black women report higher incidence of candidiasis infections compared with white women.

Key features of the common causes are listed below

Condition	Key features
Candida	• **'Cottage cheese'** discharge • Vulvitis • Itch
Trichomonas vaginalis	• Offensive, **yellow**/**green**, frothy discharge • Vulvovaginitis • Strawberry cervix
Bacterial vaginosis	• Offensive, thin, **white**/grey, 'fishy' discharge

Bacterial vaginosis (BV)

Bacterial vaginosis - overgrowth of predominately Gardnerella vaginalis

- Bacterial vaginosis (BV) describes an overgrowth of predominately anaerobic organisms such as *Gardnerella vaginalis*.
- This leads to a consequent fall in lactic acid **producing aerobic lactobacilli** resulting in a **raised vaginal pH**.
- **BV is the commonest cause of abnormal vaginal discharge** in women of childbearing age. It is twice as common as vaginal candidiasis.
- Whilst BV is not a sexually transmitted infection it is seen almost exclusively in sexually active women.

Features

- vaginal discharge: 'fishy', offensive , Gray, thin, and homogeneous
- asymptomatic in 50%

Diagnosis

Epithelial cells with a stippled border (Clue cells) are the hallmark microscopic findings of bacterial vaginosis

Amsel's criteria for diagnosis of BV - 3 of the following 4 points should be present

1. thin, white homogenous discharge
2. **clue cells** on microscopy: **stippled vaginal epithelial cells**
3. **vaginal pH > 4.5**
4. positive whiff test (addition of potassium hydroxide results in fishy odour)

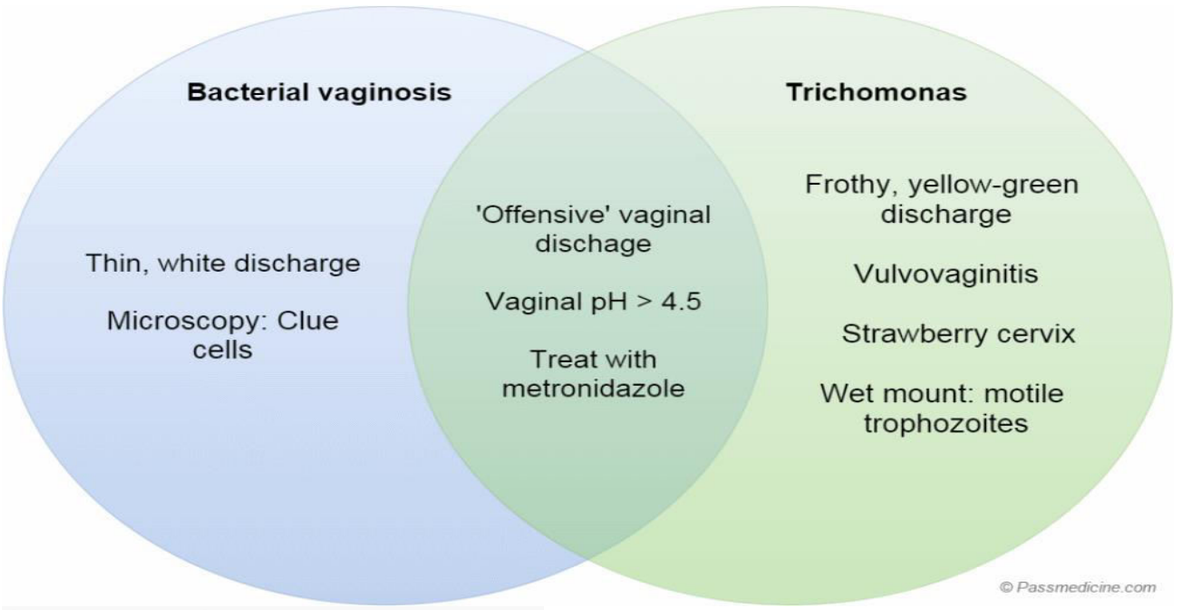
Management

Bacterial vaginosis treatment → oral metronidazole

- oral metronidazole for 5-7 days
  - initial cure rate → 70-80%
  - relapse rate > 50% within 3 months
- the BNF suggests topical metronidazole or topical clindamycin as alternatives

Bacterial vaginosis in pregnancy

- results in an increased risk of preterm labour, low birth weight and chorioamnionitis, late miscarriage
- it was previously taught that oral metronidazole should be avoided in the first trimester and **topical clindamycin** used instead. **Recent guidelines however recommend that oral metronidazole is used throughout pregnancy.** The BNF still advises against the use of high dose metronidazole regimes



Comparison of bacterial vaginosis and *Trichomonas vaginalis*

January 2015 exam: H/O offensive vaginal discharge. Diagnosed as bacterial vaginosis. What is the most appropriate initial management? Oral metronidazole

Trichomonas vaginalis

- anaerobic flagellated protozoan, which thrive in more **alkaline** conditions.
- incubation period is 5 to 28 days.
- transmitted directly, for example, through sexual transmission.

Feature:

- asymptomatic (in most men and 50% of women)
- yellow-green, frothy vaginal discharge
- vulvar pruritus
- dysuria, dyspareunia, and lower abdominal pain.
- Punctuate hemorrhages on the cervix, i.e. "**strawberry cervix**", or along the vaginal wall are less common signs, but are highly suggestive of infection with *Trichomonas vaginalis*.
- The **PH** of the discharge is **greater than 4.5**

Diagnosis

- The most rapid and practical method for detection is the use of a **wet mount** in clinic, which demonstrates **motile flagellated protozoans**.

Differential diagnosis:

- **Whilst bacterial vaginosis is also associated with a discharge with a fishy odour, classically there is no soreness or irritation associated with it.**

Treatment:

- A large dose of **metronidazole** (2 g as a single course), or a seven day course at lower dose is the treatment of choice.
  - Single-dose therapy increases drug adherence.
  - If standard treatment with either single-dose or multidose therapy fails, a regimen of 2 g of oral metronidazole or tinidazole for 5 days may be considered
  - Patients should not consume alcohol during the course of treatment or during the 24 hours after the completion of the medication.
  - Patients on tinidazole therapy should not consume alcohol during therapy or for 72 hours after completion of the medication.

- ❖ Drinking alcohol while taking tinidazole causes **disulfiram-like reaction**, which includes (nausea, vomiting, headache, ↑BP, flushing, and shortness of breath).
- ➢ Tinidazole has a longer half-life (12-14 h) than metronidazole (6-7 h).
- ➢ metronidazole and tinidazole are equally effective

- **Partner**
  - ➢ **Partners** should be identified and also screened for infection as men rarely exhibit symptoms of a *T. vaginalis* infection.
    - ❖ The epithelial damage caused by *T. vaginalis* increases susceptibility to HIV virus infection and transmission.
  - ➢ Both patient and partner should abstain from sex until pharmacological treatment has been completed and they have no symptoms.
- **HIV-positive women with Trichomoniasis.**
  - ➢ the CDC recommends considering the **multidose treatment in HIV-positive women with Trichomoniasis.**
    - ▪ (metronidazole 500 mg twice daily for 7 days) are more effective in treating *T vaginalis* in HIV-positive women than a single-dose treatment (metronidazole 2 g single dose).
- **In pregnant women**
  - ➢ The CDC recommends that infected **symptomatic** pregnant women be considered for treatment, as metronidazole has not been definitively shown to be harmful during pregnancy and may prevent transmission to the newborn.
  - ➢ Infected **asymptomatic** pregnant women may wish to defer treatment to after 37 weeks' gestation.
  - ➢ Pregnant women should be treated with 2 g metronidazole in a single dose, according to the CDC.
  - ➢ The safety of tinidazole in pregnancy is not known.
  - ➢ Tinidazole is a pregnancy class C agent; animal studies have demonstrated adverse effects on fetal development. Its use is not recommended in pregnant women.
- **In breastfeeding women**
  - ➢ In breastfeeding women, the CDC recommends stopping breastfeeding during the course of metronidazole treatment and for 12-24 hours after the last day. For treatment with tinidazole, the CDC recommends stopping breastfeeding for the course of treatment and for 3 days after the last dose.
- **Screening and Rescreening**
  - ➢ Patients should be **screened for other sexually transmitted infections**.
  - ➢ the CDC recommends **rescreening at 3 months post therapy** for sexually active women, as they have a high rate of reinfection.

Brucellosis

- Brucellosis is a zoonosis more common in the Middle East and in farmers.
- Gram negative bacilli
- It is considered a class B bioterrorist agent, is easily spread by aerosol, and is a significant hazard in microbiology laboratories.
- Four major species cause infection in humans: B melitensis (sheep), B abortus (cattle), B canis and B suis (pigs).
- incubation period 2 - 6 weeks
- Most cases of brucellosis in Northern Europe and North America are acquired overseas and/or from consuming unpasteurised milk products, including cheese.

Features

- non-specific:
  - ➢ fever, (prolonged fever of unknown origin)
  - ➢ malaise

- hepatosplenomegaly
- sacroilitis: spinal tenderness may be seen. **Brucellosis is a recognised cause of spondylitis**
  - associated rheumatic features in about 50% of cases.
- complications: osteomyelitis, infective endocarditis, meningoencephalitis, orchitis
- leukopenia is common

Diagnosis

- the Rose Bengal plate test can be used for screening but other tests are required to confirm the diagnosis
- **Brucella serology is the best test for diagnosis**
- blood and bone marrow cultures may be suitable in certain patients, but these tests are often negative
  - 75% have a positive blood culture (90% of bone marrow cultures will be positive).

Management

- doxycycline and streptomycin

Cat scratch disease (CSD)

Cat scratch disease - caused by *Bartonella henselae*

Cat scratch disease is generally caused by the Gram negative rod *Bartonella henselae*

Features

- fever
- history of a cat scratch
- regional lymphadenopathy
- headache, malaise

Treatment:

- **immunocompromised patient:**
  - Self-limiting → only supportive therapy **(paracetamol and NSAID)**
  - Systemic features resolve over few days
  - Lymph nodes regress in size over 2 – 5 months
- Immunocompromised or patient with sever systemic symptoms
  - Severe disease was defined as persistent high fever (>39.5˚C) with severe systemic signs (eg, malaise, fatigue, blindness, headache) and lymphadenitis.
  - the following 4 antibiotics were the most effective for patients with severe CSD:
    - Rifampin - Efficacy of 87%
    - Ciprofloxacin - Efficacy of 84%
    - Gentamicin intramuscularly - Efficacy of 73%
    - Trimethoprim/sulfamethoxazole (TMP-SMZ) - Efficacy of 58%
  - azithromycin administered for 5 days decreased lymph node size within the first month of treatment. No other differences in clinical outcome were noted.

Cellulitis

- ***Staphylococcus aureus* and *Streptococci* are the commonest causative organisms.**
- **Group B *Streptococcus* has a predilection for diabetic patients**

Definition

- inflammation of the skin and subcutaneous tissues,

causes

- ***Staphylococcus aureus* and *Streptococci* are the commonest causative organisms.**
- **Group B *Streptococcus* has a predilection for diabetic patients and is the likeliest causative organism in diabetics**

Features

- commonly occurs on the shins
- erythema, pain, swelling
- systemic upset such as fever
- Cellulitis **does not** have sharp, well-defined borders, unlike an erysipelas infection.

Eron classification
NICE Clinical Knowledge Summaries recommend we use the Eron classification to guide how we manage patients with cellulitis:

Class	Features
I	There are no signs of systemic toxicity and the person has no uncontrolled co-morbidities
II	The person is either systemically unwell or systemically well but with a co-morbidity (for example peripheral arterial disease, chronic venous insufficiency, or morbid obesity) which may complicate or delay resolution of infection
III	The person has significant systemic upset such as acute confusion, tachycardia, tachypnoea, hypotension, or unstable co-morbidities that may interfere with a response to treatment, or a limb-threatening infection due to vascular compromise
IV	The person has sepsis syndrome or a severe life-threatening infection such as necrotizing fasciitis

Management

- **Criteria for admission** for intravenous antibiotics
  - **Eron Class III or Class IV cellulitis**.
  - severe or rapidly deteriorating cellulitis (for example extensive areas of skin).
  - very young (under 1 year of age) or frail.
  - immunocompromised.
  - significant lymphoedema.
  - facial cellulitis (unless very mild) or periorbital cellulitis.
- Management **Eron Class II cellulitis**:
  - *Admission may not be necessary if the facilities and expertise are available in the community to give intravenous antibiotics and monitor the person.*
- Other patients can be treated with oral antibiotics.
- **Antibiotics**
  - **mild/moderate cellulitis**
    - **First line → flucloxacillin** (BNF recommendation)
      - first choice to treat sensitive staphylococcal infections
      - MRSA is resistant to flucloxacillin
    - **in patients allergic to penicillin → Clarithromycin or clindamycin.**
    - in patients who have **failed to respond to flucloxacillin → oral clindamycin**
      - **The most appropriate treatment is clindamycin and flucloxacillin**, which covers the majority of organisms responsible for cellulitis.
        - **Flucloxacillin** is bactericidal for both Staphylococcus and Streptococcus, whereas clindamycin has an anti-toxin effect for both these groups of organisms (in addition to Clostridium perfringen). Their effect is therefore synergistic, and they should be used together where rapid control is required (e.g. in finger cellulitis) or in severe cases
        - Although **clindamycin** is a bacteriostatic antibiotic, it acts by switching off protein synthesis within bacteria; this in turn will lead to decreased exotoxin expression, thereby removing the mediators of toxic shock syndrome (TSS).
    - If **no significant improvement within 48 hours**, the patient should be **readmitted for intravenous antibiotics**.
  - **Severe cellulitis**

- should be treated with **intravenous benzylpenicillin + flucloxacillin**.
- If there is any suspicion of tendon involvement (Intact joint movements make this less likely) → the plastics or orthopaedics team should be asked to review and **intravenous antibiotics** initiated.

Methicillin-resistant *Staphylococcus aureus* (MRSA)

Mechanism of resistance

- **Penicillin binding proteins are the characteristic mutated proteins in methicillin-resistant *Staphylococcus aureus*.**

Who should be screened for MRSA?

- all patients awaiting elective admissions
  - exceptions include:
    - terminations of pregnancy
    - ophthalmic surgery
    - Patients admitted to mental health trusts.
- all emergency admissions.

Where is the site of most concern for staff carriage of MRSA?

- **The nose** is the area of carriage for MRSA which gives most area for concern with respect to carriage by staff.

How should a patient be screened for MRSA?

- nasal swab and skin lesions or wounds
  - the swab should be wiped around the inside rim of a patient's nose for 5 seconds
  - the microbiology form must be labelled 'MRSA screen'

Suppression of MRSA from a carrier once identified

- nose:
  - mupirocin 2% in white soft paraffin, TDS for 5 days
- skin:
  - chlorhexidine gluconate, OD for 5 days.
    - Apply all over but particularly to the axilla, groin and perineum

The following antibiotics are commonly used in the treatment of MRSA infections:

- **Vancomycin**
  - **the first line**
- **teicoplanin**
- linezolid
  - Linezolid is the only oral medication available against MRSA.
- Ceftaroline
  - fifth generation cephalosporin
  - Ceftaroline is the only cephalosporin to cover MRSA.
- Some strains may be sensitive to the antibiotics listed below but they **should not generally be used alone** because resistance may develop:
  - rifampicin
  - macrolides
  - tetracyclines
  - aminoglycosides
  - clindamycin
- Relatively new antibiotics such as **linezolid**, **quinupristin /dalfopristin combinations** and **tigecycline** have activity against MRSA but should be reserved for resistant cases

January 2009 exam: **What is the most effective single step to reduce the incidence of MRSA ? Hand hygiene**

What is the most appropriate antibiotic regimen for possible line sepsis from an indwelling permacath?

➔ **Vancomycin + Gentamicin**

- The antibiotic chosen should have both gram-positive and gram-negative cover, including MRSA.
- vancomycin and doxycycline are able to treat MRSA, but doxycycline has limited gram-negative cover, unlike gentamicin.

Necrotising fasciitis

Overview

- Necrotising fasciitis is a medical emergency that is difficult to recognise in the early stages.

Classification (according to the causative organism):

- **Type 1** is caused by mixed anaerobes and aerobes (often occurs post-surgery in diabetics)
- **Type 2** is caused by *Streptococcus pyogenes*
  - commonly caused by group A *Streptococci*

Features

- acute onset
- painful, erythematous lesions
- extremely tender over infected tissue

Management

- **urgent surgical referral debridement**
- intravenous antibiotics
  - **Clindamycin and Tazocin**
    - Clindamycin
      - bacteriostatic
      - **inhibits** formation of peptides bonds at **50S ribosomal subunit**
      - It is also a potent suppressor of bacterial toxin synthesis.
    - Group A *Streptocooci* are usually very sensitive to benzylpenicillin so this is frequently added though this does not neutralises the toxin.

Toxic shock syndrome (TSS)

Causes

- exotoxin-mediated illness caused by bacterial infection, most commonly group A streptococcus or *Staphylococcus aureus*.

Risk factors include:

- Recent menstruation
  - Although the earliest described cases involved mostly menstruating women using highly absorbent tampons, only 55% of current cases are associated with menstruation.
- Recent use of barrier contraceptives such as diaphragms and vaginal sponges
- Vaginal tampon use (especially prolonged)
- Recent childbirth
- Recent surgery, and
- Current S. aureus infection.

Features

- can be non-specific
- toxicity occurs early, resulting in serious life-threatening disease
- multi-organ system failure.

Types

- **Streptococcal toxic shock syndrome (TSS)** can occur with infection at any site but is more **commonly associated with an infected cutaneous site**.
- **Staphylococcal TSS** (menstrual or non-menstrual)

- severe systemic reaction to staphylococcal exotoxins.
- associated with extended tampon use, postpartum infections, and other sites of infection with the organism.

Diagnosis:

Centers for Disease Control and Prevention diagnostic criteria

- fever: temperature > 38.9 C
- hypotension: systolic blood pressure < 90 mmHg
- diffuse erythematous rash
- desquamation of rash, especially of the palms and soles
- involvement of three or more organ systems: e.g. gastrointestinal (diarrhoea and vomiting), mucous membrane erythema, renal failure, hepatitis, thrombocytopenia, CNS involvement (e.g. confusion)

Treatment

- supportive care in an ICU,
- early empirical antibiotic treatment, and further culture-sensitive antibiotic treatment.
  - Although clindamycin is a bacteriostatic antibiotic, it acts by switching off protein synthesis within bacteria; this in turn will lead to decreased exotoxin expression, thereby removing the mediators of TSS.
- Surgical debridement may be needed for deep-seated streptococcal infections.

Ludwig's angina

Definition

- Ludwig's angina is a form of severe diffuse **cellulitis** that presents an acute onset and spreads rapidly, bilaterally affecting the submandibular, sublingual and submental spaces resulting in a state of emergency.

Overview

- The majority of cases of Ludwig's angina are odontogenic in etiology, primarily resulting from infections of the second and third molars teeth.
- the submandibular space is the primary site of infection
- the most life-threatening complication of Ludwig's angina is airway obstruction.

Treatment

- IV antibiotic against streptococci and oral anaerobes and take care of airway (call anaesthesiologist).
- Combinations of penicillin, clindamycin, and metronidazole are typically used.
- Up to 65% require surgical drainage
  - Physical examination alone is insufficient in determining which patients require a surgical procedure.
  - As a result, a **CT scan with intravenous contrast** is recommended to detect patients who have developed suppurative complications

Prognosis

- Without a treatment, it is frequently fatal from the risk of asphyxia with a mortality rate of 50%.
- The aggressive surgical intervention, the antibiotic introduction, and the improvement of dental care have determined a significant reduction of the mortality rate to less than 10%

Chickenpox (Varicella-zoster virus)

- Chickenpox is caused by primary infection with varicella zoster virus.
- Shingles is reactivation of dormant virus in dorsal root ganglion
- Chickenpox is highly infectious (infection rate in household contacts of 90%).
- spread via the respiratory route
- can be caught from someone with shingles
- infectivity = 4 days before rash, until 5 days after the rash first appeared*
- incubation period = 10-21 days

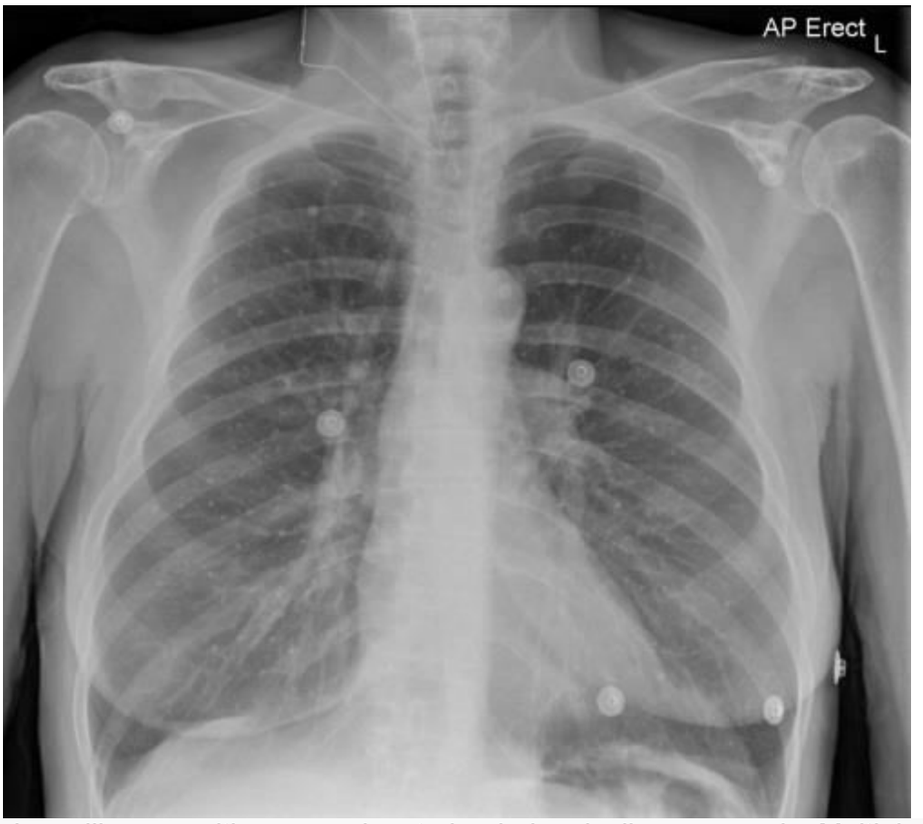
- It is commonest in spring time
- **Causes congenital limb deformity**
- **HIV**
  - **HIV-positive patients are more prone to herpes zoster regardless of their CD4 count.**
  - In addition to the typical dermatomal distribution of the vesicular rash, HIV patients occasionally have vesicles scattered in adjacent dermatomes.
  - In advanced HIV disease VZV can manifest as severe disseminated disease.

Clinical features (tend to be more severe in older children/adults)
- fever initially
- itchy, rash starting on head/trunk before spreading. Initially macular then papular then vesicular
- systemic upset is usually mild

Management is supportive
- keep cool, trim nails
- calamine lotion
- school exclusion: current HPA advice is 5 days from start of skin eruption. They also state 'Traditionally children have been excluded until all lesions are crusted. However, **transmission has never been reported beyond the fifth day of the rash.'**
- immunocompromised patients and newborns with peripartum exposure should receive varicella zoster immunoglobulin (VZIG). If chickenpox develops then IV aciclovir should be considered
  - **Aciclovir** (also famciclovir, and ganciclovir) acts through **inhibition of viral (DNA) polymerase** but it is a **pro-drug** and first **requires phosphorylation by thymidine kinase**.
    - Resistance arises when the virus lacks thymidine kinase
  - **For thymidine kinase-deficient varicella-zoster virus strain:**
    - **Cidofovir does not require activation by viral thymidine kinase; therefore, it would be best suited to treat the thymidine kinase-deficient varicella-zoster virus.**
- adults chicken pox should be treated with acyclovir within 24 hours of the appearance of rash because it can lessen the occurrence of post herpetic neuralgia.

Complications
- Common complication is secondary bacterial infection of the lesions.
- Chicken pox in the first and second trimester can produce a syndrome of skin scarring, hypoplastic limbs, eye and central nervous system impairments.
- Rare complications include
  - Pneumonia
    - Varicella pneumonia occurs in up to 20% of adults with chickenpox,
    - appearing three to five days into the course of the illness.
    - Pneumonitis is uncommon in children
    - incidence 0.3% in immunocompetent adults.
    - The risk is higher in smokers and pregnancy.
    - **Symptoms include tachypnoea, cough, dyspnoea, and fever.**
    - Cyanosis, pleuritic chest pain and haemoptysis are common.
    - In adults with pneumonitis, treatment with aciclovir is warranted.
  - encephalitis (cerebellar involvement may be seen)
  - disseminated haemorrhagic chickenpox
  - arthritis, nephritis and pancreatitis may very rarely be seen

mechanism of acyclovir resistance → reduced production of viral thymidine kinase



Chest x-ray showing miliary opacities secondary to healed varicella pneumonia. Multiple tiny calcific miliary opacities noted throughout both lungs. These are of uniform size and dense suggesting calcification. There is no focal lung parenchymal mass or cavitating lesion seen.The appearances are characteristic for healed varicella pneumonia.

*it was traditionally taught that patients were infective until all lesions had scabbed over

Chickenpox exposure in pregnancy

Chickenpox exposure in pregnancy - first step is to check antibodies

- In pregnancy there is a risk to both the mother and also the fetus, a syndrome now termed fetal varicella syndrome

Risks to the fetus and neonate relate to the time of infection:

- **Less than 20 weeks pregnancy:**
  - congenital varicella (limb hypoplasia, microcephaly, cataracts, growth retardation, skin scarring). High mortality.
  - The incidence of congenital varicella syndrome is about 2% in mothers who develop primary chickenpox in the first half of the pregnancy.
- **Second to third trimester:**
  - herpes zoster in an otherwise healthy infant.
- **Minus seven days to plus seven days after delivery:**
  - severe and even fatal disease (30% mortality).

Risks to the mother

- 5 times greater risk of pneumonitis

Fetal varicella syndrome (FVS)

- risk of FVS following maternal varicella exposure is around 1% if occurs before 20 weeks gestation
- studies have shown a very small number of cases occurring between 20-28 weeks gestation and none following 28 weeks
- features of FVS include skin scarring, eye defects (microphthalmia), limb hypoplasia, microcephaly and learning disabilities

Other risks to the fetus

- shingles in infancy: 1-2% risk if maternal exposure in the second or third trimester

- severe neonatal varicella: if mother develops rash between 5 days before and 2 days after birth there is a risk of neonatal varicella, which may be fatal to the newborn child in around 20% of cases

Management of chickenpox exposure

- if there is any doubt about the mother previously having chickenpox maternal blood should be urgently **checked for varicella antibodies**
- if the pregnant women is not immune to varicella she should be given varicella zoster immunoglobulin (VZIG) as soon as possible. RCOG and Greenbook guidelines suggest **VZIG is effective up to 10 days post exposure**
- consensus guidelines suggest oral aciclovir should be given if pregnant women with chickenpox present within 24 hours of onset of the rash

Varicella zoster immunoglobulin (VZIG)

- prepared from pooled plasma of UK blood donors with a history of recent chickenpox or herpes zoster.
- Donors are screened for HIV, hepatitis B and hepatitis C.
- VZIG prophylaxis is recommended for patients who fulfil all the following criteria:
  1. A clinical condition that increases the risk of severe varicella, (for example, immunosuppression, neonates, **pregnant women**)
  2. No antibodies to varicella zoster
  3. Significant exposure to chickenpox or herpes.
- VZIG prophylaxis is of no benefit if chickenpox has already developed.
- Severe or fatal varicella can occur despite VZIG prophylaxis. Active immunisation should therefore be used for susceptible immunosuppressed patients at long term risk.

Chlamydia

***Chlamydia* - treat with azithromycin or doxycycline**

- *Chlamydia* is the most prevalent sexually transmitted infection in the UK
- Approximately 1 in 10 young women in the UK have *Chlamydia*.
- Caused by *Chlamydia trachomatis*, an obligate intracellular pathogen.
- The incubation period is around 7-21 days, although it should be remembered a large percentage of cases are asymptomatic
- **persistent discharge in spite of adequately treated gonorrhoea → there is a co-infection with *Chlamydia*.**

Features

- asymptomatic in around 70% of women and 50% of men
- women: cervicitis (discharge, bleeding), dysuria
- men: urethral discharge, dysuria

Potential complications

- epididymitis
- pelvic inflammatory disease
- endometritis
- increased incidence of ectopic pregnancies
- infertility
- reactive arthritis
- perihepatitis (Fitz-Hugh-Curtis syndrome)

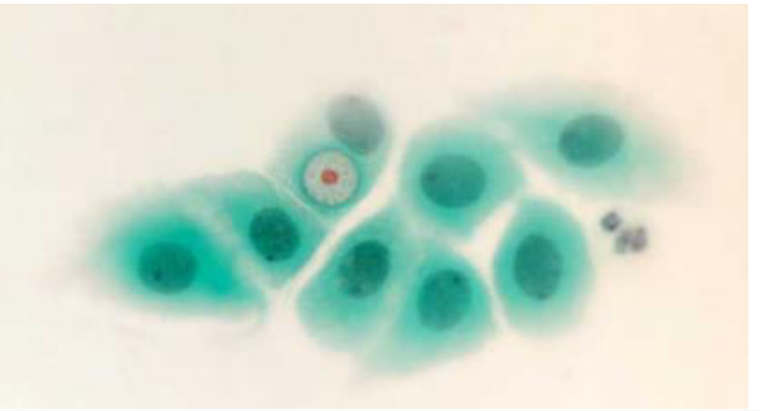
Investigation

- traditional cell culture is no longer widely used
- nuclear acid amplification tests (NAATs) are now rapidly emerging as the investigation of choice
- urine (first void urine sample), vulvovaginal swab or cervical swab may be tested using the NAAT technique

Screening

- in England the National *Chlamydia* Screening Programme is open to all men and women aged 15-24 years
- the 2009 SIGN guidelines support this approach, suggesting screening all sexually active patients aged 15-24 years

- relies heavily on opportunistic testing



Pap smear demonstrating infected endocervical cells. Red inclusion bodies are typical

Management

- doxycycline (7 day course) or azithromycin (single dose). The 2009 SIGN guidelines suggest **azithromycin should be used first-line** due to potentially poor compliance with a 7 day course of doxycycline
- if pregnant then erythromycin or amoxicillin may be used. The SIGN guidelines suggest considering azithromycin 'following discussion of the balance of benefits and risks with the patient'
- patients diagnosed with *Chlamydia* should be offered a choice of provider for initial partner notification - either trained practice nurses with support from GUM, or referral to GUM
- for men with symptomatic infection all partners from the four weeks prior to the onset of symptoms should be contacted
- for women and asymptomatic men all partners from the last six months or the most recent sexual partner should be contacted
- **contacts of confirmed *Chlamydia* cases should be offered treatment prior to the results of their investigations being known (treat then test)**

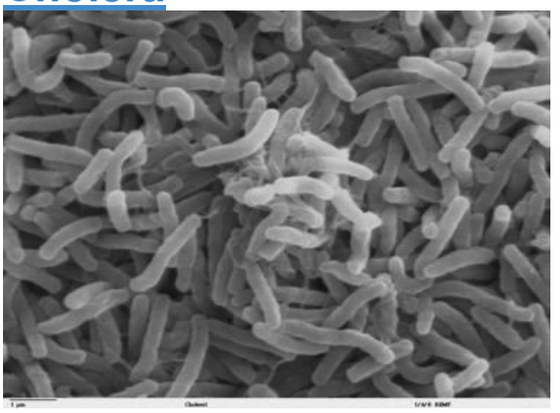
September 2008 exam: A swab taken in the clinic showed a Gram-negative diplococcus and treatment with IM ceftriaxone was given. his symptoms have not resolved. What is the most likely explanation? Co-existent *Chlamydia* infection (Co-existent infection with *Chlamydia* is extremely common in patients with gonorrhoea).

September 2012 exam: A 27-year-old pregnant woman is found to have *Chlamydia*. She has had a previous adverse reaction to azithromycin. What is the most appropriate treatment? Erythromycin

Trachoma

- **caused by Chlamydia** trachomatis,
- the leading infectious cause of blindness worldwide.
- Transmission is commonly through five routes (five Fs): Flies; Fomites; Fingers; within the Family; or among close Friends.
- Cases are rare in high-income countries, but the condition is endemic in many low- and middle-income countries; risks are increased in rural areas without good water supplies and sanitation.
- Features
  - May be asymptomatic,
  - inflammatory conjunctivitis
  - punctate keratitis.
  - Repeated infection → immune response → gradual scarring of the eyelid → blindness.
- Treatment
  - single dose of azithromycin
- WHO aims to eliminate trachoma by 2020, using the SAFE strategy (Surgery, Antibiotics, Facial cleanliness, and Environmental improvement).

Cholera



electron microscope image of Vibrio cholerae bacteria

Overview

- caused by Vibro cholerae - Gram negative bacteria
- Because the organism is not acid-resistant, it **depends on its large inoculum size** (infectious dose) to **withstand gastric acidity.**
  - If ingested with water, a higher infectious dose is needed. When ingested with food, fewer organisms are required to produce disease.
  - ↓ gastric acidity (anti-acid drugs, gastrectomy) → ↑risk of cholera infection and severity

Mechanism by which cholera leads to fluid loss:

- Cholera toxin has two parts, A and B.
  - B subunits are responsible for binding to a ganglioside (monosialosyl ganglioside, **GM1 receptor**) located on the surface of the cells that line the intestinal mucosa.
  - B binds while A activates **G protein** → **activates adenylate cyclase** → **↑(cAMP)** → unrestricted chloride secretion from villous **crypts**.

cholera toxin stimulates the generation of cyclic AMP as the second messenger

Features

- profuse 'rice water' diarrhoea
- dehydration

- hypoglycaemia
  - After dehydration, hypoglycemia is the most common lethal complication of cholera in children.

Management

- oral rehydration therapy
- antibiotics: doxycycline, ciprofloxacin

Congenital infections

Congenital rubella
- sensorineural deafness
- congenital cataracts

The major congenital infections encountered in examinations are rubella, toxoplasmosis and cytomegalovirus

Cytomegalovirus is the most common congenital infection in the UK. Maternal infection is usually asymptomatic

	Rubella	Toxoplasmosis	Cytomegalovirus
Characteristic features	Sensorineural deafness Congenital cataracts Congenital heart disease (e.g. patent ductus arteriosus) Glaucoma	Cerebral calcification Chorioretinitis Hydrocephalus	Growth retardation Purpuric skin lesions
Other features	Growth retardation Hepatosplenomegaly Purpuric skin lesions 'Salt and pepper' chorioretinitis Microphthalmia Cerebral palsy	Anaemia Hepatosplenomegaly Cerebral palsy	Sensorineural deafness Encephalitis/seizures Pneumonitis Hepatosplenomegaly Anaemia Jaundice Cerebral palsy

Cytomegalovirus

- Cytomegalovirus (**CMV, HHV-5)**, is one of the herpes viruses.
- **Herpes viridae** is the family of viruses to which cytomegalovirus belongs.
- Double stranded **DNA** virus.
- **Mononuclear cells** are the class of leukocytes in which cytomegalovirus **lies dormant.**
- It is thought that around 50% of people have been exposed to the CMV virus although it only usually causes disease in the immunocompromised, for example people with HIV or those on immunosuppressants following organ transplantation.

Diagnosis

- **infected cells have a 'Owl's eye' appearance due to intranuclear inclusion bodies**

Patterns of disease

Congenital CMV infection
- features include growth retardation, pinpoint petechial 'blueberry muffin' skin lesions, microcephaly, sensorineural deafness, encephalitis (seizures) and hepatosplenomegaly

CMV mononucleosis
- infectious mononucleosis-like illness
- may develop in immunocompetent individuals

CMV retinitis

- common in HIV patients with a low CD4 count (< 50)
- presents with visual impairment e.g. 'blurred vision'. Fundoscopy shows retinal haemorrhages and necrosis, often called 'pizza' retina
- **IV ganciclovir is the treatment of choice**
  - **Valganciclovir is an oral pro-drug for ganciclovir, with similar bioavailability but without the need to deliver it IV, making it the preferred option here.**
  - The efficacy of valganciclovir is similar to ganciclovir without the need for IV administration, and this drives ganciclovir as the option where oral therapy isn't tolerated.
  - The toxicity profile for valganciclovir is the same as that for ganciclovir, with bone marrow suppression the main concern.
- **Foscarnet** is the drug of choice for **ganciclovir-resistant cytomegalovirus retinitis**.

CMV encephalopathy

- seen in patients with HIV who have low CD4 counts

CMV pneumonitis

CMV colitis

- HIV+ bloody diarrhea+ no abdominal pain +normal stool examination → Do Colonoscopy to diagnose CMV colitis
- Patients with inflammatory bowel disease are at increased risk of CMV colitis particularly those on immunosuppression.
- COLONOSCOPY finding → multiple ulcer and mucosal erosion
- **The most appropriate investigation is → Flexible sigmoidoscopy and biopsy**
  - in severe colitis endoscopy should be limited to flexible sigmoidoscopy only due to an increased risk of perforation.
  - Biopsy shows: cytomegalic cell+ intranuclear **inclusion body**

Dengue fever

Dengue fever is a viral infection which can progress to viral haemorrhagic fever (also yellow fever, Lassa fever, Ebola)

Basics

- caused by an arthropod-borne *Flavivirus*.
- transmitted by the Aedes aegyti mosquito
- incubation period 4-10 days.
- a form of disseminated intravascular coagulation (DIC) known as dengue haemorrhagic fever (DHF) may develop. Around 20-30% of these patients go on to develop dengue shock syndrome (DSS)

Features

- causes headache (often retro-orbital)
- fever
- myalgia (severe musculoskeletal pain is a prominent feature)
- pleuritic pain
- facial flushing (dengue)
- maculopapular rash (confluent erythematous rash over the precordium)

Treatment is entirely symptomatic e.g. fluid resuscitation, blood transfusion etc

Epididymo-orchitis

- Epididymo-orchitis describes an infection of the epididymis +/- testes resulting in pain and swelling.
- It is most commonly caused by local spread of infections from the genital tract (such as *Chlamydia trachomatis* and *Neisseria gonorrhoeae*) or the bladder.
- **The most important differential diagnosis is testicular torsion. This needs to be excluded urgently to prevent ischaemia of the testicle.**

Features

- unilateral testicular pain and swelling
- urethral discharge may be present, but urethritis is often asymptomatic
- factors suggesting testicular torsion include patients < 20 years, severe pain and an acute onset

Management

- the British Association for Sexual Health and HIV (BASHH) produced guidelines in 2010
- if the organism is unknown BASHH recommend: **ceftriaxone 500mg intramuscularly single dose, plus doxycycline 100mg by mouth twice daily for 10-14 days**
- further investigations following treatment are recommended to exclude any underlying structural abnormalities

Genital warts

Genital warts - 90% are caused by HPV 6 & 11

Genital wart treatment

- multiple, non-keratinised warts: topical podophyllum
- solitary, keratinised warts: cryotherapy

- Genital warts (also known as condylomata accuminata) are a common cause of attendance at genitourinary clinics.
- They are caused by the many varieties of the human papilloma virus HPV, especially types 6 & 11.
- It is now well established that HPV (primarily types 16,18 & 33) predisposes to cervical cancer.
- **HPV 16 is an oncogenic virus** and causes squamous cell carcinomas in the oral cavity, cervix, anus and penis.

Features

- small (2 - 5 mm) fleshy protuberances which are slightly pigmented
- may bleed or itch

Management

- **first-line** → topical podophyllum or cryotherapy, depending on the location and type of lesion.
  - Multiple, non-keratinised warts → best treated with topical agents
  - solitary, keratinised warts → respond better to cryotherapy
- **second line** → **topical imiquimod**
- genital warts are often resistant to treatment and recurrence is common although the majority of anogenital infections with HPV clear without intervention within 1-2 years

Gonorrhoea

Cephalosporins are now the treatment of choice for Gonorrhoea

- Gonorrhoea is the second most common bacterial STI in the UK after chlamydia.
- caused by the **Gram negative diplococcus** *Neisseria* gonorrhoea.
- Acute infection can occur on any mucous membrane surface, typically genitourinary but also rectum and pharynx.
- The incubation period of gonorrhoea is 2-5 days
- immunisation is not possible
- reinfection is common due to antigen variation of type IV **pili** (proteins which adhere to surfaces) and **Opa** proteins (surface proteins which bind to receptors on immune cells)
- There is an increased risk of acquiring HIV infection if patient is infected with gonococcus.

Features

More commonly patients present with co-infection with *Chlamydia trachomatis*.

- Primary infection is symptomatic in 90-95% of men, but only 50% of women.
- males: urethral discharge, dysuria
- females: cervicitis e.g. leading to vaginal discharge
- rectal and pharyngeal infection is usually asymptomatic
- Spread can occur to involve the epididymis, prostate, endometrium and pelvic organs although this is rare (<10%).
- **haematological dissemination is less common, which results in skin lesions, arthralgia, arthritis and meningitis.**
- ***Neisseria gonorrhoeae* may cause either a purulent arthritis without skin lesions *or* a triad of polyarthritis (migratory), tenosynovitis, and dermatitis.**

Microbiology

- Standard aerobic and anaerobic cultures often fail to grow the organism; selective media are often required and the organism grows best in an atmosphere containing 3-10% CO_2.
- Investigations
  - Culture is the traditional first line diagnosis test, but rapid diagnosis can be undertaken using light microscopy of genital specimens to detect the bacteria.
  - **The negative culture of urethral discharge on Thayer-Martin medium, excluding gonococcal infection.**
  - Increasingly, nucleic acid amplification tests are used but if positive it should be followed by culture to confirm diagnosis and check antibiotic sensitivities.

Complications:

Acute monoarthritis, a pustular rash and synovial fluid analysis suggestive of joint sepsis in a young woman make gonococcal arthritis the most likely diagnosis.

- **local complications** may develop include
  - urethral strictures,
  - epididymitis
  - and salpingitis (hence may lead to infertility).
- **Disseminated gonococcal infection (DGI)** and **gonococcal arthritis**,
  - gonococcal infection being the **most common cause of septic arthritis in young adults.**
    - Fever, rashes, and migratory arthritis is the main presenting feature.
    - Diagnosis is made by **culture** of synovial fluid, skin lesions, and specimen from urethral swab.
  - The **pathophysiology** of DGI thought to be due to haematogenous spread from mucosal infection (e.g. Asymptomatic genital infection).
  - **Key features of disseminated gonococcal infection:**
    1. tenosynovitis
    2. migratory polyarthritis

3. dermatitis (lesions can be maculopapular or vesicular)

- Later **complications** include septic arthritis, endocarditis and perihepatitis (Fitz-Hugh-Curtis syndrome)
- **management** of DGI is **IV ceftriaxone 1 g od**. This should continue **for seven days**.

Management

- the 2011 British Society for Sexual Health and HIV (BASHH) guidelines recommend **ceftriaxone 500 mg intramuscularly as a single dose with azithromycin 1 g oral as a single dose**. The azithromycin is thought to act synergistically with ceftriaxone and is also useful for eradicating any co-existent Chlamydia infections
- if ceftriaxone is refused or contraindicated other options include **cefixime** 400mg PO (single dose)
- A test of cure (with culture >72 hours or nucleic acid amplification testing >2 weeks) is recommended in all cases, and treatment failure should be reported to Public Health England or your local Health Protection Agency.

Non-gonococcal urethritis:

- The smear of urethral discharge which shows **neutrophils without visible organisms**, is typical of nongonococcal urethritis.
- Purulent nongonococcal urethritis can be caused by *Chlamydia* and *Trichomonas vaginalis*.
- The treatment of choice for chlamydial urethritis is azithromycin (single-dose course) or doxycycline (seven-day course).
- **However if the infection is not resolved with doxycycline then it likely is not chlamydia and is most likely *Trichomonas vaginalis* and metronidazole should be prescribed.**

May 2014 exam: **H/O a purulent urethral discharge. A sample of the discharge is shown to be a Gram negative diplococcus. What is the most appropriate antimicrobial therapy? Intramuscular ceftriaxone stat dose + oral azithromycin stat dose**

January 2016 exam: **What is the most likely complication from repeated *Neisseria gonorrhoea* infection? Infertility**
(Infertility secondary to pelvic inflammatory disease (PID) is the most common complication of gonorrhoea)

Helminths

Nematodes (roundworms)

Worm	Notes	Treatment
Strongyloides stercoralis	Larvae are present in soil and gain access to the body by penetrating the skin Features include diarrhoea, abdominal pain, papulovesicular lesions where the skin has been penetrated by infective larvae e.g. soles of feet and buttocks, larva currens: pruritic, linear, urticarial rash, if the larvae migrate to the lungs a pneumonitis similar to Loeffler's syndrome may be triggered	Ivermectin and -bendazoles are used
Enterobius vermicularis (pinworm)	asymptomatic in 90% of cases, possible features include perianal itching, particularly at night; girls may have vulval symptoms	**-bendazoles**

Worm	Notes	Treatment
	Diagnosis may be made by the applying sticky plastic tape to the perianal area and sending it to the laboratory for microscopy to see the eggs	
Ancylostoma duodenale, *N ecator americanus*(hookworms)	Larvae penetrate skin of feet; gastrointestinal infection → anaemia Thin-shelled ova	-bendazoles
Loa loa	Transmission by deer fly and mango fly Causes red itchy swellings below the skin called 'Calabar swellings', may be observed when crossing conjunctivae	Diethylcarbamazine
Trichinella spiralis	Typically develops **after eating raw pork.** Features include fever, **periorbital oedema** and **myositis** (larvae encyst in muscle)	-bendazoles
Onchocerca volvulus	Causes 'river blindness'. Spread by female blackflies Features include blindness, hyperpigmented skin and possible allergic reaction to microfilaria	Ivermectin r**IVER**blindness = **IVER**mectin
Wuchereria bancrofti	Transmission by female mosquito Causes blockage of lymphatics → elephantiasis	Diethylcarbamazine
Toxocara canis (dog roundworm)	Transmitted through ingestion of infective eggs. Features include visceral larva migrans and retinal granulomas VISCious dogs → blindness	Diethylcarbamazine
Ascaris lumbricoides(giant roundworm)	• the most common nematode parasite of humans. • Eggs are visible in faeces • large roundworm, growing up to 35 cm in length • result of pneumonitis caused by the worm's migration through the lungs • May cause intestinal obstruction and occasional migrate to lung (Loffler's syndrome) • biliary/pancreatic duct obstruction.	-bendazoles **Piperazine is the treatment of choice in patients presenting with bowel obstruction**; **mebendazole** may be used to treat other infections.

Cestodes (tapeworms)

Worm	Notes	Treatment
Echinococcus granulosus	• Responsible for **hydatid disease** • Transmission through **ingestion of eggs in dog faeces.** • Definite host is dog, which ingests hydatid cysts from sheep, who act as an intermediate host. • **Often seen in farmers**. • Features include **liver cysts** and **anaphylaxis if cyst ruptures** (e.g. during surgical removal)	-bendazoles
Taenia solium	Often transmitted after eating undercooked pork. Causes cysticercosis and neurocysticercosis, mass lesions in the brain 'swiss cheese appearance'	-bendazoles
Fasciola hepatica (the liver fluke)	May cause biliary obstruction	Triclabendazole

Trematodes (flukes)

Worm	Notes	Treatment
Schistosoma haematobium	Hosted by snails, which release cercariae that penetrate skin. Causes 'swimmer's itch' - frequency, haematuria. Risk factor for squamous cell bladder cancer	Praziquantel
Paragonimus westermani	Caused by undercooked crabmeat, results in secondary bacterial infection of lungs	Praziquantel
Clonorchis sinensis	Caused by undercooked fish Features include biliary tract inflammation. **Known risk factor for cholangiocarcinoma**	Praziquantel

Paragonimiasis or (lung fluke infection)

- Paragonimiasis is a common tropical disease, which often presents in a similar fashion to tuberculosis.
- **Trematodes (flukes)** organism → *Paragonimus westermani*
- Caused by undercooked crabmeat, results in secondary bacterial infection of lungs
- The patient will have a productive cough of classically brown or red sputum (which may be misinterpreted as haemoptysis).
- also present with fever and night sweats as well as rashes or urticaria.
- Constitutional symptoms will often not be as severe as in tuberculosis and the patient may also have an eosinophilia.
- **Treatment of paragonimiasis is with praziquantel**

Herpes simplex virus

- There are two strains of the herpes simplex virus (HSV) in humans:

1. **HSV-1**
    - **most commonly cause orofacial disease**
2. **HSV-2.**
    - **most commonly cause genital disease**.

- Whilst it was previously thought HSV-1 accounted for oral lesions (cold sores) and HSV-2 for genital herpes it is now known there is considerable overlap
- Worldwide seroprevalence is high, with antibodies detectable in over 90% of the population.
    - Of these cases, approx. 60% are caused by HSV-1.
- **Incubation period** → 2 days to 2 weeks.
- Recurrent attacks tend to be shorter and less severe.
- Viral shedding can occur in the absence of lesions.
- Transmission
    - Only from direct contact
    - Because the virus dies quickly outside of the body, it's nearly impossible to get the infection through contact with toilets, towels or other objects used by an infected person
- Antiviral treatment reduces the severity of episodes but is not curative.

Features

- Up to **80%** of herpes simplex infections are **asymptomatic**.
- Gingivostomatitis
    - In orofacial HSV infections, the **trigeminal ganglia** are most commonly involved
- cold sores
- painful genital ulceration
    - Blistering and ulceration of the external genitalia or perianal region (cervix/rectum)
    - Tender inguinal lymphadenitis, usually bilateral.
    - in genital HSV infection, the **sacral nerve root ganglia (S2-S5)** are involved.

Investigations

- **nucleic acid amplification test (NAAT)** are recommended as the preferred diagnostic method for genital herpes. now regarded as **the test of choice**.
    - **PCR** (a type of NAAT) : detects HSV RNA; identification of virus genotype
- **Western blot**
    - the gold standard for the detection of antibodies to HSV, but it is not commercially available.
    - expensive, time consuming and requires skilled interpretation.
    - high sensitivity
    - have ability to discriminate between HSV-1 and HSV-2 antibodies.
- **Viral culture**:
    - gold standard for definitive diagnosis;
    - 100% specificity for HSV-1 or HSV-2
    - Sensitivity
        - depends on the stage of the lesion at the time of specimen collection.
        - varies from 75% for first episodes to 50% for recurrences
            - results available in 48 hours
- **Tzanck smear**
    - rarely used now for diagnosis.
    - can be performed when an urgent result is needed and no alternative test is immediately available
    - Microscopic examination of scrapings from the base of a lesion to look for Tzanck cells
    - Positive if **multinucleated giant cells** are present
        - Tzanck cells (multinucleated giant cells) are present in:
            - **Herpes simplex type 1 (HSV-1) infection**
            - Varicella zoster virus infection (chickenpox or shingles)

- ❖ Cytomegalovirus
- ❖ Pemphigus vulgaris

- **No** detection of Tzanck cells in:
  - ❖ Bullous pemphigoid
  - ❖ Dermatitis herpetiformis

- ➢ Results available within 1 hour
- ➢ Unable to differentiate between HSV-1 and HSV-2

Management

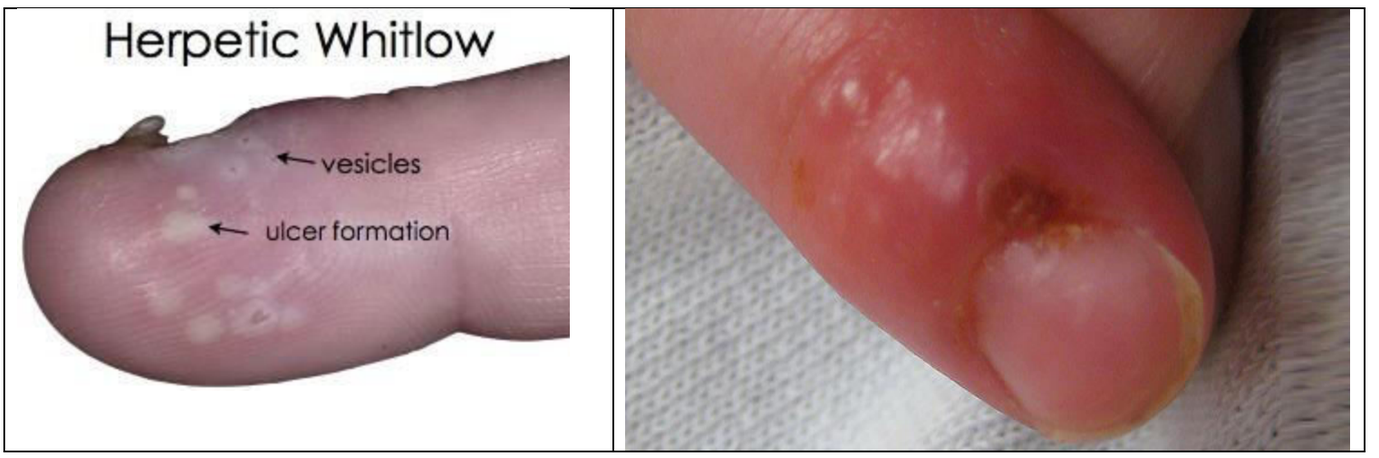
- gingivostomatitis:
  - ➢ oral aciclovir,
  - ➢ chlorhexidine mouthwash
- cold sores:
  - ➢ topical aciclovir although the evidence base for this is modest
- **genital herpes: oral aciclovir**.
  - ➢ Topical anaesthetic agents, e.g. 5% lidocaine (lignocaine) ointment
  - ➢ Recommended regimens (all for 5 days):
    - Preferred regimens:
      - ❖ Aciclovir 400 mg three times daily
      - ❖ Valaciclovir 500 mg twice daily
    - Alternative regimens:
      - ❖ Aciclovir 200 mg five times daily
      - ❖ Famciclovir 250 mg three times daily
  - ➢ Some patients with frequent exacerbations may benefit from longer term aciclovir
    - **more than six herpes episodes over the past 12 months → trial of suppressive therapy (aciclovir 400 mg BD for 12 months).**
    - Following cessation of suppressive therapy, reactivation may occur and patients therefore are counselled that up to two episodes of reactivation can present before the impact on the long-term pattern of recurrence can be evaluated.
  - ➢ **genital herpes in pregnant lady:**
    - Aciclovir is not licensed for use in pregnancy but is considered **safe and well tolerated.**
    - Recommend caesarean to all women presenting with primary episode genital herpes lesions at the time of delivery, or within 6 weeks expected delivery date.
    - if genital herpes is not recurrent and healed after a course of aciclovir:
      - ❖ there is no need to continue suppressive therapy throughout the pregnancy.
      - ❖ **She should take acyclovir 400 mg TDS from week 36**
        - ➔ Restarting a suppressive dose from week 36 is, however, appropriate to prevent active lesions being present at the time of delivery, where caesarean would definitely be needed.
    - If there is a history of recurrent genital herpes
      - ❖ She should continue taking acyclovir 400 mg TDS until the end of the pregnancy
    - If there are active lesions or prodromal symptoms at the time of delivery.
      - ❖ A caesarean section should be considered

Early treatment of herpes infections is essential to prevent complications because antiviral drugs only inhibit the virus during its replication phase

Ref: ((BASH guidelines (British Association for Sexual Health and HIV – ano-genital herpes 2014))

Herpetic whitlow

- **Pathogen**:
  - HSV-1 in 60% of cases; HSV-2 in 40% of cases (in the adult population)
- Etiology
  - Direct contact with infected secretions
- Main groups:
  - **Children** (via sucking of thumb/fingers (may have a history of labial herpes)
  - **Health care workers** exposed to oral secretions (e.g., **dentists**)
- **Incubation period**: 2–20 days
- **Clinical features**
  - Possibly history of fever and malaise
  - Infection of the dermal and subcutaneous tissue
  - One or more fingers involved (**especially the thumb and index fingers**); mostly found on terminal phalanx
  - Feeling of pain, tingling, and burning in infected finger; edema
  - **Grouped, non-purulent vesicles on an erythematous base**
  - Vesicles may rupture or ulcerate
  - Axillary and epitrochlear **lymphadenopathy**
- **Management**
  - **oral acyclovir**



HIV and pregnancy

Efavirenz is the only antiretroviral medication that is contraindicated in pregnancy (teratogenic)

- In London the incidence may be as high as 0.4% of pregnant women.
- The aim of treating HIV positive women during pregnancy is to minimise harm to both the mother and fetus, and to reduce the chance of vertical transmission.

Factors which reduce vertical transmission (from 25-30% to 2%)

- maternal antiretroviral therapy
- mode of delivery (caesarean section)
- neonatal antiretroviral therapy
- infant feeding (bottle feeding)

Screening

- NICE guidelines recommend offering HIV screening to all pregnant women

Antiretroviral therapy

- all pregnant women should be offered antiretroviral therapy regardless of whether they were taking it previously
- if women are not currently taking antiretroviral therapy the RCOG recommend that it is commenced between 28 and 32 weeks of gestation and should be continued intrapartum.

BHIVA recommend that antiretroviral therapy may be started at an earlier gestation depending upon the individual situation

Mode of delivery

- vaginal delivery is recommended if viral load is less than 50 copies/ml at 36 weeks, otherwise caesarian section is recommended
- a zidovudine infusion should be started four hours before beginning the caesarean section

Neonatal antiretroviral therapy

- zidovudine is usually administered orally to the neonate if maternal viral load is <50 copies/ml. Otherwise triple ART should be used. Therapy should be continued for 4-6 weeks.

Infant feeding

- in the UK all women should be advised not to breast feed

HIV: anti-retrovirals

HIV drugs, rule of thumb:

- NRTIs end in 'ine'
- PIs: end in 'vir'
- NNRTIs: nevirapine, efavirenz

Anti-retroviral therapy for HIV is now started at the time of diagnosis, rather than waiting for the CD4 count to drop to a particular level

HIV: anti-retrovirals - P450 interaction

- nevirapine (a NNRTI): induces P450
- protease inhibitors: inhibits P450

- Highly active anti-retroviral therapy (HAART) involves a combination of at least three drugs, typically two nucleoside reverse transcriptase inhibitors (NRTI) and either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). This combination both decreases viral replication but also reduces the risk of viral resistance emerging
- Following the 2015 BHIVA guidelines it is now recommended that patients **start HAART as soon as they have been diagnosed with HIV**, rather than waiting until a particular CD4 count, as was previously advocated.
- ART should be made up of two nucleoside reverse transcriptase inhibitors (NRTIs) and one other agent;
  - Atripla® (efavirenz, tenofovir, emtricitabine) is an acceptable choice.

Nucleoside analogue reverse transcriptase inhibitors (NRTI) (**ine** at the end)

Emtricitabine causes hyperpigmentation of skin including palmar creases in 8% of black patients.

- examples: zido**vudine** (AZT), lami**vudine**, sta**vudine**, didanos**ine**, zalcitab**ine**
- general NRTI side-effects: peripheral neuropathy
- **zidovudine**: anaemia, myopathy, black nails
  - **most frequently causes anaemia, usually by bone marrow suppression and patients can become transfusion-dependent in severe cases.**
    - **Macrocytosis is a typical finding in patients on zidovudine and can be used as a parameter to monitor adherence to therapy.**
  - Other side-effects of zidovudine include:
    - Myalgia, Myopathy, Myositis

- Pancytopenia,
- Lactic acidosis.
- Blue or black discolouration of the nails is a rare side-effect. May be misdiagnosed as cyanosis and melanoma.

- didanosine: pancreatitis (Didanosine and stavudine cause mitochondrial toxicity, hence peripheral neuropathy, pancreatitis and hyperlactataemia.)
- **NRTIs - in particular stavudine, didanosine and zidovudine - classically cause mitochondrial toxicity as an unwanted side effect. This can result in nausea, pancreatitis, lactic acidosis and lipoatrophy**
- Truvada → combination of two (Nucleoside analog reverse-transcriptase inhibitors (NRTIs) : tenofovir disoproxil and emtricitabine
  - tenofovir may cause:
    1. life-threatening liver damage
    2. lactic acidosis
    3. sudden worsen of hepatitis B after stopping tenofovir → lab tests regularly for several months after stop.

Non-nucleoside reverse transcriptase inhibitors (NNRTI) (**vir** in the middle)

- Currently four drugs of NNRTIs have been approved. These are the first generation NNRTIs ne**vir**apine, dela**vir**dine and efa**vir**enz and the next generation NNRTI etravirine. examples: nevirapine, efavirenz
- side-effects: P450 enzyme interaction (nevirapine **induces**), rashes
- **Nevirapine** can cause **acute hepatitis** and **skin rash** as a part of **hypersensitive reaction** .this is the rationale for starting low-dose therapy with nevirapine in the first 2 weeks
  - **Rashes are common on starting treatment with nevirapine, occurring in ~15% of patients.**
  - **Acute hepatitis is also common** and fatal reactions have occurred with this drug.
  - Serious side effects are more common in patients with relatively well preserved immune function.

Protease inhibitors (PI) (**vir** at the end)

- examples: indi**navir**, nelfi**navir**, rito**navir**, saqui**navir**
- side-effects:
  - diabetes,
  - **hyperlipidaemia**, **Hypertriglyceridaemia**
  - buffalo hump, central obesity,
  - P450 enzyme inhibition
  - **lipodystrophy**
- indinavir: **renal stones**, asymptomatic hyperbilirubinaemia
- ritonavir: a potent inhibitor of the P450 system (3A4 inhibitor)
  - **produces very significant elevations in plasma fluticasone (even an inhaled preparation).**
    - These levels are sufficient to suppress endogenous cortisol levels and **produce Cushing's syndrome.**

co-trimoxazole prophylaxis for *Pneumocystis* (PCP) is not necessary unless the CD4 count is below 200

Patient who have high viral load despite treatment:

- Causes of treatment failure:
  - poor adherence
  - drug interactions or absorption issues
  - primary resistance or superinfection with a new resistant strain.
- **All patients should have had a resistance test at baseline**
  - The most appropriate course of action is to **arrange an urgent resistance test** and manage the antiretrovirals accordingly with this result.

Preventing Opportunistic Infections in Patients With HIV

- Initiation of Prophylaxis and Treatment
  - Patients not taking ART who present with disseminated *Mycobacterium avium* complex (MAC) infection should be treated for the infection without ART for 2 weeks, and then started as soon as possible on ART while monitored closely for symptoms of the immune reconstitution inflammatory syndrome (IRIS).
  - Severe IRIS has also been reported after early ART in the management of **cryptococcal and tuberculous meningitis**, and it has been suggested that such patients **delay ART until 4-6 weeks after control of the opportunistic infection.**
  - Patients with CD4 counts of less than 50 cells/μL at presentation should be considered for cryptococcal antigen testing,
  - among **those diagnosed with cryptococcal meningitis, initial ART should be delayed at least 2 weeks** into cryptococcal therapy and as long as 10 weeks.
    - which must be treated initially with amphotericin and flucytosine.
- CD4 counts are useful landmarks for initiation of antimicrobial prophylaxis:
  - Less than 250 cells/μL - Coccidioidomycosis prophylaxis if seropositive in high-risk area
    - Patients with a new positive immunoglobulin M (IgM) or IgG serologic test result who live in endemic areas and have a CD4 count of less than 250 cells/μL should receive fluconazole 400 mg PO daily
  - Less than 200 cells/μL - PCP prophylaxis
    - The preferred regimen is trimethoprim-sulfamethoxazole 1 double-strength tablet orally daily or 1 double-strength tablet orally 3 times weekly.
  - Less than 150 cells/μL - Histoplasmosis prophylaxis if high-risk exposure
    - Patients with a CD4 count of less than 150 cells/μL at high risk for exposure or who live in a hyperendemic area should receive itraconazole 200 mg PO daily
  - Less than 100 cells/μL - Toxoplasmosis prophylaxis (if seropositive)
    - Trimethoprim-sulfamethoxazole, one double-strength tablet orally once daily is preferred
  - Less than 100 cells/μL - Penicilliosis prophylaxis if living in high-risk area
  - Less than 50 cells/μL - MAC infection prophylaxis
    - Patients with CD4 count of fewer than 50 cells/μL should be given **azithromycin** 1200 mg orally **weekly** after ruling out disseminated MAC infection on clinical assessment
    - Alternatives include clarithromycin 500 mg orally twice daily or rifabutin 300 mg orally daily
- Clinical Landmarks for Terminating Primary Prophylaxis
  - ***Mycobacterium avium****-intracellulare* (MAI) infection prophylaxis:
    - should be continued with antiretroviral therapy (ART) until the CD4 count exceeds 100 cells/μL **for 3 months**.
  - *P carinii* pneumonia (**PCP**) and **toxoplasmosis** prophylaxis:
    - should be continued until the CD4 count exceeds 200 cells/μL **for 3 months**.
  - Histoplasmosis prophylaxis:
    - can be discontinued when the CD4 count has exceeded 150 cells/μL for 6 months,
  - coccidioidomycosis prophylaxis:
    - can be discontinued when CD4 counts exceed 250 cells/μL for 6 months,
  - penicilliosis prophylaxis:
    - can be discontinued when CD4 counts exceed 100 cells/μL for 6 months.

HIV lipodystrophy (Antiretroviral-related lipodystrophy)

Lipodystrophy

- Lipodystrophy, lipoatrophy and alterations in serum lipid values have been observed in patients with human immunodeficiency virus (HIV) disease taking highly active antiretroviral therapy (HAART).
- **Consequences**
  - Elevated serum lipid levels have been associated with premature coronary artery disease.
  - Hypertriglyceridaemia is also thought to contribute to central fat deposition and insulin resistance.
- Causes
  - Abnormalities of serum lipid levels are likely to be **multifactorial** in patients with HIV disease but appear **much commoner in patients taking protease inhibitors.**
  - Isolated **hypertriglyceridaemia** can occur in HIV disease in the absence of **protease inhibitors** but extremely high serum triglycerides have been documented in some patients treated with these drugs.
  - In addition, patients with HIV disease may also have elevated serum lipid levels due to familial hyperlipidaemia.
- **Treatment**
  - If the elevation in lipid levels is modest, measures such as dietary modification and exercise may be tried first.
  - predominant **hypercholesterolaemia** or with a mixed picture → statin
    - caution must be exercised since some **protease inhibitors** interact with some **statins** due to metabolism by CYP3A4 pathway.
    - Simvastatin is contraindicated in patients on protease inhibitors and plasma levels of atorvastatin are also greatly elevated in these patients.
    - For this reason, **pravastatin is usually the drug of choice.**
      - **Pravastatin is preferred because its metabolism is not as dependent on the CP450s** as other agents in this group.
  - **hypertriglyceridaemia → fenofibrate**
  - Omega-3 fatty acids may also be beneficial in reducing modestly-elevated serum triglycerides.
  - Switching therapy might be an option, to non-nucleoside reverse transcriptase inhibitors (NNRTIs)

- Lipodystrophy refers to the loss of adipose tissue

Antiretroviral insulin-resistance syndrome

- Long-term use of combination antiretroviral therapy including protease inhibitor regimens is associated with a re-distribution of body fat in some patients
- HIV lipodystrophy follows an insulin-resistance pattern, with:
  - loss of fat on the face,
  - increasing abdominal fat
  - increase in the size of the dorsocervical fat pad (buffalo hump).
  - deposition of subcutaneous fat on the back
  - low high-density lipoprotein (HDL) cholesterol
  - high triglyceride levels,
  - hypertension
  - impaired glucose tolerance or frank type-2 diabetes

- there is some evidence that the insulin sensitisers (glitazones) may be effective in some patients

- **Acquired partial lipodystrophy**, also known as Barraquer-Simons syndrome
  - usually begins in childhood, at a median age of 7 years. The median age at presentation has been about 25 years.
  - It predominantly affects females
  - often follows an acute febrile illness, most commonly measles.
  - Most patients are asymptomatic until the development of advanced renal impairment or acute decompensation.
  - Fat loss is usually limited to the face, trunk, and upper extremities. Simultaneously, fat hypertrophy occurs in the lower extremities.
  - Characteristic fat distribution, as measured by skinfold thickness or images from magnetic resonance imaging (MRI) studies
  - Hepatomegaly has been reported in over 60%
  - Membranoproliferative glomerulonephritis in about 20%
    - Patients with membranoproliferative glomerulonephritis are more likely to have **low C3** levels and the **presence of C3 nephritic factor (C3NeF).**
    - **low C3** reported in about 70%
    - Presence of C3NeF in about 80%, a polyclonal (IgG), able to break down C3 in normal human serum
  - Activation of alternate complement pathway
  - Associated with Autoimmune diseases (eg: SLE most commonly)
  - Propensity to bacterial infections
  - Increased circulating free fatty acids
  - Excessive accumulation of triglycerides in multiple sites, especially the liver and muscles
  - Diabetes
    - mechanisms that may explain insulin resistance
      - Inability to store triglycerides: Leads to abnormal deposition of triglycerides in other tissues (eg, liver, skeletal muscle, and pancreas [lipotoxicity]), resulting in hypertriglyceridemia, insulin resistance, hepatic steatosis (fatty liver), impaired insulin secretion, and, eventually, type 2 diabetes
      - Absent or immature adipocytes: Inability to synthesize and release adipocytokines (eg, leptin, adiponectin) that may be important to maintain normal metabolism
  - Pathophysiology
    - Activation of an alternate complement pathway, C3 hypocomplementemia with lysis of adipocytes induced by C3NeF, has been implicated.
- Other causes of acquired lipodystrophy: **Aggressive treatment of patients infected with HIV, particularly with protease inhibitors**
- In women with lipoatrophy syndromes, oral estrogens should be avoided as they can exacerbate the hypertriglyceridemia and result in acute pancreatitis.

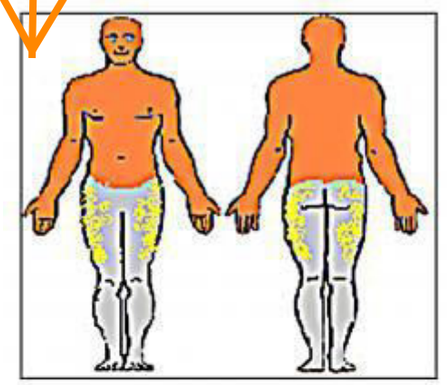


Figure Fat distribution in Acquired partial lipodystrophy

Normal

Lipodystrophy

Lipohypertrophy

Immune reconstitution syndrome

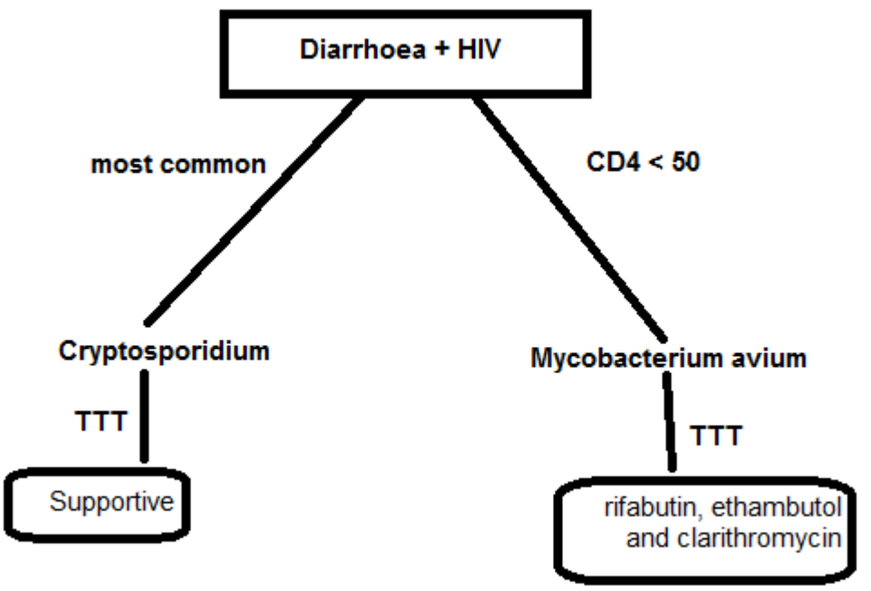
- due to activation of the immune system following HIV therapy against persisting antigen
- **typically occurs a few weeks after commencing anti-retroviral therapy in a patient with underlying tuberculosis**

HIV: biliary and pancreatic disease

- The most common cause of biliary disease in patients with HIV is sclerosing cholangitis due to infections such as CMV, Cryptosporidium and Microsporidia
- **Pancreatitis in the context of HIV infection may be secondary to anti-retroviral treatment (especially didanosine)** or by opportunistic infections e.g. CMV

HIV: diarrhoea

Supportive therapy is the mainstay of treatment in Cryptosporidium diarrhoea



- Diarrhoea is common in patients with HIV. This may be due to the effects of the virus itself (HIV enteritis) or opportunistic infections
- Possible causes
  - Cryptosporidium + other protozoa (most common)
  - Cytomegalovirus

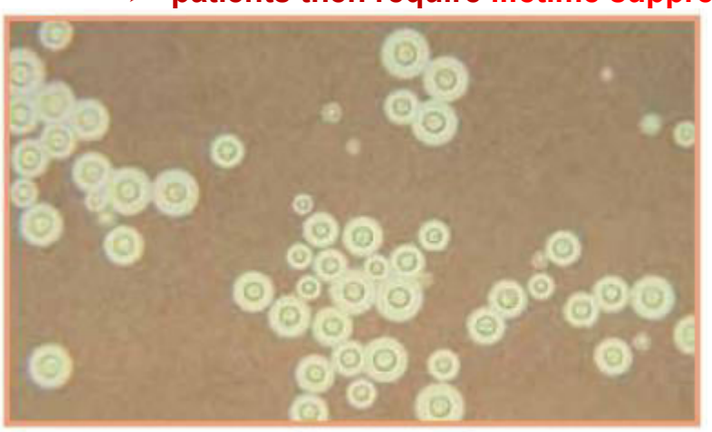
  - *Mycobacterium avium intracellulare*
  - Giardia
- Both *Cryptosporidium* and *Cytomegalovirus* are found in patients with CD4 count less than 300 cells/μL. It causes chronic diarrhoea (more than four week's duration).
- **Cryptosporidium is the most common infective cause of diarrhoea in HIV patients.**
  - It is an intracellular protozoa and has an incubation period of 7 days.
  - Presentation is very variable, ranging from mild to severe diarrhoea.
  - A modified Ziehl-Neelsen stain (acid-fast stain) of the stool may reveal the characteristic red cysts of Cryptosporidium.
  - Treatment is difficult, with the mainstay of management being **supportive therapy***
    - *nitazoxanide is licensed in the US for immunocompetent patients
- ***Mycobacterium avium intracellulare***
  - is an atypical mycobacteria seen with the CD4 count is below 50.
  - Typical features include fever, sweats, abdominal pain and diarrhoea.
  - There may be hepatomegaly and deranged LFTs.
  - Diagnosis is made by blood cultures and bone marrow examination.
  - Management is with rifabutin, ethambutol and clarithromycin

HIV nephropathy

- HIV nephropathy is characterised by:
  - raised creatinine
  - nephrotic range proteinuria
  - normal sized kidneys on ultrasound scan, and
  - **focal segmental glomerulosclerosis on renal biopsy.**
  - Somewhat surprisingly the blood pressure of patients with HIV nephropathy is usually normal.
  - raised immunoglobulins and raised cholesterol.

Cryptococcal disease in AIDS (Cryptococcosis)

- the most common fungal infection of the CNS
- the most common fungal disease in HIV
- **may present as:**
  - a space-occupying lesion,
  - meningitis, or
  - meningoencephalitis.
- **Risk factor:**
  - usually develops only when CD4+ lymphocyte counts fall below 100 cells/mL.
- **Diagnosis**
  - MRI, with and without contrast, is the preferred diagnostic imaging modality.
- **Treatment**
  - **Treatment is with amphotericin B and flucytosine (5FC);**
  - **patients then require lifetime suppression with fluconazole.**



Microscopy of *Cryptococcus neoformans*.

HIV: immunisation

The Department of Health 'Greenbook' on immunisation defers to the British HIV Association for guidelines relating to immunisation of HIV-infected adults

Vaccines that can be used in all HIV-infected adults	Vaccines that can be used if CD4 > 200	Contraindicated in HIV-infected adults
• Hepatitis A • Hepatitis B • *Haemophilus influenzae* B (Hib) • Influenza-parenteral • Japanese encephalitis • Meningococcus-MenC • Meningococcus-ACWY I • Pneumococcus-PPV23 • Poliomyelitis-parenteral (IPV) • Rabies • Tetanus-Diphtheria (Td)	• **M**easles, **M**umps, **R**ubella (**MMR**) • Varicella • Yellow Fever	• Cholera CVD103-HgR • Influenza-intranasal • **Poliomyelitis-oral (OPV)** • Tuberculosis (BCG)

HIV: Kaposi's sarcoma

Kaposi's sarcoma - caused by HHV-8 (human herpes virus 8)

- Kaposi sarcoma is a **neoplasm of endothelial cells** (vascular tumor) that is **caused by human herpes virus 8 (HHV-8)**
- most commonly seen in patients with HIV and transplant patients.
  - can be seen in HIV patients with a CD4+ cell count of less than $500/mm^3$.
- Human herpes virus 8, which causes Kaposi sarcoma in HIV patients, is **transmitted by sexual contact.**
- Aside from affecting the skin, Kaposi sarcoma can also affect the gastrointestinal tract and lungs.

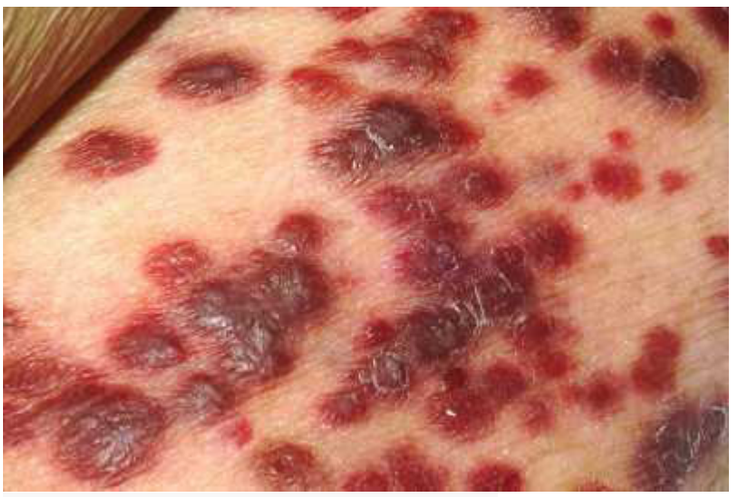
Feature

- presents as purple papules or plaques on the skin or **mucosa** (e.g. gastrointestinal and respiratory tract)
- lesions occur most commonly on the face
- skin lesions may later ulcerate
- respiratory involvement may cause massive haemoptysis and pleural effusion, Chest x ray may show pulmonary nodules.
- Histopathology classically show
  - **lymphocytic inflammation**.
  - proliferation of endothelial cells (**spindle cells**)

Treatment

- radiotherapy + resection
  - Radiotherapy may be used to treat painful or highly visible lesions.
- AIDS-related Kaposi's sarcoma becomes smaller as immune function improves such as with treatment with highly active antiretroviral therapy (HAART).
- In some circumstances chemotherapy may be added to HAART.

- **Human herpes virus 8** is also associated with:
  - primary effusion lymphoma (a rare lymphoma of serous cavities)
  - Castleman's disease.


Kaposi's sarcoma in a patient with HIV

Human immunodeficiency virus (HIV)

Etiology

- Consists of the two species :
  - HIV-1: most common species worldwide
  - HIV-2: restricted almost completely to West Africa

Mechanisms

- The **gp41** protein mediates fusion and entry of HIV into host cells, and is the structural component that first physically invades the host cell wall.
- The **gp120** protein of HIV allows its attachment to host CD4+ T cells.
- **gp120** is the HIV glycoprotein that can cross the placenta and infect the fetus.
- **Site of replication**
  - The lymph nodes are the organs in which HIV replicates during the latent phase.

Associations

- Epstein-Barr virus reactivation, leading to B-cell lymphoma, typically occurs in AIDS patients with a CD4+ cell count less than 100/mm^3.

Acute HIV disease (seroconversion illness)

Man returns from trip abroad with maculopapular rash and flu-like illness - think HIV seroconversion

- HIV seroconversion is symptomatic in 60-80% of patients
- typically presents as a glandular fever type illness.
  - The presentation may mimic glandular fever, though the pharyngitis associated with acute HIV is usually more severe and a **rash only occurs in glandular fever when ampicillin has been given.**
- Increased symptomatic severity is associated with poorer long term prognosis.
- It typically occurs 2-12 weeks after infection
  - The time from exposure to onset of symptoms is usually 2-4 weeks, but the incubation may be as long as 10 months in rare cases.

Features

- Fever
- sore throat
- maculopapular rash
- lymphadenopathy
- malaise, myalgia, arthralgia
- diarrhoea

- mouth ulcers
- rarely meningoencephalitis

Diagnosis

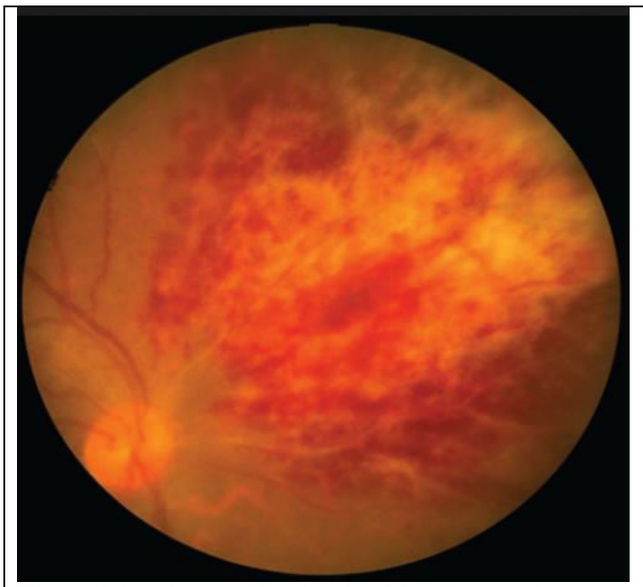
- **HIV PCR and p24 antigen tests can confirm diagnosis**
  - **P24 antigen testing may detect HIV infection one to three weeks after the event and is the most appropriate option when earlier result is needed**
    - p24 is the **capsid** protein of HIV, coded for by the *gag* gene.
  - The alternative is HIV RNA testing to estimate viral load.
    - the diagnosis is made by (PCR) of peripheral blood for HIV (RNA);
      - in acute HIV the viral load is very high.

- Flow cytometry is the lab technique used to measure CD4 cell count in HIV patients.
  - The **CD4** (T-helper cell) count is a reliable indicator of HIV-related immune impairment.
    - **The most useful investigation in estimating his risk of developing an opportunistic infection (OI)**
    - CD4 of **<** 350 cells/μl is associated with an increase in the risk of some opportunistic infections
    - CD4 **<** 200 cells/μl indicates an 80% risk of developing an (OI) over the next 3 years.
    - oesophageal candidiasis and Pneumocystis pneumonia are common at CD4 100–200 cells/μl;
    - disseminated Mycobacterium avium complex infection and cytomegalovirus retinitis are rarely seen until CD4 **<** 50 cells/μl.
      - **Blood cultures → the best investigation to confirm the diagnosis**
  - Since late 2015, the World Health Organization (WHO) has recommended **starting ART in every HIV-positive individual, regardless of CD4 count**.

- antibodies to HIV may not be present
  - During seroconversion it is likely that the HIV antibody test will be negative
  - HIV antibody testing by western blot has a lower false positive rate than HIV antibody by ELISA and may be an option when a false positive result is suspected.

CMV retinitis in a patient with HIV

- AIDS retinitis is typically caused by cytomegalovirus.



The slide shows the typical 'cottage cheese and tomato ketchup' or 'pizza' appearance of CMV retinitis in a patient with HIV disease.

Toxoplasmosis

Congenital toxoplasmosis
- cerebral calcification
- chorioretinitis

- Toxoplasma gondii is an obligate intracellular protozoa which infects the body via the GI tract, lung or broken skin.
- It's oocysts release trophozoites which migrate widely around the body including to the eye, brain and muscle.

Transmission (fecal-oral route)
- Toxoplasmosis can be contracted through:
  1. cysts in meat, (**from undercooked meat**)
     - The usual animal reservoir is the cat, although other animals such as rats carry the disease.
     - Kittens are the primary host (mature cats are less likely to secrete toxoplasma)
     - sheep and cattle eat food contaminated with soil contaminated by kitten faeces; and humans ingest the organisms in poorly cooked meat.
     - Oocysts excreted with cat faeces can remain in soil for months.
  2. oocysts in cat feces,
     - ingestion of fresh food contaminated by toxoplasma excreted in cats' faeces.
  3. transplacental → **Congenital toxoplasmosis** .

Epidemiology
- 30% risk of **reactivation** in immunocompromised (especially CD4+ count < 100 cells/μL)
  - in those not receiving prophylaxis or antiretroviral therapy
- ~ 30% of the worldwide population is infected

Risk factors
- HIV patients when the CD4+ count is less than 100cells/microL
  - Toxoplasmosis is the most common central nervous system protozoal infection that presents with brain abscesses in patients with HIV.

Pathophysiology
- HIV is associated with **reactivation** of the disease.

Feature
- Most infections are asymptomatic.
- often **features resembling infectious mononucleosis** (fever, malaise, lymphadenopathy).
  - Highly characteristic of toxoplasmosis is **asymmetrical lymphadenopathy** limited to an isolated lymph node group.
- Other less common manifestations include meningio-encephalitis and myocarditis.
- **Can present with fits in patients with AIDS**
  - **Most common infection of the central nervous system in patients with AIDS**
    - **ring-enhancing lesion on head imaging**
      - **MRI is more sensitive and preferred**
    - CD4+ count < 100 cells/μL
- Eye manifestations include:
  - Focal choroido-retinitis
  - Granulomatous uveitis
  - Optic atrophy
  - Retinal detachment
  - Cataract
  - Posterior uveitis

- Glaucoma.

- **Congenital toxoplasmosis** presents with a classic **triad** of:
  1. **chorioretinitis**,
  2. hydrocephalus and
  3. **intracranial calcifications**.

Investigation

- antibody test: **Serology testing** for anti-toxoplasma IgM and IgG antibodies via **ELISA**
  - The serologic diagnosis of toxoplasmosis in immunocompromised patients is based on the presence of **IgG** antibodies.
- Sabin-Feldman dye test
- Congenital toxoplasmosis is associated with elevated platelet count.
- HIV patients usually presents with **multiple ring-enhancing lesions on brain MRI.**

Treatment

- Symptomatic patients usually have a self-limiting infection,
- Treatment usually reserved for those with severe infections or patients who are immunosuppressed
  - **pyrimethamine plus sulphadiazine for at least 6 weeks**
    - Folinic acid, (also known as leucovorin), should be added to prevent pyrimethamine- associated hematologic toxicity

Prevention

- Trimethoprim-sulfamethoxazole is the therapy of choice for prophylaxis against toxoplasmosis reactivation.
- pregnant women
  - Since the protozoal infection is commonly contracted through the handling of cat feces, pregnant women should be advised to **avoid contact with cat litter** to reduce their fetus's risk for congenital infection.
- for infected **pregnant** to **prevent maternal-fetal transmission** → **spiramycin**,
  - Risk of fetopathy is reduced by more than 50% if spiramycin, which can prevent maternal-fetal transmission, is given to mothers

Pyrimethamine

- MOA → Dihydrofolate Reductase (DHFR) Inhibitor (competitive inhibitor)
  - DHFR is a key enzyme for production of tetrahydrofolate, a cofactor that is required for the synthesis of DNA and proteins.
- Indications:
  - used as an antimalarial or
  - with a sulfonamide to treat toxoplasmosis.

Sulfadiazine

- bacteriostatic, inhibits bacterial folic acid synthesis by competing with para amino benzoic acid.

spiramycin

- Macrolide antibiotics inhibit bacterial growth by targeting the 50S ribosomal subunit
- Resistance to spiramycin is commonly attributed to mutations in 50S rRNA

January 2008 exam: **HIV positive man is admitted with right-sided hemiplegia. CT scan shows multiple ring enhancing lesions. A diagnosis of cerebral toxoplasmosis is suspected. What is the most suitable management? Pyrimethamine and sulphadiazine**

At which CD4 count should prophylaxis against toxoplasmosis begin?
→ **<100 cells/µL** (with trimethoprim-sulfamethoxazole).

- although prophylaxis for toxoplasmosis is not required until the CD4 count is <100 cells/microL, the patient will be covered at a CD4 count <200 cells/microL when prophylaxis against *P. jiroveci* is instituted.

What is risk of transmission of HIV to a health care worker after percutaneous exposure?

- **0.3% with** no prophylaxis**.**
  - the risk is reduced by ~80% when post exposure prophylaxis is administered.

HIV- white lesion in oral mucosa

- **Oral hairy leukoplakia** are white oral lesions **caused by the Epstein-Barr virus**. Unlike oral candidiasis (thrush), these lesions **cannot be scraped off** the tongue and buccal mucosa.

H1N1 influenza pandemic

- The H1N1 virus is a subtype of the influenza A virus
- **the most common cause of flu in humans.**
- Only influenza type A viruses are known to have caused **pan**demics.
- Influenza A and B viruses circulate and cause outbreaks and **epi**demics.
- The 2009 pandemic was caused by a new strain of the H1N1 virus.
- incubation period is about 2 days.
- In temperate climates, seasonal epidemics occur mainly during winter, while in tropical regions, influenza may occur throughout the year, causing outbreaks more irregularly.

The following groups are particularly at risk:

- patients with chronic illnesses and those on immunosuppressants
- pregnant women
- young children under 5 years old

Features: The majority of symptoms are typical of those seen in a flu-like illness:

- fever greater than 38ºC
- myalgia
- lethargy
- headache
- rhinitis
- sore throat
- cough
- diarrhoea and vomiting

A minority of patients may go on to develop an acute respiratory distress syndrome which may require ventilatory support.

Treatment

There is evidence to support the use of oseltamivir as a prophylactic agent against influenza

There are two main treatments currently available:

Oseltamivir (Tamiflu)

- **For critically ill patients with confirmed or suspected H1N1, oseltamivir 150 mg bd for ten days is the recommended treatment.**
- **oral** medication
- a **neuraminidase inhibitor** which prevents new viral particles from being released by infected cells. thus, slowing viral replication down rather than directly killing the virus particle.
- This slowing down of replication is important in permitting time for the body's own immune system to deal with the virus.
- **It is of value in prophylaxis against influenza. may be used in the prophylactic treatment of healthcare workers during flu epidemics.**
- However, viral replication is rapid and to be effective the drug must be given as early as possible after the development of symptoms of flu and **preferably within 48 hours.**
- common side-effects include nausea, vomiting, diarrhoea and headaches. **Gastrointestinal symptoms are the most common side-effects of oseltamivir (Tamiflu).**

Zanamivir (Relenza)

- **inhaled** medication*
  - *intravenous preparations are available for patients who are acutely unwell
    - The only parenteral alternative is zanamivir **(300 mg IV for 10 days).**
    - can be safely given using peripheral venous access.
    - For **hospitalized influenza patients** with suspected or known gastric statis, **gastric malabsorption**, gastrointestinal bleeding, or for patients suspected or confirmed with oseltamivir-resistant influenza virus infection, intravenous zanamivir should be considered.
- also a neuraminidase inhibitor
- may induce bronchospasm in asthmatics

Intensive Care Management of Pandemic (H1N1) Influenza

- Ideally patients should be nursed in a negative pressure room.
- NIV
  - Whilst there is no evidence that NIV prevents invasive ventilation in H1N1 patients, it is commonly used as bridging therapy.
  - It is important to remember that these are open circuits and **still require personal protection for staff.**
  - **NIV should be started after the mask is secured to the face**
    - Ensuring that a well-fitting mask is in place before airflow starts can reduce the amount of aerosol production.
  - Experience with helmet devices is limited but increasing, and it has been successful in patients who are unable to tolerate the nasal or orofacial devices. The advantage is that it may provide a tighter seal than nasal or orofacial devices.
- avoiding water humidification and use of a closed hood(غطاء الرأس) is also advised.

Infectious mononucleosis & (Epstein-Barr virus)

Atypical lymphocytes - ?glandular fever

Aetiology

- Infectious mononucleosis (glandular fever) is caused by the **Epstein-Barr virus** (also known as human herpesvirus 4, HHV-4).
- The incubation period of EBV infectious mononucleosis is 1-2 months.

Epidemiology

- most common in adolescents and young adults.

Pathophysiology

- The **CD8+ T-cell response** caused by infectious mononucleosis, leads to generalized lymphadenopathy, splenomegaly, and high WBC count with atypical lymphocytes.

Features

EBV infectious mononucleosis → **triad of fever, pharyngitis, and lymphadenopathy.**

- sore throat
- lymphadenopathy
  - Bilateral posterior cervical adenopathy is most highly suggestive of EBV infectious mononucleosis.
- pyrexia
- malaise, anorexia, headache
- palatal petechiae
  - Palatal petechiae of the posterior oropharynx distinguish infectious mononucleosis from other causes of viral pharyngitis but do not distinguish it from group A streptococcal pharyngitis, in which palatal petechiae may occur.

- Uvular edema is an uncommon, but, if present, it is a helpful sign in distinguishing EBV infectious mononucleosis from other causes of viral pharyngitis or from group A streptococcal pharyngitis.
- splenomegaly - occurs in around 50% of patients and may rarely predispose to splenic rupture
- hepatitis
- **haemolytic anaemia secondary to cold agglutins (IgM)**
- a maculopapular, pruritic rash develops in around 99% of patients **who take ampicillin/amoxicillin** whilst they have infectious mononucleosis
  - Drug-induced rash is usually pruritic and is prolonged, in contrast to the viral rash of EBV infectious mononucleosis.
  - Early infectious mononucleosis may present with a maculopapular generalized rash.It is nonpruritic and rapidly disappears.
- Because **leukocytosis** is the rule in infectious mononucleosis, the presence of a **normal or decreased WBC count should suggest an alternative diagnosis.**
- Lymphocytosis
  - Relative lymphocytosis (≥ 60%) plus atypical lymphocytosis (≥ 10%) are the characteristic findings of EBV infectious mononucleosis.
- presence of 50% lymphocytes with at least 10% **atypical lymphocytes**
  - **Atypical lymphocytes**
    - **most commonly** seen in patients who have **infectious mononucleosis.**
    - Other causes
      - drug reactions (phenytoin),
      - stress,
      - **viral** or bacterial **infections**,
      - allergies,
      - autoimmune diseases, thyroid problems
      - malignancy.
- ESR is most useful in differentiating group A streptococcal pharyngitis from EBV infectious mononucleosis.
  - (ESR elevated with EBV infectious mononucleosis, not elevated in group A streptococcal pharyngitis).

atypical lymphocytosis point towards a viral illness

Diagnosis

- **heterophile antibody test (Monospot test)** (immunoglobulin IgM to EBV)
  - **the initial screening test**
  - sensitivity 85% and specificity 100%.
  - Cytomegalovirus is a herpesvirus that causes **infectious mononucleosis with a negative monospot test**.
- EBV serological tests
  - **Definitive diagnosis**
  - should be obtained in patients with a mononucleosis-like illness and a negative finding on the Monospot test.

Management is supportive and includes:

- rest during the early stages, drink plenty of fluid, avoid alcohol
- simple analgesia for any aches or pains
- consensus guidance in the UK is to **avoid playing contact sports for 8 weeks after having glandular fever to reduce the risk of splenic rupture**
- unfortunately on clinical appearances it is not possible to distinguish bacterial from viral or throat infections with any degree of reliability.
- **If the child has EBV infection, then the administration of Amoxicillin will give an erythematous rash.** Non-vomiting patients can be treated with oral penicillin-v.'
- Patients with EBV infectious mononucleosis who have positive throat cultures for group A streptococci should not be treated because this represents colonization rather than infection
- complicated EBV infectious mononucleosis :

- Short courses of corticosteroids are indicated for EBV infectious mononucleosis with:
  - hemolytic anemia,
  - thrombocytopenia,
  - CNS involvement, or
  - extreme tonsillar enlargement (impending airway obstruction).

EBV: associated malignancies:
- Burkitt's lymphoma
- Hodgkin's lymphoma
- nasopharyngeal carcinoma

In which structure is the immune response most likely localized? → Paracortex
- immune response to the virus takes place through T-cell mediated immune responses, which take place in the **lymphocyte-rich areas of the lymph node**, namely the **paracortex.**
- A biopsy of the lymph node of this patient would show reactive hyperplasia due to increased activity of the paracortex.

Influenza

- **Methods used in the laboratory diagnosis of respiratory viral infections:**
  - (ELISA):Enzyme-linked immunosorbent assay is used to look for antibodies in acute and convalescent sera.
  - Haemagglutination: Influenza is a haemagglutinating virus as red cells stick to the infected cells after addition to the culture.
  - Immunofluorescence: Rapid antigen detection kits utilising direct immunofluorescence are used to demonstrate the following in respiratory secretions:
    - Respiratory syncytial virus (RSV)
    - Influenza
    - Parainfluenza, and

Single radial haemolysis (SRH) test is used to screen for rubella antibodies in pregnant women. NOT used in diagnosis of respiratory viral infections.

Treatment
- Adenovirus.Oseltamivir (tamiflu) is the first line treatment recommended for patients with suspected or confirmed Influenza A.
- Ribavirin has not be shown to be efficacious in the management of influenza.
- Zanamivir is useful in patients with poor swallow or in those with suspected or confirmed exposure to oseltamivir-resistant influenza.
- Salbutamol nebulisers can be useful in patients with wheeze, however appropriate isolation precautions should be secured prior to the administration of nebulisers in patients with Influenza infection.

Parvovirus B19

- Parvovirus B19 is a single-strand DNA virus.
- The most widely known clinical manifestation of parvovirus B19 is erythema infectiosum ('slapped cheek syndrome'), a mild viral illness of childhood characterised by a classic exanthema in which both cheeks appear bright red as though they had been slapped.
- Although usually a benign self-limiting viral illness, parvovirus B19 infection may have more serious sequelae.

- The virus has a tropism for rapidly dividing erythrocyte precursors which they infect and destroy. Thus, no reticulocytes (immature erythrocytes) are available to replace aging or damaged erythrocytes as they are cleared by the reticuloendothelial system. This may not have any significant impact on otherwise healthy individuals, but can trigger an aplastic crisis - particularly in patients with haemoglobinopathies.
- Parvovirus B19 infection may also be associated with a symmetrical post-infectious arthritis, affecting the small joints of the hands and feet. The knees or elbows are rarely involved.
- The arthritis is much more common in adults, particularly in women, and may persist for weeks to months (even years in a small number of patients). The arthritis may mimic rheumatoid arthritis. Unlike rheumatoid arthritis, the post-infectious arthritis associated with parvovirus B19 does not cause permanent damage to bones or joints.

Leishmaniasis

Mucocutaneous ulceration following travel? - Leishmania brasiliensis

- Leishmaniasis is caused by the intracellular protozoa Leishmania, (intra-macrophage protozoa)
- transmitted to humans by phlebotomine sand flies.
- There are four main clinical syndromes: cutaneous, muco-cutaneous, visceral (also known as kala-azar) and post kala-azar dermal leishmaniasis.

Cutaneous leishmaniasis

- caused by *Leishmania tropica* or *Leishmania mexicana*
- crusted lesion at site of bite
- present with ulcers or nodules.
- usually heal spontaneously, but slowly, in immuncompetent individuals with resultant disfiguring scars.

Mucocutaneous leishmaniasis

- caused by *Leishmania braziliensis*
- skin lesions may spread to involve mucosae of nose, pharynx etc
- characterised by progressively destructive ulcerations of the mucosa extending from the nose and mouth to the pharynx and larynx,
- are not self-healing.

Visceral leishmaniasis (kala-azar)

- mostly caused by *Leishmania donovani*
- caused by the Leishmania donovani complex
  - (L. donovani sensu stricto in East Africa and India,
  - L. infantum in Europe, North Africa and Latin America).
- incubation period of 2-6 months
- patients present with persistent systemic infection (fever, sweating, rigor, malaise, loss of appetite and weight loss) (*occasionally patients may report increased appetite with paradoxical weight loss)
- parasitic infection of the blood and reticulo-endothelial system → lymphadenopathy, massive splenomegaly and hepatomegaly
- grey skin - 'kala-azar' means black sickness
- **investigations**
  - pancytopaenia secondary to hypersplenism
  - There is also often marked polyclonal hypergammaglobulinaemia.
  - **Visualisation of the parasite (amastigote form) from lymph nodes, bone marrow or spleen is used as a confirmatory test.**
  - PCR can be used to detect the parasite in the blood.
  - Anti-leishmanial antibodies can be detected, but they remain positive up to several years after cure and therefore cannot be used to detect relapse.
- **Treatment**

- First line antimonials are sodium stibogluconate and meglumine antimoniate. Adverse effects influde cardiac arrhythmias and acute pancreatitis.
- Amphotericin B is increasingly being used.

Post kala-azar dermal leishmaniasis

- a complication of visceral leishmaniasis
- characterised by a macular, maculo-papular or nodular rash
- frequently observed after treatment.It can also occur in immunosuppressed individuals.
- highly infectious.

Leptospirosis (Also known as **Weil's disease***)

Leptospirosis - give penicillin or doxycycline

- *the term Weil's disease is sometimes reserved for the most severe form
  - If the infection causes jaundice, kidney failure and bleeding, it is then known as **Weil's disease.**
  - If it affects the lung and causes pulmonary haemorrhage, then it is known as **severe pulmonary haemorrhage syndrome.**
- leptospirosis is commonly seen in questions referring to sewage workers, **farmers**, vets or people who work in abattoir.
- It is caused by the spirochaete Leptospira interrogans (serogroup L icterohaemorrhagiae),
- classically being spread by contact with infected rat urine.
- Weil's disease should always be considered in high-risk patients with **hepato-renal failure**

Features

- fever
- flu-like symptoms
- **renal failure (seen in 50% of patients)**
- **jaundice**
- headache, may herald the onset of meningitis
- subconjunctival haemorrhage
- Haemorrhagic tendencies with purpura or petechiae, and
- Enlargement of liver and spleen.
- Presentation with heart failure is uncommon but has been described in severe leptospirosis.

Management

- high-dose benzylpenicillin or doxycycline
- other options: cefotaxime or ceftriaxone.

Leprosy

Leprosy is a granulomatous disease primarily affecting the peripheral nerves and skin. It is caused by *Mycobacterium leprae*.

Features

- patches of hypopigmented skin typically affecting the buttocks, face, and extensor surfaces of limbs
- sensory loss

The degree of cell mediated immunity determines the type of leprosy a patient will develop:

- Low degree of cell mediated immunity → lepromatous leprosy ('multibacillary')
  - extensive skin involvement

- symmetrical nerve involvement
- High degree of cell mediated immunity → tuberculoid leprosy ('paucibacillary')
  - limited skin disease
  - asymmetric nerve involvement

Management

- WHO-recommended triple therapy: rifampicin, dapsone and clofazimine
- BNF advice:
  - **multibacillary leprosy (>6 lesions) → rifampicin, dapsone and clofazimine for 12 months.**
  - paucibacillary leprosy (5 or less lesions) → rifampicin and dapsone for 6 months.

Filariasis

- **Manifestations of filariasis**
  - **Remember 3 L's:**
    - **L**ymphatic filariasis (caused by Wuchereria bancrofti and Brugia malayi)
    - **L**oiasis (caused by Loa loa)
    - **L**ight (light, sight, blindness - river blindness caused by Onchocerca volvulus)
  - **Tropical eosinophilia:**
    - Tropical eosinophilia is an allergic reaction to microfilaria of Wuchereria bancrofti.
    - Characteristic features include:
      - myalgia; fatigue;
      - weight loss;
      - cough and dyspnoea with wheeze;
      - fever;
      - current or previous residence in an area endemic for filariasis (southern Asia, Africa, India, South America);
      - lymphadenopathy;
      - marked peripheral blood eosinophilia
      - high titres of anti-filarial antibodies.
    - The chest x ray shows bilateral reticulonodular shadowing.
    - This condition is commonly accompanied by false positive serological tests for syphilis and high titres of cold agglutinins.
    - There is typically a rapid response to treatment with diethylcarbamazine.
- Diagnosis
  - finger prick test
    - identifying microfilariae on Giemsa stained, thin and thick blood film smears,
  - "Filariasis fills the blood at night."
  - To remember that Microfilaria can be demonstrated in peripheral smear only at night.
    - *W. bancrofti*, whose vector is a mosquito; night is the preferred time for blood collection.
    - *Loa loa's* vector is the deer fly; daytime collection is preferred.
- **Which immune mechanisms does the body employ against the live filarial worms ?**
  → Antibody-dependent cell-mediated cytotoxicity

Loiasis

- Loiasis is a filarial infection caused by Loa Loa.
- It is transmitted by the Chrysops deerfly and tends to occur in rainforest regions of Western and Central Africa.
- It has less pathological features than other the microfilarial infections Onchocerciasis and Lymphatic Filariasis.

Clinical features

- pruritus

- urticaria
- Calabar swellings: transient, non-erythematous, hot swelling of soft-tissue around joints
- 'eye worm' - the dramatic presentation of subconjuctival migration of the adult worm.

Treatment

- Ivermectin is currently the drug of choice for control of both Onchocerciasis and Lymphatic Filariasis in Africa.
- **high loa loa microfilaraemia is associated with encephalopathy following treatment with either Ivermectin** or DEC. This occurs due to the death of vast numbers of blood microfilaria. Both of these drugs are contraindicated if loa loa microfilaraemia exceeds 2500 mf/ml.

Adult Loa loa parasite. Loa loa is the filarial nematode (roundworm) species that causes loa loa filariasis. It is commonly known as the 'eye worm.' Its geographic distribution includes Africa and India. Credit: NIAID

Lyme disease

- Lyme disease is caused by the spirochaete ***Borrelia burgdorferi*** and is spread by ticks of the **genus Ixodes**
  - ***Ixodes ricinus* is predominantly responsible for its transmission in Europe.**
  - *Ixodes pacificus* and *Ixodes scapularis* are the ticks responsible for transmission of in the USA.

Features

Bilateral facial weakness can occur with Lyme disease, myasthenia gravis, sarcoidosis and bilateral Bell's palsy.

Early features

- **erythema chronicum migrans** (small papule often at site of the tick bite which develops into a larger annular lesion with central clearing, 'bulls-eye'. Occurs in 70% of patients)
  - **Erythema migrans is often the presenting sign of Lyme disease**
- systemic symptoms: malaise, fever, arthralgia

Later features

- CVS: heart block, myocarditis
- neurological: cranial nerve palsies, meningitis
- polyarthritis

Investigation

- serology: antibodies to *Borrelia burgdorferi* **(ELISA test for antibodies to *Borrelia burgdorferi*)**
  - Serological tests are the most appropriate first line investigation for diagnosing Lyme disease.
  - ELISA tests are preferred to Western blots as they are more sensitive.

Management

The treatment of choice in those aged over 8 years and non-pregnant females is a 2–3 week course of doxycycline.

- doxycycline if early disease. Amoxicillin is an alternative if doxycycline is contraindicated (e.g. pregnancy)
- **ceftriaxone if disseminated disease**
- Jarisch-Herxheimer reaction is sometimes seen after initiating therapy: fever, rash, tachycardia after first dose of antibiotic (more commonly seen in syphilis, another spirochaetal disease)

September 2013 exam: **H/O returning from a camping holiday in the New Forest. C/O lethargy, arthralgia, rash consistent with erythema chronicum migrans. What is the most appropriate test to perform given the likely diagnosis? ELISA test for antibodies to *Borrelia burgdorferi***

Lymphadenopathy

There are many causes of generalised lymphadenopathy

Infective

- infectious mononucleosis
- HIV, including seroconversion illness
- eczema with secondary infection
- rubella
- toxoplasmosis
- CMV
- tuberculosis
- roseola infantum

Neoplastic

- leukaemia
- lymphoma

Others

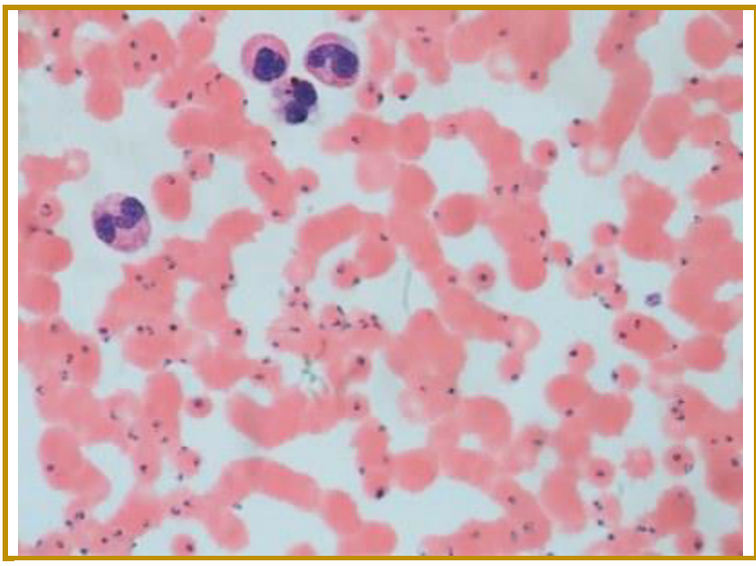
- autoimmune conditions: SLE, rheumatoid arthritis
- graft versus host disease
- sarcoidosis
- **drugs: phenytoin and to a lesser extent allopurinol, isoniazid**

Malaria

Malaria: Falciparum

Severe falciparum malaria - intravenous artesunate

- *P. falciparum* typically presents **within the first three months** of return from an endemic area.



In the slide shown, the blood film shows ring forms within erythrocytes; some erythrocytes contain two to three parasites per cell - **typical of falciparum**; other forms of malaria seldom have more than one parasite per red cell.

Feature of severe malaria

- schizonts on a blood film
- parasitaemia > 2%
- hypoglycaemia
- acidosis
- temperature > 39 C
- severe anaemia
- complications as below
- **Complications**
  - cerebral malaria: seizures, coma
  - acute renal failure: blackwater fever, secondary to intravascular haemolysis, mechanism unknown
  - acute respiratory distress syndrome (ARDS) → (**Respiratory rate 30 per minute**)
  - hypoglycaemia
  - disseminated intravascular coagulation (DIC)

Uncomplicated falciparum malaria

- strains resistant to chloroquine are prevalent in certain areas of Asia and Africa
- the 2010 WHO guidelines recommend artemisinin-based combination therapies (ACTs) as first-line therapy
- examples include artemether plus lumefantrine, artesunate plus amodiaquine, artesunate plus mefloquine, artesunate plus sulfadoxine-pyrimethamine, dihydroartemisinin plus piperaquine

Severe falciparum malaria

- a parasite counts of more than **2%** will usually need parenteral treatment irrespective of clinical state
- **Hyperparasitemia**, where **more than 5%** of the red blood cells are infected by malaria parasites
  - In 2010, WHO defined hyperparasitemia as >2%/100 000/μL in low intensity transmission areas or >5% or 250 000/μL in areas of high stable malaria transmission intensity.

- intravenous artesunate is now recommended by WHO in preference to intravenous quinine
  - I.V quinine is reserved for severe or cerebral malaria (most deaths from *M. falciparum* occur in first 96 hours of starting treatment).
  - The initial dose should NOT be reduced in those severely ill with renal/hepatic impairment.
  - High doses of quinine in pregnancy are teratogenic in the first trimester. However in malaria, the benefit of treatment outweighs the risk.
  - WHO Guidelines (2006) recommend artemisinins are first line in the second and third trimester. In the first trimester, both artesunate and quinine are considered treatment options.
  - **Hypoglycaemia is an important side effect of quinine**
    - Quinine → ↑ insulin secretion and the sensitivity of cells to insulin → hypoglycaemia
    - Malaria itself can cause hypoglycaemia too, so blood glucose should be monitored every 2 h.
- if parasite count > 10% then exchange transfusion should be considered
- shock may indicate coexistent bacterial septicaemia - malaria rarely causes haemodynamic collapse

Malaria: non-falciparum

Non-falciparum malarias are almost always chloroquine sensitive

- The **most common cause of non-falciparum malaria is *Plasmodium vivax***, with *Plasmodium ovale* and *Plasmodium malariae* accounting for the other cases.
- *Plasmodium vivax* is often found in Central America and the Indian Subcontinent whilst *Plasmodium ovale* typically comes from Africa
- **The Duffy antigen on RBCs acts as a receptor for *P. vivax*. → facilitate the entry of P. vivax in to RBCs.**
  - Duffy negative individuals are therefore resistant to this strain
  - West Africans lack the Duffy blood group and therefore *P. ovale* replaces *P. vivax* in this region.
- Both *P. vivax* and *P. ovale* have a liver hypnozoite stage which can cause repeated relapses.
  - May present **six months** after return from an endemic area

Features

- fever,
  - *Plasmodium vivax/ovale*: cyclical fever every 48 hours.
  - *Plasmodium malariae*: cyclical fever every 72 hours
- headache,
- splenomegaly
- ***Plasmodium malariae*: is associated with nephrotic syndrome**

Investigations

- ***Plasmodium ovale*,**
  - **all stages of the parasite and not just trophozoites and gametocytes are visible in the peripheral blood.**
- In *P. falciparum* malaria, only trophozoite-ring forms and gametocytes are usually seen.

Treatment

- non-falciparum malarias are almost always chloroquine sensitive
- patients with ovale or vivax malaria should be given primaquine following acute treatment with chloroquine to destroy liver hypnozoites and prevent relapse.
  - all individuals should be screened for glucose-6-phosphate dehydrogenase (G6PD) deficiency, as primaquine may cause haemolysis in those without the enzyme.

fast-acting	intermediate-acting	slow-acting
high-efficacy blood schizonticides that may be effective as monotherapy		low-efficacy schizonticides that normally need to be administered in combination.
Artemesinin Mepacrine	Quinine Mefloquine	**Pyrimethamine** Doxycycline is also a very slow-acting antimalarial.

Pyrimethamine

- used in the treatment of uncomplicated malaria, particularly for chloroquine-resistant *P. falciparum*.
- It acts on both the erythrocytic and hepatic phases of infection.
- It inhibits dihydrofolate reductase in the parasite thus preventing the biosynthesis of purines and pyrimidines, and thereby halting the processes of DNA replication, cell division and reproduction.
- It is normally used alongside a sulfonamide.

Malaria: prophylaxis

- There are around 1,500-2,000 cases each year of malaria in patients returning from endemic countries.
- The majority of these cases (around 75%) are caused by the potentially fatal *Plasmodium falciparum* protozoa.
- The majority of patients who develop malaria did not take prophylaxis.
- It should also be remembered that UK citizens who originate from malaria endemic areas quickly lose their innate immunity.

Drug	Side-effects + notes	Time to begin before travel	Time to end after travel
Atovaquone + proguanil (Malarone)	**GI upset**	**1 - 2 days**	**7 days**
Chloroquine	Headache Contraindicated in epilepsy Taken weekly	1 week	4 weeks
Doxycycline	**Photosensitivity Oesophagitis**	**1 - 2 days**	**4 weeks**
Mefloquine (Lariam)	Dizziness Neuropsychiatric disturbance Contraindicated in epilepsy Taken weekly	2 - 3 weeks	4 weeks
Proguanil (Paludrine)		1 week	4 weeks
Proguanil + chloroquine	See above	1 week	4 weeks

- **In certain parts of South-East Asia there is widespread chloroquine resistance. Chemoprophylaxis using atovaquone + proguanil (Malarone), mefloquine (Lariam) or doxycycline is therefore recommended.**
- Pregnant women should be advised to avoid travelling to regions where malaria is endemic. Diagnosis can also be difficult as parasites may not be detectable in the blood film due to placental sequestration. However, if travel cannot be avoided:
  - chloroquine can be taken
  - proguanil: folate supplementation (5mg od) should be given
  - Malarone (atovaquone + proguanil): the BNF advises to avoid these drugs unless essential. If taken then folate supplementation should be given
  - mefloquine: caution advised
  - doxycycline is contraindicated
- It is again advisable to avoid travel to malaria endemic regions with children if avoidable. However, if travel is essential then children should take malarial prophylaxis as they are more at risk of serious complications.
  - diethyltoluamide (DEET) 20-50% can be used in children over 2 months of age
  - doxycycline is only licensed in the UK for children over the age of 12 years

May 2013 exam: H/O vivax malaria treated initially with chloroquine then later given primaquine. What is the benefit of the primaquine? Destroy liver hypnozoites and prevent relapse

May 2014 exam: A 25-year-old man with a history of epilepsy presents for advice regarding malarial prophylaxis. Next month he plans to travel to Vietnam. What is the most appropriate medication to prevent him developing malaria? Atovaquone + proguanil

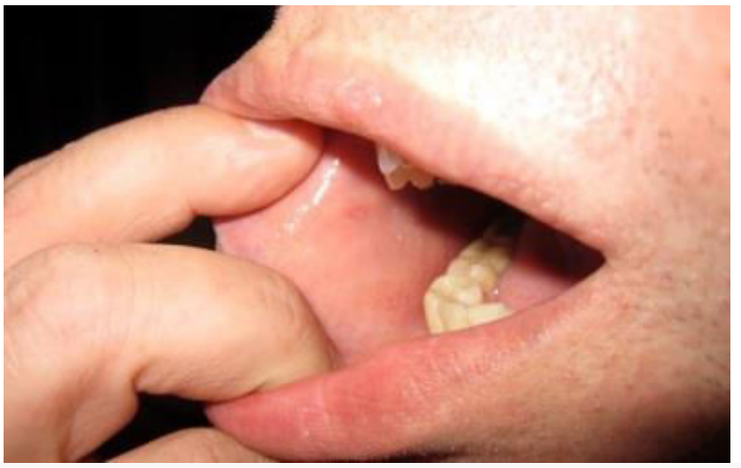
Measles

Overview

- RNA paramyxovirus
- spread by droplets
- infective from prodrome until 4 days after rash starts
- incubation period = 10-14 days

Features

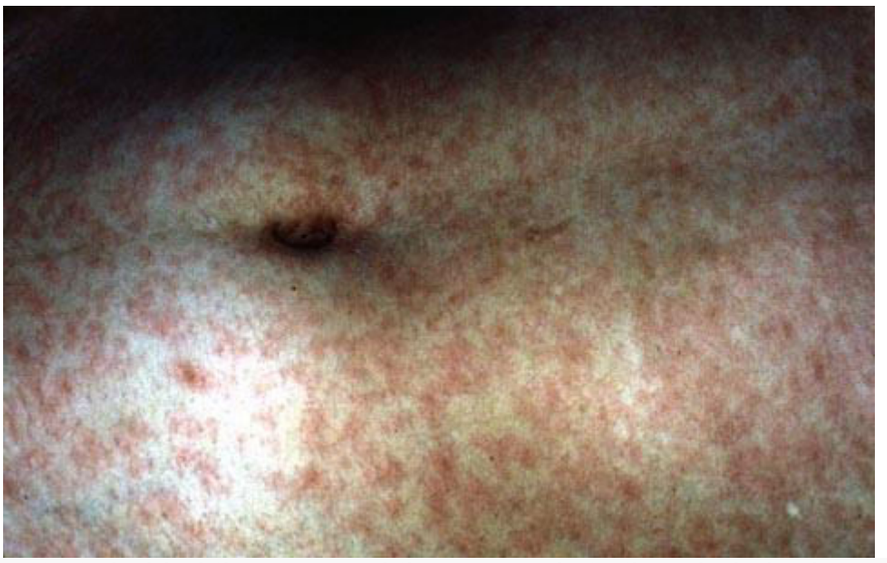
- prodrome: irritable, conjunctivitis, fever
  - **Patients present with the three C's: cough, coryza, and conjunctivitis.**
  - Rash usually develops on the head and torso, typically sparing the wrists and hands.
- Koplik spots (before rash): white spots ('grain of salt') on buccal mucosa
  - Koplik's spots are small, irregular, bright red spots with blue-white centres, occurring on the inside of the cheek next to the premolars.Seen only in measles, they are diagnostic.
  - The spots usually occur briefly after the fever begins and a couple of days before the generalised rash appears.
  - Not infrequently, the spots disappear as the eruption develops.
- rash: starts behind ears then to whole body, discrete maculopapular rash becoming blotchy & confluent



Koplik spots

Complications

- encephalitis: typically occurs 1-2 weeks following the onset of the illness)
- subacute sclerosing panencephalitis: very rare, may present 5-10 years following the illness
- febrile convulsions
- giant cell pneumonia
- keratoconjunctivitis, corneal ulceration
- diarrhoea
- increased incidence of appendicitis
- myocarditis



The rash typically starts behind the ears and then spreads to the whole body

Management of contacts

- if a child not immunized against measles comes into contact with measles then MMR should be offered (vaccine-induced measles antibody develops more rapidly than that following natural infection)
- this should be given within 72 hours

Rubella

- also known as german measles.
- RNA virus , part of the togavirus family
  - **rubella** has **positive single-stranded RNA**.
  - **rubeola virus (measles)** contains **negative** single-stranded RNA
- affects unimmunized children and presents with a rash that begins at the head and moves down with postauricular lymphadenopathy.

- **A positive rubella haemagglutination inhibition (HAI) combined with a negative rubella IgM** is consistent with:
  1. **Early acute infection with rubella**
     - **The IgM may take several days to rise and the test should be repeated one to two weeks later.**
  2. Previous vaccination, or
  3. Previous rubella infection.

Meningitis

Causes

The most common cause of bacterial meningitis is Streptococcus pneumoniae (Gram positive diplococci), accounting for >50% cases.
Listeria is a less common Gram positive cause of meningitis.

0 - 3 months	3 months - 6 years	6 years - 60 years	> 60 years	Immunosuppressed
Group B *Streptococcus* (most common cause in neonates)	*Neisseria meningitides*	*Neisseria meningitides*	***Streptococcus pneumoniae***	***Listeria*** *monocytogenes*
E. coli	*Streptococcus pneumoniae*	*Streptococcus pneumoniae*	*Neisseria meningitides*	
Listeria monocytogenes	*Haemophilus influenzae*		***Listeria*** *monocytogenes*	

Coxsackie virus is the most common viral cause of meningitis.

Pneumococcal meningitis

- caused by the Gram positive coccus *Strep. pneumoniae*.
- the second commonest cause of bacterial meningitis (commonest in the elderly)
- associated with the highest mortality (20%) and highest morbidity, such as deafness which may occur in 50% **(Nerve deafness is a common complication)**
- Chronic adhesive arachnoiditis is a complication of pneumococcal meningitis characterized by fibrosis of the arachnoid granulations.
- Contacts do not require treatment
- there is no rash associated with pneumococcal meningitis.

In the context of septic meningitis, **the petechial rash is diagnostic for infection with Neisseria meningitidis**

Listeria meningitis

- **Risk factors for listeria meningitis include**
  - neonates
  - Older age
  - immunosuppression.
- It is typically associated with brain stem signs.
- **Beta-hemolysis** is the type of hemolysis exhibited by *Listeria monocytogenes*, an organism showing tumbling motility that causes meningitis in newborns.

- Cerebrospinal fluid shows:
  - Neutrophilic pleocytosis
  - Low glucose, and
  - High protein.

Fungal meningitis

- Patients at risk for fungal **meningitis** include:
  - those who are significantly immunocompromised,
  - **those who have received intrathecal injections in the past.**
- Cerebrospinal fluid analysis
  - elevated opening pressure
  - detectable b-D-glucan
- **Testing for b-D-glucan has been an approved blood test to detect systemic fungal infection.**

Partially treated bacterial meningitis

Partial treatment of bacterial meningitis can result in **false negative CSF culture** and **Gram stain**, but **the CSF white cell count should be unaffected.**

- The assessment of children with suspected bacterial meningitis who have already received antibiotic therapy from their GP is a common diagnostic problem.
- Partial treatment may reduce the incidence of positive CSF Gram stains to less than 60%, and it also reduces the ability to grow the bacteria, particularly meningococcus.
  - Partial treatment may induce:
    - negative CSF culture
    - negative Gram stain
- CSF glucose, protein, neutrophils and bacterial antigen testing or polymerase chain reaction (PCR) should be completely unaffected.
- **A normal white cell count would make the diagnosis very unlikely.**
- In normal CSF the glucose is usually > 65% of blood glucose.

Meningitis: Investigations

- **Investigations suggested by NICE**
  - full blood count
  - CRP
  - coagulation screen
  - blood culture
  - whole-blood PCR
  - blood glucose
  - blood gas
  - Lumbar puncture if no signs of raised intracranial pressure

Meningitis: CSF analysis

Mumps meningitis is associated with a low CSF glucose

The table below summarises the characteristic cerebrospinal fluid (CSF) findings in meningitis:

	Bacterial	Viral	Tuberculous
Appearance	Cloudy	Clear/cloudy	Slight cloudy, fibrin web
Glucose	Low (< 1/2 plasma)	60-80% of plasma glucose*	Low (< 1/2 plasma)
Protein	High (> 1 g/l)	Normal/raised	High (> 1 g/l)
White cells	10 - 5,000 polymorphs/mm³	15 - 1,000 lymphocytes/mm³	10 - 1,000 lymphocytes/mm³

*mumps is unusual in being associated with a low glucose level in a proportion of cases. A low glucose may also be seen in herpes encephalitis

- The Ziehl-Neelsen stain is only 20% sensitive in the detection of tuberculous meningitis and therefore PCR is sometimes used (sensitivity = 75%)
- **Bacterial culture of cerebrospinal fluid** is the **gold-standard** test for determining if a case of **meningitis** is bacterial in etiology.

The CSF lymphocytosis combined with a glucose greater than half the serum level points towards a viral meningitis.

Management

In patients presenting with symptoms and signs of meningitis, treat empirically for bacterial meningitis while awaiting test results from the lumbar puncture.

- All patients should be transferred to hospital urgently.
- If patients are in a pre-hospital setting (for example a GP surgery) and meningococcal disease is suspected then intramuscular benzylpenicillin may be given, as long as this doesn't delay transit to hospital.
- **In bacterial meningitis, dexamethasone should also be given with the first dose of antibiotics**.

BNF recommendations on antibiotics

Scenario	BNF recommendation
Initial empirical therapy aged < 3 months	Intravenous cefotaxime + amoxicillin
Initial empirical therapy aged 3 months - 50 years	Intravenous cefotaxime
Initial empirical therapy aged > 50 years	**Intravenous cefotaxime + amoxicillin**
Meningococcal meningitis	Intravenous benzylpenicillin or cefotaxime
Pneuomococcal meningitis	Intravenous cefotaxime
Meningitis caused by *Haemophilus influenzae*	Intravenous cefotaxime
Meningitis caused by Listeria	Intravenous amoxicillin + gentamicin

- **If the patient has a history of immediate hypersensitivity reaction to penicillin or to cephalosporins the BNF recommends using chloramphenicol.**

- **Ceftriaxone does not cover *Listeria* well, and in the over 60s or immunosuppressed, amoxicillin should be added in to empirical meningitis management to cover this.**

Management of contacts

- prophylaxis needs to be offered to household and close contacts of patients affected with meningococcal meningitis
- oral ciprofloxacin or rifampicin may be used.
  - The BNF recommends a twice a day dose of rifampicin for two days, based on the patients weight.
  - The Health Protection Agency (HPA) guidelines now state that whilst either may be used **ciprofloxacin is the drug of choice as it is widely available and only requires one dose**
  - **Rifampicin may reduce the efficacy of the oral contraceptive through liver enzyme induction. So not preferred in sexually active. Therefore ciprofloxacin would be the most appropriate agent as it does not induce cytochrome p450.**
- the risk is highest in the first 7 days but persists for at least 4 weeks
- meningococcal vaccination should be offered to close contacts when serotype results are available, including booster doses to those who had the vaccine in infancy
- **for pneumococcal meningitis no prophylaxis is generally needed.** There are however exceptions to this. If a cluster of cases of pneumococcal meninigitis occur the HPA have a protocol for offering close contacts antibiotic prophylaxis.

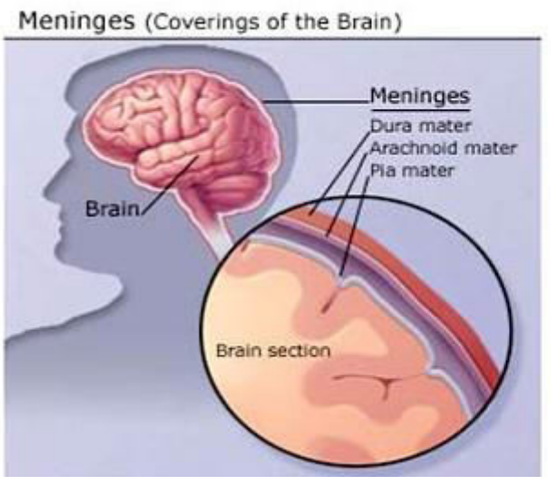
September 2010 exam. A 57-year-old female presents with headache, fever, neck stiffness with a positive Kernig's sign. CSF culture: Gram positive bacilli. ***What is the most likely causative organism?*** ***Listeria monocytogenes***

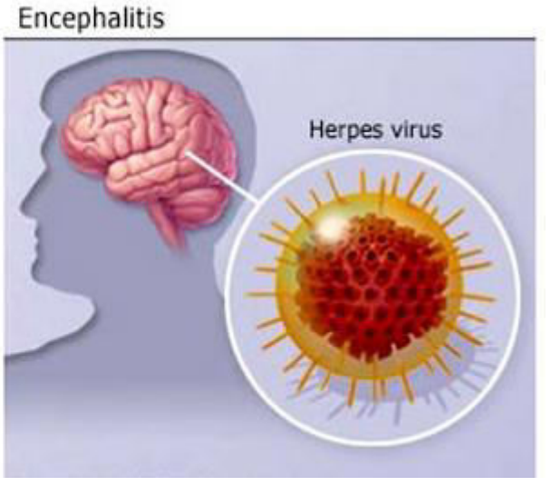
January 2013 exam: A 47-year-old lady with Feature of fever, headache and nuchal rigidity. Lumbar puncture reveals: Appearance: Cloudy. Glucose:1.7 mmol/l. Protein:1.9 g/l. White cells: 900 / mm³ (90% polymorphs). What is the most likely infective agent? ***Streptococcus pneumoniae*** (CSF →results bacterial meningitis (low glucose, high protein, high polymorphs). In this age group Streptococcus pneumoniae and Neisseria meningitidis are the most common causes of bacterial meningitis)

May 2014 exam: A diagnosis of pneumococcal meningitis is made. There are no other reports of meningitis in the local area over the past 4 weeks. How should the close contacts of this boy be managed? No action is needed (unless cluster of cases develop)

May 2009 exam: A 23-year-old man is admitted with purpuric rash, pyrexia and confusion. His GP had given him intramuscular benzylpenicillin. Which one of the following investigations is most likely to reveal the diagnosis? Blood PCR for meningococcus
(The blood cultures are likely to be negative as antibiotics have already been given. PCR has a sensitivity of over 90%)

Encephalitis





Encephalitis usually presents with altered mental status, erratic behavior, etc (brain parenchyma involved).

Etiology.
- The most common cause is herpes simplex, usually type I (HSV-1).

Clinical Presentation.
- Altered mental status with fever and headache is the primary clue to the diagnosis.
- Neck stiffness similar to that found in meningitis can occur, making it difficult to distinguish encephalitis from meningitis.
- Seizures may also occur.

Diagnosis.
- Although CT or MRI scan of the head should be performed, it cannot give a specific diagnosis. HSV has a predilection for involvement of the temporal lobes, which can sometimes be seen on CT.
- A lumbar puncture is the key to the diagnosis.
- PCR (polymerase chain reaction) for HSV has a 98% sensitivity and >95% specificity, making it at least equal to the biopsy.

Treatment.
- HSV encephalitis is best treated with IV acyclovir.
- Acyclovir-resistant herpes is treated with foscarnet

Meningococcal septicaemia

- It is associated with a high morbidity and mortality unless treated early
- meningococcal disease is the leading infectious cause of death in early childhood.
- A high index of suspicion is therefore needed.

Presentation of meningococcal disease:
- 15% - meningitis
- 25% - septicaemia
- 60% - a combination of meningitis and septicaemia

Investigations
- blood cultures
- blood PCR
- lumbar puncture is usually contraindicated
- full blood count and clotting to assess for disseminated intravascular coagulation

management
- **the most important initial step → administration of intravenous antibiotics (cefotaxime) is the greatest priority, regardless of whether cultures have been sent.**

Sepsis (Nice guidelines 2016)

- Sepsis is a life-threatening organ dysfunction due to a dysregulated host response to infection.
- Sepsis with shock is a life-threatening condition that is characterised by low blood pressure despite adequate fluid replacement, and organ dysfunction or failure.

Definition

- The new definition attempts to draw upon up-to-date pathobiology and distinguish between sepsis and uncomplicated infection. A new tool has been developed for this purpose - the SOFA or qSOFA.
  - The qSOFA (Quick SOFA) criteria are:
    - Respiratory rate > or equal to 22/min
    - Altered GCS
    - Systolic blood pressure < or equal to 100mmHg
- Septic shock is defined as "a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality. This changes from the previous definition to recognise the importance of cellular abnormalities.
- Septic shock is defined by persisting hypotension requiring vasopressors to maintain a mean arterial pressure of 65 mm Hg or higher and a serum lactate level greater than 2 mmol/L (18 mg/dL) despite adequate volume resuscitation.

Risk factors for sepsis

- Age (< 1 year and > 75 years)
- very frail people
- Immunocompromised
  - impaired immune function (eg, DM, splenectomy, sickle cell disease)
  - drugs(long-term steroids, chemotherapy, immunosuppressant)
- surgery, or other invasive procedures, in the past 6 weeks
- any breach of skin integrity (eg, cuts, burns, blisters or skin infections)
- misuse drugs intravenously
- indwelling lines or catheters

Risk stratification tool for adults, children and young people aged 12 years and over with suspected sepsis

High risk criteria	Moderate to high risk criteria
Objective evidence of new altered mental state	• History from patient or relative of new onset of altered behaviour or mental state • History of acute deterioration of functional ability • Impaired immune system (illness or drugs including oral steroids) • Trauma, surgery or invasive procedures in the last 6 weeks
• respiratory rate: ≥ 25 breaths per minute • New need for oxygen (more than 40% FiO_2) to maintain saturation more than 92% (or more than 88% in known chronic obstructive pulmonary disease)	Raised respiratory rate: 21–24 breaths per minute
Systolic blood pressure ≤ 90 mmHg or more than 40 mmHg below normal	Systolic blood pressure 91–100 mmHg
heart rate: > 130 beats per minute	heart rate: 91–130 beats per minute (for pregnant women 100–130 beats per minute) or new onset arrhythmia
Not passed urine in previous 18 hours. For catheterised patients, passed less than 0.5 ml/kg of urine per hour	Not passed urine in the past 12–18 hours For catheterised patients, passed 0.5–1 ml/kg of urine per hour
-	Tympanic temperature less than 36°C
• Mottled or ashen appearance • Cyanosis of skin, lips or tongue • Non-blanching rash of skin	Signs of potential infection, including redness, swelling or discharge at surgical site or breakdown of wound.

Low risk criteria:

- Normal behavior
- No high risk or moderate to high risk criteria met

Temperature in suspected sepsis

- Do not rely on fever or hypothermia to rule sepsis either in or out.
- Some people with sepsis may not develop a raised temperature:
  - older or very frail
  - severely ill
  - people having treatment for cancer
  - young infants or children.
- a rise in temperature can be a physiological response (eg: after surgery or trauma).

Heart rate in suspected sepsis

- baseline heart rate may be lower in young people and adults who are fit
- baseline heart rate in pregnancy is 10–15 beats per minute more than normal
- older people with an infection may not develop an increased heart rate
- older people may develop a new arrhythmia in response to infection rather than an increased heart rate
- may be affected by medicines such as beta-blockers.

Management

1 or more high risk criteria:

- **blood test** for blood gas including glucose and lactate measurement, blood culture, full blood count, C-reactive protein, urea and electrolytes, creatinine, clotting screen.
  - **Sepsis may be complicated by disseminated intravascular coagulation**

- give a broad-spectrum antimicrobial at the maximum recommended dose without delay (within 1 hour)

any high risk criteria and lactate > 4 mmol/litre, or systolic BP < 90 mmHg:

- I.V fluid bolus without delay (within 1 hour)
- refer to critical care for review of management including need for central venous access , inotropes or vasopressors.

any high risk criteria and lactate between 2 and 4 mmol/litre:

- I.V fluid bolus without delay (within 1 hour)

any high risk criteria and lactate < 2 mmol/litre:

- consider I.V fluid bolus

failure to respond within 1 hour of initial antibiotic and/or intravenous fluid resuscitation

- **Failure to respond is indicated by any of:**
  - systolic blood pressure persistently below 90 mmHg
  - reduced level of consciousness despite resuscitation
  - respiratory rate over 25 breaths per minute or a new need for mechanical ventilation
  - lactate not reduced by more than 20% of initial value within 1 hour.

2 or more moderate to high risk criteria

- blood test for blood gas including glucose and lactate measurement, blood culture, full blood count, C-reactive protein, urea and electrolytes, creatinine
- review the person's condition and venous lactate results within 1 hour

2 or more moderate to high risk criteria and lactate > 2 mmol/litre or evidence of acute kidney injury

- treat as high risk

2 or more moderate to high risk criteria, have lactate < 2 mmol/litre, no evidence of acute kidney injury and in whom a definitive condition cannot be identified:

- repeat structured assessment at least hourly
- review by a senior within 3 hours for consideration of antibiotics.

2 or more moderate to high risk criteria, have lactate < 2 mmol/litre, no evidence of acute kidney injury and in whom a definitive condition or infection can be identified and treated:

- manage the definitive condition
- if appropriate, discharge

Intravenous fluids in people with suspected sepsis

- If patients over 16 years need intravenous fluid resuscitation, use crystalloids that contain sodium in the range 130–154 mmol/litre with a bolus of **500 ml over less than 15 minutes.**

management

- The Surviving Sepsis Campaign (a partnership of the Society of Critical Care Medicine, the European Society of Intensive Care Medicine, and the International Sepsis Forum) has teamed up with the Institute for Healthcare Improvement to develop severe sepsis bundles. A 'bundle' is a group of interventions related to a disease process that, when executed together, result in better outcomes than when implemented individually.

<u>Sepsis Resuscitation Bundle:</u>

- Should begin immediately, but must be accomplished within the first six hours of presentation.
  1. Serum lactate measured.
  2. **Blood cultures obtained prior to antibiotic administration.**
  3. From the time of presentation, broad-spectrum antibiotics administered within three hours for ED admissions and one hour for non-ED ICU admissions.
  4. In the event of hypotension and/or lactate > 4 mmol/l (36 mg/dl):
     - Deliver an initial minimum of 30 ml/kg of crystalloid (or colloid equivalent).

- Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) > 65 mm Hg.

5. In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate > 4 mmol/l (36 mg/dl):
   - Achieve central venous pressure (CVP) of > 8 mm Hg.
   - Achieve central venous oxygen saturation (ScvO2) of > 70%.

Sepsis Management Bundle:

To be accomplished as soon as possible may be completed within twenty-four hours of presentation.

1. **Steroids administered for septic shock** in accordance with a standardised ICU policy. ACTH stimulation test not required prior to this.
2. Glucose control maintained > lower limit of normal, but < 150 mg/dl (8.3 mmol/l).
3. Inspiratory plateau pressures maintained < 30 cm H2O for mechanically ventilated patients.

H/O sepsis secondary to pneumonia. treated with 4.5 L sodium chloride 0.9%. blood pressure was 82/40 mmHg. In attempting to restore the blood pressure, what is the most appropriate intravenous therapy?

➔ **noradrenaline (norepinephrine)**

Ref: www.mrcpuk.org/ Acute Medicine Specialty Certificate Examination/ sample questions

Nematodes

- **most common cause of cutaneous larva migrans → Ancylostoma braziliense**
- **commonest cause of visceral larva migrans → Toxocara canis**

Ancylostoma braziliense

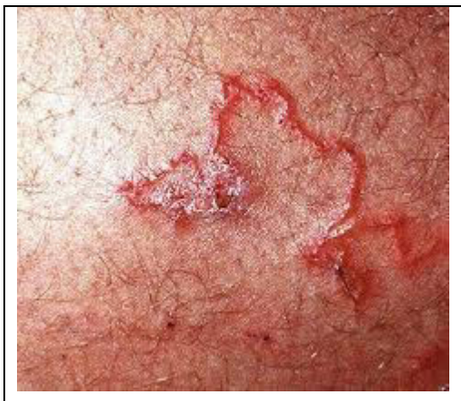
- **most common cause of cutaneous larva migrans**
- common in Central and Southern America
- The infection is acquired by direct contact with dog or cat faeces - often acquired when sunbathing on contaminated sand, etc. The larvae burrow in the dermo-epidermal junction.
- **Symptoms** include pruritus and a raised, serpiginous erythematous rash that migrates at a rate of up to 1 cm/day.
- **Treatment** i
  - The disease is self-limiting but the duration of disease varies considerably
  - **Oral ivermectin** in a single dose of 200 µg/kg body weight is the main treatment.
  - Other treatment options include oral albendazole or topical thiabendazole.

Strongyloides stercoralis

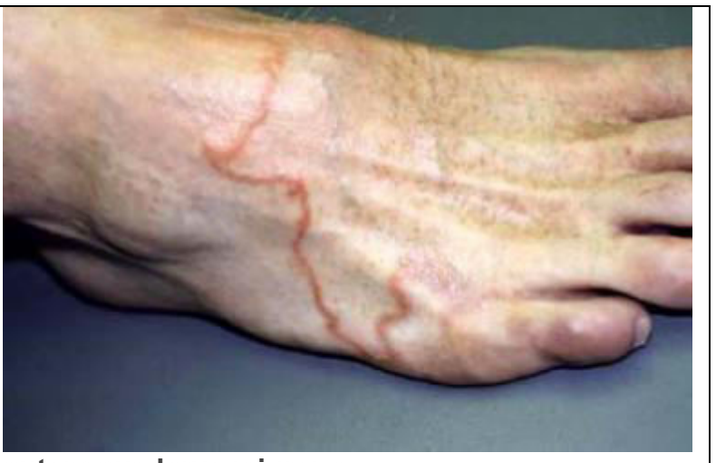
- acquired percutaneously (e.g. walking barefoot)
- causes pruritus and larva currens - this has a similar appearance to cutaneous larva migrans but moves through the skin at a far greater rate
- abdo pain, diarrhoea, pneumonitis
- may cause Gram negative septicaemia due carrying of bacteria into bloodstream
- eosinophilia sometimes seen
- management: thiabendazole, albendazole. Ivermectin also used, particularly in chronic infections

Toxocara canis

- commonly acquired by ingesting eggs from soil contaminated by dog faeces
- **commonest cause of visceral larva migrans**
- other features: eye granulomas, liver/lung involvement



cutaneous larva migrans



cutaneous larva migrans

Orf

Orf is generally a condition found in sheep and goats although it can be transmitted to humans. It is caused by the **parapox virus.**

In animals

- 'scabby' lesions around the mouth and nose

In humans

- generally affects the hands and arms
- initially small, raised, red-blue papules
- later may increase in size to 2-3 cm and become flat-topped and haemorrhagic

Pelvic inflammatory disease

Pelvic inflammatory disease (PID) is a term used to describe infection and inflammation of the female pelvic organs including the uterus, fallopian tubes, ovaries and the surrounding peritoneum. It is usually the result of ascending infection from the endocervix

Causative organisms

- *Chlamydia trachomatis* - the most common cause
- *Neisseria gonorrhoeae*
- *Mycoplasma genitalium*
- *Mycoplasma hominis*

Features

- lower abdominal pain
- fever
- deep dyspareunia
- dysuria and menstrual irregularities may occur
- vaginal or cervical discharge
- cervical excitation

Investigation

- screen for Chlamydia and Gonorrhoea

Management

- due to the difficulty in making an accurate diagnosis, and the potential complications of untreated PID, consensus guidelines recommend having a low threshold for treatment

- Consensus guidelines recommend treatment once a diagnosis of pelvic inflammatory disease is suspected, rather than waiting for the results of swabs
- oral **ofloxacin + oral metronidazole** or intramuscular ceftriaxone + oral doxycycline + oral metronidazole
- RCOG guidelines suggest that in mild cases of PID intrauterine contraceptive devices may be left in. The more recent BASHH guidelines suggest that the evidence is limited but that *' Removal of the IUD should be considered and may be associated with better short term clinical outcomes'*

Complications

- infertility - the risk may be as high as 10-20% after a single episode
- chronic pelvic pain
- ectopic pregnancy
- **Fitz-Hugh-Curtis syndrome**
  - is a rare complication of pelvic inflammatory disease, resulting in liver capsule inflammation.
  - It is most often caused by untreated sexually transmitted infections including *Chlamydia trachomatis* and *Neisseria gonorrhoeae*.
  - a patient may present with septic shock secondary to the untreated liver capsule infection.

Psittacosis (ornithosis)

- *Chlamydia psittaci* is endemic in birds including psittacine birds, canaries, finches, pigeons and poultry.
- Pet owners, vets and zoo keepers are most at risk. It is rare in children.
- **Person to person transmission occurs** especially in a hospital environment.
- Sputum Gram stain reveals a few leucocytes and no predominant bacteria.
- There are few signs and few laboratory/x ray findings.
- Positive serology is with complement-fixing antibodies.
- It is treated with tetracycline.

Pyogenic liver abscess

- The most common organisms found in pyogenic liver abscesses are *Staphylococcus aureus* in children and ***Escherichia coli* in adults.**

Management

- **amoxicillin + ciprofloxacin + metronidazole**
- if penicillin allergic: ciprofloxacin + clindamycin

January 2008 exam: **What is the most appropriate antibiotic therapy to accompany drainage of liver abscess? Amoxicillin + ciprofloxacin + metronidazole**

Pyrexia of unknown origin

Defined as a prolonged fever of > 3 weeks which resists diagnosis after a week in hospital

Neoplasia

- lymphoma
- hypernephroma
- preleukaemia
- atrial myxoma

Infections

- abscess
- TB

Connective tissue disorders

Q fever

Q fever - *Coxiella burnetti*

- Q fever is a zoonotic disease caused by **Coxiella burnetii** an obligate gram-negative intracellular bacterium.
- The organism is very resistant to drying.
- does not grow on standard culture media.

Transmission

- **The organism is usually inhaled from infected dust** (animal products)
- acquired through contact with animals.
  - Cattle, sheep and goats are the primary reservoirs of *C. burnetii*.
- drinking unpasteurised milk from infected cows.

Risk factors

- It is not notifiable, but can occur in outbreaks in **farming communities** and in abattoirs. and therefore an **occupational history** is very important.

Features:

- high fevers, chills, sweats
- severe headache, (typically retrobulbar)
- general malaise, myalgia,
- confusion,
- sore throat, ,
- non-productive cough,
- nausea, vomiting, diarrhoea, abdominal pain
- chest pain.
- Between 30% and 50% of patients with a symptomatic infection will develop pneumonia.
- may be complicated by immune complex-mediated glomerulonephritis
- Chronic infection can manifest as hepatitis, osteomyelitis or endocarditis.
- In **Q fever endocarditis**:
  - the aortic valve is involved in over 80% of cases.
  - A murmur is not always present, but augmentation of an existing murmur may occur.
  - **Low-grade fever (or no fever**),
  - signs of heart failure,
  - hepatosplenomegaly,
  - clubbing,
  - arterial emboli,
  - **leukocytoclastic vasculitic rash**.

Diagnosis:

- Confirming a diagnosis of Q fever requires **serological testing** to detect the presence of C. burnetii.
  - phase I antibody titre to *Coxiella burnetti* (IgG and/or IgA) greater than 1:200 is virtually diagnostic of Q fever.
- chest X-ray might show multilobar consolidation.
- Anaemia
- Thrombocytopenia
- Elevated erythrocyte sedimentation rate
- Hypergammaglobulinaemia
- liver function tests
  - the majority of patients have abnormal results on and some will develop hepatitis.
- Microscopic haematuria may be present.

Treatment :

- Most patients will recover within a few months with no treatment.

- **Doxycycline** is the treatment of choice for acute Q fever. OR prolonged courses of **tetracyclines**.

Prognosis

- Only 1–2% of people with acute Q fever die of the disease.
- Chronic Q fever
  - Endocarditis with **negative culture** findings and **seropositivity** is the main clinical presentation of **chronic Q fever**,
    - usually occurring in patients with preexisting cardiac disease including valve defects, rheumatic heart disease, and prosthetic valves.

Rabies

Rabies - following possible exposure give immunglobulin + vaccination

Rabies is a viral disease that causes an acute encephalitis. The rabies virus is classed as a RNA rhabdovirus and has a bullet shaped capsid. It is commonly transmitted by bat, raccoon and skunk bites. Following a bite the virus travels up the nerve axons towards the central nervous system in a retrograde fashion.

Features

- prodrome: headache, fever, agitation
- hydrophobia: water-provoking muscle spasms
- hypersalivation
- Negri bodies: cytoplasmic inclusion bodies found in infected neurons

There is now considered to be 'no risk' of developing rabies following an animal bite in the UK and the majority of developed countries.

Following an animal bite in at risk countries:

- if an individual is already immunised then 2 further doses of vaccine should be given
- if not previously immunised then human rabies immunoglobulin (HRIG) should be given along with a full course of vaccination
- Lyssaviruses such as rabies **cannot cross intact skin** and humans are regarded as an end-host (outside of transplantation-associated transmission). **Therefore**, **only standard infection-prevention precautions such as gloves and gowns are required.**

Salmonella &(Typhoid fever)

Humans are the main reservoir for *Salmonella typhi*

Bacteriology

- **Gram negative rods**
- grow under both an **aerobic** and **anaerobic** conditions.
- not normally present as commensals in the gut.
- Incubation period
  - 5–30 days (most commonly 7–14 days)
- **Transmission**:
  - fecal-oral

Types

- *Salmonella typhi* causes Typhoid
- *Salmonella paratyphi* (types A, B & C) causes paratyphoid
  - They are often termed enteric fevers.

- Blood and bone **infections caused by non-typhi salmonella (NTS) are typically associated with malaria and homozygous sickle cell disease**, especially in children. The reason for this perceived susceptibility is not fully understood - but it may be in part due to the haemolysis and subsequent iron availability to the bacteria, which is 'siderophilic' in nature.

Pathophysiology

- **Lifecycle**
  1. Oral uptake of pathogen
  2. Distal ileum: migration into the Peyer patches
  3. Infection of macrophages and reticuloendothelial system → nonspecific symptoms
  4. Spread from macrophages to the bloodstream: septicemia → systemic disease
  5. Migrates back to intestine → excretion in feces

Typhoid vaccines

- typhoid vaccines are currently available
  - (Typhoid vaccine does not protect from paratyphoid infection)
- There are 3 types of typhoid vaccine:
  1. parenteral (Typh-I),→ inactivated vaccine (i.e. killed)
  2. parenteral combined with hepatitis A (HA-Typh-I), and
  3. oral (Typh-O) → **Live-attenuated vaccine**
- These vaccines provide approximately **50% protection** against clinical disease.
- No vaccine is available against paratyphoid fever.
- Vaccinated individuals who develop the disease will **have a higher threshold** but the **same disease.**

Features

- initially systemic upset (headache, fever, arthralgia)
- relative bradycardia
- abdominal pain, distension
- diarrhoeal disease
  - Yellow-green diarrhea, comparable to pea soup (caused by purulent, bloody necrosis of the Peyer patches)
- constipation:
  - **although *Salmonella* is a recognised cause of diarrhoea, constipation is more common in typhoid**
  - obstipation and ileus (as a result of swollen Peyer patches in the ileum)
- **Rose spots**:
  - present on the trunk in 40% of patients,
    - (most commonly around the navel) حول السرة
  - more common in paratyphoid
- Neurological symptoms (delirium, coma)
- Rarely causes sepsis, meningitis, myocarditis, and renal failure

Complication

- **Chronic Salmonella carrier**
  - Definition:
    - positive stool cultures 12 months after overcoming the disease
  - Incidence:
    - up to 6% of the patients become chronic carriers
  - Presentation:
    - typically asymptomatic
  - Treatment:
    - fluoroquinolones (e.g., ciprofloxacin) administered for at least 1 month
  - Chronic carriers are not allowed to work in the food industry.
  - Increased risk for cholangiocarcinoma (bile duct cancer)

Investigations:

- normal or low leukocyte count with **eosinopenia**
- Blood culture,
  - the most effective investigation for diagnosis

  - (should be done prior to starting antibiotic)
- Bone marrow culture
  - highly sensitive diagnostic test even in later stages of infection after antibiotic therapy has begun.
  - indicated for all patients with prolonged pyrexia if routine investigations have not provided a diagnosis.
- **in chronic carriers**
  - **Blood cultures** will be **negative** in chronic carriers because the organism resides mainly in the gallbladder.
  - **Salmonella typhi can be cultured from intestinal secretions, faeces or urine**
- Widal's test
  - Serological test
  - poor sensitivity
  - negative in early infection.
    - indicated only after 5 to 7 days of fever.
  - not useful for detecting chronic carriage.
- Faecal culture
  - positive in only 50% of cases during the first week of illness.

Complications

- osteomyelitis
  - (especially in sickle cell disease where *Salmonella* is one of the most common pathogens)
- GI bleed/perforation
- meningitis
- cholecystitis
- chronic carriage (1%)
  - **more likely if adult females**)

Treatment

- best treated with quinolones, chloramphenicol or cotrimoxazole.
- However, with breast feeding chloramphenicol is relatively contraindicated as are quinolones due to potential risk even if small.
- Also cotrimoxazole is safe in breast feeding except with infants less than 2 months due to possible risk of increased bilirubin.
- **In pregnancy or children the drug of choice is parenteral ceftriaxone.**
- The gallbladder may act as a reservoir of infection and cause relapse in individuals treated with antibiotics. Cholecystectomy may be indicated.
- According to the NICE guidelines, anyone above the age of 50, immunocompromised or has cardiac valve disease/endovascular abnormalities should be treating empirically with ciprofloxacin 500mg BD when they have been diagnosed with non-typhoidal *Salmonella* gastroenteritis.

Scabies

Scabies should be suspected in any sexually active young person who presents with generalised pruritus without any specific signs.

Overview

- Scabies is **caused by** the mite Sarcoptes scabiei and is **spread by** prolonged skin contact.
- It typically affects children and young adults.

Pathophysiology

- The scabies mite burrows into the skin, laying its eggs in the stratum corneum.

- The intense pruritus associated with scabies is due to a delayed type IV hypersensitivity reaction to mites/eggs which occurs about 30 days after the initial infection.

Features

- widespread pruritus
- linear burrows on the side of fingers, interdigital webs and flexor aspects of the wrist
  - The tiny erythematous burrows in the web spaces of the fingers are almost **pathognomonic**
- in infants the face and scalp may also be affected
- secondary features are seen due to scratching: excoriation, infection

Investigation

- **Skin scrapings →** demonstrate *Sarcoptes scabiei*

Management

- first-line is → permethrin 5%
- second-line is → malathion 0.5%
- Application should be repeated seven days after initial treatment to kill any mites hatched from eggs in that time
- give appropriate guidance on use (see below)
- pruritus persists for up to 4-6 weeks post eradication

Patient guidance on treatment (from Clinical Knowledge Summaries)

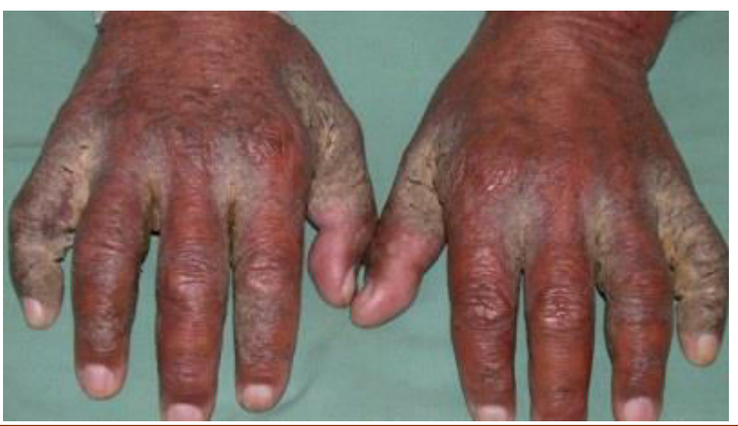
- avoid close physical contact with others until treatment is complete
- all household and close physical contacts should be treated at the same time, even if asymptomatic
  - **Re-infection most likely means → Other household members were not treated**
- launder, iron or tumble dry clothing, bedding, towels, etc., on the first day of treatment to kill off mites.

Patients should be given the following instructions:

- The BNF advises to apply the insecticide to all areas, including the face and scalp, contrary to the manufacturer's recommendation.
- apply the insecticide cream or liquid to cool, dry skin
- pay close attention to areas between fingers and toes, under nails, armpit area, creases of the skin such as at the wrist and elbow
- allow to dry and **leave on the skin for 8-12 hours for permethrin,** or **for 24 hours for malathion**, before washing off
- reapply if insecticide is removed during the treatment period, e.g. If wash hands, change nappy, etc
- repeat treatment 7 days later

Crusted (Norwegian) scabies

- **Crusted scabies** is seen in patients with **suppressed immunity, especially HIV**.
- The crusted skin will be teeming with hundreds of thousands of organisms.
- **Ivermectin** is the treatment of choice and isolation is essential



Schistosomiasis

Schistosoma haematobium causes haematuria

Schistosomiasis, or bilharzia, is a parasitic flatworm infection. The following types of schistosomiasis are recognised:

- Schistosoma mansoni and Schistosoma intercalatum: intestinal schistosomiasis
- Schistosoma haematobium: urinary schistosomiasis

Schistosoma haematobium

This typically presents as a 'swimmer's itch' in patients who have recently returned from Africa. Schistosoma haematobium is a risk factor for squamous cell bladder cancer

Features

- frequency
- haematuria
- bladder calcification

Management

- single oral dose of praziquantel

Complications:

- ***S. mansoni*** Eggs can migrate to liver through the portal venous system where they can elicit a granulomatous fibrosing reaction → venous blockade → Portal venous hypertension → varicies and upper GIT bleeding.
- ***S. haematobium*** leads to granulomatous inflammation, ulceration of the vesicle and ureteral walls. Subsequent fibrosis can cause bladder neck obstruction, hydroureter and hydronephrosis. These changes can cause a chronic renal impairment and predispose to secondary bacterial infection as well as squamous cell carcinoma.
- **all schistosome species** can result in immune complex deposition in the kidneys leading to a proteinuria and nephrotic syndrome.

Shigella

Overview

- causes bloody diarrhoea, abdo pain
- severity depends on type: S sonnei (e.g. from UK) may be mild, S flexneri or S dysenteriae from abroad may cause severe disease
- **treat with ciprofloxacin**

Splenectomy

- Following a splenectomy patients are particularly at risk from pneumococcus, Haemophilus, meningococcus and Capnocytophaga canimorsus* infections
  - *usually from dog bites

Vaccination

- if elective, should be done 2 weeks prior to operation
- Hib, meningitis A & C
- annual influenza vaccination
- pneumococcal vaccine every 5 years

Antibiotic prophylaxis

- penicillin V: unfortunately clear guidelines do not exist of how long antibiotic prophylaxis should be continued. It is generally accepted though that penicillin should be continued for at least 2 years and at least until the patient is 16 years of age, although the majority of patients are usually put on antibiotic prophylaxis for life

January 2011 exam: H/O emergency splenectomy. Following this he takes penicillin V on a daily basis. He is unsure of his vaccination history. Which organism is he particularly suscepitble to? *Haemophilus influenza* *(Penicillin V would protect him against Streptococcus pneumoniae but notHaemophilus influenzae due to the production of beta-lactamases by the organism)*

September 2009 exam: A 12-year-old boy who had a splenectomy following RTA , he had his full immunisation course as a child and was given a repeat pneumococcal vaccination 5 days following surgery. What is the most appropriate ongoing management? Booster dose of Hib and MenC vaccine + annual influenza vaccination + lifelong penicillin V

Strongyloides stercoralis

Strongyloides stercoralis is a human parasitic nematode worm. The larvae are present in soil and gain access to the body by penetrating the skin. Infection with *Strongyloides stercoralis* causes strongyloidiasis.

Features

- diarrhoea
- abdominal pain/bloating
- papulovesicular lesions where the skin has been penetrated by infective larvae e.g. soles of feet and buttocks
- larva currens: pruritic, linear, urticarial rash
- if the larvae migrate to the lungs a pneumonitis similar to Loeffler's syndrome may be triggered

Treatment

- ivermectin and albendazole are used

STI: ulcers

Genital ulcers

- painful: herpes much more common than chancroid
- painless: syphilis more common than lymphogranuloma venereum + granuloma inguinale

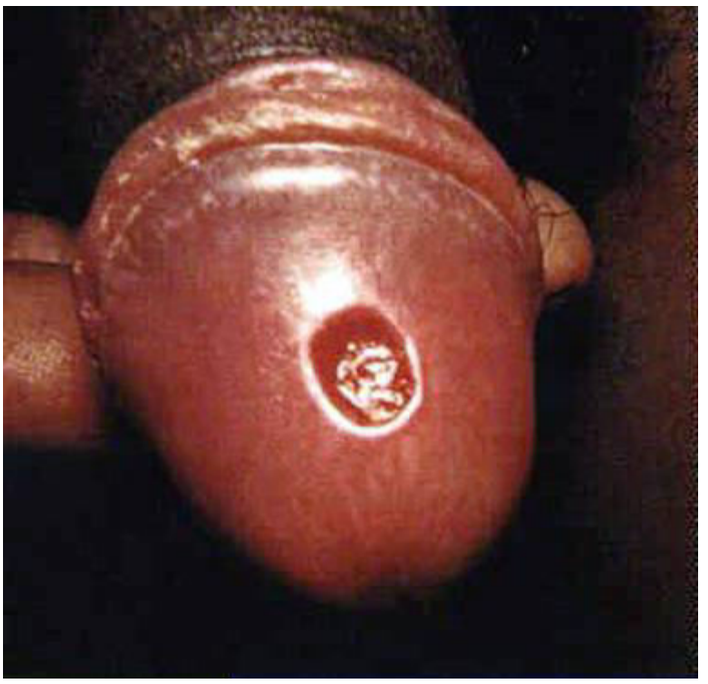
Genital herpes

- most often caused by the herpes simplex virus (HSV) type 2 (cold sores are usually due to HSV type 1).
- **Multiple painful penile vesicles and ulcers are characteristic.**
- Primary attacks are often severe and associated with fever whilst subsequent attacks are generally less severe and localised to one site.
- The lesions generally heal within 2 weeks.
- Recurrence of painful genital lesions is a characteristic.
- **Oral Acyclovir is the treatment of choice.**

Syphilis

- is a sexually transmitted infection caused by the spirochaete *Treponema pallidum*.
- Infection is characterised by primary, secondary and tertiary stages.
- A **painless ulcer** (chancre) is seen in the primary stage.
- The incubation period= 9-90 days
- Treatment
  - IM penicillin is the intervention of choice

- **In case of severe penicillin allergy, a single dose of (2 g) azithromycin is the preferred option because it is effective and doesn't raise compliance issues.**



primary chancre associated with syphilis

Chancroid

- is a tropical disease **caused by *Haemophilus ducreyi*.**
- It causes **painful genital ulcers** associated with unilateral, painful inguinal lymph node enlargement.
  - (Remember the saying: "You do cry with *ducreyi*".)
- The ulcers typically have a sharply defined, ragged, undermined border, which readily bleeds on contact.
- Treatment
  - Antibiotic treatment: single dose oral azithromycin or IM ceftriaxone
  - Examine and treat sexual partner(s).

Lymphogranuloma venereum (LGV)

- caused by *Chlamydia trachomatis*.
  - caused by infection with the L1, L2 or L3 serovars of *Chlamydia trachomatis*.
- It infects phagocytes rather than epithelium, which accounts for the rapid spread of infection to regional lymph nodes.
- The bacterium gains entry through breaches in the epithelial/mucous membranes, travelling through the lymphatics via macrophages to local nodes.
- Typically, infection comprises of three stages
  - stage 1: small painless pustule which later forms an ulcer. at the site of inoculation 3-12 days later.
  - stage 2: painful inguinal lymphadenopathy (Presents 1-6 months later).
    - Enlarged lymph nodes are known as buboes, they are often painful and can lead to thinning of the overlying skin causing abscesses.
    - Groove sign is separation inguinal nodes by the inguinal ligament and is characteristic of the disease.
  - stage 3: proctocolitis (if rectally, then tenesmus, proctocolitis, strictures and fistulas can ensue. Cervicitis and urethritis are also common features.)
- LGV is treated using doxycycline.
- Diagnosis is achieved by enzyme linked immunoassays or polymerase chain reaction of infected sample areas/pus. Acute and convalescent sera can be used, but requires two samples 2 weeks apart.
- **Treatment:**
  - Antibiotics either doxycycline or macrolides (azithromycin or erythromycin)
    - **the most appropriate intervention → Doxycycline for 21 days**

        - In patients where this is unsuitable, azithromycin is also thought to be effective.
    - surgical drainage/aspiration of the buboes or abscesses.
- Complications include: genital elephantiasis, hepatitis, infertility, pelvic inflammatory disease, arthritis and fitz hugh curtis syndrome.

Other causes of genital ulcers

- Behcet's disease
- carcinoma
- granuloma inguinale: *Klebsiella granulomatis* (previously called *Calymmatobacterium granulomatis*)

Syphilis

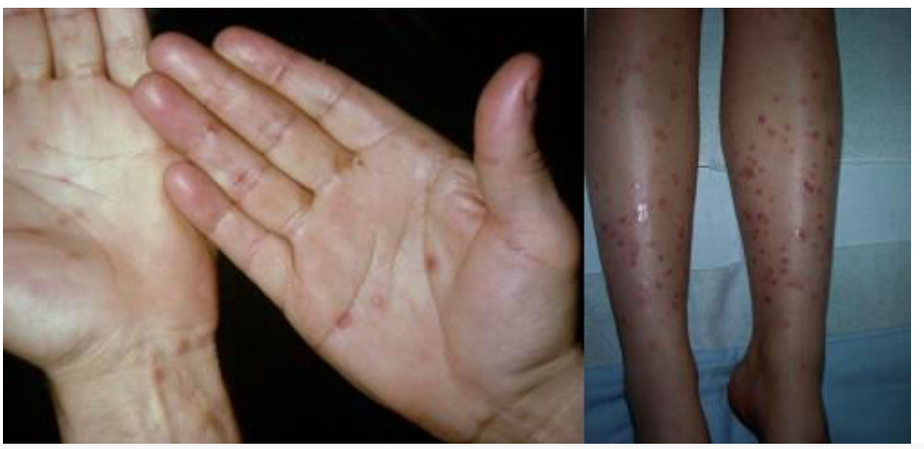
- **Definition:** Syphilis is a sexually transmitted infection caused by the spirochaete *Treponema pallidum*.
- Approximately one-third of sexual contacts of infectious syphilis will develop the disease.
- **The incubation period** is between 9-90 days
- **Stages:** Infection is characterised by primary, secondary and tertiary stages.

Primary features

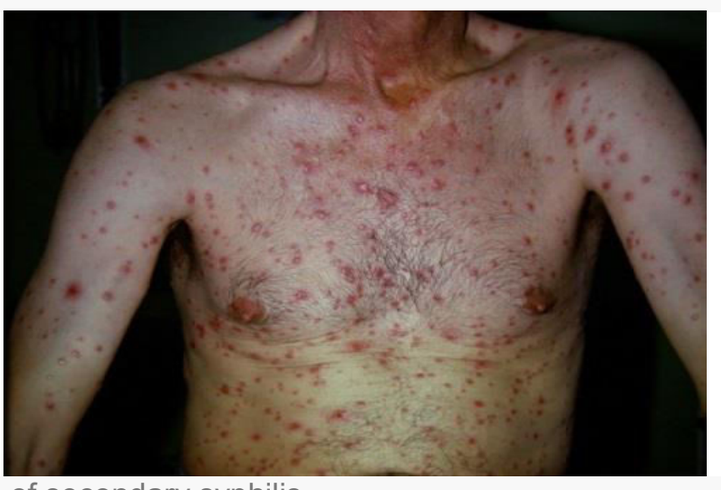
- chancre - painless ulcer at the site of sexual contact
- local non-tender lymphadenopathy
- often not seen in women (the lesion may be on the cervix)

Secondary features - occurs 6-10 weeks after primary infection

- systemic symptoms: fevers, lymphadenopathy
- rash on trunk, palms and soles
- buccal 'snail track' ulcers (30%)
- condylomata lata



Classical palm lesions of secondary syphilis



More generalised rash of secondary syphilis

Tertiary features

- occurs in one-third of untreated patients around 15–30 years after initial infection.
- gummas (granulomatous lesions of the skin and bones) most common (15% of patients)
- ascending aortic aneurysms
- general paralysis of the insane
- tabes dorsalis
- Argyll-Robertson pupil

Features of congenital syphilis

- blunted upper incisor teeth (Hutchinson's teeth), 'mulberry' molars
- rhagades (linear scars at the angle of the mouth)
- keratitis
- saber shins
- **saddle nose**
- deafness

Investigation

The diagnosis usually based on clinical features, serology and microscopic examination of infected tissue

Serological tests can be divided into

- cardiolipin tests (not treponeme specific)
- treponemal specific antibody tests

Cardiolipin tests

- syphilis infection leads to the production of non-specific antibodies that react to cardiolipin
- examples include VDRL (Venereal Disease Research Laboratory) & RPR (rapid plasma reagin)
- insensitive in late syphilis
- becomes negative after treatment
- **Causes of false positive cardiolipin tests**
  - pregnancy
  - SLE, anti-phospholipid syndrome
  - TB
  - leprosy
  - malaria
  - HIV

Treponemal specific antibody tests

- example: TPHA (*Treponema pallidum* Haem Agglutination test)
- **remains positive after treatment**

Management

- **benzylpenicillin**
  - First line treatment
  - benzathine penicillin 2.4 million units given intramuscularly. This is administered either as a single dose or two doses given one week apart.
- alternatives: doxycycline or erythromycin
  - may be given in patients with allergies to penicillins.
- **the Jarisch-Herxheimer reaction**
  - **This is an acute febrile illness with headache, myalgia, chills and rigors starting within 12 hours of the first dose of treatment and resolving within 24 hours**
  - Fever, rash, tachycardia after first dose of antibiotic.
  - It is thought to be due to the release of endotoxins following bacterial death
  - It is usually not important in early syphilis unless there is neurological or ophthalmic involvement or in pregnancy when it may cause fetal distress and premature labour.
  - It occurs in ~50% of patients with primary syphilis, **90% with secondary syphilis** and 25% with early latent syphilis.
  - also occurs in **Lyme disease** and **Q fever**.
  - Patients should be counselled about the reaction prior to receiving therapy for syphilis.

- **the appropriate management** → **reassurance** and paracetamol for symptom control

UK national guidelines on the management of syphilis 2015

- Infected patient should be advised to abstain from sex until any lesions (if any) have resolved or until two weeks after treatment completion
- first-line: Procaine penicillin is now an alternative treatment where benzathine penicillin is suitable. due to the pain and multiple injections associated
  - Benzathine dose: 2.4 Mega units IM weekly for up to 3 weeks
  - Procaine dose: 1.8–2.4 mega units IM daily for 14 days.
- second-line → oral azithromycin single dose.
- **Treatment during pregnancy**:
  - first and second trimesters → give single dose benzathine penicillin;
  - third trimester → two doses of benzathine penicillin one week apart.
- **Neurosyphilis:** procaine penicillin 1.8-2.4 units once daily (IM, for 14 days) with oral probenecid 500 mg four times a day.
- Tests for monitoring the effect of treatment → RPR/VDRL test
- Treponemal enzyme immunoassay (EIA)/chemiluminescent assay (CLIA), preferably detecting both IgM and IgG is the screening test of choice.
- Treatment during pregnancy: depends upon which trimester the presentation is in:
  - first and second trimesters - give single dose benzathine penicillin;
  - third trimester - two doses of benzathine penicillin one week apart.

Tape worms

Tape worms are made up of repeated segments called proglottids. These are often present in faeces and are useful diagnostically

Cysticercosis

- caused by Taenia solium (from pork) and Taenia saginata (from beef)
- These may affect any tissue in the body but are commonest in subcutaneous tissues and (CNS) →patient with a palpable nodule who has an epileptic seizure
- management: niclosamide

Hydatid disease

- caused by the dog tapeworm *Echinococcus granulosus*
- life-cycle involves dogs ingesting hydatid cysts from sheep liver
- often seen in farmers
- may cause liver cysts
- management: albendazole

Tetanus

- Tetanus is caused by the tetanospasmin exotoxin released from *Clostridium tetani*.
- Tetanus spores are present in soil and may be introduced into the body from a wound, which is often unnoticed. Absence of a wound does not exclude tetanus.
- Tetanospasmin prevents release of GABA
- The absence of a wound does not exclude tetanus.
- The toxin tetanospasmin does not cross the blood brain barrier, it diffuses through the blood to bind to receptors containing gangliosides on the neuronal membranes of presynaptic nerve terminals in muscles. The toxin does reach the brain by axonal transport.
- **Tetanus toxin cleaves specific sites of synaptobrevin (VAMP)**

Features

- prodrome fever, lethargy, headache
- trismus (lockjaw)
- risus sardonicus
- opisthotonus (arched back, hyperextended neck)
- spasms (e.g. **dysphagia**).

Management

- supportive therapy including ventilatory support and muscle relaxants
- intramuscular human tetanus immunoglobulin for high-risk wounds (e.g. compound fractures, delayed surgical intervention, significant degree of devitalised tissue)
  - While *Clostridium*-specific intravenous immunoglobulin is ineffective once the toxin is attached to nervous tissue **it may prevent progression.**
- **metronidazole is now preferred to benzylpenicillin as the antibiotic of choice**

Tetanus: vaccination

- The tetanus vaccine is a cell-free purified toxin that is normally given as part of a combined vaccine.
- Tetanus vaccine is currently given in the UK as part of the routine immunisation schedule at:
  - 2 months
  - 3 months
  - 4 months
  - 3-5 years
  - 13-18 years
- This therefore provides 5 doses of tetanus-containing vaccine.
- Five doses is now considered to provide adequate long-term protection against tetanus.
- A tetanus booster is not recommended in the UK if the patient is already immunized. Tetanus antitoxin may be used in developing countries as it is cheaper but it has a higher rate of anaphylaxis and a shorter half life so is not recommended in the UK.
- Intramuscular **human tetanus immunoglobulin** should be given to patients with high-risk wounds (e.g. Compound fractures, delayed surgical intervention, significant degree of devitalised tissue) irrespective of whether 5 doses of tetanus vaccine have previously been given
- High risk wounds
  - Wounds burns needing surgery delayed more than 6 hours
  - Wounds contaminated with soil
  - Compound fractures
  - Wounds containing foreign bodies
  - Wounds/burns in people with systemic sepsis
- **If vaccination history is incomplete or unknown** then a dose of tetanus vaccine should be given combined with intramuscular human tetanus immunoglobulin **for high-risk wounds**

January 2015 exam: H/O 4 cm laceration to the dorsum of left hand after cutting using a Stanley knife. no sign of a foreign body. He has 'no idea' about his tetanus vaccination. What is the most appropriate action with respect to tetanus? Requires tetanus vaccine + complete vaccine course at a later date
(This wound is not high risk for tetanus)

Trypanosomiasis

- Two main form of this protozoal disease are recognised:
  1. African trypanosomiasis (sleeping sickness) and
  2. American trypanosomiasis (Chagas' disease)

1. African trypanosomiasis, or **sleeping sickness**

- Two forms of **African trypanosomiasis**, or **sleeping sickness**, are seen:
  1) *Trypanosoma brucei gambiense* in **West** Africa
     - West African trypanosomiasis has a slower course. Symptoms start several weeks or even months after the tsetse fly bite.
  2) *Trypanosoma brucei rhodesiense* in **East** Africa.
     - *Trypanosoma rhodesiense* tends to follow a more **acute** course.
     - progression is more rapid - starting within days of infection. Death may occur within weeks or months.

- Rash is a more prominent feature and lymphadenopathy is less frequently present.

- Both types are spread by the tsetse fly.
- **Clinical features** include:
  - Trypanosoma chancre - painless subcutaneous nodule at site of infection
  - intermittent fever
  - enlargement of posterior cervical lymph nodes
  - later: central nervous system involvement e.g. somnolence, headaches, mood changes, meningoencephalitis
  - The reversal of the sleep wake cycle is typical and can be accompanied by behavioural changes.

- **Stages**
  - The **first stage** of disease is haematolymphatic spread and is accompanied by fever, and lymphadenopathy (discrete, rubbery, non-tender nodes). A rash sometimes occurs and mild hepatosplenomegaly may develop.
  - The **second stage** is the meningoencephalitic stage. This occurs months or years after the acquisition of infection. Manifestations include personality change and progressive indifference with daytime somnolence. Extrapyramidal signs and ataxia are common.
- **Management**
  - early disease: IV pentamidine or **suramin**
  - later disease or central nervous system involvement: **IV melarsoprol**

2. American trypanosomiasis, or **Chagas' disease**

- caused by the protozoan *Trypanosoma cruzi*.
- Transmitted by triatomine bug bite.
- **Features:**
  - acute phase:
    - asymptomatic (95%)
    - chagoma (an erythematous nodule at site of infection)
    - periorbital oedema
  - Chronic Chagas' disease mainly affects the heart, gastrointestinal tract and CNS.
    - Cardiac feature → myocarditis may lead to dilated cardiomyopathy (with apical atophy) and arrhythmias.
      - ➔ **Cardiac involvement is the leading cause of death in patients with Chagas' disease**
    - GIT feature:
      - ➔ Mega-oesophagus (causing dysphagia)
      - ➔ Mega-colon (causing constipation)
    - CNS feature → meningoencephalitis
- **Management**
  - treatment is most effective in the acute phase using azole or nitroderivatives such as **benznidazole** or nifurtimox
  - chronic disease management involves treating the complications e.g., heart failure.

Tuberculosis

Definition

- Tuberculosis (TB) is an infection caused by *Mycobacterium tuberculosis* that most commonly affects the lungs.
- *Mycobacterium tuberculosis* is a small aerobic non-motile bacillus. It is classified as a Gram positive organism

Pathophysiology

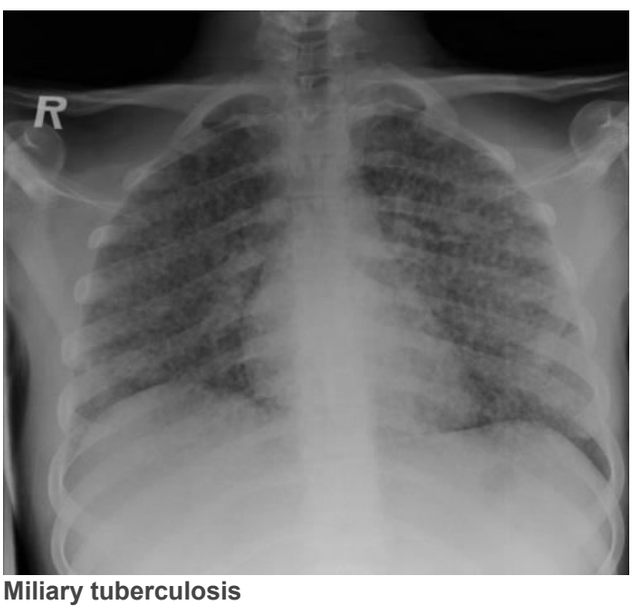
- the key of pathophysiology is to differentiate between primary and secondary disease.

Primary tuberculosis

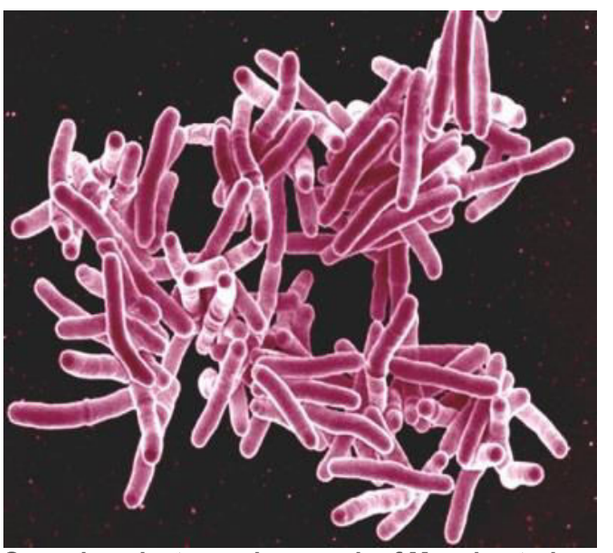
- A **non-immune host** who is exposed to M. tuberculosis may develop primary infection of the lungs. A small lung lesion known as a **Ghon** focus develops. The Ghon focus is composed of tubercle-laden macrophages. The combination of a Ghon focus and hilar lymph nodes is known as a Ghon complex
- In **immunocompetent** people the intially lesion usually heals by fibrosis.
- Those who are **immunocompromised** may develop disseminated disease (miliary tuberculosis).
- Primary TB is usually asymptomatic
- Bacilli are transported via lymphatics early in the disease process to regional lymph nodes to cause marked lymphadenopathy.
- Pleural and pericardial infections (which can result in effusions) occur at or shortly after primary infection.
- Positive tuberculin test occurs between three weeks and three months after primary infection.
- ***Mycobacterium avium* causes disseminated infection in patients with advanced HIV, typically when the CD4 count is less than 50 cells/mm^3.**
- **Positive tuberculin test occurs between three weeks and three months after primary infection**.

Secondary (post-primary) tuberculosis

- If the host becomes immunocompromised the initial infection may become reactivated.
- Reactivation generally occurs in the apex of the lungs and may spread locally or to more distant sites.
- Possible causes of immunocomprise include:
  - immunosuppressive drugs including steroids
  - HIV
  - malnutrition
- The lungs remain the most common site for secondary tuberculosis.
- Extra-pulmonary infection may occur in the following areas:
  - central nervous system (tuberculous meningitis - the most serious complication)
  - vertebral bodies (Pott's disease)
  - cervical lymph nodes (scrofuloderma)
  - renal
  - gastrointestinal tract
- **tuberculosis may be associated with an inflammatory polyarthritis that may follow a similar pattern to rheumatoid arthritis**



Miliary tuberculosis


Scanning electron micrograph of Mycobacterium tuberculosis bacteria, which cause TB.

Patients should be routinely screened for TB exposure before treatment with Etanercept with the tuberculin skin test

Transmission

- **Non-sputum producing patients are non-infectious** . Only untreated smear-positive pulmonary TB is likely to be infectious.

Screening

- **The Mantoux test** is the main technique used to screen for latent tuberculosis.
  - **The most commonly used screening test for contacts of a patient with recently diagnosed TB**
  - It measures the T cell-mediated immune response to TB antigen. Immune complexes are not involved (these result from antibody mediated immune responses).

- In recent years the interferon-gamma blood test has also been introduced. It is used in a number of specific situations such as:
  - the Mantoux test is positive or equivocal
  - people where a tuberculin test may be falsely negative (see below)
- Tuberculin skin tests are an example of type IV (delayed) hypersensitivity reactions. These are largely **mediated by interferon-γ secreted by T_h1 cells** which in turn stimulates macrophage activity.

Mantoux test (tuberculin test) (**p**urified **p**rotein **d**erivative (**PPD**) test)

- **It is a cell mediated immune response.**
  - measures the T cell-mediated immune response to TB antigen
- **Memory TH1 cells previously formed against *M. tuberculosis* recognize peptide: MHC class II complexes on the surface of antigen presenting cells**
- It is a **type IV**, hypersensitivity reaction.
- 0.1 ml of 1:1,000 purified protein derivative (PPD) injected intradermally
- result read 2-3 days later
- The left forearm is typically used.
- Only the induration, not surrounding erythema, is used in the measurement and the longest diameter is measured in millimetres:

Diameter of induration	Positivity	Interpretation
< 6mm	Negative - no significant hypersensitivity to tuberculin protein	Previously unvaccinated individuals may be given the BCG
6 - 15mm	Positive - hypersensitive to tuberculin protein	Should not be given BCG. May be due to previous TB infection or BCG or atypical mycobacteria. However, in other contexts **(e.g. immigrant screening and contact tracing),** further investigation should and follow-up may be indicated.
> 15mm	Strongly positive - strongly hypersensitive to tuberculin protein	Suggests tuberculosis infection. → do chest x-ray

- Active disease may be indicated by grade III/IV response to tuberculin.
- Eighty percent of individuals with history of BCG vaccination have grade I/II response.

False negative tests may be caused by: (→ ↓reaction to tuberculin protein)

- miliary TB

- sarcoidosis
- **immunosuppression (HIV , corticosteroids)**
- lymphoma
- very young age (e.g. < 6 months)
- Viral infections,
- live viral vaccines
- poor nutrition.

January 2012 exam: Which cytokines is most involved in the response of a Mantoux test?
- **Interferon-γ**

Heaf test

- The Heaf test was previously used in the UK but has been since been discontinued.
- It involved injection of PPD equivalent to 100,000 units per ml to the skin over the flexor surface of the left forearm. It was then read 3-10 days later.
- Patients who exhibited a negative reaction to the test were considered for BCG vaccination.
- Heaf test was used to test for tuberculosis in adolescents aged around 13–14
- Until 2005, the test was used in the United Kingdom to determine if the BCG vaccine was needed; the Mantoux test is now used instead.
- Heaf tests are graded as follows:

0	no reaction
1	4-6 small dots
2	dots coalesce, normal skin in centre
3	dots coalesce, central skin filled in
4	solid induration >10 mm, with or without vesiculation or ulceration

- Interpretation of results:
  - **grade 0**,indicating no TB;
    - An HIV-positive patient without active tuberculosis would likely have a grade 0 reaction.
    - Without prior BCG vaccination in an HIV-negative patient with no previous exposure to TB a grade 0 reaction would be expected.
  - **Grade 2** is a normal response in the presence of a previous BCG vaccination.
  - **grade 3-4**, indicating active disease.

BCG

- is a live attenuated vaccine derived from a strain of *Mycobacterium. bovis*.
- BCG is currently used as a form of immunotherapy for treating bladder cancer; which can lead to disseminated *M. bovis* infection (systemic 'BCG-it is')
- **it also has effects against leprosy *(Mycobacterium* (*M. leprae*)) (up to 80% protection)**
- updates now recommend that it should be given to neonates in high risk groups.
- It should not be given to children who have a strongly positive tuberculin test.
- A Mantoux should be documented before administration.
- **In case of increased risk of HIV, NICE advises that an HIV test should be done prior to vaccination.**

Diagnosis

- In adults induction of sputum or bronchoscopy and lavage may be used in patients who cannot produce sputum

- **If patient is unable to produce sputum, bronchoscopy with bronchial washings for microscopy staining and culture is the investigation of choice.**
- Gastric lavage for AFB is unpleasant for the patient has a lower yield than bronchoscopy and is therefore rarely undertaken now.

- In children who are unable to cough up sputum, the gold standard is gastric washings for M tuberculosis culture
- Smear-positive tuberculosis → **(Patient needs treatment and isolation from casual contacts, his close contacts need screening)**
  - **Smear-positive tuberculosis** means the patient is highly infectious to both close contacts (more than 8 hours spent together per day) and casual contacts, such as other patients on the ward and healthcare workers.
    - He therefore needs to be isolated in a negative-pressure room and contacts should wear particulate masks until he has received anti-tuberculous therapy for 2 weeks.

    The sputum might remain positive after this time, but the organisms will be dead.
  - **Culture-positive tuberculosis** means the immediate smear is negative, but prolonged culture has shown tuberculosis.
- **The definitive diagnosis**: requires the growth of Mycobacterium tuberculosis from respiratory secretions.
- **A probable diagnosis**: can be based on:
  - Typical clinical and chest X-ray findings, together with either
  - sputum (or other specimens) positive for acid-fast bacilli,
    - stains very weakly on testing. When using the **Ziehl-Neelsen test** it stains **bright red** against a blue background.
  - typical histopathological findings on biopsy material

Management

- Should only be carried out in hospitals with appropriate isolation facilities.
  - Smear-positive tuberculosis means the patient is highly infectious to both **close contacts (more than 8 hours spent together per day)** and casual contacts, such as other patients on the ward and healthcare workers.
  - He therefore needs to be isolated in a negative-pressure room,
  - contacts should wear particulate masks until he has received anti-tuberculous therapy **for 2 weeks**. The sputum might remain positive after this time, but the organisms will be dead.
- **Length of treatment:**
  - All forms of pulmonary TB may be treated equally except tuberculous pleural effusion which may require drainage (with large effusions causing breathlessness) and adjunct corticosteroids to delay reaccumulation.
  - A 6-month course of treatment is adequate for all non-CNS disease.
  - Length of treatment for other forms are:
    - bone TB – 6 months
      - Treatment for bone and joint tuberculosis is recommended to continue for 2 months with the initial phase consisting of quadruple therapy and the remaining 4 months of dual therapy.
      - It is recommended not to extend treatment for residual complications such as collapsed discs or bending of the spine, although there is some debate about this.
    - meningitis - 1 year
      - **Antituberculous treatment for 12 months is recommended for TB meningitis.**
      -
    - drug resistance - 2 years.
      - Treatment must be continued for a minimum of 18 months, with **at least 9 months of treatment after the patient becomes culture-negative.**

- **TB with strider:**
  - If patient of **TB** presents with worsening breathlessness and stridor due to mediastinal lymph nodes compressing the carina, **the next step - after commencing steroid - is urgent (CT) scan**, first to confirm the degree of airway compression and second to assess the response to chemotherapy.
- **Patients on long term steroids with TB:**
  - **Patients on long term steroids should have their dose of steroids increased when starting antituberculous therapy.**
    - **The metabolism of corticosteroids is increased by rifampicin. (P450 inducer)**
- **Failing regimen in the treatment of TB:**
  - reactivation of (TB) infection during treatment course.
  - Evidence of failing treatment:
    - worsening symptoms,
    - elevated C-reactive protein,
    - progression of chest X-ray changes
  - **what is the most appropriate next treatment step?**
    - Most guidelines recommend **progression to five agents – rifampicin, pyrazinamide, isoniazid, ethambutol and streptomycin.**

TB Drug therapy

Treatment for active tuberculosis is:

- **Initial phase - first 2 months (RIPE)**
  1. Rifampicin
  2. Isoniazid
  3. Pyrazinamide
  4. Ethambutol
     - (the 2006 NICE guidelines now recommend giving a 'fourth drug' such as ethambutol routinely - previously this was only added if drug-resistant tuberculosis was suspected)
     - either ethambutol or streptomycin.
- **Continuation phase - next 4 months**
  1. Rifampicin
  2. Isoniazid
     - After 2 months of therapy (for a fully susceptible isolate), pyrazinamide can be stopped. Isoniazid plus rifampicin are continued as daily or intermittent therapy for 4-or-more months.
     - Therapy must be extended if the patient has cavitary disease or remains culture positive after 2 months of treatment.

Treatment for latent tuberculosis

- isoniazid alone for 6 months

Treatment for meningeal tuberculosis

- treated for a prolonged period (at least **12 months**)
- 4 drugs for the first 2 months, followed by isoniazid and rifampicin 10 months.
- addition of **steroids** (equivalent to prednisolone 20-40 mg) is recommended for the first 2-3 weeks, then with gradual reduction.
  - (use of steroids is recommended to ensure adequate brain penetration and to prevent cranial nerve compression by meningeal scarring.

Extra-pulmonary TB (e.g. bone, CNS)

- requires a longer duration of treatment, usually 9-12 months.

Directly observed therapy

- with a three times a week dosing regimen may be indicated in certain groups, including:
  - homeless people with active tuberculosis
  - patients who are likely to have poor concordance
  - all prisoners with active or latent tuberculosis

Tuberculosis: drug side-effects and mechanism of action

- **Rifampicin**
  - mechanism of action:
    - **inhibits** bacterial DNA dependent **RNA polymerase preventing transcription** of DNA into mRNA
  - **mechanism of resistance for rifampicin resistant *Mycobacterium tuberculosis***
    - **Mutations in rpoB gene cause alterations in the bacterial DNA dependent RNA transcriptase, which prevents the binding of rifampicin**.
  - In patients with HIV/TB co-infection:
    - Rifampicin is a potent inducer of liver enzymes (cytochrome P450). Furthermore, it up-regulates the expression of P-glycoprotein in the gastrointestinal tract.
    - Co-administration of a protease inhibitor with rifampicin therefore will often lead to sub-therapeutic levels of the protease inhibitor.
    - the British HIV Association suggest the **substitution of rifampicin for an alternative rifamycin agent (rifabutin or rifapentine), which has less inducing action of cytochrome P450**
  - Side effects
    - potent liver enzyme inducer
    - hepatitis,
    - orange secretions (Red or orange discoloration of the urine and other body fluids)
    - flu-like symptoms
    - Rifampicin and isoniazid can cause a relative vitamin D deficiency
- **Isoniazid**
  - mechanism of action:
    - Prevents cell wall synthesis by **inhibiting the synthesis of mycolic acid**
    - Bactericidal
  - Side effects
    - **Hepatotoxicity**
      - **INH is the most common drug associated with toxicity.**
      - INH metabolites are responsible for INH hepatotoxicity
      - *N*-acetyltransferase 2 (NAT2) is the primary enzyme that contributes to INH metabolism.
      - NAT2 deficiency increases the risk of INH-induced liver injury.
      - **slow acetylators are prone to develop more severe hepatotoxicity than rapid acetylators.**
    - Peripheral neuropathy:
      - prevent with pyridoxine (Vitamin B6)
    - agranulocytosis
    - Drug-induced lupus erythematosus
    - liver enzyme inhibitor

INH Injures **N**eurons and **H**epatocytes

- **Pyrazinamide**
  - mechanism of action:
    - converted by pyrazinamidase into pyrazinoic acid which in turn inhibits fatty acid synthase (FAS)
    - Bactericidal
    - Streptomycin has high activity against extracellular organisms whilst **pyrazinamide have high activity against intracellular organisms**.
  - **side effects**
    - **hyperuricaemia causing gout**
    - arthralgia, myalgia
      - **the most common cause of arthralgia after starting antituberculous**
    - Hepatotoxicity
- **Ethambutol**
  - mechanism of action:
    - Prevents cell wall synthesis by **inhibiting arabinosyltransferase** (which polymerizes arabinose into arabinan)
    - **Bacteriostatic**
  - side effects
    - optic neuritis: **check visual acuity before and during treatment**
    - **Ocular side-effects of ethambutol**
      - Loss of acuity
      - Colour blindness
      - Restriction of visual fields
  - **dose needs adjusting in patients with renal impairment**
    - Ethambutol is **renally excreted** and therefore dose adjustment is necessary to minimise the risk of toxic effects (optic neuropathy). The remaining drugs are mainly metabolised in the liver and can be given in normal doses in renal failure.
- **Anti-tuberculosis drug and LFTs :**
  - **All tuberculosis patients should have pre-treatment LFTs.**
  - rifampicin/isoniazid/pyrazinamide all are associated with liver toxicity, **but isoniazid are most commonly implicated** (this fact are tested in MRCPI website - part 1, sample question)
  - Up to **20%** of the patients receiving **isoniazid** either in single or combination therapy develop **transient asymptomatic elevation in liver enzymes**, which **settle with continued use of the drug.**
    - while some patients (less than 1%–3%) develop severe liver injury and even liver failure
  - If there is no pre-existing liver disease, LFTs are only repeated (and treatment stopped) if fever, malaise, vomiting , jaundice or unexplained deterioration occurs during treatment.
  - Regular LFTs should be performed in patients with previously known chronic liver disease.
  - define hepatotoxicity → rifampicin/isoniazid/pyrazinamide **should be stopped**
    - If AST/ALT levels rise **by 5 times** upper limit of normal range **without symptoms**
    - If ALT/AST levels rise **by 3 times** upper limit of normal range **with symptoms** (abdominal pain, nausea, vomiting, unexplained fatigue or jaundice)

- If the patient is not unwell and/or has non-infectious TB, no treatment until LFT returns to normal.
- If clinically unwell or sputum smear is positive within two weeks of starting treatment, consider **streptomycin and ethambutol until LFT returns to normal.**
- Once LFT is back to normal, challenge dosages can be reintroduced sequentially in order of isoniazid, rifampicin and pyrazinamide with daily monitoring of patient's condition and LFT.
- If there is a further reaction , the offending drug should be excluded and a suitable alternative regimen used.

- **Immune reconstitution disease**
  - **Immune reconstitution inflammatory syndrome** (**IRIS**) (also known as **immune recovery syndrome**) is a condition seen in some cases of AIDS or immunosuppression, in which the immune system begins to recover, but then responds to a previously acquired opportunistic infection with an overwhelming inflammatory response that paradoxically makes the symptoms of infection worse
  - **occurs typically 3-6 weeks after starting treatment**
  - **often presents with enlarging lymph nodes**

Latent tuberculosis infection (LTBI)

Definition

- screening tests indicating previous infection with *M. tuberculosis are* positive without any pathological findings on radiological imaging.

Risk for developing active tuberculosis

- The lifetime risk of reactivation TB for a person with LTBI is about 5–10%.
- **Risk factors for developing active tuberculosis** include:
  - silicosis
  - chronic renal failure
  - HIV positive
  - solid organ transplantation with immunosuppression
  - intravenous drug use
  - haematological malignancy
  - anti-TNF treatment
  - previous gastrectomy

Diagnosis

- **positive Mantoux test**
  - can be positive with both active and latent TB, but can also by a previous BCG vaccination.
  - Recommended for close contacts of a person with TB.
  - If positive (**induration ≥ 5 mm**, **regardless of BCG history**) → assess for active TB
- **Interferon gamma release assay (IGRA)**
  - Indications
    - Quantaferon testing (interferon gamma testing) is recommended as a second-line test for people whose Mantoux testing may be less reliable - for example, BCG-vaccinated people.
    - If the Mantoux test is positive + active TB is excluded, and evidence of infection is needed to decide on treatment. for example:
      - if the person needs enhanced case management or
      - if there could be adverse events from treatment.

- **In people with HIV and a CD4 count of less than 200 cells/mm^3 an interferon-gamma test should be done alongside the Mantoux** as it will be unreliable.
  - ❖ If either test is positive a clinical assessment should be performed to exclude active TB,
  - ❖ if no active disease found consideration made to treating a latent infection.
- For immunocompromised, (HIV and CD4 < 200 cells/mm3, or after transplant),→ **Interferon- gamma release assay and a concurrent Mantoux test:**
  - ❖ If either test is positive → assess for active TB.
  - ❖ If assess for active TB is negative, → treatment for latent TB infection.

➢ Advantage
- Quantaferon testing is not influenced by BCG vaccination status
- **A positive test would, therefore, indicate prior exposure to M. tuberculosis (active or latent TB)**

➢ Disadvantage
- The main disadvantage of the IGRA is its inability to distinguish between active and latent TB.

- **Chest x-ray**
  - ➢ **NO** TB-related findings on chest x-ray (e.g., hilar lymphadenopathy, upper lobe opacification, or cavitation),

Treatment

- NICE now give two choices for treating latent tuberculosis:
  - ➢ **3 months of isoniazid (with pyridoxine) and rifampicin**
    - For people younger than 35 years if hepatotoxicity is a concern after an assessment of both liver function (including transaminase levels) and risk factors.
  - ➢ **6 months of isoniazid (with pyridoxine)**
    - if interactions with rifamycins are a concern, for example, in people with HIV or who have had a transplant.

NICE advises that once a diagnosis of pulmonary TB has been made then **close contacts** should be managed as follow:

- If **asymptomatic** and **younger than 65 years** then:
  - ➢ test for latent TB.
    - If Mantoux-negative and unvaccinated then offer vaccination.
      - ❖ **If at risk of HIV then test for HIV first (HIV testing and if negative then BCG vaccination).**
- If **asymptomatic** and **older than 65 years** then assess with a chest X-ray.

Ref: NICE guidelines 2016
www.nice.org.uk

Miliary TB

Overview

- miliary TB most likely occur in young children.

Features

- presents with a gradual onset of vague ill health, loss of weight and then fever.
- TB meningitis

  - 15 - 20% of patients who have miliary TB also have TB meningitis at the time of presentation.
  - 33% of patient with TB meningitis have concomitant miliary TB.
- Hepatosplenomegaly is seen in advanced disease.
- Choroidal tubercles can be seen in the eyes.

Investigations

- tuberculin test is often negative.
  - negative in up to half of patients with severe disease
- chest x ray
  - may be normal in up to one third of patients.
  - The classic millet seed nodules are small measuring about 1-2 mm.
- Not all patients will be **sputum** positive and with evidence supporting a diagnosis of tuberculosis treatment should be commenced swiftly.
- Transbronchial biopsy – positive at an early stage.
- Biopsy of liver and bone marrow might be required.

Non-tuberculous mycobacterial infections

Opportunistic mycobacteria

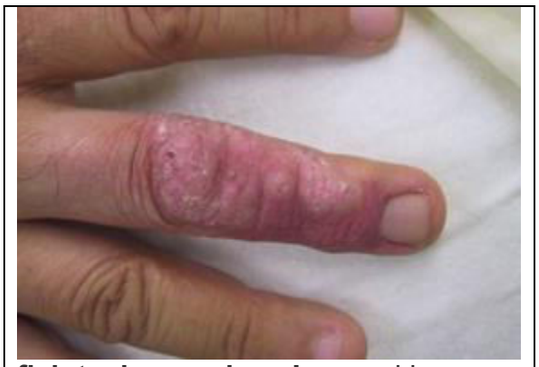
- Mycobacterium kansasii
- Mycobacterium malmoense
- Mycobacterium xenopi
- Mycobacterium avium intracellular(The presence of acid fast bacilli (AFB) and absence of TB (*Mycobacterium tuberculosis* negative on culture.) suggests an atypical AFB such as *M. avium*.)
  - **The presence of AFB yet absence of TB suggests an atypical AFB such as *M. avium*.**
  - *Mycobacterium avium* causes disseminated infection in patients with advanced HIV, typically when the CD4 count is less than 50 cells/mm^3.

Mycobacterium malmoense

- is a non-tuberculous mycobacterium
- most commonly causes pulmonary infection in middle-aged and older adults with pre-existing lung disease or immunodeficiency and can also cause local invasion from a skin lesion.
- It causes nonspecific symptoms, such as malaise and weight loss, or chest symptoms that take an atypical course.

Pathophysiology

- they can colonise structurally abnormal lung, for example in patients with:
  - Cavitary disease
  - Bronchiectasis
  - Chronic obstructive pulmonary disease
  - Such patients might not always require treatment. However, if treatment is required, then it is usually for longer than the standard 6 months needed to treat pulmonary tuberculosis
- 'atypical' mycobacteria differ from *M. tuberculosis* in that they are ubiquitous organisms and have no person-to-person spread.
- ***Mycobacterium marinum*** infection
  - It is an uncommon atypical mycobacterium infection
  - The skin is the most common site of infection, where it usually produces a **solitary indolent granulomatous lesion - the 'fish tank granuloma'.**
  - usually seen in **patients who handle fish** or swim in freshwater or saltwater.
  - occurs when contaminated water is exposed to skin that has experienced open trauma.



fish tank granuloma' caused by ***Mycobacterium marinum***

Diagnosis

- A single isolate from a non-sterile site might not be significant and can just represent contamination. **More than two isolates from a non-sterile site are required to establish disease.**
- Chest X-ray => (like other mycobacterium) upper-zone fibrosis and cavitation.

Treatment

- No need to isolate patients or notify public health authorities.

Multidrug-resistant tuberculosis (MDR-TB).

- **Definition**
  - Defined as resistance to rifampicin and isoniazid, with or without resistance to other anti-TB drugs.
  - defined as **positive cultures after 4 months of therapy**.
- **Epidemiology**
  - Rare in previously untreated white patients born in the UK(< 2%).
  - Higher levels of resistance occur in Indian subcontinent and black, with isoniazid resistance occurring in 4-6% of such patients.
- **Risk factors**
  - Poor compliance (the most common reason)
  - Previous anti-TB treatment
  - Contact with a known case of drug-resistant TB
  - Birth in a foreign country, particularly high-incidence countries
  - **HIV infection**
  - Residence in London
  - Age profile, with highest rates between ages 25 and 44,
  - Male gender.
  - Homelessness
  - Intravenous drug use
  - Infection acquired in institutions (eg prison)
- **Treatment**
  - **Directly observed therapy is recommended**
  - should be treated with an injectable agent such as amikacin, kanamycin or capreomycin, in combination with a fluoroquinolone and at least three other agents.
    - At least 5 drugs, one of which is a quinolone, is the recommended
  - Ideally the **injectable agent is administered daily for the first 6-8 months**, forming an intensive phase of treatment, with other drugs then continued for a total of **18-24 months.**
  - In practice, unwanted effects may lead to intravenous therapy being discontinued early.

Vaccinations

Live attenuated vaccines

- **BCG**
- **measles, mumps, rubella (MMR)**
- **oral polio**
- **oral rotavirus**
- **oral typhoid**
- **influenza (intranasal)**
- **yellow fever**
- **Varicella**

Live attenuated vaccines are contraindicated in all HIV positive and immunocompromised patients.

- *whole cell typhoid vaccine is no longer used in the UK

Inactivated preparations

- rabies
- influenza (intramuscular)

Detoxified exotoxins

- tetanus

Extracts of the organism/virus (sometimes termed fragment) (may also be produced using recombinant DNA technology)

- diphtheria
- pertussis ('acellular' vaccine)
- hepatitis B
- meningococcus, pneumococcus, haemophilus

Notes

- influenza:
  - different types are available, including whole inactivated virus, split virion (virus particles disrupted by detergent treatment) and sub-unit (mainly haemagglutinin and neuraminidase)
- cholera:
  - contains inactivated Inaba and Ogawa strains of Vibrio cholerae together with recombinant B-subunit of the cholera toxin
- hepatitis B:
  - contains HBsAg adsorbed onto aluminium hydroxide adjuvant and is prepared from yeast cells using recombinant DNA technology

contraindications to pertussis immunisation include:

- Acute illness - until recovered
- Previous reaction to pertussis:
  1. **Local:** an extensive area of redness and swelling which becomes indurated, involving most of the anterolateral surface of the thigh or a major part of the circumference of the upper arm
  2. **General: fever equal to or more than 39.5°C within 48 hours of vaccine**, anaphylaxis, bronchospasm, laryngeal oedema, generalised collapse, prolonged hyporesponsiveness, prolonged inconsolable or high-pitched screaming of more than four hours, convulsions or encephalopathy occurring within 72 hours.

Splenectomised patients

- Splenectomised patients are at **increased risk of infection with**:
  - encapsulated bacteria
    - A popular mnemonic to remember most of the encapsulated bacteria is the **SHiNE SKiS** bacteria (**S**. pneumo, **Hi**b, **N**. meningitidis, **E**. Coli, **S**almonella, **K**lebs**i**ella, Group B **S**trep).
  - infections that are filtered by the spleen (for example, malaria).
- When **elective splenectomy** is planned, vaccines to pneumococcus and meningiococcus should be given **two weeks pre-surgery** to allow an antibody response to evolve.

- Patients who have **emergency splenectomies** should be vaccinated post-operatively (most effective if performed **at least 14 days after surgery**)

Post-exposure prophylaxis

Post-exposure prophylaxis for HIV: oral antiretroviral therapy for 4 weeks

Hepatitis A

- Human Normal Immunoglobulin (HNIG) or hepatitis A vaccine may be used depending on the clinical situation

Hepatitis B

- **HBsAg positive source**:
  - if the person exposed is a known responder to HBV vaccine then a booster dose should be given.
  - If they are in the process of being vaccinated or are a non-responder they need to have hepatitis B immune globulin (HBIG) and the vaccine
- **unknown source:**
  - for known responders the green book advises considering a booster dose of HBV vaccine.
  - For known non-responders → HBIG + vaccine should be given
  - those in the process of being vaccinated should have an accelerated course of HBV vaccine.
  - accelerated course of HBV vaccine → given at zero, one and two months. For those who are at continued risk, a fourth dose is recommended at 12 months.

	Source person	
Exposed person	**HBsAg positive**	**unknown**
responder to HBV vaccine	booster HBV vaccine	booster HBV vaccine
non-responder	(HBIG) + vaccine	HBIG + vaccine
in the process of vaccination	(HBIG) + vaccine	accelerated course of HBV vaccine (given at zero, one and two months)

Hepatitis C

- monthly PCR - if seroconversion then interferon +/- ribavirin

HIV

- **Three antiretroviral agents for 1 month**
  - New guidelines in 2014 recommend three-agent PEP with **Truvada® (tenofovir and emtricitabine) and raltegravir**, which should both be taken for 1 month.
  - (i.e. Within 1-2 hours, but may be started up to 72 hours following exposure) for 4 weeks
- serological testing at 12 weeks following completion of post-exposure prophylaxis
- reduces risk of transmission by 80%

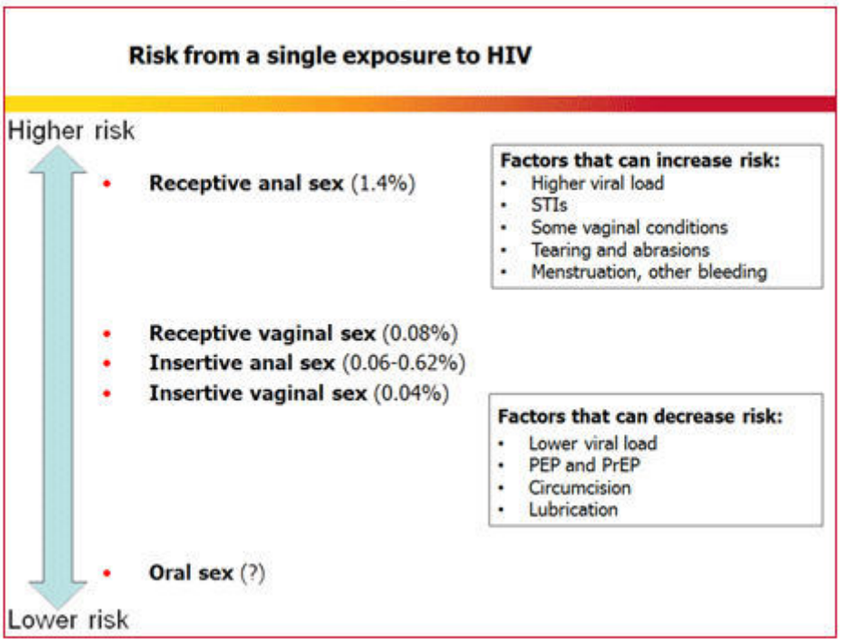
Varicella zoster

- VZIG for IgG negative pregnant women/immunosuppressed

Estimates of transmission risk for single needle stick injury

Hepatitis B	**20-30%**
Hepatitis C	0.5-2%
HIV	0.3%

First line management of needle stick injuries includes immediate washing of the affected area under running water.



UK Guideline for the use of HIV Post-Exposure Prophylaxis Following Sexual Exposure (PEPSE) 2015

- If the source is of unknown status: → establish the HIV status of the source.
- Source individual known to be HIV-positive: → determine the HIV viral load, resistance profile and treatment history.
- if the source is on antiretroviral therapy (ART) with a confirmed and sustained (>6 months) undetectable plasma HIV viral load → PEPSE is no longer recommended
  - However, if there are any doubts about the HIV viral load history or the source's adherence to ART → PEP should be given following unprotected receptive anal intercourse.
  - Initiation of PEPSE is recommended as soon as possible after exposure, preferably within 24 hours of exposure but can be offered up to 72 hours.
  - The first-line regimen is Truvada and raltegravir
    - Truvada → fixed-dose combination of two antiretroviral medications: tenofovir disoproxil and emtricitabine (both are Nucleoside analog reverse-transcriptase inhibitors (NRTIs)
    - Raltegravir (integrase inhibitors, a new class of HIV drugs) targets integrase, an HIV enzyme that integrates the viral genetic material into human chromosomes, a critical step in the pathogenesis of HIV.
  - PEPSE beyond 72 hours are not recommend
  - duration of PEPSE should be 28 days
  - follow-up HIV testing at 8-12 weeks after exposure
  - pregnancy should not alter the decision to start PEPSE. Women must be counselled that antiretroviral agents used for PEPSE are unlicensed in pregnancy and risks / benefits must be carefully discussed
  - In the event of a further high-risk sexual exposure in the last two days of the PEPSE course the PEP should be continued for 48 hours after the last high-risk exposure
  - If the recipient has missed more than 48 hours of PEPSE then the course should be discontinued.

Virulence factors

- Bacteria employ a large number of virulence factors which enable them to colonize the host and evade/suppress the immune response.
- The table below shows a select number of virulence factors which are important for the exam.

Virulence factor	Example organisms
IgA protease	*Streptococcus pneumoniae* *Haemophilus influenzae* *Neisseria gonorrhoeae*
M Protein	*Streptococcus pyogenes*
Polyribosyl ribitol phosphate capsule	*Haemophilus influenzae*
Bacteriophage	*Corynebacterium diphtheriae*
Spore formation	*Bacillus anthracis* *Clostridium perfringens* *Clostridium tetani*
Lecithinase alpha toxin	*Clostridium perfringens*
D-glutamate polypeptide capsule	*Bacillus anthracis*
Actin rockets	*Listeria monocytogenes*

- **New Delhi metallo-beta-lactamase 1**
  - is the mutation that leads to carbapenem resistance.
  - Typically found in Klebsiella pneumoniae, Escherichia Coli (E. Coli), Enterobacter cloacae and others.
  - First line of management is the old antibiotic **colistin** and second line may be **tigecycline.**

- **D-alanyl-D-lactate**
  - **D-alanyl-D-lactate** variation leading to loss of affinity to antibiotics is the mechanism of VRE (vancomycin resistant enterococci).
  - Vancomycin binds to D-ala-D-ala.

- **MexAB-OprM efflux pumps**
  - The presence of **MexAB-OprM efflux pumps** is one of the mechanisms by which pseudomonas aeruginosa is resistant to -lactams, chloramphenicol, fluoroquinolones, macrolides, novobiocin, sulfonamides, tetracycline, and trimethoprim.

- **penicillin binding protein 2**
  - Alteration to the **penicillin binding protein 2** is the mechanism behind methicillin-resistant staphylococcus aureus.
  - **Mutations in the MEC gene** which codes the penicillin binding proteins give staphylococcus aureus its resistance.

Viral haemorrhagic fever

- The Viral Haemorrhagic Fevers describe infection by a group of RNA viruses which include Yellow fever, Lassa fever and Ebola virus.
- Examples of viral haemorrhagic fever include:
  - Flaviviridae: dengue, yellow fever
  - Arenaviridae: Lassa fever
  - Filoviridae: Ebola virus

- this group of infections must be considered as a differential in returning travellers presenting with a fever.
- They are characterised by initially non specific symptoms such as fever, headache, vomiting, sore throat, diarrhoea and myalgic muscle pains, progressing to shock, renal failure and the presence of disseminated intravascular coagulation (DIC).
- Investigations characteristically reveal an anaemia with thrombocytopaenia, low lymphocyte count, deranged liver function and the presence of DIC.

West Nile virus

- West Nile virus is a mosquito-borne zoonotic arbovirus belonging to the genus *Flavivirus*.
- It is thought it is spread when a mosquito bites an infected bird and then bites a human.
- Few of those bitten develop symptoms and even fewer progress to severe disease.
- West Nile virus can be spread via vertical transmission as well as blood transfusions and organ transplant.
- If infected with the virus there are generally three different outcomes:
  1. Asymptomatic (estimated 90%)
  2. A mild febrile syndrome known as West Nile fever, or rarely
  3. Neuro-invasive disease termed West Nile meningitis or encephalitis.
- West Nile fever can present with several vague 'generally unwell' symptoms that tend to last three to six days such as:
  - Abdominal pain
  - Diarrhoea
  - Fever
  - Headache
  - Arthralgia
  - Nausea and vomiting
  - Rash
  - Sore throat, and
  - Lymphadenopathy.
- The following symptoms are suggestive of West Nile encephalitis/meningitis and prompt medical attention is required:
  - Confusion and seizures
  - Loss of consciousness or coma
  - Muscle weakness
  - Stiff neck, and
  - **Weakness of one arm or leg (a poliomyelitis-like paralysis). May be associated with poliomyelitis-like paralysis**
- Diagnosis can be via blood or cerebral spinal fluid serology for West Nile antibodies. More rapid techniques using polymerase chain reaction may be used.
- Due to the viral nature of the infection the current best treatment is supportive. In general it has an excellent prognosis. For those rare cases with severe infection it may lead to brain damage and death. Approximately 10% of patients with brain inflammation do not survive.
- In 2003 there were 276 deaths attributed to West Nile virus.
- Interestingly, West Nile Virus is endemic in the avian population. The deaths of large numbers of birds in an area may thus herald an imminent epidemic of West Nile virus.

Whooping cough (pertussis)

- caused by the bacterium *Bordetella pertussis*. gram-negative aerobic coccobacillus
- Lymphocytosis is typically found.
  - **it causes a profound leucocytosis by inhibiting chemokines that normally remove white cells from the blood stream.**

- **Pertussis toxin inactivates Gi, an inhibitory protein. Gi normally inhibits activation of adenylate cyclase. Therefore, the pertussis toxin inhibits an inhibitor leading to increased activity of adenylate cyclase.**
  - **Pertussis toxin → ↓ Gi → ↑adenylate cyclase**
- The pertussis vaccine is estimated to be 63% to 94% effective in the diphtheria-pertussis-tetanus (DPT) shot
- **A rare complication is a hemiseizure-hemiplegia syndrome**, which is thought to be related to post-immunisation hyperthermia rather than direct neurological toxicity.
- infants under the age of 3 months who are at the highest risk of severe complications, hospitalisation and death.
- Although it is a bacterial disease, antibiotics do not alter the clinical course once the disease is established.
- Erythromycin, clarithromycin and azithromycin may be given however as they have been shown to reduce the period the patient is infective for.

Yellow fever

- Type of viral haemorrhagic fever (also dengue fever, Lassa fever, Ebola).

Aetiology

- Pathogen: yellow fever virus (genus Flavivirus)
- linear RNA virus
- spread by *Aedes* mosquitos (primarily Aedes aegypti)
- incubation period = 2 - 14 days

Epidemiology

- endemic in large parts of South America and Africa **but not in Asia.**

Features

- Most patients remain asymptomatic
- In symptomatic patients: classic progression in three stages
  1. Period of infection (3–4 days)
     - Sudden onset of fever (up to 41°C)
     - Headaches, chills
     - Nausea, vomiting
     - Bradycardia may develop
  2. Period of remission (up to 2 days)
     - Easing of symptoms and decline in fever
  3. Period of intoxication (only in ~ 15% of symptomatic patients)
     - Hemorrhage
     - Multiorgan dysfunction (e.g., acute kidney and liver failure)
       - Nausea, (bloody) vomiting, abdominal pain, severe jaundice
       - Zone 2 of the liver is most affected in Yellow fever.

yellow fever is suggested by:
1. Travel to endemic area (West Africa and Central America)
2. Fever, with initial resolution
3. Progression to jaundice and renal failure

Investigations

- Leukopenia
- Thrombocytopenia, ↑ PTT
- Signs of organ failure (acute liver failure, acute renal failure)
- Virus detection
  - PCR
    - **The best test to rule out yellow fever infection is PCR**
  - ELISA
- Liver biopsy
  - Used for **definitive diagnosis** (e.g., postmortem)
  - Must not be done while the patient has an active yellow fever infection

- May show Councilman bodies
  - **Councilman bodies (inclusion bodies) may be seen in the hepatocytes**
    - For exam purposes **Councilman bodies (eosinophilic inclusion in the liver on post mortem) are diagnostic** of yellow fever, although they can occasionally be seen in other Viral Haemorrhagic Fevers such as Crimean Congo Haemorrhagic Fever, (but this is nosocomially spread)

Treatment

- Symptomatic treatment
- No specific antiviral treatment is available

Prevention

- **Yellow fever vaccine**
  - **the vaccination is the only intervention which could prevent death .**
  - **a live, attenuated vaccine** that consists of the 17D strain of the virus, **grown in hens' eggs**.
  - Administration
    - A single dose is provides life-long protection
    - administer at least 10 days before traveling to endemic area.
  - Its use is contraindicated in:
    - Under six months
    - With previous confirmed anaphylactic reaction to the vaccine
    - **previous confirmed anaphylactic reaction to egg**
    - thymus disorder
    - immunocompromised due to a congenital condition, disease process or treatment.

Sepsis

- A 'bundle' is a group of interventions related to a disease process that, when executed together, result in better outcomes than when implemented individually.

Sepsis Resuscitation Bundle:

- Should begin immediately, but must be accomplished **within the first six hours** of presentation.
  1. Serum lactate measured.
  2. **Blood cultures obtained prior to antibiotic administration.**
  3. From the time of presentation, broad-spectrum antibiotics administered within three hours for ED admissions and one hour for non-ED ICU admissions.
  4. in the event of hypotension and/or lactate > 4 mmol/l (36 mg/dl):
     - Deliver an initial minimum of 20 ml/kg of crystalloid (or colloid equivalent).
     - Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) > 65 mm Hg.
  5. In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate > 4 mmol/l (36 mg/dl):
     - Achieve central venous pressure (CVP) of > 8 mm Hg.
     - Achieve central venous oxygen saturation ($ScvO_2$) of > 70%.

Sepsis Management Bundle:

- To be accomplished as soon as possible may be completed **within twenty-four hours** of presentation.
  1. Low-dose steroids administered for septic shock in accordance with a standardised ICU policy.
  2. Glucose control maintained > lower limit of normal, but < 150 mg/dl (8.3 mmol/L).
  3. Inspiratory plateau pressures maintained < 30 cm H_2O for mechanically ventilated patients

Acute epiglottitis

- Acute epiglottitis is rare but serious infection caused by **Haemophilus influenzae type B.**
- Prompt recognition and treatment is essential as airway obstruction may develop.
- Epiglottitis was generally considered a disease of childhood but in the UK it is now more common in adults due to the immunisation programme.
- The incidence of epiglottitis has decreased since the introduction of the Hib vaccine

Features

- Rapid onset
- High temperature, generally unwell
- Stridor
- Drooling of saliva **(the most specific sign)**

Diagnosis

- the preferred method of diagnosis → **direct visualization of the epiglottis** using nasopharyngoscopy/laryngoscopy → cherry-red epiglottis
  - No attempt should be made to visualise the epiglottis until an **anaesthetist is present** as there is a high risk of causing acute airway obstruction by touching the inflamed tissue.
- Lateral neck soft-tissue radiography
  - useful screening tool in suspected stable patient.
  - Only 79% of epiglottis cases are diagnosed by neck soft-tissue radiographs
  - The classic findings are:
    - swollen epiglottis (ie, a thumb sign),
    - thickened aryepiglottic folds, and
    - obliteration of the vallecula (pre-epiglottic space). (vallecula sign).
      - The vallecula is the air pocket found at the level of the hyoid bone just anterior to the epiglottis.
- blood culture

Differential

- cough is specific for croup
- drooling is specific for epiglottitis
- laryngomalacia improves in the prone position

Treatment:

- Unstable patients → immediate airway management.
  - Early intubation is essential, especially in cases where there is respiratory distress.
- Stable patients
  - Patients without signs of airway compromise, respiratory difficulty, stridor, or drooling, and who have only mild swelling on laryngoscopy may be managed without immediate airway intervention by close monitoring in the intensive care unit (ICU).
- **Third generation cephalosporin is the treatment of choice.**
  - Ceftriaxone is the antibiotic of choice for epiglottitis.
- **Close contacts** of patients in whom *Haemophilus influenzae* type b is isolated should receive **rifampin prophylaxis** (20 mg/kg; not to exceed 600 mg/d for 4 d).
- recurrent episodes of acute epiglottitis in adults is unusual and, when present, warrants **immune system** investigation

Haemophilus influenzae requires hemin (**factor X**) and NAD+ (**factor V**) for growth. Other *Haemophilus* species require only NAD+ and therefore grow on blood agar.

Haemophilus *influenzae* : culture requirements:
➔ Read Hemophilus as "HemoFive": · Needs Heme with Factors Five and Ten.

Animal bites

Animal bite - co-amoxiclav

- The majority of bites seen in everyday practice involve dogs and cats.
- Dog bites become infected in 10% of cases.
- These are generally polymicrobial but **the most common isolated organism is *Pasteurella multocida*.**

Management

- cleanse wound
- current BNF recommendation is co-amoxiclav
- if penicillin-allergic then doxycycline + metronidazole is recommended

January 2011 exam: H/O a dog bite to right hand. What is the most appropriate antibiotic therapy? Co-amoxiclav

Rocky Mountain spotted fever

- Rocky Mountain spotted fever (RMSF) is a systemic vasculitis **caused by infection with *Rickettsia rickettsii*,** a tick-borne, gram-negative, intracellular bacterium, that primarily infects vascular endothelial cells.
- It is the most common fatal tick-borne infection in the USA
- Transmitted by bites of the dog or wood tick, which predominantly occur in spring and summer throughout much of the United States.

Feature

- Fever, headache, myalgia, rash, vomiting, and history of tick bite are commonly reported; however, the absence of any of these does not exclude diagnosis. A history of tick bite may not be elicited in up to 45% of cases.
- The rash usually sparing the face and may involve palms and soles.
- Signs and symptoms may be difficult to distinguish from those of common viral illnesses, leading to delayed diagnosis.
- Diagnosis should be considered in any person with a compatible clinical presentation and recent outdoor exposure.
- Late-stage manifestations, such as noncardiogenic pulmonary edema (acute respiratory distress syndrome [ARDS]) and cerebral edema, are consequences of microvascular leakage.

Investigation

- PCR (polymerase chain reaction) is the most appropriate test

Treatment

- **Doxycycline is the drug of choice** for *adults and children* and is almost always curative, especially if given in the first 5 days of illness.
  - Tetracyclines acts on 30S ribosomes to prevent protein synthesis in the infecting organism.
  - **Aluminium hydroxide can complex with this antibiotic in the gastrointestinal tract, preventing absorption.** Dairy products ingested at the same time can also cause this.
  - **Aluminium hydroxide medication should be stoped till the antibiotic course is finished**
- Because the risk of death rises if appropriate therapy is not started before the fifth day of illness, doxycycline should be prescribed for suspected Rocky Mountain spotted fever before confirmatory diagnostic test results are available.

Typhus (Rickettsial infection)

- caused by Rickettsia typhi (endemic typhus) or Rickettsia prowazekii (epidemic typhus). T
- **Rickettsia prowazekii (epidemic typhus)** is transmitted via human-to-human contact through body lice.
- Arthropod vectors transmit the etiologic agents to humans.
- Presented with fever and rash
- Both forms of typhus consist of a **rash that classically begins centrally, and spreads outwardly sparing the palms and soles** (unlike Rocky Mountain spotted fever)
- Rocky Mountain Spotted Fever can be distinguished from typhus because its rash begins peripherally, and spreads centrally to the palms, soles, and trunk.
- Doxycycline is the drug of choice for treatment in patients of all ages.

Histoplasmosis

- Histoplasmosis is one of the most common systemic fungal infections in the United States. It is endemic to the Ohio and Mississippi river valleys
- often associated with spelunkers (**cave divers**) or patients recently exposed to bird and bat droppings.

Feature

- The majority are asymptomatic.
- can closely mimic tuberculosis in symptomatology and imaging.
  - dry cough, shortness of breath, fatigue, and fever
- **Disseminated infection causes bilateral adrenal enlargement in 80% of** cases and it can result in adrenal insufficiency.
  - **Diagnosis: Adrenal biopsy or FNA with Groccott stain (Groccott-stained adrenal biopsy**).

Investigation

- Chest X-ray often reveals a solitary lung lesion.
- Disseminated histoplasmosis can cause systemic granulomatous inflammation and cavitation, which may be fatal.
- The organisms can be visualized using methenamine silver or periodic acid-Schiff staining.
- **On histology → *Macrophages containing yeast***
  - *Histoplasma capsulatum* is a small intracellular yeast that is phagocytosed by alveolar macrophages.

Treatment

- Itraconazole for 3-6 months

Actinomycosis

Predisposing conditions include:

- tooth extractions,
- fractures of the jaw,
- periodontal abscesses,
- foreign bodies penetrating the mucosal barrier (bone splinters, fish bones) or
- suppurating tonsillar crypts.
- impaired immunity

Features

- cervicofacial actinomycosis
  - the most common manifestation of infection with Actinomyces spp.
- Initially, cervicofacial actinomycosis presents either as an acute, usually odontogenic, abscess or cellulitis of the floor of the mouth, or as a slowly developing hard, painless, reddish or livid swelling.

- Small, acute actinomycotic abscesses may heal after surgical drainage alone. More often, however, the acute initial stage is followed by a subacute to chronic course if no specific antimicrobial treatment is administered.
- Chronic disease is characterised by regression of central suppurative foci while the infection progresses peripherally; it can spread to involve other parts of the head and neck, including the meninges.
- A quick and comparatively reliable diagnosis is possible microscopically, when sulphur granules are present; this is not conclusive, however, as nocardiosis may present similarly and has a similar appearance on microscopy.
- One way to differentiate Actinomyces spp. from Nocardia spp. is through culture: the former grow in anaerobic conditions and the latter do not.

Malignant otitis externa

- Malignant otitis externa is a necrotizing infection of the ear that is **commonly caused by *Pseudomonas aeruginosa*.**
- *Pseudomonas* species are often found swimming pools and hot tubs, and can also cause “hot tub folliculitis”.
- Susceptible individuals include diabetics and other immunosuppressed patients.
- **Feature**
  - Physical exam may reveal discharge from the ear
  - severe pain, out of proportion to physical findings, on manipulation of the ear.
  - The disease can affect surrounding bony architecture and cause cranial nerve palsies. Such involvement suggests poor prognosis.
- **Treatment** for suspected *Pseudomonas* infections → anti-**pseudomonal penicillin such as piperacillin-tazobactam,** which is a penicillin paired with a beta-lactamase inhibitor.

Parotid swelling

- causes of bilateral parotid swelling include:
  - Infection with viruses, including mumps, parainfluenza virus type 3, Coxsackie viruses and influenza A virus
  - Metabolic diseases, such as:
    - diabetes mellitus
    - uraemia
  - Drugs, such as:
    - phenylbutazone
    - **thiouracil**
- Other conditions associated with **chronic parotid swelling** include:
  - Alcoholic liver disease
  - Sarcoidosis
  - Sjögren syndrome
  - Lymphoma
  - Infection with HIV

Notes & Notes

For MRCP part 1 & 11

By

Dr. Yousif Abdallah Hamad

Dermatology

updated

Contains:

1/ Passmedicine 2017 (white & black fields)

2/ on examination 2016 (green fields)

3/ pastest 2016 (yellow fields)

4/ **Red fonts --> previous exams**

5/ other colours: updated UK sources

Epidermis

Epidermis - 5 layers - bottom layer = stratum germinativum which gives rise to keratinocytes and contains melanocytes

- The epidermis is the outermost layer of the skin and is composed of a stratified squamous epithelium with an underlying basal lamina
- It may be divided in to five layers:

Layer	Description
Stratum corneum	Flat, dead, scale-like cells filled with keratin Continually shed
Stratum lucidum	Clear layer - present in thick skin only
Stratum granulosum	Cells form links with neighbours
Stratum spinosum	Squamous cells begin keratin synthesis Thickest layer of epidermis
Stratum germinativum	The basement membrane - single layer of columnar epithelial cells **Gives rise to keratinocytes** Contains melanocytes

Definitions

- **plaque is a descriptive term for a skin lesion that is raised and greater than 1 cm in diameter.**
- **macule** → An area of altered skin colour is irrespective of the size.
- **papule** is a raised lesion less than 1 cm in diameter.
- **ulcer** is a discontinuity of the skin with complete loss of the epidermis and often portions of the dermis and subcutaneous fat.
- **vesicle** is a fluid-filled, well-circumscribed raised lesion.
- **Pustule are small elevation of the skin containing cloudy or purulent material, usually consisting of necrotic inflammatory cells**.
- **Bulla** are large vesicle containing serous fluid.
- **Fissure** are cracks in the skin that are narrow but deep.
- **Telangiectasia** are collection of enlarged capillaries visible on the skin or mucous membranes.

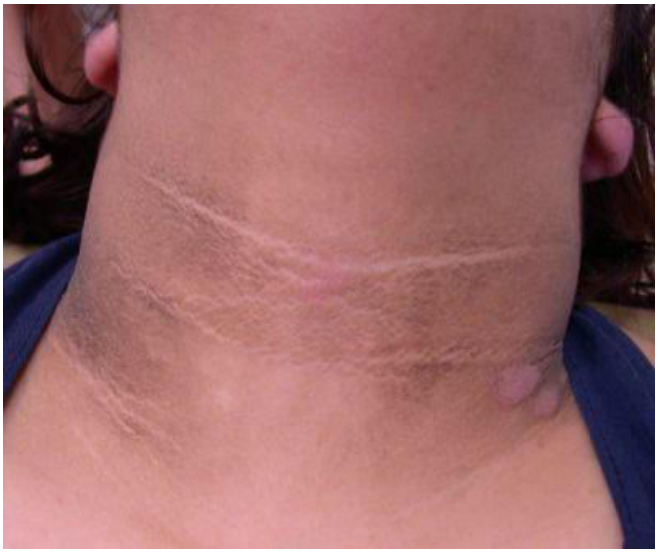
- **Lichenification of the skin is due to epidermal thickening characterised by visible and palpable thickening of the skin with accentuation of skin markings.**
- **Atrophy** of the skin may be due to loss of epidermis, dermis or subcutaneous tissue. Thinning of the epidermis presents as skin that appears thin and translucent. Thinning of the dermis and subcutaneous tissue leads to a depression in the skin.

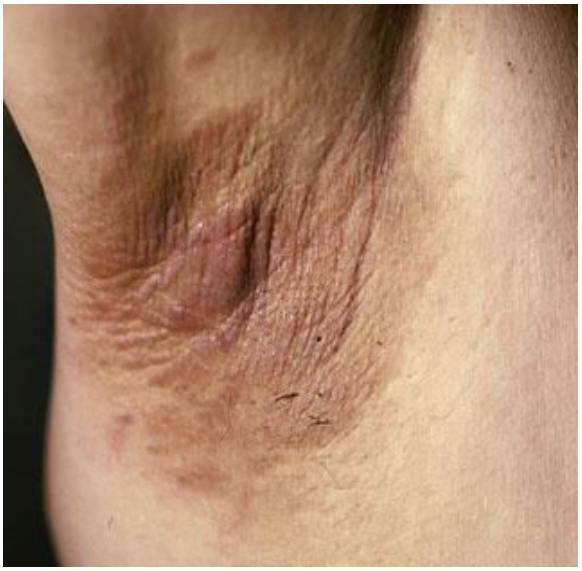
Acanthosis nigricans

Describes symmetrical, brown, velvety plaques that are often found on the neck, axilla and groin

Causes

- paraneoplastic phenomenon (usually tumours of the GI tract, especially **adenocarcinoma of the stomach**).
- diabetes mellitus
- obesity
- polycystic ovarian syndrome
- acromegaly
- Cushing's disease
- hypothyroidism
- familial
- Prader-Willi syndrome
- drugs: oral contraceptive pill, nicotinic acid





Acne rosacea is a chronic skin disease of unknown aetiology

Features

- typically affects nose, cheeks and forehead
- flushing is often first symptom
- telangiectasia are common
- later develops into persistent erythema with papules and pustules

- rhinophyma
- ocular involvement: blepharitis

Management

Acne rosacea treatment:
- mild/moderate: topical metronidazole
- severe/resistant: oral tetracycline

- topical metronidazole may be used for mild symptoms (i.e. Limited number of papules and pustules, no plaques)
- more severe disease is treated with systemic antibiotics e.g. Oxytetracycline
- recommend daily application of a high-factor sunscreen
- camouflage creams may help conceal redness
- laser therapy may be appropriate for patients with prominent telangiectasia

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Acne vulgaris

- Acne vulgaris is a common skin disorder which usually occurs in adolescence.
- It typically affects the face, neck and upper trunk
- characterised by the obstruction of the pilosebaceous follicle with keratin plugs which results in comedones, inflammation and pustules.

Epidemiology

- affects around 80-90% of teenagers, 60% of whom seek medical advice
- acne may also persist beyond adolescence, with 10-15% of females and 5% of males over 25 years old being affected

Pathophysiology is multifactorial

- follicular epidermal hyperproliferation → formation of a keratin plug → obstruction of pilosebaceous follicle.
- hormonal activation of sebaceous glands
  - Activity of sebaceous glands may be controlled by androgen,
  - although levels are often normal in patients with acne
  - Acne accompanying polycystic ovarian syndrome is caused by modestly raised circulating androgen levels.
  - Acne presenting at beyond aged 20 years should always prompt investigation of a possible secondary cause.
- colonisation by the anaerobic bacterium → Propionibacterium acnes
- inflammation

Classification: Acne may be classified into mild, moderate or severe:

- mild acne : open and closed comedones with or without sparse inflammatory lesions
- moderate acne: widespread non-inflammatory lesions and numerous papules and pustules
- severe acne: extensive inflammatory lesions, which may include nodules, pitting, and scarring

Features

Management: A simple step-up management scheme often used in the treatment of acne is as follows:

- single topical therapy (topical retinoids, benzyl peroxide)
- topical combination therapy (topical antibiotic, benzoyl peroxide, topical retinoid)
- oral antibiotics: e.g. Oxytetracycline, doxycycline.
  - Improvement may not be seen for 3-4 months.
  - Minocycline is now considered less appropriate due to the possibility of irreversible pigmentation.
  - Gram negative folliculitis may occur as a complication of long-term antibiotic use
    - high-dose oral trimethoprim is effective if this occurs
  - **Oral erythromycin may be used for acne in pregnancy**. The other drugs are contraindicated
- oral isotretinoin: only under specialist supervision
- Ethinylestradiol with cyproterone acetate (Dianette) is useful in some female patients with acne unresponsive to standard treatment.
- **There is no role for dietary modification in patients with acne**

Weight loss is the most important intervention.

Isotretinoin

- Isotretinoin is an oral retinoid used in the treatment of severe acne. Two-thirds of patients have a long term remission or cure following a course of oral isotretinoin

Adverse effects

- teratogenicity: females should ideally be using two forms of contraception (e.g. Combined oral contraceptive pill and condoms)
- dry skin, eyes and lips: the most common side-effect of isotretinoin
- low mood
- raised triglycerides
- hair thinning
- nose bleeds (caused by dryness of the nasal mucosa)
- benign intracranial hypertension: isotretinoin treatment should not be combined with tetracyclines for this reason
- photosensitivity

Alopecia

divided into scarring (destruction of hair follicle) and non-scarring (preservation of hair follicle)

Scarring alopecia

- trauma, burns
- radiotherapy
- lichen planus
- discoid lupus
- tinea capitis*
  - *scarring may develop in untreated tinea capitis if a kerion develops

Non-scarring alopecia

- male-pattern baldness
- drugs: cytotoxic drugs, carbimazole, heparin, oral contraceptive pill, colchicine
- nutritional: iron and zinc deficiency
- autoimmune: alopecia areata
- telogen effluvium (hair loss following stressful period e.g. surgery)
- trichotillomania
  - psychological disorder where patients are compelled to pull their own hair, resulting in alopecia.
  - It is typically encountered in teenage females and children

Cicatricial alopecia (also known as scarring alopecia)

- inflammation injures hair follicles resulting in permanent bald patches with no visible follicles.
  - inflammation can be seen as redness, scaling and crusting.
- Common causes include:
  - discoid lupus erythematosus, and
  - lichen planopilaris (a variant of lichen planus).
- Treatment is dependent on the underlying causes but often requires topical corticosteroids.

Alopecia areata

- Alopecia areata is a presumed autoimmune condition causing localised, well demarcated patches of hair loss.

Feature

- localised patches of non-scarring hair loss.
- Remaining hairs have a characteristic 'exclamation mark' appearance, and are tapered towards the base.
  - small, broken hairs at the edge of the hair loss
- More severe involvement may present as alopecia totalis (total loss of scalp hair) or alopecia universalis (total loss of all body hair).

Treatment

- Hair will regrow in 50% of patients by 1 year, and in 80-90% eventually. Careful explanation is therefore sufficient in many patients.
- **Other treatment options include**:
  - topical or intralesional corticosteroids
    - **the most appropriate treatment for area of hair loss → Intra-lesional triamcinolone**
  - topical minoxidil
  - phototherapy
  - dithranol
  - contact immunotherapy
  - wigs

Differential diagnosis

- **Androgenetic alopecia**

  - presents after puberty as a more diffuse slow hair loss with characteristic loss over the temporal regions and vertex in males.
- **Discoid lupus erythematosus (DLE)**
  - presents as scarring alopecia.
  - Areas of alopecia are usually atrophic with visible loss of hair follicles.
  - Patients may have DLE lesions elsewhere.
  - If not treated early, hair loss is usually irreversible.
- **Telogen effluvium**
  - presents with diffuse hair loss and usually presents one to three months after a stressful episode, for example, viral illness, surgery, childbirth, emotional stress.
  - Hair loss is never complete and usually stops after three to five months.
  - Subsequent hair regrowth is usually complete.
- **Trichotillomania**
  - more commonly seen in children compared to adults.
  - Patients also present with localised hair loss but in a bizarre pattern.
  - Hairs of differing lengths are usually seen within and at the edges of the patches.
  - Patients may or may not volunteer a history of hair pulling.

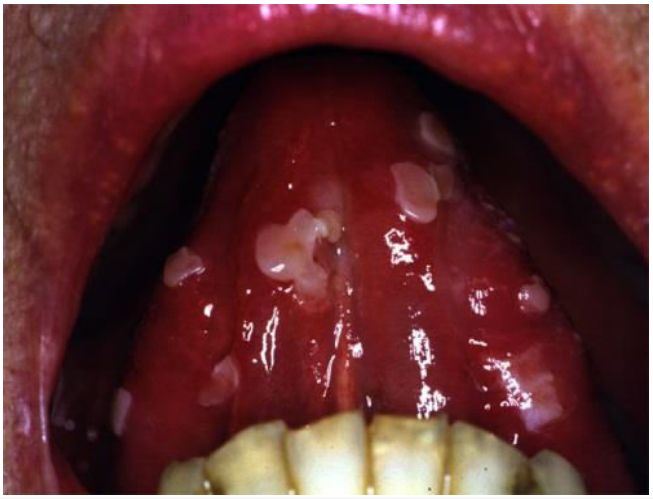
Pemphigus vulgaris

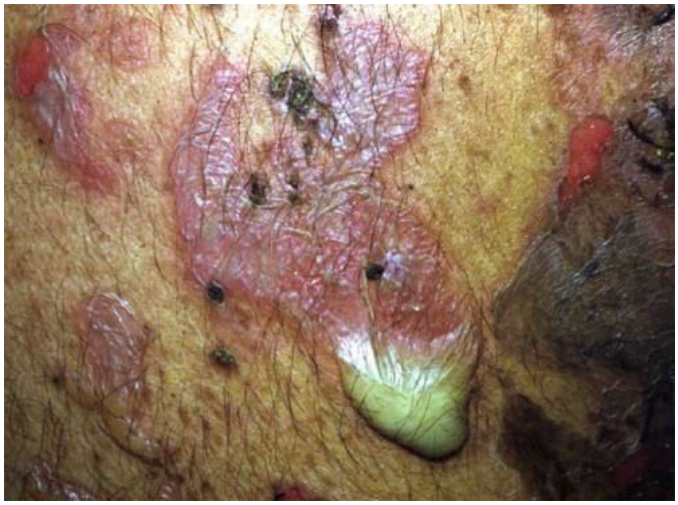
Blisters/bullae
- no mucosal involvement: bullous pemphigoid
- mucosal involvement: pemphigus vulgaris

- Pemphigus vulgaris is an autoimmune disease caused by antibodies **(IgG) directed against desmoglein 3**, a cadherin-type epithelial cell adhesion molecule.
- The binding of autoantibodies results in a loss of cell-to-cell adhesion, a process termed acantholysis.
- It is more common in the Ashkenazi Jewish population
- seen predominantly in patients ages 50-60, but can affect many ages.

Features

- **mucosal ulceration is common and often the presenting symptom.** Oral involvement is seen in 50-70% of patients
- skin blistering - flaccid, easily ruptured vesicles and bullae.
  - Blisters are thin-walled and rupture easily (intact blisters are rarely seen).
- Lesions are typically painful but not itchy. These may develop months after the initial mucosal symptoms.
- Nikolsky's describes the spread of bullae following application of horizontal, tangential pressure to the skin
- Immunofluorescent staining of a biopsy sample shows deposition of immunoglobulin (IgG) directed against to keratinocyte desmosomes and to desmosome-free areas of the keratinocyte cell membrane, resulting in a 'chicken wire' appearance.
- acantholysis on biopsy





Mucosal ulceration is common with pemphigus

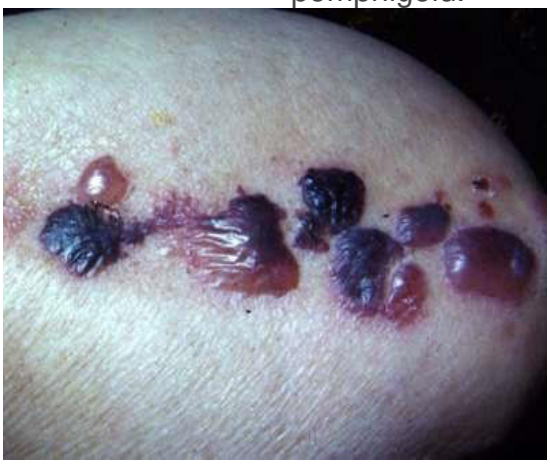
Management

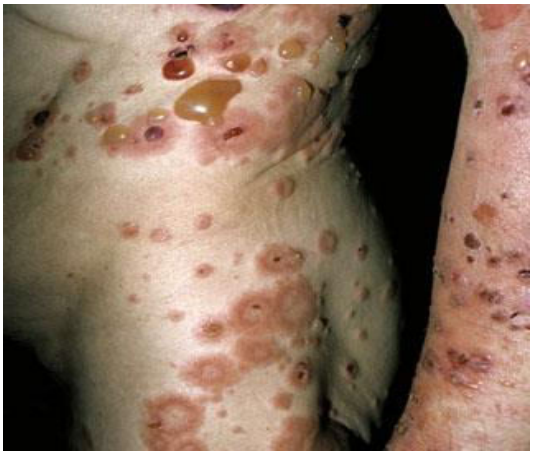
- steroids
- immunosuppressants

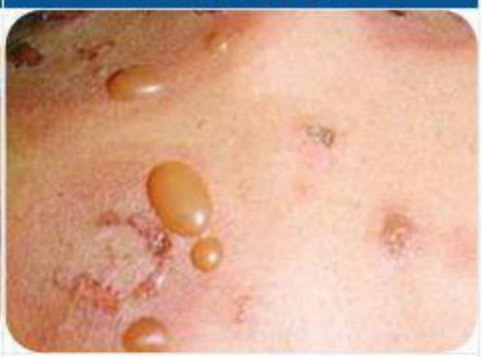
Bullous pemphigoid

- Pemphigoid, erythema multiforme, and herpes are the commonest causes of a blistering rash.
- Bullous pemphigoid is an autoimmune condition causing sub-epidermal blistering of the skin.
- This is secondary to the development of **antibodies against hemidesmosomal proteins BP180 and BP230**
  - caused by (IgG) autoantibodies against components of the basement membrane.
- Bullous pemphigoid is more common in elderly patients (over 60 years).
- **Features** include
  - itchy, tense blisters typically around flexures
  - the blisters usually heal without scarring
  - mouth is usually spared*
    - *in reality around 10-50% of patients have a degree of mucosal involvement. It would however be unusual for an exam question to mention mucosal involvement as it is seen as a classic differentiating feature between pemphigoid and pemphigus.
- **Skin biopsy:** immunofluorescence shows IgG and C3 at the dermoepidermal junction
- **Differential diagnosis**
  - Blistering in pemphigoid occurs at the sub-epidermal level - deeper than the blisters of pemphigus vulgaris (which occur at the dermal-epidermal junction); hence the tense blisters seen in pemphigoid. Blisters are thin-walled and fragile in pemphigus - few intact blisters are ever seen.
  - In pemphigus vulgaris, mucous membrane involvement is more common, and intact bullae are rare. Skin biopsy for routine and direct immunofluorescence is needed to differentiate from bullous pemphigoid.
- **Management**
  - referral to dermatologist for biopsy and confirmation of diagnosis
  - oral corticosteroids are the mainstay of treatment
  - topical corticosteroids, immunosuppressants and antibiotics are also used

- Topical corticosteroids may be attempted in patients with mild, localised bullous pemphigoid.





	Pemphigus vulgaris	Bullous pemphigoid
Appearance		
Age	Younger	Older
Mucous membrane involvement	Yes	Rare
Autoantibodies	Against desmoglein 3	Against hemidesmosomes
Blister location	Intraepidermal (superficial)	Subepidermal (deep)
Blister quality	Flaccid, rupture easily	Tense and firm
Nikolsky's sign	Nikolsky **positive**	Nikolsky **negative**
Prognosis	Poor	Favorable

Dermatitis herpetiformis

- autoimmune blistering skin disorder **associated with coeliac disease** and gluten sensitivity.
- it is caused by deposition of IgA in the dermis.

Features

- itchy, vesicular skin lesions on the extensor surfaces (e.g. elbows, knees, buttocks)

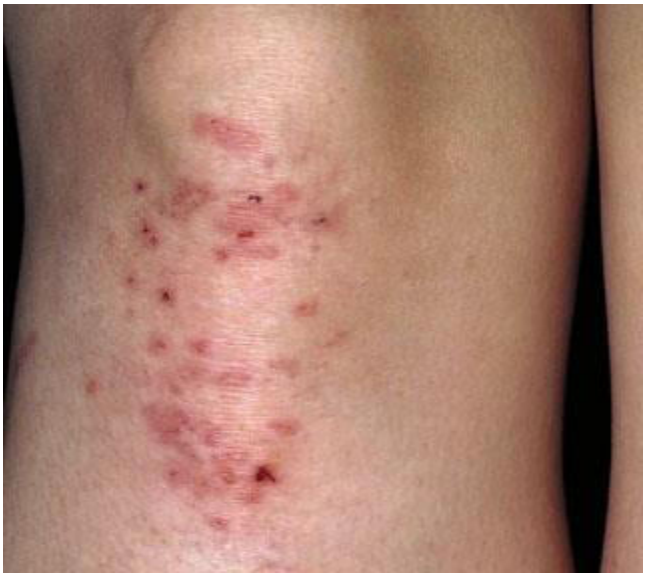
Diagnosis

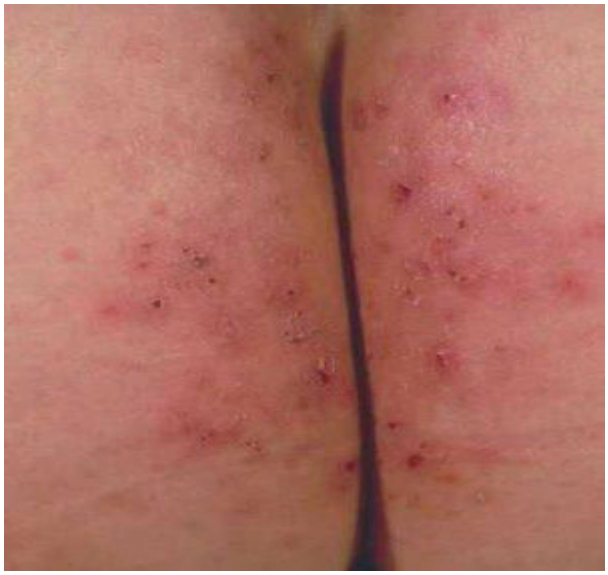
Dermatitis herpetiformis - caused by IgA deposition in the dermis

- skin biopsy:
  - direct immunofluorescence shows **deposition of IgA** in a **granular pattern** in the upper **dermis** (in the **dermal papillae**)(Granular IgA deposits at the basement membrane zone)

Management

- gluten-free diet
- dapsone





Discoid lupus erythematous

Pathology

- it is a chronic type of Cutaneous lupus erythematosus (CLE)
- **characterised by follicular keratin plugs**
- characterised by a well-demarcated macular rash with erythema, scales, and plaques that often results in scarring and atrophy.

Aetiology

- thought to be **autoimmune** in aetiology

Association

- may occur in the absence or in association with systemic SLE.
  - Approximately 10% of patients may have signs of SLE.

Epidemiology

- generally seen in younger females.
- occurs 2-3 times more frequently in women than in men
- more common in African–Caribbean female.

Features

- erythematous, raised rash, sometimes scaly
- may be photosensitive
- more common on face, neck, ears and scalp
- lesions heal with atrophy, scarring (may cause scarring alopecia), and pigmentation

Diagnosis

- made by biopsy of the lesion.

Management

Discoid lupus erythematous - topical steroids → oral hydroxychloroquine

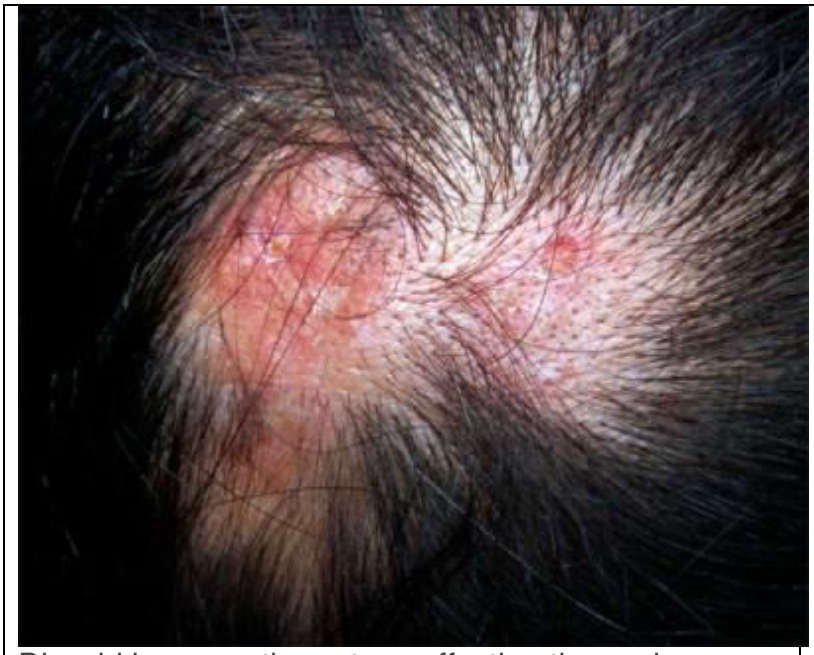
- **1st line** → topical potent steroid cream
- **2nd line** → oral antimalarials e.g. hydroxychloroquine
  - other options
    - Topical calcineurin inhibitors
    - Intralesional corticosteroids
    - Oral corticosteroids.
- avoid sun exposure

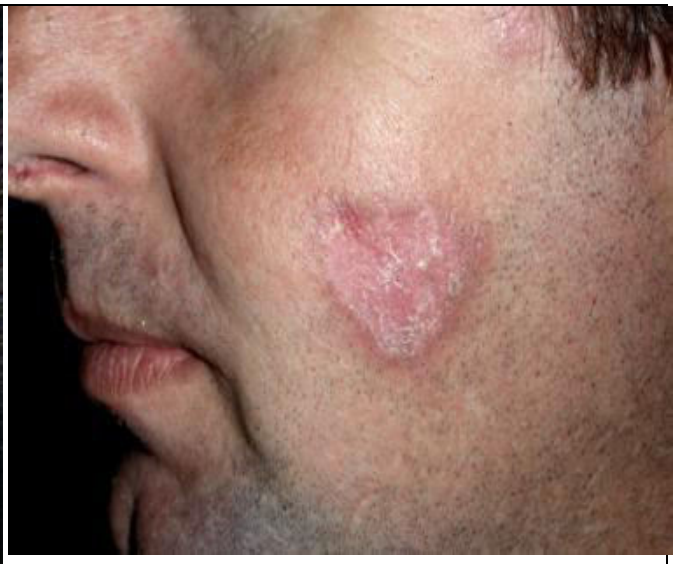
Prognosis

- **The risk of progression to SLE** in patients with DLE was demonstrated to be higher than previously reported (**16.7% progression within 3 years of diagnosis,** as compared with previous data indicating that <5-10% of patients with DLE progress to SLE).
- **children** with DLE seem to have a higher early rate of progression to SLE (up to **25%**) indicating that the **age at onset might influence disease severity**

According to a recent epidemiologic study, approximately 16% of patients with discoid lupus erythematosus (DLE) may develop systemic involvement within 3 years of diagnosis.

Ref: emedicine.medscape.com .Updated: May 10, 2017
https://emedicine.medscape.com/article/1065529-clinical


Discoid lupus erythematous affecting the scalp


Discoid lupus erythematous affecting the face

Contact dermatitis

There are two main types of contact dermatitis

1. **Irritant contact dermatitis**:
   - common
   - non-allergic reaction due to weak acids or alkalis (e.g. detergents).
   - Often seen on the hands.
   - Erythema is typical, crusting and vesicles are rare
2. **Allergic contact dermatitis**:
   - type IV hypersensitivity reaction.
   - Uncommon
   - often seen on the head following hair dyes.
   - Presents as an acute weeping eczema, which predominately affects the margins of the hairline rather than the hairy scalp itself.
   - Topical treatment with a potent steroid is indicated

Cement is a frequent cause of contact dermatitis. The alkaline nature of cement may cause an irritant contact dermatitis whilst the dichromates in cement also can cause an allergic contact dermatitis

The main difference between allergic contact dermatitis and irritant contact dermatitis:

- The rash caused by allergic contact dermatitis **confined to contacted area**, whereas in irritant contact dermatitis, the rash is more **widespread**.
- In allergic contact dermatitis the rash usually appears **after a day or two** after exposure to the allergen, unlike irritant contact dermatitis that appears **immediately** after the contact with the trigger.

Pruritus

The table below lists the main characteristics of the most important causes of pruritus

Liver disease	**History of alcohol excess** **Stigmata of chronic liver disease: spider naevi, bruising, palmar erythema, gynaecomastia etc** **Evidence of decompensation: ascites, jaundice, encephalopathy**
Iron deficiency anaemia	Pallor Other signs: koilonychia, atrophic glossitis, post-cricoid webs, angular stomatitis
Polycythaemia	Pruritus particularly after warm bath 'Ruddy complexion' Gout Peptic ulcer disease
Chronic kidney disease	Lethargy & pallor Oedema & weight gain Hypertension
Lymphoma	Night sweats Lymphadenopathy Splenomegaly, hepatomegaly Fatigue

Other causes:

- hyper- and hypothyroidism
- diabetes
- pregnancy
- 'senile' pruritus
- Urticaria
  - Uritcaria can be classified into idiopathic, immune, or non-immune.
  - **Up to 50% of cases are idiopathic**, and no trigger is readily identifiable.
- skin disorders: eczema, scabies, psoriasis, pityriasis rosea

Eczema herpeticum

- Eczema herpeticum describes a severe primary infection of the skin by herpes simplex virus 1 or 2.

Features

- It is more commonly seen in children with atopic eczema.
- **Typically, the child has a high fever for seven days,** and recurrent attacks can occur.
- It may affect any site but is most often seen on face and neck.

Treatment

- Eczema herpeticum is considered as one of the few dermatological emergencies.

- As it is potentially life threatening children should be admitted for IV acyclovir

Complications

- Death can result from physiological disturbances (loss of fluid electrolytes and protein through the skin) or dissemination of the virus to brain and other organs or from secondary bacterial sepsis.
- may be further complicated by secondary staphylococcal infection. This is treated by adding oral antibiotics, for example, flucloxacillin 500 mg q.i.d.

Eczema: topical steroids

Topical steroids
- moderate: Clobetasone butyrate 0.05%
- potent: Betamethasone valerate 0.1%
- very potent: Clobetasol propionate 0.05%

Use weakest steroid cream which controls patients symptoms

The table below shows topical steroids by potency

Mild	Moderate	Potent	Very potent
Hydrocortisone 0.5-2.5%	Betamethasone valerate 0.025% (Betnovate RD) Clobeta**sone** butyrate 0.05% (Eumovate)	Fluticasone propionate 0.05% (Cutivate) Betamethasone valerate 0.1% (Betnovate)	Clobeta**sol** propionate 0.05% (Dermovate)

Finger tip rule

- 1 finger tip unit (FTU) = 0.5 g, sufficient to treat a skin area about twice that of the flat of an adult hand

Topical steroid doses for eczema in adults

Area of skin	Fingertip units per dose
Hand and fingers (front and back)	1.0
A foot (all over)	2.0
Front of chest and abdomen	7.0

Area of skin	Fingertip units per dose
Back and buttocks	7.0
Face and neck	2.5
An entire arm and hand	4.0
An entire leg and foot	8.0

The BNF makes recommendation on the quantity of topical steroids that should be prescribed for an adult for a single daily application for 2 weeks:

Area	Amount
Face and neck	15 to 30 g
Both hands	15 to 30 g
Scalp	15 to 30 g
Both arms	30 to 60 g
Both legs	100 g
Trunk	100 g
Groin and genitalia	15 to 30 g

Pompholyx

Pompholyx is a type of eczema which affects both the hands (cheiropompholyx) and the feet (pedopompholyx). It is also known as dyshidrotic eczema

Features

- small blisters on the palms and soles
- pruritic, sometimes burning sensation
- once blisters burst skin may become dry and crack

Management

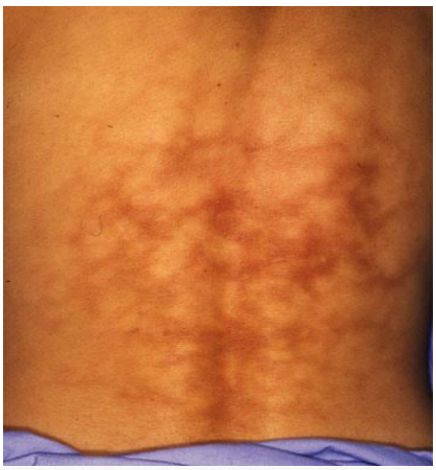
- cool compresses
- emollients
- topical steroids

Nickel dermatitis

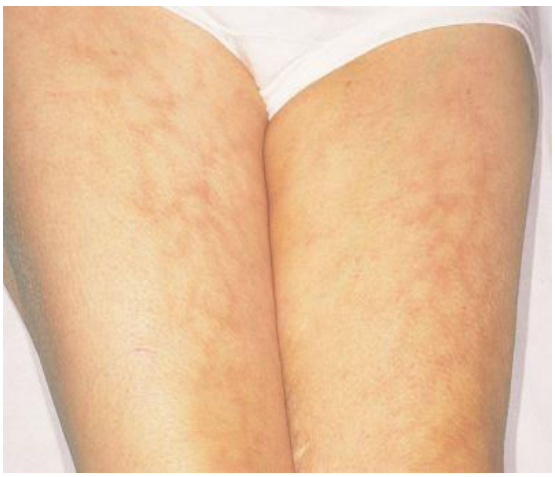
- Nickel is a common cause allergic contact dermatitis and is an example of a type IV hypersensitivity reaction. It is often caused by jewellery such as watches
- It is diagnosed by a skin patch test

Erythema ab igne

- Erythema ab igne is a skin disorder caused by over exposure to infrared radiation.
- It classically presents on the front of the legs due to the patient sitting too close to a fire or heater. It may also arise as a response to chronic hot water bottle use.
- Characteristic features include reticulated, erythematous patches with hyperpigmentation and telangiectasia.
- A typical history would be an elderly women who always sits next to an open fire.
- **Hypothyroidism can make patients feel cold and hence more likely to sit next a heater / fire.**
- **If the cause is not treated then patients may go on to develop squamous cell skin cancer.**



Erythema ab igne



Erythema ab igne

Erythema multiforme

Herpes simplex virus infection is the commonest cause of **Erythema multiforme**

- mucocutaneous inflammatory condition, characterised by target lesions that resemble a bull's eye. These usually erupt over 24 to 48 hours and last for 1 to 2 weeks.
- considered to be a type IV hypersensitivity reaction
- Typically presents in a symmetrical distribution of lesions over the dorsal surfaces of the extensor extremities with minimal mucous membrane involvement.

Causes

- viruses: herpes simplex virus (**the most common cause**), Orf
- idiopathic
- bacteria: **Mycoplasma**, *Streptococcus*
- drugs: penicillin, sulphonamides, sulphonylureas, barbiturates, carbamazepine, allopurinol, NSAIDs, oral contraceptive pill, nevirapine
- connective tissue disease e.g. Systemic lupus erythematosus, inflammatory bowel disease
- sarcoidosis
- malignancy

Classification

- **Erythema multiforme minor** (typical targets or raised oedematous papules, with acral distribution, without involvement of mucosal sites, and involving <10% total body surface area)
- **Erythema multiforme major** (typical targets or raised oedematous papules, with acral distribution, plus involvement of 1 or more mucosal sites, and involving <10% total body surface area)

Features

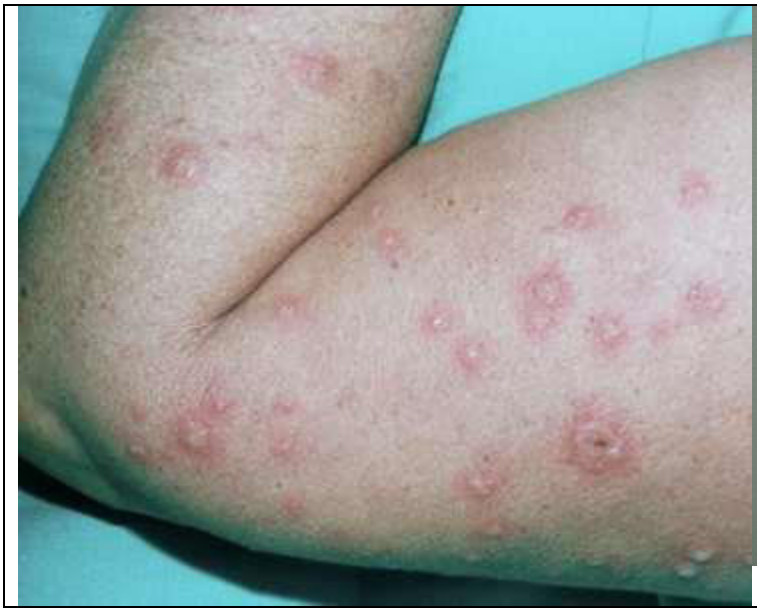
- target lesions
- initially seen on the back of the hands / feet before spreading to the torso
- upper limbs are more commonly affected than the lower limbs
- pruritus is occasionally seen and is usually mild
- If symptoms are severe and involve blistering and mucosal involvement the term Stevens-Johnson syndrome is used.

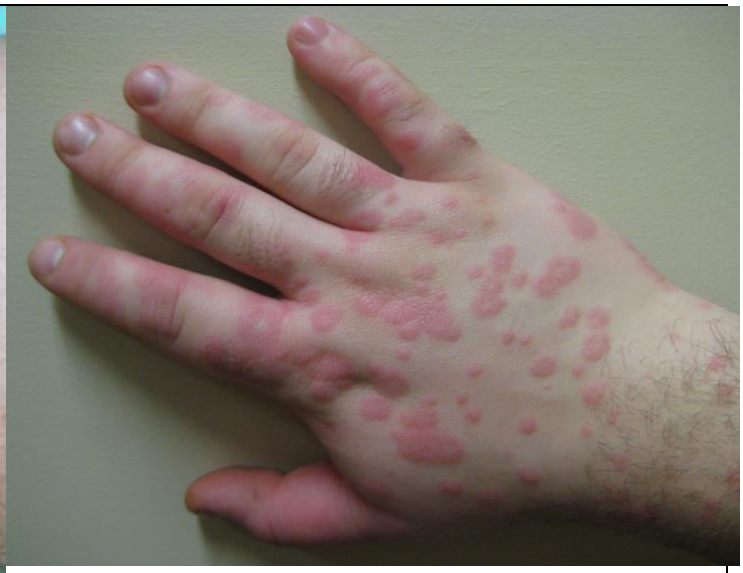
Treatment

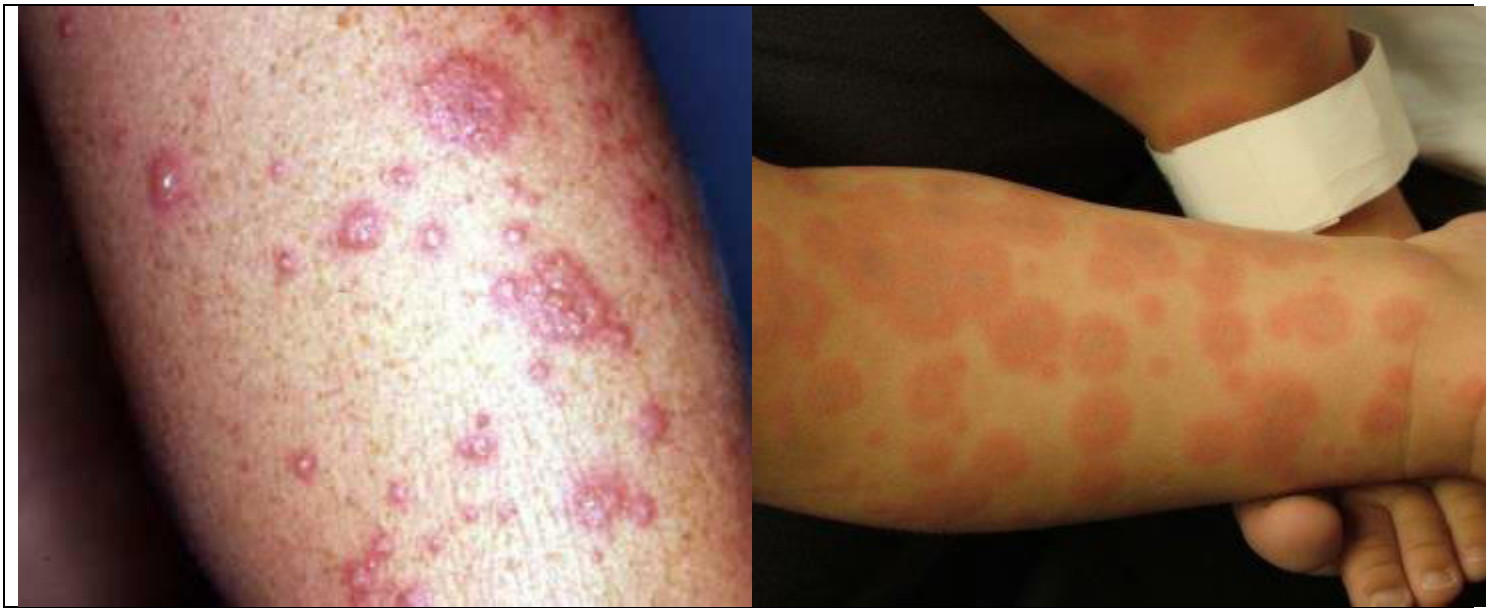
- Supportive care and treatment of underlying infection.

Prognosis

- usually mild and self-limiting disease with the lesions healing within 2 to 3 weeks without scarring.







Related dermatitides

- **Stevens-Johnson syndrome**: severe macular (atypical target) lesions that coalesce, resulting in epidermal blistering, necrosis, and sloughing. No typical targets. Less than 10% total body surface area affected. May present with only mucosal involvement..
- **Toxic epidermal necrolysis**: severe macular (atypical target) lesions that coalesce, resulting in epidermal blistering, necrosis, and sloughing. No typical targets. More than 30% total body surface area affected.
- **Stevens-Johnson/toxic epidermal necrolysis overlap**: severe macular (atypical target) lesions that coalesce, resulting in epidermal blistering, necrosis, and sloughing. No typical targets. Between 10% and 30% total body surface area affected.\

Erythema multiforme	Stevens-Johnson syndrome
lesions begin on the extremities	Lesions typically begin on the face and trunk.
Commonly related to infectious diseases and not drug exposure.	More than 50% of cases are due to medications
typical targets.	No typical targets.
Histology → high density of cell infiltrate rich in T-lymphocytes.	Histology → poor infiltrate of macrophages and dendrocytes with strong tumor necrosis factor (TNF)

Stevens-Johnson syndrome

- severe form of erythema multiforme associated with mucosal involvement and systemic symptoms
- It is now known also as erythema multiforme major

Features

- rash is typically maculopapular with target lesions being characteristic. May develop into vesicles or bullae
- mucosal involvement
- systemic symptoms: fever, arthralgia

Causes

- idiopathic
- bacteria: Mycoplasma, *Streptococcus*
- viruses: herpes simplex virus, Orf
- drugs: penicillin, sulphonamides, carbamazepine, allopurinol, NSAIDs, oral contraceptive pill
- connective tissue disease e.g. SLE
- sarcoidosis
- malignancy

Toxic epidermal necrolysis (TEN)

- TEN is a severe mucocutaneous exfoliative disease with an uncertain pathogenesis and a high mortality rate.
- TEN is a potentially life-threatening skin disorder that is most commonly seen secondary to a drug reaction.
- In this condition the skin develops a scalded appearance over an extensive area.
- Some authors consider TEN to be the severe end of a spectrum of skin disorders which includes erythema multiforme and Stevens-Johnson syndrome
- It is often idiopathic but may be associated with:
  - Viral infections
  - Leukaemia
  - Lymphoma, and
  - Drugs (in particular sulphonamides and anticonvulsants).

Features

- systemically unwell e.g. pyrexia, tachycardic
- positive Nikolsky's sign: the epidermis separates with mild lateral pressure

Drugs known to induce TEN

- phenytoin
- sulphonamides
- allopurinol
- penicillins
- **carbamazepine**
- NSAIDs

Management

- stop precipitating factor
  - **is most likely to improve prognosis**
- supportive care, often in intensive care unit
- intravenous immunoglobulin has been shown to be effective and is now commonly used first-line
- other treatment options include: immunosuppressive agents (ciclosporin and cyclophosphamide), plasmapheresis

Prognosis

- The risk of death in patients with toxic epidermal necrolysis can be accurately predicted by the toxic epidermal necrolysis-specific severity-of-illness score (SCORTEN).

- Each of the following independent **prognostic factors** is given a score of one:
  - Age of greater than 40 years;
  - Heart rate of greater than 120 beats per minute;
  - Cancer/hematologic malignancy;
  - Involved body surface area of greater than 10%;
  - Serum urea level of more than 10 mmol/L;
  - Serum bicarbonate level of less than 20 mmol/L;
  - Serum glucose level of more than 14 mmol/L.
- A score of 0-1 indicates a mortality risk of 3.2%;
- score of 2, 12.1%;
- score of 3, 35.3%;
- score of 4, 58.3%;
- score of 5 or more, 90%.

Erythema nodosum

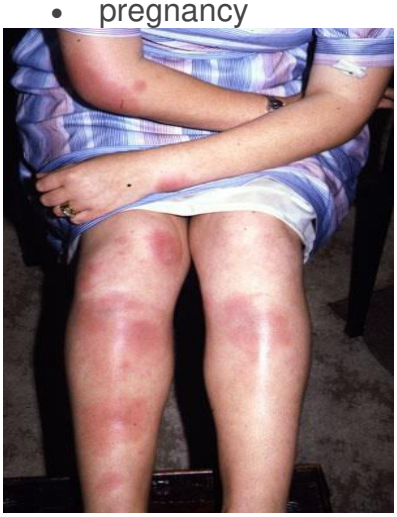
Always do a chest x-ray on a patient with erythema nodosum, to exclude sarcoidosis

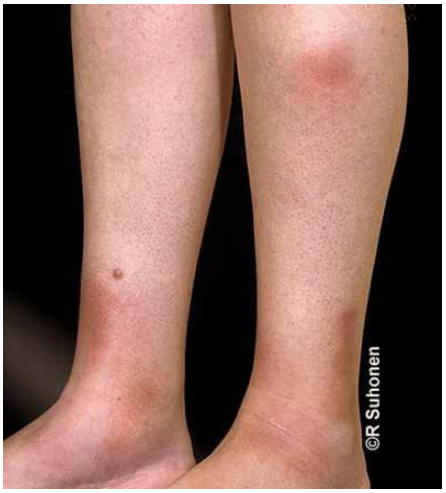
Overview

- inflammation of subcutaneous fat
- Histology of these lesions shows a vasculitis of small venules and panniculitis.
- typically causes tender, erythematous, nodular lesions
- usually occurs over shins, may also occur elsewhere (e.g. forearms, thighs)
- **usually resolves within 6 weeks**
- **lesions heal without scarring**

Causes

- infection: streptococci, TB, brucellosis
  - **The commonest cause is streptococcal infection.**
- systemic disease: sarcoidosis, inflammatory bowel disease (**ulcerative colitis**), Behcet's , SLE
- malignancy/lymphoma
- Drugs (oral contraceptive, sulfonamides, penicillins, antipyretics, montelukast, Hep B vaccination, omeprazole).
- pregnancy





Erythema induratum (EI)

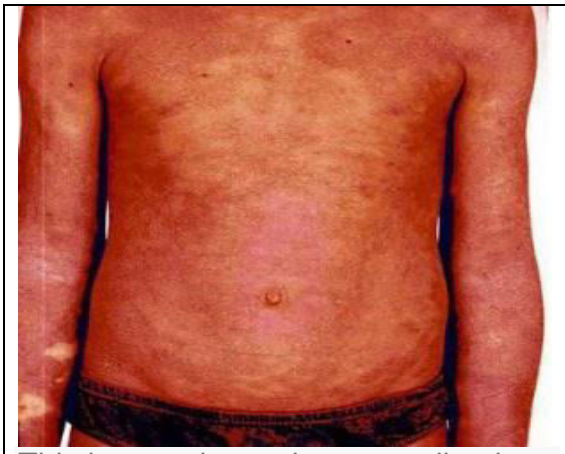
- EI is a form of panniculitis characterised by chronic, recurrent, tender, subcutaneous, and sometimes **ulcerated** nodules on the lower legs that may also appear elsewhere.
    - **(Erythema nodosum also commonly associated with TB but do not ulcerate)**
- Females are more frequently affected, with a female: male ratio of 7:1 and it is more frequent in younger females.
- **It is found in association with tuberculosis.**

Erythrasma

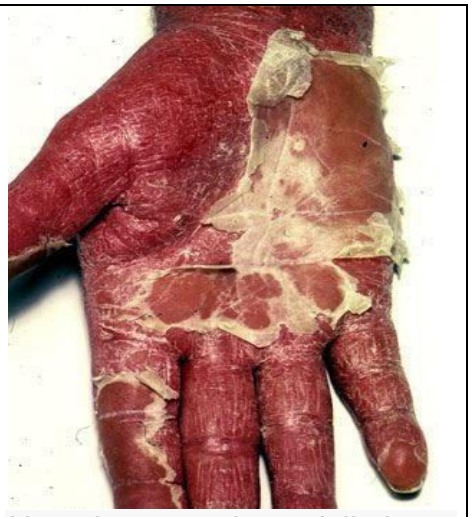
- Erythrasma is a generally asymptomatic, flat, slightly scaly, pink or brown rash usually found in the groin or axillae.
- It is caused by an overgrowth of the diphtheroid Corynebacterium minutissimum
- Examination with Wood's light reveals a coral-red fluorescence.
- Topical miconazole or antibacterial are usually effective. Oral erythromycin may be used for more extensive infection

Erythroderma

- Erythroderma is a term used when more than 95% of the skin is involved in a rash of any kind
- **Mechanism**
    - The mechanism behind erythroderma is most likely from cutaneous thermal dysregulation.
        - **Increased blood flow to the skin** leads to heat and fluid loss, and increased rate of skin cell turnover and skin sloughing.
- **Causes** of erythroderma
    - Eczema (40%)
    - Psoriasis (25%)
    - drugs e.g. gold
    - lymphoma, leukaemia
    - pityriasis rubra pilaris
    - idiopathic
- often accompanied with fever, shivering and malaise.
- **Erythrodermic psoriasis**
    - may result from progression of chronic disease to an exfoliative phase with plaques covering most of the body. Associated with mild systemic upset
    - more serious form is an acute deterioration. This may be triggered by a variety of factors such as withdrawal of systemic steroids. Patients need to be admitted to hospital for management



This image shows the generalised erythematous rash seen in patients with erythroderma, sometimes referred to as 'red man syndrome'



Note the extensive exfoliation seen in this patient

Polymorphous light eruption

- presents most commonly in young females.
- **commonly occurs a few hours after sun-exposure and resolves after a few days, without scarring.**
- Various morphologies have been described, for example, macules, papules, patches or plaques.

Fungal nail infections

Onychomycosis is fungal infection of the nails. This may be caused by

- dermatophytes - mainly Trichophyton rubrum, accounts for 90% of cases
- yeasts - such as *Candida*
- non-dermatophyte moulds

Features

- 'unsightly' nails are a common reason for presentation
- thickened, rough, opaque nails are the most common finding

Investigation

- nail clippings
- scrapings of the affected nail
- **Wood's lamp**
  - **useful, rapid and easy way to confirm the diagnosis**
  - Yellow to yellow-green fluorescence is characteristic of fine scales taken from active fungal lesions
  - the sensitivity of this procedure is reduced when patients have taken a recent shower

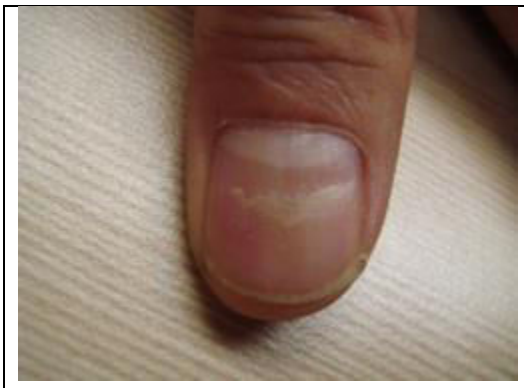
Management

Dermatophyte nail infections - use oral terbinafine

- treatment is successful in around 50-80% of people
- diagnosis should be confirmed by microbiology before starting treatment
- dermatophyte infection:
  - **first-line: oral terbinafine**
  - alternative: oral itraconazole.
  - Treatment duration:
    - for fingernail infections → 6 weeks - 3 months
    - for toenails → 3 - 6 months
- *Candida* infection: mild disease should be treated with topical antifungals (e.g. Amorolfine) whilst more severe infections should be treated with oral itraconazole for a period of 12 weeks

Beau's lines

- Beau's lines is a benign nail condition that presents as a jagged transverse groove on the nail plate corresponding to an episode of nail growth arrest, which can **occur during an episode of severe medical illness**. It usually affects several nails.



Beau's lines

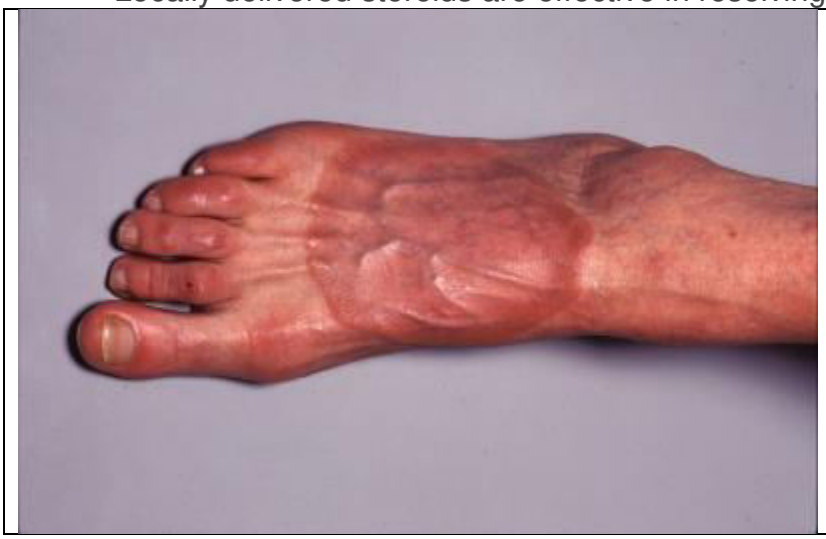
Nail conditions

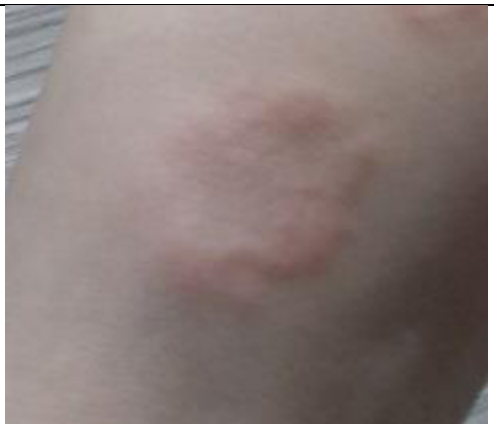
- **Fungal nail infections** present with thickening and discolouration of the nail plate with prominent subungual debris. It usually only affects one or several nails.
- **Nail psoriasis** presents with pitting, onycholysis, subungual debris and yellowish nail discolouration.

Granuloma annulare

Basics

- Granuloma annulare is a benign inflammatory condition of unknown aetiology
- characterised by dermal papules which can coalesce to form annular plaques.
- papular lesions that are often slightly hyperpigmented and depressed centrally
- typically occur on the dorsal surfaces of the hands and feet, and on the extensor aspects of the arms and legs
- Histology reveals foci of degenerative collagen surrounded by areas of granulomatous inflammation.
- A number of associations have been proposed to conditions such as diabetes mellitus but there is only weak evidence for this
- **Treatment → Observation** (The eruption should disappear spontaneously.)
- Locally delivered steroids are effective in resolving the condition.





Granuloma annulare

Herpes simplex virus

There are two strains of the herpes simplex virus (HSV) in humans: HSV-1 and HSV-2. Whilst it was previously thought HSV-1 accounted for oral lesions (cold sores) and HSV-2 for genital herpes it is now known there is considerable overlap

Features

- primary infection: may present with a severe gingivostomatitis
- cold sores
- painful genital ulceration

Management

- gingivostomatitis: oral aciclovir, chlorhexidine mouthwash
- cold sores: topical aciclovir although the evidence base for this is modest

- genital herpes: oral aciclovir. Some patients with frequent exacerbations may benefit from longer term aciclovir

Pregnancy

- elective caesarean section at term is advised if a primary attack of herpes occurs during pregnancy at greater than 28 weeks gestation

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Molluscum contagiosum

- common skin infection caused by molluscum contagiosum virus (MCV), a member of the Poxviridae family (DNA) pox virus.
- The majority of cases occur in children (often in children with atopic eczema), with the maximum incidence in preschool children aged 14 years.

Transmission

- occurs directly by close personal contact, or
- indirectly via fomites (contaminated surfaces) such as shared towels and flannels.
- may be spread following scratching to other sites.

Presentation

- Typically presents with characteristic pinkish or pearly white papules with a central umbilication, which are up to 5 mm in diameter.
- Lesions appear in clusters in areas anywhere on the body (except the palms of the hands and the soles of the feet).
- In children, lesions are commonly seen on the trunk and in flexures, but anogenital lesions may also occur.
- In adults, sexual contact may lead to lesions developing on the genitalia, pubis, thighs, and lower abdomen.
- Rarely, lesions can occur on the oral mucosa and on the eyelids.
- seen in patients with advanced HIV/AIDS (CD4 count less than 200 cells/mm^3). → **HIV antibody test hould be performed**

Self-care advice:

- Reassure people that molluscum contagiosum is a self-limiting condition.
- Spontaneous resolution usually occurs within 18 months
- Explain that lesions are contagious, and it is sensible to avoid sharing towels, clothing, and baths with uninfected people (e.g. siblings)
- Encourage people not to scratch the lesions. If it is problematic, consider treatment to alleviate the itch
- Exclusion from school, gym, or swimming is not necessary

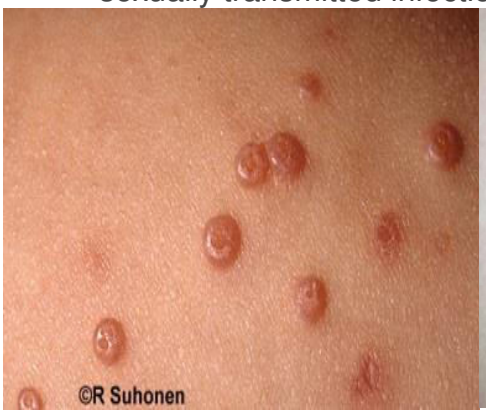
Treatment

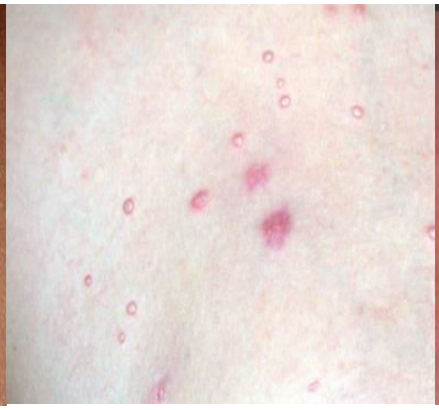
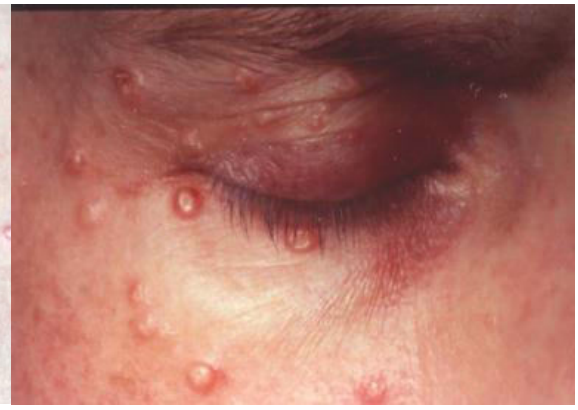
- usually not recommended → **Watchful waiting** (especially in children)
- for troublesome lesions → use simple trauma or cryotherapy, depending on the parents' wishes and the child's age:
  - simple trauma
    - Squeezing (with fingernails) or piercing (orange stick) lesions may be tried, following a bath.
    - Treatment should be limited to a few lesions at one time

  - Cryotherapy may be used in older children or adults, if the healthcare professional is experienced in the procedure
- topical imiquimod
- topical cantharidin.
- Oral cimetidine may be attempted in some patients with widespread lesions.
- Eczema or inflammation can develop around lesions prior to resolution.
  - Treatment may be required if:
    - → Itching is problematic; prescribe an emollient and a mild topical corticosteroid (e.g. hydrocortisone 1%)
    - → The skin looks infected (e.g. oedema, crusting); prescribe a topical antibiotic (e.g. fusidic acid 2%)

Referral may be necessary in some circumstances:

- HIV-positive with extensive lesions → urgent referral to a HIV specialist
- eyelid-margin or ocular lesions and associated red eye → urgent referral to an ophthalmologist
- ano-genital lesions → should be referred to genito-urinary medicine, for screening for other sexually transmitted infections



Impetigo

Impetigo - topical fusidic acid → oral flucloxacillin / topical retapamulin

Impetigo is a superficial bacterial skin infection usually caused by either *Staphylcoccus aureus* or *Streptococcus pyogenes*.

Features

- 'golden', crusted skin lesions typically found around the mouth
- very contagious

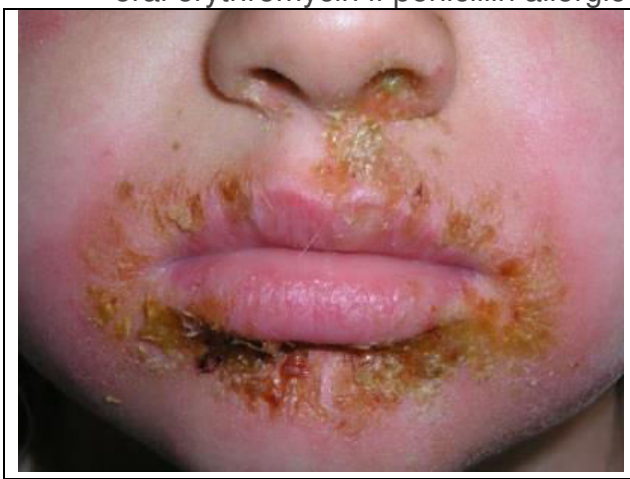
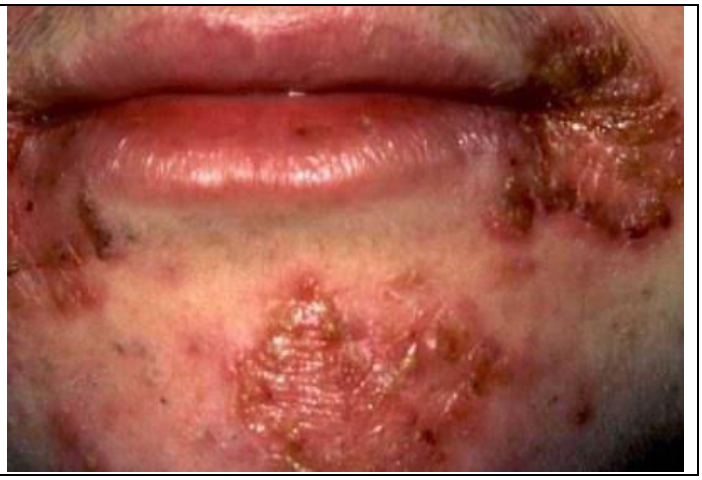
Management

Limited, localised disease

- **topical fusidic acid is first-line**
- topical retapamulin is used second-line if fusidic acid has been ineffective or is not tolerated
- MRSA is not susceptible to either fusidic acid or retapamulin. Topical mupirocin (Bactroban) should therefore be used in this situation

Extensive disease

- oral flucloxacillin
- oral erythromycin if penicillin allergic

Erysipelas

- Erysipelas is a *Streptococcus pyogenes* (a group A streptococcal bacterium) infection of the deep dermis and subcutis.

Feature

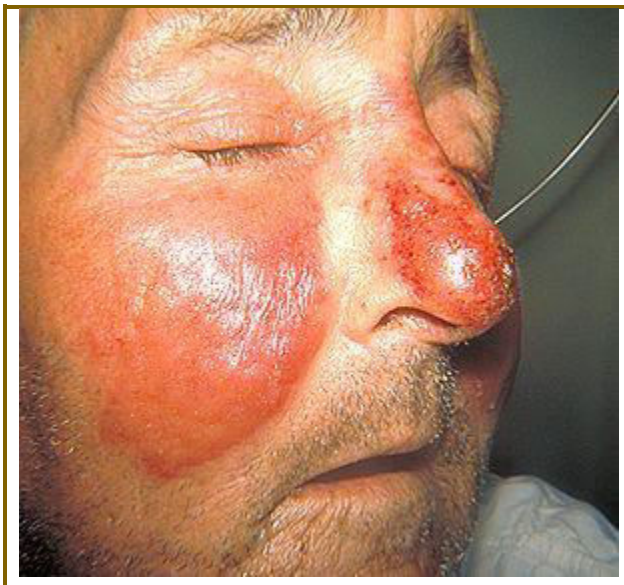
- It is a tender, intensely erythematous, indurated plaque with a sharply demarcated border.
- Its well-defined margin can help differentiate it from other skin infections (eg, cellulitis).

Treatment

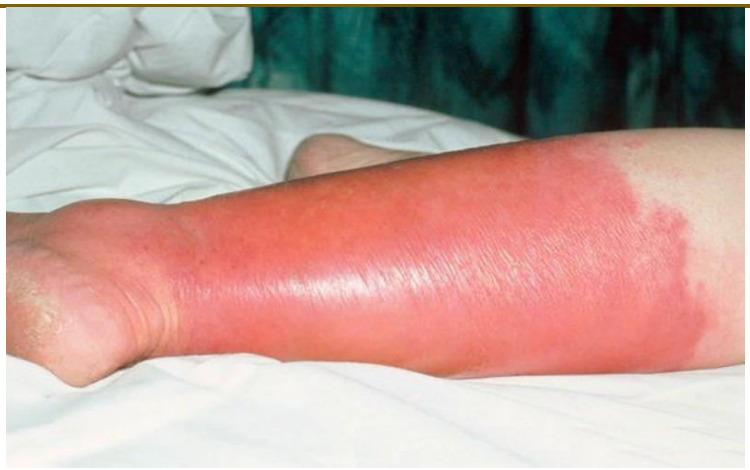
- IV antibiotics such as benzylpenicillin and erythromycin.
- **In a penicillin allergic patient a macrolide is the drug of choice** .There is a 10% cross allergy between cephalosporins and penicillins.

Complications

- sepsis
- cerebral abscess
- venous sinus thrombosis.



Well-demarcated, erythematous plaque of **erysipelas**.



Leprosy

- Leprosy is a granulomatous disease primarily affecting the peripheral nerves and skin.
- It is caused by *Mycobacterium leprae*.
- **Features**
  - patches of hypopigmented skin typically affecting the buttocks, face, and extensor surfaces of limbs
  - sensory loss
- The degree of cell mediated immunity determines the type of leprosy a patient will develop.
- Low degree of cell mediated immunity → lepromatous leprosy ('multibacillary')
  - extensive skin involvement
  - symmetrical nerve involvement
- High degree of cell mediated immunity → tuberculoid leprosy ('paucibacillary')
  - limited skin disease
  - asymmetric nerve involvement
- **Management:** WHO-recommended triple therapy: rifampicin, dapsone and clofazimine

Koebner phenomenon describes skin lesions which appear at the site of injury. It is seen in:

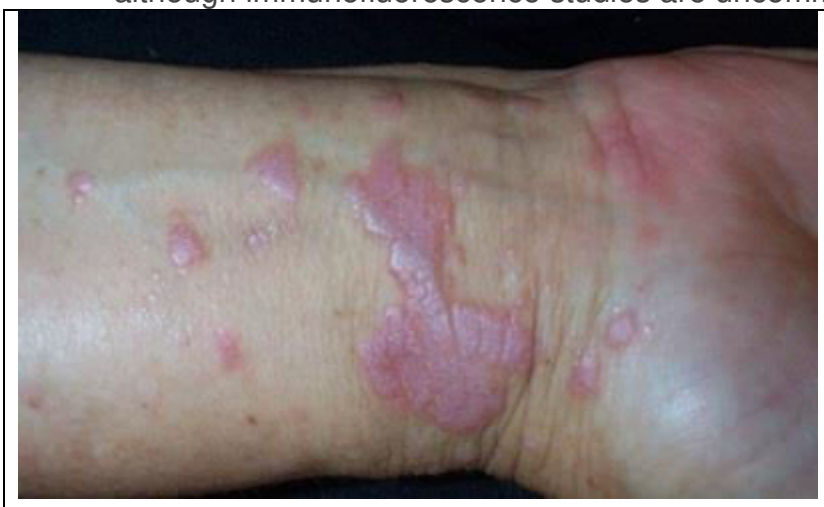
- psoriasis
- vitiligo
- warts
- lichen planus
- lichen sclerosus
- molluscum contagiosum

Lichen planus

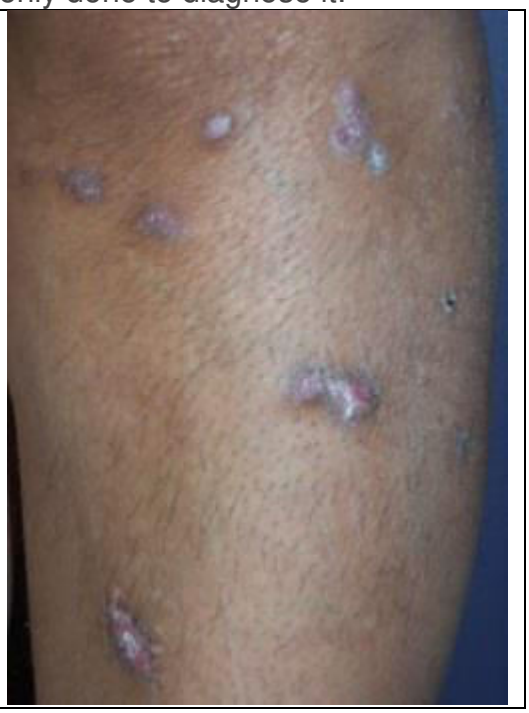
Lichen
- planus: purple, pruritic, papular, polygonal rash on flexor surfaces. Wickham's striae over surface. Oral involvement common
- sclerosus: itchy white spots typically seen on the vulva of elderly women

Lichen planus is a skin disorder of unknown aetiology, most probably being immune mediated.

Features
- itchy, papular rash most common on the palms, soles, genitalia and flexor surfaces of arms
- rash often polygonal in shape, 'white-lace' pattern on the surface (Wickham's striae)
- Koebner phenomenon may be seen (new skin lesions appearing at the site of trauma)
- oral involvement in around 50% of patients
- nails: thinning of nail plate, longitudinal ridging
- **Fibrin deposits at the basement membrane zone** are found in cases of lichen planus , although immunofluorescence studies are uncommonly done to diagnose it.



Lichen planus



Lichenoid drug eruptions - causes:
- gold
- quinine
- thiazides

Management

- topical steroids are the mainstay of treatment
- extensive lichen planus may require oral steroids or immunosuppression

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Lichen sclerosus

- Lichen sclerosus was previously termed lichen sclerosus et atrophicus.
- It is an inflammatory condition which usually **affects the genitalia and is more common in elderly females.**
- Lichen sclerosus leads to atrophy of the epidermis with white plaques forming

Features

- itch is prominent

Diagnosis

- usually made on clinical grounds but a biopsy may be performed if atypical features are present*

Management

- topical steroids and emollients

Follow-up

- increased risk of vulval cancer

***the RCOG advise the following**

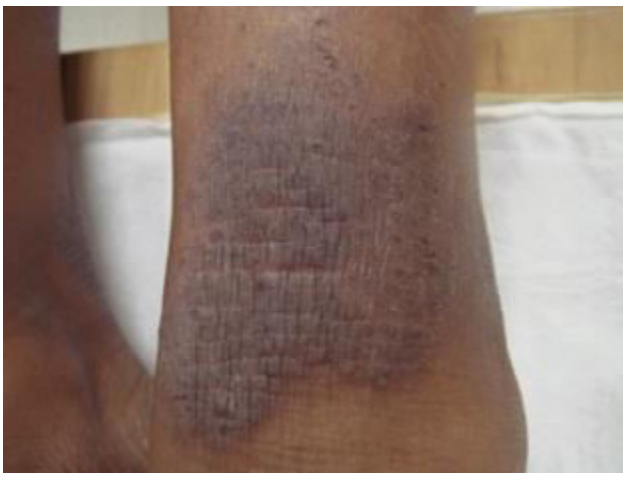
- *Skin biopsy is not necessary when a diagnosis can be made on clinical examination. Biopsy is required if the woman fails to respond to treatment or there is clinical suspicion of VIN or cancer.*

and the British Association of Dermatologists state the following:

- *A confirmatory biopsy, although ideal, is not always practical, particularly in children. It is not always essential when the clinical features are typical. However, histological examination is advisable if there are atypical features or diagnostic uncertainty and is mandatory if there is any suspicion of neoplastic change.*
- ***Patients under routine follow-up will need a biopsy if:***
  - *(i) there is a suspicion of neoplastic change, i.e. a persistent area of hyperkeratosis, erosion or erythema, or new warty or papular lesions;*
  - *(ii) the disease fails to respond to adequate treatment;*
  - *(iii) there is extragenital LS, with features suggesting an overlap with morphoea;*
  - *(iv) there are pigmented areas, in order to exclude an abnormal melanocytic proliferation;*
  - *(v) second-line therapy is to be used.*

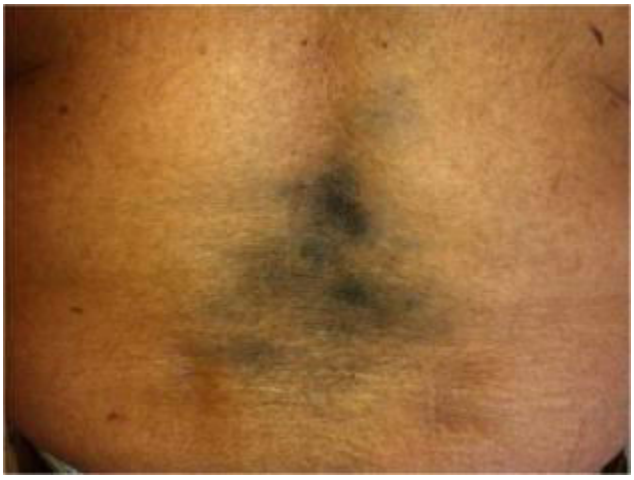
Lichen simplex chronicus (LSC)

- *LSC presents with hyperpigmented, scaly, lichenified plaques.*
- *Patients may volunteer a history of chronic scratching or manipulation, especially during times of stress.*
- *The ankles are common sites for LSC.*



Lichen amyloidosis

- Lichen amyloidosis is a primary, localised cutaneous amyloidosis (amyloid deposition in the skin).
- It results in intensely itchy shiny or hyperkeratotic, pigmented macules and occurs most commonly in South East Asia.
- It appears that itching drives further amyloid deposition, and treatments are therefore directed at reducing the sensation of itching - for example, with the use of antihistamines and intra-lesional/topical corticosteroids.



Lichen amyloidosis

Onycholysis

Onycholysis describes the separation of the nail plate from the nail bed

Causes

- idiopathic
- trauma e.g. Excessive manicuring
- infection: especially fungal
- skin disease: psoriasis, eczema, dermatitis
- impaired peripheral circulation e.g. Raynaud's
- systemic disease: hyper- and hypothyroidism
- **Tetracycline**

Parvovirus B19

Parvovirus B19 is a DNA virus which causes a variety of clinical presentations. It was identified in the 1980's as the cause of erythema infectiosum

Erythema infectiosum (also known as fifth disease or 'slapped-cheek syndrome')

- most common presenting illness
- systemic symptoms: lethargy, fever, headache
- 'slapped-cheek' rash spreading to proximal arms and extensor surfaces

Other presentations

- asymptomatic
- pancytopaenia in immunosuppressed patients
- aplastic crises e.g. in sickle-cell disease (parvovirus B19 suppresses erythropoiesis for about a week so aplastic anaemia is rare unless there is a chronic haemolytic anaemia)

Pityriasis rosea

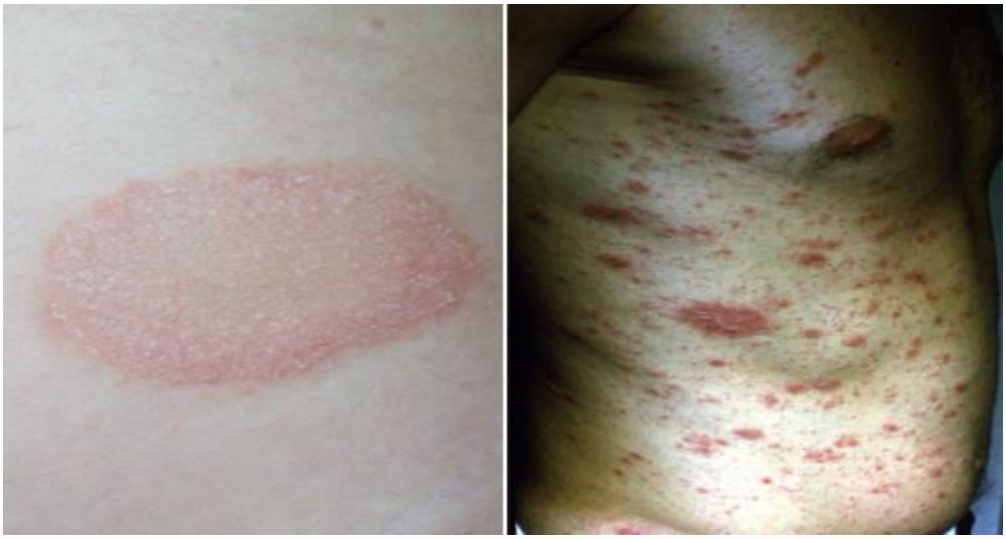
- describes an acute, self-limiting rash which tends to affect young adults. occurs most commonly in people between the ages of 10 and 35 years.
- The aetiology is not fully understood but is thought that herpes hominis virus 7 (HHV-7) may play a role. does not appear to be contagious;
- aetiology is unknown

Features

- herald patch (usually on trunk)
- followed by **erythematous, oval, scaly patches** which follow a characteristic distribution with the longitudinal diameters of the oval lesions running parallel to the line of Langer. This may produce a 'fir-tree' appearance
- can be pruritic or asymptomatic

Management

- self-limiting, usually disappears after 4-12 weeks
- moisturisers can help the pruritus



On the left a typical herald patch is seen. After a few days a more generalised 'fir-tree' rash appears

Pityriasis versicolor

also called tinea versicolor, is a superficial cutaneous fungal infection caused by Malassezia furfur (formerly termed Pityrosporum ovale)

Features

- most commonly affects trunk
- patches may be hypopigmented, pink or brown (hence versicolor)
- scale is common
- mild pruritus

Predisposing factors

- occurs in healthy individuals
- immunosuppression
- malnutrition
- Cushing's

Management

- topical antifungal. NICE Clinical Knowledge Summaries advise ketoconazole shampoo as this is more cost effective for large areas
- **Topical selenium sulphide**
- if extensive disease or failure to respond to topical treatment then consider oral itraconazole 200 mg once a day for seven days.

Psoriasis

Definition

- Psoriasis is a chronic relapsing inflammatory skin disorder most commonly characterised by erythematous, sharply demarcated papules and rounded plaques covered by silvery scales.

Epidemiology

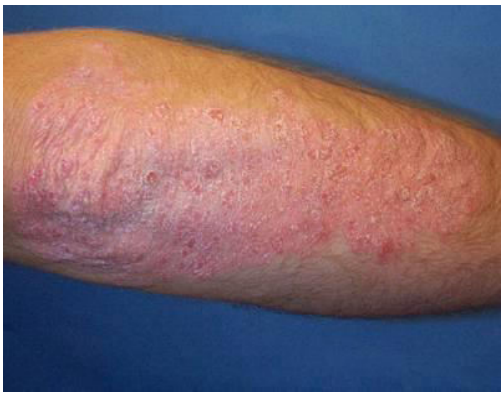
- prevalence around 2%.
- there are two peaks of incidence at 16-22 years and 57-60 years.
- Males and females are equally affected.

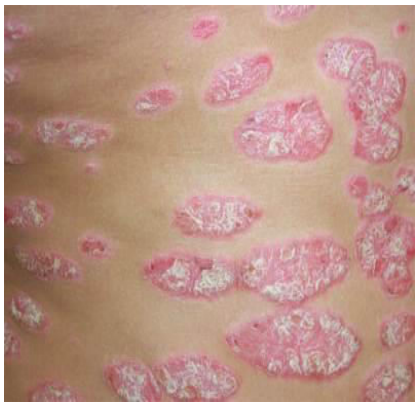
Pathophysiology

- multifactorial and not yet fully understood
  - genetic:
    - polygenic inheritance
    - associated HLA-B13, -B17, and -Cw6.
    - European populations are commonly affected,
    - Strong concordance (70%) in identical twins
  - immunological:
    - abnormal T cell activity stimulates keratinocyte proliferation.
      - may be mediated by T helper cells producing **IL-17**.
      - IL-17 is a pro-inflammatory cytokine which is expressed at high levels in psoriasis lesions.
      - Ixekizumab is an **anti-IL-17 antibody** which binds to IL-17, it is effective in treating active psoriasis and in reducing the risk of recurrence.
  - environmental:
    - psoriasis may be worsened (e.g. Skin trauma, stress), triggered (e.g. Streptococcal infection) or improved (e.g. Sunlight) by environmental factors
- increase in mitotic activity of the cells in the malpighian layer of the epidermis
  - The Malpighian layer of the skin is generally defined as both the stratum basalis and stratum spinosum as a unit.

Recognised subtypes of psoriasis

- **plaque psoriasis**: the most common sub-type resulting in the typical well demarcated red, scaly patches affecting the extensor surfaces, sacrum and scalp
- **flexural psoriasis**: in contrast to plaque psoriasis the skin is smooth
- **guttate psoriasis**: transient psoriatic rash frequently triggered by a streptococcal infection. Multiple red, teardrop lesions appear on the body
- **pustular psoriasis**: commonly occurs on the palms and soles





Features

- **Salmon colored skin plaques with silvery scales**
- Psoriasis may occur in **hidden sites**, such as the scalp (where psoriasis frequently is mistaken for dandruff), perineum, intergluteal cleft, and umbilicus
  - The scalp is often involved in psoriasis. Most commonly, it causes a telogen effluvium, that is, the hair follicles are forced into the telogen resting stage.

Other features

- nail signs: pitting, onycholysis
- arthritis
- New lesions often appear at sites of injury or trauma **(Koebner phenomenon),** which typically occurs one to two weeks after the skin has been damaged.
- Auspitz sign: small bleeding spots when psoriasis scales are scraped off.
- Psoriasis can be associated with an anterior uveitis

Complications

- psoriatic arthropathy (around 10%)
  - This can range from mild distal interphalangeal joint involvement with nail pitting to severe arthritis mutilans.
- increased incidence of metabolic syndrome
- **increased incidence of cardiovascular disease**
- increased incidence of venous thromboembolism
- psychological distress

Diagnosis

- usually clinical
- skin biopsy is rarely required to confirm psoriasis.
  - Hyperkeratosis (described as an increased thickness of the stratum corneum),
  - Parakeratosis, defined as hyperkeratosis with retention of nuclei in the stratum corneum,
  - **Munro's microabscess** (or neutrophils) in the **stratum corneum** of the epidermis are a **cardinal sign**

Exacerbating factors

Psoriasis: common triggers are beta-blockers and lithium

- trauma
- alcohol
- drugs:
  - **beta blockers**,
  - **lithium**,
  - **antimalarials (chloroquine and hydroxychloroquine),**
  - gold salts,
  - NSAIDs,
  - ACE inhibitors,
  - infliximab
  - antibiotics such as tetracycline and penicillin
- withdrawal of systemic steroids
- **Notes**
  - Reactions may occur from less than one month to one year after the medication is initiated.
  - the effect of antimalarials on trans-glutaminase activity leads to stimulation of epidermal proliferation

- **beta blockers** is more common than ACEi

Management

Topical potent corticosteroid + vitamin D analogue is first-line for chronic plaque psoriasis

Management of chronic plaque psoriasis (NICE guidelines 2012**)**

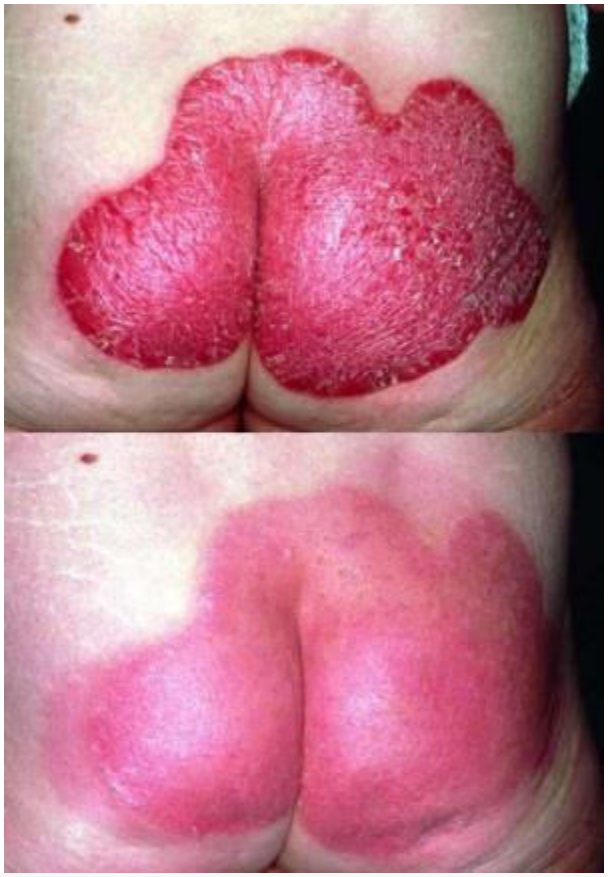
- regular emollients may help to reduce scale loss and reduce pruritus
- **First-line**:
  - **potent corticosteroid applied once daily plus vitamin D analogue applied once daily** (applied separately, one in the morning and the other in the evening) for up to 4 weeks as initial treatment
- **Second-line**:
  - if no improvement after 8 weeks then offer a **vitamin D analogue twice daily**
- **Third-line**:
  - if no improvement after 8-12 weeks then offer either: a potent **corticosteroid applied twice daily** for up to 4 weeks or a coal tar preparation applied once or twice daily
- short-acting dithranol can also be used

Using topical steroids in psoriasis

- as we know topical corticosteroid therapy may lead to skin atrophy, striae and rebound symptoms
- systemic side-effects may be seen when potent corticosteroids are used on large areas e.g. > 10% of the body surface area
- NICE recommend that we aim for a 4 week break before starting another course of topical corticosteroids
- they also recommend using potent corticosteroids for no longer than 8 weeks at a time and very potent corticosteroids for no longer than 4 weeks at a time

What should I know about vitamin D analogues?

- examples of vitamin D analogues include calcipotriol (Dovonex), calcitriol and tacalcitol
- they work by reducing cell division and differentiation
- adverse effects are uncommon
- unlike corticosteroids they may be used long-term
- unlike coal tar and dithranol they do not smell or stain
- they tend to reduce the scale and thickness of plaques but not the erythema
- they should be avoided in pregnancy
- the maximum weekly amount for adults is 100g



A 'before and after' image showing the effect of 6 weeks of calcipotriol therapy on a large plaque. Note how the scale has improved but the erythema remains

Steroids in psoriasis

- topical steroids are commonly used in flexural psoriasis and there is also a role for mild steroids in facial psoriasis. If steroids are ineffective for these conditions vitamin D analogues or tacrolimus ointment should be used second line
- patients should have 4 week breaks between course of topical steroids
- very potent steroids should not be used for longer than 4 weeks at a time. Potent steroids can be used for up to 8 weeks at a time
- the scalp, face and flexures are particularly prone to steroid atrophy so topical steroids should not be used for more than 1-2 weeks/month

Scalp psoriasis

Scalp psoriasis - first-line treatment is topical potent corticosteroids

- First line
  - potent topical corticosteroids used once daily for 4 weeks
  - if no improvement after 4 weeks go to second line
- Second line
  - use different formulation of the potent corticosteroid (for example, a shampoo or mousse) **and/or**
  - topical agents to remove adherent scale (for example, agents containing salicylic acid, emollients and oils) before application of the potent corticosteroid

Face, flexutal and genital psoriasis

Flexural psoriasis - topical steroid

- mild or moderate potency corticosteroid applied once or twice daily for a maximum of 2 weeks **eg: clobetasone butyrate once a day**

Secondary care management

Phototherapy

- narrow band ultraviolet B-light is now the treatment of choice. If possible this should be given 3 times a week
- photochemotherapy is also used - psoralen + ultraviolet A light (PUVA)
- adverse effects: skin ageing, squamous cell cancer (not melanoma)

Systemic therapy

- **Indications**
  - topical are not effective **and**
  - person is impacted physically, psychologically, or socially by the problem **and**
  - one or more of the following apply:
    - extensive psoriasis (eg, **>** 10% of body surface area affected or a PASI score of **>** 10) **or**
    - localised psoriasis and associated with significant functional impairment and/or high levels of distress (for example severe nail disease or involvement at high-impact sites) **or**
    - phototherapy has been ineffective, cannot be used or has resulted in rapid relapse (rapid relapse is defined as greater than 50% of baseline disease severity within 3 months).
- **Methotrexate**
  - **Oral methotrexate is used first-line.** It is particularly useful if there is associated joint disease
- Ciclosporin
  - Offer ciclosporin as the first choice in patients who need rapid or short-term disease control (for example a
    - psoriasis flare
    - palmoplantar pustulosis
    - or considering conception (both men and women) and systemic therapy cannot be avoided.
  - Consider changing from methotrexate to ciclosporin (or vice-versa) when response to the first-choice systemic treatment is inadequate.
- Systemic retinoids (acitretin)
  - if methotrexate and ciclosporin are not appropriate or have failed or
  - for people with pustular forms of psoriasis.
- biological agents: infliximab, etanercept and adalimumab
  - **In situation with uncontrolled psoriasis and psoriatic arthritis**, early instigation of a biological is recommended.

- TNF alpha is a pro-inflammatory cytokine closely linked to the severity of psoriasis, and **etanercept, a TNF alpha antagonist is the most appropriate intervention**.
- Tuberculosis and viral hepatitis should be ruled out prior to starting therapy.
- Brodalumab is an anti-IL17 monoclonal antibody which has completed registration trials for psoriasis. It's likely to be reserved however for patients who fail to gain control on other interventions.

- **ustekinumab** (IL-12 and IL-23 blocker) is showing promise in early trials
  - it is not an anti- TNF agent (so did not reactivate TB)
  - side effects:
    - **common → dental infection**
    - uncommon → depression and injection site reaction

Mechanism of action of commonly used drugs:

- coal tar: probably inhibit DNA synthesis
- calcipotriol: vitamin D analogue which reduces epidermal proliferation and restores a normal horny layer
- dithranol: inhibits DNA synthesis, wash off after 30 mins, SE: burning, staining

Contra-indication:

- Oral steroids are contraindicated in psoriasis and although one may see an initial improvement, a very serious rebound effect may be seen.

Question:
An elderly man with learning difficulties, is admitted to hospital with an acute exacerbation of congestive cardiac failure and severe raised plaques of psoriasis covering his chest, elbows, knees and scalp. he has been treating it with topical creams for years but has seen no improvement. What treatment would you recommend for his psoriasis?

→ **Refer for PUVA**

- The safest treatment - that which produces the best clinical effect with minimal side effects in this patient - would be psoralen and ultraviolet light (PUVA).
- Emollients, baths and use of methotrexate require a fair amount of input from the patient in order to be effective and safe, which may not be the best option in this man.

MRCPUK-part-1-sep 2017: Which medication is of most concern with respect to worsening of psoriasis?

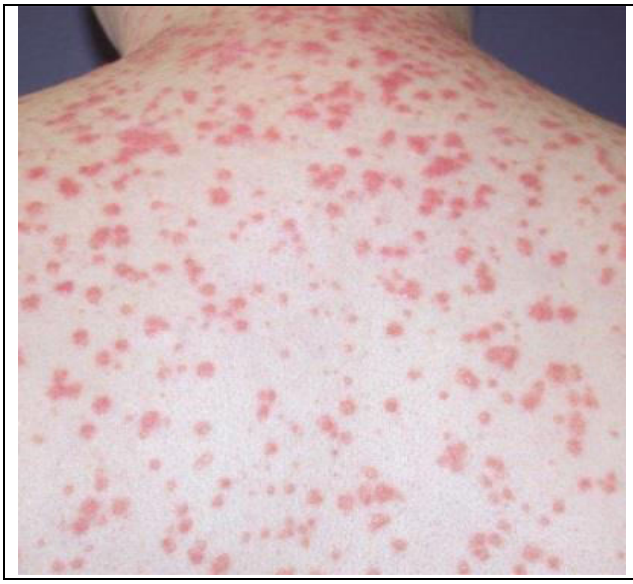
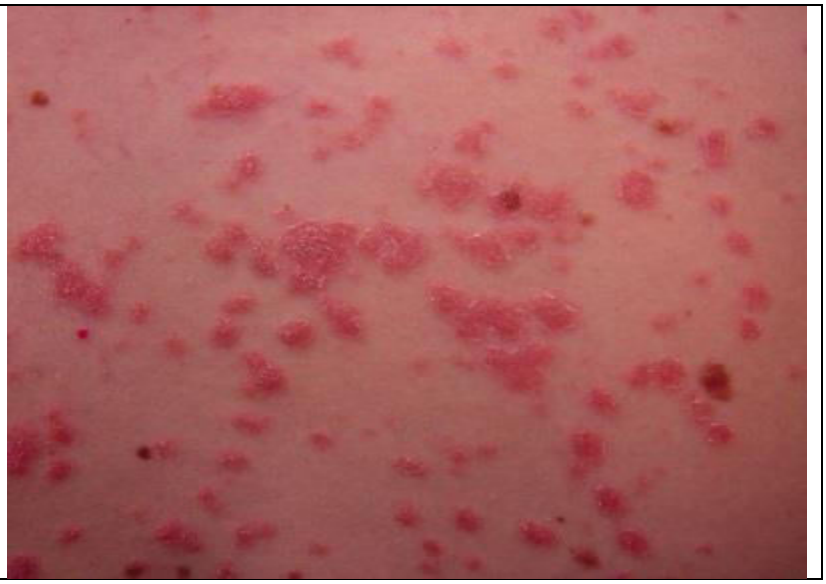
→ **Atenolol**

Psoriasis: guttate

- Guttate psoriasis is more common in children and adolescents.
- It may be precipitated by a streptococcal infection 2-4 weeks prior to the lesions appearing

Features

- tear drop 'drop-like' papules on the trunk and limbs

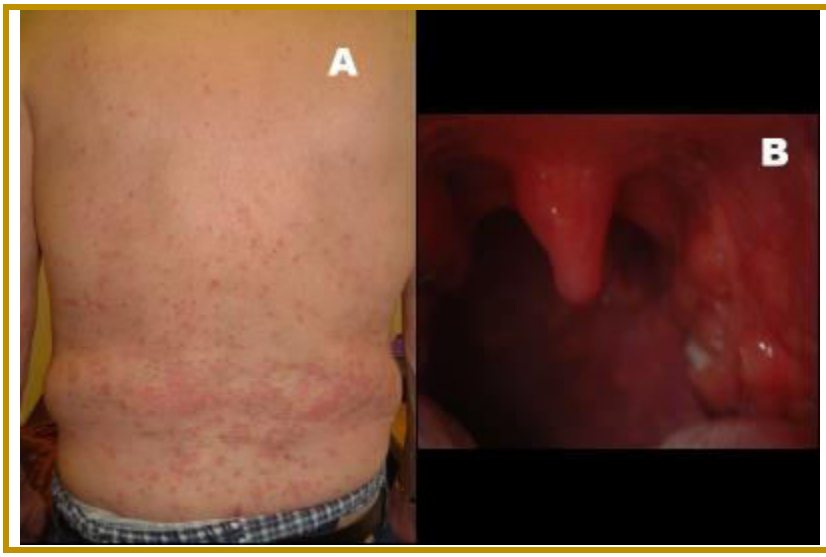



Management

- **if lesions are not widespread (<10% body surface area) and the person is not impacted physically, psychologically, or socially by the problem:**
  - **No treatment required**
    - most cases resolve spontaneously within 2-3 months
- If the lesions are not widespread (<10% body surface area) and treatment is desired:
  - topical agents as per psoriasis.
- If lesions are widespread **(>10% body surface area**):
  - **refer urgently to a dermatologist** as phototherapy (UVB phototherapy) can be considered.
- **with recurrent episodes → referral to ENT should be considered → tonsillectomy may be necessary**
- Although guttate psoriasis can be triggered by an acute sore throat, it is not recommended to treat guttate psoriasis with anti-streptococcal antibiotics.

Differentiating guttate psoriasis and pityriasis rosea

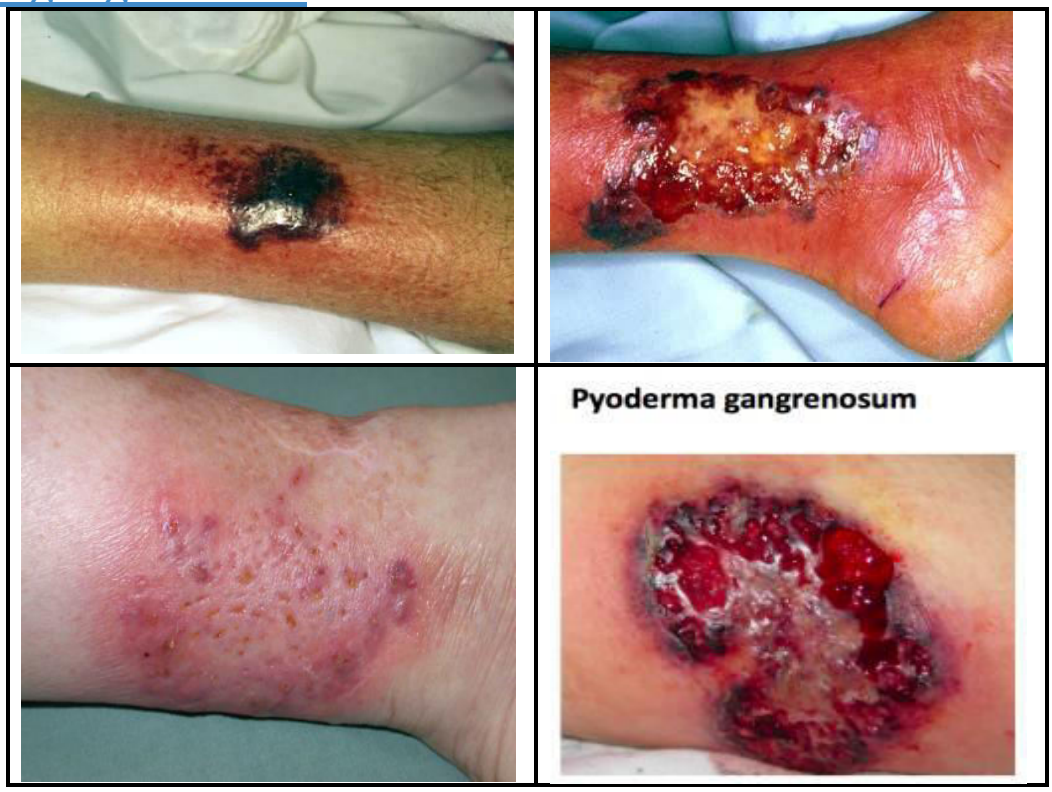
	Guttate psoriasis	Pityriasis rosea
Prodrome	Classically preceded by a streptococcal sore throat 2-4 weeks	Many patients report recent respiratory tract infections but this is not common in questions
Appearance	'Tear drop', scaly papules on the trunk and limbs	Herald patch followed 1-2 weeks later by multiple erythematous, slightly raised oval lesions with a fine scale confined to the outer aspects of the lesions. May follow a characteristic distribution with the longitudinal diameters of the oval lesions running parallel to the line of Langer. This may produce a 'fir-tree' appearance
Treatment / natural history	Most cases resolve spontaneously within 2-3 months Topical agents as per psoriasis UVB phototherapy	Self-limiting, resolves after around 6 weeks



Guttate psoriasis

- A 46-year-old man presents with an extensive pruritic rash shown in picture A.
- Two weeks previously he had a sore throat with the appearance shown in picture B.

Pyoderma gangrenosum



Overview

- Pyoderma gangrenosum typically is an expanding ulcer with a polycyclic or serpiginous outline and a characteristic undermined bluish edge.
- The pathogenesis is unknown, and is presumed to be immunological.

Features

- typically on the lower limbs
  - It is most common on the lower limb and in scars or sites of previous trauma.
- initially small red papule
- later deep, red, necrotic ulcers with a violaceous border
- may be accompanied systemic symptoms e.g. Fever, myalgia

Causes*

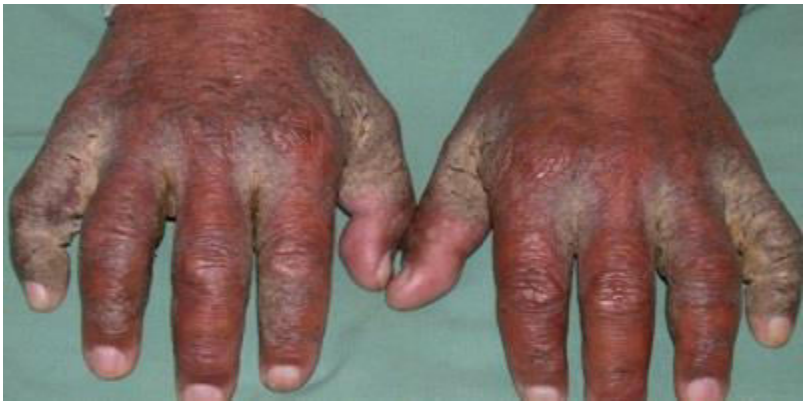
- idiopathic in 50%
- inflammatory bowel disease: **ulcerative colitis**, Crohn's
  - Estimates of the prevalence in inflammatory bowel disease (IBD) range between 2% and 5%.
  - It tends to be associated with colonic involvement and is perhaps **slightly more common in patients with UC.**
- rheumatoid arthritis, SLE
- myeloproliferative disorders
- lymphoma, myeloid leukaemias
- monoclonal gammopathy (IgA)
- primary biliary cirrhosis

*note whilst pyoderma gangrenosum can occur in diabetes mellitus it is rare and is generally not included in a differential of potential causes

Management

- the potential for rapid progression is high in most patients and most doctors advocate oral steroids as first-line treatment
- other immunosuppressive therapy, for example ciclosporin and infliximab, have a role in difficult cases

Scabies



- Scabies is caused by the mite Sarcoptes scabiei and is spread by prolonged skin contact.
- It typically affects children and young adults.
- The scabies mite burrows into the skin, laying its eggs in the stratum corneum.
- The intense pruritus associated with scabies is due to a delayed type IV hypersensitivity reaction to mites/eggs which occurs about 30 days after the initial infection.

Features

- widespread pruritus
  - **Scabies can present with an itchy dermatitic-looking rash on the body, but the clues are at certain sites (soles, genitalia, buttocks)**
- linear burrows on the side of fingers, interdigital webs and flexor aspects of the wrist
  - **Burrows (linear crusted lesions of a few millimetres in length) are pathognomonic**
  - **It has a predilection for the web-spaces and around the nipples.**
- in infants the face and scalp may also be affected
- secondary features are seen due to scratching: excoriation, infection

Management

- permethrin 5% is first-line
- malathion 0.5% is second-line
- give appropriate guidance on use (see below)
- pruritus persists for up to 4-6 weeks post eradication

Patient guidance on treatment (from Clinical Knowledge Summaries)

- permethrin cream doesn't have any direct effect on the pruritis itself but helps to settle symptoms indirectly by killing the mite, which is the root cause.
- You should counsel your patients that it may take longer for the itching to settle as the allergic reaction to the mite abates
- the cream should be applied everywhere below the neck, not merely where there is rash present.
- avoid close physical contact with others until treatment is complete
- all household and close physical contacts should be treated at the same time, even if asymptomatic
- launder, iron or tumble dry clothing, bedding, towels, etc., on the first day of treatment to kill off mites.

The BNF advises to apply the insecticide to all areas, including the face and scalp, contrary to the manufacturer's recommendation.
Patients should be given the following instructions:

- apply the insecticide cream or liquid to cool, dry skin
- pay close attention to areas between fingers and toes, under nails, armpit area, creases of the skin such as at the wrist and elbow
- allow to dry and leave on the skin for 8-12 hours for permethrin, or for 24 hours for malathion, before washing off
- reapply if insecticide is removed during the treatment period, e.g. If wash hands, change nappy, etc
- repeat treatment 7 days later

Crusted (Norwegian) scabies

- Crusted scabies is seen in patients with suppressed immunity, especially HIV.
- The crusted skin will be teeming with hundreds of thousands of organisms.
- Ivermectin is the treatment of choice and isolation is essential

Seborrhoeic dermatitis

- Seborrhoeic dermatitis in adults is a chronic dermatitis thought to be caused by an inflammatory reaction related to a proliferation of a normal skin inhabitant, a fungus called **Malassezia furfur** (formerly known as Pityrosporum ovale).
- It is common, affecting around **2% of the general population**

Features

- eczematous lesions on the sebum-rich areas: scalp (may cause dandruff), periorbital, auricular and nasolabial folds
- otitis externa and blepharitis may develop

Associated conditions include

- **HIV**
  - **in patients with HIV the prevalence of seborrheic dermatitis may be as high as 80%.**
  - **the most useful next step → HIV testing**
- Parkinson's disease

Scalp disease management

- Dandruff is an uninflamed form of seborrheic dermatitis and presents as scaly patches scattered within hair-bearing areas of the scalp.
- over the counter preparations containing zinc pyrithione ('Head & Shoulders') and tar ('Neutrogena T/Gel') are first-line
- the preferred second-line agent is ketoconazole
- selenium sulphide and topical corticosteroid may also be useful

Face and body management

Seborrhoeic dermatitis - first-line treatment is topical ketoconazole

- topical antifungals: e.g. Ketoconazole
- topical steroids: best used for short periods
- difficult to treat - recurrences are common

Shin lesions

The differential diagnosis of shin lesions includes the following conditions:

- erythema nodosum
- pretibial myxoedema
- pyoderma gangrenosum
- necrobiosis lipoidica diabeticorum

Below are the characteristic features:

Erythema nodosum

- symmetrical, erythematous, tender, nodules which heal without scarring
- most common causes are streptococcal infections, sarcoidosis, inflammatory bowel disease and drugs (penicillins, sulphonamides, oral contraceptive pill)

Pretibial myxoedema

- symmetrical, erythematous lesions seen in Graves' disease
- shiny, orange peel skin

Pyoderma gangrenosum

- initially small red papule
- later deep, red, necrotic ulcers with a violaceous border
- idiopathic in 50%, may also be seen in inflammatory bowel disease, connective tissue disorders and myeloproliferative disorders

Necrobiosis lipoidica diabeticorum

- shiny, painless areas of yellow/red skin typically on the shin of diabetics
- often associated with telangiectasia

Skin disorders associated with diabetes

Note whilst pyoderma gangrenosum can occur in diabetes mellitus it is rare and is often not included in a differential of potential causes

Necrobiosis lipoidica

- a disorder of collagen degeneration with a granulomatous response, thickening of blood vessel walls, and fat deposition.
- It is usually related to diabetes, **but can also occur in patients with rheumatoid arthritis**
- The exact cause of necrobiosis lipoidica is unknown, but the leading theory of necrobiosis lipoidica in diabetes has focused on diabetic microangiopathy.
- shiny, painless areas of yellow/red/brown skin typically on the shin
- often associated with surrounding telangiectasia
- Necrobiosis is often mistaken for eczema, but rather than responding to steroids it may actually deteriorate.
- Occasionally ulceration of the lesion may occur.
- Necrobiosis is typically painless.

Infection

- candidiasis
- staphylococcal

Neuropathic ulcers

Vitiligo

Lipoatrophy

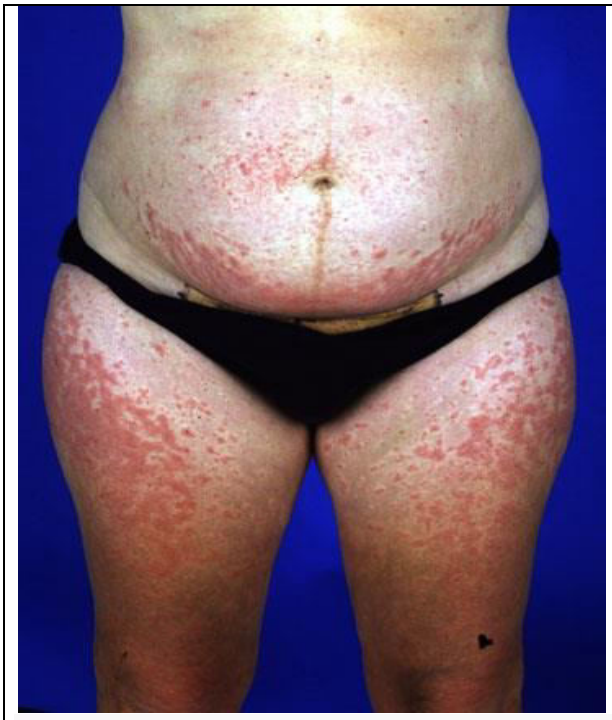
Granuloma annulare*

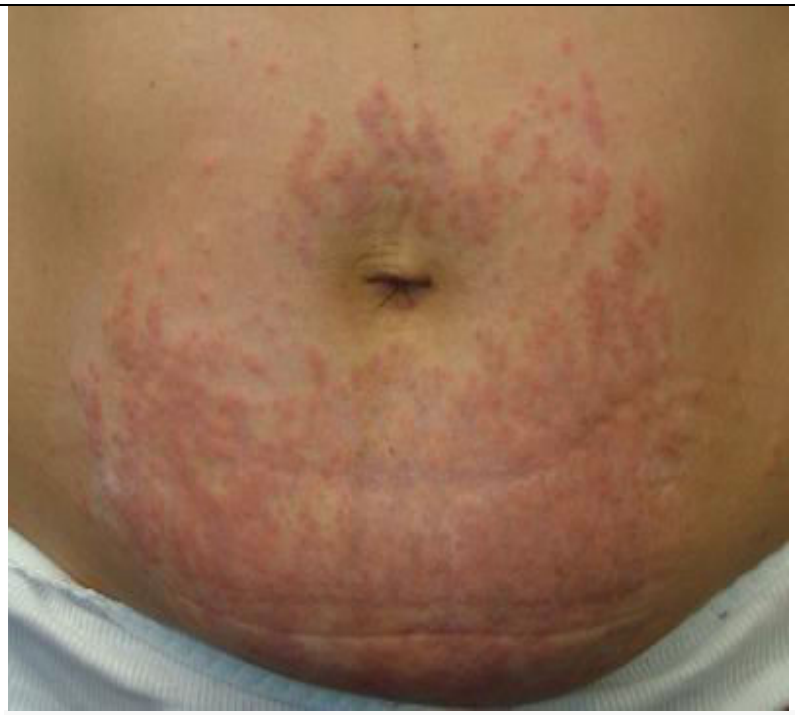
- papular lesions that are often slightly hyperpigmented and depressed centrally
- *it is not clear from recent studies if there is actually a significant association between diabetes mellitus and granuloma annulare, but it is often listed in major textbooks

Polymorphic eruption of pregnancy

Polymorphic eruption of pregnancy is not associated with blistering

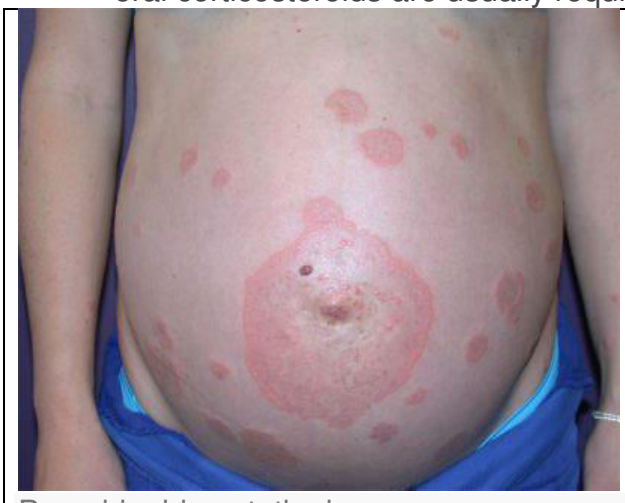
- also known as Pruritic Urticarial Papules and Plaques of Pregnancy (PUPPP)
- pruritic condition associated with last trimester
- lesions often first appear in abdominal striae
- management depends on severity: emollients, mild potency topical steroids and oral steroids may be used

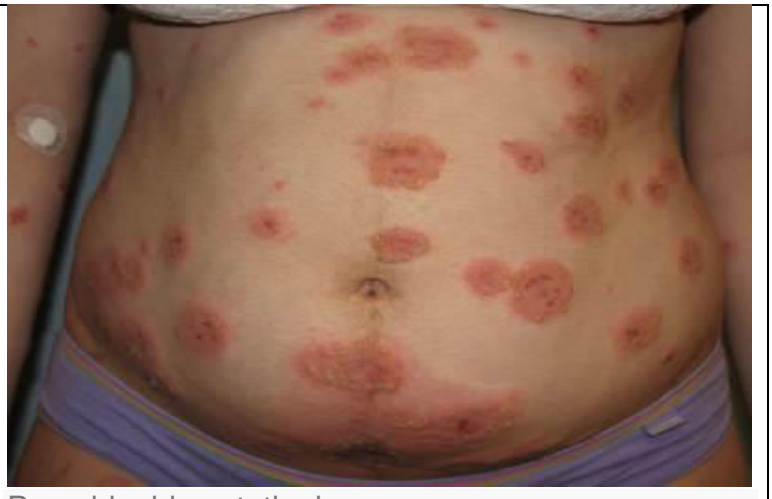

Polymorphic eruption of pregnancy


Polymorphic eruption of pregnancy

Pemphigoid gestationis

- pruritic blistering lesions
- often develop in peri-umbilical region, later spreading to the trunk, back, buttocks and arms
- usually presents 2nd or 3rd trimester and is rarely seen in the first pregnancy
- oral corticosteroids are usually required


Pemphigoid gestationis


Pemphigoid gestationis

Melasma

- Melasma is a benign but relatively common skin condition which can appear in pregnancy.
- it may resolve a few months after delivery.

Chloasma

- Chloasma is a hormonally stimulated increase in melanogenesis that mainly appears on the face.
- The pigment is augmented by sunlight
- On testing, levels of melanocyte-stimulating hormone are normal
- more likely to occur in women with darker skin tones

Causes

- **Pregnancy**
- combined oral contraceptive pill

Treatment:

- The pigmentation may take many months to resolve after parturition or pill discontinuation
- avoid prolonged sunlight exposure or to use a sunblock

Skin disorders associated with tuberculosis

Possible skin disorders

- lupus vulgaris (accounts for 50% of cases)
- erythema nodosum
- scarring alopecia
- scrofuloderma: breakdown of skin overlying a tuberculous focus
- verrucosa cutis
- gumma

Lupus vulgaris

- the most common form of cutaneous TB seen in the Indian subcontinent.
- Cutaneous TB usually occurs due to spread from an endogenous source
- It generally occurs on the face and is common around the nose and mouth.
  - more than 80% of cases occur on the face and neck.
- The initial lesion is an erythematous flat plaque which gradually becomes elevated and may ulcerate later
- Diagnosis: On diascopy, it shows characteristic "apple-jelly" color. Biopsy will reveal tuberculoid granuloma with few bacilli. Mantoux test is positive.
- Treated with combination of drugs used for tuberculosis, such as Rifampicin, Isoniazid and Pyrazinamide (with either streptomycin or ethambutol)

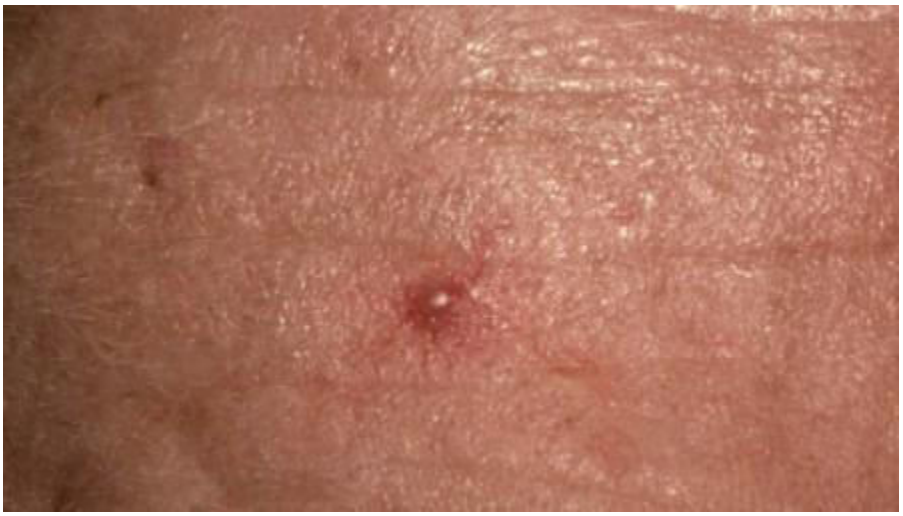
Spider nevi

- most common on the face and upper chest.
- typically asymptomatic
- usually resolve spontaneously.
- Causes
  - chronic liver disease
    - the presence of more than five lesions is likely to be due to chronic liver disease.
    - may resolve when liver function increases or when a liver transplant is performed.

- **the cause of the spider nevi → patients cannot metabolize circulating estrogen**

➢ pregnancy
- may resolve after childbirth.

➢ oral contraceptives,
- may resolve after stopping the contraceptives.



forehead lesion (spider nevus (nevus araneus))

Tinea

- Tinea is a term given to dermatophyte fungal infections.
- Three main types of infection are described depending on what part of the body is infected
  1. tinea capitis - scalp
  2. tinea corporis - trunk, legs or arms
  3. tinea pedis - feet

Tinea capitis (scalp ringworm)

- a cause of scarring alopecia mainly seen in children
- if untreated a raised, pustular, spongy/boggy mass called a kerion may form
- **Causes**
  - **most common cause is *Trichophyton tonsurans*** in the UK and the USA (>90% of cases)
  - may also be caused by *Microsporum canis* acquired from cats or dogs
- **Diagnosis**:
  - the most useful investigation is scalp scrapings
  - lesions due to *Microsporum canis* green fluorescence under Wood's lamp (but do not fluoresce if caused by *Trichophyton tonsurans*.)*.
    - *lesions due to *Trichophyton* species do not readily fluoresce under Wood's lamp
- **Management** (based on CKS guidelines): oral antifungals:
  - **T**erbinafine for ***T****richophyton tonsurans* infections
    - Although not licensed in young children, a **four-week** course of the **fungicidal** drug terbinafine is often preferred.
  - griseofulvin for *Microsporum* infections.

- Griseofulvin is **fungistatic**, so a prolonged course of **2-4 months** is required.

➢ Topical ketoconazole shampoo should be given for the first two weeks to reduce transmission

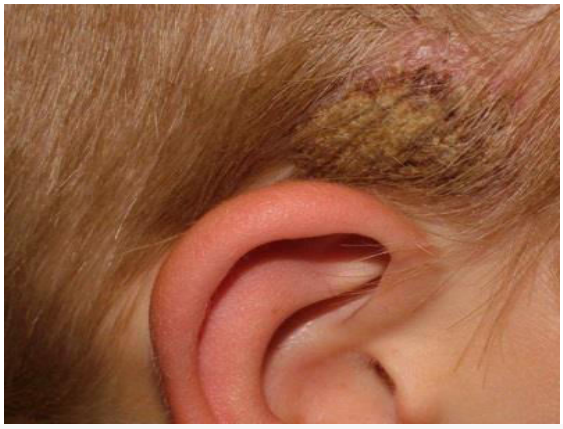


Image showing a kerion

griseofulvin

The enzyme that is most likely induced by griseofulvin requires which of the following cofactors?

➔ **Vitamin B_6**

- Griseofulvin is a microtubule poison that is used to treat skin and nail dermatophytoses
- strong inducer of cytochrome P450 enzymes.
  - CYP450 enzymes require heme for proper function, and thus inducers of CYP450 increase heme synthesis.

Tinea corporis (ringworm)

- causes include *Trichophyton rubrum* and *Trichophyton verrucosum* (e.g. From contact with cattle)
- well-defined annular, erythematous lesions with pustules and papules
- may be treated with oral fluconazole

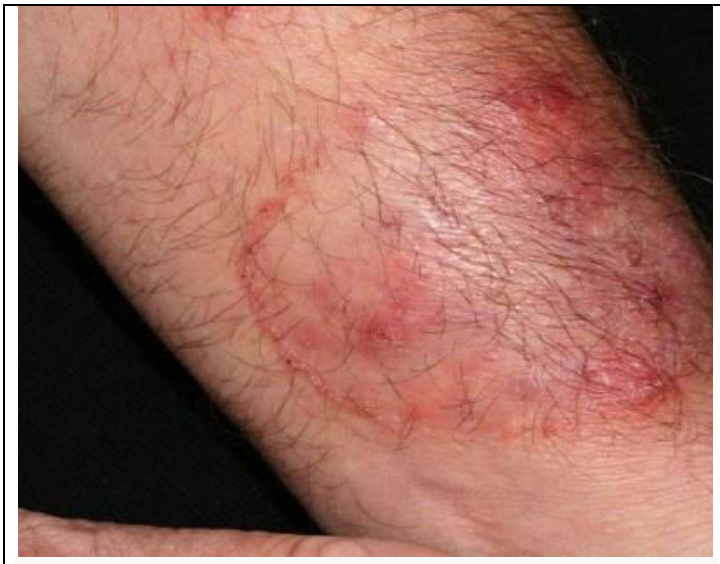


Image showing tinea corporis

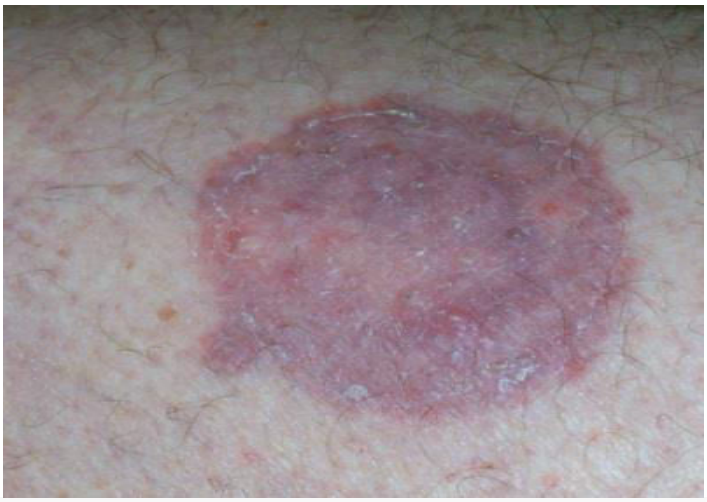


Image showing tinea corporis. Note the well defined border

Tinea pedis (athlete's foot)

- characterised by itchy, peeling skin between the toes
- common in adolescence

Tinea incognito

- **What is the cause for tinea incognito?**
  - **Inappropriate treatment with steroid cream**
- Tinea incognito is the name given to tinea when the clinical appearance has been altered by inappropriate treatment, usually a topical steroid cream
- The result is that the original infection slowly extends Often the patient and/or their doctor believe they have a dermatitis, hence the use of a topical steroid cream
- The steroid cream dampens down inflammation so the condition feels less irritable But when the cream is stopped for a few days the itch gets worse, so the steroid cream is promptly used again
- The more steroid applied, the more extensive the fungal infection becomes

---

Vitiligo

Definition

- Vitiligo is an autoimmune condition which results in the loss of melanocytes and consequent depigmentation of the skin.

Epidemiology

- It is thought to affect around 1% of the population
- symptoms typically develop by the age of 20-30 years.

Features

- well demarcated patches of depigmented skin
- the peripheries tend to be most affected
- trauma may precipitate new lesions (Koebner phenomenon)

Associated conditions

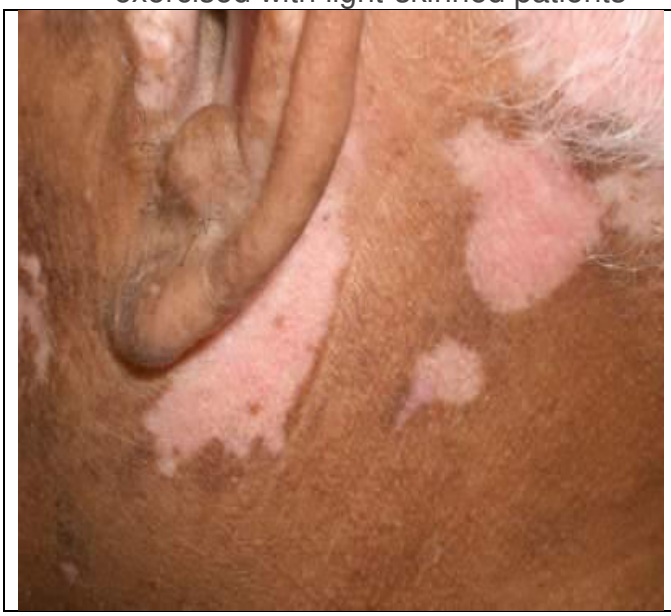
- type 1 diabetes mellitus
- Addison's disease
- autoimmune thyroid disorders
- pernicious anaemia
- alopecia areata

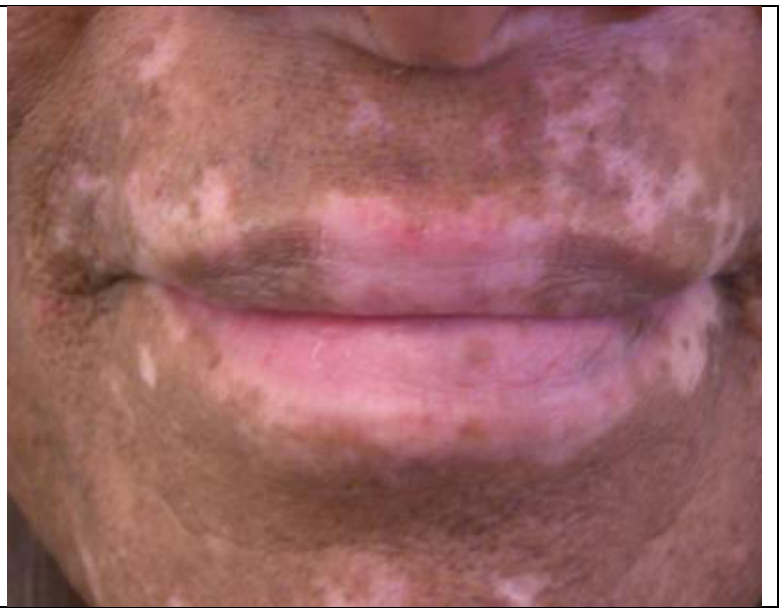
Diagnosis

- Diagnosis is made clinically
- anti-melanocyte antibodies
- can be confirmed using a skin biopsy.

Management

- sun block for affected areas of skin
- camouflage make-up
- topical corticosteroids may reverse the changes if applied early
- there may also be a role for topical tacrolimus and phototherapy, although caution needs to be exercised with light-skinned patients





Yellow nail syndrome

Slowing of the nail growth leads to the characteristic thickened and discoloured nails seen in yellow nail syndrome.

Associations

- congenital lymphoedema
- pleural effusions
- bronchiectasis
- chronic sinus infections

Atopic dermatitis (AD)

- Cyclosporin is a well used drug in the treatment of atopic dermatitis (AD). It is usually at doses of 2-5 mg/kg.
- The pathophysiology of AD is complex but the T lymphocytes are involved and it is known that there is an increased production of cytokines particularly IL-4.
- Cyclosporin is a suppressor of T cells and in that respect works very well in atopic dermatitis and psoriasis. The side effects of hypertension and renal toxicity limit its use.
- These patients are seen monthly to have their blood pressure and urea and electrolytes checked.

Angular stomatitis

- Angular stomatitis describes erythema and fissuring of the skin adjacent to the angle of the mouth.
- The most common cause is *Candida* infection,
- also associated with:
  - allergy,
  - seborrhoeic dermatitis,
  - vitamin B deficiencies,
  - iron deficiency.

leg ulcers

- Diuretics may reduce oedema but have not been demonstrated per se to reduce healing time.
- Gravitational ulcers are not usually painful.
- If there are no obvious features of surrounding cellulitis, antibiotic therapy is usually unnecessary and has not been shown to improve healing in superficial infection which is common in ulceration.
- **In diabetic ulcers, the dressing should be left in situ for no more than one week**

Venous ulceration

- Venous ulcers are secondary to venous stasis and chronic stretching of the walls of the superficial veins. These eventually become thinner and ulcerate.
- **typically seen above the medial malleolus**

The incidence of venous leg ulceration is higher in:

- obese patients
- history of varicose veins
- **history of deep vein thrombosis**

Ulcers occur owing to:

- venous stasis
- secondary increase in capillary pressure
- fibrosis
- poorly nourished skin particularly over areas such as the medial malleolus

Investigations

- **ankle-brachial pressure index (ABPI)** is important in non-healing ulcers to assess for poor arterial flow which could impair healing
  - a 'normal' ABPI may be regarded as between 0.9 - 1.2.
  - Values below 0.9 indicate arterial disease.
  - Interestingly, values above 1.3 may also indicate arterial disease, in the form of false-negative results secondary to arterial calcification (e.g. In diabetics)

Management

Management of venous ulceration - compression bandaging

- compression bandaging, usually four layer **(only treatment shown to be of real benefit)**
- **The mainstay of treatment of venous ulceration is compression therapy**, which aims to improve venous return and thereby reduce venous hypertension.
- The patient should always have their Doppler's and ABPI (ankle brachial pressure index) prior to compression. The ABPI should be greater than 1 before compression bandaging is used (this excludes significant arterial disease.
- oral pentoxifylline, a peripheral vasodilator, improves healing rate
- small evidence base supporting use of flavinoids
- little evidence to suggest benefit from hydrocolloid dressings, topical growth factors, ultrasound therapy and intermittent pneumatic compression

Pressure ulcers

Waterlow score - used to identify patients at risk of pressure sores

- Pressure ulcers develop in patients who are unable to move parts of their body due to illness, paralysis or advancing age.
- They typically develop over bony prominences such as the sacrum or heel. The following factors predispose to the development of pressure ulcers:
  - malnourishment
  - incontinence
  - lack of mobility
  - pain (leads to a reduction in mobility)

- The **Waterlow score** is widely used to screen for patients who are at risk of developing pressure areas. It includes a number of factors including body mass index, nutritional status, skin type, mobility and continence.

Grading of pressure ulcers

the following is taken from the European Pressure Ulcer Advisory Panel classification system.

Grade	Findings
Grade 1	Non-blanchable erythema of intact skin. Discolouration of the skin, warmth, oedema, induration or hardness may also be used as indicators, particularly on individuals with darker skin
Grade 2	Partial thickness skin loss involving epidermis or dermis, or both. The ulcer is superficial and presents clinically as an abrasion or blister
Grade 3	Full thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to, but not through, underlying fascia.
Grade 4	Extensive destruction, tissue necrosis, or damage to muscle, bone or supporting structures with or without full thickness skin loss

Management

- a moist wound environment encourages ulcer healing. Hydrocolloid dressings and hydrogels may help facilitate this. The use of soap should be discouraged to avoid drying the wound
- wound swabs should not be done routinely as the vast majority of pressure ulcers are colonised with bacteria. The decision to use systemic antibiotics should be taken on a clinical basis (e.g. Evidence of surrounding cellulitis)
- consider referral to the tissue viability nurse
- surgical debridement may be beneficial for selected wounds

Keloid scars

Keloid scars are most common on the sternum

Keloid scars are tumour-like lesions that arise from the connective tissue of a scar and extend beyond the dimensions of the original wound

Predisposing factors

Keloid scars - more common in young, black, male adults

- ethnicity: more common in people with dark skin
- occur more commonly in young adults, rare in the elderly

- common sites (in order of decreasing frequency): sternum, shoulder, neck, face, extensor surface of limbs, trunk
- Keloid scars are less likely if incisions are made along relaxed skin tension lines*
  - *Langer lines were historically used to determine the optimal incision line. They were based on procedures done on cadavers but have been shown to produce worse cosmetic results than when following skin tension lines

Treatment

- early keloids may be treated with intra-lesional steroids e.g. triamcinolone
- excision is sometimes required

Increased skin fragility

- Increased skin fragility is seen in a number of disorders and is used as a clinical test in bullous disorders (Nikolsky's sign).
- Other causes include:
  - pemphigus vulgaris
  - porphyria cutanea tarda
  - drug reactions (especially pseudoporphyria).
- Other causes of increased skin fragility (not associated with bullae) include:
  - long term corticosteroid therapy,
  - Ehlers-Danlos syndrome
  - curvy (vitamin C deficiency).

Basal cell carcinoma (BCC)

- Basal-cell carcinomas are the most common malignant skin tumour and are related to excessive sun exposure
  - most commonly occurs in elderly patients with sun-damaged skin.

- Lesions are also known as rodent ulcers
- characterised by slow-growth and **local invasion**. Metastases are extremely rare.
- **BCC is the most common type of cancer in the Western world.**
- BCC is more commonly seen on the upper lip.

Genetics

- environmental and genetic factors are believed to predispose patients to BCC
- Basal cell carcinoma is associated with mutations in the Hedgehog signaling pathway.
- Up to 70% of people with sporadic BCC without Gorlin syndrome have patched **PTCH1 gene** mutations as a result of UV radiation exposure.

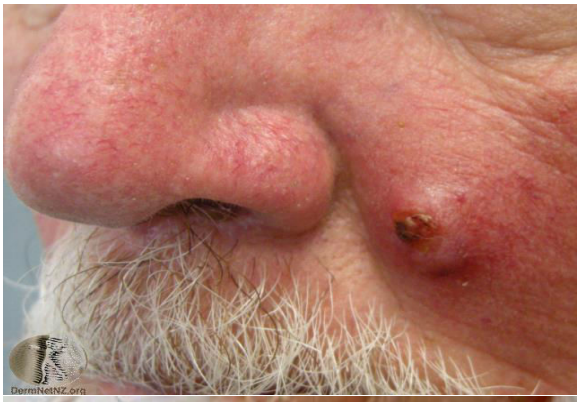
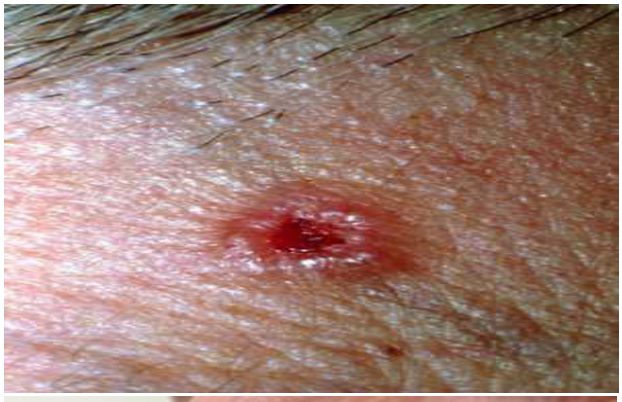
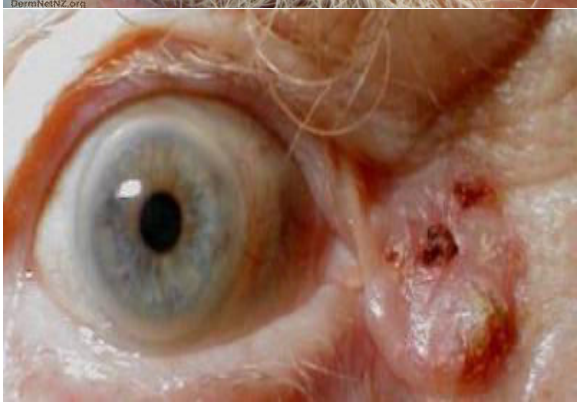
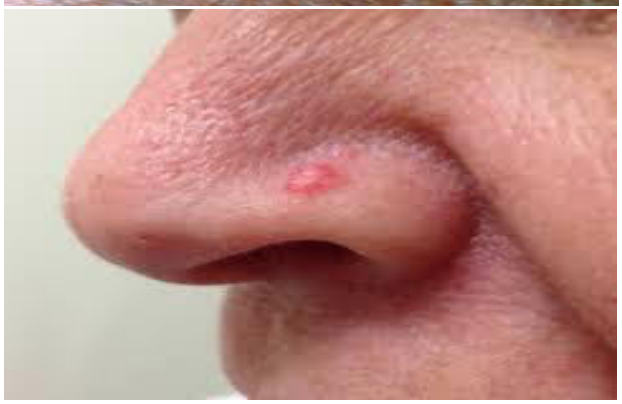
Features

- many types of BCC are described. The most common type is nodular BCC.
- sun-exposed sites, especially the head and neck account for the majority of lesions
- initially a pearly, flesh-coloured papule with telangiectasia

- may later ulcerate leaving a central 'crater'
- characterized histologically by **palisading nuclei**.
  - Palisading nuclei consist of parallel rows of elongated nuclei.

Management options:

- surgical removal
  - Mohs surgery for is useful for minimizing the amount of safety margin excised.
- curettage
- cryotherapy
- topical cream: imiquimod, **5- fluorouracil**
- radiotherapy

(BCC) VS (SCC)

Basal cell carcinoma	**Squamous cell carcinoma**
Most common	2nd most common
Present in upper part of face	Present in lower part of face (appear most often on the lower lip, ear, and nose.)
Does not metastasize and kill by local invasion(rodent ulcer)	Can metastasize
presents as a **"pearly"** papule or nodule that grows slowly with **shiny** appearance with telangiectasias and an umbilicated center or ulcer	usually hyperkeratotic **scaly** lesion with crusting and ulceration. often well-defined, superficial, discrete, and hard lesions arising from an indurated, rounded, and elevated base

Basal cell nevus syndrome (Gorlin syndrome)

Consider nevoid basal cell carcinoma syndrome (NBCCS) in any young patient with multiple basal-cell carcinomas (BCC), or with BCC and palmar pitting.

overview

- autosomal dominant condition caused by the loss of the tumor suppressor gene PTCH on chromosome 9q22.

Feature

- broad forehead,
- palmar pits
- multiple basal cell carcinomas under the age of 20,
- calcified falx cerebri, an odontogenic keratocyte, or polyostotic bone cyst located in the jaw.

Diagnosis

- Diagnosis of NBCCS is a clinical determination, based on the presence of two major or one major and two minor criteria.
- Major criteria:
  - More than 2 instances of basal cell carcinoma (BCCs), or 1 BCC in a patient younger than 20 years old
  - Odontogenic keratocysts of the jaw
  - Three or more palmar or plantar pits
  - Bilamellar calcification of the falx cerebri
  - Bifid, fused, or markedly splayed ribs
  - First-degree relative with NBCCS
- Minor criteria:
  - Macrocephaly
  - Ovarian fibroma or medulloblastoma
  - Congenital malformations – cleft lip or palate, frontal bossing, etc
  - Skeletal abnormalities
  - Radiological abnormalities

Management

- Management of this condition depends on the manifestations of the disease, in the particular individual affected.
- It may include chemotherapy, resection of meduloblastoma in a child, and/or removal of basal cell carcinomas and jaw cysts in patients in adolescence and adulthood.

Squamous cell carcinoma (SCC)

Overview

- SCC is the second most common non-melanoma skin cancer worldwide (after basal cell cancer).
- SCC is the most common oral cancer.
- More common in elderly males.

- It is possible to get SCC on any part of the body, including the inside of the mouth, lips, and genitals.
- Women frequently get SCC on their lower legs.

Precursor and variants of SCC:

- **Actinic keratosis** presents as hyperkeratotic grey-white plaques and is a precursor lesion to squamous cell carcinoma of the skin.
  - Precursor lesions for SCCs are called actinic (or sun-damage) keratosis
- **Keratoacanthoma** is a cup-shaped form of squamous cell carcinoma of the skin that develops rapidly and resolves spontaneously.

Risk factors

- photo-exposed skin such as face and lower lips.
  - often caused by **ultraviolet B-light**, which can mutate DNA via the formation of pyrimidine dimers.
  - exposure to ultraviolet radiation (UV), especially UVB → **Mutations in the p53** tumour suppression gene
  - commonly affects the lower lip.
- The incidence of skin cancer has been increasing among Caucasians but remains relatively low in people of color.
  - Light-skinner, non-Hispanic white populations experience higher rates of SCC than darker people of color.
  - Low incidence in darker skins due to photo-protection provided by increased epidermal melanin, which filters twice as much ultraviolet (UV) radiation
  - When skin cancer occurs in **people of color**, patients often present with an advanced stage, and thus, **worse prognosis** in comparison to Caucasian patients
- Chronic **immunosuppression**
  - more common in patients who have received an **organ transplant**.
- **old scars** or burns
  - may arise from areas of Bowen's disease and sometimes in the margin of a chronic leg ulcer.
  - (SCC) arising on a scar is termed a **Marjolin ulcer**.
    - **Marjolin ulcer is typically aggressive** and associated with a poor prognosis.
- **arsenic exposure**
- ionizing radiation
- HPV infection
- chronic infections, particularly those associated with chronically draining sinuses.
- actinic keratoses and Bowen's disease
- Inherited syndromes: eg: xeroderma pigmentosum and albinism
- smoking

Features

- usually appears as a **scaly** or crusty area of skin, with a red, inflamed base.

Diagnosis

- Excision biopsy is essential for accurate diagnosis.
  - shows keratin pearl appearance.

- The presence of **keratin pearls** indicates that the tumor is well-differentiated and **carries a better prognosis**.
  - undifferentiated tumor would contain almost entirely atypical cells that have lost their keratin producing function and thus keratin pearls would be absent.

Treatment

- Treatments include non-surgical destruction (e.g., using cryotherapy), topical chemotherapy, traditional surgical excision, and Mohs micrographic surgery.
- Surgical excision with 4mm margins if lesion <20mm in diameter. If tumour >20mm then margins should be 6mm.
- Mohs surgery is the best surgical treatment to minimize the loss of normal tissue.
- Radiotherapy is the treatment of choice in patients who are poor surgical candidates.
- Chemotherapy is used as adjuvant therapy in high risk patients

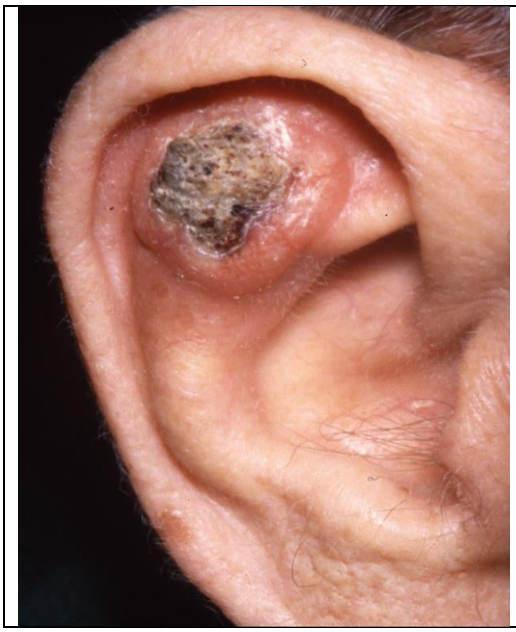
Prevention

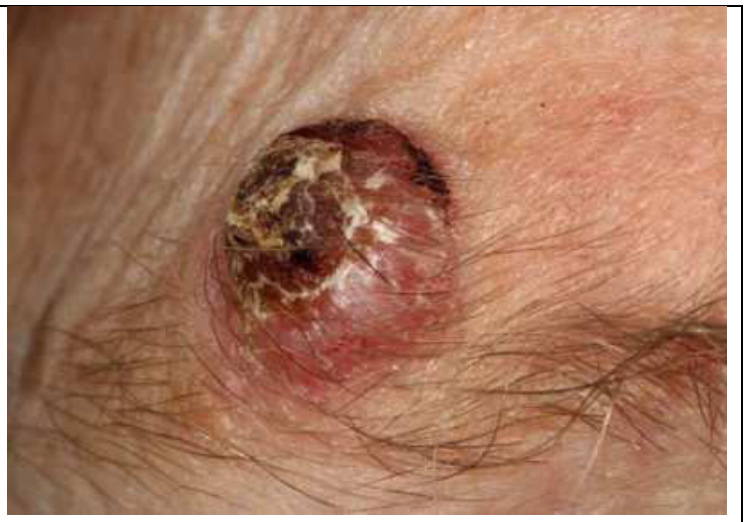
- Sunscreen is used to minimize risk of developing SCC.

Prognosis

Good Prognosis	Poor prognosis
Well differentiated tumours	Poorly differentiated tumours
<20mm diameter	>20mm in diameter
<2mm deep	>4mm deep
No associated diseases	Immunosupression for whatever reason

Keratoacanthoma(KA)





- Keratoacanthoma (KA) is a relatively common low-grade malignancy that originates in the pilosebaceous glands and resembles squamous cell carcinoma (SCC) pathologically.
- Some experts support classifying KA as a variant of invasive SCC.
- Keratoacanthoma is a benign epithelial tumour.
- It is believed to develop from the hair follicle,
- more common in males.
- They are more frequent in middle age and do not become more common in old age (unlike basal cell and squamous cell carcinoma)
- KA is characterised by rapid growth over a few weeks to months, followed by spontaneous resolution over four to six months in most cases.
- Lesions typically are solitary and begin as firm, roundish, skin-coloured or reddish papules that rapidly progress to dome-shaped nodules with a smooth shiny surface and a central crateriform ulceration or keratin plug that may project like a horn.

Features - said to look like a volcano or crater

- initially a smooth dome-shaped papule
- rapidly grows to become a crater centrally-filled with keratin

Treatment

- **The most suitable management → Urgent referral to dermatology**
- Spontaneous regression of keratoacanthoma within 3 months is common, often resulting in a scar.
- Should be urgently excised as it is difficult clinically to exclude squamous cell carcinoma. Removal also may prevent scarring.

Actinic keratoses

- Actinic, or solar, keratoses (AK) is a common premalignant skin lesion that develops as a consequence of chronic sun exposure
- Less than 10% of actinic keratoses progress to invasive squamous cell carcinoma.

Features

- small, crusty or scaly, lesions
- may be pink, red, brown or the same colour as the skin
- typically on sun-exposed areas e.g. temples of head
- multiple lesions may be present

Management

- prevention of further risk: e.g. sun avoidance, sun cream
- **fluorouracil cream**: typically a 2 to 3 week course. The skin will become red and inflamed - sometimes topical hydrocortisone is given following fluorouracil to help settle the inflammation
- topical diclofenac: may be used for mild AKs. Moderate efficacy but much fewer side-effects
- topical imiquimod: trials have shown good efficacy
- cryotherapy
- curettage and cautery

Malignant melanoma:

- **Melanocytes are positioned in the basal layer of the epidermis**
- Melanoma is the third most common skin cancer, but is the most common cause of skin cancer-related death.
- Up to 20% of patients develop metastatic disease.

The mnemonic of ABCDE regarding characteristics of a melanoma are as follows:

- **A** - Asymmetry - one half of the lesion does not match the other half
- **B** - Border irregularity
- **C** - Colour variegation - pigmentation is not uniform
- **D** - Diameter- a diameter 7 mm warrants investigation although changes in size are also important
- **E** - Evolution - evolving size or changes in characteristics such as nodules.

Prognostic factors

Melanoma: the invasion depth of the tumour is the single most important prognostic factor

The invasion depth of a tumour (Breslow depth) is the single most important factor in determining prognosis of patients with malignant melanoma

Breslow Thickness	Approximate 5 year survival
< 1 mm	95-100%
1 - 2 mm	80-96%
2.1 - 4 mm	60-75%
> 4 mm	50%

Treatment

- Vemurafenib is a small molecule inhibitor of *BRAF* oncogene that can be found in melanoma. As such, Vemurafenib is used to treat metastatic melanoma.

Lentigo maligna

- Lentigo maligna is a type of melanoma in-situ.
- It typically progresses slowly but may at some stage become invasive causing lentigo maligna melanoma.

- Lentigo maligna melanoma occurs on the sun-exposed skin areas (usually the face) of elderly patients

Acral lentiginous melanoma

- **The acral lentiginous melanoma is normally seen on the sole of the foot**, and occasionally on the palm of the hand
- It is **characterised by a raised darker area surrounded by a paler macular (lentiginous) area** that may extend for several centimetres around the raised area

Other notes

- Periungual melanomas occur in the area of the nailbed
- Hutchinson's sign (brown pigmentation on the nailfold) is an important pointer to malignant melanoma
- Superficial spreading melanoma is the commonest type, consisting of an irregular brown, black or blue–black lesion with some intermingled inflammation
- Nodular melanoma is the most rapidly growing and aggressive variant and may contain relatively little melanin pigment

Moles

- **Uniform pigmentation is not in itself a suspicious feature of a mole, but colour variegation and irregular border are two of many suspicious features.**

Systemic mastocytosis results from a neoplastic proliferation of mast cells

Features

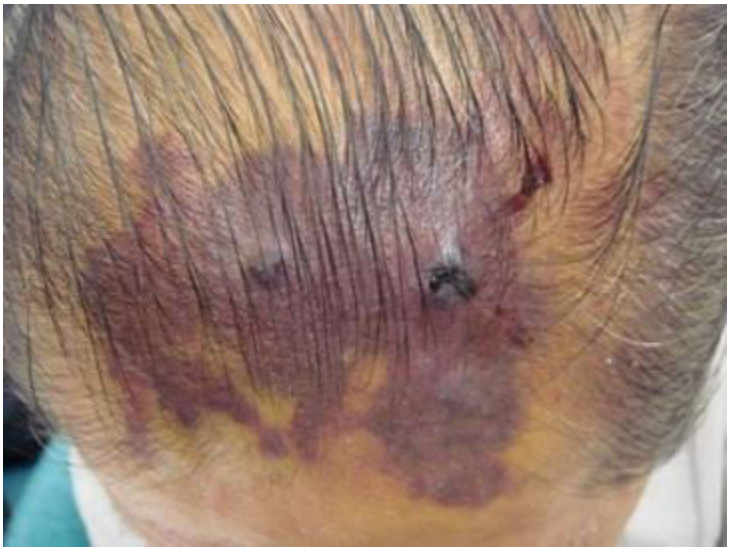
- urticaria pigmentosa - produces a wheal on rubbing (Darier's sign)
- flushing
- abdominal pain
- monocytosis on the blood film

Diagnosis

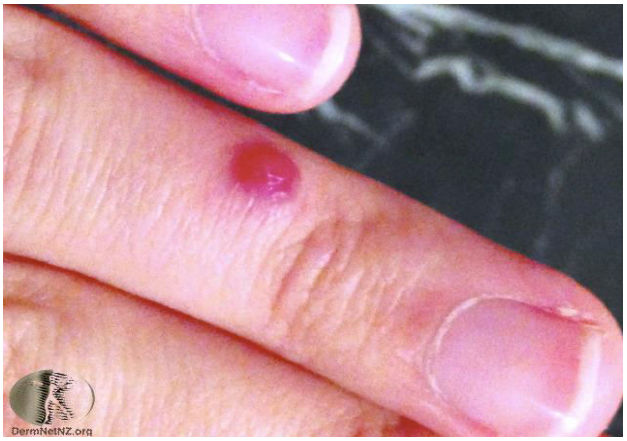
- raised serum tryptase levels
- urinary histamine

Angiosarcoma

- Angiosarcomas are malignant vascular tumours most commonly seen in elderly men.
- most commonly occur on the scalp and forehead.
- present an infiltrative vascular patch or plaque with super-imposed nodules which may bleed with minor trauma.
- poor prognosis.
- Angiosarcomas can also occur in areas of chronic lymphoedema.



Pyogenic granuloma



overview

- relatively common benign skin lesion
- benign vascular lesion of the skin and mucosa.
- The name is a double misnomer - the lesion is neither pyogenic nor a granuloma.
- There are multiple alternative names but perhaps 'eruptive haemangioma' is the most useful.
- Pathologically, it is an inflammatory lesion composed of granulation tissue and chronic inflammatory cells.

Etiology:

- unknown,
- **associated with trauma and pregnancy**

Epidemiology

- more common in women and young adults

Features

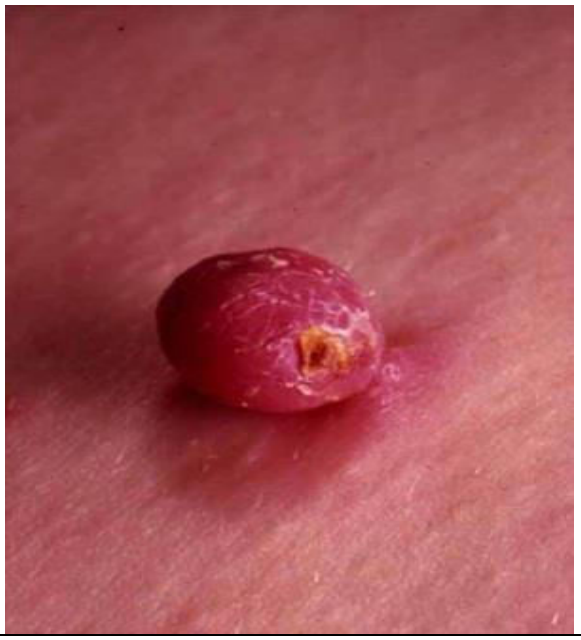
- initially soft, round, bright red spot
- usually solitary lesions,
- Lesions often grow rapidly (**over weeks**),
- **tender and bled easily when touched.**

Localization:

- The most common location are:
  - fingers **(commonly involve the digits)**
  - mucosal surfaces of the mouth
  - inner surfaces of the nose.

Treatment:

- lesions associated with pregnancy often resolve spontaneously post-partum
- other lesions usually persist.
- surgical excision
  - Removal methods include curettage and cauterisation, cryotherapy, excision



Skin disorders associated with malignancy

Paraneoplastic syndromes associated with internal malignancies:

Skin disorder	Associated malignancies
Acanthosis nigricans	Gastric cancer
Acquired ichthyosis	Lymphoma

Skin disorder	Associated malignancies
Acquired hypertrichosis lanuginosa	Gastrointestinal and lung cancer
Dermatomyositis	Ovarian and lung cancer
Erythema gyratum repens	Lung cancer
Erythroderma	Lymphoma
Migratory thrombophlebitis	Pancreatic cancer
Necrolytic migratory erythema	Glucagonoma
Pyoderma gangrenosum (bullous and non-bullous forms)	Myeloproliferative disorders
Sweet's syndrome	Haematological malignancy e.g. Myelodysplasia - tender, purple plaques
Tylosis	Oesophageal cancer

Acrokeratosis paraneoplastica

A widespread psoriatic-type rash involving the ears is suggestive of acrokeratosis paraneoplastica.

- Most acrokeratosis paraneoplastica cases are **associated with squamous cell carcinoma** of the upper one third of the respiratory or GI tract, i.e. the oropharynx, larynx, lungs or oesophagus.
  - The symptoms of indigestion and food sticking fit best with a diagnosis of oesophageal carcinoma.

Cellulitis see infectious diseases

Otitis externa

Otitis externa is a common reason for primary care attendance in the UK.

Causes of otitis externa include:

- infection: bacterial (*Staphylococcus aureus*,*Pseudomonas aeruginosa*) or fungal
- seborrhoeic dermatitis
- contact dermatitis (allergic and irritant)

Features

- ear pain, itch, discharge

- otoscopy: red, swollen, or eczematous canal

The recommend initial management of otitis externa is:

- topical antibiotic or a combined topical antibiotic with steroid
- if the tympanic membrane is perforated aminoglycosides are traditionally not used*
  - *many ENT doctors disagree with this and feel that concerns about ototoxicity are unfounded
- if there is canal debris then consider removal
- if the canal is extensively swollen then an ear wick is sometimes inserted

Second line options include

- consider contact dermatitis secondary to neomycin
- oral antibiotics if the infection is spreading
- taking a swab inside the ear canal
- empirical use of an antifungal agent

Malignant otitis externa

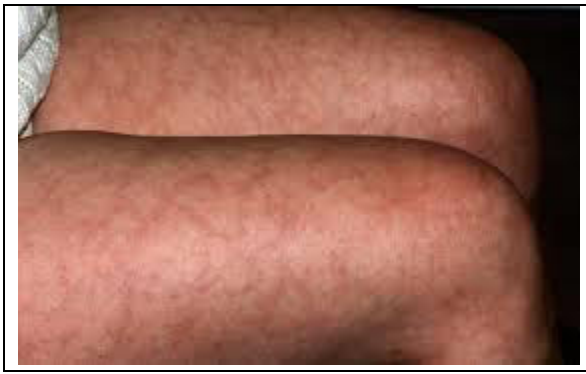
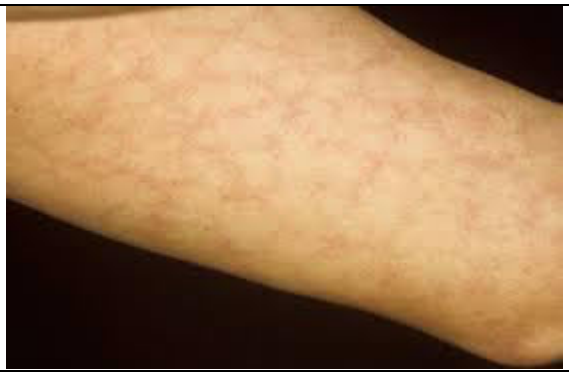
- more common in elderly diabetics.
- In this condition there is extension of infection into the bony ear canal and the soft tissues deep to the bony canal.
- Intravenous antibiotics may be required.

Drugs causing photosensitivity

- thiazides
- tetracyclines, sulphonamides, ciprofloxacin
- amiodarone
- NSAIDs e.g. piroxicam
- psoralens
- sulphonylureas

Livedo reticularis

- **Livedo reticularis is due to superficial capillary dilatation, resulting in characteristic mottling of the skin.**
- appears as a lace-like purplish discoloration of the skin
- **It is mainly idiopathic. (primary livedo reticularis is the most common cause)**
- occur more in women than in men and usually in the 3rd decade of life.
- It is thought to be due to spasms of the blood vessels or an abnormality of the local circulation.
- It may be aggravated by exposure to cold,
- occurs most often in the lower extremities
- idiopathic livedo reticularis may improve with warming the area.
- bath PUVA is a therapeutic option with the possibility of some success.
- Exercise is the best remedy. Increased circulation helps to dilate the blood vessels throughout the body.

Causes Secondary Livedo reticularis:

- **Obstruction / vasculopathy**
  - Antiphospholipid syndrome
  - Cryoglobulinaemia
  - Polycythaemia rubra vera
  - Multiple myeloma
  - Cold agglutinin disease
  - Protein C and S deficiency
  - Antithrombin III deficiency
  - Disseminated intravascular coagulation
  - Haemolytic uraemic syndrome
  - Emboli (DVT , cholesterol emboli and septic emboli)
  - Hypercalcaemia (calcium deposits)
  - Infections (syphilis, tuberculosis, Lyme disease)
- **Autoimmune / vasculitis / connective tissue disease**
  - Small, medium and large vessel vasculitis.
  - SLE
  - Dermatomyositis
  - Rheumatoid arthritis
  - Polyarteritis nodosa
- **Drugs**
  - Amantadine (dopamine agonist used to treat Parkinson disease) causes livedo through arteriolar vasospasm associated with depletion of catecholamines.
  - Minocycline

Reactions to drugs

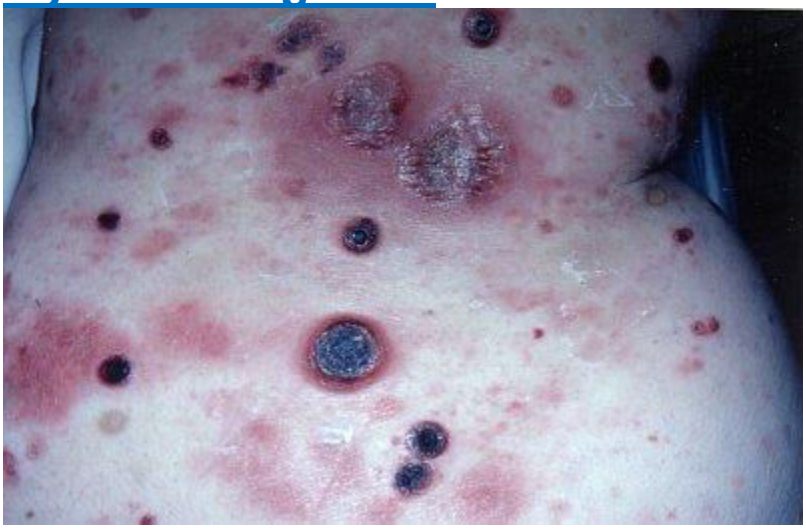
- **Psoriatic-type reactions are most commonly caused by beta-blockers**
- Antibiotics may cause lupus-type reactions, erythema multiforme, Stevens–Johnson syndrome and erythroderma
- Warfarin is associated with alopecia, as are cytotoxic agents and antithyroid agents
- Phenytoin may cause both acne and gingival hyperplasia

Hyperhidrosis describes the excessive production of sweat

Management options include

- topical aluminium chloride preparations are first-line. Main side effect is skin irritation
- iontophoresis: particularly useful for patients with palmar, plantar and axillary hyperhidrosis
- botulinum toxin: currently licensed for axillary symptoms
- surgery: e.g. Endoscopic transthoracic sympathectomy. Patients should be made aware of the risk of compensatory sweating

Mycosis fungoides



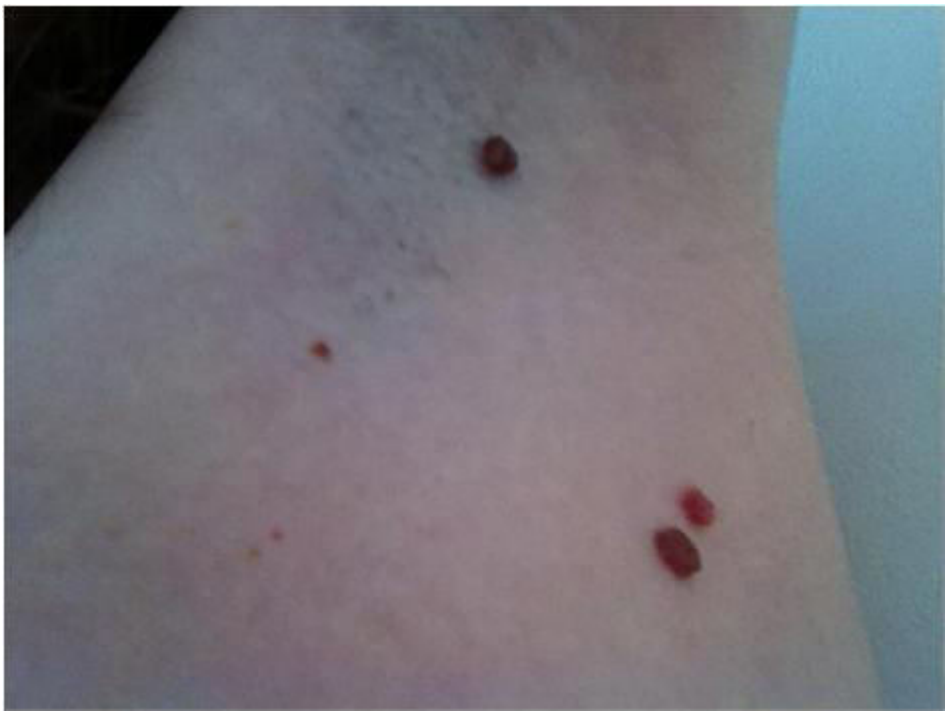
- **a cutaneous T cell lymphoma.**
- The disease presents as a pruritic eczematous rash (the pre-malignant stage) and develops telangiectasias and areas of 'cigarette paper' atrophy.
- As malignancy develops, nodular lesions appear and proceed to become necrotic.

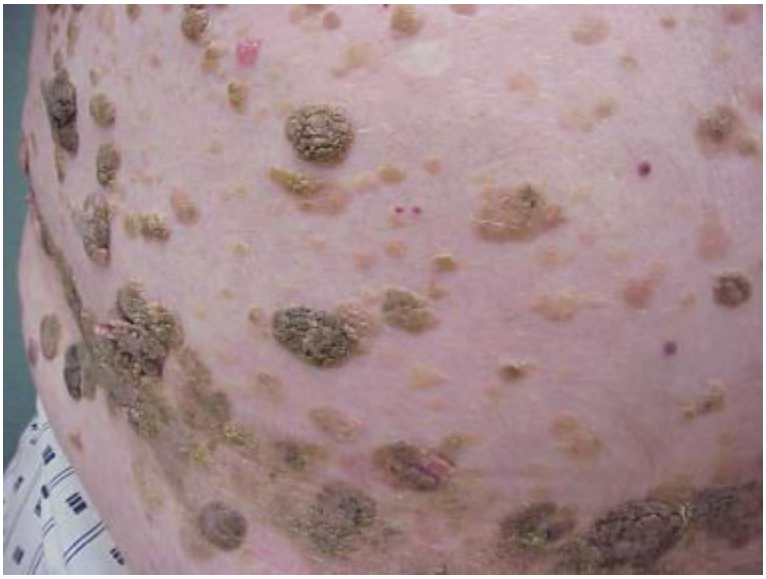
Narrow-band phototherapy (NBUVB)

- skin disorders can be treated with narrow-band phototherapy (**NBUVB**) includes:
  - Psoriasis
  - **Mycosis fungoides patch stage** (NOT tumor stage)
  - Vitiligo
  - Eczemas

Seborrheic keratosis

- Seborrheic keratoses are the most common benign tumor in older individuals.
- and they develop from the proliferation of epidermal cells.
- No specific etiologic factors have been identified.
- Typical features include a warty and waxy surface with surface crypts and a stuck on appearance.
- They typically have an appearance of being stuck on the skin surface.
- Because they begin at a later age and can have a wart-like appearance, seborrheic keratoses are often called the “barnacles of aging.
- Most commonly they are several
- Can growths anywhere on the skin, except the palms and soles. Most often on the chest, back, head, or neck.
- Commonly used treatments include Curettage and cautery (C&C), and cryotherapy (for thinner lesions).

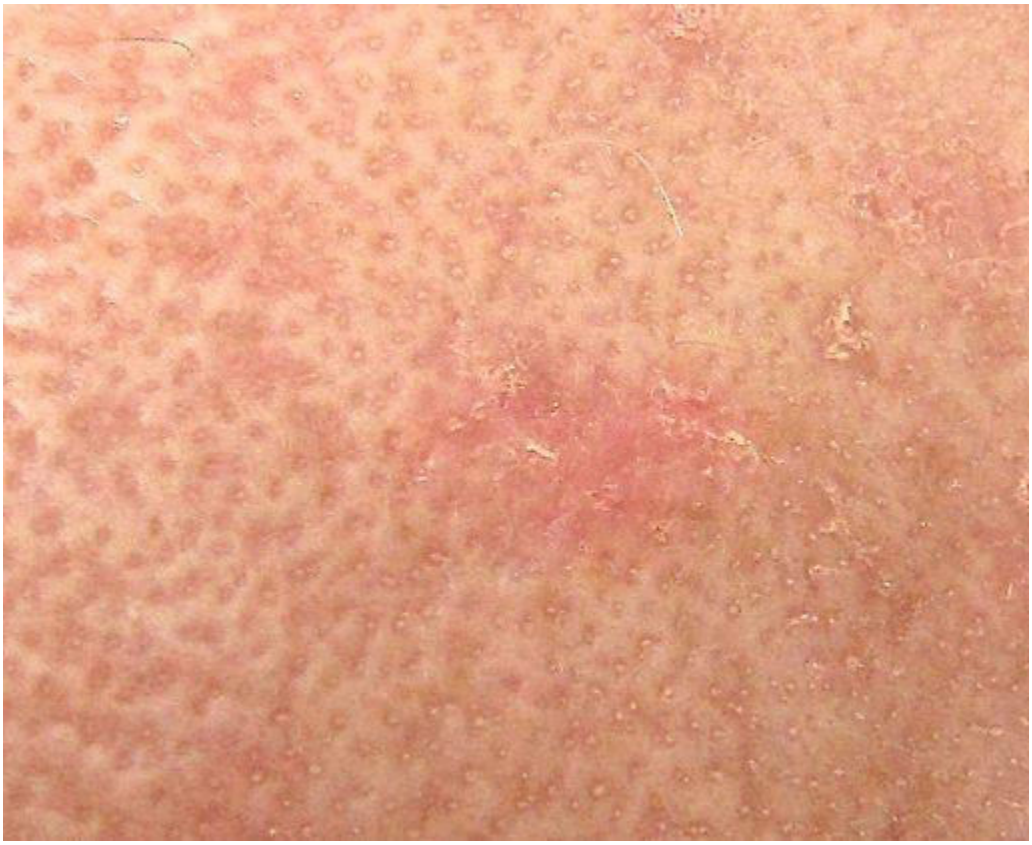




multiple seborrheic keratoses in an autosomally dominant mode of inheritance.

Solar keratosis

- hyperkeratotic lesion with underlying erythema.
- bleed when scratched
- Progression of these lesions to squamous cell skin cancer is slow,
- **Topical 5-FU cream** used twice a day for 3–4 weeks usually achieves clearance of the lesion.
- Diclofenac gel requires a more prolonged treatment period (up to 12 weeks), meaning that it is the second-choice option for compliance reasons. It is useful where coverage of a larger area of skin is required.



solar keratosis (on scalp of elderly)

Xeroderma pigmentosum

- inherited skin disorder

Aetiology

- autosomal recessive
- **defect in nucleotide excision repair (NER),** leading to deficient repair of DNA damaged by UV radiation, and chromosome breakage.

Features

- photosensitivity with severe sunburn in infancy,
- numerous pigmented spots resembling freckles,
- larger atrophic lesions associated with telangiectasis and multiple solar keratosis.

Complications

- multiple malignant cutaneous neoplasms at an early age,
- severe ophthalmic and neurological abnormalities.

Diagnosis

- Cellular hypersensitivity to UV radiation studies
- chromosomal breakage studies

Treatment

- Avoidance of sun exposure

Notes & Notes

For MRCP part 1 & 11

By

Dr. Yousif Abdallah Hamad

Ophthalmology

Updated

2017

Contains:

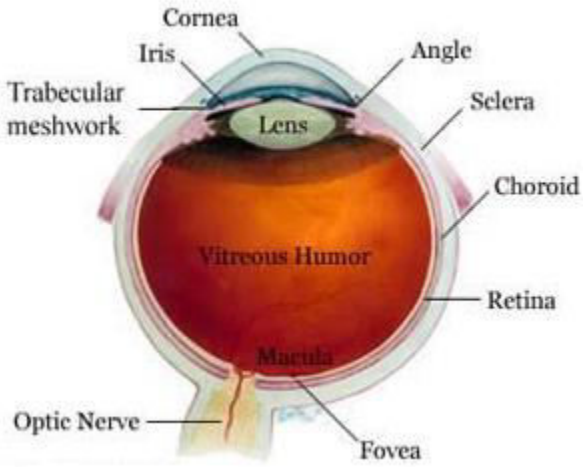
1/ Passmedicine 2017

2/ On examination 2017

3/ Pastest 2017

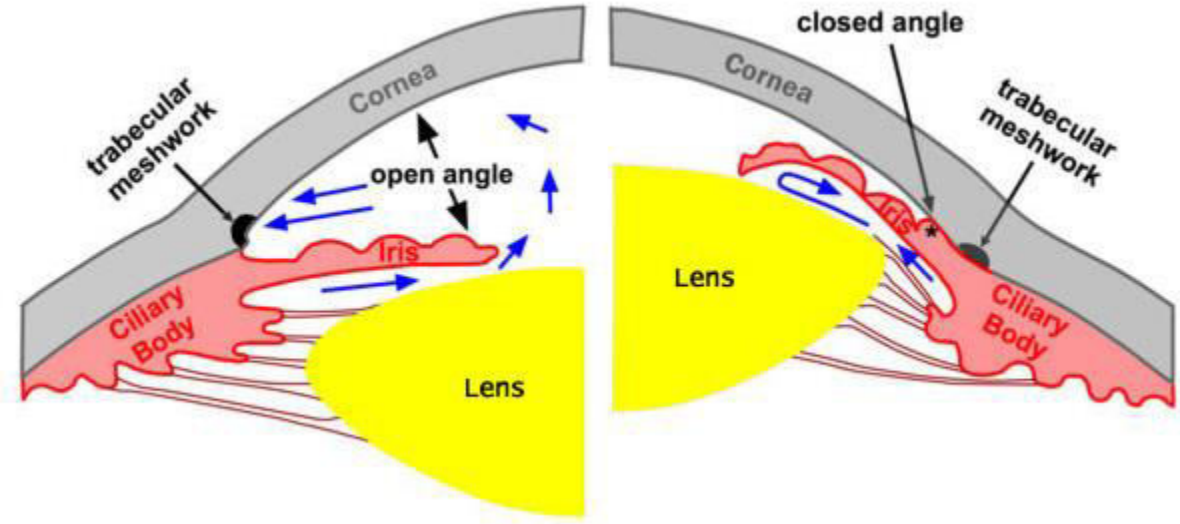
4/ **Red fonts --> previous exams**

5/ Other updated UK sources



Acute angle closure glaucoma

Acute angle closure glaucoma is associated with hypermetropia, where as primary open-angle glaucoma is associated with myopia



- **Glaucoma** is a group disorders characterised by optic neuropathy due, in the majority of patients, to **raised intraocular pressure (IOP).** It is now recognised that a minority of patients with raised IOP do not have glaucoma and vice versa
- In acute angle closure glaucoma (AACG) there is a rise in IOP secondary to an impairment of aqueous outflow.

Factors predisposing to AACG include:

- hypermetropia (long-sightedness)
- pupillary dilatation (Mydriatic drops are a known precipitant of acute angle closure glaucoma)
- lens growth associated with age
- **Drugs which may precipitate acute glaucoma include anticholinergics and tricyclic antidepressants**

Features

- severe pain: may be ocular or headache
- decreased visual acuity
- symptoms worse with mydriasis (e.g. watching TV in a dark room)
- hard, red eye
- haloes around lights
- semi-dilated non-reacting pupil.The oval shape is due to the iris sphincter ischaemia from the high intraocular pressure.
- corneal oedema results in dull or hazy cornea
- systemic upset may be seen, such as nausea and vomiting and even abdominal pain

Management

Treatment of acute glaucoma - acetazolamide + pilocarpine

- urgent referral to an ophthalmologist
- management options include reducing aqueous secretions with acetazolamide and inducing pupillary constriction with topical pilocarpine

---

Primary open-angle glaucoma

- Primary open-angle glaucoma (POAG), is the **most common type of glaucoma**.
- Primary open-angle glaucoma (POAG, also referred to as (chronic simple glaucoma) is present in around 2% of people older than 40 years.
- POAG may present insidiously and for this reason is often detected during routine optometry appointments.

Risk factors (Other than age) include:

- family history
- black patients
- myopia
- hypertension
- diabetes mellitus

Features:

- **peripheral visual field loss - nasal scotomas progressing to 'tunnel vision'**
  - **Loss of nasal visual field is the most consistent feature with POAG**
- decreased visual acuity
- ophthalmoscopic exam → optic disc cupping

management

- Most patients are managed with eye drops.
- These aims to lower intra-ocular pressure which in turn has been shown to prevent progressive loss of visual field.
- **A prostaglandin analogue (e.g. Latanoprost) should be used first-line in patients with a history of asthma.**

Medication	Mode of action	Notes
Prostaglandin analogues (e.g. Latanoprost)	Increases uveoscleral outflow	Once daily administration SE: brown pigmentation of the iris
Beta-blockers (e.g. Timolol)	Reduces aqueous production	Should be avoided in asthmatics and patients with heart block
Sympathomimetics (e.g. brimonidine, an alpha2-adrenoceptor agonist)	Reduces aqueous production and increases outflow	Avoid if taking MAOI or tricyclic antidepressants Adverse effects include hyperaemia
Carbonic anhydrase inhibitors (e.g. Dorzolamide)	Reduces aqueous production	Systemic absorption may cause sulphonamide-like reactions
Miotics (e.g. pilocarpine, a muscarinic receptor agonist)	Increases uveoscleral outflow	Adverse effects included a constricted pupil, headache and blurred vision

Rubeosis iridis

What is the most important preventative intervention to reduce the risk of glaucoma?

➔ **Pan-retinal photocoagulation**

- An important part of the work-up of rubeosis iridis is with fluorescein angiography to assess the extent of retinal ischaemia, and ultrasound.
- Once eye disease has progressed to rubeosis, the mainstay of therapy is pan-retinal photocoagulation to reduce the area of viable retina.
- Anti-VEGF agents and topical steroids may also be of value, but ultimately the prognosis is poor because of late stage at presentation.

Surgery in the form of a trabeculectomy may be considered in refractory cases.

Age related macular degeneration

Drusen = Dry macular degeneration

- Age related macular degeneration is the most common cause of blindness in the UK.
- Degeneration of the central retina (macula) is the key feature with changes usually bilateral.

Classification

- Traditionally two forms of macular degeneration are seen:
  1. **dry** (geographic atrophy) macular degeneration: **characterised by drusen** - yellow round spots in Bruch's membrane
  2. **wet** (exudative, neovascular) macular degeneration: characterised by choroidal neovascularisation. Leakage of serous fluid and blood can subsequently result in a rapid loss of vision. Carries worst prognosis

- Recently there has been a move to a more updated classification:
  - early age related macular degeneration (non-exudative, age related maculopathy): drusen and alterations to the retinal pigment epithelium (RPE)
  - late age related macular degeneration (neovascularisation, exudative)

Risk factors

Macular degeneration - smoking is risk factor

- age: most patients are over 60 years of age
- smoking
- family history
- more common in Caucasians
- high cumulative sunlight exposure
- female sex

Features

- reduced visual acuity: 'blurred', 'distorted' vision, **central vision is affected first**
- **central scotomas**
- fundoscopy: drusen, pigmentary changes

Investigation and diagnosis

- optical coherence tomography: provide cross sectional views of the macula
- **if neovascularisation is present fluorescein angiography is performed**

General management

- stop smoking
- high dose of beta-carotene, vitamins C and E, and zinc may help to slow down visual loss for patients with established macular degeneration. **Supplements should be avoided in smokers due to an increased risk of lung cancer**
- Having a balanced diet, with plenty of fresh fruits and vegetables may also slow the progression of macular degeneration.

Dry macular degeneration - no current medical treatments

Wet macular degeneration

- photocoagulation
- photodynamic therapy
- anti-vascular endothelial growth factor (anti-VEGF) treatments: intravitreal ranibizumab

Cataracts

A cataract is an opacity of the normally clear lens which may develop as a result of aging, metabolic disorders, trauma or heredity

Definition

- **opacification of the lens**

Causes

- **Majority**
  - age related (Senile cataracts)
    - the most common cause
      - 17% of people older than 40 years
      - 50% of people older than 75 years
  - UV light
- **Systemic**
  - diabetes mellitus
  - steroids
    - **Inhaled steroids can cause cataracts**
  - infection (congenital rubella)
  - metabolic:
    - diabetes
    - hypocalcaemia,
    - galactosaemia
      - but if the galactosaemia is treated, the cataract is reversible.
  - myotonic dystrophy,
  - Down's syndrome
- **Ocular**
  - trauma
  - uveitis
  - high myopia
  - topical steroids

Feature

- Symptoms
  - painless, progressive, and slow vision loss
- Physical exam

- absent red reflex

Classification

- **Nuclear sclerosis**:
  - **the most common type** of cataract,
  - involves the central or 'nuclear' part of the lens.
  - **common in old age**
  - reduction of vision is the major symptom.
  - change lens refractive index,
    - often leads to an **increase in refractive power of the lens** causing **nearsightedness (problems with distance vision**).
- Polar: localized, commonly inherited, lie in the visual axis
- **Subcapsular:**
  - glare is the major symptom
    - **Glare** is difficulty seeing in the presence of bright light such as direct or reflected sunlight or artificial light such as car headlamps at night. (صعوبة الرؤية في الضوء الساطع)
  - due to steroid use, just deep to the lens capsule, in the visual axis
  - **Posterior subcapsular cataracts** are associated with:
    - **retinitis pigmentosa**
    - **chronic steroid** use.
  - Anterior subcapsular cataracts are associated with:
    - idiopathic or
    - secondary to trauma and iotragenic causes.
- Dot opacities
  - common in normal lenses,
  - also seen in:
    - diabetes
    - myotonic dystrophy

Diabetic retinopathy **See endocrinology**

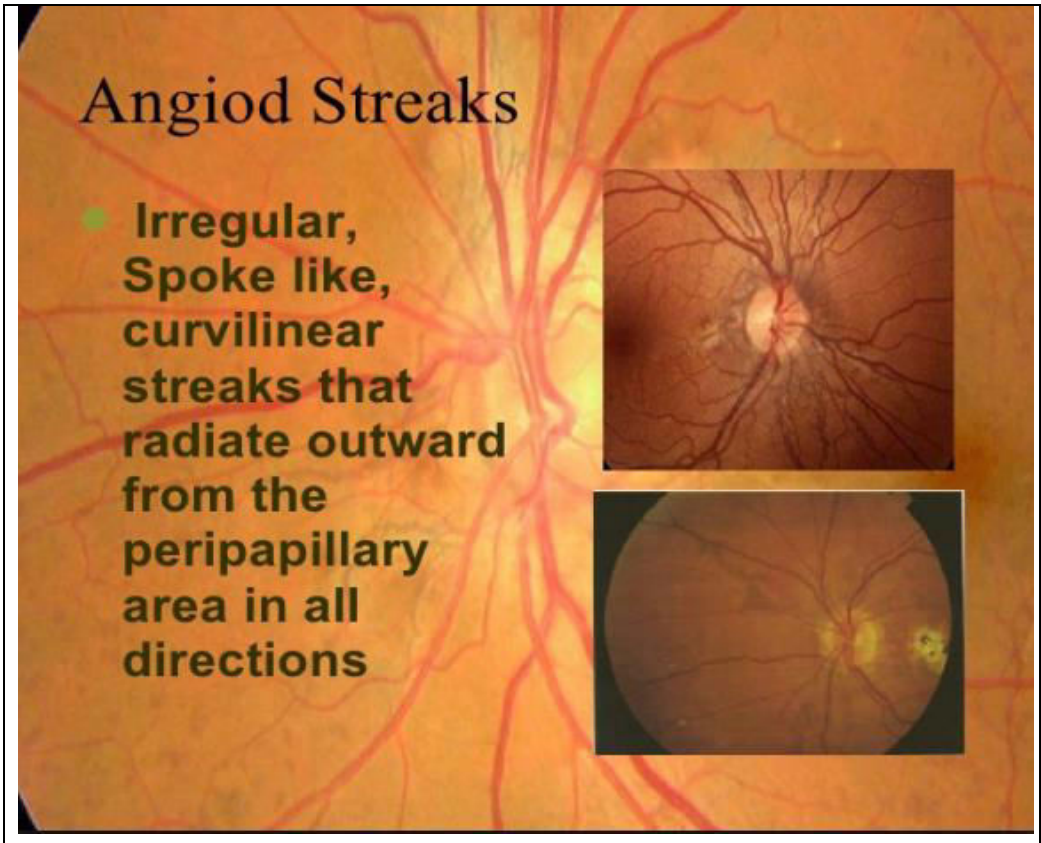
Angioid retinal streaks

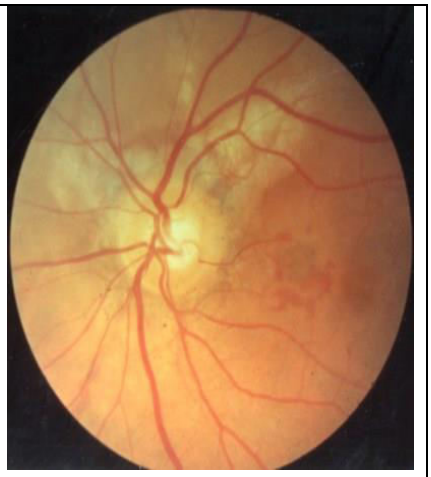
- Angioid retinal streaks are seen on fundoscopy as irregular dark red streaks radiating from the optic nerve head. They are caused by degeneration, calcification and breaks in Bruch's membrane .

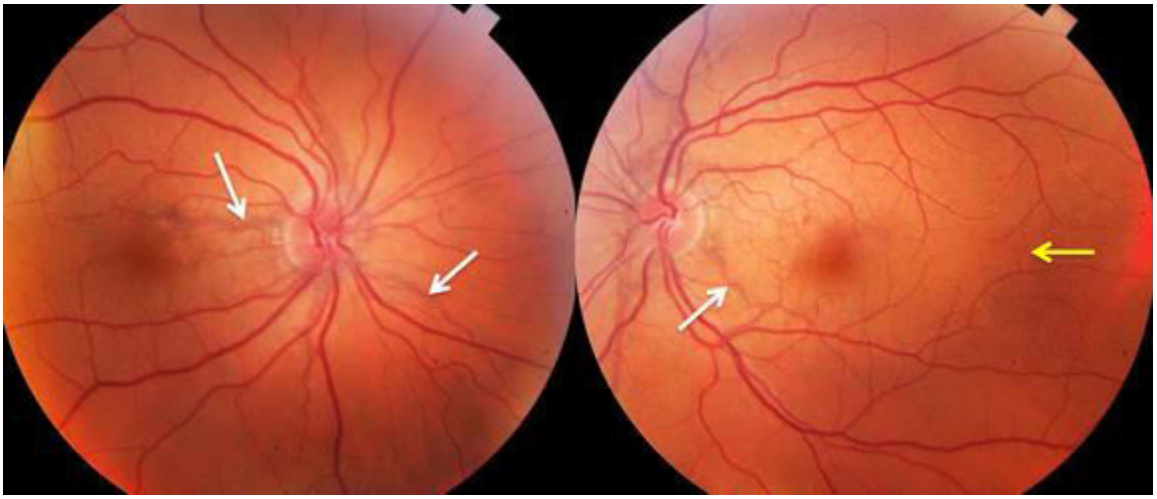
Causes

A useful mnemonic for angioid retinal streak is **SLAPPERS**:

- S - **Sickle-cell anaemia**
- L - Lead poisoning
- A - Abetalipoproteinaemia/acromegaly
- P - **Paget's disease** /phacomatoses (tuberous, sclerosis, neurofibromatosis, Sturge-Weber)
- P - **Pseudoxanthoma elasticum**
- E - Ehlers-Danlos syndrome
- R - Raised calcium or phosphate
- S - Short people (dwarfism).


Angiod Streaks
Irregular, Spoke like, curvilinear streaks that radiate outward from the peripapillary area in all directions





Mydriasis

Causes of mydriasis (large pupil)

- third nerve palsy
- Holmes-Adie pupil
- traumatic iridoplegia
- phaeochromocytoma
- congenital
- **Drug causes of mydriasis**
  - topical mydriatics: tropicamide, atropine
  - sympathomimetic drugs: amphetamines, pseudoephedrine, amphetamines and **cocaine,**
  - anticholinergic drugs: eg antihistamines, atropine and tricyclic antidepressants
  - Poisons (atropine, CO, ethylene glycol).

Miosis

Causes of small pupils include:

- Horner's syndrome
- Old age
- **Pontine haemorrhage**
- Argyll Robertson pupil
- Drugs, and
- Poisons (opiates, organophosphates).

Holmes-Adie pupil

Holmes ADIe = DIlated pupil, females, absent leg reflexes

Abnormally dilated pupil (mydriasis) which does not constrict in response to light, loss of deep tendon reflexes, and abnormalities of sweating.

Holmes-Adie pupil is a benign condition most commonly seen in women. It is one of the differentials of a dilated pupil.

Overview

- unilateral in 80% of cases
- dilated pupil (**tonically dilated pupil**)
- slowly reactive to accommodation but very poorly (if at all) to light
- once the pupil has constricted it remains small for an abnormally long time
- associated with absent ankle/knee reflexes and impaired sweating
  - The cause of the associated arreflexia is unknown.

pathophysiology

- Viral or bacterial infection causes → damage to neurons in the **ciliary ganglion**, **located in the posterior orbit**, that provides parasympathetic control of eye constriction.
- damage to the **dorsal root ganglia of the spinal cord** → problems with autonomic control of the body**.**

Diagnosis

- **testing with low dose (1/8%) pilocarpine may constrict the tonic pupil due to cholinergic denervation super-sensitivity. A normal pupil will not constrict with the dilute dose of pilocarpine.**

Argyll-Robertson pupil

- the prostitute's pupil - accommodates but doesn't react.
- Another mnemonic used for the Argyll-Robertson Pupil (ARP) is Accommodation Reflex Present (ARP) but Pupillary Reflex Absent (PRA)

Features

- small, irregular pupils
- no response to light but there is a response to accommodate

Causes

- diabetes mellitus
- syphilis (neurosyphilis)

Optic atrophy

- Optic atrophy is a descriptive term, it is the optic neuropathy that results in visual loss
- Usually bilateral and causes a gradual loss of vision.
- On fundoscopy optic atrophy is seen as pale, well demarcated disc.
- Causes may be acquired or congenital

Acquired causes

- multiple sclerosis
- papilloedema (longstanding)
- raised intraocular pressure (e.g. glaucoma, tumour)
- retinal damage (e.g. choroiditis, retinitis pigmentosa)
- ischaemia
- toxins: tobacco amblyopia, quinine, methanol, arsenic, lead
- nutritional: vitamin B1, B2, B6 and B12 deficiency

Congenital causes

- Friedreich's ataxia
- **mitochondrial disorders e.g. Leber's optic atrophy**
  - usually affects young men.
  - It causes sequential optic neuropathies in days to weeks.
  - It is typically painless and severe.
  - Visual acuity fails to improve.
  - Mutations in the MT-ND1, MT-ND4, MT-ND4L, and MT-ND6 genes
    - These genes are contained in mitochondrial DNA.
  - Specifically, more than 50% of males with a mutation and more than 85% of females with a mutation never experience vision loss or related medical problems.
- DIDMOAD - the association of cranial Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness (also known as Wolfram's syndrome)

Optic neuritis

The patient sees nothing and the doctor sees nothing

- Optic neuritis is a broad term which can be used to describe inflammation, degeneration or demyelination of the optic nerve.
- Optic neuritis is very rare in people over the age of 50.
- It encompasses a number of conditions, including:
  - Papillitis (anterior optic neuritis) - the intraocular portion of the nerve is affected, and the **optic disc is swollen**
    - It is important to note that the disc changes in papilloedema may closely resemble those of papillitis but visual acuity is markedly reduced in papillitis and not papilloedema.
  - Retrobular neuritis - the distal portion of the optic nerve is affected, and the disc is therefore not swollen
  - Neuroretinitis - optic disc and adjacent temporal retina are affected.

Causes

- multiple sclerosis
- diabetes
- syphilis

Features

- unilateral decrease in visual acuity over hours or days
  - Visual loss typically **occurs over days rather than hours.** Sudden visual loss due to optic neuritis is very unusual.
  - **Optic neuritis presents with a particular type of central visual loss - a central scotoma.**
- poor discrimination of colours, 'red desaturation' - ie when red looks paler to one eye than the other -
- **The retrobulbar neuritis seen with ethambutol may be unilateral or bilateral; as such unilateral symptoms do not preclude the diagnosis.**
- pain worse on eye movement
- relative afferent pupillary defect during the 'swinging flashlight test'.
- central scotoma
- **Most cases of optic neuritis are retrobulbar and hence there are no abnormalities on fundoscopy.**
  - **the most likely finding on fundoscopy → Normal optic disc**

Diagnosis

- **MRI with gadolinium of the brain** will likely show → **enhancement of the optic nerve**
- **Abnormal visual evoked potentials (VEP)**

Management

- high-dose steroids
  - Methylprednisolone pulse therapy is the standard treatment
    - slightly shortens the time of recovery but does not prevent neurodegeneration and persistent visual impairment.

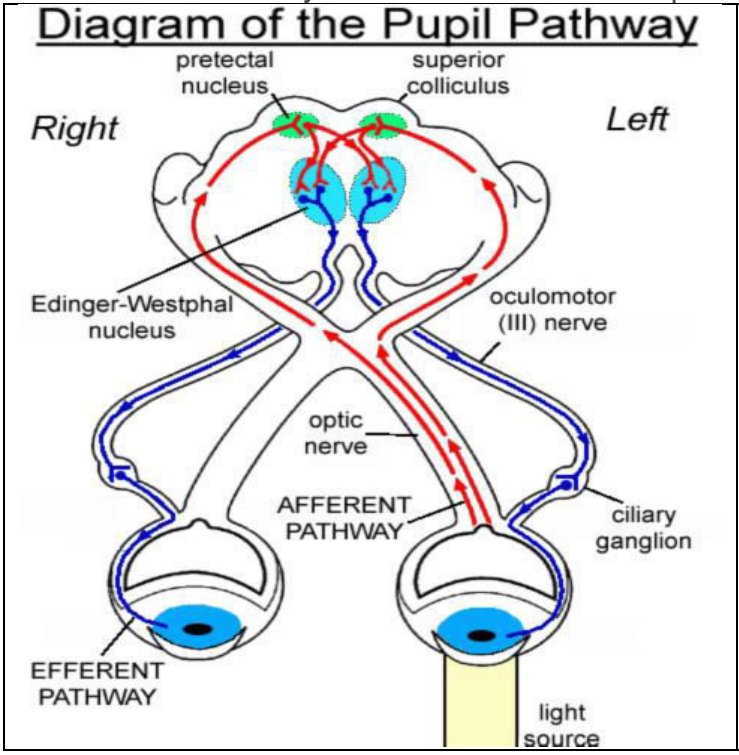
- recovery usually takes 4-6 weeks
- erythropoietin may have neuroprotective effects in autoimmune optic neuritis

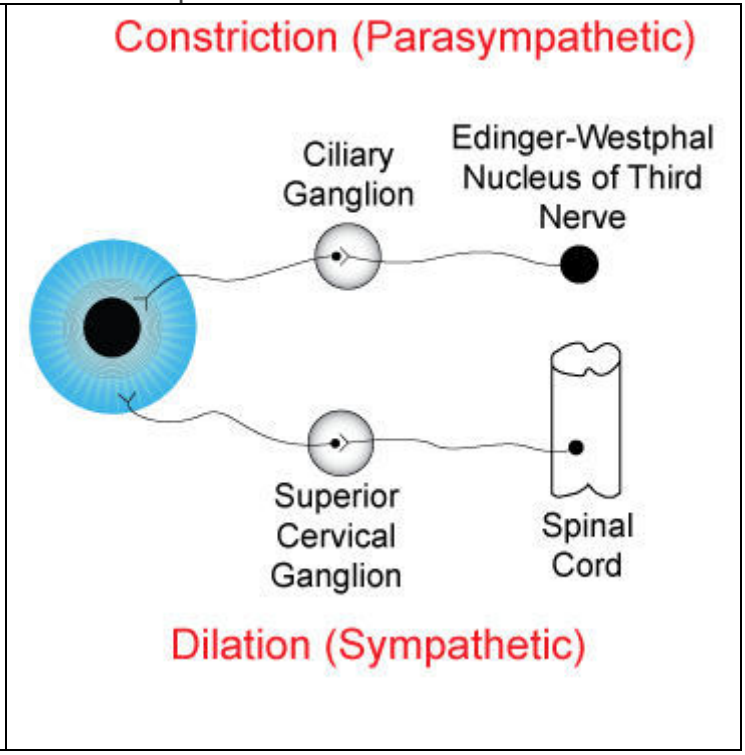
Prognosis

- **MRI: if > 3 white-matter lesions, 5-year risk of developing multiple sclerosis is c. 50%**
- Retrobulbar neuritis has the same systemic implications as optic neuritis, in that an episode of optic or retrobulbar neuritis can contribute to a diagnosis of multiple sclerosis

Relative afferent pupillary defect

- Also known as the **Marcus-Gunn pupil**, a relative afferent pupillary defect is found by the 'swinging light test'.
- It is caused by a lesion anterior to the optic chiasm i.e. optic nerve or retina





Causes

- retina: detachment
- optic nerve: optic neuritis e.g. multiple sclerosis

Pathway of pupillary light reflex

- afferent: retina → optic nerve → lateral geniculate body → midbrain
- efferent: Edinger-Westphal nucleus (midbrain) → oculomotor nerve

Swinging flashlight test & Relative afferent pupillary defect RAPD **(**Marcus Gunn pupil**)**

- The Marcus Gunn pupil is a relative afferent pupillary defect indicating a decreased pupillary response to light in the affected eye
- In the swinging flashlight test, a light is alternately shone into the left and right eyes.
- A normal response would be equal constriction of both pupils, regardless of which eye the light is directed at. This indicates an intact direct and consensual pupillary light reflex.
- When the test is performed in an eye with an afferent pupillary defect, light directed in the affected eye will cause only mild constriction of both pupils (due to decreased response to light

from the afferent defect), while light in the unaffected eye will cause a normal constriction of both pupils (due to an intact efferent path, and an intact consensual pupillary reflex). Thus, light shone in the affected eye will produce less pupillary constriction than light shone in the unaffected eye.

- A **positive** RAPD is due to retinal or optic nerve disease.

due to the consensual response of the pupillary light reflex, shining light in the unaffected eye will produce bilateral miosis.

- shining light in the affected eye will not produce miosis because the afferent limb of the pupillary light reflex pathway is damaged (eg: optic neuritis)
- However, **due to the bilateral projections of nerves from the Edinger-Westphal nucleus**, light shined in the **unaffected eye** will produce **bilateral miosis**. This phenomenon is called a **consensual response**.

Herpes simplex keratitis

- Herpes simplex keratitis most commonly presents with a dendritic corneal ulcer

Features

- red, painful eye
- photophobia
- epiphora
- visual acuity may be decreased
- fluorescein staining may show an epithelial ulcer (dendritic corneal ulcer)

Management

- immediate referral to an ophthalmologist
- topical aciclovir

Herpes zoster ophthalmicus

- Herpes zoster ophthalmicus (HZO) describes the reactivation of the varicella zoster virus in the area supplied by the ophthalmic division of the trigeminal nerve.
- It accounts for around 10% of case of shingles.

Features

- vesicular rash around the eye, which may or may not involve the actual eye itself
- Hutchinson's sign: rash on the tip or side of the nose. Indicates nasociliary involvement and is a strong risk factor for ocular involvement

Management

- **Oral antiviral** treatment for 7-10 days, ideally started within 72 hours. **Topical antiviral treatment is not given in HZO**
- oral corticosteroids may reduce the duration of pain but do not reduce the incidence of post-herpetic neuralgia
- ocular involvement requires urgent ophthalmology review

Complications

- ocular: conjunctivitis, keratitis, episcleritis, anterior uveitis
- ptosis
- post-herpetic neuralgia

Blepharitis

- Blepharitis is inflammation of the eyelid margins.
- It may due to either meibomian gland dysfunction (common, posterior blepharitis) or seborrhoeic dermatitis/staphylococcal infection (less common, anterior blepharitis).
- Blepharitis is also more common in patients with rosacea
- The meibomian glands secrete oil on to the eye surface to prevent rapid evaporation of the tear film. Any problem affecting the meibomian glands (as in blepharitis) can hence cause drying of the eyes which in turns leads to irritation

Features

- symptoms are usually bilateral
- grittiness and discomfort, particularly around the eyelid margins
- eyes may be sticky in the morning
- eyelid margins may be red. Swollen eyelids may be seen in staphylococcal blepharitis
- styes and chalazions are more common in patients with blepharitis
- secondary conjunctivitis may occur

Management

- softening of the lid margin using hot compresses twice a day
- mechanical removal of the debris from lid margins - cotton wool buds dipped in a mixture of cooled boiled water and baby shampoo is often used*
  - *an alternative is sodium bicarbonate, a teaspoonful in a cup of cooled water that has recently been boiled
- artificial tears may be given for symptom relief in people with dry eyes or an abnormal tear film

Keratitis

- Keratitis refers to inflammation of one or more of the three corneal layers, the most common of which is epithelial keratitis. This is **characterised by dendritic ulcers**. Rarer forms involve the stroma or endothelium.
- *Pseudomonas aeruginosa* is commonly associated with contact lens related infections.
- The management must also include advising the patient to discontinue wearing contact lenses and referral to a specialist ophthalmic unit.
- Recurrence is common.

Features

- red eye: pain and erythema (**sharp ocular pain**)
- photophobia
- blurred vision (in many cases).
- Microbial keratitis, **causing a white corneal infiltrate**
- foreign body, gritty sensation
- hypopyon may be seen

Infective

- **Viral: herpes simplex keratitis**
  - Treated with topical antivirals, e.g. aciclovir 5 times per day.
  - Topical steroids or oral antivirals can be used in some cases.
- bacterial:
  - typically *Staphylococcus aureus*.
  - *Pseudomonas aeruginosa* is seen in contact lens wearers.

- more likely if there is a history of contact lens wear or trauma, such as a corneal abrasion or a corneal foreign body.
- **first line treatment of corneal ulcer → Levofloxacin hourly**

- fungal
- amoebic: acanthamoebic keratitis
- parasitic: onchocercal keratitis ('river blindness')

Enviromental

- photokeratitis: e.g. welder's arc eye
- exposure keratitis
- contact lens acute red eye (CLARE)

Acanthamoeba keratitis

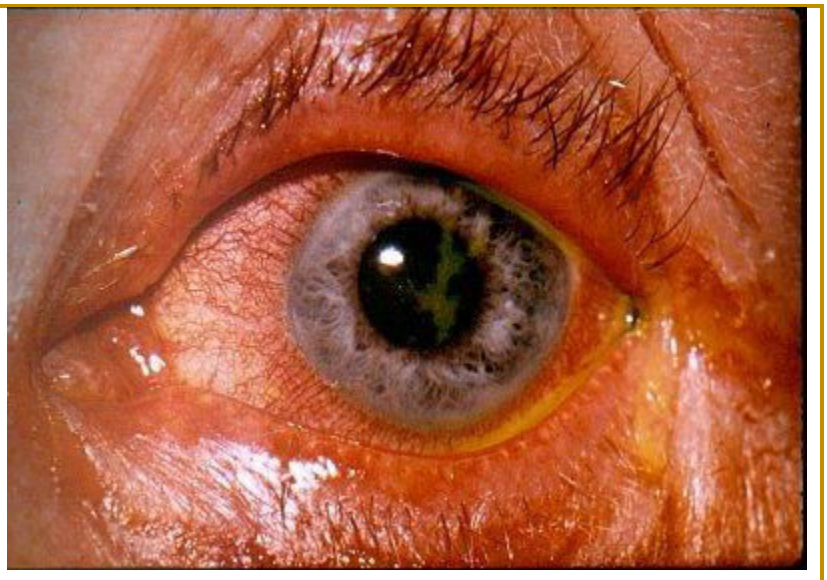
- rare and serious keratitis associated with contact lens (CL) wear.
- Risk factors are exposure of CL to contaminated water, for example, using tap water to clean CL or swimming in lenses.
- Clinical features include pain out of proportion to clinical signs, ring infiltrates and radial kerato-neuritis.
- management → Brolene drops

Marginal keratitis

- Marginal keratitis is areas of peripheral corneal infiltrates/ulcers associated with blepharitis.
- classically causes an infiltrate near the limbal edge with an area of clear cornea. There may be limbal vessels growing towards the lesion(s).
- caused by a hypersensitivity reaction to staphylococcal exotoxins from *Staphylococcus aureus* present on the lid margins in blepharitis.
- Treatment:
  - topical steroids for the keratitis
  - lid hygiene advice
  - topical antibiotics to treat the underlying blepharitis.
  - In severe cases oral doxycycline can also be used.

Dendritic ulcers

- **caused by** herpes simplex virus.
- **Presentation** is usually with pain, photophobia, blurred vision, conjunctivitis and chemosis.
- Steroid eye drops are contraindicated as they may induce massive amoeboid ulceration and blindness.
- **treated with aciclovir eye drops,** which should be continued for three days after the ulcer has healed.



Lacrimal duct problems

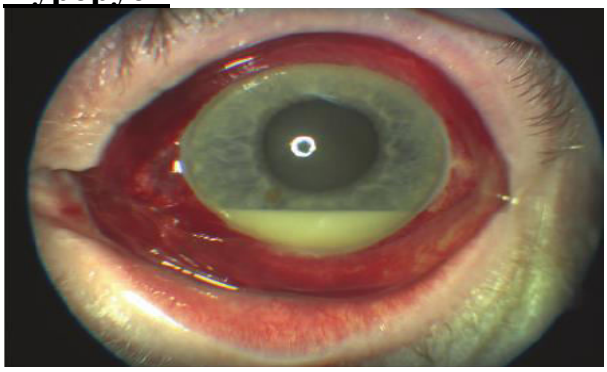
Dacryocystitis is infection of the lacrimal sac

- **Features**
  - watering eye (epiphora)
  - swelling and erythema at the inner canthus of the eye
- **Management**
  - systemic antibiotics.
  - Intravenous antibiotics are indicated if there is associated periorbital cellulitis

Congenital lacrimal duct obstruction

- affects around 5-10% of newborns.
- It is bilateral in around 20% of cases
- **Features**
  - watering eye (even if not crying)
  - secondary infection may occur
- Symptoms resolve in 99% of cases by 12 months of age

Hypopyon



- **Hypopyon** is the collection of pus in the bottom of the anterior chamber of the eye.
- It can be clearly visualized as a fluid level and the sedimentation is governed by the gravity.
- The composition of the pus would be only white cells or leucocytes without any pathogens of bacterial, fungal or even viral origin.

causes

- inflammatory process in that region, mainly the iris and the uvea.
- usually implies infective endophthalmitis (eg following cataract surgery),
- sterile hypopyon can occur in cases of severe iritis (eg Behcet's disease).

Red eye

Red eye - glaucoma or uveitis?
- glaucoma: severe pain, haloes, 'semi-dilated' pupil
- uveitis: small, fixed oval pupil, ciliary flush

There are many possible causes of a red eye. It is important to be able to recognise the causes which require urgent referral to an ophthalmologist. Below is a brief summary of the key distinguishing **features**

Acute angle closure glaucoma

- severe pain (may be ocular or headache)
- decreased visual acuity, patient sees haloes
- semi-dilated pupil
- hazy cornea

Anterior uveitis

• acute onset • pain • blurred vision and photophobia	• small, fixed oval pupil, ciliary flush • **sign on ocular examination → Hypopyon**

Iritis is associated with conditions such as:
- Reiter's
- Behcet's
- **Psoriatic arthropathy (about 20%)**
- and inflammatory bowel disease.

A chronic iritis is rarely described in association with Lyme disease.

Signs of anterior uveitis

- **Keratic precipitates**: (opaque aggregates of inflammatory cells deposited on the endothelium in anterior uveitis. They are typically located inferiorly.
- Cells +/- flare +/- fibrin in the anterior chamber
- Ciliary injection - localised conjunctival injection (redness) around the limbus
- Posterior synechiae - where part of the pupil margin becomes stuck to the lens
- Hypopyon (in severe anterior uveitis).

Scleritis

- Scleritis : inflammation that occurs throughout the entire thickness of the sclera,
- **severe pain** (may be worse on movement) and tenderness
  - **pain** in scleritis is more evident and severe than episcleritis.
  - **Tenderness** to palpation of the globe can differentiate it from episcleritis. After asking the patient to look down with eyelids closed, the physician gently presses the globe. Patients with scleritis have tenderness on palpation, while those with episcleritis do not.
  - Unlike scleritis, patients with episcleritis do not complain of **blurred vision or photophobia.**
  - Studies have shown that patients with RA-associated scleritis have **more widespread systemic disease** and a higher mortality rate than those episcleritis.
- 50% of cases are bilateral.
- Pain often radiates to the forehead, brow and jaw. This pain worsens with movement of the eye, and is classically worse at night.
- There is associated watering, photophobia and a gradual decrease in vision (sometimes with diplopia).
- Systemic symptoms such as fever, headache and vomiting can occur.
- may be underlying autoimmune disease e.g. rheumatoid arthritis
  Around 50% of patients with scleritis have an underlying disease, of which the majority are connective tissue disorders. **Rheumatoid arthritis is the most common.**
- On examination the globe is tender, and the sclera can have a bluish tinge.
- **Application of topical phenylephrine 2.5% leads to blanching of episcleral vessels in episcleritis but not in scleritis.**
- Management ultimately depends on the underlying cause, but includes NSAIDs and prednisolone.
- **The patient should be referred urgently to the ophthalmology clinic**

Episcleritis

Scleritis is painful, episcleritis is not painful

- Results in ocular irritation with nodules.
- acute in onset, with **mild pain** or discomfort / grittiness.
- can be unilateral or bilateral, with localised or diffuse red eye.
- There may be **mild** photophobia and watering. **The lack of photophobia and discharge, and normal vision, makes episcleritis the most likely option**

Ocular manifestation of rheumatoid arthritis (see rheumatology)

Conjunctivitis

- purulent discharge if bacterial, clear discharge if viral
- **Viral conjunctivitis**
  - causes redness, soreness and watering.
  - In severe cases it can cause a keratitis which may affect vision.

- It is highly contagious so patients should be advised to practise strict hand hygiene, to avoid sharing towels and to take time off work.
- It is a self-limiting disease which may take several weeks to resolve.
- Patients are treated with topical lubricants and some ophthalmologists give topical chloramphenicol to protect against secondary bacterial infections.

Subconjunctival haemorrhage

- history of trauma or coughing bouts
- **adverse effect of aspirin** therapy (and other antiplatelets).
- It usually resolves over 10-14 days.
- If the haematoma is large it may be worth considering prophylactic antibiotic eyedrops.

Posterior uveitis

- Posterior uveitis describes inflammation of the choroid, which can involve the retinal vessels.
- presents with gradual visual loss and floaters, which is often bilateral.
- Discomfort and erythema are rare.
- Slit light examination can demonstrate inflammatory lesions on the retina or choroid, with inflammation of the retinal vessels and oedema of the optic nerve.

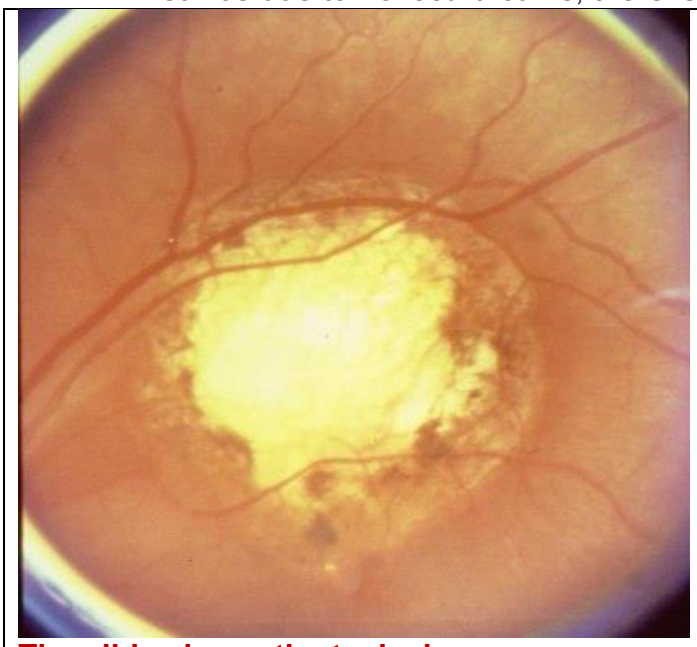
Retinitis

CMV Retinitis: causes hemorrhage at the edge of the area of retinal necrosis

- **Retinitis** is inflammation of the retina in the eye, which may lead to blindness.
- may be caused by several infectious agents, toxoplasmosis, cytomegalovirus and candida.
- Cytomegalovirus retinitis is the most common cause of vision loss in AIDS patients.

Toxocara retinitis

- In retinitis due to *Toxocara canis*, there is usually only a single, well demarcated lesion.



The slide shows the typical appearance of *Toxocara* retinitis with a lesion at the macula.

Retinitis pigmentosa

Retinitis pigmentosa - night blindness + funnel vision

Definition

- Retinitis pigmentosa is a **degenerative** disease involving retinal receptors and pigment cells.

Pathophysiology

- **degeneration of rod photoreceptor cells** in the retina → night blindness and low peripheral vision
  - There are two types of photoreceptors, called rods and cones.
    - **Rods** are in the outer regions of the retina, and allow us to see in dim and dark light.
      - Died early → night blindness
    - **Cones** reside mostly in the central portion of the retina, and allow us to perceive fine visual detail and color.
      - Died in the late stages

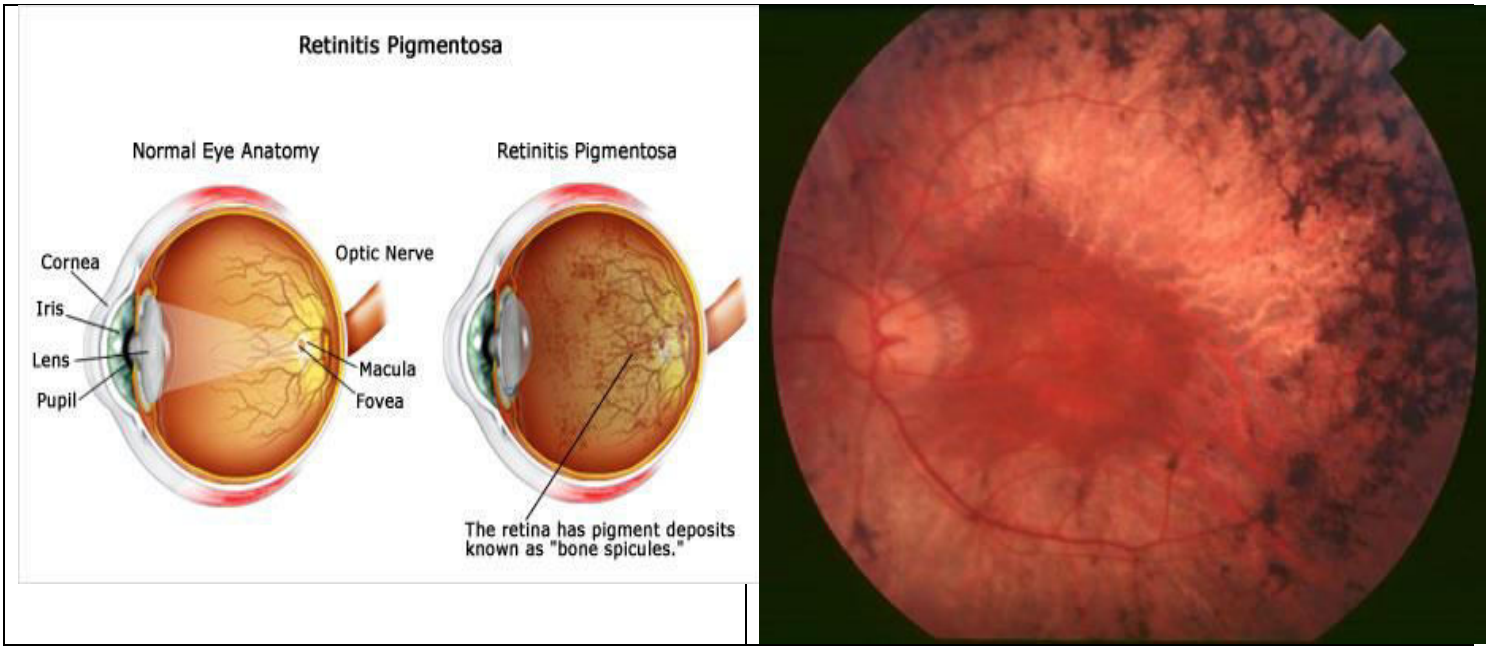
Features

- **night blindness is often the initial sign**
- funnel vision (the preferred term for tunnel vision)

- fundoscopy:
  - black bone spicule-shaped pigmentation in the peripheral retina,
  - mottling of the retinal pigment epithelium

Associated diseases

- Refsum disease:
  - cerebellar ataxia, peripheral neuropathy, deafness, ichthyosis
- Usher syndrome
- abetalipoproteinemia
- Lawrence-Moon-Biedl syndrome
- Kearns-Sayre syndrome
- Alport's syndrome
- mitochondrial myopathy
- drug-induced
  - Thioridazine
    - (typical antipsychotic drug belonging to the phenothiazine group and was previously widely used in the treatment of schizophrenia and psychosis; withdrawn worldwide in 2005 because it caused severe cardiac arrhythmias,)
    - It is important to differentiate this from corneal deposits that may develop with the use of chlorpromazine.
      - Thioridazine → **retinal** deposits (**retinitis pigmentosa**).
      - **ch**lorpromazine → **corneal** deposits



Fundus showing changes secondary to retinitis pigmentosa

Deficiency of ornithine- δ-aminotransferase

- Deficiency of ornithine- **δ**-aminotransferase causes atrophy of the choroid and retina,
- beginning as a small yellowish spot and increasing to a circular lesion edged with pigment giving an atypical retinitis pigmentosa appearance

- **Children** present with **myopia** and **decreased night vision**, which progresses to blindness in middle life
- Cataracts also develop but the optic discs, cornea and iris remain normal
- A few patients develop mild proximal muscle weakness

CHRPE - congenital hypertrophy of the retinal pigment epithelium.

- These can be typical' or 'atypical'.
- **Typical CHRPE** are grey or black, with depigmented lacunas, and are found in one quadrant of one eye. They do not affect vision.
- **Atypical CHRPE** have a white fishtail and are bilateral. They do not affect vision, but if there are more than four atypical CHRPE in each eye, then familial adenosis polyposis or Gardner syndrome might be suspected as an association. **Colonoscopy and examination of all family members would therefore be appropriate.**
  A referral to gastroenterology is the best next step.

Sudden painless loss of vision

Flashes and floaters - vitreous/retinal detachment

An elderly patient with acute visual loss has giant cell arteritis until proved otherwise

The most common causes of a sudden painless loss of vision are as follows:

- ischaemic optic neuropathy (e.g. temporal arteritis or atherosclerosis)
- occlusion of central retinal vein
- occlusion of central retinal artery
- vitreous haemorrhage
- retinal detachment

Ischaemic optic neuropathy

- may be due to arteritis (e.g. temporal arteritis) or atherosclerosis (e.g. hypertensive, diabetic older patient)
- due to occlusion of the short posterior ciliary arteries, causing damage to the optic nerve
- altitudinal field defects are seen

Central retinal vein occlusion

Central retinal vein occlusion - sudden painless loss of vision, severe retinal haemorrhages on fundoscopy

- incidence increases with age, **more common than arterial occlusion**
- causes: glaucoma, polycythaemia, hypertension, DM
- severe retinal haemorrhages are usually seen on fundoscopy
- hypertension and diabetes are risk factors
- In central retinal vein occlusion there are **widespread dot-blot and flame hemorrhages throughout the fundus and disc edema.** In branch vein occlusion the hemorrhages are found in a single zone.

Nasal branch retinal vein occlusion → sudden blurring (not total visual loss) of the temporal field in the affected eye.

Central retinal artery occlusion

- due to thromboembolism (from atherosclerosis) or arteritis (e.g. temporal arteritis)
- features include afferent pupillary defect, 'cherry red' spot on a pale retina
- Retinal artery occlusions lead to amaurosis fugax, often describes as a 'black curtain' descending over the vision.
- In retinal artery occlusion, **the area of retina involved is pale** and interrupted columns of blood may be seen in retinal arteries. If the macula is involved, the center of the macula (blood supply from the intact underlying choroid) stands out as a cherry-red spot.

Vitreous haemorrhage

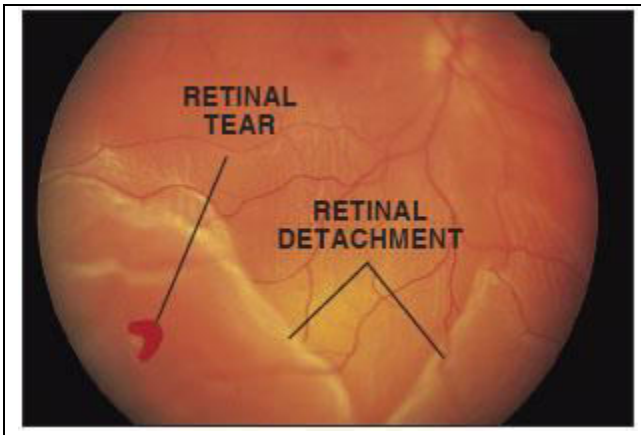
- The history of diabetes, complete loss of vision in the affected eye and inability to visualise the retina point towards a diagnosis of vitreous haemorrhage.
- causes: diabetes, bleeding disorders. the most likely source of bleeding in a diabetic patient is fragile neovascular tissue (**Proliferative retinopathy)**
- features may include sudden visual loss, dark spots

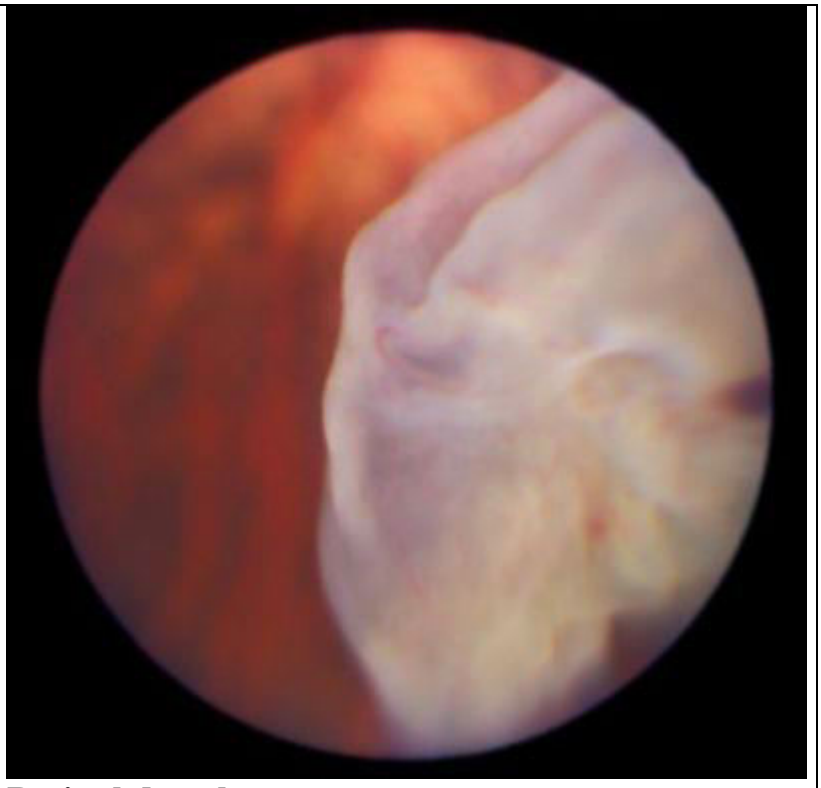
Retinal detachment

- features of vitreous detachment, which may precede retinal detachment, include flashes of light or floaters (see below)

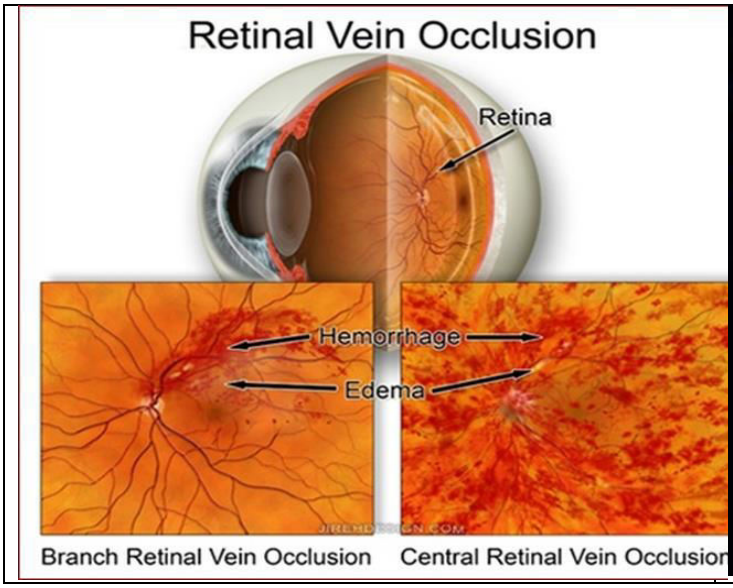
Differentiating posterior vitreous detachment, retinal detachment and vitreous haemorrhage

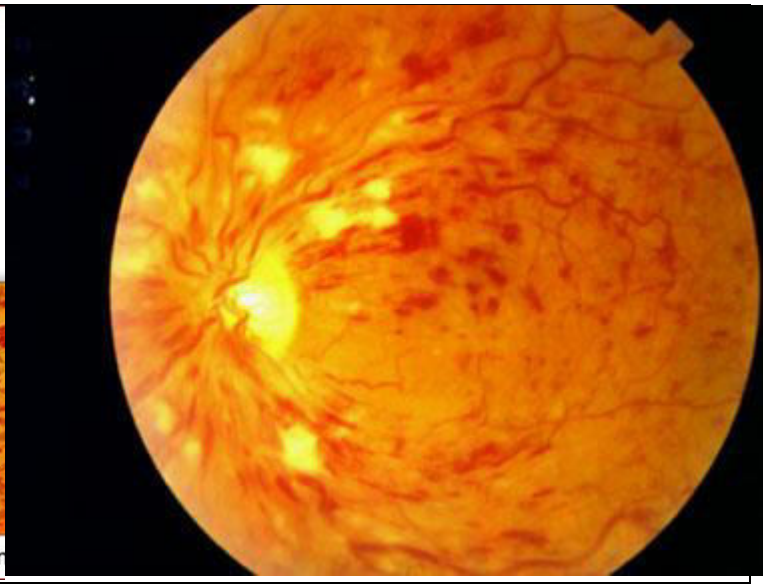
Posterior vitreous detachment	Retinal detachment	Vitreous haemorrhage
♦ Flashes of light (photopsia) - in the peripheral field of vision ♦ Floaters, often on the temporal side of the central vision ♦ occur in up to 50-75% of the population **over 65 years**	♦ Dense shadow that starts peripherally progresses towards the central vision ♦ A veil or curtain over the field of vision ♦ Straight lines appear curved Central visual loss	♦ Large bleeds cause sudden visual loss ♦ inability to visualise the retina ♦ Moderate bleeds may be described as numerous dark spots ♦ Small bleeds may cause floaters





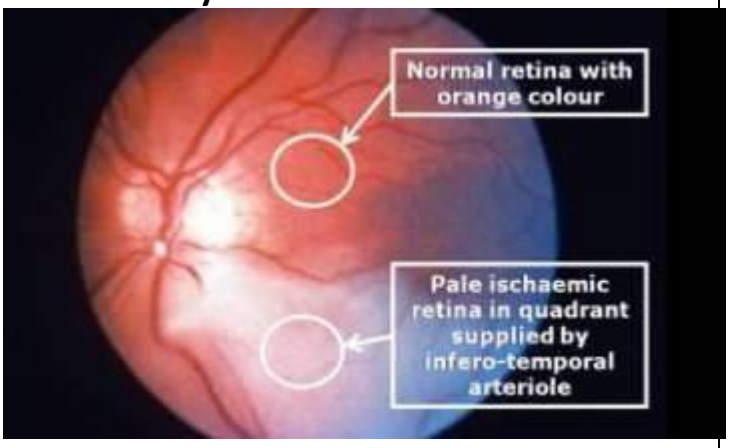
Retinal detachment

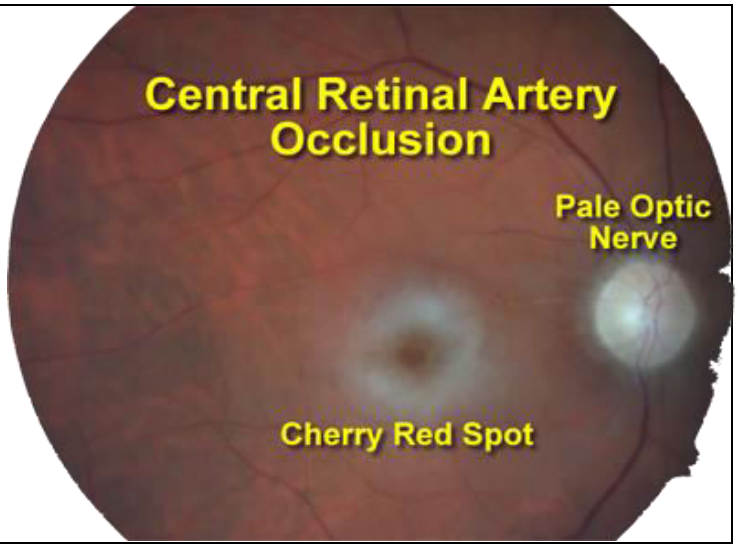




Central retinal vein occlusion

Retinal artery occlusion





Central Retinal Artery Occlusion

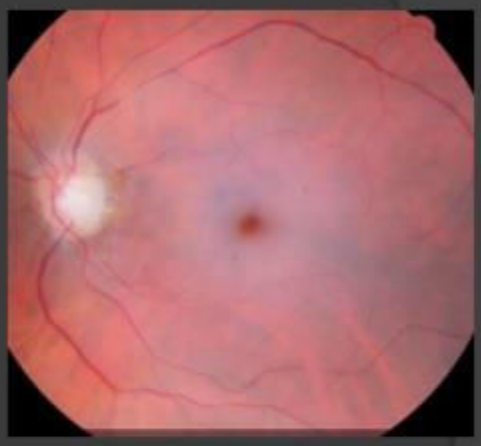
Ocular emergency

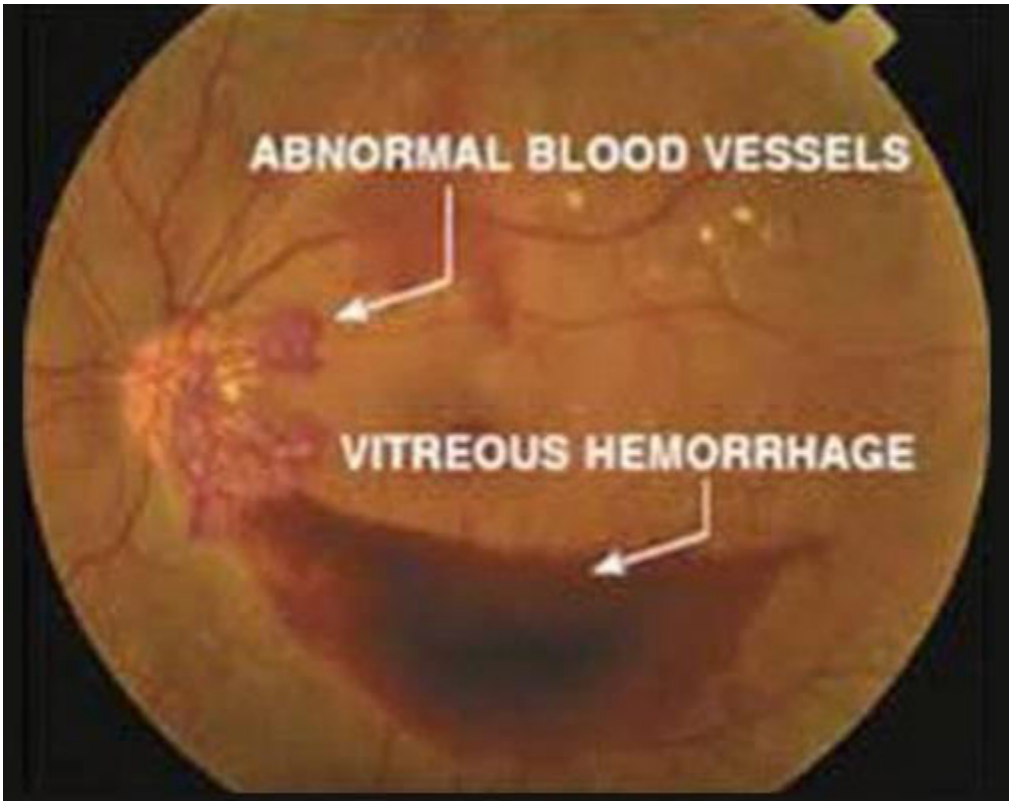
Sudden painless unilateral vision loss

Emboli, thrombotic plaque, vascultitis

Cherry red spot (perifoveal atrophy), box cars (arteriolar narrowing)

Tx: emergency ophtho referral, poor prognosis, atherosclerotic wkup





Tunnel vision

Tunnel vision (also known as **Kalnienk vision**) is the loss of peripheral vision with retention of central vision, resulting in a constricted circular tunnel-like field of vision.

Causes

- papilloedema
- glaucoma
- retinitis pigmentosa
- choroidoretinitis
- optic atrophy secondary to tabes dorsalis
- hysteria

Keratoconus

Keratoconus, meaning, "cone shaped," describes a condition in which the cornea (the clear front window of the eye) becomes thin and protrudes. This abnormal shape can cause serious distortion of visual images.

Retinoblastoma

- The incidence is 1 in 16,000 live births.
- Genetic predisposition occurs in 20% of patients with unilateral disease, and 30% of patients with bilateral disease.
- The gene has been localised to 13q and the inherited form is associated with an increased risk of malignancy such as osteosarcoma and pineal tumours.
- It may be inherited as autosomal dominant.

- **The commonest presentation is leucocoria (yellowish white pupil reflex),** and there may be diminished or absent vision or strabismus.
- Late symptoms are:
  - pupil irregularity
  - hyphema
  - pain
  - proptosis
  - signs of raised intracranial pressure.
- The tumours have rarely metastasised before they are detected.

Ectopia lentis

Ectopia lentis/subluxation of the lens is associated with:

- Ehlers-Danlos syndrome
- Marfan's syndrome
- Weill-Marchesani syndrome (short stature, skeletal abnormalities and ectopia lentis), and
- Refsum's disease.

Fundoscopic features

- ***Cytomegalovirus* (CMV) retinitis**
  - secondary to human immunodeficiency virus (HIV)
  - Fundoscopy of the left eye revealed an extensive **'brushfire-like' lesion** in the major superior temporal arcade with a large patch of white fluffy lesion mixed with extensive **retinal haemorrhages.**
- **Ocular histoplasmosis and syphilitic choroiditis** would give a fundus picture of **multiple whitish lesions**.
- **Syphilitic neuroretinitis** would normally give a picture of a **macular star exudation**.
- **Tuberculous periphlebitis** gives a picture of **perivenous sheathing and minimal retinal haemorrhages**.

Anisocoria

- is a condition characterized by an unequal size of the eyes' pupils.
- Affecting 20% of the population,
- it can be an entirely harmless condition or a symptom of more serious medical problems
- **The history of anisocoria, with headaches and diplopia should ring alarm bells, in that a life-threatening posterior communicating artery aneurysm/berry aneurysm needs to be excluded urgently**.

Eye signs in Systemic diseases

- **Lisch nodules of the iris are golden nodules occurring bilaterally in the teenage years onwards in Neurofibromatosis type 1 (NF-1). Axillary freckles** appear at 10 years of age, while cafe au lait spots increase in size and number throughout childhood.
- **Brushfield spots** of the iris are found in people with Down syndrome.

- **Kayser-Fleischer rings** are due to copper deposition in Descemet's membrane of the cornea.
- **Band keratopathy is caused by calcium deposition in Bowman's layer of the cornea. Patients who present with band keratopathy should have a serum calcium and phosphate level**
- **Ectopia lentis with aortic regurgitation → Marfan syndrome (Lens dislocation (classically upwards)).**
  Inferior dislocated lens → consistent with a diagnosis of homocytinstinuria.
- **Roth's spots haemorrhages in the retina → associated with subacute bacterial endocarditis.** also, seen in leukaemia.
- **'black sunburst' - a chorioretinal scar, which is one of the commoner retinal manifestations of Sickle cell disease (SCD) and pathognomonic.**

Immune reconstitution uveitis

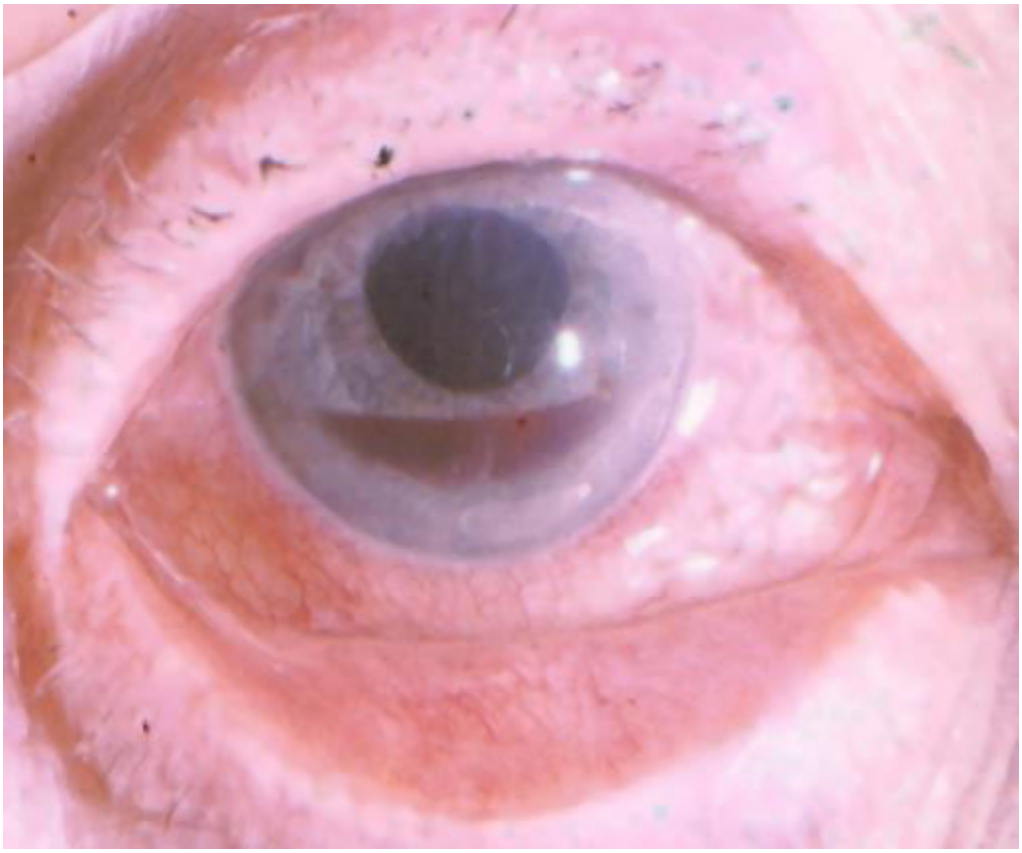
associated with recovery of the CD4 count in HIV. In this condition a granulomatous uveitis appears as the immune system recovers as a result of autoimmune mechanisms.

Hyphaema

- Occurs when bleeding from iris vessels fills the anterior chamber with blood and if there is enough blood
- the main risk in the acute stage is of raised intraocular pressure (IOP).
- It is usually caused by trauma - often small objects (champagne corks, squash balls) hitting the eye.

Treatment

- Strict rest is vital if a hyphaema is present, as there is an increased risk of a second bleed in the initial period.
- **Intravenous carbonic anhydrase inhibitors is the most appropriate treatment**
- Aspiration may be required to prevent loss of vision.
- avoid drops that dilate the pupil (such as anticholinergics) the iris remains stable and a second bleed is therefore less likely.



The slide shows hyphaema: blood in the anterior chamber.

Acute corneal hydrops

- Acute corneal hydrops occurs in advanced keratoconus, which is the most common cause of corneal ectasia.
- The cornea is made of three main layers:
  - Epithelium
  - Stroma
  - Endothelium
- The transparency of the cornea is maintained by the endothelium which constantly pumps water out from the stroma.
- Descemet's membrane is a specialised basement membrane which lies between the endothelium and stroma, which helps to provide structural integrity to the cornea.
- In acute corneal hydrops the endothelium and Descemet's membrane split which allows aqueous to enter the corneal stroma.
- Stromal and epithelial oedema results in corneal opacification and formation of epithelial bullae.
- Patient present with **painful loss of vision**
- **cornea is opaque and appears to be protruding**
- Keratoconus is associated with atopic conditions (for example, asthma, hay fever, eczema) and Down syndrome.

Subtarsal foreign body

- history of 'gritty pain' in the eye with pain on blinking.
- The appropriate management would be to **examine underneath the lid to search for and remove a foreign body.**
- Further management would involve topical chloramphenicol ointment three to four times a day for five days.

Retinoblastoma

- Physical examination shows a **white pupillary reflex** **in both eyes**.
- The responsible gene, RB1, coding for pRb, is **located on chromosome 13.**
- Definition
  - malignancy of the retina of the eye
  - often presents in children less than 3 years of age
- Genetics
  - 60% are sporadic.
  - There is no significant family history of disease.
  - 40% are heritable.
  - Rb is a tumor suppressor gene located on chromosome 13
  - loss of heterozygosity
    - both alleles must be deleted/mutated before the development of cancer and expression of disease ("two-hit hypothesis")
      - as opposed to oncogenes which require just one mutation
    - mutation in a tumor suppressor gene leads to increased cancer risk
    - inhertied loss of Rb protein results in bilateral disease
  - mechanism
    - regulates cell growth and repair damage
      - see Tumor suppressor gene topic
      - see Cell cycle topic
  - associations
    - familial retinoblastoma is a predisposing factor to the development of osteosarcoma

Presentation

- Symptoms
  - visual loss
- Physical exam
  - leukocoria
    - absence of red-light reflex
  - unilateral exophthalmos
  - strabismus

Evaluation

- Referral to opthamologist if seen in general pediatric screening

Treatment

- Surgical
  - enucleation of the eye

Notes & Notes

For MRCP part 1 & 11

By

Dr. Yousif Abdallah Hamad

Psychiatry

Updated

2017

Contains:

1/ Passmedicine 2017

2/ On examination 2017

3/ Pastest 2017

4/ **Red fonts --> previous exams**

5/ Other updated UK sources

Unexplained symptoms

Unexplained symptoms
- Somatisation = Symptoms
- hypoChondria = Cancer

There are a wide variety of psychiatric terms for patients who have symptoms for which **no organic cause can be found:**

Somatisation disorder
- multiple physical **SYMPTOMS** present for at least 2 years
- patient refuses to accept reassurance or negative test results

Hypochondrial disorder
- persistent belief in the presence of an underlying serious **DISEASE**, e.g. cancer
- patient again refuses to accept reassurance or negative test results
- more common in those who have lost a close family member to a serious illness.

Conversion disorder
- typically **involves loss of motor or sensory function**
- the patient doesn't consciously feign the symptoms (factitious disorder) or seek material gain (malingering)
- patients may be indifferent to their apparent disorder - la belle indifference - although this has not been backed up by some studies

Dissociative disorder
- dissociation is a process of 'separating off' certain memories from normal consciousness
- in contrast to conversion disorder **involves psychiatric symptoms e.g. Amnesia, fugue, stupor**
- dissociative identity disorder (DID) is the new term for multiple personality disorder as is the most severe form of dissociative disorder

Munchausen's syndrome
- also, known as factitious disorder
- the intentional production of physical or psychological symptoms

Malingering
- fraudulent simulation or exaggeration of symptoms with the intention of financial or other gain

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Anorexia nervosa

Anorexia features
- most things low
- G's and C's raised: growth hormone, glucose, salivary glands, cortisol, cholesterol, carotinaemia

Anorexia nervosa is the most common cause of admissions to child and adolescent psychiatric wards.

Epidemiology

- 90% of patients are female
- predominately affects teenage and young-adult females
- prevalence of between 1:100 and 1:200

Features

- Reduced body mass index
- Phobic avoidance of normal weight
- Relentless dieting
- Self-induced vomiting
- Laxative use
- Excessive exercise
- Amenorrhoea
- enlarged salivary glands
- Lanugo hair
- Hypotension
- bradycardia
- Denial
- Concealment
- Over-perception of body image
- Enmeshed families.

Physiological abnormalities

- **Hypokalaemia**
  - (it is the most likely abnormality to be seen on routine laboratory testing with both induced vomiting and abuse of diuretics).
- low FSH, LH, oestrogens and testosterone
- raised cortisol and growth hormone
  - ↑↑ Cortisol,
  - ↑↑ growth hormone (due to GH resistance)
- impaired glucose tolerance
  - **↑↑ glucose (impaired glucose tolerance)**
- hypercholesterolaemia
- hypercarotinaemia
- low T3
  - though thyroxine (T4) and TSH may be normal.
- hypoalbuminaemia,
- anaemia,
- Ferritin levels are low in a state of malnutrition.
- leukopaenia,

Diagnosis (based on the DSM-IV criteria)

- person chooses not to eat - BMI < 17.5 kg/m^2, or < 85% of that expected
- intense fear of being obese
- disturbance of weight perception
- amenorrhoea = 3 consecutive cycles

Investigation

- **Use of laxatives to drive weight loss is common, and a purgative screen is therefore a logical next step.**

Prognosis

- remains poor
- Up to 10% of patients will eventually die because of the disorder.

Bulimia nervosa

- **Definition**
  - Bulimia nervosa is a type of eating disorder characterised by episodes of **binge eating followed by intentional vomiting** to prevent weight gain.
- **Epidemiology**
  - Most common in women in their 20s and 30s.
- **Clinical features**
  - usually appear physically normal,
  - low self-esteem
  - depressive thoughts,
  - lack of confidence.
  - **Parotid hypertrophy** and **erosion of the teeth** are the most common physical signs and may prompt diagnosis.
- **Lab Features**
  - hypokalaemic metabolic alkalosis
  - Hyponatraemia.
  - Hypocalcaemia.
  - **Alkaline phosphatase is often raised**, due to bone loss resulting from nutritional deficiencies.
- **Treatment**
  - first-line treatment → Cognitive behavioural therapy (CBT) is considered the optimal primary treatment
  - pharmacological treatments have a limited role
    - Selective serotonin-reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) (used adjunctively to CBT, or as an alternative when CBT is not available).
    - a trial of **high-dose fluoxetine** is currently licensed for bulimia but long-term data is lacking

Hypomania vs. mania

The presence of psychotic symptoms **differentiates mania from hypomania**

Mania → Psychotic symptoms	**mania and hypomania**	
• delusions of grandeur	Mood	• predominately elevated • irritable
• auditory hallucinations	Speech and thought	• pressured • flight of ideas • poor attention
	Behaviour	• insomnia • loss of inhibitions: ➢ sexual promiscuity, ➢ overspending, ➢ risk-taking • increased appetite

Antipsychotics

Antipsychotics in the elderly - increased risk of stroke and VTE

- Antipsychotics act as **dopamine D2 receptor antagonists**, blocking dopaminergic transmission in the mesolimbic pathways.
- Conventional antipsychotics are associated with problematic extrapyramidal side-effects which has led to the development of atypical antipsychotics such as clozapine

Extrapyramidal side-effects

- Parkinsonism
- acute dystonia (e.g. torticollis, oculogyric crisis)
  - ➢ affects about 2% of patients.
  - ➢ **Administer procyclidine**
- **akathisia (severe restlessness)**
- tardive dyskinesia (late onset of choreoathetoid movements, abnormal, involuntary),
  - ➢ may occur in 40% of patients,
  - ➢ may be irreversible,
  - ➢ most common is chewing and pouting of jaw

Specific warnings when antipsychotics are used in elderly patients:

- increased risk of stroke (especially olanzapine and risperidone)
- increased risk of venous thromboembolism

Other side-effects

- antimuscarinic: dry mouth, blurred vision, urinary retention, constipation
- sedation,
- weight gain
- **raised prolactin**: galactorrhoea,

- block dopamine D2 receptors → block dopamine's action on the pituitary →**reduces inhibition of prolactin** secretion→ hyperprolactinaemia.

- Amenorrhoea, infertility
- loss of libido, and erectile dysfunction.
- impaired glucose tolerance
- neuroleptic malignant syndrome: pyrexia, muscle stiffness
- reduced seizure threshold (greater with atypicals)
- **prolonged QT** interval (particularly **haloperidol**)

Typical antipsychotics

Typical Antipsychotics			
High Potency Antipsychotics (in Descending Order)	**Advantages**	**Disadvantages**	**Unique Features**
Haloperidol	Fewer side effects of sedation and hypotension	High association with extrapyramidal symptoms	• Able to use as long-acting depot injections • Can be given IM in acute situations
Fluphenazine			
Perphenazine			
Chlorpromazine	Lower frequency of extrapyramidal side effects	Greater incidence of anticholinergic side-effects, hypotension, sedation	**Corneal** deposits
Thioridazine			• **Retinal** deposits • QT prolongation

Atypical antipsychotics

Atypical antipsychotics commonly cause weight gain

atypical antipsychotics such as olanzapine/risperidone/clozapine have been associated with hyperglycaemia and insulin resistance.

- Atypical antipsychotics should now be used first-line in patients with schizophrenia, according to 2005 NICE guidelines.

- The main advantage of the atypical agents is a significant reduction in extra-pyramidal side-effects.

Adverse effects of atypical antipsychotics

- **weight gain**
- clozapine is associated with agranulocytosis (see below)

Examples of atypical antipsychotics

- cloz**apine**
- olanz**apine**
- queti**apine**
- risperidone
- amisulpride

Atypical Antipsychotics	
Medication	**Unique features and side effects**
Risperidone	• High potency • Usually first line • Hyperprolactinemia • Weight gain
Olanzapine	• Severe weight gain • Very sedating
Zip**rasidone**	• **Minimal to no weight gain** • Increased QTc
Quetiapine	• Low potency • Sedating • Weight gain • Useful in bipolar depression and augmentation of major depression therapy
Lu**rasidone**	• **Minimal weight gain** • Useful in bipolar depression
Clozapine	• Weight gain • **Most effective anti-psychotic** • **Decreased suicide risk** • **Agranulocytosis** • Myocarditis • Sialorrhea • Orthostatic hypotension • Increased seizures
Aripiprazole	• D2 partial agonist • Augmentation of major depression therapy

Clozapine

Clozapine is no longer used first-line due to the risk of agranulocytosis

Indication

- should only be used in patients resistant to other antipsychotic medication **(**due to significant risk of agranulocytosis**)**

Adverse effects of clozapine

- agranulocytosis (1%), neutropenia (3%)
- reduced seizure threshold - can induce seizures in up to 3% of patients

Monitoring: (full blood count monitoring is therefore essential during treatment)

- A white cell count with differential is checked **prior to treatment**,
- then **weekly** for the first 18 weeks,
- then **two weekly** from week 18 to 52,
- then **four weekly** after one year of clozapine with stable blood results.
- then checked for **four weeks after discontinuation of treatment.**

Risperidone

- Risperidone is a novel antipsychotic belonging to the benzisoxazole derivative class
- **It is a high-affinity D2 and 5-HT-2 receptor antagonist**
- To a lesser extent, risperidone is also an antagonist at α-p adrenergic receptors, H1-histaminergic and α2- adrenergic receptors
- Common adverse effects include:
  - Insomnia
  - Agitation
  - Anxiety
  - Headache
  - Risperidone may also lead to impaired glucose tolerance, although the incidence of abnormalities in glucose metabolism is less than that seen with other antipsychotics

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Neuroleptic malignant syndrome

- Neuroleptic malignant syndrome is a rare but dangerous condition seen in patients taking antipsychotic medication.
- It carries a mortality of up to 10%
- can also occur with atypical antipsychotics.
- **It may also occur with dopaminergic drugs (such as levodopa) for Parkinson's disease, usually when the drug is suddenly stopped or the dose reduced.**
- Concomitant treatment with lithium or anticholinergics may increase the risk of NMS.

A patient with P/H/O parkinson's disease, deteriorate 1 – 2 days after admission to hospital for other condition → neuroleptic malignant syndrome (NMS) as a result of not taking her parkinson's medication → **do Creatine kinase to confirm the diagnosis**

Features

- more common in young male patients
- **onset usually in first 10 days of treatment or after increasing dose**
- pyrexia
- rigidity
- tachycardia
- Renal failure may occur secondary to rhabdomyolysis
- **Raised creatine kinase** in most cases.
  - **the most important investigation to be performed**
  - always elevated (>1000 IU/L^{-1}), reflecting myonecrosis secondary to intense muscle contracture.
- leukocytosis may also be seen

differential diagnosis

- **serotonin syndrome**
  - **Myoclonus is the distinguishing feature of serotonin syndrome (found only in serotonin syndrome).** All the other features can be present in both conditions.
  - Features of both NMS and serotonin syndrome.
    - Severe muscular rigidity
    - Hyperthermia (temperature >38°C)
    - Autonomic instability
    - Changes cognition or in the level of consciousness
    - Rhabdomyolysis
    - Recent commencement or change of dose of a medication
  - **Causes of Serotonin syndrome**
    - in those taking therapeutic doses of SSRIs, as part of **drug-drug interaction** (e.g. the addition of:
      - ondansetron,
      - amphetamine, cocaine, meperidine(Pethidine),
      - dextromethorphan, fentanyl, buspiron, ergot alkaloids, lithium, L-dopa, LSD, St. John's Wort),
    - or following intentional **self-poisoning** with SSRI.
  - **treatment** for serotonin syndrome:
    - **stopping any serotinergic agents,**
    - **using benzodiazepines for agitation**
    - **consideration of use of serotonin antagonists such as cyproheptadine if there is severe autonomic disturbance.**

Management

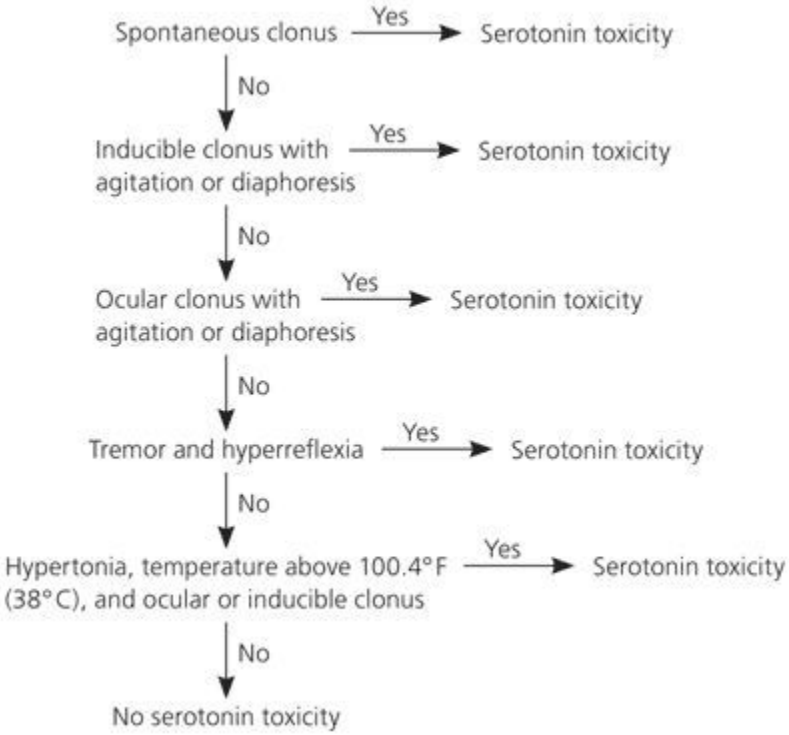
- stop antipsychotic
- IV fluids to prevent renal failure
- **dantrolene** may be useful in selected cases

- thought to work by decreasing excitation-contraction coupling in skeletal muscle by binding to the ryanodine receptor, and decreasing the release of calcium from the sarcoplasmic reticulum

- **bromocriptine**, dopamine agonist, may also be used
- levodopa preparations may be beneficial

Neuroleptic malignant syndrome	Serotonin syndrome
• develops over days to weeks.	• develops over 24 hours.
• characterized by sluggish neuromuscular responses (rigidity, bradyreflexia).	• characterized by neuromuscular hyperreactivity (**tremor, hyperreflexia**, **myoclonus**).
• resolution typically requires an average of nine days.	• resolution typically requires less than 24 hours .

Hunter's Decision Rules for Diagnosis of Serotonin Toxicity



Antidepressants

- **Classes**
  1. selective serotonin reuptake inhibitors (**SSRIs**),
  2. selective serotonin-norepinephrine reuptake inhibitors (SS**N**RIs),
  3. Serotonin antagonist and reuptake inhibitors (**SARIs**)
  4. monoamine oxidase inhibitors (**MAOIs**),
  5. tricyclic antidepressants (**TCAs**).
  6. Atypical antidepressants
- Most of these drugs work by increasing the levels of serotonin, norepinephrine, or dopamine within the synaptic cleft.
- **SSRIs are the first-line treatment for the vast majority of patients with depression**
- MAOIs and TCAs are similarly efficacious but are rarely used today due to their large number of potentially severe adverse effects.

Selective serotonin reuptake inhibitors (SSRIs)

SSRI + NSAID = GI bleeding risk - give a PPI

- **Mechanism of action**
  - inhibition of serotonin reuptake in synaptic cleft → ↑ serotonin levels
  - primarily act at the **5HT** transporter protein
- **Drugs**
  - Flu**oxetine**
  - Par**oxetine**
  - Sertraline
  - Citalopram
  - Escitalopram
- **Indications**
  - **First-line treatment for major depressive disorder**
  - **Generalized anxiety disorder**
  - Obsessive-compulsive disorder
  - Post-traumatic stress disorder
  - Somatic symptom disorder
  - Panic disorder
  - Gambling disorder
  - Premature ejaculation
  - Premenstrual dysphoric disorder
  - Binge-eating disorder
- **Side effects**
  - Sexual disorders (anorgasmia, erectile or ejaculatory dysfunction, ↓ libido)
  - Diarrhea, nausea, vomiting
    - **gastrointestinal symptoms are the most common side-effect**

- Sleep disorders
- Headache
- Increased risk of bleeding
  - proton pump inhibitor should be prescribed if a patient is also taking a NSAID
- Serotonin syndrome
- patients should be counselled to be vigilant for **increased anxiety and agitation after starting a SSRI**

- **Contraindications**
  - risk of serotonin syndrome if given concomitantly within 14 days of **MAOIs**, **linezolid**, or **methylene blue** use
- **Additional information**
  - must usually be taken for 4–6 weeks before symptom reduction is seen
  - citalopram (although ↑ QT interval) and fluoxetine are currently the preferred SSRIs
  - **sertraline is useful post myocardial infarction** as there is more evidence for its safe use in this situation than other antidepressants
  - nice advice 2017 → For people who also have a chronic physical health problem, consider using **citalopram or sertraline** as these have a lower propensity for interactions.
  - SSRIs should be used with caution in children and adolescents. Fluoxetine is the drug of choice when an antidepressant is indicated

- **Citalopram and the QT interval**
  - citalopram and escitalopram are associated with dose-dependent QT interval prolongation and should not be used in those with: congenital long QT syndrome; known pre-existing QT interval prolongation; or in combination with other medicines that prolong the QT interval
  - the maximum daily dose is now 40 mg for adults; 20 mg for patients older than 65 years; and 20 mg for those with hepatic impairment
- **Interactions**
  - NSAIDs: NICE guidelines advise 'do not normally offer SSRIs', but if given co-prescribe a proton pump inhibitor
  - **warfarin / heparin:** NICE guidelines recommend avoiding SSRIs and considering **mirtazapine**
    - **the SSRIs least likely to cause drug interactions with warfarin appear to be sertraline and citalopram**.
  - aspirin: see above
  - **triptans: avoid SSRIs**
  - fluoxetine and paroxetine have a higher propensity for drug interactions

- **Antidepressant Follow-up**
  - After initiation of antidepressant therapy patients should normally be reviewed by a doctor after 2 weeks.
  - For patients under the age of 30 years or at increased risk of suicide they should be reviewed after 1 week.

- If a patient makes a good response to antidepressant therapy they should continue on treatment for at least 6 months after remission as this reduces the risk of relapse.

- **Selective serotonin reuptake inhibitor discontinuation syndrome**

Paroxetine - higher incidence of discontinuation symptoms

- When stopping a SSRI the dose should be gradually reduced over a 4 week period (this is not necessary with fluoxetine). This not necessary with fluoxetine due to its longer half-life.
- **Paroxetine has a higher incidence of discontinuation symptoms.**
- **Discontinuation symptoms**
  - increased mood change
  - restlessness
  - difficulty sleeping
  - unsteadiness
  - sweating
  - gastrointestinal symptoms: pain, cramping, diarrhoea, vomiting
  - paraesthesia

while not as selective as the SSRIs, drugs of abuse such as cocaine, fenfluramine, and (3,4-methylenedioxy) methamphetamine (**MDMA** or ecstasy) are **inhibitors of serotonin uptake**.

Selective serotonin-norepinephrine reuptake inhibitors (SSNRIs)

- **Mechanism of action**
  - inhibition of serotonin and norepinephrine reuptake in synaptic cleft → ↑ serotonin and norepinephrine levels
- **Drugs**
  - Venlafaxine
  - Duloxetine
- **Indications**
  - Major depressive disorder (**second-line therapy**)
  - Generalized anxiety disorder
  - Panic disorder
  - Duloxetine: stress incontinence in women
- **Side effects**
  - Similar profile to SSRIs (see “Selective serotonin reuptake inhibitors” above)
  - Increased blood pressure
- **Contraindications**: risk of serotonin syndrome if given concomitantly within 14 days of MAOIs, linezolid, or methylene blue use
- **Additional information**:
  - Blood pressure should be controlled before initiating SSNRI therapy.

Serotonin antagonist and reuptake inhibitors (SARIs)

- **Mechanism of action**
  - Inhibition of serotonin reuptake → ↑ serotonin levels
  - Antagonist of H_1- and α_1-receptors
- **Drugs**
  - **Trazodone**
  - Nefazodone
- **Indications**:
  - major depressive disorder, especially in patients with insomnia
- **Side effects**
  - **Priapism**
  - Sedation (due to H_1 antagonism)
  - Orthostatic hypotension
- Contraindications:
  - risk of serotonin syndrome if given concomitantly within 14 days of **MAOIs**, **linezolid**, or **methylene blue** use
- **Additional information**
  - Mainly used as adjunct to other antidepressants for treatment of insomnia associated with depression
  - Off-label use: insomnia in patients without depression

Monoamine oxidase inhibitors (MAOIs)

- **Mechanism**
  - inhibition of monoamine oxidase → ↓ breakdown of epinephrine, norepinephrine, and serotonin → ↑ levels of epinephrine, norepinephrine, and serotonin
- **Drugs**
  - Tranylcypromine
  - Phenelzine
  - **Selegiline**
  - Isocarboxazid
- **Indications**
  - Major depressive disorder (**third- or fourth-line therapy**)
    - due to its potentially severe side effects, interaction with foods containing tyramine, and numerous drug interactions
  - particularly effective for treating atypical symptoms of depression (↑ appetite and weight gain, ↑ sleep, leaden paralysis)
  - Selegiline: Parkinson's disease (as an adjunct to carbidopa-levodopa)
    - For the treatment of depression, Selegiline is available as a transdermal patch
    - (oral form is only used for Parkinson's disease)
- **Side effects**
  - Hypertensive crisis with ingestion of **foods containing tyramine** (e.g. aged cheeses, smoked/cured meats, alcoholic beverages, dried fruits)
  - Serotonin syndrome
- **Contraindications**

- risk of serotonin syndrome if given concomitantly within 14 days of MAOIs, linezolid, or methylene blue use

Tricyclic antidepressants (TCA)

Dosulepin - avoid as dangerous in overdose

- **Mechanism of action**
  - inhibition of serotonin and norepinephrine reuptake in synaptic cleft → ↑ serotonin and norepinephrine levels
- **Drugs**

Tertiary amines	Secondary amines
Amitriptyline Clomipramine Doxepin Imipramine Trimipramine	Nortriptyline Desipramine Protriptyline

- **Indications**
  - less commonly now for depression due to their side-effects and toxicity in overdose.
  - used widely in the treatment of neuropathic pain, where smaller doses are typically required.
  - prophylaxis of headache (both tension and migraine)
  - Major depressive disorder (**third- or fourth-line therapy**)
  - Neuropathy (diabetic neuropathy, post-herpetic neuralgia, etc.)
  - Chronic pain (including fibromyalgia)
- **Side effects**
  - Orthostatic hypotension
  - Sedation and delirium
  - Anticholinergic symptoms
    - **Cardiovascular symptoms:**
      - **wide QRS complex, tachycardia, arrhythmia (including ventricular fibrillation),**
      - **hypotension**
    - CNS symptoms: drowsiness, confusion, hallucinations, sedation, coma, seizures
    - Gastrointestinal symptoms: intestinal ileus, **constipation**
    - Genitourinary symptoms: **urinary retention**
    - General:
      - Xerostomia (dry mouth)
      - blurred vision
      - mydriasis,
      - hyperthermia/dry skin

More sedative	Less sedative
Amitriptyline Clomipramine **Dosulepin** Trazodone (is technically a 'tricyclic-related)	Imipramine **Lofepramine** Nortriptyline

- **Overdose**

> Lofepramine - the safest TCA in overdosage

  - **lofepramine has a lower incidence of toxicity in overdose**
  - amitriptyline and **dosulepin** (dothiepin) are considered the most dangerous in overdose
  - **Clinical features:** caused by anticholinergic effects
  - **Management**
    - Secure airways, oxygenation, monitoring, fluid resuscitation
    - ECG: cardiac arrhythmia (e.g., tachycardia, QRS prolongation)
    - Urine immunoassay: detection of TCA in the body
    - Activated carbon in first 2 hours after ingestion as soon as the airways are secured
    - **Sodium bicarbonate for cardiac arrhythmia** (QRS ≥ 100 ms or ventricula arrhythmias)
    - Benzodiazepines for seizures
- **Contraindications**
  - Risk of serotonin syndrome if given concomitantly within 14 days of MAOIs, linezolid, or methylene blue use
  - Tertiary amines are high-risk medications in the elderly population as they can cause confusion due to sedative and anticholinergic side effects.
- **Additional information**
  - Rarely used as a first- or second-line antidepressant today due to extensive side effect profile and risk of lethal overdose (ingestion of a one week supply can be fatal)
  - Physostigmine should not be given to patients with suspected TCA overdose because it can precipitate cardiac arrest
  - **Antimuscarinic side-effects are more common with imipramine than other types of tricyclic antidepressants.**

Atypical antidepressants

Mirtazapine

- **Mechanism of action**
  - α_2-adrenergic antagonist → ↑ serotonin and norepinephrine release
  - **5-HT_2 and 5-HT_3 receptor antagonist → ↑ effect of serotonin on free 5-HT_1 receptor → likely responsible for antidepressant effects**
  - H_1 antagonist
- **Indications**
  - major depressive disorder, especially in underweight and insomniac patients

- **Side effects**
  - ↑ appetite and weight gain
  - Sedation (due to H_1 antagonism)
- **Contraindications**
  - risk of serotonin syndrome if given concomitantly within 14 days of MAOIs, linezolid, or methylene blue use

Bupropion

- **Mechanism of action**
  - not fully understood, but thought to **increase dopamine and norepinephrine levels via reuptake inhibition**
- **Indications**
  - **Smoking cessation**:
    - used in conjunction with counseling and nicotine replacement
  - Major depressive disorder
  - Depressive disorders with seasonal pattern
- **Side effects**
  - **Reduction of seizure threshold**
  - Tachycardia, palpitations, agitation
  - Weight loss
  - Neuropsychiatric symptoms (including depression, mania, psychosis, and paranoia)
- **Contraindications**
  - Patients with ↑ risk for seizure (epilepsy, anorexia/bulimia, alcohol or benzodiazepine withdrawal, etc.)
  - Risk of serotonin syndrome if given concomitantly within 14 days of MAOIs, linezolid, or methylene blue use
- **Additional information**
  - Bupropion has **no sexual side effects**, which makes it a viable alternative to SSRIs or SSNRIs for patients who experience sexual dysfunction.

Benzodiazepines

$GABA_A$ drugs
- benzodiazipines increase the frequency of chloride channels
- barbiturates increase the duration of chloride channel opening

Frequently Bend - During Barbeque

...or...

Barbidurates increase duration & Frendodiazepines increase frequency

Benzodiazepines enhance the effect of GABA, the main inhibitory neurotransmitter

Action:

- Benzodiazepines (lorazepam, diazepam, chlordiazepoxide) enhance the effect of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA).

Indications

- Sedation
- Hypnotic
- Anxiolytic
- Anticonvulsant
- Muscle relaxant

Prescription

- Patients commonly develop a tolerance and dependance to benzodiazepines and care should therefore be exercised on prescribing these drugs.
- The Committee on Safety of Medicines advises that benzodiazepines are only prescribed for a short period of time (2-4 weeks).

Benzodiazepine withdrawal

- **The BNF gives advice on how to withdraw a benzodiazepine**:
- The dose should be withdrawn in steps of about 1/8 (range 1/10 to 1/4) of the daily dose every fortnight(أسبوعين).
- A suggested protocol for patients experiencing difficulty is given:
  - Switch patients to the equivalent dose of diazepam
  - Reduce dose of diazepam every 2-3 weeks in steps of 2 or 2.5 mg
  - Time needed for withdrawal can vary from 1 month to 1 year or more

benzodiazepine withdrawal syndrome:

- If patients withdraw too quickly from benzodiazepines they may experience benzodiazepine withdrawal syndrome, a condition very similar to alcohol withdrawal syndrome.
- This may occur up to 3 weeks after stopping a long-acting drug.
- **Features** include:
  - Insomnia
  - Irritability
  - Anxiety
  - Tremor
  - Loss of appetite
  - Tinnitus
  - Perspiration
  - Perceptual disturbances
  - Seizures

Flumazenil

- **Flumazenil, a benzodiazepine antagonist, is used to reverse the central sedative effects of benzodiazepines** after anaesthetic and similar procedures
- Flumazenil has a shorter half-life than that of diazepam and midazolam and there is a risk that patients may become re-sedated - in which case a repeat dose of flumazenil should be given

- Diazepam has a long half-life, principally because of its active metabolites.
- Midazolam is short-acting but is only used intravenously.
- Promethazine is an antihistamine with a 12-hour half-life and may cause daytime sedation.
- Clomethiazole is less safe in overdose, has dependence potential and is only licensed for sedation in the elderly.
- **Loprazolam is short-acting (half-life 6–12 hours) .**

Post-traumatic stress disorder

- Post-traumatic stress disorder (PTSD) can develop in people of any age following a traumatic event, for example a major disaster or childhood sexual abuse.
- It encompasses what became known as 'shell shock' following the first world war.
- One of the DSM-IV diagnostic criteria is that symptoms have been present for more than one month
- the onset of symptoms is usually delayed and it tends to run a prolonged course

Features

- re-experiencing: flashbacks, nightmares, repetitive and distressing intrusive images
- avoidance: avoiding people, situations or circumstances resembling or associated with the event
- hyperarousal: hypervigilance for threat, exaggerated startle response, sleep problems, irritability and difficulty concentrating
- emotional numbing - lack of ability to experience feelings, feeling detached from other people
- depression
- drug or alcohol misuse
- anger
- unexplained physical symptoms

Management

- following a traumatic event single-session interventions (often referred to as debriefing) are not recommended
- watchful waiting may be used for mild symptoms lasting less than 4 weeks
- military personnel have access to treatment provided by the armed forces
- trauma-focused cognitive behavioural therapy (CBT) or eye movement desensitisation and reprocessing (EMDR) therapy may be used in more severe cases
- drug treatments for PTSD should not be used as a routine first-line treatment for adults. **If drug treatment is used then paroxetine or mirtazapine are recommended**

Post-concussion syndrome

Post-concussion syndrome is seen after even minor head trauma

Typical features include

- headache
- fatigue
- anxiety/depression
- dizziness

Grief reaction

- It is normal for people to feel sadness and grief following the death of a loved one and this does not necessarily need to be medicalised.

- **Grief stages:** One of the most popular models of grief divides it into 5 stages.
    1. Denial: this may include a feeling of numbness and also pseudohallucinations of the deceased, both auditory and visual. Occasionally people may focus on physical objects that remind them of their loved one or even prepare meals for them
    2. Anger: this is commonly directed against other family members and medical professionals
    3. Bargaining
    4. Depression
    5. Acceptance
- It should be noted that many patients will not go through all 5 stages.
- **risk factors of Abnormal, or atypical, grief reactions**
    - more likely occur in women
    - if the death is sudden and unexpected.
    - problematic relationship before death
    - if the patient has not much social support.
- **Features of atypical grief** reactions include:
    - delayed grief: sometimes said to occur when more than 2 weeks passes before grieving begins
    - prolonged grief: difficult to define. Normal grief reactions may take up to and beyond 12 months

Depression: screening and assessment

Screening

The following two questions can be used to screen for depression

- 'During the last month, have you often been bothered by feeling down, depressed or hopeless?'
- 'During the last month, have you often been bothered by having little interest or pleasure in doing things?'

A 'yes' answer to either of the above should prompt a more in depth assessment.

Assessment

There are many tools to assess the degree of depression including the Hospital Anxiety and Depression (HAD) scale and the Patient Health Questionnaire (PHQ-9).

Hospital Anxiety and Depression (HAD) scale

- consists of 14 questions, 7 for anxiety and 7 for depression
- each item is scored from 0-3

- produces a score out of 21 for both anxiety and depression
- severity: 0-7 normal, 8-10 borderline, 11+ case
- patients should be encouraged to answer the questions quickly

Patient Health Questionnaire (PHQ-9)

- asks patients 'over the last 2 weeks, how often have you been bothered by any of the following problems?'
- 9 items which can then be scored 0-3
- includes items asking about thoughts of self-harm
- depression severity: 0-4 none, 5-9 mild, 10-14 moderate, 15-19 moderately severe, 20-27 severe

NICE use the **DSM-IV** criteria to grade depression:

- 1. Depressed mood most of the day, nearly every day
- 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
- 3. Significant weight loss or weight gain when not dieting or decrease or increase in appetite nearly every day
- 4. Insomnia or hypersomnia nearly every day
- 5. Psychomotor agitation or retardation nearly every day
- 6. Fatigue or loss of energy nearly every day
- 7. Feelings of worthlessness or excessive or inappropriate guilt nearly every day
- 8. Diminished ability to think or concentrate, or indecisiveness nearly every day
- 9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

Subthreshold depressive symptoms	**Fewer than 5 symptoms**
Mild depression	Few, if any, symptoms in excess of the 5 required to make the diagnosis, and symptoms result in only minor functional impairment
Moderate depression	Symptoms or functional impairment are between 'mild' and 'severe'
Severe depression	Most symptoms, and the symptoms markedly interfere with functioning. Can occur with or without psychotic symptoms

- Psychotic symptoms such as delusions and hallucinations may occur in depression, and when they do, treatment with both an antidepressant and an antipsychotic is indicated.

Psychotic depression

- Psychotic depression: severe depression accompanied by psychotic features
- is uncommon but important due to high risk of suicide.
- **The history of low mood predating the psychotic symptoms, also the fact that the auditory hallucinations and delusions are consistent with the depressive feelings of guilt, distinguish this from schizophrenia.**

Electroconvulsive therapy (ECT)

- **Electroconvulsive therapy (ECT) would usually be avoided if he had a recent cerebrovascular accident.** Most guidelines state that a recent CVA (within 1 to 3 months) is a contraindication.

Early morning waking is a classic somatic symptom of depression and often develops earlier than general insomnia.

Suicide

Factors associated with **risk of suicide** following an episode of deliberate self-harm:

- efforts to avoid discovery
- planning
- leaving a written note
- final acts such as sorting out finances
- violent method

These are in addition to **standard risk factors for suicide**

- male sex
- advancing age
- unemployment or social isolation
- divorced or widowed
- history of mental illness (depression, schizophrenia)
- history of deliberate self harm
- alcohol or drug misuse

Treatment

- In an Emergency Department the suicidal patient who declines to be admitted for observation and treatment should be managed as follows:
  - Ensure that a member of staff stays with them at all times
  - Call the duty psychiatrist
  - **If they attempt to abscond before or during psychiatric assessment, the staff of the Emergency Department have a duty under Common Law to restrain the patient**

A suicidal patient became agitated and insisted that she wanted to go home immediately. How should you proceed?

- **Call the duty psychiatrist, and with other staff in the Emergency Department attempt to restrain her until they arrive**

Depression in older people

- Older patients are less likely to complain of depressed mood
- Depression in elderly can depress cognitive function, hence cognition may be inaccurately depressed on measurement scales.
- In elderly patients, geriatric depression scale (GDS) is more appropriate than Becks depression scale, as the latter focuses heavily on somatic symptoms that frequently under-score depression in elderly patients.

Features

- physical complaints (e.g. hypochondriasis)
- agitation
- insomnia

Management

- SSRIs are first line (adverse side-effect profile of TCAs more of an issue in the elderly)

Mood disorder

cyclothymic disorder

- characterised by the presence of numerous periods of both depression (but not major depressive episodes) and hypomania for at least two years.
- The crucial feature of a major depressive disorder is a severe dysphoric mood and persistent loss of interest or pleasure in all usual activities.

dysthymic disorder

- In dysthymic disorder, the patient's mood is chronic depression with never a manic or hypomanic episode, for at least two years.

Bipolar I disorder

- characterised by severe alterations in mood (**mania and depression**) that are usually episodic and recurrent.
- Treatment
  - Sodium valproate and carbamazepine are efficacious as first line treatment in the prophylaxis of manic and depressive episodes in bipolar I disorder. Lithium may be used if these anticonvulsants are ineffective.
  - However, in the initial stages of manic episodes, the addition of drugs with potent sedative effects are often required, for example, clonazepam, lorazepam and haloperidol.
    - These drugs can be tapered and then discontinued as soon as the initial phase of the manic episode has subsided and the effects of the anticonvulsants or lithium are seen clinically.

Bipolar II disorder

- characterised by one or more major **depressive** episodes, at least one **hypomanic** episode and **NO manic** episodes.

Cognitive behavioural therapy

Main points

- useful in the management of depression and anxiety disorders
- usually consists of one to two hour sessions once per week
- should be completed within 6 months
- patients usually get around 16-20 hours in total

Seasonal affective disorder

- Seasonal affective disorder (SAD) describes depression which occurs predominately around the winter months.
- Bright light therapy has been shown to be more effective than placebo for patients with SAD

Body dysmorphic disorder

- Body dysmorphic disorder (sometimes referred to as dysmorphophobia) is a mental disorder where patients have a significantly distorted body image
- **Diagnostic and Statistical Manual (DSM) IV criteria:**
    - Preoccupation with an imagine defect in appearance. If a slight physical anomaly is present, the person's concern is markedly excessive
    - The preoccupation causes clinically significant distress or impairment in social, occupational, or other important areas of functioning
    - The preoccupation is not better accounted for by another mental disorder (e.g., dissatisfaction with body shape and size in Anorexia Nervosa)

Post-partum mental health problems

Post-natal depression is seen in around 10% of women

Post-partum mental health problems range from the 'baby-blues' to puerperal psychosis.

The **Edinburgh Postnatal Depression Scale** may be used to screen for depression:

- 10-item questionnaire, with a maximum score of 30
- indicates how the mother has felt over the previous week
- score > 13 indicates a 'depressive illness of varying severity'
- sensitivity and specificity > 90%
- includes a question about self-harm

'Baby-blues'	Postnatal depression	Puerperal psychosis
Seen in around 60-70% of women Typically seen 3-7 days following birth and is more common in primips Mothers are characteristically anxious, tearful and irritable	Affects around 10% of women Most cases start within a month and typically peaks at 3 months Features are similar to depression seen in other circumstances	Affects approximately 0.2% of women Onset usually within the first 2-3 weeks following birth Features include severe swings in mood (similar to bipolar disorder) and disordered perception (e.g. auditory hallucinations)
Reassurance and support, the health visitor has a key role	As with the baby blues reassurance and support are important Cognitive behavioural therapy may be beneficial. Certain SSRIs such as sertraline and paroxetine* may be used if symptoms are severe** - whilst they are secreted in breast milk it is not thought to be harmful to the infant	Admission to hospital is usually required There is around a 20% risk of recurrence following future pregnancies

*paroxetine is recommended by SIGN because of the low milk/plasma ratio
**fluoxetine is best avoided due to a long half-life

Sleep paralysis

- Sleep paralysis is a common condition characterized by transient paralysis of skeletal muscles which occurs when awakening from sleep or less often while falling asleep.
- It is thought to be related to the paralysis that occurs as a natural part of REM (rapid eye movement) sleep.
- Sleep paralysis is recognised in a wide variety of cultures

Features

- paralysis - this occurs after waking up or shortly before falling asleep
- hallucinations - images or speaking that appear during the paralysis

Management

- if troublesome clonazepam may be used

Alcohol - problem drinking: management

- **Alcohol is a common cause of hypoglycaemia**, and can be rapidly life-threatening if not recognised. Common initial symptoms are tachycardia and sweating.
- patients who abuse alcohol often are relatively hypotensive as they are often relatively dehydrated and are thin due to minimal food intake.

Nutritional support

- SIGN recommends alcoholic patients should receive oral thiamine if their 'diet may be deficient'

Drugs used

- benzodiazepines for acute withdrawal
- **Disulfram**: promotes abstinence - alcohol intake causes severe reaction due to inhibition of acetaldehyde dehydrogenase. Patients should be aware that even small amounts of alcohol (e.g. In perfumes, foods, mouthwashes) can produce severe symptoms. Contraindications include ischaemic heart disease and psychosis
- **acamprosate**: reduces craving, known to be a weak antagonist of NMDA receptors, improves abstinence in placebo controlled trials
  - is derived from taurine
  - increases the γ-aminobutyric acid (GABA) level, which inhibits CNS activity
  - **has relatively few side-effects**
- **Naltrexone:** reduces the pleasure that alcohol brings and craving when it is withdrawn, and can halve the relapse rates; however, it is associated with a number of **adverse effects, including:**
  - nausea, vomiting, anxiety, nervousness, insomnia, lethargy, arthralgia, increased sweating and lacrimation, diarrhoea or constipation, increased thirst and liver and kidney dysfunction
  - particularly the GI symptoms recognised with naltrexone may discourage use in a patient with a previous history of IBS

Alcohol withdrawal

Alcohol withdrawal is the most common cause of paranoid psychosis with visual hallucination

Mechanism

- chronic alcohol consumption **enhances GABA mediated inhibition in the CNS** (similar to benzodiazepines) and **inhibits NMDA-type glutamate receptors**
- alcohol withdrawal is thought to be lead to the opposite (decreased inhibitory GABA and increased NMDA glutamate transmission)

Features

- symptoms start at 6-12 hours
- **peak incidence of seizures at 36 hours**
- peak incidence of delirium tremens is at 72 hours

- **if patients continue to abstain from alcohol they usually peak after about 72 hours and may last a week or more, but usually have resolved by 3 weeks.**

	Minor Withdrawal	Alcoholic Hallucinosis	Withdrawal Seizure	Delirium Tremens
Time Since Last Drink	6-12 hours	12-24 hours	24-48	48-72 hours
Features	• Insomnia • Tremor • Anxiety • Nausea • Vomiting • Headache • Sweating • Palpitations	visual, auditory and tactile hallucinations.	generalised tonic-clonic seizures.	• **Autonomic instability** (tachycardia, hypertension, and pyrexia), • Disorientation • Hallucinations • Agitation

- **Withdrawal Seizure**
  - Most patients will have single or few fits, and complete spontaneous disappearance is anticipated within 6-12 hours.
  - The presence of focal fits, more than six fits, a prolonged post-ictal phase or development of status epilepticus should suggest another diagnosis.
  - Around 30% of patients will go on to develop delirium tremens and prophylactic doses of diazepam or chlodiazepoxide are indicated.
- **Delirium tremens**
  - the most severe form of alcohol withdrawal.
  - Onset is typically three to seven days after cessation of chronic alcohol ingestion.
  - characterised by
    - visual hallucinations,
    - autonomic instability (tachycardia, hypertension, pyrexia),
    - obtundation and confusion.
    - Sweating, tremors and agitation are also features.

Management

- benzodiazepines
  - **In hepatic impairment benzodiazepines with a shorter half-life (e.g. lorazepam and oxazepam) are preferred**
- carbamazepine also effective in treatment of alcohol withdrawal
  - at a starting dose of 800 mg per 24 hours
- phenytoin is said not to be as effective in the treatment of alcohol withdrawal seizures
  - best avoided because of the risk of causing hypotension.
- Thiamine is also indicated in chronic alcoholism but is not as immediately important as diazepam.

Schizophrenia

Epidemiology

Risk of developing schizophrenia

- **monozygotic twin has schizophrenia = 50%**
- parent has schizophrenia = 10-15%
- sibling has schizophrenia = 10%
- no relatives with schizophrenia = 1%
- Schizophrenia is more common in social classes IV and V.
- Temporal lobe epilepsy
- Amphetamines may cause a state resembling hyperactive paranoid schizophrenia with hallucinations.

Schizophrenia: features

Schneider's first rank symptoms may be divided into auditory hallucinations, thought disorders, passivity phenomena and delusional perceptions:

Auditory hallucinations of a specific type:

- two or more voices discussing the patient in the third person
- thought echo
- voices commenting on the patient's behaviour

Thought disorder: occasionally referred to as thought alienation

- thought insertion
- thought withdrawal
- thought broadcasting

Passivity phenomena:

- bodily sensations being controlled by external influence
- actions/impulses/feelings - experiences which are imposed on the individual or influenced by others

Delusional perceptions

- a two stage process) where first a normal object is perceived then secondly there is a sudden intense delusional insight into the objects meaning for the patient e.g. 'The traffic light is green therefore I am the King'.

Other features of schizophrenia include

- impaired insight
- incongruity/blunting of affect (inappropriate emotion for circumstances)
- decreased speech
- neologisms: made-up words
- catatonia
- **Concrete thinking where a patient cannot use abstraction to understand the meaning of a sentence.** It is more common in schizophrenia.
- negative symptoms: incongruity/blunting of affect, anhedonia (inability to derive pleasure), alogia (poverty of speech), avolition (poor motivation)

Prognostic indicators

Factors associated with poor prognosis

- strong family history

- gradual onset
- low IQ
- premorbid history of social withdrawal
- lack of obvious precipitant

Schizophrenia: management

Key points: (NICE guidelines 2009)

- oral atypical antipsychotics are first-line
- **cognitive behavioural therapy should be offered to all patients**
- close attention should be paid to cardiovascular risk-factor modification due to the high rates of cardiovascular disease in schizophrenic patients (linked to antipsychotic medication and high smoking rates)

Electroconvulsive therapy

- Electroconvulsive therapy is a useful treatment option for patients with severe depression refractory to medication or those with psychotic symptoms.
- The only absolute contraindications is raised intracranial pressure.

Short-term side-effects

- headache
- nausea
- short term memory impairment
- memory loss of events prior to ECT
- cardiac arrhythmia

Long-term side-effects

- some patients report impaired memory

Charles Bonnet syndrome

- Charles Bonnet syndrome (CBS) is characterised by persistent or recurrent complex **hallucinations (usually visual or auditory), occurring in clear consciousness.**
- This is generally against a background of visual impairment (although visual impairment is not mandatory for a diagnosis).
- **Insight is usually preserved.**
- Well-formed complex visual hallucinations are thought to occur in 10-30 percent of individuals with severe visual impairment.
- Around a third find the hallucinations themselves an unpleasant or disturbing experience.
- This must occur in the absence of any other significant neuropsychiatric disturbance.

Epidemiology

- CBS is equally distributed between sexes and does not show any familial predisposition.
- Prevalence of CBS in visually impaired people is thought to be between 11 and 15 percent.

Risk factors include:

- Advanced age
- Peripheral visual impairment

- Social isolation
- Sensory deprivation
- Early cognitive impairment

Associated conditions

- The most common ophthalmological conditions associated with this syndrome are age-related macular degeneration, followed by glaucoma and cataract.

Prognosis

- In a large study published in the British Journal of Ophthalmology, 88% had CBS for 2 years or more, resolving in only 25% at 9 years (thus it is not generally a transient experience).

Treatment

- **Reassurance is usually the best treatment**

Aphonia

- Aphonia describes the inability to speak.
- Causes include:
  - recurrent laryngeal nerve palsy (e.g. Post-thyroidectomy)
  - psychogenic

De Crambault's syndrome

- De Crambault's syndrome, also known as erotmania, is a form of paranoid delusion with an amorous quality.
- The patient, often a single **woman, believes that a famous person is in love with her.**

Bouffée délirante is an acute psychotic disorder in which hallucinations, delusions or perceptual disturbances are obvious but markedly variable, changing from day to day or even from hour to hour.

Fregoli delusion is the mistaken belief that some person currently present in the deluded person's environment (typically a stranger) is a familiar person in disguise.

Capgras delusion is the belief that significant others have been replaced by impostors, robots or aliens.

Couvade is the common but poorly understood phenomenon whereby the expectant father experiences somatic symptoms during the pregnancy for which there is no recognised physiological basis.

Delusions

Cotard syndrome

- Cotard syndrome is a rare mental disorder where the affected **patient believes that they (or in some cases just a part of their body) is either dead or non-existent.**
- This delusion is often difficult to treat and can result in significant problems due to patients stopping eating or drinking as they deem it not necessary.

Othello syndrome is a delusional belief that a patients partner is committing infidelity despite no evidence of this. It can often result in violence and controlling behaviour.

De Clerambault syndrome (otherwise known as erotomania), is where a **patient believes that a person of a higher social or professional standing is in love with them.** Often this presents with people who believe celebrities are in love with them.

Ekbom syndrome is also known as delusional parasitosis and is the **belief that they are infected with parasites or have 'bugs' under their skin.** This can vary from the classic psychosis symptoms in narcotic use where the user can 'see' bugs crawling under their skin or can be a patient who believes that they are infested with snakes.

Capgras delusion is the belief that friends or family members have been replaced by an identical looking imposter.

Personality disorders

Disorder	Features
Antisocial	• Failure to conform to social norms with respect to lawful behaviors as indicated by repeatedly performing acts that are grounds for arrest; • Deception, as indicated by repeatedly lying, use of aliases, or conning others for personal profit or pleasure; • Impulsiveness or failure to plan ahead; • Irritability and aggressiveness, as indicated by repeated physical fights or assaults; • Reckless disregard for safety of self or others; • Consistent irresponsibility, as indicated by repeated failure to sustain consistent work behavior or honor financial obligations; • Lack of remorse, as indicated by being indifferent to or rationalizing having hurt, mistreated, or stolen from another
Avoidant	• Avoidance of occupational activities which involve significant interpersonal contact due to fears of criticism, or rejection. • Unwillingness to be involved unless certain of being liked

Disorder	Features
	• Preoccupied with ideas that they are being criticised or rejected in social situations • Restraint in intimate relationships due to the fear of being ridiculed • Reluctance to take personal risks due to fears of embarrassment • Views self as inept and inferior to others • Social isolation accompanied by a craving for social contact
Borderline	• Efforts to avoid real or imagined abandonment • Unstable interpersonal relationships which alternate between idealization and devaluation • Unstable self image • Impulsivity in potentially self damaging area (e.g. Spending, sex, substance abuse) • Recurrent suicidal behaviour • Affective instability • Chronic feelings of emptiness • Difficulty controlling temper • Quasi psychotic thoughts Borderline - think nightmare girlfriend/boyfriend
Dependent	• Difficulty making everyday decisions without excessive reassurance from others • Need for others to assume responsibility for major areas of their life • Difficulty in expressing disagreement with others due to fears of losing support • Lack of initiative • Unrealistic fears of being left to care for themselves • Urgent search for another relationship as a source of care and support when a close relationship ends • Extensive efforts to obtain support from others • Unrealistic feelings that they cannot care for themselves
Histrionic	• Inappropriate sexual seductiveness • Need to be the centre of attention • Rapidly shifting and shallow expression of emotions • Suggestibility • Physical appearance used for attention seeking purposes • Impressionistic speech lacking detail • Self dramatization • Relationships considered to be more intimate than they are
Narcissistic	• Grandiose sense of self importance • Preoccupation with fantasies of unlimited success, power, or beauty

Disorder	Features
	• Sense of entitlement • Taking advantage of others to achieve own needs • Lack of empathy • Excessive need for admiration • Chronic envy • Arrogant and haughty attitude **Narcissistic - Steve Jobs's ex-wife thought he had this**
Obsessive-compulsive	• Is occupied with details, rules, lists, order, organization, or agenda to the point that the key part of the activity is gone • Demonstrates perfectionism that hampers with completing tasks • Is extremely dedicated to work and efficiency to the elimination of spare time activities • Is meticulous, scrupulous, and rigid about etiquettes of morality, ethics, or values • Is not capable of disposing worn out or insignificant things even when they have no sentimental meaning • Is unwilling to pass on tasks or work with others except if they surrender to exactly their way of doing things • Takes on a stingy spending style towards self and others; and shows stiffness and stubbornness
Paranoid	• Hypersensitivity and an unforgiving attitude when insulted • Unwarranted tendency to questions the loyalty of friends • Reluctance to confide in others • Preoccupation with conspirational beliefs and hidden meaning • Unwarranted tendency to perceive attacks on their character
Schizoid	• Indifference to praise and criticism • Preference for solitary activities • Lack of interest in sexual interactions • Lack of desire for companionship • **Emotional coldness** • Few interests • Few friends or confidants other than family **Schizoid - think Bruce Wayne/Batman from recent Christopher Nolan films**

Disorder	Features
Schizotypal	• Ideas of reference (differ from delusions in that some insight is retained) • Odd beliefs and magical thinking • Unusual perceptual disturbances • Paranoid ideation and suspiciousness • Odd, eccentric behaviour • Lack of close friends other than family members • Inappropriate affect • Odd speech without being incoherent

Haptic hallucinations are hallucinations involving skin sensation in the absence of stimuli, and are common in situations of alcohol withdrawal and stimulant drug overdose. In this situation medication with a benzodiazepine is the most appropriate intervention.

Borderline personality disorder is marked out by instability in moods, behaviour and relationships.

Diagnosis is confirmed by the presence of at least 5 of the following symptoms;

1) Extreme reactions including panic, depression, rage, or frantic actionsto abandonment, whether real or perceived

2) A pattern of intense and stormy relationships with family, friends, and loved ones, often veering from extreme closeness and love to extreme dislike or anger

3) Distorted and unstable self-image or sense of self, which can result in sudden changes in feelings, opinions, values, or plans and goals for the future (such as school or career choices).

4) Impulsive and often dangerous behaviours, such as spending sprees, unsafe sex, substance abuse, reckless driving, and binge eating.

5) Recurring suicidal behaviours or threats or self-harming behaviour, such as cutting
Intense and highly changeable moods, with each episode lasting from a few hours to a few days.

6) Chronic feelings of emptiness and/or boredom.

7) Inappropriate, intense anger or problems controlling anger

8) Having stress-related paranoid thoughts or severe dissociative symptoms, such as feeling cut off from oneself, observing oneself from outside the body, or losing touch with reality.

There are no features consistent with endogenous depression, such as early morning wakening or loss of appetite, and no features consistent with hypomania such as pressure of speech, flight of

ideas, or over exuberant behaviour. We are given no indication of drug abuse which may indicate drug induced psychosis. Anti-social personality disorder is characterised by a failure to conform to social norms, and repeated law breaking. There is consistent irresponsibility, impulsivity and disregard for both their own safety and that of others.

Panic disorder

- The patient is suffering from panic disorder - sudden, discrete **attacks of intense anxiety or fear accompanied by physical symptoms, for example, palpitations and a feeling of suffocation.**
- Abnormal discharge from the **locus caeruleus in the midbrain has been implicated in panic attacks.** The locus caeruleus is the origin of most brain noradrenergic pathways.
- To distinguish it from a specific phobia, some of the attacks must occur without an environmental trigger.

Acute confusional state (delirium) (NICE 2014)

- A sudden change in the mental state or sudden onset of behaviour that is out of character in an older person is most likely to be due to an acute confusional state (delirium).
- Recent changes in behavior (within hours or days)

Risk factors

- Older people (≥ 65)
- cognitive impairment or dementia
- severe illness
  - 20–30% of people on **medical wards** in hospital have delirium,
  - 10% - 50% of people who have **surgery** develop delirium
- Current hip fracture

delirium vs dementia

- It can be difficult to distinguish between delirium and dementia because symptoms overlap, and some people may have both conditions.
- Dementia tends to develop slowly, whereas delirium is characterised by sudden changes.
- Dementia is generally a chronic, progressive disease for which there is no cure. Delirium is a potentially reversible condition if the causes are identified and they are treatable.
- If clinical uncertainty exists over the diagnosis, initial management should be for delirium.

Diagnosis

- By clinical assessment based on:
  - Diagnostic and Statistical Manual of Mental Disorders **(DSM-IV)** criteria **or**
  - short Confusion Assessment Method **(short CAM)** to confirm the diagnosis.
    - In critical care or in the recovery room after surgery, **CAM-ICU** should be used.

Treatment

- **the first intervention → Interview the patient, take a history, assess mental state and try to reassure the patient.**
- Adults with delirium who are distressed or are a risk to themselves or others are not prescribed antipsychotic medication unless de-escalation techniques (Communication approaches) are ineffective or inappropriate.
- Sedation should only be used as a last resort and preferably only once the cause of the delirium has been established.
- short-term (usually for 1 week or less) haloperidol or olanzapine
- avoid antipsychotics in patients Parkinson's disease or dementia with Lewy bodies.
- **Mirtazapine, which enhances both noradrenergic and serotinergic transmission, would be a good antidepressant choice for an emaciated agitated elderly patients.** (medical-masterclass.com 2017 mrcp part 2)
  - Mirtazapine blocks alpha-2, 5-HT2A and 5-HT3 receptors, thus increasing the amounts of both noradrenaline and serotonin in the synaptic gap. It also has a high affinity for H1 receptors so it tends to cause weight gain and drowsiness, a good choice for a thin agitated patient.

Chronic fatigue syndrome

- also been called myalgic encephalomyelitis (ME) and, more recently, systemic exertion intolerance disease (SEID).
- extreme fatigue that can't be explained by any underlying medical condition.
- The fatigue may worsen with physical or mental activity, but doesn't improve with rest.
- The cause is unknown, although there are many theories — ranging from viral infections to psychological stress.

Risk factors

- Age (most commonly affects people in their 40s and 50s)
- Sex (more common in female)
- stress

Diagnosis

- rule out other conditions with similar symptoms.

Treatment

- **Graded exercise programmes** and cognitive-behavioural therapy are the only two treatments shown to be of definite benefit.

Notes & Notes

For MRCP part 1 & 11

By

Dr. Yousif Abdallah Hamad

Basic sciences

Cell biology

Updated

2017

Contains:

1/ Passmedicine 2017

2/ On examination 2017

3/ Pastest 2017

4/ **Red fonts --> previous exams**

5/ Other updated UK sources

Membrane receptors

There are four main types of membrane receptor:

1. ligand-gated ion channels,
2. tyrosine kinase receptors,
3. guanylate cyclase receptors and
4. G protein-coupled receptors

Ligand-gated ion channel receptors

- generally mediate fast responses
- e.g. **nicotinic acetylcholine**, GABA-A & GABA-C, glutamate receptors

Tyrosine kinase receptors

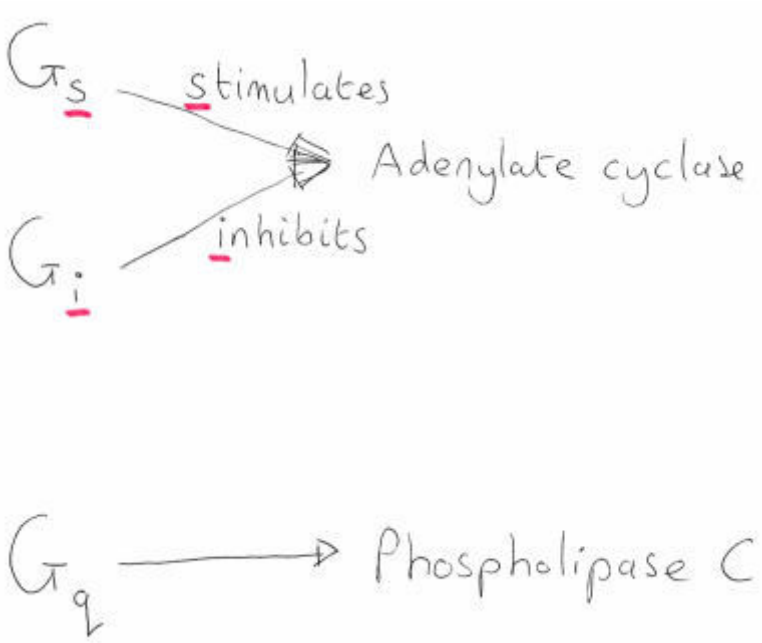
- intrinsic tyrosine kinase: insulin, insulin-like growth factor (IGF), epidermal growth factor (EGF)
- receptor-associated tyrosine kinase: growth hormone, prolactin, interferon, interleukin

Guanylate cyclase receptors

- contain intrinsic enzyme activity
- e.g. atrial natriuretic factor, brain natriuretic peptide

G protein-coupled receptors

- **located on Cell membrane**
- generally mediate slow transmission and affect metabolic processes
- activated by a wide variety of extracellular signals e.g. Peptide hormones, biogenic amines, lipophilic hormones, light
- 7-helix membrane-spanning domains
- consist of 3 main subunits: alpha, beta and gamma
- the alpha subunit is linked to GDP (guanine diphosphate). Ligand binding causes conformational changes to receptor, **GDP is phosphorylated to GTP (Ligand binding leads to GDP replacement by GTP)**, and the alpha subunit is activated
- **The muscarinic acetylcholine receptor is an example of a G protein-coupled receptor**
- G proteins are named according to the alpha subunit (G_s, G_i, G_q)



	G_s	G_i	G_q
Mechanism	**S**timulates adenylate cyclase → increases cAMP → activates protein kinase A	**I**nhibits adenylate cyclase → decreases cAMP → inhibits protein kinase A	Activates phospholipase C → splits PIP_2 to IP_3 & DAG → activates protein kinase C
Examples	• **Beta-1** receptors (epinephrine, norepinephrine, dobutamine) • **Beta-2** receptors (epinephrine, salbuterol) • **H2** receptors (histamine) • **D1** receptors (dopamine) • **V2** receptors (vasopressin) • Receptors for ACTH, LH, FSH, glucagon, PTH, calcitonin, prostaglandins	• **M2** receptors (acetylcholine) • **Alpha-2** receptors (epinephrine, norephinephrine) • **D2** receptors (dopamine) • GABA-B receptor	• **Alpha-1** receptors (epinephrine, norepinephrine) • **H1** receptors (histamine) • **V1** receptors (vasopressin) • **M1, M3** receptors (acetylcholine)

Adenosine interact with ➔ G protein-coupled receptor

G protein-coupled receptors	
Gs	B1, B2 , H2, D1, V2 , prostaglandins, (ACTH, LH, FSH), PTH, Calcitonin
Gi	M2, α2, D2, Adenosine in nodal tissue
Gq	α1, H1, V1, M1, M3, Adenosine in bronchial smooth muscle

Nucleus receptors:

The nucleus is the site of RNA transcription and DNA replication. **Active vitamin D** and **steroid hormones** such as cortisol, estrogen, and progesterone **act by binding receptors that localize to the nucleus** and alter gene transcription.

Cell signalling

- **Phosphorylation of specific tyrosine residues is often a key event in the activation of the Cell signalling pathways**

Intracellular signalling proteins (Ras protein)

- The Ras family of oncogenes are important intracellular signalling proteins which transmit signals from receptor tyrosine kinase proteins in the cell membrane down to the nucleus.
- Ras is controlled by the activity of a GTPase binding site; when guanosine triphosphate (GTP) is bound **Ras** is active and **it slowly hydrolyses the GTP to guanosine diphosphate (GDP) resulting in an inactive state.**
- Mutations in codon 12 result in decreased GTPase activity and a Ras protein which is 'always on' resulting in increased proliferation of the cell.
  - **Mutation in codon 12 of the Ras oncogene often results in** → Decreased GTP hydrolysis → increased proliferation of the cell.

G proteins

the location of G-proteins? In the cytoplasm

- Their ligand-binding site is exposed outside the surface of the cell
- Their effector site extends into the cytosol
- Many ligands bind to the GPCR, including thyroid-stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), serotonin and γ-aminobutyric acid (GABA)

Diseases caused by GPCR loss-of-function mutations

Receptor	Disease	Inheritance
Cone opsins	Color blindness	X-linked; autosomal recessive
Rhodopsin	Retinitis pigmentosa	Autosomal dominant; recessive
V2 vasopressin	Nephrogenic diabetes insipidus	X-linked
Ca2+ sensing	Familial hypocalciuric hypercalcemia	Autosomal dominant
Melanocortin 4	Extreme obesity	Codominant
TRH	Central hypothyroidism	Autosomal recessive

GPCR Gene Gain-of-Function Mutations

- gain-of-function mutations in the LH and TSH receptor genes may mimic states of hormone excess, familial male precocious puberty, and familial nonautoimmune hyperthyroidism, respectively.
- Women inheriting gain-of-function mutations in the LH receptor gene do not show precocious puberty because, unlike in males, **the combined action of LH and FSH is required for female pubertal development.**

Diseases caused by GPCR gain-of-function mutation

Receptor	Disease	Inheritance
Rhodopsin	**Congenital night blindness**	**Autosomal dominant**
LH	**Familial male precocious puberty**	**Autosomal dominant**
LH	**Sporadic Leydig cells tumors**	**Somatic**
TSH	**Familial nonautoimmune hyperthyroidism**	**Autosomal dominant**
Ca2+ sensing	**Familial hypocalcemia**	**Autosomal dominant**

Adrenoceptors

	Agonists	Antagonists	Pathways
Alpha-1	• **vasoconstriction** • **relaxation of GI smooth muscle** • salivary secretion • hepatic glycogenolysis	**Doxazosin (α-1)** (for HTN & BPH) **Tamsulosin** (**α-1a**) (acts mainly on urogenital tract)	activate phospholipase C → IP3 → DAG
Alpha-2	• mainly presynaptic: inhibition of transmitter release • inhibits insulin • platelet aggregation	yohimbine	inhibit adenylate cyclase
Beta-1	• mainly located in the heart • increase heart rate + force	atenolol	stimulate adenylate cyclase
Beta-2	• vasodilation • bronchodilation • relaxation of GI smooth muscle		stimulate adenylate cyclase
Beta-3	• lipolysis		stimulate adenylate cyclase

Alpha antagonists

- non-selective: phenoxybenzamine (previously used in peripheral arterial disease)

Beta antagonists

- non-selective: propranolol
- Carvedilol and labetalol are mixed alpha and beta antagonists

Second messengers

Overview

- many different types
- allow amplification of external stimulus

	cAMP system	Phosphoinositol system	cGMP system	Tyrosine kinase system
Ligand: Neurotransmitters (Receptor)	Epinephrine (α2, β1, β2) Acetylcholine (M2)	Epinephrine (α1) Acetylcholine (M1, M3)	-	-
Ligand: Hormones	ACTH, ADH, calcitonin, FSH, glucagon, hCG,LH, MSH, **PTH**, TSH, GHRH*	angiotensin II, GnRH, GHRH*, Oxytocin, TRH	ANP, **Nitric oxide**	insulin, growth hormone, I**GF**, PD**GF**, prolactin
Primary effector	Adenylyl cyclase	Phospholipase C	Guanylate cyclase	Receptor tyrosine kinase
Secondary messenger	cAMP (cyclic adenosine monophosphate)	IP3 (inositol 1,4,5 trisphosphate) and DAG (Diacylglycerol)	cGMP	Protein phosphatase

*the cAMP pathway is the most important

Molecules that freely pass through the cell membrane include:

- **cholesterol,**
- **steroid hormones** (progesterone, testosterone, oestradiol and cortisol)**, and**
- **vitamin D.**

other ionic hormones such as the following are unable to pass the plasma membrane

Act through cyclic adenosine monophosphate (cAMP) as the second messenger:

- adrenaline
- growth hormone-releasing hormone (GHRH)
- glucagon
- luteinising hormone (LH)
- follicle stimulating hormone (FSH)
- parathyroid hormone (PTH), and
- thyroid-stimulating hormone (TSH).

Acts through mitogen-activated protein (MAP) kinase pathway

- Insulin
- growth hormone (GH)
- prolactin.

Act through calcium/phosphoinositide:

- Thyroid releasing hormone (TRH)
- gonadatrophin-releasing hormone (GnRH), and
- antidiuretic hormone (ADH).

Act through cyclic guanosine monophosphate (cGMP).

- Nitric oxide
- atrial natriuretic peptide (ANP)

Acts by binding to intracellular receptors.

- Triiodothyronine (T3)

Cell organelles

The table below summarises the main functions of the major cell organelles:

Organelle/macromolecule	Main function
Endoplasmic reticulum	**Rough endoplasmic reticulum (RER)** • translation and folding of new proteins • manufacture of lysosomal enzymes • site of N-linked glycosylation • Hydroxylation of proline and lysine residues in procollagen chains occurs in the RER and requires vitamin C • examples of cells with extensive RER include pancreatic cells, goblet cells, plasma cells **Smooth endoplasmic reticulum (SER)** • steroid, lipid synthesis • SER is the site of drug detoxification • examples of cells with extensive SER include those of the adrenal cortex, hepatocytes, testes, ovaries • Drugs such as barbiturates can increase the amount of SER in cells
Golgi apparatus	Modifies, sorts, and packages these molecules that are destined for cell secretion Site of O-linked glycosylation
Mitochondrion	Aerobic respiration. Contains mitochondrial genome as circular DNA. **has its own self-replicating DNA**
Nucleus	DNA maintenance and RNA transcription
Lysosome	Breakdown of large molecules such as proteins and polysaccharides. **breakdown of oligopeptides**
Nucleolus	Ribosome production
Ribosome	Translation of RNA into proteins
Peroxisome	Catabolism of very long chain **fatty acids and amino acids** Results in the formation of hydrogen peroxide
Proteasome	Along with the lysosome pathway involved in degradation of protein molecules that have been tagged with ubiquitin **(degradation of polypeptides)**

Tumour suppressor genes

Tumour suppressor genes - loss of function results in an increased risk of cancer

Oncogenes - gain of function results in an increased risk of cancer

Basics

- genes which normally control the cell cycle
- loss of function results in an increased risk of cancer
- both alleles must be mutated before cancer occurs

Examples

Gene	Associated cancers
p53	Common to many cancers, Li-Fraumeni syndrome
APC	Colorectal cancer
BRCA1	Breast and ovarian cancer
BRCA2	Breast and ovarian cancer
NF1	Neurofibromatosis
Rb	Retinoblastoma
WT1	Wilm's tumour
Multiple tumor suppressor 1 (MTS-1, p16)	Melanoma

p53

- p53 is a tumour suppressor gene located on chromosome 17p.
- It is the most commonly mutated gene in breast, colon and lung cancer
- p53 is thought to play a crucial role in the cell cycle, preventing entry into the S phase until DNA has been checked and repaired.
- It may also be a key regulator of apoptosis
- **Li-Fraumeni syndrome is** a rare autosomal dominant disorder characterised by the early onset of a variety of cancers such as sarcomas and breast cancer. It is **caused by mutation in the p53 gene**

Eukaryotic cell cycle

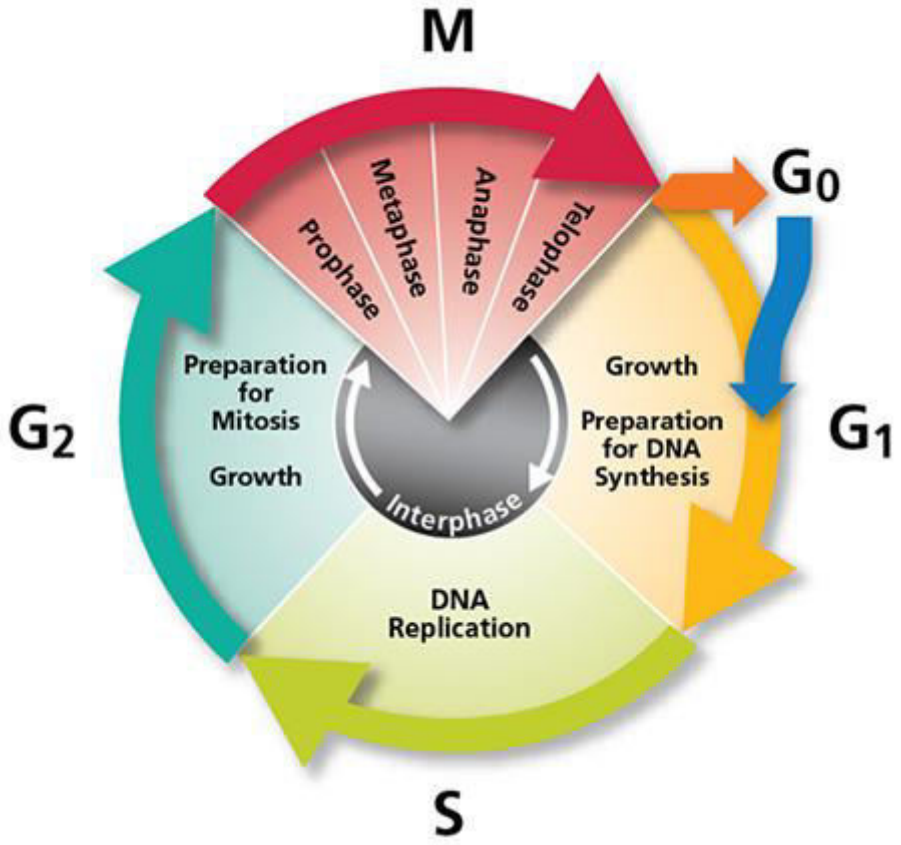
Eukaryotes (higher organisms) vs prokaryotic cells

- **nuclear membranes**
  - Eukaryotes have muliple chromosomes in the genome, which is separated from the rest of the cell by nuclear membranes.
  - Prokaryotes lack a membrane bound nucleus, and their DNA occurs in a circular form.
- Transcription
  - Transcription of eukaryotic genes requires non-coding sequences (introns) in the mRNA to be spliced out before translation at the ribosome.
- **Ribosomes**
  - **Ribosomes are found in eukaryotic and prokaryotic cells**
  - Both eukaryotes and prokaryotes have a ribosome, though the **ribosome is significantly larger in eukaryotes.**

Phases of cell cycle

- The cell cycle is regulated by proteins called cyclins which in turn control cyclin-dependent kinase (CDK) enzymes.

Phase	Notes	Regulatory proteins
G_0	• 'resting' phase • quiescent cells such as hepatocytes and more permanently resting cells such as neurons	
G_1	• **G**ap 1, cells increase in size • determines length of cell cycle • under influence of p53	Cyclin D / CDK4, Cyclin D / CDK6 and Cyclin E / CDK2: regulates transition from G1 to S phase. **determine the length of the cell cycle**
S	• **S**ynthesis of DNA, RNA and histone • centrosome duplication	Cyclin A / CDK2: active in S phase
G_2	• **G**ap 2, cells continue to increase in size	Cyclin B / CDK1: regulates transition from G_2 to M phase
M	• **M**itosis - cell division • the shortest phase of the cell cycle	



G0 phase

- G0 is a resting stage with non-dividing cells
- Cells can enter the **G0 phase** from G1 if they are not preparing for cell division. This may occur if the **cell has reached its final differentiation**

G1 phase

- G1 and G2 are gap phases
- **G1 is a gap phase under the influence of the p53 gene**
- G1 phase determines the variability of the cycle length
- In normal tissues, cells with significant damage to their DNA are arrested at the G1 phase

S phase

- During the S phase the cell prepares itself for division by duplicating the chromosomes.
- **DNA is synthesised in the S phase**

M phase

- **Mitosis occurs during the M phase of the cell cycle.**

- Mitosis describes the process in which somatic cells divide and replicate producing genetically identical diploid daughter cells. This allows tissue to grow and renew itself.

Radio-sensitivities during phases of the cell cycle.

- Normal and cancerous cells exhibit different radiosensitivities during different phases of the cell cycle.
- They are **most sensitive in G2-M phase** when the cell is preparing to and actively dividing due to the fragile nature of the intracellular structure during this event.
- **Cells are most resistant in G0, early G1 and the late S phase of the cell cycle**.
- Resistance in S phase is thought to be due to elevated levels of glutathione, as well as rapid DNA synthesis and repair enzymes.

Cell division

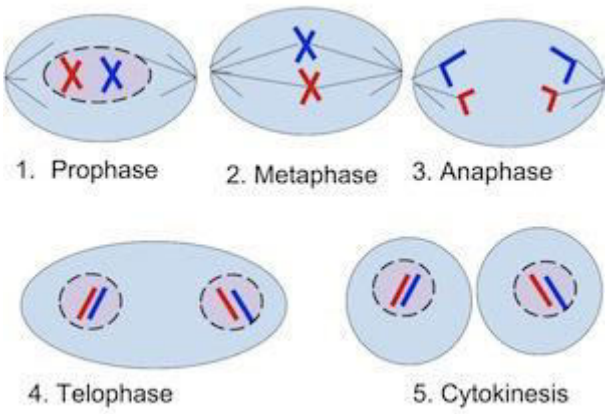
There are two types of cell division; mitosis and meiosis.
The table below demonstrates the key differences:

Mitosis	Meiosis
Occurs in somatic cells	Occurs in gametes
Results in 2 diploid daughter cells	Results in 4 haploid daughter cells
Daughter cells are genetically identical to parent cell	Daughter cells contain one homologue of each chromosome pair and are therefore genetically different

Remember:

- somatic cells have 22 pairs of autosomes and 1 pair of sex chromosomes, i.e. 46XY or 46XX
- cells with a normal chromosome complement are known as diploid cells
- gametes (ova or spermatozoa) have a single copy of each chromosome and are known as haploid cells

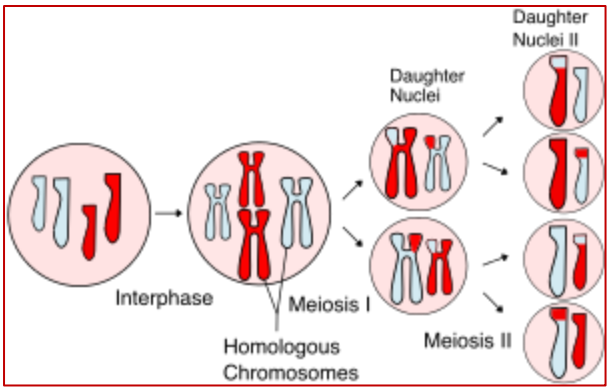
Mitosis



The table below shows the phases of mitosis:

Prophase	**Chromatin in the nucleus condenses**
Prometaphase	**Nuclear membrane breaks down allowing the microtubules to attach to the chromosomes**
Metaphase	Chromosomes aligned at middle of cell
Anaphase	The paired chromosomes separate at the kinetochores and move to opposite sides of the cell
Telophase	Chromatids arrive at opposite poles of cell
Cytokinesis	Actin-myosin complex in the centre of the cell contacts resulting in it being 'pinched' into two daughter cells

Meiosis



- Meiosis is the form of cell division that produces gametes.
- It is divided into two parts, meiosis 1 and meiosis 2.
- **D**eoxyribo**n**ucleic **a**cid (DNA) replication occurs before meiosis 1, and the cell begins division with twice the normal cellular amount of DNA.
- In meiosis 1, each daughter cell gets one of the duplicated chromosomes of each pair.
- At the beginning of meiosis 2, each cell contains 23 chromosomes each with a duplicated pair of chromatids.
- In meiosis 2, the duplicated pair separate and each daughter cell ends up with one of each of the 23 chromosomes (4 hapolid daughter cells).
- Two common errors of cell division occurring during meiosis are:
    1. **non-disjunction** (2 chromosomes fail to separate, so both copies of the chromosome go to one of the daughter cells);
        - In Down's syndrome, non-disjunction accounts for 94% of cases. The incidence of this increases with increasing maternal age.
        - 5% of cases are due to translocation, and 1% to mosaicism.
        - **Non-disjunction at mitosis (meisois 2) results in mosaicism.**
    2. **anaphase lag** in which a chromatid is lost because it fails to move quickly enough during anaphase to become incorporated into one of the new daughter cells.

Matrix metalloproteinases (MMPs)

- Matrix metalloproteinases (MMPs) are a group of enzymes responsible for the degradation of most extracellular matrix proteins during organogenesis, growth and normal tissue turnover.
- **(MMPs) are calcium-dependent zinc-containing endopeptidases**
- They are distinguished from other endopeptidases by their **dependence on metal ions as cofactors**, their **ability to degrade extracellular matrix**, and their specific evolutionary DNA sequence.

- All are involved in normal remodelling processes, such as embryonic development, postpartum involution of the uterus, bone and growth-plate remodelling, ovulation and wound healing
- The activity of MMPs in adult tissues is normally quite low.
- ↑ activity of MMPs →unwanted tissue destruction (inflammatory diseases & tumours)
  - ↑MMPs → degrade the structural proteins of the aortic wall →Aortic Aneurysm.
  - ↑collagenases, especially MMP-8 → periodontitis and peri-implantitis
  - ↑MMP-2 and MMP-9 → metastasis.
  - ↑MMP-1 → rheumatoid arthritis and osteoarthritis.
- Disregulation of the balance between MMPs and TIMPs (Tissue Inhibitor of Metallo-Proteinases) is also a characteristic of acute and chronic cardiovascular diseases.
- A range of MMP inhibitors is currently under development for the treatment of solid tumours.
- **Doxycycline, at sub-antimicrobial doses, inhibits MMP activity, and has been used in various experimental systems for this purpose, such as for recalcitrant recurrent corneal erosions. It is used clinically for the treatment of periodontal disease and is the only MMP inhibitor that is widely available clinically.**

Normal wound healing

- **Phase 1 : hemostasis (1 – 24 h)**
  - The initiating factor originate from platelets activated by mature collagen exposed in the wound
  - Platelets first aggregate then release a variety of active agents including lysosomal enzymes, ATP, serotonin and wound cytokines
  - A fibrin clot develops, which completes haemostasis and provides strength and support to the wound
  - platelets are integral to initiating wound healing → release cytokines that cause leukocyte migration and chemotaxis into the wound
- **Phase 2 : inflammation (1 – 5 days)**
  - **mast cells**
    - native cells **initiate the inflammatory phase**
    - secrete cytokines that cause vasodilation and increase vascular permeability
    - allows influx of neutrophils and macrophages to the wound bed
  - neutrophils
    - present early in inflammatory phase
    - clear intralesional pathogens
    - prepare the wound bed by removing damaged cells
    - secrete cytokines that stimulate infux of macrophages
  - macrophages
    - present late in inflammatory phase
    - secrete cytokines and growth factors that **drive fibroblast proliferation** and angiogenesis
- **Phase 3: proliferation (3 – 7 days)**
  - fibroblasts lay down type III collagen

- **myofibroblasts** (fibroblasts with contractile filaments) **initiate wound contraction**
- **macrophages become active as the main agents of demolition, removing unwanted fibrin, dead cells and bacteria and creating fluid-filled spaces for granulation tissue**
- **Which cell initiates granulation of the wound? → Macrophages**
- Macrophages also release factors that **stimulate the formation of new capillary buds** during this phase, and later they **initiate and control fibroblast activity during repair**
- angiogenesis and vasculogenesis lay down new blood vessels
- granulation tissue (newly laid collagen with neovascularization) forms
- epithelialization occurs from surrounding basal keratinocytes and hair follicle basal cells
- Within the connective tissue, **randomly orientated collagen** begins to form after a few days, reaching a peak of activity after 5-7 days

- **Phase 4 : maturation and remodeling** (up to 1 year)
  - **the phase of maturation and remodeling lasts for up to 12 months**.
  - type III collagen remodeled to type I collagen

Difference between 1° & 2° union of wound

FEATURES	PRIMARY	SECONDARY
CLEANLINESS	CLEAN	NOT CLEAN
INFECTION	NOT INFECTED	INFECTED
MARGINS	SURGICALLY CLEAN	IRREGULAR
SUTURES	USED	NOT USED
HEALING	SMALL GRANULATION TISSUE	LARGE GRANULATION TISSUE
OUT COME	LINEAR SCAR	IRREGULAR WOUND
COMPLICATION	NOT FREQUENT	FREQUENT

Molecular biology techniques

Molecular biology techniques

- SNOW (**S**outh - **NO**rth - **W**est)
- DROP (**D**NA - **R**NA - **P**rotein)

The following table shows a very **basic summary of molecular biology techniques**

Technique	Description
Southern blotting	Detects DNA
Northern blotting	Detects RNA
Western blotting	Detects proteins Uses gel electrophoresis to separate native proteins by 3-D structure Examples include the **confirmatory** HIV test commonly used as a confirmatory test following a positive ELISA.

Enzyme-linked immunosorbent assay (ELISA)

- a type of biochemical assay used to detect antigens and antibodies
- a colour changing enzyme is attached to the antibody if looking for an antigen and to an antigen if looking for an antibody
- the sample therefore changes colour if the antigen or antibody is detected
- an example includes the **initial** HIV test
  - the first step in screening for HIV in adults.
  - It can detect antibodies against HIV, but not the genetic material.

- **initial** HIV test → **ELISA**
- **confirmatory** HIV test → Western blotting
- **Polymerase chain reaction (PCR) is the only technique that would allow for the detection of the genetic material from HIV.**
- **Maternal antibodies usually cross the placenta during pregnancy, therefore any test that detects antibodies to HIV could give a false positive reading.**

Polymerase chain reaction (PCR)

the main action of PCR → DNA amplification

- Polymerase chain reaction (PCR) is a molecular genetic investigation technique.
- **Used** in:
  - prenatal diagnosis
    - Pre-implantation diagnosis uses IVF and genetic analysis of 3-day-old embryos before selective transfer of unaffected embryos to uterus.
  - detection of mutated oncogenes
  - diagnosis of infections
    - PCR is used to determine viral load
  - forensics.
- The main advantage of PCR is its sensitivity: only one strand of sample DNA is needed to detect a particular DNA sequence.
- Prior to the procedure **it is necessary to have two DNA oligonucleotide primers**. These are complimentary to specific DNA sequences at either end of the target DNA. **To do this the DNA double helix must first be split into two strands by Heating to nearly 100°C.**
- **Initial prep**
  - sample of DNA is added to test tube along with two DNA primers
  - a thermostable DNA polymerase (Taq) is added
- **The following cycle then takes place**
  - mixture is heated to almost boiling point causing denaturing (uncoiling) of DNA
  - mixture is the allowed to cool: complimentary strands of DNA pair up, as there is an excess of the primer sequences they pair with DNA preferentially
  - The above cycle is then repeated, with the amount of DNA doubling each time

- **advantages of PCR over ELISA in HIV testing:**
  - PCR becomes positive earlier in disease course
    - Positive ELISA result is dependent on antibody formation
  - PCR does not require that the patient have a competent immune system
    - ELISA requires the host to make antibodies
  - important specific cases when PCR should always be used
  - a newborn whose mother is HIV+
    - will have antibodies even if not infected, so ELISA does not work
  - when earliest possible detection is required

Reverse transcriptase PCR

- used to measure the amount of RNA present in a sample
- **used to amplify RNA**
- **RNA is converted to DNA by reverse transcriptase**
- gene expression in the form of mRNA (rather than the actually DNA sequence) can therefore be analyzed
- Using the enzyme reverse transcriptase, the cDNA (complementary (cDNA) is then amplified by conventional polymerase chain reaction (PCR).
- **Reverse transcriptase-PCR (RT-PCR) is able to identify the transcripts of a given gene by detecting the messenger(m) RNA coding for the gene**

MRCPUK-part-1-sep 2017: what is the function of reverse transcriptase?
➔ **Generation of cDNA from an RNA template**

Positron Emission Tomography (PET)

Positron Emission Tomography (PET) is a form of nuclear imaging which **uses fluorodeoxyglucose (FDG) as the radiotracer.** This allows a 3D image of metabolic activity to be generated using glucose uptake as a proxy marker. The images obtained are then combined with a conventional imaging technique such as CT to decide whether lesions are metabolically active.

Uses

- evaluating primary and possible metastatic disease
- cardiac PET: not used mainstream currently

Oncogenes and proto-oncogenes

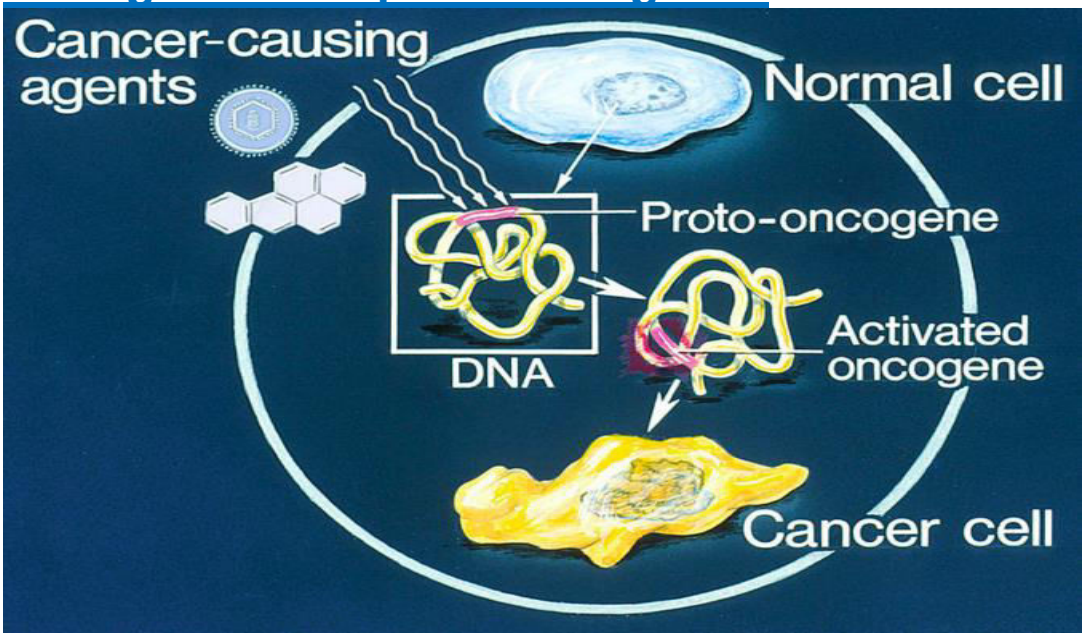


Illustration of how a normal cell is converted to a cancer cell, when an oncogene becomes activated

- **oncogene** is a gene that has the potential to cause cancer.
- Oncogenes are endogenous human deoxyribonucleic acid (DNA) sequences that arise from normal genes called proto-oncogenes.
- Proto-oncogenes are normally expressed in many cells, particularly during fetal development, and are thought to play an important regulatory role in cell growth and development.
- Alterations in the proto-oncogene can activate an oncogene, which produces unregulated gene activity, contributing directly to tumourogenesis.
- myc is an oncogene which encodes a transcription factor
- The **bcr-abl** fusion protein is the proto-oncogene from the Philadelphia chromosome found in CML. It is a **potent tyrosine kinase** which stimulates signal transduction and hence mitosis.

Oncogene alterations are important causes of:

- Rhabdomyosarcomas (ras oncogene)
- Burkitt's lymphoma (C-myc is translocated intact from its normal position on chromosome 8 to chromosome 14)
- Neuroblastoma **(N-myc proto-oncogene is seen in a proportion of patients with poor prognosis).**

They should be contrasted with tumour suppressor genes. In this situation, the genes normally down regulate cell growth, and require inactivation to allow malignant growth. Examples include retinoblastoma.

In situ hybridisation

- **gene mapping technique, denatured (DNA) from metaphase chromosomes is hybridised with a radioactively labelled probe. This DNA is then exposed to film to reveal the approximate chromosomal location of the DNA in the probe.**
- It uses a labelled complementary DNA or RNA probe to localise a specific sequence within a tissue.
- Firstly, the tissues are treated to fix the target, then the probe is added. This then hybridises to the target, following which, excess probe is washed away.
- In the classical form, the probe is labelled with radio-labelled bases, which can then be identified using plain film.

FISH (fluorescence in situ hybridization)

- **FISH** is a form of in situ hybridisation in which the probe is labelled with fluorescent bases, which can then be visualised under a fluorescent microscope.
- **Gene amplifications and chromosomal translocations are best detected by FISH (fluorescence in situ hybridization),** a technique that employs the use of DNA probes linked to fluorescent markers to visualize chromosomes.
- **eg :** Detection of Her2/neu
  - HER2/neu encodes human epidermal growth factor receptor protein, a transmembrane receptor tyrosine kinase that participates in cellular growth signaling.
  - HER2/neu is often amplified in breast cancer.

Other notes:

- **DNA amplification** is used to detect deletions and insertions in single genes.
- Metaphase **karyotype analysis** is often used for the detection of large chromosomal abnormalities including a trisomy like Down syndrome or Patau syndrome.

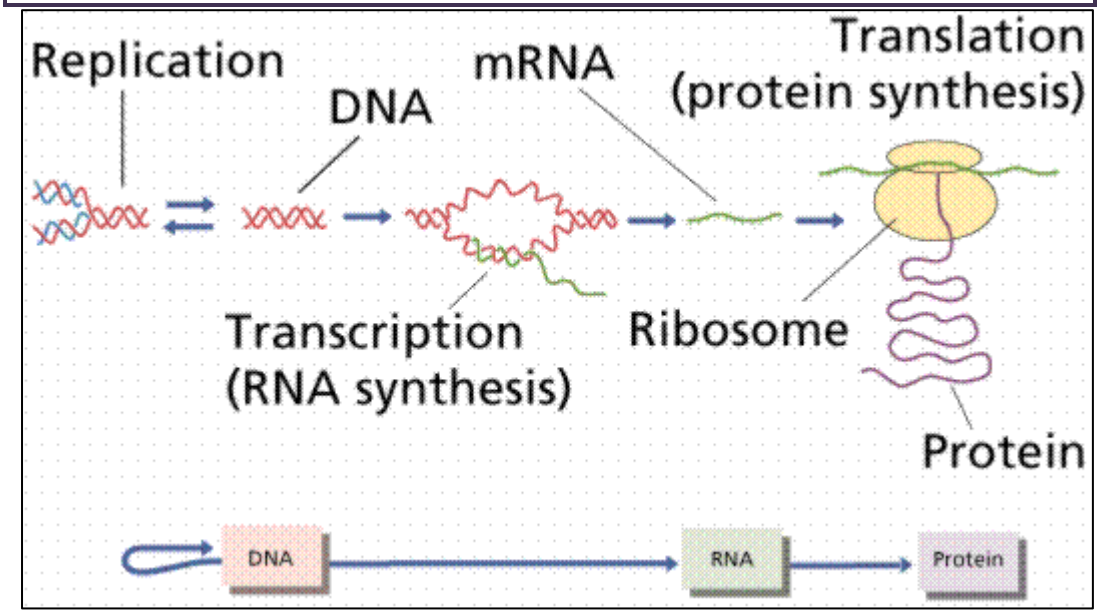
Recombination

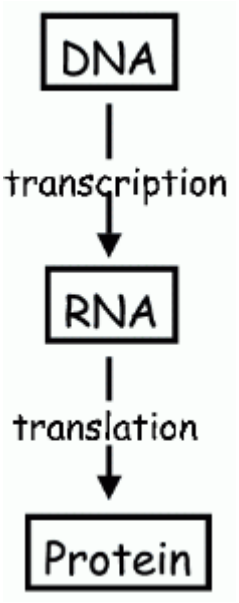
- **Recombination is the production of genetic combinations not found in either of the parents.**
- In humans, this is predominantly created by crossing-over between homologous chromosomes during meiosis.
- The maximum possible recombination distance between two genes (or any two markers on a chromosome) is 50%, because they may be inherited together at random on 50% of occasions. If two genes (or markers) have a recombination fraction of 50%, then they either lie on different chromosomes, or a long distance apart on the same chromosome

Ref: medical-masterclass.com 2017 mrcp part 1

Protein synthesis

In DNA, Adenine is paired with Thymine and Cytosine with Guanine.



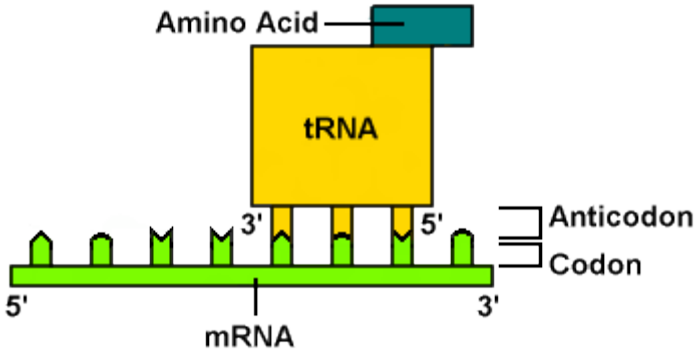


messenger RNA produced in the nucleus, matures in the cytoplasm, binds to the ribosome and initiates protein synthesis

- Protein synthesis consists of two phases.
  - **Transcription** is where one strand of the deoxyribonucleic acid (DNA) double helix is used as a template by ribonucleic acid (RNA) polymerase to synthesise messenger RNA from RNA nucleotides.The mRNA then migrates into the cytoplasm maturing, for example, by the splicing of non-coding sequences.
  - **Translation** occurs when the ribosome binds to mRNA at the start codon and transfer RNA brings amino acids into position along the mRNA template.
  - Ribosomal RNA interacts with transfer RNA during translation by providing peptidyl transferase activity.The ribosome moves from codon to codon along the mRNA producing a polypeptide sequence.
  - Transfer RNA (tRNA) binds to messenger RNA (mRNA) codons **by the specific area called (anticodons)** during translation of protein synthesis. ((mRNA) → has acodon & (tRNA) → has anticodon)
- Each type of RNA consists of nucleotides, which are made up of phosphate, ribose sugar and nitrogen bases.
- **RNA polymerase is the enzyme which is responsible for synthesing RNA molecules**.
- A purine always pairs with a pyrimidine (adenine with thymine; guanine with cytosine).
- DNA is much more stable than RNA. This property is exploited in forensic pathology
- The bases in RNA and DNA differ. RNA contains uracil in place of thymidine; they are structurally similar. **In RNA ribose is hydroxylated at the 2' and 3' positions**; in DNA only at the 3' position (hence 'deoxyribonucleic').

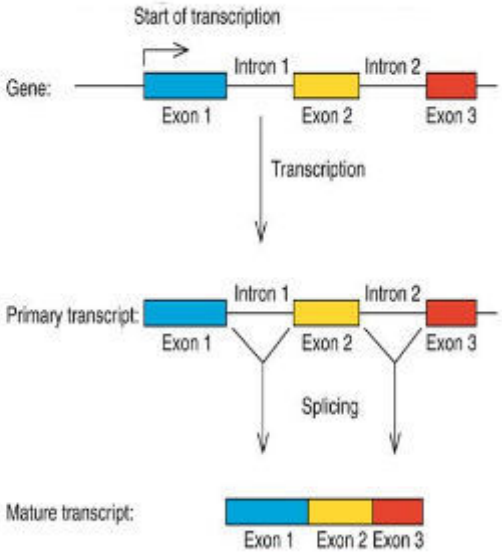
Other notes about protein synthesis

- **codon** is a three-base sequence (three nitrogen bases in a row) **on mRNA**. It calls for a specific amino acid to be brought to the growing polypeptide.
- **anticodon is a three-base sequence on Transfer RNA (tRNA) .**
  - mRNA has codons which are bound by the anticodons on tRNA during translation of protein synthesis.



- **RNA splicing**

- Process of cutting introns out of immature RNAs and stitching together the exons to form final **product is RNA splicing**
- **Introns are transcribed along with exons in the primary transcript**
- **Introns are removed as the exons are spliced together**



Removal of the introns in RNA transcript modification is called RNA splicing. **Splicing occurs in the nucleus** before transport to the cytoplasm.

- **Telomere**
  - **telomere** is a DNA sequence at the end of each chromosome which becomes progressively shorter with each division the cell undergoes.
  - When it is reduced to a critical length the cell is not capable of dividing.
  - The enzyme telomerase is able to lengthen the telomere thus preventing this occurring.
  - **The level of cellular telomerase activity will affect → The number of cell divisions**
- **Exons** are coding sequences in the mRNA
- **introns** are areas of unknown function.
- **Transposons** are genetic sequences that have been transposed from one part of DNA to another.
- **Cyclins** are key regulators of the cell cycle; **different cyclins are expressed at different stages of the cell cycle**.

- **Restriction enzymes → cut DNA** at sequences specific for each restriction enzyme.
  - They are vital tools for molecular biology and molecular genetic research.

Apoptosis

- Apoptosis is a physiological process of programmed cell death (in contrast to necrosis which is pathological).
- A key event in the initiation of apoptosis is the activation of a cascade of cysteine-aspartate specific proteases known as caspases**. (Apoptosis is induced by Activation of caspases)**
- **A mediator of this process is p53 a tumour suppressor gene** that inhibits mitosis and promotes apoptosis
- BCL-2 is an inhibitor of apoptosis.
- Fas is a cell receptor and caspases are present in all cells; both promote apoptosis but are not tumour suppressor genes.

Notes & Notes

For MRCP part 1 & 11

By

Dr. Yousif Abdallah Hamad

Basic sciences

Biochemistry & metabolism

Updated

2017

Contains:

1/ Passmedicine 2017

2/ On examination 2017

3/ Pastest 2017

4/ **Red fonts --> previous exams**

5/ Other updated UK sources

Anion gap (AG)

Renal tubular acidosis causes a normal anion gap

- The anion gap allows for the differentiation of 2 groups of metabolic acidosis.
  1. **Metabolic acidosis with a high AG** is associated with the **addition of** endogenously or exogenously **generated acids**.
  2. **Metabolic acidosis with a normal AG** is associated with the **loss of HCO_3 or the failure to excrete H^+ from the body.**
- The anion gap is calculated by: (sodium + potassium) - (bicarbonate + chloride)
- A normal anion gap is **8-14 mmol/L**
- It is useful to consider in patients with a metabolic acidosis:
  - **Causes of a normal anion gap or hyperchloraemic metabolic acidosis**
    - gastrointestinal bicarbonate loss: diarrhoea, uretero-sigmoidostomy, fistula
    - **renal tubular acidosis**
    - **drugs: e.g. acetazolamide**
    - ammonium chloride injection
    - Addison's disease
  - **Causes of a raised anion gap metabolic acidosis**
    - lactate: shock, hypoxia
    - ketones: diabetic ketoacidosis, alcohol
    - urate: renal failure
    - acid poisoning: salicylates, methanol

mnemonic of high anion gap acidosis:
- DR. MAPLES: D-DKA; R-renal; M-methanol; A-alcoholic ketoacidosis; P-paraldehyde, phenformin; L-lactic (ie, CO, HCN); E-ethylene glycol; S-salicylates

Remember the mnemonic MUDPILES → high anion gap acidosis

M	Methanol
U	Uremia
D	Diabetic ketoacidosis
P	Paraldehyde
I	Infection
L	Lactic acidosis
E	Ethylene glycol
S	Salicylates

Metabolic acidosis associated with bladder reconstruction (e.g: for carcinoma of the bladder).

- Hyperchloraemic metabolic acidosis is a documented complication of neobladder formation. However, it usually improves with time and is mild.
- Severe and persistent metabolic acidosis may manifest when patients undergo further surgery for other reasons, as is the case in this patient.
- Neobladder formation following radical cystectomy or cystoprostatectomy is becoming increasingly more common, and medical staff treating patients with neobladders should recognise and **treat metabolic acidosis with intravenous fluids and bicarbonate**.

Metabolic alkalosis

Overview

- Metabolic alkalosis may be caused by a **loss of hydrogen ions** or a **gain of bicarbonate**.
- It is due mainly to problems of the **kidney** or **gastrointestinal tract**
- The initial disturbance of metabolic alkalosis is an increased HCO_3^- concentration, followed by a compensatory response of increased Pco_2.
- Hypoventilation is an immediate compensatory response to metabolic alkalosis.
- All renal tubular defects result in metabolic alkalosis, except for Fanconi syndrome.

Causes

- vomiting / aspiration (e.g. peptic ulcer leading to pyloric stenos, nasogastric suction)
- **diuretics**
- liquorice, carbenoxolone
- hypokalaemia
- Bulimia nervosa
- primary **hyperaldosteronism**
  - Liddle syndrome
  - Con syndrome
- Cushing's syndrome
- Bartter's syndrome
- Gitelman syndrome
- congenital adrenal hyperplasia

Mechanism of metabolic alkalosis

- **the main mechanisms of metabolic alkalosis in the setting of vomiting are increased H+ excretion in the distal tubule and increased bicarbonate reabsorption in the proximal tubule.**
- activation of renin-angiotensin II-aldosterone (RAA) system is a key factor
- ECF depletion (vomiting, diuretics) → Na^+ and Cl- loss → activation of RAA system → raised aldosterone levels → reabsorption of Na^+ in exchange for H+ in the distal convoluted tubule
- in hypokalaemia, K^+ shift from cells → ECF, alkalosis is caused by shift of H+ into cells to maintain neutrality

A patient with liver cirrhosis develops metabolic alkalosis. What **is the most likely pathological mechanism?** → **Reduced urea synthesis**

A patient in the intensive care unit following liver transplant surgery has a metabolic alkalosis.

What is the most likely cause?

➔ **Diuretic-induced volume depletion**

- Cirrhosis → hypoalbuminaemia → low colloid osmotic pressure → Relative volume depletion → ↑aldosterone, (which is not adequately metabolised by an impaired liver).
- **Furosemide use in the post-operative period further exacerbates alkalosis driven by hyperaldosteronism .**

Prognosis

- plasma pH of 8.0 is incompatible with life
- when the pH is greater than 7.65 → mortality rate is 80%

Treatment

- Acetazolamide is a diuretic used to alkalinize the urine or treat metabolic alkalosis as it inhibits carbonic anhydrase.

Buffering agents in plasma

- Buffers are substances or solutions that accept a proton or hydroxyl group with very little change in overall pH.
- Blood buffers include:
    1. bicarbonate,
    2. **haemoglobin**
        - Haemoglobin is a protein and has imidazole side chains which can buffer H+ ions.
        - Along with bicarbonate, it is one of the most important buffering agents in plasma.
        - Haemoglobin is a much more effective buffer in its deoxygenated form; this contributes to the Haldane effect where carbon dioxide is offloaded more easily at the lungs (when haemoglobin is oxygenated) but is easily picked up and transported from the tissues when haemoglobin has been deoxygenated.
        - Deoxyhaemoglobin is a much more effective buffer than oxyhaemoglobin which accounts for some proportion of the Haldane effect (the effect of oxygen on haemoglobin, reducing its ability to transport carbon dioxide).
    3. protein.
    4. phosphate
        - Technically is also a serum buffer but so little of it is present in the plasma that it has no significant contribution to the body's acid-base balance mechanisms.

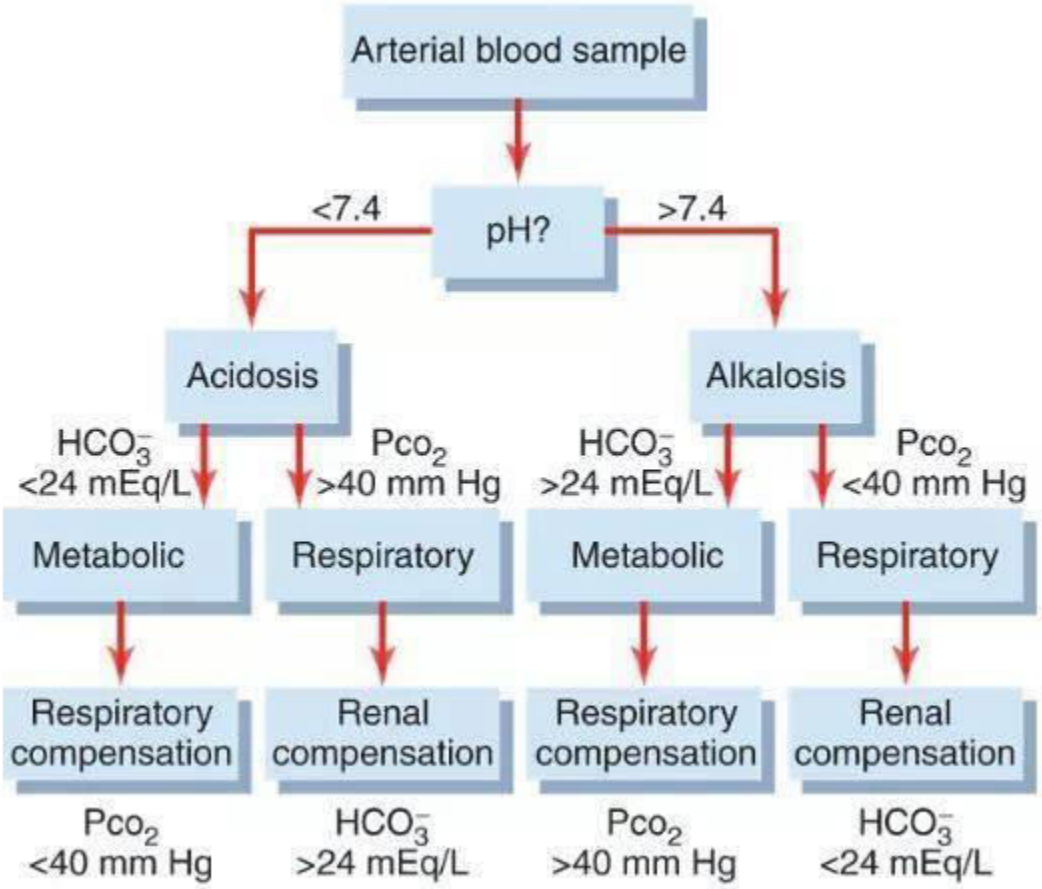
Arterial blood gas interpretation

The Resuscitation Council (UK) advocate a 5 step approach to arterial blood gas interpretation.

1. How is the patient?

2. Is the patient hypoxaemic?
   - the $Pa0_2$ on air should be >10 kPa
3. Is the patient acidaemic (pH <7.35) or alkalaemic (pH >7.45)

4. Respiratory component: What has happened to the $PaCO_2$?
   - $PaCO_2$ > 6.0 kPa suggests a respiratory acidosis (or respiratory compensation for a metabolic alkalosis)
   - $PaCO_2$ < 4.7 kPa suggests a respiratory alkalosis (or respiratory compensation for a metabolic acidosis)
5. Metabolic component: What is the bicarbonate level/base excess?
   - bicarbonate < 22 mmol/l (or a base excess < - 2mmol/l) suggests a metabolic acidosis (or renal compensation for a respiratory alkalosis)
   - bicarbonate > 26 mmol/l (or a base excess > + 2mmol/l) suggests a metabolic alkalosis (or renal compensation for a respiratory acidosis)



Calcium metabolism see endocrinology
Hypercalcaemia see endocrinology
Hypocalcaemia see endocrinology
Vitamin D see endocrinology

Hyperkalaemia

- Plasma potassium levels are regulated by a number of factors including:
  - Aldosterone
  - acid-base balance
  - insulin levels.
- Metabolic acidosis is associated with hyperkalaemia as hydrogen and potassium ions compete with each other for exchange with sodium ions across cell membranes and in the distal tubule.

Causes of hyperkalaemia:

- acute renal failure
  - Chronic kidney disease alone generally will not cause hyperkalemia until the eGFR is less than 20-25 mL/min.
- **drugs*:** Can be due to:
  - Potassium being shifted out of cells, for example:
    - β-blockers
      - *beta-blockers interfere with potassium transport into cells and can potentially cause hyperkalaemia in renal failure patients - remember beta-agonists, e.g. Salbutamol, are sometimes used as emergency treatment
    - acidosis
  - Reduced renal excretion, for example:
    - potassium sparing diuretics : spironolactone,
    - angiotensin converting enzyme (ACE) inhibitors
    - angiotensin 2 receptor blockers
    - ciclosporin
    - lithium
    - heparin**

    **both unfractionated and low-molecular weight heparin can cause hyperkalaemia. This is thought to be caused by inhibition of aldosterone secretion →↓↓renal potassium excretion, particularly in patients with diabetes or those who are acidotic
  - Other causes, for example:
    - fluoride
    - digoxin
- metabolic acidosis
- Addison's
- rhabdomyolysis
- massive blood transfusion

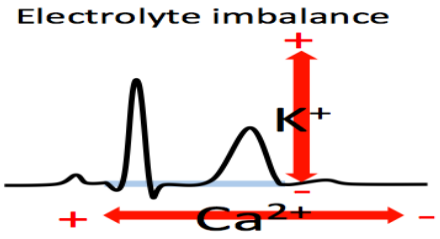
Foods that are high in potassium:

- salt substitutes (i.e. Contain potassium rather than sodium)

- bananas, oranges, kiwi fruit, avocado, spinach, tomatoes

Features

- Weakness and fatigue are the most common complaints
- May be asymptomatic
- Cardiac: Palpitations, Chest pain, Dyspnea
- Neuromuscular: Frank muscle paralysis, Depressed or absent deep tendon reflexes, Paresthesias
- Nausea or vomiting
- ECG changes seen in hyperkalaemia include:
  - **Early changes** (typically seen at a serum potassium level of 5.5-6.5 mEq/L)
    - tall, peaked **T** waves
    - shortened Q**T** interval
    - S**T**-segment depression.
  - At a serum potassium level of 6.5-8.0 mEq/L, in addition to peaked T waves:
    - Decreased or disappearing **P** wave
    - Prolonged **PR** interval
    - Widening of the QRS
    - Amplified **R** wave



Treatments

Immediate treatment principles include:

1. Providing calcium salts to reduce the risk of arrhythmia (‘**protect the heart’**);
2. Administering intravenous glucose and insulin (‘**shift potassium into cells’**);
3. Reducing intake and increasing output of potassium (‘**remove potassium from the body’**).

Untreated hyperkalaemia may cause life-threatening arrhythmias.

- Precipitating factors should be addressed (e.g. acute renal failure) and aggravating drugs stopped (e.g. ACE inhibitors).
- **Mild chronic hyperkalaemia (eg: 5.6 mmol/l) is well tolerated and not a cause for concern.** If serum potassium rise to >6.0 mmol/l, standard practice would be to stop the ACEi and - if K >6.0 mmol/l were to persist - to advise a low potassium diet.
- Management may be categorised by the aims of treatment**:**
  - **Stabilisation of the cardiac membrane**
    - intravenous 10 ml 10% calcium gluconate (or calcium chloride)

- The effects of intravenous calcium occur within 1 to 3 minutes but last for only 30 to 60 minutes.

➢ **Short-term shift in potassium from extracellular to intracellular fluid compartment**
- combined insulin/dextrose infusion
  - ❖ the most effective agent
  - ❖ In hyperglycaemic patients (serum glucose >15 mmol/L) insulin may be given without additional intravenous glucose
  - ❖ The dose: **10 units of soluble insulin**
- nebulised salbutamol
  - ❖ salbutamol is not recommended as monotherapy for hyperkalaemia but is a useful adjunct to intravenous insulin and glucose.
  - ❖ ineffective in up to 40% of patients with end-stage renal disease.
  - ❖ Patients prescribed beta blockers may be 'resistant' to the hypokalaemic effects of salbutamol.
- **Sodium bicarbonate** has little use in the routine treatment of hyperkalemia unless severe metabolic acidosis is present.
  - ❖ Sodium bicarbonate → ↑ blood pH → H+ shift out of the cell to buffer the alkalinizing units. In exchange, K will move from the blood into the cell.

➢ **Removal of potassium from the body**
- calcium resonium (orally or enema)
- loop diuretics
- dialysis

May 2012 exam: H/O muscle weakness and lethargy. K+ = 6.3 mmol/l. What is the most appropriate initial treatment to lower the serum potassium level? Insulin/dextrose infusion

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Pseudohyperkalaemia

High cell counts and high potassium: consider pseudohyperkalaemia

- Pseudohyperkalaemia is a rise in serum potassium that occurs due to excessive leakage of potassium from cells, during or after blood is taken.
- It is a laboratory artefact and does not represent the true serum potassium concentration.
- The majority of potassium is intracellular and thus leakage from cells can significantly impact serum levels.

Causes include:
- haemolysis during venepuncture (excessive vacuum of blood drawing or too fine a needle gauge)
- delay in the processing of the blood specimen
- abnormally high numbers of platelets, leukocytes, or erythrocytes (such as myeloproliferative disorders)
  - ➢ **essential thrombocytosis**
- familial causes

Management
- **Re-check a fresh sample at the hospital**

- Measuring an arterial blood gas will give a quick and accurate measure of true serum potassium.
- For obtaining a lab sample, using a lithium heparin tube, requesting a slow spin (on the lab centrifuge) and walking the sample to the lab should ensure an accurate result.

Hypokalaemia and acid-base balance

Hypokalaemia - U waves on ECG

- Potassium and hydrogen can be thought of as competitors.
- Hyperkalaemia tends to be associated with acidosis because as potassium levels rise fewer hydrogen ions can enter the cells

Causes

Hypokalaemia with alkalosis

- Vomiting
- Diuretics
- Cushing's syndrome
- Conn's syndrome (primary hyperaldosteronism)

Hypokalaemia with acidosis

- Diarrhoea
- Renal tubular acidosis
- Acetazolamide
- Partially treated diabetic ketoacidosis

Drug induced hypokalaemia

- Intracellular shifts of potassium with normal total body potassium, for example:
  - theophylline
  - β-agonists
  - caffeine
  - insulin
- Loss of potassium stores, for example:
  - chronic diuretic use

Magnesium deficiency may also cause hypokalaemia. In such cases, **normalizing the potassium level may be difficult until the magnesium deficiency has been corrected**

Features

symptoms associated with hypokalaemia of less than 3.0 mmol/L include:

- Tiredness
- General weakness
- Muscle pain, and
- Constipation.

ECG changes: When potassium falls below 3 mmol/l, the ECG often demonstrates:

- Flattening of the T waves
- **ST depression**
- QT prolongation, and
- Prominent U waves.

Treatment

- if K>2.5 with no symptoms or ECG changes → oral potassium
- if K<2.5 with symptoms or ECG changes → IV potassium
- **in life-threatening cases → 1L IV 0.9% NaCL with 40 mmol/l KCl infused over four hours**
  - Cardiac monitoring.
  - Potassium should be given in NaCl.
  - Concentration should not exceed 40 mmol/l
  - No more than 10-20 mmol/hour should be given.

Daily maintenance requirements

amounts prescribed for patients on maintenance fluids (NICE guidelines):

- Water → 1500-2500 ml/ day
  - 25-30 ml/kg/day
- Potassium, Sodium and Chloride → **1 mmol/kg/day**
  - **Sodium → 70 mmol**
  - **potassium → (40-80 mmol/day)** In the absence of kidney disease or hyperkalaemia (around 1 mmol/kg per day)

Estimation of total body potassium loss:

- **a drop in 1 mmol/L K^+ of serum potassium in approximately equivalent to a 200 mmol K^+ total body loss.**

Hypernatraemia

Causes

- excess of hypertonic fluids (IV saline, enteral or parenteral nutrition);
- excessive free water loss:
  - renal (**diabetes insipidus**, diuretics, osmotic diuresis as with hyperglycaemia),
  - GI (diarrhoea, vomiting),
  - skin (sweating, burns)
- reduced thirst - seen in very old and very young patients.
- dehydration

Treatment

- Treatment is aimed at the underlying cause.
- Hypernatraemia should be corrected with great caution.
- Although brain tissue can lose sodium and potassium rapidly, lowering of other osmolytes (and importantly water) occurs at a slower rate, predisposing to cerebral oedema, resulting in seizures, coma and death.
- acute hypernatraemia can be corrected quickly but if chronic (>24hours) then it should be corrected at <0.5mmol/L/hr.
- Fluid resuscitation should involve oral water, 0.45% saline or 5% dextrose IV.

Free water deficit in litres = (**Serum sodium -**140)/ 140) **x total body water**

Hyponatraemia

- Hyponatraemia may be caused by water excess or sodium depletion.
- Causes of pseudohyponatraemia include hyperlipidaemia (increase in serum volume) or a taking blood from a drip arm.
- Urinary sodium and osmolarity levels aid making a diagnosis.

Cause of hyponatraemia

Urinary sodium > 20 mmol/l		**Urinary sodium < 20 mmol/l**	
Sodium depletion, renal loss (patient often **hypovolaemic**)	Patient often **euvolaemic**	Sodium depletion, extra-renal loss (**hypovolaemic**)	Water excess (patient often **hypervolaemic** and oedematous)
• diuretics • Addison's • diuretic stage of renal failure	• SIADH (urine osmolality > 500 mmol/kg) • hypothyroidism	• diarrhoea, vomiting, sweating • burns, adenoma of rectum	• secondary hyperaldosteronism : heart failure, cirrhosis • reduced GFR: renal failure • IV dextrose, psychogenic polydipsia

Nice guidelines 2013➔

- Additional monitoring of urinary sodium may be helpful in patients with high-volume gastrointestinal losses.
- (Reduced urinary sodium excretion [less than 30 mmol/l] may indicate total body sodium depletion even if plasma sodium levels are normal.
- Urinary sodium may also indicate the cause of hyponatraemia, and guide the achievement of a negative sodium balance in patients with oedema.
  However, urinary sodium values may be misleading in the presence of renal impairment or diuretic therapy.)

Features

- Fatigue
- Muscle weakness
- Gait disturbance
- Falls
- Disorientation
- Cerebral oedema

- Seizures
- And death if untreated.

Management

- It is important with hyponatraemia to ascertain volume status as this will determine management.
- The management of each is as follows:

  - **Hypovolaemic hyponatraemia**
    - **Diagnosis may supported by an elevated urea suggesting dehydration.**
    - **rehydration with sodium chloride 0.9%** or a balanced crystalloid (Hartmann's)
    - avoid rapid correction of sodium in order to reduce the risk of osmotic complications such as central pontine myelinolysis
  - **Euvolaemic hyponatraemia**
    - check urine and serum osmolality. Does the patient meet the criteria for SIADH?
    - treat the underlying cause where possible in SIADH
    - fluid restriction (500-750mls/day)
    - monitor fluid balance and perform daily weights
    - consider demeclocycline or tolvaptan (under specialist supervision). Both inhibit the action of antidiuretic hormone.
  - **Hypervolaemic hyponatraemia**
    - fluid and salt restriction
    - consider diuretics
    - treat the underlying cause (e.g. cardiac failure)

Hyponatraemia: correction

Acute hyponatraemia is that which occurs within a duration of 48 hours.

Acute hyponatraemia

- predisposing factors to acute hyponatraemia:
  - Over consumption of fluids,
  - prolonged race duration and inadequate training
- Pathophysiology
  - When hyponatraemia develops over a short duration the ability of the brain to adapt is exceeded and cerebral oedema can result which may lead to confusion, seizures and coma. As a result patients may die from brain herniation.
- Treatment
  - The correct treatment to give is hypertonic saline.
  - Decompressive craniotomy would help alleviate raised intracranial pressure due to cerebral oedema however is not an appropriate first line treatment.

- A small, quick increase in the serum sodium is required in order to decrease intracranial pressure. **Hypertonic saline (3%) boluses are the most appropriate treatment to improve neurological status in such patients.**

Central pontine demyelinolysis

- demyelination syndrome caused by rapid correction of **chronic hyponatraemia**
- Pathological changes are not confined to the pons (despite the name of the condition).
- In 10%, demyelination also occurs in extrapontine regions, including the mid brain, thalamus, basal nuclei, and cerebellum.
- Occur more frequently in females than in males.
- **Risk factors** for central pontine myelinolysis
  - alcoholism,
  - liver disease,
  - malnutrition, and
  - hyponatremia.
- Risk factors for central pontine myelinolysis in the hyponatremic patient:
  - Serum sodium of less than 120 mEq/L for more than 48 hours
  - Aggressive IV fluid therapy with hypertonic saline solutions
  - Development of hypernatremia during treatment
- **Features**
  - Consciousness is usually impaired.
  - quadriparesis and bulbar palsy
    - The most consistent examination findings are those of **pseudobulbar palsy** and **spastic quadriplegia** caused by demyelination of corticospinal and corticobulbar tracts within the pons.
  - Delirium is extremely common.
  - Lesions within the pons cause **horizontal gaze paralysis**.
  - locked-in syndrome
    - includes paralysis of lower cranial nerves and limb musculature.
    - Vertical eye movements, blinking, breathing, and alertness may remain intact in these patients.
- **Diagnosis**: MRI brain
  - MRI is the imaging modality of choice
  - (MRI) usually shows changes within the pons, however the appearances are not diagnostic.
  - Typically, T2-weighted MRI images demonstrate hyperintense or bright areas where demyelination has occurred and has been caused by relatively increased water content in those regions.
- **Treatment**
  - Treatment is supportive only.
  - Avoid hypernatremia
    - Many authorities recommend that increases in serum sodium of **<12 mmol/24 hours** are likely to be safe for the majority of patients.

- Certain patients with hypokalaemia, liver disease, poor nutritional state or burns are at higher risk of demyelination and should have a rate of sodium correction of **<8 mmol/24 hours.**

Which fluid should be used to resuscitate a patient with diuretic-induced hyponatraemia and dehydration?

➔ **Hartmann's solution**

"Saline depletion, for example due to excessive diuretic exposure, is best managed with a balanced electrolyte solution such as Hartmann's."

Fluid resuscitation in other clinical situations:

- Losses from diarrhoea/ileostomy/small bowel fistula/ileus/obstruction should be replaced volume for volume with Hartmann's or Ringer's lactate/acetate type solutions.
- Excessive losses from gastric aspiration/vomiting should be treated pre-operatively with an appropriate crystalloid solution which includes an appropriate potassium supplement.
- Hypochloraemia is an indication for the use of 0.9% saline, with appropriate additions of potassium and care not to produce sodium overload.

Osmolar gap

- **Osmolar gap is the difference between the calculated osmolarity and the measured osmolality**.
- The normal value is 10-15 but may be increased in the presence of unmeasured 'abnormal' osmotically active ions in the plasma.
- An elevated osmolar gap provides indirect evidence for the presence of an abnormal solute that may be present in significant amounts.
- To have much effect on the osmolar gap, this substance needs to have a low molecular weight and be uncharged so it can be present in a form and in a concentration (measured in mmol/l) sufficient to elevate the osmolar gap.
- Ethanol, ethylene glycol (anti-freeze), acetone and methanol are solutes that will cause elevation of the osmolar gap in this way.
- Osmolarity is the measure of solute concentration, defined as the number of osmoles (Osm) of solute per litre (l) of solution (Osmol/l).
- **Calculated osmolarity = 2 (Na + K) + Glucose + Urea (all in mmol/L).**
- Normal serum osmolarity is 285-295 mOsm/L.
- Osmolarity can be affected by temperature and pressure and for a given solution, this calculated variable is less than the osmolality.
- **Osmolality** is also a measure of solute concentration but is defined as the number of osmoles (Osm) of solute per kilogram (Osm/Kg).The value is independent of temperature and pressure. **It is measured in the laboratory using an osmometer**. Osmometers use the colligative properties of a solution such as depression of freezing point or vapour pressure.

Magnesium (Mg):

- 99% of total body magnesium is intracellular or bone-deposited, with only 1% present in the extracellular space.
- Normal plasma magnesium → (0.7-0.9 mmol)
- magnesium homeostasis: The main controlling factors in magnesium homeostasis → GIT absorption and renal excretion.
  - Renal absorption
    - Unlike most ions, the majority of magnesium is not reabsorbed in the proximal convoluted tubule (PCT). **the thick ascending limb (TAL) of the loop of Henle is the major site of reabsorption (60-70%).**
    - **In the TAL, magnesium is passively reabsorbed** with calcium through paracellular tight junctions
    - Claudins are the major components of tight-junction strands in the TAL, where the reabsorption of magnesium occurs
    - In the distal convoluted tubule (DCT), magnesium is reabsorbed via an active, transcellular process that is thought to involve **TRPM6**
      - The TRPM6 channel is embedded in the membrane of epithelial cells of large intestine, distal convoluted tubules, lungs, and testes.

Hypomagnesaemia

- Low magnesium → (below 0.7 mmol/L)

Uses for magnesium include:

- polymorphic ventricular tachycardia (torsade de pointes),
- acute asthma
- prevention/treatment of seizures in pre-eclampsia.
- **Magnesium salts can be given as laxatives**

Causes of low magnesium

- Inadequate intake:
  - Malnutrition, and
  - Alcohol dependence.
    - hypomagnesemia is the most common electrolyte abnormality observed in alcoholic patients
  - **total parenteral nutrition**
- Malabsorption:
  - Inflammatory bowel disease
  - Long term PPI therapy
  - Gluten enteropathy

  - Intestinal bypass, and
  - Radiation enteritis.
- Renal tubular disease:
  - Hyperaldosteronism
  - Hyperparathyroidism
  - Obstructive uropathy
  - Potassium depletion, and
  - Drugs (including diuretics, amphotericin, cisplatin, ciclosporin, amikacin, gentamicin, laxatives, and tacrolimus).
- Intracellular shift:
  - Post myocardial infarction
  - Post parathyroidectomy
  - Recovery from diabetic ketoacidosis (K+ and PO_4- also enter cells)
  - Refeeding syndrome (PO_4- also enters cells),
  - Acute pancreatitis.

- **Drugs:**
  - **cisplatin,**
  - **diuretics,**
  - **cyclosporine**
  - **cardiac glycosides**
  - **Colorectal cancer treatment with cetuximab/panitumumab (EGF receptor inhibitors) → ↓ TRPM6 → hypomagnesemia.**
  - **Omeprazole** → **hypomagnesaemia** → hypoparathyroidism → hypocalcaemia.
    - The reasons for this are unclear, but it may be due to reduced uptake of Mg^{2+} ions in the gut.
      - Omeprazole reduces acid production and raises stomach pH.
      - An acid environment can aid release of metal ions from their binding sites in food molecules which facilitate absorption.
- diarrhoea
- Metabolic acidosis
  - Chronic metabolic acidosis → ↓renal TRPM6 expression in the DCT → ↓ Mg reabsorption →↓ serum Mg.
- **Hypercalcaemia**
  - Hypercalcemia → activation of **calcium-sensing receptor (CaSR)** → ↓ Mg reabsorption
- hypokalaemia, hypocalcaemia
- **Genetic diseases**
  - **Hypomagnesemia with secondary hypocalcemia (HSH):**
    - autosomal recessive
    - caused by mutations in the TRPM6 gene → ↓↓ intestinal magnesium reabsorption→ ↓↓ serum magnesium → ↓↓ (PTH) → ↓↓ serum calcium levels (hypocalcemia).

- manifests in early infancy with generalized convulsions refractory to anticonvulsant treatment or with other symptoms of increased neuromuscular excitability, such as muscle spasms or tetany.
- Laboratory evaluation reveals extremely low serum magnesium and serum calcium levels.

➢ **familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC)**
- Mutations in the **claudin-16 and claudin-19** genes
- characterized by:
  - ❖ excessive renal magnesium and calcium wasting,
  - ❖ polyuria,
  - ❖ recurrent urinary tract infections,
  - ❖ bilateral nephrocalcinosis,
  - ❖ progressive renal failure.

➢ autosomal-dominant hypocalcemia with hypercalciuria (ADHH),
- due to activating mutations of the CaSR
  - ❖ **(CaSR),** is a G-protein–coupled receptors.
  - ❖ The CaSR is expressed in TAL.
- characterized by hypocalcemia, hypercalciuria, and hypomagnesemia and by low, but detectable, levels of PTH.

Features

- **General**
  - ➢ **lack of appetite.**
  - ➢ **Lethargy**
  - ➢ **fatigue**
- **neuromuscular hyper-excitability**
  - ➢ **muscle weakness including fasciculations**
  - ➢ **changes in personality**
  - ➢ **paraesthesia**
  - ➢ **tetany**
  - ➢ **seizures**
- cardiac
- **arrhythmias**
- **ECG features similar to those of hypokalaemia**
- The ECG change most typically associated with hypomagnesaemia is QT prolongation.
- **exacerbates digoxin toxicity**
- **decreased PTH secretion → hypocalcaemia**
- **Hypokalemia (in 40-60%)**

- **Associations with hypomagnesemia**
  - ➢ hypoparathyroidism
    - ↓ Mg →↓ magnesium-dependent adenyl cyclase generation of cyclic adenosine monophosphate (cAMP) → ↓PTH → hypoparathyroidism
  - ➢ DM (↓ Mg →↓ insulin sensitivity and secretion)
  - ➢ Cardiac:
    - CAD
    - Hypertension (Mg plays a role in BP regulation).
    - cardiac arrhythmia
      - ❖ prolongation of the QT interval
      - ❖ Torsade de pointes

Investigation

- blood magnesium levels can guide but do not accurately reflect total body magnesium status. Attempts to find a marker of cellular magnesium status include measuring erythrocyte or monocyte Mg but these are not generally available.
- Urine Mg excretion is a useful guide. When there is inadequate intake or malabsorption, the kidneys would normally conserve Mg, giving urine Mg concentrations <7 mmol/24 hours. The reference range is around 2-7 mmol/24 hours.

Treatment

- <0.4 mmol/l
  - intravenous replacement is commonly given. An example regime would be 40 mmol of magnesium sulphate over 24 hours
- >0.4 mmol/l
  - oral magnesium salts (10-20 mmol orally per day)
  - diarrhoea can occur with oral magnesium salts

Hypermagnesaemia

- Hypermagnesaemia is much less common than hypomagnesaemia and is often iatrogenic in cause.

Causes of hypermagnesaemia:

- **Iatrogenic**:
  - Treatment with magnesium sulphate to prevent/treat seizures in patients with eclampsia or pre-eclampsia
  - Treatment with Mg containing antacids
  - Use of citrate-glucuronic acid solutions to dissolve renal calculi either through bladder irrigation or via a nephrostomy tube
  - Over-zealous IV treatment of hypomagnesaemia
  - Chronic use of Mg-containing enemas.
- **Other causes:**
  - **Acute or chronic renal failure**
    - release of Mg from tissues,
    - Mg in dialysate,
    - Mg in phosphate binding drugs
  - Familial hypocalciuric hypercalcaemia.

Lithium can cause hypermagnesaemia

Interpretation of serum Mg results:

- 0.7-1.5 mmol/L: reference range
- 1.5-2.5 mmol/L: mild hypermagnesaemia - symptoms uncommon
- 2.5-5.0 mmol/L: moderate hypermagnesaemia - symptoms develop including hypotension, prolonged PR and QRS intervals on ECG, arreflexia
- >5.0 mmol/L: severe hypermagnesaemia - at risk of respiratory paralysis through inhibition of acetylcholine release and cardiac arrest.

Features

- Signs of hypermagnesaemia include:
  - Nausea
  - Vasodilatation, and
  - Hypotension (myocardial depression + vasodilatation).
- In severe cases it can also include:
  - Double vision
  - Drowsiness
  - Loss of deep tendon reflexes
  - Respiratory depression
  - Bradycardia
  - Coma, and
  - Cardiac arrest.

Treatment:

- if mild/moderate and iatrogenic, often it is enough to identify and stop the cause.
- In an emergency, dialysis or administration of IV calcium glucuronate (10 ml of 10%) will reduce the effects of hypermagnesaemia.

Hypophosphataemia

Definition

- serum phosphate level of less than 2.5 mg/dL (0.8 mmol/L).

Causes	Consequences
• alcohol excess • acute liver failure • diabetic ketoacidosis • refeeding syndrome • **primary hyperparathyroidism** • **osteomalacia** • **Hyperventilation**	• red blood cell haemolysis • white blood cell and platelet dysfunction • muscle weakness and rhabdomyolysis • central nervous system dysfunction

Mechanisms

- The three major mechanisms of hypophosphataemia are:
  1. Redistribution of extracellular phosphate into cells
     - **hyperventilation** → respiratory alkalosis → activating phosphofructokinase → moves phosphate into cells → stimulates intracellular glycolysis.
     - Glycolysis leads to phosphate consumption as phosphorylated glucose precursors are produced.
     - Any cause of hyperventilation (eg, sepsis, **anxiety**, **pain**, heatstroke, alcohol withdrawal, diabetic ketoacidosis [**DKA**], hepatic encephalopathy, salicylate

toxicity, neuroleptic malignant syndrome [NMS]) can precipitate hypophosphatemia.

2. Decreased intestinal absorption,
   - chronic diarrhea,
   - malabsorption syndromes,
   - severe vomiting,
   - nasogastric (NG) tube suctioning.
3. Depletion due to increased urinary loss.
   - the most common cause of hypophosphatemia
     - primary and secondary hyperparathyroidism.
     - Osmotic diuresis, such as seen in hyperosmolar hyperglycemic syndrome (HHS)
     - Fanconi syndrome (proximal tubule dysfunction)
     - X linked hypophosphataemic rickets
     - Oncogenic hypophosphataemic osteomalacia

Sep 2017 part 1: **what is the mechanism of Hypophosphataemia during treatment of DKA?**

➔ **Shift from extracellular to intracellular space**

Sep 2017 part 1: **what is the mechanism of Hypophosphataemia in alcoholic patients after hospital admission ?**

➔ **Shift from extracellular to intracellular space**

- The alcoholic patient often has chronic phosphate depletion, and, after admission to the hospital, is prone to severe hypophosphatemia resulting from redistribution of extracellular phosphate into the cells.
- Two factors may contribute to this shift:
  1. I.V therapy with dextrose-containing solutions or refeeding → ↑Glucose → ↑ insulin release → ↑ phosphate uptake by the cells
  2. alcohol withdrawal → hyperventilation →acute respiratory alkalosis →intracellular alkalosis → stimulates intracellular phosphofructokinase →↑ glycolysis → movement of phosphate into cells

Ref: uptodate.com 2017

Hyperphosphataemia

- The healthy adult usually ingests about **8400 mg per week of phosphate through their diet**
- Absorption occurs mainly in the jejunum
- Renal absorption
  - The **majority** (70%) of filtered phosphate is reabsorbed by **type 2a sodium phosphate cotransporters** located on the apical membrane of the renal **proximal tubule**.

        - expression of these cotransporters is increased by:
            - low dietary phosphate intake
            - several growth factors to enhance phosphate absorption.
        - expression is decreased by:
            - high dietary phosphate intake,
            - parathyroid hormone (PTH),
            - FGF23, and
            - dopamine.
        - Impaired expression or function of these transporters is associated with nephrolithiasis.
    - absorption in the **remainder of the nephron** is generally mediated by **type 3** sodium phosphate cotransporters.
- The normal adult range for phosphorus is 2.5-4.5 mg/dL (0.81-1.45 mmol/L).
    - Levels are 50% higher in infants and 30% higher in children, because of growth hormone effects.
- **Renal excretion**
    - **About 5400 mg of phosphate is excreted per week through the kidneys.**

Mechanisms

- increased phosphate intake,
- decreased phosphate excretion,
- disorder that shifts intracellular phosphate to extracellular space.
    - Tumor lysis
    - Rhabdomyolysis

Foods that are characteristically rich in phosphate include:

- **dairy products, (Cheddar cheese)**
- fibre rich foods,
- chocolate, and
- processed meats.

Causes

- usually iatrogenic
- rhabdomyolysis
- ↓calcium + ↑ phosphate levels seen in:
    - renal failure,
    - hypoparathyroidism, and pseudohypoparathyroidism
- ↑calcium + ↑phosphate seen in:
    - vitamin D intoxication (↓PTH + ↑ vitamin D)
    - milk-alkali syndrome (↓PTH + ↓vitamin D)
- Laxative (Phospho-soda) abuse

Features

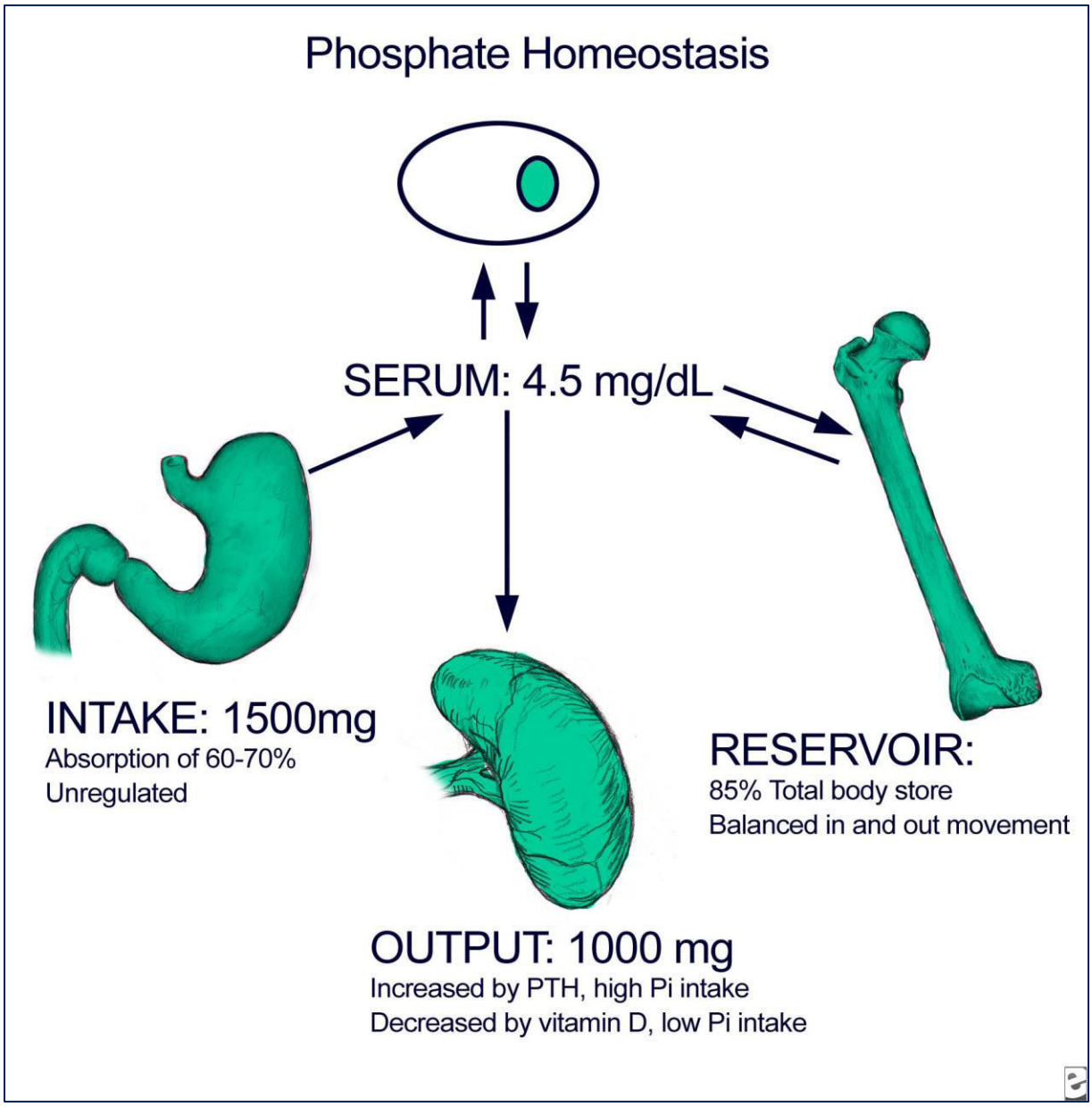
- most are asymptomatic
- hypocalcemic symptoms, such as muscle cramps, tetany, and perioral numbness or tingling.
- Other symptoms include bone and joint pain, pruritus, and rash.
- heart block
- soft tissue calcification

Investigations

- 24-hour measurement of urinary phosphate
  - Fractional renal excretion > 15%: → Suggests:
    - massive phosphate ingestion (eg, laxative [Phospho-soda] abuse) or
    - lysis of tissue and resulting release of intracellular phosphate
- Fractional renal excretion > 15%: Suggests that renal excretion is impaired because of:
  - renal failure or
  - hypoparathyroidism

Management

- Phosphate level is important to control in patients with chronic renal failure.
- Decrease dietary phosphorous
- Aluminum hydroxide
- Hydration and acetazolamide
- Dialysis


Phosphate Homeostasis
SERUM: 4.5 mg/dL
INTAKE: 1500mg
Absorption of 60-70%
Unregulated
RESERVOIR:
85% Total body store
Balanced in and out movement
OUTPUT: 1000 mg
Increased by PTH, high Pi intake
Decreased by vitamin D, low Pi intake

Collagen synthesis

- Collagen synthesis starts with the synthesis of preprocollagen, which is the same process as translation of alpha chains. This process occurs in the rough endoplasmic reticulum.
- Hydroxylation of proline and lysine residues is the second step of collagen synthesis. It also occurs in the rough endoplasmic reticulum, and this process is impaired in Vitamin C deficiency leading to scurvy.
- Glycosylation of pro-alpha-chain hydroxylysine residues and formation of procollagen, via hydrogen and disulfide bonds, yielding a triple helix. Problems in this step of collagen I synthesis leads to *osteogenesis imperfecta*.
- **The final step of collagen synthesis occurs extracellular and includes the cross-linking** of lysine-hydroxylysine residues in collagen by lysyl oxidase. This creates collagen fibrils and is impaired in diseases like Ehlers-Danlos syndrome or Menkes disease.

Collagen Types

Type I

- strongest tensile form of collagen
- majority of collagen in the body (approx. 90%)
- found in bone, fascia, tendons, teeth (dentin), cornea, skin
- type III of early wound repair converted to type I in late wound repair
- defective in osteogenesis imperfecta (OI) type I
- defective in various forms of Ehlers-Danlos syndrome

Type II

- spongy collagen to absorb shock
- found in cartilage (including hyaline), vitreous body of the eye, nucleus pulposus of vertebral disc

Type III

- web-like fibers
- found in skin, blood vessels, uterus, fetal tissue
- granulation tissue
- type III of early wound repair converted to type I in late wound repair
- defective in Ehlers-Danlos type IV
  - associated with joint dislocation, berry aneurysms, organ rupture

Type IV

- basement membrane, especially kidney, ears, eyes, skin
- defective in Alport's syndrome
  - kidney → progressive hereditary nephritis
  - ears → deafness
  - eyes → ocular disturbances
- one of the causes of epidermolysis bullosa
  - weak union of dermis and epidermis of the skin
  - easily formed blisters
- Goodpasture's syndrome involves an auto-antibody against collagen type IV in pulmonary and glomerular capillaries
  - presents with hemoptysis and glomerular disease

Vitamin B3 (Niacin) deficiency

Basics

- Niacin is present in two forms - nicotinamide and its precursor molecule, nicotinic acid.

Causes

- poor diets (diets low in tryptophan or niacin) or malabsorption
  - niacin is present in a wide range of plant and animal foodstuffs. However, sometimes the form of the vitamin is not readily absorbable in humans - such as occurs in maize.
  - Deficiency can occur in places where maize constitutes the main dietary carbohydrate. (corn staple diets)
- more common in alcoholics.
- **Diseases affecting the availability of tryptophan (Niacin is manufactured via metabolism of tryptophan)**
  - **Hartnup disease**
    - autosomal recessive →↓ tryptophan absorption in kidneys and small intestine → Niacin deficiency
      - ↑ tryptophan in urine.
    - also known as "pellagra-like dermatosis"
    - treatment
      - high-protein diet
      - protection from sunlight
      - avoid other aggravating factors, such as photosensitizing drugs,
  - **carcinoid tumor**.
    - Tryptophan is used by carcinoid tumours to produce 5-hydroxytryptamine.
    - As the carcinoid tumour mass increases→ more and more of the available tryptophan is consumed, and less is available for niacin production.
- isoniazid therapy
  - isoniazid inhibits the conversion of tryptophan to niacin
  - ↓ vitamin B6 leading to ↓ niacin synthesis

Presentation

- glossitis
- severe deficiency leads to pellagra

Atrophic glossitis

- the tongue is pink or red
- appears glossy and smooth due to the atrophy of papillae.
- can be painful.

Pellagra

The classical features are the 3 D's - Dermatitis, Diarrhoea and Dementia

Causes

- Pellagra is a caused by **nicotinic acid (niacin) deficiency**.

Features

- Initially non-specific features such as nausea, fatigue, reduced appetite, gastrointestinal disturbance
- Dermatitis
  - bilateral, symmetric and typically on sun-exposed areas (neck, arms).
  - progresses to hyperpigmented, dry, rough skin.
  - brown scaly rash on sun-exposed sites - termed Casal's necklace if around neck
  - **aggravated by exposure to sunlight** (photosensitivity dermatitis)
- diarrhoea
- dementia, depression
- death if not treated

Vitamin C (ascorbic acid) (scurvy)

- Vitamin C is a water soluble vitamin.
- Dehydroascorbic acid, the oxidative product of ascorbic acid metabolism, passively penetrates cellular membranes and is the preferred form for erythrocytes and leukocytes.

Functions

- Antioxidant (Ascorbic acid provides electrons needed to reduce molecular oxygen. These anti-oxidant capabilities also **stabilize vitamin E and folic acid.**)
- It is a cofactor for reduction of folate to dihydro-and-tetrahydrofolate.
  - Therefore **macrocytic anaemia** in scurvy may occur due to two reasons:
    - oxidative hemolysis and
    - **folate metabolism defects.**
- collagen synthesis: acts as a cofactor for enzymes that are required for the hydroxylation proline and lysine in the synthesis of collagen
  - Vitamin C deficiency (scurvy) leads to defective synthesis of collagen resulting in capillary fragility (bleeding tendency) and poor wound healing
- **facilitates iron absorption**
- cofactor for norepinephrine synthesis
- cofactor for reduction of folate to dihydro-and-tetrahydrofolate.

Causes

- occurs in people with poor dietary intake, who eat little or no fruit and vegetables, commonly alcoholics and elderly people existing on a ‘tea and toast’ diet.
- Pregnancy, lactation and thyrotoxicosis increase ascorbic acid requirements and may precipitated scurvy.

Features vitamin C deficiency

- gingivitis, loose teeth
- **poor wound healing**

- bleeding from gums, haematuria, epistaxis
- general malaise
- anaemia
  - **macrocytic anaemia in scurvy may occur due to two reasons: oxidative hemolysis and folate metabolism defects.**
  - normochromic, normocytic anaemia reflects bleeding into tissues

Continued deficiency leads to:

• Anaemia • Myalgia • Bone pain • Bruising • Petechial and perifollicular haemorrhages • Corkscrew hairs • Mood changes	• Fragility • scleral icterus (late, probably secondary to haemolysis), and • pale conjunctiva. • Fractures, dislocations and tenderness of bones are common in children. • Bleeding into muscles and joints may be seen

Late stages can lead to:

• Generalised oedema • Severe jaundice • Haemolysis • Haemorrhage	• Neuropathy • Convulsions, and • Death.

The classical skin manifestations of scurvy are:

- perifollicular hyperkeratotic papules
- perifollicular haemorrhages
- purpura, and
- ecchymoses.

Treatment

- vitamin C supplementation,
- recovery is usually complete within three months.

Vitamin B12 deficiency

- Vitamin B12 is mainly used in the body for red blood cell development and also maintenance of the nervous system.
- It is absorbed after **binding to intrinsic factor** (secreted from parietal cells in the stomach) and is actively **absorbed in the terminal ileum**.
- A small amount of vitamin B12 is passively absorbed without being bound to intrinsic factor.
  - Approximately 1 percent of a large oral dose of vitamin B_{12} is absorbed by this second mechanism. This pathway is important in relation to oral replacement.
- Once absorbed, vitamin B_{12} binds to **transcobalamin II** and is transported throughout the body.
- Exhaustion of vitamin B12 stores usually occurs after 12 to 15 years of absolute vitamin B12 deficiency.

Causes of vitamin B12 deficiency

- pernicious anaemia (the most common cause)

- post gastrectomy
- poor diet eg: vegetarians and vegans (sources of vitamin B12 are limited to animal foods)
- disorders of terminal ileum (site of absorption): Crohn's, blind-loop etc
- Atrophic gastritis (affect10%–30% of older adults) → ↓ HCL → ↓ absorption of vit B12.
  - ↓ HCL → ↑ growth of normal intestinal bacteria that use vitamin B12 → ↓ vit B12
  - They are unable to absorb the vitamin B12 that is naturally present in food. however, they can absorb the synthetic vitamin B12.
- **metformin** (rare)
  - Chronic metformin use results in vitamin B12 deficiency in 30% of patients.

Features of vitamin B12 deficiency

- macrocytic anaemia
- sore tongue and mouth
- neurological symptoms: e.g. Ataxia
  - include paresthesias, peripheral neuropathy, and demyelination of the corticospinal tract and dorsal columns (subacute combined systems disease).
  - The neurological symptoms can occur without anemia
- psychiatric disorders symptoms: including impaired memory, irritability, depression, dementia and, rarely, psychosis
- cardiovascular effect:
  - Similar to folic acid deficiency, vitamin B_{12} deficiency produces hyperhomocysteinemia, which is an independent risk factor for atherosclerotic disease.
  - Serum high concentrations of homocysteine and low levels of folic acid and vitamin B_{12} are significantly correlated with the categories of coronary artery diseases

investigations

- Serum cobalamin levels are the initial test
  - A normal serum cobalamin level does not exclude cobalamin deficiency.
- **Diagnosis of vitamin B_{12} deficiency is typically based on measurement of serum vitamin B_{12} levels; however, about 50 percent of patients with subclinical disease have normal B_{12} levels.**
- **A more sensitive method of screening for vitamin B_{12} deficiency is measurement of serum methylmalonic acid and homocysteine levels, which are increased early in vitamin B_{12}deficiency.**
  - **elevated methylmalonic acid level is more specific for vitamin B_{12} deficiency than an elevated homocysteine level.**
  - Vitamin B_{12} or folic acid deficiency can cause the homocysteine level to rise, so folic acid levels also should be checked in patients with isolated hyperhomocysteinemia.
  - two enzymatic reactions are known to be dependent on vitamin B_{12}.
    1. methylmalonic acid is converted to succinyl-CoA using vitamin B_{12} as a cofactor. Vitamin B_{12} deficiency, therefore, can lead to **increased levels of serum methylmalonic acid.**
    2. homocysteine is converted to methionine by using vitamin B_{12} and folic acid as cofactors. In this reaction, a deficiency of vitamin B_{12} or folic acid may lead to **increased homocysteine levels.**

Management

- if no neurological involvement 1 mg of IM hydroxocobalamin 3 times each week for 2 weeks, then once every 3 months
  - **oral vitamin B_{12} has been shown to have an efficacy equal to that of injections** in the treatment of pernicious anemia and other B_{12} deficiency states.
    - Although the daily requirement of vitamin B_{12} is approximately 2 mcg, the initial oral replacement dosage consists of a single daily dose of 1,000 to 2,000 mcg.
    - This high dose is required because of the variable absorption of oral vitamin B_{12} in doses of 500 mcg or less.
    - This regimen has been shown to be safe, cost-effective, and well tolerated by patients.
- if a patient is also deficient in folic acid then it is important to treat the B12 deficiency first to avoid precipitating subacute combined degeneration of the cord
  - Large amounts of **folic acid can mask the damaging effects of vitamin B12 deficiency** by correcting the megaloblastic anemia caused by vitamin B12 deficiency without correcting the neurological damage that also occurs

Schedule for Vitamin B_{12} Therapy

ROUTE OF ADMINISTRATION	*INITIAL DOSAGE*	*MAINTENANCE DOSAGE*
Oral	1,000 to 2,000 mcg per day for one to two weeks	1,000 mcg per day for life
Intramuscular	100 to 1,000 mcg every day or every other day for one to two weeks	100 to 1,000 mcg every one to three months

Sep 2017 part 1: **Which structure in the body are able to synthesize vitamin B12?**

➔ **gut bacteria**

- It is synthesized by gut bacteria in humans, but humans cannot absorb the B_{12} made in their guts, as it is made in the colon which is too far from the small intestine, where absorption of B_{12} occurs
- Therefore diet is the only source of vit B12.

Vitamin B1 (Thiamine) deficiency

- the biologically active form of this vitamin is **thiamine pyrophosphate** (TPP)
- **Thiamine function**
  - the most important biochemical reactions requiring the availability of thiamine includes
    - glycolysis and
    - tricarboxylic acid (TCA) cycle.
  - There are three enzymes that require the presence of thiamine pyrophosphate as a co-factor:
    1. a-ketoglutarate **dehydrogenase**,

2. branched chain amino acid **dehydrogenase**, and
3. pyruvate **dehydrogenase**.

- **Causes of thiamine deficiency**
  - chronic alcoholism due to inadequate dietary intake or impaired absorption
  - diet mainly composed of polished rice (non-enriched rice)
- **Diagnosis**
  - mainly by history
  - can be made by measuring **increased transketolase activity after thiamine administration**
    - mechanism
      - thiamine is a cofactor necessary for the function of transketolase
- **Complications**
  - **Wernicke's encephalopathy**
    - Wernicke's encephalopathy is a result of thiamine deficiency.
    - Most cases occur in those with a history of chronic alcohol ingestion however malnutrition of any cause is a risk factor.
    - The classic triad of features is
      1. Encephalopathy
      2. Ataxia and
      3. Oculomotor dysfunction ((usually nystagmus but also lateral rectus palsies or conjugate gaze palsies (ophthalmoplegia)).
  - **Korsakoff's psychosis**
    - Korsakoff's psychosis is a chronic condition resulting from untreated thiamine deficiency
    - characterised by:
      - both anterograde and retrograde amnesia with confabulation.
      - psychosis,
      - **mammillary body hemorrhage**
  - **Beriberi:** can be divided into
    - wet beriberi
      - high-output cardiac failure (**dilated cardiomyopathy**)
      - edema
    - dry beriberi
      - resulting in symmetrical **peripheral neuropathy due to demyelination**
      - symmetrical **muscle wasting**
      - no fluid retention

What happens if you do not give the thiamine first before starting an intravenous glucose infusion?

- ATP failing to be adequately generated,
- The inability of pyruvate to enter the TCA cycle causes the cell to convert the pyruvate to lactate (or lactic acid) in order to be able to maintain glycolysis.
  - **pyruvate is accumulating → ↑acidosis.**
    - The reason the cell converts pyruvate to lactate is to regenerate the NAD+ required for the process of glycolysis to continue and to generate a net balance of at least 2 ATP.
- **inability of the pentose phosphate pathway to protect the cell from reactive oxygen species** that damage cellular structures, results in either **cell death or activation of apoptosis**.

Vitamin function as a co-factors:

- → Biotin for carboxylase reactions.
- → **Thiamine for dehydrogenase reactions**
- → B9 (folate) for transferases.
- → Vit C for hydroxylases.

Vitamin E

- **Forms and Sources of Vit E:**
  1. γ-tocopherol:
     - the most common form.
     - found in corn oil, soybean oil, margarine, and dressings.
  2. α-tocopherol:
     - the most biologically active form of vitamin E,
     - the second-most common form of vitamin E in the diet.
     - found in wheat germ oil, sunflower, and safflower oils
     - The nutritional content of vitamin E is defined by α-tocopherol activity.
- consumption of more than 1,000 mg (1,500 IU) of tocopherols per day may cause hypervitaminosis E, → **interfere with vitamin K metabolism → vitamin K deficiency → increased tendency to bleed.**
- Function:
  - lipid-soluble antioxidant in the glutathione peroxidase pathway → removes the free radical intermediates → protects cell membranes from oxidation by reacting with lipid radicals produced in the lipid peroxidation chain reaction.

Vitamin K Deficiency

- Disruption of all vitamin K-dependent factors
  - II, VII, IX, X, protein C, protein S
- See *Vitamin* topic
- Deficiency most commonly seen in
  - newborns
    - **lack gut colonization by bacteria that produce vitamin K**
    - newborns are given IM vitamin K shot at birth for prophylaxis
  - malabsorptive conditions
  - long-term antibiotic therapy
    - kills gut bacteria that produce vitamin K
- Symptoms
  - bleeding
- Labs
  - ↑ PTT, PT
  - normal bleeding time
- Treatment
  - Administer vitamin K

Vitamin deficiency

The table below summarises vitamin deficiency states

Vitamin	Chemical name	Deficiency state
A	Retinoids	Night-blindness (nyctalopia). dry skin.
B1	Thiamine	Beriberi • polyneuropathy, Wernicke-Korsakoff syndrome • heart failure (dilated cardiomyopath)
B2	(riboflavin)	Angular stomatitis, cheilosis, corneal vascularization
B3	Niacin	Pellagra • dermatitis • diarrhoea • dementia
B6	Pyridoxine	Anaemia, irritability, seizures
B7	Biotin	Dermatitis, seborrhoea
B9	Folic acid	Megaloblastic anaemia, deficiency during pregnancy - neural tube defects
B12	Cyanocobalamin	Megaloblastic anaemia, peripheral neuropathy
C	Ascorbic acid	Scurvy • gingivitis • bleeding • **poor wound healing**
D	Ergocalciferol, cholecalciferol	Rickets, osteomalacia
E	Tocopherol, tocotrienol	↑ fragility of RBCs. Mild haemolytic anaemia in newborn infants, ataxia, peripheral neuropathy
K	Naphthoquinone	Haemorrhagic disease of the newborn, bleeding diathesis
Selenium	Selenium	Keshan disease (cardiomyopathy).

Vitamin A

- **Which substances in vitamin A is most likely to be maximally involved in correcting the visual disturbance?**
  - ➔ **Retinaldehyde**
    - Retinaldehyde is derived from the oxidation of retinol
    - light causes retinaldehyde to change to its trans isomer, and this leads to changes in membrane potentials that are transmitted to the brain
    - Retinol and retinoic acid are involved in the control of cell proliferation and differentiation
    - Retinyl phosphate is a cofactor in the synthesis of most glycoproteins containing mannose
- **What would you give the patient who taking long term steroids to help his wound heal faster?**
  - ➔ **Vitamin A**
    - Vitamin A is believed to counteract the effect of steroids on slowing wound healing by stimulating TGF-beta and IGF-I, as well as collagen production.
    - However, high levels (which can accumulate because vitamin A is fat soluble) can also be toxic and inhibit collagen synthesis, such as in the skin.

Other notes

- β-Carotene is the main carotenoid found in green vegetables, carrots and other yellow and red fruits
- Its conversion to retinol in humans is inefficient - 6 mg of beta-carotene is equivalent to 1 mg of preformed retinol

Zinc deficiency

Features

- **perioral dermatitis**: red, crusted lesions
- (rough and dry skin)
- acrodermatitis
- alopecia
- short stature (dwarfism)
- hypogonadism
- hepatosplenomegaly
- geophagia (ingesting clay/soil)
- cognitive impairment

Zn supplementation has been shown to improve neuropsychological function in Chinese children.

Zn deficiency is associated with adverse pregnancy outcomes.

Pyruvate kinase

- **Pyruvate kinase is the rate-limiting step in glycolysis** and gluconeogenesis
- It catalyses the transfer of a phosphate group from phosphoenolpyruvate to ADP, yielding a molecule of pyruvate and a molecule of ATP
- **Deficient pyruvate kinase activity may result in the development of hereditary haemolytic anaemias**

Which biochemical processes is likely to contribute most to energy creation in long distance running?
➔ **Fatty acid oxidation**

Daily requirement

- **daily intake** of **calories**
  - for a man → 10,500kJ **(2,500kcal) a day**.
  - for a woman → 8,400kJ (2,000kcal) a day.
  - These values can vary depending on age, metabolism and levels of physical activity, among other things.
- Normal daily **fluid and electrolyte** requirements (nice):
  - 25–30 ml/kg/d water
  - 1 mmol/kg/day sodium, potassium, chloride
  - 50–100 g/day glucose (e.g. glucose 5% contains 5 g/100ml).
- FDA state that → In general, Americans should limit daily sodium consumption to 2,300 milligrams, but this is an upper safe limit, not a recommended daily allowance. Even active people who lose lots of sodium through sweating require no more than 1,500 milligrams of sodium per day.

Essential amino acids
Humans can synthesise 11 of the basic set of 20 amino acids. The rest must be obtained from the diet: histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine are therefore known as 'essential' amino acids.

Carnitine

- Carnitine is a naturally occurring hydrophilic amino acid derivative,
- produced endogenously in the kidneys and liver and derived from meat and dairy products in the diet.
- Function
  - transfer of long-chain fatty acids into the mitochondria for beta-oxidation.
  - Carnitine binds acyl residues and helps in their elimination.
- **Carnitine deficiency** may be primary or secondary

- **Primary carnitine deficiency** is caused by a deficiency in the plasma membrane carnitine transporter, with urinary carnitine wasting causing systemic carnitine depletion.
- intracellular carnitine deficiency impairs the entry of long-chain fatty acids into the mitochondrial matrix. Consequently, long-chain fatty acids are not available for beta-oxidation and energy production, and the production of ketone bodies (which are used by the brain) is also impaired.
- The 3 areas of involvement include:
    1. the cardiac muscle, which is affected by progressive cardiomyopathy (by far, the most common form of presentation),
    2. the CNS, which is affected by encephalopathy caused by hypoketotic hypoglycemia,
    3. the skeletal muscle, which is affected by myopathy.

- **Feature**
    - hypoketotic hypoglycemic encephalopathy, accompanied by
    - hepatomegaly, elevated liver transaminases, and hyperammonemia.
    - Cardiomyopathy
    - Muscle weakness
- **secondary carnitine deficiency:** caused by:
    - other metabolic disorders (eg, fatty acid oxidation disorders, organic acidemias),
    - secondary to the formation of acylcarnitine adducts and the inhibition of carnitine transport in renal cells by acylcarnitines.
    - drugs associated with secondary carnitine deficiency (eg, valproate, pivampicillin, emetine, zidovudine).
        - **Valproic acid** →secondary carnitine deficiency by directly impairing renal tubular reabsorption of carnitine.
        - **Zidovudine** → ↓carnitine uptake in muscle → ↓muscle carnitine levels → Muscle mitochondrial impairment.

Carnitine deficiency will cause significant impairment of B-oxidation
why hypoglycemia? --> because B-oxidation provides energy for gluconeogenesis in the liver.
why hypoketosis? --> because the primary source of ketone bodies is acetyl CoA from B-oxidation.

- **Deferential diagnosis**
    - A good way to differentiate between Myophosphorylase deficiency (McArdle) and Carnitine deficiency, is by remembering that **in McArdle you have difficulty in the beginning of the exercise** while in **myopathic carnitine acyl transferase deficiency** you have a problem after a prolonged exercise.
    - The explanation for this is that glycogen is utilized first by muscles as a source of energy so in McArdle (Muslce glycogen phosphorylase deficiency) you have a problem in the beginning and patients will have muscle cramps after few seconds of starting the exercise. However once the beta oxidation kicks in they will experience the classical "second wind".
    - While in Muslce carnitine deficiency you have a problem later on when Fatty acids oxidation is needed.
    - Both conditions may have myoglobinuria

- In muscle carnitine you'll see accumulated triglycerides in biopsy while in McArdle (also called Type V glycogen storage disease) you will have accumulated glycogen in muscle biopsy.

Acid maltase deficiency

- typically presents with insidious onset of **proximal myopathy and early respiratory muscle weakness.**
- Respiratory failure in inflammatory myopathies (polymyositis, dermatomyositis, inclusion body myositis) and limb girdle muscular dystrophy are rare.
- Muscle biopsy shows vacuolation in muscle fibres.

Notes & Notes

For MRCP part 1 & 11

By

Dr. Yousif Abdallah Hamad

Basic sciences

Immunology

Updated

2017

Contains:

1/ Passmedicine 2017

2/ On examination 2017

3/ Pastest 2017

4/ **Red fonts --> previous exams**

5/ Other updated UK sources

human leukocyte antigen (HLA) associations

- The human leucocyte antigen (HLA) system is the name given to the major histocompatibility complex (MHC) in humans.
- HLA antigens are encoded for by genes on short arm of chromosome 6.
- HLA A, B and C are class I antigens whilst DP, DQ, DR are class II antigens.
- Class-I molecules (subtypes A, B and C) are expressed on all cell types **except erythrocytes and trophoblasts**
  - They interact with CD8-positive T-cells and are involved in driving cytotoxic reactions
- Class II matching is particularly important when it comes to transplant matching,
- Studies in renal transplantation indicate that mismatches at the A, B, and DR loci are associated with worse allograft survival.
- **when HLA matching for a renal transplant the relative importance of the HLA antigens are as follows DR > B > A**
- Anti-HLA antibodies are typically not naturally occurring, only occur post transplantation
- MHC class II is only expressed on immune cells. MHC I is expressed on any cell type.

The golden notes:

HLA (MHC):

- Found on chromosome 6
- 2 classes:
  - Class I → HLA A , B, C
    - expressed on all cells, except erythrocytes and trophoblasts
    - interact with CD8+
- class II → HLA DP, DQ, DR
  - expressed on B cells, dendritic cells, and monocytes
  - most important in transplant → (DR)

The most important HLA associations are listed below:

HLA type	Associated diseases
HLA-**A3**	Hemochromatosis
HLA-**B5**	Behcet's disease HLA B51 is a split of B5
HLA-**B47**	21-hydroxylase deficiency
HLA-CW6	Psoriasis
HLA-**DR3 + DR4** combined	Diabetes mellitus type 1(but more with HLA-DR4)
HLA-**DR7**	steroid-responsive nephrotic syndrome
HLA-**DR2**	Narcolepsy Goodpasture's hay fever, systemic lupus erythematosus, multiple sclerosis.
HLA-**DR4**	**Felty's syndrome (90%)** => most common Rheumatoid arthritis (70%) Diabetes mellitus type 1 (> DR3) **Drug-induced SLE** IgA nephropathy HOCM
HLA-**B27**	Ankylosing spondylitis Postgonococcal arthritis Reiter's syndrome (reactive arthritis) Acute anterior uveitis
HLA-**DR3**	Autoimmune hepatitis Primary biliary cirrhosis Coeliac disease (95% associated with HLA-DQ2) Diabetes mellitus type 1 Primary Sjögren syndrome Dermatitis herpetiformis

HLA-A3101

- **Toxic epidermal necrolysis and Stevens–Johnson syndrome** are associated with HLA-A3101 in patients of Japanese and European descent.
- In patients who develop **SJS on carbamazepine**, A3101 HLA type should be suspected.

HLA-B1502

- HLA-B1502 is strongly associated with the development of SJS in patients of Han Chinese and Thai ethnic origin.

Clusters of differentiation

Function and usage of CDs:

- Commonly used as cell markers in **immuno-phenotyping**, allowing cells to be defined based on what molecules are present on their surface.
- often acting as **receptors** or ligands (the molecule that activates a receptor)
- **cell signaling:** Errors in cellular information processing are responsible for diseases such as cancer, autoimmunity, and DM
- **Cell adhesion**: essential for the pathogenesis of infectious organisms. Eg:
  - *Plasmodium falciparum* uses adhesion molecules to bind to liver cells and RBCs.
  - Cancer metastases by mechanisms of cell adhesion.
  - Adhesion of bacteria is the first step in colonization and regulates **tropism** (tissue- or cell-specific interactions).
- **Pemphigus** is the result of auto-antibodies which target **desmosomal cadherins**, resulting in loss of cell adhesion.
- viruses also have adhesion molecules required for viral binding to host cells. For example:
  - influenza virus has a hemagglutinnin on its surface that is required for recognition of the sugar sialic acid on host cell surface molecules.
  - **HIV** has an **adhesion molecule termed gp120** that binds to **its ligand CD4**, which is expressed on lymphocyte.

Leukocyte adhesion deficiency-1 (LAD-1) is an example of genetic diseases caused by an inability to express a specific adhesion molecule (β2-integrin subunit precursor).This integrin is required for leukocytes to adhere to the blood vessel wall during inflammation in order to fight infection. The leukocytes from LAD-I patients fail to adhere and patients exhibit serious infections.

The table below lists the major clusters of differentiation (CD) molecules

Cluster of differentiation	Function
CD1	MHC molecule that presents lipid molecules
CD2	Found on thymocytes, T cells, and some natural killer cells that acts as a ligand for CD58 and CD59 and is involved in signal transduction and cell adhesion
CD3	The signalling component of the T cell receptor (TCR) complex
CD4	Found on helper T cells. Co-receptor for **MHC class II** **Used by HIV to enter T cells**
CD5	Found in the majority of mantle cell lymphomas
CD8	Found on cytotoxic T cells. **Co-receptor for MHC class I** Found on a subset of myeloid dendritic cells
CD14	Cell surface marker for macrophages
CD15	Expressed on Reed-Sternberg cells (along with CD30)
CD28	Interacts with B7 on antigen presenting cell as costimulation signal
CD95	Acts as the FAS receptor, involved in apoptosis

The number of **CD4** and **CD8** T cells in blood is often used to **monitor the progression of HIV** infection.

CD4:

- encoded by a gene on chromosome 12.
- They are helper cells → send signals to other immune cells, including CD8 killer cells, which then destroy the infectious particle.
- If CD4 cells become depleted, (eg: HIV, immunosuppressive) → ↑ vulnerable to infections
- .GP 41 , GP 120 fuses to CD4 receptor , this allow GP41 to penetrate the cell membrane **(GP41 is the HIV peptide which play a role in initial step for HIV entry to the cells) (Jan 2015 exam)**
- **CD4** uses its D_1 domain to interact with the β_2-domain of **MHC class II** molecules
- Normal values for CD4 cells being 500-1200 cells/mm^3
- The newest National Institute of Health guidelines recommend **treatment of any HIV-positive individuals, regardless of CD4 count.**
- PCP, disseminated fungal disease, and CMV infection almost always occur when the CD4 counts are very low, usually **below 200 cells/mm^3.**

- **CD4** continues to be expressed in most neoplasm derived from T-helper cells. It is therefore possible to use CD4 immunohistochemistry on tissue biopsy samples **to identify most forms of peripheral T cell lymphoma** and related malignant conditions. The antigen has also been associated with a number of autommune diseases such as vitiligo and type I diabetes mellitus

CD8:

- encoded by genes on chromosome 2
- **CD8** is specific for the **class I MHC** protein
- CD8+ T lymphocytes are otherwise known as cytotoxic T lymphocytes.
- The T cell receptor on the surface of the CD8+ T cell recognises virus peptides in the context of self **HLA class I** molecules on the surface of virus infected antigen presenting cells. The infected cell is then lysed.
- The CD8 co-receptor is predominantly expressed on the surface of cytotoxic T class cytotoxic T cells, but can also be found on natural killer cells, cortical thymocytes, and dendritic cells.

Which of the following HIV peptides is thought to play a role in the initial step for HIV entry into cells?

GP41

Gp120 fuses to the CD4 receptor, this then allows GP41 to penetrate the cell membrane.

The golden notes

Clusters of differentiation

- CD4 →
  - Found on helper T cells.
  - Co-receptor for MHC class II
  - Used by HIV to enter T cells
    - GP120 → fuses to CD4 → allow GP41 to penetrate the cell membrane
- CD 8 →
  - Found on cytotoxic T cells.
  - **Co-receptor for MHC class I**
  - Found on a subset of myeloid dendritic cells
- CD14 → Cell surface marker for macrophages
- CD18 → the absence of it causes Leukocyte adhesion deficiency

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Complement pathways

- Activation may occur via three pathways:
  1. **Classical pathway**:
     - Triggered by antigen-antibody complexes containing IgM or IgG.
     - **IgG** and **IgM** are the main antibody classes that activate the classical pathway

- C1 is the initiating protein, and after binding to an Fc is able to activate C4 and C2, which in turn activate multiple C3 molecules.
- C1q binds to the Fc (Fc, **c**rystallisable **F**ragment)
- **C2 is involved in activation via the classical pathway**

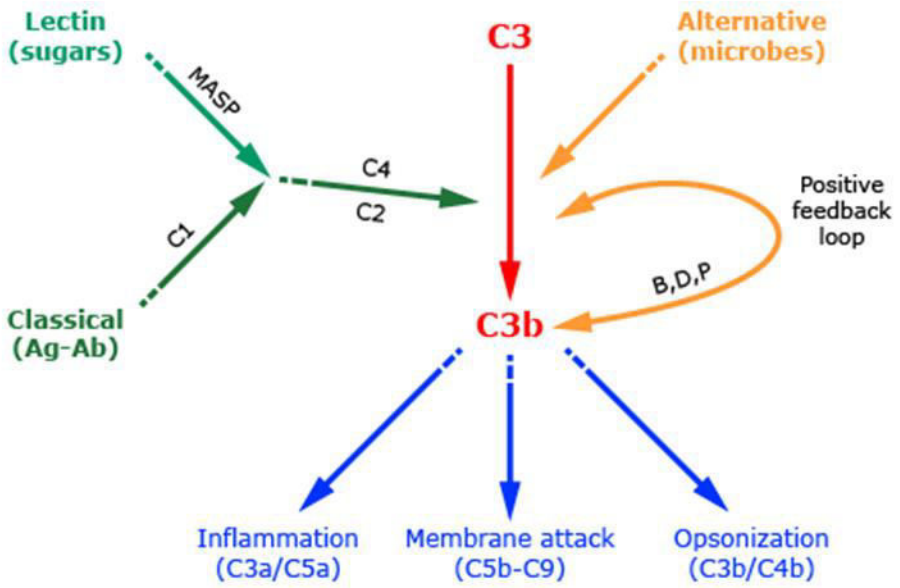
2. **Alternative pathway**:
   - Initiated by certain antigens (lipopolysaccharide, endotoxin) and IgA complexes on cell surfaces which activate C3.
   - **the alternative**, (not the classical) C3, convertase enzyme involves **C3b**
   - Generates early innate response that does not require antibody for activation.
3. **Lectin pathway** :**Mannose-binding lectin (MBL)** : lectin proteins bind to carbohydrates present on bacteria. This indirectly activates the next complement components. C2 and C4.

A child has recurrent pyogenic infection. What is the most likely diagnosis**?**

➔ Mannose binding lectin deficiency

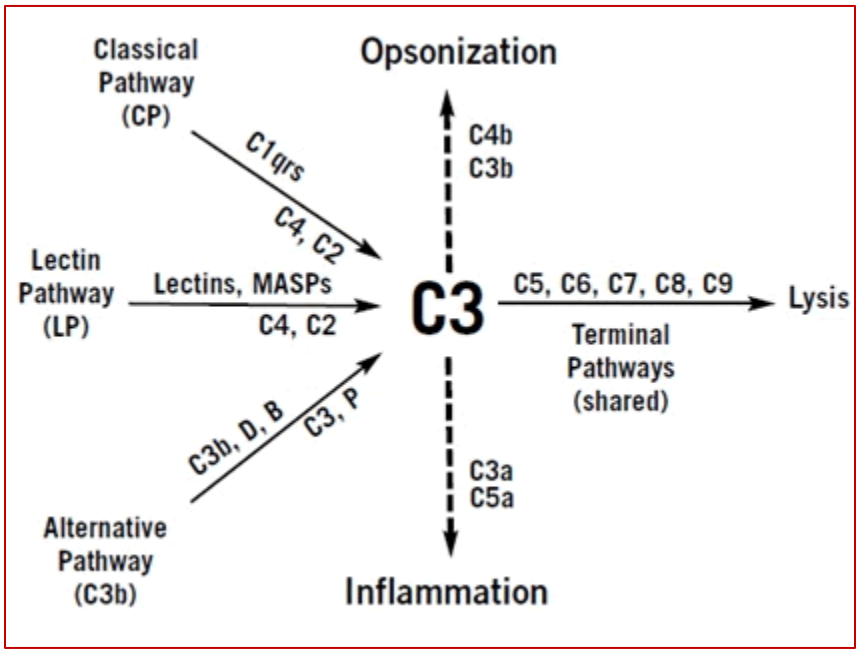
- **Mannose-binding lectin (MBL) (an acute phase protein secreted by the liver)**
- **MBL deficiency is thought to be the most common complement deficiencies**
- low MBL result from mutations in MBL2 gene (3 - 5 % of population. Heterozygosity in 30 % of population).
- deficiency of MBL is associated with:
  - ↑pyogenic infections, especially encapsulated bacteria, due to defective opsonization.
  - ↑severity of chronic inflammatory conditions.

Pathways of complement activation



The three pathways of complement activation are shown. Each leads to generation of activated C3b. The classical pathway is triggered by antibody interacting with antigen, and the lectin pathway by a lectin binding to a sugar. The alternative pathway turns over continuously. Activation of the complement system leads to inflammation (release of anaphylatoxins C3a and C5a), membrane perturbation and lysis (via the membrane attack complex, C5b-9), and opsonization (deposition of C3b and C4b).

MASP: mannose-binding lectin (MBL)-associated serine protease.



- All complement pathways have one final common pathway at C3.

Complement inhibitor

membrane bound complement inhibitor

- **CD59**
- complement receptor 1
- decay accelerating factor
- membrane cofactor protein.

soluble complement inhibitors

- factor H
- C4 binding protein
- C1 inhibitor
- factor I

Hypersensitivity

The Gell and Coombs classification divides hypersensitivity traditionally divides reactions into 4 types:

Type	Mechanism	Examples
Type I - Anaphylactic	Antigen reacts with **IgE** bound to mast cells (**IgE-mediated**)	• Anaphylaxis • Atopy (e.g. asthma, eczema and hayfever) **Diagnosed by plasma tryptase** (protease released from mast cell).
Type II - Cell bound	IgG or IgM binds to antigen on cell surface (**antibody-mediated**)	• Autoimmune haemolytic anaemia • ITP • Goodpasture's syndrome • Pernicious anaemia • Acute haemolytic transfusion reactions • Rheumatic fever • Pemphigus vulgaris / bullous pemphigoid
Type III - Immune complex	Free antigen and antibody (IgG, IgA) combine (**Immune complex deposition**)	• Serum sickness • Systemic lupus erythematosus • Post-streptococcal glomerulonephritis • Extrinsic allergic alveolitis (especially **acute phase**)
Type IV - Delayed hypersensitivity	T-cell mediated (**cell-mediated**)	• Tuberculosis / tuberculin skin reaction • Graft versus host disease • Allergic contact dermatitis • Scabies • Extrinsic allergic alveolitis (especially **chronic phase**) • Multiple sclerosis • Guillain-Barre syndrome

In recent times a further category has been added:

Type	Mechanism	Examples
Type V	Antibodies that recognise and bind to the cell surface receptors. This either stimulating them or blocking ligand binding	• **GraVes**' disease • Myasthenia **graVis**

What is the hallmark signs of mast cell degranulation?
➔ **Classical wheal and flare**

Anaphylaxis

Anaphylaxis = type I hypersensitivity reaction

Anaphylaxis - serum tryptase levels rise following an acute episode

- Anaphylaxis may be defined as a severe, life-threatening, generalised or systemic hypersensitivity reaction.
- caused by type I hypersensitivity.
- **Immunoglobulin E is the most common immunoglobulin involved in the pathogenesis of anaphylaxis.**
- mediated by histamine 1 receptor stimulation.
- antigen ➔production of IgE ➔ initiates events
- can be associated with leukotrienes B4, C4, D4 and E4
- (B4, C4, D4)are the mediators that make up the slow-reacting substance of anaphylaxis (SRSA)
- Usually takes 15-30 minutes from the time of exposure to the antigen.
- Flushing, warmth and tingling are typical initial symptoms
- At least 50% of fatalities are due to respiratory complications, and more than 20% of patients will have a second episode within 8 hours
- **Mediators involved in the development of anaphylaxis** include:
  - histamine, leukotrienes, prostaglandins and platelet aggregating factor, which are generated by mast cell degranulation.
  - Additional factors include:
    - Tryptase
    - Chondroitin sulphate
    - Chimase
    - **IL4**
    - Heparin
    - IL13.
  - IL4 and IL13 are thought to be important in driving the onward cascade of inflammation to other immune system cells and contribute to the severity of anaphylaxis.
  - Th2 CD4 positive lymphocytes are involved in the pathogenesis of anaphylaxis, via the production of IL-4/IL-13 that act on B cells to increase IgE production and precipitate the development of acute hypersensitivity.
  - **IL-4 also exacerbates anaphylaxis by acting synergistically with other vasoactive mediators to increase vascular permeability.**

Causes

Common identified causes of anaphylaxis.

Mast cell mediator release can be triggered by both IgE and non-IgE-mediated factors. Therefore, anaphylaxis may be termed anaphylaxis (IgE mediated) or anaphylactoid (non--IgE mediated).

1. **anaphylaxis (IgE mediated) :**
   - food (e.g. Nuts) - the most common cause in children
   - drugs
     - The most common IgE-mediated triggers are drugs, typically penicillin or other beta-lactam antibiotics.
     - Neuromuscular blocking agents (eg **vecuronium) are responsible for 60-70% of allergic reactions related to anaesthesia.** The antigen responsible is thought to be the quaternary ammonium group that is found in other drugs, foods, cosmetics and hair products
   - venom (e.g. Wasp sting)
2. **Anaphylactoid (non--IgE mediated).**
   - Anaphylactoid reactions are defined as those reactions that produce the same **clinical picture** as anaphylaxis **but are not IgE mediated**.'
   - Non-IgE-mediated causes include: plasma proteins or compounds, which act directly on the mast cell membrane, such as
     - vancomycin,
     - quinolone antibiotics,
     - aspirin or other non-steroidal anti-inflammatory drugs
     - opiates,
     - radiographic contrast media

Anaphylaxis following a blood transfusion can be due to immunoglobulin A deficiency.

anaphylaxis VS Anaphylactoid

Is it anaphylactic OR anaphylactoid reaction?

	Anaphylactic (IgE-mediated anaphylactic reactions)	Anaphylactoid (Non IgE-mediated anaphylactic reactions)
Is sensitization required?	Yes	**No**
Can reaction occur in first exposure?	**No**	Yes
How much exposure is needed to elicit reaction?	very little (dose independent)	usually more than for anaphylaxis
Is reaction predicted by skin allergy test?	Yes	**No**

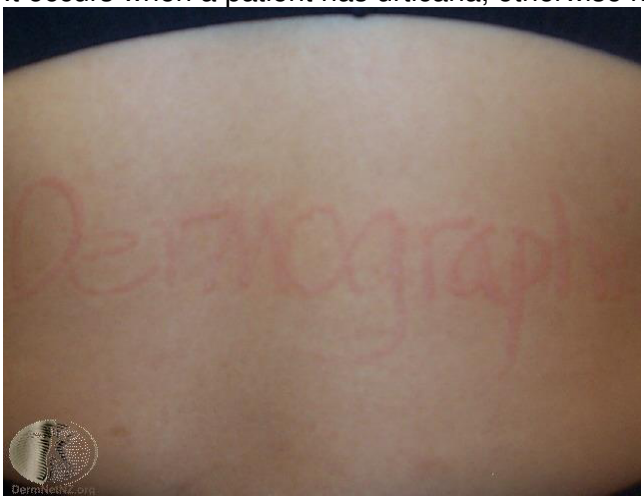
Triggers for anaphylactic reactions

- heat, cold,

- sexual activity.
- **Anaphylaxis may be exacerbated by exercise**

Features

- The most common presentation of anaphylaxis is due to involvement of the skin.
- **Dermatographism** is a physical examination sign that signifies a type I hypersensitivity
  - **When the examiner applies pressure to the skin of a patient and writes a word, it remains imprinted as erythematous wheals.**
  - It occurs when a patient has urticaria, otherwise known as hives.



Dermatographism

Investigations

- **Plasma tryptase activity is the most likely investigation to confirm the nature of the reaction**
  - Tryptase is a mast cell – specific protease
  - Elevated Tryptase imply mast cell degranulation
  - The greater the severity of anaphylaxis, the more likely that serum tryptase levels will be elevated.
  - Elevated serum **tryptase** levels demonstrate that **mast cell activation** with mediator release has occurred whether triggered by IgE-mediated anaphylaxis or non-IgE-mediated anaphylactoid reactions.
  - has a half-life of 2 h, peaking at 1 h after anaphylaxis onset and return to baseline by 6 hours.
  - Both sensitivity and specificity to confirm diagnosis is → 95%
  - Tryptase levels, may be **helpful in confirming the diagnosis** of anaphylaxis, **but does not elucidate the cause.**
  - **Normal tryptase results do not exclude anaphylaxis** and can be seen in serious reactions.
    - Typically the increase is less marked in non-allergic reactions (non-IgE mediated anaphylaxis).
- skin test
  - skin prick (SPT)
    - usually carried out 4–6 weeks after a reaction to allow replenishment of histamine in mast cell granules.

        - Antihistamine drugs must be stopped for 5 days though steroids may be continued.
        - A wheal of >3 mm in diameter than the negative control is considered positive and the presence of a flare or itching is also significant.
    - intradermal (IDT)
        - IDT is indicated if there is clinical suspicion but negative SPT.
        - A 4-mm bleb of diluted solution is injected under the skin and read after 15 min by measuring the wheal and flare.
        - IDT is considered positive if the bleb doubles or exceeds 8 mm.
        - IDT are more sensitive but less specific than SPT.
- Others
    - Total serum IgE level is **non-specific and unhelpful.**

Management

- **Adrenaline** is by far the most important drug in anaphylaxis and **should be given as soon as possible**. The recommended doses for adrenaline, hydrocortisone and chlorphenamine are as follows:

	Adrenaline	Hydrocortisone	Chlorphenamine
< 6 months	150 micrograms (0.15ml 1 in 1,000)	25 mg	250 micrograms/kg
6 months - 6 years	150 micrograms (0.15ml 1 in 1,000)	50 mg	2.5 mg
6-12 years	300 micrograms (0.3ml 1 in 1,000)	100 mg	5 mg
Adult and child > 12 years	500 micrograms (0.5ml 1 in 1,000)	200	10 g

    - Adrenaline can be repeated every 5 minutes if necessary.
    - The best site for IM injection is the anterolateral aspect of the middle third of the thigh.
- It is recommended to observe patients after resolution of an anaphylactic episode for 24 hours **for possible second-phase reactivation.**

Late-phase reaction

In IgE mediated reactions such as asthma or anaphylaxis what therapy inhibits the important late-phase reaction? steroids

- The late phase reaction is due to attraction of T cell, release of leukotrienes and prostaglandins often characterised by asthma
- prevented by the administration of steroids **(Hydrocortisone**).
- Approximately **30% of deaths related to anaphylaxis occur as a consequence of this late-phase reaction**

Exercised induced anaphylaxis

Definition

- a rare disorder in which anaphylaxis occurs after physical activity.

Features

- usually occur around 10 minutes after exercise and follow a sequence of pruritus, widespread urticaria and then subsequently respiratory distress and vascular collapse.

Pathophysiology

- may be related to endorphin release during exercise. The endorphin causes excessive histamine release from mast cells in susceptible individuals.

Associations

- Co-factors such as foods, alcohol, temperature, drugs (eg, aspirin and other nonsteroidal anti-inflammatory drugs), humidity, seasonal changes, and hormonal changes are important in the precipitation of attacks.
- most associated with wheat ingestion.
- The foods most commonly implicated in food-dependent exercise-induced anaphylaxis are wheat, shellfish, tomatoes, peanuts, and corn.
- The patients can usually eat the causative food without problems so long as they do not exercise afterwards.

Treatment

- managed in the same manner as anaphylaxis.
- usually resolves on stopping exercise
- Reducing physical activity to a lower level may diminish the frequency of attacks.
- Patients should be instructed on the proper use of emergency injectable epinephrine and have one available at all times.
- Patients should wear a medical alert bracelet with instructions on the use of epinephrine.

Anaphylactic Reactions Associated with Anaesthesia

- Neuromuscular blocking drugs and latex appear to cause anaphylaxis more commonly in female patients
- Individuals with a **history of atopy, asthma or allergy to some** foods appear to be at **increased risk of latex allergy** **but not anaphylaxis to neuromuscular blocking drugs or antibiotics**
- **Anaphylaxis associated with radiographic contrast media** appears to be associated with **atopy**
- Patients with **asthma** or taking **b-blocking drugs** may suffer a more severe reaction.
- **Neuromuscular blocking agents (NMBAs)**
  - **60% of cases of anaesthesia-related anaphylaxis are due to neuromuscular blocking agents**.
  - anaphylactic reactions to neuromuscular blocking agents (NMBAs) is more frequent
  - 80% of NMBA reactions occur without prior exposure
  - Quaternary ammonium ions (QAI) are proposed to be the allergenic epitopes in NMBAs.
  - Common environmental chemicals such as toothpastes, washing detergents, shampoos, and **cough medicines** share these allergenic epitopes with the NMBAs, predisposed individual to become sensitised to QAIs and thus be at **risk of developing anaphylaxis to NMBAs during anaesthesia.**
  - **succinylcholine** is the NMBA **most likely** to be associated with **allergic anaphylaxis**
    - Succinylcholine carries the highest risk because of its molecular shape and size.
  - Miv**acurium** and atr**acurium** are associated with non-allergic anaphylaxis

- If clinical suspicion has been raised, **all types of NMBAs should be tested** by SPT ± IDT because of **extensive cross-reactivity.**
- Future anaesthesia if allergic to one NMBA:
  - Rocuronium and vecuronium are contraindicated.
  - The negative intradermal testing to atracurium and succinylcholine does not guarantee their safety and therefore all relaxants must be avoided because of the incidence of cross-reactivity.
  - If future NMBA use is clinically **unavoidable**, then a **relaxant with negative SPT and IDT should be used**

- Latex hypersensitivity is the second most common cause of anaesthesiarelated anaphylaxis in many studies (up to 20% of cases). **But now decreased due to decline in the use of latex gloves.**
- Approximately 15% of anaesthesia-related anaphylactic episodes are due to **antibiotics**.
  - Skin testing is only approximately 60% predictive of clinical hypersensitivity. Penicillins and
  - cephalosporins which share the b-lactam ring are responsible for approximately 70% of antibiotic-induced anaphylaxis.
  - There is a higher rate of antibiotic allergy in smokers,
- Anaesthetic induction agents
  - Anaphylaxis to **propofol** is **very uncommon.**
  - Anaphylaxis to thiopental has become extremely uncommon, probably reflecting the decline in its use.
- Antiseptics and disinfectants
  - Reactions to **chlorhexidine** have come into greater prominence in recent years.
    - Anaphylaxis has occurred when chlorhexidine was used as an antiseptic for urological and gynaecological procedures as well as insertion of central venous and epidural catheters.
    - Allowing chlorhexidine to dry before beginning a procedure may reduce the risk of reaction.
  - Anaphylaxis to other antiseptics is rare.

Diagnosis

- Timings:
  - Type I reactions typically occur within seconds to minutes after i.v. exposure. An insidious or delayed onset may occur (e.g. with latex, antibiotics, and colloids[1]and a tourniquet may delay onset until after surgery).
  - History of atopy and asthma has a clear link with latex allergy.

Ref: Association of Anaesthetists of Great Britain and Ireland GUIDELINES 2009
https://www.aagbi.org/sites/default/files/anaphylaxis_2009_0.pdf

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Allergy

- **Birch-associated oral allergy syndrome**
  - occurs with stoned fruits, apples, carrots and potatoes
  - However, this only happens with the raw form as cooking denatures the allergen
  - The birch-tree pollen season is usually in April/May, giving the typical rhinitis symptoms
- **Latex allergy** can be associated with certain foods such as bananas, avocado, kiwi and melon, **but this allergen is heat-stable**
- Most apples contain a considerable amount of salicylate, which can induce urticaria in aspirin-sensitive individuals; however, this is not usually associated with pharyngeal itching
- **Allergic contact dermatitis** is caused by a type 4 delayed hypersensitivity reaction to a chemical in contact with the skin

- Initial sensitisation can occur 7-10 days after first contact with a potent allergen
- However, it is more usually a consequence of many months or years of exposure to small amounts of the allergen
- Once sensitised, contact with the allergen can produce dermatitis within 24-48 h, and all areas of the body are equally susceptible
- Urticaria is a common condition and usually responds very well to **systemic antihistamines which are the correct first line treatment.** Oral steroids can be given for severe cases but only as a last resort.
- Blood testing including allergy screening is not routinely recommended in the management of urticaria, which may occur as part of an allergic or non-allergic process.
- **Cetirizine may have greater pharmacodynamic effect in certain individuals than desloratidine.**

Allergy tests

Skin prick test	• **Most commonly used test as an easy to perform and inexpensive.** • **the first line for detection of allergen-specific IgE** • **Drops of diluted allergen are placed on the skin after which the skin is pierced using a needle.** • **A large number of allergens can be tested in one session.** • **Normally includes a histamine (positive) and sterile water (negative) control.** • **A wheal will typically develop if a patient has an allergy.** • **Can be interpreted after 15 minutes** • **Useful for food allergies and also pollen** • **It can induce anaphylaxis, and must therefore be done in an environment where resuscitation facilities are available.**
Radioallergosorbent test (RAST)	• Determines the amount of IgE that reacts specifically with suspected or known allergens, for example IgE to egg protein. • Results are given in grades from 0 (negative) to 6 (strongly positive) • Useful for food allergies, inhaled allergens (e.g. Pollen) and wasp/bee venom • Blood tests may be **used when skin prick tests are not suitable, for example if there is extensive eczema or if the patient is taking antihistamines**
Skin patch testing	• Useful for **contact dermatitis**. • Around 30-40 allergens are placed on the back. • Irritants may also be tested for. • The patches are **removed 48 hours later** with the results being read by a dermatologist after a further 48 hours

If a history of anaphylaxis is given it would not be appropriate to perform a skin prick test, thus Radioallergosorbent test (RAST) is the most appropriate first-line test to investigate the cause of the reaction

Reasons for a false negative RAST test:

- Immediately following anaphylaxis / allergic reaction (transient drop in IgE)

- Waning of allergen-specific IgE with time following a reaction.
- Unstable allergens in the RAST substrates (especially food allergens)

Latex allergy

- Nearly 1 in 5 anaphylactic reactions may be due to latex allergy, (more common than peanuts allergy)
- NHS trusts in the UK have moved away from the routine use of latex gloves precisely because of the risk of allergy. As a result, **latex allergy in hospital is now very rare in the UK.**
- **it is very unlikely that a latex allergy would explain an anaphylaxis during anaesthetic induction** (latex allergies typically used to commence when a surgeon began handling internal organs).
- Sensitivity to latex may cause a number of problems:
  - type I hypersensitivity (anaphylaxis)
  - type IV hypersensitivity (allergic contact dermatitis)
  - irritant contact dermatitis
- Latex allergy is more common in children with myelomeningocele spina bifida.
- Latex can induce allergy through IgE bound to mast cells
- Morphine, radiocontrast media and colloid plasma expanders induce histamine release via their direct effects on mast cells

Latex-fruit syndrome

- It is recognised that many people who are allergic to latex are also allergic to fruits, particularly **banana**, pineapple, avocado, chestnut, kiwi fruit, mango, passion fruit and strawberry. **However, bananas are the most commonly associated with latex/rubber allergy**

MRCPUK part-1-May 2016 exam: A nurse who is known to have an allergy to latex develops a widespread urticarial rash and facial oedema shortly after eating lunch. Which food is she most likely to have consumed? Banana

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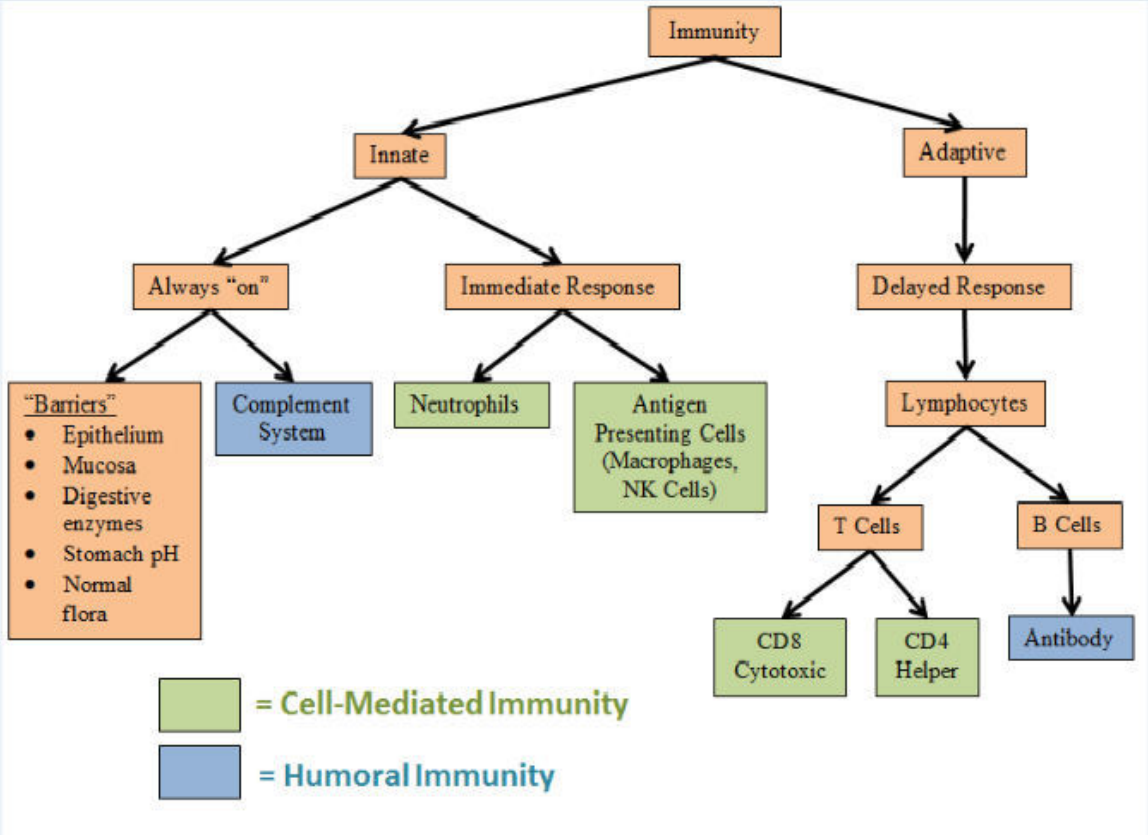
Peanut allergy

- The sensitivity of a negative **skin prick test** to foods is high: that is, for all nuts, skin prick tests miss only 0.5% of cases, whereas specific IgE will miss 22%
- Less than 20% of individuals will grow out of peanut allergy, but they are usually those in whom the reactions are mild and started under 1 year of age
- **The wheal size resulting from the skin prick test is an excellent predictor of a positive food challenge to peanuts**
- **Which feature is the most important predictor of anaphylaxis in asthmatic patient with peanut allergy?**
  - ⇨ **Poorly controlled asthma**
    - Poorly controlled asthma is an important risk factor for fatal anaphylaxis in this situation.
    - Patients such as this should have their asthma well controlled and have ready access to, and knowledge of how to use, self-injectable adrenaline.

Serum Sickness

- an example of immune complex mediated hypersensitivity.
- **Drugs are the most common cause**.
- Classical features are rash, fever, and polyarthralgias or polyarthritis, which **begin one to two weeks after first exposure** to the responsible agent.
- Symptoms resolve quickly upon discontinuation of the offending agent and prognosis is excellent.
- Treatment is symptomatic. Short courses of steroids are used for severe arthritis.

Immune system



Immune system cells: innate immune response

The following cells are mostly involved in the innate immune response:

Cell type	Functions and properties
Neutrophil	Primary phagocytic cell in acute inflammation Granules contain **myeloperoxidase** and **lysozyme** Most common type of white blood cell Multi-lobed nucleus
Basophil	Releases histamine during allergic response Granules contain **histamine** and **heparin** Expresses IgE receptors on the cell surface Bi-lobed nucleus
Mast cell	Present in tissues and are similar in function to basophils but derived from different cell lines Granules contain histamine and heparin Expresses IgE receptors on the cell surface
Eosinophil	Defends against protozoan and helminthic infections Bi-lobed nucleus
Monocyte	Differentiates into macrophages Kidney shaped nucleus
Macrophage	Involved in phagocytosis of cellular debris and pathogens Acts as an antigen presenting cell Major source of IL-1
Natural killer cell	Induce apoptosis in virally infected and tumour cells
Dendritic cell	Acts as an **antigen presenting cell**, but have no cytotoxic potential.

Which cell type is the most important antigen-presenting cell during sensitisation?

- **Dendritic cells**
  - dendritic cells is a key antigen-presenting cell.
  - After uptake of antigen, it migrates from the site of antigen uptake to the regional draining lymph node, where it presents processed antigen to T cells, stimulating either proliferation of established memory cells or differentiation of naive T cells reactive to the antigen presented.

Innate (non-specific system)	*Adaptive (acquired system)*
Components 1. Anatomical and physiological barriers 2. Inflammatory response with leakage of antibacterial serum proteins (acute-phase proteins) and phagocytic cells 3. Phagocytosis by neutrophils and macrophages 4. Complement system	**Components** 1. Cell-mediated response effected by T cells 2. Humeral immune response effected by B cells
Properties 1. Rapid: responds within minutes to infection 2. No antigenic specificity, i.e. the same molecules and cells respond to range of pathogens 3. No memory, i.e. the response does not change after repeated exposure exposure 4. Preformed or rapidly formed components	**Properties** 1. Slow: response over days to weeks 2. Antigenic specificity i.e. each cell is a programmed genetically to respond to a single antigen 3. Immunological memory, i.e. on repeated the response is faster, stronger and qualitatively different 4. Diversity: ability to recognize and respond to a vast number of different antigens 5. Self/non-self recognition: i.e. lack of response (tolerance) to self-antigens but response to foreign antigens

Macrophages

- Macrophages are defined as a lymphocyte that is able to phagocytose debris, toxins, cells or pathogens.
- Most macrophages in the body are tissue macrophages; i.e. they are allocated to specific tissues where they will patrol for pathogens, or “house-keep”, removing cellular debris.
- Most tissue macrophages are positioned at the most likely entry points for pathogens.
- **Types**
  - Tissue macrophages are either fixed (i.e. their location is fixed in connective tissue) or wandering (able to scavenge or move in response to signalling).
    - Fixed macrophages include:
      - **Kupffer cells (liver)**
        - lining the sinusoids of the liver
        - they account for nearly 90% of the tissue macrophages of the body.
        - Pathogens from the intestine will first travel to the liver via the portal venous system, and consequently, the Kupffer cells are positioned to engulf bacteria, debris and endotoxins.
      - Microglial cells (CNS)
      - Mesangial cells (kidney)

- ❖ Osteoclasts
- ❖ Macrophages of the reticuloendothelial system

▪ Wandering macrophages include:

- ❖ Macrophages of the serosal cavities (pleura, peritoneum, pericardium)
- ❖ Alveolar macrophages

Immunoglobulins

IgD is involved in the activation of B-cells

The table below summarises the characteristics of the 5 types of immunoglobulin found in the body:

Type	Frequency	Shape	Notes
IgG	75%	Monomer	• **comprises the majority of circulating antibody in serum** • the major antibody produced in the **secondary** immune response. • Enhance pha**G**ocytosis of bacteria and viruses • half-life: 7-23 days • Fixes **classical** complement • **can bind to NK cells** for antibody-dependent cytotoxicity (ADCC). • **the only antibody that can cross the placenta and enter the fetal circulation** • Most abundant isotype in blood serum • **G**amma is the type of heavy chain found in Ig**G**.
IgA	15%	Monomer/ dimer	• Found in secretions such as saliva, tears and mucous • made primarily in the mucosal-associated lymphoid tissues (MALT). • Provides localized protection on mucous membranes • The Fc portion of secretory IgA binds to components of mucous and contributes to the ability of mucous to trap microbes. • Most commonly produced immunoglobulin in the body (but blood serum concentrations lower than IgG) • half-life ≈ 5 days • Transported across the interior of the cell via transcytosis • can activate the **alternative** complement pathway. (Ig**A** ≈ **A**lternate) • Low levels of IgA are associated with an increased incidence of Coeliac Disease. • **A**lpha is the type of heavy chain found in Ig**A**.
IgM	10%	**Pentamer**	• First immunoglobulins to be secreted in response to an infection (primary response) • Fixes **classical** complement pathway (**most efficient**) • Anti-A, B blood antibodies (note how they cannot pass to the fetal circulation, which could of course result in haemolysis) • Monomeric forms of IgM are found on the surface of B-lymphocytes as B-cell receptors or sIg.

Type	Frequency	Shape	Notes
			• half-life: about 5 days • **M**u is the type of heavy chain found in Ig**M**.
IgD	1%	Monomer	• **Involved in activation of B cells** (as a surface receptor on B cells) • may play a role in eliminating B-lymphocytes generating self-reactive autoantibodies. • **D**elta is the type of heavy chain found in Ig**D**. • Hyper-lgD is associated with **periodic fever** (attacks of fever every 4-8 weeks, with each attack lasting 3-7 days)
IgE	0.1%	Monomer	• **produced by plasma cells** • Mediates type 1 hypersensitivity reactions • Binds to Fc receptors found on the surface of mast cells and basophils • Provides immunity to parasites such as helminths • Least abundant isotype in blood serum • half-life of 2 days • IgE may protect external mucosal surfaces by promoting inflammation, enabling IgG, complement proteins, and leucocytes to enter the tissues. • Cross linking of cell-bound IgE by antigen triggers the release of vasodilators for an inflammatory response. • The Fc portion of IgE made against parasitic worms and arthropods can bind to eosinophils enabling opsonization. This is a major defense against parasitic worms and arthropods. • **E**psilon is the type of heavy chain found in Ig**E**.

Each day an average adult produces approximately 3gm of antibodies, about two-thirds of this IgA

Acute organ rejection is due to anti-IgG antibodies to the human leukocyte antigen (HLA) incompatible tissues with primary activation of T cells.

Rhesus antibodies are **IgG** , wherese **ABO** antibodies are ***IgM***

Commonly recognized immunoglobulin changes in liver disease (usually accompanied by a decrease in albumin) are:

- **IgG** ↑ in: chronic active hepatitis, cryptogenic cirrhosis
- **IgM** ↑ in: 1° biliary cirrhosis, alcoholic cirrhosis
- **IgA** ↑ in: alcoholic cirrhosis.

Which one of the immunoglobulin structure forms antigen binding site?
➔ **The variable region of one heavy and one light chain**

Complement fixation
- **IgA** can fix complement via the **alternative** pathway
- **IgG** and **IgM** can fix complement via the **classical** pathway through the Fc portion of the immunoglobulin

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Hyper-IgM syndrome

- also known as CD40 ligand deficiency
- an X-linked condition
- a T-cell defect
- presenting in a similar way to X-linked agammaglobulinaemia with recurrent sinopulmonary disease
- affected individuals are susceptible to
  - **Pneumocystis jirovecii pneumonia**
  - chronic Cryptosporidial infection, leading to sclerosing cholangitis and liver failure
  - increased risk of malignancy, particularly abdominal cancers

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Hypergammaglobulinaemia

Causes of polyclonal hypergammaglobulinaemia:

1. Artefactual, e.g. prolonged venous stasis before venepuncture
2. Haemoconcentration secondary to dehydration
3. Chronic infection, e.g. TB, infective endocarditis, leishmaniasis
4. Autoimmune disease, e.g. SLE, rheumatoid arthritis
5. Ulcerative colitis and Crohn's disease
6. Sarcoidosis
7. Hepatic disease.

Causes of monoclonal hypergammaglobulinaemia

1. Multiple myeloma, Waldenstrom's macroglobulinaemia and heavy chain disease
2. Leukaemia, lymphoma or carcinoma
3. Bence Jones proteinuria
4. 'Benign' paraproteinaemia
5. Amyloidosis.

Cryoglobulinaemia

- Immunoglobulins which undergo reversible precipitation at 4 deg C, dissolve when warmed to 37 deg C.
- One third of cases are idiopathic

Three types

- **Type I** (25%):
  - monoclonal - IgG or IgM

  - associations: multiple myeloma, Waldenstrom macroglobulinaemia
- **Type II :** (25%):
  - mixed monoclonal and polyclonal: usually with RF
  - associations: hepatitis C, RA, Sjogren's, lymphoma
- **Type III**(50%):
  - polyclonal: usually with RF
  - associations: RA, Sjogren's

Symptoms (if present in high concentrations)

- Raynaud's only seen in type I
- cutaneous: vascular purpura, distal ulceration, ulceration
- arthralgia
- renal involvement (diffuse glomerulonephritis)

Tests

- low complement (esp. C4)
- high ESR

Treatment

- immunosuppression
- plasmapheresis

Immunoglobulins: therapeutics

Basics

- formed from large pool of donors (e.g. 5,000)
- IgG molecules with a subclass distribution similar to that of normal blood
- half-life of 3 weeks

Uses

- primary and secondary immunodeficiency
- idiopathic thrombocytopenic purpura
- myasthenia gravis
- Guillain-Barre syndrome
- **Kawasaki disease**
- toxic epidermal necrolysis
- pneumonitis induced by CMV following transplantation
- low serum IgG levels following haematopoietic stem cell transplant for malignancy
- dermatomyositis
- chronic inflammatory demyelinating polyradiculopathy

Leukotrienes

- mediators of inflammation and allergic reactions

Production

- secreted by leukocytes
- formed from arachidonic acid by action of lipoxygenase

- it is thought that the NSAID induced bronchospasm in asthmatics is secondary to the express production of leukotrienes due to the inhibition of prostaglandin synthetase

Function

- **cause bronchoconstriction,**
- **mucous production (**an important consideration in the pathophysiology of bronchial asthma**)**
- increase vascular permeability, attract leukocytes
- leukotriene D4 has been identified as the SRS-A (slow reacting substance of anaphylaxis) which causes bronchial wall and intestinal smooth muscle contraction

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Acute phase proteins

Acute phase proteins

- CRP
- procalcitonin
- ferritin
- fibrinogen
- alpha-1 antitrypsin
- caeruloplasmin
- serum amyloid A
- serum amyloid P component*
  - *plays a more significant role in other mammals such as mice
- haptoglobin
- complement

During the acute phase response the **liver decreases the production of other proteins** (sometimes referred to as negative acute phase proteins). Examples include:

- albumin
- transthyretin (formerly known as prealbumin)
- transferrin
- retinol binding protein
- cortisol binding protein

ANCA

cANCA = Wegener's; pANCA = Churg-Strauss + others

- There are two main types of anti-neutrophil cytoplasmic antibodies (ANCA):
  1. cytoplasmic (cANCA) and
  2. perinuclear (pANCA)
- For the exam, remember:
  - cANCA - Wegener's granulomatosis
  - pANCA - Churg-Strauss syndrome + others (see below)

cANCA

- most common **target serine proteinase 3 (PR3)**

- some correlation between cANCA levels and disease activity
- Wegener's granulomatosis, positive in > 90%
  - In Wegener's, the level of PR3 antibody and ANCA titre are **related to disease activity** and the antibodies typically disappear when the disease is in remission.
- microscopic polyangiitis, positive in 40%

pANCA

- most common **target is myeloperoxidase (MPO)**
- cannot use level of pANCA to monitor disease activity
- associated with immune crescentic glomerulonephritis (positive in c. 80% of patients)
- microscopic polyangiitis, positive in 50-75%
- Churg-Strauss syndrome, positive in 60%
- primary sclerosing cholangitis, positive in 60-80%
- Wegener's granulomatosis, positive in 25%
- **Other causes of positive ANCA (usually pANCA)**
  - inflammatory bowel disease (UC > Crohn's)
  - connective tissue disorders: RA, SLE, Sjogren's
  - autoimmune hepatitis

May 2006 exam: Which one of the following statements is true regarding cytoplasmic anti-neutrophil cytoplasmic antibodies (cANCA)? Associated with Wegener's granulomatosis

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Rheumatoid factor (see rheumatology)

Antibodies

antibody	Associated condition
Antinuclear antibodies (ANA)	• Younger women often have low **(ANAs)** • **increase with age** • ANA positivity with antiphospholipid antibody syndrome (APL) suggests secondary APL, ie in association with a connective tissue disease. • The common tests used for detecting and screening ANAs are indirect immunofluorescence and enzyme-linked immunosorbent assay (ELISA). • Although positive titres of 1:160 or higher are strongly associated with autoimmune disorders, they are also found in 5% of healthy individuals • Positive titres of less than 1:160 are present in up to 20% of the healthy population, especially the elderly.
Anti-Ro (SS-A) and **anti-La** (SS-B)	**Anti-Ro** Sjögren's syndrome (50–70%) SLE with cutaneous involvement (30%) anti-Ro can cross the placenta and cause neonatal lupus in babies.
Anti-Smith (Anti-Sm)	**very specific marker for SLE** (99%) sensitivity (20%) **not associated with disease activity.**

Anti-nuclear ribonucleoprotein (anti-nRNP) also known as anti-U1-RNP	highly associated with **mixed connective tissue disease.** SLE (30 – 40%)
Anti-double stranded DNA (anti-dsDNA)	**very specific marker for SLE, (nearly 100%).** sensitivity (85%). **Correlate with disease activity in SLE**. also linked with lupus nephritis.
Anti-histone	**drug induced lupus (75–95%)** idiopathic SLE (75%) Unlike anti-dsDNA, these antibodies do not fix complement.
anti-glycoprotein-210 (anti-gp210) and anti-nucleoporin 62 (anti-p62)	primary biliary cirrhosis (PBC) (25–30%).
Anti-centromere	**limited cutaneous systemic sclerosis**, also known as CREST syndrome, primary biliary cirrhosis
Thyroid autoantibodies (microsomal and thyroglobulin)	**Hashimoto's thyroiditis (70-90% microsomal: 75-95% thyroglobulin)** Pernicious anaemia (55% microsomal)
Anti-Scl-70	**diffuse cutaneous scleroderma (40%),** limited cutaneous involvement (10%). SLE (5%) The antigenic target of anti-Scl-70 antibodies is topoisomerase I
Antireticulin	Coeliac disease (37%) Crohn's disease (24%)
Gastric parietal cell antibody	**Pernicious anaemia (>90%)** Atrophic gastritis(60%) Autoimmune thyroid disease (33%)
Anti-mitochondrial antibody	**Primary biliary cirrhosis (60-94%)**
Anti-smooth muscle antibody	**Chronic active hepatitis** (40-90%) Primary biliary cirrhosis (30-70%) Idiopathic cirrhosis (25-30%) Viral infections (80%)
Anti-sp100	primary biliary cirrhosis (PBC) (20–30%). **very specific marker of the disease.**
Anti-PM-Scl	polymyositis/systemic sclerosis (PM/SSc) overlap syndrome (50%).

The only two auto-antibodies which have a role in monitoring disease activity
(there is correlation between levels and disease activity**)**

1. Anti-ds DNA antibodies in systemic lupus erythematosus (SLE)
2. Circulating anti-neutrophil cytoplasmic antibody (cANCA) in Wegener's granulomatosis.

Interleukin

- **Interleukin** are a group of cytokines (secreted proteins and signal molecules) that were first seen to be expressed by white blood cells (leukocytes).
- The function of the immune system depends in a large part on interleukins,
- **The majority of interleukins are synthesized by helper CD4 T lymphocytes, as well as through monocytes, macrophages,** and endothelial cells.
- They promote the development and differentiation of T and B lymphocytes, and hematopoietic cells.
- Interleukin receptors on astrocytes in the hippocampus are also known to be involved in the development of spatial memories in mice

Mnemonic Hot T-Bone stEAk
IL-1: fever (Hot)
IL-2: stimulates T lymphocytes
IL-3: stimulates Bone marrow
IL-4: stimulates IgE
IL-5: stimulates IgA

Interleukin 1 (IL-1) (α, β)

- Interleukin 1 (IL-1) is a key mediator of the immune response.
- **It is secreted mainly by macrophages and monocytes** and acts as a costimulator of T cell and B cell proliferation. (Stimulation of acute phase response)
- Other effects include increasing the expression of adhesion molecules on the endothelium.
- By stimulating the release by the endothelium of vasoactive factors such as PAF (platelet-activating factor), nitric oxide and prostacyclin it also causes vasodilation and increases vascular permeability.
- It is therefore one of the mediators of shock in sepsis.
- Along with IL-6 and TNF, it acts on the hypothalamus causing pyrexia.
- IL-1 β levels in the circulation are only detectable in the following situations:
  - after strenuous exercise,
  - in ovulating women,
  - sepsis,
  - acute organ rejection,
  - acute exacerbation of rheumatoid arthritis.
- **IL-1 play a role in the formation of the atherosclerotic plaque.**
  The uptake of oxidized low-density lipoproteins (LDL) by vascular endothelial cells results in → IL-1 expression → stimulates the production of platelet-derived growth factor.

Interleukin-2 (IL-2)

- IL-2 is a member of a cytokine family. It is a protein that regulates the activities of white blood cells (leukocytes, often lymphocytes) that are responsible for immunity.
- IL-2 is part of the body's natural response to microbial infection, and in discriminating between foreign ("non-self") and "self".
- Through its role in the development of T cell immunologic memory, it also has a key role in enduring cell-mediated immunity.
- there is some evidence that IL-2 may be involved in itchy psoriasis
- **High-dose interleukin-2 can produce a high rate of response and durable remissions in patients with metastatic renal cancer.**

Cytokine disorders

Both cytokine overexpression and underexpression or their receptors 'can be pathogenic:

1. **Septic shock**: production of IL-1, IL-6 and TNF due to endotoxin stimulation of macrophages following Gram-negative infection.

2. **Toxic shock syndrome**: massive release of cytokines due to super antigen stimulation of T-cells by TSST-1, a bacterial exotoxin.

3. **Chagas' disease** (T. *cruzi* infection): causes reduced expression of IL-2 receptor, leading to marked immune suppression.

Interferon

- Interferons (IFN) are cytokines released by the body in response to viral infections and neoplasia.
- They are classified according to cellular origin and the type of receptor they bind to.
- **IFN-alpha and IFN-beta bind to type 1 receptors** whilst IFN-gamma binds only to type 2 receptors.

IFN-alpha

- produced by leucocytes
- antiviral action
- useful in hepatitis B & C, Kaposi's sarcoma, metastatic renal cell cancer, hairy cell leukaemia
- adverse effects include flu-like symptoms and depression

IFN-beta

- produced by fibroblasts
- antiviral action
- reduces the frequency of exacerbations in patients with relapsing-remitting MS

IFN-gamma

- produced by T lymphocytes & NK cells
- weaker antiviral action, more of a role in immunomodulation particularly macrophage activation
- may be useful in chronic granulomatous disease and osteopetrosis

Chemokines

- **Chemokines** are a family of small cytokines, or signaling proteins secreted by cells.
- Their name is derived from their ability to induce directed chemotaxis in nearby responsive cells; they are **chemo**tactic cyto**kines**.
- have four cysteine residues in conserved locations that are key to forming their 3-dimensional shape.

Types and function

- Homeostatic chemokines:
  - responsible for basal leukocyte migration.
  - include: CCL14, CCL19, CCL20, CCL21, CCL25, CCL27, CXCL12 and CXCL13.
- Inflammatory chemokines:
  - Released under pathological conditions (on pro-inflammatory stimuli, such as IL-1, TNF-alpha, LPS, or viruses)
  - attracting immune cells to the site of inflammation.
  - Examples are: **CXCL8 (IL-8)**, CCL2, CCL3, CCL4, CCL5, CCL11, CXCL10
- May promote wound healing.
- promote angiogenesis (the growth of new blood vessels)
- The major role of chemokines is to act as a chemoattractant to guide the migration of cells.
- CXC chemokines have two cysteine residues separated by another amino acid. They are mainly chemoattractive for neutrophils.
- **IL-8 is an example of a CXC chemokine.**
- CC chemokines do not have the separating amino acid and mainly act on monocytes and lymphocytes.

Ref: medical-masterclass.com 2017 mrcp part 1

Nitric oxide

- Previously known as **endothelium derived relaxation factor**, nitric oxide (NO) has emerged as a molecule which is integral to many physiological and pathological processes.
- It is **formed from L-arginine** and oxygen by nitric oxide synthetase (NOS).
- An inducible form of NOS has been shown to be present in macrophages.
- Nitric oxide has a very short half-life (seconds), being inactivated by oxygen free radicals
- Nitric oxide generates cyclic guanosine monophosphate (cGMP) as the second messenger

Effects

- acts on guanylate cyclase leading to raised intracellular cGMP levels and therefore decreasing Ca2+ levels
- vasodilation, mainly venodilation
- **inhibits platelet aggregation**

Clinical relevance

- underproduction of NO is implicated in hypertrophic pyloric stenosis
- lack of NO is thought to promote atherosclerosis
- in sepsis increased levels of NO contribute to septic shock

- organic nitrates (metabolism produces NO) is widely used to treat cardiovascular disease (e.g. angina, heart failure)
- sildenafil is thought to potentiate the action of NO on penile smooth muscle and is used in the treatment of erectile dysfunctions
- N2O, also known as 'laughing gas', is often used in obstetrics and trauma for pain relief

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Endothelin-1

- It is a 21-amino-acid **polypeptide**
- It is a highly potent vasoconstrictor and plays a part in the modulation of vascular tone
- It may have a role in diseases such as Raynaud's phenomenon
- Its levels increase when the endothelium is stressed, for example in trauma or oxidative stress

Other proteins activated during tissue stress

- ICAM-1 is a cellular adhesion molecule (I = intercellular), which is increased during inflammation and by IL-1, an interleukin
- Heat-shock proteins (HSPs) are also increased during tissue stress

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Kinins

- kinins are potent vasoactive basic peptides involved in the inflammatory response
- **Their activation leads to release of chemotactic cytokines**
- Their properties including the ability to
  - increase vascular permeability
  - cause vasodilation, pain, and the contraction of smooth muscle
  - stimulate arachidonic acid metabolism

Erythrocyte sedimentation rate (ESR)

The ESR is a non-specific marker of inflammation and depends on both the size, shape and number of red blood cells and the concentration of plasma proteins such as fibrinogen, alpha2-globulins and gamma globulins

Causes of a high ESR

- temporal arteritis
- myeloma
- other connective tissue disorders e.g. systemic lupus erythematosus
- other malignancies
- infection
- other factors which raise ESR: increasing age, female sex, anaemia

Causes of a low ESR

- **polycythaemia**
- afibrinogenaemia/ hypofibrinogenaemia

Tumour necrosis factor (TNF)

- Tumour necrosis factor **(TNF) is a pro-inflammatory cytokine** with multiple roles in the immune system
- TNF is secreted mainly by macrophages and has a number of effects on the immune system, acting mainly in a paracrine fashion:
  - activates macrophages and neutrophils
  - acts as co-stimulator for T cell activation
  - key mediator of bodies response to Gram negative septicaemia
  - similar properties to IL-1
  - anti-tumour effect (e.g. phospholipase activation)
  - is a key cytokine in the pathogenesis of multi-organ failure.
  - exerts an interferon-like effect against viruses
  - Enhanced HLA class I expression
  - Stimulation of acute phase response
- TNF-alpha binds to both the p55 and p75 receptor. These receptors can induce apoptosis. It also cause activation of NFkB
- Endothelial effects include increase expression of selectins and increased production of platelet activating factor, IL-1 and prostaglandins
- TNF promotes the proliferation of fibroblasts and their production of protease and collagenase. It is thought fragments of receptors act as binding points in serum
- Systemic effects include pyrexia, increased acute phase proteins and disordered metabolism leading to cachexia
- TNF is important in the pathogenesis of rheumatoid arthritis - TNF blockers (e.g. infliximab, etanercept) are now licensed for treatment of severe rheumatoid

TNF blockers

- infliximab: monoclonal antibody, IV administration
- etanercept: fusion protein that mimics the inhibitory effects of naturally occurring soluble TNF receptors, subcutaneous administration
- adalimumab: monoclonal antibody, subcutaneous administration
- adverse effects of TNF blockers include reactivation of latent tuberculosis and demyelination
- Infliximab is also used in active Crohn's disease unresponsive to steroids

Contraindications of usage of TNF- alpha antagonist:

- Active infection
- Active TB
- MS (Multiple sclerosis)
- Heart failure (NYHA grade 3-4).
- Pregnancy and Breast feeding

Growth factors

Transforming growth factor-beta (TGF-β)

- Generally limits inflammatory response.
- Enhances IgA synthesis.
- Initiates and terminates tissue repair.
- Undergoes autoinduction.
- **Released by platelets at the site of tissue injury and promotes the formation of extracellular matrix.**
- Implicated in diseases of tissue fibrosis such as cirrhosis and glomerulosclerosis.

Leukocyte alkaline phosphatase

Raised in	Low in
• Myelofibrosis • Leukemoid reactions • Polycythemia rubra vera • Infections • Steroids, Cushing's syndrome • Pregnancy, oral contraceptive pill	• Chronic myeloid leukemia • Pernicious anemia • Paroxysmal nocturnal hemoglobinuria • Infectious mononucleosis

Monoclonal antibodies

Rituximab - monoclonal antibody against CD20

- manufactured by a technique called somatic cell hybridization.
- This involves the fusion of myeloma cells with spleen cells from a mouse that has been immunized with the desired antigen. The resulting fused cells are termed a hybridoma and act as a 'factory' for producing monoclonal antibodies.
- The main limitation to this is that mouse antibodies are immunogenic leading to the formation of human anti-mouse antibodies (HAMAs). This problem is overcome by combining the variable region from the mouse body with the constant region from an human antibody.

Clinical examples of monoclonal antibodies:

MONOCLONAL AB	TYPE	USES
Rituximab	Anti-CD20	non-Hodgkin's lymphoma
Infliximab	anti-**TNF**	rheumatoid arthritis and Crohn's
Cetuximab	anti-epidermal growth factor receptor	metastatic colorectal cancer and head and neck cancer
Trastuzumab	anti-**HER**2, anti EGF receptor	metastatic **breast** cancer
Alemtuzumab	anti-CD52	chronic lymphocytic leukemia
Abciximab	anti-glycoprotein IIb/IIIa receptor	undergoing PCI, prevention of ischemic events in patients
OKT3	anti-CD3	prevent organ rejection

Monoclonal antibodies are also used for:

- medical imaging when combined with a radioisotope
- identification of cell surface markers in biopsied tissue
- diagnosis of viral infections

Diagnostic antibody testing

AB	Association
Anti-Hu	small-cell lung cancer, neuroblastoma and prostatic cancer
Intrinsic factor antibodies	pernicious anaemia, and hence (subacute combined degeneration of the spinal cord) secondary to vitamin B12 deficiency
Anti-Ri	neuroblastoma (children) and fallopian or breast cancer (adults), resulting in paraneoplastic opsoclonus myoclonus ataxia (POMA).
Anti-Yo	gynaecological tumours and breast cancer,
Anti-Tr	Hodgkin's disease, resulting in cerebellar degeneration.
Anti-Ta (Ma2)	testicular tumours, and can lead to limbic or brain stem encephalomyelitis.
Anti-endomysial / **gliadin** / **transglutaminase**	coeliac disease, and related vitamin B-1 deficiency may lead to Wernicke's encephalopathy and Korsakoff's psychosis
Tissue transglutaminase antibody ('tTGA') **&** Endomysial antibody ('EMA')	The most accurate blood tests for coeliac disease
Antimitochondrial antibodies (M2 pattern)	primary biliary cirrhosis (PBC)
double-stranded DNA (ds-DNA) **Anti-dsDNA**	highly specific for SLE.
Antibodies that bind single-stranded denatured DNA (ss-DNA)	present in 90% of patients with SLE, but also in drug-induced lupus and other connective tissue disorders.
Antihistone antibody	seen in SLE and drug-induced lupus.
Anticentromere antibody	present in 70% of patients with CREST and 15% of patients with diffuse scleroderma. CREST syndrome: calcinosis, Raynaud's phenomenon, oesophageal dysfunction, sclerodactyly and telangiectasia.
ASMA – Anti- smooth muscle antibody	**Chronic active hepatitis**
pANCA	**Ulcerative Colitis**
cANCA	**Wegner's granulomatosis**
Anti-centromere	**CREST / Scleroderma**
Anti-Ro	**Sjogren's Syndrome**
Anti-La	**Sjogren's syndrome**
Anti-Jo	**Polymyositis**
Rheumatoid factor	**Rheumatoid arthritis, Sjogren's (90%), SLE (30%)** ***5% of normal population***

Lymphocytes

	B lymphocytes	T lymphocytes
Site of production	**bone marrow**. **germinal centre** of lymph nodes and spleen.	produced in the bone marrow but mature in the **thymus** **Paracortical region** of lymph nodes and spleen.
Functions	**Humoral immunity** ➢ antibody production (immunoglobulins) ➢ control of pyogenic bacteria prevention of blood-borne infections. ➢ neutralization of toxins.	**Cell-mediated immunity;** ➢ protection against intracellular organisms, protozoa and fungi; ➢ graft rejection; ➢ control of neoplasms.
% of total lymphocytes:	➢ 12% ➢ **mainly fixed.**	➢ 70-80% **(the majority of circulating lymphocytes in plasma).** ➢ **mainly circulating;** ➢ long-lived memory cells.

Thymus

- The thymus is composed of two identical lobes and is located anatomically in the anterior superior mediastinum, in front of the heart and behind the sternum.
- Histologically, each lobe of the thymus can be divided into a central medulla and a peripheral cortex which is surrounded by an outer capsule.
- The thymus is largest and most active during the neonatal and pre-adolescent periods. By the early teens, the thymus begins to atrophy and thymic stroma is mostly replaced by adipose (fat) tissue. Nevertheless, residual T lymphopoiesis continues throughout adult life.
- Cells in the thymus can be divided into thymic stromal cells and cells of hematopoietic origin (derived from bone marrow resident hematopoietic stem cells). Developing T-cells are referred to as thymocytes and are of hematopoietic origin. Stromal cells include epithelial cells of the thymic cortex and medulla, and dendritic cells.
- Cortical thymocytes are immature forms, and either do not express CD4 or CD8 (double negative cells) or express both CD4 and CD8 (double positive cells).
- As the cells mature, they pass to the thymic medulla, where they lose expression of either CD4 or CD8, to become single positive cells.
- Negative selection occurs at the stage when thymocytes express both CD4 and CD8, but co-expression of these markers does not mediate negative selection.

- Negative selection occurs when a thymocyte expresses a TcR with high affinity for self antigen:MHC complexes in the thymic micro-environment.
- Once a thymocyte has successfully rearranged and expressed an alpha/beta or gamma/delta TcR it is committed to that lineage.
- **Thymocytes whose TcR bind with high affinity to self Ag/MHC complexes are clonally deleted** by a process of negative selection.

Immune cell antigen receptors

- T and B lymphocytes express receptors on their surface that recognise antigen in a specific manner.
- Each individual lymphocyte expresses a single type of receptor with unique specificity (except dual specificity T cells
- The receptor on the B lymphocyte is membrane bound immunoglobulin (IgM and IgD isotype) and recognises particulate antigen, whilst the TCR is a heterodimer that recognises peptide fragments presented by MHC molecules.
- T cells with dual specificities have been reported although their function is unknown.

B-cells and plasma cells

- B-cells have surface IgG and major histocompatibility complex (MHC) class II
- **B cells express immunoglobulin on their surface**
- **B-cells undergo somatic hypermutation and isotype switching** (ie switching through the immunoglobulin classes)
- Plasma cells are fully differentiated cells from B-cells and hence lack these features
- **Multiple myeloma is a cause of isolated B-cell immune deficiency**
- B cells usually require T cell help for full activation.
- B cells activated in the primary immune response initially produce IgM. With continuing T cell help B cells then undergo heavy chain class switching and enter germinal centres in secondary lymphoid organs.
- The germinal centres are the sites of immunoglobulin affinity maturation and memory B cell formation.
- CD40 and CD40L are required for co-stimulation by T cells. Deficiency of either CD40 or CD40L impairs class switching.
- Certain antigens can activate B cells in the absence of T cell help - thymus independent antigen. T cell independent B cell responses are mainly to carbohydrate antigen, for example, pneumococcal polysaccharide. These antigens are not processed and presented in association with MHC molecules, and therefore cannot activate T helper cells.
- The influenza virus will activate T and B cells, and result in memory cell production.
- **Affinity maturation of the B cell receptor is an important process initiated during the primary immune response**
- **IgD are surface receptors of B lymphocytes**

Class II MHCs are present on all antigen presenting cells, for example,

- B cells
- Dendritic cells
- Macrophages

- Langerhans cells.

They are also present on activated T cells.

CD4 T-cells interact with B-cells via MHC class II

Class I major histocompatibility complexes (MHCs) react with CD 8 on T cells to result in immune system activation

Proteins are displayed on the cell surface by **MHC I** human leukocyte antigen (HLA) antigens.

If the MHC I is presenting material recognised as foreign, then it is detected and destroyed by CD 8 plus T cells

Antigen presenting cells (APCs)

- Extracellular antigen which is not directly recognised as foreign requires processing by APCs to generate an immune response. This process involves these cells expressing antigenic peptides in conjunction with MHC class II.
- Antigen is presented via MHC class II complexes,
- MHC class I aids in the recognition of virally infected cells.
- Direct stimulation of an immune response may occur in the absence of APCs.
- APCs are not required before an immune response to viral infection can be successfully mounted.

T cells

- **Co-operation with other cell types is required for T cell recognition of antigen**
- T cells recognise antigen only when presented by (self) MHC molecules on an antigen presenting cell.
- Autoreactive T cells exist in the periphery and other mechanisms are responsible for the protection of the body against autoimmunity.
- The antigen specificity of T and B cells is generated during development in the thymus (T lymphocytes) and in the bone marrow (B lymphocytes).
- **Patients with HIV have a deficiency of T-cells (**CD4 T-cell lymphocytes**)**
- T lymphocytes are involved in cell-mediated acquired immune responses, whereas B lymphocytes are involved in humoral immunity and produce immunoglobulins.
- **T lymphocytes compose the majority of circulating lymphocytes in plasma.**
- **Within lymph nodes:**
  - **The paracortical areas**➔ contain T cells and accessory cells.
  - **Cortex** ➔ B cells are found within the cortex in follicles, which have central areas known as germinal centres.
  - **The medulla** ➔ contains large blood vessels and sinuses, and medullary cords that contain plasma cells secreting antibody.

Which is the predominant site in the lymph node that contains T cells? Paracortex

T-Helper cells

There are two major subsets of T-Helper cells:

Th1

- involved in the cell mediated response and delayed (type IV) hypersensitivity
- secrete IFN-gamma, IL-2, IL-3

Th2

- involved in mediating humoral (antibody) immunity
- e.g. stimulating production of IgE in asthma
- secrete IL-4, IL-5, IL-6, IL-10, IL-13

An increase in the Th1:Th2 ratio is associated with a reduction in the risk of allergic/hypersensitivity reactions.

May 2012 exam: Which one of the following is most commonly secreted by T-helper cells subset 2 (Th2 cells) ? Interleukin 4

Mast cells

Mast cells are basophilic cells in the connective and subcutaneous tissues, which are involved in inflammatory and immune responses.

They contain storage granules that contain lytic enzymes (for example, tryptase) and inflammatory mediators, for example:

- Histamine
- Heparin
- 5-Tryptase hydroxytryptamine (5-HT)
- Leukotrienes
- Platelet aggregating factor
- Leukocyte chemotactic factor
- Hyaluronidase.

Release of these mediators occurs during mast cell degranulation, which can be triggered by:

- Tissue injury
- Drugs
- Complement activation
- Foreign antigenic material.

An anaphylactic reaction occurs when a previously sensitised individual is re-exposed to the antigen. It is an IgE mediated immune response.

Mastocytosis occurs when excess mast cells are present in the circulation or as tissue infiltrates.

Degranulation releases lytic enzymes and inflammatory mediators from storage granules

Immunity to viruses

- Natural killer cells are activated faster than cytotoxic T-cells
- Infected non-immune cells produce interferon-α and -β, whereas interferon-γ is produced by T-cells
- Influenza virus mutates its surface neuraminidase and haemagglutinin to avoid antibody recognition
- Enveloped viruses are susceptible to complement attack
- **IgA can offer protection at mucosal surfaces**

Immunity to bacteria

- **Cellular immunity** is essential in protection against intracellular bacteria, eg mycobacteria
- Phagocytes interact directly but weakly with bacteria, or strongly if they are complement-opsonised
- Endotoxin activates macrophages by binding to CD14
- **bacteria opsonised by antibodies and complement are more effectively phagocytosed than those opsonised by antibodies alone**

Congenital immunodeficiency disorders

Types

- B-cell immunodeficiencies
  - **B-cell defects** (**humoral immunity** deficiencies) account for **50–60%** of all primary immunodeficiencies.
  - Include
    - Bruton agammaglobulinemia (X-linked agammaglobulinemia)
    - Selective IgA deficiency (SIgAD)
    - Common variable immunodeficiency (CVID)
- T-cell immunodeficiencies
  - **T cell defects** (**cellular immunity** deficiencies) are responsible for **5–10%** of primary immunodeficiencies.
  - Include:
    - DiGeorge syndrome (22q11.2 deletion syndrome)
- mixed immunodeficiencies
  - Severe combined immunodeficiency (SCID)
  - Wiskott-Aldrich syndrome
  - Ataxia telangiectasia
- Congenital complement deficiencies
  - C1-esterase inhibitor deficiency (hereditary angioedema)
  - Terminal complement deficiency (C5–C9 deficiency)
- phagocyte deficiencies
  - Phagocytic defects are characterized by impaired ability of phagocytic cells (e.g., monocytes, macrophages, granulocytes such as neutrophils and eosinophils) to kill pathogens
  - account for **10–15%** of primary immunodeficiencies.
  - Include:
    - Chronic granulomatous disease (CGD)
    - Leukocyte adhesion deficiency type 1
    - Chediak-Higashi syndrome

Primary immunodeficiency

disorders may be classified according to which component of the immune system they affect.

Neutrophil disorders

Disorder	Underlying defect	Notes
Chronic granulomatous disease	Lack of NADPH oxidase reduces ability of phagocytes to produce reactive oxygen species	**Caused by** a failure of intracellular killing (no respiratory burst). Causes recurrent pneumonias and abscesses, particularly due to catalase-positive bacteria (e.g. *Staphylococcus aureus* and fungi (e.g. *Aspergillus*) Negative nitroblue-tetrazolium test Screening is by the nitroblue tetrazolium (NBT) test Abnormal dihydrorhodamine flow cytometry test
Chediak-Higashi syndrome	Microtubule polymerization defect which leads to a decrease in phagocytosis	Affected children have 'partial albinism' and peripheral neuropathy. Recurrent bacterial infections are seen Giant granules in neutrophils and platelets
Leukocyte adhesion deficiency	Defect of LFA-1 integrin (CD18) protein on neutrophils	Recurrent bacterial infections. Delay in umbilical cord sloughing may be seen Absence of neutrophils/pus at sites of infection

B-cell disorders

Disorder	Underlying defect	Notes
Common variable immunodeficiency **CVID**	Many varying causes	Hypogammaglobulinemia is seen. May predispose to autoimmune disorders and lymphona
Bruton's (x-linked) congenital agammaglobulinaemia	Defect in Bruton's tyrosine kinase (BTK) gene that leads to a severe block in B cell development	X-linked recessive. Recurrent bacterial infections are seen Absence of B-cells with reduce immunoglogulins of all classes
Selective immunoglobulin A deficiency	Maturation defect in B cells	• **Most common primary antibody deficiency**. • Recurrent sinus and respiratory infections • Associated with coeliac disease and **may cause false negative coeliac antibody screen**

T-cell disorders

Disorder	Underlying defect	Notes
DiGeorge syndrome	22q11.2 deletion, failure to develop 3rd and 4th pharyngeal pouches	Common features include congenital heart disease (e.g. tetralogy of Fallot), learning difficulties, hypocalcaemia, recurrent viral/fungal diseases, cleft palate

Combined B- and T-cell disorders

Combined B- and T-cell disorders: SCID WAS ataxic (SCID, Wiskott-Aldrich syndrome, ataxic telangiectasia)

Disorder	Underlying defect	Notes
Severe combined immunodeficiency	Most common **(X-linked)** due to defect in the common gamma chain, a protein used in the receptors for IL-2 and other interleukins. **Other causes include adenosine deaminase deficiency**	Recurrent infections due to viruses, bacteria and fungi. Reduced T-cell receptor excision circles **Stem cell transplantation may be successful**
Ataxia telangiectasia	Defect in DNA repair enzymes	• Autosomal recessive. • Features include: 1. cerebellar ataxia, 2. telangiectasia (spider angiomas), 3. recurrent chest infections 4. and 10% risk of developing malignancy, lymphoma or leukaemia
Wiskott-Aldrich syndrome	Defect in WAS gene	X-linked recessive. Features include recurrent bacterial infections, eczema, thrombocytopaenia. Low IgM levels Increased risk of autoimmune disorders and malignancy

Antibody deficiency

- The most common type of primary immunodeficiency (>50% of cases) involves being deficient in antibody production
- Selective IgG deficiencies include the decreased production of IgA and/or the various IgG subclasses and impaired antibody responses to polysaccharide antigens
- Normal immunoglobulin serum levels, including subclasses, do not exclude antibody deficiency

- Hence in patients with a good history of recurrent (proven) bacterial infections, IgG responses to Haemophilus influenzae, Pneumococcus spp, and tetanus toxoid should all be assessed, as should postimmunisation responses if required
- **Good IgG antibody responses to immunisations ➔ excludes IgG subclass deficiency.**

Which disease occurring during pregnancy is most likely to lead to the neonate having low immunoglobulin levels and hence being prone to bacterial infections?
Intestinal lymphangiectasia

Selective IgA deficiency (SIgAD)

Definition

- total absence or severe deficiency of IgA, serum levels are usually less than 0.05g/L (with a normal adult range of 0.9 - 4.5 g/L).

Epidemiology

- the **most common primary antibody deficiencies**
- prevalence: 1 in 700
- high incidence in Arab and Spanish

Causes

- unknown
- occurs more frequently in first degree relatives of patients with common variable immunodeficiency (CVID).

Features

- Often asymptomatic,
- Recurrent infections
  - ➢ most commonly present with otitis media, chronic rhinosinusitis and pneumonia.
  - ➢ chronic diarrhea (*Giardia*), steatorrhea

Associated conditions

- coeliac disease
  - ➢ 10-fold increased risk of coeliac disease
- **gluten-sensitive enteropathy (GSE)**
- IgG subclass or specific antibody deficiency:
  - ➢ **The possibility of IgG2 deficiency should always be investigated in IgA-deficient individuals with a history of recurrent bacterial infections, but Staphylococcus aureus is the exception**
- **pernicious anaemia and hence gastric carcinoma**
- Allergy and autoimmune conditions
- ↑ **adverse reactions to blood products**.
  - ➢ Patients with selective IgA deficiency should be tested for the presence of anti-IgA antibodies prior to transfusion with blood products.
- may progress to **common variable immune deficiency** (involving low levels of both IgA and IgG, and sometimes also IgM),

Diagnosis

- **low serum IgA level, with normal IgG and IgM levels**

Treatment

- no specific treatment
- Prophylactic antibiotics
- **Intravenous infusion of IgA is not recommended** because:
  - ➢ the risk of anaphylactic reactions (caused by the production of anti-IgA antibodies).

- the short half-life of IgA and the relative paucity of IgA in commercial immunoglobulin preparations

Ref:

- medical-masterclass.com 2017 mrcp part 1
- pastest part 1
- www.amboss.com 2017

Common variable immunodeficiency (CVID)

Epidemiology

- **The most common clinically significant primary immunodeficiency** is CVID.
  - IgA deficiency is more common, but most are asymptomatic.
- Sex: ♀ = ♂
- Onset: present later than other B cell defects (usually 20–35 years of age)

Pathogenesis

- **immunodeficiency arising from B-cell dysfunction**
- B cells are phenotypically normal but unable to differentiate into Ig-producing cells
  - defect in B-cell **differentiation** (cannot differentiate to plasma cells which produces antibodies).
- **no clear pattern of inheritance**
- Can be acquired in young adulthood

Definition

- A well-accepted definition of CVID includes three key features:
  1. the presence of hypogammaglobulinaemia of two or more immunoglobulin isotypes (low IgG, IgA, or IgM),
  2. recurrent sinopulmonary infections
  3. impaired functional antibody responses.
     - include absent isohaemagglutinins (eg. antibodies associated with blood transfusion reactions),
     - poor responses to protein (diphtheria, tetanus) or polysaccharide vaccines (S pneumoniae), or both.
- **Features**
  - Symptoms
    - recurrent sinopulmonary infections
    - persistent diarrhea
      - Giardia lamblia
  - Physical exam
    - generalized lymphadenopathy
    - splenomegaly
- **Associated conditions and complications:**
  - ↑risk for autoimmune diseases (~20%)
    - (e.g., rheumatoid arthritis, autoimmune hemolytic anemia, immune thrombocytopenia, vitiligo)
    - alopecia areata
    - granulomatous diseases
  - ↑risk for lymphoma
    - **common cause of death in patients with CVID → lymphoma**
    - especially non-Hodgkin's lymphoma [NHL], and gastrointestinal [GI] carcinoma).
    - Lymphoma occurs 300 times more frequently in women with CVID than in affected men.
    - Most lymphomas are of these are of the B cell immunophenotype

        - frequently associated with Epstein-Barr virus (EBV).
    - permanent damage to lungs → **bronchiectasis**
    - severe gastroenteropathy with severe malabsorption (20%), resembling coeliac sprue, nodular lymphoid hyperplasia, and chronic inflammatory bowel disease such as ulcerative colitis and Crohn's disease.
    - Granulomas in 5-10%.
        - Granulomas are indistinguishable from those of classic sarcoidosis
        - are found in the: Lung, Liver, Spleen, and Conjunctivae.
- **Investigations**
    - Quantitative Ig levels (low levels of IgG, IgA, IgM)
        - ↓ All immunoglobulin classes, especially IgA and IgG
        - **IgG is more likely to be deficient than IgM.**
    - Flow cytometry shows normal B and T cell subsets
    - Lymph node biopsy – to exclude malignancy
        - reactive follicular hyperplasia
- **Treatment**
    - IVIG replacement therapy (first line)
        - **the best option would best prevent recurrent chest infections → Intravenous immunoglobulin**
    - Prophylactic antibiotics
- **Vaccination**
    - Poor response to immunizations
    - Patients with common variable immunodeficiency should receive killed vaccines for prophylaxis against infections.

Question
H/O **recurrent Giardia lamblia diarrhea and multiple upper respiratory infections** since birth. serum analysis reveals **normal levels of mature B lymphocytes**. What other finding on serum analysis predisposes the patient to recurrent diarrheal infections?
Answer
➔ **Deficiency in IgA**
- The patient has **common variable immunodeficiency disorder (CVID)**
- IgA plays an important role in mucosal immunity. By its presence on the surface of intestinal mucosal cells, IgA is able to prevent the binding of pathogens to the epithelial cells; thus, preventing protozoa like Giardia lamblia from causing inflammation. Its absence, therefore, leads to the increased likelihood of repeat infection of the GI mucosa and repeat episodes of non-bloody diarrhea

CVID → B-cell Cannot differentiate into plasma cells → low immunoglobulins but **normal or decreased B cells.**
Bruton's → Pre-B lymphocytes are increased because there's a maturation defect.

Bruton's (x-linked) congenital agammaglobulinaemia (XLA)

- **Definition**
    - **X-linked recessive** disease that causes a **complete deficiency of B lymphocytes**
- **Etiology**
    - mutations in the gene coding for **Bruton tyrosine kinase** (BTK).
        - BTK is critical to the maturation of pre–B cells to differentiating mature B cells.

        - The most common genetic event is a **missense mutation** (substitution in one amino acid in a protein).
    - Males with XLA have a total or almost total absence of B lymphocytes and plasma cells.
- **Epidemiology**
    - appears in boys only
- **Features**
    - frequent infections
        - Infections begin once transferred maternal immunoglobulin G (IgG) antibodies have been catabolized, typically at about 6 months of age. (because transplacentally transferred maternal IgG is no longer active)
        - Recurrent, severe pyogenic infections (e.g., pneumonia, otitis media); especially by encapsulated organisms (S. pneumoniae, N. meningitidis, and H. influenzae)
        - Hepatitis viruses and enteroviruses (e.g., Coxsackie virus)
    - small or absent tonsils, adenoids, lymph nodes, and Peyer patches in the intestines, due to absence of B lymphocytes which is normally make most of the bulk of these tissues.
- **Diagnosis**
    - flow cytometry
        - showing absent or low B cells and **normal T cells**
        - **low B cell count** in the blood is the most reliable indicator of XLA
    - Quantitative Ig levels
        - immunoglobulins (IgG, IgM, and IgA) are absent or very low
    - Diagnosis confirmed by absence of Bruton's tyrosine kinase (BTK), or by detection of an abnormality in the BTK gene.
- **Treatment**
    - IV immunoglobulins
    - Prophylactic antibiotics

Severe combined immunodeficiency disease (SCID)

- **Combined B- and T-cell disorder** causing immunodeficiency
- multiple variants found
    - most common is X-linked defective common gamma chain
        - found in IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21
    - autosomal recessive adenosine deaminase deficiency
        - 2nd most common
        - ↑ deoxyadenosine, which is toxic to lymphocytes
            - Mutations in adenosine deaminase gene → ↓adenosine deaminase → ↑deoxyadenosine
        - ↓ DNA synthesis

Features

- most patients present before age 3 months. Without intervention, SCID usually results in severe infection and death in children by age 2 years.
- recurrent infections, diarrhea, dermatitis, and failure to thrive.
- common cutaneous manifestations and typical infections can provide clinical clues in diagnosing this pediatric emergency.

Diagnosis

- ↓ Lymphocyte count (< 3000/μL)
- Chest radiography with no thymic shadow
- Flow cytometry
    - absent T-cells

- abnormal function of B-cells

DiGeorge syndrome

DiGeorge syndrome - a T-cell disorder

- DiGeorge syndrome is a primary immunodeficiency disorder caused by **T-cell** deficiency and dysfunction.
- Results from maldevelopment of thymic epithelial elements derived from the third and fourth pharyngeal pouches. (abnormal development of the 3rd and 4thbranchial pouches.) → thymic aplasia and defective parathyroid
  - **The thymus arises from the 3rdpharyngeal pouch,**
  - **the parathyroid glands receive contribution from both 3rd and 4th pouches.**
- It is an example of a microdeletion syndrome.
- The gene defect mapped to **chromosome 22**q11.

Features

- risk of viral and fungal infections
- parathyroid gland hypoplasia → hypocalcaemic tetany
- thymus hypoplasia → **T-lymphocyte deficiency/dysfunction** → susceptible to opportunistic infections such as yeast.
- cardiac defects
  - interrupted aortic arch,
  - truncus arteriosus
  - tetralogy of Fallot
  - isolated VSD.
- Facial abnormalities may include abnormal ears, a shortened philtrum, micrognathia and hypertelorism
- high and broad nasal bridge
- Affected individuals usually have a **small**, **histologically** normal thymus **located near the base of the tongue or in the neck**, allowing most patients to develop functional T-cells in numbers that may or may not be adequate for host defence
- **X-ray shows absence of the thymic shadow.**
- **low levels of serum calcium and parathormone**

May 2013 exam: In a patient having DiGeorge syndrome, which infection is he most at risk from, secondary to his immune system dysfunction? ***Cryptococcus neoformans*** (T-cell dysfunction → ↑↑ risk from recurrent viral and fungal infections)

Wiskott-Aldrich syndrome

Wiskott-Aldrich syndrome

- **recurrent bacterial infections (e.g. Chest)**
- **eczema**
- **thrombocytopaenia**

- Wiskott-Aldrich syndrome causes primary immunodeficiency due to a combined **B- and T-cell** dysfunction.
- It is inherited in a **X-linked recessive** fashion
- and is thought to be **caused by mutation in the WASP gene**.(which responsible for ensuring proper functioning of the actin cytoskeleton in haematopoietic cells)
- **Features include**:
  - recurrent bacterial infections (e.g. chest),
  - eczema
  - thrombocytopenia
  - low IgM levels
  - humoral immunodeficiency,
  - autoimmune disease
  - haematological malignancy

- The disease have **variable penetrance**, which means that life expectancy can range from 6 - 30 years.

Complement deficiencies

C3 deficiency is associated with recurrent bacterial infections,
C5 deficiency is more characteristically associated with disseminated meningococcal infection

- Complement is a series of proteins that circulate in plasma and are involved in the inflammatory and immune reaction of the body.
- Complement proteins are involved in chemotaxis, cell lysis and opsonisation.

C1 inhibitor (C1-INH) protein deficiency

- causes hereditary angioedema
- C1-INH is a multifunctional serine protease inhibitor
- probable mechanism is uncontrolled release of bradykinin resulting in oedema of tissues

C1q, C1rs, C2, C4 deficiency (classical pathway components)

- predisposes to immune complex disease
- e.g. SLE, Henoch-Schonlein Purpura, vasculitidies
- mechanism
  - complement activity is associated with clearance of circulating immune complexes
  - If immune complexes are not cleared, they undergo → tissue deposition where an inflammatory process is triggered, leading to SLE

C3 deficiency

- causes recurrent bacterial infections
- Deficiencies of C3 is more commonly associated with **haemolytic uraemic syndrome**

C5 deficiency

- predisposes to Leiner disease
- recurrent diarrhoea, wasting and seborrhoeic dermatitis

C5-9 deficiency

- encodes the membrane attack complex (MAC)
- particularly prone to ***Neisseria meningitidis*** infection
- **Absent classical and alternate pathway activity**

Decay-accelerating factor (DAF) deficiency is associated with → Paroxysmal nocturnal haemoglobinuria (PNH).

Diagnosis

- **CH50 assay screening test**

Question

Post splenectomy what type of immunodeficiency is occurs?

→ **Humoral** . Post splenectomy there is increased susceptibility to H. Influenzae, N. Meningitidis and Strep pneumonia which are encapsulated organisms **due to the loss of splenic macrophages which are part of the humoral response.**

If adenosine deaminase is absent from a cell i.e. in severe combined immunodeficiency disease, what does this result in?

Leads to accumulation of deoxyadenosine**.** Adenosine deaminase enzyme leads to the breakdown of deoxyadenosine, which is a breakdown product of DNA. Deoxyadenosine is toxic to lymphocytes, thus accumulation of this leads to apoptosis of lymphocytes.

How to exclude antibody deficiency?

→ **Presence of Specific antibodies to haemophilus and pneumococci**

May 2009 exam: A 23-year-old man is admitted with sepsis. Blood cultures are reported as *Neisseria gonorrhoeae* .Which complement protein is the patient most likely to deficient in? C5-9

Membrane attack complex (MAC)

- Structure
  - formed by C5b, C6, C7, C8, and multiple copies of C9 complement proteins on pathogen cell membranes
- function → lyses pathogens
- Inhibition
  - CD59 inhibit the complex.
    - This exists on body cells to protect them from MAC.
    - paroxysmal nocturnal haemoglobinuria, results in red cells that lack CD59. These red cells can, therefore, be lysed by MAC.

Hereditary angioedema

Hereditary angioedema - C1-INH deficiency

Hereditary angioedema - C4 is the best screening test inbetween attacks

- Hereditary angioedema is an **autosomal dominant** condition associated with **low plasma levels of the C1 inhibitor (C1-INH) protein**.
- C1-INH is a multifunctional serine protease inhibitor

Pathophysiology

- deficiency of C1 esterase inhibitor leads to persistent activation of the classical complement pathway and C4 levels are frequently low secondary to activation and consumption.
  - ↓C1 inhibitor allow C1 to act on C4 and C2
- Mechanism of attacks : uncontrolled release of **bradykinin** resulting in oedema of tissues.

Investigation

- C1-INH level is low during an attack
- Low C2 and C4 levels are seen, even between attacks.
- **Serum C4 is the most reliable and widely used screening tool**

Symptoms

- painless, non-pruritic swelling of subcutaneous/submucosal tissues
  - urticaria is not usually a feature
  - attacks may be proceeded by painful macular rash
- may affect upper airways, skin, genital or abdominal organs (can occasionally present as abdominal pain and vomiting due to visceral oedema)
- Membrane-attack complex deficiencies leave patients particularly susceptible to neisserial infection
- Triggers include stress, infection and menstruation

Management

- **acute**: IV C1-inhibitor concentrate (1000-1500 units given intravenously over 20-30 min),
  - fresh frozen plasma (FFP) if this is not available
- **prophylaxis**:
  - anabolic steroid, synthetic androgen: Danazol may help
  - aminocaproic acid

Other Causes of angioedema

- Angioedema associated with angiotensin-converting enzyme (ACE) inhibitors is the commonest cause of these swellings involving the face and tongue; it often begins several years after starting an ACE inhibitor
- Salicylate- and/or aspirin-associated angioedema ➔ more likely to coexist with urticaria
- Idiopathic angioedema

Complication

- **If treatment fails to normalise the C4 levels and they remain persistently low, these patients are at an increased risk of developing SLE.**

The granulomatous response

- A granuloma is a collection of macrophages: giant cells as a nidus of chronic inflammation
- The centre may necrotise to form caseation, classically in tuberculosis
- **Granuloma is seen in :**
  - **tertiary syphilis**
  - sarcoidosis
  - Crohn's
  - Wegener's granulomatosis

IgG deficiency

- In IgG subclass deficiency, the overall level of IgG may be normal or slightly reduced
- **IgG2 deficiency** ➔increase susceptibility to infections with polysaccharide-coated bacteria, including Haemophilus influenzae, ➔ multiple presentations with otitis media and respiratory tract infections
- If these patients are vaccinated with Pneumovax, they are still unable to mount a response to S. pneumoniae antigens
- IgG3 deficiency ➔ increase susceptibility to infections with Moraxella catarrhalis,➔frequent chronic sinusitis
- IgG1 deficiency normally occurs as part of a wider picture of common variable immunodeficiency

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IgG4-related disease

- IgG4-related disease has been described in virtually every organ system: the biliary tree, salivary glands, periorbital tissues, kidneys, lungs, lymph nodes, meninges, aorta, breast, prostate, thyroid, pericardium, and skin.
- The histopathological features are similar across organs, regardless of the site.
- IgG4-related disease is analogous to sarcoidosis, in which diverse organ manifestations are linked by similar histopathological characteristics.
- **Raised concentrations of IgG4 in tissue and serum can be helpful in diagnosing IgG4 disease**, but neither is a specific diagnostic marker.

Examples include:

- Riedel's Thyroiditis
- Autoimmune pancreatitis
- Mediastinal and Retroperitoneal Fibrosis
- Periaortitis/periarteritis/Inflammatory aortic aneurysm

- Kuttner's Tumour (submandibular glands) & Mikulicz Syndrome (salivary and lacrimal glands)
- Possibly sjogren's and primary biliary cirrhosis

Isolated IgD deficiency

- No specific signs or symptoms
- **increased viral respiratory tract infections**,
  - **IgE** deficiency leads to both **viral and parasitic infections**
- IgA, IgG and IgM levels are entirely normal
- isolated IgD deficiency has been identified amongst people of Basque origin, hence the link to northern Spain
- not require any specific treatment

Notes & Notes

For MRCP part 1 & 11

By

Dr. Yousif Abdallah Hamad

Basic sciences

Genetics

Updated

2017

Contains:

1/ Passmedicine 2017

2/ On examination 2017

3/ Pastest 2017

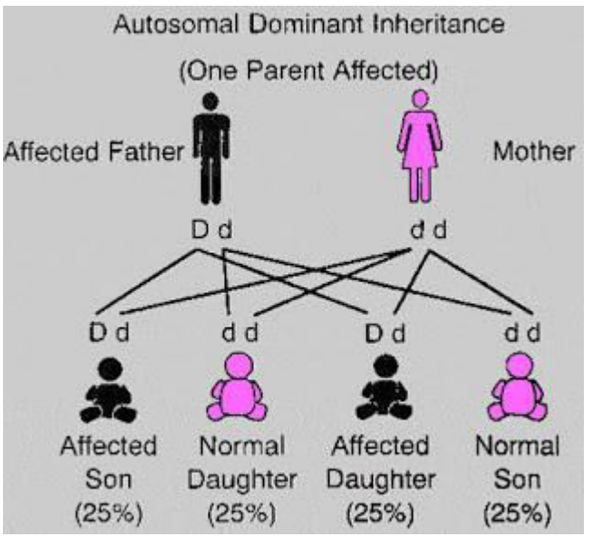
4/ **Red fonts --> previous exams**

5/ Other updated UK sources

Autosomal dominant conditions

Autosomal recessive conditions are often thought to be 'metabolic' as opposed to autosomal dominant conditions being 'structural', notable exceptions:

- some 'metabolic' conditions such as Hunter's and G6PD are X-linked recessive whilst others such as hyperlipidemia type II and hypokalemic periodic paralysis are autosomal dominant
- some 'structural' conditions such as ataxia telangiectasia and Friedreich's ataxia are autosomal recessive



The following conditions are **autosomal dominant:**

- **Achondroplasia**
- Acute intermittent porphyria
- Adult polycystic disease
- Antithrombin III deficiency
- Ehlers-Danlos syndrome
- Familial adenomatous polyposis
- Hereditary haemorrhagic telangiectasia
- Hereditary spherocytosis
- Hereditary non-polyposis colorectal carcinoma
- Huntington's disease
- Hyperlipidaemia type II
- Hypokalaemic periodic paralysis
- Malignant hyperthermia
- Marfan's syndromes
- Myotonic dystrophy
- Neurofibromatosis
- **Noonan syndrome**
- Osteogenesis imperfecta
- Peutz-Jeghers syndrome
- Retinoblastoma
- Romano-Ward syndrome
- **Tuberose sclerosis**
- Von Hippel-Lindau syndrome
- Von Willebrand's disease*

As an autosomal dominant condition, two affected parents can expect:

- **1 in 4 chance of an unaffected child**
- 1 in 2 chance of an affected heterozygous child
- 1 in 4 chance of an affected homozygous child.

Which disease demonstrates autosomal co-dominant inheritance?

➔ **Alpha-1-antitrypsin deficiency**

*type 3 von Willebrand's disease (most severe form) is inherited as an autosomal recessive trait. Around 80% of patients have type 1 disease

Achondroplasia

Etiology

- **Mutation in fibroblast growth factor receptor 3 gene (FGFR3) → reduced endochondral ossification**
- **autosomal dominant**
- The homozygous form is usually fatal.

Epidemiology

- Most common type of skeletal dysplasia and disproportionate short stature (1:40,000 children worldwide affected)
- The incidence **increases with paternal age**.

Pathophysiology

- Epiphyseal growth cartilage fails,
- there is **normal bone formation and repair**.
  - Therefore **NO** increased risk of fracture.

Features

becomes obvious within the first year with disparity between a large skull, normal trunk length and short limbs.

- short stature
- short limbs (rhizomelia) with shortened fingers (brachydactyly)
  - The fingertips may only come down to the iliac crest, and the shortness of the limbs is often most marked proximally.
  - short stature due to shortening of the limbs, but spinal length is maintained.
  - The limbs appear broad with deep creases.
- large head (Macrocephaly) with frontal bossing
- midface hypoplasia with a flattened nasal bridge
- 'trident' hands
- lumbar lordosis
- Normal intelligence

Complications

- Small foramen magnum → compression of the cervical medulla
- Spinal canal stenosis and radiculopathy (of the lower back)
  - low back and leg pain,
  - paresthesias, dysesthesia,
  - incontinence
- Secondary scoliosis
- **Recurrent otitis media**
- Cardiopulmonary complications (due to a small chest wall)

Diagnostics

- **X-ray**
  - **It may be diagnosed radiographically at birth**,
  - Lateral skull
    - midface hypoplasia,
    - frontal prominence
  - pelvis
    - narrow in anteroposterior diameter with deep sacroiliac notches and short iliac wings.
  - Spine
    - progressive narrowing of the interpedicular distance from top to bottom (reverse of normal).
      - abnormally narrow interpedicular distance → spinal canal stenosis; scoliosis
  - Extremities
    - bones are short and broad;
    - short fingers
    - metaphyseal irregularity,
    - flaring in the long bones,
    - late-appearing irregular epiphyses.

Management

- medical
  - Early administration of **growth hormone** (1–6 years)
- Surgical corrections:
  - spinal stenosis, secondary scoliosis, genu varum, foramen magnum decompression

Osteogenesis imperfecta ("brittle bone disease")

- **Etiology**
  - rare, **autosomal dominant mutation** in **COL**1A1 or **COL**1A2 genes;
  - results in **defective type I collagen synthesis** due to decreased synthesis of **pro-alpha 1** or **pro-alpha 2** collagen polypeptides.
- **Clinical features**
  - **Growth retardation**
  - **Skeletal deformities, brittle bones, and recurrent fractures from minimal trauma**
  - **Blue sclerae due to visible choroidal pigment.**
  - **Progressive hearing loss** secondary to **otosclerosis**
  - **Brittle, opalescent teeth** (dental imperfections)
- **Types**
  - type 1:The most common, and milder form.
  - Type II: most severe form; lethal perinatally or within the first year
- **Diagnostics**
  - DNA test
  - Ultrasonography before birth and radiographic skeletal survey afterwards (fractures, callus, deformities)
  - **Bone or skin biopsy → type 1 collagen mutation**
- **Therapy**
  - No cure available
  - IV **bisphosphonates** to increase cortical thickness
  - Surgery for functional improvement

May 2009 exam: A pregnant woman is known to have polycystic kidney disease. What is the chance her child will also have the disease? 50% (Polycystic kidney disease is usually inherited in an autosomal dominant fashion and hence 50% of her children will be affected, regardless of gender)

Down's syndrome (trisomy 21)

Epidemiology and genetics

- the most common autosomal abnormality

Risk of Down's syndrome with increasing maternal age

Age (years)	Risk
20	**1 in 1,500**
30	1 in 800
35	1 in 270
40	1 in 100
45	1 in 50 or greater

One way of remembering this is by starting at 1/1,000 at 30 years and then dividing the denominator by 3 (i.e. 3 times more common) for every extra 5 years of age

Cytogenetics

Mode	% of cases	Risk of recurrence
Non-disjunction	**94%**	1 in 100 if under mother < 35 years
Robertsonian translocation (usually onto 14)	5%	10-15% if mother is translocation carrier 2.5% if father is translocation carrier
Mosaicism	1%	

- The chance of a further child with Down's syndrome is approximately 1 in 100 if the mother is less than 35 years old. If the trisomy 21 is a result of a translocation the risk is much higher.
- Down syndrome have one of the two karyotypes:
  1. 47,XX,+21 (trisomy 21)
     - ❖ more common
  2. 46,XY,der(14;21).
     - ❖ characterized by the presence of two normal chromosomes 21, one normal chromosome 14 and a product of Robertsonian translocation between chromosomes 14 and 21 (der(14;21); der stands for derivative).

Features

Clinical features

- face: upslanting palpebral fissures, epicanthic folds, Brushfield spots in iris, protruding tongue, small ears, round/flat face
- flat occiput
- single palmar crease, pronounced 'sandal gap' between big and first toe
- hypotonia
- congenital heart defects (40-50%, see below)
- duodenal atresia **can be diagnosed by U/S at gestation → double bubble sign**
- Hirschsprung's disease

associations

- **Children with Down syndrome are at increased risk for developing acute myeloid leukemia (AML)** (approximately 1-2% of children with Down syndrome develop AML, the great majority < 5 y) rather than acute lymphoblastic leukemia (ALL), which is a more common form of leukemia in children.
- Other haematological disorders associated with Down's syndrome include:
  - ➢ Fanconi's anaemia,
  - ➢ Patients with learning disabilities may be prone to lead poisoning due to pica.

Cardiac complications

- 50% of children with Down's syndrome have a cardiac defect.
- multiple cardiac problems may be present

- **endocardial cushion defect (c. 40%, also known as atrioventricular septal canal defects)**
- ventricular septal defect (c. 30%)
- secundum atrial septal defect (c. 10%)
- tetralogy of Fallot (c. 5%)
- isolated patent ductus arteriosus (c. 5%)

Later complications

- subfertility: males are almost always infertile due to impaired spermatogenesis. **Females are usually subfertile,** and have an increased incidence of problems with pregnancy and labour
- learning difficulties
- short stature
- repeated respiratory infections (+hearing impairment from glue ear)
- acute lymphoblastic leukaemia
- hypothyroidism
- Alzheimer's
- atlantoaxial instability

Diagnosis

Screening tests

- **Increased nuchal translucency is a finding on ultrasound** that may suggest trisomy 21 or other chromosomal defects such as trisomy 18 or 45 XO, thus additional testing is required to confirm the diagnosis.
- Alpha-fetoprotein **(AFP),** human chorionic gonadotropin **(hCG),** urine unconjugated **estriol**, and **inhibin** are components of the **quad screen** for Down syndrome.
  - **↓ AFP ↓ unconjugated estriol ↑ hCG ↑ inhibin is consistent with the diagnosis of Down syndrome.**
  - **quad screen** done between the 15th and 22nd weeks of the pregnancy.
  - In pregnancies where the fetus has **Edwards syndrome (trisomy 18),** unconjugated estriol and **hCG** levels are **low** and AFP levels can be variable.
  - Anencephaly will have a low hCG and a high AFP value.
  - Beta hCG should double in value every 48-72 hours and a decreased hCG should raise suspicion for an ectopic pregnancy or a missed abortion.
  - **Elevations of AFP** are associated with **neural tube defects**, multiple gestations or **abnormal dating.**

Diagnostic tests

- amniocentesis

Down Versus Edwards Syndrome

	Down Syndrome	Edwards Syndrome
Distinguishing characteristics	**Upward slanting palpebral fissures,** speckled iris, inner epicanthal fold; **simian crease**	**Low-set, malformed ears, clenched fist, rocker-bottom feet**
Gastrointestinal anomalies	**Duodenal atresia**	**Omphalocele**
Lifespan	Most survive Long-term sequelae include increased risk of **acute lymphocytic leukemia.**	Do not survive first year of life (rare)

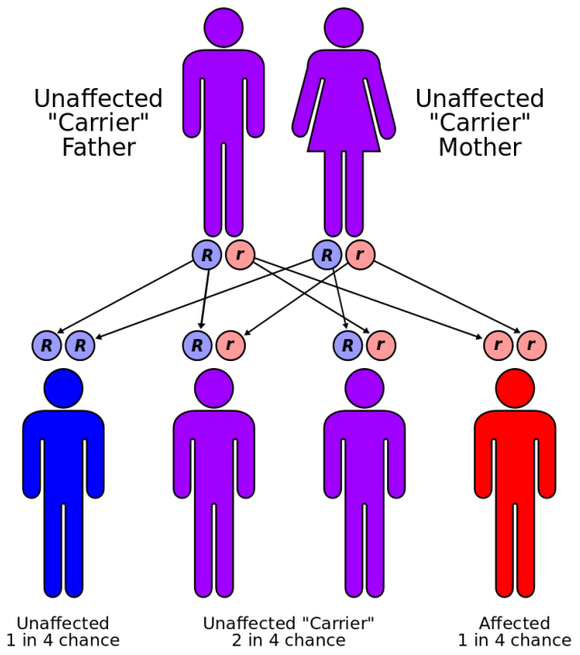
Noonan's syndrome

- Noonan's syndrome is a mutation affecting the RAS-MAPK pathway.
- It is an autosomal dominant disorder

feature

- short stature,
- learning disabilities,
- pectus deformity and
- congenital cardiac defects **(typically pulmonary stenosis, atrial septal defect (ASD)** and occasionally hypertrophic cardiomyopathy).

Autosomal recessive conditions



Two copies of the defective gene (one inherited from each parent) are required in order to be born with the disorder.

Autosomal recessive conditions are often thought to be '**metabolic**' as opposed to autosomal dominant conditions being 'structural', notable exceptions:

- some '**metabolic**' conditions such as Hunter's and G6PD are X-linked recessive whilst others such as hyperlipidemia type II and hypokalemic periodic paralysis are autosomal dominant
- some **'structural'** conditions such as ataxia telangiectasia and Friedreich's ataxia are autosomal recessive

The following conditions are **autosomal recessive**:

- Albinism
- Ataxia telangiectasia
- **Congenital adrenal hyperplasia**
- Cystic fibrosis
- Cystinuria
- Familial Mediterranean Fever
- Fanconi anaemia
- Friedreich's ataxia
- Gilbert's syndrome*
- Glycogen storage disease
- Haemochromatosis
- Homocystinuria
- Lipid storage disease: Tay-Sach's, Gaucher, Niemann-Pick
- Mucopolysaccharidoses: Hurler's
- PKU
- Sickle cell anaemia
- Thalassaemias
- Wilson's disease

*this is still a matter of debate and many textbooks will list Gilbert's as autosomal dominant

May 2012 exam: A man diagnosed as having hereditary hemochromatosis. His wife is not a carrier. What is the chance his child will develop haemochromatosis? 0% (Haemochromatosis is an autosomal recessive condition. If one of the parents has haemochromatosis (i.e. is homozygous) and the other is not a carrier/affected then all the children will inherit one copy of the gene from the affected parent and hence will be carriers)

Pseudoxanthoma elasticum

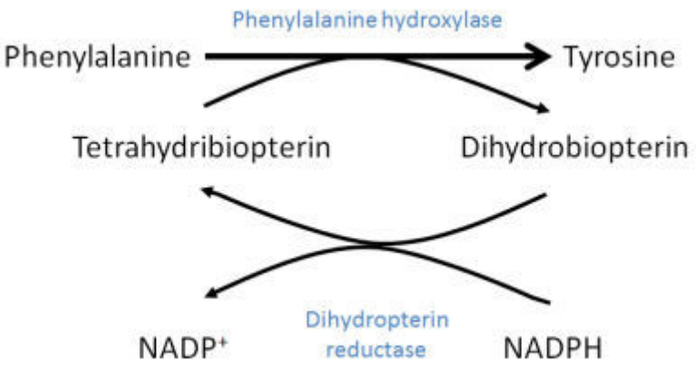
- inherited condition (**usually autosomal recessive***) characterised by an abnormality in elastic fibres
  - *there are reports of autosomal dominant inheritance in a minority of cases

Features

- retinal angioid streaks
- **'plucked chicken skin' appearance** - small yellow papules on the neck, antecubital fossa and axillae
- cardiac: mitral valve prolapse, increased risk of ischaemic heart disease
  - Due to loss of elastic tissue, patients have an increased incidence of mitral regurgitation, aortic regurgitation and aortic dissection.
- **gastrointestinal haemorrhage**

Phenylketonuria (PKU)

- Phenylalanine is an essential amino acid.
- Phenylketonuria (PKU) is an autosomal recessive condition
- Caused by a disorder of phenylalanine metabolism.
  - usually **due to defect in phenylalanine hydroxylase**, an enzyme which converts phenylalanine to tyrosine .
  - In a small number of cases the underlying defect is a deficiency of the tetrahydrobiopterin-deficient cofactor, e.g. secondary to defective dihydrobiopterin reductase.
- The gene for phenylalanine hydroxylase is located on chromosome 12.
- The incidence of PKU is around 1 in 10,000 live births.
- High levels of phenylalanine lead to problems such as learning difficulties and seizures.



Features

- usually presents by 6 months e.g. with developmental delay, infantile spasms
- child classically has fair hair and blue eyes
- learning difficulties
  - **Even with dietary treatment some degree of cognitive impairment is seen**
- Microcephaly, prominent maxilla, growth retardation and wide-spaced teeth are found in untreated children.
- seizures, typically infantile spasms
  - About 25% of infants have seizures, but over 50% have an abnormal EEG.
- Cerebral white matter changes are seen in older patients and may reflect a combination of late diagnosis and dietary indiscretion.
- eczema
- **'musty' odour** to urine and sweat* (*secondary to phenylacetate, a phenylketone)

Diagnosis

- Diagnosis of classic PKU requires raised Phe levels, **increased urinary Phe metabolites** and normal cofactor (tetrahydrobiopterin) concentrations.
  - plasma levels of tyrosine are difficult to measure, and have diurnal variation. Whilst the levels are often low in patients with PKU, the levels can be normal depending on what time of the day the sample is taken and whether or not the patients are being treated.
- Guthrie test: the 'heel-prick' test done at 5-9 days of life - also looks for other biochemical disorders such as hypothyroidism
- hyperphenylalaninaemia
- phenylpyruvic acid in urine

Management

- poor evidence base to suggest strict diet prevents learning disabilities
- dietary restrictions are however important during pregnancy as genetically normal fetuses may be affected by high maternal phenylalanine levels

Alkaptonuria

The **black** discoloration of sclera and urine becoming **black** on standing should alert you to the likelihood of **Alkaptonuria**.

- autosomal recessive disorder of phenylalanine and tyrosine metabolism

- **caused by** a **deficiency of homogentisic acid oxidase** responsible for the degradation of homogentisic acid produced from phenylalanine and tyrosine.
- Accumulation of homogentisic acid causes pigmentation of the urine, sclera and connective tissues.
- Alkaptonuria is generally a benign and often asymptomatic condition.

Features

- pigmented sclera
- **urine turns black if left exposed to the air**
- Deposition in the joints causes cartilage pigmentation (ochronosis) and degeneration.
  - **Patients develop arthritis at 40 years of age.**
  - intervertebral disc calcification may result in back pain
  - The knees and spine are commonly affected.
  - The sacroiliac joint may be spared.
- renal stones
- Homogentisic acid is a reducing agent, therefore it gives a false **positive Glucostix test** but normal Clinitest.

Treatment

- high-dose vitamin C
- dietary restriction of phenylalanine and tyrosine

X-linked recessive

X-linked recessive conditions - there is no male-to-male transmission. Affected males can only have unaffected sons and carrier daughters.

X-linked conditions: Duchenne/Becker, haemophilia, G6PD

- The abnormal gene is carried on the X chromosome, and in the carrier female, the normal allele on her other X chromosome protects her from the disease. Since the male does not have this protection, he manifests the disease.
- only males are affected. An exception to this seen in examinations are **patients with Turner's syndrome, who are affected due to only having one X chromosome.**
- Females only occasionally show mild sign of disease
- X-linked recessive disorders are transmitted by heterozygote females (carriers) and male-to-male transmission is not seen.
- **Affected males can only have unaffected sons and carrier daughters.**
- heterozygous female carrier →
  - 50% of male children are affected
  - 50% of female children are carrier
- The possibility of an affected father having children with a heterozygous female carrier is generally speaking extremely rare. However, in certain Afro-Caribbean communities G6PD deficiency is relatively common and homozygous females with clinical manifestations of the enzyme defect are seen.
- **Many of the inherited eye disorders such as retinitis pigmentosa and ocular albinism are inherited in an x-linked recessive pattern.**
- **The following conditions are inherited in a X-linked recessive fashion:**
  - Androgen insensitivity syndrome
  - Becker muscular dystrophy
  - Colour blindness
  - Duchenne muscular dystrophy
  - **Fabry's disease**
  - G6PD deficiency
  - Haemophilia A,B
  - Hunter's disease
  - Lesch-Nyhan syndrome
  - Nephrogenic diabetes insipidus
  - Ocular albinism
  - Retinitis pigmentosa
  - Wiskott-Aldrich syndrome
  - Fragile X syndrome

- **The following diseases have varying patterns of inheritance, with the majority being in an X-linked recessive fashion:**
  - Chronic granulomatous disease (in > 70%)

Fabry's disease

Definition

- **X-linked recessive,** lysosomal storage disorder characterised by myelin deposits in tubular epithelium and vascular endothelium, resulting in ischaemic nephropathy

Aetiopathogenesis

- The molecular defect is a **deficiency of α-galactosidase A**
  - The affected lysosomal enzyme, α-galactosidase A, converts trihexosyl ceramide to lactosyl ceramide.
  - **Accumulation of trihexosyl ceramide** in the endothelial smooth muscle cells of blood vessels causes ischemia and infarction, particularly in the kidneys, which explains the elevated BUN and proteinuria.

Features and Complications

The disorder has three distinct clinical entities:

1. Classical presentation in the male homozygote with early presentation in childhood - angiokeratomas, heart failure, cataracts and renal disease
2. **Male homozygotes with atypical presentation in adulthood with proteinuria, acroparaesthesia, angiokeratomas and cardiomegaly**
3. Female heterozygotes can present again in adulthood with similar mild symptoms.
   - An X linked recessively inherited condition can exist in female carriers who may exhibit mild to moderate symptoms. This is due to variable expression according to random X inactivation of the affected gene in embryogenesis

- often start in childhood or adolescence
- **Opacity of the lens and cornea**,
- **skin lesions** with telangiectasia and a warty, hyperkeratinized covering (**angiokeratoma**),
  - Angiokeratomas are present in 66% of male and 36% of female
  - They are non-blanching, red to blue-black lesions 1-5 mm in diameter.
  - The earliest lesions are observed on the hands, knees, elbows and flanks.
- **Peripheral neuropathy**
  - paresthesias in the extremities,
  - usually burning in nature,
  - painful stocking-glove neuropathy
  - Patients may complain of pain and burning in the hands and feet that worsens with exercise or hot weather
- **hypohidrosis** (decreased sweating)
- Complications
  - vascular diseases of the brain, heart, and kidneys.
    - accumulation of the sphingolipids can lead to systemic vasculopathy
    - Often, renal disease is progressive and can lead to death.
  - cardiac conduction defects

most common symptoms → peripheral neuropathy, angiokeratomas, and hypohidrosis.

Diagnosis

- The diagnosis is confirmed by demonstration of **absent or deficient levels of alpha-galactosidase A** in leucocytes, plasma or cultured fibroblasts.
- The most efficient means of diagnosis is by **slit-lamp examination** of the cornea, which reveals microscopic lipid deposits
- Microscopy of the spun urine sediment may demonstrate 'Maltese cross' lipid globules
- Further clues to the diagnosis include **skin angiokeratomas**, **decreased sweating** and leg lymphedema

In Fabry disease, tissue accumulation of which is most likely to occur?

➡ **Trihexosyl ceramide**

X-linked dominant disorders

➡ **No carrier (the carrier of a defective gene associated with a disorder, will have the**

disorder)
- **affected woman → Half of the daughters and sons are affected**
- **affected father → all his daughters are affected but none of his sons.**

- The gene responsible for a genetic disorder is located on the X chromosome, and only one copy of the allele is sufficient to cause the disorder when inherited from a parent who has the disorder.
- X linked dominant disorders are rare (for example, **vitamin D-resistant rickets**).
- They affect both sexes but **females more than males.**
  - Males can only get an X chromosome from their mother whilst females get an X chromosome from both parents. As a result, females tend to show higher prevalence of X-linked dominant disorders because they have more of a chance to inherit a faulty X chromosome.
- Homozygous mother → All children are affected.
- An affected mother with the trait → half the sons and half the daughters inherit the disorder
- when the mother alone is the carrier ; she herself will have the disorder.
  - 50% Of her daughters and sons will have the disorder,
  - 50% will be unaffected.
- **Affected females will transmit the condition to 50% of their children**, **whether male or female.**
- When the father alone is the carrier of a defective gene associated with a disorder, he too will have the disorder.
  - 100% Of his daughters will have the disorder, since all of his daughters will receive one copy of his single X chromosome.
  - none of his sons will have the disorder; sons do not receive an X chromosome from their father.
  - **affected father → all his daughters are affected but none of his sons.**

Vitamin D-resistant rickets

- Vitamin D-resistant rickets is a **X-linked dominant** condition
  - affected female will transmit the disease to 50% of her sons and 50% of her daughters.
  - affected male will transmit the condition to all of his daughters but none of his sons.
- usually presents in infancy with failure to thrive.
- It is caused by impaired phosphate reabsorption in the renal tubules

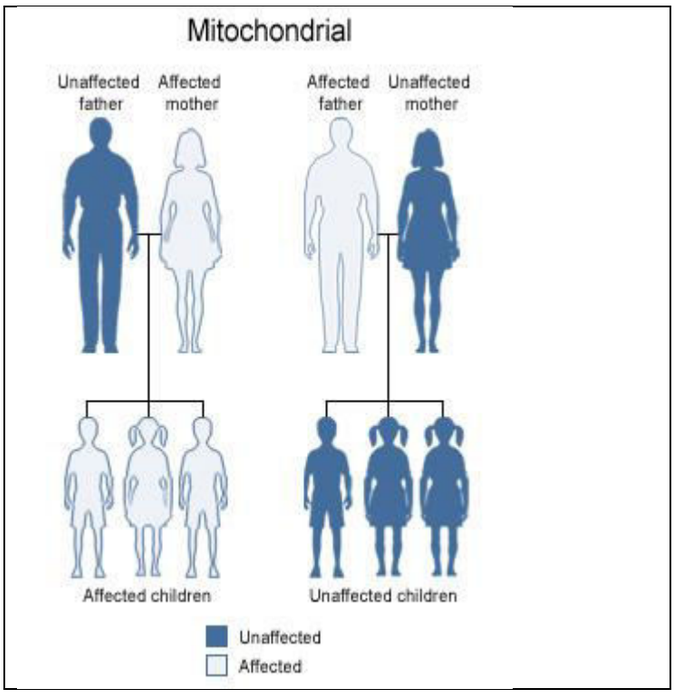
Features
- failure to thrive
- normal serum calcium, low phosphate, elevated alkaline phosphotase
- x-ray changes: cupped metaphyses with widening of the epiphyses

Diagnosis is made by demonstrating increased urinary phosphate

Management
- high-dose vitamin D supplements
- oral phosphate supplements

Mitochondrial diseases

Mitochondrial diseases follow a maternal inheritance pattern



myoclonic epilepsy with ragged red fibres (MERRF):
a young patient presenting with cognitive impairment developing after a period of normal development, seizures, myoclonic jerks, Wolff-Parkinson White syndrome and worsening vision (consistent with optic atrophy). diagnosis → **(MERRF),** which is a mitochondrial DNA disorder **diagnosed by → ragged red fibres on muscle biopsy.**

- Whilst most DNA is found in the cell nucleus, a small amount of double-stranded DNA is present in the mitochondria. It encodes protein components of the respiratory chain and some special types of RNA

Mitochondrial inheritance has the following characteristics:

- inheritance is only via the maternal line as the sperm contributes no cytoplasm to the zygote
- all children of affected males will not inherit the disease
- all children of affected females will inherit it
- generally encode rare neurological diseases
- **poor genotype: phenotype correlation** - within a tissue or cell there can be different mitochondrial populations - this is known as heteroplasmy)

Histology

- muscle biopsy classically shows **'red, ragged fibres'** due to increased number of mitochondria

Examples include:

- **Leber's optic atrophy**
  - Cyanocobalamin (a form of B12) should be avoided as it may lead to blindness in Leber's disease patients.
- MELAS syndrome: mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes
- MERRF syndrome: myoclonus epilepsy with ragged-red fibres
- sensorineural hearing loss

Kearns-Sayre syndrome:

Kearns-Sayre syndrome produces the classic triad of:

- Progressive external ophthalmoplegia
- Pigmentary degeneration of the retina and
- Heart block.

- mitochondrial DNA mutation.
- It is a slowly progressive neuromuscular disorder **associated with progressive external ophthalmoplegia and heart conduction defect.**
- onset in patients < 20 years old
- external ophthalmoplegia
- retinitis pigmentosa
- Ptosis may be seen
- sensorineural hearing loss is almost universal in those who survive into the fourth decade of life; this may not be fully corrected with hearing aids.
- Other associated features: cerebellar ataxia, cardiac conduction block, raised cerebrospinal fluid (CSF) proteins, and proximal myopathy.

- short stature and **multiple endocrinopathies** including diabetes mellitus, hypoparathyroidism, and Addison disease.
- **Muscle biopsy may reveal ragged red fibers.**
- Muscle histochemistry reveals deficiency of cytochrome c oxidase (mitochondrial respiratory chain enzyme).

Kearns-Sayre syndrome
- mitochondrial inheritance
- onset < 20-years-old
- external ophthalmoplegia
- retinitis pigmentosa

Kallman's syndrome

Klinefelter's - LH & FSH raised
Kallman's - LH & FSH low-normal

- Kallman's syndrome is a recognised cause of delayed puberty secondary to hypogonadotrophic hypogonadism.
- It is usually inherited as an **X-linked recessive** trait.
  - Whilst the majority of cases are sporadic, perhaps up to 50% of cases are due to genetic inheritance.
- caused by failure of GnRH-secreting neurons to migrate to the hypothalamus → gonadotrophin releasing hormone (GnRH) deficiency
- may arise due to abnormalities of the KAL-1 or KAL-2 gene (encoding anosmin-1 and FGF-1).
- There is isolated gonadotrophic deficiency (may be evidenced by a normal prolactin).
- The clue given in many questions is lack of smell (anosmia) in a boy with delayed puberty

Incidence

- 1 in 10,000 males,
- More common in men: male to female ratio of 4:1.

Features

- delayed puberty
- hypogonadotrophic hypogonadism
  - sex hormone levels are low
  - LH, FSH levels are inappropriately low/normal
  - Lack of development of secondary sexual characteristics
  - Primary amenorrhoea.
- cryptorchidism **(Cryptorchidism is more suggestive of Kallman's than Klinefelter's syndrome)**
  - Cryptorchidism is the absence of one or both testes from the scrotum (undescended testis).
- anosmia **(Lack sense of smell) due to failure of the olfactory bulb to develop, leading to loss of gonadotropin releasing hormones.**
  - Anosmia is present in 75%
- Cleft lip/palate
- visual defects : colour blindness,
- deafness.
- patients are typically of normal or above average height
- **no mental retardation**

Diagnosis

- **Diagnostic test → Fluorescent in situ hybridisation (FISH) is currently the best means of a genetic diagnosis**
- Absent olfactory bulbs are present on 75% of MRI scans in these patients.

- **The appearance on cerebral MRI → Absent olfactory bulbs**

Treatment

- **For a male who begin a relationship with a woman**
  - **Pulsed (NOT Continuous) GnRH treatment** is needed to restore LH and FSH release.
    - It needs to be continued for as long as fertility is required.
    - As natural GnRH release is pulsatile, continuous therapy fails to lead to LH and FSH release.
    - Once his family is complete, switching to testosterone therapy may be more convenient for him.
    - Although Testosterone supplementation will restores secondary sexual characteristics, it doesn't restore fertility and is therefore not appropriate here.
    - FSH can be used to induce fertility, but it is less effective than pulsed GnRH therapy.
- LH can be used in conjunction with FSH **to induce fertility in women with Kallmann syndrome**.
- **For a woman who wants to start a family:**
  - **HCG** to drive production of gonadal steroid hormones, **FSH** to drive ovulation, harvesting of eggs, and **IVF**. This process is most effective in achieving successful pregnancy.

Klinefelter's syndrome

Klinefelter's? - do a karyotype

- Klinefelter's syndrome is associated with male phenotype and **47, XXY karyotype**
- the commonest form of which is XXY, is the result of chromosomal non-dysjunction; as such, it does not follow a mendelian pattern of inheritance.
- Population studies suggest that the rate of occurrence in live male births is between **1 in 500** and 1 in 1000.
- The rate of chromosomal non-dysjunction increases with increasing maternal age and increasing paternal age, each parent contributing 50% of the risk. Around 60% of Klinefelter cases do not survive the fetal period.
- **has no specific genetic pattern of inheritance**
  - **chances of inheriting the disorder → < 1%**

Features

- often taller than average
- lack of secondary sexual characteristics
- small, firm testes
- infertile, azoospermia
- gynaecomastia
  - **increased incidence of breast cancer** (20 times higher than a normal male).
- elevated gonadotrophin levels **(↑↑LH/FSH)** due to testicular failure
- Low testosterone levels
- **Low HDL cholesterol**, elevated triglyceride ,normal or increased (LDL)
- increased cardiovascular risk due to lipid abnormality.
- decrease libido
- decrease bone mineral density → increased risk of osteoporotic fractures.

Investigation

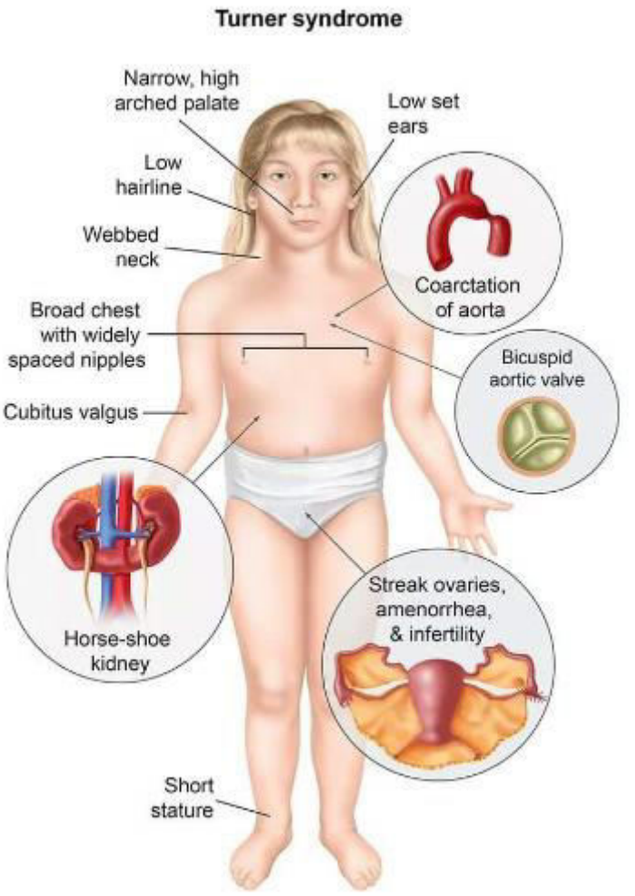
- **Diagnosis is by chromosomal analysis**
- **the most appropriate investigation in suspected cases → FSH, LH**
  - Both FSH and LH are raised in Klinefelter syndrome, and elevation would be a strong pointer to confirming the underlying diagnosis.

- more useful than Testosterone (wouldn't indicate whether the defect was at the level of the pituitary or the testes)

Treatment with testosterone

- **Testosterone is known to improve bone mineralization and is the treatment of choice**

Turner's syndrome



- Turner's syndrome is a chromosomal disorder affecting around 1 in 2,500 females.
- It is caused by either the presence of only one sex chromosome (X) or a deletion of the short arm of one of the X chromosomes.
- **Turner's syndrome is denoted as 45,XO or 45,X**

Features

- short stature
- shield chest, widely spaced nipples
- webbed neck
- cardiac defects: bicuspid aortic valve (15%), coarctation of the aorta (5-10%)
- **primary amenorrhoea**
- **associated absent uterus and streak ovaries**
- cystic hygroma (often diagnosed prenatally)
- high-arched palate
- short fourth metacarpal
- multiple pigmented naevi
- **keloid scars**
- lymphoedema in neonates (especially feet)
- **Horseshoe kidney** is strongly associated with Turner's syndrome
  - often initially presents with stone disease, pelviureteric junction (PUJ) obstruction, trauma, infections and tumors.
  - In a pediatric patient with multiple urinary tract infections or renal stones, imaging must be performed to rule out this congenital anomaly.

- **Which anatomical structures is responsible for horseshoe kidney anomaly during normal embryological development?**
  - **Inferior mesenteric artery**
  - occurs when the isthmus of the kidney becomes trapped behind the inferior mesenteric artery as the kidneys ascend during embryonic life.

Associated conditions

- autoimmune diseases:
  - autoimmune thyroiditis **(hypothyroidism (much more common in Turner's))**
  - and Crohn's disease
- **Hypertension is quite common in Turner syndrome (10%) and is typically idiopathic - essential.** In a **small proportion** causes can include:
  - coarctation of the aorta
  - and renal dysfunction due to horsehoe kidney.
- metabolic abnormalities (dyslipidaemia and glucose intolerance)
- recurrent otitis media.

Diagnosis

- **→ made by → karyotype → identification of 45X0 .**

Marfan's syndrome

- **autosomal dominant** connective tissue disorder.
- caused by a defect in the fibrillin-1 gene on chromosome 15
- affects around 1 in 3,000 people.
- may occur as a spontaneous mutation, (1/3rd of cases), and this occurs more commonly to offspring of older males.

Features

- tall stature with arm span to height ratio > 1.05
- high-arched palate
- arachnodactyly
- pectus excavatum
- pes planus
- scoliosis of > 20 degrees
- crowded teeth.
- **Heart:**
  - **dilation of the aortic sinuses (seen in 90%)** which may lead to aortic aneurysm, aortic dissection, aortic regurgitation, mitral valve prolapse (75%),
- lungs: repeated pneumothoraces
- eyes:
  - upwards lens dislocation (superotemporal ectopia lentis)
    - seen in 50% of patients,
  - **Retinal detachment**
  - blue sclera,
  - myopia
  - early glaucoma, and early cataracts.
  - increased axial globe length
- dural ectasia (ballooning of the dural sac at the lumbosacral level)
  - Dural ectasia affects around 60% of patients with Marfan's syndrome.
  - **It may cause lower back pain associated with neurological problems such as bladder and bowel dysfunction.**

Diagnosis

- Unfortunately **DNA testing for fibrillin gene mutations, whilst helpful, cannot exclude a diagnosis of Marfan because a number of mutations exist (at least 130**).
- Hence **diagnosis is made on the major and minor features associated with the syndrome.**

Prognosis & treatment :

- The life expectancy of patients used to be around 40-50 years.
- With the advent of regular echocardiography monitoring and beta-blocker/ACE-inhibitor therapy this has improved significantly over recent years.

- Treatment with β-blockers reduces the rate of aortic dilatation and the risk of rupture
- Aortic dissection and other cardiovascular problems remain the leading cause of death however.
- Pregnancy is associated with increased risk of aortic rupture

Homocystinuria

- autosomal recessive disease
- caused by **deficiency of cystathionine beta synthase** which is responsible for converting homocysteine to cystathionine. Cystathionine is later converted to cysteine, so patients who have this enzyme deficiency **need to supplement their diets with exogenous cysteine**.
- Results in an accumulation of homocysteine which is then oxidized to homocystine.

Types

- **homocystinuria type 1 → a defect in cystathionine synthetase is responsible.**
- homocystinuria type 2 → defects in methylene tetrahydrofolate reductase
  - However, individuals with this condition rarely survive the neonatal period or, if they survive longer than this, they often have more severe mental retardation.

Features

- fine, fair hair
- musculoskeletal: may be similar to Marfan's - arachnodactyly etc
- neurological: learning difficulties, mild to moderate mental handicap ,seizures
- ocular: downwards (inferonasal) dislocation of lens
- The sudden visual deterioration could either be due to a thrombotic episode or to the lens dislocation associated with this condition.
- **increased risk of arterial and venous thromboembolism** (atherosclerosis, thrombosis, MI)
  - the most common cause of death.
- malar flush,
- **livedo reticularis**

Diagnosis

- made by the **cyanide-nitroprusside test**, which is also positive in cystinuria

Treatment

- dietary modification aim to:
  - reduce intake of methionine
  - increase intake of cysteine.
- vitamin B6 (pyridoxine) supplements
  - Folate and vitamin B12 are facilitate the conversion of homocysteine to methionine.

Homocystinuria VS Marfan's

	homocystinuria	Marfan's syndrome
inheritance	autosomal recessive	autosomal dominant
lens dislocation	downward lens dislocation	upward lens dislocation
aortic incompetence	heart rarely affected	aortic incompetence may occur
intellectual development	**mental retardation** (nearly 50%)	**normal**
livedo reticularis	**seen** due to the venous thrombosis in the small vessels of the skin	**NO**
other principle features	**osteoporosis**, recurrent thromboembolism; **characteristic laboratory features**: plasma methionine and homocystine levels are elevated, homocystine is excreted in the urine, plasma cystine levels are reduced, positive urine cyanide-nitroprusside test; response to treatment with pyridoxine	flat feet, herniae, scoliosis; there is a 50% reduction in life expectancy

Fragile X syndrome

Characteristics of individuals with Fragile X syndrome may include:

- moderate to severe mental retardation large ears

- macroorchidism
- prognathism
- speech delays
- prominent forehead
- double-jointedness
- autistic symptoms, and
- occasional self-mutilation.
- The face is typically long and narrow, with a high arched palate and large ears.
- Otitis media, strabismus, and dental problems may be present
- hyperextensible joints
- hypotonia, and
- heart problems, including mitral valve prolapse.
- **In post pubertal males, abnormally large testes are a distinctive feature.**

The following can occur In young children:

- delayed motor development
- hyperactivity
- behavioural problems
- toe walking, and
- occasional seizures.

Porphyrias

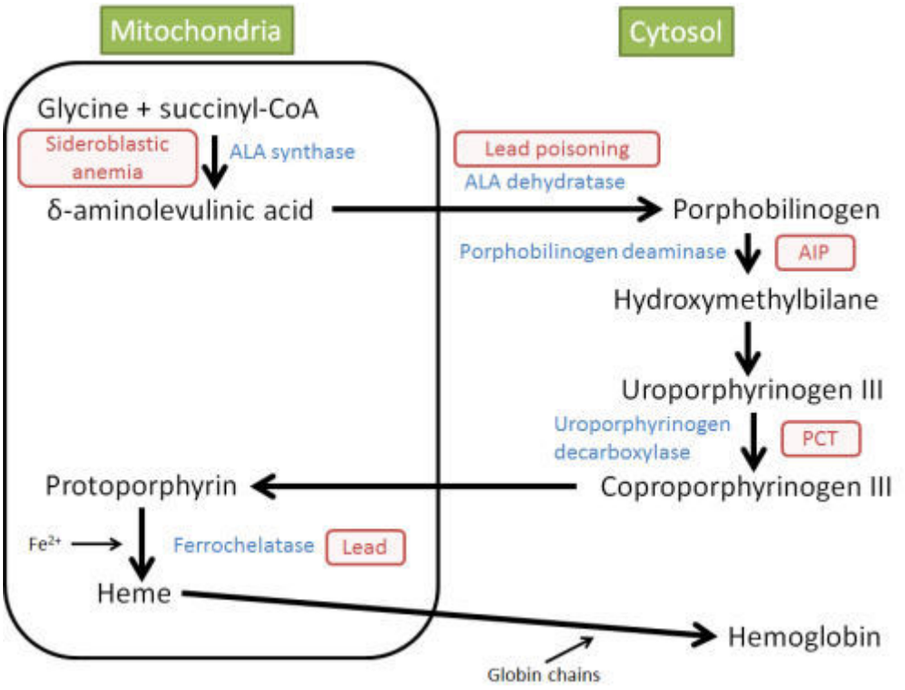
AIP - porphobilinogen deAminase; PCT - uroporphyrinogen deCarboxylase

Overview

Acute intermittent porphyria: 6 P's

- **Porphobilinogen deaminase deficiency**
- **Pain in abdomen** (most common, 95% of patients experience)
- **Psychological symptoms** (Anxiety, agitation, hallucination, hysteria, delirium, depression)
- **Peripheral neuropathy** (Patchy numbness and paresthesias)
- **Pee abnormality** (Dysuria, urinary retention/incontinence or dark urine)
- **Precipitated by drugs** (e.g. barbiturates, oral contraceptives, Sulfa drugs)

- Porphyria is a group of diseases characterised by excess production and excretion of porphyrins and their precursors.
- They are caused by enzyme defects within the haem metabolic pathway.
- **Stress, infection, pregnancy, menstruation, starvation, and certain drugs may precipitate acute attacks.**
- **Definite precipitants include sulphonamides, barbiturates, and phenytoin.**
- may be acute or non-acute
- **The most common presenting sign of PCT is fragility of sun exposed skin after mechanical trauma, leading to erosions and bullae, worst on dorsal hands, forearms, and face.**



Acute intermittent porphyria (AIP)

- autosomal dominant
- defect in porphobilinogen deaminase
- caused by a defect in porphobilinogen deaminase, an enzyme involved in the biosynthesis of haem.
- 20-40 year olds more likely to be affected (**only rarely presents before puberty)**
- AIP is more common in females (5:1)
- **90% of affected individuals remain asymptomatic throughout their lives.**
- typically present with abdominal symptoms, neuropsychiatric symptoms
  - Seizures occur in 10-20% of patients with acute intermittent porphyria (AIP).
  - A range of psychiatric symptoms, including hypomania and delirium may be seen.
- hypertension and tachycardia common
- urine turns deep red on standing
- **Patients excrete urinary porphobilinogen (PBG) between and during acute attacks.**
- Faecal porphyrin excretion is usually normal or slightly increased.
- Photosensitivity is **unusual in AIP**
- All attacks of porphyria increase the activity of hepatic 5-aminolevulinate (ALA) synthase.
- Lab features
  - hyponatraemia,
  - mild leukocytosis.

Factors precipitate an acute attack:

treatment of seizures in AIP → Gabapentin

- Stress,
- Infection
- Pregnancy
- Menstruation
- starvation
- Drugs
  - sulphonamides,
  - barbiturates
  - phenytoin.
    - **Most anti-epileptics should not be given, but gabapentin is safe and the most appropriate choice for seizures occur in (AIP).**
  - **ACE inhibitors** and calcium channel blockers
  - **Ibuprofen is safe for use in acute intermittent porphyria, but diclofenac should be avoided.**

Acute intermittent porphyria: drugs

Drugs which may precipitate attack		Safe Drugs
• Alcohol • Barbiturates • Benzodiazepines • Tricyclic antidepressants • Halothane • Oral contraceptive pill • Sulphonamides • Cephalosporins • Erythromycin • Isoniazid • **flu**cloxacillin • Anabolic steroids	• Sulphonylureas • Theophylline • Antihistamines • MAOIs • Amiodarone • Simvastatin. • Diuretics • calcium channel blockers • **ACE inhibitors**	• Paracetamol • Aspirin • Ibuprofen • Codeine • Morphine • Chlorpromazine • β-blockers • **Gabapentin** • Penicillin • Metformin • **amoxicillin**

Diagnosis

- **Urinary porphobilinogen assay is the optimal way to establish the diagnosis.**

Treatment:

- **glucose and heme**, which inhibit delta-aminolevulinic acid synthase, thereby decreasing heme precursor synthesis.
  - Two procedures have been shown to decrease the activity of ALA synthase in animals:
    1. **carbohydrate** loading and
    2. parenteral infusion of **haem arginate.**
       Consequently, these two procedures are the mainstay of the treatment along with opiate analgesia.
  - **The treatment of choice in acute porphyria is intravenous haem arginate**
  - high-glucose diets or infusions have been used for mild attacks of pain without neurological symptoms

Distinguishing between lead poisoning and acute intermittent porphyria

Which one of the following features in an adult patient presenting with porphyrinuria would most suggest lead poisoning rather than acute intermittent porphyria as a cause?

- ➔ **Anaemia**
- ➔ **Anaemia occurs only in lead poisoning and is due to:**
  - ➢ inhibition of ferrochelatase (the activity of this enzyme is normal in acute intermittent porphyria)
  - ➢ a decrease in red cell lifespan
  - ➢ enzyme inhibition (pyrimidine 5'-nucleotidase) leading to the accumulation of pyrimidine nucleotides in red cells, which in turn reduces the stability of the cell membrane (and is seen on a blood film as basophilic stippling)

Porphyria cutanea tarda (PCT)

- most common hepatic porphyria
- defect in uro-porphyrinogen decarboxylase
- **can be both acquired and inherited**
- may be caused by hepatocyte damage e.g. alcohol, oestrogens (oral contraceptive pill)
- **classically photosensitive rash with bullae**,
  - ➢ Bullae develop on sun-exposed areas
  - ➢ When exposed to light, uroporphyrinogen generates free radicals that cause blistering of the skin.
  - ➢ lesions heal slowly, leaving scars.

- skin fragility on face and dorsal aspect of hands
- Factors contributing to PCT are:
  - alcohol (the commonest cause),
  - excess iron and
  - excess oestrogens.
- Urine: elevated uroporphyrinogen (Urinary porphyrins)and pink fluorescence of urine under Wood's lamp
- Porphyrins are increased in liver, plasma, urine and stool.
- Porphobilinigen (PBG) is normal.
- Assay of red blood cells for uroporphyrinogen decarboxylase (UROD) activity is now available
- **Antinuclear antibodies are frequently seen**
- manage with Chloroquine
- PCT can be treated with phlebotomy to deplete the excess iron stores that exacerbate the porphyria.

Variegate porphyria

- autosomal dominant
- defect in protoporphyrinogen oxidase
- photosensitive blistering rash
- abdominal and neurological symptoms
- more common in South Africans

Trinucleotide repeat disorders

Anticipation in trinucleotide repeat disorders = earlier onset in successive generations

Genetic anticipation is seen in inherited neurological disorders. It occurs because of expansion of trinucleotide repeat sequences across successive generations. Huntington's disease, myotonic dystrophy and spinal cerebellar ataxias are examples of diseases where genetic anticipation is seen.

- Trinucleotide repeat disorders are genetic conditions caused by an abnormal number of repeats (expansions) of a repetitive sequence of three nucleotides.
- These expansions are unstable and may enlarge which may lead to **an earlier age of onset in successive generations - a phenomenon known as anticipation.** In most cases, an increase in the severity of symptoms is also noted

Examples - note dominance of neurological disorders

- Fragile X (CGG)
- Huntington's (CAG)
- myotonic dystrophy (CTG)
- Friedreich's ataxia* (GAA) (*Friedreich's ataxia is unusual in not demonstrating anticipation)
- spinocerebellar ataxia
- spinobulbar muscular atrophy
- **Kennedy disease**, also known as 'X-linked bulbospinal neuronopathy'
- dentatorubral pallidoluysian atrophy

Human genome

Human genome - 25,000 protein-coding genes

- The human genome is stored on 23 chromosome pairs.
- The haploid human genome has a total of 3 billion DNA base pairs, making up an estimated 20,000-25,000 protein-coding genes

Polygenic diseases

- genetic disorder that is caused by the combined action of more than one gene.
- Examples of polygenic conditions include:
  - hypertension,
  - coronary heart disease,

  - diabetes
  - **Amyotrophic lateral sclerosis (ALS)**
- Because such disorders depend on the presence of several genes, they are not inherited as simply as are single-gene diseases.

Pseudoxanthoma elasticum

- Pseudoxanthoma elasticum is an inherited condition (usually autosomal recessive*) characterised by an abnormality in elastic fibres.
  - *there are reports of autosomal dominant inheritance in a minority of cases

Features

- retinal angioid streaks
- 'plucked chicken skin' appearance - small yellow papules on the neck, antecubital fossa and axillae
- cardiac: mitral valve prolapse, increased risk of ischaemic heart disease
- gastrointestinal haemorrhage

Causes of early developmental delay and learning difficulties

Chromosomal abnormalities and fragile X syndrome are among the commonest causes of early developmental delay and learning difficulties.
Other potential causes of intellectual impairment include:

- birth asphyxia
- intraventricular haemorrhage
- rhesus disease
- congenital infections (toxoplasmosis, CMV, rubella, herpes)
- hypoglycaemia
- meningitis
- congenital hypothyroidism
- tuberous sclerosis
- trisomy 21
- Tay-Sachs
- Cornelia De Lange
- homocystinuria
- phenylketonuria
- tryptophanuria, and
- galactosaemia.
- **Maple syrup urine disease**

Autosomal recessive conditions

Hurler's syndrome (MPS-1) & Hunter's syndrome (MPS-2)

Which feature suggests a diagnosis of Hurler's syndrome rather than Hunter's syndrome? ➔ Cloudy cornea.

- **Hunter's syndrome (MPS-2)** is of X linked inheritance. The corneas are clear. The skeletal involvement tends to be mild with no gibbous present, though scoliosis is often found.Mental retardation and heart involvement are less severe than in Hurler's syndrome.
- **Hurler's syndrome (MPS-1)** is autosomal recessive in inheritance and is associated with cloudy cornea. There is severe mental retardation, and gibbous deformation of the spine is characteristic. There is the characteristic coarse facies with hepatosplenomegaly.

Gaucher's disease

- autosomal recessive mutation in a gene located on chromosome 1
  - Both parents must be carriers for a child to be affected.
  - If both parents are carriers, the chance of the disease is one in four, or 25%, with each pregnancy for an affected child
- **Caused by deficiency of the enzyme glucocerebrosidase** (also known as glucosylceramidase),(also known as **beta**-glucosidase) which acts on glucocerebroside.
- When the enzyme is defective, glucocerebroside accumulates in white blood cells spleen, liver, kidneys, lungs, brain, and bone marrow.
- Gaucher's disease is the most common of the lysosomal storage diseases.It is a form of sphingolipidosis (a subgroup of lysosomal storage diseases), as it involves dysfunctional metabolism of sphingolipids.

- About one in 100 people in the United States are carriers of the most common type of Gaucher disease. The carrier rate among Ashkenazi Jews is 8.9% while the birth incidence is one in 450.
- **Parkinson's disease is more common in Gaucher's disease patients (**the most common known genetic risk factor for Parkinson's**)**
- Cancer risk may be increased, particularly myeloma.
- Patients with all types of disease have hepatosplenomegaly and large glucocerebroside-rich cells (Gaucher cells) infiltrating the bone marrow.

Types

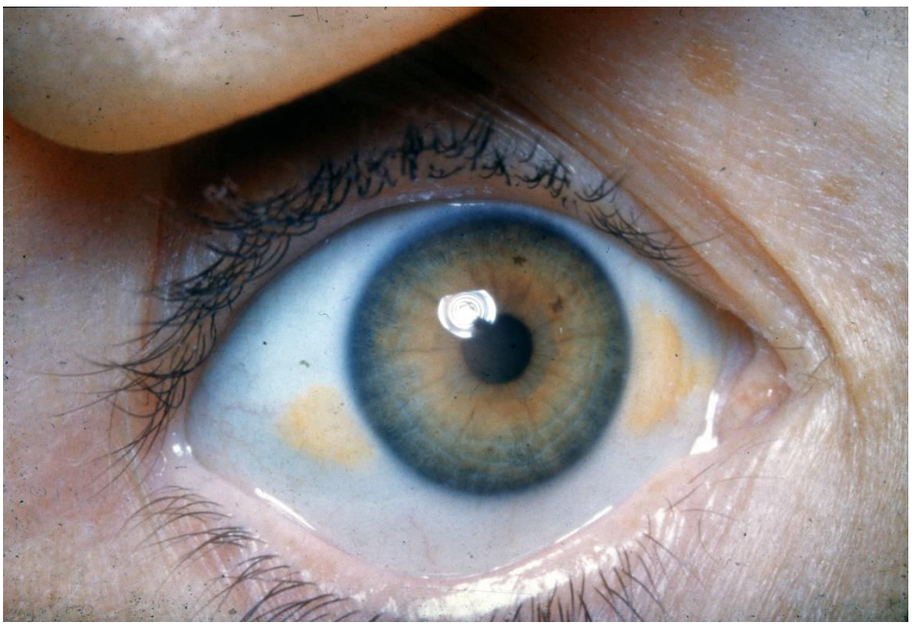
- **GD type I** (Chronic non-neuropathic; adult Gaucher disease)
  - **most common form** of the disease, occurring in about one in 40,000 live births.
  - It occurs most often among persons of **Ashkenazi Jewish** heritage.
  - **patients may live well into adulthood.**
  - Symptoms:
    - massive hepatosplenomegaly; the spleen may rupture
    - bone weakness (Osteoporosis , aseptic necrosis of the femur joint).
    - pancytopaenia .Spleen enlargement and bone marrow replacement cause anemia, thrombocytopenia, and leukopenia. bruise easily (due to low levels of platelets).
    - Yellowish-brown skin pigmentation
    - **Characteristic yellow or yellow-brown papules (pingueculae) develop at the sclerocorneal junctions.**
    - The brain is not affected pathologically.
- GD type II (Acute neuropathic; infantile Gaucher disease)
  - typically begins within 6 months of birth
  - incidence : 1 in 100,000 live births.
  - Symptoms include, hepatosplenomegaly, progressive brain damage, eye movement disorders, spasticity, seizures, limb rigidity, and a poor ability to suck and swallow.
  - carries the worst prognosis, Affected children **usually die by age two**.
- GD type III (Subacute neuropathic; juvenile Gaucher disease)
  - can begin at any time in childhood or even in adulthood,
  - occurs in about one in 100,000 live births.
  - characterized by slowly progressive, but milder neurologic symptoms compared to the acute or type II version.
  - **Patients often live into their early teen years and adulthood**

Investigations

- **Diagnosis → enzyme analysis (Enzyme studies of blood leucocytes)**
- Some lysosomal enzymes are elevated, including:
  - tartrate-resistant **acid phosphatase**,
  - hexosaminidase,
  - chitinase
  - **chitotriosidase → very useful for monitoring Gaucher's disease activity in response to treatment, and may reflect the severity of the disease**
- biochemical abnormalities : high alkaline phosphatase, angiotensin-converting enzyme, and immunoglobulin levels
- cell analysis showing "crinkled paper" cytoplasm and glycolipid-laden macrophages.

Treatment

- recombinant glucocerebrosidase.



The slide shows yellow papules (pingueculae) in the cornea; these are characteristic of Gaucher disease.

Glycogen storage disorders (GSD)

Glycogen

- Glycogen is the storage form of carbohydrate, found predominantly in muscle and liver.
- **Chains of glucose residues are linked by alpha-1,4 glycosidic bonds, i.e. between the first carbon of one glucose and the fourth carbon of the next. Branches occur about every ten residues, and are formed by alpha-1,6 glycosidic linkages.**
- Glycogen synthesis and degradation occur at the tips of branches, with the branching structure increasing the number of sites at which glucose residues can be added or removed.

Pompe's disease or acid maltase deficiency **(glycogen storage disorder type 2): is a deficiency in alpha-glucosidase**. It produces a myopathy , restrictive cardiomyopathy and hepatomegaly.

- **Muscle involvement (muscle glycogenoses): Types II, III, IV, V**
- **Liver involvement (liver glycogenoses): Types I, III, IV**
- **Types III and IV (late-onset type) may present with both muscle and liver involvement**
- **NO liver involvement → V**

- All types of glycogen storage diseases result in abnormal metabolism and product accumulation within cells.
- **autosomal recessive**
- Type IV(Andersen's disease) is the only one **GSD** involved in Glycogen Synthesis. The rest are involve in Glycogen degradation.

Diagnosis

- **Periodic acid-Schiff stain is helpful in diagnosing glycogen storage disorders.**

Type I (Von Gierke's disease)

- Relative frequency
  - ~25%
- Deficient enzyme
  - **Type 1a**
    - Glucose-6-phosphatase
      - Role of the enzyme → Hydrolysis of glucose-6-phosphate to glucose and inorganic phosphate
  - **Type 1b**
    - Glucose-6-phosphate translocase
      - Role of the enzyme → Transport of glucose-6-phosphate into the endoplasmic reticulum where it is hydrolyzed by glucose-6-phosphatase

- Characteristic features
  - Hepatomegaly
  - Severe fasting hypoglycemia, mild ketosis
  - Severe hyperlipidemia → doll-like facies
  - Hyperuricemia
  - Lactic acidosis
  - Anemia
  - Failure to thrive

Type II (Pompe's disease)

- Relative frequency
  - ~15%
- Deficient enzyme
  - Lysosomal acid maltase deficiency
- Role of the enzyme
  - Glycogenolysis within the lysosome
- Characteristic features
  - Hypertrophic cardiomyopathy and/or conduction blocks
  - Proximal myopathy
  - Macroglossia
  - Failure to thrive

Type III (**Cori's disease**)

- Relative frequency
  - ~25%
- Deficient enzyme
  - deficiency of debranching enzyme (alpha-1,6-glucosidase).
- Role of the enzyme
  - Glycogenolysis
- Characteristic features
  - Generalized muscle weakness and/or cramps
  - Hepatomegaly
  - Possibly cirrhosis (ascitis, splenomegaly)
  - Mild, fasting hypoglycemia and ketosis
  - Hyperlipidemia

Type IV (Andersen's disease)

- Relative frequency
  - ~3%
- Deficient enzyme
  - **Glycogen branching enzyme**
- Role of the enzyme
  - **Glycogenesis**
- Characteristic features
  - Proximal myopathy
  - Hepatomegaly
  - Possibly cirrhosis (ascites, splenomegaly)

Type V (McArdle's disease)

- Relative frequency
  - ~2%
- Deficient enzyme
  - Muscle phosphorylase (myophosphorylase)
- Role of the enzyme
  - Glycogenolysis
- Characteristic features
  - Generalized muscle weakness, exercise intolerance (with a second wind phenomenon) ,
  - Rhabdomyolysis and myoglobinuria

McArdle's disease

Overview

- **autosomal recessive type V glycogen storage disease**
- **caused by myophosphorylase deficiency**

- which is responsible for glycogen storage in skeletal muscles.
- Myophosphorylase is involved in the breakdown of glycogen to glucose.
  - ↓ myophosphorylase → unable to release glucose from glycogen in muscle.
- The gene for myophosphorylase (PYGM) is on chromosome 11.

- this causes **decreased muscle glycogenolysis**

Epidemiology

- It is now known as one of the most common disorders of muscle metabolism
- prevalence :1 per 100,000 people.

Features

- **muscle pain and stiffness following exercise** (reversible)
  - in the first few minutes of activity.
  - Characterised by **'second wind' phenomenon**
    - after about 8 minutes most patients achieve a 'second wind' and can then continue exercise with less difficulty.
    - **Second wind** is a phenomenon in distance running, such as marathons (an athlete who is too tired to continue suddenly finds the strength to press on at top performance with less exertion).
    - **Mechanism → metabolic switch**
      - When non-aerobic glycogen metabolism is insufficient to meet energy demands, physiologic mechanisms utilize alternative sources of energy such as fatty acids and proteins via aerobic respiration.
      - muscle fibers use fat as a source of energy.
- muscle cramps
- **myoglobinuria**
- low lactate levels during exercise

Investigations

- A history of painful muscle cramps that occur within a few minutes of initiating actvity and which subside rapidly with rest, in conjunction with a raised serum CK, is highly suggestive of McArdle's disease
- Creatine kinase levels are elevated in more than 90%
- NO increase in venous lactic acid levels following exercise testing.
- Urine study → myoglobinuria following exercise
- muscle biopsy, which shows an excess of glycogen and absence of the muscle enzyme phosphorylase
- In the UK, "hot spot" DNA testing for the two most common mutations.
  - Up to 85% of patients can be confirmed without muscle biopsy.
- The **gold standard** for the diagnosis of McArdle disease is **gene sequencing.**

Management

- No specific treatment exists.
- Tourniquets should not be used during operative procedures
- advised to ingest snacks containing **sucrose** before exercise.

The exertional thigh cramps, the presence of myoglobin and change in colour of urine after exercise suggests glycogen storage disease type V - McArdle's syndrome. the next most appropriate investigation →Muscle biopsy which reveals subsarcolemmal deposits of glycogen appearing at the periphery of fibres.

Which one of the following is most prevalent genetic disease in patients of Finnish/Scandinavian origin?

Alpha-1 antitrypsin deficiency (A1AD)

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linkage disequilibrium

- **linkage disequilibrium is the non-random association of alleles at different loci in a given population.**

- Loci are said to be in linkage disequilibrium when the frequency of association of their different alleles is higher or lower than what would be expected if the loci were independent and associated randomly.
- Consider the scenario of two separate genetic loci A and B, where each locus carries two possible alleles. If these two loci A and B are in linkage disequilibrium → An **individual with locus A is likely to have locus B**
- Linkage disequilibrium almost always, but not invariably, occurs between alleles at genetic loci that are closely linked in the genome.

Imprinting

Definition

- **imprinting** is a phenomenon by which certain genes are expressed in a parent-of-origin-specific manner.
  - Genomic imprinting is a principle in which certain genes on a chromosome are only expressed depending on the maternal or paternal origins of the chromosome.
  - **the term 'imprinting' refers to → Differential expression of alleles contingent on their parental origin**
    - If the allele inherited from the father is imprinted, it is thereby silenced, and only the allele from the mother is expressed.
    - If the allele from the mother is imprinted, then only the allele from the father is expressed.

Mechanism

- poorly understood, but does **involve DNA methylation**.
- Disease may occur as a result of a defect in one allele if the other allele is imprinted and hence not expressed.

Examples

- diseases involving genomic imprinting include:
  - Prader–Willi syndrome (paternally imprinted)
  - Angelman syndrome (maternally imprinted)

Prader-Willi syndrome

Deletion of chromosome 15
- Prader-Willi - paternal
- Angelman syndrome - maternal

- Prader-Willi syndrome is an example of **genetic imprinting** where the phenotype depends on whether the deletion occurs on a gene inherited from the mother or father:
  - Prader-Willi syndrome if gene deleted from father
  - Angelman syndrome if gene deleted from mother
- Prader-Willi syndrome is associated with the absence of the active **Prader-Willi gene on the long arm of chromosome 15.** This may be due to:
  - **microdeletion of paternal 15q11-13 (70% of cases)**
  - maternal uniparental disomy of chromosome 15
- **the mode of inheritance is → Non-Mendelian**

Features

- **hypotonia during infancy**
- dysmorphic features
- **short stature** (Growth hormone deficiency)
- **hypogonadism and infertility**
  - **(risk factor for osteoporosis)**
- **cryptorchidism** (undescended testis)
- **learning difficulties**
- **childhood obesity**
  - **due to Hyperphagia** (abnormally desire for food → overeating → obesity)
- behavioural problems in adolescence

Treatment

- **administration of growth hormone and sex hormones (testosterone) is the treatment of choice**

September 2007 exam: Which one of the following is the most common genetic cause of Prader-Willi syndrome? Microdeletion of the paternal 15q11-13

Chromosome 15 is implicated in Prader-Willi, Angelman, and Marfan syndromes.

Angelman syndrome

- Angelman syndrome is a genetic condition characterized by a mutation on the **maternal copy** of **chromosome 15**.
- occurs as a result of a phenomena known as genomic **imprinting**.
- The imprinted copy of the gene is silenced through methylation or histone modification.
- Normally, certain paternal alleles on chromosome 15 are silenced and only the maternal alleles are expressed. However, in Angelman syndrome, the maternal alleles are mutated. Hence, the patient will have disease since only the mutated maternal alleles are active.

Features

- developmental delay,
- seizures,
- hypo-pigmentation with blond hair,
- ataxia,
- **unprovoked laughter,**
- large mouth with tongue protrusion.

Diagnosis

- genetic studies showing loss of function of the UBE3A gene.

Mutations

- **Missense mutation**
  - substitution in one amino acid in a protein
  - e.g: glutamic acid is substituted by valine in sickle-cell disease
- **nonsense mutation**
  - the altered DNA sequence prematurely signals the cell to stop building a protein. This type of mutation results in a shortened protein that may function improperly or not at all.
- **insertion mutation**
  - changes the number of DNA bases in a gene by **adding a piece of DNA**. As a result, the protein made by the gene may not function properly.

McCune–Albright syndrome

- due to a mutation in a G-protein.

Features

- Precocious puberty (typically gonadotropin-independent). This includes:
  - breast development,
  - genital maturation (with or without pubic hair growth),
  - increased height velocity
  - macro-orchidism in males.
- Café-au-lait pigmentation.
  - This consists of spots ranging from light brown to dark brown in colour.
  - often display a segmental distribution and frequently are predominant on one side of the body without crossing the midline;
  - these spots must be differentiated from those characteristic of neurofibromatosis.
- Polyostotic fibrous dysplasia.
- Multiple pathological fractures may be prominent early in the history; in many cases, bony involvement is found to predominate clinically on one side; clinical manifestations include gait anomalies, visible bony deformities (including abnormal bone growths of the skull), bone pain and joint stiffness with pain.
- Hyperthyroidism, which in infants can result in failure to thrive.

- increased risk of osteosarcoma and other connective tissue tumours,
- In relation to precocious puberty, the patient is at increased risk of developing breast carcinoma.

Notes & Notes

For MRCP part 1 & 11

By

Dr. Yousif Abdallah Hamad

Basic science

Biostatistics & EBM

Updated

2017

Contains:

1/ Passmedicine 2017
2/ On examination 2017
3/ Pastest 2017
4/ **Red fonts --> previous exams**
5/ Other updated UK sources

Significance tests

Null hypothesis (H_0)

- A null hypothesis (H_0) states that two treatments are equally effective (and is hence negatively phrased).
- A significance test uses the sample data to assess how likely the null hypothesis is to be correct.
- The null hypothesis is always that there is no difference between the variables we would like to test for a difference.
- For example:
  - 'there is no difference in the prevalence of colorectal cancer in patients taking low-dose aspirin compared to those who are not'

The alternative hypothesis (H_1)

- is the opposite of the null hypothesis, i.e. There is a difference between the two treatments

P value

- The **p value** is the probability of obtaining a result by chance at least as extreme as the one that was actually observed, assuming that the null hypothesis is true.
- It is therefore equal to the chance of making a type I error (see below).
- **the p-value is the probability of obtaining the observed results or results which are more extreme if the null hypothesis is true**

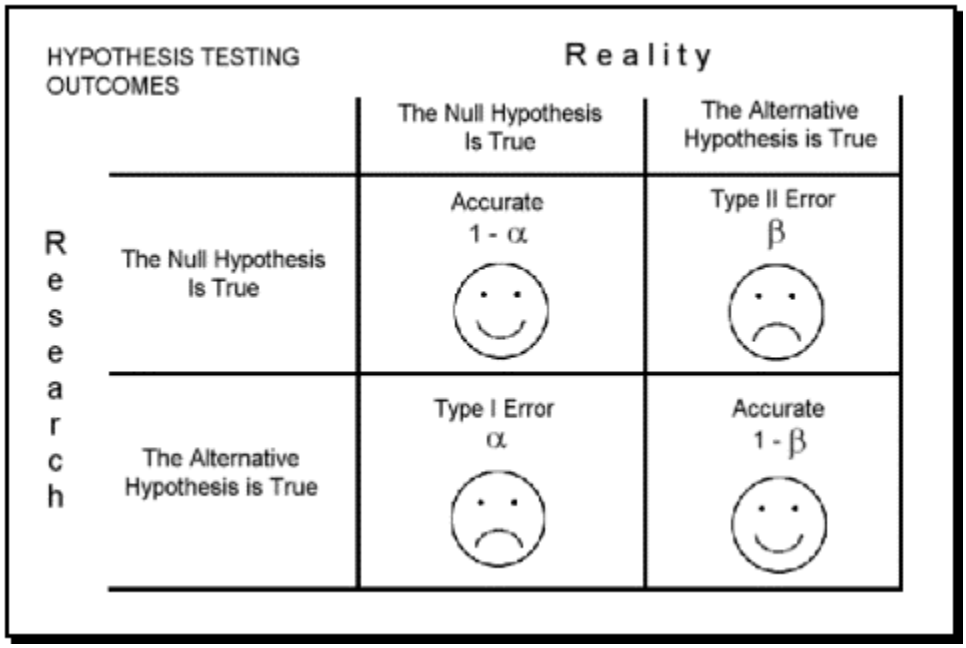
- **Example**: **if p=0.03. What does 'p=0.03' mean?**
- **It means →the probability that a difference between the two sample groups occurred by chance is 3%**

Statistical errors

- Two types of errors may occur when testing the null hypothesis
  1. type I:
     - **the null hypothesis is rejected when it is true,**
       - 'the null hypothesis is falsely rejected'. –
       - i.e. Showing a difference between two groups when it doesn't exist,
       - a false positive.
     - This is determined against a preset significance level (termed alpha).
     - As the significance level is determined in advance the chance of making a type I error is not affected by sample size.
     - It is however increased if the number of end-points are increased. For example if a study has 20 end-points it is likely one of these will be reached, just by chance. i.e. the result is just a statistical fluke (صدفة).
  2. type II:
     - **the null hypothesis is accepted when it is false**,
       - 'the null hypothesis is falsely accepted'.-
       - i.e. Failing to spot a difference when one really exists,
       - a false negative.
     - The probability of making a type II error is termed beta.
     - It is **determined by both sample size** and alpha. This can happen if the sample size is too small.
       - **Increasing the sample size** reduces the standard error, meaning the estimate is more precise and the **probability of a type-2 error is reduced.**

- This type of error can be avoided by making explicit power calculations before embarking on any study. This will answer the question 'if I am studying an outcome that occurs in (say) 20% of a conventionally treated group and want to show a (say) halving in the rate of this outcome, then how many patients do I need to study?'

	Study accepts H_0	**Study rejects H_0**
Reality H_0		Type 1 error (alpha)
Reality H_1	Type 2 error (beta)	Power (1 - beta)



Error: type I (alpha) vs. type II (beta)

- Type I (Alpha) Error: "There Is An Effect" where in reality there is none.

The power

- The power of a study is the probability of (correctly) rejecting the null hypothesis when it is false, i.e. the probability of detecting a statistically significant difference
  - power = 1 - the probability of a type II error
  - power can be increased by increasing the sample size
- **As the power decreases, type II error (= 1-power) will increase. Therefore, the chance of type II error will increase if the same sample size is used.**
- The statistical power will decrease if the standard deviation increases.
- **Power of the study' refer ➔ The probability of a statistically significant treatment effect if the true treatment difference is at a prespecified level**
- Power is determined by sample size, effect size, and its standard error.

- **The statistical significance** of a result is the probability ('p value') that the observed relationship (eg between variables) or a difference (eg between means) in a sample occurred by pure chance and that in the population from which the sample was drawn, no such relationship or differences exist
- The sample size can be reduced if the level of significance is increased.
- The power increases with the set level of significance, if other variables remain the same.

Significance tests: types

Correlation

- **parametric (normally distributed): Pearson's coefficient**
- **non-parametric: Spearman's coefficient**

- The type of significance test used depends on whether the data is parametric (something which can be measured, usually normally distributed) or non-parametric
  - **Parametric tests**
    - Student's t-test - paired or unpaired*
    - Pearson's product-moment coefficient – correlation
  - **Non-parametric tests**
    - Mann-Whitney U test - unpaired data
    - Wilcoxon signed-rank test - compares two sets of observations on a single sample
    - chi-squared test - used to compare proportions or percentages
    - Spearman, Kendall rank - correlation
- *paired data refers to data obtained from a single group of patients, e.g. Measurement before and after an intervention. Unpaired data comes from two different groups of patients, e.g. Comparing response to different interventions in two groups

Parametric & non-parametric methods

- Theoretical distributions are described by quantities called parameters, notably the mean and standard deviation.
  - Methods that use distributional assumptions are called **parametric** methods, because we estimate the parameters of the distribution assumed for the data.
  - Methods which do not require us to make distributional assumptions about the data, are called **non-parametric** methods.
- A parametric test is a statistical test which assumes the data are normally distributed.
- Data which are not normally distributed can still be subject to a parametric test, but it need to be transformed first.
- The parametric assumption of normality is particularly worrisome for small sample sizes($n < 30$). Nonparametric tests are often a good option for these data with a very small sample size.
- Non-parametric methods are most often used to analyse data which do not meet the distributional requirements of parametric methods. In particular, skewed data are frequently analysed by non-parametric methods, although data transformation can often make the data suitable for parametric analyses
- **Nonparametric tests have two main drawbacks:**
  1- "Less powerful" than parametric (a nonparametric test will require a slightly larger sample size to have the same power as the corresponding parametric test).
  2- their results are often less easy to interpret than the results of parametric tests

Parametric tests and analogous nonparametric procedures

Analysis Type	Example	Parametric Procedure	Nonparametric Procedure
Compare means between two distinct/independent groups	Is the mean systolic blood pressure (at baseline) for patients assigned to placebo different from the mean for patients assigned to the treatment group?	**Two-sample t-test**	Wilcoxon ranksum test
Compare two quantitative measurements taken from the same individual	Was there a significant change in systolic blood pressure between baseline and the six-month followup measurement in the treatment group?	Paired t-test	Wilcoxon signedrank test
Compare means between three or more distinct/independent groups	If our experiment had three groups (e.g., placebo, new drug #1, new drug #2), we might want to know whether the mean systolic blood pressure at baseline differed among the three groups?.	Analysis of variance (ANOVA)	Kruskal-Wallis test
Estimate the degree of association between two quantitative variables	Is systolic blood pressure associated with the patient's age?	Pearson coefficient of correlation	Spearman's rank correlation

- Categorical variables are not continuous, e.g. drug / placebo, dead / alive. They should be described as percentages or proportions and compared with a Chi-squared test.
- Normally distributed continuous data should be described as mean and standard deviation and compared with a Student's t-test.
- Skewed continuous data should be described as median and range and compared using a test such as the Wilcoxon rank-sum test or the Mann-Whitney U-test.

Choosing the appropriate test

- Choosing of a test to examine a statistical problem depends upon the scale of measurement (nominal, ordinal, interval, ratio) and the type of question being asked
- a non-parametric test would give less power

Student's t- test

- ***t* -test can only be used for parametric (normally distributed) data.**
- *t*-test can be used, for example, to determine if two sets of data are significantly different from each other.
- The t-tests are applicable to quantitative variables
- **Paired *t* test**
  - Compares a **single measure** (variable) recorded **on a single group** of individuals **on two different occasions.**
  - Is used to compare **means in a single sample**, **for example, before and after treatment**.
  - ➔ comparing **means** (**not** proportions) in the **same subjects**
  - **paired *t*-test is used to compare post-treatment and pre-treatment result of a single group.**

- eg: the same subject measured before and after a process change, or the same subject measured at different times.
- As both sets of measurements were made on the same patients, the measurements are not independent

- **unpaired t-test (independent sample *t*-test)**
  - is the most appropriate statistical test to compare means of two independent samples.
    - compare the **means of two** different populations
  - An independent sample *t*-test may be used in a study of two **independent** treatment groups, and the **sample sizes are relatively large** (>30 in each group) and the variable is **Normally distributed**.
  - eg: Blood pressure is a continuous variable which is normally distributed; as such Student's *t* test is the most appropriate way to test for **differences in the mean BPs between the two groups.**
  - For example, suppose we are evaluating the effect of a medical treatment, and we enroll 100 subjects into our study, then randomly assign 50 subjects to the treatment group and 50 subjects to the control group. In this case, we have two independent samples and would use the unpaired form of the *t*-test.
  - eg: 2 groups (treatment group & placebo group) In a randomised controlled trial of drug A for treatment of hypercholesterolemia

Pearson test

- is used to assess the correlation (strength of association) between two variables
- **Pearson correlation coefficient is inappropriate if the data do not approximately follow normal distribution**
- (often called 'R')
- R is a measure of association between two continuous scale measurements

Chi square test

- is used for nominal data to find out if there is a significant difference between the proportion of observations falling in each group - for example, comparing the proportion of children developing measles between a group receiving a new measles vaccine and a group not given the vaccine
- (used to test for independence between two categorical variables)
- It is a 2 × 2 contingency table for which there is a special chi squared formula that gives a value that can be looked up in a table giving the p value.
- Is used to test categorical variables for **association**.
- Should be used for 2 **independent** samples.
- **In order to compare the prevalence in two groups, the chi square test is most appropriate.**

Log-rank test

- Is the most appropriate test to **compare two survival curves** with censored data.
- Logrank test should be used to compare survival data between two groups, but not compare median survival. Mean survival is not known unless all patients have died.
- If a question presented survival data and some observations are censored(ex: not came for follow up) and the outcomes are not known. We need to use survival analysis for such data and the log-rank test is the appropriate test to use **to compare survivals in two independent groups**.
- **can be used to test the difference in relapse rate between the two groups**

Mann-Whitney U-test

- is a non-parametric comparison of two distributions
- used to compare medians or rank orders of two groups with **non-normal distribution**.

Spearman's rank correlation coefficient

- measures the correlation between the ranks of two variables
- as it only compares ranks and not values, it is appropriate for use on an ordered categorical (ordinal) variable such as the perception of pain (ranked on a scale of
  - 1-10)

- Spearmann's correlation is the best method to determine two variables which do not follow a normal distribution.

ANOVA (analysis of variance)

- **is used for more than two means**
- tests for a difference in mean values between a **number of groups**
- **Is the most appropriate to compare the means of more than two groups.**
- **One-way analysis of variance** is identical mathematically to the unpaired Student t-test when just two groups are being compared.
- **The one-way (analysis of variance) (ANOVA)** compares the means of the **groups**
- The means should be presented with confidence intervals to give the reader an idea of whether the differences between the groups were significant

McNemar's test

- is applied to binary data, but is only applicable to paired data, used to compare proportions
- McNemar's test is used to compare paired samples - either case control studies where each case is matched to a control, or to studies where two treatments are given to matched subjects.
- It cannot be used where the sample size differs.
- is used to test for agreement of repeated observations.

The Cox (proportional odds) regression (Cox proportional hazards regression):

- this method was devised specifically for the type of study in which many patients fail to reach the end-point (ie in statistical terms, are 'censored') and in which follow-up time varies.
- Cox regression is designed specifically for the analysis of time to an event occurring.

Multiple regression

- is used to analyse the relationship between one dependent variable and one or more independent variables.

Logistic regression

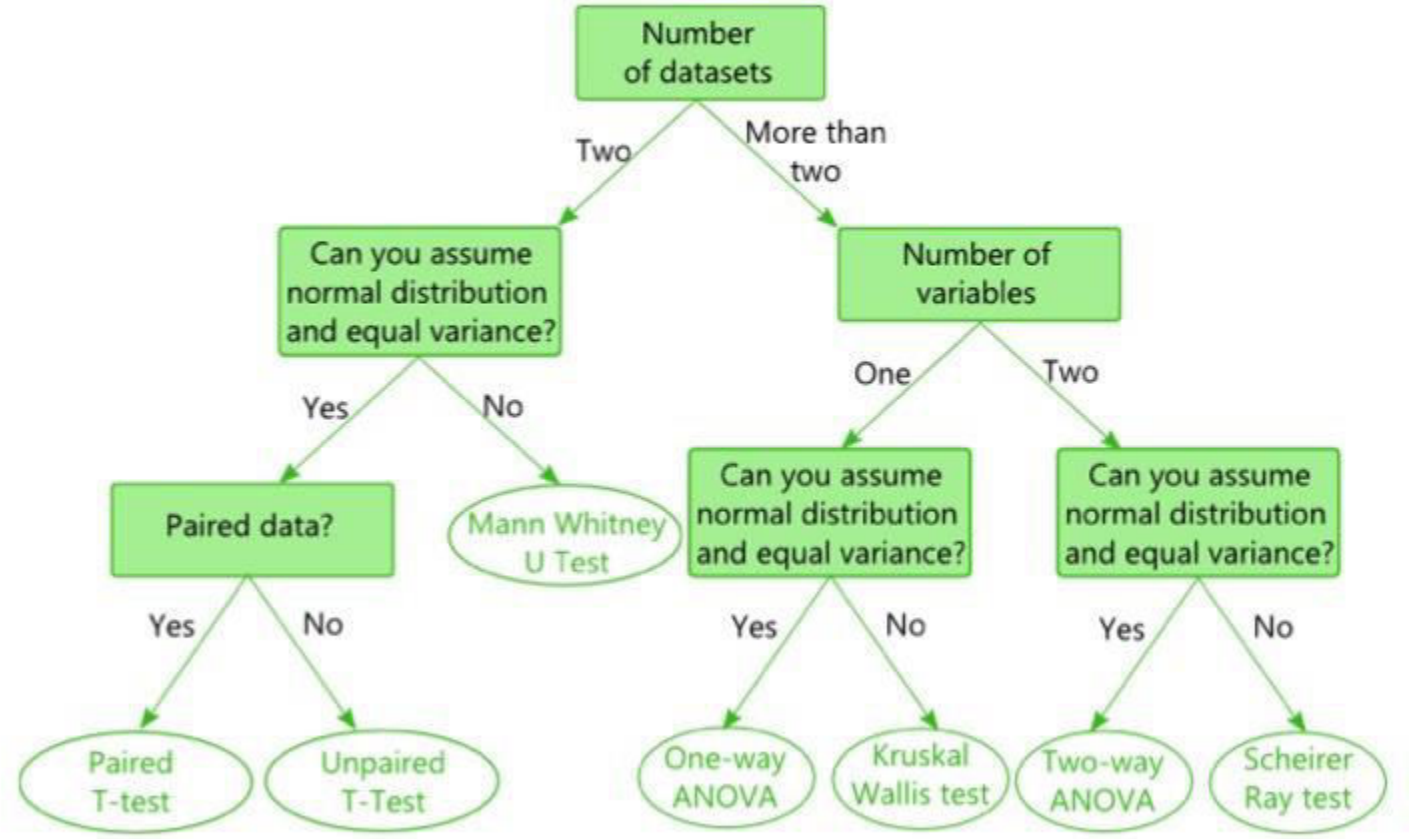
- This would allow us to determine whether one variable is dependent on another, ex: in case whether drug concentration was dependent on body surface area.
  - ANOVA is an example of logistic regression analysis.

ANCOVA

- is a statistical test which tests for co-variance between populations and is useful when variables such as age, sex or race may be expected to affect the treatment's effectiveness.

Regression techniques

- are used to predict the value of one variable based on the other



May 2012 exam: A study is designed to assess severity of snoring before and after using a new mandibular device. What is the most appropriate statistical test to apply to this data? Wilcoxon signed-rank test

Normal distribution

- The normal distribution is also known as the Gaussian distribution or 'bell-shaped' distribution. It describes the spread of many biological and clinical measurements
- Properties of the Normal distribution
  - symmetrical i.e. Mean = mode = median
  - **68.3% of values lie within 1 SD of the mean**
  - **95.4% of values lie within 2 SD of the mean**
  - **99.7% of values lie within 3 SD of the mean**
  - this is often reversed, so that within 1.96 SD of the mean lie 95% of the sample values
  - the range of the mean - (1.96 *SD) to the mean + (1.96 * SD) is called the 95% confidence interval, i.e. If a repeat sample of 100 observations are taken from the same group 95 of them would be expected to lie in that range

January 2009 exam: **A study is designed to assess the efficacy of a new antihypertensive drug. Two groups of patients are randomly assigned, one to take the established drug for 3 months whilst the other takes the new drug for 3 months. blood pressure is measured before and 3 months .After period off medication the drug swapped around and again, blood pressure is measured before and 3 months later. Which one of the following significance tests is it most appropriate to apply?** **Student's paired t-test** (comparing parametric data from the same patients (they swapped medication halfway through the study))

Standard deviation

SD = square root (variance)

Remember that around two-thirds of values lie within 1 SD of the mean, one-third will therefore lie outside 1 SD, and half of these (one-sixth) will be less than 1 SD below the mean

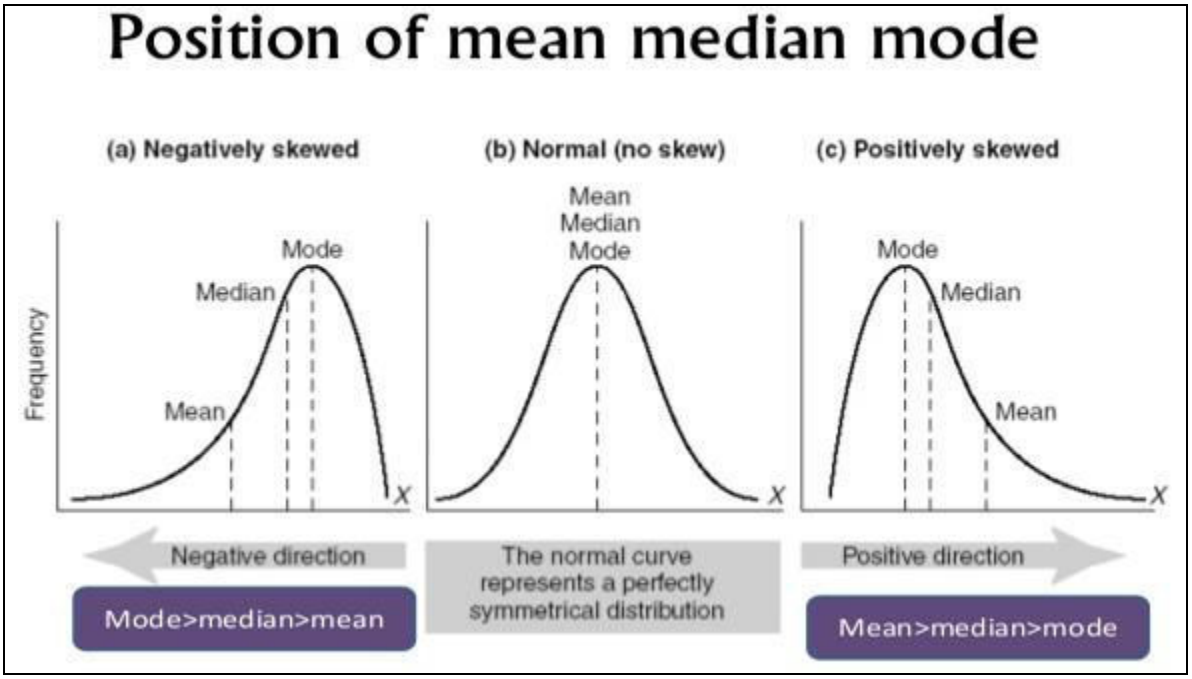
- the standard deviation (SD) is a measure of how much dispersion exists from the mean
- **It is a measure of the spread of the sample distribution**
- SD = square root (variance)
- **The standard deviation** is a sort of average of the deviations of each observation from the mean, whereas **the range** is simply the difference between the largest and smallest observations.
- The standard deviation is affected by outliers and would be larger than expected if outliers are present
- If the data are skewed, the standard deviation will tend to overestimate the spread in the data
- If the standard deviation is reduced, the sample size required is smaller.
- **If SD increased the power of study is reduced .**
- **The standard deviation would give the best estimate of a spread of a measurement about the mean**
- Variance is the square of standard deviation. Standard deviation is the square root of variance.

Skewed distributions

Skewed distributions

- alphabetical order: mean - median - mode
- '>' for positive, '<' for negative

- Normal (Gaussian) distributions: mean = median = mode (**bell-shaped**)
- Positively skewed distribution: mean > median > mode
- Negatively skewed distribution mean < median < mode
- To remember the above note how they are in alphabetical order, think positive going forward with '>', whilst negative going backwards '<'



- Mean, median and mode are measures of central tendency
- **Descriptive statistics provide mean, median and mode values for a distribution**

Example: The annual numbers of reported cases of leptospirosis in the USA over the 5-year period from 1985 to 1990 were: 2, 1, 3, 4, 1, . What was the mean, median and modal number of cases per year?
Answer:

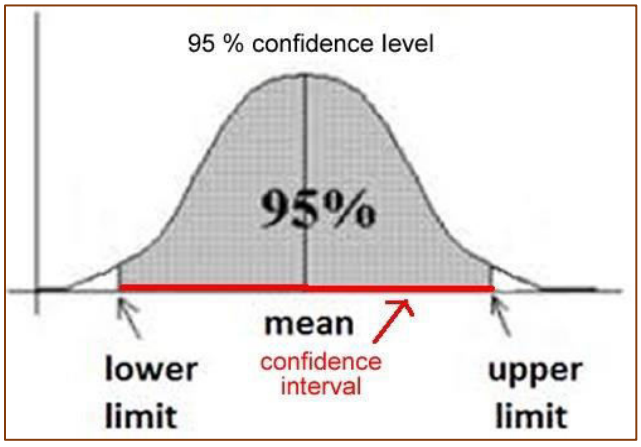
- **The mean** is found by ➔ summing all the values and dividing by 5; this gives a mean = 11/5=2.2
  - **The mean is the average value of observations, and therefore very sensitive to extreme values in a distribution**
  - If the mean is greater than the median, this indicates a positive skew.
- For the median and mode ➔ rewrite the values in ascending order: ie 1,1,**2**,3,4,
- **The median** is the middle value when the values are placed in order = **2**
  - For an even number of values it is halfway between the two middle values,
  - If you forgot to sort the values before looking for the middle value, you will have got the incorrect answer = 3
  - The median is the observation that divides the frequency distribution by half and is equal to the 50th centile (lies exactly between each end of a range of values)
  - It responds to the number of extreme observations but not their value, and therefore is useful as a measure of central tendency in extremely skewed distributions
  - In a normal distribution the median equals the mean
- **The mode** is the most common value; this is ➔ 1 , which occurs twice, whereas all other values occur only once
  - **mode is the most commonly observed value**

- **The distribution sample means will be normally distributed even if the population values are not normally distributed.**
- The random sampling distribution of means would always tend to be normal, irrespective of the population distribution for which the samples were drawn. Hence, even if the population distribution is skewed or in any non-normal distribution, the sample means would be normally distributed.'
- the mean of the random sampling distribution of means is equal to the mean of the original population.
- **In a distribution skewed by the presence of a number of positive outliers➔ Mean increases, median may increase, mode remains the same**

Confidence interval and standard error of the mean

Standard error of the mean = standard deviation / square root (number of patients)

- Definition of **confidence interval**
  - *a range of values for a variable of interest constructed so that this range has a specified probability of including the true value of the variable.*
  - *The specified probability is called the confidence level, and the end points of the confidence interval are called the confidence limits**
  - in simpler terms: a range of values within which the true effect of intervention is likely to lie
- **A confidence interval is needed for almost all statistical estimates, including sensitivity or specificity of a diagnostic test.**
- Confidence intervals relate to values of the population mean and tell you how precisely you have determined the mean.
- If the confidence interval includes the number 1,➔ the trial did not find a statistically **significant** difference between the variables (this does not mean there was no difference)
- A narrow confidence interval **emphasises the significance** of the result, but it is the p-value that **describes significance**, not the confidence interval around it.
- If confidence interval of any study includes 1, This means the association is not statistically significant and therefore the p value should be above 0.05.
- If confidence interval does not include 1. This means the association is statistically significant and therefore the p value should be below 0.05.



Key point

- **A 95% confidence interval:**
  - Most commonly, the 95% confidence level is used
  - **What is the best interpretation of the 95% confidence interval?**

        - **We are 95% confident that the mean in the value is between confidence limits**
    - confidence interval at the 95% confidence level means that the confidence interval should contain the true effect of intervention 95% of the time.
    - **A 95% confidence interval means that there is only a 5% chance that the true mean value for the variable lies outside the ranges quoted**
    - The 95% confidence limits will be the mean plus or minus 1.96 standard errors
        - lower limit = mean - (1.96 * SEM)
        - upper limit = mean + (1.96 * SEM)
    - For example, in a study the mean height in a sample taken from a population is 183cm. You know that the standard error (SE) (the standard deviation of the mean) is 2cm. This gives a 95% confidence interval of 179-187cm (+/- 2 SE).
    - **meaning that there is a 5% chance that the true population mean is not included in this range, in other words a 95% chance that the true population mean is included within this range**
    - **If the 95% confidence interval does not include 0 (zero), the difference is statistically significant**
    - If the p value is less than 0.05, ➔ statistically significant ➔ the 95% confidence interval should not include 0.
- **Standard error of the mean (SEM)**
    - The standard error of the mean (SEM) is a measure of the spread expected for the mean of the observations - i.e. how 'accurate' the calculated sample mean is from the true population mean
    - **SEM = SD / square root (n)**
        - where SD = standard deviation and n = sample size
        - therefore the SEM gets smaller as the sample size (n) increases
    - **standard error of the mean➔ Gets smaller as the sample size increases**
    - **Increasing the sample size will reduce the standard error of the mean and the width of the confidence interval.**
    - **The standard error is → Smaller than the standard deviation**

Confounding variable

- Is an extraneous **variable** in a statistical model that correlates (directly or inversely) with both the dependent **variable** and the independent **variable**.
- To give a hypothetical **example** of a confounding variable:
- A study shows that wearing sunglasses and putting on sun cream are linked - increases in sun cream sales are higher when sales of sunglasses increase. It could be that sun cream makes individuals wear sunglasses or that wearing sunglasses reminds people that they need to put on sun cream. However, there is a third "confounding" variable that affects BOTH sales of sunglasses and sun cream - the weather. It could be that hot, sunny weather makes people both put on sunglasses and apply sun cream.
- **Another example**: In a case-control study on the association between cola drinking and type 2 diabetes **=> BMI is likely to be a confounding variable**
- In general, **a randomised controlled trial eliminates confounding** by known and unknown factors.
- **Stratified analysis eliminates the confounding of the stratified data.**

- Multivariable logistic regression can control and minimise confounding by simultaneous adjustment for multiple factors.

Correlation and linear regression

- The terms correlation and regression are related but are not synonymous.
- Correlation is used to test for association between variables (e.g. whether salary and IQ are related).
- Once correlation between two variables has been shown regression can be used to predict values of other dependent variables from independent variables.
- **Regression is not used unless two variables have firstly been shown to correlate.**

Correlation

- The degree of correlation is summarised by the correlation coefficient (r). This indicates how closely the points lie to a line drawn through the plotted data. In parametric data this is called Pearson's correlation coefficient and can take any value between -1 to +1.
- **The value of 'r' (coefficient of variation) ranges from -1 to +1**
- For example
  - r = 1 - strong positive correlation (e.g. systolic blood pressure always increases with age)
  - r = 0 - no correlation (e.g. there is no correlation between systolic blood pressure and age)
  - r = - 1 - strong negative correlation (e.g. systolic blood pressure always decreases with age)
- Whilst correlation coefficients give information about how one variable may increase or decrease as another variable increases they do not give information about how much the variable will change. They also do not provide information on cause and effect.
- Correlation is summarised when using parametric variables by Pearson's correlation coefficient (represented by a small r).
- In the situation of non parametric variables, Spearman's correlation coefficient is used. Spearman's correlation coefficient is usually represented by the Greek letter p (rho), or by rs.
- In the case of dichotomous variables logistic regression is used.
- Linear (or simple linear) regression is used when looking for association between two continuous variables, and multiple regression is used when looking for association between more than two continuous variables.

Linear regression

- In contrast to the correlation coefficient, linear regression may be used to predict how much one variable changes when a second variable is changed.
- A regression equation may be formed, y = a + bx, where:
  - y = the variable being calculated
  - a = the intercept value, when x = 0
  - b = the slope of the line or regression coefficient. Simply put, how much y changes for a given change in x
  - x = the second variable

Correlation coefficient

- The correlation coefficient measures the strength (and direction, if linear) of the relationship between two variables.
- Correlation coefficient does not follow normal distribution.
- Calculation of correlation coefficient does not need to assume normal distribution.
- If there is perfect linear relationship with positive slope between the two variables, the correlation coefficient is 1.

- If there is a perfect linear relationship with negative slope between the two variables, the correlation coefficient is -1.
- A correlation coefficient of 0 means that there is no linear relationship between the variables.
- The correlation is not necessarily linear
- Correlation coefficient describes the linear relationship between two variables. If the relationship between them is not linear, it can be misleading and should not be used.
- **The correlation coefficient does not depend on sample size.** Increasing the sample size will not change the correlation coefficient as its value does not depends on sample size.
- **The correlation coefficient can be a negative number**.
- The correlation coefficient can range from -1 to +1.
- Correlation and regression are different.
  - **Correlation** describes how closely two variables are associated.
  - **Regression** allows you describe one variable with respect to the other in terms of an equation.

Screening test statistics

Sensitivity = true positives / (true positives + false negatives)

Specificity = true negatives / (true negatives + false positives)

The rule of thumb is that a high sensitivity helps to **rule out** disease (SnOut) and a high specificity helps to **rule in** (SpIn) disease (Mnemonic "spin and snout")

Contingency tables

- also known as 2 * 2 tables, are used to illustrate and calculate test statistics such as sensitivity.
- TP = true positive; FP = false positive; TN = true negative; FN = false negative

	Disease present	**Disease absent**
Test positive	TP	FP
Test negative	FN	TN

The table below lists the main statistical terms used in relation to screening tests:

Measure	Formula	Plain English
Sensitivity	TP / (TP + FN)	Proportion of patients with the condition who have a positive test result
Specificity	TN / (TN + FP)	Proportion of patients without the condition who have a negative test result
Positive predictive value	**TP / (TP + FP)**	The chance that the patient has the condition if the diagnostic test is positive
Negative predictive value	TN / (TN + FN)	The chance that the patient does not have the condition if the diagnostic test is negative
Likelihood ratio for a positive test result	sensitivity / (1 - specificity)	How much the odds of the disease increase when a test is positive
Likelihood ratio for a negative test result	(1 - sensitivity) / specificity	How much the odds of the disease decrease when a test is negative

Incidence and prevalence

- **The incidence equals the number of newly affected individuals divided by the number of people at risk for the disease for a given duration.**
- Prevalence equals the total number of cases divided by the total number of at risk.
- Prevalence may be lower than incidence if the condition has high fatality or cure rate.

Sensitivity and specificity

- **Essentially a knowledge of the sensitivity/specificity is based on the *disease state* itself, whereas predictive values are based on the *test result*.**
- **Sensitivity and specificity** will not change with sample size. They will change only with:
  - composition of the sample (especially if subjects in the sample have different risks of disease)
  - performance of the test
  - diagnostic threshold, and
  - The "gold standard" to be compared with.
- **The reliability** of estimates of sensitivity, specificity, positive and negative predictive value will all **increase with increasing sample size**, which will reduce their confidence intervals.
- Increasing the cut-off of a positive test result will decrease the number of false positives and hence increase the specificity.

Positive and negative predictive values

- **Positive and negative predictive values are prevalence dependent.**
  - **The positive predictive value will increase and negative predictive value will decrease if the prevalence of the disease increases.**

Likelihood ratios

- Likelihood ratios are not prevalence dependent.

- **If the sensitivity increases, the likelihood ratio of a positive test will increase. If the specificity decreases, the likelihood ratio of a positive test will decrease.**
- **The likelihood ratio of negative test will increase if the specificity of the test is decreased.**
- **The lower the likelihood ratio of a negative test, the less likely is the presence of disease**
- The likelihood ratio of a positive test helps to rule in disease and the likelihood ratio of a negative test helps to rule out disease.

Posterior probability

- **Posterior probability = posterior odds / (1 + posterior odds)**
  - Posterior odds of having disease = prior odds × likelihood ratio.
  - Prior odds of having disease = Prevalence(P) / (1 − P)

Precision

- quantifies a tests ability to produce the same measurements with repeated tests.

September 2009 exam: What is the correct formula to calculate the negative predictive value of a screening test? TN / (TN + FP)

Incidence and prevalence

Incidence is the number of new cases per population in a given time period.	**Prevalence** is the total number of cases per population at a particular point in time.

- These two terms are used to describe the frequency of a condition in a population.
- The **incidence** is the number of new cases per population in a given time period.
- For example, if condition X has caused 40 new cases over the past 12 months per 1,000 of the population the annual incidence is 0.04 or 4%.
- The **prevalence** is the total number of cases per population at a particular point in time.
- For example, imagine a questionnaire is sent to 2,500 adults asking them how much they weigh. If from this sample population of 500 of the adults were obese then the prevalence of obesity would be 0.2 or 20%.

Relationship

- prevalence = incidence * duration of condition
- in chronic diseases the prevalence is much greater than the incidence
- in acute diseases the prevalence and incidence are similar. For conditions such as the common cold the incidence may be greater than the prevalence

Relative risk

Relative risk ratio (RRR) = EER / CER

- **Relative risk (RR)** is the ratio of risk in the experimental group (experimental event rate, EER) to risk in the control group (control event rate, CER).
  - EER = rate at which events occur in the experimental group
  - CER = rate at which events occur in the control group
- For example, if we look at a trial comparing the use of paracetamol for dysmenorrhoea compared to placebo we may get the following results

	Total number of patients	Experienced significant pain relief
Paracetamol	100	60
Placebo	80	20

- Experimental event rate, EER = 60 / 100 = 0.6
  Control event rate, CER = 20 / 80 = 0.25
  Therefore the relative risk ratio = EER / CER = 0.6 / 0.25 = 2.4
- If the risk ratio is > 1 then the rate of an event (in this case experiencing significant pain relief) is increased compared to controls. It is therefore appropriate to calculate the relative risk increase if necessary (see below).
- If the risk ratio is < 1 then the rate of an event is decreased compared to controls. The relative risk reduction should therefore be calculated (see below).
- **The relative risk is always positive**
- **Relative risk reduction (RRR) or relative risk increase (RRI) is calculated by dividing the absolute risk change by the control event rate**
  Using the above data, RRI = (EER - CER) / CER = (0.6 - 0.25) / 0.25 = 1.4 = 140%
- **Relative risk reduction = 1 − relative risk**

Remember that risk and odds are different. If 20 patients die out of every 100 who have a myocardial infarction then the risk of dying is 20 / 100 = 0.2 whereas the odds are 20 / 80 = 0.25.

Numbers needed to treat and absolute risk reduction

Absolute risk reduction = (Control event rate) - (Experimental event rate)

NNT = 1 / Absolute Risk Reduction

- **Numbers needed to treat (NNT)** is a measure that indicates how many patients would require an intervention to reduce the expected number of outcomes by one.
- **Example: if a study for stroke reveals that 20 patients need to be treated to prevent one event.**
- **That means, if you treat a 1000 patients then you will expect to have 50 fewer strokes**
- It is calculated by 1/(Absolute risk reduction)
  Experimental event rate (EER) = (Number who had particular outcome with the intervention) / (Total number who had the intervention)
- **Control event rate (CER)** = (Number who had particular outcome with the control/ (Total number who had the control)
- **Absolute risk reduction = CER-EER or EER-CER**
- ARR = risk in control group - risk in treated group.
  - **For example**: If a drug reduces the incidence of heart attacks from 12% to 8% then:
    - The control event rate (CER) is 12%
    - The experimental event rate (EER) is 8%
    - The relative risk reduction (RRR) is 33% ([EER-CER/CER] x 100)
    - The absolute risk reduction (ARR) is 4% (CER-EER)
    - The number needed to treat (NNT) is 25 ([1/ARR] x 100)

Number needed to harm

- For many studies now, papers quote the number needed to harm. This uses the same principle to establish the difference in absolute risk of an adverse event occurring between two treatment strategies, **calculating a number needed to harm by dividing 100 by the absolute risk.**

Hazard ratio

- The hazard ratio (HR) is similar to relative risk but is used when risk is not constant to time. It is typically used when analysing survival over time
- Example: A study is performed comparing two chemotherapy regimes for patients with small cell lung cancer. The end point of the study is survival time. Which one of the following types statistical measures is it most appropriate to compare survival time with? → Hazard ratio

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Odds and odds ratio

Odds - remember a ratio of the number of people who incur a particular outcome to the number of people who do not incur the outcome
NOT a ratio of the number of people who incur a particular outcome to the total number of people

- **Odds are a ratio of the number of people who incur a particular outcome to the number of people who do not incur the outcome.** The odds ratio may be defined as the ratio of the odds of a particular outcome with experimental treatment and that of control.

Odds vs. probability

In contrast, probability is the fraction of times you'd expect to see an event in many trials. When expressed as a single number probability is always between 0 and 1. So, if we take the example of rolling a dice:

- the probability of rolling a six is 1/6 or 0.166666
- the odds of rolling a six is 1/5 or 0.2
- Odds ratios are the usual reported measure in case-control studies. It approximates to relative risk if the outcome of interest is rare.

For example, if we look at a trial comparing the use of paracetamol for dysmenorrhoea compared to placebo we may get the following results

	Total number of patients	Achieved = 50% pain relief
Paracetamol	60	40
Placebo	90	30

The odds of achieving significant pain relief with paracetamol = 40 / 20 = 2
The odds of achieving significant pain relief with placebo = 30 / 60 = 0.5
Therefore the odds ratio = 2 / 0.5 = 4

Pre- and post- test odds and probability

Pre-test probability

- the proportion of people with the target disorder in the population at risk at a specific time (point prevalence) or time interval (period prevalence).
- For example, the prevalence of rheumatoid arthritis in the UK is 1%.

Post-test probability

- The proportion of patients with that particular test result who have the target disorder.
  Post-test probability = post test odds / (1 + post-test odds).

Pre-test odds

- The odds that the patient has the target disorder before the test is carried out.
- Pre-test odds = pre-test probability / (1 - pre-test probability).

Post-test odds

- The odds that the patient has the target disorder after the test is carried out.
- Post-test odds = pre-test odds x likelihood ratio.
- where the likelihood ratio for a positive test result = sensitivity / (1 - specificity).

Screening: Wilson and Junger criteria

1. The condition should be an important public health problem
2. There should be an acceptable treatment for patients with recognised disease
3. Facilities for diagnosis and treatment should be available
4. There should be a recognised latent or early symptomatic stage
5. The natural history of the condition, including its development from latent to declared disease should be adequately understood
6. There should be a suitable test or examination
7. The test or examination should be acceptable to the population
8. There should be agreed policy on whom to treat
9. The cost of case-finding (including diagnosis and subsequent treatment of patients) should be economically balanced in relation to the possible expenditure as a whole
10. Case-finding should be a continuous process and not a 'once and for all' project

R-values

- A positive R-value means that as one variable increases, so does the other
- A negative R-value means that as one variable decreases, the other increases ie the correlation is inversed (**A negative R-value indicates an inverse association**)
- An association or lack of association is indicated by how close the value of R is to zero and its statistical
- significance is denoted by its p-value
- P-values < 0.05 are considered to be significant

Scales of measurement

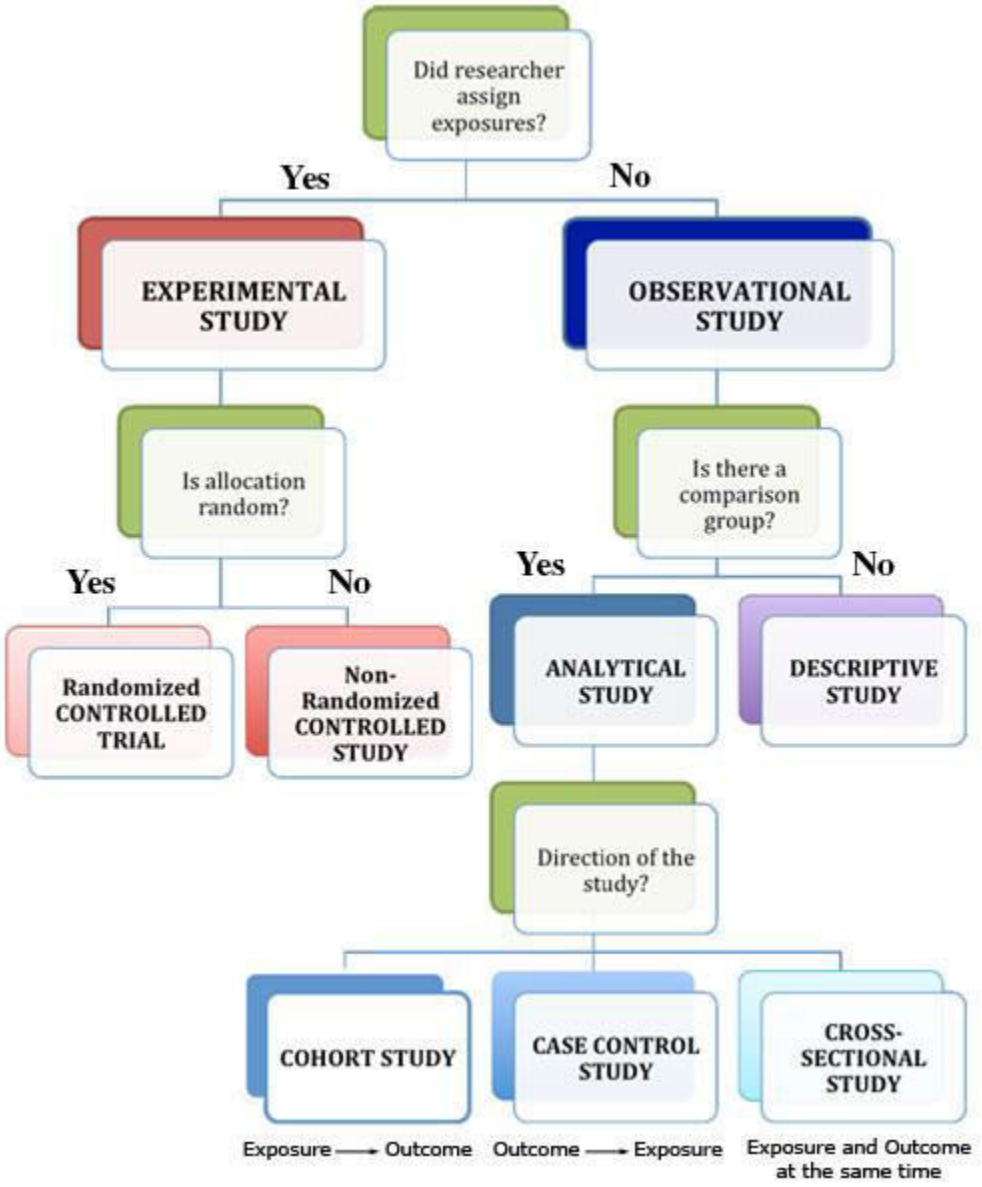
Data always come in one of the four scales of measurement:

Nominal	Data are divided into qualitative groups, such as hot/cold, with no implication of order.
Ordinal	Data are placed in an order (hot/hotter/hottest), although the absolute levels are unknown and no conclusion can be made about the size of the interval.
Interval	**dividing a continuous measurement into groups (eg age groups).**Data are placed in an order; and the exact value of the measurement is given, usually in measured quantities representing the difference between two measurements (81-90/91-100/101-110 °C). That is, differences between arbitrary pairs of measurements can be meaningfully compared. Ratios between numbers of the scale are not meaningful, so operations such as multiplication and division cannot be carried out directly. But ratios of differences can be expressed; for example, one difference can be twice Another If the measurement scale does not have an absolute zero (ie no numbers exist below the zero) this is called interval data.
Ratio	Here, there is a value of 0 kelvin, and it isn't possible to get below this (ie absolute zero), therefore, the ratio between the values is meaningful, eg 271-280/281-290/291-300 kelvin.

Select Study Design to Match the Research Goals

Objective	Study design
Describe of disease or spectrum	Case series or report Cross sectional study
Determine operating characteristics of a new diagnostic test	Cross sectional study
Describe prognosis	Cohort study
Determine cause-effect	Cohort study Case control study
Compare new interventions	Randomised clinical trial
summarize literature	Meta-analysis

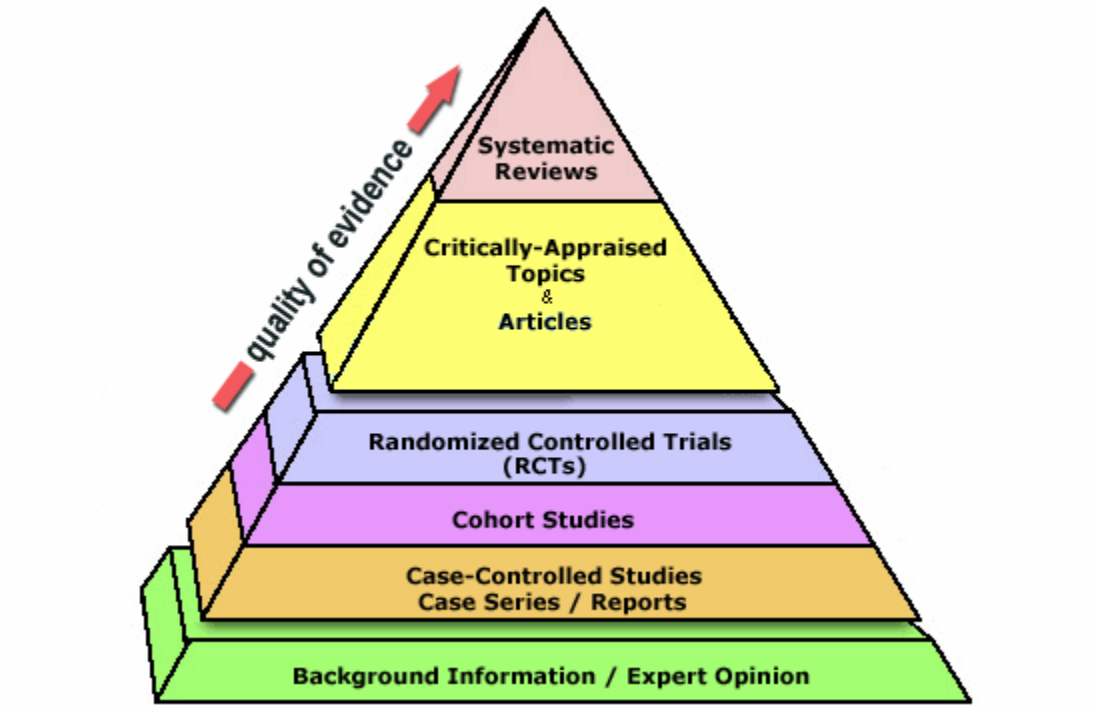
Select Study Design



The following table highlights the main features of the main types of study:

Study type	Key features
Randomised controlled trial	Participants randomly allocated to intervention or control group (e.g. standard treatment or placebo) Practical or ethical problems may limit use
Cohort study	Observational and prospective. Two (or more)are selected according to their exposure to a particular agent (e.g. medicine, toxin) and followed up to see how many develop a disease or other outcome. **The usual outcome measure is the relative risk.** Examples include Framingham Heart Study
Case-control study	Observational and retrospective. Patients with a particular condition (cases) are identified and matched with controls. Data is then collected on past exposure to a possible causal agent for the condition. **The usual outcome measure is the odds ratio.** Inexpensive, produce quick results Useful for studying rare conditions Prone to confounding
Cross-sectional survey	Provide a 'snapshot', sometimes called prevalence studies Provide weak evidence of cause and effect

Grade of evidence



Randomised controlled trial (RCT)

- is the 'gold standard' for evaluating a new intervention
- **The purpose of randomisation is to prevent systematic differences between treatment groups.**
- **Classic errors in randomisation** are:
  - Consecutive sampling, which may well not be representative if the study time is short.
  - Convenience sampling: strong potential for bias, with volunteers generally healthier than others.
  - Judgmental sample: including those that you want only. The potential for systematic error is enormous.
- **In RCT, the results best summarised as ➔ Mean and confidence interval for the difference between the active intervention group and the control that is of importance**
- **In RCT, data analysed by analysis of covariance provides an efficient analysis without introducing bias**
- **An imbalance in a baseline variable will inevitably sometimes occur in well-conducted, randomised controlled trials, so analysis should be undertaken to see if the imbalance alters the conclusions of the trial**
- A 'double-blind, randomised, placebo controlled study' would be time consuming, expensive and unlikely to be powered enough to detect what may be a **rare** toxic effect.

With rare diseases and exposures, **case control studies** are the best option. Although cohort studies are good for **rare exposures**, they are **not good for rare diseases**.

To test relative potency:

- **Biological assays are designed to measure the relative potency of different preparations.**

To test efficacy:

- Blood pressure is highly variable and is subject to variability because of the patient's level of anxiety and the method used by the observer to measure it.
- In a test of **efficacy** of an antihypertensive drug, a double blind, **randomised design would be favourable.**

A sequential trial

- a trial in which the data are analysed after each participant's results become available and the trial continues until a clear benefit is seen in one of the comparison groups, could also be used to assess efficacy, but there would have to be a large expected difference from placebo.
- 'Sequential' trial would be comparing one therapy to another sequentially (usually with wash out periods in between).

Advantages of case-control studies are that:

- **They are particularly suitable for rare diseases**
- A wide range of risk factors can be investigated
- There is no loss to follow up, and
- They are relatively cheap and quick to perform.

Disadvantages of case-control studies:

Have the greatest problems with recall bias

Cohort advantages and disadvantages

Disadvantages include:

- Relatively time consuming
- expensive to perform.
- **When the outcome of interest is rare a very large sample size is needed (Insufficient for rare disease)**

Advantages include

- able to study exposure factors that are rare
- Less susceptible to recall bias than case-control studies.
- Able to measure the incidence/risk of a disease.

Disadvantages of observational studies

- **From association in an observational study, we cannot infer cause and effect**

Crossover trial

- The principle of a crossover design is that a patient has one drug or treatment, then a washout period, and then another drug, and the effect is compared between the two in a single individual.
- For this reason it is a good **study design for treatment of chronic conditions (eg: comparing analgesics in arthritis**) but not appropriate for acute conditions.

- **In a crossover trial, the patient (who usually has a chronic stable disease) receives one drug (or placebo) and then the other drug after a washout period**
- **Each patient will usually receive all drugs within the study**
- In this way, confounding can be greatly reduced
- If a drug had long-lasting effects it may not be easy to see which of the trial drugs was having an effect
- A self-limiting illness is difficult to study in this way
- Because each person is acting as their own control, it is usually possible to use smaller numbers to get the same power.
- **If any treatment in a cross-over trial is a disease-modifier (in the most extreme case, kills or cures the patient), then the interpretation of results in any subsequent period becomes impossible.** This is because disease modification implies that one course of the drug will permanently change the future timecourse of that patient's disease in some way, making a cross-over study un-interpretable. In this case a parallel trial is the only appropriate option.

Intention to treat analysis (ITT)

- Intention to treat analysis is a method of analysis for randomized controlled trials in which all patients randomly assigned to one of the treatments are analysed together, regardless of whether or not they completed or received that treatment. **Include the patients who drop out in the final data set**
- Intention to treat analysis is done to avoid the effects of crossover and drop-out, which may affect the randomization to the treatment groups.
- Intention to treat helps to reduce bias by sticking to the original allocation of treatment and analysing the patient in that treatment group even if they do not recieve the treatment
- ITT is considered to be the analysis which is least subject to bias. **Considered the most robust**

Per protocol analysis

- **A per protocol analysis** may exclude patients who suffered an event but then did not follow the protocol accurately, for example, a patient treated with the diabetes agent who was admitted to hospital, but missed one to two doses of medication.

Sampling

- Sampling error arises when only a portion of the population is studied
- **Random sampling** implies that the sample has been selected from a sampling frame in such a way that every individual has the same chance of being selected

- In random sampling, defined criteria for sample selection are laid down
- **The standard error of the mean** is the standard deviation divided by the square root of the sample size, hence it must always be smaller than the standard deviation
- **Inference** is the process of drawing conclusions about the population using the sample information
- **a sample statistic is a point estimate of a population parameter**

Bias

Bias occurs when there is a systematic difference between the results from a randomised controlled trial and the true state of affairs.

- **a selection bias** occurs when the study population is different from the population to whom the results will be applied and there is therefore said to be
- **Allocation bias** occurs when patients are not randomly assigned to a particular treatment.
- **Assessment bias** occurs when the observer knows which treatment the subject is taking.
- **Observer bias** is when one observer consistently under or over reports a particular variable.
- **Recall bias** applies to case-control studies when a patient is more likely to remember a particular detail of exposure if they go on to develop the disease.

Study design: evidence and recommendations

Levels of evidence

- Ia - evidence from meta-analysis of randomised controlled trials
- Ib - evidence from at least one randomised controlled trial
- IIa - evidence from at least one well designed controlled trial which is not randomised
- IIb - evidence from at least one well designed experimental trial
- III - evidence from case, correlation and comparative studies
- IV - evidence from a panel of experts

Grading of recommendation

- Grade A - based on evidence from at least one randomised controlled trial (i.e. Ia or Ib)
- Grade B - based on evidence from non-randomised controlled trials (i.e. IIa, IIb or III)
- Grade C - based on evidence from a panel of experts (i.e. IV)

Study design: new drugs

Superiority trial ➔ a large sample size is required to demonstrate a significant difference

When a new drug is launched there are a number of options available in terms of study design. One option is a placebo controlled trial. Whilst this may provide robust evidence it may be considered unethical if established treatments are available and it also does not provide a comparison with standard treatments.

If a drug is therefore to be compared to an existing treatment a statistician will need to decide whether the trial is intended to show superiority, equivalence or non-inferiority:

- **Superiority**: whilst this may seem the natural aim of a trial one problem is the large sample size needed to show a significant benefit over an existing treatment

- **Equivalence**: an equivalence margin is defined (-delta to +delta) on a specified outcome. If the confidence interval of the difference between the two drugs lies within the equivalence margin then the drugs may be assumed to have a similar effect
- **Non-inferiority**: similar to equivalence trials, but only the lower confidence interval needs to lie within the equivalence margin (i.e. -delta). Small sample sizes are needed for these trials. Once a drug has been shown to be non-inferior large studies may be performed to show superiority

It should be remembered that drug companies may not necessarily want to show superiority over an existing product. If it can be demonstrated that their product is equivalent or even non-inferior then they may compete on price or convenience.

Post-marketing surveillance (PMS)/observational studies (phase IV studies):

- **designed to assess the potential side effects of new drugs**
- In contrast to the randomised controlled trials, PMS typically includes patients from more extreme age groups and patients with comorbidity or other risk factors.
- In order to cover a wide spectrum of patients and to observe rare events with sufficiently high probability, PMS enrolls a large number of patients, typically several thousands.

Phases of new drug development

phase	goal	notes
Animal trial	Safety for testing the drug in humans	
Phase I	• Initial safety ❖ most frequent side effects ❖ How the drug is metabolized and excreted.	• conducted in healthy volunteers. • The number of subjects ranges from 20 to 80.
Phase II	Effectiveness (RCTs)	The number of subjects ranges from a few dozen to about 300.
Phase III	Comparative efficacy (Effectiveness compared to commonly used treatment)	• The number of subjects ranges from several hundred to about 3,000 • The best study for phase 3 is a randomised control study.
Phase IV (post marketing)	Side effects	Enrolls a large number of patients, typically several thousands.

Systematic review (meta-analysis)

- a study of studies.
- statistical (quantitative) combination of results from two or more studies addressing the same research question.
- Metanalysis= systematic reviews + Quantitative measures.
- Usually used to treatment studies.
- **A 'meta-analysis' would look at combining all previous data,. This is likely to be the quickest option to complete, and also produces the highest level of evidence.**
- **rapid and efficient**

- **Publication bias might be present** (positive results are published more often than the negative ones).
- Publication bias can be examined by funnel plots if a sufficient number of studies is found.
- Non-randomised or other studies may or may not be included.
- However, randomised controlled trials usually have lower risk of bias and hence give us more confidence about validity of results and are preferred primary sources for systematic review.
- Critical appraisal is an important part of systematic review and it has to be objectively performed using well-defined criteria or appraisal tools.
- Meta-analysis, that is, combining results numerically in a statistically appropriate way, though desirable, is not always feasible, depending on the availability of usable data and heterogeneity. **(Meta-analysis is not always performed)**
- The search strategy in systematic review should be comprehensive involving electronic databases and other sources and using well-defined search terms.
- **Case-control studies are not usually included in the search of literature in systematic review**
- The research question is always focused
- there are at least two authors to independently appraise the search results and primary studies.
- It is not mandatory to exclude studies with missing data.
- The effect size should not affect the weight of each study, although it will affect the final result.
- Trial quality is usually not incorporated into meta-analysis nowadays since the weightings can be subjective and arbitrary.
- **The weight of each study should depend on the sample size**
- **Funnel plots**
  - **show publication bias in meta-analyses**
- **Forest plot**
  - **The most appropriate way of graphically depicting the results of meta-analysis.**

Fixed vs random effect model for meta-analysis

The fixed effect model	The random effects model
the most commonly used model for meta-analysis. **Provides the best estimate of the treatment effect**	
attempts to provide one single best estimate of treatment effect.	attempts to find an average treatment effect.
assumes there is no heterogeneity between the trials.	assumes heterogeneity
assumes a single treatment effect	allows multiple treatment effects.

Graphical representation of data

Charts and diagrams

Quantitative data	Qualitative data
Histogram Scatter diagram	Bar diagram Pie diagram

The interpretation of novel findings in a published clinical research study

- The trustworthiness of a study should depend solely on its scientific validity, that is, whether it is free of bias.
- **The conclusion should be treated with skepticism even if it is extensively peer-reviewed**

Notes & Notes

For MRCP part 1 & 11

By

Dr. Yousif Abdallah Hamad

Pharmacology

Updated

2017

Contains:

1/ Passmedicine 2017

2/ On examination 2017

3/ Pastest 2017

4/ **Red fonts --> previous exams**

5/ Other updated UK sources

Basic pharmacology

Pharmacokinetics: metabolism

Drug metabolism
- phase I: oxidation, reduction, hydrolysis
- phase II: conjugation

Drug metabolism usually involves two types of biochemical reactions - phase I and phase II reactions.
The majority of phase I and phase II reactions take place in the liver

- **phase I reactions:** oxidation, reduction, hydrolysis.
  - Mainly performed by the P450 enzymes but some drugs are metabolised by specific enzymes, for example alcohol dehydrogenase and xanthine oxidase.
  - Products of phase I reactions are typically more active and potentially toxic
- **phase II reactions:** conjugation.
  - Products are typically inactive and excreted in urine or bile.
  - Glucuronyl, acetyl, methyl, sulphate and other groups are typically involved

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Drug absorption

- **Diffusion.**
  - **Most drug absorption** in the gastrointestinal tract occurs **by diffusion**.
  - For diffusion to occur:
    - the drug must be dissolved so that individual drug molecules come into contact with the gut epithelium,
    - **the drug must be lipid soluble so that it can cross the cell membrane**.
      - Because the cell membrane is lipoid, lipid-soluble drugs diffuse most rapidly.
      - **Drugs that are not ionized are lipid soluble and most likely to be well absorbed from the gastrointestinal tract.**
        - The ionized form has low lipid solubility (but high water solubility—ie, hydrophilic) and high electrical resistance and thus cannot penetrate cell membranes easily.
- Theoretically, **weakly acidic drugs (eg, aspirin) are more readily absorbed from an acid medium (stomach)** than are weakly basic drugs (eg, quinidine). However, whether a drug is acidic or basic, most absorption occurs in the small intestine because the surface area is larger and membranes are more permeable

Ref: medical-masterclass.com 2017 mrcp part 1

lipid soluble drug vs lipid insoluble drug

lipid soluble drug	lipid insoluble drug
have good gastrointestinal absorption	**have poor gastrointestinal absorption**
can be given orally	**may need to be given parenterally**
will be widely distributed in the body (large volume of distribution)	has limited distribution (may not cross blood-brain barrier or placenta and less likely to be stored in fat tissue)
usually requires metabolism before elimination (to decrease lipid solubility)	**may be eliminated without metabolism**
often have a **long plasma half-life** (prolonged by 'reservoir' of drug in tissues and by requirement for metabolism).	often have a short plasma half-life as elimination does not require metabolism.

Ref: medical-masterclass.com 2017 mrcp part 1

Sep 2017 part 1: What is the mechanism that make salmeterol acts as a LABA?
➔ **Its long duration results from its high lipid solubility**

	Chemical nature	Clinical significance	Example
Lipophilic	• Predominantly **nonpolar** compounds	• can easily **diffuse across the lipid** bilayer of the cell membrane. ➢ **can be administered topically** ➢ **can across the blood-brain barrier** • Metabolised in the liver and then excreted **through the bile duct**	• Scopolamine (hydroscine) ➢ Tertiary amine ➢ Used to treat motion sickness
Hydrophilic	• Predominantly **polar** compounds	• can only cross the lipid bilayer **via facilitated transport** • Smaller hydrophilic molecules can diffuse along a concentration gradient through pores in the membrane • **eliminated by the kidneys**	• Butylscopolamine (hyoscine butylbromide) ➢ Quarternary amine ➢ Used as an antispasmodic to treat GI colic
Amphiphilic	• Both lipophilic and hydrophilic		Local anesthetics, e.g., lidocaine

Drug metabolism in patients with advanced liver disease

- Plasma proteins fall in liver disease and may negatively affect drug **distribution**
- Both intrahepatic and extrahepatic cholestasis may affect the **metabolism** of drugs that are actively secreted into bile, eg ciprofloxacin
- **Conjugation reactions are affected to a lesser extent by advanced liver disease and only occur in very late stage disease**

Pharmacokinetics in chronic reprnal failure

- Renal failure disturbs virtually every kinetic parameter including:
  - ➢ gastric absorption
  - ➢ hepatic metabolism of some drugs
  - ➢ protein binding
  - ➢ volume of distribution
- **The bioavailability of an intravenously administered drug is 100% and does not change in renal failure**

What is the reason for phenytoin toxicity in patient with chronic renal failure?
→ Decreased protein binding of phenytoin

- In CRF, drugs lose some of their affinity for protein binding → ↑↑ availability of free drug at any given dose → toxicity
- Because laboratory assays for **phenytoin** usually measure total drug concentration, this give a false re-assurance (**drug level may be within therapeutic range**)
- In CRF dose reduction of phenytoin is therefore required
- Other drugs may cause same problem → **sodium valporate** and **warfarin**

Effects of age on drug metabolism

- All of the following may account for differences in drug metabolism in the elderly:
  - ➢ diminished renal function
  - ➢ altered proportions of body fat and water
  - ➢ **reduced cardiac output**
  - ➢ some degree of altered hepatic metabolism
  - ➢ diseases
  - ➢ general debility
  - ➢ concomitant medication use
- For these reasons, 'box-ticking' healthy elderly studies are rarely able to detect problems associated with the use of new drugs in the elderly age group
- Many problems associated with the use of new drugs in the elderly may only be discovered through adverse event reporting during the post-launch period
- **Which medications would require greatest caution when prescribed for older adults?**

- **diuretics,**
  - Older adults are more susceptible to the volume depletion and hyponatraemic effects of diuretics.
- digoxin,
- antihypertensives,
- anti-inflammatory agents
- drugs acting on the central nervous system (CNS).

First-pass metabolism

- This is a phenomenon where the concentration of a drug is greatly reduced before it reaches the systemic circulation due to **hepatic** metabolism.
  - As a consequence much larger doses are need orally than if given by other routes.
- This effect is seen in many drugs, including:
  - Aspirin
  - isosorbide dinitrate
  - glyceryl trinitrate
  - lignocaine
  - propranolol
  - verapamil
  - isoprenaline
  - testosterone
  - hydrocortisone
  - morphine
- **Drugs with high first-pass metabolism should be used with caution in liver disease**, since poor hepatic function may lead to their accumulation because of increased bioavailability

What is the reason for a different dose of sublingual glyceryl trinitrate (GTN) and oral isosorbide mononitrate?

⇨ **First-pass metabolism**

Saturation kinetics (first order + zero order kinetics)

- In drugs which have saturation kinetics→ initially Small doses of the drug lead to a linear increase in serum drug concentration(follow a linear line) → **(first order kinetics)**
- Then their metabolism slows down leading to a plateau of the line, for example due to enzyme depletion. Small doses in the drug then lead to large increases in plasma concentration → (**zero order kinetics).**This response is typical of drugs such as phenytoin (saturates liver metabolism).
- **Types of drug kinetics**
  1. **Zero order kinetics**: The rate of metabolism and/or elimination remains constant and is independent of the concentration of the drug (e.g., metabolism of alcohol)
  2. **First order kinetics**: The rate of metabolism and/or elimination is directly proportional to the plasma concentration of the drug (applies to most drugs)

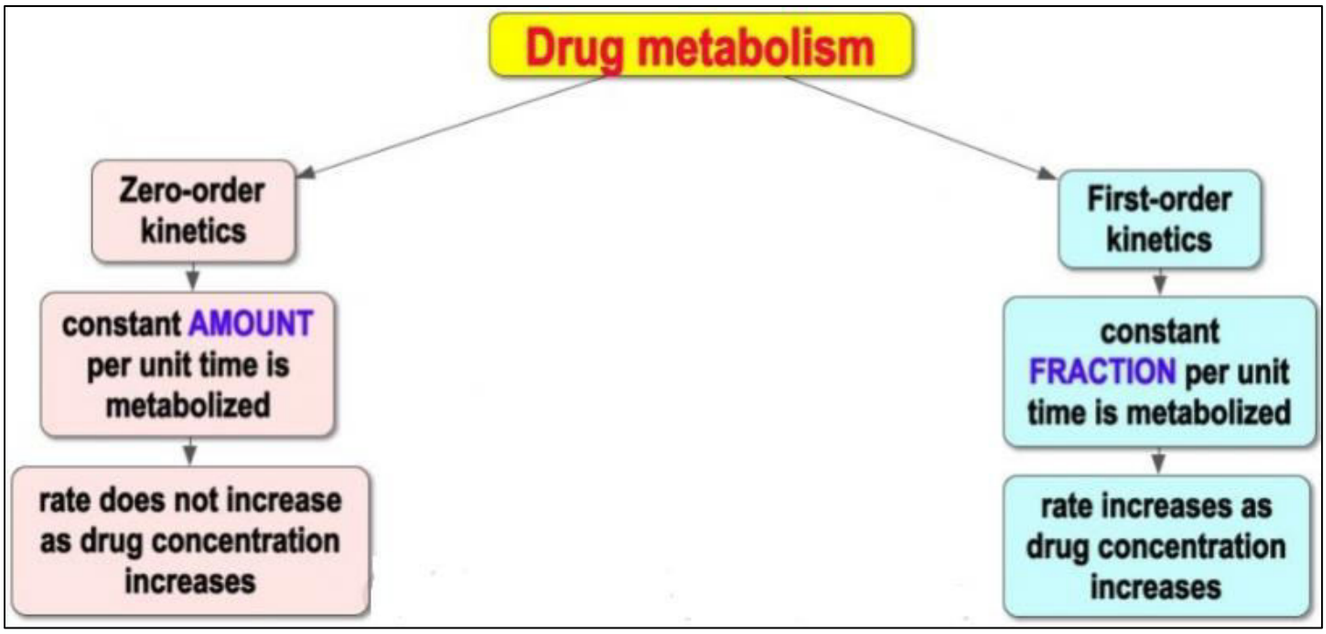
Zero-order kinetics

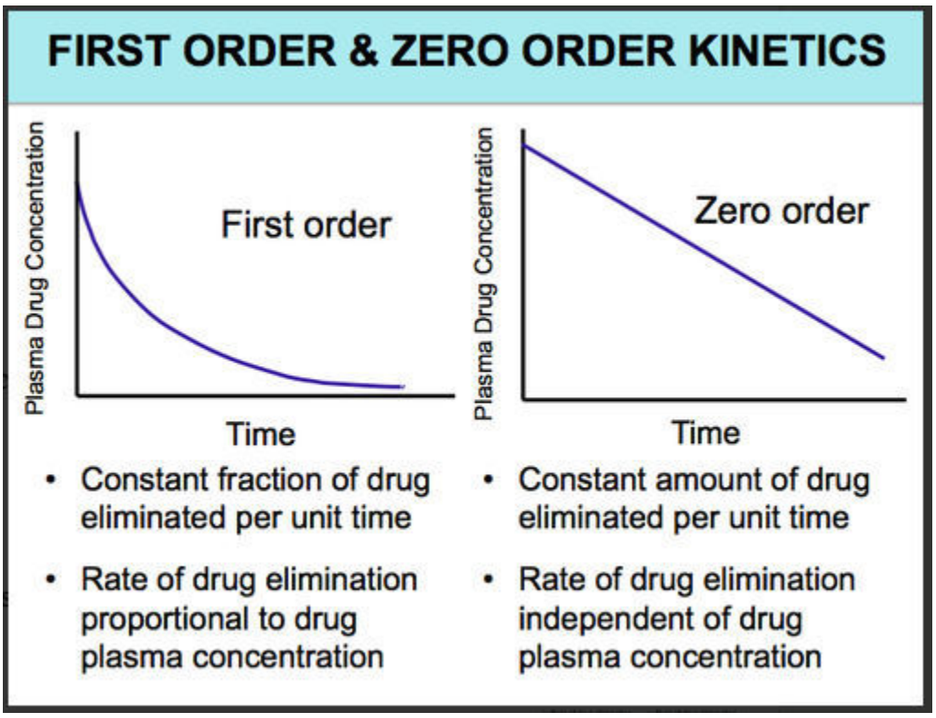
Zero-order (saturation) kinetics
- phenytoin
- alcohol

- Zero-order kinetics describes:
  - metabolic pathways becoming saturated resulting in → constant **amount** of drug being eliminated per unit time (metabolism which is independent of the concentration of the reactant).
- This explains why people may fail a breathalyser test in the morning if they have been drinking the night before
- Drugs following zero order kinetics continue to be metabolised at a steady rate, independent of the concentration of the substrate.
- **The plot of metabolism against time is linear**.

Drugs exhibiting zero-order kinetics

- phenytoin
- salicylates (e.g. high-dose aspirin)
- heparin
- ethanol





Acetylator status

- 50% of the UK population are deficient in hepatic N-acetyltransferase
- Greater than 60% of Japanese are recognised to be fast acetylators
- Approximately 50% of black and Caucasian people are 'slow acetylators' and the rest are 'rapid acetylators'.
- The majority of Eskimos and Orientals are 'rapid acetylators'.
- **Slow acetylation** → ↑↑**drug concentrations** → ↑↑toxicity from drugs adverse effects.
- **fast acetylation** →
  - ↓↓response to the drug effect
  - ↑↑ **blood levels of the toxic metabolite**

Drugs affected by acetylator status (slow acetylators → increased unwanted effects)

1. isoniazid
   - **Slow acetylation** →↑↑**drug concentrations** → (peripheral neuropathy and **toxic hepatitis**
2. hydralazine →(drug-induced lupus)
3. dapsone →(haemolysis and neuropathy but not fibrosis)
4. **sulfasalazine →(haemolysis)**
5. procainamide

Drug transporter : P-glycoprotein (P-gp)

P-glycoprotein (P-gp)

- **(P-gp)** is an efflux transporter that takes drug molecules from the cell cytoplasm and transports them back into the intestinal lumen for excretion. thus ↓↓ their bioavailability.
- P-gp transports many drugs that are substrates of CYP3A4.
- P-gp and CYP3A4 act as barriers to the systemic exposure of exogenous substances including drugs.
- P-gp prevent saturation of CYP3A4. This results in an increase in the efficiency of first-pass drug metabolism.العلاقة بينهما عكسية
- CYP3A4 concentrations decrease from the proximal to distal portions of the intestine. P-gp content increases from the proximal to distal intestine. Thus, where an excess of CYP3A4 is available for metabolism, less P-gp is present. Conversely, where CYP3A4 concentrations are lower, more P-gp is found to prevent saturation of the enzyme.
- An inhibitor of P-gp will increase the bioavailability of a P-gp substrate, whereas induction of P-gp will reduce the bioavailability of a substrate drug.
- P-gp inhibits digoxin bioavailability .
  - Co-administration of the P-gp inhibitors (eg: erythromycin or clarithromycin) to patients receiving chronic digoxin →↑ serum digoxin → ↑central nervous system side effects
  - Conversely, P-gp inducers → ↓ serum digoxin.

Substrates, Inhibitors, and Inducers of P-glycoprotein

Substrates	Inhibitors	Inducers
Colchicine	**Amiodarone**	Carbamazepine
Digoxin	Clarithromycin	Rifampin
Fexofenadine	Erythromycin	St. John's wort
Indinavir	Ketoconazole	Tipranavir
Morphine	Quinidine	
Sirolimus	Saquinavir	
	Verapamil	

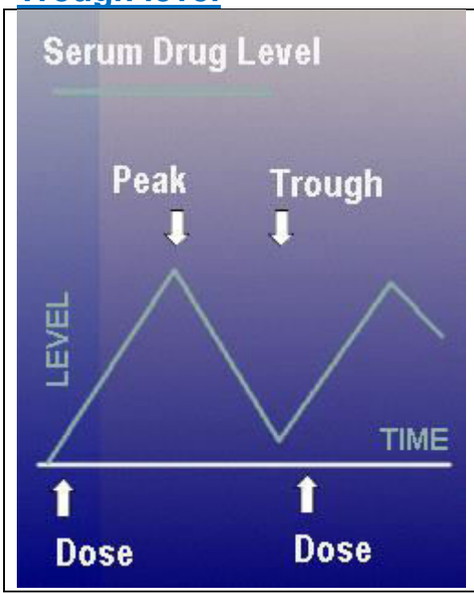
Half-life

↑↑ lipid solubility → ↑↑tissue binding of the drug → ↓↓ renal and hepatic clearance rate → ↑↑ half life

- **The half-life is the time taken for the concentration of a drug to reduce by 50%**
- **Plasma half-life is the most important pharmacokinetic factor in determining the appropriate timing between doses**
- **The half-lives are related to**:
  1. lipid solubility (amiodarone, fluoxetine and diazepam are very lipid-soluble)
  2. the rate of drug clearance
- **Amiodarone the longest half-life = 25 days** , fluoxetine 53 h; diazepam 43 h; gentamicin 2-3 h; and bumetanide 0.8 h

After 4 half-lives, more than 90% of the drug is eliminated

Trough level



- The **lowest concentration** reached by a drug **before the next dose** is administered, often used in therapeutic drug monitoring.
- Half-life is the major determinant of trough concentration

Affinity & efficacy

- **Affinity** is the measure of the attraction between a drug and its receptor.
  - (the **affinity of a drug for its receptor ➔ Potency**)
  - Affinity and intrinsic activity are determinants of potency.
- **Potency**
  - 'Potency' is a term often used incorrectly to describe dose-response
  - Potency is merely the **effect of a drug**, weight for weight, **compared against another**
- **Efficacy**
  - contributes both to potency and to the maximum effect of the agonist.
  - Efficacy is a measure of the efficiency of the drug-receptor complex in initiating the signal transduction process.
  - Therapeutic efficacy (eg in a change in mmHg) is a much better measure of dose-response
  - dose-response curves can be plotted for efficacy and toxic effects
- **Therapeutic index** → (the maximum tolerated dose divided by the minimum effective dose)

Dose-response

- **The dose-response curve** for loop diuretics such as furosemide is steeply rising and prolonged, indicating a **large improvement in drug effect across a range of increasing doses**
- In contrast, the dose-response curve for thiazide diuretics rapidly reaches a plateau after the use of relatively low doses, indicating that there is no point in increasing doses above 2.5 mg in the case of bendrofluazide for instance
- The dose-response curve reaches a plateau for pioglitazone at above 45 mg (licensed doses 30 mg and 45 mg)
- With respect to losartan, two doses are available, but the dose increment between 50 and 100 mg only results in a relatively modest further drop in blood pressure

loading dose

Why is a loading dose used in amiodarone? Because Amiodarone is widely bound in body tissues

- Tissue-binding sites must be 'filled up' by a loading dose before a therapeutic plasma concentration can be achieved.
- Metabolism/elimination/clearance rates and plasma half-life determine the time taken to achieve a steady-state plasma concentration and the level of that steady-state concentration when a steady dosing regimen is established.
- The loading dose is calculated (using various models) by taking into account age, creatinine clearance, body surface area, etc.
- **The loading dose is mainly dependent on the volume of distribution of a drug but in patient with moderate renal failure it depends on renal clearance.**
- Volume of distribution becomes important particularly when body weight is 40 kg or less.
- **What is the main factor that determines the choice of loading dose of digoxin in patient with high creatinine?**
  - **➔ Renal clearance**
    - Digoxin is cleared by the kidneys so the maintenance dose would require adjustment in renal failure.
    - **In digoxin both the initial loading dose and the maintenance dose must be reduced in patients with underlying renal disease.**
- most useful for drugs which have a long half-life such as:
  - **Amiodarone**
  - digoxin,
  - teicoplanin,
    - antibiotic → inhibit bacterial cell wall synthesis.
    - spectrum of activity similar to vancomycin → against Gram-positive bacteria including *Staphylococci* and *Clostridium* spp.
      - Oral teicoplanin is effective in the treatment of pseudomembranous colitis
  - voriconazole,
  - procainamide and
  - fulvestrant.
    - selective estrogen receptor degrader (SERD)
    - used to treat hormone receptor (HR)-positive metastatic breast cancer

Loading dose vs maintenance dose:

- **Loading doses** usually do not need to be adjusted in patients with chronic kidney disease, but **maintenance doses** should be adjusted by: dose reduction, lengthening the dosing interval, or both.
- in renal or liver disease, dosage of the same drug when given as **maintenance dose** is decreased and when it is given as **loading dose** is usually unchanged.

Bioavailability

- Bioavailability is a measure of **the proportion of an oral administered dose that reaches the systemic circulation**
- Where a drug is administered intravenously, it has 100% bioavailability
- Bioavailability is affected by two mechanisms:
  1. **First pass effect**:
     - Orally administered drugs are absorbed from the GI tract and reach the liver via the portal circulation, where they undergo some degree of metabolism before they enter systemic circulation. This decreases the bioavailability of the drug.
  2. **Ability to pass through lipid membranes**

Extraction ratio

- The extraction ratio is a measure of how much drug is extracted from the plasma by the kidney
- It determines the **clearance** (= renal plasma flow **X** extraction ratio)
- **The extraction ratio is determined by assessing drug concentration on the arterial and venous sides of the renal circulation**

Drug level and elimination

Example: if the half-life of a drug is 4 h , what percentage of the drug will be eliminated after 20 h?

- The concentration of the drug reduces by 50% over each 4-h period
- After 4 h → 50% remaining
  After 20 h → X % remaining
  X% = (0.5 x 20) /4 = 2.5 (remaining after 20 h)
- This means that approximately 97% of the drug concentration has been **eliminated after 20 h**

Example: 630 mg of a drug with half-life of 30 min, **how much time will it take before the drug level falls below 20 mg?**

- 20/630 = approximately 1/32 = 1/2x1/2x1/2x1/2x1/2 = 5 half-lives (for less than 20 mg to remain)
- 5 half-lives equals 5 x 30 min = **150 min**

Example: The half-life of a drug is 4 h, **calculate the plasma concentration** 12 h after administration of drug that gives a peak initial plasma concentration of 2 mg/dl**?**

- the half-life here, which is 4 h,
- 12 h is equal to three half-lives
- Therefore, the plasma concentration at 12 h will be 2/(2 x 2 x 2) = 0.25

Example: On admission the lithium level was 2.4 mmol/l; **After what period of time post admission is the lithium level likely to be approaching 0?**

- **The half-life of lithium is around 20 h**
- The level would be 1.2 mmol/l after 20 h, 0.6 mmol/l after 40 h, 0.3 mmol/l after 60 h and 0.15 mmol/l after 80 h

Clinical trial: phases

Clinical trials are commonly classified into 4 phases;

Phase	Goal	Notes
I	Determines pharmacokinetics and pharmacodynamics and side-effects prior to larger studies	Conducted on healthy volunteers
II	Assess efficacy + dosage	Involves small number of patients affected by particular disease May be subdivided into:

Phase	Goal	Notes
		• IIa - assesses optimal dosing • **IIb - assesses efficacy**
III	Assess effectiveness	Typically involves 100-1000's of people, often as part of a randomised controlled trial, comparing new treatment with established treatments
IV	Postmarketing surveillance	Monitors for long-term effectiveness and side-effects

How many patients would need to be recruited to detect one adverse event?

- Roughly speaking, to detect one adverse event in a clinical trial you would need to enrol **three times** as many patients as the expected event frequency
- **So If the frequency expected was 1 in 10 000, then you would need to recruit 30 000 patients**

Testing of a new drug pharmacokinetic

In designing a new drug, which of the following compounds, according to its mode of clearance, is most likely to show stable pharmacokinetic properties when tested between patients?

- CYP2D6 shows the greatest genetic variability → ↑↑ pharmacokinetic differences between patients in drugs metabolised down this route
- CYP3A4 is the P450 isoform pathway → significant drug interaction
- **Therefore, the preferred pathway for drug clearance is one-third via the kidneys and two-thirds via P450 isoforms, but not CYP2D6**
- the ideal profile of our candidate drug should be neither an inhibitor nor an inducer of the P450 system
- To maximise drug absorption, the ideal compound should be:
  - small molecular weight (of less than 300 kDa)
  - have intermediate lipophilicity and hydrophilicity

Bioequivalence

- **Bioequivalence means that → the two drugs compared have the same pharmacokinetic and pharmacodynamic effects**
- A pharmaceutical company wants to bring generic drug to the market. **What kind of study is needed to obtain approval to market the drug?**
  - → **Phase-I bioequivalence study.** Generic medicines have to be therapeutically equivalent to their branded product.

Some definitions

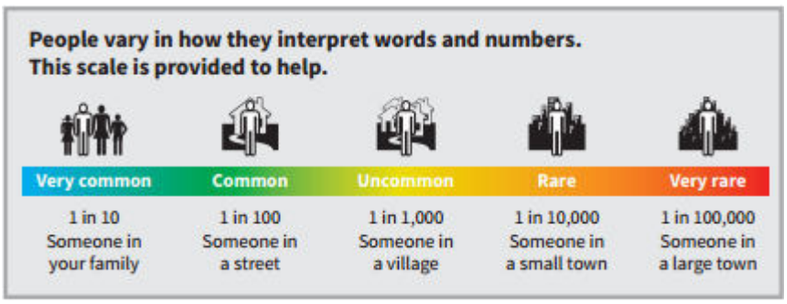
- **Competitive antagonists** bind to the site of action for the endogenous receptor ligand and can be displaced, (eg prazosin)
- **Non-competitive antagonists** (eg phenoxybenzamine) cannot be displaced or have their effects diminished by an endogenous receptor ligand
- **A partial agonist** (eg acebutolol) may exhibit strong receptor-binding activity, but have a limited physiological response

Adverse drug reactions

- **Type A** (**a**ugmented) reactions occur owing to a **pharmacological effect of the drug**
  - they are dose-related and can occur in anyone
- **Type B** (**b**izarre) reactions are **unpredictable** and not related to a pharmacological effect of the drug
- **Type C** (**c**ontinuous) reactions occur because of **prolonged drug use** (eg analgesic nephropathy or **visual-field defects with vigabatrin**,)
- **Type D** (**d**elayed) reactions are **teratogenic or carcinogenic** reactions (eg thalidomide)
- **Type E** (**e**nd of use) reactions are **withdrawal phenomena** identified after a drug is discontinued

Side-effects Classification

- **Very common side-effects are said to occur with a frequency of greater than 1 in 10 patients**
- Common side-effects: in 1 in 100 to 1 in 10
- Uncommon side-effects: in 1 in 1000 to 1 in 100
- Rare side-effects: in 1 in 10 000 to 1 in 1000
- Very rare side-effects: in less than 1 in 10 000 patients



The Yellow Card recording system of drug adverse effects:
Only 10% of serious adverse drug reactions are identified by Yellow Cards

Prodrugs

Prodrug	Active form	Note
Levodopa	Dopamine	converted by dopa decarboxylase to dopamine in the brain (in the striatum).
Enalapril	Enalaprilat	
S-methyldopa	Alpha methylnorepinephrine	It is converted to α-methylnorepinephrine by dopamine beta-hydroxylase → activation of α_2 adrenergic receptors in the brainstem →↓sympathetic output → ↓ BP.
Loratadine	desloratadine	non-sedating antihistamine
Terfenadine	fexofenadine	• non-sedating antihistamine • Terfenadine, withdrawn from the market because of serious side effect. • fexofenadine, is safe, does not carry the same risks as the parent compound.
salicin	salicylic acid	salicin is a β-D-glucopyranoside that is cleaved by esterases to release salicylic acid.
codeine and morphine	(morphine-glucuronides)	codeine and morphine is enzymatically activated to form sugar derivatives (morphine-glucuronides) that are more active than the parent compound
Mercaptopurine	Methymercaptopurine ribonucleotide	
Fluouracil	Fluororidine monophosphate	
Cyclophosphamide	Aldophosphamide, Phosphormide mustard	
Sulfasalazine	5-Aminosalicyclic acid	
Becampicillin	Ampicillin	
Prednisone	Prednisolone	
Proguanil	Proguanil triazine	Antimalarial is an inhibitor of dihydrofolate reductase
Hydrazide MAO inhibitors	Hydrazine derivatives	
Dipivefrine	Epinephrine	used to treat open-angle glaucoma

- Prodrugs can be classified into two major types:
  - **Type I prodrugs** are bioactivated intracellularly.
    - Examples of these are:
      - anti-viral nucleoside analogs that must be phosphorylated
      - lipid-lowering statins.
  - **Type II prodrugs** are bioactivated extracellularly, in GIT or blood.
    - Examples:
      - salicin

- ❖ antibody-, gene- or virus-directed enzyme prodrugs used in chemotherapy or immunotherapy.

P450 enzyme system

3 "**O**" antibiotics inhibit**O**rs → is**O**niazid , cipr**O**floxacine , erythr**O**mycin
1 "**C** " antibiotic indu**C**er → rifampi**C**ine

Induction usually requires prolonged exposure to the inducing drug, as opposed to P450 inhibitors, where effects are often seen rapidly

Inhibitors of the P450 system include

Isoniazid inhibits the P450 system

- antibiotics: ciprofloxacin, erythromycin
- isoniazid
- cimetidine, omeprazole
- **amiodarone**
- allopurinol
- imidazoles: ketoconazole, fluconazole
- SSRIs: fluoxetine, sertraline
- sulphonamides
- Disulfiram
- ritonavir
- **sodium valproate**
- acute alcohol intake
- quinupristin

Inducers of the P450 system include:

- antiepileptics: phenytoin, carbamazepine
- barbiturates: phenobarbitone
- rifampicin
- St John's Wort
- chronic alcohol intake
- griseofulvin
- smoking (affects CYP1A2, reason why smokers require more aminophylline)

Carbamazepine is an inducer of the P450 system. This in turn increases the metabolism of carbamazepine itself - auto- induction

P450 drug interactions: more detail

the most important and common reason for drug interactions is the P450 **CYP3A4 system**.
The table below shows the main enzyme systems that are affected by common drugs.

P450 system	Substrates	Inhibitors	Inducers
CYP3A4	Macrolides Antiretrovirals **Calcium channel blockers** simvastatin	Macrolides Protease inhibitors (including ritonavir) Imidazoles **grapefruit juice**	Carbamazepine Phenytoin Phenobarbitone Rifampicin St John's Wort
CYP2D6	Tricyclic antidepressants Antipsychotics	SSRIs Ritonavir	
CYP2C9	**Warfarin** Sulfonylureas	Imidazoles Amiodarone Sodium valproate	Rifampicin
CYP1A2	Theophylline	**Ciprofloxacin**	Smoking Omeprazole
CYP2E1	Alcohol		Chronic alcohol Isoniazid

Interestingly, **codeine** and **dihydrocodeine** are metabolised by cytochrome **P450 2D6** to morphine, which provides the analgesic effect; therefore, those patients who are CYP-2D6 poor metabolisers will have a reduced analgesic effect with codeine or Dihydrocodeine

CYP-2C8	CYP-2C18/19	CYP-2D6
Omeprazole	Diazepam	Tricyclic antidepressants
Diazepam	Tricyclic antidepressants	β-blockers
Barbiturates	Omeprazole	Dihydrocodeine
	Proguanil	Ecstasy (MDMA)
		Selective serotonin reuptake inhibitors

Drug interactions with cytochrome P450

- Drug interactions with the cytochrome P450 system are only clinically significant for drugs that have a narrow therapeutic index (ie small changes in plasma concentrations lead to the drug concentration being either sub-therapeutic or toxic)
- Examples of these drugs include:
  - **Ciclosporin**
  - warfarin
  - theophylline and
  - phenytoin
- Lithium has a narrow therapeutic index owing to changes in absorption and excretion and does not interact with cytochrome P450

Drugs required therapeutic monitoring

Antiepileptics • Carbamazepine • Phenobarbital • Phenytoin • Valproic Acid	**Antiarrhythmics** • Digitoxin • Digoxin • Lidocaine • NAPA • Procainamide	**Antibiotics** • Gentamicin • Tobramycin • **Vancomycin**
Immunosuppressants • Cyclosporine • Mycophenolic Acid • Sirolimus • Tacrolimus	**Antimanics** • Lithium	**Bronchodilators** • Theophylline

Drug induced manifestations

Drug causes gingival hyperplasia

Gingival hyperplasia: phenytoin, ciclosporin, calcium channel blockers and AML

Drug causes of gingival hyperplasia

- phenytoin
- Ciclosporin
- **calcium channel blockers** (especially nifedipine)

Other causes of gingival hyperplasia include

- acute myeloid leukaemia (myelomonocytic and monocytic types)

Drug affects folic acid metabolism

Drugs which inhibit dihydrofolate reductase are:

- Methotrexate
- **Pyrimethamine,** and
- Trimethoprim.

Drugs which interfere with absorption/storage of folate are:

- Phenytoin
- Primidone, and
- Oral contraceptives.

Drug causes SIADH

most commonly causes SIADH	Other causes
• Thiazide diuretics • Vincristine • Vinblastine • Cyclophosphamide	• Chlorpropamide • Carbamazepine • Phenothiazines • Tricyclic antidepressants • Clofibrate • Oxytocin • Vasopressin • Morphine • Barbiturates • Nicotine

Drug causes of urticaria

The following drugs commonly cause urticaria:

- **aspirin**
- penicillins
- NSAIDs
- opiates

Drugs induced galactorrhoea

Drug causes of raised prolactin

- **metoclopramide**, Domperidone
  - **Domperidone is a dopamine antagonist producing large rises in prolactin concentrations.**
- phenothiazines
- haloperidol
- Cimetidine produces hyperprolactinaemia **only** when given intravenously (IV).
- very rare: SSRIs, opioids

Drugs associated with gynaecomastia.

- **Spironolactone (the** most common**),** causes gynaecomastia by several **mechanisms.**
  - **block androgen production** by inhibiting enzymes in the testosterone synthetic pathway,
  - **block recceptor binding of testosterone** and dihydrotestosterone.
  - **increases free oestrogen levels** by displace oestradiol from sex hormone binding globulin (SHBG)

Other causes

- inhibitors of testosterone synthesis:
  - ketoconazole
  - metronidazole
  - cimetidine, Omeprazole
  - etomidate, and
  - cisplatin.
- Oestrogens:
  - **Digoxin** → direct action at oestrogen receptors.
- LHRH analogues
- Finasteride.
- marijuana
- heroin
- isoniazid
- Ciclosporin
- calcium-channel blockers
- **ACE inhibitors**
- tricyclic antidepressants
- busulphan
- diazepam

Drug-induced impaired glucose tolerance

- Drugs which are known to cause impaired glucose tolerance include:
  - thiazides, furosemide (less common)
  - steroids

  - tacrolimus, ciclosporin
  - interferon-alpha
  - nicotinic acid
  - atypical antipsychotics e.g. olanzapine
- Beta-blockers an glycemic status:
  - beta -2-adrenergic antagonism → inhibition of hepatic gluconeogenesis
    - **unselective beta-blockade associated with hypoglycemia** (e.g. **propranolol** rather than the use of beta-1 selective blockers e.g. atenolol, metoprolol).
    - **selective beta-1 blockers** would not lead to hypoglycaemia - however "...in patients with abnormal energy requirements or metabolism, administration of beta 1-selective-adrenergic antagonists may be associated with hypoglycaemia
  - Beta-blockers cause a slight impairment of glucose tolerance.
  - They should also be used with caution in diabetics as they can interfere with the metabolic and autonomic responses to hypoglycaemia

Drug-induced liver disease

Hepatocellular Picture	Cholestasis (+/- Hepatitis)	Liver Cirrhosis
• Alcohol • Amiodarone • Anti-tuberculosis: isoniazid, rifampicin, pyrazinamide • Halothane • MAOIs • Methyldopa • Paracetamol • Sodium valproate, phenytoin • **Statins** • nitrofurantoin	• Anabolic steroids, testosterones • Antibiotics: flucloxacillin, co-amoxiclav*, erythromycin**, nitrofurantoin • **Fibrates** • Oral contraceptive pill • Phenothiazines: ➢ chlorpromazine, ➢ prochlorperazine • Rarely: nifedipine • Sulphonylureas	• Amiodarone • Methotrexate • Methyldopa

* A four-week delay in symptoms and signs is not unusual.
**risk may be reduced with erythromycin stearate

Prescribing in patients with renal failure

See nephrology

Drug-induced lupus erythematosus

The most commonly associated drugs

- procainamide
- hydralazine 2,
- anti-TNF alpha agents,
- statins
- isoniazid
- **minocycline**.

Drug-induced pancytopaenia

Trimethoprim may cause pantcytopaenia

Drug causes of pancytopaenia

- cytotoxics
- antibiotics: **trimethoprim**, chloramphenicol
- anti-rheumatoid: gold, penicillamine
- carbimazole (causes both agranulocytosis and pancytopaenia)
- anti-epileptics: carbamazepine

- sulphonylureas: tolbutamide
- Although both **azathioprine** and **mesalazine** cause pancytopenia, it is **more commonly seen in patients undergoing azathioprine therapy**.

Drug-induced thrombocytopenia

Drug-induced thrombocytopenia (probable immune mediated)

- quinine
- abciximab
- NSAIDS
- diuretics: furosemide
- antibiotics: penicillins, sulphonamides, rifampicin
- anticonvulsants: carbamazepine, valproate
- heparin

Sulfa drugs

- Hypersensitivity reactions to sulfa medications are common and are usually limited to pruritic rashes.
- An acronym for remembering sulfa drugs is **P**opular **FACTSSS:**
  - **P**robenecid,
  - **F**urosemide,
  - **A**cetazolamide,
  - **C**elecoxib,
  - **T**hiazides,
  - **S**ulfonamide antibiotics,
  - **S**ulfasalazine,
  - **S**ulfonylureas.
- **Furosemide,**
  - Most loop diuretic, such as furosemide are sulfa-containing drugs,
  - sulfa-containing drugs can cause interstitial nephritis.
    - **Interstitium is the site of furosemide toxicity.**
    - For these patients, **ethacrynic acid** can be used instead, because it does not contain a sulfa group.

Disulfiram

- alcohol antagonist drug used to treat chronic alcoholism

Action

- Ethanol is metabolized by two enzymes:
  1. Alcohol dehydrogenase, which is located in the cytosol, converts ethanol to acetaldehyde.
  2. **Aldehyde dehydrogenase, which is located in the mitochondria** , converts acetaldehyde to acetyl CoA. Both enzymes require NAD+ for function.
- **Disulfiram is an inhibitor of aldehyde dehydrogenase** and causes accumulation of acetaldehyde, leading to severe nausea and vomiting if alcohol is consumed.

Disulfiram reaction

- The elevations in serum acetaldehyde levels cause the **symptoms of disulfiram reaction** which include:
  - flushing,
  - headache,
  - nausea, vomiting
  - sweating
  - blurred vision,
  - dyspnea,
  - palpitations, hypotension, chest pain and syncope.
- avoid all alcohol-containing products (e.g., cough and cold syrups, mouthwash, or foods containing alcohol) while taking this medication.
- **Disulfiram typically causes an acute hepatitis like syndrome 2 to 12 weeks after starting the medication** that can be severe and lead to acute liver failure or need for liver transplantation.

Disulfiram → inhibitor of Aldehyde dehydrogenase, which is located in the mitochondria
Fomepizole → inhibitor of Alcohol dehydrogenase, which is located in the cytosol

The target of disulfiram is located in which cellular compartments?
⇨ **Mitochondria**

Drug-induced ethanol intolerance (disulfiram-like reaction)

- As in the case with disulfiram, the underlying mechanism is believed to be the accumulation of acetaldehyde in the blood, due to inhibition of the hepatic aldehyde dehydrogenases.
- drugs which can produce DISULFIRAM like reaction when taken with Alcohol:
  - chloramphenicol,
  - furazolidone,
  - **nitroimidazole antibiotics, including metronidazole**, and
  - quinacrine,
  - First-generation sulfonylureas, e.g. tolbutamide and chlorpropamide
  - cephalosporins, including cefoperazone, cefamandole and cefotetan
  - antifungal eg: Griseofulvin
  - Procarbazine

Drug-induced long QT

Commonly medications that cause QT prolongation		
class	**Examples**	
Antiarrhythmic	• Amiodarone • Disopyramide • Ibutilide	• Procainamide • Quinidine • Sotalol
antipsychotics	• Chlorpromazine • Clozapine • Haloperidol	• Quetiapine • Risperidone • Thioridazine
antibiotics	• Azithromycin • Clarithromycin • Erythromycin • Ciprofloxacin • Levofloxacin	• Ofloxacin • Trimethoprim – sulpha • Ketoconazole • Fluconazole • itraconazole
Antidepressants	• Amitriptyline • Citalopram • Desipramine • Doxepin • fluoxetine	• Imipramine • Nortriptyline • Paroxetine • Sertraline • venlavaxine
Antiemetics	• Ondansetron	• prochlorperazine

Drugs causing ocular problems

Visual disturbance	cataract	Corneal opacities	Optic neuritis	Retinopathy	Blue tinge in vision	Yellow-green tinge
Drug	steroids	Amiodarone Indomethacin	Ethambutol Amiodarone Metronidazole	Chloroquine, quinine	**Sildenafil**	**Digoxin**

Visual changes secondary to drugs
- blue vision: Viagra ('the blue pill')
- yellow-green vision: digoxin

Sildenafil can cause both blue discolouration and non-arteritic anterior ischaemic neuropathy

Drug induced photosensitivity

Rash on the forearms and face is typical of a photosensitivity rash

- Thiazides
- Tetracyclines, sulphonamides, ciprofloxacin
- Amiodarone
- NSAIDs e.g. Piroxicam
- Psoralens
- Sulphonylureas

Mnemonic: **FAST-N** (**F**luoroquinolones eg: cipro. **A**miodarone. **S**ulfo.Tetracyclines. **N**SAIDs)

Drug induced ototoxicity

- Causes
  - Aminoglycosides
    - Streptomycin → irreversible cochlear and vestibular dysfunction
  - platinum-based antineoplastic agents,
  - salicylates,
  - quinine,
  - loop diuretics.
- Ototoxicity is typically associated with bilateral high-frequency sensorineural hearing loss and tinnitus.
- The time of onset is unpredictable:
  - marked hearing loss can occur even after a single dose.
  - may occur several weeks or months after completion of antibiotic or antineoplastic therapy.
- usually irreversible with most agents.

Drug induced seizures

Drugs that cause seizures as a drug reaction include isoniazid (vitami
B6 deficiency), bupropion, imipenem/cilastatin, tramadol, and enflurane.

Isoniazid, Bupropion, Imipenem/cilastatin, Tramadol, Enflurane.

With seizures, I BITE my tongue.

Drug causes erythema multiforme, and the Stevens-Johnson syndrome subtype.

- **Allopurinol → (the Most commonly associated)**
- Recent drugs - nevirapine, lamotrigine, sertraline, pantoprazole, tramadol
- Antibiotics - sulphonamides, co-trimoxazole, penicillin, cephalosporins, fluoroquinolones, vancomycin
- NSAIDs - piroxicam, fenbufen, ibuprofen, ketoprofen, naproxen, tenoxicam, diclofenac, sulindac
- Anti-TB - rifampicin, ethambutol, isoniazid, pyrazinamide
- Anticonvulsants - barbiturates, carbamazepine, phenytoin, valproate, lamotrigine
- Antifungals - fluconazole, nystatin, griseofulvin
- Antidepressants - lamotrigine, sertraline.
- **Sulfasalazine**

Drugs causes weight loss

- **Thyroxine,**
  - Abuse of thyroxine by doctors used to be more common as a method of keeping awake and active, before the European Working Time Directive was introduced.
  - Excessive use results in **proximal muscle weakness** , tachycardic cardiomyopathy, arrhythmias, palpitations, muscle cramps, diarrhoea, tremors, restlessness, sweating, headaches and **insomnia**.
  - Causes features of hyperthyroidism
- Laxatives
  - cause weight loss by volume depletion, not reduced fat.
- Metformin
  - can cause diarrhoea and headaches but does not cause muscle weakness.

Drugs which act on serotonin receptors

- Below is a summary of drugs which are known to act via modulation of the serotonin (5-HT) system.
- It should be noted that 5-HT receptor agonists are used in the acute treatment of migraine whilst 5-HT

receptor antagonists are used in prophylaxis.

Agonists

- sumatriptan is a 5-HT1D receptor agonist which is used in the acute treatment of migraine
- ergotamine is a partial agonist of 5-HT1 receptors

Antagonists

- pizotifen is a 5-HT2 receptor antagonist used in the prophylaxis of migraine attacks.
- Methysergide is another antagonist of the 5-HT2 receptor but is rarely used due to the risk of retroperitoneal fibrosis
- **cyproheptadine is a 5-HT2 receptor antagonist which is used to control diarrhoea in patients with carcinoid syndrome**
- ondansetron is a 5-HT3 receptor antagonist and is used as an antiemetic

5HT-2 receptor inhibition

- 5HT-2 receptor inhibition also reduces platelet aggregation
- one example is sarpogrelate developed in North East Asia primarily as an alternative to aspirin because of its association with a lower risk of haemorrhage.

Drugs that can be cleared with Hemodialysis - mnemonic: **BLAST**

• **B**arbiturate • **L**ithium • **A**lcohol (inc methanol, ethylene glycol) • **S**alicylates • **T**heophyllines (charcoal hemoperfusion is preferable)	**Drugs which cannot be cleared with HD include** • Tricyclics • Benzodiazepines (diazepam,midazolam,alprazolam) • Dextropropoxyphene (co-proxamol) • Digoxin, β-blockers

Drug fever

- 'Drug fever' as an isolated phenomenon can occur with
  - Penicillins,
  - phenytoin,
  - **hydralazine**
  - and quinidine
- Such fevers are usually of low grade and the patient is generally not very ill
- The fever subsides within a few days of stopping the drug

Cardiovascular drugs

Prescribing in patients with heart failure

The following medications may **exacerbate heart failure:**

- **thiazolidinediones**: pioglitazone is contraindicated as it causes fluid retention
  - pioglitazone is now the only thiazolidinedione on the market
- **verapamil:** negative inotropic effect
- **NSAIDs & glucocorticoids**: should be used with caution as they cause fluid retention
  - low-dose aspirin is an exception - many patients will have coexistent cardiovascular disease and the benefits of taking aspirin easily outweigh the risks
- **class I antiarrhythmics; flecainide** (negative inotropic and proarrhythmic effect)
- **Celecoxib** (rofecoxib has been withdrawn) acts by inhibiting prostaglandin synthesis via inhibition of cyclo-oxygenase-2 (COX-2).It causes fluid retention and can worsen an already pre-existing heart failure. The CSM reminds prescribers that **celecoxib is contraindicated** in:
  - patients with severe congestive heart failure,
  - active peptic ulceration
  - or gastrointestinal bleeding.

Antiarrhythmics: Vaughan Williams classification

The Vaughan Williams classification of antiarrhythmics is still widely used although it should be noted that a number of common drugs are not included in the classification e.g. adenosine, atropine, digoxin and magnesium
AP = action potential

Class	Examples	Mechanism of action
Ia	**Quinidine** **Procainamide** **Disopyramide**	1. Block sodium channels 2. Increases AP duration **Notes:** • Quinidine toxicity causes cinchonism (headache, tinnitus, thrombocytopaenia) • Procainamide may cause drug-induced lupus • **Disopyramide toxicity → Urinary retention**
Ib	**Lidocaine** **Mexiletine** **Tocainide**	1. Block sodium channels 2. Decreases AP duration
Ic	**Flecainide** **Encainide** **Propafenone**	1. Block sodium channels 2. No effect on AP duration
II	**Propranolol** **Atenolol** **Bisoprolol** **Metoprolol**	Beta-adrenoceptor antagonists
III	**Amiodarone** **Sotalol** **Ibutilide** **Bretylium**	Block potassium channels
IV	**Verapamil** **Diltiazem**	Calcium channel blockers

Antiarrhythmic agents

- **Calcium-channel blockers act mainly on (SA) (AV) nodes (direct membrane effect),** as these structures are almost exclusively depolarised by the slow calcium channels
- **Flecainide** binds to the sodium channel and decreases the speed of depolarisation (in other words, decreases conduction velocity) **(Slows the upstroke of the action potential)**
- **Atenolol** decreases sympathetic tone
- **Amiodarone** and **sotalol** increase the action-potential duration and therefore the refractory periods
  - they have little effect on conduction velocity
  - **Sotalol have a high risk of producing torsades de pointe**
- **Class V agents (digitalis agents)** affect SA and AV nodes by increasing vagal tone

Atropine

Action

- Atropine is an antagonist of the muscarinic acetylcholine receptor

Uses*

- treatment of organophosphate poisoning
- *atropine is no longer used in resuscitation

Physiological effects

- tachycardia
- mydriasis

January 2008 exam: Which physiological effect would be expected following administration of atropine?
Tachycardia + mydriasis

Adenosine

Adenosine
- dipyridamole enhances effect
- aminophylline reduces effect

Mechanism of action

- causes transient heart block in the AV node
- agonist of the A1 receptor which inhibits adenylyl cyclase thus reducing cAMP and causing hyperpolarization by increasing outward potassium flux
- Acts on specific adenosine cell surface receptors (A1 and A2)
- Stress testing: A2A adenosine receptor agonist;
  - activation of the A2A adenosine receptor produces coronary vasodilation and increases coronary blood flow
- ↑ coronary vasodilatation (**Adenosine is an important mediator of metabolic vasodilatation)**
- Increasing O_2 demands are met by → adenosine production → vasodilatation → increased blood supply.
- Adenosine effect on renal
  - In the renal vasculature, in contrast, adenosine can produce vasoconstriction
  - However, the vasoconstriction elicited by an intravenous infusion of adenosine is only short lasting, being replaced within 1-2 min by vasodilatation.
  - It appears that the steady-state response to the increase of plasma adenosine levels is global renal vasorelaxation that is the result of A2A receptor activation
  - Adenosine lowers glomerular filtration rate (GFR) by constricting afferent arterioles, especially in superficial nephrons. In contrast, it leads to vasodilation in deep cortex and medulla.
- ↓↓ sinus node automaticity and AVN conduction.
- adenosine has a very short half-life of about 8-10 seconds
- Inactivated by adenosine deaminase.

Adverse effects

- transient facial **flushing** (18%) (most common)
- bronchospasm
  - Dyspnea (12%)
  - It should be avoided in asthmatics
- choking sensation, where patients often clutch their chest
- chest pain
- can enhance conduction down accessory pathways, resulting in increased ventricular rate (e.g. WPW syndrome)

Interaction

- The effects of adenosine are enhanced by dipyridamole (anti-platelet agent)
  - Adenosine transported out of the cell to the extracellular space by specific bi-directional nucleoside transporters. **Inhibitors of these transporters**, such as dipyridamole, increase the extracellular concentrations of adenosine and are useful clinically to treat certain cardiovascular complications.
- Adenosine effects blocked by theophyllines.
- **Unlike verapamil it may be used following β-blockade**

Adenosine is a coronary vasodilator (which is why we use it in cardiac stress testing) and a bronchoconstrictor (action opposed by theophylline).

Adenosine receptors (ARs)

- ARs are classified based on their differential coupling to adenylyl cyclase to regulate cyclic AMP levels.
  - The A_1 and A_3ARs
    - are coupled to $G_{i/o}$ proteins
    - In contrast, activation of the A_1 and A_3AR inhibits cyclic AMP production and decreases PKA activity
  - A_{2A}AR and A_{2B}AR
    - are coupled to $G_{s/olf}$ proteins
    - activation of the A_{2A} and A_{2B}ARs increase cyclic AMP production, resulting in activation

of protein kinase A (PKA)

Flecainide

Action

- Flecainide is a Vaughan Williams class 1c antiarrhythmic.
- It slows conduction of the action potential by acting as a potent **sodium channel blocker**.
  - **Slows the upstroke of the action potential**
  - does not alter the overall length of the action-potential duration.
- This may be reflected by widening of the QRS complex and prolongation of the PR interval

Indications

- atrial fibrillation
- SVT associated with accessory pathway e.g. Wolf-Parkinson-White syndrome

Contraindications

- post myocardial infarction → increase mortality

Adverse effects

- negatively inotropic
- bradycardia
- proarrhythmic
- oral paraesthesia
- visual disturbances

Amiodarone

Amiodarone - MOA: blocks potassium channels

- Amiodarone is a **class III antiarrhythmic agent**
- used in the treatment of atrial, nodal and ventricular tachycardias.
- metabolized in the liver via cytochrome **P450 3A4**.

Action

- The main mechanism of action is by blocking potassium channels which inhibits repolarisation and hence prolongs the action potential.
  - Amiodarone **prolongs the refractory period** of the cardiac conducting system.
  - Its antiarrhythmic effects are due mostly to the **inhibition of the rapid component of the delayed potassium rectifier IKr channel** (as with sotalol) but also have an effect on the slow component.
- Amiodarone also has other actions such as blocking sodium channels (a class I effect)

Several factors limit the use of amiodarone:

- long half-life (20-100 days)
  - Because of its long half-life there is a potential for drug interactions to occur for several weeks after amiodarone has been stopped.
- should ideally be given into central veins (causes thrombophlebitis)
- has proarrhythmic effects due to lengthening of the QT interval
- interacts with drugs commonly used concurrently e.g. Decreases metabolism of warfarin
- numerous long-term adverse effects.

Monitoring of patients taking amiodarone

- TFT, LFT, U&E, CXR prior to treatment
- TFT, LFT every 6 months
  - and for up to 12months after discontinuation of amiodarone
  - An **increase of up to 40% above the baseline T4 is a normal effect of amiodarone**. This occurs approximately 2 months after initiation of therapy & **does not require discontinuation**.

Administration

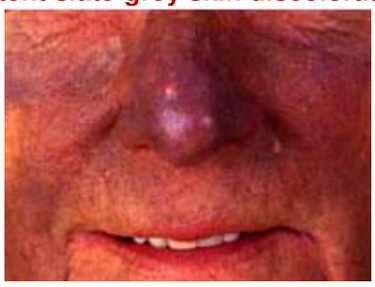
- 300 mg of amiodarone made up to 20 ml with 5% dextrose given as an intravenous bolus is the drug of choice in treating refractory ventricular fibrillation or pulseless ventricular tachycardia (100 mg of lidocaine may be given intravenously when amiodarone is unavailable).

Adverse effects

- thyroid dysfunction: both hypothyroidism and hyperthyroidism
  - Amiodarone blocks the peripheral conversion of thyroxine (T4) to triiodothyronine (T3)→ **hypo**
    - hypothyroidism occurs in up to 20% of patients taking amiodarone.
      - ↑T4 , reverse T3 and TSH
      - ↓T3.
  - It is also a potential source of large amounts of inorganic iodine→ **hyper**
    - Hyperthyroidism occurs in 3% of patients in iodine-deficient areas, but in 20% in areas in

areas where iodine is sufficient.

- **Corneal deposits**:
  - **present in most patients**,
    - almost universal in patients taking amiodarone therapy (at least **90%).**
  - rarely interfere with vision, becomes manifest by the presence of night-time visual glare, noticed while driving.
  - usually reversible on withdrawal of drug
- **photosensitivity**
  - **Skin deposits result in photodermatitis and a greyish-blue discoloration on sun-exposed areas** ('slate-grey' appearance (Skin sensitivity)
  - **can be prevented by using a sun block**
- **pulmonary fibrosis/pneumonitis**
- 5-7%.
- liver cirrhosis/hepatitis
- peripheral neuropathy, myopathy
- prolonged QT interval
- thrombophlebitis and injection site reactions
- bradycardia
- **Persistent slate-grey skin discoloration (ceruloderma)**



  - more common in males than females.
  - the pigmentation consists of brownish-yellow deposits of amiodarone, **iron** and others (not including melanin or hemosiderin)
  - On biopsy of these lesions, which cell type is laden with pigment?
    - ➔ **histiocytes** of the dermis
  - **appears in sun-exposed areas** and is thought to be activated by an UVA-related hypersensitivity response.
    - Sun exposure is not recommended for patients on amiodarone.
  - Treatment
    - discontinuation of the drug
    - if not disappeared after discontinuation → laser-based therapy.
- Neutropenia
- Nightmares, sleep disturbance

Important drug interactions of amiodarone include:

- decreased metabolism of warfarin, therefore increased INR
  - Decrease warfarin dose by 33- 50% and monitor the INR weekly
- increased digoxin levels
  - the dose of digoxin should be halved when patients are started on amiodarone.
- There is an increased **risk of ventricular arrhythmias when amiodarone is given with tricyclics**, hence concomitant use should be avoided.

Amiodarone and the thyroid gland

- Around 1 in 6 patients taking amiodarone develop thyroid dysfunction
- Amiodarone contains 75 mg of iodine per 200 mg tablet.
- In addition, the half-life is very long (100 days) and can result in prolonged effects even after stopping therapy for several months.

Amiodarone-induced hypothyroidism (AIH)

pathophysiology

- high iodine content of amiodarone causing a Wolff-Chaikoff effect (an autoregulatory phenomenon where thyroxine formation is inhibited due to high levels of circulating iodide)
- amiodarone **inhibits the peripheral conversion of T4 to T3** (Normal T4 , ↓ T3 , ↑ TSH) ➔These

results are typical of amiodarone-induced hypothyroidism)

Amiodarone-induced thyrotoxicosis (AIT)

Amiodarone-induced thyrotoxicosis (AIT) may be divided into two types:

Differentiating between the two forms of Amiodarone-Induced Thyrotoxicosis (AIT)

	AIT type 1	AIT type 2
Epidemiology	Most often seen in iodine-deficient areas.	most common in Europe and North America
Pathophysiology	Amiodarone contains↑ iodine → ↑ thyroid hormone synthesis (Jod-Basedow effect)	Amiodarone-related destructive thyroiditis
history	Occurs in patients with underlying thyroid pathology, such as a nodular goitre or Graves disease.	Occurs in patients without underlying thyroid disease.
Goitre	Present	Absent
Color Doppler	↑ Blood flow	↓ Blood flow
iodine-131 uptake scan	**normal or high**	minimal or none
IL-6 levels	**Low or normal**	markedly elevated
Management	Carbimazole ± potassium perchlorate or lithium carbonate	Corticosteroids ± Antithyroid

- **Differentiation between type 1 and type 2**
  - **Colour flow Doppler is most likely test to differentiate between Amiodarone induced thyrotoxicosis (AIT) type 1 and type 2.**
    - It appears to be superior to IL-6.
      - Interleukin 6 levels may be markedly elevated in AIT type 2, although this is not invariable and IL-6 may also be raised by concurrent non-thyroidal illness.
- Unlike in AIH, amiodarone should be stopped if possible in patients who develop AIT
  - **Jod-Basedow effect but in cases such as VT, this decision should be considered carefully in conjunction with a cardiologist, so the next management step will be Start carbimazole 40 mg od.**
- Mild amiodarone-induced hyperthyroidism can resolve spontaneously on stopping amiodarone. However, the majority of cases require treatment.
- In both types, if amiodarone cannot be withdrawn then total thyroidectomy should be considered.
- **AIT type 1** should be treated when stable with either radioiodine therapy or thyroidectomy,
- Type 2 amiodarone-induced thyrotoxicosis:
  - **the most appropriate treatment is withdrawal of the amiodarone and steroid therapy.**
  - eventually may progress to hypothyroidism, and patients should be monitored for this possibility.

The presence of markedly elevated serum IL-6 concentrations and low thyroidal radioiodine uptake (RAIU) values in patients with AIT without underlying thyroid disease suggests the presence of **amiodarone-induced thyroiditis** as the etiology of thyrotoxicosis.

Dobutamine

Action

- Direct Sympathomimetics
- $\beta_1 > \beta_2$, agonist
- positive inotropic effect

Indications

- Cardiogenic shock
- Acute heart failure
- Cardiac stress testing

Which of the following fits with the main mode of action of dobutamine?

Beta-1 receptor agonist

Dobutamine is predominantly a beta-1 adrenergic agonist, with weak beta-2 activity, and alpha-1 selective activity. It is used in the treatment of cardiogenic shock because of its effect in increasing cardiac contractility and cardiac output. It can of course increase the risk of both arrhythmias and myocardial ischaemia.

Antiplatelets: summary of latest guidance

The table below summarises the most recent guidelines regarding antiplatelets:

Diagnosis	1st line	2nd line
NSTEMI	Aspirin (lifelong) & clopidogrel (12 months)	If aspirin contraindicated, clopidogrel (lifelong)
STEMI	Aspirin (lifelong) & clopidogrel (1m if no/bare stent, 12 m if drug-eluting stent)	If aspirin contraindicated, clopidogrel (lifelong)
TIA*	Clopidogrel (lifelong)	Aspirin (lifelong) & dipyridamole (lifelong)
Ischaemic stroke	Clopidogrel (lifelong)	Aspirin (lifelong) & dipyridamole (lifelong)
Peripheral arterial disease	Clopidogrel (lifelong)	Asprin (lifelong)

*the guidelines for TIA are based on the 2012 Royal College of Physicians National clinical guideline for stroke. These guidelines corrected the anomaly where patients who've had a stroke were given clopidogrel, but those who'd suffered a TIA were given aspirin + dipyridamole.

Peri-Operative Management of Anticoagulation and Antiplatelet Therapy

(British society for Haematology guidelines 2016)

- **Warfarin and other vitamin K antagonists**
  - Emergency surgery in patients on warfarin
    - If surgery can wait for 6–8 h then 5 mg of intravenous **phytomenadione** can restore coagulation factors;
    - if this is not possible, anticoagulation can be reversed with 25–50 u/kg of four-factor **prothrombin complex concentrate**
  - ***Consider*** **bridging with treatment dose heparin in:**
    1) Patients with a VTE **within previous 3 months**.
    2) Very high risk patients such as patients with a previous VTE whilst on therapeutic anticoagulation who now have a target INR of 3·5.
    3) Patients with a previous stroke/TIA **in last 3 months.**
    4) Patients with a previous stroke/TIA and three or more of the following risk factors:
       - Congestive cardiac failure
       - Hypertension (>140/90 mmHg or on medication)
       - Age >75 years
       - Diabetes mellitus
    5) mechanical heart valve (MHV) patients other than those with a bileaflet aortic valve and no other risk factors
  - the post-operative bridging (i.e. full dose anticoagulation) should not started until **at least 48 h after high bleeding risk surgery** although thromboprophylaxis should be given if indicated.
  - Warfarin should be stopped for **5 days before an elective procedure** if anticoagulation needs to be discontinued
- **Antiplatelet therapy**
  - aspirin monotherapy (for secondary prevention of cardiovascular disease) can be continued for most invasive non-cardiac procedures
  - Aspirin can be continued both before and after coronary artery bypass surgery

Ref: http://www.b-s-h.org.uk/guidelines/guidelines/peri-operative-management-of-anticoagulation-and-antiplatelet-therapy/

Aspirin

Aspirin is a common cause of urticaria

- **Aspirin works by blocking the action of both cyclooxygenase-1 and 2.**
- Cyclooxygenase is responsible for prostaglandin, prostacyclin and thromboxane synthesis.
- Cyclo-oxygenase is an enzyme that converts arachidonic acid to thromboxane A2 (TXA2), a strong platelet agonist
- Because the platelet has no protein synthetic apparatus the effects of aspirin are irreversible and last for the life of the platelet (8-10 days)
- ↑ bleeding time (PT and PTT unchanged)
- The blocking of thromboxane A2 formation in platelets reduces the ability of platelets to aggregate which has lead to the widespread use of low-dose aspirin in cardiovascular disease.
- Until recent guidelines changed all patients with established cardiovascular disease took aspirin if there was no contraindication. Following the 2010 technology appraisal of clopidogrel this is no longer the case.
- Two recent trials (the Aspirin for Asymptomatic Atherosclerosis and the Antithrombotic Trialists Collaboration) have cast doubt on the use of aspirin in primary prevention of cardiovascular disease. Guidelines have not yet changed to reflect this.
- However the Medicines and Healthcare products Regulatory Agency (MHRA) issued a drug safety update in January 2010 reminding prescribers that aspirin is not licensed for primary prevention.

What do the *current* guidelines recommend?

- first-line for patients with ischaemic heart disease
- Current NICE guidelines advise that **people with acute upper gastrointestinal bleeding who take aspirin for secondary prevention of vascular events and in whom haemostasis has been achieved continue on low dose aspirin.**
- the U.S. Preventive Services Task Force (USPSTF), recommended that, for some people, aspirin can be used to help reduce their risk of cardiovascular disease **and colorectal cancer.**

Potentiates

- oral hypoglycaemics
- warfarin
- steroids

In hypersensitive patients aspirin can cause:

- Angioedema
- Bronchospasm, and
- Urticaria (skin rashes).

ASA can be continued normally if patient is going for dental procedure

Avoid aspirin in children < 16 years as risk of Reye's syndrome

Aspirin is not considered to be safe in breast-feeding due to the risk of causing Reye's syndrome in the baby.

Salicylate overdose

The mixed respiratory alkalosis and metabolic acidosis in a sweaty, confused patient point towards salicylate overdose.
The development of pulmonary edema suggests severe poisoning and is an indication for hemodialysis

- A key concept for the exam is to understand that salicylate overdose leads to a mixed respiratory alkalosis and metabolic acidosis.

- Early stimulation of the respiratory centre leads to a respiratory alkalosis whilst later the direct acid effects of salicylates (combined with acute renal failure) may lead to an acidosis.
- In children metabolic acidosis tends to predominate.
- The metabolic acidosis can increase the transfer of salicylates across the blood-brain barrier, thereby increasing CNS toxicity

Features

early features:

- hyperventilation (centrally stimulates respiration) → respiratory alkalosis
  - the most prominent feature of the early period after aspirin overdose
- tinnitus: typically occurs at plasma salicylate concentrations above 400-500 mg/l
- vertigo
- lethargy
- **sweating, pyrexia**
  - salicylates cause the uncoupling of oxidative phosphorylation leading to decreased adenosine triphosphate production, increased oxygen consumption and increased carbon dioxide and heat production
- peripheral vasodilatation and bounding pulse
- nausea/vomiting → dehydration

later features:

- metabolic acidosis
  - by **uncoupling oxidative phosphorylation**, leading to a build- up of organic acids in the blood.
- hyperglycaemia and hypoglycaemia
  - Hypoglycaemia is commonly seen in children but not in adults
- seizures
- coma
  - Although decreased consciousness is seen in aspirin overdose, it is seen late, and is associated with severe metabolic acidosis and hypokalaemia.
  - **Early presentation with coma will suggest that another drug has been taken in addition to aspirin.**

Treatment

- no specific antidote
- The management is supportive, with measures to prevent further absorption from the gastrointestinal tract and enhance excretion.
- general (ABC, charcoal) **Multi-dose activated charcoal may be indicated**
  - activated charcoal should be repeated as bezoars may form, resulting in delayed absorption of salicylate. This **should continue until salicylate levels have peaked.**
- **urinary alkalinization**
  - alkalinisation of the urine should be considered in patients with a plasma level > 300 mg/L.
  - **urine and serum alkalinization through intravenous sodium bicarbonate** (1.25% or 8.4%)
  - By alkalinizing the urine, charged salicylic acid will become protein bound and secreted through the proximal tubule, which minimizes the diffusion of uncharged salicylate back into the renal epithelium.
    - The ionisation of a weak acid, such as salicylic acid, is increased in an alkaline environment.
    - The administration of an intravenous infusion of sodium bicarbonate aiming for a urinary pH of 7.5-8 will increase the excretion of the acid 10-fold.
  - Alkalinization of the serum further promotes diffusion of salicylate out of the brain.
- Haemodialysis
  - **Indications for haemodialysis in salicylate overdose**
    - serum concentration > 700mg/L
    - metabolic acidosis resistant to treatment
    - acute renal failure
    - pulmonary oedema
    - neurological impairment (coma, hallucinations or seizures)

Clopidogrel

most (PPIs) ↓ Clopidogrel effect but lansoprazole is OK

- Clopidogrel is an antiplatelet agent used in the management of cardiovascular disease.
- Clopidogrel belongs to a class of drugs known as thienopyridines which have a similar mechanism of action. Other examples include:
  - prasugrel
  - ticagrelor
  - ticlopidine

Mechanism (Inhibition of the platelet ADP receptor)

- antagonist of the $P2Y_{12}$ adenosine diphosphate (ADP) receptor, inhibiting the activation of platelets

Indications:

- clopidogrel is used in addition to aspirin in patients with an acute coronary syndrome. The dose is 300 mg.
- NICE now recommend clopidogrel first-line following an ischaemic stroke and for peripheral arterial disease.
- Recent Royal College of Physician (RCP) guidelines support the use of clopidogrel in TIAs. However the older NICE guidelines still recommend aspirin + dipyridamole

Interactions

- concurrent use of proton pump inhibitors (PPIs) may make clopidogrel less effective (MHRA July 2009)
- this advice was updated by the MHRA in April 2010, evidence seems inconsistent but omeprazole and esomeprazole still cause for concern. **Other PPIs such as lansoprazole should be OK**

The golden notes

Clopidogrel

- action → antagonist of the **P2Y12** adenosine diphosphate **(ADP) receptor**, inhibiting the activation of platelets
- other members of the same class (thienopyridines):
  - prasugrel
  - ticagrelor
  - ticlopidine
- Indications → 1st line for : ACS , an ischaemic stroke , TIA and peripheral arterial disease.
- Interaction → **most (PPIs) ↓ Clopidogrel effect but lansoprazole is OK**

Prasugrel

- a third-generation thienopyridine antiplatelet agent
- ADP receptor inhibitors
- advantages compared with clopidogrel
  - faster onset of action,
  - greater potency in the inhibition of adenosine-induced platelet aggregation,
  - more consistent antiplatelet response
- **Prasugrel is contra-indicated in patients with prior transient ischaemic attack or stroke.**
  - In the TRITON-TIMI 38 trial, patients in this group had a higher rate of stroke when taking Prasugrel compared with those taking Clopidogrel.

IIb/IIIa inhibitors (eg: Abciximab)

- Other members of this drug group
  - abciximab
  - eptifibatide
  - tirofiban
- action
  - monoclonal antibody **antagonizes IIb/IIIa glycoprotein receptor** on activated platelets
- prevents platelet aggregation
- Abciximab is a humanised monoclonal antibody

Phosphodiesterase III (PDE) inhibitors (dipyridamole & cilostazol)

Dipyridamole is a non-specific phosphodiesterase inhibitor and decreases cellular uptake of adenosine

Dipyridamole may provoke bronchospasm. Avoid in asthmatics.

Mechanism of action

- **inhibits phosphodiesterase** → increase platelet cAMP (due to decreased breakdown of cAMP) → reduce intracellular calcium levels → inhibition of platelet aggregation.
- direct arterial vasodilation
  - inhibits cellular uptake of adenosine → more available to act on coronary vessels → vasodilation
- inhibition of thromboxane synthase

Indications

- Dipyridamole is an antiplatelet mainly used in combination with aspirin after an ischaemic stroke or transient ischaemic attack
- **Cilostazol** is currently licensed for the **management of patients with intermittent claudication without rest pain and with no signs of tissue necrosis.**
  - It is a first-line medication for the treatment of claudication caused by peripheral artery disease (PAD).
  - Trials show an improvement in time to initial pain on walking and maximal walking distance when compared to placebo.
  - **metabolised by cytochrome P450 3A4.**

Contraindications

- known bleeding tendencies (e.g. active peptic ulcer disease, previous haemorrhagic stroke in the last 6 months).
- Asthmatics (may provoke bronchospasm)

Adrenaline

Adrenaline induced ischaemia - phentolamine

Recommend Adult Life Support (ALS) adrenaline doses
- anaphylaxis: 0.5ml 1:1,000 IM
- cardiac arrest: 10ml 1:10,000 IV or 1ml of 1:1000 IV

Adrenaline is a sympathomimetic amine with **both alpha and beta** adrenergic stimulating properties.
The β- effect will cause significant **tachycardia**

Indications

- anaphylaxis
- cardiac arrest

Recommend Adult Life Support (ALS) adrenaline doses

- **anaphylaxis: 0.5ml 1:1,000 IM**
- cardiac arrest: 10ml 1:10,000 IV or 1ml of 1:1000 IV

Management of accidental injection

- **local infiltration of phentolamine**
- An alternative possibility is locally applied GTN paste

Anaphylaxis

- Where there is a history of a typical allergic reaction, current United Kingdom resuscitation guidelines **suggest adrenaline if there is**:
  - Stridor
  - Wheeze
  - Respiratory distress, or
  - Clinical evidence of shock.
- Adrenalin is **used for its alpha-agonist effects** that include increased peripheral vascular resistance and reversed peripheral vasodilatation, systemic hypotension, and vascular permeability.
- **Beta-agonist effects** include bronchodilatation, chronotropic cardiac activity, and positive inotropic effects.
- IM administration is preferred because of a superior safety profile with respect to cardiac adverse events compared with the IV route, although 1:10000 adrenalin IV may be used in a life-threatening situation.
- **The intramuscular (IM) route for adrenaline is the route of choice** for most healthcare providers.
- Adult **EpiPen** which allergy sufferers can carry with them contains 0.3 mg or 0.15 mg adrenaline in a 1:1000 dilution for intramuscular (IM) injection.

Angiotensin-converting enzyme (ACE) inhibitors

Mechanism of action:

- Inhibit the conversion angiotensin I to angiotensin II

Indications

- hypertension
  - first-line treatment in younger patients with hypertension and are also extensively used to treat
  - less effective in treating hypertensive Afro-Caribbean patients.
- diabetic nephropathy
- heart failure.
- secondary prevention of IHD.

Side-effects:

- Cough:
  - occurs in around 15% of patients
  - may occur up to a year after starting treatment.
  - Thought to be **due to increased bradykinin levels**
  - The enzyme ACE is also responsible for the metabolism of bradykinin in mast cells and ACEi leads to its bradykinin accumulation
  - This phenomenon is not seen in subjects taking angiotensin receptor blockers such as losartan.
- Angioedema:
  - may occur up to a year after starting treatment
  - ACE inhibitors are the most common cause of **drug-induced angioedema (swelling of his lips and tongue)**
- Hyperkalaemia
- ACEi → **dilate the efferent arteriole** of the glomerulus,→ ↓GFR → ↑ **creatinine and BUN.**
- 1st-dose hypotension: more common in patients taking diuretics

Cautions and contraindications

- Pregnancy and breastfeeding – avoid (ACEi & ARB → renal dysgenesis in the fetus)
  Exposure to ACE inhibitors in the first trimester → showed a significant increase in major (in particular, cardiovascular) congenital malformation.
- Renovascular disease - significant renal impairment may occur in patients who have undiagnosed bilateral renal artery stenosis
- Aortic stenosis - may result in hypotension
- Patients receiving high-dose diuretic therapy (more than 80 mg of furosemide a day) - signficantly increases the risk of hypotension
- Hereditary of idiopathic angioedema

- The co-administration of a **potassium-sparing diuretic** and an ACE inhibitor, may result in profound **hyperkalaemia**. Thus patients on both these drugs should have their potassium monitored closely.

Monitoring

- Urea and electrolytes should be checked before treatment is initiated and after increasing dose
  - Monitoring of renal function and potassium is important after commencement of an ACE inhibitor.
    - **The optimum period to check this is one to two weeks after commencing the medication.**
- A rise in the creatinine and potassium may be expected after starting ACE inhibitors.
  - **Acceptable increases are an increase in serum creatinine, up to 50% from baseline or up to 265µmol/l (whichever is smaller) and an increase in potassium up to 5.5 mmol/l.**
  - NICE guidelines state that when initiating ACE inhibitor therapy a **25% reduction in the eGFR or 30% increase in the serum creatinine** is **tolerable** and **should not lead to changes in dosing.**
  - ACE inhibitors should also be stopped or dose adjusted if is there is a rise in the serum potassium level to greater than 6 mmol/l.
  - Other causes of a deterioration in renal function should be excluded first before stopping the ACE inhibitor.
    - **e.g:** patient taking trimethoprim
      - This drug **competes with creatinine for excretion in the nephron** → ↑ serum creatinine.
      - **the appropriate option would be to re-check the blood tests in one to two weeks once trimethoprim has been discontinued to see whether the level of renal dysfunction is sustained or improves.**

Usage of ACEi & ARB as combination (NICE January 2015)

- **Do not combine an ACE inhibitor with an ARB to treat hypertension.**
- no significant benefits of ACEi & ARB combination were seen in people who did not have heart failure and there was an increased risk of hyperkalaemia, hypotension, and impaired renal function.
- The NICE guideline on **chronic heart failure** recommends that, after seeking specialist advice, the addition of an ARB licensed for heart failure is an option that could be considered for people who remain symptomatic despite optimal therapy with an ACE inhibitor and a beta-blocker
  - Candesartan and valsartan are the only ARBs licensed as add-on therapy to ACE inhibitors in this situation.
  - Other options are adding an aldosterone antagonist licensed for heart failure or hydralazine in combination with nitrate.

direct renin inhibitors

- **Aliskiren** (branded as Rasilez) → **Direct renin inhibitor**
- **Action:** by inhibiting renin blocks the conversion of angiotensinogen to angiotensin I
- **indication:** only current role would seem to be in patients who are intolerant of more established antihypertensive drugs
- no trials have looked at mortality data yet. Trials have only investigated fall in blood pressure. Initial trials suggest aliskiren reduces blood pressure to a similar extent as angiotensin converting enzyme (ACE) inhibitors or angiotensin-II receptor antagonists
- **adverse effects** were uncommon in trials although diarrhoea was occasionally seen

Other notes

- Enalapril is a prodrug for enalaprat, the active agent
- **irbesartan : the dose response is linear, as such dose can be titrated more easily from a base of 75 mg to a maximum of 300 mg.**

Adrenoceptor antagonists

Doxazosin is an α-1 adrenoceptor antagonist used in the treatment of hypertension and benign prostatic hypertrophy

Alpha antagonists

- alpha-1: doxazosin
  - **cause → orthostatic hypotension**
- alpha-1a: tamsulosin - acts mainly on urogenital tract

- alpha-2: yohimbine
- non-selective: phenoxybenzamine (previously used in peripheral arterial disease)
  Phenoxybenzamine → presurgical management of hypertension in phaeochromocytoma.

Beta antagonists

- beta-1: atenolol
- non-selective: propranolol

Carvedilol and labetalol are mixed alpha and beta antagonists

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Beta-blockers

3 Generations of beta-blockers

	Properties	Drugs
1st Generation	Non-selective No vasodilatation	Propranolol, Timolol, Pindolol, Nadolol, Sotalol
2nd Generation	β1-selective without vasodilation β1selective with vasodilation	Atenolol, Bisoprolol, Metoprolol Nebivolol, Acebutolol
3rd Generation	Non-selective with vasodilation	Carvedilol, Bucindolol

Indications

- angina
- post-myocardial infarction
- Heart failure: there is now strong evidence that certain beta-blockers improve both symptoms and mortality. Especially Bisoprolol
- arrhythmias: beta-blockers have now replaced digoxin as the rate-control drug of choice in atrial fibrillation
- hypertension: the role of beta-blockers has diminished in recent years due to a lack of evidence in terms of reducing stroke and myocardial infarction.
- thyrotoxicosis
- migraine prophylaxis
- anxiety

Beta- blocker in heart failure

- NICE recommends β blockers in all HF patients.
- In chronic obstructive pulmonary disease (COPD) patients with HF, cardioselective β blockers appear safer at **lower doses** than higher doses or non-selective β blockers.
- Bisoprolol 5 mgs is too high an initial starting dose, a low dose can always be titrated up later, if tolerated. (**starting dose → Bisoprolol 1.25 mg od**)
- Carvedilol though effective treatment for heart failure is not selective and therefore carries a greater risk of causing bronchospasm.
- Atenolol though cardioselective has no clinical evidence for prognostic benefit in heart failure.
- The patient should be closely monitored for deterioration in lung function post-administration.

Examples

Atenolol:

- Atenolol is a water soluble beta-blocker,
- taken once daily
- not associated with drowsiness/sleep disturbance like the lipid-soluble beta-blockers.

Propranolol:

- one of the first beta-blockers to be developed.
- Lipid soluble therefore crosses the blood-brain barrier

Nebivolol:

- has a vasodilatory action in addition to β-blocking effects
- associated with a lower incidence of erectile dysfunction compared with other β-blocking agents

Bisoprolol:

- **the most cardio-selective beta-blocker**

Metoprolol:

- **the most lipid-soluble and therefore has the largest volume of distribution**
- ↑lipid solubility → greater penetration across the blood-brain barrier (and also into other tissues), and therefore a greater incidence of **night terrors**
- Maximal gastrointestinal absorption of drugs occurs when there is intermediate lipid and water solubility, so that drugs with **greater lipid solubility, although allowing greater tissue penetration, may be more poorly absorbed**
- Metoprolol though **selective** is **shorter acting**.

Oxprenolol

- has an intrinsic sympathomimetic properties.

Carvedilol	Bisoprolol
Not β1- selective	Highly β1- selective
Vasodilatation due to α-1- blockade	No α-1- blocking activity
Lipids effects Positive lipid effect → ↑↑HDL & ↓↓LDL Negative lipid effect → ↑↑ cholesterol , TG, VLDL	Lipid profile almost not affected
Oral bioavailability of digoxin increased	No interaction with other CV drugs known
Sensitive to liver enzyme induction	Not sensitive to liver enzyme induction
Extensive metabolism in the liver (CYP2D6)(dose adjustment in liver impairment)	No dose adjustment required

Side-effects

- bronchospasm
- cold peripheries
- β-Blockers cause a rise in peripheral vascular resistance due to the unopposed α-adrenoceptor effects (vasoconstriction)
- Fatigue
  - **fatigue is a frequent side effect**
  - **typically is felt two hours and beyond after taking the drug.**
- sleep disturbances, including nightmares
- β-blockers associated with increased dreams/possible night terrors

Contraindications

- uncontrolled heart failure
- asthma
- sick sinus syndrome
- concurrent verapamil use: may precipitate severe bradycardia
- There is a theoretical risk of **intrauterine growth retardation** with the use of atenolol in pregnancy although the studies which showed this effect were done **with very large doses** of **atenolol**.

Beta-blocker overdose

Beta-blocker overdose management: atropine + glucagon

Features

- bradycardia
- hypotension
- heart failure
- syncope

Management

- if bradycardic then atropine
- **in resistant cases glucagon may be used**
- Glucagon acts by bypassing the blocked β-receptor, thus activating adenyl cyclase → formation of cyclic AMP from ATP. Cyclic AMP in turn exerts a direct stimulant action on the heart.
- **The action of glucagon, essential for reversing the effect of beta-blocker overdose → Promotes the formation of cyclic AMP.**
  - Doses of glucagon used are much higher than those conventionally used for reversing hypoglycaemia in diabetes, with a bolus of 3-10 mg being required, then 2-5 mg/hr by infusion.
- Haemodialysis is not effective in beta-blocker overdose

Calcium channel blockers

Calcium channel blockers - side-effects: headache, flushing, ankle oedema

- Voltage-gated calcium channels are present in myocardial cells, cells of the conduction system and those of the vascular smooth muscle.
- The various types of calcium channel blockers have varying effects on these three areas and it is therefore important to differentiate their uses and actions.

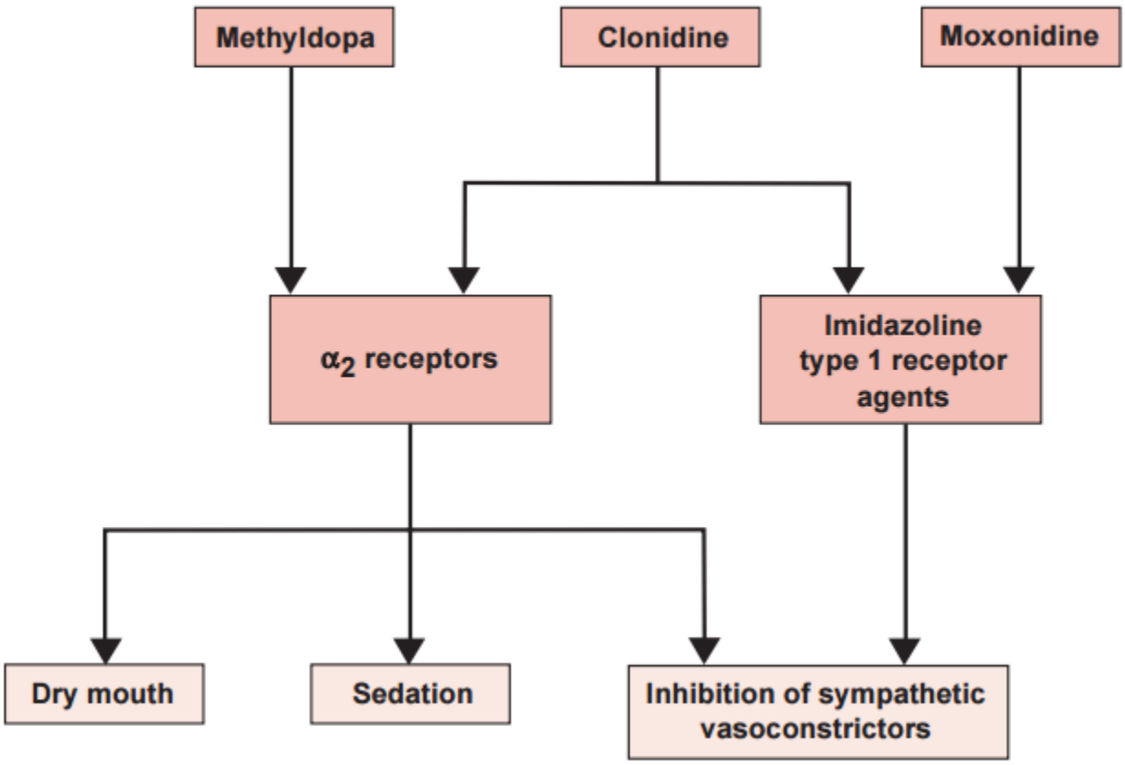
Examples	Indications & notes	Side-effects and cautions
Verapamil	Angina, hypertension, arrhythmias Highly negatively inotropic Should not be given with beta-blockers as may cause heart block	Heart failure, constipation, hypotension, bradycardia, flushing
Diltiazem	Angina, hypertension Less negatively inotropic than verapamil but caution should still be exercised when patients have heart failure or are taking beta-blockers	Hypotension, bradycardia, heart failure, ankle swelling
Nifedipine, amlodipine, felodipine (dihydropyridines)	Hypertension, angina, Raynaud's Affects the peripheral vascular smooth muscle more than the myocardium and therefore do not result in worsening of heart failure	Flushing, headache, ankle swelling

Centrally acting antihypertensives

Methyldopa ➔ not utilised in a patient with abnormal LFTs

Examples of centrally acting antihypertensives include:

- methyldopa: used in the management of hypertension during pregnancy
- moxonidine: used in the management of essential hypertension when conventional antihypertensives have failed to control blood pressure
- clonidine: the antihypertensive effect is mediated through stimulating alpha-2 adrenoceptors in the vasomotor centre



Bosentan

- Bosentan is a competitive antagonist of **both endothelin-A (ETa) and endothelin-B (ETb) receptors**, leading to falls in both pulmonary and systemic vascular resistances without an increase in heart rate
- effective in patients with pulmonary arterial hypertension
- It is excreted in bile following metabolism by the cytochrome P450 enzymes and this is a potential source of interaction with drugs metabolised by the same isoenzyme
- **Common unwanted effects** include
  - flushing
  - **hypotension**
  - dyspepsia
  - fatigue
  - Haemoglobin concentrations can **fall** by up to 1 g/dl during bosentan treatment
  - Hepatotoxicity:
    - The most serious unwanted effect is dose-dependent hepatotoxicity, and it is therefore contraindicated in patients with moderate to severe liver disease
    - Generally, hepatotoxicity occurs within the first 3-4 months of treatment
  - teratogenic and therefore contraindicated in pregnancy

Nitroglycerin

- Nitroglycerin products are both venous capacitance dilators and coronary and systemic artery dilators
- Administration of nitroglycerin results in:
  - **dilation of systemic veins**
  - decreased myocardial wall tension
  - decreased oxygen demand
  - vasodilation of large and medium-sized coronary arteries
  - increased coronary blood flow to the subendocardium
  - reduced afterload
  - reduced preload
  - increased ventricular compliance
- **Nitrates may cause→ haemolytic anaemia**

Nicorandil

Action

- **acts through the opening of potassium channels .**
- Nicorandil is an activator of ATP-dependent potassium channels
- Effect → relaxation of smooth muscle in veins → venodilatation → ↓ ventricular filling pressures + dilatation of the coronary arterioles
- It relaxes vascular smooth muscle through membrane hyperpolarisation via increased transmembrane

potassium conductance and, like nitrates, through an increase in intracellular cyclic guanosine monophosphate (GMP).

Indication

- **now second-line treatment for angina**
- Use nicorandil for treatment of stable angina only in patients whose angina is inadequately controlled by first line anti-anginal therapies, or who have a contraindication or intolerance to first line anti-anginal therapies such as beta-blockers or calcium antagonists

Side effects

- Headache
  - **The most common** unwanted effect (- 35% of patients),
  - appears to be dose-dependent
  - resolves with continued treatment
- **Ulcerations**
  - oral ulceration, flushing and gastrointestinal disturbances
  - **(ulceration of the upper and lower gastrointestinal tract and may present with life threatening bleeding)**
  - Nicorandil can cause serious skin, mucosal, and eye ulceration, including gastrointestinal ulcers which may progress to perforation, haemorrhage, fistula, or abscess

Contraindication

- **Use with phosphodiesterase inhibitors such as sildenafil is contraindicated since they can potentiate the hypotensive effects of nicorandil**

Digoxin and digoxin toxicity

The half-life of digoxin is around 36-48 hours. This results in a delay before steady plasma levels are seen, it may take a week to start its action

Digoxin - inhibits the Na^+/K^+ ATPase pump

- Digoxin is a cardiac glycoside now mainly used for rate control in the management of atrial fibrillation.
- As it has positive inotropic properties it is sometimes used for improving symptoms (but not mortality) in patients with heart failure.
- **digoxin is highly water-soluble**
- Digoxin has a high volume of distribution and long half-life (36-48 h), which means that loading doses are required to allow the drug to reach a steady-state concentration more quickly.
  - If initiated on a maintenance dose (without loading), it will take several days to reach a steady state.
- Digoxin is almost exclusively renally cleared; as a result, renal impairment will significantly alter the half-life of this medication.

Mechanism of action

- decreases conduction through the atrioventricular node which slows the ventricular rate in atrial fibrillation and flutter
- Increases the force of cardiac muscle contraction due to inhibition of the Na^+/K^+ATPase pump which is located in the sarcolemmal membrane.
- Also stimulates vagus nerve

What is the pharmacokinetic reason that drives the practice of loading with digoxin?

➔ **Volume of distribution.**

- The volume of distribution for Digoxin is very large (510 litres). This means that administered doses are rapidly distributed to body tissues.
- The initial distribution lasts for some 6-8hrs, which drives the typical loading regimen for Digoxin of two larger doses (500mcg) some 6-12hrs apart.
- Without loading Digoxin typically takes a few days to reach therapeutic effect.

Digoxin can worsen hyperkalaemia

- Translocation of potassium from the cells into the extracellular space can occur from digoxin overdose due to its dose-dependent Na-K-ATPase pump inhibition.

Drug Interactions Associated with Digoxin

Drug	Effect*	Mechanism
Quinidine	Increase	Decreases renal clearance of digoxin
Verapamil, diltiazem	Increase	Decreases renal clearance of digoxin
Cholestyramine, colestipol	Decrease	Binds digoxin in gastrointestinal tract; interferes with enterohepatic circulation
Spironolactone	Increase	Inhibits tubular secretion of digoxin
Thiazides, furosemide	Increase	Diuretic-induced hypokalemia and/or bumetanide hypomagnesemia potentiates digitalis action

*Increase indicates enhances digitalis effect; decreases diminishes digitalis effect.

Digoxin toxicity

- Plasma concentration alone does not determine whether a patient has developed digoxin toxicity.
- The BNF advises that the likelihood of toxicity increases progressively from 1.5 to 3 mcg/l.
  - Samples taken after 6 h will be more accurate in estimating the body's digoxin
- **the mechanism of action leading to tachy-arrhythmias in digoxin toxicity → Inhibition of the sodium pump**

Features

- generally unwell, lethargy, anorexia,
  - **The earliest features** of digitalis toxicity include: Nausea, vomiting, anorexia.
- cholinergic effects : nausea, vomiting, diarrhea
- confusion,
- **yellow-green** vision
- arrhythmias (e.g. AV block, bradycardia)
  - **(Digoxin toxicity can result in any abnormal cardiac rhythm <u>except</u> type-II second-degree atrioventricular (AV) block)**

Precipitating factors

- **classically: hypokalaemia**
  - (hyperkalaemia may also worsen digoxin toxicity, although this is very small print)
- increasing age
- renal failure
- myocardial ischaemia
- hypomagnesaemia,
- **hyper**calcaemia,
- **hyper**natraemia,
- acidosis
- hypoalbuminaemia
- hypothermia
- hypothyroidism
- amyloidosis
- drugs: amiodarone, quinidine, **verapamil**, diltiazem, spironolactone (competes for secretion in distal convoluted tubule therefore reduce excretion), ciclosporin. Also drugs which cause hypokalaemia e.g. thiazides and **loop diuretics**
  - **Bumetanide is a loop diuretic and may cause hypokalaemia as a side effect. The potassium loss caused by bumetanide increases the toxicity of digoxin.**

Management

Antidote "KLAM"

- slowly normalize **K**+
- **L**idocaine
- digoxin **A**ntibodies (anti-dig Fab fragments)
- **M**g2+

Phenytoin may be used as an alternative to lidocaine (both are class IB agents) if immune therapy is unsuccessful or unavailable in the treatment of tachyarrhythmias secondary to digoxin toxicity.

- Treatment of digoxin toxicity should be guided by the patient's signs and symptoms and the specific toxic effects and not necessarily by digoxin levels alone.
- Activated charcoal if presented within 1 h of an overdose
  - The first-line treatment for acute ingestion is repeated dosing of activated charcoal to reduce absorption and interrupt enterohepatic circulation.
- Binding resins (eg, cholestyramine)
  - may bind enterohepatically-recycled digoxin.
  - may be more appropriately used for treatment of chronic toxicity in patients with renal insufficiency.
- correct arrhythmias
- severe sinus bradycardia (hemodynamically unstable bradyarrhythmic patients) → Atropine
- ventricular tachycardia → responds best to digoxin immune therapy, but phenytoin and lidocaine are useful if immune therapy is ineffective or unavailable.
  - These drugs depress the enhanced ventricular automaticity without significantly slowing AV conduction
- Magnesium sulfate, 2 g IV over 5 minutes, has been shown to terminate dysrhythmias in digoxin-toxic patients with and without overt cardiac disease.
  - Magnesium is contraindicated in the setting of bradycardia or AV block and should be used cautiously in patients with renal failure.
- Premature ventricular contractions (PVCs), bigeminy, or trigeminy may require only observation unless the patient is hemodynamically unstable, in which case lidocaine may be effective.
- Digibind
  - **Its brand name of Digoxin immune fab** or **Digoxin-specific antibody** is an antidote for overdose of digoxin
  - Action: bind to the digoxin → unable to bind to its action sites
  - is an immunoglobulin fragment that binds with digoxin.
  - first-line treatment for significant dysrhythmias from digitalis toxicity
  - Indications for digoxin-specific antibodies include:
    - Hemodynamically unstable arrhythmia
      - **Tachyarrhythmias** with hypotension
      - bradycardia with hypotension that do not respond to atropine treatment.
    - End organ damage
    - digoxin level > 4ng/ml if chronic ingestion
    - digoxin level > 10 ng/ml if acute ingestion (taken 6 h after the last dose)
    - **Hyperkalaemia** (if not respond to insulin-dextrose infusions): potassium > 5 mEq/L and symptomatic
  - **SE → Serum sickness**
- **If digoxin-specific antibodies not available → lidocaine or phenytoin**
- **Digoxin toxicity related ventricular tachycardia:**
  - **Phenytoin and lidocaine are useful for ventricular tachycardia if immune therapy is ineffective or unavailable**
    - Phenytoin is thought to suppress the pro-arrhythmic properties of digoxin without diminishing its inotropic effects.
    - **lidocaine is useful for chemical cardioversion of digoxin toxicity related ventricular tachycardia.** This is because it can reduce ventricular automaticity without significantly slowing AV conduction.
  - Calcium channel blockers are contraindicated because they may increase digoxin levels.
  - Amiodarone is shown to increase digoxin levels and as such can worsen the risk of rhythm

disturbance further.
  - VT in digoxin toxicity is resistant to electrical cardioversion, which may actually precipitate VF and asystole.
  - Bretylium is contraindicated in the treatment of digoxin induced arrhythmias as it can actually precipitate ventricular tachycardia.
  - Quinidine worsens AV and SA conductivity and reduces digoxin tissue binding and is therefore also contraindicated.
- conventional dialysis is ineffective
- monitor potassium
  - Electrolytes
    - In **acute toxicity**, **hyperkalemia** is common
      - Although calcium is often used to ameliorate cardiac toxicity from hyperkalemia, it is not recommended in patients with digoxin toxicity because it can delay after-depolarization and may precipitate ventricular tachycardia or fibrillation. This is based on the fact that intracellular calcium levels are already high in this setting.
      - potassium level > 5 mEq/L → digoxin Fab fragments
    - **Chronic toxicity** is often accompanied by **hypokalemia** and hypomagnesemia
      - Concomitant hypomagnesemia may result in refractory hypokalemia
    - Correction of electrolyte imbalances may reverse dysrhythmias.

Which measurement would be most useful when monitoring patient for digoxin efficacy?

➔ **Pulse rate**

- Measuring drug plasma concentration will tell you whether digoxin is at therapeutic concentrations in the blood, but not whether it is having a therapeutic effect.

Diuretics

Class	Compound	Action	Side effects
Loop Diuretics	Furosemide Bumetanide ethacrynic acid	inhibit **NKCC2** in the thick ascending loop of Henle	Deafness
Thiazides	hydrochlorothiazide, indapamide	inhibit **NaCl** co-transporter in early distal tubule	hyponatraemia, hypokalaemia, hypercalcaemia
K+ sparing agents	spironolactone	Aldosterone receptor antagonist	Hyperkalemia
	amiloride, **triamterene**	inhibit **Na** channel in late distal tubule	Hyperkalemia
Osmotic Diuretics	mannitol	Inhibit water reabsorption throughout the tubules, but mostly in the proximal tubule	Pulmonary edema

Loop diuretics

Action

- Furosemide and bumetanide are loop diuretics that act by inhibiting the Na-K-Cl cotransporter (NKCC) in the thick ascending limb of the loop of Henle, reducing the absorption of NaCl.
- There are two variants of NKCC; **loop diuretics act on NKCC2**, which is more prevalent in the kidneys.

Indications

- heart failure: both acute (usually intravenously) and chronic (usually orally)
- resistant hypertension, particularly in patients with renal impairment

Adverse effects

- hypotension
- hypocalcaemia

- hyponatraemia
- hypokalaemia
- hypochloraemic alkalosis
- ototoxicity
- renal impairment (from dehydration + direct toxic effect)
- hyperglycaemia (less common than with thiazides)
- gout

- **Loop diuretics induces ototoxicity by affecting Na+/K+/2Cl- cotransporters present in the inner ear.**
- **Explanation of respond to i.v furosemide but not oral in heart failure → Increased bioavailability**
  - In right heart failure → The patient has a lot of gut oedema which would → reduce the absorption of oral furosemide. Intravenous furosemide would have a much better bioavailability and thus therapeutic effect.
  - Protein binding of drugs may be reduced in elderly patients, this may be due to malnutrition.
- **Explanation of not responding to furosemide in chronic kidney disease (CKD) → Tubular secretion of furosemide is reduced in CKD**
  - Organic acids accumulate in renal failure and compete for tubular secretion with furosemide. This competition can be overcome by using a larger dose of the drug.

A 76-year-old lady taking perindopril 2 mg, bisoprolol 1.25 mg and had recently had her dose of furosemide increased from 40 mg to 80 mg. C/O dizziness, particularly when standing upright after being seated. There were no clinical signs of cardiac failure. Serum urea: 13.3 mmol/L. **Serum creatinine: 221** µmol/L. What is the next step in her management?

➔ **Stop the furosemide temporarily and restart at a lower dose within a few days**

- This lady is developing postural hypotension after the recent increase in furosemide dose.
- She has moderate renal impairment.
- Stopping either her beta-blocker or **ACE inhibitor** is not the best option for treatment at this stage.

Bendroflumethiazide

Bendroflumethiazide - site of action = proximal part of the distal convoluted tubules

the target of action of thiazide diuretics → **NaCl** co-transporter
the target of action of loop diuretics → **NKCC2**

- Bendroflumethiazide (bendrofluazide) is a thiazide diuretic which works by inhibiting sodium absorption at the beginning of the distal convoluted tubule (DCT).
- **The NaCl co-transporter**:
  - **the target of thiazide diuretics**
  - it contributes to the reabsorption of about 10% of the filtered load of sodium.
  - Mutations causing loss of function of the NaCl co-transporter cause Gitelman's syndrome, the commonest monogenic cause of hypokalaemia in adults.
- Potassium is lost as a result of more sodium reaching the collecting ducts.
- Bendroflumethiazide has a role in the treatment of mild heart failure although loop diuretics are better for reducing overload.
- The main use of bendroflumethiazide was in the management of hypertension but recent NICE guidelines now recommend other thiazide-like diuretics such as indapamide and chlortalidone.

Bendroflumethiazide - mechanism of Hypokalemia:

- ↑ sodium reaching the collecting ducts
- Activation of the renin-angiotensin-aldosterone

Common adverse effects	Rare adverse effects
• dehydration • postural hypotension • hyponatraemia, hypokalaemia, Hypomagnesaemia, **hypercalcaemia** • gout • impaired glucose tolerance • impotence	• thrombocytopaenia • agranulocytosis • photosensitivity rash • pancreatitis • hypochloraemic alkalosis

Amiloride

- The potassium-sparing diuretic **amiloride**→ inhibits sodium channels in the distal segment of the distal convoluted tubule
- **Amiloride** →inhibits the action of aldosterone on the distal convoluted tubule producing potassium reabsorption.
- **In treating a patient with congestive heart failure who develops hypokalaemia, the best choice is to add a small dose of amiloride to his furosemide therapy**

Triamterene

- Triamterene, a potassium sparing diuretic similar to amiloride.
- occasionally prescribed with thiazide or loop diuretics, to prevent hypokalaemia.
- It inhibits the movement of sodium through channels towards the end of the distal tubule and collecting ducts, preventing the passage of sodium from the urinary space into the tubular cells. This action causes hyperpolarisation of the apical plasma membrane, preventing the secretion of potassium into the collecting ducts.
- **Hyperkalaemia is common** (>5%), and is unaffected by concurrent potassium depleting diuretics.
- **In mild hyperkalaemia, (eg: K = 5.9 mmol/l) with no evidence of cardiac toxicity. The management involves stopping the triamterene, and repeating the U&E in one week.**

Spironolactone

- Spironolactone is an aldosterone antagonist
- acts in the cortical **distal convoluted tubule** and collecting duct.

Indications

- ascites: patients with cirrhosis develop a secondary hyperaldosteronism. Relatively large doses such as 100 or 200mg are often used
- hypertension: used in some patients as a NICE 'step 4' treatment
- heart failure (see RALES study below)
- nephrotic syndrome
- Conn's syndrome
- **Spironolactone** is a diuretic with **anti-androgen effects**. This makes it a useful agent in the treatment of hormonal acne and hirsutism.
  - ➢ It blocks the androgen receptor and 5α-reductase enzyme that is responsible for the synthesis of dihydrotestosterone (DHT) and **can be used to treat hirsutism.**

Adverse effects

- **hyperkalaemia**
- gynaecomastia
  - ➢ Spironolactone and **eplerenone** are both aldosterone receptor antagonists that have shown survival benefit in patients with NYHA III/IV systolic heart failure.
  - ➢ **Eplerenone has a lower antiandrogenic effect compared to spironolactone and may, therefore, be preferable if patient develops erectile dysfunction and bilateral gynecomastia.**

RALES

- NYHA III + IV, patients already taking ACE inhibitor
- low dose spironolactone reduces all-cause mortality

Eplerenone

Indications

- Eplerenone is a **spironolactone-like agent** indicated as an add-on to standard therapy after a myocardial infarction, and heart failure

Side-effects

- **Common side-effects**: **hyperkalaemia**, dizziness, hypotension, diarrhoea, nausea and prerenal renal dysfunction
- **Uncommon side-effects** : eosinophilia, dehydration, hypercholesterolemia and hypertriglyceridaemia

Cautions

- The drug is metabolised via the CYP3A4 system, so that inducers or inhibitors of the 3A4 enzyme subtype may precipitate drug interactions

Diuretic abuse

- Diuretic abuse is not uncommon amongst athletes and jockeys as a means of weight loss.
- **The patient has a hypokalaemic alkalosis, and urine potassium excretion is high despite the hypokalaemia.**

Proto-oncogene stimulation

- **β-Agonists and angiotensin II** → augment proto-oncogene expression, → stimulate protein synthesis and induce the synthesis of fetal forms of actin and myosin, → **leading to hypertrophy of smooth muscle**
- Thyroxine acts directly via nuclear receptors to regulate myosin heavy-chain gene transcription

Respiratory drugs

Theophylline

- Theophylline, like caffeine, is one of the naturally occurring methylxanthines.
- The main use of theophyllines in clinical medicine is as a bronchodilator in the management of asthma and COPD

Action

- The exact mechanism of action has yet to be discovered.
- One theory suggests theophyllines may be a non-specific **inhibitor of phosphodiesterase** resulting in an increase in cAMP.
- **antagonism of adenosine** and prostaglandin inhibition
  - **It blocks the adenosine receptor**
  - Blockade of the receptors by theophylline results in:
    - relaxation of smooth muscles, especially bronchial muscles
    - constriction of cerebral blood vessels
    - stimulation of the cardiac pacemaker
    - stimulation of gastric secretions
- Theophylline also releases calcium ions from the sarcoplasmic reticulum in skeletal and cardiac muscle, thus enhancing their contractility, including diaphragmatic contractility
- plasma theophylline concentration of between 10 and 20 mg/l is required for satisfactory bronchodilatation.

Side effect

- **At therapeutic doses, the side-effect of Aminophylline → Jitteriness**
- adverse effects can occur within the range 10-20 mg/l and both the frequency
- **severity increase at concentrations above 20 mg/l**

Factors increasing the plasma theophylline concentration:

- heart failure
- cirrhosis
- viral infections
- increased age (the elderly)
- Diet:
  - Obesity
  - High carbohydrate intake
  - High methylxanthine intake (for example, tea, coffee)
- drugs that **inhibit** its metabolism
  - Commonly prescribed drugs that can increase serum theophylline levels include:
    - clarithromycin, **erythromycin**
    - **ciprofloxacin**,
    - cimetidine,
    - oral contraceptives
    - allopurinol.
    - Fluvoxamine
  - Consideration should be given to reducing theophylline dose when these drugs are prescribed.
- cessation of enzyme-inducing drugs.

Factors decreasing the plasma theophylline concentration: (increasing theophylline clearance):

- Diet:
  - Low carbohydrate
  - High protein intake
- Social:
  - chronic alcoholism without cirrhosis
  - **smoking**
    - **Smoking cessation → sudden increase in theophylline level**
      - Regular tobacco use up-regulates hepatic enzyme activity; cessation will be associated with a decrease of hepatic enzyme activity, such that theophylline concentrations may increase.
- Drugs: drugs that **induce** liver metabolism: eg:
  - Rifampicin
  - Carbamazepine.

Theophylline poisoning

- **Theophylline has a narrow therapeutic window and needs close monitoring of its serum level to avoid toxicity**
- Symptoms of toxicity may be delayed following the ingestion of sustained-release preparations for up to 48 h
- Theophylline toxicity occurs with concomitant use of clarithromycin **due to inhibition of cytochrome P450 (CYP1A2 and CYP3A4) by clarithromycin.**
- Features of mild to moderate theophylline toxicity include nausea, vomiting, epigastric, tremor, tachycardia, restlessness and hallucinations. Severe toxicity can cause convulsions, arrhythmias and metabolic acidosis.
- Studies have shown an approximate 20% increase in both peak and trough theophylline levels with concomitant use of clarithromycin and it is recommended that theophylline levels should be monitored prior, during and on cessation of clarithromycin and dosage adjustment of theophylline made accordingly.
- **Features**
  - mild to moderate theophylline toxicity
    - nausea, vomiting, epigastric,
    - tremor,
    - tachycardia,
    - restlessness and
    - hallucinations.
  - Severe toxicity:
    - convulsions,
    - arrhythmias
    - metabolic acidosis, **hypokalaemia** and hyperglycaemia
- **Management**
  - activated charcoal
  - charcoal haemoperfusion is preferable to haemodialysis

In cases of severe theophylline toxicity, charcoal haemoperfusion can be used

Antimuscarinic agent

- Muscarinic antagonists (antimuscarinic agents) are a group of anticholinergic drugs that competitively inhibit postganglionic muscarinic receptors.
- Which organ systems are most affected by an antimuscarinic agent **depends on** the specific characteristics of the agent, particularly **its lipophilicity**.
  - Lipophilic agents (i.e., atropine or benztropine) are able to cross the blood-brain barrier and therefore affect the central nervous system (CNS) in addition to other organ systems.
  - Less lipophilic agents (i.e., ipratropium or butylscopolamine) are administered if the CNS does not need to be targeted, specifically for respiratory (e.g., asthma), gastrointestinal (e.g., irritable bowel syndrome), or genitourinary applications (e.g., urinary incontinence).

Action

- Muscarinic antagonists (the majority of anticholinergic drugs) inhibit the effect of acetylcholine on muscarinic receptors,

Effects of muscarinic antagonists

Muscarinic receptors	Organ/Tissue	Effects
M1, M4, M5	**Central nervous system**	• Influences neurologic function (e.g., cognitive impairment)
M2	**Heart**	• ↑ Heart rate • Increases AV-node conduction → arrhythmias

M3	**Smooth muscle**	• **Gastrointestinal tract**
		  • ↓ Intestinal peristalsis ,
		  • ↓ Salivary and gastric secretions
		• **Urinary tract**
		  • ↓ Bladder contraction (decreases detrusor muscle tone, increases the internal urethral sphincter tone)
		• **Airway**
		  • Bronchodilation
		  • ↓ Bronchial secretions
		• **Eye**
		  • Mydriasis → narrowing of the iridocorneal angle
		  • Impaired accommodation
		• **Blood vessels**: minimal effect on vascular tone and blood pressure

	Exocrine glands	• ↓ Secretions (sweat)

Antimuscarinic side effects

"Blind as a bat (mydriasis), mad as a hatter (delirium), red as a beet (flushing), hot as a hare (hyperthermia), dry as a bone (decreased secretions and dry skin), the bowel and bladder lose their tone (urinary retention and paralytic ileus), and the heart runs alone (tachycardia)."

	Side effect	Contraindications
Impaired secretion by exocrine glands	• Dry mouth and sore throat • ↓ Respiratory tract secretions • Hyperthermia und warm, dry skin	• Acute asthma • Respiratory distress
Cardiovascular system	• Tachycardia	• Tachyarrhythmias • Heart failure • Myocardial infarction • Hyperthyroidism
Decreased smooth muscle tone	• Gastroesophageal reflux • Obstipation or ileus • Impaired micturition/urinary retention • Vasodilatation and flush	• Hiatal hernia associated with reflux esophagitis • Ulcerative colitis • Paralytic ileus • Obstructive disease of the gastrointestinal tract (e.g., achalasia, pyloric stenosis or duodenal stenosis) • Obstructive uropathy (e.g., benign prostatic hyperplasia, urinary retention)
Eye	• Mydriasis and photophobia • Blurred vision	• Narrow-angle glaucoma
CNS	• Excitement, agitation, and hallucinations with the	• Myasthenia gravis

	Side effect	Contraindications
	use of lipophilic parasympatholytics (e.g., atropine), especially in elderly patients • Confusion, disorientation • Coma, seizure, and rarely death	

Lipophilic antimuscarinic (good oral bioavailability and CNS penetration) (Tertiary amines)

Drug	Effect	Indication
• Atropine	• ↑ Heart rate • ↓ Secretions of exocrine glands • ↓ Tone and motility of smooth muscles • ↓Cholinergic overactivity in CNS • Mydriasis and cycloplegia	• First drug of choice in unstable (symptomatic) sinus bradycardia (IV) • Premedication: prior to intubation to decrease salivary, respiratory, and gastric secretions • Ophthalmology: uveitis • Antidote for anticholinesterase poisoning • Scorpion stings
• Scopolamine(hyoscine)	• ↓ Vestibular disturbances (**antiemetic**)	• Motion sickness

• Homatropine
• Tropicamide
	• Mydriasis
	• Impair accommodation
		• Ophthalmology
		  • Therapeutic use: in patients with uveitis
		  • Diagnostic use: pupillary dilation to allow ocular fundus examination and cycloplegia to allow refractory testing

• Benztropine • Biperiden • Trihexyphenidyl	• ↓ **Cholinergic overactivity in CNS**	• Antiparkisonian effect (Parkinson disease) • ↓ Extrapyramidal symptoms (EPS) caused by antipsychotics
• Oxybutynin • Tolterodine • Solifenacin • Dicyclomine	• ↓ **Tone and motility of smooth muscle cells**	• Oxybutynin, tolterodine, and solifenacin: overactive bladder incontinence • Dicyclomine: irritable bowel syndrome
• Darifenacin	• ↑ Sphincter tone	• Urinary urgency, urge incontinence, urinary frequency, and/or nocturia(symptoms resulting from, e.g., overactive bladder)

Hydrophilic (poor oral bioavailability and CNS penetration) (Quarternary amines)

Drug	Effect	Indication
• Glycopyrrolate	• Decreases secretions of exocrine glands	• Peptic ulcer disease treatment

• Ipratropium bromide
• Tiotropium bromide
	• **Bronchodilation**	• COPD and bronchial asthma
		  • Ipratropium bromide:
		  • COPD grade I and higher
		  • Acute management of refractory asthma
		  • Tiotropium bromide:
		  • Longer duration of action
		  • Long-term treatment of COPD (grade II and above)

Anticholinergic syndrome (overdose)

- Etiology
  - Belladonna poisoning
  - Jimson weed/Angel's trumpet (*Datura stramonium*) poisoning
  - Medications
    - Anticholinergic agents (e.g., atropine, benztropine, trihexyphenidyl)
    - Drugs with anticholinergic properties
      - Tricyclic antidepressives (predominantly doxepin, amitriptyline, imipramine, and trimipramine)
      - Antipsychotics (e.g., clozapine, quetiapine)
      - First-generation antihistamines (e.g., promethazine, dimenhydrinate)
- **Clinical features**
  - Dry mouth, warm, flushed skin, thirst, tachycardia, arrhythmias, mydriasis, confusion, and agitation
  - Possibly anticholinergic delirium: Excessive use of tricyclic antidepressants (or other medications with significant anticholinergic effects) can cause life-threatening delirium, hallucinations, and psychomotor symptoms.
- **Treatment**: **antidote for purely anticholinergic poisoning** (e.g. atropine): **physostigmine**

One mnemonic used to remember the symptoms of anticholinergic toxicity is:

Hot as a hare: increased body temperature
Blind as a bat: mydriasis (dilated pupils)
Dry as a bone: dry mouth, dry eyes, decreased sweat
Red as a beet: flushed face
Mad as a hatter: delirium

Tiotropium

Indications

- Tiotropium is a specific long-acting **antimuscarinic** agent indicated as maintenance therapy for patients with (COPD)

Cautions

- Caution is advised in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction

Side-effects

- Dry mouth
- Paradoxical bronchospasm
- Rarer side-effects include tachycardia, blurred vision, urinary retention and constipation

Doxapram

Indications

- Doxapram is a centrally acting respiratory stimulant, used in patients with severe respiratory disease who are deemed unsuitable for admission to the Intensive Therapy Unit
- Intravenous doxapram only used if the patient is not suitable for either intubation or non-invasive ventilation.
- The main purpose in using doxapram is to allow time for recovery from an acute respiratory event
- The usual dosing regimen is 1-4 mg/min given as an intravenous infusion

Contraindications

- heart disease,
- epilepsy, cerebral oedema, stroke,
- status asthmaticus,
- hypertension, **hyperthyroidism** and phaeochromocytoma

Side-effects

- hypertension,
- exacerbation of apparent dyspnoea,
- agitation,
- confusion,
- sweating,
- cough,
- headache,
- dizziness,
- nausea, vomiting
- urinary retention

Sodium cromoglicate

- Sodium cromoglicate principally acts by reducing the degranulation of mast cells triggered by the interaction of antigen and IgE
- The **inhibitory effect on mast cells** appears to be cell-type specific, since cromoglicate has little inhibitory effect on mediator release from human basophils
- More recent research has also shown that cromoglicate may act on eosinophils to reduce their inflammatory response to inhaled allergens, but this is not the most probable mechanism of action of sodium cromoglicate **in the prophylaxis of asthma**

Magnesium treatment in asthma

- Intravenous magnesium (1.2 - 2 g given over 20 minutes) is now indicated in the management of severe life threatening acute asthma attacks

Its principal actions are to:

- inhibit acetylcholine release at the neuromuscular junction
- **relax bronchial smooth muscle**
- stabilise mast cells

Unwanted effects are uncommon following single-dose therapy, although a slight decrease in blood pressure can be noticed and flushing can occur

Symptoms of hypermagnesaemia include:

- nausea
- diarrhoea
- flushing
- hypertension
- confusion
- coma
- loss of tendon reflexes

CNS & Psychiatric drugs

Anti-convulsants

Remarkable side effects of anti-epileptic drugs are:

- SIADH and rash (carbamazepine)
- Liver toxicity (sodium valproate)
- Severe rash (lamotrigine)
- Retinal damage (vigabatrin)
- Aplastic anaemia (felbamate).
- **Topiramate**
  - anticonvulsant ,most frequently prescribed for the prevention of migraines
  - **Side effects:**
    - Renal stones
      - topiramate causes systemic metabolic acidosis, lowers urinary citrate excretion, and increases urinary pH. These changes increase the propensity to form **calcium phosphate stones.**
    - weight loss (weight gain with sodium valproate),
    - impaired taste sensation,
    - cognitive dysfunction
    - depression.
    - Tingling in extremities.

- **Felbamate**
  - Because of its **potentially fatal toxic effects** (especially **aplastic anemia** and hepatic failure), the use of felbamate should be restricted to patients with severe partial epilepsy or Lennox-Gastaut syndrome who do not respond to other medications.
- **Lamotrigine**
  - Lamotrigine has a black box warning because of its association with Stevens-Johnson syndrome.
    - **the risk of tevens-Johnson syndrome increases if it is co-administered with valproate .**
    - When co-administered with valproate, the dosage of lamotrigine should be half that required in the absence of valproate and should be very slowly escalated.

Epilepsy medication in pregnancy

- There is an increased risk of neural tube defects associated with anti-convulsants during pregnancy.
- However, the risks associated with treatment are outweighed by the benefits in preventing seizures, so the drug should be continued.
- The risks may be minimised through use of folate supplements.
- **If a patient is planning on pregnancy, then registry studies suggest that lamotrigine would be the best choice**
- **lamotrigine** is the most appropriate choice in women of child-bearing age because:
  - low risk of congenital malformations.
  - it does not affect the effectiveness of the oral contraceptive pill
- **Percentage of Congenital malformations associated with Anti-epileptics**
  - Valproate → 6% (neural tube defects in the fetus)
    - **Valproate should be avoided in pregnancy if possible**
    - NICE guidance suggests that **phenytoin** should be avoided in women of child-bearing age because of the risk of congenital malformations.
  - Topiramate → 4.3%
  - Phenytoin → 3.5% (fetal hydantoin syndrome with facial dysmorphism)
  - Carbamazepine → 2.5%
  - General population →1.5%
  - Primidone and phenobarbital → withdrawal symptoms in the newborn

Breast feeding is acceptable with nearly all anti-epileptic drugs

Contraception in epilepsy

- Phenytoin induces liver enzymes, thereby increasing oestrogen breakdown and reducing the effectiveness of oestrogen-containing contraceptives
- Where the combined contraceptive pill is used in conjunction with phenytoin, the contraceptive should contain high dose oestrogen: 50 mg ethinylestradiol or more
- **Lamotrigine** is a suitable first-line treatment for partial epilepsy, and **does not alter oestrogen metabolism**
- Whilst **Carbamazepine** is a potent enzyme inducer and therefore **can't be used in combination with the pill**

Antiepileptic and weight (medical-masterclass.com 2017 part 2)

- **Two antiepileptic medications have been found to induce weight loss; topiramate and zonisamide**.
- Valproate, vigabatrin, gabapentin, carbamazepine, and pregabalin **induce weight gain**.
- Levetiracetam, lamotrigine, and phenytoin are **weight neutral.**

Sodium valproate

- Sodium valproate is used in the management of epilepsy and is first line therapy for generalised seizures.
- It works by increasing GABA activity.

Adverse effects

- gastrointestinal: nausea
- hepatitis

- increased appetite and weight gain
- alopecia: regrowth may be curly
  (note that phenytoin → hirsutism while valporate → alopecia)
- ataxia
- **tremor**
- **pancreatitis**
- thromobcytopaenia
- **teratogenic**
- hyponatraemia
- **polycystic ovarian (PCOS) syndrome**

Sodium valproate can lead to severe hepatic toxicity. more commonly if the patient has a metabolic or degenerative disorder, organic brain disease or severe seizures associated with mental retardation. Usually this reaction occurs within the first three months of therapy.

Phenytoin

Phenytoin is used in the management of seizures.

Mechanism of action

- refractory period of voltage-gated Na+ channels **decreasing the sodium influx into neurons** which in turn decreases excitability

Side effects

Phenytoin is associated with a large number of adverse effects. These may be divided into acute, chronic, idiosyncratic and teratogenic

Acute

- initially: dizziness, diplopia, nystagmus, slurred speech, ataxia
- later: confusion, seizures

Chronic

- common: **gingival hyperplasia** (secondary to increased expression of platelet derived growth factor, PDGF), **hirsutism**, coarsening of facial features, drowsiness
- megaloblastic anaemia (secondary to altered folate metabolism)
- peripheral neuropathy
- enhanced vitamin D metabolism causing osteomalacia
- lymphadenopathy
- dyskinesia

Idiosyncratic

- fever
- rashes, including severe reactions such as toxic epidermal necrolysis
- hepatitis
- Dupuytren's contracture (although not listed in the BNF)
- aplastic anaemia
- drug-induced lupus
- Hypocalcaemia
- Pseudolymphoma or, rarely, malignant lymphoma and mycosis-fungoides-like lesions.

Teratogenic

- associated with cleft palate and congenital heart disease

Interaction

- Phenytoin would speed up metabolism of ethinyloestradiol making the pill less effective.
- **Cimetidine increases the efficacy of phenytoin by reducing its hepatic metabolism**
- Sucralfate may decrease the pharmacological effects of phenytoin when administered concurrently
- **Effect on other anti-epileptic:**
  - Phenytoin usually lowers the serum concentration of carbamazepine, clonazepam, topiramate and sodium valproate,
  - **elevates the serum level of phenobarbitone**.
  - Phenytoin does not appear to influence the serum concentration of levetiracetam.

In renal failure

Renal failure → ↓ drug affinity for protein binding → ↑ free drug → toxicity (drug level may be within the therapeutic range)

- In patients with renal failure, dose reduction of phenytoin is therefore required.
- Other drugs where this may be a problem include sodium valproate and warfarin.

There is no oral preparation of fosphenytoin; it is used in status epilepticus only.

Phenytoin toxicity typically gives rise to a cerebellar-like syndrome. Nystagmus is present even in mild toxicity.

Carbamazepine

Carbamazepine is chemically similar to the tricyclic antidepressant drugs.

Indications:

- most commonly used in the treatment of epilepsy, particularly partial seizures, where carbamazepine remains a first-line medication.
- Other uses include
  - neuropathic pain (e.g. trigeminal neuralgia, diabetic neuropathy)
  - bipolar disorder

Mechanism of action

- binds to sodium channels increases their refractory period

Adverse effects

- P450 enzyme inducer
  - **Auto-induction of carbamazepine metabolism → need to increase the dose to achieve a therapeutic plasma concentration.**
  - In patients on carbamazepine who develop Hashimoto's thyroiditis the dose of thyroxine should be increased to maintain therapeutic levels
- dizziness and ataxia
- drowsiness
- headache
- nystagmus
- visual disturbances (especially diplopia)
  - **The most common dose-related adverse effects of carbamazepine are diplopia and ataxia**
- **Steven-Johnson syndrome**
  - **HLA-B*1502 in individuals of Han Chinese and Thai origin** has been shown to be strongly associated with the risk of developing Stevens-Johnson syndrome (SJS) when treated with carbamazepine.
  - The prevalence of the HLA-B*1502 carrier is about 10% in Han Chinese and Thai populations.
  - Whenever possible, these individuals should be screened for this allele before starting treatment with carbamazepine
- leucopenia and agranulocytosis
- syndrome of inappropriate ADH secretion
- Carbamazepine is nephrotoxic and may cause **proteinuria.**

Carbamazine overdose presents with:

- Drowsiness
- Slurred speech
- Ataxia
- Hallucinations
- Nausea
- Vomiting
- Tremor
- Blurred vision
- Seizures
- Oliguria, and
- Bullous skin lesions.

Contraindications:

- atrioventricular (AV) conduction abnormalities
- porphyria
- history of bone marrow depression

Vigabatrin

Vigabatrin → **Vi**sual field defects

V for Vigabatrin - V for Visual field defects

Indication:

- Vigabatrin should be used only in combination with other anti-epileptic drugs for patients with resistant partial epilepsy when all other appropriate drug combinations have proved inadequate or have not been tolerated.
- **Vigabatrin** is the drug of choice for infantile spasms, is not generally used outside the situation of infantile spasms

Adverse effects:

- **reduced peripheral vision**
  - **40% of patients develop visual field defects, which may be irreversible**
  - The pattern of the field defect is typically a bilateral, absolute concentric constriction of the visual field, the severity of which varies from mild to severe.
  - **visual fields should be checked** before the start of treatment and **every 6 months**
- aggression
- alopecia
- retinal atrophy

Topiramate

The patient with epilepsy and hepatic impairment → Topiramate

- Topiramate is one of the few antiepileptic drugs (also including gabapentin) with almost exclusively renal metabolism
- It would be less likely to cause worsening of hepatic function
- **adverse effects** of topiramate include
  - **renal stones**
  - weight loss
  - and neuropsychiatric side-effects

Gabapentin

- **used for add-on therapy** in partial or generalised seizures.
- does not induce cytochrome P450 unlike other anticonvulsants such as phenytoin and phenobarbitone.
- **Requires dose adjustment in renal disease**

Levetiracetam (Keppra)

- Is an adjunctive treatment for partial seizures with or without secondary generalisation.
- mechanism of action is unknown.
- rapidly absorbed orally, it does not affect hepatic enzymes but dose reduction is required in renal failure.
- The drug appears to be well tolerated with few side effects.
- has least interactions and is **safe with warfarin .**

Procyclidine

- action
  - antimuscarinic
- indication
  - used to treat the Parkinsonian side effects of neuroleptics;
- Signs of **procyclidine overdose** include:
  - Agitation
  - Confusion
  - Sleeplessness lasting up to 24 hours or more
  - Pupils are dilated and unreactive to light.
  - Visual and auditory hallucinations and tachycardia have also been reported.

Barbiturates

- Examples
  - phenobarbital, pentobarbital, thiopental, and secobarbital
- Mechanism
  - increases $GABA_A$ action by ↑ duration of Cl^- channel opening resulting in ↓ neuron firing
    - barbitDURATE
- Clinical use
  - CNS depressant for anxiety and seizures
  - induction of anesthesia (thiopental)
- kinetics
  - induction of P450
  - tolerance/dependence
- Phenobarbitone suppress the central nervous system causing:
  - Hypoventilation (and therefore a respiratory acidosis)
  - Hypotension, and
  - Hypothermia.

Anticholinergic syndrome

common causes	Signs and symptoms	Management
• tricyclic antidepressants • atropine • H-1-antihistamines	• hot, dry skin • hypertension • tachycardia • urinary retention • **dilated pupils (**mydriasis**)** • Agitated delirium can also occur	supportive

- Although physostigmine, a reversible inhibitor of acteylcholinesterase, is effective in treating symptoms, there is a significant risk of cardiac toxicity (bradycardia, AV conduction defects and asystole).
- Treatment therefore consists of withdrawal of the precipitating drug and supportive care.

Serotonin syndrome

Causes

- monoamine oxidase inhibitors
- SSRIs
- ecstasy
- amphetamines
- The serotonin syndrome occurs primarily because of interactions between monoamine-oxidase inhibitors (MAOI) and drugs that enhance serotonin function (eg selective serotonin-reuptake inhibitors (SSRIs))

Features

- neuromuscular excitation (e.g. hyperreflexia, myoclonus, Tremor, rigidity)
- autonomic nervous system excitation (e.g. hyperthermia)
- altered mental state
- sweating
- tachycardia

Management (Cyproheptadine may be useful in treatment)

- stopping the precipitating drugs
- instituting generalised cooling measures and diazepam to reduce agitation
- Studies have suggested that drugs possessing serotonin-antagonist activity (eg **cyproheptadine**, methysergide) may provide some benefit in the management of patients with the serotonin syndrome

Oculogyric crisis

An oculogyric crisis is a dystonic reaction to certain drugs or medical conditions

Features

- restlessness, agitation
- involuntary upward deviation of the eyes

Causes

- phenothiazines
- haloperidol
  - Usually a consequence of **typical neuroleptic drugs** such as haloperidol or chlorpromazine, but

is **unusual with newer agents** such as olanzapine or clozapine.

- metoclopramide
- postencephalitic Parkinson's disease

The condition is often precipitated by re-introduction of the agent.

Management

- procyclidine (usually IV or IM)
- Benztropine

St John's Wort

Overview

- shown to be as effective as tricyclic antidepressants in the treatment of mild-moderate depression
- mechanism: thought to be similar to SSRIs (although noradrenaline uptake inhibition has also been demonstrated)
- NICE advise 'may be of benefit in mild or moderate depression, but its use should not be prescribed or advised because of uncertainty about appropriate doses, variation in the nature of preparations, and potential serious interactions with other drugs'

Adverse effects

- profile in trials similar to placebo
- can cause serotonin syndrome
- **inducer of P450 system**, therefore decreased levels of drugs such as warfarin, ciclosporin. The effectiveness of the combined oral contraceptive pill may also be reduced.

Dopamine receptor agonists

Overview

- e.g. bromocriptine, cabergoline , ropinirole, apomorphine
- ergot-derived dopamine receptor agonists (bromocriptine, cabergoline, pergolide*) have been associated with pulmonary, retroperitoneal and cardiac **fibrosis**.
  - The Committee on Safety of Medicines advice that an ESR, creatinine and chest x-ray should be obtained prior to treatment and patients should be closely monitored
  - *pergolide was withdrawn from the US market in March 2007 due to concern regarding increased incidence of valvular dysfunction

Action:

- L-DOPA is a precursor of dopamine. Dopamine iteself does not cross the blood-brain barrier and so is no effective as a drug.
- Levodopa exerts its therapeutic action after being converted by dopa decarboxylase to dopamine in the brain (in the striatum).
- It is also converted to dopamine in the periphery, causing nausea and vomiting through action at the area postrema, which lies outside the blood-brain barrier in the brain stem.

Indications

- Parkinson's disease
  - Currently treatment is delayed until the onset of disabling symptoms
  - If the patient is elderly, L-dopa is sometimes used as an initial treatment
- prolactinoma/ galactorrhoea
- cyclical breast disease
- acromegaly

Adverse effects

- nausea/vomiting
- postural hypotension
- hallucinations
- daytime somnolence

Dopa-decarboxylase inhibitors

- **Reduce the extracerebral complications of L-dopa therapy.** These include nausea, vomiting, postural hypotension and cardiac arrhythmias.
- When given in combination with dopamine agonists dyskinetic movements are more likely.

- Carbidopa is an inhibitor of dopa decarboxylase that does not cross the blood-brain barrier, so it reduces peripheral, but not central, metabolism of levodopa to dopamine, thereby reducing the unwanted side effect but not the therapeutic action.
- Benserazide is another peripheral dopa decarboxylase inhibitor that is commonly used in combination with levodopa (as co-beneldopa (Madopar)).

Amitriptyline (tricyclic antidepressants)

Adverse effects

Antimuscarinic effects: relatively common and occur before an antidepressant effect is obtained.

• Dry mouth • Constipation → paralytic ileus • **Urinary retention**	• Blurred vision and disturbances in accommodation • Increased intraocular pressure, and • Hyperthermia.

- Tolerance is often achieved if treatment is continued
- adverse effects may be less troublesome if treatment is begun with small doses and then increased gradually, although this may delay the clinical response.

Neurological adverse effects:

• Drowsiness • Headache • Peripheral neuropathy • Tremor • Ataxia • Epileptiform seizures • Tinnitus	• extrapyramidal symptoms including speech difficulties (dysarthria).Confusion, hallucinations, or delirium may occur, particularly in the elderly, and mania or hypomania, and behavioural disturbances (particularly in children) have been reported.

Gastrointestinal complaints include:

- Sour or metallic taste
- Stomatitis, and
- Gastric irritation with nausea and vomiting.
- rarely, cholestatic jaundice

cardiovascular

- Orthostatic hypotension and tachycardia can occur in patients without a history of cardiovascular disease, and may be particularly troublesome in the elderly.

blood disorders:

- Eosinophilia
- Bone marrow depression
- Thrombocytopenia
- Leucopenia, and
- Agranulocytosis.

Endocrine effects

- testicular enlargement
- gynaecomastia and breast enlargement, and galactorrhoea.
- Sexual dysfunction.
- Changes in blood sugar concentrations
- hyponatraemia associated with inappropriate secretion of antidiuretic hormone.
- increased appetite with weight gain (or occasionally anorexia with weight loss).
- Sweating may be a problem.

Others

- Hypersensitivity reactions, such as urticaria and angioedema, and photosensitisation have been reported

Tricyclic overdose

Tricyclic overdose - give IV bicarbonate

- Overdose of tricyclic antidepressants is a common presentation to emergency departments. Amitriptyline and dosulepin (dothiepin) are particularly dangerous in overdose.
- Other tricyclic antidepressants includes **imipramine**
- Early features relate to anticholinergic properties: dry mouth, dilated pupils, agitation, sinus tachycardia, blurred vision.

Features of severe poisoning include:

- Hypertension
  - results from the blockade of norepinephrine reuptake
  - is an early and transient finding.
  - Catecholamines are eventually depleted and in most patients hypertension is mild and self-limiting and is best left untreated.
- Orthostasis and hypotension
  - are the result of direct myocardial depression, catecholamine depletion, alpha-adrenergic blockade, and arrhythmias.
  - The combination of decreased contractility and vasodilation produce decreased preload and can result in severe and refractory hypotension.
- Arrhythmias
  - secondary to blockage or slowing of fast sodium channels (causing a quinidine-like effect)
  - the most serious consequence of TCA overdose.
  - **Mild overdoses** produce **sinus tachycardia**, mostly as a result of **anticholinergic effects**.
  - **More severe overdoses** result in **prolonged QRS and QTc intervals**, followed by a **prolonged PR interval**, and, finally, **ventricular arrhythmias**, including **ventricular tachycardia** and **ventricular fibrillation**.
- seizures
- metabolic acidosis
- coma

ECG changes include: (ECG is the most appropriate initial action)

- sinus tachycardia
- widening of QRS
- prolongation of QT interval

Widening of QRS > 100ms is associated with an increased risk of seizures whilst QRS > 160ms is associated with ventricular arrhythmias

Management

- Check U&Es, looking specifically for hypokalaemia, and ABG looking for acidosis. Hypokalaemia should be corrected. ECG should be done to assess the QRS interval.
- Gastric lavage should only be considered if it is within one hour a potentially fatal overdose. 50 g of charcoal can be given if it is within one hour of ingestion.
- 50 ml of 8.4% sodium bicarbonate should be given if the pH is less than 7.1, QRS interval is more than 0.16 s, or there are cardiac arrhythmias or hypotension.

  - **Indication for sodium bicarbonate in tricyclic poisoning includes wide QRS complex.**
  - **Intravenous sodium bicarbonate is the standard initial therapy for patients who develop cardiotoxicity (usually a QRS > 100ms or a ventricular arrhythmia) as a result of tricyclic antidepressant (TCA) overdose.**
    - **Mechanism of Sodium bicarbonate action:**
      - alkalinisation of blood to a pH of 7.45-7.55 **uncouples TCA from myocardial sodium channels;**

- ❖ also, additional sodium increases extracellular sodium concentration, thereby improving the gradient across the channel.
- ➢ Intravenous magnesium sulphate can be used as a second-line agent in refractory arrhythmias.
- ➢ IV bicarbonate may reduce the risk of seizures and arrhythmias in severe toxicity

- arrhythmias: class 1a (e.g. Quinidine) and class Ic antiarrhythmics (e.g. Flecainide) are contraindicated as they prolong depolarisation. Class III drugs such as amiodarone should also be avoided as they prolong the QT interval. Response to lignocaine is variable and it should be emphasized that correction of acidosis is the first line in management of tricyclic induced arrhythmias
- intravenous lipid emulsion is increasingly used to bind free drug and reduce toxicity
- dialysis is ineffective in removing tricyclics
- Patients who display signs of toxicity should be monitored for a minimum of 12 hours.

Tricyclic Withdrawal symptoms rare and include:

- **cholinergic** effects such as: abdominal cramps, diarrhoea, vomiting and dehydration
- **extrapyramidal** symptoms such as: anxiety, psychosis, delirium and mania

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Monoamine oxidase (MAO) inhibitors

Overview

- serotonin and noradrenaline are metabolised by monoamine oxidase in the presynaptic cell

Non-selective monoamine oxidase inhibitors

- e.g. tranylcypromine, phenelzine
- used in the treatment of atypical depression (e.g. hyperphagia) and other psychiatric disorder
- not used frequently due to side-effects
- Abrupt withdrawal of phenelzine leads to panic, shaking, sweats and nausea

Adverse effects of non-selective monoamine oxidase inhibitors

- hypertensive reactions with tyramine containing foods e.g. cheese, pickled herring, Bovril, Oxo, Marmite, broad beans
- anticholinergic effects

Selective serotonin reuptake inhibitors (SSRIs)

Selective serotonin reuptake inhibitors (SSRIs) are considered first-line treatment for the majority of patients with depression.

- citalopram and fluoxetine are currently the preferred SSRIs
- **sertraline is useful post myocardial infarction** as there is more evidence for its safe use in this situation than other antidepressants
- SSRIs should be used with caution in children and adolescents. Fluoxetine is the drug of choice when an antidepressant is indicated

Adverse effects

- gastrointestinal symptoms are the most common side-effect
- there is an increased risk of gastrointestinal bleeding in patients taking SSRIs. A proton pump inhibitor should be prescribed if a patient is also taking a NSAID
- patients should be counselled to be vigilant (حذر) for increased anxiety and agitation after starting a SSRI
- fluoxetine and paroxetine have a higher propensity for drug interactions
- The Committee on Safety of Medicines (CSM) have reported that **hyponatraemia is associated with all types of antidepressants;** however it has been reported **more frequently with selective serotonin reuptake inhibitors (SSRIs)** than with other antidepressants.
- Hyponatraemia should be considered in all patients who develop drowsiness, confusion or convulsions whilst taking an antidepressant.

Citalopram and the QT interval

- citalopram and escitalopram are associated with dose-dependent QT interval prolongation and should not be used in those with:
  - ➢ congenital long QT syndrome;
  - ➢ known pre-existing QT interval prolongation;
  - ➢ or in combination with other medicines that prolong the QT interval
- the maximum daily dose is now 40 mg for adults; 20 mg for patients older than 65 years; and 20 mg for those with hepatic impairment

Interactions

- NSAIDs: NICE guidelines advise 'do not normally offer SSRIs', but if given co-prescribe a proton pump inhibitor
- **warfarin / heparin: NICE guidelines recommend avoiding SSRIs and considering mirtazapine**
- aspirin: see above
- triptans: avoid SSRIs
- monoamine oxidase inhibitor (MAOI)→ serotonin syndrome

follow up

- Following the initiation of antidepressant therapy patients should normally be reviewed by a doctor after 2 weeks.
- For patients under the age of 30 years or at increased risk of suicide they should be reviewed after 1 week.
- If a patient makes a good response to antidepressant therapy they should continue on treatment for at least 6 months after remission as this reduces the risk of relapse.

Discontinuation symptoms

- When stopping a SSRI the dose should be gradually reduced over a 4 week period (**this is not necessary with fluoxetine).**
- **Paroxetine has a higher incidence of discontinuation symptoms**
  - Withdrawal of paroxetine can lead to deterioration in mood and cognition and orofacial dystonias
- Symptoms:
  - increased mood change
  - restlessness
  - difficulty sleeping
  - unsteadiness
  - sweating
  - gastrointestinal symptoms: pain, cramping, diarrhoea, vomiting
  - paraesthesia

Lithium

Lithium: fine tremor in chronic treatment, coarse tremor in acute toxicity

- Lithium is mood stabilising drug used most commonly prophylactically in bipolar disorder but also as an adjunct in refractory depression.
- It has a very narrow therapeutic range (0.4-1.0 mmol/L) and a long plasma half-life being excreted primarily by the kidneys.

Mechanism of action - not fully understood, two theories:

- interferes with inositol triphosphate formation
- interferes with cAMP formation

Adverse effects

Chronic lithium use is recognised to reduce both cAMP- and non-cAMP-related upregulation of *aquaporin-2* gene expression. The role of aquaporin-2 is to drive reuptake of water from the urine, and the number of aquaporin-2 channels is increased in response to vasopressin. Blockade of the upregulation of *aquaporin-2* gene expression reduces the effect of vasopressin causing nephrogenic diabetes insipidus.

- nausea/vomiting, diarrhoea
- fine tremor
- polyuria (secondary to nephrogenic diabetes insipidus)
- thyroid enlargement, may lead to hypothyroidism
- ECG: T wave flattening/inversion
- weight gain
- **Hypercalcaemia** and primary hyperparathyroidism.
  - It has been suggested that lithium → alters the sensitivity of the parathyroid cells to calcium → hyperplasia.
  - Other studies have however failed to confirm an excess of parathyroid hyperplasia in this population, suggesting instead that lithium selectively stimulates growth of parathyroid adenomas in susceptible patients, who are best treated therefore with adenoma excision rather than total parathyroidectomy.

Pregnancy

- **Exposure to lithium in utero is associated with Ebstein's anomaly.**
- **Lithium is contraindicated during the first trimester and when breast-feeding.**
- In the first trimester lithium can cause atrialisation of the right ventricle.
- During the second and third trimesters lithium can be used, but dose requirements are increased.
- Immediately after delivery lithium dose requirements return to normal abruptly. Lithium levels can rise dangerously if a high dose is continued.
- Lithium is excreted in breast milk and if the infant becomes dehydrated, then toxic lithium levels develop rapidly.

Monitoring of patients on lithium therapy

- NICE and the National Patient Safety Agency (NPSA) recommends:
  1. lithium blood level should 'normally' be checked every 3 months. Levels should be taken 12 hours post-dose
  2. thyroid and renal function should be checked before starting treatment and then every 6 months
  3. patients should be issued with an information booklet, alert card and record book
  4. monitor serum lithium levels 1 week after treatment starts and every dose change, and then every 3 months.

Lithium monitoring (NICE 2017):

thyroid and renal function	serum lithium levels	ECG
before treatment	1 week after treatment starts	For people at high risk of cardiovascular disease
every 6 months	every dose change	
	every 3 months	

Sodium valproate is the second line therapy for bipolar disorder in patients who don't tolerate lithium or where it's contraindicated.

Interaction:

- **Acetazolamide leads to decreased lithium concentration**
  - Osmotic diuretics and carbonic anhydrase inhibitors such as acetazolamide lead to decreased lithium concentration because of increased excretion
- Calcium channel blockers combined with lithium may cause a syndrome of ataxia, confusion and sleepiness, which is reversible on stopping the drug.
- ACE inhibitors lead to increased lithium concentration because of decreased excretion.
- thiazide diuretics increased lithium reabsorption and may cause lithium intoxication.
- Methyldopa also leads to increased risk of neurotoxicity.

Lithium toxicity

Toxicity may be precipitated by dehydration, renal failure, diuretics (Especially bendroflumethiazide) or ACE inhibitors and ARBs

- Lithium has a very narrow therapeutic range (0.4-1.0 mmol/L)
- long plasma half-life (20 h)
- excreted primarily by the kidneys.
- Lithium toxicity generally occurs following concentrations > 1.5 mmol/L.
- Toxicity may be precipitated by dehydration, electrolyte imbalance, renal failure, , and drugs

Drugs that may precipitate lithium toxicity include:

- diuretics (especially bendroflumethiazide),
- ACE inhibitors & **ARB**
- NSAIDs
- Metronidazole
- Tetracycline
- Phenytoin
- Ciclosporin
- Methyldopa

Features of toxicity

- **coarse tremor (a fine tremor is seen in therapeutic levels)**
- hyperreflexia
- acute confusion
- **dysarthria**
- **ataxia**
- seizure
- coma

Mild to moderate toxicity (levels less than 2 mmol/L)	severe toxicity (levels more than 2 mmol/L)
• anorexia • vomiting • ataxia • dysarthria • blurring of vision • coarse tremor • diarrhoea • drowsiness, and • muscle weakness.	• circulatory failure • coma • convulsions • hyper-reflexia • oliguria • psychosis, and • death (in severe cases).

Management

- mild-moderate toxicity may respond to volume resuscitation with normal saline.
  - In case of significant hypernatraemia , 5% dextrose is an initial option for fluid replacement
- haemodialysis may be needed in severe toxicity
  - indication of Haemodialysis:
    - if serum lithium levels > 4 mmol/l or
    - serum lithium levels > 2.5 mmol/l with signs of significant lithium toxicity (e.g. seizures, depressed mental status) or inability to excrete lithium (e.g. renal disease, decompensated heart failure).
- sodium bicarbonate is sometimes used but there is limited evidence to support this. By increasing the alkalinity of the urine it promotes lithium excretion
- Activated charcoal does not bind lithium effectively and is therefore ineffective except where co-ingestion of other poisons is suspected.

Prognosis

- 10% of patients who survive severe lithium toxicity will be left with a neurological deficit.

Therapeutic drug monitoring

Lithium

- range = 0.4 - 1.0 mmol/l
- take 12 hrs post-dose

Digoxin

- at least 6 hrs post-dose

Ciclosporin

- trough levels immediately before dose

Phenytoin

- trough levels immediately before dose

Baclofen

- The primary site of action is the spinal cord by depressing monosynaptic and polysynaptic transmission.
- It can hyperpolarise cells by increasing K^+ conductance and inhibit Ca^{2+} channels in others.
- Avoid abrupt **withdrawal** as it can cause serious side-effects including:
  - Autonomic dysreflexia.
  - **hallucinations**

Baclofen toxicity

- Onset of toxicity is rapid and its effect can last up to 35-40 hours post ingestion.

- Features include:
  - Drowsiness
  - Coma
  - Respiratory depression
    - CO2 retention is likely to be due to central nervous system depression and reduction in diaphragmatic contraction secondary to baclofen toxicity.
  - Hyporeflexia
  - Hypotonia
  - Hypothermia, and
  - Hypotension.
  - Bradycardia with first degree heart block and prolongation of Q-T interval can occur.
- Treatment is usually supportive and often requires intensive care.
  - **Intubation and mechanical ventilation**
- Patients with a high risk of aspiration pneumonia (↓ glasgow coma scale (GCS)) are a contraindication to non-invasive ventilation.

Endocrinology drugs

For all diabetic drugs → See endocrinology

lipid-lowering agents

See endocrinology (Hyperlipidaemia: management)

Octreotide

Octreotide → Stimulation of the somatostatin (SMS) receptor

Overview

- long-acting analogue of somatostatin
- somatostatin is released from D cells of pancreas and inhibits the release of growth hormone, glucagon and insulin

Uses

- acute treatment of variceal haemorrhage
- acromegaly
- gastrinomas
- carcinoid syndrome
- prevent complications following pancreatic surgery
- VIPomas
- refractory diarrhoea

Adverse effects

- gallstones (secondary to biliary stasis)

Orlistat → Reduces fat absorption from the intestine

- Orlistat promotes weight loss and improves co-morbidities in obese patients
- Orlistat operates by preventing the absorption of fat molecules in the intestinal tract
- Approximately 30% of fat that would otherwise have been absorbed passes straight through the bowel and is excreted in the faeces
- As a result it can cause 'fatty stools', urgency and increased frequency of defaecation often with anal leakage or oily spotting
- these effects encourage people taking the drug to limit fat intake
- Orlistat itself is not absorbed, except in very small quantities and thus its side-effects are restricted to the gastrointestinal tract
- Patients taking orlistat may require concomitant vitamin supplements because of malabsorption of fat-soluble vitamins such as vitamins A, D, K and E
- Orlistat is shown to be clinically efficacious in reducing a person's weight over a period of a year
- Study results also showed significant improvement in reducing fasting glucose, total cholesterol, LDL-

cholesterol and blood pressure

Obs & Gyna drugs

Prescribing in pregnant patients

Very few drugs are known to be completely safe in pregnancy. The list below largely comprises of those known to be harmful.

Drugs	Antibiotics
• ACE inhibitors, ARBs • Statins • Warfarin • Sulfonylureas • Retinoids (including topical) • Cytotoxic agents	• Tetracyclines • Aminoglycosides • Sulphonamides • Trimethoprim • Quinolones: the BNF advises to avoid due to arthropathy in some animal studies

- The majority of antiepileptics including valproate, carbamazepine and phenytoin are known to be potentially harmful. The decision to stop such treatments however is difficult as uncontrolled epilepsy is also a risk.
- **Verapamil is relatively safe in pregnancy** and has been widely used to treat maternal and fetal supraventricular tachycardias.
- Amiodarone is associated with fetal hypothyroidism,
- lisinopril with oligohydramnios,
- lithium with Ebstein's anomaly,
- and warfarin with facial / CNS abnormalities.

Combined oral contraceptive pill: contraindications

Breakthrough bleeding is most commonly associated with low-dose combined oral contraceptive pills, especially those containing 20 micrograms ethinylestradiol.

The decision of whether to start a women on the combined oral contraceptive pill is now guided by the UK Medical Eligibility Criteria (UKMEC). This scale categorises the potential cautions and contraindications according to a four point scale, as detailed below:

- UKMEC 1: a condition for which there is no restriction for the use of the contraceptive method
- UKMEC 2: advantages generally outweigh the disadvantages
- UKMEC 3: disadvantages generally outweigh the advantages
- UKMEC 4: represents an unacceptable health risk

Examples of UKMEC 3 conditions include

- more than 35 years old and smoking less than 15 cigarettes/day
- BMI > 35 kg/m^2*
- migraine without aura and more than 35 years old
- family history of thromboembolic disease in first degree relatives < 45 years
- controlled hypertension
- immobility e.g. wheel chair use
- breast feeding 6 weeks - 6 months postpartum

Examples of UKMEC 4 conditions include

- more than 35 years old and smoking more than 15 cigarettes/day
- migraine with aura
- history of thromboembolic disease or thrombogenic mutation
- history of stroke or ischaemic heart disease
- breast feeding < 6 weeks post-partum
- uncontrolled hypertension
- breast cancer
- major surgery with prolonged immobilisation

Diabetes mellitus diagnosed > 20 years ago is classified as UKMEC 3 or 4 depending on severity

Progestogen only pill: advantages/disadvantages

Advantages

- highly effective (failure rate = 1 per 100 woman years)
- doesn't interfere with sex
- contraceptive effects reversible upon stopping
- can be used whilst breast-feeding
- can be used in situations where the combined oral contraceptive pill is contraindicated e.g. in smokers > 35 years of age and women with a history of venous thromboembolic disease

Disadvantages

- irregular periods: some users may not have periods whilst others may have irregular or light periods. This is the most common adverse effect
- doesn't protect against sexually transmitted infections
- increased incidence of functional ovarian cysts
- common side-effects include **breast tenderness,** weight gain, acne and headaches. These symptoms generally subside after the first few months

Breast feeding: contraindications

Breast feeding is acceptable with nearly all anti-epileptic drugs

The major breastfeeding contraindications tested in exams relate to drugs (see below). Other contraindications of note include:

- galactosaemia
- viral infections - this is controversial with respect to HIV in the developing world. This is because there is such an increased infant mortality and morbidity associated with bottle feeding that some doctors think the benefits outweigh the risk of HIV transmission

SAFE	DANGEROUS
• Antibiotics: penicillins, cephalosporins, trimethoprim • Endocrine: glucocorticoids (avoid high doses), levothyroxine* • Epilepsy: sodium valproate, carbamazepine • Asthma: salbutamol, theophyllines • Psychiatric drugs: tricyclic antidepressants, antipsychotics** • Hypertension: β-blockers, hydralazine, methyldopa • Anticoagulants: warfarin, heparin • Digoxin	• Antibiotics: ciprofloxacin, **tetracycline,** chloramphenicol, sulphonamides • Psychiatric drugs: lithium, benzodiazepines, clozapine • Aspirin • Carbimazole • Sulphonylureas • Cytotoxic drugs • Amiodarone • vitamin A derivatives.

*the BNF advises that the amount is too small to affect neonatal hypothyroidism screening

**clozapine should be avoided

Drug causes teratogenesis

Some common drugs and their potential teratogenic effect are given below:

drug	teratogenic effect
Androgens	cardiac deformities
Alcohol	fetal alcohol syndrome
Carbamazepine	microcephaly
Diethylstilbestrol	vaginal carcinoma
Lithium	cretinism
Phenobarbital	cleft palate
Sodium valproate	neural tube defects
Thalidomide	phocomelia
Warfarin	chondrodysplasia punctata

Unwanted drug effects in pregnancy

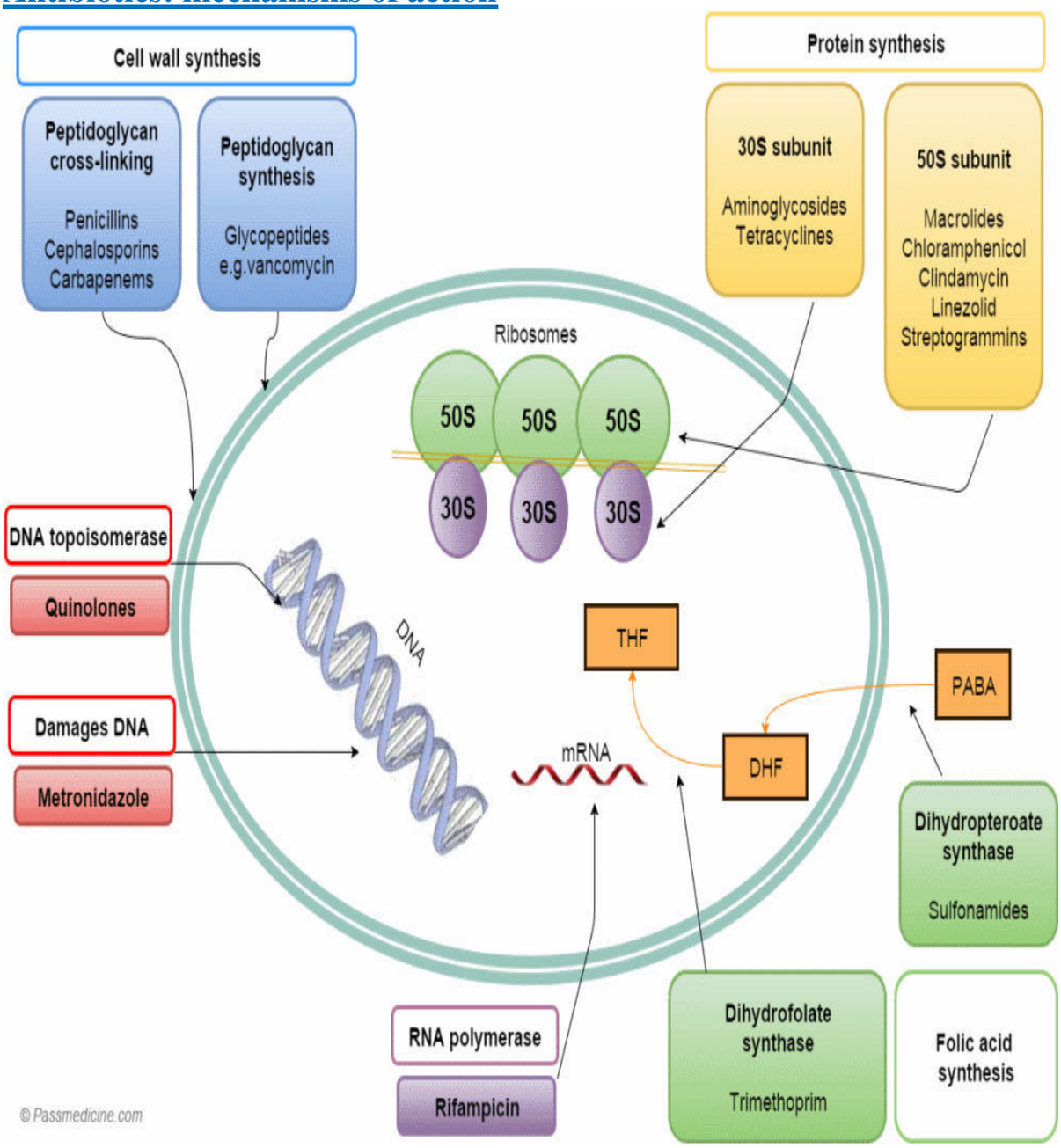
drug	effects in pregnancy
ACE inhibitors	oligohydramnios, impaired renal function
Aspirin	kernicterus
β-Blockers	hypoglycaemia, intrauterine growth retardation, fetal bradycardia
Carbimazole	neonatal goitre
NSAIDs	close ductus arteriosus
Sulphonamides	kernicterus
Thiazide diuretics:	neonatal thrombocytopenia

Antimicrobial

Antibiotics: bactericidal vs. bacteriostatic

Bactericidal antibiotics	Bacteriostatic antibiotics
• penicillins • cephalosporins • aminoglycosides • nitrofurantoin • metronidazole • quinolones • rifampicin • isoniazid	• chloramphenicol • macrolides • tetracyclines • sulphonamides • trimethoprim

Antibiotics: mechanisms of action



The lists below summarise the site of action of the commonly used antibiotics

Inhibit cell wall formation	Inhibit protein synthesis (by acting on ribosome)	Inhibit DNA synthesis	Inhibit RNA synthesis
peptidoglycan cross-linking • β-lactams ➢ Penicillins ➢ Cephalosporins • carbopenems **↓peptidoglycan synthesis** • glycopeptides ➢ Vancomycin ➢ teicoplanin • Isoniazid (Those organisms lacking a cell wall are resistant to these drugs eg. Chlamydia's)	**50S subunit** 1. chloramphenicol 2. macrolides (e.g. erythromycin) 3. fusidic acid 4. (Quin/Dalfo)pristin 5. Linezolid **30S subunit** 1. aminoglycosides (cause misreading of mRNA) 2. tetracyclines	• quinolones (e.g. ciprofloxacin) **Damages DNA** 1. metronidazole **Inhibits folic acid formation** 1. sulphonamides 2. trimethoprim	•Rifampicin

Antibiotics: anaerobic activity

antibiotics have anti-anaerobic activity	antibiotics do not have anti-anaerobic activity
• penicillins • cephalosporins (except ceftazidime) • erythromycin • metronidazole • tetracycline	• gentamicin • ciprofloxacin • ceftazidime

Skin rash with antibiotics

- Ampicillin and amoxicillin can cause skin rashes that are **not allergic** in nature
- Erythromycin, benzylpenicillin, cefuroxime and cefadroxil all produce a diffuse, papular, non-purpuric rash that may be **intensely pruritic**
- A maculopapular rash is also seen when tonsillitis/pharyngitis is related to EBV infection

Cephalosporins

- Cephalosporins are safe in penicillin allergy if it is only a rash.
- Only ceftazidime and cefepime will cover Pseudomonas

Co-trimoxazole

The sulfamethoxazole in co-trimoxazole causes haemolysis in G6PD, not the trimethoprim

Indications

- now only indicated for oral prophylaxis against Pneumocystis pneumonia, toxoplasmosis and nocardiosis
- It should only be considered in the treatment of chronic bronchitis or urinary tract infection where there is no other alternative

Side-effects

- nausea, vomiting,
- allergy : rash (including Stephens-Johnson syndrome), toxic epidermal necrolysis and photosensitivity
- Blood disorders: **neutropenia**, thrombocytopenia and, rarely, agranulocytosis

Cautions/contraindications

- used with caution (or avoided) in renal or hepatic impairment

Aminoglycosides

Action

- bactericidal antibiotics that bind to the **30S** ribosome and inhibit bacterial protein synthesis.
- active **only** against aerobic **gram-negative** bacilli and cocci.

- **ineffective against anaerobic bacteria** as they require O_2 to enter bacterial cells.

Indications

- endocarditis in combination with penicillin (gentamycin)
- added to a beta-lactam antibiotic when serious *Pseudomonas aeruginosa* (cystic fibrosis)
- tuberculosis (streptomycin)

Side effects

- nephrotoxicity
  - The reversible acute tubular necrosis after aminoglycoside reflects a concurrent impairment in the concentrating ability, and most patients are non-oliguric.
  - Irreversible tubulointerstitial damage, however, is uncommon after discontinuing aminoglycoside.
  - We expect a diagnosis of **acute renal failure beginning more than five days after the initiation of gentamicin;**
  - **Aminoglycoside nephrotoxicity correlates with → Frequency of aminoglycoside dosing**
- ototoxicity:
  - Streptomycin, tobramycin, and gentamycin are primarily **vestibulotoxic**
  - Kanamycin, amikacin, neomycin, and dihydrostreptomycin are preferentially **cochleotoxic**.
  - Cochlear toxicity that results in hearing loss usually begins in the high frequencies and is secondary to irreversible destruction of outer hair cells in the organ of Corti, predominantly at the basal turn of the cochlea
  - What is the explanation of progression of hearing loss or onset of hearing loss after cessation of aminoglycoside treatment?
    - Aminoglycosides are cleared more slowly from inner ear fluids than from serum
    - monitor the patient for cochleotoxic and vestibulotoxic effects **up to 6 months after cessation of aminoglycoside** treatment is important.
  - What is the **initial** manifestation of early hearing loss?
    - increase in the threshold of highest frequencies (>4000 Hz).
  - what is the main teratogenic effect of aminoglycosides.
    - CN VIII toxicity
- **What is the mechanism of resistance of Aminoglycosides?**
  - Bacterial transferase enzymes;
    - they inactivate the drug by acetylation, phosphorylation or adenylation
- **Why is the gentamycin trough level likely to be too high in patients with chronic renal failure?**
  - **Prolongation of the half-life**
    - The usual half-life of gentamicin is between 2 and 3 h, although this can be considerably prolonged in patients with renal failure.

Administration

- **There are two commonly used regimens** for dosing gentamicin. Both require the patient's body weight to ensure accurate dosing. For patients who are over their ideal body weight, this value rather than the patient's actual weight should be used. Ideal body weight can be calculated using age, sex and height on a number of online applications.
  1. The most commonly used dosing regimen in the UK is the **once daily regime**, which is thought to be associated with reduced toxicity whilst being effective against gram-negative infections.
     - It is not recommended for patients with a creatinine clearance of less than 60 ml/min.
     - The dose used is 7 mg/kg IV every 24 hours.
     - Levels should be monitored for patients on this regimen for 3 days or more, with a level taken 6-14 hours following the third dose. A nomogram is then used to determine whether the interval between doses should be altered.

2. Patients with creatinine clearance of less than 60 ml/min are usually given a reduced dose of gentamicin with a multiple-daily dosing regimen. This may also be recommended by microbiologists for the treatment of serious gram-negative infections such as Pseudomonas. Dosing is dependent on creatinine clearance:
   - >60 ml/min: 1.5-1.7 mg/kg IV every 8 hours
   - 40-60 ml/min: 1.2-1.5 mg/kg IV every 12 hours
   - 20-40 ml/min: 1.2-1.5 mg/kg IV every 12-24 hours
   - <20 ml/min: 2 mg/kg loading dose then discuss with microbiology and pharmacy

- On this regimen monitoring is typically initiated after the 3rd or 4th dose, which allows a steady-state to be reached. Peak levels should be taken 30 minutes following the end of the infusion, and a trough level taken before the next dose. The desired trough level is less than 2 micrograms/ml, with a peak level of 5-8 micrograms/ml.

Administering gentamicin in conjunction with loop diuretics →↑↑ risk of exacerbating renal and ototoxicity

- **Aminoglycosides Ototoxicity:**
  - mechanism:
    - **cochlear dysfunction** (e.g., tinnitus, hearing impairment) **by damaging cochlear cells**, and/or
    - **vestibulopathy** (e.g., nausea, vomiting, dizziness, vertigo, **oscillopsia**, ataxia) **by damaging hair cells of the inner ear**.
      - **nystagmus** may be present as an early sign.
      - The vestibular dysfunction of gentamicin toxicity is typically bilateral; accordingly, there is no imbalance between right-sided and left-sided input to the central nervous system, so patients do not typically experience vertigo.
      - However, patients can experience oscillopsia and an abnormal head thrust test in both horizontal directions.
        - Oscillopsia is a visual disturbance in which stationary objects appear to oscillate.
          - occur only when the head is moving.
          - Quick movements of the head are associated with transient visual blurring.
          - This can cause difficulties with seeing signs while driving or recognizing people's faces while walking.
        - Head thrust test (Head impulse test)
          - a physical examination maneuver to test for vestibular neuritis.
          - While the patient fixates on a target, the examiner administers brisk, horizontal head rotations to the side.
          - Considered positive if the patient is unable to maintain visual fixation, in which case the patient requires corrective saccades (quick eye movements) to re-fixate back to the target).

Macrolides

- Erythromycin was the first macrolide used clinically. Newer examples include clarithromycin and azithromycin.
- They are used against intracellular pathogens, including Mycoplasma and Legionella, and can also be used as alternatives in case of penicillin allergy.

Action

- Macrolides act by inhibiting bacterial protein synthesis by blocking translocation.
- Macrolides are **bacteriostatic** agents that **inhibit protein synthesis by binding to the 50S subunit of the bacterial ribosome**. If used in high doses, they may be bactericidal.
- If pushed to give an answer they are bacteriostatic in nature, but in reality this depends on the dose and type of organism being treated.
  - **bacteriostatic at low doses and bactericidal at high doses**

Macrolides (erythromycin, azithromycin and clarithromycin), **aminoglycosides** and **chloramphenicol → bind to bacterial ribosomes and disrupt protein synthesis**

- Clarithromycin is a macrolide antibiotic with good gram positive cover and that of atypical organisms. **It's mechanism of action is via reversible inhibition of 50s ribosome subunit.**

Mechanism of resistance

- post-transcriptional methylation of the 23S bacterial ribosomal RNA

Adverse effects

- gastrointestinal side-effects are common. Nausea is less common with clarithromycin than erythromycin
- cholestatic jaundice: risk may be reduced if erythromycin stearate is used
- P450 inhibitor (see below)

Common interactions

- statins should be stopped whilst taking a course of macrolides. Macrolides inhibit the cytochrome P450 isoenzyme CYP3A4 that metabolises statins. Taking macrolides concurrently with statins significantly increases the risk of myopathy and rhabdomyolysis.
- Clarithromycin enhances anticoagulant effect of coumarins This is because warfarin is metabolised by the same CYP3A isozyme as clarithromycin. Clarithromycin, known to inhibit CYP3A, and a drug primarily metabolised by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant drug.
- Clarithromycin is a potent inhibitor of CYP3A4, and as such may interfere significantly with metabolism of a number of medications, including **theophylline**, **simvastatin**, and **cyclosporine** as the most important drug interactions.
- The effect of **warfarin** and **digoxin** may also be potentiated by clarithromycin.

Erythromycin

- Was the 1st macrolide used clinically. Newer examples include clarithromycin and azithromycin.
- Erythromycin may **potentially interact with amiodarone, warfarin and simvastatin**
- **Erythromycin would inhibit the metabolism of theophylline.**
- Macrolides act by inhibiting bacterial protein synthesis.
- If pushed to give an answer they are bacteriostatic in nature, but in reality this depends on the dose and type of organism being treated.

Erythromycin is used in gastroparesis as it has prokinetic properties, Promotes gastric emptying

Used in diabetic gastropathy,

Adverse effects of erythromycin

- GI side-effects are common
- Cholestatic jaundice: risk may be ↓ if erythromycin stearate is used
- P450 inhibitor
- associated with prolonged QT interval and torsades de pointes,

Quinolones

Ciprofloxacin - tendinopathy

Quinolones are a group of antibiotics which work by inhibiting DNA synthesis and are bactericidal in nature.

Examples include:

- ciprofloxacin
- levofloxacin

Mechanism of action

- inhibit topoisomeras II (DNA gyrase) and topoisomerase IV

Mechanism of resistance

- mutations to DNA gyrase, efflux pumps which reduce intracellular quinolone concentration

Adverse effects

- lower seizure threshold in patients with epilepsy

- tendon damage (including rupture) - the risk is increased in patients also taking steroids
  - Rupture has been reported in the achilles, shoulder and hand.
  - This may occur due to disruption of the extracellular matrix and depletion of collagen which is observed in animal models.
- cartilage damage has been demonstrated in animal models and for this reason quinolones are generally avoided (but not necessarily contraindicated) in children

Interaction & contraindication

- It should not be used with drugs that prolong the QT interval (eg erythromycin, tricyclic antidepressants) since there is an increased risk of cardiac arrhythmias
- Contraindicated in left heart failure with reduced ejection fraction
- It should not be given at the same time as bivalent or trivalent cations (eg aluminium, iron) as these reduce absorption. **Antacids** → reduce quinolones absorption leading to therapeutic failure.
- Quinolone absorption is markedly reduced with **antacids** containing aluminium, magnesium and/or calcium and therapeutic failure may result. Other metallic **ion-containing drugs**, such as sucralfate, **iron salts**, and zinc salts, can also reduce absorption.
- The affinity of quinolones for the gamma-aminobutyric acid (GABA) receptor may induce CNS adverse effects; these effects are enhanced by some nonsteroidal anti-inflammatory drugs (NSAIDs).

Co-amoxiclav

- **Because of cholestatic jaundice, prescription of co-amoxiclav is not recommended for longer than 14 days.**
- **If patient developed cholestatic jaundice → the co-amoxiclav should be withdrawn, and the combination avoided in future.**

Probenecid

- Drugs can be excreted into the proximal convoluted tubule of the nephron by cation or anion transporters:
  - cation transporters: basic drugs, eg quinine, pethidine, morphine
  - anion transporters: acidic drugs, eg penicillins, bendroflumethiazide, furosemide, cephalosporins
- The anion transporters are inhibited by probenecid, which can lead to increased plasma concentrations of acidic drugs
- probenecid used clinically to increase the plasma half-life and therefore the therapeutic duration of the drug
- For example, in the management of gonorrhoea infection, probenecid may be combined with oral penicillin to **increase the half-life of the penicillin**

Sulfonamides

Antibacterial sulfonamides act as competitive inhibitors of the enzyme dihydropteroate synthetase (DHPS), an enzyme involved in folate synthesis.

Other uses

- The sulfonamide chemical moiety is also present in other medications that are not antimicrobials, including thiazide diuretics (including hydrochlorothiazide, metolazone, and indapamide, among others), loop diuretics (including furosemide, bumetanide and torsemide) sulfonylureas (including glipizide, glyburide, among others), some COX-2 inhibitors (e. g. celecoxib) and acetazolamide.
- Sulfasalazine, in addition to its use as an antibiotic, is also utilized in the treatment of inflammatory bowel disease.
- **Co-trimoxazole:** sulfonamide antibiotic combination of trimethoprim and sulfamethoxazole, in the ratio of 1 to 5, used in the treatment of a variety of bacterial infections. The name co-trimoxazole is the British Approved Name, and has been marketed worldwide under many trade names including Septra, Bactrim, and various generic preparations. Sources differ as to whether co-trimoxazole usually is bactericidal or bacteriostatic

Vancomycin

Spectrum of the drug – MEC
- **M** – MRSA
- **E** – Enterococcus
- **C** - Cl. difficle

Side effects – RON
- **R** - Red man syndrome
- **O** – Ototoxicity
- **N** - Nephrotoxicity

Action
- Bactericidal
  - inhibits formation of peptidoglycan in bacterial cell walls, but a step earlier in the process compared to β-lactams
    - binds D-ala-D-ala moities of the peptides

Resistance
- D-ala-D-ala mutates to D-ala-D-lac, conferring resistance

Indications
- IV administration for serious, multidrug resistant Gram-positive infections
  - including methicillin-resistant *Staphylococcus aureus* infections (MRSA)
  - including Enterococcus
  - including multidrug resistant Staph epidermidis
- Given orally for C. difficile → not systemically absorbed when given orally

Side effects
- Red man syndrome
  - infuse drug too fast → release of histamine → red rash
- **Ototoxicity**
  - more likely in patients with high plasma concentrations, renal impairment or pre-existing hearing loss.
  - may progress after drug withdrawal,
  - may be irreversible.
  - Hearing loss may be preceded by tinnitus, which must be regarded as a sign to stop treatment.
- Nephrotoxicity
- Thrombophlebitis

Monitoring
- **Vancomycin → requires plasma level monitoring** (after three or four doses if the renal function is normal, or earlier if renal impairment is present)
- The important level to measure here is the **trough level** as opposed to the peak level with gentamicin.
- The trough level toxic threshold (30 mg/l).
  - **If trough level > 30 mg/l → Omit dose and restart when level <15 mg/l**
    - dose omission is required to reduce the risk of significant complications (including ototoxicity and nephrotoxicity).
    - The BNF recommends trough levels of 15-20 mg/l for endocarditis.

Which molecular change is responsible for vancomycin resistance?
- → **D-ala D-ala to D-ala D-lac**
  - Vancomycin resistance is involves its Binding sites the D-Ala-D-Ala.
  - terminal D-Ala is replaced by D-Lactate(D-Lac).

Linezolid

- is a type of oxazolidinones antibiotic class

Action
- **inhibits bacterial protein synthesis** by binding at the **50S subunit of the bacterial ribosome**
  - linezolid occupies the A site of the 50S ribosomal subunit, inducing a conformational change that **prevents tRNA from entering the site** and ultimately **forcing tRNA to separate from the ribosome**

  - work on the first step of protein synthesis, ***initiation***, unlike most other protein synthesis inhibitors, which inhibit ***elongation***
- bacteriostatic

Spectrum, highly active against **Gram positive** organisms including:

- MRSA (Methicillin-resistant *Staphylococcus aureus*)
- VRE (Vancomycin-resistant enterococcus)
- GISA (Glycopeptide Intermediate *Staphylococcus aureus*)

Advantages

- **high bioavailability** (close to 100%) when given by mouth:
  - the entire dose reaches the bloodstream, as if it had been given intravenously.

Adverse effects

- Bone marrow suppression (especially **thrombocytopenia**)
  - (reversible on stopping)
- Peripheral neuropathy
- GI upset
- **Serotonin syndrome**

Contraindications

- Concurrent use with monoamine oxidase inhibitors (**MAOI)** and selective serotonin reuptake inhibitors (**SSRIs**)
- tyramine **diet**

Carbapenems

- **Carbapenems** are antibiotics used for multidrug-resistant (MDR) bacteria.
- members
  - imipenem (+ cilastatin)
    - normal kidneys break down imipenem with a dihydropeptidase
    - cilastatin, a selective dihydropeptidase inhibitor, is always given with imipenem
    - inhibits renal dihydropeptidase I, thereby decreasing inactivation of drug in renal tubules
    - cilastatin not needed for meropenem
  - meropenem
- Their use is primarily in people who are hospitalized.
- Like the penicillins and cephalosporins, they are members of the **beta lactam** class of antibiotics, which kill bacteria by binding to penicillin-binding proteins and **inhibiting cell wall synthesis**.
- Side effect
  - Gastrointestinal distress, skin rash and **seizures** are three common complications of carbapenem administration when there are high plasma levels.
  - 5-10% of patients with penicillin allergy are also allergic to carbapenems

Meropenem

- Which Carbapanem antibiotic has less CNS toxicity? → **Meropenem**
- Meropenem is a carbapanem antibiotic that does not need to be coadministered with Cilastatin.

Trimethoprim

- Trimethoprim is an antibiotic, mainly used in the management of urinary tract infections.
- **It is combined with sulfamethoxazole for synergistic reasons**

Mechanism of action

- interferes with DNA synthesis by inhibiting dihydrofolate reductase

Adverse effects

- myelosuppression
- **transient rise in creatinine**: trimethoprim competitively inhibits the tubular secretion of creatinine resulting in a temporary increase which reverses upon stopping the drug
  - Trimethoprim interferes with tubular handling of creatinine and thereby leads to an increase in serum creatinine, without impairment of GFR.
- Megaloblastic anaemia may occur owing to folate deficiency

Quinupristin & dalfopristin antibiotics

Overview

- injectable streptogrammin antibiotic Only administered via a central line.
- combination of group A and group B streptogrammin respectively.
- inhibits bacterial protein synthesis by blocking tRNA complexes binding to the ribosome

Spectrum

- most Gram positive bacteria
- **Particularly useful against multi- resistant *Strep. pneumoniae* and *Staph. aureus*.**
- exception: *Enterococcus faecalis**

Adverse effects

- thrombophlebitis (give via a central line)
- arthralgia
- P450 inhibitor

*not to be confused with Enterococcus faecium, which is sensitive to Quinupristin & dalfopristin

Tuberculosis: drug side-effects and mechanism of action

Drug	Most common side effects
Rifampicin	Orange bodily fluids, rash, hepatotoxicity, drug interactions
Isoniazid	Peripheral neuropathy, psychosis, hepatotoxicity
Pyrazinamide	Arthralgia, gout, hepatotoxicity, nausea
Ethambutol	Optic neuritis, rash

Rifampicin

- mechanism of action: inhibits bacterial DNA dependent RNA polymerase preventing transcription of DNA into mRNA
- potent liver enzyme inducer
- hepatitis,
- orange secretions
  Patients on rifampicin should be warned that their urine, tears and other secretions will develop a bright orange-red colour
- flu-like symptoms
- **acute interstitial nephritis (pt may present with acute renal failure after 1 month of starting rifampicin)**

Interaction

- **Interact with oral contraceptive induces → failure of the oral contraceptive treatment**
- Rifampicin is a potent hepatic enzyme inducer that increases the metabolism of many drugs, including all the steroid hormones
- Barrier contraceptives must be used during treatment with rifampicin and for 4-8 weeks after a course of rifampicin is completed

Isoniazid

Isoniazid inhibits the P450 system

Isoniazid causes peripheral neuropathy

- mechanism of action: inhibits mycolic acid synthesis
- peripheral neuropathy:
  - Occurs in less than 1%

- **Those with N-acetyltransferase type-2 gene defect → resulting in abnormal isoniazid metabolism → predisposed to neuropathy**
- Prevented with 10 mg pyridoxine (Vitamin B6)

- hepatitis, raised transaminases in 10-20%
  - **Isoniazid-induced hepatitis** occurs in ~1% of individuals and is much commoner in people more than 35-years-old (risk of hepatitis is less than 0.3% in patients under 20 years; 2-3% risk in individuals over 50 years).
- agranulocytosis
- liver enzyme inhibitor
- isoniazid inhibits the conversion of tryptophan to niacin → nicotinic acid (niacin) deficiency → Pellagra (the 3 D's - dermatitis, diarrhoea and dementia)
- systemic lupus erythematosus (SLE)-like syndrome.
- **Isoniazid toxicity**
  - **Isoniazid toxicity should be suspected in any patient with intractable seizures and profound metabolic acidosis with an elevated anion gap.**
  - Intravenous pyridoxine (vitamin B6) is the treatment of choice.
  - The acidosis may need to be corrected with bicarbonate.

Pyrazinamide

- mechanism of action: converted by pyrazinamidase into pyrazinoic acid which in turn inhibits fatty acid synthase (FAS) I
- hyperuricaemia causing gout
- arthralgia, myalgia
- hepatitis

Ethambutol

- mechanism of action: inhibits the enzyme arabinosyl transferase which polymerizes arabinose into arabinan
- optic neuritis: check visual acuity before and during treatment
- dose needs adjusting in patients with renal impairment

The main adverse effects of ethambutol are:

- loss of visual acuity
- restriction of visual fields
- colour blindness
- retrobulbar neuritis
- arthralgia.

Uncommonly it may be associated with

- hyperuricaemia, and with interstitial nephritis. This is thought to **occur less frequently than with rifampicin.**

Antiviral agents

Drug	Mechanism of action	Indications	Adverse effects/toxicity
Aciclovir	Guanosine analog, phosphorylated by thymidine kinase which in turn **inhibits the viral DNA polymerase**	HSV, VZV	Crystalline nephropathy
Ganciclovir	Guanosine analog, phosphorylated by thymidine kinase which in turn **inhibits the viral DNA polymerase**	CMV	Myelosuppression/ agranulocytosis
Ribavirin	Guanosine analog which inhibits inosine monophosphate (IMP) dehydrogenase, **interferes with the capping of viral mRNA**	Chronic hepatitis C, RSV	Haemolytic anaemia
Amantadine	Inhibits uncoating (M2 protein) of virus in cell. Also releases dopamine from nerve endings	Influenza, Parkinson's	Confusion, ataxia, slurred speech

Drug	Mechanism of action	Indications	Adverse effects/toxicity
		disease	
Oseltamivir	Inhibits neuraminidase	Influenza	
Foscarnet	Pyrophosphate analog which inhibits viiral DNA polymerase	CMV, HSV if not responding to aciclovir	Nephrotoxicity, hypocalcaemia, hypomagnasaemia, seizures
Interferon-α	Human glycoproteins which **inhibit synthesis of mRNA**	Chronic hepatitis B & C, hairy cell leukaemia	Flu-like symptoms, anorexia, myelosuppression
Cidofovir	Acyclic nucleoside phosphonate, and is therefore independent of phosphorylation by viral enzymes (compare and contrast with aciclovir/ganciclovir)	CMV retinitis in HIV	Nephrotoxicity

Which one of the following best describes the step required for aciclovir activation?

Conversion to monophosphate form by viral thymidine kinase

HIV: anti-retrovirals

Highly active anti-retroviral therapy (HAART) involves a combination of at least three drugs, typically two nucleoside reverse transcriptase inhibitors (NRTI) and either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). This combination both decreases viral replication but also reduces the risk of viral resistance emerging

Anti-retroviral agent used in HIV	About
Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTI)	Examples: zalcitabine, zidovudine (AZT), didanosine, lamivudine, stavudine,
Protease inhibitors (PI)	• Inhibits a protease needed to make virus able to survive outside the cell • Examples: indinavir, nelfinavir, ritonavir, saquinavir
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)	examples: nevirapine, efavirenz

Nucleoside analogue reverse transcriptase inhibitors (NRTI)

- examples: zidovudine (AZT), didanosine, lamivudine, stavudine, zalcitabine
- general NRTI side-effects: peripheral neuropathy
- zidovudine: anaemia, myopathy, black nails
- didanosine: pancreatitis

Non-nucleoside reverse transcriptase inhibitors (NNRTI)

- examples: nevirapine, efavirenz
- side-effects: P450 enzyme interaction (nevirapine induces), rashes

Protease inhibitors (PI)

- Protease inhibitors are multi-pathway **inhibitors of rivaroxaban clearance and elimination.**
- examples: indinavir, nelfinavir, ritonavir, saquinavir
- side-effects: diabetes, **hyperlipidaemia**, buffalo hump, central obesity, P450 enzyme inhibition
- indinavir: renal stones, asymptomatic hyperbilirubinaemia
- ritonavir: a potent inhibitor of the P450 system

HIV: anti-retrovirals - P450 interaction
- **nevirapine (NNRTI): induces P450**
- **protease inhibitors: inhibits P450**

Abnormalities of serum lipid levels are likely to be multifactorial in patients with HIV disease, but appear much commoner in patients taking protease inhibitors.

Isolated hypertriglyceridaemia can occur in HIV disease in the absence of protease inhibitors, but extremely high serum triglycerides have been documented in some patients treated with these drugs.

Oseltamivir (Tamiflu)

- **Oseltamivir (Tamiflu)** like its predecessor zanamivir (Relenza) functions as an antiviral through inhibition of the enzyme neuraminidase, thus slowing viral replication down rather than directly killing the virus particle.
- This slowing down of replication is important in permitting time for the body's own immune system to deal with the virus.
- Unlike inhaled zanamivir, oseltamivir is administered orally.
- **Oseltamivir ➔It is of value in prophylaxis against influenza**
- However, viral replication is rapid and to be effective the drug must be given as early as possible after the development of symptoms of flu and preferably within 48 hours.

Anti-fungal

- **Nystatin** is poorly absorbed through mucous membranes and is thus useful in oral, vaginal and enteric candidiasis
- **Terbinafine** is used to treat superficial mycoses such as dermatophyte infections
- **Fluconazole** is useful in candidiasis and central nervous system infections with Cryptococcus neoformans and is usually commenced after initial treatment with amphotericin and flucytosine
- **Itraconazole** is the agent of choice for non-life threatening blastomycosis and histoplasmosis it is also moderately effective against invasive aspergillosis
- **Amphotericin B → treatment of Aspergilloma**
  - The drug may exert either fungicidal or fungistatic activity, depending on its concentration at the site of infection and sensitivity of the organism
  - increases the permeability of the fungal cell wall by binding to ergosterol and forming micropores
  - side effect→ nephrotoxicity associated with **hypokalaemia** and hypomagnesaemia
  - **To decrease toxicity, newer lipid-bound preparations are now available**

Griseofulvin

- Is not active against *Candida albicans*. It is active against trichophytons (tinea) and other dermatophytes.
- It is metabolised in the liver (note also it's an enzyme inducer). Only 0.1-0.2% excreted in urine.
- Treatment with griseofulvin is often needed for a long period, sometimes years, depending on the rate of nail growth.
- **It is associated with drug-induced Stevens-Johnson syndrome**

Diethylcarbamazine

Indication:
- Treatment of individual patients with certain filarial diseases.
- These diseases include: lymphatic filariasis caused by infection with Wuchereria bancrofti, Brugia malayi, or Brugia timori; (ELEPHANTiasis) tropical pulmonary eosinophilia, and loiasis.

Overdose of antimalarial medications

Chloroquine

Symptoms

- Nausea
- Headaches
- Visual disturbances
- Cardiac arrhythmias
- Convulsions
- Coma

Treatment

- Activated charcoal should be given to patients who present within 1 h
- The initial **hypokalemia that occurs appears to be cardio-protective** and should not be corrected for at least 8 h after the ingestion
- **In patients with severe toxicity, high-dose (2 mg/kg) diazepam and adrenaline (0.25 pg/kg per min) have been shown to reduce mortality**

Quinine toxicity (cinchonism)

- Quinine is a remarkably toxic drug; something which is not so readily acknowledged. It is used as an antimalarial drug and also as a prophylactic agent against leg cramps, although both uses are increasingly falling from vogue due to the availability of better, safer agents.
- Quinine toxicity, known as cinchonism, may be fatal, usually by cardiac arrhythmia or flash pulmonary oedema in the short term, although incipient renal failure may be fatal more long-term.
- Cardiac arrhythmia is a common finding in cinchonism due to blockade of sodium and potassium channels prolonging QRS and QT intervals respectively and these rhythms may degenerate into ventricular tachyarrhythmias or fibrillation causing death.
- Hypoglycaemia is also a common finding in cinchonism since quinine stimulates pancreatic insulin secretion and this should be corrected rapidly if present.
- Flash pulmonary oedema may develop causing hypoxia and necessitating positive pressure ventilation.
- Classical hallmarks of cinchonism are tinnitus, visual blurring, flushed and dry skin and abdominal pain.
- Other visual complications, including **blindness,** can occur and **may be permanent**
- Clinically, quinine toxicity is difficult to distinguish from aspirin poisoning and so measurement of serum salicylate levels is important when this clinical picture is seen.
- In terms of management however, whereas aspirin can be cleared from overdose victims by haemofiltration, quinine cannot be extracted easily by extracorporeal methods.
- Central nervous symptoms such as tinnitus, deafness and visual defects which may occur with aspirin are usually transient whereas quinine leaves permanent neural damage, if the patient survives.
- **Management** of quinine poisoning is largely supportive with fluids, inotropes and bicarbonate as needed as well as positive pressure ventilation for pulmonary oedema.
- Lidocaine (lignocaine) should not be used in the management of cardiac arrhythmias as this can increase the risk of seizures
- Urine acidification is not recommended as whilst it increases quinine elimination, it also increases the risk of cardiotoxicity

Immunosuppressants

Ciclosporin (Cyclosporine)

Ciclosporin + tacrolimus - MOA: inhibit calcineurin thus decreasing IL-2

Ciclosporin side-effects: everything is increased - fluid, BP, K^+, hair, gums, glucose

Mode of action

- It acts by **binding to cyclophilin** forming a complex which → **inhibits calcineurin**, (a phosphotase that activates various transcription factors in T cells) → **reducing IL-2** release → decreases clonal proliferation of T cells → immunosuppression

Indications

- following organ transplantation
- rheumatoid arthritis
- psoriasis (has a direct effect on keratinocytes as well as modulating T cell function)
- ulcerative colitis
- pure red cell aplasia
- **atopic dermatitis (AD)** (T lymphocytes are involved in the pathophysiology of AD and increased production of cytokines particularly IL-4)

Adverse effects (note how **everything is increased - fluid, BP, K^+, hair, gums, glucose**)

- Nephrotoxicity
  - **Chronic interstitial nephritis is a major side-effect of ciclosporin**
  - **Fluconazole inhibits the metabolism of ciclosporin which increases the risk of ciclosporin nephrotoxicity.**
- hepatotoxicity
- fluid retention
- hypertension
- hyperkalaemia
- hypertrichosis
- gingival hyperplasia
- impaired glucose tolerance
- hyperlipidaemia
- increased susceptibility to severe infection
- **Tremor**
  - cause **coarse tremor**.
  - In the **first** instance the **dose should be reduced**.
    - Usually the neurological side effects of cyclosporin are **dose dependent**.
- **increased risk for Squamous cell carcinoma**
  - Cutaneous squamous cell carcinoma (SCC) is the second most common human cancer
  - transplant-associated SCC (TSCC), which occurs in immune-suppressed solid organ transplant recipients (OTRs) may be considerably more aggressive than SCC in immune competent patients, with metastatic rates as high as 8%
  - IL-22 receptor is most highly expressed in TSCC and is induced by cyclosporine A.
  - Treatment with anti–IL-22 antibody decreases SCC tumor number and tumor burden.

Note:

- Interestingly for an immunosuppressant, ciclosporin is noted by the BNF to be '**virtually non-myelotoxic'**.

Cyclosporine A immunosuppression drives catastrophic squamous cell carcinoma through IL-22 **(September 2016)**

Monitoring

- These patients are seen monthly to have their blood pressure, urea, and electrolytes checked.

Tacrolimus

Mode of action

- similar to the action of ciclosporin

Tacrolimus vs Ciclosporin:

- It has a very similar action to ciclosporin (**inhibits calcineurin**, **reducing IL-2 release**)
- The action of tacrolimus differs from ciclosporin in that it **binds to a protein called FKBP rather than cyclophilin**
- Tacrolimus is more potent than ciclosporin and hence the incidence of organ rejection is less.
- However, nephrotoxicity and impaired glucose tolerance is more common

Indications

- immunosuppressant to prevent transplant rejection.
- Other T-cell medicated diseases
  - Eczema (as ointment)
  - Sever refractory uveitis after bone marrow transplant
  - Vitiligo

Monitoring

- Tacrolimus levels can be affected by concomitant use of other drugs and changes in gut absorption, and so **need to be monitored carefully.**

Many side effects of tacrolimus are similar to cyclosporine A, but tacrolimus does not cause gingival hyperplasia or hirsutism

Sirolimus

Overview

- A macrolide compound
- Also known as rapamycin

Mode of action

- binding with intracellular FKBP-12 protein → **inhibition of mTORC1**→ ↓ cytokine-induced T-cell proliferation → immunosuppression
- Sirolimus binds to the immunophilin FK **b**inding **p**rotein 12 (FKBP12), and the drug-immunophilin complex acts on the Target of Rapamycin (rapamycin being the original name of sirolimus) to **interrupt stimulation of cell proliferation via the interleukin-2 receptor.**
- **What is the target of action of sirolimus?**
  - ⇨ **FK binding protein 12 (FKBP12)**

Indications

- treatment of acute rejection.

Adverse Effects

- **Pancytopenia**
- **Hyperlipidemia**
- Peripheral edema
- Insulin resistance
  - Inhibition of mTORC2 → diabetes- like symptoms

Azathioprine

Azathioprine → check thiopurine methyltransferase deficiency (TPMT) before treatment

- Azathioprine is metabolised to the active compound mercaptopurine, a purine analogue that inhibits purine synthesis → **Impaired DNA synthesis**
- A thiopurine methyltransferase (TPMT) test may be needed to look for individuals prone to azathioprine toxicity.
  - The enzyme activity of thiopurine methyltransferase (TPMT) is under the control of a genetic polymorphism.
  - **90 % of the population have normal or high (TPMT) enzyme activity**. 10 % have intermediate levels
  - One in 300 people have no functional enzyme activity.
  - Several groups of patients have developed azathioprine induced myelosuppression linked to TPMT deficiency.

Adverse effects include

- bone marrow depression → Pancytopenia
  - **It suppresses lymphocyte numbers and function**
- nausea/vomiting
- pancreatitis
- Hepatotoxicity
- 100-fold increased risk of skin cancers and lymphomas.

Monitoring

- (BNF) suggest monitoring CBC, LFTs and U&E every 3 months once patients are established and stable on azathioprine treatment.

interaction

- Azathioprine and 6-MP are metabolized by xanthine oxidase. Therefore, allopurinol–a xanthine oxidase inhibitor–increases the risk of azathioprine and 6-MP toxicity.
- A significant interaction may occur with allopurinol and hence lower doses of azathioprine should be used.
  - Allopurinol acts by inhibition of xanthine oxidase and thus inhibits the metabolism of 6-mercaptopurine, an active metabolite of azathioprine.
  - The prodrug azathioprine is metabolised to its active compound 6-mercaptopurine (6-MP). 6-MP undergoes catabolic oxidation to 6-thiouric acid by xanthine oxidase.
  - Allopurinol has a peak onset of action of one to two weeks and works by inhibiting xanthine oxidase.
  - Co-administration of (Azathioprine + Allopurinol) → accumulation of 6-MP (6-MP toxicity) → ↑ risk of myelosuppression (aplastic anaemia)
  - if concomitant use is to occur, a **dose reduction in azathioprine by 25%** is advised with regular blood count monitoring.

Usage in pregnancy

- **Azathioprine can be used in pregnancy without significant risk to the fetus**

Methotrexate

Action

- Methotrexate is an **antimetabolite** which **inhibits dihydrofolate reductase**, an enzyme essential for the synthesis of purines and pyrimidines
  - Methotrexate inhibits dihydrofolate reductase , thereby inhibiting the production of tetrhydrofolate required for thymidine and purine synthesis.
  - inhibits purine and pyrimidine synthesis **by competing for the active site** of dihydrofolate reductase (by **competitive inhibition**).
  - It is cytotoxic **during the S-phase of the cell cycle**, and has a greater toxic effect on rapidly dividing cells.
  - **Take 6 -12 weeks to achieve full affect**

Indications

- rheumatoid arthritis
- psoriasis (Methotrexate would be the only correct treatment for someone with **erythrodermic psoriasis**)
- acute lymphoblastic leukaemia

Adverse effects

- mucositis
- myelosuppression
- **Macrocytosis is seen as a consequence of long term methotrexate therapy.**
- pneumonitis
- pulmonary fibrosis
- liver cirrhosis
  - **What is the toxicity of Methotrexate (MTX) at the liver?**
    - **Macrovesicular fatty change**

Pregnancy

- women should avoid pregnancy for at least 3 months after treatment has stopped
- the BNF also advises that men using methotrexate need to use effective contraception for at least 3 months after treatment

Prescribing methotrexate

- methotrexate is taken weekly, rather than daily
- FBC, U&E and LFTs need to be regularly monitored.
  - The Committee on Safety of Medicines recommend **'FBC and renal and LFTs before starting treatment and repeated weekly until therapy stabilised, thereafter patients should be monitored every 2-3 months'**

- **Folic acid 5mg once weekly should be co-prescribed**, taken more than 24 hours after methotrexate dose
- the starting dose of methotrexate is 7.5 mg once weekly, can be increased by 2.5 mg every 6 weeks, to a maximum of 20 mg weekly (Ref: oxford handbook of practical drug therapy)
- only one strength of methotrexate tablet should be prescribed (usually 2.5 mg)
- do not prescribe with aspirin or NSAIDs → ↓ methotrexate excretion → ↑ toxicity
- **avoid prescribing anti-folate antibiotics trimethoprim or cotrimoxazole concurrently - increases risk of marrow aplasia**
- **In the circumstances of infection one should consider temporarily stopping methotrexate as it is an immunosuppressant.**

Interaction

- OAT-1 inhibitors
  - Methotrexate is a substrate for the OAT-1 renal transporter and levels of methotrexate are therefore affected by decreased renal function.
  - OAT-1 inhibitors include drugs such as **probenecid**, and therefore should not be used in conjunction with methotrexate.
- **Omeprazole**
  - **Omeprazole is also known to affect clearance of methotrexate**; this interaction is not thought to be via OAT-1, but is **thought to be related to inhibition of breast cancer resistance protein**, which is responsible for methotrexate transport.

Monitoring

- Clinicians are recommended to check **FBC fortnightly until 6 weeks** after the last dose increase.
  - Provided it is **stable**, it can be checked **monthly** thereafter until the dose and disease is stable for one year.
  - Thereafter, monitoring is guided by clinical judgement. If white cell count is less than 3.5, neutrophils less than 2 or platelets less than 150, methotrexate should be withheld pending discussion with the specialist team.
  - An MCV greater than 105 fL warrants checking B12, folate and TSH and treating any abnormality. If these are normal, discuss with the specialist team.
- **Liver function tests** should be checked **three monthly**. If there is an unexplained decrease in albumin, or AST/ALT twice the upper limit of normal, the specialist team should be informed.
- **Urea, creatinine and electrolytes** should be checked **six monthly**. If the estimated glomerular filtration rate falls below 50 mL/minute, methotrexate should be withheld until the result has been discussed with the specialist team.

Drug	MOA
Mycophenolate mofetil	inhibits inosine monophosphate dehydrogenase
Azathioprine	metabolised to the active compound mercaptopurine a purine analogue that inhibits DNA synthesis. purine synthesis inhibitor
Methotrexate	antimetabolite which inhibits dihydrofolate reductase

Methotrexate overdose

Methotrexate overdose → Folinic acid

- Methotrexate is a folic acid antagonist which can result in multi-organ failure in overdose.
- medication errors with respect to rheumatoid arthritis are not uncommon.
  - Patients occasionally find it difficult to understand that they must take their medication weekly as opposed to daily.
- **Calcium folinate is a potent antagonist for the effects of methotrexate** on the haematopoeic system, given by IV infusion at doses up to 75mg in the first 12hrs. This can then be followed by doses of 6-12mg every 4hrs.
- **Folinic acid is the antidote** and should be given intravenously as soon as possible, regardless of the liver function tests.
- Blood transfusion may also be required in exceptional circumstances.
- Where massive overdose of methotrexate has occurred, hydration and urinary alkalinisation may be an option.
- Standard dialysis is ineffective in removing methotrexate, although intermittent high flux dialysis may be of value.

Mycophenolate mofetil

Mode of action

- inhibits inosine monophosphate dehydrogenase, which is needed for purine synthesis
- as T and B cells are particularly dependent on this pathway it can reduce proliferation of immune cells
- adverse effects
  - Pancytopenia
  - Hypertension
  - Hyperglycemia

Hydroxychloroquine

- Hydroxychloroquine ocular toxicity includes:
  - Keratopathy
  - Ciliary body involvement
  - Lens opacities (Lenticular deposits)
  - Retinopathy.
    - Retinopathy is the major concern; the others are more common but benign.
    - The incidence of true hydroxychloroquine retinopathy is exceedingly low.
    - Risk factors include:
      - Daily dosage of hydroxychloroquine
      - Cumulative dosage
      - Duration of treatment
      - Coexisting renal or liver disease
      - Patient age, and
      - Concomitant retinal disease.
    - Patients usually complain of difficulty in reading, decreased vision, missing central vision, glare, blurred vision, light flashes, and metamorphopsia.
    - They can also be asymptomatic.
    - Most patients with advanced retinopathy have a bull's eye (also known as target, as in darts) fundoscopic appearance. All patients have field defects including paracentral, peri-central, and central and peripheral field loss.
- Regular screening may be necessary to detect reversible premaculopathy.
- Cessation of the drug is the only effective management of the toxicity.

Sulfasalazine

Side effects

- hypersensitivity,
- myelosuppression,
- macrocytosis, and
- azoospermia in males.

sulfasalazine toxicity

- There are numerous signs of sulfasalazine toxicity.
- **Rash and oral ulceration** should be asked about and, if severe, the drug should be withheld until specialist advice has been sought.
- Nausea, dizziness and headache can be common and sometimes necessitate dose reduction.
- If patients present with abnormal bruising or sore throat an urgent CBC should be done, and sulfasalazine withheld until results are available.

Monitoring

- **CBC**
  - CBC should be monitored monthly for the first 3 months.
  - Sulphasalazine should be withheld until discussion with the specialist team if:
    - The white cell count is less than 3.5
    - Neutrophils is less than 2, or

        - Platelets are less than 150.
    - If (MCV) **>** 105 fl, vitamin B12, folate and TSH should be checked and treated if found to be abnormal. If these are all normal it should be discussed with the specialist team.
    - If counts remain normal within the first 3 months, CBC can be checked 3 monthly.
- **Liver function tests (LFTs)**
    - should also be checked monthly for the first 3 months.
    - If either AST or ALT are **more than twice the upper limit of normal**, sulfasalazine should be withheld until discussion with the specialist team.
    - If the LFTs remain normal for the first 3 months, monitoring can be decreased to 3 monthly.
    - If, following the first year, the dose has not been increased and blood results have been stable, the frequency of monitoring can be reduced to every six months for the second year of treatment. Thereafter monitoring is not required, although CBC and LFTs should be checked one month after any dose increase.

Leflunomide

- an immunosuppressive disease-modifying antirheumatic drug (DMARD), used in active moderate-to-severe rheumatoid arthritis and psoriatic arthritis.
- It is a **pyrimidine synthesis inhibitor**.
- achieves its effects by **inhibiting the mitochondrial enzyme dihydroorotate dehydrogenase (DHODH),** which plays a key role in the *de novo* synthesis of uridine monophosphate (rUMP), which is required for the synthesis of DNA and RNA. Hence, leflunomide inhibits the reproduction of rapidly dividing cells, especially lymphocytes.

Side effects

- Hepatotoxicity (occurring in 15-20% of cases)
    - most hepatic events occur within the first 6 months of use.
- signs of leflunomide toxicity should be monitored. If the patient develops a **rash or itch** dose reduction should be considered, with or without the addition of antihistamines. If severe, leflunomide should be stopped and washout considered.
- **Hair loss, headaches and gastrointestinal upset** may also warrant dose reduction or washout.
- **A blood pressure of greater than 140/90** mmHg should be treated as per NICE guidelines. If it remains elevated, stop leflunomide and consider washout.
- Weight should be monitored, and a **weight loss** of greater than 10% should be identified. If no other cause can be found, consider dose reduction or washout.
- If there is increasing shortness of breath, **pneumonitis** should be considered and leflunomide should be stopped.
- Leflunomide **reduces sperm count**.

Monitoring

- **LFT**
    - (LFTs) should be checked monthly for 6 months and, if stable, 2 monthly thereafter.
    - If AST or ALT is between 2 and 3 times the upper limit of normal, and the leflunomide dose is more than 10 mg daily, the dose should be reduced to 10 mg and LFTs rechecked weekly until normalised. If the ALT and AST are returning to normal, the patient should be left on 10 mg per day. It the LFTs remain elevated, leflunomide should be stopped and discussed with the specialist team.
    - If the AST or ALT is more than 3 times the upper limit of normal, the LFTs should be rechecked within 72 hours. If they remain more than 3 times the reference range, leflunomide should be stopped and washout considered (cholestyramine and activated charcoal).
    - It is important to note that the half-life of leflunomide is usually 2 weeks (mean 14) therefore if a rapid response is required, washout should be considered.

- **CBC**
  - (CBC) should be checked monthly for six months and, if stable, two monthly thereafter.
  - White cell count less than 3.5, neutrophils less than 2 or platelets less than 150 should be discussed with the specialist team, and leflunomide withheld until this has taken place.

Poisoning &Toxicology

Overdose and poisoning: management

The table below outlines the main management for common overdoses:

Toxin	Treatment
Paracetamol	Management • activated charcoal if ingested < 1 hour ago • N-acetylcysteine (NAC) • liver transplantation
Salicylate	Management • urinary alkalinization is now rarely used - it is contraindicated in cerebral and pulmonary oedema with most units now proceeding straight to haemodialysis in cases of severe poisoning • haemodialysis
Opioid/opiates	Naloxone
Benzodiazepines	Flumazenil
Tricyclic antidepressants	Management • IV bicarbonate may reduce the risk of seizures and arrhythmias in severe toxicity • arrhythmias: class 1a (e.g. Quinidine) and class Ic antiarrhythmics (e.g. Flecainide) are contraindicated as they prolong depolarisation. Class III drugs such as amiodarone should also be avoided as they prolong the QT interval. Response to lignocaine is variable and it should be emphasized that correction of acidosis is the first line in management of tricyclic induced arrhythmias • dialysis is ineffective in removing tricyclics
Lithium	Management • mild-moderate toxicity may respond to volume resuscitation with normal saline • haemodialysis may be needed in severe toxicity • sodium bicarbonate is sometimes used but there is limited evidence to support this. By increasing the alkalinity of the urine it promotes lithium excretion
Warfarin	Vitamin K, prothrombin complex
Heparin	Protamine sulphate
Beta-blockers	Management • if bradycardic then atropine

Toxin	Treatment
	• in resistant cases glucagon may be used
Ethylene glycol	Management has changed in recent times • ethanol has been used for many years • works by competing with ethylene glycol for the enzyme alcohol dehydrogenase • this limits the formation of toxic metabolites (e.g. Glycoaldehyde and glycolic acid) which are responsible for the haemodynamic/metabolic features of poisoning • **fomepizole**, an inhibitor of alcohol dehydrogenase, is now used first-line in preference to ethanol • haemodialysis also has a role in refractory cases
Methanol poisoning	Management • fomepizole or ethanol • haemodialysis
Organophosphate insecticides	Management • atropine • the role of pralidoxime is still unclear - meta-analyses to date have failed to show any clear benefit
Digoxin	Digoxin-specific antibody fragments
Iron	Desferrioxamine, a chelating agent
Lead	Dimercaprol, calcium edetate
Carbon monoxide	Management • 100% oxygen • hyperbaric oxygen
Cyanide	Hydroxocobalamin; also combination of amyl nitrite, sodium nitrite, and sodium thiosulfate
Sarin (organophosphorus)	**Pralidoxime** ➔ reactivates acetyl cholinesterase enzyme. It should be used in the first few hours.

Drug poisoning: Hypersalivation

Hypersalivation is seen with:

- Parasympathomimetic agents
- Insecticides
- Arsenic
- Strychnine
- Chlormethiazole, and
- Clozapine.

Other poisoning signs

Acneiform rash around the buccal cavity ➔ Solvent abuse

Nasal septum perforation (and hypertension) ➔ Cocaine abuse

Drug poisoning: Altered serum glucose in unknown overdose

Alteration in serum glucose concentration, in addition to other clinical signs and symptoms, can be helpful in diagnosing the ingestion of an unknown drug:

Drugs induce hyperglycaemia	Drug induce hypoglycaemia
• Corticosteroids, • thiazide diuretics, • theophylline, • **iron** (during the **initial** period after overdose), • caffeine and • B2-agonists	• insulin, sulphonylureas, • **Salicylates** • sodium valproate, • **propranolol,** • iron (later if hepatic failure ensues)

Drugs cleared by alkalization of the urine

The clearance of which drug would be increased by alkalization of the urine?

- Weak acids are ionized in an alkaline environment, and this lessens their tubular absorption.
- Alkalization of urine, achieved by IV infusion of sodium bicarbonate, can thereby be used to increase the urinary elimination of:
    1. barbiturates,
    2. salicylates and
    3. **isoniazid.**

Ref → www.medical-masterclass.com 2017 part 2

Measurement of drug concentrations

- Measurement of drug concentrations is clinically important for relatively few compounds.
- Drug concentrations are particularly important for those compounds where the concentration is predictive of serious toxicity in an otherwise asymptomatic patient.

Compounds where measurement of drug concentration is clinically indicated:

- **Paracetamol**
- **Theophylline**
    - Theophylline concentrations predict the risk of seizures and cardiac toxicity in both acute and chronic toxicity
    - Patients who have ingested more than 10 mg kg^{-1} of theophylline should receive repeated doses of activated charcoal.
- **Digoxin**
- **Iron**
- **Lithium**
- **Salicylate**
- **Ethylene glycol**
    - An ethylene glycol concentration of >50 mg dl^{-1} is a possible indication for haemodialysis and a definite indication for 4-methylpyrazole (4MP) or ethanol infusion
- **Methanol**
    - A methanol level of greater than 50 mg dl−1 is a possible indication for haemodialysis and a definite indication for 4MP or ethanol infusion.
        - haemodialysis usually considered at methanol concentrations **above 20 mmol/l** (approximately 90 mg/dl).
- **Ethanol**
- **Anticonvulsants**
    - Measurement of anticonvulsant concentrations will confirm ingestion but do not substantially influence treatment in overdose, which is supportive care.
- **Paraquat**
    - non-selective contact herbicide
    - paraquat concentrations are useful for confirming ingestion and defining prognosis but do not influence treatment, which is predominantly supportive care

Drug toxicity in renal failure

- A wide range of drug-handling processes occur in the kidney:
  - Filtration
  - tubular secretion
  - active and passive tubular reabsorption
- The overall renal clearance of drugs declines in parallel with falls in the glomerular filtration rate and creatinine clearance

Norpethidine

- In patients with renal impairment pethidine is metabolised to norpethidine, but at this stage metabolism stops and **norpethidine accumulates** rather than being excreted through the kidneys
- **Norpethidine is toxic and is associated with a risk of seizures**

Morphine

- A similar accumulation of morphine 6-glucuronide occurs after morphine administration in patients with renal impairment, **which may lead to narcosis**
- **fluid overloaded + pin point pupils in a patient taking morphine with renal impairment → the most likely cause of his symptoms → Renal failure leading to accumulation of morphine** (not overdose) (masterclass 2017 part 2)
  - Patients with relapsed ovarian cancer may develop an obstructive nephropathy due to pelvic recurrence. If they are on morphine they may get accumulation of this drug and signs of opiate toxicity superimposed on the signs of renal failure.

Other drugs

- Other drugs where physiologically active metabolites accumulate leading to toxicity in renal failure include:
  - nitroprusside (active metabolite thiocyanate)
  - allopurinol (accumulation of oxypurinol leads to rash and allergy)

Characteristic smells of toxins/poisons

Certain toxins/poisons have characteristic smells that can assist in the identification of substances taken. Below is a list of well-recognised smells/odours and the poisons/toxins for which they are characteristic.

- Garlic: Arsenic, selenium
- Bitter almonds: Cyanide
- **Rotten eggs: Hydrogen sulphide, mercaptans**
- Wintergreen: Methyl salicylate
- Mothballs: Naphthalene

Arsenic toxicity

The combination of mixed sensorimotor polyneuropathy in the presence of possible exposure to pesticides in a farmer would suggest a diagnosis of chronic arsenic poisoning.

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- Arsenic is a heavy metal which is a natural component of the earth's crust.
- exists in organic or inorganic . It is highly toxic in its inorganic form.
  - organic arsenics found in fish and seafood are non-toxic
- Arsenic exposure is usually occupational or environmental
- **routes of exposure include:**
  - Groundwater most often becomes contaminated naturally
    - Arsenic contamination of groundwater is widespread
    - most common in Bangladesh, West Bengal and india
  - **Occupational exposures:** toxic waste sites and traditional medicines.
- Features
  - Acute
    - GI (nausea, vomiting, hemorragic gastroenteritis, garlic breath)
    - CNS (coma, seizures)
  - Chronic
    - Skin changes: dermatitis, hyperkeratosis & hyperpigmentation
      - **The first symptoms of long-term exposure**
      - **the most common effect of chronic exposure**
      - Keratoses on the palms and soles are characteristic.
      - occur after a minimum exposure of approximately five years
      - may be a precursor to skin cancer.
    - **Mees lines: leukonychia striata (transverse white lines on the finger nails)**
    - Abdominal pain
    - Sensory-motor **Peripheral neuropathy**
    - Diabetes

        - Cancers (lung, bladder, skin).
- Arsenic can interfere with the mechanism of hemoglobin synthesis and the ribosomes may **form dot-like precipitates, called basophilic stippling**, **at the periphery of RBCs.**
- Basophilic stippling is also found in:
    - thrombotic thrombocytopenic purpura, in hemoglobin H disease (rarely)
    - megaloblastic anemia.
        - It indicates a RBC cell line maturation defect in the bone marrow.
- The hematological effects of arsenic toxicity include:
    - Anemia
    - Pancytopenia
    - Hemolysis in some cases
- Management
    - Acute exposure → Chelation:
        - Consider chelation therapy in patients who are symptomatic and/or have urine concentration >200 mcg/L.
            - DMPS is the chelation agent of choice.
            - DMSA is an alternative (oral preparation only, so unsuitable if the patient is vomiting).
    - Chronic exposure
        - arsenic-free drinking water, to reduce the risk of further disease
        - It is recommended that all patients with skin lesions be given multivitamins.

Drugs altered pupil size

Many drugs can cause changes in pupil size as detailed below:

- **Dilated pupils (mydriasis):**
    - sympathomimetic drugs, eg cocaine, dopamine, amphetamines
    - anticholinergic drugs, eg antihistamines, atropine, tricyclic antidepressants
- **Constricted pupils (miosis):**
    - sympatholytic drugs, eg opiates, phenothiazines, clonidine, sodium valproate
    - cholinergic drugs, eg organophosphates, pilocarpine

Charcoal

- reduce drug absorption from the gastrointestinal tract, and interrupting enterohepatic recirculation.
- **Which factor would be most strongly influence your decision to administer or avoid oral activated charcoal?**
    - **Absence of bowel sounds**
        - It is generally safe, but should be administered only in patients who are able to protect their airway. The absence of bowel sounds may indicate a paralytic ileus, which is surprisingly common after overdose, and which is associated with an increased risk of charcoal aspiration and pneumonitis.
- Iron, lithium and other cations are not adsorbed by charcoal; alcohols including ethanol, methanol and ethylene glycol are not adsorbed either.
- Activated charcoal is capable of adsorbing around 10% of its own weight, so administration of charcoal 50 g might be expected to adsorb around 5 g of drug.
- should normally be administered within 1 hour of drug overdose, but may be effective when administered after a longer interval, particularly after modified-release preparations.

Multi-dose activated charcoal

When Activated charcoal can be repeatedly given to increase elimination of the poison?

⇨ **When the drug circulates through the enterohepatic circulation**

- Multi-dose activated charcoal means giving 50 g of activated charcoal every 3-4 h
- It is useful in patients who have taken significant amounts of salicylates, and should be continued until plasma salicylate concentrations have peaked
- It is also useful in the management of patients who have taken drugs with significant enterohepatic circulation (carbamazepine, phenobarbital, theophylline and quinine) and sustained-/modified-release preparations
- It is contraindicated in patients with signs of bowel obstruction,

Methanol poisoning

- Methanol, like ethanol, is **metabolised by alcohol dehydrogenase to form formaldehyde**.
  Formaldehyde is then further metabolised by **aldehyde dehydrogenase** to **formic acid**.
- Formate formation leads to:
  - severe **metabolic acidosis**, and
  - crystals forming within the eye can lead to so called **'snow field' cataract formation**.

Feature

- **Early signs** (are due to methanol) include:
  - Nausea and vomiting
  - Headache,
  - Confusion.
- **later signs** (are due to its metabolite, formic acid)
  - high gap metabolic acidosis
    - Anion gap = (Na + K) - (Cl + HCO_3); normal range 7-17 mmol/L.
    - Although elevated, the lactate level does not account for the anion gap.
  - visual problems, retinal injury, including blindness (methanol-associated visual loss)
    - accumulation of formic acid → a form of optic neuropathy

Differential diagnosis

- The differential diagnosis of this form of a **high anion gap metabolic acidosis** is (**SLUMPED**) (**s**alicylates, **l**actic acidosis, **u**remia, **m**ethanol/ethylene glycol, **p**araldehyde, **e**thanol, and **d**iabetic ketoacidosis).

Similarities between Methanol and ethylene glycol intoxication

- Both are causes a very similar biochemical and clinical picture.
- Both require the enzyme alcohol dehydrogenase for metabolism.
- Both are treated with fomepizole or ethanol, which inhibit alcohol dehydrogenase
- Both can present with metabolic acidosis, hyperpnea and tachypnea, coma, seizures, and hypotension.
- The fruity smell suggests ketosis.

Differences between Methanol and ethylene glycol intoxication

- From history
  - Methanol is pure distilled alcohol, more likely to be consumed by those with a history of alcohol abuse.
  - Ethylene glycol is antifreeze, usually consumed by those with suicidal intent or history of deliberate self-harm.
- From examination
  - **eye signs (macular oedema and poor pupillary responses) → methanol**
    - In exams, cases involving methanol toxicity often involve patients not meeting your gaze or asking for the lights to be switched on, as well as the more traditional visual acuity results.
    - Methanol leads to the formation of **formate**, which causes retinal damage with optic disc hypemia and edema, blindness, and basal ganglia infarcts.
  - Ethylene glycol causes the formation of calcium oxalate crystals, leading to renal failure and **hypocalcemia** (→ tetany)
    - **Oxalate crystals** are a specific sign of ethylene glycol toxicity.

- **formate is the toxic metabolite of methanol**
- **oxalic acid is the toxic metabolite of ethylene glycol**

Management

- fomepizole or ethanol → Inhibition of methanol metabolism by alcohol dehydrogenase **is the treatment of choice.**
  - 1st line → fomepizole which is an inhibitor of alcohol dehydrogenase.
  - 2nd line → If fomepizole is not available, then ethanol is recommended.
- sodium bicarbonate if necessary to correct severe acidaemia (pH <7.20)
- Haemodialysis

Treatment is aimed at:
1. Eliminating formic acid (alkaline diuresis or **haemodialysis**).
2. Correcting acidosis with IV bicarbonate.
3. Preventing metabolism of methanol to formic acid by administering IV ethanol.

Ethylene glycol toxicity

Ethylene glycol toxicity management - fomepizole. Also ethanol / haemodialysis

- Ethylene glycol is a type of alcohol used as a coolant or antifreeze

Features of toxicity are divided into 3 stages:
- Stage 1: symptoms similar to alcohol intoxication: confusion, slurred speech, dizziness
- Stage 2: metabolic acidosis with high anion gap and high osmolar gap. Also tachycardia, hypertension
- Stage 3: acute renal failure
  - renal, respiratory and cardiac failure.
  - Multi-organ failure is thought to occur at least in part **due to widespread deposition of calcium oxalate crystals** around 12 h after the initial insult.

Management
- treatment is often given based on clinical suspicion due to a delay in obtaining ethylene glycol levels in most centres.
- **fomepizole**, an inhibitor of alcohol dehydrogenase, is now used **first-line** in preference to ethanol
  - prevents metabolism of ethylene glycol to **oxalic acid**, responsible for the **acidosis and renal failure**
  - Because of the potential formation of calcium oxalate, **calcium levels should also be assessed**.
- **ethanol** has been used for many years
  - works by competing with ethylene glycol for the enzyme alcohol dehydrogenase
  - this limits the formation of toxic metabolites (e.g. **glycoaldehyde and glycolic acid**) which are responsible for the **haemodynamic/metabolic features** of poisoning
- **IV fluids with bicarbonate** to correct the **metabolic acidosis** in **severe lactic acidosis**.
- **Calcium gluconate for hypocalcemia,**
- **haemodialysis** also has a role in refractory cases

Fomepizole - used in ethylene glycol and methanol poisoning - competitive inhibitor of alcohol dehydrogenase

Isopropyl alcohol (Isopropanol) intoxication

- It is a clear colorless liquid with a BITTER TASTE and **fruity odor**.
- commonly used as a rubbing alcohol and as a solvent in hair-care products, skin lotions and home aerosols.
- Also found in products including cleaners, disinfectants, antifreezes, cosmetics, solvents, inks, and pharmaceuticals.
- Inexpensive and can be a substitute for ethanol.
- the second most common alcohol intoxication next to ethanol.
- It is twice as potent as ethanol as a central nervous system depressant but without an early elation phase.

Feature:
- Severe isopropanol poisoning results in CNS and respiratory depression and circulatory collapse.
- GIT and CNS symptoms are predominates,
- **alcohol**, benzodiazepines, **isopropyl alcohol**, lithium, and organophosphates may all lead to **miosis** (constriction of the pupil)
- Large ingestions can result in coma.

- The most common metabolic effects are an increased osmol (osmolal) gap, ketonemia, and ketonuria
- **metabolic acidosis - unlike in other alcohols intoxication - is not present**, this is because isopropyl alcohol is metabolized by alcohol dehydrogenase to acetone, (a ketone is not an acid).
  - ➢ therefore ketone appear in breath and in urine.
- Isopropyl alcohol intoxication can be remembered as **"ketosis without acidosis".**
- Another unique finding is **"pseudo renal failure" or ISOLATED false elevation of creatinine with a normal BUN.**

Diagnosis:

- An osmol gap, ketonemia, and/or ketonuria **without metabolic acidosis**, along with a fruity or sweet odor on the breath and CNS depression support the diagnosis.
- Although ethylene glycol, methanol, and ethanol ingestions result in anion gap **and** osmolar gap, **isopropyl alcohol results in only an osmolar gap.**
  - ➢ Osmolar gap = Osmola**lity** – Osmola**rity**
    - Osmola**lity** is **measured** in laboratory by osmometers
    - Osmola**rity** is **calculated** = (2 x [Na+]) + [glucose] + [urea]
    - normal = < 10
    - the units of osmola**lity** are mOsm/**kg** of solute
    - the units of osmola**rity** are mOsm/**L**

Treatment:

- supportive care (is the mainstay of management)→ Patients usually make a full recovery
- hemodialysis → elimination of isopropanol and acetone → only in severe life-threatening poisonings.

Acidosis + eye signs → methanol poisoning
Acidosis without eye signs → ethylene glycol poisoning
Ketosis without acidosis → isopropyl alcohol poisoning

Ecstasy poisoning

- Ecstasy is an amphetamine derivative (MDMA, 3,4-**M**ethylene-**D**ioxy-**M**eth-**A**mphetamine) use became popular in the 1990's during the emergence of dance music culture
- is a semi-synthetic hallucinogen used as a recreational drug.

Clinical features

- neurological: agitation, anxiety, confusion, ataxia
- cardiovascular: tachycardia, hypertension
- **hyponatraemia**
- Hyperventilation
- **hyperthermia**
- rhabdomyolysis

Management → supportive (no specific antidote)

- Cold intravenous fluids if the core temperature is over 39 °C
- dantrolene may be used for hyperthermia if simple measures fail
- and/or paralysis and ventilation
- Treatment of associated hyperthermia

Opioid misuse

Acute confusion and visual hallucinations are common symptoms of opioid toxicity and pin point pupils and myoclonas are common signs.

Opioids are substances which bind to opioid receptors. This includes both naturally occurring opiates such as morphine and synthetic opioids such as buprenorphine and methadone.

Features of opioid misuse

- rhinorrhoea
- needle track marks
- pinpoint pupils
- drowsiness
- watering eyes
- yawning

Complications of opioid misuse

- viral infection secondary to sharing needles: HIV, hepatitis B & C
- bacterial infection secondary to injection: infective endocarditis, septic arthritis, septicaemia, necrotising fasciitis
- venous thromboembolism
- overdose may lead to respiratory depression and death
- psychological problems: craving
- social problems: crime, prostitution, homelessness

Emergency management of opioid overdose

- IV or IM **naloxone**: has a rapid onset and relatively short duration of action
- intravenous naloxone (0.4 mg), repeated up to a total dose of 2 mg depending on clinical response.
- **The half-life of naloxone is shorter than that of opioids**, hence if the patient wakes up it can be anticipated that he will 're-narcose'. A naloxone infusion may be necessary.

Harm reduction interventions may include

- needle exchange
- offering testing for HIV, hepatitis B & C

Management of opioid dependence

- patients are usually managed by specialist drug dependence clinics although some GPs with a specialist interest offer similar services
- patients may be offered maintenance therapy or detoxification
- NICE recommend methadone or buprenorphine as the first-line treatment in opioid detoxification
- compliance is monitored using urinalysis
- detoxification should normally last up to 4 weeks in an inpatient/residential setting and up to 12 weeks in the community

Dihydrocodeine

- Dihydrocodeine is an opiate analgesic and when taken in overdose has a number of toxic effects.
- It acts as a respiratory depressant leading to reduced respiratory rate.
- **It can cause bradycardia and hypotension in large doses.**
- Pupillary constriction is a diagnostic feature in opiate overdose.
- It is also a central nervous system depressant and therefore causes coma in overdose.

Pain relief

- Titrating the dose of morphine needed for analgesia should be done with rapidly acting formulations of morphine, and once adequate analgesia is obtained sustained-release morphine can then be substituted (at the same total daily dose)

Analgesia in opiate users (eg: on methadone)

- Discontinuation of methadone may result in symptoms of acute opiate withdrawal and this is not recommended
- **Continuation of methadone and consideration of analgesics with a different mode of action (ie non-steroidals such as parenteral diclofenac) is recommended**

Opioid withdrawal

- The symptoms and signs of opioid withdrawal include dysphoric mood, yawning, insomnia, nausea, vomiting, diarrhoea, muscle aches, lacrimation / rhinorrhoea, pupillary dilatation, piloerection, sweating and fever.
- Initially give 10 mg of methadone syrup and wait about 60 min to determine its effect. Continue administering in 10 mg doses until symptoms are under control. It is rare to exceed a total dose of 40 mg over 24 hours.

Morphine

Side-effects including:

- Nausea, vomiting
  - Nausea affects up to two-thirds of patients starting morphine but in the majority of these it is self-limiting to within 1 week.
  - **Haloperidol is the first-line drug for opioid-induced nausea**, kidney disease and hypercalcaemia
- **constipation**
- drowsiness, confusion
- others, including: bronchospasm, angioedema, urinary retention, ureteric or biliary spasm, dry mouth, **sweating**, rash, facial flushing, vertigo, tachycardia, bradycardia, palpitations, orthostatic hypotension, hypothermia, restlessness, mood change, hallucinations, seizures (adults and children) and miosis,

headache and allergic reactions (including anaphylaxis) and decreased libido or potency
- raised intracranial pressure
- Muscle rigidity may occur with high doses
- biliary sphincter constriction → Elevated liver enzymes
- Large doses can lead to respiratory depression, circulatory failure and coma

Morphine vs pethidine

- **Morphine acts for four to five hours while pethidine works for two to three hours.**
  - This means that pethidine would have to be given at more frequent intervals to produce the same analgesic effects as morphine.

Pethidine

- Meperidine (Pethidine) is a full opioid agonist at mu receptors.
  - the only opioid that acts as an **antimuscarinic**
- **Pethidine is contraindicated in most cases of sickle cell pain**. It is metabolized into a cerebral irritant that can lead to clonus, seizures, or altered mental status.
- Pethidine is preferred to morphine in the **preoperative management** of biliary colic and in the management of acute diverticulitis.
  - Pethidine is comparable to morphine in its sedative and tranquillizing effects, **but the analgesia and respiratory depression it produces are of shorter duration**, and it **induces less smooth muscle spasm.**
- It is largely metabolized in the liver and the end-products are excreted in the urine.
- Contraindications
  - Bronchial asthma, emphysema or heart failure secondary to chronic lung disease.
  - Increased intracranial pressure, head injury or brain tumour.
  - Severe hepatic impairment, adrenocortical insufficiency, hypothyroidism.
  - Convulsive disorders, acute alcoholism, delirium tremens.
  - Use of monoamine oxidase inhibitors within the previous 14 days.

Buprenorphine

Action

- **partial** opiate agonist at mu and kappa opioid receptors.
  - meaning that by occupying the receptor, it **doesn't achieve the effects of full agonism**, and thus has **less addictive potential versus other opiates**.
  - Due to the fact that buprenorphine is a partial agonist, at higher doses it displays "functional antagonism", meaning that **by occupying the receptor it blunts the effects of other full opiate agonists.**
- It also has a long half-life of up to 32hrs.
  - This means that it can be utilised in cases of addiction to short-acting opiates such as diamorphine because it reduces the highs, and thus addictive potential, associated with these agents.

Interaction

- Since **buprenorphine** is a **partial agonist at opioid receptors**, **it will antagonise the action of a full agonist such as morphine**
- therefore it is appropriate to substitute morphine for buprenorphine, but not to add the two together

MRCPUK- part-1- jan- 2017: What is the mode of action of buprenorphine?
➔ **Partial mu opioid receptor agonist**

Cocaine

- Cocaine is an alkaloid derived from the coca plant.
- cocaine toxicity becoming a much more frequent clinical problem.

Mechanism of action

- cocaine blocks the uptake of dopamine, noradrenaline and serotonin

The use of cocaine is associated with a wide variety of adverse effects:

Cardiovascular effects

- myocardial infarction
  - cocaine-induced MI is thought to be related to coronary artery spasm
  - It is probably caused by stimulation of the α-adrenergic receptors in smooth muscle cells. In addition, cocaine increases endothelin-1 (a vasoconstrictor) and decreases nitric oxide

(vasodilator).

- both tachycardia and bradycardia may occur
- hypertension
  - (Blockage of noradrenaline (norepinephrine) re-uptake leads to →tachycardia, & ↑↑BP)
- QRS widening and QT prolongation
- aortic dissection

Neurological effects

- seizures
- mydriasis
- hypertonia
- hyperreflexia
- haemorrhagic stroke
- **cocaine-induced spinal cord infarct**:
  - **The constellation of quadriparesis, spinothalamic sensory loss with sparing of posterior columns and sphincter dysfunction is most suggestive of an anterior spinal cord syndrome.**
    - The areflexia may reflect spinal cord shock.
    - With a C3/4 spinal cord lesion, it is not surprising that the patient has respiratory difficulties.
    - detection of cocaine in the urine suggesting he was using it

Psychiatric effects

- agitation (inhibition of dopamine re-uptake → psychomotor agitation)
- psychosis
- hallucinations (serotonin re-uptake blockade leads to → hallucinations)

Others

- hyperthermia which may lead to rhabdomyolysis and renal failure
- **metabolic acidosis**
- rhabdomyolysis

Management of cocaine toxicity

- in general benzodiazipines are generally first-line for most cocaine related problems
  - **Agitation, seizures and hypertension are best treated with benzodiazepines (such as midazolam) initially.**
  - Diazepam is useful for the treatment of anxiety and may precipitate a small reduction in blood pressure, **but will not treat coronary artery vasospasm.**
  - Calcium channel blockers (such as nifedipine) can be used as a **second line treatment for hypertension** if benzodiazepines are ineffective.
- chest pain:
  - benzodiazipines + **glyceryl trinitrate**.
    - Other option include calcium antagonists,
  - If myocardial infarction develops then primary percutaneous coronary intervention
- hypertension:
  - benzodiazipines + sodium nitroprusside
- Beta blockers should be avoided in cocaine associated myocardial ischaemia or infarction as they can potentiate coronary vasoconstriction.
  - Beta blockers are contraindicated as they can cause unopposed alpha activity and worsen hypertension.
- **Intubation and ventilation** will lower blood pressure and improve the ischaemia
  - **the most appropriate next intervention if diazepam fail to control the acute symptoms (eg: seizure)**
    - Whilst IV sodium valproate and IV phenytoin may be effective in terminating the recurrent seizures, these options would cost precious time with respect to controlling blood pressure and pyrexia

January 2016 exam: A 23-year-old man found 'collapsed' in the bathroom at a house party. Then C/O severe abdominal pain + blood in his stool. What is the single most likely cause of his abdominal pain? Ischaemic colitis (Ischaemic colitis is a recognised phenomenon following cocaine ingestion and should be considered if patients develop abdominal pain or rectal bleeding)

Heroin withdrawal

- The following are all signs of heroin withdrawal:
  - rhinorrhoea
  - diarrhoea
  - nausea and vomiting
  - lacrimation
  - irritability and restlessness, which are cardinal features

Heroin substitutes in medical management of withdrawal

- Both buprenorphine and methadone may be considered for use as heroin replacements
- Buprenorphine may be associated with less risk in overdose, but NICE recommends that unless circumstances dictate otherwise, **methadone should be the first-choice therapy**
- Co-abuse of alcohol and benzodiazepines may drive preferential use of buprenorphine, as these agents increase the risk of significant CNS depression

Benzodiazepine overdose

- Benzodiazepine overdose is very rarely life-threatening unless associated with the co-ingestion of alcohol or other respiratory depressants
- **Clinical features**:
  - **CNS depression**: lethargy, somnolence, hyporeflexia
  - Respiratory depression
  - Mild hypotension
  - Ataxia
  - Slurred speech
- **Treatment**
  - **Supportive therapy**
    - GCS ≤ 8: endotracheal intubation
    - Hypotension: fluid resuscitation
  - **Antidote**: flumazenil
    - Indications
      - Severe respiratory depression
      - Overdose in benzodiazepine-naive patients (e.g., accidental ingestion in children, periprocedural oversedation with benzodiazepines)
    - **Routine use of flumazenil for benzodiazepine overdose is not recommended**
    - Most cases of benzodiazepine overdose occur in patients who are on chronic benzodiazepine therapy. Flumazenil can precipitate withdrawal symptoms and seizures in patients with benzodiazepine dependence.

Cathinone toxicity

- NRG-1 is a synthetic cathinone drug which is increasingly used recreationally.
- Pharmacologically it is a derivative of phenylpropanone which is a naturally occurring psychotrope in khat (*Catha edulis*).
- Synthetic cathinones became increasingly popular in the last ten years as an alternative to ecstasy since they were cheaper, easier to produce and initially were unrestricted. As legislation changes, chemical substitutions are made to molecular moieties to create similar drugs to avoid restrictions.
- All exert their effect by increasing synaptic concentrations of noradrenaline, dopamine and serotonin, giving users the sensation of euphoria, detachment and wellbeing as well as upregulation of the sympathetic system.
- Toxicity is often seen due to lack of regulation of constituents and active ingredients

Features

- Tachycardia and hypertension may be seen due to the sympathomimetic effects of the drug and in some cases myocardial ischaemia can be seen.
- In the majority of cases of toxicity, however, similar to ecstasy toxicity, **hyponatraemia** and **serotonin syndrome** are seen. Hyponatraemia occurs as a consequence of significant water intake to reduce body temperature. Serum sodium levels may be markedly low and patients may present seizing.
- **Serotonin syndrome** is due to massive flooding of synapses with liberated serotonin and causes agitation, confusion, muscle hyperactivity with fasciculations, hypertonia and clonus.
- Creatine kinase and white cell counts are often raised and body temperature may be extremely high.

Treatment

- If there is evidence of neurological compromise with an accompanying hyponatraemia, rapid correction

of sodium is recommended with infusion of 3% saline solution at a maximum rate of 1ml/kg/hour.
- 0.9% saline solution is not recommended in patients with hyponatraemia and agitation due to the risk of worsening the hyponatraemia.

Cannabinoids

- Cannabinoids are derived from the resin of cannabis sativa,
- 9-tetrahydrocannabinol (9-THC) is its most important pharmacologically active constituent.
- Oral bioavailability of THC, whether given in the pure form or as THC in marijuana, is low and extremely variable, ranging between 5% and 20%, with effects occurring 0.5-3 hours later.
- Bioavailability of THC in a marijuana cigarette or pipe also rarely exceeds 10-20%.
- Naloxone and other opioid receptor antagonists block the analgesic actions of cannabinoids.
- Synthetic cannabinoids reduce arachidonic acid-induced inflammation by inhibiting eicosanoid production.

Cyanide poisoning

cyanide mechanism of action → Inhibition of enzyme cytochrome oxidase c

- Cyanide may be used in:
  - insecticides,
  - photograph development and
  - production of certain metals.
- **Acute cyanide toxicity may occur secondary to burning plastics in the house fire.**
- Toxicity results from reversible inhibition of cellular oxidising enzymes
- **Cyanide ions inhibit mitochondrial cytochrome oxidase**, preventing aerobic respiration, which is an essential part of the mitochondrial electron transfer chain (ETC). It therefore interferes with the basic process of cellular respiration, preventing the formation of ATP and causing rapid cell death.

Presentation (classical features: brick-red skin, smell of bitter almonds)

- manifests in normal oxygen saturations, a high pO2 and flushing (or 'brick red' skin) brought on by the excess oxygenation of venous blood. (it is important to note that the blood gas sample given is venous rather than arterial)
- acute: hypoxia, hypotension, headache, confusion
  - increased anion gap, consistent with high lactate (generated by anaerobic respiration due to the inability to use available oxygen).
  - very high lactate and high venous pO2 fit better with cyanide toxicity.
- chronic: ataxia, peripheral neuropathy, dermatitis

Management

- supportive measures: 100% oxygen
- definitive: **hydroxocobalamin** (intravenously), also combination of **amyl nitrite** (inhaled), sodium nitrite (intravenously), and sodium thiosulfate (intravenously)
- The recommended treatment for moderate cyanide toxicity in the UK is one of three options:
  1. Hydroxocobalamin,
     - has the best side-effect profile and speed of onset compared with other treatments
  2. dicobalt edetate,
     - only given when the patient is tending to lose or has lost consciousness.
       - When the patient is fully conscious, it is unlikely that the extent of poisoning warrants the use of Dicobalt Edetate Injection.
     - Dangerous if given without confirmed cyanide poisoning
     - Other antidotes such as hydroxocobalamin or sodium thiosulphate are preferred.
  3. sodium thiosulfate

Hydroxocobalamin

- also known as **vitamin B12a** and hydroxycobalamin,
- is an injectable form of vitamin B 12
- indications
  - vitamin B 12 deficiency
  - cyanide poisoning,
  - Leber's optic atrophy,
  - toxic amblyopia (Nutritional optic neuropathy)
    - a condition where a **toxic** reaction in the optic nerve results in visual loss.
    - Various poisonous substances may cause the condition as well as nutritional factors.
    - Tobacco **amblyopia** is a form of **toxic amblyopia** caused by tobacco containing cyanide.

Sarin gas

- **Sarin gas** and related agents cause inhibition of the enzyme acetylcholinesterase, causing levels of acetylcholine to build up in the nervous system causing prolonged sustained contraction of the diaphragm. This hinders and eventually paralyses normal breathing.
- Sarin has muscarinic and nicotinic effects.
  - Muscarinic effects:
    - Paralysis
    - Fasciculations
    - Hyperglycaemia, and
    - Ketosis.
  - Nicotinic effects:
    - Hypotension
    - Meiosis
    - Dyspnoea, and
    - GI disturbance.

Arsenic

- **Arsenic** causes inhibition of the enzyme pyruvate dehydrogenase which is necessary for the conversion of pyruvate to acetyl CoA. This also interferes with the basic process of cellular respiration, as pyruvate formed during glycolysis cannot be changed to acetyl CoA to enter the Kreb's cycle.
- Arsenic and mustards → cause mutational damage to DNA → ↑ risks of skin and haematological malignancy in the longer term.
- Arsenic can also accelerate atherosclerosis.

Acid poisoning

Pathology

- Acids cause injury by coagulative necrosis

Presentation

- Acid effects are mainly topical, with corrosive burns to the mouth, oropharynx and stomach
- They are less likely than alkalis to cause significant localised damage to the oesophagus
- Aspiration can lead to inflammation and a chemical pneumonitis

Management

- Neutralisation of acids is not appropriate, since this can generate increased heat and so exacerbate any injury sustained
- Gastric lavage is contraindicated due to the increased risk of oesophageal perforation
- Management consists of **supportive** care and **early endoscopy**
- Early surgical intervention is required to prevent mediastinitis, from which there is a high mortality, in those patients with signs or symptoms of perforation
- **Hydrofluoric acid** causes significant hypocalcaemia as it binds calcium,
  - even small amounts (topically or ingested) can produce significant hypocalcaemia and be rapidly fatal
  - in cases of significant topical exposure, patients should be monitored for signs of systemic hypocalcaemia
  - patient treated with intravenous calcium supplementation if required .
  - Calcium gluconate applied both topically and injected around the burn may be required
  - **Systemic fluorosis may occur as a complication**

Alkali poisoning

- Alkalis cause saponification (liquefactive necrosis) of tissue
- Neutralisation of alkalis is not appropriate, as this can generate increased heat and so exacerbate any injury sustained
- Assuming survival, fluorosis may lead to further problems later on

Radiosensitiser drugs

Radiosensitiser drugs → radiation toxicity

• **dactinomycin,** • metronidazole • 5-fluorouracil • gemcitabine • cisplatin	• hydroxyurea • paclitaxel • mitomycin C • topotecan

Radioprotector

- Amifostine is a radioprotector

Management of body packers

- The management of body packers and body stuffers is relatively straightforward
- Abdominal radiographs may show **some** packages in the gastrointestinal tract - they appear as air halos trapped within the packages, **but not all packages** may contain trapped air
- In patients with no signs of drug-associated toxicity, whole-bowel irrigation with polyethylene glycol will clear the gastrointestinal tract of all the swallowed packages
- Endoscopy may also be useful in removing packages that are still in the stomach, but packages should be carefully removed to prevent damage and drug release
- Gastric lavage may increase the risk of package rupture
- Laxatives may also help the packages to pass naturally, but paraffin-based laxatives should not be used since they increase the risk of package rupture
- Surgical intervention to remove all the remaining packages may be necessary in patients who start to develop signs of drug toxicity, since the strength and amount of drug in each package is unknown

Heavy metal poisoning

Causes

- **lead: most common**
- mercury
- manganese
- cadmium
- thallium

Lead poisoning

- Along with acute intermittent porphyria, lead poisoning should be considered in questions giving a combination of abdominal pain and neurological signs
- Lead can also be absorbed through the skin and by inhalation.

Aetiology: ingestion of:

- lead-containing compounds, deliberate (pica) or inadvertent
  - ➢ Patients with learning disabilities may be prone to lead poisoning due to pica.
- contaminated water from old lead water pipes
- occupation, such as a painter have a lead exposure while stripping the walls in old houses.
- certain traditional remedies such as ayurvedic medicines

Features

- abdominal pain
- nausea
- constipation
- peripheral neuropathy (mainly motor) due to demyelination

- fatigue
- blue lines on gum margin (only 20% of adult patients, very rare in children)
- may be associated with **anterior** uveitis or iritis

Laboratory tests

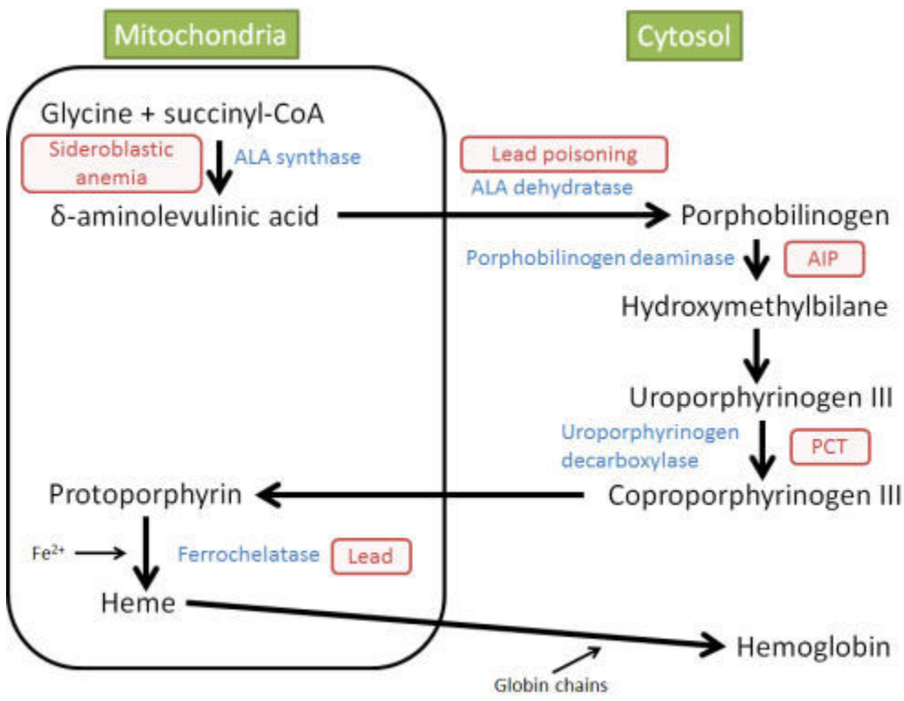
- Whole blood lead levels:
  - <10 µg/dL - normal.
  - >10 µg/dL - may cause impaired cognitive development in children.
  - >45 µg/dL - GI symptoms in adults and children.
  - >70 µg/dL - high risk of acute CNS symptoms.
  - >100 µg/dL - may be life-threatening.

Investigations

- Abdominal radiographs are essential to see if there is any unabsorbed lead present, which can be removed by whole-bowel irrigation
- The blood lead level is usually used for diagnosis. **Levels greater than 10 mcg/dl are considered significant**
- full blood count:
  - microcytic anaemia.
  - Blood film shows red cell abnormalities including:
    - **basophilic stippling** and
      - This occurs due to accumulation of (RNA) in the RBCs due to inhibition of pyrimidine 5 nucleotidase by lead.
    - clover-leaf morphology
- raised serum and urine levels of delta aminolaevulinic acid may be seen making it sometimes difficult to differentiate from acute intermittent porphyria
- urinary coproporphyrin is also increased (urinary porphobilinogen and uroporphyrin levels are normal to slightly increased)

Management - various chelating agents are currently used:

- dimercaptosuccinic acid (DMSA)
  - **the most appropriate intervention**
  - The recommended dose is 10 mg/kg three times per day for five days, followed by 10 mg/kg twice per day for two weeks.
- EDTA
  - This is used IV or IM, which makes administration less convenient than DMSA.
  - It is considered for patients with symptoms of severe acute lead poisoning.
- dimercaprol



- containing foods

Mercury poisoning

Features

- paraesthesia
- visual field defects
- ataxia
- dysarthria
- hearing loss
- irritability
- renal tubular acidosis
- Chronic poisoning from the inhalation of mercury vapour results in a classic **triad** of tremor, neuropsychiatric disturbance and gingivostomatitis

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Cadmium (Cd) poisoning

- **Workers in zinc factories are at risk of cadmium (Cd) poisoning.**

Feature

- Bone pain, osteopenia
- Renal failure.
  - The Cd-protein complex is mainly taken up by proximal tubular cells. This may give rise to a tubular **proteinuria**
  - may also cause a Fanconi syndrome-like presentation, with **amino aciduria** and **phosphaturia**.
  - Prolonged renal tubular toxicity may cause glomerular damage.
  - Another renal effect of prolonged Cd exposure is **calcium phosphate stones**.

Thallium poisoning

Features

- painful polyneuropathy
- mood change
- alopecia

Treatment is chelation therapy with oral Prussian Blue.

Iron overdose

- Undissolved iron tablets are radio-opaque

Presentation

- Early features of iron overdose are due to the direct corrosive effects of iron and include vomiting, diarrhoea and gastrointestinal bleeding
- Typically, there is then a latent phase of up to 24 h when the patient is asymptomatic
- This is then followed by widespread organ failure
- **Initial hyperglycaemia can occur following significant ingestion of iron**, but hypoglycaemia can be seen later in cases of severe poisoning with associated hepatic failure
- In patients who recover, there may be long-term GI strictures and possible gastrointestinal obstruction due to the initial corrosive effects of iron

Treatment

- Iron is a metal and therefore will not be adsorbed by activated charcoal
- Patients with serum iron concentrations over 90 mmol/l, as well as those with signs of severe toxicity, require chelation therapy with desferrioxamine

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LSD intoxication

Lysergic acid diethylamide (LSD)

- No medicinal use.
- Recreationally used as a hallucinogen and for its ability to alter human perception and mood.

Pharmacodynamics:

- LSD is primarily a non-selective 5-HT agonist.
- LSD may exert its hallucinogenic effect by interacting with 5-HT2A receptors as a partial agonist and modulating the NMDA receptor-mediated sensory, perceptual, affective and cognitive processes.
- LSD mimics 5-HT at 5-HT1A receptors, producing a marked slowing of the firing rate of serotonergic neurons.

Features

- hallucinations
- heightened sense of awareness
- synaesthesia
- palinopsia

New recreational drugs

Drug types	Street names
Gamma-hydroxybutyric acid (GHB) and gamma-butyrolactone (GBL)	G, Geebs or Liquid Ecstasy
Synthetic agonists of the CB1 receptor	Spice
Methoxetamine (derivative of ketamine)	Mexxy
Benzylpiperazine	Exodus, Legal X, Legal E
Nitrous oxide	Hippie crack

Paracetamol overdose

- it is the most common agent of intentional self-harm
- it is the most common cause of acute liver failure
- As little as 10–15 g (20–30 tablets) in an adult or 150 mg/kg of paracetamol taken within 24 h may cause severe hepatocellular necrosis and, less frequently, renal tubular necrosis.

Pathophysiology

➔Paracetamol is conjugated to glucuronic acid and sulphate under normal conditions.
➔In overdose these processes become saturated and the drug is then results in a toxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI)
➔(NAPQI) inactivated by glutathione, rapidly preventing any harm.
➔If the glutathione supply is depleted then a toxic metabolite is formed.

After ingestion of a therapeutic dose:

- The liver normally conjugates paracetamol with glucuronic acid/sulphate.
- and the resulting non-toxic metabolites are excreted in the urine.
- About 4% of a therapeutic dose is metabolised by the cytochromes P450, mainly CYP2E1, to a potentially toxic intermediate metabolite N-acetyl-p-benzoquinone imine (NAPQI).
- NAPQI combines with intracellular glutathione to become a non-toxic mercapturate derivative with urinary excretion.

after ingestion of an overdose:

- the conjugation system becomes saturated leading to oxidation by P450 mixed function oxidases*.
- the normally minor CYP2E1 pathway becomes important.
- This produces a toxic metabolite (N-acetyl-B-benzoquinone imine)
  - *this explains why there is a lower threshold for treating patients who take P450 inducing medications e.g. phenytoin or rifampicin
- Normally glutathione acts as a defence mechanism by conjugating with the toxin forming the non-toxic mercapturic acid.
- If glutathione stores run-out, the toxin leads to cell death of hepatocytes and renal tubules

Paracetamol overdose: risk factors

The following groups of patients are at an increased **risk of developing hepatotoxicity** following a paracetamol overdose:

- patients taking liver enzyme-inducing drugs (rifampicin, phenytoin, carbamazepine, chronic alcohol excess, St John's Wort)
- malnourished patients (e.g. anorexia or bulimia, cystic fibrosis, hepatitis C, alcoholism, HIV

⇨ ↓ glutathione stores

- patients who have not eaten for a few days
- Human immunodeficiency virus (HIV) positive patients.

Investigations

- Paracetamol level: take paracetamol level
    1. **four hours post-ingestion**, or
    2. as soon as the patient arrives if:
        - Time of overdose is greater than four hours.
        - Staggered overdose (in staggered overdoses, the level is not interpretable except to confirm ingestion).

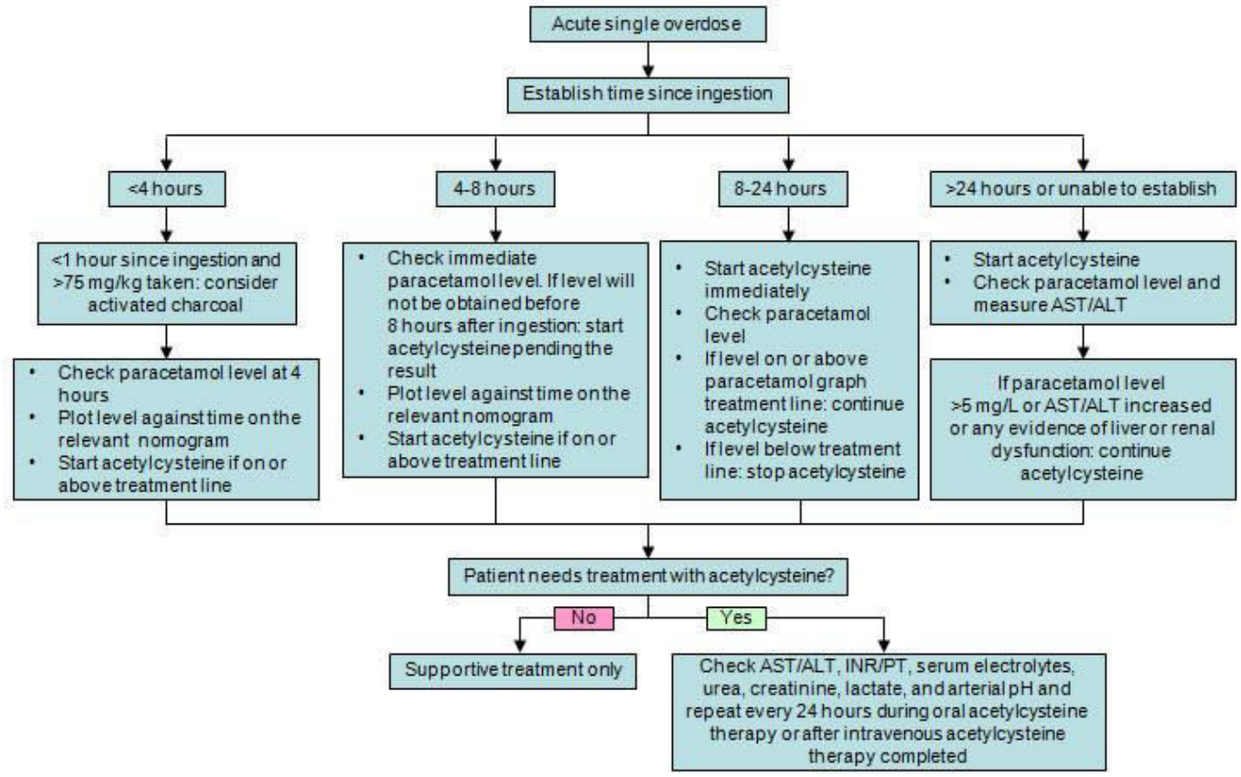
Management

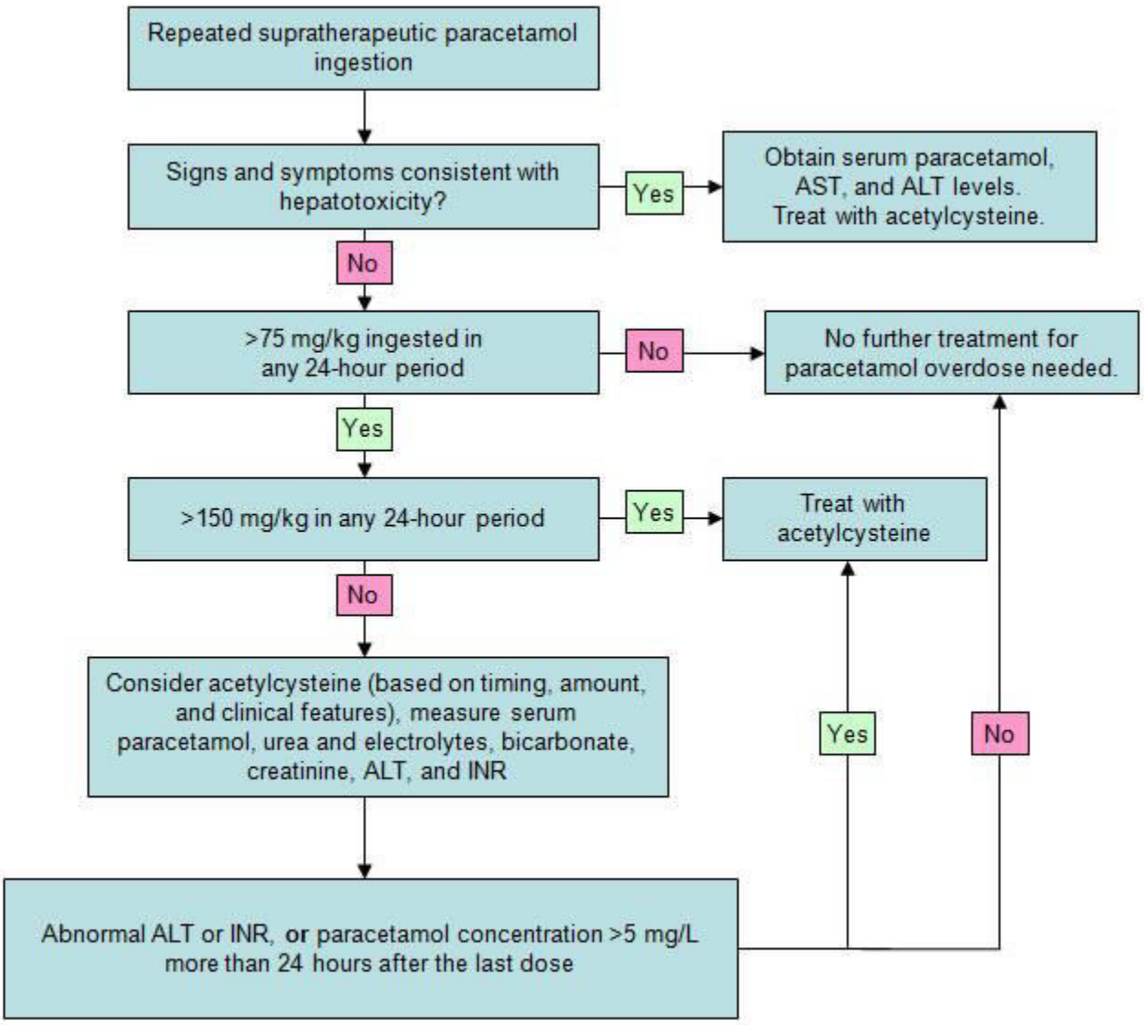
The essentials of management are:

1. Check paracetamol level four hours after ingestion, check levels against the Rumack-Matthew nomogram.
2. Gastric lavage if large dose ingested (more than 7.5 g) and/or presenting within eight hours of ingestion; consider oral charcoal.
3. Give N-acetylcysteine or methionine.
4. Hourly BMs monitored.
5. Check INR 12 hourly.

if patient present with ingestion of non-significant amount (<150mg/kg) and timing of ingestion is known (1- 4 hrs) → **No immediate action**

- A single dose of activated charcoal (50g for adults) can be given **up to 1 hour after ingestion**
- Acetylcysteine should be **started immediately** or empirically when:
    - if a significant amount has been taken (>150mg/kg).
    - Serum paracetamol level: 100 mg/L at 4 hours and 15 mg/L at 15 hours after ingestion
    - patients who present late (8-24 hours)
    - Serum paracetamol level is not available within an 8-hour time window
    - If there is any doubt about the timing of the ingestion (including a staggered overdose over one hour or more).
    - Patients are unconscious or have a suspected overdose.
- Hepatotoxicity is unlikely if it is >24 hours since last ingestion of paracetamol and all the following apply:
    1. Patient is asymptomatic.
    2. Paracetamol concentration is <5 mg/L.
    3. INR is 1.3 or less.
    4. ALT is less than 2 times upper limit of normal.
    - If all of the above criteria are fulfilled then acetylcysteine may be stopped, and the patient discharged with the advice to return if he or she becomes symptomatic (vomiting, abdominal pain).
- **Repeated supratherapeutic ingestion**
    - Patients who have ingested <75 mg/kg in a period of 24 hours are very unlikely to develop hepatotoxicity.
    - Those who have ingested 75 mg or less/kg/24 hours of paracetamol require no treatment.
    - Those who have ingested 75-150 mg/kg/24 hours should be considered for acetylcysteine (based on amount ingested, timing, and other relevant features)
    - Those who have ingested >150 mg/kg/24 hours are treated with acetylcysteine.





Prescribing N-acetyl cysteine (NAC)

- Acetylcysteine is the treatment of choice and is given intravenously (in the US and some other places it

is still occasionally given orally).

- Although the oral route is simpler, it frequently causes nausea and vomiting and is unpleasant. Additionally, the standard oral regimen is 72 hours in duration compared with 21 hours intravenously,
- N-acetyl cysteine is used in the management of paracetamol overdose as it is a precursor of glutathione and hence can increase hepatic glutathione production
- Acetylcysteine should be administered by intravenous infusion **preferably using Glucose 5%** as the infusion fluid. Sodium Chloride 0.9% solution may be used if Glucose 5% is not suitable.
- The full course of treatment with acetylcysteine comprises of 3 consecutive intravenous infusions.
- The new guidelines have increased the recommended **duration of the first infusion to 60** minutes from 15 minutes previously.
- The patient should receive a **total dose of 300 mg/kg body weight over a 21 hour period.**
  - First infusion
    - Add the appropriate volume of acetylcysteine injection to **200 mL of infusion fluid** and infuse **over 1 hour.**
  - Second infusion
    - Add the appropriate volume of acetylcysteine injection to **500 mL of infusion** fluid and infuse **over the next 4 hours**.
  - Third infusion
    - Add the appropriate volume of acetylcysteine injection to **1 litre** of infusion fluid and infuse over the next 16 hours.
- **N-acety lcysteine is most effective when administered within 8 h of ingestion**
  - If acetylcysteine is started within 8 hours of the ingestion, hepatotoxicity is extremely unlikely.
- N-Acetylcysteine is recommended in all cases where the paracetamol overdose exceeds 150 mg/kg body weight
- All patients with a plasma paracetamol level ≥ 100 mg/L at 4 hours or ≥ 15 mg/L at 15 hours after ingestion should receive acetylcysteine regardless of risk factors for hepatotoxicity.
- The paracetamol level is not used to guide treatment in the setting of a **staggered overdose,** and N-acetylcysteine should be given without delay to reduce the risk of liver failure.
  - **In the case of staggered overdose or unclear timing of overdose, acetylcysteine should be given.**
- The urgency of treatment is underlined by the fact that the **incidence of hepatotoxicity is worse if treatment is delayed.**
  - Trials of N-acetylcysteine suggest that the incidence of hepatotoxicity is 1% in those treated within eight hours as opposed to 46% in those treated after 16 hours.

Reactions to NAC (eg: patient became flushed and hypotensive)**:**

- Reactions to NAC are well recognized and are not related to hypersensitivity.
- The majority of dose-related adverse reactions occur within the first hour of the initial infusion of acetylcysteine.
- The MHRA **now recommends extending the time of the initial infusion from 15 minutes to 60 minutes** in order to reduce the incidence of adverse reactions.
- **Even if a patient has a history of a previous reaction to intravenous acetylcisteine, the benefits outweigh the risks and patient should receive treatment**.
- Any 'hypersensitivity-like' reactions are more likely to be anaphylactoid in nature (i.e. not immunologically mediated) and therefore may not occur on repeated exposure.
- **Management: IV chlorpheniramine and restart NAC infusion once symptoms resolved**
- NAC can almost always be safely restarted and total dose safely administered after symptomatic treatment.
- Oral methionine may be an alternative but is definitely second line.

Paracetamol overdose during pregnancy

- resulting toxic metabolites can cross the placenta and lead to hepatocellular necrosis of maternal and fetal liver cells.
- NAC can bind the toxic metabolites in the mother and fetal circulation as it crosses the placenta.
- NAC appears to be safe during pregnancy and therefore should be administered.

King's College Hospital criteria for liver transplantation in paracetamol-induced acute liver failure
List for transplantation if:

- Arterial pH <7.3 or arterial lactate >3.0 mmol/L after adequate fluid resuscitation; **OR**
- If all three of the following occur in a 24-hour period:
  - Creatinine >300 µmol/L.
  - PT >100 seconds (INR >6.5).
  - Grade III/IV encephalopathy.

Strongly consider transplantation if:

- Arterial lactate >3.5 mmol/L after early fluid resuscitation.

The criteria for transfer to a specialist liver unit are: (poor prognostic factors)

- Encephalopathy
- **INR**: >2.0 at **<** 48 hours, or **>** 3.5 at **<** 72 hours
  - synthetic function (as determined by INR or PT) is the best indicator.
- Serum creatinine: >200 µmol/L
- **Blood pH: <7.3**
- Systolic BP: <80 mmHg.

Monitoring and endpoints for treatment

Hepatotoxicity

- In patients being treated with acetylcysteine for liver toxicity the acetylcysteine should be continued until the INR is 1.3 or less **OR** INR is falling towards normal on two consecutive blood tests, and less than 3.0.
- Blood tests (urea and electrolytes, creatinine, INR, and ALT) should be re-checked every 8 to 16 hours to assess the progress of the hepatic injury. There is no clinical benefit in continuing treatment with acetylcysteine for a rise in ALT if the INR has normalised.

Time-sensitive treatment issues

- 8-hour window
  - the need for acetylcysteine treatment should be based on a serum paracetamol concentration determined within this 8-hour window.
  - acetylcysteine within 8 hours of an acute ingestion → prevent hepatic injury in nearly all patients
  - Empiric acetylcysteine therapy should be initiated for patients who:
    - present later than 8 hours after ingestion;
    - when serum paracetamol concentrations cannot be determined within 8 hours;
    - or if the exact timing of the ingestion is uncertain.

adverse effects

- oral acetylcysteine → nausea and vomiting.
- intravenous acetylcysteine → anaphylactoid reaction (e.g., nausea, flushing, vomiting, rash, urticaria, pruritus, angio-oedema, dyspnoea, wheezing, bronchospasm, tachycardia, and hypotension),
- Previous anaphylactoid reaction to acetylcysteine is not a contraindication to receiving acetylcysteine.
  - Patients with a previous anaphylactoid reaction should be given an H1 and an H2 antagonist.
  - Patients with previous bronchospasm reaction to acetylcysteine can be given nebulised salbutamol.
  - Patients considered at risk of anaphylactoid reactions (e.g., those with atopy, bronchospasm, asthma, or a previous reaction) should be administered prophylactic medication such as antihistamines to reduce adverse reactions.
- **Methionine is used as an oral antidote for paracetamol poisoning in those who cannot tolerate N-acetylcysteine**

Paracetamol and smoking

- Enzyme induction with cigarette smoking does affect paracetamol metabolism. Its importance however, is in toxicity.
- Smokers would be classified as in a high risk for paracetamol overdose and are assessed using a different time - paracetamol level curve.

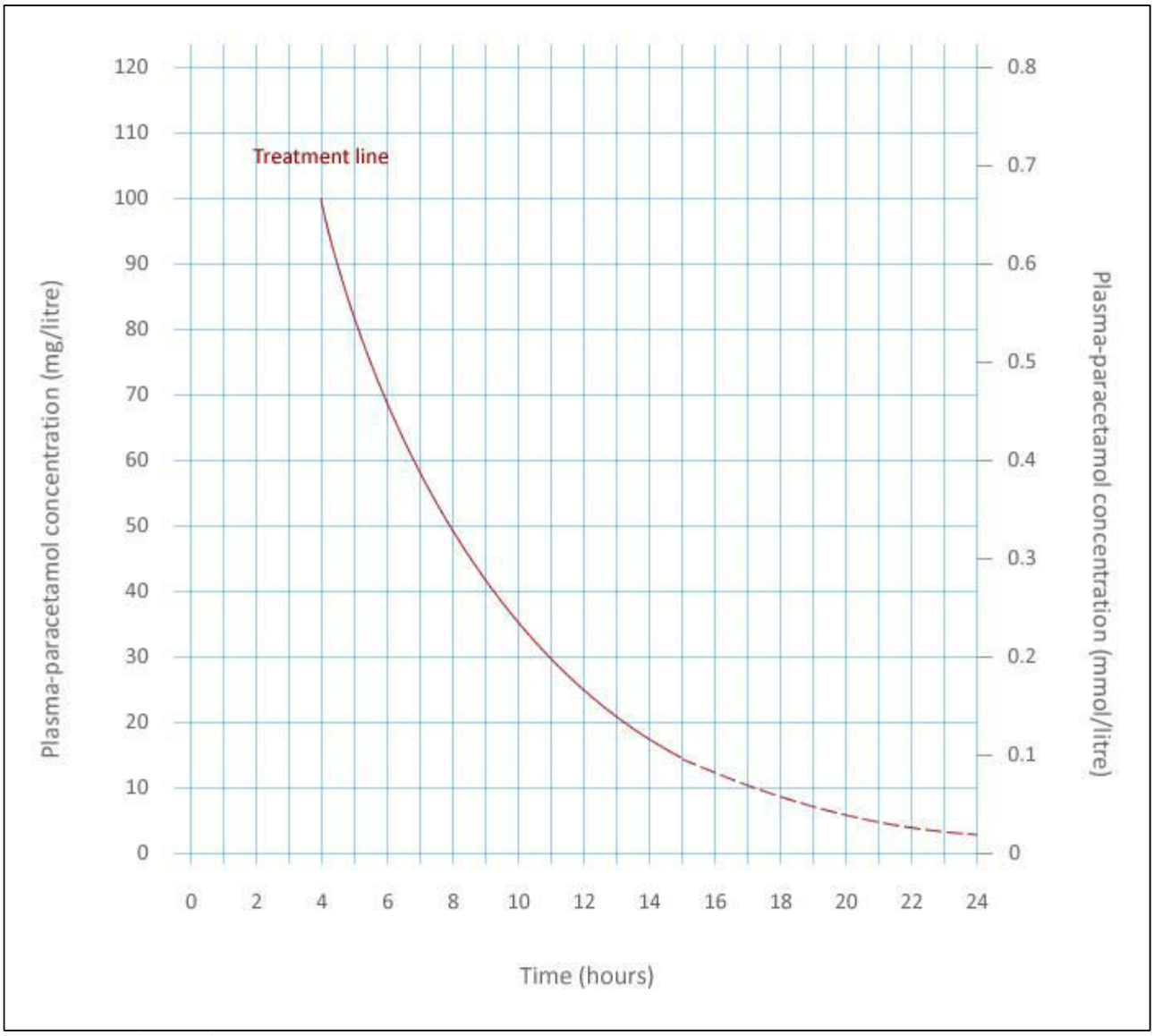
Complications

- Untreated paracetamol poisoning may cause varying degrees of liver injury over the 2 to 4 days following ingestion, including fulminant hepatic failure.
  - **Hepatotoxicity is extremely rare in patients treated with acetylcysteine within 8 hours of an acute paracetamol overdose.**
- **Lactic acidosis is recognised complication**
- **Hypoglycaemia is seen when paracetamol toxicity leads to significant impairment of hepatic synthetic function**
  - Severe hypoglycaemia affects 40% of patients with fulminant liver failure, which exacerbates encephalopathy.
- Paracetamol nephrotoxicity
  - can develop later than liver toxicity
  - The mechanism of kidney injury is similar to that of the liver,
  - there is little evidence that N-acetyl cysteine confers any renal protection.
  - usually the renal function returns to baseline after a few weeks.
  - Haemodialysis may be required to support the patient during the acute episode.

Prognosis

The prognosis is poor in those with

- Blood PH less than 7.0
- Prolonged prothrombin time (more than 100s) and
- Serum creatinine more than 300 uM.
- Mortality is greater if the patient is more than 40 years of age.



paracetamol overdose treatment nomogram

Adult Dosage Table (Royal College of Emergency Medicine Guidance. http://www.rcem.ac.uk)

Regimen	First Infusion	Second Infusion	Third Infusion
Infusion fluid	200 mLs 5% glucose or sodium chloride 0.9%	500 mLs 5% glucose or sodium chloride 0.9%	1000 mLs 5% glucose or sodium chloride 0.9%
Duration of infusion	1 hour	4 hours	16 hours
Drug dose	150 mg/kg acetylcysteine	50 mg/kg acetylcysteine	100 mg/kg acetylcysteine

Although hepatotoxic in high doses **even in fairly advanced chronic liver disease paracetamol can be used safely** as long as doses do not exceed 2-3 g per day. **The main exception to this is alcoholic liver disease** where the patient continues to drink, in this setting induction of enzymes and depletion of glutathione **increases the chances of hepatotoxicity**.

Paraquat poisoning

Properties of Paraquat

- Paraquat is a very toxic compound
- As little as 2 g is potentially fatal (10 ml of a concentrated 20% solution)

Presentation

- Initial signs of toxicity are due to its corrosive effects on the gastrointestinal tract and oropharynx

Pathology

- Paraquat is rapidly absorbed and is sequestered in the lungs, where it reacts with oxygen to form hydrogen peroxide and superoxide anions
- Hydrogen peroxide and superoxide anions are responsible for cell death, which leads to an acute alveolitis

Prognosis

- Death tends to occur within hours to days in patients who have ingested more than 6 g of Paraquat
- Death tends to occur within days in those who have ingested 3-6 g of Paraquat
- Illness following ingestion of 1.5-3 g Paraquat follows a much more protracted course and delayed pulmonary
- fibrosis can lead to death up to 6 weeks after ingestion

Management

- supportive care
- activated charcoal to reduce absorption
- **oxygen supplementation can increase pulmonary toxicity**, by increasing the rate of hydrogen peroxide and superoxide anion production

- Measurement of plasma paraquat concentration can help in assessing prognosis and can aid treatment
- Plasma concentration measurements are also useful in the management of poisoning with paracetamol, salicylates, lithium, iron, methanol, ethylene glycol and theophylline

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Organophosphate insecticide poisoning

Organophosphate is an anticholinesterase, thus prolonging the effects of acetylcholine.

One of the effects of organophosphate poisoning is inhibition of acetylcholinesterase

Organophosphates are rapidly absorbed through the gastrointestinal and respiratory tracts and the skin

Mechanism

- The principal action of organophosphates is inhibition of acetylcholinesterases
- This results in the accumulation of acetylcholine at muscarinic receptors, nicotinic receptors and in the central nervous system

Features can be predicted by the accumulation of acetylcholine (mnemonic = SLUD)

Hypersalivation and miosis are the specific clues to acetycholine overactivity.

- Salivation
- Lacrimation
- Urination
- Defecation/diarrhoea
- cardiovascular: hypotension, bradycardia
- also: small pupils, muscle fasciculation

Presentation

The presentation relates to the sites of accumulation of acetylcholine

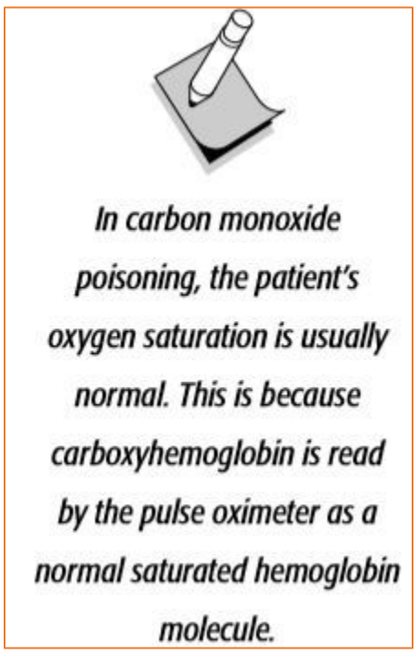
- Accumulation at muscarinic receptors leads to:
  - miosis
  - hypersalivation
  - sweating
  - diarrhoea
  - excessive bronchial secretions
- Accumulation at nicotinic receptors leads to:
  - muscle fasciculations
  - tremor
- Accumulation in the central nervous system leads to:
  - anxiety
  - loss of memory
  - headache
  - coma
- Organophosphate-induced neuropathy starts to develop 2 weeks after exposure
  - Initial presentation of neuropathy is a flaccid paralysis

- Later, hypertonia, hyperreflexia and a spastic paralysis occur

Management

- atropine
- the role of pralidoxime(an activator of cholinesterase) is still unclear - meta-analyses to date have failed to show any clear benefit

Carbon Monoxide Poisoning



- A hypoxemic poisoning syndrome seen in patients who have been exposed to automobile exhaust, smoke inhalation, barbecues, or old appliances in poorly ventilated locations.
- Presents with hypoxemia, cherry-red skin (rare), confusion, and headaches. Coma or seizures occur in severe cases.
- Chronic low-level exposure may cause fl ulike symptoms with generalized myalgias, nausea, and headaches. Ask about symptoms in others living in the same house.
- Suspect smoke inhalation in the presence of singed nose hairs, facial burns, hoarseness, wheezing, or carbonaceous sputum.

Diagnosis

- Check an ABG and serum carboxyhemoglobin level (normal is < 5% in nonsmokers and < 10% in smokers).
- Check an ECG in the elderly and in patients with a history of cardiac disease.

Treatment

- 100% O2
- Patients with airway burns or smoke inhalation may require early intubation, since upper airway edema can rapidly lead to complete obstruction.

Antiemetic

Antiemetics

- **Aprepitant → is a neurokinin receptor blocker used in the prevention of chemotherapy induced nausea.**
- **Ondansteron ➔ is a selective 5-HT3 (**5-hydroxytryptamine 3A receptor**) antagonist both centrally and peripherally and as such is a potent antiemetic.**
  - Ondansetron is the first line drug for chemotherapy related nausea and vomiting.
  - Its effects are thought to be on both **peripheral** and **central nerves**.
    - One part is to reduce the activity of the vagus nerve, which is a nerve that activates the

vomiting center in the medulla oblongata,
- the other is a blockage of serotonin receptors in the chemoreceptor trigger zone.

➢ Common side effects of ondansetron are headache, drowsiness, and dizziness.

- **Hyoscine → antiemetics functions as a cholinergic muscarinic antagonist**
  - ➢ It acts as a competitive antagonist at muscarinic acetylcholine receptors; it is thus classified as an anticholinergic or as an antimuscarinic drug.
- **Metoclopramide** is a dopamine receptor antagonist that **can induce parkinsonism.** It can also worsen control in patients with idiopathic Parkinson's disease to its antagonistic effect on dopamine receptors.
- **Domperidone** is also a dopamine antagonist but acts peripherally.
  - ➢ **Best drug for nausea and vomiting associated with Parkinson treatment.**
  - ➢ Drugs such as apomorphine and bromocriptine cause vomiting through peripheral stimulation of the chemoreceptor trigger zone. Worsening of Parkinson's disease may result from the use of dopamine antagonists; however, **domperidone is much less likely to cross the blood–brain barrier and is therefore the preferred agent in this case.**
- **Haloperidol: the main site of action for haloperidol with regards anti-emetic effects --> Chemoreceptor trigger zone**
  - ➢ Haloperidol is an anti-dopaminergic agent licensed for and used mainly as an anti-psychotic agent
  - ➢ It does result in more extrapyramidal side-effects than phenothiazine-type agents, but is associated with less hypotension
- **Phenothiazines** (e.g. promethazine) and domperidone are also used as anti-emetic agents and act at the chemoreceptor trigger zone
- **Cyclizine** is an anticholinergic antihistamine acting through the vomiting centre.

5-HT3 antagonists

- 5-HT3 antagonists are antiemetics used mainly in the management of chemotherapy related nausea. They mainly act in the chemoreceptor trigger zone area of the medulla oblongata.

Examples

- ondansetron
- granisetron

Adverse effects

- constipation is common

Metoclopramide

Indications

Metoclopramide is a D2 receptor antagonist mainly used in the management of nausea. Other uses include:

- gastro-oesophageal reflux disease
- prokinetic action is useful in gastroparesis secondary to diabetic neuropathy
- often combined with analgesics for the treatment of migraine (migraine attacks result in gastroparesis, slowing the absorption of analgesics)

Adverse effects

- extrapyramidal effects: oculogyric crisis. This is particularly a problem in children and young adults , especially girls , usually subsides within 24 hours following cessation of treatment and can be **treated with procyclidine 5-10 mg i.m. (antimuscarinic).**
- hyperprolactinaemia
- tardive dyskinesia

Acute dystonic-dyskinetic reactions

- mostly occur in children and young adults and about 70% of cases are female.
- It occurs more commonly when excess of the recommended dose of metoclopramide is administered.
- The effects usually occur within 72 hours but have been reported to occur within 30 minutes of starting treatment.
- Symptoms include:
  - ➢ oculogyric crisis
  - ➢ opisthotonus
  - ➢ torticollis
  - ➢ trismus, and
  - ➢ tetanus-like reactions.

- A blue discolouration of the tongue has also been described.
- Although generally self-limiting, the reaction can be reversed by an anticholinergic such as **benzatropine** or procyclidine or an antihistamine such as diphenhydramine.

Other drugs

Antihistamines

- Antihistamines (H_1 inhibitors) are of value in the treatment of allergic rhinitis and urticaria.
- Sedation and headaches are the most common adverse effects of antihistamines
- First generation antihistamines (chlorpheriramine and diphenhydramine) are more sedating than the newer agents.

Examples of sedating antihistamines

- **Cyproheptadine**
- Chlorpheniramine
  - As well as being sedating these antihistamines have some antimuscarinic properties (e.g. urinary retention, dry mouth).

Examples of non-sedating antihistamines

- loratidine
- cetirizine
- **Desloratadine**
  - is a long-acting H-1-receptor antagonist
  - has poor penetration into the central nervous system
  - does not interact with antibiotics or other co-administered medications
- Of the non-sedating antihistamines there is some evidence that cetirizine may cause more drowsiness than other drugs in the class.
- Of the newer antihistamines, cetirizine and levocetirizine are more sedating than loratadine and desloratadine, and possibly more sedating than fexofenadine.

Other notes

- **Terfenadine (a pro-drug) has been associated with cardiac arrhythmias (torsades de pointes) especially in individuals with prolonged QT intervals.**
  - Fexofenadine is the active metabolite of terfenadine and does not appear to have the same arrhythmogenic effects as terfenadine.
- Cetirizine, desloratadine and fexofenadine are prescribed for allergic rhinitis (hay fever) and all three are equally effective
- cetirizine and fexofenadine interact with erythromycin and other macrolides
- Chlorphenamine maleate and terfenadine cause drowsiness and also interact with erythromycin

Human and animal bite

- **Co-amoxiclav** is recommended as first-line treatment for all cat or human bites and other complicated animal bites.
- In patients who are pencillin allergic, doxycycline plus metronidazole is a typical first choice regimen.
- Only 15 - 20% of dog bites become infected, and providing the wound is appropriately cleaned and not considered at risk (for example, crush or deep wounds) then antibiotic prophylaxis may not be required.

Botox → Paralysis of frontalis → eyebrows are drooping (eyebrow ptosis).

- Botox (onabotulinumtoxinA) is an injectable neuro-toxin used for the treatment of chronic migraines, limb spasticity, axillary hyperhidrosis, cervical dystonia, strabismus, and blepharospasm.
- Botox is a neurotoxin derived from the bacteria, *Clostridium botulinum*. It blocks neuromuscular transmission inhibition of acetylcholine release at the presynaptic membrane. The end result is that the muscle contraction is inhibited.
- The action of Botox is not permanent because collateral axonal sprouting establishes new neuromuscular junctions, restoring muscle function.

- Frontalis is a quadrilateral muscle found on the forehead that elevates the eyebrows; hence paralysis of this muscle can lead to eyebrow ptosis.

D-Penicillamine

- used to reduce the body copper in Wilson's disease & as a chelating agent in lead poisoning
- **D-Penicillamine** is associated with → **pancytopenia and tubulointerstitial nephritis**

Isotretinoin

Isotretinoin adverse effects
- teratogenicity - females MUST be taking contraception
- low mood
- dry eyes and lips
- raised triglycerides
- hair thinning
- nose bleeds

- Isotretinoin is an oral retinoid used in the treatment of severe acne.
- Two-thirds of patients have a long term remission or cure following a course of oral isotretinoin

Adverse effects

- **Teratogenicity**: ♀s **MUST** be using two forms of contraception (e.g. COCP and condoms).
  - Women must have a negative pregnancy test before treatment
  - and be on effective contraception **for at least a month before the course begins**, during the course **and for a month after it finishes**
  - Congenital **deafness** , **CNS** and **heart** defects may occur in children exposed to isotretinoin in utero
- Dry skin, eyes and lips: the most common side-effect of isotretinoin
- Low mood, depression
- Raised triglycerides
- Hair thinning
- Nose bleeds (caused by dryness of the nasal mucosa)
- Benign intracranial hypertension: isotretinoin treatment should not be combined with tetracyclines for this reason

Cinnarizine

- Cinnarizine is thought to be particularly **useful for the treatment of motion sickness** as it has a dual action:
  - it acts as a depressant of the vestibular system
  - it dampens down smooth muscle contraction in the gut

Ergotamine

- Ergotamine is an old drug and a member of the family of ergot alkaloids.
- It is licensed as a treatment and prophylaxis for migraines but has been largely superseded by newer agents despite its efficacy, cost and relatively benign side effect profile.
- A derivative of the drug, ergometrine, is used in obstetrics to reduce the incidence of post partum haemorrhage.
- Ergotamine, like all ergot alkaloids, is a potent vasoconstrictor which is partly how it exerts its clinical effects, however in overdosage it can cause significant peripheral vasoconstriction causing critical ischaemia and gangrene. Coronary vasoconstriction may occur, with or without flow limiting lesions causing cardiac ischaemia which may be manifest as chest pain, arrhythmia or even sudden death.
- Contraindications to the use of ergotamine are flow limiting coronary lesions or peripheral vascular disease.
- Additionally, ergotamine has a complex series of effects on central nervous neurotransmitter systems including serotonergic, dopaminergic and noradrenergic systems which can cause excitement, confusion, paranoia, visual and auditory hallucinations and delusions in overdose.

- It is also a metabolic precursor to the highly hallucinogenic chemical lysergic acid diethylamide (LSD) which inactivates 5-HT2A receptors in the brain.
- At normal doses, side effects of ergotamine are relatively minor and unlikely to cause significant clinical signs in the absence of underlying pathology. However, metabolism of ergot alkaloids is predominantly by the hepatic enzyme CYP3A4 which is almost totally inhibited by macrolide antibiotics. Co-administration of ergotamine and clarithromycin may be expected to produce a rapid picture of ergotism with confusion, psychosis, muscle cramps, seizures, peripheral and coronary vasospasm, severe headache and gastrointestinal symptoms of bowel ischaemia, cramps, diarrhoea and GI haemorrhage. Myocardial infarction, renal infarction, stroke and critical limb ischaemia may occur if not treated.
- Interestingly, ergot alkaloid derivatives are naturally produced by the fungus Claviceps purpurea which may infect crops.
- Historically, significant outbreaks of ergotism have been seen due to ingestion of crops contaminated with ergot and there is some historical evidence that claims of witchcraft are ascribable to the psychosis of ergot poisoning.

Finasteride

Finasteride treatment of BPH may take 6 months before results are seen

- Finasteride is an inhibitor of 5 alpha-reductase.
- **5-α-Reductase converts testosterone to dihydrotestosterone (DHT)**
- DHT is much more active than testosterone and binds more avidly to cytoplasmic receptors
- DHT stimulates prostate growth and may be responsible for benign prostatic hyperplasia in the elderly

Indications

- benign prostatic hyperplasia
- male-pattern baldness

Adverse effects

- impotence
- decrease libido
- ejaculation disorders
- gynaecomastia and breast tenderness

Finasteride causes decreased levels of serum prostate specific antigen

Acetazolamide

Action

- **carbonic anhydrase inhibitor**, hence causing the accumulation of carbonic acid
- Inhibits **proximal tubule** **bicarbonate reabsorption** in a similar fashion to type-2 renal tubular acidosis (RTA) → associated with metabolic acidosis
- By excreting bicarbonate, the blood becomes acidic, causing compensatory hyperventilation with deep respiration (Kussmaul respiration), increasing levels of oxygen and decreasing levels of carbon dioxide in the blood. Hence used in treatment of high altitude sickness.

Indications

- intracranial hypertension
  - post-haemorrhagic hydrocephalus (often with furosemide)
  - primary idiopathic pseudotumour cerebri (benign intracranial hypertension)
- reducing intraocular pressure
- **prevent acute mountain sickness**
- preventative agent for contrast nephropathy

Side effects

- metabolic acidosis, due to bicarbonate loss in the proximal and distal tubules through inhibition of reabsorption
  - **hyperchloraemic, normal anion gap metabolic acidosis**.
- Hypokalaemia
- **Acute interstitial nephritis (AIN)**
- Agranulocytosis and thrombocytopenia
- hyponatremia,

- hyperglycemia, hypoglycemia, glycosuria,
- **crystalluria** (and hematuria), and polyuria.
- **peripheral paresthesiae**

carbonic anhydrase works to control the equilibrium between carbon dioxide and carbonic acid in order to maintain proper blood pH. Through which mechanism does **carbonic anhydrase** exert its influence on reaction kinetics?

➔ **Lowers the activation energy**
- Enzymes like **carbonic anhydrase** lower the energy of activation that is needed to initiate a reaction.
  - ❖ Inhibition of carbonic anhydrase prevents the conversion of carbon dioxide (CO_2) and water (H_2O) to carbonic acid (H_2O_3) thus affecting the blood pH.

Bicarbonate therapy

- Can increase extracellular pH only if the carbon dioxide (CO_2) produced can be removed by adequate ventilation.
- Indeed, if hypercapnia occurs then as CO_2 crosses cell membranes easily, intracellular pH may decrease even further with further deterioration of cellular function.
- Bicarbonate has a negative inotropic effect,
- reducing cerebral blood flow;
- It shifts the oxygen dissociation curve to the left, inhibiting oxygen release to tissues.
- **Exacerbates intracellular acidosis in cardiorespiratory arrest**

Bisphosphonates

Bisphosphonates inhibit osteoclasts

Bisphosphonates are analogues of pyrophosphate, a molecule which decreases demineralisation in bone. They **inhibit osteoclasts** by reducing recruitment and promoting apoptosis.

The mechanism of action of bisphosphonates involves the inhibition of farnesyl diphosphate synthase within osteoclasts. In doing this they interfere with geranylgeranylation (attachment of the lipid to regulatory proteins), which causes osteoclast inactivation. This leads to reduced bone turnover, increased bone mass and improved mineralisation.

Clinical uses
- prevention and treatment of osteoporosis
  - ➢ Bisphosphonates licensed for the prevention and treatment of osteoporosis **include** alendronate, risedronate and ibandronate.
- hypercalcaemia
- Paget's disease
- pain from bone metastases
  - ➢ The bisphosphonates zoledronate and pamidronate are used for the treatment of metastatic bone disease and short term management of hypercalcaemia.

Adverse effects

Bisphosphonates can cause a variety of oesophageal problems

- oesophageal reactions: oesophagitis, oesophageal ulcers (especially alendronate)
- **osteonecrosis of the jaw:**
  - ➢ This is a consequence of potent anti-resorptive action of the nitrogen containing bisphosphonates.

- Most cases have been associated with **zoledronic acid** and pamidronate given intravenously for metastatic bone disease.
- The reported incidence in patients with malignancy treated with these drugs is between 1.3-4.0%.
- Dental disease is a recognised predisposing factor.
- The lesions usually heal with minimal surgical debridement, chlorhexidine mouthwashes, antibiotics and analgesia.

- **Bisphosphonate infusions can lead to hypocalcaemia** although it is more common when using larger doses in malignancy induced hypercalcaemia as oppose to the smaller dose used in osteoporosis.
- increased risk of atypical stress fractures of the proximal femoral shaft in patients taking alendronate

The BNF suggests the following counselling for patients taking oral bisphosphonates

- 'Tablets should be swallowed whole with plenty of water while sitting or standing; to be given on an empty stomach at least 30 minutes before breakfast (or another oral medication); patient should stand or sit upright for at least 30 minutes after taking tablet'

Botulinum toxin

As well as the well publicised cosmetic uses of Botulinum toxin ('Botox') there are also a number of licensed **indications:**

- blepharospasm
- hemifacial spasm
- focal spasticity including cerebral palsy patients, hand and wrist disability associated with stroke
- spasmodic torticollis
- severe hyperhidrosis of the axillae
- achalasia

Immunoglobulins: Therapeutics

The Department of Health issued guidelines on the use of intravenous immunoglobulins in May 2008

Uses

- Primary and secondary immunodeficiency
- Idiopathic thrombocytopenic purpura (ITP)
- Myasthenia gravis
- Guillain-Barre syndrome
- Kawasaki disease
- Toxic epidermal necrolysis (TEN)
- Pneumonitis induced by CMV following transplantation
- Low serum IgG levels following hematopoietic stem cell transplant for malignancy
- Dermatomyositis
- Chronic inflammatory demyelinating polyradiculopathy

Basics

- Formed from large pool of donors (e.g. 5,000)
- IgG molecules with a subclass distribution similar to that of normal blood
- Half-life of 3 weeks

Malignant hyperthermia (MH)

Overview

- condition often seen following administration of anaesthetic agents
- characterised by increased temperature and muscle rigidity during anaesthesia, which results from abnormal skeletal muscle contraction and increased metabolism.
- caused by excessive release of Ca^{2+} from the sarcoplasmic reticulum of skeletal muscle
- associated with defects in a gene on chromosome 19 encoding the ryanodine receptor, which controls Ca^{2+} release from the sarcoplasmic reticulum
- neuroleptic malignant syndrome may have a similar aetiology

Causative agents

- halothane (volatile anaesthetic agents)

- suxamethonium
- other drugs: antipsychotics (neuroleptic malignant syndrome)

Investigations

- Serum creatine kinase(CK) elevation and myoglobinuria are suggestive but not diagnostic of MH.(both known to increase after giving suxamethonium to normal patients)
- Contracture tests with halothane and caffeine **are the investigations of choice.**
- **Muscle biopsies may appear histologically normal.**

Management

- dantrolene - prevents Ca2+ release from the sarcoplasmic reticulum
  - Intravenous dantrolene (up to 10 mg/kg) is the only available specific treatment
  - Care must be taken when administering as the solution has a pH of 9-10.

Prognosis

- The prognosis of malignant hyperpyrexia is good when the appropriate treatment is instigated early, mortality being less than 5% (prior to dantrolene the mortality was 80%).

Intravenous fluid therapy

Composition of electrolytes in commonly used crystalloids

Content	Plasma	Sodium chloride 0.9%*	Sodium chloride 0.18%/ 4% glucose(a)	0.45% NaCl/ 4% glucose(a)	5% glucose(a)	Hartmann's	Lactated Ringer's (USP)	Ringer's acetate
Na^+ (mmol/l)	135-145	154	31	77	0	131	130	130
Cl^- (mmol/l)	95-105	154	31	77	0	111	109	112
$[Na^+]:[Cl^-]$ ratio	1.28 - 1.45:1	1:1	1:1	1:1	-	1.18:1	1.19:1	1.16:1
K^+ (mmol/l)	3.5-5.3	*	*	*	*	5	4	5
$HCO3^-$ / Bicarbonate	24-32	0	0	0	0	29 (lactate)	28 (lactate)	27 (acetate)
Ca^{2+} (mmol/l)	2.2-2.6	0	0	0	0	2	1.4	1
Mg^{2+} (mmol/l)	0.8-1.2	0		0		0	0	1
Glucose (mmol/ l)	3.5-5.5	0	222(40 g)	222 (40g)	278(50 g)	0	0	0
pH	7.35-7.45	4.5-7.0	4.5		3.5-5.5	5.0-7.0	6-7.5	6-8
Osmolarity (mOsm/l)	275-295	308	284		278	278	273	276

Intravenous fluid therapy in adults in hospital (NICE guidelines 2013)

- **Indicators for urgent fluid resuscitation**:
  - systolic blood pressure is less than 100 mmHg
  - **heart rate is more than 90 beats per minute**
  - capillary refill time is more than 2 seconds or peripheries are cold to touch
  - respiratory rate is more than 20 breaths per minute
  - National Early Warning Score (NEWS) is 5 or more
  - passive leg raising suggests fluid responsiveness
- Resuscitation
- If patients need IV fluid resuscitation, use crystalloids that contain sodium in the range 130–154 mmol/l, **with a bolus of 500 ml over less than 15 minutes.**
- Consider human albumin solution 4–5% for fluid resuscitation only in patients with severe sepsis.
- Routine maintenance
- ➔If patients need IV fluids for routine maintenance alone, restrict the initial prescription to:
- 25–30 ml/kg/day of water **and**
- approximately 1 mmol/kg/day of potassium, sodium and chloride **and**
- approximately 50–100 g/day of glucose to limit starvation ketosis. (This quantity will not address patients' nutritional needs)

(patients rarely need more than a total of 3 litres of fluid per day)

- ➔Consider prescribing less fluid (for example, 20–25 ml/kg/day fluid) for patients who:
- are older or frail
- have renal impairment or cardiac failure
- are malnourished and at risk of refeeding syndrome
- ➔When prescribing for routine maintenance alone, consider using 25–30 ml/kg/day sodium chloride 0.18% in 4% glucose with 27 mmol/l potassium on day 1.
- ➔Prescribing more than 2.5 litres per day increases the risk of hyponatraemia. **These are initial prescriptions and further prescriptions should be guided by monitoring.**
- ➔Consider delivering IV fluids for routine maintenance during daytime hours to promote sleep and wellbeing.

British Consensus Guidelines on Intravenous Fluid Therapy (2011) Recommendation

- Because of the risk of inducing **hyperchloraemic acidosis** in routine practice, when crystalloid resuscitation or replacement is indicated, balanced salt solutions e.g. **Ringer's lactate/acetate or Hartmann's solution should replace 0.9% saline**, except in cases of hypochloraemia e.g. from vomiting or gastric drainage.
- Hypochloraemia is an indication for the use of 0.9% saline, with sufficient additions of potassium and care not to produce sodium overload.
- Losses from diarrhoea/ileostomy/small bowel fistula/ileus/obstruction should be replaced volume for volume with Hartmann's or Ringer-Lactate/acetate type solutions.
- "Saline depletion," for example due to excessive diuretic exposure, is best managed with a balanced electrolyte solution such as Hartmann's.

Daily requirement

- The typical daily requirement is:
  - 1.5 ml/kg/hr fluid - for a 80kg man around 2-3 litres/day
  - 70-150mmol sodium
  - 40-70mmol potassium
- This is why the typical regime prescribed for patients is:
  - 1 litre 5% dextrose with 20mmol potassium over 8 hours
  - 1 litre 0.9% normal saline with 20mmol potassium over 8 hours

The table below shows the electrolyte concentrations (in millimoles/litre) of plasma and the most commonly used fluids:

	Na^+	Cl^-	K^+	$HCO3^-$	Ca^{2+}
Plasma	135-145	98-105	3.5-5	22-28	2.3-2.6
0.9% normal saline	150	150	-	-	-
5% dextrose	-	-	-	-	-
Hartmann's solution	131	111	5	29	2

Normal saline has a pH of 5 and may produce a mild metabolic acidosis with significant infusions.

Lactulose

- **Lactulose MOA → Osmotic laxative**
- Causes hypomagnesaemia associated with diarrhoea
- Is not absorbed
- Does not affect the absorption of spironolactone and
- May be used in diabetics.
- **It reduces proliferation of ammonia producing bacteria**

It is used in patients with cirrhosis/hepatic encephalopathy to limit the proliferation of ammonia-forming gut organisms and increase the clearance of protein load in the gut.

- lactulose broken down by colonic bacteria → production of lactic acid and other organic acids → contents of the gut become more acidic (↓ PH) → ↓↓ **absorption of ammonia** → ↑↑ ammonia in the gut → ↑↑ water drawn into the lower bowel

laxative abuse

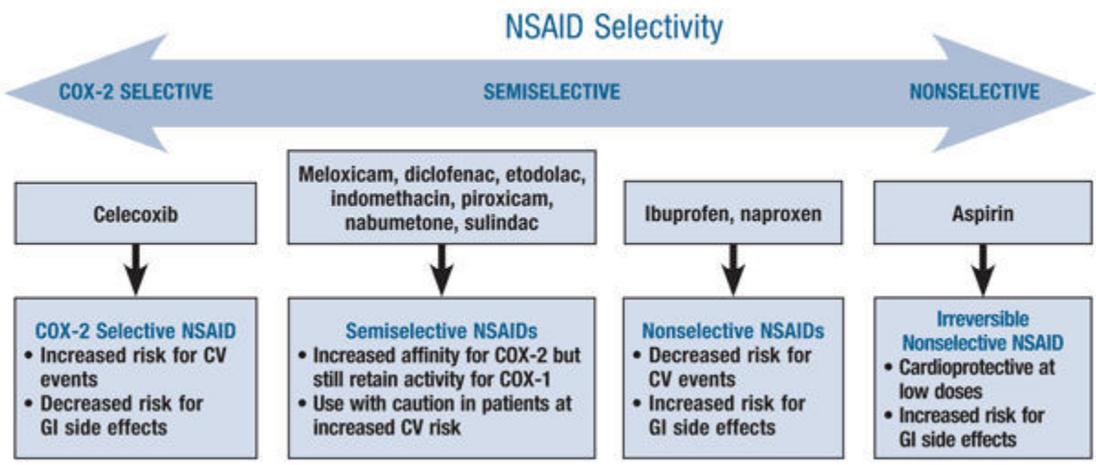
Features

- most commonly seen in young female patients complaining of chronic diarrhoea.
  - **The diarrhoea is frequently high volume**
- underweight girl with calluses on her knuckles may point towards induced vomiting and a diagnosis of bulimia, which would fit with possible laxative abuse.
- **Hypokalaemia**
  - Due to increased GI potassium loss
  - symptoms of fatigue which are consistent with hypokalaemia.
  - GI loss leads to renal conservation of potassium, a **urinary concentration of potassium of less than 1 mmol/l being highly suggestive of laxative abuse.**

Bismuth

- subsalicylate is a colloidal substance frequently included in over-the-counter treatments for gastrointestinal discomfort.
- It has anti-secretory, anti-inflammatory, and antibacterial properties.
- It may be included in multidrug regimens against *H. pylori*.
- Its most unique side-effect is the appearance of black stool or a black tongue, both secondary to the drug's interaction with sulfur.

Non-steroidal anti-inflammatory drugs (NSAID)



Non-steroidal anti-inflammatory drugs (Nice 2015)

- If an NSAID is needed, use ibuprofen (1200 mg a day or less) or naproxen (1000 mg a day or less).
- Naproxen (1000 mg a day or less) and low-dose ibuprofen (1200 mg a day or less) are considered to have the most favourable thrombotic cardiovascular safety profiles of all NSAIDs.
- Co-prescribe gastroprotective treatment (a proton pump inhibitor) with NSAIDs
- In October 2012, a European Medicines Agency (EMA) review on the cardiovascular safety of NSAIDs confirmed that diclofenac is associated with cardiovascular risks that are higher than ibuprofen and naproxen, and similar to the COX-2 inhibitors.
- etoricoxib should not be prescribed to people whose blood pressure is persistently above 140/90 mmHg
- the arterial thrombotic risk with diclofenac is similar to that of COX-2 inhibitors.
- diclofenac is now contraindicated in patients with established:
  - ischaemic heart disease
  - peripheral arterial disease
  - cerebrovascular disease
  - congestive heart failure (New York Heart Association [NYHA] classification II–IV)

Indometacin → is an inhibitor of both prostaglandin synthase and lipoxygenase enzymes

Side effects

- **Current evidence suggests that naproxen, a nonselective NSAID, is associated with the lowest risk of cardiovascular events. Therefore, naproxen is the NSAID of choice in patients with high cardiovascular risk.**
- **Optic neuritis is described as being rarely associated with diclofenac therapy.**
- A range of other CNS side effects has also been noted on the summary of product characteristics, these include headache, dizziness, vertigo and in rare circumstances drowsiness.
- **gastrointestinal bleeding occurs due to depletion of mucosal prostaglandin E (PGE) levels**
- Endoscopic evidence of peptic ulceration is found in 20% of NSAID users even in the absence of symptoms
- The relative risk of causing GI bleeds differs with different preparations:
  - ibuprofen has a low risk
  - piroxicam and azapropazone have the highest risk
- While all NSAIDs may contribute to anaemia, usually via gastrointestinal bleeding, **mefenamic acid is particularly associated with immune haemolytic anaemia.**

Non-steroidal anti-inflammatory drugs are contraindicated in chronic liver disease for a variety of reasons:

- their gastrointestinal side effects increase the risk of bleeding, particularly in those with varices.
- Additionally due to systemic vasodilatation renal circulation is very dependent upon prostaglandin production to maintain glomerular filtration. Inhibition of this mechanism by non-steroidals, in addition to their other nephrotoxic effects, means that their use in patients with chronic liver disease, especially where there is pre-existing renal impairment, can precipitate renal failure.

Overdose with (NSAIDs)

Presentation and aetiology

- GIT upset (epigastric tenderness, nausea, vomiting and diarrhea)
  These effects are mainly due to the inhibition of cyclo-oxygenase
- **convulsions** (10-20%) → **more common in mefenamic acid over dose**

Large overdoses can present with:

- acidosis
- renal impairment
- gastrointestinal haemorrhage
- CNS effects (drowsiness, coma, cerebellar signs)

Management

- Activated charcoal in patients presenting within the first hour
- Supportive care
- Oral H2-histamine blockers and proton-pump inhibitors may reduce the symptoms of gastrointestinal toxicity

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Celecoxib (COX)-2 inhibitor)

Celecoxib is an NSAID that is safe to use in patients with gastritis or gastric ulcers as it does not affect COX1 action at the stomach.

Action

- Celecoxib is a **selective cyclo-oxygenase(COX)-2 inhibitor**
  - differing from the other non-steroidal anti-inflammatory drugs (NSAIDs) such as naproxen which affects both COX-1 and COX-2.
  - COX-1 is involved in platelet aggregation and inhibition of this by the NSAIDs produces its beneficial cardiovascular effects.
  - **platelet aggregation is not affected by COX-2.**
  - **Celecoxib has a lower level of anti-platelet activity than naproxen**

Advantages

- Naproxen and celecoxib have been shown to be as effective at reducing inflammation.
- **One of the benefits of celecoxib is its reduced incidence of upper gastrointestinal side effects.**

Side effects

- As with the non-specific NSAIDS, **hepatotoxicity** may occur with the COX-2 specific inhibitors resulting

in cholestatic, hepatocellular or mixed liver injury. Rates seem to be comparable between the traditional NSAIDs and the COX-2 selective inhibitors.

- The **cardiovascular effects** of the COX-2 inhibitors remains under study, and care should be taken before prescribing them to patients with a past medical history of significant cardiovascular disease.
- Rofecoxib (Vioxx) has been withdrawn due to its increased cardiovascular events compared with naproxen.
- **What is the mechanism of celecoxib-induced deterioration in renal function?**
  - ❖ **inhibition of afferent arteriole vasodilatation**

Interaction

- **Co-administration of diuretics** and COX-2 inhibitors should be avoided if possible, as COX-2 inhibitors may reduce the antihypertensive and diuretic effects of diuretics. This may be due to impaired prostaglandin synthesis, which results in salt and water retention. In addition, COX-2 inhibitors have nephrotoxic effects which can be exacerbated by diuretics.

Aminosalicylate drugs

- 5-aminosalicyclic acid (5-ASA) is released in the colon and is not absorbed. It acts locally as an anti-inflammatory. The mechanism of action is not fully understood but 5-ASA may inhibit prostaglandin synthesis
- The safety of the 5-aminosalicylic acid (5-ASA) drugs in pregnancy is best supported by the data on Salazopyrin which have been available for the longest.

Sulphasalazine

- a combination of sulphapyridine (a sulphonamide) and 5-ASA
- many side-effects are due to the sulphapyridine moiety: rashes, oligospermia, headache, Heinz body anaemia, megaloblastic anaemia
- other side-effects are common to 5-ASA drugs (see mesalazine)

Mesalazine

- a delayed release form of 5-ASA
- sulphapyridine side-effects seen in patients taking sulphasalazine are avoided
- side-effects: GI upset, headache, agranulocytosis, pancreatitis, interstitial nephritis
  - pancreatitis is 7 times more common in patients taking mesalazine than sulfasalazine

Olsalazine

- two molecules of 5-ASA linked by a diazo bond, which is broken by colonic bacteria

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Anti-TNF therapy (NICE January 2016)

TNF-α inhibitors may reactivate TB

Drugs

- adali**mumab**, Goli**mumab,** inflixi**mab,** certoli**zumab**, tocili**zumab**
- etaner**cept**, abata**cept**,

Action

- tumour necrosis factor alpha (TNF-α) inhibitors

Indications

- Refractory Crohn's disease,
- rheumatoid arthritis : for adults who have both the following characteristics:
  - ➢ **Active rheumatoid arthritis** as measured by **disease activity score** (**DAS**28) greater than 5.1 confirmed on at least two occasions, 1 month apart.
  - ➢ Have undergone **trials of two disease-modifying anti-rheumatic drugs (DMARDs),** including methotrexate (unless contraindicated).
    - A trial of a DMARD is defined as being normally of 6 months, with 2 months at standard dose, unless significant toxicity has limited the dose or duration of treatment.

- ❖ Use of the TNF-α inhibitors for rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs is not recommended.

➢ **Follow up**
- Continue treatment only if there is a moderate response measured using **European League Against Rheumatism (EULAR)** criteria **at 6 months after starting therapy**.
- monitored 6-monthly
  - ❖ withdraw treatment if a moderate EULAR response is not maintained.

- **Plaque psoriasis**
  - ➢ **Adalimumab** is recommended for adults with **plaque psoriasis** only if:
    - **condition is severe** and
    - **not improved with other treatments** such as ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation), or they have had side effects with these in the past or there is a medical reason why they should not be given these treatments.
  - ➢ Follow up
    - Adalimumab treatment should be continued beyond **16 weeks** only if the psoriasis has clearly improved within this time.
- **ankylosing spondylitis**
  - ➢ NICE states that adalimumab, etanercept and golimumab may be used for ankylosing spondylitis (AS) **only if:**
    - treatment with two or more NSAIDs for four weeks at the highest possible dose has not controlled the symptoms
    - confirms that **condition has not improved** by 2 methods:
      1) level of **pain is assessed twice** (using a simple scale to fill in) 12 weeks apart and confirms that condition has **not improved**
      2) **Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)** is tested twice, 12 weeks apart, and confirms that **condition has not improved**
         - ➧ BASDAI is a set of measures to evaluate condition, by asking a number of questions about symptoms

Side effects

- Reactions
  - ➢ Injection site reactions
  - ➢ Cutaneous reactions, including psoriasis
  - ➢ Infusion reactions
    - Infusion reactions with infliximab are classified as one of two types:
      - ❖ Acute reactions : occur within 24 hours.
      - ❖ Delayed reactions: develop between 1 and 14 days
- Neutropenia
- Infections
  - ➢ **risk of reactivation of tuberculosis or new infection**
    - including miliary TB and some unusual extra-pulmonary TB
    - **If patient had previous active TB, the optimal TB screening test in this situation→ Interferon gamma release assay**
- Demyelinating disease → exacerbation of neurologic disorders associated with demyelination, such as multiple sclerosis.
- Heart failure
  - ➢ Given the evidence to date, patients with symptomatic HF should be treated with strategies other than TNF-alpha inhibitors.
  - ➢ In a patient who develops HF while on a TNF-alpha inhibitor, a drug-induced cause should be suspected.
- Malignancy
- Induction of autoimmunity

Usage

- **Prior to initiating** a TNF-alpha inhibitor, all patients **should be screened for**:
  - ➢ **tuberculosis**,
  - ➢ hepatitis B, and
  - ➢ hepatitis C.

- All forms of anti-TNF therapy are given by injection.
  - **Etanercept** is given as **subcutaneous** injection twice per week.
  - **Infliximab** is given as an **infusion (intravenous).**
    - requires intravenous infusion in a hospital setting.
    - It is given 2-4 weekly initially and then on a 6-8 weekly basis and as per protocol.
    - Infliximab monotherapy induces the production of **anti-infliximab antibodies**, which may reduce its effectiveness. **Adding methotrexate to infliximab therapy may prevent this response.**
  - **Adalimumab** is given as (**subcutaneous injection**) on alternate weeks (every second week).
- **Unlike methotrexate**,
  - there is little problem with nausea.
  - Nor is there the same concern for effects on blood cells and the liver which means less blood tests are required.
- TNF-α inhibitors should normally be used in combination with methotrexate.
  - If methotrexate is intolerant, adalimumab and etanercept may be given as monotherapy.

Trastuzumab (Herceptin) - monoclonal antibody that acts on the HER2/neu receptor

Cetuximab - monoclonal antibody against the epidermal growth factor receptor

Some other monoclonal antibodies in clinical use include:

monoclonal antibodies	Action	Indication
Digibind	Digoxin-binding antibody	for treatment of overdoses (increases clearance).
Abciximab	Glycoprotein IIb,IIIa receptor	for unstable angina.
Pexelizumab	**Anti-C5** (complement) - anti-inflammatory	**reduces myocardial infarction and death following coronary artery bypass graft (CABG) and angioplasty.**

Proton pump inhibitors

- The proton pump is only contained in the tubo-vesicles of the parietal cell → **secrete acid.**
- Proton-pump inhibitors (e.g omeprazole) **binds to gastric K+/H+-ATPase proton pump irreversibly**
- However, as the half-life of the pump is 24-36 hours, the duration of the effect of proton-pump inhibitors is limited by the degradation of these pumps.

Sildenafil

Viagra? - contraindicated by nitrates and nicorandil

Action

- Sildenafil is a phosphodiesterase type V inhibitor (**PDE-5 inhibitors**) used in the treatment of impotence.
- It **increases** intracavernosal **cGMP** levels, thereby **competitively inhibiting the PDE-5 enzyme**, and **allowing nitric oxide-induced vasodilation**.
  - it **blocks cGMP phosphodiesterase**, which is normally responsible for the breakdown of cGMP. Sildenafil therefore leads to increased levels of cGMP, which has vasodilatory effects to relax smooth muscle.

Contraindications

- patients taking nitrates and related drugs such as nicorandil
- hypotension
- recent stroke or myocardial infarction (NICE recommend waiting 6 months)
- non-arteritic anterior ischaemic optic neuropathy

Side-effects

- visual disturbances e.g. blue discolouration, non-arteritic anterior ischaemic neuropathy
  Sildenafil is a PDE-5 inhibitor, but at high doses it also **inhibits PDE-6, which leads to blue discoloration of** vision.This can often be managed by reducing the dose of Sildenafil.
- nasal congestion
- flushing
- gastrointestinal side-effects
- headache

Anaesthetic drugs

halothane hepatitis (medical-masterclass.com 2017 mrcp part 2)

- There are many causes of **post-operative jaundice**, but **the fact that the surgery was uncomplicated, the time course, the presence of joint / muscle pains and an eosinophilia, all suggest halothane hepatitis as the most likely diagnosis.** This is thought to result as a hypersensitivity reaction. Treatment is supportive.

Effects on the liver

- **Halothane**
  - Halothane undergoes ~25% metabolism by oxidative phosphorylation via hepatic cytochrome P450 systems.
  - The major metabolite is trifluoroacetic acid (TFA), which is protein-bound and this TFA–protein complex can induce a T-cell-mediated immune response resulting in hepatitis ranging from mild transaminitis to fulminant hepatic necrosis and possibly death.
  - the risk of fatal hepatic necrosis → one in 10 000 anaesthetics.
  - Adult females are more commonly affected.
  - Repeated exposure increases the risk of hepatitis.
  - **Halothane and hepatitis**
    - Halothane can cause a mild liver dysfunction in approximately 30% of patients, due to the binding of reactive halothane metabolites to hepatocytes
    - Halothane oxidation by cytochrome P450 enzymes leads to the synthesis of trifluoroacetyl chloride, which covalently binds to hepatic molecules and causes an immune reaction **Fulminant hepatitis results from the reactive metabolite, trifluoroacetyl chloride**
    - Further exposure to halothane anaesthesia may lead to a fulminant hepatitis, where the mortality is approximately 90%.
- Less commonly hepatitis has been described after exposure to en**flurane** > iso**flurane** > des**flurane**.
- **Sevoflurane** is not metabolized to antigenic TFA–protein complexes.

Inhaled anaesthetic-like agent

- If patient was markedly comatose on arrival but **quickly regains consciousness.** This suggests a short acting (probably) inhaled anaesthetic-like agent → e.g **Inhaled solvent glue.**
- The inhaled solvents, due to their lipophilicity, are rapidly absorbed through the lungs and then quickly distributed to the brain and other organs. The effects therefore appear within minutes of inhalation.
- Typical substances that are inhaled include toluene, aromatic hydrocarbons and butane.

Pseudocholinesterase deficiency (emedicine.medscape.com & medical-masterclass.com 2017 part 2)

- Pseudocholinesterase is a glycoprotein enzyme, produced by the liver.
- It specifically hydrolyzes exogenous choline esters.
- most common in European; rare in Asians.
- Pseudocholinesterase deficiency results in delayed metabolism of the following:
  1. **Succinylcholine.** depolarizing neuromuscular blocking agent (the most clinically important drug)
     - **Suxamethonium** is a depolarising neuromuscular blocking agent, **metabolised by plasma pseudocholinesterases.**
     - Approximately 1 in 2500 individuals have deficiency of this enzyme, **resulting in prolonged neuromuscular blockade if they are given suxamethonium.**
  2. mivacurium.
  3. procaine.

4. cocaine.

- After an intravenous dose of succinylcholine in individuals with normal plasma levels of normally functioning pseudocholinesterase enzyme:
  - hydrolysis and inactivation of 90-95% of i.v succinylcholine occurs before it reaches the neuromuscular junction.
  - The remaining 5-10% of the dose acts as an acetylcholine receptor agonist at the neuromuscular junction, causing prolonged depolarization of the postsynaptic junction of the motor-end plate.
  - This depolarization initially triggers fasciculation of skeletal muscle.
  - As a result of prolonged depolarization, endogenous acetylcholine released from the presynaptic membrane of the motor neuron does not produce any additional change in membrane potential after binding to its receptor on the myocyte.
  - Flaccid paralysis of skeletal muscles develops within 1 minute.
- In normal subjects, skeletal muscle function returns to normal approximately 5 minutes after a single bolus injection of succinylcholine as it passively diffuses away from the neuromuscular junction.
- Pseudocholinesterase deficiency can result in higher levels of intact succinylcholine molecules reaching receptors in the neuromuscular junction, causing the duration of paralytic effect to continue for as long as 8 hours.
- This condition is recognized clinically when paralysis of the respiratory and other skeletal muscles fails to spontaneously resolve after succinylcholine is administered as an adjunctive paralytic agent during anesthesia procedures.

Diagnosis:

- by plasma assays of pseudocholinesterase enzyme activity.

Management

- prolonged ventilation until the action of the drug wears off.
- Relatives of affected patients should be screened.

Prognosis

- exposed to succinylcholine →excellent when close monitoring and respiratory support measures.
- exposed to cocaine, sudden cardiac death can occur.

Succinyl choline

- **Depolarizing Skeletal muscle relaxants**
- Also called suxamethonium
- Analogue of acetyl choline, **acts on nicotinic Nm receptors**
- Only depolarizing skeletal muscle relaxant
- Fastest onset of action, Shortest duration of action
- can stimulate autonomic ganglia
- **Side effect and contraindications (CI)**
  - **Cause hyperkalemia** in patients with nerve and muscular disorders so **CI in**:
    - nerve disorders (Paraplegia, hemiplegia, GBS) and
    - muscular disorders(muscular dystrophy, Myasthenia, crush injury, **burns**, rhabdomyolysis)
  - **Increases all pressures** so **CI in:**
    - glaucoma,
    - head injury,
    - increase BP,
    - nausea and vomiting due to intragastric pressure.
  - Trigger **malignant hyperthermia when used with halothane**

Local spinal anesthetics

Hypotension and bradycardia following spinal anesthesia suggest neurogenic shock.

- Local spinal anesthetics, can interrupt the transmission of nerve impulses in spinal sympathetic pathways, causing a **loss of sympathetic vascular tone** that ultimately results in neurogenic shock.
- Neurogenic shock is a type of distributive shock characterized by:
  - generalized vasodilation (causing **diaphoresis** and **flushed skin**).
  - This vasodilation leads to decreased preload and subsequently reduced cardiac output, which results in **hypotension** and **bradycardia**.
  - Consequently, cerebral perfusion is impaired, leading to a **loss of consciousness**.

Fentanyl

- Large, rapidly given doses of specific opioids such as fentanyl, sufentanil, remifentanil, and alfentanil are associated with systemic skeletal muscle rigidity.
  - Of most concern to the anesthesiologist is **chest wall rigidity** (**which impairs mask and bag ventilation**) and **rigidity of the jaw muscles which can prevent the insertion of an advanced airway**.

Ketamine

- Ketamine is commonly used as a recreational drug.

adverse effects include:

- stimulation, **euphoria**, depersonalisation, floating feeling
- synaesthesia (a sensory stimulus in one modality is perceived as a sensation in another), eg: being **able to 'smell sounds'**
- delirium,
- vivid dreams
- hallucinations.

Topoisomerase inhibitors

- (topoisomerase I and II) are enzymes that control the changes in DNA structure during the normal cell cycle.
- **By what mechanism does topoisomerase catalyse DNA replication?**
  - **Helix torsion release**
    - Topoisomerase releases torsion in the DNA helix during replication.
    - It accomplishes this by **cutting the DNA helix at specific points to allow it to unravel and then ligates the ends together again.** This **allows large proteins such as DNA polymerase to replicate DNA** along the sequence.
    - Topoisomerase is therefore an important target for chemotherapeutic agents such as topotecan which can **arrest cells in S-phase and induce apoptosis.**
- Topoisomerase inhibition leads to apoptosis and cell death.
- Used in:
  - chemotherapy treatments.
  - as antibacterial agents :Quinolones (including nalidixic acid and ciprofloxacin)

classification:

- Topoisomerase I inhibitors: irino**tecan**, topo**tecan**, camptothecin
- Topoisomerase II inhibitors:
  - anti-cancer: eto**poside**, teni**poside**, dox**orubicin**, daun**orubicin**,
  - anti-bacterial : Quinolones (nalidixic acid and ciprofloxacin)

Irinotecan

- Irinotecan is in topoisomerase inhibitor.
- **It works by blocking topoisomerase 1** which results in DNA damage and cell death.
- Its main use is in colon cancer
  - This includes the regimen FOLFIRI which consists of infusional 5-fluorouracil, leucovorin, and irinotecan.
- The most significant adverse effects of irinotecan are:
  - severe diarrhea
  - extreme suppression of the immune system

Sodium aurothiomalate (gold)

- used for rheumatoid arthritis.
- has been superceded by newer and less toxic DMARDs.
- **Side effects**
  - commonly causes trace proteinuria, and if present on its own is unimportant,
  - membranous glomerulonephritis
  - dermatitis, stomatitis,

Antivenom

- The adder (*Vipera berus*) is the only poisonous indigenous snake in the United Kingdom.
- Most adder bites occur in the summer months to people walking in long grass or heathland and typically occur on the ankle and lower leg.

- Only 50% of bites are associated with true envenomation as snakes do not always inject venom when they bite.
- Local symptoms and signs include:
  - pain, swelling and bruising at the site of the bite and
  - painful regional lymphadenopathy.
- Systemic features of envenomation may be divided into two types:
  - Early anaphylactoid symptoms that include:
    - nausea, vomiting, abdominal pain, diarrhoea,
    - transient hypotension with syncope,
    - angioedema or urticarial
  - Some patients later have:
    - persistent hypotension,
    - ECG abnormalities,
    - coagulopathy or spontaneous bleeding,
    - adult respiratory distress syndrome, and
    - acute renal failure.
  - There is frequently a leukocytosis (WBC > 15 $\times 10^9$/L)
  - serum creatine kinase may be elevated.
- **Complications**
  - Fatalities are rare following adder bites, though they may be associated with significant morbidity especially tissue necrosis at the site of the bite in adults.
- **Treatment**
  - usually supportive.
  - The bitten limb should be immobilised and a ligature is not necessary unless a delay is anticipated before admission to hospital.
  - Any patient who shows signs of envenomation needs to be admitted to hospital and monitored for 24 hours.
  - Regular monitoring should consist of measurement of pulse, blood pressure, urine output and the degree of swelling of the bitten limb should be recorded.
  - Early anaphylactoid symptoms may be treated with adrenaline.
  - European viper venom antiserum is available and should be considered in the following situations:
    - Persistent hypotension
    - ECG abnormalities
    - Haemostatic abnormalities
    - **Marked local tissue swelling extending proximally (extending above the ankle or wrist [if bitten on the hand/foot] within four hours of the bite).**
  - Antivenom administration
    - given by intravenous injection over 10-15 minutes or by intravenous infusion over 30 minutes
    - may be repeated after 12 hours if symptoms of systemic envenoming persist.
    - Anaphylactic reactions occur in 1% of patients during administration of antivenom
    - history of asthma or other allergy is a relative contraindication to its use.
    - Adrenaline should be available for immediate use while the antivenom is infused in case a severe anaphylactic reaction occurs.

Weeverfish (*Trachinus vipera*)

- The weeverfish (*Trachinus vipera*) lives in shallow waters around the coast of the United Kingdom.
- This small, sandy-coloured fish has sharp dorsal opercular spines that are attached to subcutaneous poison glands.
- Most stings from the weeverfish occur in the summer months in bare-footed bathers who step on the fish in shallow water, but stings also occur in anglers who attempt to grasp the fish when caught on a line.
- The sting of the fish causes intense pain at the site of the wound.
- **The toxin produced by the fish is heat-labile and is denatured at temperatures above 40°C.**
- Treatment of a weeverfish sting should include **cleansing of the wound and immersion in hot water** (as hot as can be borne), ideally around 45°C.

Jellyfish sting

- The jellyfish with the most severe sting in British waters is the Portuguese man-of-war.
- The Portuguese man-of-war *(Physalia physalis*) - actually a form of plankton and not a jellyfish - can give a fatal sting in susceptible individuals.
- Treatment
  - A slurry of **sodium bicarbonate** has been shown to be of **benefit in treating stings from all UK species** - and is therefore **a better choice when it is uncertain which species is**

responsible.