صدقه جاريه على روح أبى فاللهم تقبلها بقبول حسن وأجعلها في ميزان حسناته

برجاء الدعاء له بالمغفرة و الرحمة

د/سيد عبدالنبي مصطفى

الطبيب الذي أفنى عمره في علاج المرضى بمستشفيات وزارة الصحة في مصر

Passmedicine notes 2017

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Cardiology

Acute coronary syndrome: a very basic introduction

Acute coronary syndrome (ACS) is an umbrella term covering a number of acute presentations of ischaemic heart disease.

It covers a number of presentations, including

- ST elevation myocardial infarction (STEMI)
- non-ST elevation myocardial infarction (NSTEMI)
- unstable angina

Before we go into more detail into these presentations it's useful to take a step back and consider how such conditions develop.

ACS generally develops in patients who have ischaemic heart disease, either known or previously undetected. Ischaemic heart disease is a term synonymous with coronary heart disease and coronary artery disease. It describes the gradually build up of fatty plaques within the walls of the coronary arteries. This leads to two main problems:

- 1. Gradual narrowing, resulting in less blood and therefore oxygen reaching the myocardium at times of increased demand. This results in angina, i.e. chest pain due to insufficient oxygen reaching the myocardium during exertion
- 2. The risk of sudden plaque rupture. The fatty plaques which have built up in the endothelium may rupture leading to sudden occlusion of the artery. This can result in no blood/oxygen reaching the area of myocardium.

Remember that there are a large number of factors which can increase the chance of a patient developing ischaemic heart disease:

Unmodifiable risk factors	Modifiable risk factors
Increasing age Male gender Family history	Smoking Diabetes mellitus Hypertension Hypercholesterolaemia Obesity

Pathophysiology
Ischaemic heart disease 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.
- smooth muscle proliferation and migration from the tunica media into the intima results in formation of a fibrous capsule covering the fatty plaque.

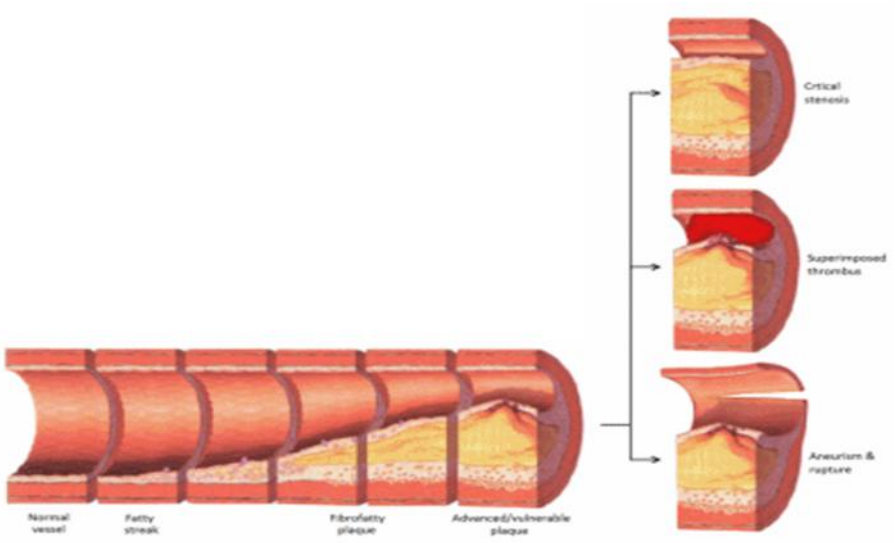
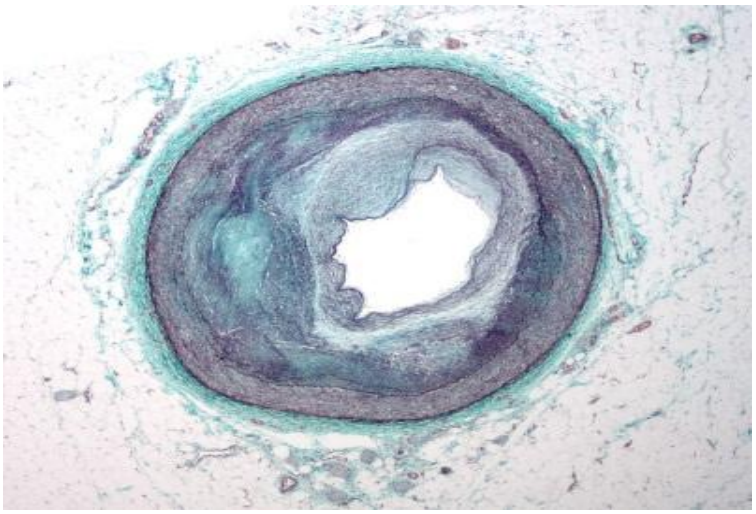


Diagram showing the progression of atherosclerosis in the coronary arteries with associated complications on the right

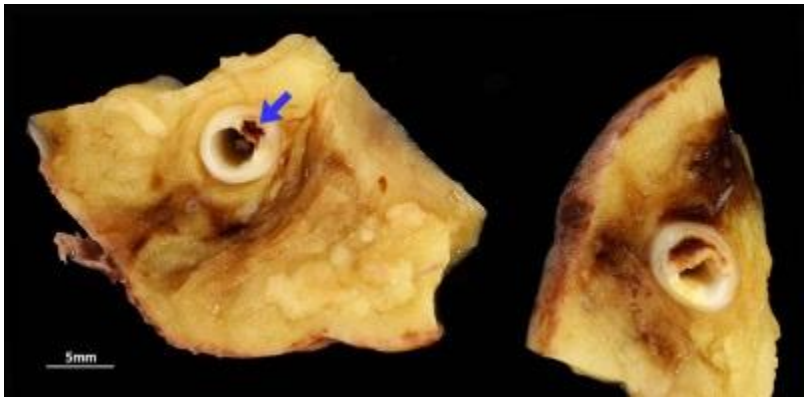


Slide showing a markedly narrowed coronary artery secondary to atherosclerosis. Stained with Masson's trichrome.

Complications of atherosclerosis

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



Ruptured coronary artery plaque resulting in thrombosis and associated myocardial infarction.

Pathological specimen showing infarction of the anteroseptal and lateral wall of the left ventricle. There is a background of biventricular myocardial hypertrophy.

Symptoms and signs
The classic and most common feature of ACS is chest pain.

- typically central/left-sided
- may radiate to the jaw or the left arm
- often described as 'heavy' or constricting, 'like an elephant on my chest'
- it should be noted however in real clinical practice patients present with a wide variety of types of chest pain and patients/doctors may confuse ischaemic pain for other causes such as dyspepsia
- certain patients e.g. diabetics/elderly may not experience any chest pain

Other symptoms in ACS include

- dyspnoea
- sweating
- nausea and vomiting

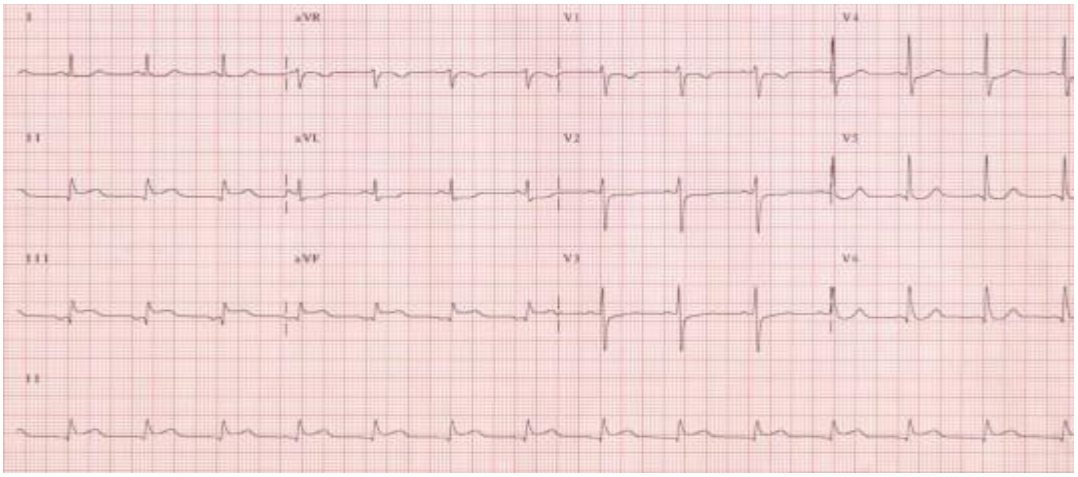
Patients presenting with ACS often have very few physical signs to ellicit:

- pulse, blood pressure, temperature and oxygen saturations are often normal or only mildly altered e.g. tachycardia
- if complications of the ACS have developed e.g. cardiac failure then clearly there may a number of findings
- the patient may appear pale and clammy

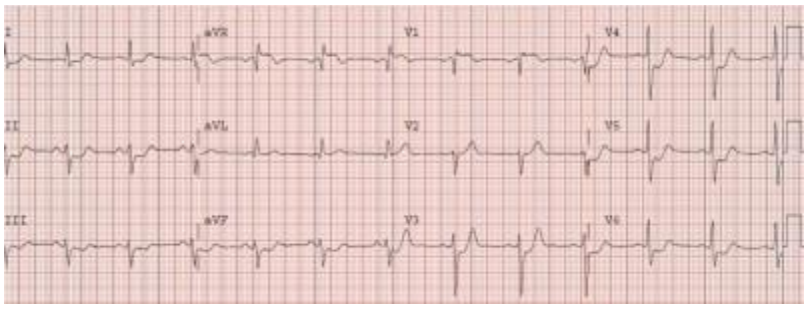
Investigations

The two most important investigations when assessing a patient with chest pain are:

- ECG
- cardiac markers e.g. troponin



ECG showing a ST elevation myocardial infarction (STEMI). Note by how looking at which leads are affected (in this case II, III and aVF) we are able to tell which coronary arteries are blocked (the right coronary artery in this case). A blockage of the left anterior descending (LAD) artery would cause elevation of V1-V4, what is often termed an 'anterior' myocardial infarction.



ECG showing a non-ST elevation myocardial infarction (NSTEMI). On the ECG there is deep ST depression in I-III, aVF, and V3-V6. aVR also has ST elevation. Deep and widespread ST depression is associated with very high mortality because it signifies severe ischemia usually of LAD or left main stem.

The table below shows a simplified correlation between ECG changes and coronary territories:

	ECG changes	Coronary artery
Anterior	V1-V4	Left anterior descending
Inferior	II, III, aVF	Right coronary
Lateral	I, V5-6	Left circumflex

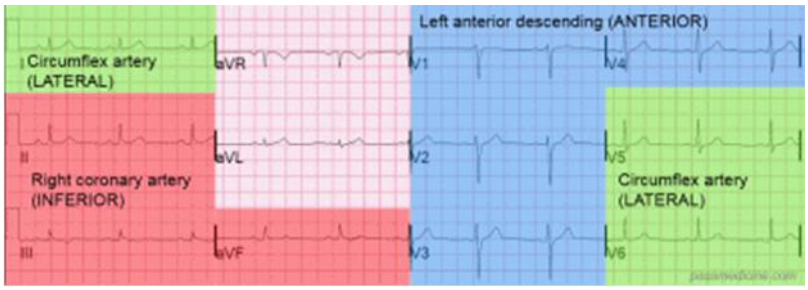


Diagram showing the correlation between ECG changes and coronary territories in acute coronary syndrome

Management

Once a diagnosis of ACS has been made there are a number of elements to treatment:

- prevent worsening of presentation (i.e. further occlusion of coronary vessel)
- revascularise (i.e. 'unblock') the vessel if occluded (patients presenting with a STEMI)
- treat pain

A commonly taught mnemonic for the treatment of ACS is MONA:

- Morphine
- Oxygen
- Nitrates
- Aspirin

Whilst useful it should be remember that not all patients require oxygen therapy. British Thoracic Society guidelines are now widely adopted and oxygen should only be given if the oxygen saturations are < 94%.

For patients who've had a **STEMI** (i.e. one of the coronary arteries has become occluded) the priority of management is to reopen, or revascularise, the blocked vessel.

- a second antiplatelet drug should be given in addition to aspirin. Options include clopidogrel, prasugrel and ticagrelor
- for many years the treatment of choice was thrombolysis. This involved the intravenous administration of a thrombolytic or 'clot-busting' drug to breakdown the thrombus blocking the coronary artery
- since the early 2000's thrombolysis has been superseded by percutaneous coronary intervention (PCI). In this procedure the blocked arteries are opened up using a balloon (angioplasty) following which a stent may be deployed to prevent the artery occluding again in the future. This is done via a catheter inserted into either the radial or femoral artery

If a patient presents with an **NSTEMI** then a risk stratification too (such as GRACE) is used to decide upon further management. If a patient is considered high-risk or is clinically unstable then coronary angiography will be performed during the admission. Lower risk patients may have a coronary angiogram at a later date.

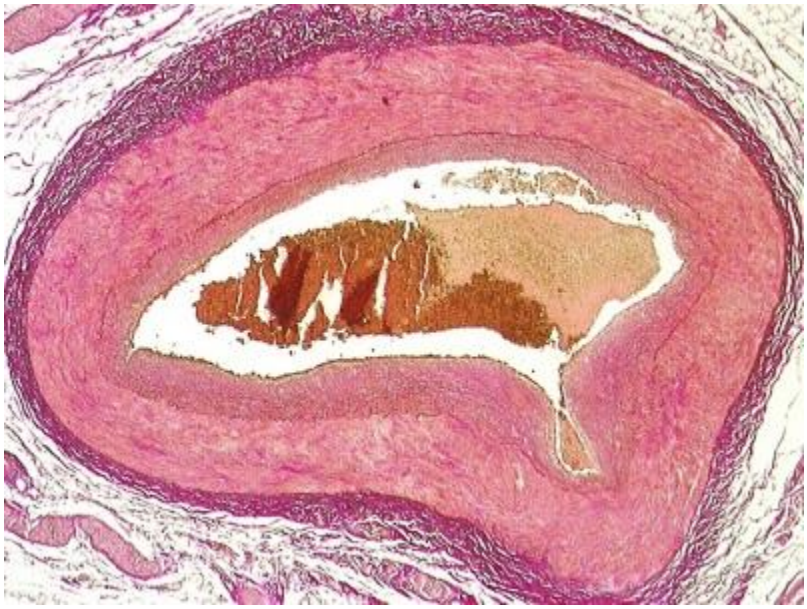
Secondary prevention

Patients who've had an ACS require lifelong drug therapy to help reduce the risk of a further event. Standard therapy comprises the following as a minimum:

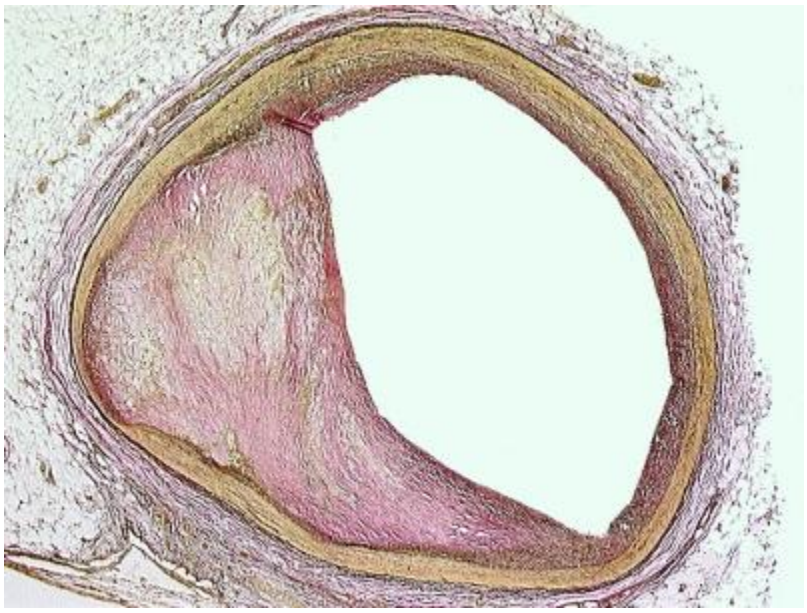
- aspirin
- a second antiplatelet if appropriate (e.g. clopidogrel)
- a beta-blocker
- an ACE inhibitor
- a statin

Further images

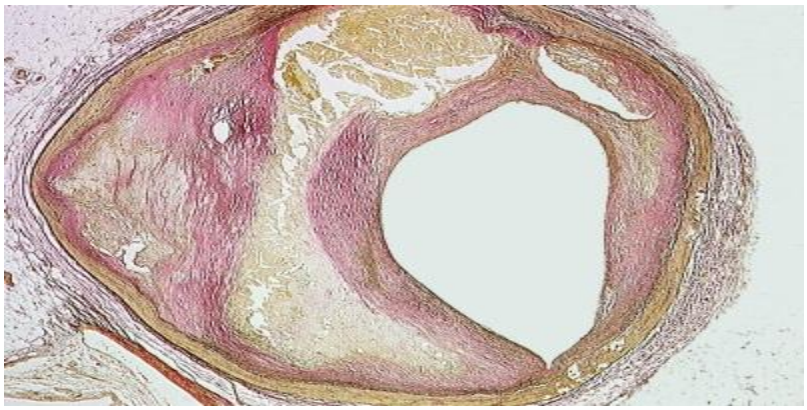
The following images show the progress of coronary artery atherosclerosis:



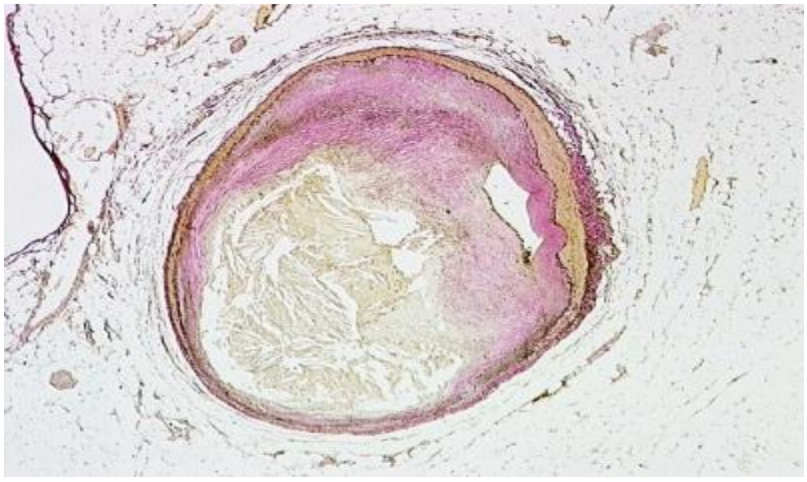
Normal coronary artery with blood in the lumen.



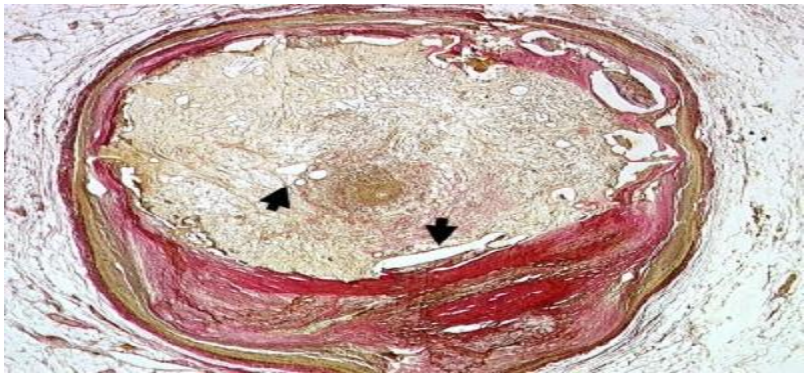
Slightly stenosed coronary artery



Moderately stenosed coronary artery, beetween 50-75%



Severely stenosed coronary artery



Recanalised old atherothrombotic occlusion of a coronary artery. Numerous small neolumina recanalising the organised occluding thrombus (indicated with arrows)

Acute coronary syndrome: management of NSTEMI

NICE produced guidelines in 2013 on the *Secondary prevention in primary and secondary care for patients following a myocardial infarction management of unstable angina and non-ST elevation myocardial infarction (NSTEMI)*. These superceded the 2010 guidelines which advocated a risk-based approach to management which determined whether drugs such as clopidogrel were given.
All patients should receive

- aspirin 300mg
- nitrates or morphine to relieve chest pain if required

Whilst it is common that non-hypoxic patients receive oxygen therapy there is little evidence to support this approach. The 2008 British Thoracic Society oxygen therapy guidelines advise not giving oxygen unless the patient is hypoxic.

Antithrombin treatment. Fondaparinux should be offered to patients who are not at a high risk of bleeding and who are not having angiography within the next 24 hours. If angiography is likely within 24 hours or a patients creatinine is > 265 µmol/l unfractionated heparin should be given.

Clopidogrel 300mg should be given to all patients and continued for 12 months.
Intravenous **glycoprotein IIb/IIIa receptor antagonists** (eptifibatide or tirofiban) should be given to patients who have an intermediate or higher risk of adverse cardiovascular events (predicted 6-month mortality above 3.0%), and who are scheduled to undergo angiography within 96 hours of hospital admission.
Coronary angiography should be considered within 96 hours of first admission to hospital to patients who have a predicted 6-month mortality above 3.0%. It should also be performed as soon as possible in patients who are clinically unstable.

The table below summaries the mechanism of action of drugs commonly used in the management of acute coronary syndrome:

Medication	Mechanism of action
Aspirin	Antiplatelet - inhibits the production of thromboxane A2
Clopidogrel	Antiplatelet - inhibits ADP binding to its platelet receptor
Enoxaparin	Activates antithrombin III, which in turn potentiates the inhibition of coagulation factors Xa
Fondaparinux	Activates antithrombin III, which in turn potentiates the inhibition of coagulation factors Xa
Bivalirudin	Reversible direct thrombin inhibitor

Acute coronary syndrome: prognostic factors

The 2006 Global Registry of Acute Coronary Events (GRACE) study has been used to derive regression models to predict death in hospital and death after discharge in patients with acute coronary syndrome

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%

Acute pericarditis

Pericarditis is one of the differentials of any patient presenting with chest pain.

Features

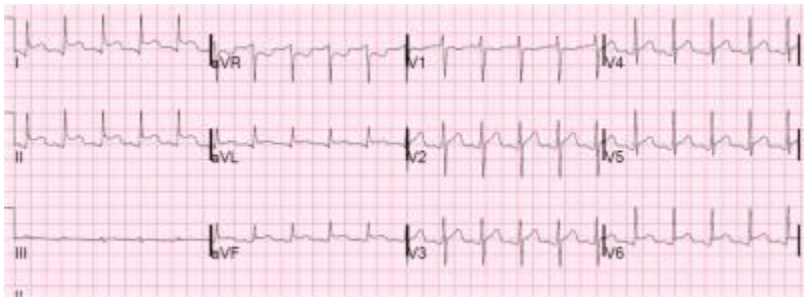
- chest pain: may be pleuritic. Is often relieved by sitting forwards
- other symptoms include non-productive cough, dyspnoea and flu-like symptoms
- pericardial rub
- tachypnoea
- tachycardia

Causes

- viral infections (Coxsackie)
- tuberculosis
- uraemia (causes 'fibrinous' pericarditis)
- trauma
- post-myocardial infarction, Dressler's syndrome
- connective tissue disease
- hypothyroidism

ECG changes

- widespread 'saddle-shaped' ST elevation
- PR depression: most specific ECG marker for pericarditis



ECG showing pericarditis. Note the widespread nature of the ST elevation and the PR depression

Adult advanced life support

The following is based on the 2015 Resus Council guidelines. Please see the link for more details, below is only a very brief summary of key points.

Major points include:

- 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).
- atropine is no longer recommended for routine use in asystole or pulseless 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
- if the cardiac arrested is witnessed in a monitored patient (e.g. in a coronary care unit) then the 2015 guidelines recommend 'up to three quick successive (stacked) shocks', rather than 1 shock followed by CPR
- asystole/pulseless-electrical activity should be treated with 2 minutes of CPR prior to reassessment of the rhythm
- 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

Angina pectoris: 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

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

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. Headache. Bradycardia, due to the mechanism of action, may also be seen
- there is no evidence currently of superiority over existing treatments of stable angina

Angiotensin II receptor blockers

Angiotensin II receptor blockers are generally used in situations where patients have not tolerated an ACE inhibitor, usually due to the development of a cough.

Examples

- candesartan
- losartan
- irbesartan

Like ACE inhibitors they should be used with caution in patients with renovascular disease. Side-effects include hypotension and hyperkalaemia.

Mechanism

- block effects of angiotensin II at the AT1 receptor

Evidence base

- shown to reduce progression of renal disease in patients with diabetic nephropathy
- evidence base that losartan reduces CVA and IHD mortality in hypertensive patients

Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme (ACE) inhibitors are now the established first-line treatment in younger patients with hypertension and are also extensively used to treat heart failure. They are known to be less effective in treating hypertensive Afro-Caribbean patients. ACE inhibitors are also used to treat diabetic nephropathy and have a role in secondary prevention of ischaemic heart disease.

Mechanism of action:

- inhibit the conversion angiotensin I to angiotensin II

Side-effects:

- cough: occurs in around 15% of patients and may occur up to a year after starting treatment. Thought to be due to increased bradykinin levels
- angioedema: may occur up to a year after starting treatment
- hyperkalaemia
- first-dose hypotension: more common in patients taking diuretics

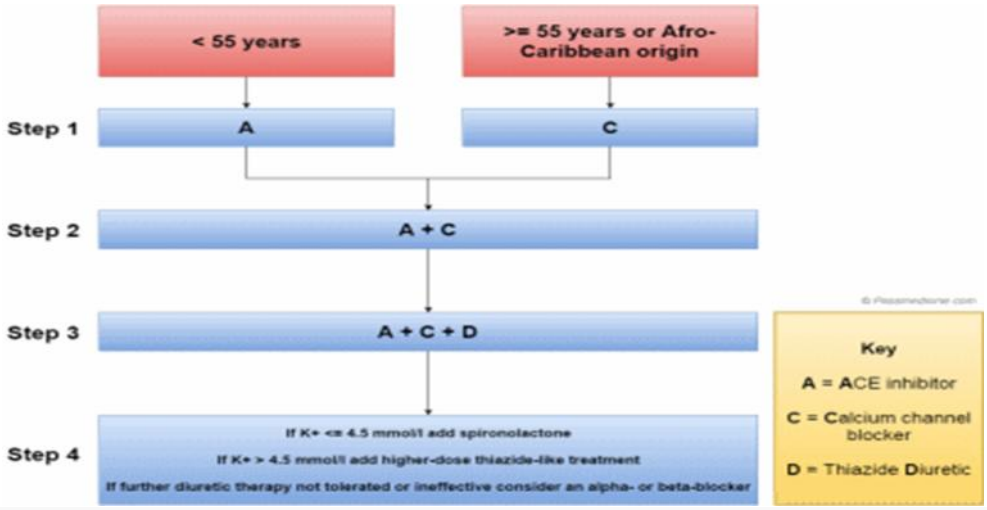
Cautions and contraindications

- pregnancy and breastfeeding - avoid
- 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) - significantly increases the risk of hypotension
- hereditary of idiopathic angioedema

Monitoring

- urea and electrolytes should be checked before treatment is initiated and after increasing the dose
- a rise in the creatinine and potassium may be expected after starting ACE inhibitors. Acceptable changes are an increase in serum creatinine, up to 30%* from baseline and an increase in potassium up to 5.5 mmol/l*.

*Renal Association UK, Clinical Knowledge Summaries quote 50% which seems rather high. SIGN advise that the fall in eGFR should be less than 20%. The NICE CKD guidelines suggest that a decrease in eGFR of up to 25% or a rise in creatinine of up to 30% is acceptable



Flow chart showing the management of hypertension as per current NICE guideliness

Antiplatelets: summary of latest guidance

The table below summarises the most recent guidelines regarding antiplatelets:

Diagnosis	1st line	2nd line
NSTEMI	Aspirin (lifelong) & clopidogrel or ticagrelor (12 months)	If aspirin contraindicated, clopidogrel (lifelong)
STEMI	Aspirin (lifelong) & clopidogrel or ticagrelor (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.

Aortic dissection

Stanford classification

- type A - ascending aorta, 2/3 of cases
- type B - descending aorta, 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

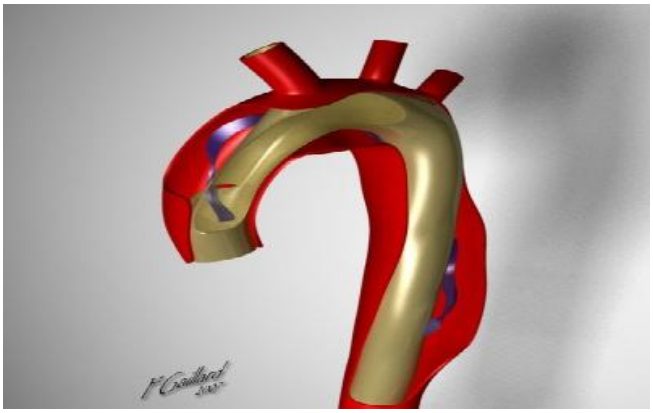
- hypertension
- trauma
- bicuspid aortic valve
- collagens: Marfan's syndrome, Ehlers-Danlos syndrome
- Turner's and Noonan's syndrome
- pregnancy
- syphilis

Complications of backward tear

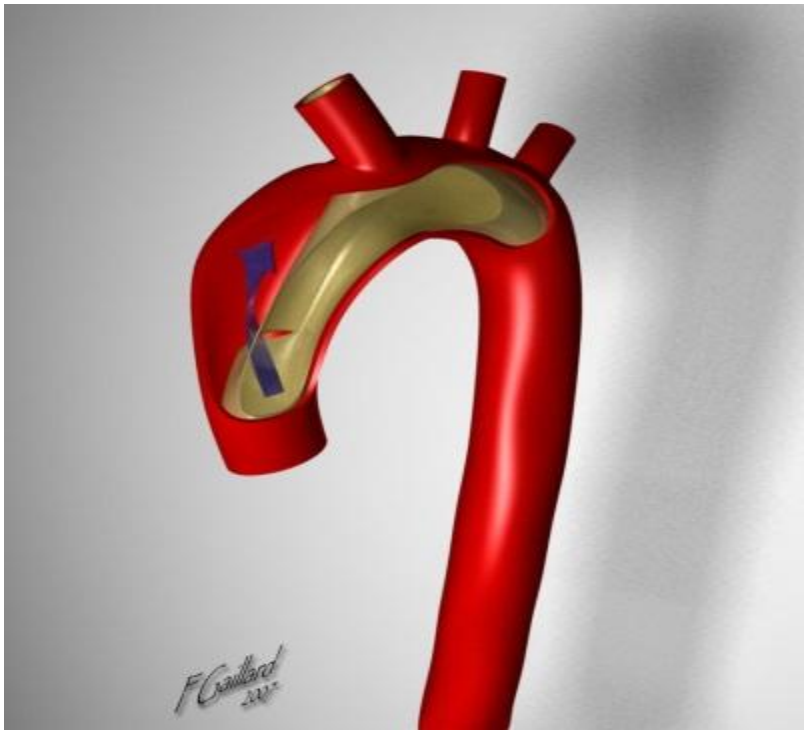
- aortic incompetence/regurgitation
- MI: inferior pattern often seen due to right coronary involvement

Complications of forward tear

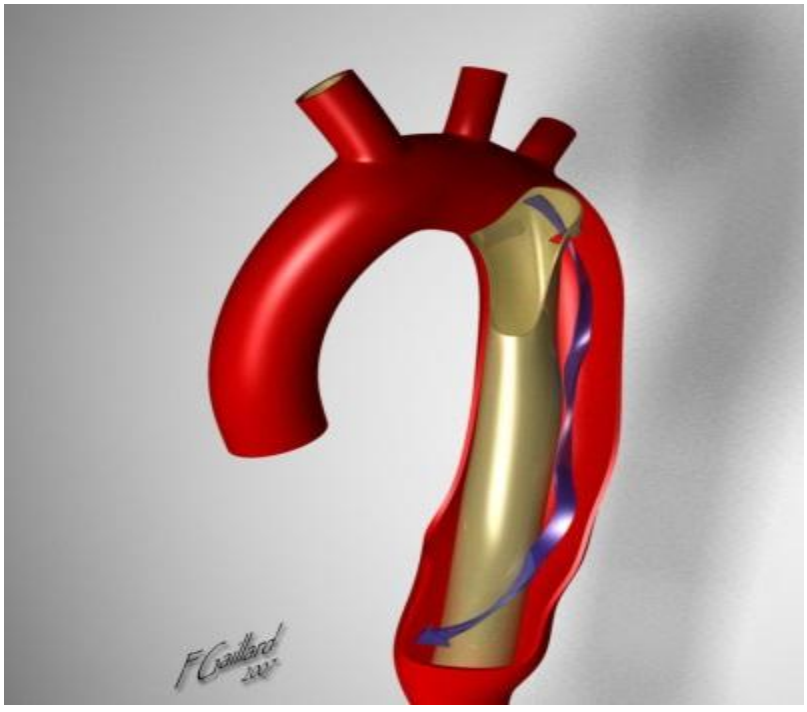
- unequal arm pulses and BP
- stroke
- renal failure



Stanford type A / DeBakey type I



Stanford type A / DeBakey type II



Stanford type B / DeBakey type III

Aortic dissection: management

Stanford classification

- type A - ascending aorta, 2/3 of cases
- type B - descending aorta, 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

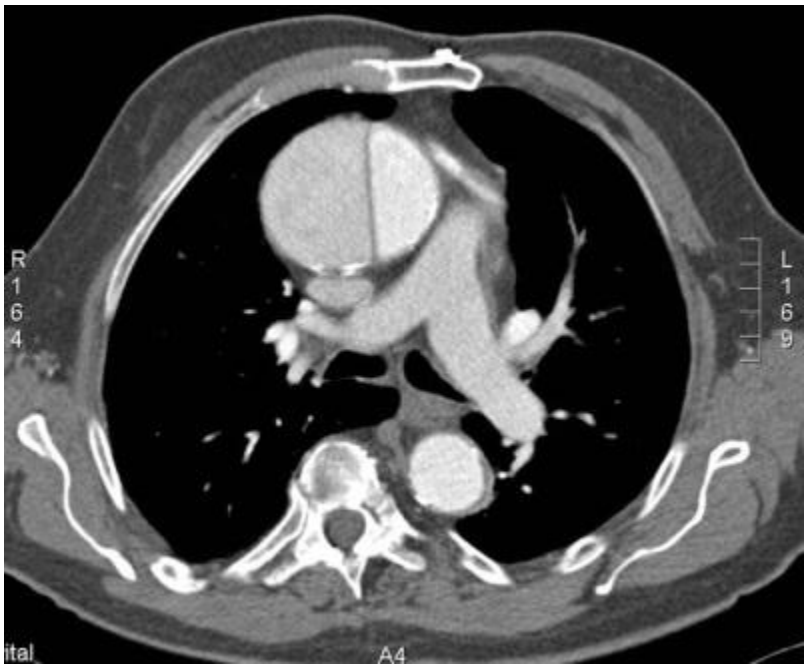
Type A

- surgical management, but blood pressure should be controlled to a target systolic of 100-120 mmHg whilst awaiting intervention

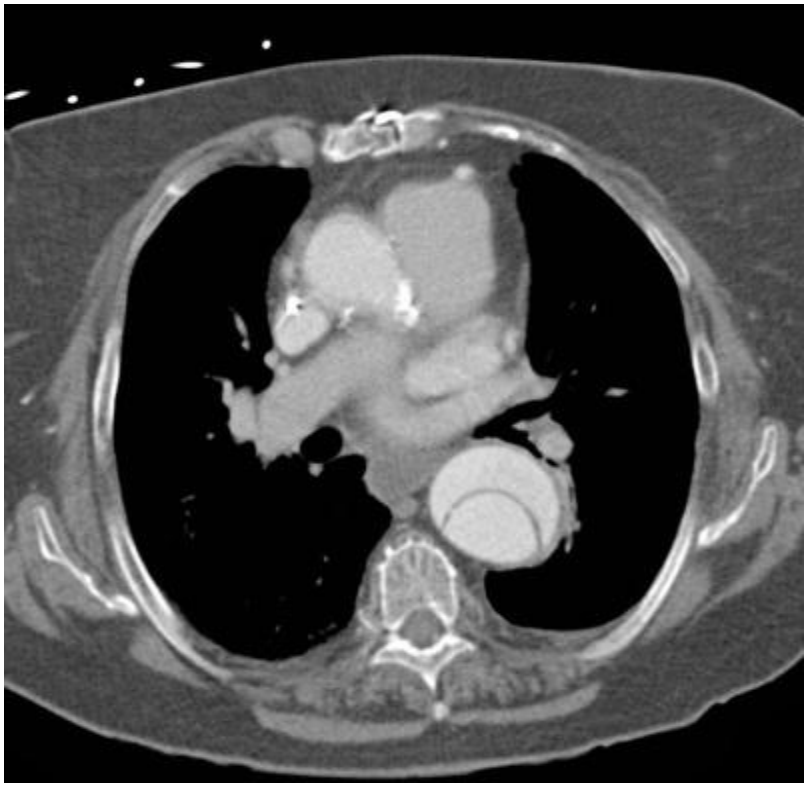
Type B*

- 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



An intraluminal tear has formed a 'flap' that can be clearly seen in the ascending aorta. This is a Stanford type A dissection



Stanford type B dissection, seen in the descending aorta

Aortic regurgitation

Features

- early diastolic murmur
- collapsing pulse
- wide pulse pressure
- mid-diastolic Austin-Flint murmur in severe AR - due to partial closure of the anterior mitral valve cusps caused by the regurgitation streams

Causes (due to valve disease)

- rheumatic fever
- infective endocarditis
- connective tissue diseases e.g. RA/SLE
- bicuspid aortic valve

Causes (due to aortic root disease)

- aortic dissection
- spondylarthropathies (e.g. ankylosing spondylitis)
- hypertension
- syphilis
- Marfan's, Ehler-Danlos syndrome

Aortic stenosis

Features of severe aortic stenosis

- narrow pulse pressure
- slow rising pulse
- delayed ESM
- soft/absent S2
- S4
- thrill
- duration of murmur
- left ventricular hypertrophy or failure

Causes of aortic stenosis

- degenerative calcification (most common cause in older patients > 65 years)
- bicuspid aortic valve (most common cause in younger patients < 65 years)
- William's syndrome (supravalvular aortic stenosis)
- post-rheumatic disease
- subvalvular: HOCM

Management

- if asymptomatic then observe the patient is general rule
- if symptomatic then valve replacement
- if asymptomatic but valvular gradient > 40 mmHg and with features such as left ventricular systolic dysfunction then consider surgery
- balloon valvuloplasty is limited to patients with critical aortic stenosis who are not fit for valve replacement

Arrhythmogenic right ventricular cardiomyopathy

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.

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

- 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
- 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: a very basic introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. It is very common, being present in around 5% of patients over aged 70-75 years and 10% of patients aged 80-85 years. Whilst uncontrolled atrial fibrillation can result in symptomatic palpitations and inefficient cardiac function probably the most important aspect of managing patients with AF is reducing the increased risk of stroke which is present in these patients.

Types of atrial fibrillation

AF may be classified as either first detected episode, paroxysmal, persistent or permanent.

- first detected episode (irrespective of whether it is symptomatic or self-terminating)
- recurrent episodes, when a patient has 2 or more episodes of AF. If episodes of AF terminate spontaneously then the term **paroxysmal AF** is used. Such episodes last less than 7 days (typically < 24 hours). If the arrhythmia is not self-terminating then the term **persistent AF** is used. Such episodes usually last greater than 7 days
- in **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
- dyspnoea
- chest pain

Signs

- an irregularly irregular pulse

Investigations

An ECG is essential to make the diagnosis as other conditions can give an irregular pulse, such as ventricular ectopics or sinus arrhythmia.

Management

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 employed in dealing with the arrhythmia element of atrial fibrillation:

- **rate control**: accept that the pulse will be irregular, but slow the rate down to avoid negative effects on cardiac function
- **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

For many years the predominant approach was to try and maintain a patient in sinus rhythm. This approach changed in the early 2000's and now the majority of patients are managed with a rate control strategy. NICE advocate using a rate control strategy except in a number of specific situations such as coexistent heart failure, first onset AF or where there is an obvious reversible cause.

Rate control

A **beta-blocker** or a **rate-limiting calcium channel blocker** (e.g. diltiazem) is used first-line to control the rate in AF.

If one drug does not control the rate adequately NICE recommend combination therapy with any 2 of the following:

- a betablocker
- diltiazem
- digoxin

Rhythm control

As mentioned above there are a subgroup of patients for whom a rhythm control strategy should be tried first. Other patients may have had a rate control strategy initially but switch to rhythm control if symptoms/heart rate fails to settle.

When considering cardioversion it is very important to remember that the moment a patient switches from AF to sinus rhythm presents the highest risk for embolism leading to stroke. Imagine the thrombus formed in the fibrillating atrium suddenly being pushed out when sinus rhythm is restored. For this reason patients must either of had a short duration of symptoms (less than 48 hours) or be anticoagulated for a period of time prior to attempting cardioversion.

Reducing stroke risk

Some patients with AF are at a very low risk of stroke whilst others are at a very significant risk. Clinicians use risk stratifying tools such as 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 their gender)
2 or more	Offer anticoagulation

NICE recommend that we offer patients a choice of anticoagulation, including warfarin and the novel oral anticoagulants (NOACs).

Atrial fibrillation: anticoagulation

NICE updated their guidelines on the management of atrial fibrillation (AF) in 2014. They suggest using the **CHA_2DS_2-VASc** score to determine the most appropriate anticoagulation strategy. This scoring system superceded the $CHADS_2$ score.

	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
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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 their gender)
2 or more	Offer anticoagulation

NICE recommend that we offer patients a choice of anticoagulation, including warfarin and the novel oral anticoagulants (NOACs). There are complicated rules surrounding which NOAC is licensed for which risk factor - these can be found in the NICE guidelines. 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: cardioversion

There are two scenarios where cardioversion may be used in atrial fibrillation:

- electrical cardioversion as an emergency if the patient is haemodynamically unstable
- electrical or pharmacological cardioversion as an elective procedure where a rhythm control strategy is preferred.

The notes below refer to cardioversion being used in the elective scenario for rhythm control. The wording of the 2014 NICE guidelines is as follows:

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

Onset < 48 hours

If the atrial fibrillation (AF) is definitely of less than 48 hours onset patients should be heparinised. Patients who have risk factors for ischaemic stroke should be put on lifelong oral anticoagulation. Otherwise, patients may be cardioverted using either:

- electrical - 'DC cardioversion'
- pharmacology - amiodarone if structural heart disease, flecainide or amiodarone in those without structural heart disease

Following electrical cardioversion if AF is confirmed as being less than 48 hours duration then further anticoagulation is unnecessary

Onset > 48 hours

If the patient has been in AF for more than 48 hours then anticoagulation should be given for at least 3 weeks prior to cardioversion. An alternative strategy is to perform a transoesophageal echo (TOE) to exclude a left atrial appendage (LAA) thrombus. If excluded patients may be heparinised and cardioverted immediately.

NICE recommend electrical cardioversion in this scenario, rather than pharmacological.

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

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

Atrial fibrillation: classification

An attempt was made in the joint American Heart Association (AHA), American College of Cardiology (ACC) and European Society of Cardiology (ESC) 2012 guidelines to simplify and clarify the classification of atrial fibrillation (AF).

It is recommended that AF be classified into 3 patterns:

- first detected episode (irrespective of whether it is symptomatic or self-terminating)
- recurrent episodes, when a patient has 2 or more episodes of AF. If episodes of AF terminate spontaneously then the term **paroxysmal AF** is used. Such episodes last less than 7 days (typically < 24 hours). If the arrhythmia is not self-terminating then the term **persistent AF** is used. Such episodes usually last greater than 7 days
- in **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

Atrial fibrillation: pharmacological cardioversion

The Royal College of Physicians and NICE published guidelines on the management of atrial fibrillation (AF) in 2006. The following is also based on the joint American Heart Association (AHA), American College of Cardiology (ACC) and European Society of Cardiology (ESC) 2012 guidelines

Agents with proven efficacy in the pharmacological cardioversion of atrial fibrillation

- amiodarone
- flecainide (if no structural heart disease)
- others (less commonly used in UK): quinidine, dofetilide, ibutilide, propafenone

Less effective agents

- beta-blockers (including sotalol)
- calcium channel blockers
- digoxin
- disopyramide
- procainamide

Atrial fibrillation: post-stroke

NICE issued guidelines on atrial fibrillation (AF) in 2006. They included advice on the management of patients with AF who develop a stroke or transient-ischaemic attack (TIA).

Recommendations include:

- 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
- 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

Atrial fibrillation: rate control and maintenance of sinus rhythm

The Royal College of Physicians and NICE published guidelines on the management of atrial fibrillation (AF) in 2006. The following is also based on the joint American Heart Association (AHA), American College of Cardiology (ACC) and European Society of Cardiology (ESC) 2012 guidelines

Agents used to control rate in patients with atrial fibrillation

- beta-blockers
- calcium channel blockers
- digoxin (not considered first-line anymore as they are less effective at controlling the heart rate during exercise. However, they are the preferred choice if the patient has coexistent heart failure)

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

Atrial flutter is a form of supraventricular tachycardia characterised by a succession of rapid atrial depolarisation waves.

ECG findings

- 'sawtooth' appearance
- 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
- radiofrequency ablation of the tricuspid valve isthmus is curative for most patients

Atrial myxoma

Overview

- 75% occur in left atrium
- more common in females

Features

- systemic: dyspnoea, fatigue, weight loss, fever, clubbing
- emboli
- atrial fibrillation
- mid-diastolic murmur, 'tumour plop'
- echo: pedunculated heterogeneous mass typically attached to the fossa ovalis region of the interatrial septum

Atrioventricular block

In atrioventricular (AV) block, or heart block, there is impaired electrical conduction between the atria and ventricles. There are three types:

First degree heart block

- PR interval > 0.2 seconds

Second degree heart block

- type 1 (Mobitz I, Wenckebach): progressive prolongation of the PR interval until a dropped beat occurs
- type 2 (Mobitz II): PR interval is constant but the P wave is often not followed by a QRS complex

Third degree (complete) heart block

- there is no association between the P waves and QRS complexes

Beta-blockers

Beta-blockers are an important class of drug used mainly in the management of cardiovascular disorders.

Indications

- angina
- post-myocardial infarction
- heart failure: beta-blockers were previously avoided in heart failure but there is now strong evidence that certain beta-blockers improve both symptoms and mortality
- 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

Examples

- atenolol
- propranolol: one of the first beta-blockers to be developed. Lipid soluble therefore crosses the blood-brain barrier

Side-effects

- bronchospasm
- cold peripheries
- fatigue
- sleep disturbances, including nightmares

Contraindications

- uncontrolled heart failure
- asthma
- sick sinus syndrome
- concurrent verapamil use: may precipitate severe bradycardia

Bicuspid aortic valve

Overview

- occurs in 1-2% of the population
- usually asymptomatic in childhood
- the majority eventually develop aortic stenosis or regurgitation
- associated with a left dominant coronary circulation (the posterior descending artery arises from the circumflex instead of the right coronary artery) and Turner's syndrome
- around 5% of patients also have coarctation of the aorta

Complications

- aortic stenosis/regurgitation as above
- higher risk for aortic dissection and aneurysm formation of the ascending aorta

Bivalirudin

Bivalirudin is a reversible direct thrombin inhibitor used as an anticoagulant in the management of acute coronary syndrome.

Broad complex tachycardia

Features suggesting VT rather than SVT with aberrant conduction

- AV dissociation
- fusion or capture beats
- positive QRS concordance in chest leads
- marked left axis deviation
- history of IHD
- lack of response to adenosine or carotid sinus massage
- QRS > 160 ms

Brugada syndrome

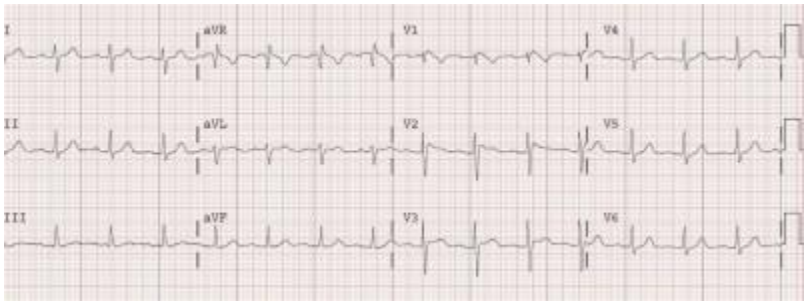
Brugada syndrome is a form of inherited cardiovascular disease with may present with sudden cardiac death. It is inherited in an autosomal dominant fashion and has an estimated prevalence of 1:5,000-10,000. Brugada syndrome is more common in Asians.

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

Buerger's disease

Buerger's disease (also known as thromboangiitis obliterans) is a small and medium vessel vasculitis that is strongly associated with smoking.

Features

- extremity ischaemia: intermittent claudication, ischaemic ulcers etc
- superficial thrombophlebitis
- Raynaud's phenomenon

Cardiac catherisation and oxygen saturation levels

Questions regarding cardiac catherisation 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%

The table below shows the **oxygen saturations** that would be expected in different scenarios:

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%

Diagnosis & notes	RA	RV	PA	LA	LV	Aorta
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%

Cardiac enzymes and protein markers

Interpretation of the various cardiac enzymes has now largely been superceded by the introduction of troponin T and I. Questions still however commonly appear in exams.

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

Cardiac tamponade

Features

- dyspnoea
- raised JVP, with an absent Y descent - this is due to the limited right ventricular filling
- tachycardia
- hypotension
- muffled heart sounds
- pulsus paradoxus
- Kussmaul's sign (much debate about this)
- ECG: electrical alternans

The key differences between constrictive pericarditis and cardiac tamponade are summarised 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

A commonly used mnemonic to remember the absent Y descent in cardiac tamponade is TAMponade = TAMpaX

Cardiomyopathies: key points

The old classification of dilated, restricted and hypertrophic cardiomyopathy has been largely abandoned due to the high degree of overlap. The latest classification of cardiomyopathy by the WHO and American Heart Association reflect this.

The tables below shows a very limited set of exam related facts for the various cardiomyopathies:

Primary cardiomyopathies - predominately involving the heart

Genetic - both conditions listed below are autosomal dominant. An implantable cardioverter-defibrillator is often inserted to reduce the incidence of sudden cardiac death.

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 and 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

Mixed - rather confusingly most of the causes of dilated and restrictive cardiomyopathy are now listed separately in the 'secondary' causes. This category servers as a reminder that many patients will have a genetic predisposition to cardiomyopathy which is then triggered by the secondary process, hence the 'mixed' category

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

Acquired

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

Secondary cardiomyopathies- pathological myocardial involvement as part of a generalized systemic disorder

Type of cardiomyopathy	Selected causes/points
Infective	Coxsackie B virus Chagas disease
Infiltrative	Amyloidosis
Storage	Haemochromatosis
Toxicity	Doxorubicin Alcoholic cardiomyopathy
Inflammatory (granulomatous)	Sarcoidosis
Endocrine	Diabetes mellitus Thyrotoxicosis Acromegaly
Neuromuscular	Friedreichs ataxia Duchenne-Becker muscular dystrophy Myotonic dystrophy
Nutritional deficiencies	Beriberi (thiamine)
Autoimmune	Systemic lupus erythematosis

Catecholaminergic polymorphic ventricular tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a form of inherited cardiac disease associated with sudden cardiac death. It is inherited in an autosomal dominant fashion and 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

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
- implantable cardioverter-defibrillator

Centrally acting antihypertensives

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

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'.

Below is a brief summary of the key points. Please see the link for more details.

Patients presenting with acute chest pain

Immediate management of suspected acute coronary syndrome (ACS)

- glyceryl trinitrate
- aspirin 300mg. NICE do not recommend giving other antiplatelet agents (i.e. Clopidogrel) outside of hospital
- do not routinely give oxygen, only give if sats < 94%*
- perform an ECG as soon as possible but do not delay transfer to hospital. A normal ECG does not exclude ACS

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

*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.

Patients presenting with stable chest pain

With all due respect to NICE the guidelines for assessment of patients with stable chest pain are rather complicated. They suggest an approach where the risk of a patient having coronary artery disease (CAD) is calculated based on their symptoms (whether they have typical angina, atypical angina or non-anginal chest pain), age, gender and risk factors.

NICE define anginal pain as the following:

- 1. constricting discomfort in the front of the chest, neck, shoulders, jaw or arms
- 2. precipitated by physical exertion
- 3. relieved by rest or GTN in about 5 minutes
- patients with all 3 features have typical angina
- patients with 2 of the above features have atypical angina
- patients with 1 or none of the above features have non-anginal chest pain

The risk tables are not reproduced here but can be found by clicking on the link.

If patients have typical anginal symptoms and a risk of CAD is greater than 90% then no further diagnostic testing is required. It should be noted that all men over the age of 70 years who have typical anginal symptoms fall into this category.

For patients with an estimated risk of 10-90% the following investigations are recommended. Note the absence of the exercise tolerance test:

Estimated likelihood of CAD	**Diagnostic testing**
61-90%	Coronary angiography
30-60%	Functional imaging, for example: - myocardial perfusion scan with SPECT - stress echocardiography - first-pass contrast-enhanced magnetic resonance (MR) perfusion - MR imaging for stress-induced wall motion abnormalities.
10-29%	CT calcium scoring

Cholestyramine

Cholestyramine is a bile acid sequestrant used in the management of hyperlipidaemia. It decreases bile acid reabsorption in the small intestine, therefore upregulating the amount of cholesterol that is converted to bile acid. The main effect it has on the lipid profile is to reduce LDL cholesterol. It is also occasionally used in Crohn's disease for treatment resistant diarrhoea.

Adverse effects

- abdominal cramps and constipation
- decreases absorption of fat-soluble vitamins
- cholesterol gallstones
- may raise level of triglycerides

Chronic kidney disease: anaemia

Patients with chronic kidney disease (CKD) may develop anaemia due to a variety of factors, the most significant of which is reduced erythropoietin levels. This is usually a normochromic normocytic anaemia and 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

Management

- the 2011 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
- 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'

Coarctation of the aorta

Coarctation of the aorta describes a congenital narrowing of the descending aorta.

Overview

- more common in males (despite association with Turner's syndrome)

Features

- infancy: heart failure
- adult: hypertension
- radio-femoral delay
- mid systolic murmur, maximal over back
- apical click from the aortic valve
- notching of the inferior border of the ribs (due to collateral vessels) is not seen in young children

Associations

- Turner's syndrome
- bicuspid aortic valve
- berry aneurysms
- neurofibromatosis

Complete heart block

Features

- syncope
- heart failure
- regular bradycardia (30-50 bpm)
- wide pulse pressure
- JVP: cannon waves in neck
- variable intensity of S1

Types of heart block

First degree heart block

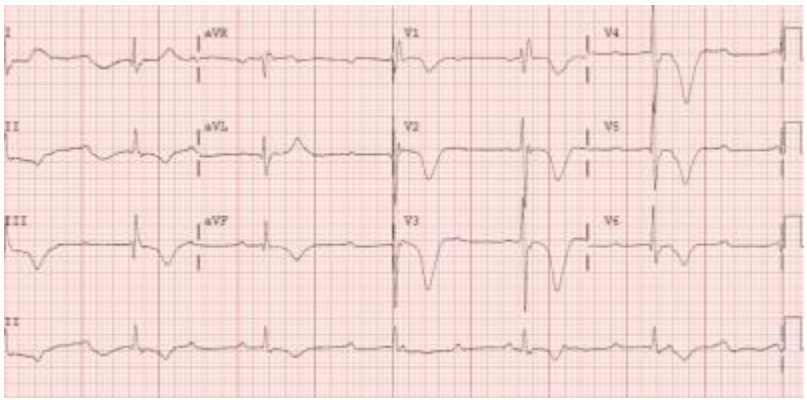
- PR interval > 0.2 seconds

Second degree heart block

- type 1 (Mobitz I, Wenckebach): progressive prolongation of the PR interval until a dropped beat occurs
- type 2 (Mobitz II): PR interval is constant but the P wave is often not followed by a QRS complex

Third degree (complete) heart block

- there is no association between the P waves and QRS complexes



ECG showing third degree (complete) heart block

Congenital heart disease: types

Acyanotic - most common causes

- ventricular septal defects (VSD) - most common, accounts for 30%
- atrial septal defect (ASD)
- 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
- transposition of the great arteries (TGA)
- tricuspid atresia

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

The presence of cyanosis in pulmonary valve stenosis depends very much on the severity and any other coexistent defects.

Constrictive pericarditis

Causes

- any cause of pericarditis
- particularly TB

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

CXR

- pericardial calcification

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

A commonly used mnemonic to remember the absent Y descent in cardiac tamponade is TAMponade = TAMpaX

*a paradoxical rise in JVP during inspiration

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%

Venous drainage of the heart

- coronary sinus drains into the right atrium

Diabetes mellitus: hypertension management

NICE recommend the following blood pressure targets for diabetics:

- if end-organ damage (e.g. renal disease, retinopathy) < 130/80 mmHg
- otherwise < 140/80 mmHg

A 2013 Cochrane review casted doubt on the wisdom of lower blood pressure targets for patients with diabetes. It compared patients who had tight blood pressure control (targets < 130/85 mmHg) with more relaxed control (< 140-160/90-100 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 than 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.

Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) basics

- dilated heart leading to systolic (+/- diastolic) dysfunction
- all 4 chambers affected but LV more so than RV
- features include arrhythmias, emboli, mitral regurgitation
- absence of congenital, valvular or ischaemic heart disease

Causes often considered separate entities

- alcohol: may improve with thiamine
- postpartum
- hypertension

Other causes

- inherited (see below)
- infections e.g. Coxsackie B, HIV, diphtheria, parasitic
- endocrine e.g. Hyperthyroidism
- infiltrative* e.g. Haemochromatosis, sarcoidosis
- neuromuscular e.g. Duchenne muscular dystrophy
- nutritional e.g. Kwashiorkor, pellagra, thiamine/selenium deficiency
- drugs e.g. Doxorubicin

Inherited dilated cardiomyopathy

- around a third of patients with DCM are thought to have a genetic predisposition
- a large number of heterogeneous defects have been identified
- the majority of defects are inherited in an autosomal dominant fashion although other patterns of inheritance are seen

*these causes may also lead to restrictive cardiomyopathy

Down syndrome: 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
- Hirschsprung's disease

Cardiac complications

- 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

DVLA: cardiovascular disorders

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
- CABG - 4 weeks off driving
- 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 prophylatically 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 of 6cm or more - notify DVLA. Licensing will be permitted subject to annual review. An aortic diameter of 6.5 cm or more disqualifies patients from driving
- heart transplant: DVLA do not need to be notified

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.

Associations

- tricuspid incompetence (pan-systolic murmur, giant V waves in JVP)
- Wolff-Parkinson White syndrome

Ebstein's anomaly may be caused by exposure to lithium in-utero

ECG: axis deviation

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

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
- normal in infant < 1 years old
- minor RAD in tall people

*in the majority of cases, or in a question without qualification, Wolff-Parkinson-White syndrome is associated with left axis deviation

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

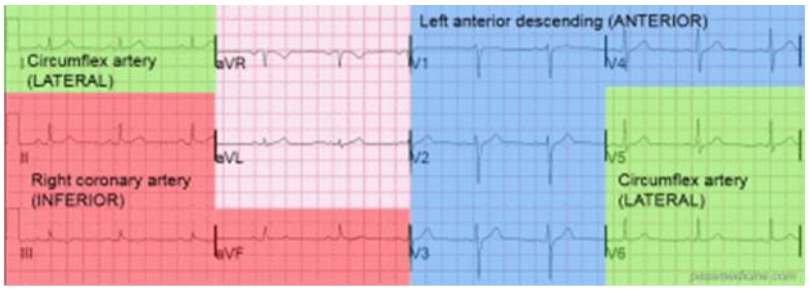


Diagram showing the correlation between ECG changes and coronary territories in acute coronary syndrome

ECG: digoxin

ECG features

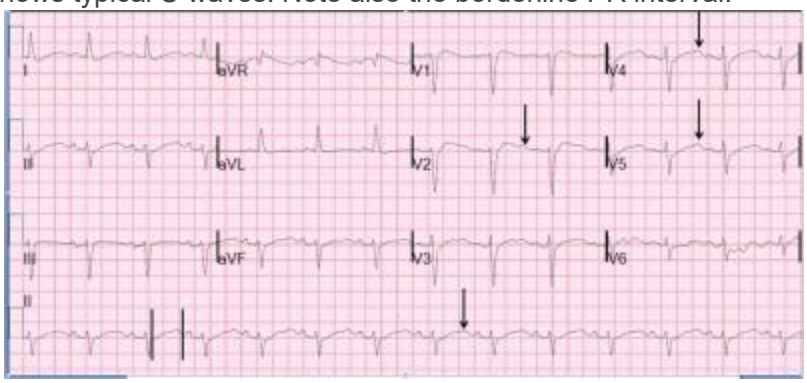
- down-sloping ST depression ('reverse tick')
- flattened/inverted T waves
- short QT interval
- arrhythmias e.g. AV block, bradycardia

ECG: hypokalaemia

ECG features of hypokalaemia

- U waves
- small or absent T waves (occasionally inversion)
- prolong PR interval
- ST depression
- long QT

The ECG below shows typical U waves. Note also the borderline PR interval.



One registered user suggests the following rhyme

- In Hypokalaemia, U have no Pot and no T, but a long PR and a long QT

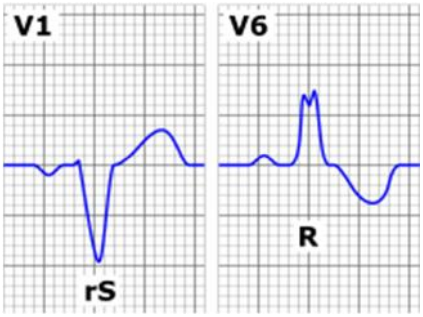
ECG: hypothermia

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

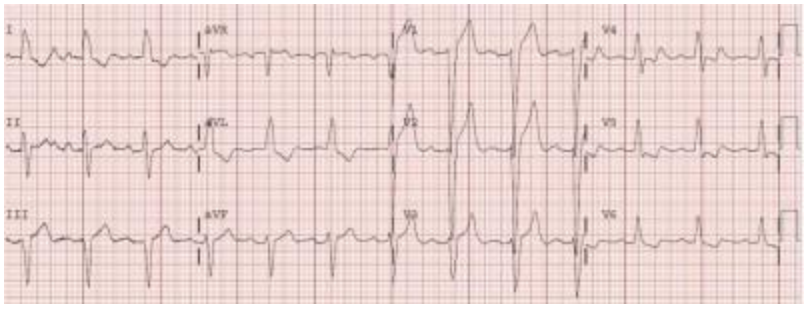
ECG: left bundle branch block

The diagram below shows the typical features of left bundle branch block (LBBB):



One of the most common ways to remember the difference between LBBB and RBBB is WiLLiaM MaRRoW

- in LBBB there is a 'W' in V1 and a 'M' in V6
- 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

New LBBB is always pathological and may be a sign of a myocardial infarction. Diagnosing a myocardial infarction for patients with *existing* LBBB is difficult. The Sgarbossa criteria can help with this. Please see the link for more details.

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: P wave changes

Increased P wave amplitude

- cor pulmonale

ECG: PR interval

Causes of a **prolonged PR interval**

- idiopathic
- ischaemic heart disease
- digoxin toxicity
- hypokalaemia*
- rheumatic fever
- aortic root pathology e.g. abscess secondary to endocarditis
- Lyme disease
- sarcoidosis
- myotonic dystrophy

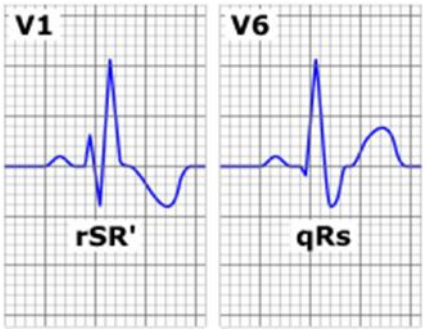
A prolonged PR interval may also be seen in athletes

A **short PR interval** is seen in Wolff-Parkinson-White syndrome

*hyperkalaemia can rarely cause a prolonged PR interval, but this is a much less common association than hypokalaemia

ECG: right bundle branch block

Right bundle branch block is a common feature seen on ECGs.



One of the most common ways to remember the difference between LBBB and RBBB is WiLLiaM MaRRoW

- in LBBB there is a 'W' in V1 and a 'M' in V6
- in RBBB there is a 'M' in V1 and a 'W' in V6

Causes of RBBB

- normal variant - more common with increasing age
- right ventricular hypertrophy
- chronically increased right ventricular pressure - e.g. cor pulmonale
- pulmonary embolism
- myocardial infarction
- atrial septal defect (ostium secundum)
- cardiomyopathy or myocarditis

ECG: ST depression

Causes of ST depression

- secondary to abnormal QRS (LVH, LBBB, RBBB)
- ischaemia
- digoxin
- hypokalaemia
- syndrome X

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

ECG: T wave changes

Peaked T waves

- hyperkalaemia
- myocardial ischaemia

Inverted T waves

- myocardial ischaemia
- digoxin toxicity
- subarachnoid haemorrhage
- arrhythmogenic right ventricular cardiomyopathy
- pulmonary embolism ('S1Q3**T3**')
- Brugada syndrome

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

Exercise tolerance tests

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
- assessing exercise tolerance
- risk stratifying patients with hypertrophic cardiomyopathy

ETT has a sensitivity of around 80% and a specificity of 70% for ischaemic heart disease.

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)
- aortic stenosis
- left bundle branch block: this would make the ECG very difficult to interpret

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

Exercise: physiological changes

Blood pressure

- systolic increases, diastolic decreases
- 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

Heart failure: diagnosis

NICE issued updated guidelines on diagnosis and management in 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

No previous myocardial infarction

- measure serum natriuretic peptides (BNP)
- if levels are 'high' arrange echocardiogram within 2 weeks
- if levels are 'raised' arrange echocardiogram within 6 weeks

Serum natriuretic peptides

B-type natriuretic peptide (BNP) is a hormone produced mainly by the left ventricular myocardium in response to strain. Very high levels are associated with a poor prognosis.

	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)

Factors which alter the BNP level:

Increase BNP levels	Decrease BNP levels
Left ventricular hypertrophy Ischaemia Tachycardia Right ventricular overload Hypoxaemia (including pulmonary embolism) GFR < 60 ml/min Sepsis COPD Diabetes Age > 70 Liver cirrhosis	Obesity Diuretics ACE inhibitors Beta-blockers Angiotensin 2 receptor blockers Aldosterone antagonists

Heart failure: drug management

A number of drugs have been shown to improve mortality in patients with chronic heart failure:

- ACE inhibitors (SAVE, SOLVD, CONSENSUS)
- spironolactone (RALES)
- beta-blockers (CIBIS)
- hydralazine with nitrates (VHEFT-1)

No long-term reduction in mortality has been demonstrated for loop diuretics such as furosemide.

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**
- 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. An alternative supported by NICE in 2012 is **ivabradine**. The criteria for ivabradine include that the patient is already on suitable therapy (ACE-inhibitor, beta-blocker + aldosterone antagonist), has a heart rate > 75/min and a left ventricular fraction < 35%
- **diuretics** should be given for fluid overload
- offer **annual influenza vaccine**
- offer one-off** **pneumococcal vaccine**

Beta-blockers licensed to treat heart failure in the UK include bisoprolol, carvedilol, and nebivolol.

*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

**adults usually require just one dose but those with asplenia, splenic dysfunction or chronic kidney disease need a booster every 5 years

Heart failure: non-drug management

Cardiac resynchronisation therapy

- for patients with heart failure and wide QRS
- biventricular pacing
- improved symptoms and reduced hospitalisation in NYHA class III patients

Exercise training

- improves symptoms but not hospitalisation/mortality

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 sounds

The first heart sound (S1) is caused by closure of the mitral and tricuspid valves whilst the second heart sound (S2) is due to aortic and pulmonary valve closure

S1

- closure of mitral and tricuspid valves
- soft if long PR or mitral regurgitation
- loud in mitral stenosis

S2

- closure of aortic and pulmonary valves
- soft in aortic stenosis
- splitting during inspiration is normal

S3 (third heart sound)

- caused by diastolic filling of the ventricle
- 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) and mitral regurgitation

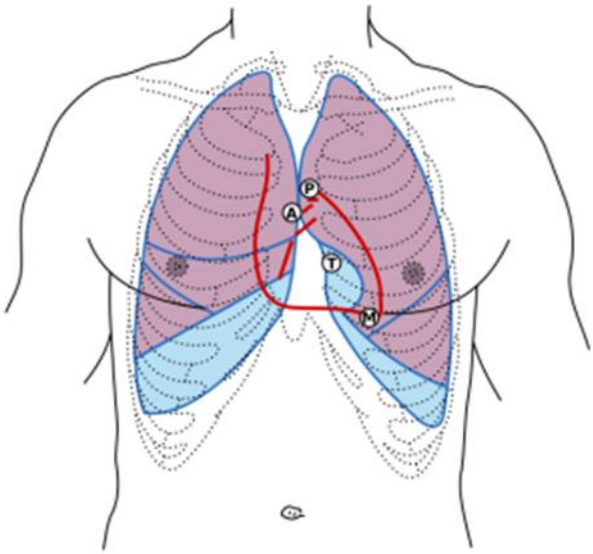
S4 (fourth heart sound)

- may be heard in aortic stenosis, HOCM, hypertension
- caused by atrial contraction against a stiff ventricle
- in HOCM a double apical impulse may be felt as a result of a palpable S4

Sites of auscultation

Valve	Site
Pulmonary valve	Left second intercostal space, at the upper sternal border
Aortic valve	Right second intercostal space, at the upper sternal border
Mitral valve	Left fifth intercostal space, just medial to mid clavicular line
Tricuspid valve	Left fourth intercostal space, at the lower left sternal border

The diagram below demonstrates where the various cardiac valves are best heard.



Heart sounds: S1

S1 is caused by closure of mitral and tricuspid valves

Causes of a loud S1

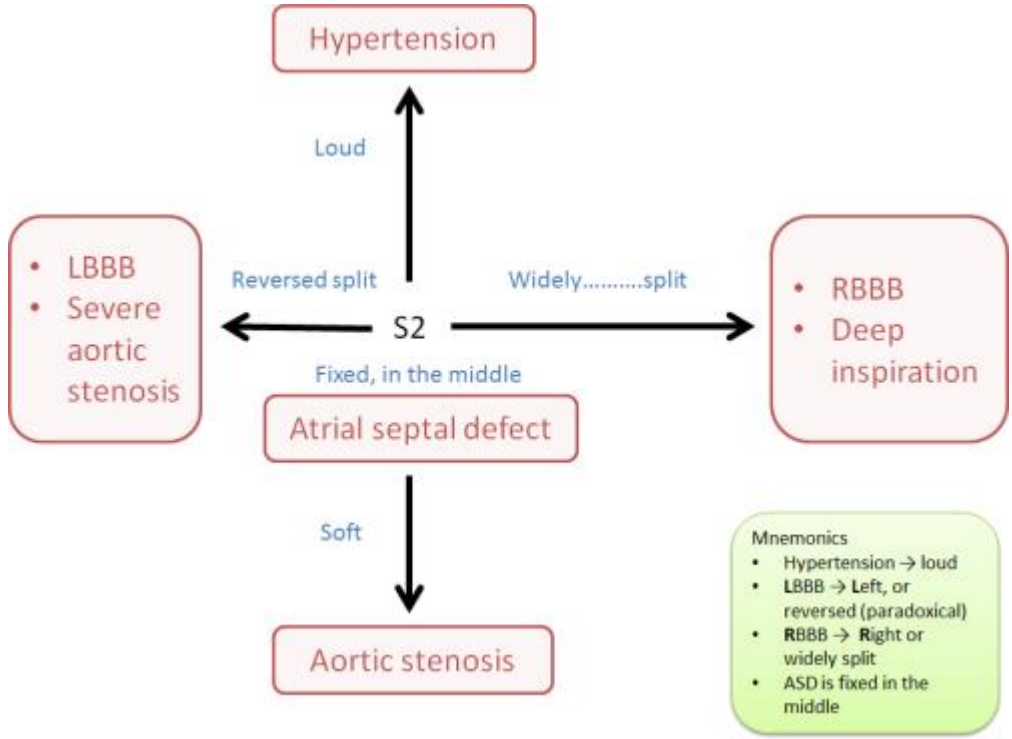
- mitral stenosis
- left to right shunts
- short PR interval, atrial premature beats
- hyperdynamic states

Causes of a quiet S1

- mitral regurgitation

Heart sounds: S2

S2 is caused by the closure of the aortic valve (A2) closely followed by that of the pulmonary valve (P2)



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

Causes of a widely split S2

- deep inspiration
- RBBB
- pulmonary stenosis
- severe mitral regurgitation

Causes of a reversed (paradoxical) split S2 (P2 occurs before A2)

- LBBB
- severe aortic stenosis
- right ventricular pacing
- WPW type B (causes early P2)
- patent ductus arteriosus

HOCM: features

Hypertrophic obstructive cardiomyopathy (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. The estimated prevalence is 1 in 500.

Features

- often asymptomatic
- dyspnoea, 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

Associations

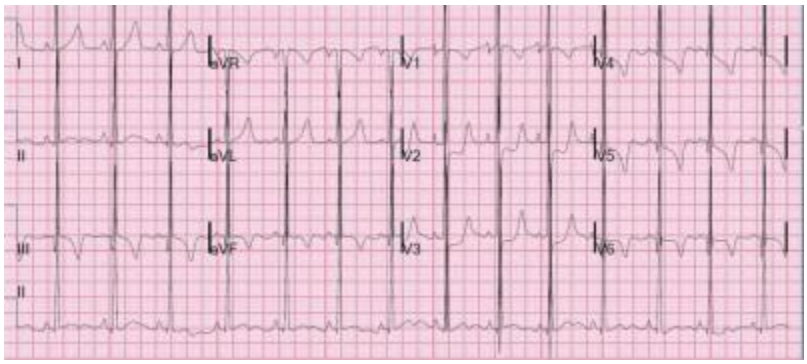
- Friedreich's ataxia
- Wolff-Parkinson White

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
- atrial fibrillation may occasionally be seen



ECG showing typical changes of HOCM including LVH and T wave inversion

HOCM: management

Hypertrophic obstructive cardiomyopathy (HOCM) is an autosomal dominant disorder of muscle tissue caused by defects in the genes encoding contractile proteins. The estimated prevalence is 1 in 500.

Management

- **A**miodarone
- **B**eta-blockers or verapamil for symptoms
- **C**ardioverter defibrillator
- **D**ual chamber pacemaker
- **E**ndocarditis prophylaxis*

Drugs to avoid

- nitrates
- ACE-inhibitors
- inotropes

*although see the 2008 NICE guidelines on infective endocarditis prophylaxis

HOCM: prognostic factors

Hypertrophic obstructive cardiomyopathy (HOCM) is an autosomal dominant disorder of muscle tissue caused by defects in the genes encoding contractile proteins. Mutations to various proteins including beta-myosin, alpha-tropomyosin and troponin T have been identified. Septal hypertrophy causes left ventricular outflow obstruction. It is an important cause of sudden death in apparently healthy individuals.

Poor prognostic factors

- syncope
- family history of sudden death
- young age at presentation
- non-sustained ventricular tachycardia on 24 or 48-hour Holter monitoring
- abnormal blood pressure changes on exercise

An increased septal wall thickness is also associated with a poor prognosis.

Hydralazine

Hydralazine is one of the 'older' antihypertensives and is not commonly used nowadays. It is still sometimes used for hypertension in pregnancy and for severe hypertension.

Mechanism of action

- increases cGMP leading to smooth muscle relaxation

Contraindications

- systemic lupus erythematous
- ischaemic heart disease

Adverse effects

- tachycardia
- palpitations
- flushing
- fluid retention
- headache
- drug-induced lupus

Hypercalcaemia: features

Features

- 'bones, stones, groans and psychic moans', also:
- corneal calcification
- shortened QT interval on ECG
- hypertension

Hyperlipidaemia: xanthomata

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 hypertriglyceridaemia
- lipoprotein lipase deficiency

Tendon xanthoma, tuberous xanthoma, xanthelasma

- familial hypercholesterolaemia
- remnant hyperlipidaemia

Xanthelasma are also seen without lipid abnormalities

Management of xanthelasma, options include:

- surgical excision
- topical trichloroacetic acid
- laser therapy
- electrodesiccation

Hypertension in pregnancy

NICE published guidance in 2010 on the management of hypertension in pregnancy. They also made recommendations on reducing the risk of hypertensive disorders developing in the first place. 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: a very basic introduction

Hypertension is one of the most common medical conditions encountered in the developed world. Whilst there is a degree of normal variation in blood pressure according to the time of day and whether we are exerting ourselves hypertension describes a chronically raised blood pressure. The main relevance of hypertension lies in the fact that it is an important risk factor for the development of cardiovascular disease such as ischaemic heart disease and stroke. Unless the blood pressure is very high it is unusual for patients to experience any symptoms.

What is a 'normal' blood pressure?

Normal blood pressure can vary widely according to age, gender and individual physiology. Most healthy people have a blood pressure between 90/60 mmHg and 140/90 mmHg.

NICE define hypertension as follows:

- a clinic reading persistently above >= 140/90 mmHg, or:
- a 24 hour blood pressure average reading >= 135/85 mmHg

Why do some patients have an elevated blood pressure?

Patients with hypertension may be divided into two categories. The vast majority (around 90-95%) have primary, or essential, hypertension. This is where there is no single disease causing the rise in blood pressure but rather a series of complex physiological changes which occur as we get older.

Secondary hypertension may be caused by a wide variety of endocrine, renal and other causes. The table below lists some of the conditions that may cause secondary hypertension

Renal disease	Endocrine disorders	Other causes
• Glomerulonephritis • Chronic pyelonephritis • Adult polycystic kidney disease • Renal artery stenosis	• Primary hyperaldosteronism • Phaeochromocytoma • Cushing's syndrome • Liddle's syndrome • Congenital adrenal hyperplasia (11-beta hydroxylase deficiency) • Acromegaly	• Glucocorticoids • NSAIDs • Pregnancy • Coarctation of the aorta • Combined oral contraceptive pill

Symptoms and signs

As mentioned earlier, hypertension does not typically cause symptoms unless it is very high, for example > 200/120 mmHg. If very raised patients may experience:

- headaches
- visual disturbance
- seizures

In terms of signs hypertension is obviously usually detected when checking someones blood pressure. For diagnosing longstanding blood pressure there has been a move in recent years to using 24 hour blood pressure monitors. These avoid cases of so called 'white coat' hypertension where a patients blood pressure rises when they are in a clinical setting, for example a GP surgery. Studies have shown that readings from 24 hour blood pressure monitors correlate better with clinical outcomes and hence should be used to guide decisions about treatment.

It also also important when assessing a patient with newly diagnosed hypertension to ensure they do not have any end-organ damage:

- fundoscopy: to check for hypertensive retinopathy
- urine dipstick: to check for renal disease, either as a cause or consequence of hypertension
- ECG: to check for left ventricular hypertrophy or ischaemic heart disease

Investigations

As mentioned previously 24 hour blood pressure is now recommend for the diagnosis of hypertension. If 24 hour blood pressure monitoring is not available then home readings using an automated sphygmomanometer are useful.

Following diagnosis patients typically have the following tests:

- urea and electrolytes: check for renal disease, either as a cause or consequence of hypertension
- HbA1c: check for co-existing diabetes mellitus, another important risk factor for cardiovascular disease
- lipids: check for hyperlipidaemia, again another important risk factor for cardiovascular disease
- ECG
- urine dipstick

Management

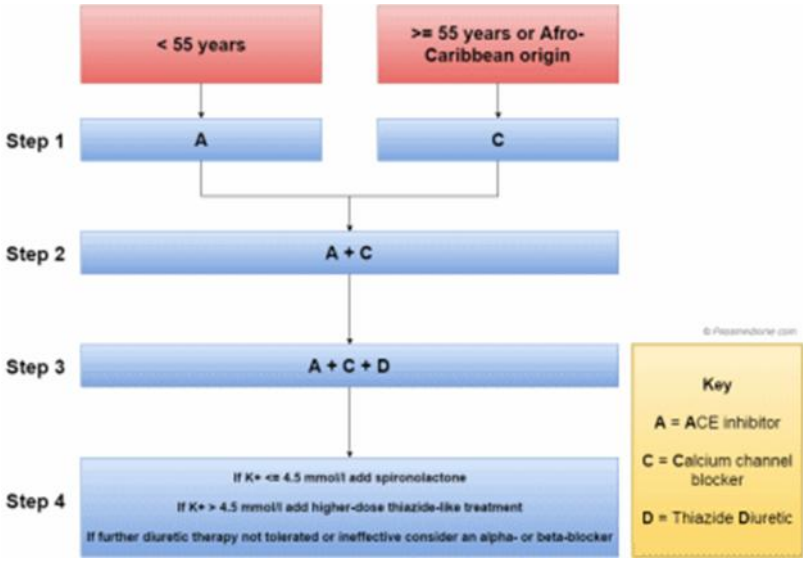
The management of patients with hypertension involves several aspects:

- drug therapy using antihypertensives
- modification of other risk factors to reduce the overall risk of cardiovascular disease
- monitoring the patient for the development of complications of hypertension

The table below shows the common drugs used to treat hypertension:

Drug	Mechanism of action	Common side-effects	Notes
Angiotensin-converting enzyme (ACE) inhibitors	Inhibit the conversion angiotensin I to angiotensin II	Cough Angioedema Hyperkalaemia	First-line treatment in younger patients (< 55 years old) Less effective in Afro-Caribbean patients Must be avoided in pregnant women Renal function must be check 2-3 weeks after starting due to the risk of worsening renal function in patients with renovascular disease Drug names end in '-pril'
Calcium channel blockers	Block voltage-gated calcium channels relaxing vascular smooth muscle and force of myocardial contraction	Flushing Ankle swelling Headache	First-line treatment in older patients (>= 55 years old)
Thiazide type diuretics	Inhibit sodium absorption at the beginning of the distal convoluted tubule	Hyponatraemia Hypokalaemia Dehydration	Although technically a diuretic, thiazides have a very weak diuretic action
Angiotensin II receptor blockers (A2RB)	Block effects of angiotensin II at the AT1 receptor	Hyperkalaemia	Angiotensin II receptor blockers are generally used in situations where patients have not tolerated an ACE inhibitor, usually due to the development of a cough Drug names end in '-sartan'

Drug therapy is decided by well established NICE guidelines, which advocate a step-wise approach:

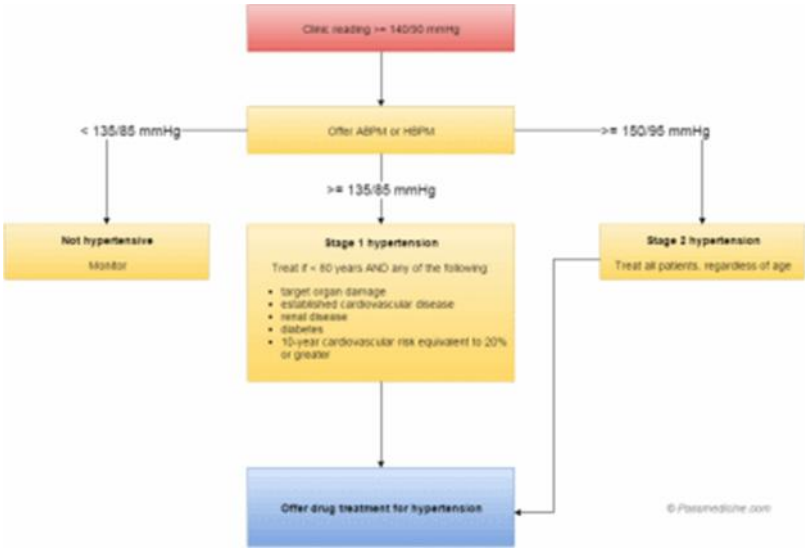


Flow chart showing the management of hypertension as per current NICE guideliness

Hypertension: 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

Why were these guidelines needed?

It has long been recognised by doctors that there is a subgroup of patients whose blood pressure climbs 20 mmHg whenever they enter a clinical setting, so called 'white coat hypertension'. If we just rely on clinic readings then such patients may be diagnosed as having hypertension when, the vast majority of the time, their blood pressure is normal.

This has led to the use of both ambulatory blood pressure monitoring (ABPM) and home blood pressure monitoring (HBPM) to confirm the diagnosis of hypertension. These techniques allow a more accurate assessment of a patients' overall blood pressure. Not only does this help prevent overdiagnosis of hypertension - 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

Firstly, NICE recommend measuring blood pressure 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 blood pressures should be recorded from the arm with the higher reading.

It should of course be remember that there are pathological causes of unequal blood pressure readings from the arms, such as supravalvular aortic stenosis. It is therefore prudent to listen to the heart sounds if a difference exists and further investigation if a very large difference is noted.

NICE also recommend taking a second reading during the consultation, if the first reading is > 140/90 mmHg. The lower reading of the two should determine further management.

NICE suggest offering ABPM or HBPM to any patient with a blood pressure >= 140/90 mmHg.

If however the blood pressure is >= 180/110 mmHg:

- immediate treatment should be considered
- if there are signs of papilloedema or retinal haemorrhages NICE recommend same day assessment by a specialist
- NICE also recommend referral if a 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 or a 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

Hypertension: management

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)
- calcium channel blockers are now considered superior to thiazides
- bendroflumethiazide is no longer the thiazide of choice

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
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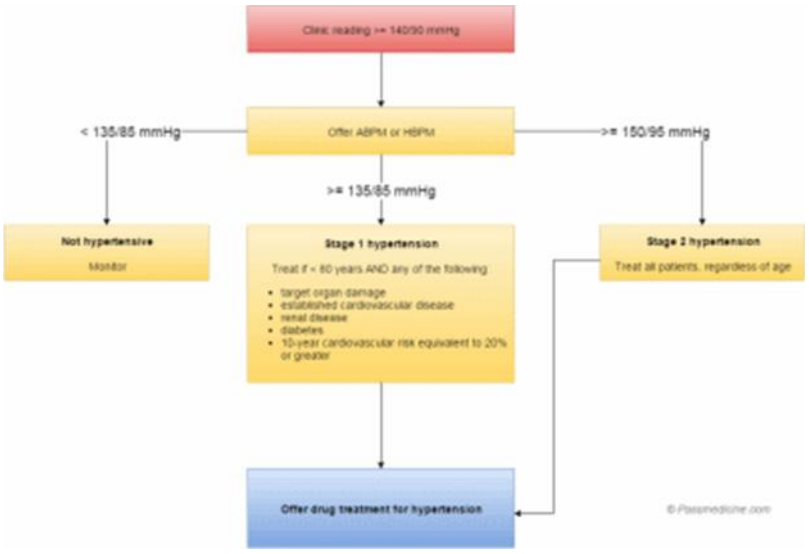


Flow chart showing simplified schematic for diagnosis hypertension following NICE guidelines

Managing hypertension

Lifestyle advice should not be forgotten and is frequently tested in exams:

- 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

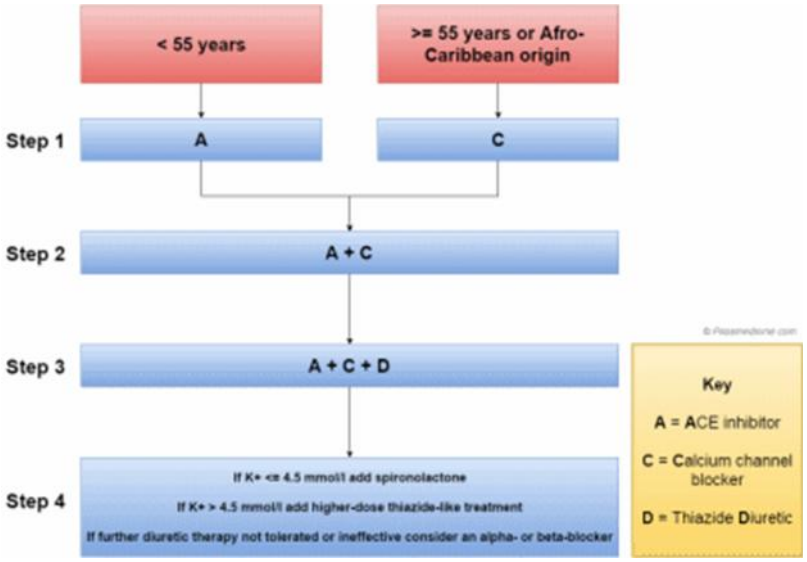
ABPM/HBPM >= 135/85 mmHg (i.e. stage 1 hypertension)

- treat if < 80 years of age AND any of the following apply; target organ damage, established cardiovascular disease, renal disease, diabetes or a 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

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

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:

If blood pressure remains uncontrolled with the optimal or maximum tolerated doses of four drugs, seek expert advice if it has not yet been obtained.

Blood pressure targets

	Clinic BP	**ABPM / HBPM**
Age < 80 years	140/90 mmHg	135/85 mmHg
Age > 80 years	150/90 mmHg	145/85 mmHg

New drugs

Direct renin inhibitors

- e.g. Aliskiren (branded as Rasilez)
- by inhibiting renin blocks the conversion of angiotensinogen to angiotensin I
- 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
- only current role would seem to be in patients who are intolerant of more established antihypertensive drugs

Hypertension: secondary causes

It is thought that between 5-10% of patients diagnosed with hypertension have **primary hyperaldosteronism**, including Conn's syndrome. This makes it the single most common cause of secondary hypertension.

Renal disease accounts for a large percentage of the other cases of secondary hypertension. Conditions which may increase the blood pressure include:

- glomerulonephritis
- pyelonephritis
- adult polycystic kidney disease
- renal artery stenosis

Endocrine disorders (other than primary hyperaldosteronism) may also result in increased blood pressure:

- phaeochromocytoma
- Cushing's syndrome
- Liddle's syndrome
- congenital adrenal hyperplasia (11-beta hydroxylase deficiency)
- acromegaly

Other causes include:

- NSAIDs
- pregnancy
- coarctation of the aorta
- the combined oral contraceptive pill
- steroids
- MAOI

Implantable cardiac defibrillators

Indications

- long QT syndrome
- hypertrophic obstructive cardiomyopathy
- previous cardiac arrest due to VT/VF
- previous myocardial infarction with non-sustained VT on 24 hr monitoring, inducible VT on electrophysiology testing and ejection fraction < 35%
- Brugada syndrome

Infective endocarditis

The strongest risk factor for developing infective endocarditis is a previous episode of endocarditis. The following types of patients are affected:

- 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)

Causes

- historically *Streptococcus viridans* was the most common cause of infective endocarditis. This is no longer the case, except in developing countries. ***Staphylococcus aureus* is now the most common cause of infective endocarditis**. *Staphylococcus aureus* is also particularly common in acute presentation and IVDUs
- coagulase-negative Staphylococci such as *Staphylococcus epidermidis* commonly colonize indwelling lines and are the most cause of endocarditis in patients following prosthetic valve surgery, usually the result of perioperative contamination. After 2 months the spectrum of organisms which cause endocarditis return to normal (i.e. *Staphylococcus aureus* is the most common cause)
- *Streptococcus viridans* still accounts for around 20% of cases. Technically *Streptococcus viridans* is a pseudotaxonomic term, referring to viridans streptococci, rather than a particular organism. The two most notable viridans streptococci are *Streptococcus mitis* and *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
- *Streptococcus bovis* is associated with colorectal cancer
- non-infective: systemic lupus erythematosus (Libman-Sacks), malignancy: marantic endocarditis

Culture negative causes

- prior antibiotic therapy
- *Coxiella burnetii*
- *Bartonella*
- *Brucella*
- HACEK: *Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella*)

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 > 38ºC
- vascular phenomena: major emboli, splenomegaly, clubbing, splinter haemorrhages, Janeway lesions, petechiae or purpura
- immunological phenomena: glomerulonephritis, Osler's nodes, Roth spots

Infective endocarditis: prophylaxis

The 2008 guidelines from NICE have radically changed the list of procedures for which antibiotic prophylaxis is recommended

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

The guidelines do however suggest:

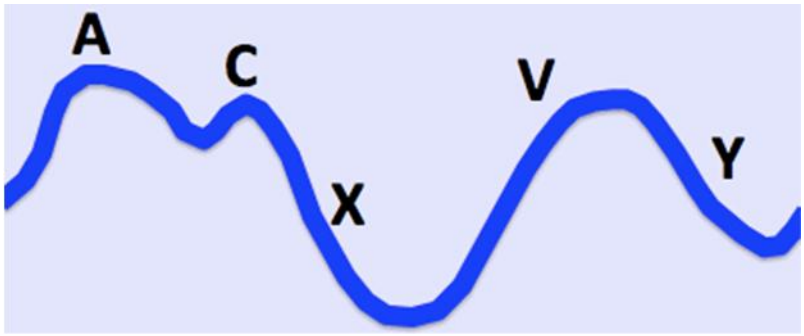
- any episodes of infection in people at risk of infective endocarditis should be investigated and treated promptly to reduce the risk of endocarditis developing
- if a person at risk of infective endocarditis is receiving antimicrobial therapy because they are undergoing a gastrointestinal or genitourinary procedure at a site where there is a suspected infection they should be given an antibiotic that covers organisms that cause infective endocarditis

Isolated systolic hypertension

Isolated systolic hypertension (ISH) is common in the elderly, affecting around 50% of people older than 70 years old. The Systolic Hypertension in the Elderly Program (SHEP) back in 1991 established that treating ISH reduced both strokes and ischaemic heart disease. Drugs such as thiazides were recommended as first line agents. This approach is contradicated by the 2011 NICE guidelines which recommends treating ISH in the same stepwise fashion as standard hypertension.

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

Long QT syndrome

Long QT syndrome (LQTS) is an inherited condition associated with delayed repolarization of the ventricles. It is important to recognise as it may lead to ventricular tachycardia and can therefore cause collapse/sudden death. The most common variants of LQTS (LQT1 & LQT2) are caused by defects in the alpha subunit of the slow delayed rectifier potassium channel. A normal corrected QT interval is less than 430 ms in males and 450 ms in females.

Causes of a prolonged QT interval:

Congenital	Drugs*	Other
⁾ Jervell-Lange-Nielsen syndrome (includes deafness and is due to an abnormal potassium channel) ⁾ Romano-Ward syndrome (no deafness)	⁾ amiodarone, sotalol, class 1a antiarrhythmic drugs ⁾ tricyclic antidepressants, selective serotonin reuptake inhibitors (especially citalopram) ⁾ methadone ⁾ chloroquine ⁾ terfenadine** ⁾ erythromycin ⁾ haloperidol	⁾ electrolyte: hypocalcaemia, hypokalaemia, hypomagnesaemia ⁾ acute myocardial infarction ⁾ myocarditis ⁾ hypothermia ⁾ subarachnoid haemorrhage

Features

- ⁾ 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

Management

- avoid drugs which prolong the QT interval and other precipitants if appropriate (e.g. Strenuous exercise)
- beta-blockers***
- implantable cardioverter defibrillators in high risk cases

*the usual mechanism by which drugs prolong the QT interval is blockage of potassium channels. See the link for more details

**a non-sedating antihistamine and 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

***note sotalol may exacerbate long QT syndrome

Malignant hypertension

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
- bed rest
- most patients: oral therapy e.g. atenolol
- if severe/encephalopathic: IV sodium nitroprusside/labetolol

Mitral regurgitation

Features

- pan-systolic murmur
- soft S1, split S2

Mitral stenosis

It is said that the causes of mitral stenosis are rheumatic fever, rheumatic fever and rheumatic fever. Rarer causes that may be seen in the exam include mucopolysaccharidoses, carcinoid and endocardial fibroelastosis

Features

- mid-late diastolic murmur (best heard in expiration)
- loud S1, opening snap
- low volume pulse
- malar flush
- atrial fibrillation

Features of severe MS

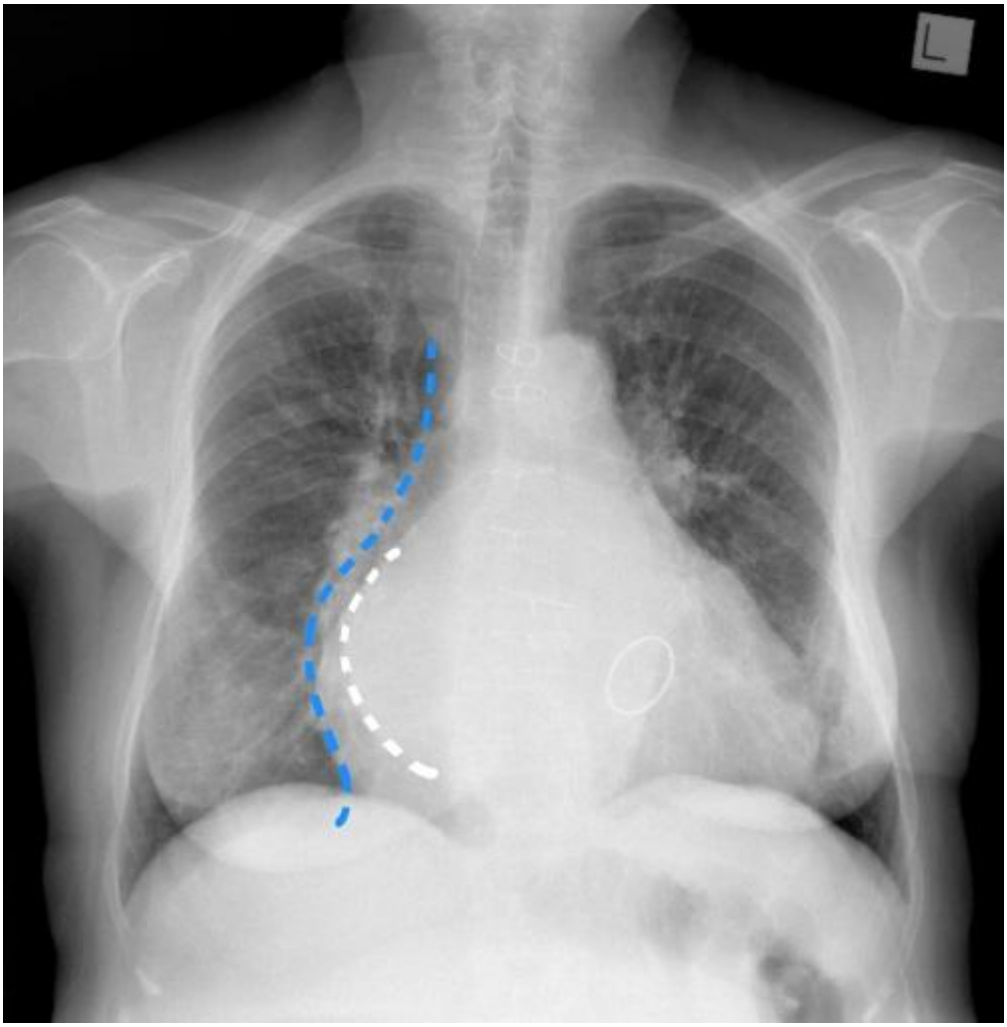
- length of murmur increases
- opening snap becomes closer to S2

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 valve prolapse

Mitral valve prolapse is common, occurring in around 5-10 % of the population. It is usually idiopathic but may be associated with a wide variety of cardiovascular disease and other conditions

Associations

- 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

- 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

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

Murmurs

Ejection systolic

- aortic stenosis
- pulmonary stenosis, HOCM
- ASD, 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

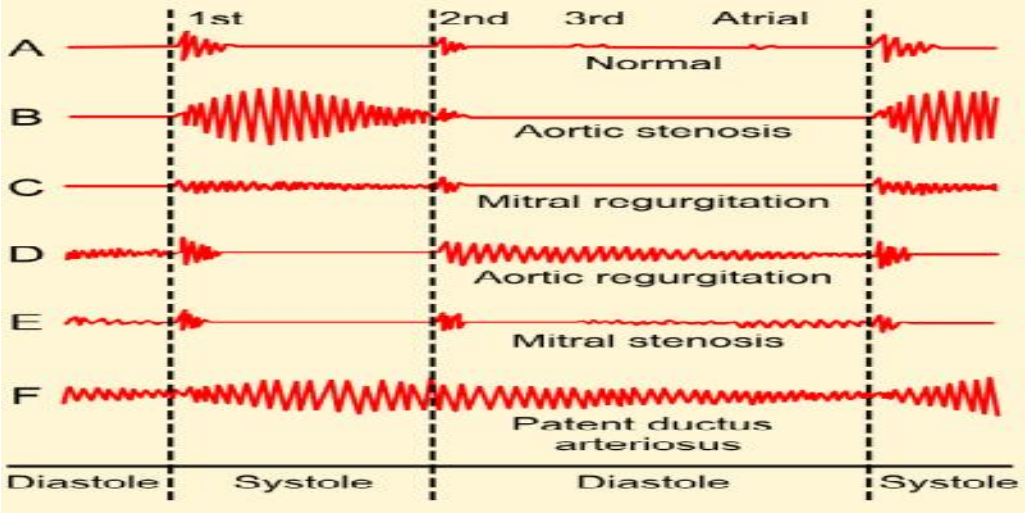
- aortic regurgitation (high-pitched and 'blowing' in character)
- Graham-Steel murmur (pulmonary regurgitation, again high-pitched and 'blowing' in character)

Mid-late diastolic

- mitral stenosis ('rumbling' in character)
- Austin-Flint murmur (severe aortic regurgitation, again is 'rumbling' in character)

Continuous machine-like mumur

- patent ductus arteriosus



Myocardial infarction: complications

Patients are at risk of a number of immediate, early and late complications following a myocardial infarction (MI).

Cardiac arrest

This most commonly occurs due to patients developing ventricular fibrillation and is the most common cause of death following a MI. Patients are managed as per the ALS protocol with defibrillation.

Cardiogenic shock

If a large part of the ventricular myocardium is damaged in the infarction the ejection fraction of the heart may decrease to the point that the patient develops cardiogenic shock. This is difficult to treat. Other causes of cardiogenic shock include the 'mechanical' complications such as left ventricular free wall rupture as listed below. Patients may require inotropic support and/or an intra-aortic balloon pump.

Chronic heart failure

As described above, if the patient survives the acute phase their ventricular myocardium may be dysfunctional resulting in chronic 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.

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 2-6 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 and a raised ESR. It is treated with NSAIDs.

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.

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. An early-to-mid systolic murmur is typically heard. Patients are treated with vasodilator therapy but often require emergency surgical repair.

Myocardial infarction: secondary prevention

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

Myocardial infarction: STEMI management

A number of studies over the past 10 years have provided an evidence for the management of ST-elevation myocardial infarction (STEMI)

In the absence of contraindications, all patients should be given

- **aspirin**
- **P2Y12-receptor antagonist**. Clopidogrel was the first P2Y12-receptor antagonist to be widely used but now ticagrelor is often favoured as studies have shown improved outcomes compared to clopidogrel, but at the expense of slightly higher rates of bleeding. This approached is supported in SIGN's 2016 guidelines. They also recommend that prasugrel (another P2Y12-receptor antagonist) could be considered if the patient is going to have a percutaneous coronary intervention
- **unfractionated heparin** is usually given for patients who're are going to have a PCI. Alternatives include low-molecular weight heparin

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.

Primary percutaneous coronary intervention (PCI) has emerged as the gold-standard treatment for STEMI but is not available in all centres. Thrombolysis should be performed in patients without access to primary PCI

With regards to thrombolysis:

- tissue plasminogen activator (tPA) has been shown to offer clear mortality benefits over streptokinase
- tenecteplase is easier to administer and has been shown to have non-inferior efficacy to alteplase with a similar adverse effect profile

An 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

Glycaemic control in patients with diabetes mellitus

- in 2011 NICE issued guidance on the management of hyperglycaemia in acute coronary syndromes
- it recommends using a dose-adjusted insulin infusion with regular monitoring of blood glucose levels to glucose below 11.0 mmol/l
- intensive insulin therapy (an intravenous infusion of insulin and glucose with or without potassium, sometimes referred to as 'DIGAMI') regimes are not recommended routinely

Myocarditis

Causes

- viral: coxsackie, HIV
- bacteria: diphtheria, clostridia
- spirochaetes: Lyme disease
- protozoa: Chagas' disease, toxoplasmosis
- autoimmune
- drugs: doxorubicin

Presentation

- usually young patient with acute history
- chest pain, SOB

Nitrates are a group of drugs which have vasodilating effects. The main indications for their use is in the management of angina and the acute treatment of heart failure. Sublingual glyceryl trinitrate is the most common drug used in patients with ischaemic heart disease to relieve angina attacks.

Mechanism of action

- cause release of nitric oxide in smooth muscle, increasing cGMP which leads to a fall in intracellular calcium levels
- in angina they both dilate the coronary arteries and also reduce venous return which in turn reduces left ventricular work, reducing myocardial oxygen demand

Side-effects

- hypotension
- tachycardia
- headaches
- flushing

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

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 - 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

Pacemakers: temporary

Indications for a temporary pacemaker

- symptomatic/haemodynamically unstable bradycardia, not responding to atropine
- post-ANTERIOR MI: type 2 or complete heart block*
- trifascicular block prior to surgery

*post-INFERIOR MI complete heart block is common and can be managed conservatively if asymptomatic and haemodynamically stable

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

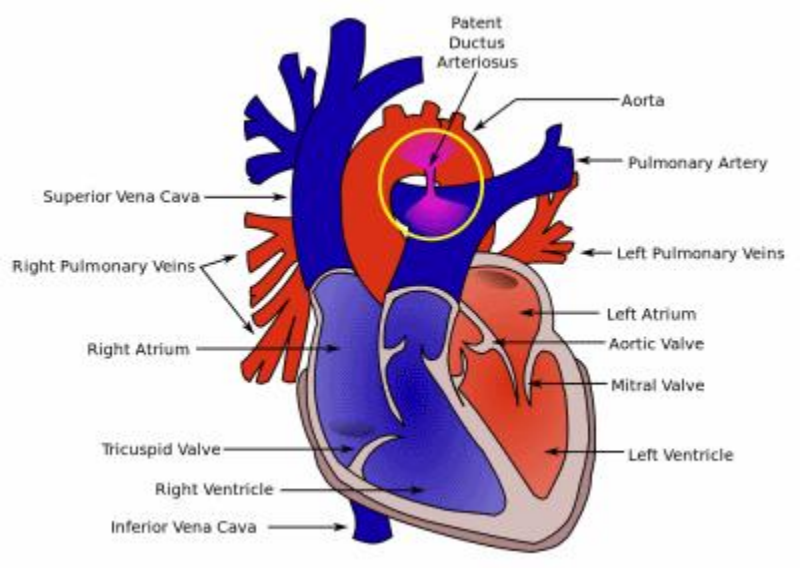
The following cardiac lesions may cause such events

- patent foramen ovale - present in around 20% of the population
- atrial septal defect - a much less common cause

Patent ductus arteriosus

Overview

- a form of congenital heart defect
- generally classed as 'acyanotic'. However, uncorrected can eventually result in late cyanosis in the lower extremities, termed differential cynaosis.
- 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
- 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

Patent foramen ovale

- Patent foramen ovale (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

Percutaneous coronary intervention

Percutaneous coronary intervention (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.

Two main complications may occur

- 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
- 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

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

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

Peri-arrest rhythms: bradycardia

The 2015 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

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

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
- adrenaline infusion titrated to response

Peri-arrest rhythms: tachycardia

The 2015 Resuscitation Council (UK) guidelines have simplified the advice given for the management of peri-arrest tachycardias. Separate algorithms for the management of broad-complex tachycardia, narrow complex tachycardia and atrial fibrillation have been replaced by one unified treatment algorithm

Following basic ABC assessment, 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 any of the above adverse signs are present then synchronised DC shocks should be given

Treatment following this is given according to whether the QRS complex is narrow or broad and whether the rhythm is regular or irregular. The full treatment algorithm can be found at the Resuscitation Council website, below is a very limited summary:

Broad-complex tachycardia

Regular

- assume ventricular tachycardia (unless previously confirmed SVT with bundle branch block)
- loading dose of amiodarone followed by 24 hour infusion

Irregular

- 1. AF with bundle branch block - treat as for narrow complex tachycardia
- 2. Polymorphic VT (e.g. Torsade de pointes) - IV magnesium

Narrow-complex tachycardia

Regular

- vagal manoeuvres followed by IV adenosine
- if above unsuccessful consider diagnosis of atrial flutter and control rate (e.g. Beta-blockers)

Irregular

- probable atrial fibrillation
- if onset < 48 hr consider electrical or chemical cardioversion
- rate control (e.g. Beta-blocker or digoxin) and anticoagulation

Primary pulmonary hypertension

The classification of pulmonary hypertension is currently changing with the term idiopathic pulmonary arterial hypertension (IPAH) becoming more widely used

Primary pulmonary hypertension (PPH, now IPAH)

- pulmonary arterial pressure > 25 mmHg at rest, > 30mmHg with exercise
- PPH is diagnosed when no underlying cause can be found
- around 10% of cases are familial: autosomal dominant
- endothelin thought to play a key role in pathogenesis
- associated with HIV, cocaine and anorexigens (e.g. fenfluramine)

Features

- more common in females, typically presents at 20-40 years old
- progressive SOB
- cyanosis
- right ventricular heave, loud P2, raised JVP with prominent 'a' waves, tricuspid regurgitation

Investigation

- echocardiography

Management

- diuretics if right heart failure
- anticoagulation
- vasodilator therapy: calcium channel blocker, IV prostaglandins, bosentan: endothelin-1 receptor antagonist
- heart-lung transplant

Prosthetic heart valves

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 Major disadvantage is structural deterioration and calcification over time. Most older patients (> 65 years for aortic valves and > 70 years for mitral valves) receive a bioprosthetic valve Long-term anticoagulation not usually needed. Warfarin may be given for the first 3 months depending on patient factors. Low-dose aspirin is given long-term.	The most common type now implanted is the bileaflet valve. Ball-and-cage valves are rarely used nowadays Mechanical valves have a low failure rate Major disadvantage is the increased risk of thrombosis meaning long-term anticoagulation is needed. Aspirin is normally given in addition unless there is a contraindication. Target INR - aortic: 3.0 - mitral: 3.5

Following the 2008 NICE guidelines for prophylaxis of endocarditis antibiotics are no longer recommended for common procedures such as dental work.

Pulmonary arterial hypertension: features and management

Pulmonary arterial hypertension (PAH) may be defined as a sustained elevation in mean pulmonary arterial pressure of greater than 25 mmHg at rest or 30 mmHg after exercise.

Features

- exertional dyspnoea is the most frequent symptom
- chest pain and syncope may also occur
- loud P2
- left parasternal heave (due to right ventricular hypertrophy)

Management should first involve treating any underlying conditions, for example with anticoagulants or oxygen. Following this, it has now been shown that **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 to acute vasodilator testing

- oral calcium channel blockers

If there is a negative response to acute vasodilator testing

- prostacyclin analogues: treprostinil, iloprost
- endothelin receptor antagonists: bosentan
- phosphodiesterase inhibitors: sildenafil

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

- aortic regurgitation
- patent ductus arteriosus
- hyperkinetic (anaemia, thyrotoxic, fever, exercise/pregnancy)

Pulsus alternans

- regular alternation of the force of the arterial pulse
- severe LVF

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

Restrictive cardiomyopathy

Features

- similar to constrictive pericarditis

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

Causes

- amyloidosis (e.g. secondary to myeloma) - most common cause in UK
- haemochromatosis
- Loffler's syndrome
- sarcoidosis
- scleroderma

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

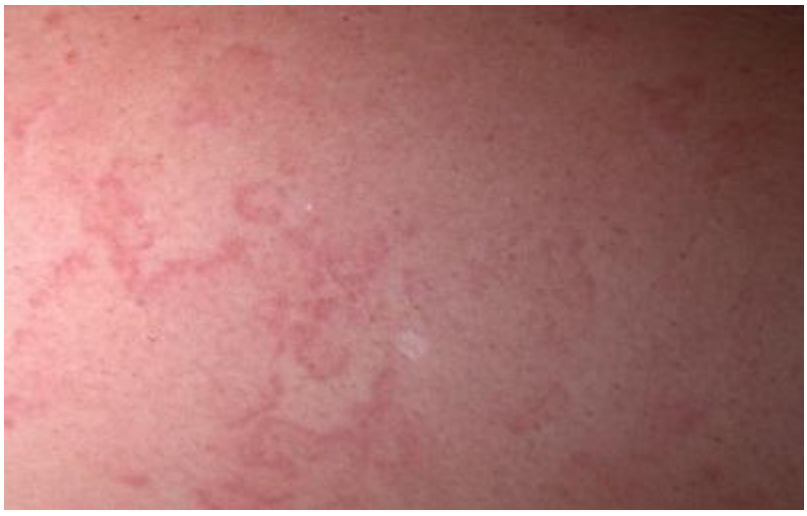
- ASOT > 200iu/mL
- history of scarlet fever
- positive throat swab
- increase in DNase B titre

Major criteria

- erythema marginatum
- Sydenham's chorea
- polyarthritis
- carditis (endo-, myo- or peri-)
- subcutaneous nodules

Minor criteria

- raised ESR or CRP
- pyrexia
- arthralgia (not if arthritis a major criteria)
- prolonged PR interval



Erythema marginatum is seen in around 10% of children with rheumatic fever. It is rare in adults

Supraventricular tachycardia

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. Episodes are characterised by the sudden onset of a narrow complex tachycardia, typically an atrioventricular nodal re-entry tachycardia (AVNRT). Other causes include atrioventricular re-entry tachycardias (AVRT) and junctional tachycardias.

Acute management

- vagal manoeuvres: e.g. Valsalva manoeuvre
- intravenous adenosine 6mg → 12mg → 12mg: contraindicated in asthmatics - verapamil is a preferable option
- electrical cardioversion

Prevention of episodes

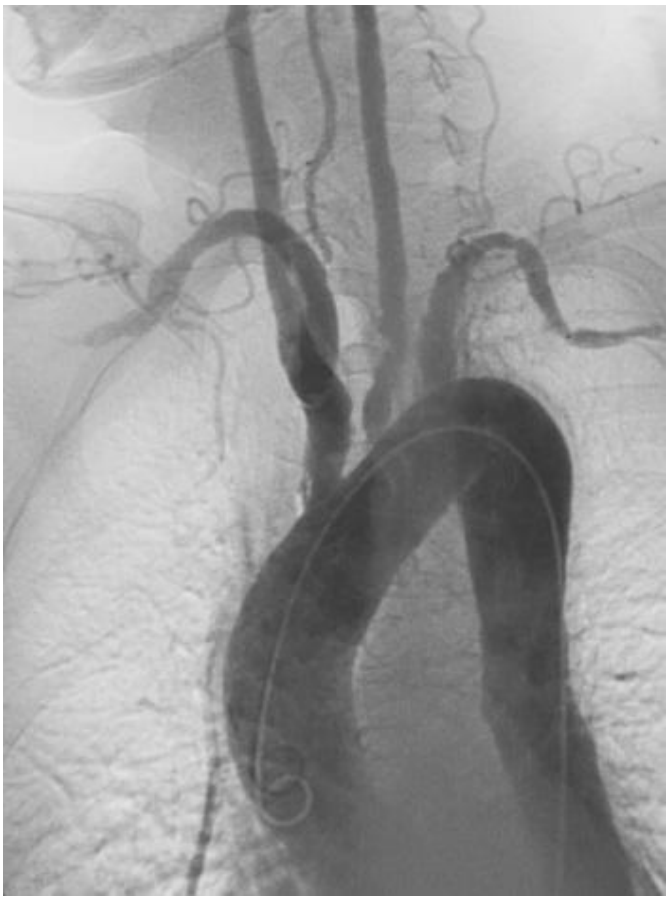
- beta-blockers
- radio-frequency ablation

Takayasu's arteritis

Takayasu's arteritis is a large vessel vasculitis. It typically causes occlusion of the aorta and questions commonly refer to an absent limb pulse. It is more common in females and Asian people

Features

- systemic features of a vasculitis e.g. malaise, headache
- unequal blood pressure in the upper limbs
- carotid bruit
- intermittent claudication
- aortic regurgitation (around 20%)



Angiography showing multiple stenoses in the branches of the aorta secondary to Takayasu's arteritis

Associations

- renal artery stenosis

Management

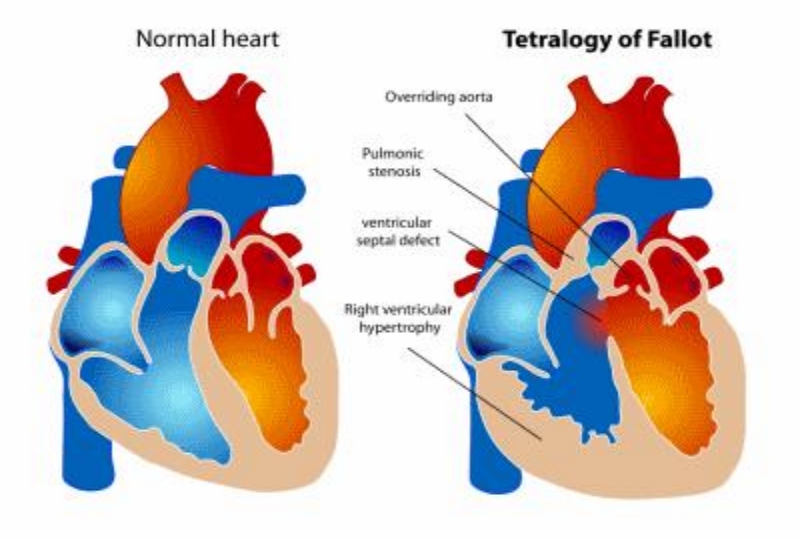
- steroids

Tetralogy of Fallot

Tetralogy of Fallot (TOF) is the most common cause of cyanotic congenital heart disease*. 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:

- ventricular septal defect (VSD)
- right ventricular hypertrophy
- right ventricular outflow tract obstruction, pulmonary stenosis
- 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

*however, at birth transposition of the great arteries is the more common lesion as patients with TOF generally present at around 1-2 months

Torsades de pointes

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

Causes of long QT interval

- congenital: Jervell-Lange-Nielsen syndrome, Romano-Ward syndrome
- antiarrhythmics: amiodarone, sotalol, class 1a antiarrhythmic drugs
- tricyclic antidepressants
- antipsychotics
- chloroquine
- terfenadine
- erythromycin
- electrolyte: hypocalcaemia, hypokalaemia, hypomagnesaemia
- myocarditis
- hypothermia
- subarachnoid haemorrhage

Management

- IV magnesium sulphate

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

Ventricular septal defects

Ventricular septal defects (VSD) are the most common cause of congenital heart disease. They close spontaneously in around 50% of cases. Congenital VSDs are associated with chromosomal disorders (e.g. Down's syndrome, Edward's syndrome, Patau syndrome) and single gene disorders such as Non-congenital causes include post myocardial infarction

Features

- classically a pan-systolic murmur which is louder in smaller defects

Complications

- aortic regurgitation*
- 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

*aortic regurgitation is due to a poorly supported right coronary cusp resulting in cusp prolapse

Ventricular tachycardia

Ventricular tachycardia (VT) is broad-complex tachycardia originating from a ventricular ectopic focus. It has the potential to precipitate ventricular fibrillation and hence requires urgent treatment.

There are two main types of VT:

- monomorphic VT: most commonly caused by myocardial infarction
- polymorphic VT: 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

Causes of a prolonged QT interval

Congenital	Drugs	Other
• Jervell-Lange-Nielsen syndrome (includes deafness and is due to an abnormal potassium channel) • Romano-Ward syndrome (no deafness)	• amiodarone, sotalol, class 1a antiarrhythmic drugs • tricyclic antidepressants, fluoxetine • chloroquine • terfenadine • erythromycin	• electrolyte: hypocalcaemia, hypokalaemia, hypomagnesaemia • acute myocardial infarction • myocarditis • hypothermia • subarachnoid haemorrhage

Management

If the patient has adverse signs (systolic BP < 90 mmHg, chest pain, heart failure or rate > 150 beats/min) then immediate cardioversion is indicated. In the absence of such signs antiarrhythmics may be used. If these fail, then electrical cardioversion may be needed with synchronised DC shocks

Drug therapy

- amiodarone: ideally administered through a central line
- lidocaine: use with caution in severe left ventricular impairment
- procainamide

Verapamil should NOT be used in VT

If drug therapy fails

- electrophysiological study (EPS)
- implant able cardioverter-defibrillator (ICD) - this is particularly indicated in patients with significantly impaired LV function

Ventricular tachycardia: management

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

If the patient has adverse signs (systolic BP < 90 mmHg, chest pain, heart failure, syncope) then immediate cardioversion is indicated. In the absence of such signs antiarrhythmics may be used. If these fail, then electrical cardioversion may be needed with synchronised DC shocks

Drug therapy

- amiodarone: ideally administered through a central line
- lidocaine: use with caution in severe left ventricular impairment
- procainamide

Verapamil should NOT be used in VT

If drug therapy fails

- electrophysiological study (EPS)
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Warfarin

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.

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.

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. There a variety of loading regimes and computer software is now often used to alter the dose.

Factors that may potentiate warfarin

- liver disease
- P450 enzyme inhibitors, e.g.: amiodarone, ciprofloxacin
- cranberry juice
- drugs which displace warfarin from plasma albumin, e.g. NSAIDs
- inhibit platelet function: NSAIDs

Side-effects

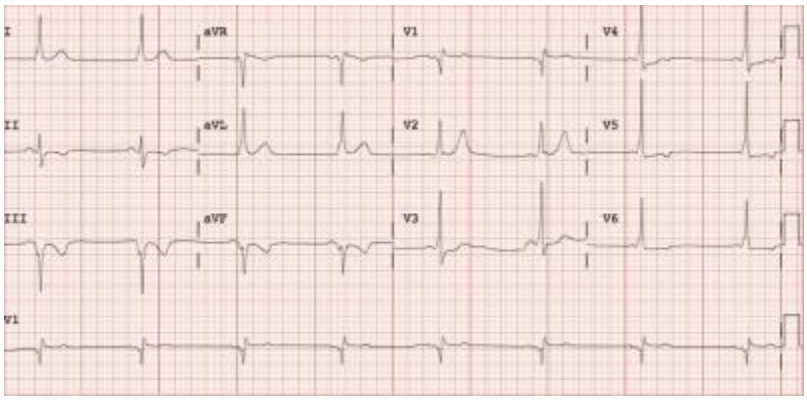
- haemorrhage
- teratogenic, although can be used in breast-feeding mothers
- skin necrosis: when warfarin is first started biosynthesis of protein C is reduced. This results in a temporary procoagulant state after initially starting warfarin, normally avoided by concurrent heparin administration. Thrombosis may occur in venules leading to skin necrosis
- purple toes

Wolff-Parkinson White

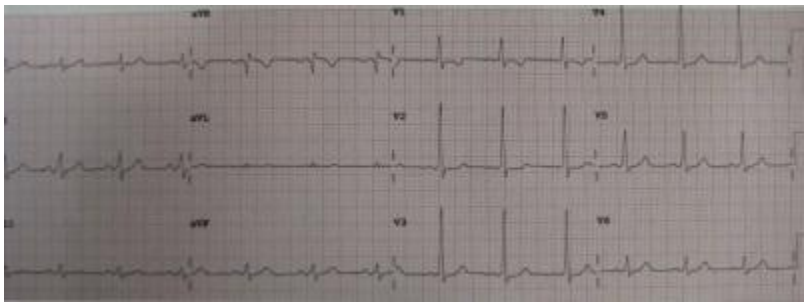
Wolff-Parkinson White (WPW) syndrome is caused by a congenital accessory conducting pathway between the atria and ventricles leading to a atrioventricular re-entry tachycardia (AVRT). As the accessory pathway does not slow conduction AF can degenerate rapidly to VF

Possible ECG features include:

- short PR interval
- wide QRS complexes with a slurred upstroke - 'delta wave'
- left axis deviation if right-sided accessory pathway*
- right axis deviation if left-sided accessory pathway*



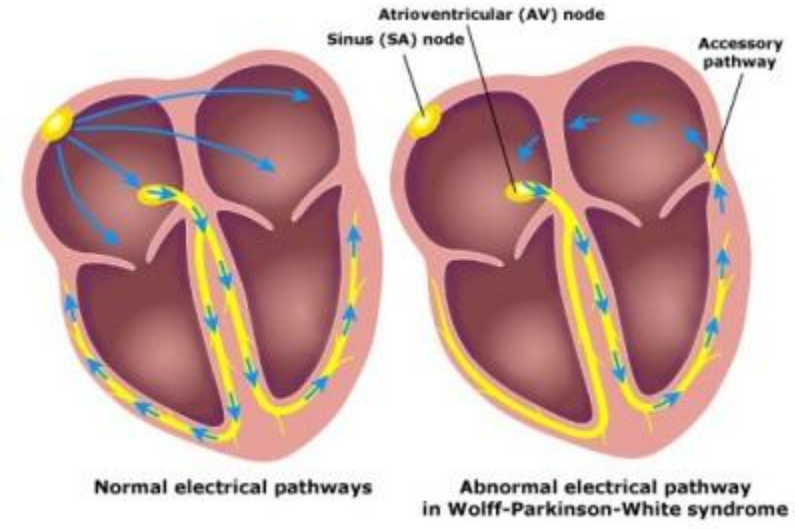
ECG showing short PR interval associated with a slurred upstroke (delta wave). Note the non-specific ST-T changes which are common in WPW and may be mistaken for ischaemia. The left axis deviation means that this is type B WPW, implying a right-sided pathway



Further example showing a characteristic delta wave

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



Associations of WPW

- HOCM
- mitral valve prolapse
- Ebstein's anomaly
- thyrotoxicosis
- secundum ASD

Management

- definitive treatment: radiofrequency ablation of the accessory pathway
- medical therapy: sotalol***, amiodarone, flecainide

*in the majority of cases, or in a question without qualification, Wolff-Parkinson-White syndrome is associated with left axis deviation

**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

***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

Clinical haematology/oncology

Acute lymphoblastic leukaemia: prognostic features

Good prognostic factors

- French-American-British (FAB) L1 type
- common ALL
- pre-B phenotype
- low initial WBC
- del(9p)

Poor prognostic factors

- FAB L3 type
- T or B cell surface markers
- Philadelphia translocation, t(9;22)
- age < 2 years or > 10 years
- male sex
- CNS involvement
- high initial WBC (e.g. > 100 * 10^9/l)
- non-Caucasian

Acute myeloid leukaemia

Acute myeloid leukaemia is the more common form of acute leukaemia in adults. It may occur as a primary disease or following a secondary transformation of a myeloproliferative disorder.

Poor prognostic features

- > 60 years
- > 20% blasts after first course of chemo
- cytogenetics: deletions of chromosome 5 or 7

Acute promyelocytic leukaemia M3

- associated with t(15;17)
- fusion of PML and RAR-alpha genes
- presents younger than other types of AML (average = 25 years old)
- Auer rods (seen with myeloperoxidase stain)
- DIC or thrombocytopenia often at presentation
- good prognosis

Classification - French-American-British (FAB)

- MO - undifferentiated
- M1 - without maturation
- M2 - with granulocytic maturation
- M3 - acute promyelocytic
- M4 - granulocytic and monocytic maturation
- M5 - monocytic
- M6 - erythroleukaemia
- M7 - megakaryoblastic

Acute promyelocytic leukaemia

You are not normally expected to be able to differentiate the different subtypes of acute myeloid leukaemia (AML) for the MRCP. An exception to this is acute promyelocytic leukaemia (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 which causes fusion of the PML and RAR-alpha genes.

Features

- presents younger than other types of AML (average = 25 years old)
- DIC or thrombocytopenia often at presentation
- good prognosis

Alpha-thalassaemia

Alpha-thalassaemia is due to a deficiency of alpha chains in haemoglobin

Overview

- 2 separate alpha-globulin genes are located on each chromosome 16

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. 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)

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
- other features: pre-eclampsia, pulmonary hypertension

Associations other than SLE

- other autoimmune disorders
- lymphoproliferative disorders
- phenothiazines (rare)

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
- 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 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

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

Antithrombin III inhibits several clotting factors, primarily thrombin, factor X and factor IX. It mediates the effects of heparin

Antithrombin III deficiency comprises a heterogeneous group of disorders, with some patients having a deficiency of normal antithrombin III whilst others produce abnormal antithrombin III

Features

- recurrent venous thromboses
- arterial thromboses do occur but are uncommon

Management

- thromboembolic events are treated with lifelong warfarinisation
- heparinisation during pregnancy*
- antithrombin III concentrates (often using during surgery or childbirth)

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

Condition	Prevalence	Relative risk of VTE
Antithrombin III deficiency	0.03	10-20

*as patients with antithrombin III deficiency have a degree of resistance to heparin anti-Xa levels should be monitored carefully to ensure adequate anticoagulation

Aplastic anaemia: 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%

Autoimmune haemolytic anaemia

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*
- neoplasia: e.g. lymphoma, CLL
- drugs: e.g. methyldopa

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. Features may include symptoms of Raynaud's and acrocynaosis. Patients respond less well to steroids

Causes of cold AIHA

- neoplasia: e.g. lymphoma
- infections: e.g. mycoplasma, EBV

*systemic lupus erythematosus can rarely be associated with a mixed-type autoimmune haemolytic anaemia

Beta-thalassaemia trait

The thalassaemias are a group of genetic disorders characterised by a reduced production rate of either alpha or beta chains. Beta-thalassaemia trait is an autosomal recessive condition characterised by a mild hypochromic, microcytic anaemia. It is usually asymptomatic

Features

- mild hypochromic, microcytic anaemia - microcytosis is characteristically disproportionate to the anaemia
- HbA2 raised (> 3.5%)

Bladder cancer: risk factors

Risk factors for transitional cell carcinoma of the bladder include:

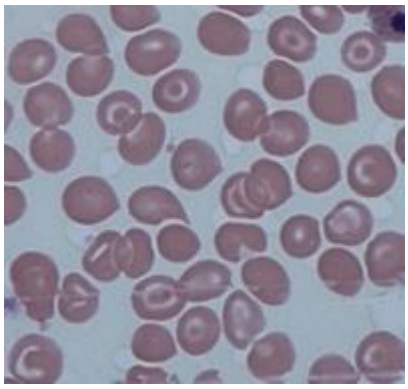
- Smoking
- Exposure to aniline dyes in the printing and textile industry
- Rubber manufacture
- Cyclophosphamide

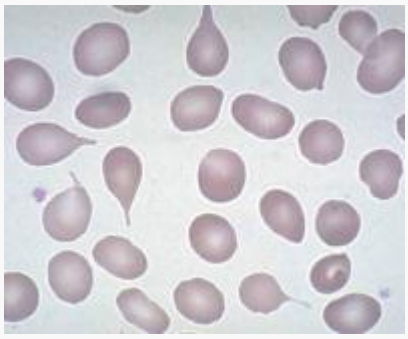
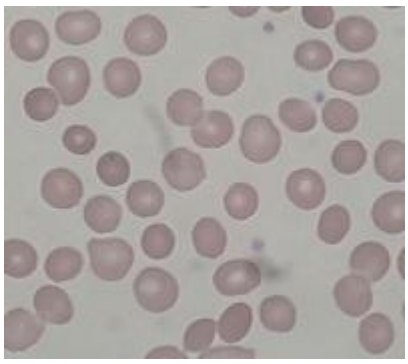
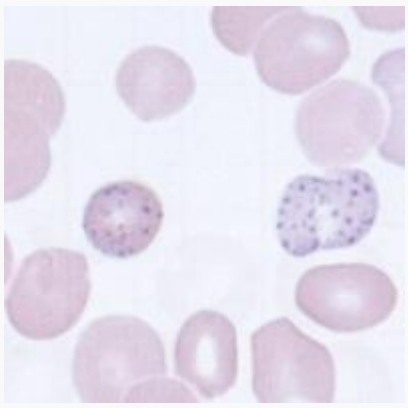
Risk factors for squamous cell carcinoma of the bladder include:

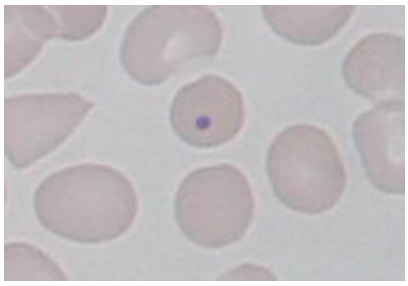
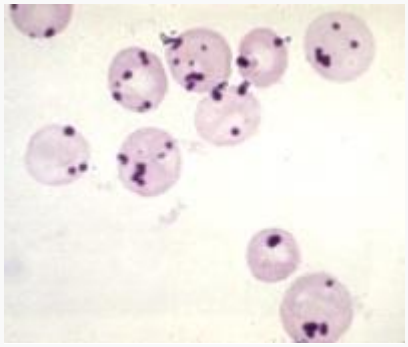
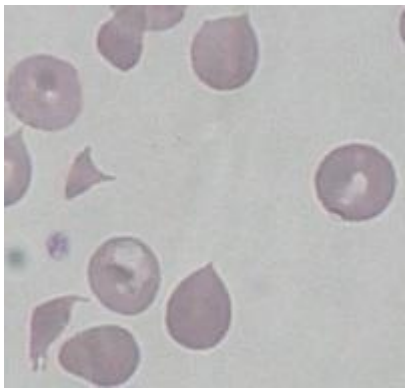
- Schistosomiasis
- Calmette-Guérin (BCG) treatment
- Smoking

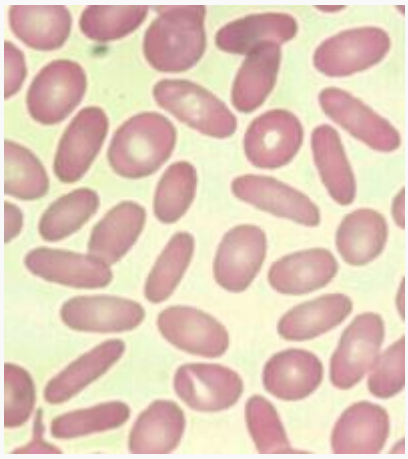
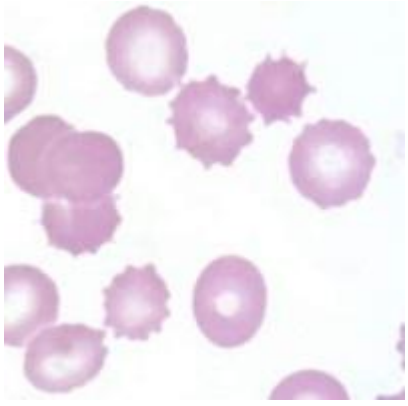
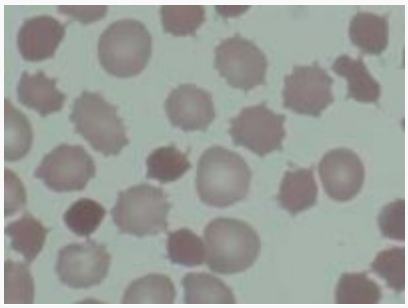
Blood films: pathological cell forms

Pathological red cell forms

Abnormality	Associated condition(s)	Appearance
Target cells	Sickle-cell/thalassaemia Iron-deficiency anaemia Hyposplenism Liver disease	

Abnormality	Associated condition(s)	Appearance
'Tear-drop' poikilocytes	Myelofibrosis	
Spherocytes	Hereditary spherocytosis Autoimmune hemolytic anaemia	
Basophilic stippling	Lead poisoning Thalassaemia Sideroblastic anemia Myelodysplasia	

Abnormality	Associated condition(s)	Appearance
Howell-Jolly bodies	Hyposplenism	
Heinz bodies	G6PD deficiency Alpha-thalassaemia	
Schistocytes ('helmet cells')	Intravascular haemolysis Mechanical heart valve Disseminated intravascular coagulation	

Abnormality	Associated condition(s)	Appearance
'Pencil' poikilocytes	Iron defiency anaemia	
Burr cells (echinocytes)	Uraemia Pyruvate kinase deficiency	
Acanthocytes	Abetalipoproteinemia	

Other blood film abnormalities:
hypersegmented neutrophils: megaloblastic anaemia

Blood films: typical pictures

Hyposplenism e.g. post-splenectomy

- target cells
- Howell-Jolly bodies
- 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

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

- e.g. ABO mismatch
- massive intravascular haemolysis

Febrile reactions

- due to white blood cell HLA antibodies
- often the result of sensitization by previous pregnancies or transfusions

Causes a degree of immunosuppression

- e.g. patients with colorectal cancer who have blood transfusions have a worse outcome than those who do not

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

Burkitt's lymphoma

Burkitt's lymphoma is a high-grade B-cell neoplasm. There are two major forms:

- endemic (African) form: typically involves maxilla or mandible
- 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 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 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. Complications of tumour lysis syndrome include:

- hyperkalaemia
- hyperphosphataemia
- hypocalcaemia
- hyperuricaemia
- acute renal failure

*allantoin is 5-10 times more soluble than uric acid, so renal excretion is more effective

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

*excludes non-melanoma skin cancer

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

Chronic lymphocytic leukaemia

Chronic lymphocytic leukaemia (CLL) is caused by a monoclonal proliferation of well-differentiated lymphocytes which are almost always B-cells (99%)

Features

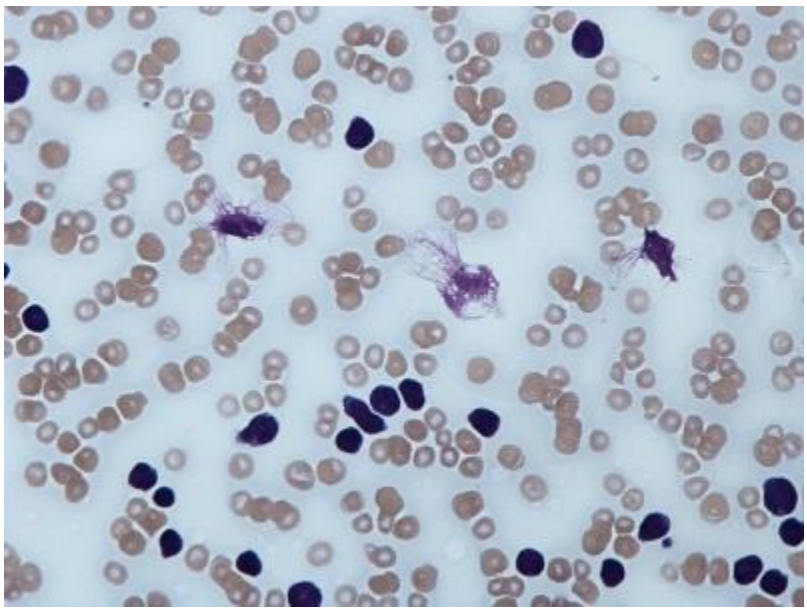
- often none
- constitutional: anorexia, weight loss
- bleeding, infections
- lymphadenopathy more marked than CML

Complications

- hypogammaglobulinaemia leading to recurrent infections
- 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)
- immunophenotyping



Peripheral blood film showing smudge B cells

Chronic lymphocytic leukaemia: management

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 >38ºC for > 2 weeks, extreme fatigue, night sweats
- autoimmune cytopaenias e.g. ITP

Management

- patients who have no indications for treatment are monitored with regular blood counts
- fludarabine, cyclophosphamide and rituximab (FCR) has now emerged as the initial treatment of choice for the majority of patients

Chronic lymphocytic leukaemia: 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

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

Chronic myeloid leukaemia

The Philadelphia chromosome is present in more than 95% of patients with chronic myeloid leukaemia (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 (40-50 years)

- middle-age
- anaemia, weight loss, abdo discomfort
- splenomegaly may be marked
- spectrum of myeloid cells seen in peripheral blood
- decreased leukocyte alkaline phosphatase
- may undergo blast transformation (AML in 80%, ALL in 20%)

Management

- imatinib is now considered first-line treatment
- hydroxyurea
- interferon-alpha
- allogenic bone marrow transplant

Imatinib

- inhibitor of the tyrosine kinase associated with the BCR-ABL defect
- very high response rate in chronic phase CML

Coagulopathy of liver disease

In liver failure all clotting factors are low, except for factor VIII which is paradoxically supra-normal. This is because factor VIII is synthesised in endothelial cells throughout the body, unlike the other clotting factors which are synthesised purely in hepatic endothelial cells. Furthermore, whilst activated factor VIII is usually rapidly cleared from the blood stream, good hepatic function is required for this to occur, further leading to increases in circulating factor VIII. This is one of many reasons why, despite conventional coagulation studies (increased PT, APTT, decreased fibrinogen) suggesting increased bleeding risk, patients with chronic liver disease are not protected from venous thrombosis formation but are paradoxically at an increased risk of thrombosis, in addition to bleeding. Other events occurring in chronic liver disease which predispose patients to thrombosis formation include reduced synthesis of the purely hepatic derived natural anticoagulants protein c and protein s (vitamin k dependent), and anti-thrombin (non-vitamin k dependent).

Colorectal cancer

Colorectal cancer is the third most common type of cancer in the UK and the second most cause of cancer deaths. Annually there are about 150,000 new cases diagnosed and 50,000 deaths from the disease.

Location of cancer (averages)

- rectal: 40%
- sigmoid: 30%
- descending colon: 5%
- transverse colon: 10%
- ascending colon and caecum: 15%

Colorectal cancer: screening

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 in England, 50 to 74 years in Scotland. IPatients aged over 74 years may request screening
- eligible patients are sent faecal occult blood (FOB) tests through the post
- patients with abnormal results are offered a colonoscopy

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

Cyclophosphamide

Cyclophosphamide is an alkylating agent used in the management of cancer and autoimmune conditions. It works by causing cross-linking of DNA

Adverse effects

- haemorrhagic cystitis: incidence reduced by the use of hydration and mesna
- myelosuppression
- transitional cell carcinoma

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

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	Myelosuppression, mucositis, dermatitis

Cytotoxic	Mechanism of action	Adverse effects
	blocking thymidylate synthase (works during S phase)	
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	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

Deep vein thrombosis: diagnosis and management

Diagnosis

NICE published guidelines in 2012 relating to the investigation and management of deep vein thrombosis (DVT).

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

Further 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.

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

Drug-induced haemolytic anaemia

Drug-induced haemolytic anaemia can be classified according to three different mechanisms:

Type I - antibody against drug-red cell membrane complex

- penicillin

Type II - deposition of complement via a drug-protein-antibody complex onto the red cell membrane

- quinidine
- rifampicin

Type III - true autoimmune haemolytic anaemia - role of drug not known

- methyldopa
- L-dopa
- mefanamic acid

Drug-induced pancytopaenia

Drug causes of pancytopaenia

- cytotoxics
- antibiotics: trimethoprim, chloramphenicol
- anti-rheumatoid: gold, penicillamine
- carbimazole*
- anti-epileptics: carbamazepine
- sulphonylureas: tolbutamide

*causes both agranulocytosis and pancytopaenia

ECOG score

The ECOG score is a 'performance status' scale, or a score that measures the functional status 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

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)

Factor V Leiden

Factor V Leiden (activated protein C resistance) is the most common inherited thrombophilia, being present in around 5% of the UK population. It is due to a mutation in the Factor V Leiden mutation. Heterozygotes have a 4-5 fold risk of venous thrombosis.

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

G6PD deficiency

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the commonest red blood cell enzyme defect. It is more common in people from the Mediterranean and Africa and is inherited in a X-linked recessive fashion. Many drugs can precipitate a crisis as well as infections and broad (fava) beans

Pathophysiology

- ↓ G6PD → ↓ glutathione → increased red cell susceptibility to oxidative stress

Features

- neonatal jaundice is often seen
- intravascular haemolysis
- gallstones are common
- splenomegaly may be present
- Heinz bodies on blood films

Diagnosis is made by using a G6PD enzyme assay

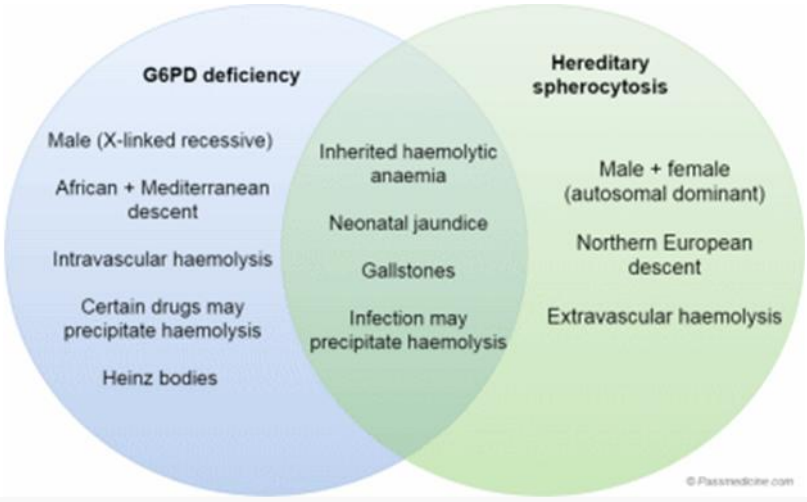
Some drugs causing haemolysis

- anti-malarials: primaquine
- ciprofloxacin
- sulph- group drugs: sulphonamides, sulphasalazine, sulfonylureas

Some drugs thought to be safe

- penicillins
- cephalosporins
- macrolides
- tetracyclines
- trimethoprim

Comparing G6PD deficiency to hereditary spherocytosis:



Comparison of 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

Gastric cancer

Epidemiology

- overall incidence is decreasing, but incidence of tumours arising from the cardia is increasing
- peak age = 70-80 years
- more common in Japan, China, Finland and Colombia than the West
- more common in males, 2:1

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
- blood group A: gAstric cAncer
- gastric adenomatous polyps
- pernicious anaemia
- smoking
- diet: salty, spicy, nitrates
- may be negatively associated with duodenal ulcer

Investigation

- diagnosis: endoscopy with biopsy
- staging: CT or endoscopic ultrasound - endoscopic ultrasound has recently been shown to be superior to CT

Gastrointestinal secretions

Up to 7 litres of gastrointestinal secretions enter the lumen of the GI tract in a 24 hour period. The absorptive function of the small bowel is such that by the time a formed stool is created, it will contain, on average 200ml water.
The common secretions together with their approximate volumes are demonstrated below:

Origin of secretion	Volume in ml / 24 hour period	Na^+ mmol/L	K^+ mmol/L	Cl^- mmol/L	HCO_3
Salivary glands	1500	10	26	10	30
Stomach	1500	60	10	130	
Duodenum	100-2000	140	80	80	
Pancreas	1000	140	5	70	115
Bile	50-800	145	50	100	35
Jejunum/ileum	3000	140	50	104	30
Colon	100	60	30	40	

The regulation of these secretions is dependent upon location. In the salivary glands a complex interaction of flow rate governed by the autonomic nervous system. The exact composition of sodium and potassium is regulated by aldosterone. In the stomach hormones such as gastrin play a role and feedback is both endocrine and neurologically mediated (vagus). In the duodenum CCK is released in response to duodenal distension and this causes contraction of the gallbladder and release of bile.

Pancreatic secretions are affected by somatostatin. The secretions in the small bowel are affected by the osmolality of the lumenal contents. This is in part due to the tightness of cellular junctions and in this regard the jejunum is more permeable than the ileum. The practical implication of this is that if an individual has an extensive intestinal resection and a high output, proximally sited stoma then administration of hypotonic rather than isotonic solutions will result in worsening of electrolyte

disturbances as electrolyte rich secretions will enter the jejunum.

In some individuals a colectomy or similar procedure results in formation of an end or loop ileostomy. Ileostomies typically lose between 500 and 1000ml over a 24 hour period and patients with high output ileostomies can rapidly become dehydrated. Ileostomy effluent typically contains 126mmol/L of sodium and 22mmol/L of potassium. Knowledge of this fluid composition should guide fluid prescribing in replacing losses.

Gingival hyperplasia

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)

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(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

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

Haemolytic anaemias: by site

In intravascular haemolysis free haemoglobin is released which binds to haptoglobin. 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: causes

- mismatched blood transfusion
- G6PD deficiency*
- red cell fragmentation: heart valves, TTP, DIC, HUS
- paroxysmal nocturnal haemoglobinuria
- cold autoimmune haemolytic anaemia

Extravascular haemolysis: causes

- 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

Haemophilia

Haemophilia is a X-linked recessive disorder of coagulation. Up to 30% of patients have no family history of the condition. Haemophilia A is due to a deficiency of factor VIII whilst in haemophilia B (Christmas disease) there is a lack of factor IX

Features

- haemoarthroses, haematomas
- prolonged bleeding after surgery or trauma

Blood tests

- prolonged APTT
- bleeding time, thrombin time, prothrombin time normal

Up to 10-15% of patients with haemophilia A develop antibodies to factor VIII treatment

Hairy cell leukaemia

Hairy cell leukaemia is a rare malignant proliferation disorder of B cells. It is more common in males (4:1)

Features

- pancytopenia
- splenomegaly
- skin vasculitis in 1/3 patients
- 'dry tap' despite bone marrow hypercellularity
- tartrate resistant acid phosphotase (TRAP) stain positive

Management

- chemotherapy is first-line: cladribine, pentostatin
- immunotherapy is second-line: rituximab, interferon-alpha

Hepatocellular carcinoma

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.

The main risk factor for developing HCC is liver cirrhosis, for example secondary* to hepatitis B & C, alcohol, haemochromatosis and primary biliary cirrhosis. 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

*Wilson's disease is an exception

Hereditary spherocytosis

Basics

- most common hereditary haemolytic anaemia in people of northern European descent
- autosomal dominant defect of red blood cell cytoskeleton
- the normal biconcave disc shape is replaced by a sphere-shaped red blood cell
- red blood cell survival reduced as destroyed by the spleen

Presentation

- failure to thrive
- jaundice, gallstones
- splenomegaly
- aplastic crisis precipitated by parvovirus infection
- degree of haemolysis variable
- MCHC elevated

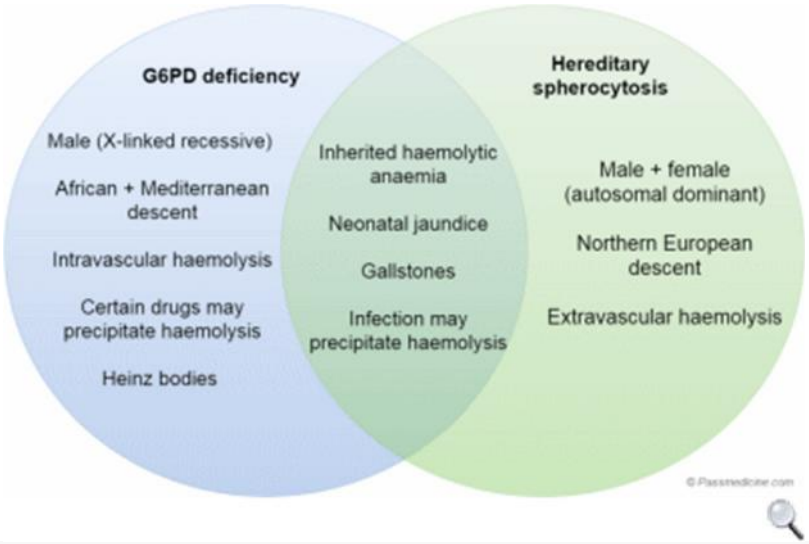
Diagnosis

- osmotic fragility test

Management

- folate replacement
- splenectomy

Comparing G6PD deficiency to hereditary spherocytosis:



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Diagnostic test	Measure enzyme activity of G6PD	Osmotic fragility test

Hodgkin's lymphoma: staging

Hodgkin's lymphoma is a malignant proliferation of lymphocytes characterised by the presence of the Reed-Sternberg cell. It has a bimodal age distributions being most common in the third and seventh decades

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
- 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)

Hyposplenism

Causes

- splenectomy
- sickle-cell
- coeliac disease, dermatitis herpetiformis
- Graves' disease
- systemic lupus erythematosus
- amyloid

Features

- Howell-Jolly bodies
- siderocytes

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

Iron deficiency anaemia

Features

- koilonychia
- atrophic glossitis
- post-cricoid webs
- angular stomatitis

Blood film

- target cells
- 'pencil' poikilocytes
- if combined with B12/folate deficiency a 'dimorphic' film occurs with mixed microcytic and macrocytic cells

ITP

Idiopathic thrombocytopenic purpura (ITP) is an immune mediated reduction in the platelet count. Antibodies are directed against the glycoprotein IIb/IIIa or Ib-V-IX complex.

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)

ITP: investigation and management

Idiopathic thrombocytopenic purpura (ITP) is an immune mediated reduction in the platelet count. Antibodies are directed against the glycoprotein IIb-IIIa or Ib complex

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

- oral prednisolone (80% of patients respond)
- splenectomy if platelets < 30 after 3 months of steroid therapy
- IV immunoglobulins
- immunosuppressive drugs e.g. cyclophosphamide

Leucocyte alkaline phosphatase

Raised in

- myelofibrosis
- leukaemoid reactions
- polycythaemia rubra vera
- infections
- steroids, Cushing's syndrome
- pregnancy, oral contraceptive pill

Low in

- 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

A relatively common clinical problem is differentiating chronic myeloid leukaemia from a leukaemoid reaction. The following differences may help:

Leukaemoid reaction:

- 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

Chronic myeloid leukaemia:

- low leucocyte alkaline phosphatase score

Macrocytic anaemia

Macrocytic anaemia can be divided into causes associated with a megaloblastic bone marrow and those with a normoblastic bone marrow

Megaloblastic causes	Normoblastic causes
• vitamin B12 deficiency • folate deficiency	• alcohol • liver disease • hypothyroidism • pregnancy • reticulocytosis • myelodysplasia • drugs: cytotoxics

MGUS

Monoclonal gammopathy of undetermined significance (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. Around 10% of patients eventually develop myeloma at 5 years, with 50% at 15 years

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)

Myelofibrosis

Overview

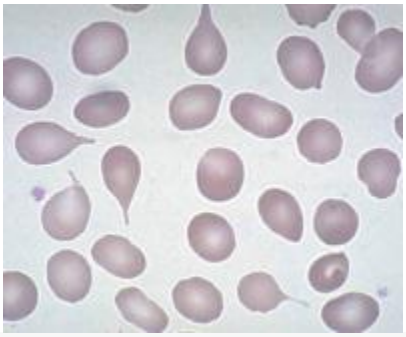
- a myeloproliferative disorder
- thought to be caused by hyperplasia of abnormal megakaryocytes
- the resultant release of platelet derived growth factor is thought to stimulate fibroblasts
- haematopoiesis develops in the liver and spleen

Features

- e.g. elderly person with symptoms of anaemia e.g. fatigue (the most common presenting symptom)
- massive splenomegaly
- hypermetabolic symptoms: weight loss, night sweats etc

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
- high urate and LDH (reflect increased cell turnover)



Blood film showing the typical 'tear-drop' poikilocytes of myelofibrosis

Myeloma: features

Multiple myeloma is a neoplasm of the bone marrow plasma cells. The peak incidence is patients aged 60-70 years.

Clinical features

- bone disease: bone pain, osteoporosis + pathological fractures (typically vertebral), osteolytic lesions
- lethargy
- infection
- hypercalcaemia (see below)
- renal failure
- other features: amyloidosis e.g. Macroglossia, carpal tunnel syndrome; neuropathy; hyperviscosity

Investigations

- monoclonal proteins (usually IgG or IgA) in the serum and urine (Bence Jones proteins)
- increased plasma cells in the bone marrow
- bone lesions on the skeletal survey

The 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

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.

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

Myeloma: prognosis

B2-microglobulin is a useful marker of prognosis - raised levels imply poor prognosis. Low levels of albumin are also associated with a poor prognosis

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

Neck lumps

The table below gives characteristic exam question features for conditions causing neck lumps:

Condition	Notes
Reactive lymphadenopathy	By far the most common cause of neck swellings. There may be a history of local infection or a generalised viral illness
Lymphoma	Rubbery, painless lymphadenopathy The phenomenon of pain whilst drinking alcohol is very uncommon There may be associated night sweats and splenomegaly
Thyroid swelling	May be hypo-, eu- or hyperthyroid symptomatically Moves upwards on swallowing
Thyroglossal cyst	More common in patients < 20 years old Usually midline, between the isthmus of the thyroid and the hyoid bone Moves upwards with protrusion of the tongue May be painful if infected
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 Typical symptoms are dysphagia, regurgitation, aspiration and chronic cough
Cystic hygroma	A congenital lymphatic lesion (lymphangioma) typically found in the neck, classically on the left side Most are evident at birth, around 90% present before 2 years of age

Condition	Notes
Branchial cyst	An oval, mobile cystic mass that develops between the sternocleidomastoid muscle and the pharynx Develop due to failure of obliteration of the second branchial cleft in embryonic development Usually present in early adulthood
Cervical rib	More common in adult females Around 10% develop thoracic outlet syndrome
Carotid aneurysm	Pulsatile lateral neck mass which doesn't move on swallowing

Neutropenic sepsis

Neutropenic sepsis is a relatively common complication of cancer therapy, usually as a consequence of 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 38ºC or
- other signs or symptoms consistent with clinically significant sepsis

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
- NICE recommend starting empirical antibiotic therapy with piperacillin with tazobactam (Tazocin) immediately
- 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 therapy antifungal therapy blindly
- there may be a role for G-CSF in selected patients

Oesophageal cancer

Until recent times oesophageal cancer was most commonly due to a squamous cell carcinoma but the incidence of adenocarcinoma is rising rapidly. 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.

Risk factors

- smoking
- alcohol
- GORD
- Barrett's oesophagus
- achalasia
- Plummer-Vinson syndrome
- squamous cell carcinoma is also linked to diets rich in nitrosamines
- rare: coeliac disease, scleroderma

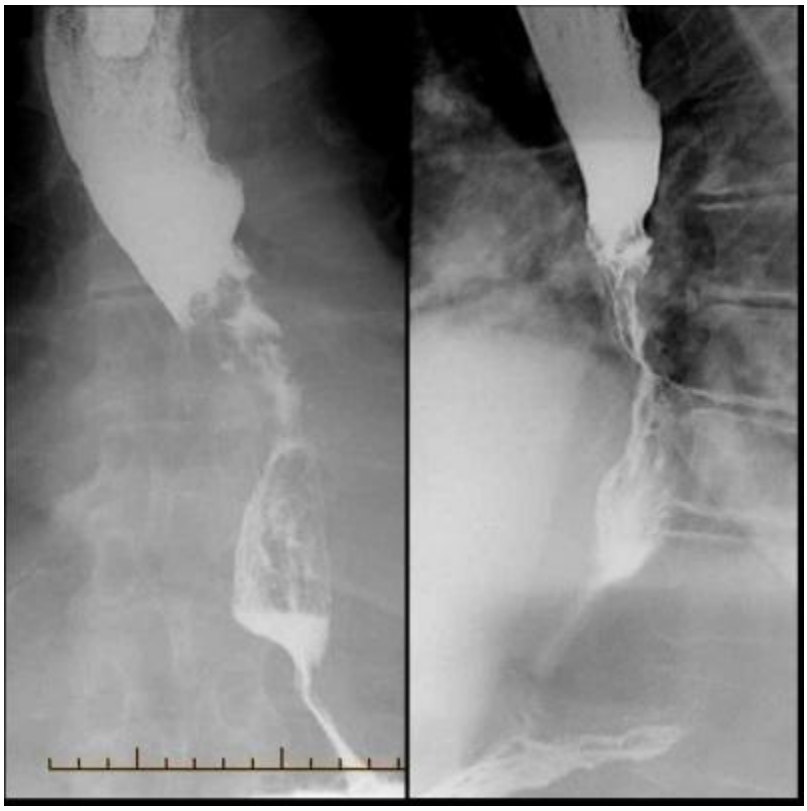
Diagnosis

- Upper GI endoscopy is the first line test
- Contrast swallow may be of benefit in classifying benign motility disorders but has no place in the assessment of tumours
- Staging is 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. Thoracoscopy is not routinely performed.

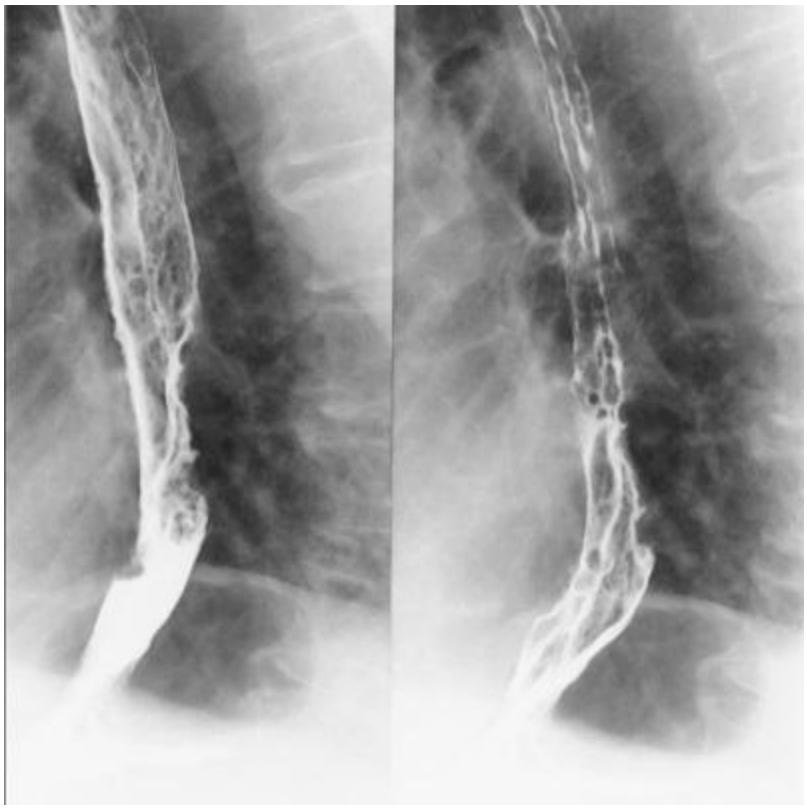
Treatment

- Operable disease is best managed by surgical resection.
- 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), a left thoraco-abdominal resection (difficult access due to thoracic aorta) and a 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.



Barium swallow - 5cm irregular narrowing of the mid-thoracic oesophagus with proximal shouldering



Fluoroscopy - a region of fixed, irregular stricturing is seen in the distal oesophagus

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)

Paroxysmal nocturnal haemoglobinuria

Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired disorder leading to haemolysis (mainly intravascular) of haematological cells. It is thought to be caused by increased sensitivity of cell membranes to complement (see below) due to a lack of glycoprotein glycosyl-phosphatidylinositol (GPI). Patients are more prone to venous thrombosis

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 (DAF), are not properly bound to the cell membrane due a lack of GPI
- thrombosis is thought to be caused by a lack of CD59 on platelet membranes predisposing to platelet aggregation

Features

- haemolytic anaemia
- red blood cells, white blood cells, platelets or stem cells may be affected therefore pancytopaenia may be present
- haemoglobinuria: classically dark-coloured urine in the morning (although has been shown to occur throughout the day)
- thrombosis e.g. Budd-Chiari syndrome
- aplastic anaemia may develop in some patients

Diagnosis

- flow cytometry of blood to detect low levels of CD59 and CD55 has now replaced Ham's test as the gold standard investigation in PNH
- Ham's test: acid-induced haemolysis (normal red cells would not)

Management

- blood product replacement
- anticoagulation
- eculizumab, a monoclonal antibody directed against terminal protein C5, is currently being trialled and is showing promise in reducing intravascular haemolysis
- stem cell transplantation

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*

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

*uterine fibroids may cause menorrhagia which in turn leads to blood loss - polycythaemia is rarely a clinical problem

Polycythaemia vera: features

Polycythaemia vera (previously called polycythaemia rubra vera) 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. It has recently been established that a mutation in JAK2 is present in approximately 95% of patients with polycythaemia vera and this has resulted in significant changes to the diagnostic criteria. The incidence of polycythaemia vera peaks in the sixth decade.

Features

- hyperviscosity
- pruritus, typically after a hot bath
- splenomegaly
- haemorrhage (secondary to abnormal platelet function)
- plethoric appearance
- hypertension in a third of patients

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

Other features that may be seen in PRV include a low ESR and a raised leukocyte alkaline phosphotase

The diagnostic criteria for polycythaemia vera have recently been updated by the BCSH. This replaces the previous polycythaemia vera Study Group criteria.

JAK2-positive polycythaemia vera - 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

Criteria	Notes
B4	Endogenous erythroid colonies or low serum erythropoietin

Polycythaemia vera: management

Polycythaemia vera 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. It has peak incidence in the sixth decade, with typical features including hyperviscosity, pruritus and splenomegaly

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
- 5-15% of patients progress to acute leukaemia (risk increased with chemotherapy treatment)

Pregnancy: DVT/PE

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)

Primary immunodeficiency

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	Causes recurrent pneumonias and abscesses, particularly due to catalase-positive bacteria (e.g. *Staphylococcus aureus* and fungi (e.g. *Aspergillus*) Negative nitroblue-tetrazolium 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	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

Disorder	Underlying defect	Notes
Severe combined immunodeficiency	Many varying causes. Most common (X-linked) due to defect in the common	Recurrent infections due to viruses, bacteria and fungi. Reduced T-cell receptor excision

Disorder	Underlying defect	Notes
	gamma chain, a protein used in the receptors for IL-2 and other interleukins. Other causes include adenosine deaminase deficiency	circles Stem cell transplantation may be successful
Ataxia telangiectasia	Defect in DNA repair enzymes	Autosomal recessive. Features include cerebellar ataxia, telangiectasia (spider angiomas), recurrent chest infections 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

Prostate cancer: PSA testing

Prostate specific antigen (PSA) is a serine protease enzyme produced by normal and malignant prostate epithelial cells. It has become an important tumour marker but much controversy still exists regarding its usefulness as a screening tool.

The NHS Prostate Cancer Risk Management Programme (PCRMP) has published updated guidelines in 2009 on how to handle requests for PSA testing in asymptomatic men. A recent European trial (ERSPC) showed a statistically significant reduction in the rate of death prostate cancer by 20% in men aged 55 to 69 years but this was associated with a high risk of over-diagnosis and over-treatment. Having reviewed this and other data the National Screening Committee have decided not to introduce a prostate cancer screening programme yet but rather allow men to make an informed choice.

Age-adjusted upper limits for PSA were recommended by the PCRMP:

Age	PSA level (ng/ml)
50-59 years	3.0
60-69 years	4.0
> 70 years	5.0

PSA levels may also be raised by*:

- benign prostatic hyperplasia (BPH)
- prostatitis and urinary tract infection (NICE recommend to postpone the PSA test for at least 1 month after treatment)
- ejaculation (ideally not in the previous 48 hours)
- vigorous exercise (ideally not in the previous 48 hours)
- urinary retention
- instrumentation of the urinary tract

Poor specificity and sensitivity

- around 33% of men with a PSA of 4-10 ng/ml will be found to have prostate cancer. With a PSA of 10-20 ng/ml this rises to 60% of men
- around 20% with prostate cancer have a normal PSA

- various methods are used to try and add greater meaning to a PSA level including age-adjusted upper limits and monitoring change in PSA level with time (PSA velocity or PSA doubling time)

*whether digital rectal examination actually causes a rise in PSA levels is a matter of debate

Protein C deficiency

Protein C deficiency is an autosomal codominant condition which causes an increased risk of thrombosis

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

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. In this case the potassium is released as the large numbers of platelets aggregate and degranulate.

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)
- familial causes

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.

Sickle-cell crises

Sickle cell anaemia is characterised by periods of good health with intervening crises

Four main types of crises are recognised:

- thrombotic, 'painful crises'
- sequestration
- aplastic
- haemolytic

Thrombotic crises

- also known as painful crises or vaso-occlusive crises
- precipitated by infection, dehydration, deoxygenation
- 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

Aplastic crises

- caused by infection with parvovirus
- sudden fall in haemoglobin

Haemolytic crises

- rare
- fall in haemoglobin due an increased rate of haemolysis

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. It may be congenital or acquired

Congenital cause: delta-aminolevulinate synthase-2 deficiency

Acquired causes

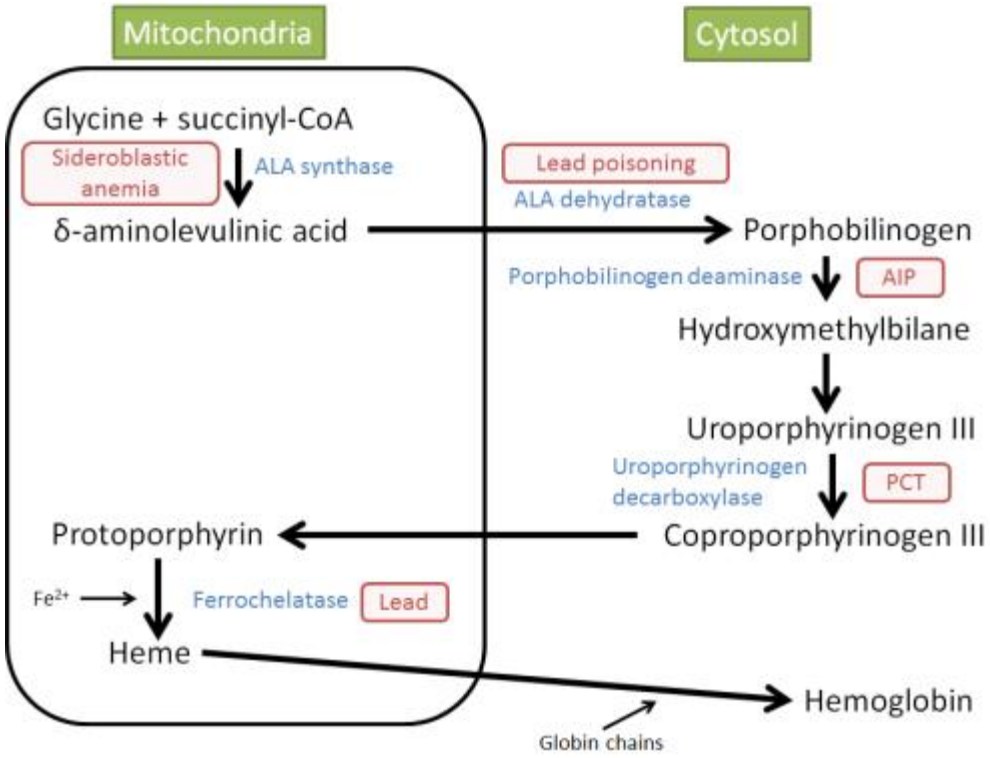
- myelodysplasia
- alcohol
- lead
- anti-TB medications

Investigations

- hypochromic microcytic anaemia (more so in congenital)
- bone marrow: sideroblasts and increased iron stores

Management

- supportive
- treat any underlying cause
- pyridoxine may help


Mitochondria
Cytosol
Glycine + succinyl-CoA
Sideroblastic anemia
ALA synthase
δ-aminolevulinic acid
Lead poisoning
ALA dehydratase
Porphobilinogen
Porphobilinogen deaminase
AIP
Hydroxymethylbilane
Uroporphyrinogen III
Uroporphyrinogen decarboxylase
PCT
Coproporphyrinogen III
Protoporphyrin
Fe2+
Ferrochelatase
Lead
Heme
Hemoglobin
Globin chains

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. Sjogren's syndrome is much 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)

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-La (SSB) antibodies in 30% of patients with PSS
- Schirmer's test: filter paper near conjunctival sac to measure tear formation
- histology: focal lymphocytic infiltration
- also: hypergammaglobulinaemia, low C4

Management

- artificial saliva and tears
- pilocarpine may stimulate saliva production

Superior vena cava obstruction

Superior vena cava (SVC) obstruction is an oncological emergency caused by compression of the SVC. It is most commonly associated with lung cancer.

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

Causes

- common malignancies: small cell lung cancer, lymphoma
- other malignancies: metastatic seminoma, Kaposi's sarcoma, breast cancer
- aortic aneurysm
- mediastinal fibrosis
- goitre
- SVC thrombosis

Management

- general: dexamethasone, balloon venoplasty, stenting
- small cell: chemotherapy + radiotherapy
- non-small cell: radiotherapy

Thrombocytosis

Thrombocytosis is an abnormally high platelet count, usually > 400 * 10^9/l.

Causes of thrombocytosis

- reactive: platelets are an acute phase reactant - platelet count can increase in response to stress such as a severe infection or surgery
- malignancy
- essential thrombocytosis (see below), or as part of another myeloproliferative disorder such as chronic myeloid leukaemia or polycythaemia rubra vera
- hyposplenism

Essential thrombocytosis

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.

Features

- platelet count > 600 * 10^9/l
- both thrombosis (venous or arterial) and haemorrhage can be seen
- a characteristic symptom is a burning sensation in the hands
- a JAK2 mutation is found in around 50% of patients

Management

- hydroxyurea (hydroxycarbamide) is widely used to reduce the platelet count
- interferon-α is also used in younger patients
- low-dose aspirin may be used to reduce the thrombotic risk

Thrombophilia: causes

Inherited

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
- 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
Antiphospholipid syndrome

Drugs
the combined oral contraceptive pill

Thrombotic thrombocytopenic purpura: management

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 protease which breakdowns large multimers of von Willebrand's factor
- overlaps with haemolytic uraemic syndrome (HUS)

Management

- no antibiotics - may worsen outcome
- plasma exchange is the treatment of choice
- steroids, immunosuppressants
- vincristine

Thymoma

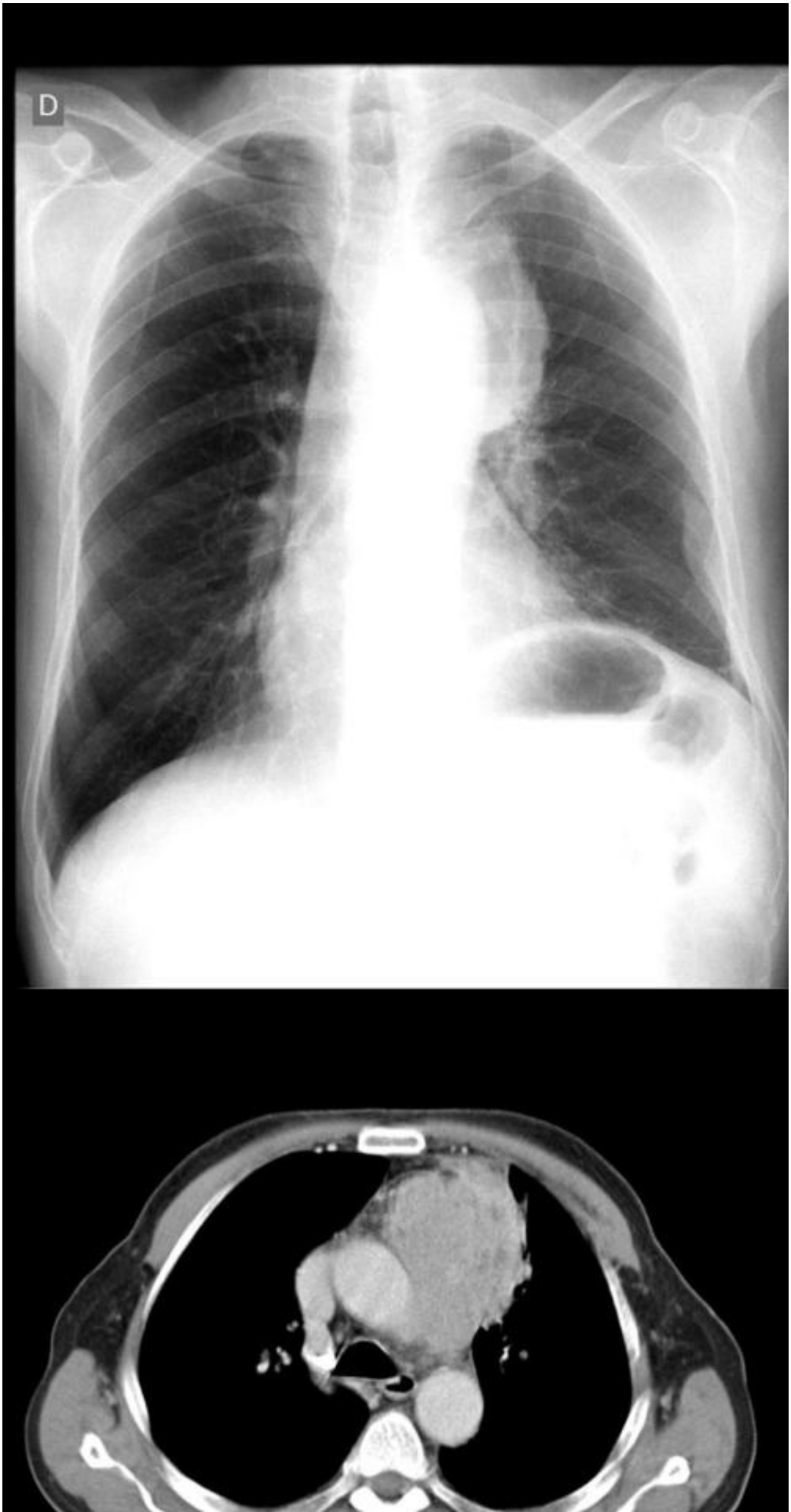
Thymomas are the most common tumour of the anterior mediastinum and is usually detected between the sixth and seventh decades of life.

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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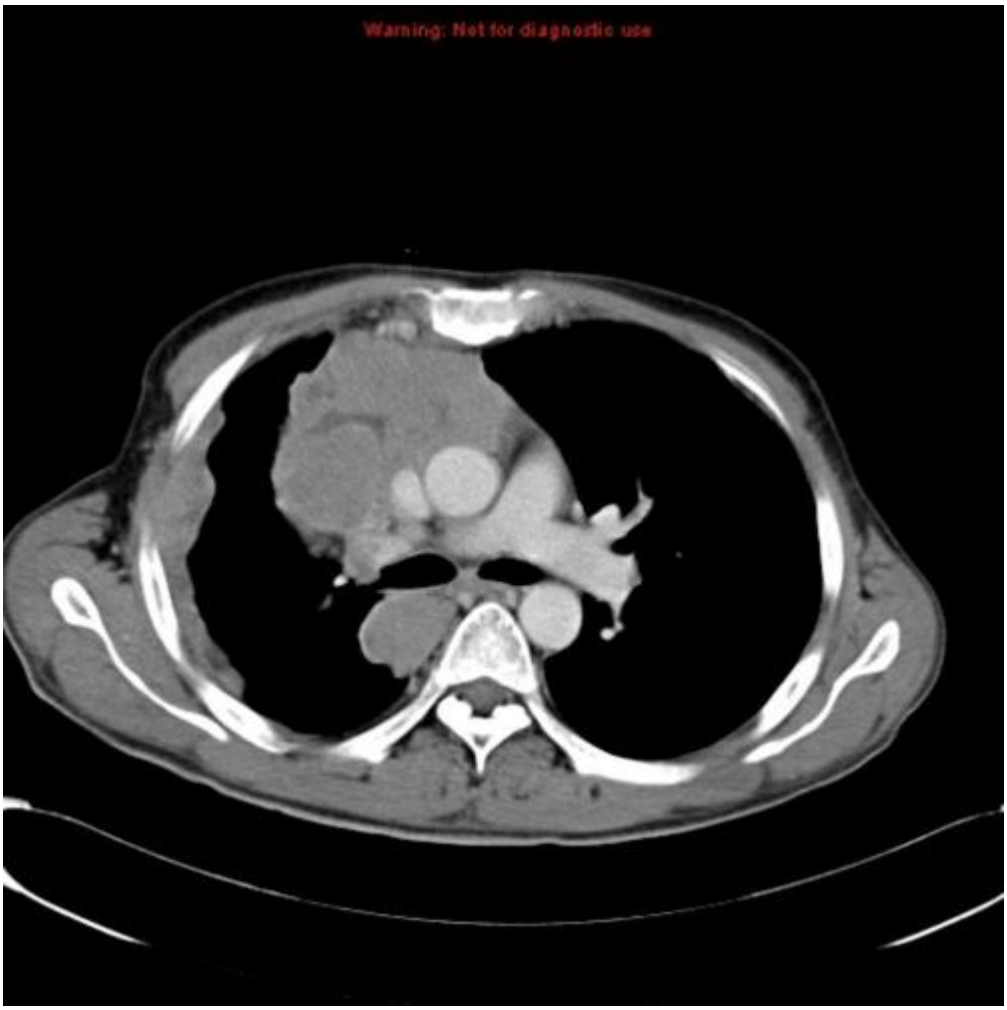
Chest x-ray and accompanying CT scan of a patient with a thymoma. In the chest x-ray there is a partially delineated mediastinal mass (anterior mediastinum) with regular borders, bulging the left upper mediastinal contour.



CT slice at the bifurcation of the main bronchus showing an invasive thymoma presenting as an anterior mediastinal mass

Tumour lysis syndrome

Tumour lysis syndrome (TLS) is a potentially deadly condition related to the 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. On occasion it can occur with steroid treatment alone. Awareness of the condition is critical as prophylactic medication can be given to prevent the potentially deadly effects of tumour cell lysis.

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. Patients in lower risk groups should be given oral allopurinol during chemotherapy cycles in an attempt to avoid the condition.

TLS occurs from the breakdown of the tumour cells and the subsequent release of chemicals from the cell. It leads to a high potassium and high phosphate level in the presence of a 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.

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

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
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
Carcinoembryonic antigen (CEA)	Colorectal cancer
S-100	Melanoma, schwannomas

Tumour marker	Association
Bombesin	Small cell lung carcinoma, gastric cancer, neuroblastoma

Venous thromboembolism: risk factors

Common predisposing factors include malignancy, pregnancy and the period following an operation. The comprehensive list below is partly based on the 2010 SIGN venous thromboembolism (VTE) guidelines:

General

- increased risk with advancing age
- obesity
- family history of VTE
- pregnancy (especially puerperium)
- immobility
- hospitalisation
- anaesthesia
- central venous catheter: femoral >> subclavian

Underlying conditions

- malignancy
- thrombophilia: e.g. Activated protein C resistance, protein C and S deficiency
- heart failure
- antiphospholipid syndrome
- Behcet's
- polycythaemia
- nephrotic syndrome
- sickle cell disease
- paroxysmal nocturnal haemoglobinuria
- hyperviscosity syndrome
- homocystinuria

Medication

- combined oral contraceptive pill: 3rd generation more than 2nd generation
- hormone replacement therapy: the risk of VTE is higher in women taking oestrogen + progestogen preparations compared to those taking oestrogen only preparations
- raloxifene and tamoxifen
- antipsychotics (especially olanzapine) have recently been shown to be a risk factor

It should be remembered however that around 40% of patients diagnosed with a PE have no major risk factors.

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.

Causes of vitamin B12 deficiency

- pernicious anaemia
- post gastrectomy
- poor diet
- disorders of terminal ileum (site of absorption): Crohn's, blind-loop etc
- metformin (rare)

Features of vitamin B12 deficiency

- macrocytic anaemia
- sore tongue and mouth
- neurological symptoms: e.g. Ataxia
- neuropsychiatric symptoms: e.g. Mood disturbances

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 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

Von Willebrand's disease

Von Willebrand's disease is the most common inherited bleeding disorder. The majority of cases are inherited in an autosomal dominant fashion* and characteristically behaves like a platelet disorder i.e. epistaxis and menorrhagia are common whilst haemoarthroses and muscle haematomas are rare

Role of von Willebrand factor

- large glycoprotein which forms massive multimers up to 1,000,000 Da in size
- promotes platelet adhesion to damaged endothelium
- carrier molecule for factor VIII

Types

- type 1: partial reduction in vWF (80% of patients)
- type 2: abnormal form of vWF
- type 3: total lack of vWF (autosomal recessive)

Investigation

- prolonged bleeding time
- APTT may be prolonged
- factor VIII levels may be moderately reduced
- 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
- factor VIII concentrate

*type 3 von Willebrand's disease (most severe form) is inherited as an autosomal recessive trait. Around 80% of patients have type 1 disease

Waldenstrom's macroglobulinaemia

Waldenstrom's macroglobulinaemia is an uncommon condition seen in older men. It is a lymphoplasmacytoid malignancy characterised by the secretion of a monoclonal IgM paraprotein

Features

- monoclonal IgM paraproteinaemia
- systemic upset: weight loss, lethargy
- hyperviscosity syndrome e.g. visual disturbance
- hepatosplenomegaly
- lymphadenopathy
- cryoglobulinaemia e.g. Raynaud's

Clinical pharmacology and toxicology

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

Acute intermittent porphyria: drugs

Acute intermittent porphyria (AIP) is an autosomal dominant condition caused by a defect in porphobilinogen deaminase, an enzyme involved in the biosynthesis of haem. It characteristically presents with abdominal and neuropsychiatric symptoms in 20-40 year olds. AIP is more common in females (5:1)

Drugs which may precipitate attack

- barbiturates
- halothane
- benzodiazepines
- alcohol
- oral contraceptive pill
- sulphonamides

Drugs considered safe to use

- paracetamol
- aspirin
- codeine
- morphine
- chlorpromazine
- beta-blockers
- penicillin
- metformin

Adenosine

The effects of adenosine are enhanced by dipyridamole (anti-platelet agent) and blocked by theophyllines. It should be avoided in asthmatics due to possible bronchospasm.

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
- adenosine has a very short half-life of about 8-10 seconds

Adverse effects

- chest pain
- bronchospasm
- can enhance conduction down accessory pathways, resulting in increased ventricular rate (e.g. WPW syndrome)

Adrenal lesions- Incidental

Incidentaloma of the adrenal glands have become increasingly common as CT scanning of the abdomen is widely undertaken. Prevalences range from 1.5-9% in autopsy studies. Overall, 75% will be non functioning adenomas. However, a thorough diagnostic work up is required to exclude a more significant lesion.

Investigation

- Morning and midnight plasma cortisol measurements
- Dexamethasone suppression test
- 24 hour urinary cortisol excretion
- 24 hour urinary excretion of catecholamines
- Serum potassium, aldosterone and renin levels

Management
The risk of malignancy is related to the size of the lesion and 25% of all masses greater than 4cm will be malignant. Such lesions should usually be excised. Where a lesion is a suspected metastatic deposit a biopsy may be considered. Smaller, innocent lesions are usually followed up by serial CT scans at 6, 12 and 24 months.

Adrenaline

Adrenaline is a sympathomimetic amine with both alpha and beta adrenergic stimulating properties

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

Alcohol - problem drinking: 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 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.

Allopurinol

Allopurinol is used in the prevention of gout. It works by inhibiting xanthine oxidase

Initiating allopurinol prophylaxis - see indications below

- allopurinol should not be started until 2 weeks after an acute attack has settled
- initial dose of 100 mg od, with the dose titrated every few weeks to aim for a serum uric acid of < 300 µmol/l
- NSAID or colchicine cover should be used when starting allopurinol

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
- prophylaxis if on cytotoxics or diuretics

*patients with Lesch-Nyhan syndrome often take allopurinol for life

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

Cyclophosphamide

- allopurinol reduces renal clearance, therefore may cause marrow toxicity

Amiodarone

Amiodarone is a class III antiarrhythmic agent used in the treatment of atrial, nodal and ventricular tachycardias. The main mechanism of action is by blocking potassium channels which inhibits repolarisation and hence prolongs the action potential. Amiodarone also has other actions such as blocking sodium channels (a class I effect)

The use of amiodarone is limited by a number of factors

- long half-life (20-100 days)
- 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 (see below)

Monitoring of patients taking amiodarone

- TFT, LFT, U&E, CXR prior to treatment
- TFT, LFT every 6 months

Adverse effects of amiodarone use

- thyroid dysfunction
- corneal deposits
- pulmonary fibrosis/pneumonitis
- liver fibrosis/hepatitis
- peripheral neuropathy, myopathy
- photosensitivity
- 'slate-grey' appearance
- thrombophlebitis and injection site reactions
- bradycardia

Amiodarone and the thyroid gland

Around 1 in 6 patients taking amiodarone develop thyroid dysfunction

Amiodarone-induced hypothyroidism

The pathophysiology of amiodarone-induced hypothyroidism (AIH) is thought to be due to the high iodine content of amiodarone causing a Wolff-Chaikoff effect*

Amiodarone may be continued if this is desirable

Amiodarone-induced thyrotoxicosis

Amiodarone-induced thyrotoxicosis (AIT) may be divided into two types:

	AIT type 1	**AIT type 2**
Pathophysiology	Excess iodine-induced thyroid hormone synthesis	Amiodarone-related destructive thyroiditis
Goitre	Present	Absent
Management	Carbimazole or potassium perchlorate	Corticosteroids

Unlike in AIH, amiodarone should be stopped if possible in patients who develop AIT

*an autoregulatory phenomenon where thyroxine formation is inhibited due to high levels of circulating iodide

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	Notes
Ia	Quinidine Procainamide Disopyramide	Block sodium channels Increases AP duration	Quinidine toxicity causes cinchonism (headache, tinnitus, thrombocytopaenia) Procainamide may cause drug-induced lupus
Ib	Lidocaine Mexiletine Tocainide	Block sodium channels Decreases AP duration	
Ic	Flecainide Encainide Propafenone	Block sodium channels No effect on AP duration	
II	Propranolol Atenolol Bisoprolol Metoprolol	Beta-adrenoceptor antagonists	

Class	Examples	Mechanism of action	Notes
III	Amiodarone Sotalol Ibutilide Bretylium	Block potassium channels	
IV	Verapamil Diltiazem	Calcium channel blockers	

Antibiotics: gross mechanism of action

The diagram and list below summarises the gross mechanism of action of the commonly used antibiotics. More detailed descriptions are found elsewhere on the site.

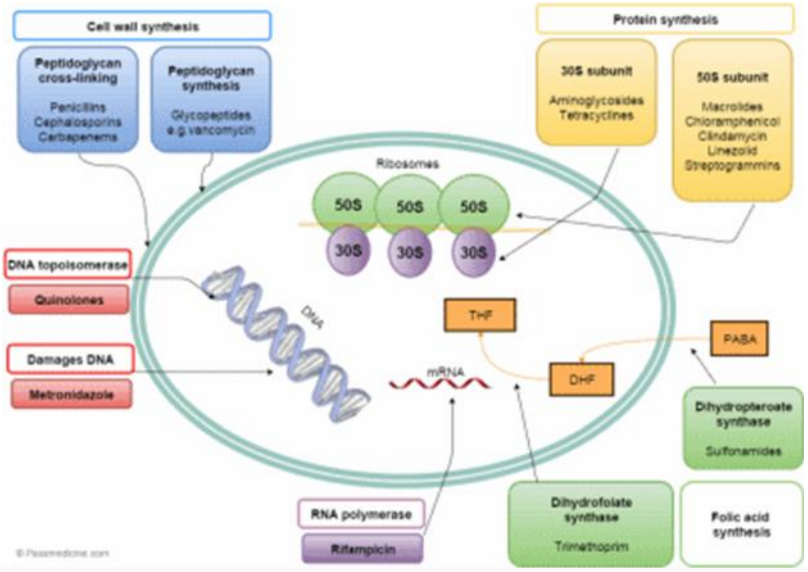


Diagram showing the gross mechanism of action of the commonly used antibiotics

Inhibits cell wall formation

- peptidoglycan cross-linking: penicillins, cephalosporins, carbopenems
- peptidoglycan synthesis: glycopeptides (e.g. vancomycin)

Inhibits protein synthesis (by acting on the ribosome)

- 50S subunit: macrolides, chloramphenicol, clindamycin, linezolid, streptogrammins
- 30S subunit: aminoglycosides, tetracyclines

Inhibits DNA synthesis

- quinolones (e.g. ciprofloxacin)

Damages DNA

- metronidazole

Inhibits folic acid formation

- sulphonamides
- trimethoprim

Inhibits RNA synthesis

- rifampicin

Antihistamines

Antihistamines (H_1 inhibitors) are of value in the treatment of allergic rhinitis and urticaria.

Examples of sedating antihistamines

- 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

Of the non-sedating antihistamines there is some evidence that cetirizine may cause more drowsiness than other drugs in the class.

Antipsychotics

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)
- 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)

The Medicines and Healthcare products Regulatory Agency has issued specific warnings when antipsychotics are used in elderly patients:

- increased risk of stroke
- increased risk of venous thromboembolism

Other side-effects

- antimuscarinic: dry mouth, blurred vision, urinary retention, constipation
- sedation, weight gain
- raised prolactin: galactorrhoea, impaired glucose tolerance
- neuroleptic malignant syndrome: pyrexia, muscle stiffness
- reduced seizure threshold (greater with atypicals)
- prolonged QT interval (particularly haloperidol)

Aspirin

Aspirin works by blocking the action of both cyclooxygenase-1 and 2. Cyclooxygenase is responsible for prostaglandin, prostacyclin and thromboxane synthesis. 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

Potentiates

- oral hypoglycaemics
- warfarin
- steroids

*NICE now recommend clopidogrel first-line following an ischaemic stroke and for peripheral arterial disease. For TIAs the situation is more complex. Recent Royal College of Physician (RCP) guidelines support the use of clopidogrel in TIAs. However the older NICE guidelines still recommend aspirin + dipyridamole - a position the RCP state is 'illogical'

Atypical antipsychotics

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)

The Medicines and Healthcare products Regulatory Agency has issued specific warnings when antipsychotics are used in elderly patients:

- increased risk of stroke (especially olanzapine and risperidone)
- increased risk of venous thromboembolism

Examples of atypical antipsychotics

- clozapine
- olanzapine
- risperidone
- quetiapine
- amisulpride

Clozapine, one of the first atypical agents to be developed, carries a significant risk of agranulocytosis and full blood count monitoring is therefore essential during treatment. For this reason clozapine should only be used in patients resistant to other antipsychotic medication

Adverse effects of clozapine

- agranulocytosis (1%), neutropaenia (3%)
- reduced seizure threshold - can induce seizures in up to 3% of patients

Benign prostatic hyperplasia

Benign prostatic hyperplasia (BPH) is a common condition seen in older men.

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

BPH typically presents with lower urinary tract symptoms (LUTS), which may be categorised 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

Management options

- watchful waiting
- medication: alpha-1 antagonists, 5 alpha-reductase inhibitors. The use of combination therapy was supported by the Medical Therapy Of Prostatic Symptoms (MTOPS) trial
- surgery: transurethral resection of prostate (TURP)

Alpha-1 antagonists e.g. tamsulosin, alfuzosin

- decrease smooth muscle tone (prostate and bladder)
- considered first-line, improve symptoms in around 70% of men
- adverse effects: dizziness, postural hypotension, dry mouth, depression

5 alpha-reductase inhibitors e.g. finasteride

- block the conversion of testosterone to dihydrotestosterone (DHT), which is known to induce BPH
- unlike alpha-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 decrease PSA concentrations by up to 50%
- adverse effects: erectile dysfunction, reduced libido, ejaculation problems, gynaecomastia

Benzodiazepines

Benzodiazepines enhance the effect of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) by increasing the **frequency** of chloride channels. They therefore are used for a variety of purposes:

- sedation
- hypnotic
- anxiolytic
- anticonvulsant
- muscle relaxant

Patients commonly develop a tolerance and dependence 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).

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. 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 4 weeks to a year or more

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

GABA$_A$ drugs

- benzodiazipines increase the **frequency** of chloride channels
- barbiturates increase the **duration** of chloride channel opening

Frequently **Ben**d - **Dur**ing **Barb**eque

...or...

Barbi**durat**es increase **durat**ion & **Fre**ndodiazepines increase **fre**quency

Beta-blocker overdose

Features

- bradycardia
- hypotension
- heart failure
- syncope

Management

- if bradycardic then atropine
- in resistant cases glucagon may be used

Haemodialysis is not effective in beta-blocker overdose

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

Breast feeding: contraindications

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

Drug contraindications

The following drugs can be given to mothers who are breast feeding:

- antibiotics: penicillins, cephalosporins, trimethoprim
- endocrine: glucocorticoids (avoid high doses), levothyroxine*
- epilepsy: sodium valproate, carbamazepine
- asthma: salbutamol, theophyllines
- psychiatric drugs: tricyclic antidepressants, antipsychotics**
- hypertension: beta-blockers, hydralazine
- anticoagulants: warfarin, heparin
- digoxin

The following drugs should be avoided:

- antibiotics: ciprofloxacin, tetracycline, chloramphenicol, sulphonamides
- psychiatric drugs: lithium, benzodiazepines
- aspirin
- carbimazole
- sulphonylureas
- cytotoxic drugs
- amiodarone

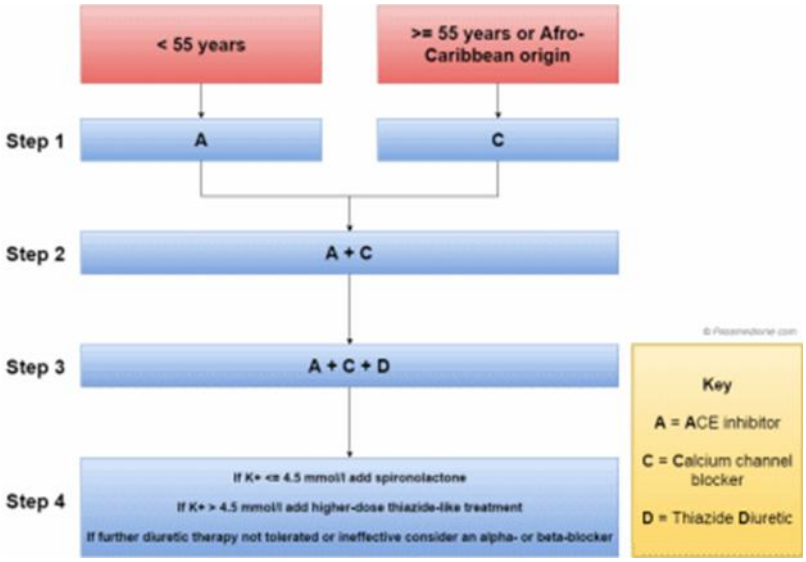
*the BNF advises that the amount is too small to affect neonatal hypothyroidism screening

**clozapine should be avoided

Calcium channel blockers

Calcium channel blockers are primarily used in the management of cardiovascular disease. 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



Flow chart showing the management of hypertension as per current NICE guideliness

Carbon monoxide poisoning

Carbon monoxide has high affinity for haemoglobin and myoglobin resulting in a left-shift of the oxygen dissociation curve and tissue hypoxia. There are approximately 50 per year deaths from accidental carbon monoxide poisoning in the UK

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%
- severe toxicity: 'pink' skin and mucosae, hyperpyrexia, arrhythmias, extrapyramidal features, coma, death

Typical carboxyhaemoglobin levels

- < 3% non-smokers
- < 10% smokers
- 10 - 30% symptomatic: headache, vomiting
- > 30% severe toxicity

Management

- 100% oxygen
- hyperbaric oxygen

Indications for hyperbaric oxygen*

- loss of consciousness at any point
- neurological signs other than headache
- myocardial ischaemia or arrhythmia
- pregnancy

*as stated in the 2008 Department of Health publication 'Recognising Carbon Monoxide Poisoning'

Ciclosporin

Ciclosporin is an immunosuppressant which decreases clonal proliferation of T cells by reducing IL-2 release. It acts by binding to cyclophilin forming a complex which inhibits calcineurin, a phosphotase that activates various transcription factors in T cells

Adverse effects of ciclosporin (note how everything is increased - fluid, BP, K^+, hair, gums, glucose)

- nephrotoxicity
- hepatotoxicity
- fluid retention
- hypertension
- hyperkalaemia
- hypertrichosis
- gingival hyperplasia
- tremor
- impaired glucose tolerance
- hyperlipidaemia
- increased susceptibility to severe infection

Interestingly for an immunosuppressant, ciclosporin is noted by the BNF to be 'virtually non-myelotoxic'.

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

Clopidogrel

Clopidogrel is an antiplatelet agent used in the management of cardiovascular disease. It was previously used when aspirin was not tolerated or contraindicated but there are now a number of conditions for which clopidogrel is used in addition to aspirin, for example in patients with an acute coronary syndrome. Following the 2010 NICE technology appraisal clopidogrel is also now first-line in patients following an ischaemic stroke and in patients with peripheral arterial 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

- antagonist of the $P2Y_{12}$ adenosine diphosphate (ADP) receptor, inhibiting the activation of platelets

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 - please see the link for more details

Combined oral contraceptive pill: contraindications

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*
- family history of thromboembolic disease in first degree relatives < 45 years
- controlled hypertension
- immobility e.g. wheel chair use
- carrier of known gene mutations associated with breast cancer (e.g. BRCA1/BRCA2)

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
- current breast cancer
- major surgery with prolonged immobilisation

Diabetes mellitus diagnosed > 20 years ago is classified as UKMEC 3 or 4 depending on severity

Changes in 2016

- breast feeding 6 weeks - 6 months postpartum was changed from UKMEC 3 → 2

Cyanide poisoning

Cyanide may be used in insecticides, photograph development and the production of certain metals. Toxicity results from reversible inhibition of cellular oxidising enzymes

Presentation

- 'classical' features: brick-red skin, smell of bitter almonds
- acute: hypoxia, hypotension, headache, confusion
- 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)

Diabetes mellitus: GLP-1 and the new drugs

A number of new drugs to treat diabetes mellitus have become available in recent years. Much research has focused around the role of glucagon-like peptide-1 (GLP-1), a hormone released by the small intestine in response to an oral glucose load

Whilst it is well known that insulin resistance and insufficient B-cell compensation occur other effects are also seen in type 2 diabetes mellitus (T2DM). 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.

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.

Glucagon-like peptide-1 (GLP-1) mimetics (e.g. exenatide)

Exenatide is an example of a glucagon-like peptide-1 (GLP-1) mimetic. These drugs increase insulin secretion and inhibit glucagon secretion. One of the major advances of GLP-1 mimetics is that they typically result in weight loss, in contrast to many medications such as insulin, sulfonylureas and thiazolidinediones.

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 is the other GLP-1 mimetic currently available. One the main advantages of liraglutide over exenatide is that it only needs to be given once a day.

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. Please see the BNF for a more complete list of licensed indications.

NICE state the following:

Consider adding exenatide to metformin and a sulfonylurea if:

- *BMI >= 35 kg/m² in people of European descent and there are problems associated with high weight, or*
- *BMI < 35 kg/m² and insulin is unacceptable because of occupational implications or weight loss would benefit other comorbidities.*

NICE like patients to have achieved a 11 mmol/mol (1%) reduction in HbA1c and 3% weight loss after 6 months to justify the ongoing prescription of GLP-1 mimetics.

The major adverse effect of GLP-1 mimetics is nausea and vomiting. The Medicines and Healthcare

products Regulatory Agency has issued specific warnings on the use of exenatide, reporting that is has been linked to severe pancreatitis in some patients.

Dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g. Vildagliptin, sitagliptin)

Key points

- oral preparation
- trials to date show that the drugs are relatively well tolerated with no increased incidence of hypoglycaemia
- do not cause weight gain

NICE guidelines on DPP-4 inhibitors

- 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

Digoxin and digoxin toxicity

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.

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. Also stimulates vagus nerve

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.

Features

- generally unwell, lethargy, nausea & vomiting, anorexia, confusion, yellow-green vision
- arrhythmias (e.g. AV block, bradycardia)
- gynaecomastia

Precipitating factors

- classically: hypokalaemia*
- increasing age
- renal failure
- myocardial ischaemia
- hypomagnesaemia, hypercalcaemia, hypernatraemia, acidosis
- hypoalbuminaemia
- hypothermia
- hypothyroidism
- 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

Management

- Digibind
- correct arrhythmias
- monitor potassium

*hyperkalaemia may also worsen digoxin toxicity, although this is very small print

Dipyridamole

Dipyridamole is an antiplatelet mainly used in combination with aspirin after an ischaemic stroke or transient ischaemic attack.

Mechanism of action

- inhibits phosphodiesterase, elevating platelet cAMP levels which in turn reduce intracellular calcium levels
- other actions include reducing cellular uptake of adenosine and inhibition of thromboxane synthase

Dopamine receptor agonists

Indications

- Parkinson's disease
- prolactinoma/galactorrhoea
- cyclical breast disease
- acromegaly

Currently accepted practice in the management of patients with Parkinson's disease is to delay treatment until the onset of disabling symptoms and then to introduce a dopamine receptor agonist. If the patient is elderly, L-dopa is sometimes used as an initial treatment

Overview

- e.g. bromocriptine, ropinirole, cabergoline, 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

Adverse effects

- nausea/vomiting
- postural hypotension
- hallucinations
- daytime somnolence

*pergolide was withdrawn from the US market in March 2007 due to concern regarding increased incidence of valvular dysfunction

Drug causes of urticaria

The following drugs commonly cause urticaria:

- aspirin
- penicillins
- NSAIDs
- opiates

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 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 thrombocytopenia

Drug-induced thrombocytopenia (probable immune mediated)

- quinine
- abciximab
- NSAIDS
- diuretics: furosemide
- antibiotics: penicillins, sulphonamides, rifampicin
- anticonvulsants: carbamazepine, valproate
- heparin

Drugs causing ocular problems

Cataracts

- steroids

Corneal opacities

- amiodarone
- indomethacin

Optic neuritis

- ethambutol
- amiodarone
- metronidazole

Retinopathy

- chloroquine, quinine

Sildenafil can cause both blue discolouration and non-arteritic anterior ischaemic neuropathy

Drugs causing photosensitivity

Causes of drug-induced photosensitivity

- thiazides
- tetracyclines, sulphonamides, ciprofloxacin
- amiodarone
- NSAIDs e.g. piroxicam
- psoralens
- sulphonylureas

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

Ecstasy poisoning

Ecstasy (MDMA, 3,4-Methylenedioxymethamphetamine) use became popular in the 1990's during the emergence of dance music culture

Clinical features

- neurological: agitation, anxiety, confusion, ataxia
- cardiovascular: tachycardia, hypertension
- hyponatraemia
- hyperthermia
- rhabdomyolysis

Management

- supportive
- dantrolene may be used for hyperthermia if simple measures fail

Ethylene glycol toxicity

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

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

Finasteride

Finasteride is an inhibitor of 5 alpha-reductase, an enzyme which metabolises testosterone into dihydrotestosterone

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

Flecainide

Flecainide is a Vaughan Williams class 1c antiarrhythmic. It slows conduction of the action potential by acting as a potent sodium channel blocker. This may be reflected by widening of the QRS complex and prolongation of the PR interval

The Cardiac Arrhythmia Suppression Trial (CAST, 1989) investigated the use of agents to treat asymptomatic or mildly symptomatic premature ventricular complexes (PVCs) post myocardial infarction. The hypothesis was that this would reduce deaths from ventricular arrhythmias. Flecainide was actually shown to increase mortality post myocardial infarction and is therefore contraindicated in this situation

Indications

- atrial fibrillation
- SVT associated with accessory pathway e.g. Wolf-Parkinson-White syndrome

Adverse effects

- negatively inotropic
- bradycardia
- proarrhythmic
- oral paraesthesia
- visual disturbances

Haemodialysis in overdose

Drugs that can be cleared with haemodialysis - mnemonic: BLAST

- Barbiturate
- Lithium
- Alcohol (inc methanol, ethylene glycol)
- Salicylates
- Theophyllines (charcoal haemoperfusion is preferable)

Drugs which cannot be cleared with haemodialysis include

- tricyclics
- benzodiazepines
- dextropropoxyphene (Co-proxamol)
- digoxin
- beta-blockers

Heparin

There are two main types of heparin - unfractionated, 'standard' heparin or low molecular weight heparin (LMWH). Heparins generally act by activating antithrombin III. Unfractionated heparin forms a complex which inhibits thrombin, factors Xa, IXa, XIa and XIIa. LMWH however only increases the action of antithrombin III on factor Xa

The table below shows the differences between standard heparin and LMWH:

	Standard heparin	**Low molecular weight heparin (LMWH)**
Administration	Intravenous	Subcutaneous
Duration of action	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 Heparin-induced thrombocytopaenia (HIT) Osteoporosis	Bleeding Lower risk of HIT and osteoporosis with LMWH
Monitoring	Activated partial thromboplastin time (APTT)	Anti-Factor Xa (although routine monitoring is not required)
Notes	Useful in situations where there is a high 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)

- immune mediated - antibodies form against complexes of platelet factor 4 (PF4) and heparin
- these antibodies bind to the PF4-heparin complexes on the platelet surface and induce platelet activation by cross-linking FcγIIA receptors
- usually does not develop until after 5-10 days of treatment
- despite being associated with low platelets HIT is actually a prothrombotic condition
- features include a greater than 50% reduction in platelets, thrombosis and skin allergy
- treatment options include alternative anticoagulants such as lepirudin and danaparoid

Both unfractionated and low-molecular weight heparin can cause hyperkalaemia. This is thought to be caused by inhibition of aldosterone secretion.

Heparin overdose may be reversed by protamine sulphate, although this only partially reverses the effect of LMWH.

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

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.

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)

- 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

Hormone replacement therapy: adverse effects

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.

Side-effects

- nausea
- breast tenderness
- fluid retention and weight gain

Potential complications

- increased risk of breast cancer: increased by the addition of a progestogen
- 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
- increased risk of venous thromboembolism: increased by the addition of a progestogen
- increased risk of stroke
- increased risk of ischaemic heart disease if taken more than 10 years after menopause

Breast cancer

- in the Women's Health Initiative (WHI) study there was a relative risk of 1.26 at 5 years of developing breast cancer
- 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

Hormone replacement therapy: indications

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.

The indications for HRT have changed significantly over the past ten years as the long-term risks became apparent, primarily as a result of the Women's Health Initiative (WHI) study.

Indications

- vasomotor symptoms such as flushing, insomnia and headaches
- premature menopause: should be continued until the age of 50 years. Most important reason is preventing the development of osteoporosis

The main indication is the control of vasomotor symptoms. The other indications such as reversal of vaginal atrophy should be treated with other agents as first-line therapies

Other benefits include a reduced incidence of colorectal cancer

Hyperlipidaemia: 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
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

Hypomagnesaemia

Cause of low magnesium

- diuretics
- total parenteral nutrition
- diarrhoea
- alcohol
- hypokalaemia, hypocalcaemia
- conditions causing diarrhoea: Crohn's, ulcerative colitis
- metabolic disorders: Gitleman's and Bartter's

Features

- paraesthesia
- tetany
- seizures
- arrhythmias
- decreased PTH secretion → hypocalcaemia
- ECG features similar to those of hypokalaemia
- exacerbates digoxin toxicity

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

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

Lead poisoning

Along with acute intermittent porphyria, lead poisoning should be considered in questions giving a combination of abdominal pain and neurological signs

Features

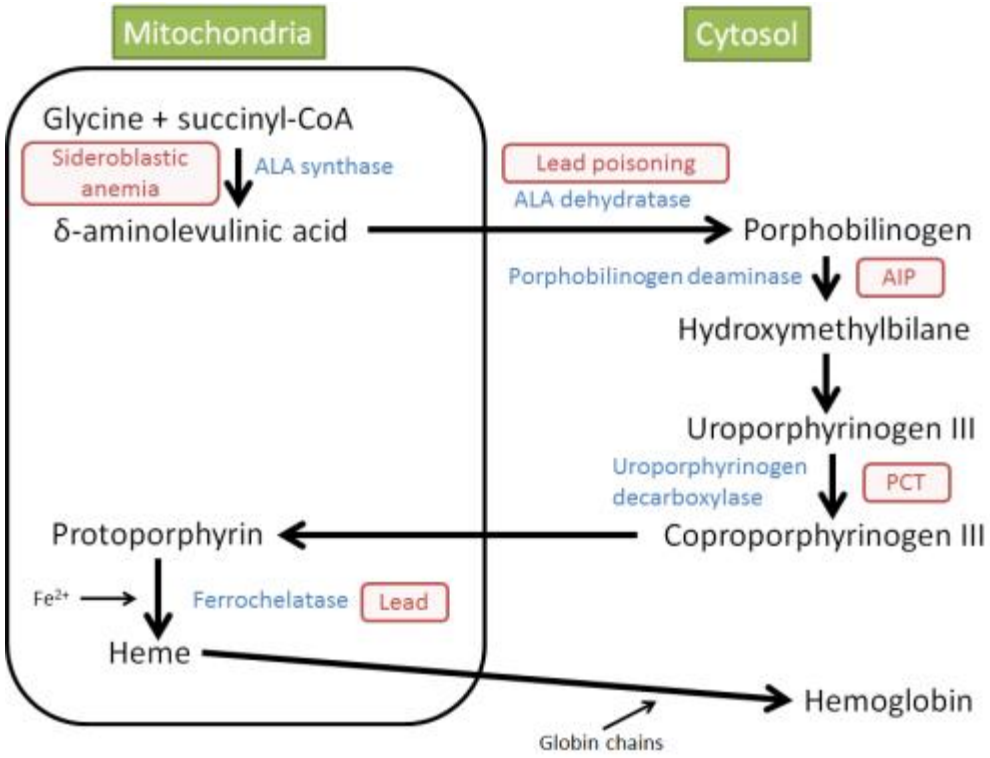
- abdominal pain
- peripheral neuropathy (mainly motor)
- fatigue
- constipation
- blue lines on gum margin (only 20% of adult patients, very rare in children)

Investigations

- 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 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)
- D-penicillamine
- EDTA
- dimercaprol



Leukotriene receptor antagonists

Basics

- e.g. Montelukast, zafirlukast
- have both anti-inflammatory and bronchodilatory properties
- should be used when patients are poorly controlled on high-dose inhaled corticosteroids and a long-acting b2-agonist
- particularly useful in aspirin-induced asthma
- associated with the development of Churg-Strauss syndrome

Lithium

Lithium is mood stabilising drug used most commonly prophylatically 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

- nausea/vomiting, diarrhoea
- fine tremor
- nephrotoxicity: polyuria, secondary to nephrogenic diabetes insipidus
- thyroid enlargement, may lead to hypothyroidism
- ECG: T wave flattening/inversion
- weight gain
- idiopathic intracranial hypertension

Monitoring of patients on lithium therapy

- inadequate monitoring of patients taking lithium is common - NICE and the National Patient Safety Agency (NPSA) have issued guidance to try and address this. As a result it is often an exam hot topic
- lithium blood level should 'normally' be checked every 3 months. Levels should be taken 12 hours post-dose
- thyroid and renal function should be checked every 6 months
- patients should be issued with an information booklet, alert card and record book

Lithium toxicity

Lithium is mood stabilising drug used most commonly prophylatically 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. Lithium toxicity generally occurs following concentrations > 1.5 mmol/L.

Toxicity may be precipitated by dehydration, renal failure, diuretics (especially bendroflumethiazide), ACE inhibitors, NSAIDs and metronidazole.

Features of toxicity

- coarse tremor (a fine tremor is seen in therapeutic levels)
- hyperreflexia
- acute confusion
- seizure
- coma

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

Loop diuretics

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
- hyponatraemia
- hypokalaemia
- hypochloraemic alkalosis
- ototoxicity
- hypocalcaemia
- renal impairment (from dehydration + direct toxic effect)
- hyperglycaemia (less common than with thiazides)
- gout

Macrolides

Erythromycin was the first macrolide used clinically. Newer examples include clarithromycin and azithromycin.

Macrolides act by inhibiting bacterial protein synthesis by blocking translocation. 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.

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.

Mercury poisoning

Features

- paraesthesia
- visual field defects
- hearing loss
- irritability
- renal tubular acidosis

Merkel cell tumours of the skin

- Rare but aggressive tumour.
- Develops from intra epidermal Merkel cells.
- Usually presents on elderly, sun damaged skin. The periorbital area is the commonest site.
- Histologically these tumours appear within the dermis and subcutis. The lesions consist of sheets and nodules of small hyperchromatic epithelial cells with high rates of mitosis and apoptosis. Lymphovascular invasion is commonly seen.
- Pre-existing infection with Merkel Cell Polyomavirus is seen in 80% cases.

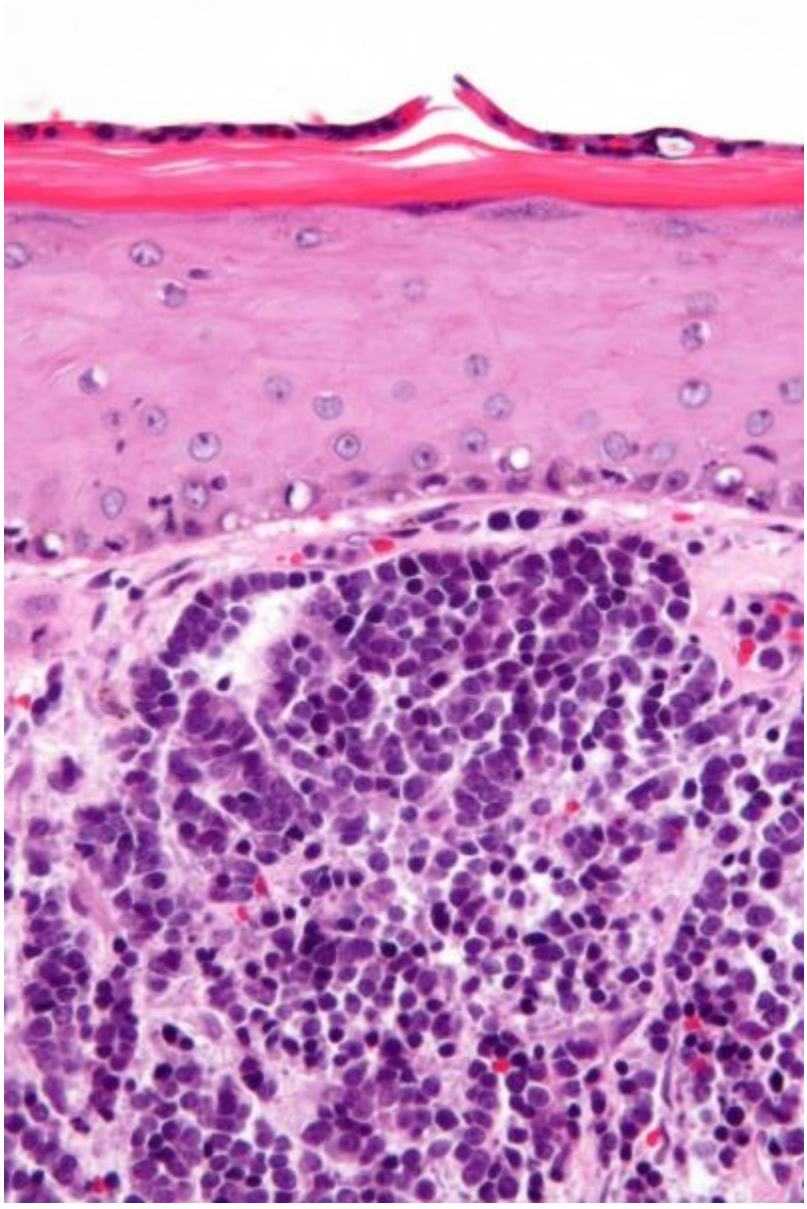
Treatment

Surgical excision is first line. Margins of 1cm are required. Lesions >10mm in diameter should undergo sentinel lymph node biopsy. Adjuvant radiotherapy is often given to reduce the risk of local recurrence.

Prognosis

- With lymph node metastasis 5 year survival is 50% or less.
- Small lesions without nodal spread are usually associated with a 5 year survival of 80%.

Skin biopsy demonstrating a Merkel Cell cancer. Note the hyperchromatic epithelial cells and high mitotic rate



Metabolic acidosis

Metabolic acidosis is commonly classified according to the anion gap. This can be calculated by: $(Na^+ + K^+) - (Cl^- + HCO_3^-)$. If a question supplies the chloride level then this is often a clue that the anion gap should be calculated. The normal range = 10-18 mmol/L

Normal anion gap (= hyperchloraemic metabolic acidosis)

- gastrointestinal bicarbonate loss: diarrhoea, ureterosigmoidostomy, fistula
- renal tubular acidosis
- drugs: e.g. acetazolamide
- ammonium chloride injection
- Addison's disease

Raised anion gap

- lactate: shock, hypoxia
- ketones: diabetic ketoacidosis, alcohol
- urate: renal failure
- acid poisoning: salicylates, methanol

Metabolic acidosis secondary to high lactate levels may be subdivided into two types:

- lactic acidosis type A: shock, hypoxia, burns
- lactic acidosis type B: metformin

Metformin

Metformin is a biguanide used mainly in the treatment of type 2 diabetes mellitus. It has a number of actions which improves glucose tolerance (see below). 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

Mechanism of action

- increases insulin sensitivity
- decreases hepatic gluconeogenesis
- may also reduce gastrointestinal absorption of carbohydrates

Adverse effects

- gastrointestinal upsets are common (nausea, anorexia, diarrhoea), intolerable in 20%
- reduced vitamin B12 absorption - rarely a clinical problem
- lactic acidosis* with severe liver disease or renal failure

Contraindications**

- chronic kidney disease: NICE recommend that the dose should be reviewed if the creatinine is > 130 µmol/l (or eGFR < 45 ml/min) and stopped if the creatinine is > 150 µmol/l (or eGFR < 30 ml/min)
- 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
- 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
- alcohol abuse is a relative contraindication

*it is now increasingly recognised that lactic acidosis secondary to metformin is rare, although it remains important in the context of exams

**metformin is now sometimes used in pregnancy, for example in women with polycystic ovarian syndrome

Methanol poisoning

Methanol poisoning causes both the effects associated with alcohol (intoxication, nausea etc) and also specific visual problems, including blindness. These effects are thought to be secondary to the accumulation of formic acid. The actual pathophysiology of methanol-associated visual loss is not fully understood but it is thought to be caused by a form of optic neuropathy

Management

- fomepizole or ethanol
- haemodialysis

Migraine: management

It should be noted that as a general rule 5-HT receptor agonists are used in the acute treatment of migraine whilst 5-HT receptor antagonists are used in prophylaxis. NICE produced guidelines in 2012 on the management of headache, including migraines.

Acute treatment

- first-line: offer combination therapy with an oral triptan and an NSAID, or an oral triptan and paracetamol
- for young people aged 12-17 years consider a nasal triptan in preference to an 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

Prophylaxis

- 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 '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' or gabapentin
- 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'
- for women with predictable menstrual migraine treatment NICE recommend either frovatriptan (2.5 mg twice a day) or zolmitriptan (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

*caution should be exercised with young patients as acute dystonic reactions may develop

Monoamine oxidase 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

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

Motion sickness

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

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% and 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.

Features

- more common in young male patients
- onset usually in first 10 days of treatment or after increasing dose
- pyrexia
- rigidity
- tachycardia

A raised creatine kinase is present in most cases. A leukocytosis may also be seen

Management

- stop antipsychotic
- IV fluids to prevent renal failure
- dantrolene* may be useful in selected cases
- bromocriptine, dopamine agonist, may also be used

*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

Nicotinic acid

Nicotinic acid is used in the treatment of patients with hyperlipidaemia, although its use is limited by side-effects. As well as lowering cholesterol and triglyceride concentrations it also raises HDL levels

Adverse effects

- flushing
- impaired glucose tolerance
- myositis

Octreotide

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
- carcinoid syndrome
- prevent complications following pancreatic surgery
- VIPomas
- refractory diarrhoea

Adverse effects

- gallstones (secondary to biliary stasis)

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
- metoclopramide
- postencephalitic Parkinson's disease

Management

- intravenous antimuscarinic: benztropine or procyclidine

Organophosphate insecticide poisoning

One of the effects of organophosphate poisoning is inhibition of acetylcholinesterase

Features can be predicted by the accumulation of acetylcholine (mnemonic = SLUD)

- Salivation
- Lacrimation
- Urination
- Defecation/diarrhoea
- cardiovascular: hypotension, bradycardia
- also: small pupils, muscle fasciculation

Management

- atropine
- the role of pralidoxime is still unclear - meta-analyses to date have failed to show any clear benefit

Osteoporosis: management

NICE guidelines were updated in 2008 on the secondary prevention of osteoporotic fractures in postmenopausal women.

Key points include

- treatment is indicated following osteoporotic fragility fractures in postmenopausal women who are confirmed to have osteoporosis (a T-score of - 2.5 SD or below). In women aged 75 years or older, a DEXA scan may not be required 'if the responsible clinician considers it to be clinically inappropriate or unfeasible'
- 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
- 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

Unfortunately, a number of complicated treatment cut-off tables have been produced in the latest guidelines for patients who do not tolerate alendronate

These take into account a patients age, theire T-score and the number of risk factors they have from the following list:

- parental history of hip fracture
- alcohol intake of 4 or more units per day
- rheumatoid arthritis

It is very unlikely that examiners would expect you to have memorised these risk tables so we've not included them in the revision notes but they may be found by following the NICE link. 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

- alendronate, risedronate and etidronate are all licensed for the prevention and treatment of post-menopausal and glucocorticoid-induced osteoporosis
- all three have been shown to reduce the risk of both vertebral and non-vertebral fractures although alendronate, risedronate may be superior to etidronate in preventing hip fractures
- ibandronate is a once-monthly oral bisphosphonate

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)

- has been shown to prevent bone loss and to reduce the risk of vertebral fractures, but has not yet been shown to reduce the risk of non-vertebral fractures
- has been shown to increase bone density in the spine and proximal femur
- may worsen menopausal symptoms
- increased risk of thromboembolic events
- may decrease risk of breast cancer

Strontium ranelate

- '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
- 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
- given as a single subcutaneous injection every 6 months
- initial trial data suggests that it is effective and well tolerated

Teriparatide

- recombinant form of parathyroid hormone
- very effective at increasing bone mineral density but role in the management of osteoporosis yet to be clearly defined

Hormone replacement therapy

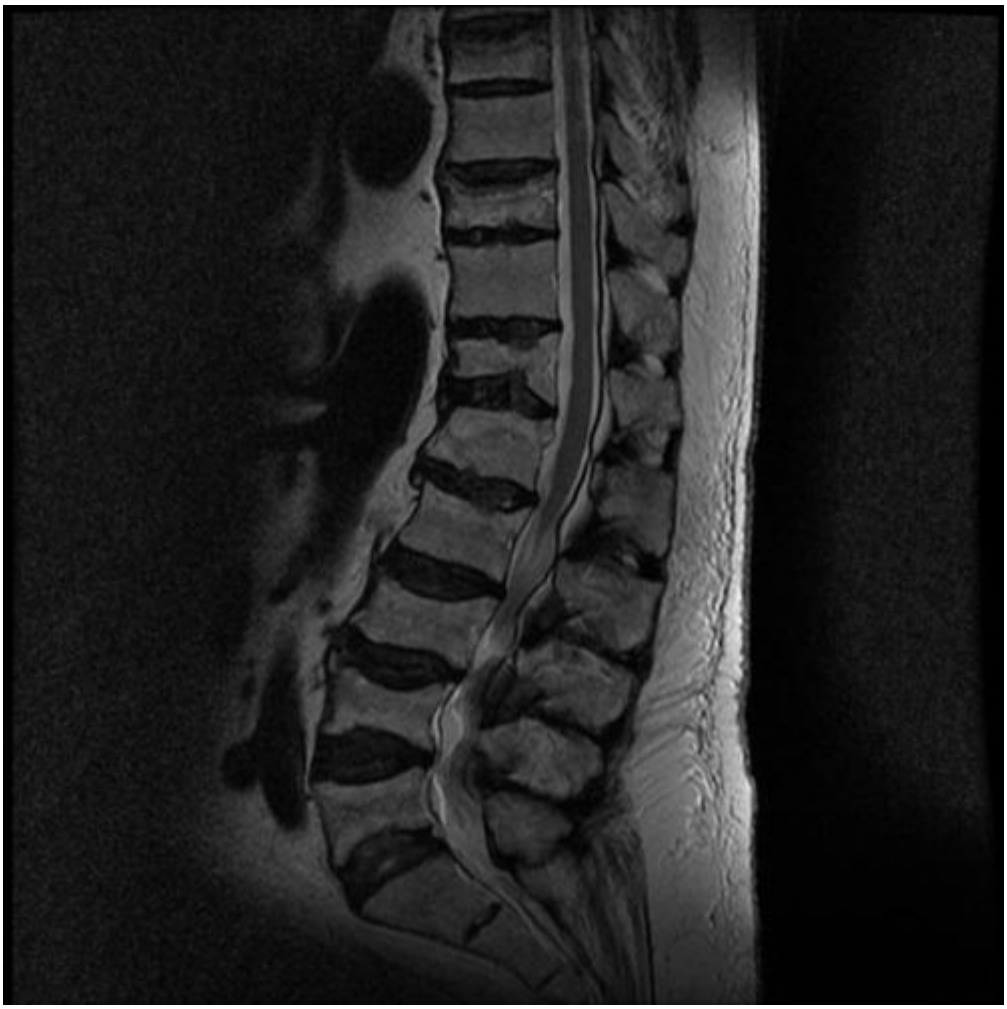
- has been shown to reduce the incidence of vertebral fracture and non-vertebral fractures
- due to concerns about increased rates of cardiovascular disease and breast cancer it is no longer recommended for primary or secondary prevention of osteoporosis unless the woman is suffering from vasomotor symptoms

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



MRI showing osteoporotic fractures of the 8th and 10th thoracic vertebrae.

P450 enzyme system

Induction usually requires prolonged exposure to the inducing drug, as opposed to P450 inhibitors, where effects are often seen rapidly

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)

Inhibitors of the P450 system include

- antibiotics: ciprofloxacin, erythromycin
- isoniazid
- cimetidine, omeprazole
- amiodarone
- allopurinol
- imidazoles: ketoconazole, fluconazole
- SSRIs: fluoxetine, sertraline
- ritonavir
- sodium valproate
- acute alcohol intake
- quinupristin

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

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 prescribing: pain

NICE guidelines

In 2012 NICE published guidelines on the use of opioids in palliative care. Selected points are listed below. Please see the link for more details.

Starting treatment

- when starting treatment, offer patients with advanced and progressive disease regular oral modified-release (MR) or oral immediate-release morphine (depending on patient preference), with oral immediate-release morphine for breakthrough pain
- 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
- oral modified-release morphine should be used in preference to transdermal patches
- laxatives should be prescribed for all patients initiating strong opioids
- 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

SIGN guidelines

SIGN issued guidance on the control of pain in adults with cancer in 2008. Selected points

- the breakthrough dose of morphine is one-sixth the daily dose of morphine
- all patients who receive opioids should be prescribed a laxative
- opioids should be used with caution in patients with chronic kidney disease. Alfentanil, buprenorphine and fentanyl are preferred
- metastatic bone pain may respond to NSAIDs, bisphosphonates or radiotherapy

Other points

When increasing the dose of opioids the next dose should be increased by 30-50%.

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*

Oxycodone generally causes less sedation, vomiting and pruritis than morphine but more constipation.

From	To	Conversion factor
Oral morphine	Oral oxycodone	Divide by 1.5-2**

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

*this has previously been stated as 5 but the current version of the BNF states a conversion of 10

**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

Paracetamol overdose: management

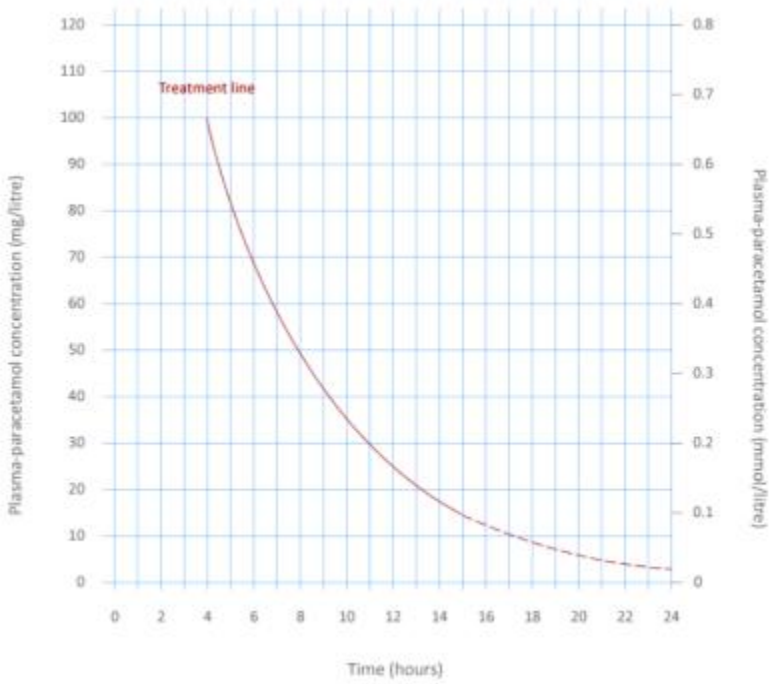
Management

The following is based on 2012 Commission on Human Medicines (CHM) review of paracetamol overdose management. The big change in these guidelines was the removal of the 'high-risk' treatment line on the normogram. All patients are therefore treated the same regardless of risk factors for hepatotoxicity. The National Poisons Information Service/TOXBASE should always be consulted for situations outside of the normal parameters.

Acetylcysteine should be given if:

- there is a staggered overdose* or there is doubt over the time of paracetamol ingestion, regardless of the plasma paracetamol concentration; or
- the plasma paracetamol concentration is on or above a single treatment line joining points of 100 mg/L at 4 hours and 15 mg/L at 15 hours, regardless of risk factors of hepatotoxicity

Acetylcysteine is now infused over 1 hour (rather than the previous 15 minutes) to reduce the number of adverse effects.



King's College Hospital criteria for liver transplantation (paracetamol liver failure)

Arterial pH < 7.3, 24 hours after ingestion

or all of the following:

- **prothrombin time > 100 seconds**
- **creatinine > 300 µmol/l**
- **grade III or IV encephalopathy**

*an overdose is considered staggered if all the tablets were not taken within 1 hour

Paracetamol overdose: metabolic pathways

The liver normally conjugates paracetamol with glucuronic acid/sulphate. During an overdose the conjugation system becomes saturated leading to oxidation by P450 mixed function oxidases*. This produces a toxic metabolite (N-acetyl-B-benzoquinone imine)

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 forms covalent bonds with cell proteins, denaturing them and leading to cell death. This occurs not only in hepatocytes but also in the renal tubules

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

*this explains why there is a lower threshold for treating patients who take P450 inducing medications e.g. phenytoin or rifampicin

Pharmacokinetics: metabolism

Drug metabolism usually involves two types of biochemical reactions - phase I and phase II reactions

- 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

The majority of phase I and phase II reactions take place in the liver

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

Questions concerning zero-order kinetics and acetylator status are also common in the exam

Zero-order kinetics

Zero-order kinetics describes metabolism which is independent of the concentration of the reactant. This is due to metabolic pathways becoming saturated resulting in a constant amount of drug being eliminated per unit time. This explains why people may fail a breathalyser test in the morning if they have been drinking the night before

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

Drugs affected by acetylator status

- isoniazid
- procainamide
- hydralazine
- dapsone
- sulfasalazine

Phenytoin

Phenytoin is used to in the management of seizures.

Mechanism of action

- binds to sodium channels increasing their refractory period

Adverse 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*
- aplastic anaemia
- drug-induced lupus

Teratogenic

- associated with cleft palate and congenital heart disease

Monitoring

Phenytoin levels do not need to be monitored routinely but **trough levels, immediately before dose** should be checked if:

- adjustment of phenytoin dose
- suspected toxicity
- detection of non-adherence to the prescribed medication

*although not listed in the BNF

Prescribing in patients with heart failure

The following medications may exacerbate heart failure:

- thiazolidinediones*: pioglitazone is contraindicated as it causes fluid retention
- verapamil: negative inotropic effect
- NSAIDs**/glucocorticoids: should be used with caution as they cause fluid retention
- class I antiarrhythmics; flecainide (negative inotropic and proarrhythmic effect)

*pioglitazone is now the only thiazolidinedione on the market

**low-dose aspirin is an exception - many patients will have coexistent cardiovascular disease and the benefits of taking aspirin easily outweigh the risks

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. Some countries have developed a grading system - see the link.

Antibiotics

- tetracyclines
- aminoglycosides
- sulphonamides and trimethoprim
- quinolones: the BNF advises to avoid due to arthropathy in some animal studies

Other drugs

- ACE inhibitors, angiotensin II receptor antagonists
- statins
- warfarin
- sulfonylureas
- retinoids (including topical)
- cytotoxic agents

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

Prostate cancer: management

Localised prostate cancer (T1/T2)

Treatment depends on life expectancy and patient choice. Options include:

- conservative: active monitoring & watchful waiting
- radical prostatectomy
- radiotherapy: external beam and brachytherapy

Localised advanced prostate cancer (T3/T4)

Options include:

- hormonal therapy: see below
- radical prostatectomy
- radiotherapy: external beam and brachytherapy

Metastatic prostate cancer disease - 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

Quinolones

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
- cartilage damage has been demonstrated in animal models and for this reason quinolones are generally avoided (but not necessarily contraindicated) in children
- lengthens QT interval

Quinupristin & dalfopristin antibiotics

Overview

- injectable streptogrammin antibiotic
- combination of group A and group B streptogrammin
- inhibits bacterial protein synthesis by blocking tRNA complexes binding to the ribosome

Spectrum

- most Gram positive bacteria
- 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

Salicylate overdose

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

Features

- hyperventilation (centrally stimulates respiration)
- tinnitus
- lethargy
- sweating, pyrexia*
- nausea/vomiting
- hyperglycaemia and hypoglycaemia
- seizures
- coma

Treatment

- general (ABC, charcoal)
- urinary alkalinization with intravenous sodium bicarbonate - enhances elimination of aspirin in the urine
- haemodialysis

Indications for haemodialysis in salicylate overdose

- serum concentration > 700mg/L
- metabolic acidosis resistant to treatment
- acute renal failure
- pulmonary oedema
- seizures
- coma

*salicylates cause the uncoupling of oxidative phosphorylation leading to decreased adenosine triphosphate production, increased oxygen consumption and increased carbon dioxide and heat production

Sildenafil

Sildenafil is a phosphodiesterase type V inhibitor used in the treatment of impotence.

Contraindications

- patients taking nitrates and related drugs such as nicorandil
- hypotension
- recent stroke or myocardial infarction (NICE recommend waiting 6 months)

Side-effects

- visual disturbances e.g. blue discolouration, non-arteritic anterior ischaemic neuropathy
- nasal congestion
- flushing
- gastrointestinal side-effects
- headache

The **blue pill**, Viagra (sildenafil), causes **blue discolouration** of vision

Smoking cessation

NICE released guidance in 2008 on the management of smoking cessation. General points include:

- 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

Nicotine replacement therapy

- adverse effects include 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

Varenicline

- a nicotinic receptor partial agonist
- should be started 1 week before the patients target date to stop
- the recommended course of treatment is 12 weeks (but patients should be monitored regularly and treatment only continued if not smoking)
- has been shown in studies to be more effective than bupropion
- nausea is the most common adverse effect. Other common problems include headache, insomnia, abnormal dreams
- varenicline should be used with caution in patients with a history of depression or self-harm. There are ongoing studies looking at the risk of suicidal behaviour in patients taking varenicline
- contraindicated in pregnancy and breast feeding

Bupropion

- a norepinephrine and dopamine reuptake inhibitor, and nicotinic antagonist
- should be started 1 to 2 weeks before the patients target date to stop
- small risk of seizures (1 in 1,000)
- contraindicated in epilepsy, pregnancy and breast feeding. Having an eating disorder is a relative contraindication

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.

Interventions

- the first-line interventions in pregnancy should be cognitive behaviour therapy, motivational interviewing or structured self-help and support from NHS Stop Smoking Services
- the evidence for the use of NRT in pregnancy is mixed but it is often used if the above measures failure. There is no evidence that it affects the child's birthweight. Pregnant women should remove the patches before going to bed
- as mentioned above, varenicline and bupropion are contraindicated

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
- increased appetite and weight gain
- alopecia: regrowth may be curly
- ataxia
- tremor
- hepatitis
- pancreatitis
- thromobcytopaenia
- teratogenic
- hyponatraemia

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

Statins

Statins inhibit the action of HMG-CoA reductase, the rate-limiting enzyme in hepatic cholesterol synthesis

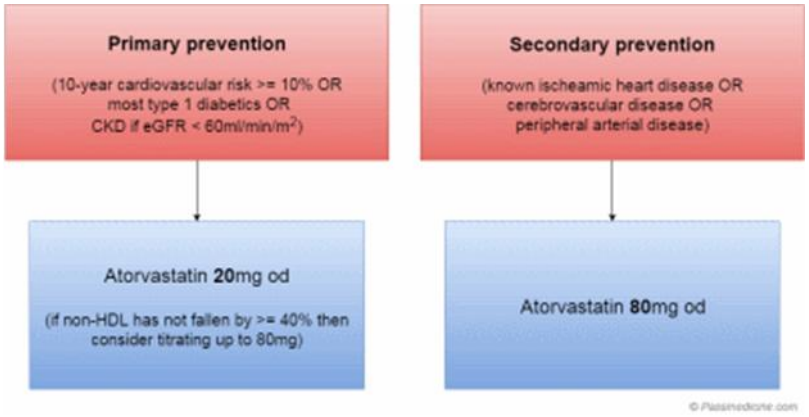
Adverse effects

- myopathy: includes myalgia, myositis, rhabdomyolysis and asymptomatic raised creatine kinase. Risks factors for myopathy include advanced age, female sex, low body mass index and presence of multisystem disease such as diabetes mellitus. Myopathy is more common in lipophilic statins (simvastatin, atorvastatin) than relatively hydrophilic statins (rosuvastatin, pravastatin, fluvastatin)
- liver impairment: 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
- there is some evidence that 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

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 statins
- patients with type 1 diabetes mellitus who were diagnosed more than 10 years ago OR are aged over 40 OR have established nephropathy

Statins 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



Graphic showing choice of statin.

Tacrolimus

Tacrolimus is a macrolide used as an immunosuppressant to prevent transplant rejection. It has a very similar action to ciclosporin:

Action of ciclosporin

- decreases clonal proliferation of T cells by reducing IL-2 release
- binds to cyclophilin forming a complex which inhibits calcineurin, a phosphotase that activates various transcription factors in T cells

The action of tacrolimus differs 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

Tamoxifen

Tamoxifen is a Selective oEstrogen 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 - 3% of patients stop taking tamoxifen due to climateric side-effects
- venous thromboembolism
- 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

*although antagonistic with respects to breast tissue tamoxifen may serve as an agonist at other sites. Therefore risk of endometrial cancer is increased cancer

Therapeutic drug monitoring

Lithium

- range = 0.4 - 1.0 mmol/l
- take 12 hrs post-dose

Ciclosporin

- trough levels immediately before dose

Digoxin

- at least 6 hrs post-dose

Phenytoin levels do not need to be monitored routinely but **trough levels, immediately before dose** should be checked if:

- adjustment of phenytoin dose
- suspected toxicity
- detection of non-adherence to the prescribed medication

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: more common when anthracyclines have also been used. An echo is usually performed before starting treatment

Tricyclic overdose

Overdose of tricyclic antidepressants is a common presentation to emergency departments. Amitriptyline and dosulepin (dothiepin) are particularly dangerous in overdose.

Early features relate to anticholinergic properties: dry mouth, dilated pupils, agitation, sinus tachycardia, blurred vision.

Features of severe poisoning include:

- arrhythmias
- seizures
- metabolic acidosis
- coma

ECG changes include:

- 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

- 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

Tuberculosis: drug side-effects and mechanism of action

Rifampicin

- mechanism of action: inhibits bacterial DNA dependent RNA polymerase preventing transcription of DNA into mRNA
- potent liver enzyme inducer
- hepatitis, orange secretions
- flu-like symptoms

Isoniazid

- mechanism of action: inhibits mycolic acid synthesis
- peripheral neuropathy: prevent with pyridoxine (Vitamin B6)
- hepatitis, agranulocytosis
- liver enzyme inhibitor

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

Urinary incontinence

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
- stress incontinence: leaking small amounts when coughing or laughing
- mixed incontinence: both urge and stress
- overflow incontinence: due to bladder outlet obstruction, e.g. due to prostate enlargement

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. NICE recommend oxybutynin (immediate release), tolterodine (immediate release) or darifenacin (once daily preparation). Immediate release oxybutynin should however be avoided in 'frail older women'

If stress incontinence 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

Warfarin: management of high INR

The following is based on the BNF guidelines, which in turn take into account the British Committee for Standards in Haematology (BCSH) guidelines. 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 Minor bleeding	Stop warfarin 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

Clinical sciences

Achondroplasia

Achondroplasia is an autosomal dominant disorder associated with short stature. It is caused by a mutation in the fibroblast growth factor receptor 3 (FGFR-3) gene. This results in abnormal cartilage giving rise to:

- short limbs (rhizomelia) with shortened fingers (brachydactyly)
- large head with frontal bossing and narrow foramen magnum
- midface hypoplasia with a flattened nasal bridge
- 'trident' hands
- lumbar lordosis

In most cases (approximately 70%) it occurs as a sporadic mutation. The main risk factor is advancing parental age at the time of conception. Once present it is typically inherited in an autosomal dominant fashion.

Treatment

There is no specific therapy. However, some individuals benefit from limb lengthening procedures. These usually involve application of Llizarov frames and targeted bone fractures. A clearly defined need and end point is the cornerstone of achieving success with such procedures.

Acute intermittent porphyria

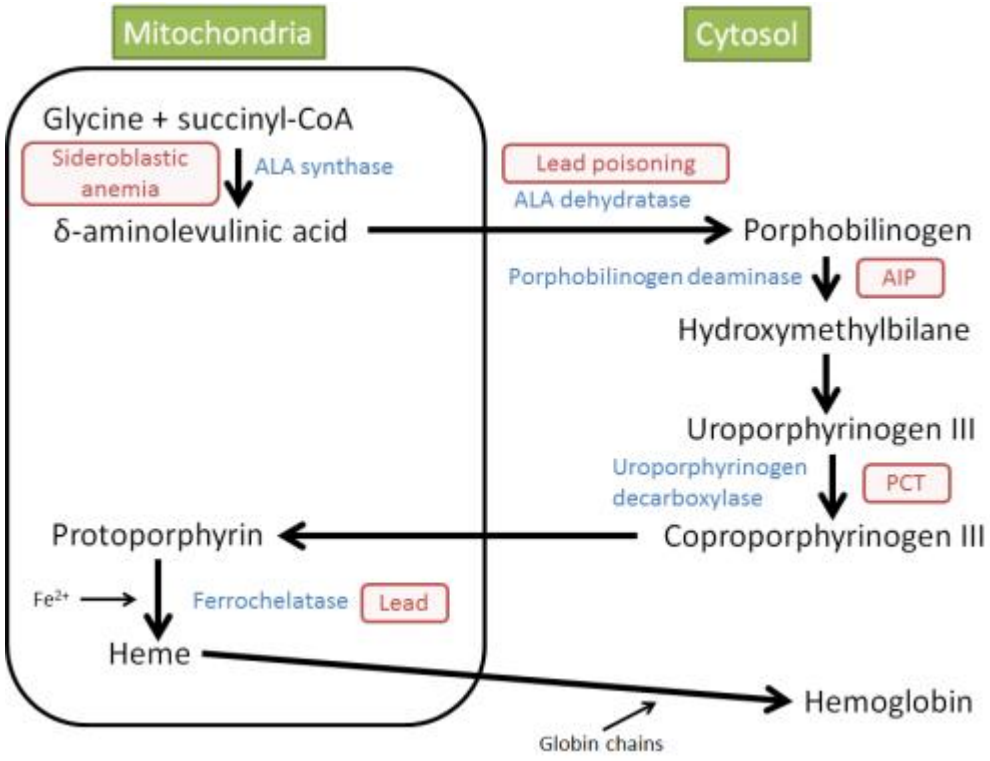
Acute intermittent porphyria (AIP) is a rare autosomal dominant condition caused by a defect in porphobilinogen deaminase, an enzyme involved in the biosynthesis of haem. The results in the toxic accumulation of delta aminolaevulinic acid and porphobilinogen. It characteristically presents with abdominal and neuropsychiatric symptoms in 20-40 year olds. AIP is more common in females (5:1)

Features

- abdominal: abdominal pain, vomiting
- neurological: motor neuropathy
- psychiatric: e.g. depression
- hypertension and tachycardia common

Diagnosis

- classically urine turns deep red on standing
- raised urinary porphobilinogen (elevated between attacks and to a greater extent during acute attacks)
- assay of red cells for porphobilinogen deaminase
- raised serum levels of delta aminolaevulinic acid and porphobilinogen



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.

Acute phase proteins

Acute phase proteins

- CRP*
- procalcitonin
- ferritin
- fibrinogen
- alpha-1 antitrypsin
- caeruloplasmin
- serum amyloid A
- serum amyloid P component**
- 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

*Levels of CRP are commonly measured in acutely unwell patients. CRP is a protein synthesised in the liver and binds to phosphocholine in bacterial cells and on those cells undergoing apoptosis. In binding to these cells it is then able to activate the complement system. CRP levels are known to rise in patients following surgery. However, levels of greater than 150 at 48 hours post operatively are suggestive of evolving complications.

**plays a more significant role in other mammals such as mice

Adrenal medulla

The adrenal medulla secretes virtually all the adrenaline in the body as well as secreting small amounts of noradrenaline. It essentially represents an enlarged and specialised sympathetic ganglion

Adrenoceptor agonists

Alpha-1 agonists

- phenylephrine

Alpha-2 agonists

- clonidine

Beta-1 agonists

- dobutamine

Beta-2 agonists

- salbutamol

Beta-3 agonists

- being developed, may have a role in preventing obesity (stimulation causes lipolysis)

Adrenoceptor antagonists

Alpha antagonists

- alpha-1: doxazosin
- alpha-1a: tamsulosin - acts mainly on urogenital tract
- alpha-2: yohimbine
- non-selective: phenoxybenzamine (previously used in peripheral arterial disease)

Beta antagonists

- beta-1: atenolol
- non-selective: propranolol

Carvedilol and labetalol are mixed alpha and beta antagonists

Adrenoceptors

Alpha-1

- vasoconstriction
- relaxation of GI smooth muscle
- salivary secretion
- hepatic glycogenolysis

Alpha-2

- mainly presynaptic: inhibition of transmitter release (inc NA, Ach from autonomic nerves)
- inhibits insulin
- platelet aggregation

Beta-1

- mainly located in the heart
- increase heart rate + force

Beta-2

- vasodilation
- bronchodilation
- relaxation of GI smooth muscle

Beta-3

- lipolysis

Pathways

- all are G-protein coupled
- alpha-1:activate phospholipase C → IP3 → DAG
- alpha-2: inhibit adenylate cyclase
- beta-1: stimulate adenylate cyclase
- beta-2: stimulate adenylate cyclase
- beta-3: stimulate adenylate cyclase

Altitude related disorders

There are three main types of altitude related disorders: acute mountain sickness (AMS), which may progress to high altitude pulmonary edema (HAPE) or high altitude cerebral edema (HACE). All three conditions are due to the chronic hypobaric hypoxia which develops at high altitudes

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

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

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
- nifedipine, dexamethasone, acetazolamide, phosphodiesterase type V inhibitors*
- oxygen if available

*the relative merits of these different treatments has only been studied in small trials. All seem to work by reducing systolic pulmonary artery pressure

Anaphylaxis

Anaphylaxis may be defined as a severe, life-threatening, generalised or systemic hypersensitivity reaction.

Anaphylaxis is one of the few times when you would not have time to look up the dose of a medication. The Resuscitation Council guidelines on anaphylaxis have recently been updated. 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 mg	10 mg

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.

Common identified causes of anaphylaxis

- food (e.g. Nuts) - the most common cause in children
- drugs
- venom (e.g. Wasp sting)

Sometimes it can be difficult to establish whether a patient had a true episode of anaphylaxis. Serum tryptase levels are sometimes taken in such patients as they remain elevated for up to 12 hours following an acute episode of anaphylaxis.

ANCA

There are two main types of anti-neutrophil cytoplasmic antibodies (ANCA) - cytoplasmic (cANCA) and perinuclear (pANCA)

For the exam, remember:

- cANCA - granulomatosis with polyangiitis (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
- granulomatosis with polyangiitis, positive in > 90%
- 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%
- granulomatosis with polyangiitis, 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

Angiodysplasia

Angiodysplasia is a vascular deformity of the gastrointestinal tract which predisposes to bleeding and iron deficiency anaemia. There is thought to be an association with aortic stenosis, although this is debated. Angiodysplasia is generally seen in elderly patients

Diagnosis

- colonoscopy
- mesenteric angiography if acutely bleeding

Management

- endoscopic cautery or argon plasma coagulation
- antifibrinolytics e.g. Tranexamic acid
- oestrogens may also be used

Anion gap

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, ureterosigmoidostomy, 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

Antidiuretic hormone

Antidiuretic hormone (ADH) is secreted from the posterior pituitary gland. It promotes water reabsorption in the collecting ducts of the kidneys by the insertion of aquaporin-2 channels.

	Notes	Further detail
Source	Synthesized in the supraoptic nuclei of the hypothalamus, released by the pituitary pituitary	
Function	Conserves body water	Promotes water reabsorption in the collecting ducts of the kidneys by the insertion of aquaporin-2 channels
Regulation	Increases secretion - extracellular fluid osmolality increase - volume decrease - pressure decrease - angiotensin II Decreases secretion - extracellular fluid osmolality decrease - volume increase - temperature decrease	Diabetes insipidus (DI) is a condition characterised by either a deficiency of antidiuretic hormone, ADH, (cranial DI) or an insensitivity to antidiuretic hormone (nephrogenic DI) Cranial DI can be treated by desmopressin, an analog of ADH

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 disease	Confusion, ataxia, slurred speech
Oseltamivir	Inhibits neuraminidase	Influenza	

Drug	Mechanism of action	Indications	Adverse effects/toxicity
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

Anti-retroviral agent used in HIV

Nucleoside analogue reverse transcriptase inhibitors (NRTI)

- examples: zidovudine (AZT), didanosine, lamivudine, stavudine, zalcitabine

Protease inhibitors (PI)

- inhibits a protease needed to make the virus able to survive outside the cell
- examples: indinavir, nelfinavir, ritonavir, saquinavir

Non-nucleoside reverse transcriptase inhibitors (NNRTI)

- examples: nevirapine, efavirenz

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)

ROME

Respiratory = **O**pposite

- low pH + high $PaCO_2$ i.e. acidosis, or
- high pH + low $PaCO_2$ i.e. alkalosis

Metabolic = **E**qual

- low pH + low bicarbonate i.e. acidosis, or
- high pH + high bicarbonate i.e. akalosis

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.
- smooth muscle proliferation and migration from the tunica media into the intima results in formation of a fibrous capsule covering the fatty plaque.

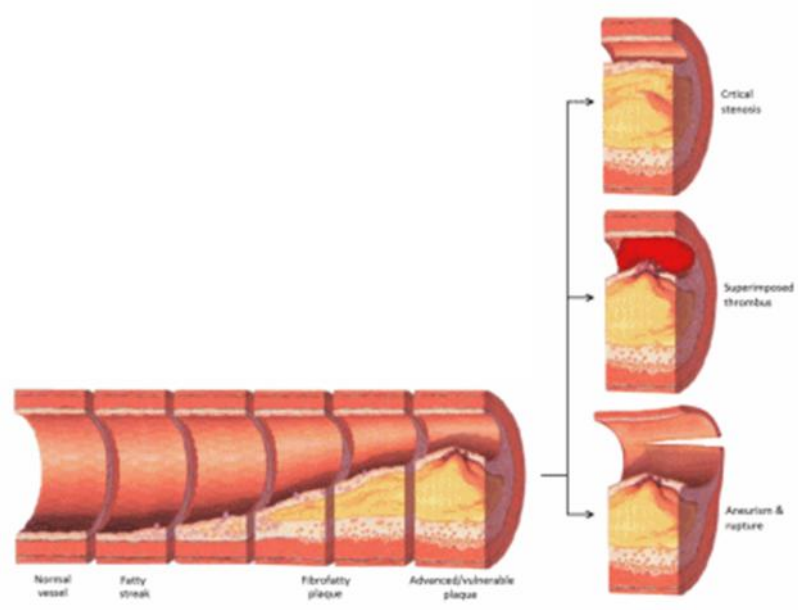
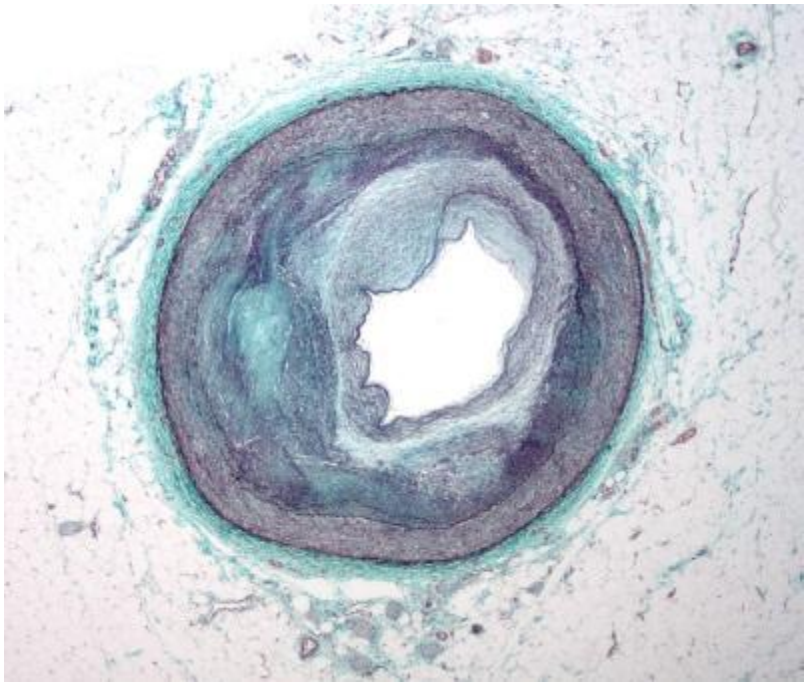


Diagram showing the progression of atherosclerosis in the coronary arteries with associated complications on the right.

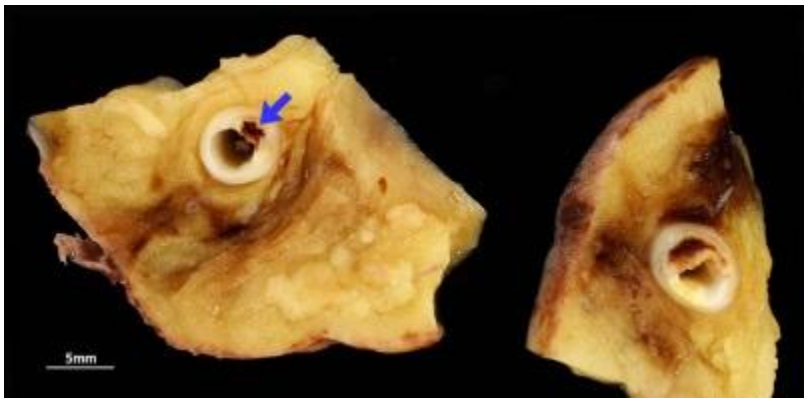


Slide showing a markedly narrowed coronary artery secondary to atherosclerosis. Stained with Masson's trichrome.

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



Ruptured coronary artery plaque resulting in thrombosis and associated myocardial infarction.

Pathological specimen showing infarction of the anteroseptal and lateral wall of the left ventricle. There is a background of biventricular myocardial hypertrophy.

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)
- 28 amino acid peptide hormone, which acts via cGMP
- degraded by endopeptidases

Actions

- natriuretic, i.e. promotes excretion of sodium
- lowers BP
- antagonises actions of angiotensin II, aldosterone

Atropine

Atropine is an antagonist of the muscarinic acetylcholine receptor

Uses*

- treatment of organophosphate poisoning

Physiological effects

- tachycardia
- mydriasis

*atropine is no longer used in resuscitation

Autosomal dominant

In autosomal dominant diseases:

- both homozygotes and heterozygotes manifest disease (there is no carrier state)
- both males and females affected
- only affected individuals can pass on disease
- disease is passed on to 50% of children
- normally appears in every generation (although see below)
- risk remains same for each successive pregnancy

Complicating factors:

- non-penetrance: lack of clinical signs and symptoms (normal phenotype) despite abnormal gene. E.g. 40% otosclerosis
- spontaneous mutation: new mutation in one of gametes e.g. 80% of individuals with achondroplasia have unaffected parents

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 hyperlipidaemia type II and hypokalaemic 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*

*type 3 von Willebrand's disease (most severe form) is inherited as an autosomal recessive trait. Around 80% of patients have type 1 disease

Autosomal recessive

In autosomal recessive inheritance

- only homozygotes are affected
- males and females are equally likely to be affected
- not manifest in every generation - may 'skip a generation'

If two heterozygote parents

- 25% chance of having an affected (homozygote) child
- 50% chance of having a carrier (heterozygote) child
- 25% chance of having an unaffected (i.e. genotypical) child

If one affected parent (i.e. homozygote for gene) and one unaffected (i.e. not a carrier or affected)

- all the children will be carriers

Autosomal recessive disorders are often metabolic in nature and are generally more life-threatening compared to autosomal dominant conditions

Autosomal recessive conditions

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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

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

B-type natriuretic peptide

B-type natriuretic peptide (BNP) is a hormone produced mainly by the left ventricular myocardium in response to strain.

Whilst heart failure is the most obvious cause of raised BNP levels any cause of left ventricular dysfunction such as myocardial ischaemia or valvular disease may raise levels. Raised levels may also be seen due to reduced excretion in patients with chronic kidney disease. Factors which reduce BNP levels include treatment with ACE inhibitors, angiotensin-2 receptor blockers and diuretics.

Effects of BNP

- vasodilator
- diuretic and natriuretic
- 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
- 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

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

*this is actually via an indirect mechanism as osteoclasts don't have PTH receptors

Cardiac action potential

Cardiac action potential

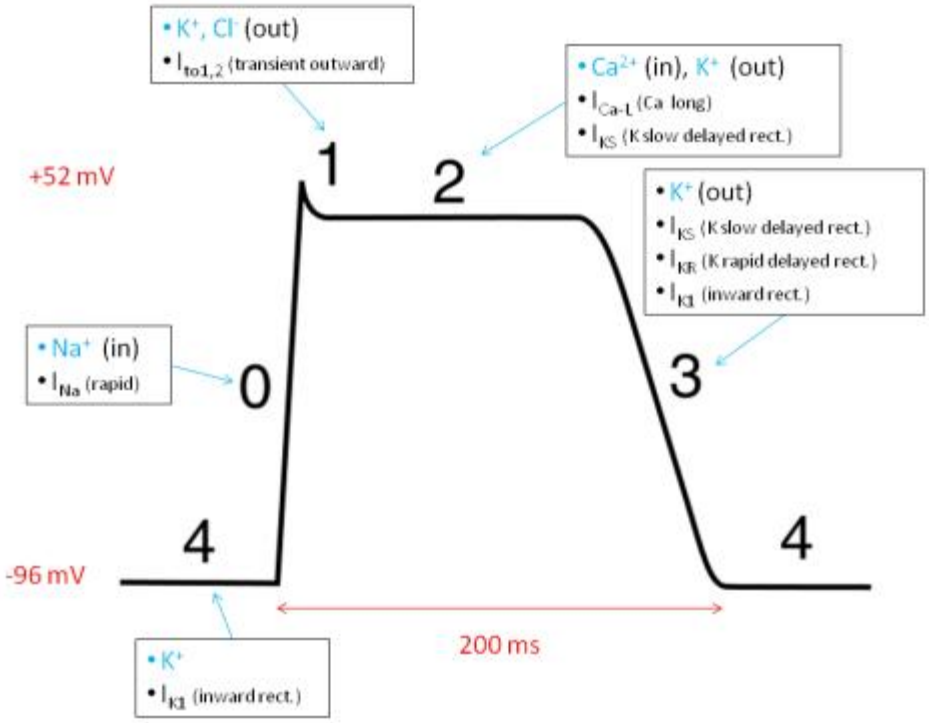


Image sourced from Wikipedia

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

Phase	Description	Mechanism
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

Cardiac imaging: non-invasive techniques excluding echocardiography

The ability to image the heart using non-invasive techniques such as MRI, CT and radionuclides has evolved rapidly over recent years.

Nuclear imaging

These techniques use radiotracers which are extracted by normal myocardium. Examples include:

- thallium
- technetium (99mTc) sestamibi: a coordination complex of the radioisotope technetium-99m with the ligand methoxyisobutyl isonitrile (MIBI), used in 'MIBI' or cardiac Single Photon Emission Computed Tomography (SPECT) scans
- fluorodeoxyglucose (FDG): used in Positron Emission Tomography (PET) scans

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). Cardiac PET is predominately a research tool at the current time

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.

Cardiac MRI

Cardiac MRI (commonly termed CMR) has become the gold standard for providing structural images of the heart. It is particularly useful when 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.

Please also see the British Heart Foundation link for an excellent summary.

Cardiovascular physiology

Left ventricular ejection fraction

Left ventricular ejection fraction = (stroke volume / end diastolic LV volume) * 100%

Stroke volume = end diastolic LV volume - end systolic LV volume

Pulse pressure

Pulse pressure = Systolic Pressure - Diastolic Pressure

Factors which increase pulse pressure

- a less compliant aorta (this tends to occur with advancing age)
- increased stroke volume

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
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	

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

Mitosis occurs during the M phase of the cell cycle. It describes the process in which somatic cells divide and replicate producing genetically identical diploid daughter cells. This allows tissue to grow and renew itself.

During the S phase of the cell cycle the cell prepares itself for division by duplicating the chromosomes. The table below shows the phases of mitosis itself:

Prophase	Chromatin in the nucleus condenses
Prometaphase	Nuclear membrane breaks down allowing the microtubules to attach to the chromosomes

Prophase	**Chromatin in the nucleus condenses**
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

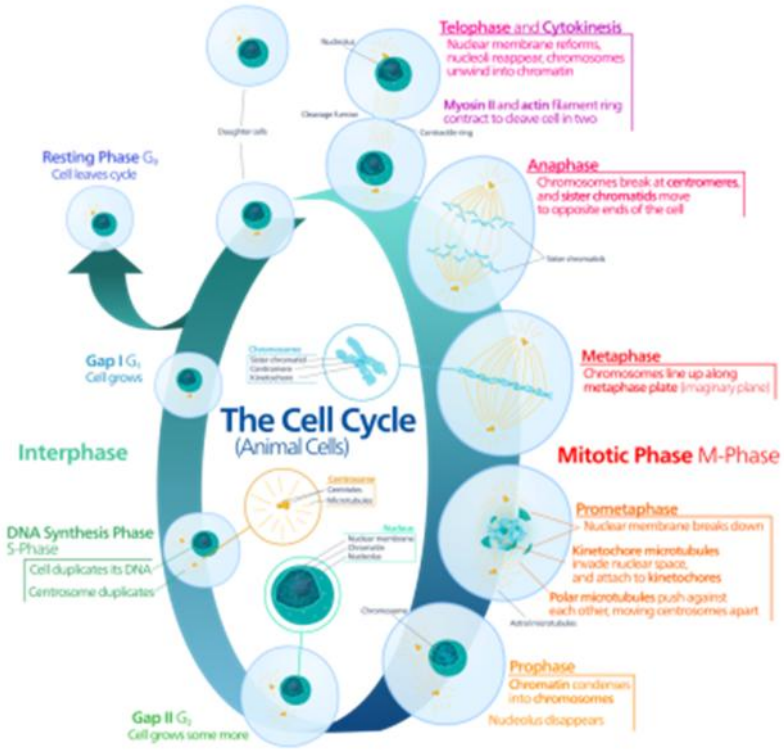


Image sourced from Wikipedia

Cell organelles

The table below summarises the main functions of the major cell organelles:

Organelle/macromolecule	Main function
Endoplasmic reticulum	Rough endoplasmic reticulum - translation and folding of new proteins - manufacture of lysosomal enzymes - site of N-linked glycosylation - examples of cells with extensive RER include pancreatic cells, goblet cells, plasma cells Smooth endoplasmic reticulum - steroid, lipid synthesis - examples of cells with extensive SER include those of the adrenal cortex, hepatocytes, testes, ovaries
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
Nucleus	DNA maintenance and RNA transcription
Lysosome	Breakdown of large molecules such as proteins and polysaccharides
Nucleolus	Ribosome production
Ribosome	Translation of RNA into proteins

Organelle/macromolecule	Main function
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

Cell surface proteins

The table below shows the most common cell surface proteins associated with particular cell types:

Type of cell	Cell surface markers
Haematopoietic stem cells	CD34
Helper T cell	CD4, TCR, CD3, CD28
Cytotoxic T cell	CD8, TCR, CD3, CD28
Regulatory T cell	CD4, CD25, TCR, CD3, CD28
B cell	CD19, CD20, CD40, MHC II, B7
Macrophage	CD14, CD40, MHC II, B7
Natural killer cell	CD16, CD56

The table below lists the major clusters of differentiation (CD) molecules and describes their function.

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

Cluster of differentiation	Function
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)
CD16	Bind to the Fc portion of IgG antibodies
CD21	Receptor for Epstein-Barr virus
CD28	Interacts with B7 on antigen presenting cell as costimulation signal
CD45	Protein tyrosine phosphatase present on all leucocytes
CD56	Unique marker for natural killer cells
CD95	Acts as the FAS receptor, involved in apoptosis

Cervical cancer

Around 50% of cases of cervical cancer occur in women under the age of 45 years, with incidence rates for cervical cancer in the UK are highest in people aged 25-29 years, according to Cancer Research UK. 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

Human papilloma virus (HPV), particularly serotypes 16,18 & 33 is by far the most important factor in the development of cervical cancer. Other risk factors include:

- smoking
- human immunodeficiency virus
- early first intercourse, many sexual partners
- high parity
- lower socioeconomic status
- combined oral contraceptive pill*

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

Chronic kidney disease: bone disease

Basic problems in chronic kidney disease

- low vitamin D (1-alpha hydroxylation normally occurs in the kidneys)
- high phosphate
- low calcium: due to lack of vitamin D, high phosphate
- secondary hyperparathyroidism: due to low calcium, high phosphate and low vitamin D

Several clinical manifestations may result:

Osteitis fibrosa cystica

- aka hyperparathyroid bone disease

Adynamic

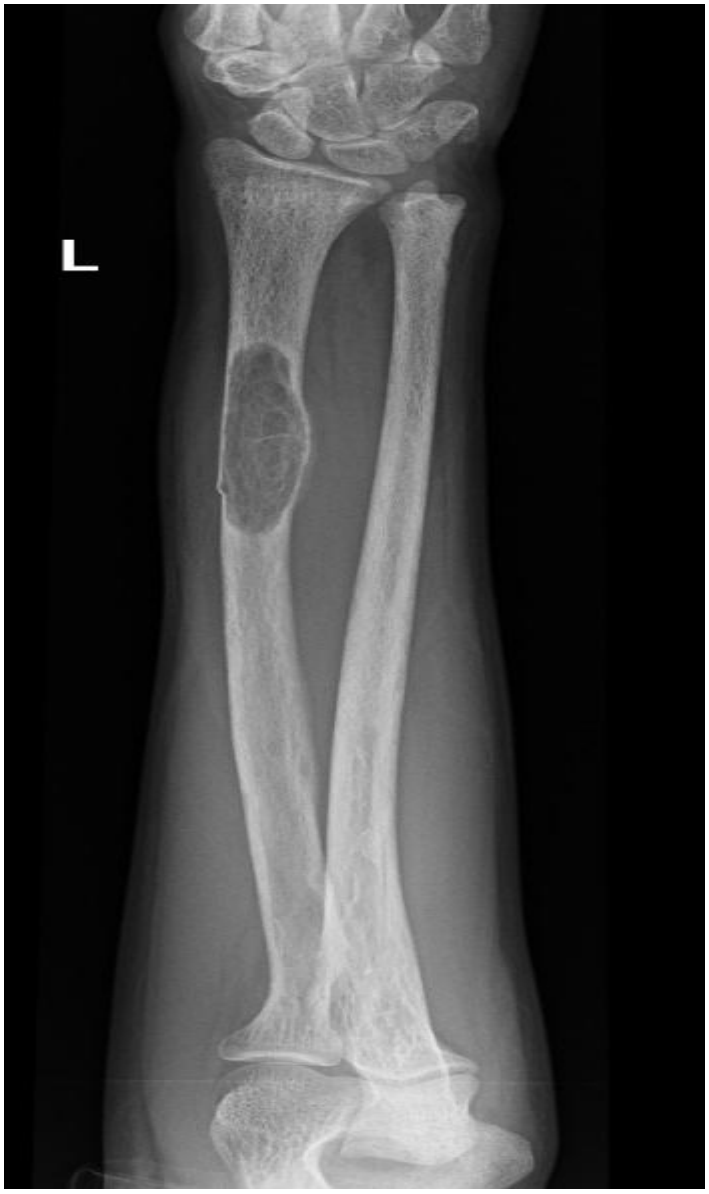
- reduction in cellular activity (both osteoblasts and osteoclasts) in bone
- may be due to over treatment with vitamin D

Osteomalacia

- due to low vitamin D

Osteosclerosis

Osteoporosis



X-ray of a Brown tumour caused by secondary hyperparathyroidism in a young female with chronic kidney disease

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) 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

Cocaine

Cocaine is an alkaloid derived from the coca plant. It is widely used as a recreational stimulant. The price of cocaine has fallen sharply in the past decade resulting in cocaine toxicity becoming a much more frequent clinical problem. This increase has made cocaine a favourite topic of question writers.

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
- both tachycardia and bradycardia may occur
- hypertension
- QRS widening and QT prolongation
- aortic dissection

Neurological effects

- seizures
- mydriasis
- hypertonia
- hyperreflexia

Psychiatric effects

- agitation
- psychosis
- hallucinations

Others

- ischaemic colitis is recognised in patients following cocaine ingestion. This should be considered if patients complain of abdominal pain or rectal bleeding
- hyperthermia
- metabolic acidosis
- rhabdomyolysis

Management of cocaine toxicity

- in general benzodiazipines are generally first-line for most cocaine related problems
- chest pain: benzodiazipines + glyceryl trinitrate. If myocardial infarction develops then primary percutaneous coronary intervention
- hypertension: benzodiazipines + sodium nitroprusside
- the use of beta-blockers in cocaine-induced cardiovascular problems is a controversial issue. The American Heart Association issued a statement in 2008 warning against the use of beta-blockers (due to the risk of unopposed alpha-mediated coronary vasospasm) but many cardiologists since have questioned whether this is valid. If a reasonable alternative is given in an exam it is probably wise to choose it

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

Common peroneal nerve lesion

The sciatic nerve divides into the tibial and common peroneal nerves. Injury often occurs at the neck of the fibula

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
- wasting of the anterior tibial and peroneal muscles

Complement deficiencies

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

C3 deficiency

- causes recurrent bacterial infections

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

Complex regional pain syndrome

Complex regional pain syndrome (CRPS) is the modern, umbrella term for a number of conditions such as reflex sympathetic dystrophy and causalgia. It describes a number of neurological and related symptoms which typically occur following surgery or a minor injury. CRPS is 3 times more common in women.

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

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

Management

- early physiotherapy is important
- neuropathic analgesia in-line with NICE guidelines
- specialist management (e.g. Pain team) is required

Confidence interval and standard error of the mean

The confidence interval is a common and sometimes misunderstood principle in medical statistics.

- a formal definition may be: *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

The likelihood of the true effect lying within the confidence interval is determined by the confidence level. For example a confidence interval at the 95% confidence level means that the confidence interval should contain the true effect of intervention 95% of the time.

How is the confidence interval calculated?

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

Key point

- SEM = SD / square root (n)
- where SD = standard deviation and n = sample size
- therefore the SEM gets smaller as the sample size (n) increases

A 95% confidence interval:

- lower limit = mean - (1.96 * SEM)
- upper limit = mean + (1.96 * SEM)

The above formula is a slight simplification:

- if a small sample size is used (e.g. n < 100) then it is important to use a 'Student's T critical value' look-up table to replace 1.96 with a different value
- if a different confidence level is required, e.g. 90% then 1.96 is replaced by a different value. For 90% this would 1.645

Results such as mean value are often presented along with a confidence interval. 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).

COPD: causes

Smoking!

Alpha-1 antitrypsin deficiency

Other causes

- cadmium (used in smelting)
- coal
- cotton
- cement
- grain

Cystic fibrosis

Cystic fibrosis (CF) is an autosomal recessive disorder causing increased viscosity of secretions (e.g. lungs and pancreas). It is due to a defect in the cystic fibrosis transmembrane conductance regulator gene (CFTR), which codes a cAMP-regulated chloride channel

In the UK 80% of CF cases are due to delta F508 on the long arm of chromosome 7. Cystic fibrosis affects 1 per 2500 births, and the carrier rate is c. 1 in 25

Organisms which may colonise CF patients

- *Staphylococcus aureus*
- *Pseudomonas aeruginosa*
- *Burkholderia cepacia**
- *Aspergillus*

*previously known as *Pseudomonas cepacia*

Cystinuria

Cystinuria is an autosomal recessive disorder characterised by the formation of recurrent renal stones. It is due to a defect in the membrane transport of cystine, ornithine, lysine, arginine (mnemonic = COLA)

Genetics

- chromosome 2: SLC3A1 gene, chromosome 19: SLC7A9

Features

- recurrent renal stones
- are classically yellow and crystalline, appearing semi-opaque on x-ray

Diagnosis

- cyanide-nitroprusside test

Management

- hydration
- D-penicillamine
- urinary alkalinization

DiGeorge syndrome

DiGeorge syndrome is a primary immunodeficiency disorder caused by T-cell deficiency and dysfunction. It is an example of a microdeletion syndrome

Features

- at risk of viral and fungal infections
- parathyroid gland hypoplasia → hypocalcaemic tetany
- thymus hypoplasia
- T-lymphocyte deficiency/dysfunction

Down's syndrome: epidemiology and genetics

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

Endothelin

Endothelin is a potent, long-acting vasoconstrictor and bronchoconstrictor. It is secreted initially as a prohormone by the vascular endothelium and later converted to ET-1 by the action of endothelin converting enzyme. It acts via interaction with a G-protein linked to phospholipase C leading to calcium release. Endothelin is thought to be important in the pathogenesis of many diseases including primary pulmonary hypertension (endothelin antagonists are now used), cardiac failure, hepatorenal syndrome and Raynaud's

Promotes release

- angiotensin II
- ADH
- hypoxia
- mechanical shearing forces

Inhibits release

- nitric oxide
- prostacyclin

Raised levels in

- MI
- heart failure
- ARF
- asthma
- primary pulmonary hypertension

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

Epidermis

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

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

Folate metabolism

Drugs which interfere with metabolism

- trimethoprim
- methotrexate
- pyrimethamine

Drugs which can reduce absorption

- phenytoin

Food energy

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.

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, please see the Wikipedia link for a full list.

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 (V1) 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)

Fourth nerve palsy

Overview

- supplies superior oblique (depresses eye, moves inward)

Features

- vertical diplopia
- classically noticed when reading book or going down stairs

Fragile X

Fragile X is a trinucleotide repeat disorder

Features in males

- learning difficulties
- large low set ears, long thin face, high arched palate
- macroorchidism
- hypotonia
- autism is more common
- mitral valve prolapse

Features in females (who have one fragile chromosome and one normal X chromosome) range from normal to mild

Diagnosis

- can be made antenatally by chorionic villus sampling or amniocentesis
- analysis of the number of CGG repeats using restriction endonuclease digestion and Southern blot analysis

Funnel plot

A funnel plot is primarily used to demonstrate the existence of publication bias in meta-analyses. Funnel plots are usually drawn with treatment effects on the horizontal axis and study size on the vertical axis.

Interpretation

- a symmetrical, inverted funnel shape indicates that publication bias is unlikely
- conversely, an asymmetrical funnel indicates a relationship between treatment effect and study size. This indicates either publication bias or a systematic difference between smaller and larger studies ('small study effects')

Galactosaemia

Galactosaemia is a rare autosomal recessive condition caused by the absence of galactose-1-phosphate uridyl transferase. This results in intracellular accumulation of galactose-1-phosphate

Features

- jaundice
- failure to thrive
- hepatomegaly
- cataracts
- hypoglycaemia after exposure to galactose
- Fanconi syndrome

Diagnosis

- urine reducing substances

Management is with a galactose free diet

Gastrointestinal hormones

Below is a brief summary of the major hormones involved in food digestion:

	Source	Stimulus	Actions
Gastrin	G cells in antrum of the stomach	Distension of stomach, vagus nerves (mediated by gastrin-releasing peptide), luminal peptides/amino acids Inhibited by: low antral pH, somatostatin	Increase HCL, pepsinogen and IF secretion, increases gastric motility, stimulates parietal cell maturation
CCK	I cells in upper small intestine	Partially digested proteins and triglycerides	Increases secretion of enzyme-rich fluid from pancreas, contraction of gallbladder and relaxation of sphincter of Oddi, decreases gastric emptying, trophic effect on pancreatic acinar cells, induces satiety
Secretin	S cells in upper small intestine	Acidic chyme, fatty acids	Increases secretion of bicarbonate-rich fluid from pancreas and hepatic duct cells, decreases gastric acid secretion, trophic effect on pancreatic acinar cells
VIP	Small intestine, pancreas	Neural	Stimulates secretion by pancreas and intestines, inhibits acid secretion

	Source	Stimulus	Actions
Somatostatin	D cells in the pancreas & stomach	Fat, bile salts and glucose in the intestinal lumen	Decreases acid and pepsin secretion, decreases gastrin secretion, decreases pancreatic enzyme secretion, decreases insulin and glucagon secretion inhibits trophic effects of gastrin, stimulates gastric mucous production

Gastrointestinal physiology: enzymes

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

GMC guidance: Confidentiality

We will not try to replicate the extensive guidance given by the General Medical Council here. There is a link available for more detailed information.

Growth hormone

Growth hormone (GH) is an anabolic hormone secreted by the somatotroph cells of the anterior lobe of the pituitary gland. It has actions on multiple organ systems and is important in postnatal growth and development. Growth hormone is also responsible for changes in protein, lipid, and carbohydrate metabolism

	Notes	Further detail
Source	Anterior pituitary	
Function	Postnatal growth and development Numerous actions on protein, carbohydrate and fat metabolism (including increasing lipolysis and gluconeogenesis)	Mechanism of action - acts on a transmembrane receptor for growth factor - binding of GH to the receptor leads to receptor dimerization - acts directly on tissues and also indirectly via insulin-like growth factor 1 (IGF-1), primarily secreted by the liver
Regulation	Increases secretion - growth hormone releasing hormone (GHRH): released in pulses by the hypothalamus - fasting - exercise - sleep Decreases secretion - glucose - somatostatin (itself increased by somatomedins, circulating insulin-like growth factors, IGF-1 and IGF-2)	Conditions associated with GH disorders - excess GH: acromegaly - GH deficiency: resulting in short stature

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

Hereditary angioedema

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 - the probable mechanism behind attacks is 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

- attacks may be proceeded by painful macular rash
- painless, non-pruritic swelling of subcutaneous/submucosal tissues
- may affect upper airways, skin or abdominal organs (can occasionally present as abdominal pain due to visceral oedema)
- urticaria is not usually a feature

Management

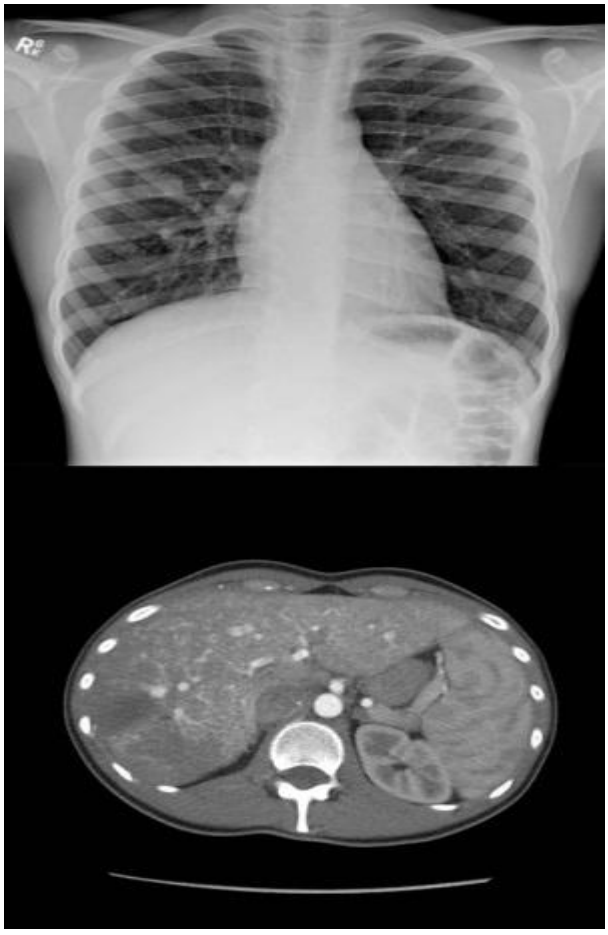
- acute: IV C1-inhibitor concentrate, fresh frozen plasma (FFP) if this is not available
- prophylaxis: anabolic steroid Danazol may help

Hereditary haemorrhagic telangiectasia

Also known as Osler-Weber-Rendu syndrome, hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant condition characterised by (as the name suggests) multiple telangiectasia over the skin and mucous membranes. Twenty percent of cases occur spontaneously without prior family history.

There are 4 main diagnostic criteria. If the patient has 2 then they are said to have a possible diagnosis of HHT. If they meet 3 or more of the criteria they are said to have a definite diagnosis of HHT:

- epistaxis : spontaneous, recurrent nosebleeds
- telangiectases: multiple at characteristic sites (lips, oral cavity, fingers, nose)
- visceral lesions: for example gastrointestinal telangiectasia (with or without bleeding), pulmonary arteriovenous malformations (AVM), hepatic AVM, cerebral AVM, spinal AVM
- family history: a first-degree relative with HHT

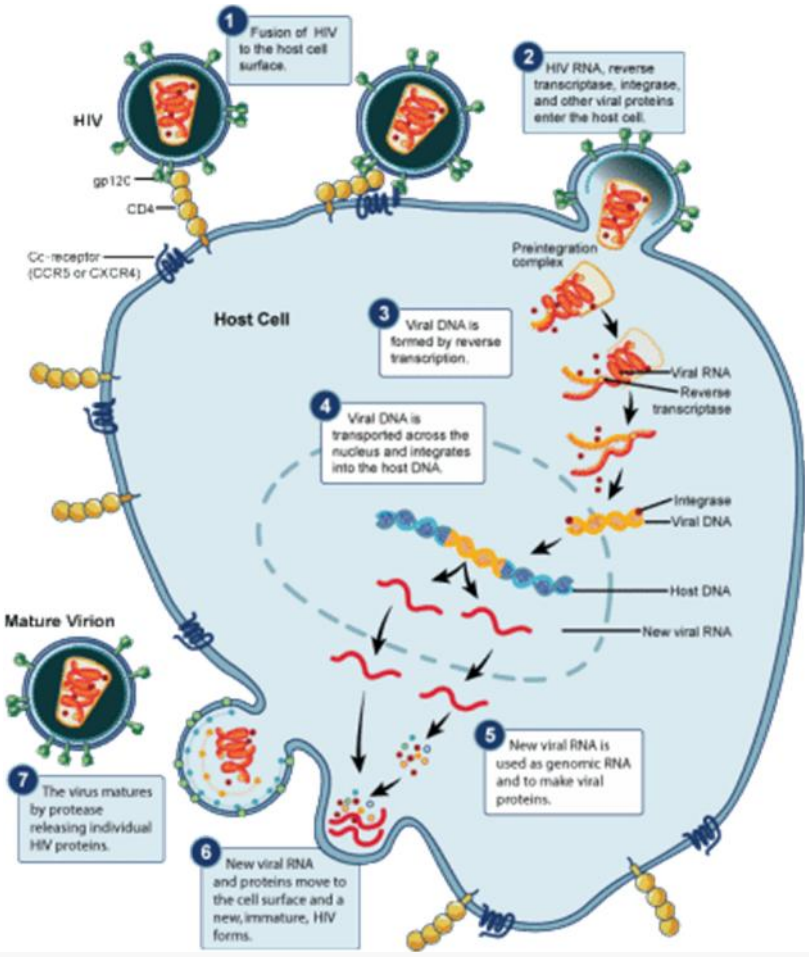


The chest x-ray shows multiple pulmonary nodules representing arteriovenous malformations, the largest in the right mid-zone. The CT scan shows multiple hepatic arteriovenous malformations

HIV: immunology

The following immunological changes are seen in progressive HIV:

- reduction in CD4 count
- increase B2-microglobulin
- decreased IL-2 production
- polyclonal B-cell activation
- decrease NK cell function
- reduced delayed hypersensitivity responses

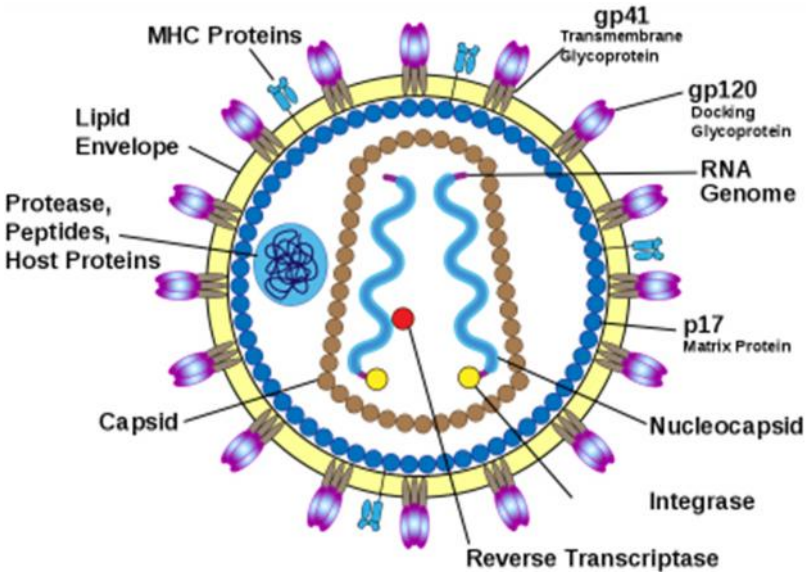


An illustration model of the HIV Replication Cycle. Each step of the cycle is numbered and concisely described. Credit: NIAID

HIV: the virus

Basics

- HIV is a RNA retrovirus of the lentivirus genus (lentiviruses are characterized by a long incubation period)
- two variants - HIV-1 and HIV-2
- HIV-2 is more common in west Africa, has a lower transmission rate and is thought to be less pathogenic with a slower progression to AIDS



Basics structure

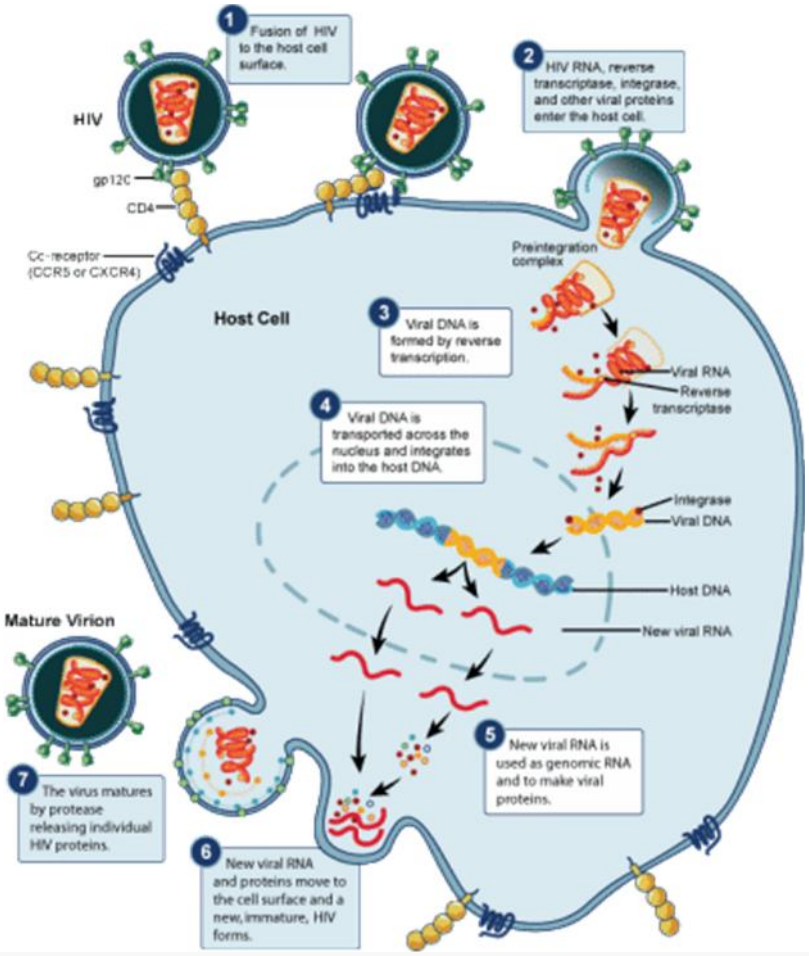
- spherical in shape with two copies of single-stranded RNA enclosed by a capsid of the viral protein p24
- a matrix composed of viral protein p17 surrounds the capsid
- envelope proteins: gp120 and gp41
- pol gene encodes for viral enzymes reverse transcriptase, integrase and HIV protease

Cell entry

- HIV can infect CD4 T cells, macrophages and dendritic cells
- gp120 binds to CD4 and CXCR4 on T cells and CD4 and CCR5 on macrophages
- mutations in CCR5 can give immunity to HIV

Replication

- after entering a cell the enzyme reverse transcriptase creates dsDNA from the RNA for integration into the host cell's genome



An illustration model of the HIV Replication Cycle. Each step of the cycle is numbered and concisely described. Credit: NIAID

HLA associations

HLA antigens are encoded for by genes on chromosome 6. HLA A, B and C are class I antigens whilst DP, DQ, DR are class II antigens. Questions are often based around which diseases have strong HLA associations. The most important associations are listed below:

HLA-A3

- haemochromatosis

HLA-B5

- Behcet's disease

HLA-B27

- ankylosing spondylitis
- Reiter's syndrome
- acute anterior uveitis

HLA-DQ2/DQ8

- coeliac disease

HLA-DR2

- narcolepsy
- Goodpasture's

HLA-DR3

- dermatitis herpetiformis
- Sjogren's syndrome
- primary biliary cirrhosis

HLA-DR4

- type 1 diabetes mellitus*
- rheumatoid arthritis

*type 1 diabetes mellitus is associated with HLA-DR3 but is more strongly associated with HLA-DR4.

Hypercalcaemia: management

The initial management of hypercalcaemia is rehydration with normal saline, typically 3-4 litres/day. Following rehydration bisphosphonates may be used. They typically take 2-3 days to work with maximal effect being seen at 7 days

Other options include:

- calcitonin - quicker effect than bisphosphonates
- 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

Hyperkalaemia

Plasma potassium levels are regulated by a number of factors including aldosterone, acid-base balance and 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. ECG changes seen in hyperkalaemia include tall-tented T waves, small P waves, widened QRS leading to a sinusoidal pattern and asystole

Causes of hyperkalaemia:

- acute kidney injury
- drugs*: potassium sparing diuretics, ACE inhibitors, angiotensin 2 receptor blockers, spironolactone, ciclosporin, heparin**
- 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

*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

**both unfractionated and low-molecular weight heparin can cause hyperkalaemia. This is thought to be caused by inhibition of aldosterone secretion

Hypernatraemia

Causes of hypernatraemia

- dehydration
- osmotic diuresis e.g. hyperosmolar non-ketotic diabetic coma
- diabetes insipidus
- excess IV saline

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 death1. Although there are no clinical guidelines by NICE or Royal College of Physicians at present, it is generally accepted that a rate of no greater than 0.5 mmol/hour correction is appropriate.

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	• Anaphylaxis • Atopy (e.g. asthma, eczema and hayfever)
Type II - Cell bound	IgG or IgM binds to antigen on cell surface	• 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	• Serum sickness • Systemic lupus erythematosus • Post-streptococcal glomerulonephritis • Extrinsic allergic alveolitis (especially acute phase)
Type IV - Delayed hypersensitivity	T-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

Hyperuricaemia

Increased levels of uric acid may be seen secondary to either increased cell turnover or reduced renal excretion of uric acid. Hyperuricaemia may be found in asymptomatic patients who have not experienced attacks of gout

Hyperuricaemia may be associated with hyperlipidaemia and hypertension. It may also be seen in conjunction with the metabolic syndrome

Increased synthesis

- Lesch-Nyhan disease
- myeloproliferative disorders
- diet rich in purines
- exercise
- psoriasis
- cytotoxics

Decreased excretion

- drugs: low-dose aspirin, diuretics, pyrazinamide
- pre-eclampsia
- alcohol
- renal failure
- lead

Hypocalcaemia: causes and management

The clinical history combined with parathyroid hormone levels will reveal the cause of hypocalcaemia in the majority of cases

Causes

- vitamin D deficiency (osteomalacia)
- chronic renal failure
- hypoparathyroidism (e.g. post thyroid/parathyroid surgery)
- pseudohypoparathyroidism (target cells insensitive to PTH)
- rhabdomyolysis (initial stages)
- magnesium deficiency (due to end organ PTH resistance)
- massive blood transfusion

Acute pancreatitis may also cause hypocalcaemia. Contamination of blood samples with EDTA may also give falsely low calcium levels

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

Hypocalcaemia: features

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
- if chronic: depression, cataracts
- ECG: prolonged QT interval

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 normocalcaemic people

Chvostek's sign

- tapping over parotid causes facial muscles to twitch
- seen in around 70% of patients with hypocalcaemia and around 10% of normocalcaemic people

Hypokalaemia

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

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

Magnesium deficiency may also cause hypokalaemia. In such cases, normalizing the potassium level may be difficult until the magnesium deficiency has been corrected

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

Urinary sodium > 20 mmol/l

Sodium depletion, renal loss (patient often hypovolaemic)

- diuretics
- Addison's
- diuretic stage of renal failure

Patient often euvolaemic

- SIADH (urine osmolality > 500 mmol/kg)
- hypothyroidism

Urinary sodium < 20 mmol/l

Sodium depletion, extra-renal loss

- diarrhoea, vomiting, sweating
- burns, adenoma of rectum

Water excess (patient often hypervolaemic and oedematous)

- secondary hyperaldosteronism: heart failure, cirrhosis
- reduced GFR: renal failure
- IV dextrose, psychogenic polydipsia

Hyponatraemia: correction

Central pontine myelinolysis

- demyelination syndrome caused by rapid correction of chronic hyponatraemia
- may lead to quadriparesis and bulbar palsy
- diagnosis: MRI brain

Hypophosphataemia

Causes

- alcohol excess
- acute liver failure
- diabetic ketoacidosis
- refeeding syndrome
- primary hyperparathyroidism
- osteomalacia

Consequences

- red blood cell haemolysis
- white blood cell and platelet dysfunction
- muscle weakness and rhabdomyolysis
- central nervous system dysfunction

IL-1

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.

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, 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.

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 Releases histamine during allergic response Granules contain histamine and heparin Expresses IgE receptors on the cell surface
Eosinophil	Defends against protozoan and helminthic infections Bi-lobed nucleus
Monocyte	Diffferentiates 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

Immunoglobulins

The table below summarises the characteristics of the 5 types of immunoglobulin found in the body:

Type	Frequency	Shape	Notes
IgG	75%	Monomer	• Enhance phagocytosis of bacteria and viruses • Fixes complement and passes to the fetal circulation • Most abundant isotype in blood serum
IgA	15%	Monomer/ dimer	• IgA is the predominant immunoglobulin found in breast milk. It is also found in the secretions of digestive, respiratory and urogenital tracts and systems • Provides localized protection on mucous membranes • Most commonly produced immunoglobulin in the body (but blood serum concentrations lower than IgG.) • Transported across the interior of the cell via transcytosis
IgM	10%	Pentamer	• First immunoglobulins to be secreted in response to an infection • Fixes complement but does not pass to the fetal circulation • Anti-A, B blood antibodies (note how they cannot pass to the fetal circulation, which could of course result in haemolysis) Pentamer when secreted
IgD	1%	Monomer	• Role in immune system largely unknown • Involved in activation of B cells

Type	Frequency	Shape	Notes
IgE	0.1%	Monomer	• 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

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
- 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

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

Incidence and prevalence

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

Inherited metabolic disorders

Glycogen storage disease

Disorder	Deficient enzyme	Notes
Von Gierke's disease (type I)	Glucose-6-phosphatase	Hepatic glycogen accumulation. Key features include hypoglycaemia, lactic acidosis, hepatomegaly
Pompe's disease (type II)	Lysosomal alpha-1,4-glucosidase	Cardiac, hepatic and muscle glycogen accumulation. Key features include cardiomegaly
Cori disease (type III)	Alpha-1,6-glucosidase (debranching enzyme)	Hepatic, cardiac glycogen accumulation. Key features include muscle hypotonia
McArdle's disease (type V)	Glycogen phosphorylase	Skeletal muscle glycogen accumulation. Key features include myalgia, myoglobulinaemia with exercise

Lysosomal storage disease

Disorder	Defect	Notes
Gaucher's disease	Beta-glucocerebrosidase	Most common lipid storage disorder resulting in accumulation of glucocerebrosidase in the brain, liver and spleen. Key features include hepatosplenomegaly, aseptic necrosis of the femur
Tay-Sachs disease	Hexosaminidase A	Accumulation of GM_2 ganglioside within lysosomes. Key features include developmental delay, cherry red spot on the macula, liver and spleen normal size (*cf.* Niemann-Pick)
Niemann-Pick disease	Sphingomyelinase	Key features include hepatosplenomegaly, cherry red spot on the macula
Fabry disease	Alpha-galactosidase-A	Accumulation of ceramide trihexoside. Key features include angiokeratomas, peripheral neuropathy of extemeties, renal failure
Krabbe's disease	Galactocerebrosidase	Key features include peripheral neuropathy, optic atrophy, globoid cells
Metachromatic leukodystrophy	Arylsulfatase A	Demyelination of the central and peripheral nervous system

Mucopolysaccharidoses

Disorder	Defect	Notes
Hurler syndrome (type I)	Alpha-1-iduronidase	Accumulation of glycosaminoglycans (heparan and dermatan sulfate). Key features include gargoylism, hepatosplenomegaly, corneal clouding
Hunter syndrome (type II)	Iduronate sulfatase	Accumulation of glycosaminoglycans (heparan and dermatan sulfate). Key features include coarse facial features, behavioural problems/learning difficulties short stature, no corneal clouding

Intention to treat analysis

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

Intention to treat analysis is done to avoid the effects of crossover and drop-out, which may affect the randomization to the treatment groups

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, gastric acid
- decreased by proton pump inhibitors, tetracycline, gastric achlorhydria, tannin (found in tea)

Distribution in body

- total body iron = 4g
- haemoglobin = 70%
- ferritin and haemosiderin = 25%
- myoglobin = 4%
- plasma iron = 0.1%

Transport

- carried in plasma as Fe3+ bound to transferrin

Storage

- stored as ferritin in tissues

Excretion

- lost via intestinal tract following desquamation

Kallman's syndrome

Kallman's syndrome is a recognised cause of delayed puberty secondary to hypogonadotrophic hypogonadism. It is usually inherited as an X-linked recessive trait. Kallman's syndrome is thought to be caused by failure of GnRH-secreting neurons to migrate to the hypothalamus.

The clue given in many questions is lack of smell (anosmia) in a boy with delayed puberty

Features

- 'delayed puberty'
- hypogonadism, cryptorchidism
- anosmia
- sex hormone levels are low
- LH, FSH levels are inappropriately low/normal
- patients are typically of normal or above average height

Cleft lip/palate and visual/hearing defects are also seen in some patients

Klinefelter's syndrome

Klinefelter's syndrome is associated with karyotype 47, XXY

Features

- often taller than average
- lack of secondary sexual characteristics
- small, firm testes
- infertile
- gynaecomastia - increased incidence of breast cancer
- elevated gonadotrophin levels

Diagnosis is by chromosomal analysis

Latex allergy

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-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.

Leukotrienes

Function

- mediators of inflammation and allergic reactions
- cause bronchoconstriction, mucous production
- increase vascular permeability, attract leukocytes
- leukotriene D4 has been identified as the SRS-A (slow reacting substance of anaphylaxis)

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

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. 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

Lower back pain: prolapsed disc

A prolapsed lumbar disc usually produces clear dermatomal leg pain associated with neurological deficits.

Features

- leg pain usually worse than back
- pain often worse when sitting

The table below demonstrates the expected features according to the level of compression:

Site of compression	Features
L3 nerve root compression	Sensory loss over anterior thigh Weak quadriceps Reduced knee reflex Positive femoral stretch test
L4 nerve root compression	Sensory loss anterior aspect of knee Weak quadriceps Reduced knee reflex Positive femoral stretch test
L5 nerve root compression	Sensory loss dorsum of foot Weakness in foot and big toe dorsiflexion Reflexes intact Positive sciatic nerve stretch test
S1 nerve root compression	Sensory loss posterolateral aspect of leg and lateral aspect of foot Weakness in plantar flexion of foot Reduced ankle reflex Positive sciatic nerve stretch test

Management

- similar to that of other musculoskeletal lower back pain: analgesia, physiotherapy, exercises
- if symptoms persist then referral for consideration of MRI is appropriate

Lung cancer: referral

The 2015 NICE cancer referral guidelines gave the following advice:

Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for lung cancer if they:

- have chest x-ray findings that suggest lung cancer
- are aged 40 and over with unexplained haemoptysis

Offer an urgent chest x-ray (to be performed within 2 weeks) to assess for lung cancer in people aged 40 and over if they have 2 or more of the following unexplained symptoms, or if they have ever smoked and have 1 or more of the following unexplained symptoms:

- cough
- fatigue
- shortness of breath
- chest pain
- weight loss
- appetite loss

Consider an urgent chest x-ray (to be performed within 2 weeks) to assess for lung cancer in people aged 40 and over with any of the following:

- persistent or recurrent chest infection
- finger clubbing
- supraclavicular lymphadenopathy or persistent cervical lymphadenopathy
- chest signs consistent with lung cancer
- thrombocytosis

Macroglossia

Causes

- hypothyroidism
- acromegaly
- amyloidosis
- Duchenne muscular dystrophy
- mucopolysaccharidosis (e.g. Hurler syndrome)

Patients with Down's syndrome are now thought to have apparent macroglossia due to a combination of mid-face hypoplasia and hypotonia

Marfan's syndrome

Marfan's syndrome is an autosomal dominant connective tissue disorder. It is caused by a defect in the fibrillin-1 gene on chromosome 15 and affects around 1 in 3,000 people.

Features

- tall stature with arm span to height ratio > 1.05
- high-arched palate
- arachnodactyly
- pectus excavatum
- pes planus
- scoliosis of > 20 degrees
- 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), blue sclera, myopia
- dural ectasia (ballooning of the dural sac at the lumbosacral level)

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. Aortic dissection and other cardiovascular problems remain the leading cause of death however.

Membrane receptors

There are four main types of membrane receptor: ligand-gated ion channels, tyrosine kinase receptors, guanylate cyclase receptors and 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

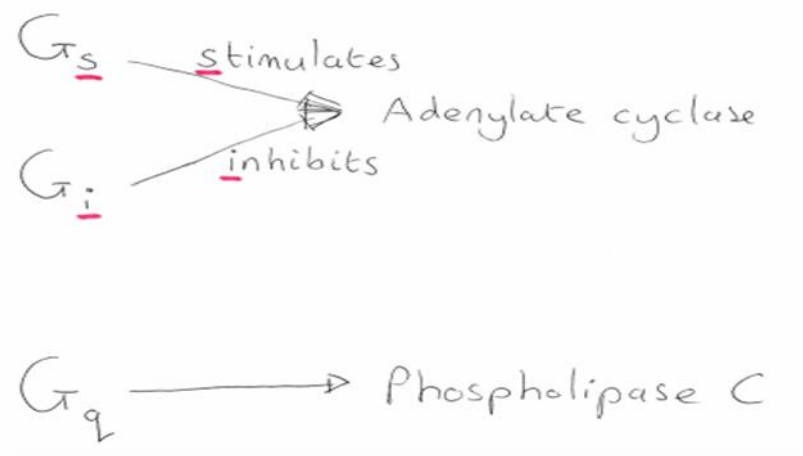
- intrinsic tyrosine kinase: insulin, insulin-like growth factor (IGF), epidermal growth factor (EGF)
- receptor-associated tyrosine kinase: growth hormone, prolactin, interferon, interleukin

Guanylate cyclase receptors

- contain intrinsic enzyme activity
- e.g. atrial natriuretic factor, brain natriuretic peptide

G protein-coupled receptors

- 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.Ligand binding causes conformational changes to receptor, GDP is phosphorylated to GTP,and the alpha subunit is activated
- G proteins are named according to the alpha subunit (G_s, G_i, G_q)

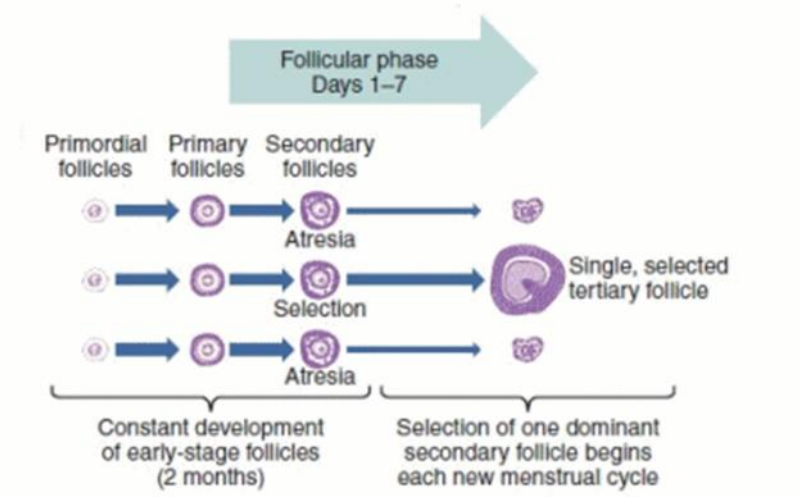


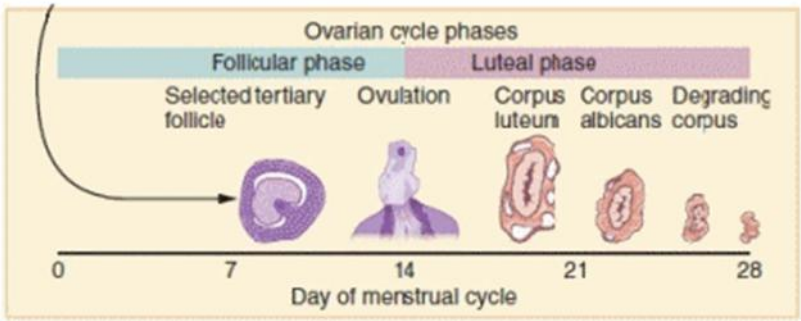
	G_s	G_i	G_q
Mechanism	**S**timulates adenylate cyclase → increases cAMP → activates protein kinase A	**I**nhibits adenylate cyclase → decreases cAMP → inhibits protein kinase A	Activates phospholipase C → splits PIP_2 to IP_3 & DAG → activates protein kinase C
Examples	• Beta-1 receptors (epinephrine, 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)

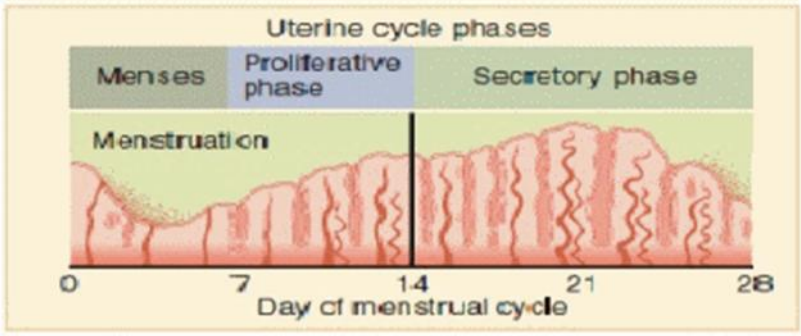
Menstrual cycle

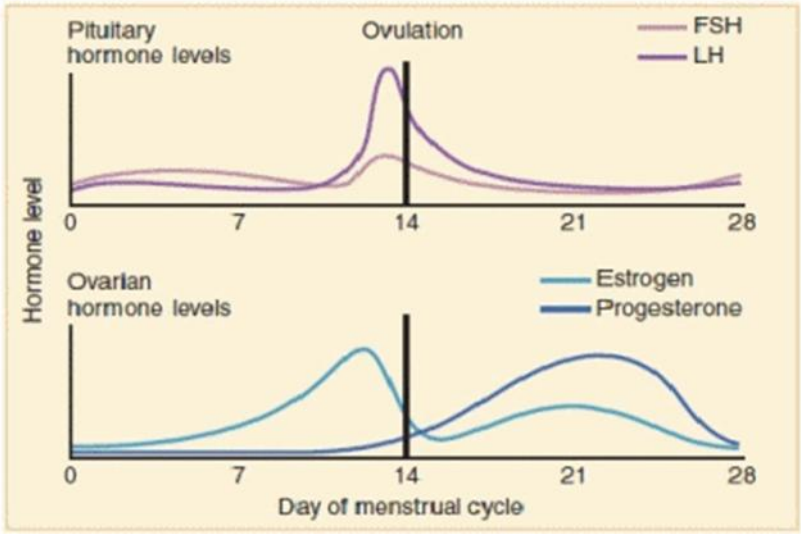
The menstrual cycle may be divided into the following phases:

	Days
Menstruation	1-4
Follicular phase (proliferative phase)	5-13
Ovulation	14
Luteal phase (secretory phase)	15-28


Follicular phase
Days 1–7
Primordial follicles
Primary follicles
Secondary follicles
Atresia
Selection
Single, selected tertiary follicle
Atresia
Constant development of early-stage follicles (2 months)
Selection of one dominant secondary follicle begins each new menstrual cycle


Ovarian cycle phases
Follicular phase
Luteal phase
Selected tertiary follicle
Ovulation
Corpus luteum
Corpus albicans
Degrading corpus
0
7
14
21
28
Day of menstrual cycle


Uterine cycle phases
Menses
Proliferative phase
Secretory phase
Menstruation
0
7
14
21
28
Day of menstrual cycle


Pituitary hormone levels
Ovulation
FSH
LH
Hormone level
0
7
14
21
28
Ovarian hormone levels
Estrogen
Progesterone
0
7
14
21
28
Day of menstrual cycle

Further details are given in the table below

	Follicular phase (proliferative phase)	Luteal phase (secretory phase)
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	Progesterone secreted by corpus luteum rises through the luteal phase. If fertilisation does not occur the corpus luteum will degenerate and progesterone levels fall Oestradiol levels also rise again during the luteal phase
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. It also becomes 'stretchy' - a quality termed spinnbarkeit	Under the influence of progesterone it becomes thick, scant, and tacky

	Follicular phase (proliferative phase)	Luteal phase (secretory phase)
Basal body temperature	Falls prior to ovulation due to the influence of oestradiol	Rises following ovulation in response to higher progesterone levels

Metabolic alkalosis

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

Causes

- vomiting / aspiration (e.g. peptic ulcer leading to pyloric stenos, nasogastric suction)
- diuretics
- liquorice, carbenoxolone
- hypokalaemia
- primary hyperaldosteronism
- Cushing's syndrome
- Bartter's syndrome
- congenital adrenal hyperplasia

Mechanism of metabolic alkalosis

- activation of renin-angiotensin II-aldosterone (RAA) system is a key factor
- aldosterone causes reabsorption of Na^+ in exchange for H+ in the distal convoluted tubule
- ECF depletion (vomiting, diuretics) → Na^+ and Cl- loss → activation of RAA system → raised aldosterone levels
- in hypokalaemia, K^+ shift from cells → ECF, alkalosis is caused by shift of H+ into cells to maintain neutrality

Methaemoglobinaemia

Methaemoglobinaemia describes haemoglobin which has been oxidised from Fe2+ to Fe3+. This is normally regulated by NADH methaemoglobin reductase, which transfers electrons from NADH to methaemoglobin resulting in the reduction of methaemoglobin to haemoglobin. There is tissue hypoxia as Fe3+ cannot bind oxygen, and hence the oxidation dissociation curve is moved to the left

Congenital causes

- haemoglobin chain variants: HbM, HbH
- NADH methaemoglobin reductase deficiency

Acquired causes

- drugs: sulphonamides, nitrates, dapsone, sodium nitroprusside, primaquine
- chemicals: aniline dyes

Features

- 'chocolate' cyanosis
- dyspnoea, anxiety, headache
- severe: acidosis, arrhythmias, seizures, coma
- normal pO2 but decreased oxygen saturation

Management

- NADH - methaemoglobinaemia reductase deficiency: ascorbic acid
- IV methylene blue if acquired

Mitochondrial diseases

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
- MELAS syndrome: mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes
- MERRF syndrome: myoclonus epilepsy with ragged-red fibres
- Kearns-Sayre syndrome: onset in patients < 20 years old, external ophthalmoplegia, retinitis pigmentosa. Ptosis may be seen
- sensorineural hearing loss

Molecular biology techniques

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

Molecular biology techniques

- SNOW (**S**outh - **NO**rth - **W**est)
- DROP (**D**NA - **R**NA - **P**rotein)

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

Monoclonal antibodies

Monoclonal antibodies have an increasing role in medicine. They are 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:

- infliximab (anti-TNF): used in rheumatoid arthritis and Crohn's
- rituximab (anti-CD20): used in non-Hodgkin's lymphoma and rheumatoid arthritis
- cetuximab (epidermal growth factor receptor antagonist): used in metastatic colorectal cancer and head and neck cancer
- trastuzumab (HER2/neu receptor antagonist): used in metastatic breast cancer
- alemtuzumab (anti-CD52): used in chronic lymphocytic leukaemia
- abciximab (glycoprotein IIb/IIIa receptor antagonist): prevention of ischaemic events in patients undergoing percutaneous coronary interventions
- OKT3 (anti-CD3): used to 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

Neurofibromatosis

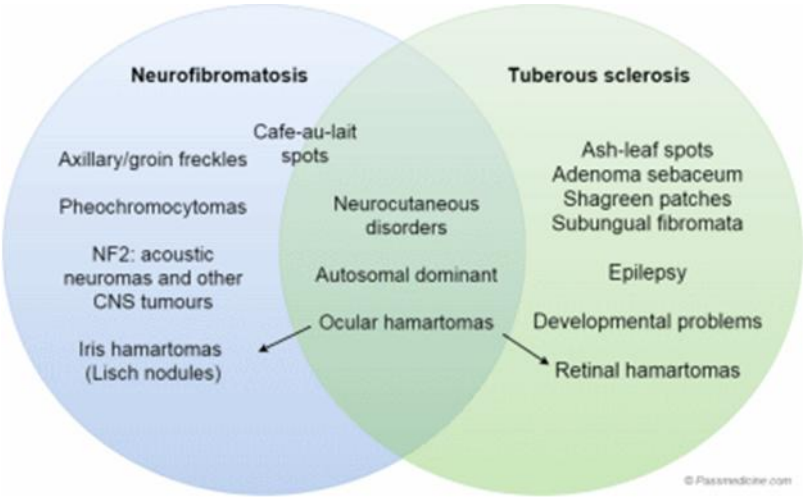
There are two types of neurofibromatosis, NF1 and NF2. Both are inherited in an autosomal dominant fashion

NF1 is also known as von Recklinghausen's syndrome. It is caused by a gene mutation on chromosome 17 which encodes neurofibromin and affects around 1 in 4,000

NF2 is caused by gene mutation on chromosome 22 and affects around 1 in 100,000

Features

NF1	NF2
Café-au-lait spots (>= 6, 15 mm in diameter) Axillary/groin freckles Peripheral neurofibromas Iris hamatomas (Lisch nodules) in > 90% Scoliosis Pheochromocytomas	Bilateral acoustic neuromas Multiple intracranial schwannomas, mengiomas and ependymomas



Comparison of neurofibromatosis and tuberous sclerosis. Note that whilst they are both autosomal dominant neurocutaneous disorders there is little overlap otherwise

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

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

Noonan's syndrome

Often thought of as the 'male Turner's', Noonan's syndrome is an autosomal dominant condition associated with a normal karyotype. It is thought to be caused by a defect in a gene on chromosome 12

As well as features similar to Turner's syndrome (webbed neck, widely-spaced nipples, short stature, pectus carinatum and excavatum), a number of characteristic clinical signs may also be seen:

- cardiac: pulmonary valve stenosis
- ptosis
- triangular-shaped face
- low-set ears
- coagulation problems: factor XI deficiency

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

Standard deviation

- the standard deviation (SD) is a measure of how much dispersion exists from the mean
- SD = square root (variance)

Numbers needed to treat and 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

It is calculated by 1/(Absolute risk reduction) and is rounded to the next highest whole number

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?

The absolute risk reduction (ARR) may be calculated by finding the absolute difference between the control event rate (CER) and the experimental event rate (EER). You will often find both versions of the above listed in different sources. In some ways in doesn't matter which you use as you will end up with the same answer but from a technical point of view:

- if the outcome of the study is undesirable then ARR = CER - EER
- if the outcome of the study is desirable then ARR* = EER - CER

*this may be more accurately termed absolute benefit increase, rather than absolute risk reduction

Obesity: physiology

Leptin

Leptin is thought to play a key role in the regulation of body weight. It is produced by adipose tissue and acts on satiety centres in the hypothalamus and decreases appetite. More adipose tissue (e.g. in obesity) results in high leptin levels.

Leptin stimulates the release of melanocyte-stimulating hormone (MSH) and corticotrophin-releasing hormone (CRH). Low levels of leptin stimulates the release of neuropeptide Y (NPY)

Ghrelin

Where as leptin induces satiety, ghrelin stimulates hunger. It is produced mainly by the P/D1 cells lining the fundus of the stomach and epsilon cells of the pancreas. Ghrelin levels increase before meals and decrease after meals

Odds and odds ratio

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

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

Osteomalacia

Basics

- normal bony tissue but decreased mineral content
- rickets if when growing
- osteomalacia if after epiphysis fusion

Types

- vitamin D deficiency e.g. malabsorption, lack of sunlight, diet
- renal failure
- drug induced e.g. anticonvulsants
- vitamin D resistant; inherited
- liver disease, e.g. cirrhosis

Features

- rickets: knock-knee, bow leg, features of hypocalcaemia
- osteomalacia: bone pain, fractures, muscle tenderness, proximal myopathy

Investigation

- low calcium, phosphate, 25(OH) vitamin D
- raised alkaline phosphatase
- x-ray: children - cupped, ragged metaphyseal surfaces; adults - translucent bands (Looser's zones or pseudofractures)

Treatment

- calcium with vitamin D tablets

Oxygen dissociation curve

The oxygen dissociation curve describes the relationship between the percentage of saturated haemoglobin and partial pressure of oxygen in the blood. It is not affected by haemoglobin concentration

Basics

- shifts to left = for given oxygen tension there is increased saturation of Hb with oxygen i.e. decreased oxygen delivery to tissues
- shifts to right = for given oxygen tension there is reduced saturation of Hb with oxygen i.e. enhanced oxygen delivery to tissues

Shifts to Left = Lower oxygen delivery	**Shifts to Right = Raised oxygen delivery**
HbF, methaemoglobin, carboxyhaemoglobin Low [H+] (alkali) Low pCO2 Low 2,3-DPG Low temperature	Raised [H+] (acidic) Raised pCO2 Raised 2,3-DPG* Raised temperature

The **L** rule

Shifts to **L** → **L**ower oxygen delivery, caused by

- **L**ow [H+] (alkali)
- **L**ow pCO2
- **L**ow 2,3-DPG
- **L**ow temperature

Another mnemonic is '**CADET**, face Right!' for **C**O2, **A**cid, 2,3-**D**PG, **E**xercise and **T**emperature

*2,3-diphosphoglycerate

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

PCR

Polymerase chain reaction (PCR) is a molecular genetic investigation technique. The main advantage of PCR is its sensitivity: only one strand of sample DNA is needed to detect a particular DNA sequence. It now has many uses including prenatal diagnosis, detection of mutated oncogenes and diagnosis of infections. PCR is also extensively used in forensics. 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

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

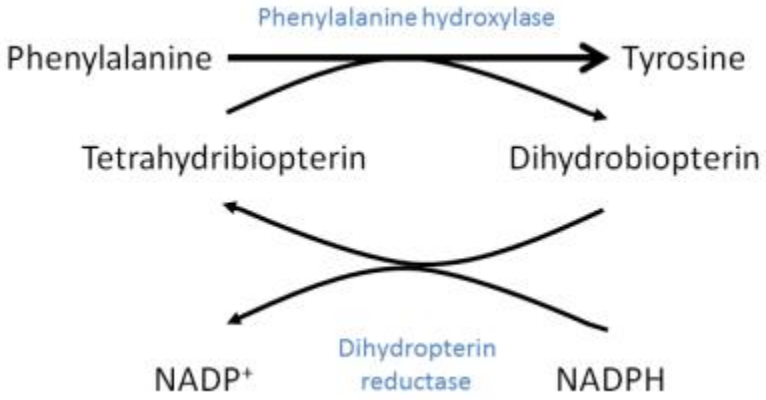
The above cycle is then repeated, with the amount of DNA doubling each time

Reverse transcriptase PCR

- 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

Phenylketonuria

Phenylketonuria (PKU) is an autosomal recessive condition caused by a disorder of phenylalanine metabolism. This is 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. High levels of phenylalanine lead to problems such as learning difficulties and seizures. The gene for phenylalanine hydroxylase is located on chromosome 12. The incidence of PKU is around 1 in 10,000 live births.



Features

- usually presents by 6 months e.g. with developmental delay
- child classically has fair hair and blue eyes
- learning difficulties
- seizures, typically infantile spasms
- eczema
- 'musty' odour to urine and sweat*

Diagnosis

- 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

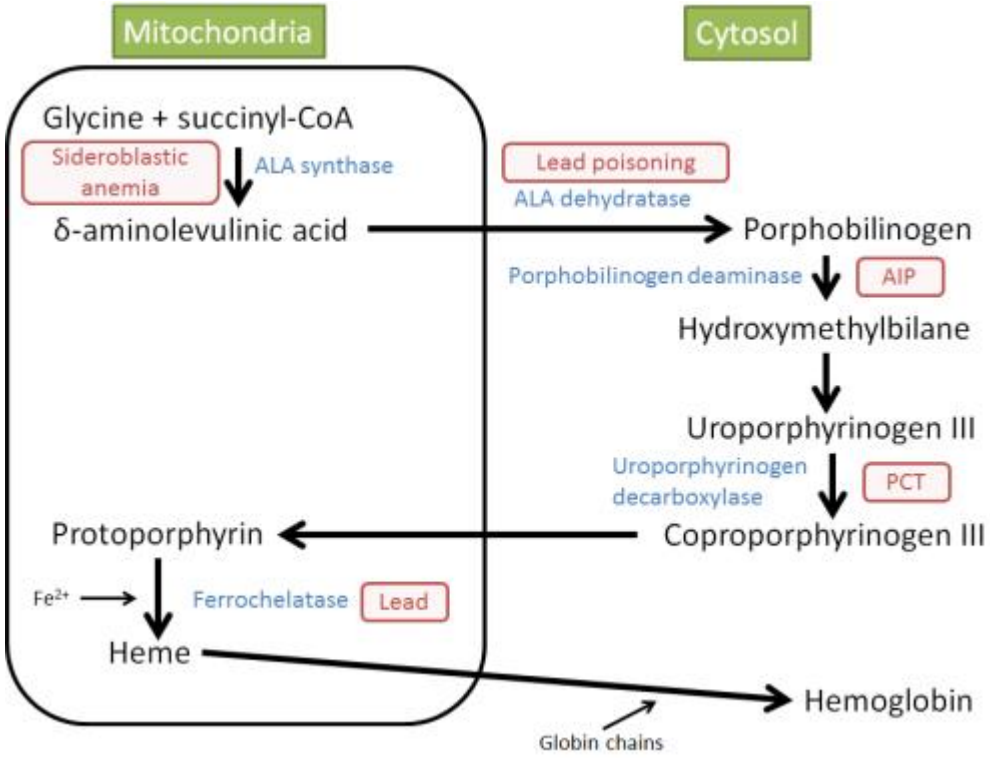
- poor evidence base to suggest strict diet prevents learning disabilities
- dietary restrictions are however important during pregnancy as genetically normal fetuses may be affected by high maternal phenylalanine levels

*secondary to phenylacetate, a phenylketone

Porphyrias

Overview

- abnormality in enzymes responsible for the biosynthesis of haem
- results in overproduction of intermediate compounds (porphyrins)
- may be acute or non-acute



Acute intermittent porphyria (AIP)

- autosomal dominant
- defect in porphobilinogen deaminase
- female and 20-40 year olds more likely to be affected
- typically present with abdominal symptoms, neuropsychiatric symptoms
- hypertension and tachycardia common
- urine turns deep red on standing

Porphyria cutanea tarda (PCT)

- most common hepatic porphyria
- defect in uroporphyrinogen decarboxylase
- may be caused by hepatocyte damage e.g. alcohol, oestrogens
- classically photosensitive rash with bullae, skin fragility on face and dorsal aspect of hands
- urine: elevated uroporphyrinogen and pink fluorescence of urine under Wood's lamp
- manage with chloroquine

Variegate porphyria

- autosomal dominant
- defect in protoporphyrinogen oxidase
- photosensitive blistering rash
- abdominal and neurological symptoms
- more common in South Africans

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

Prader-Willi syndrome

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

Features

- hypotonia during infancy
- dysmorphic features
- short stature
- hypogonadism and infertility
- learning difficulties
- childhood obesity
- behavioural problems in adolescence

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)

Pre-eclampsia

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

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
- delivery of the baby is the most important and definitive management step. The timing depends on the individual clinical scenario

Prediabetes and impaired glucose regulation

Prediabetes is a term which is increasingly used where there is impaired glucose levels which are above the normal range but not high enough for a diagnosis of diabetes mellitus. The term includes patients who have been labelled as having either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Diabetes UK estimate that around 1 in 7 adults in the UK have prediabetes. 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.

Terminology

- Diabetes UK currently recommend using the term prediabetes when talking to patients and impaired glucose regulation when talking to other healthcare professionals
- research has shown that the term 'prediabetes' has the most impact and is most easily understood

Identification of patients with prediabetes

- NICE recommend using a validated computer based risk assessment tool for all adults aged 40 and over, people of South Asian and Chinese descent aged 25-39, and adults with conditions that increase the risk of type 2 diabetes
- patients identified at high risk should have a blood sample taken
- a fasting plasma glucose of 6.1-6.9 mmol/l or an HbA1c level of 42-47 mmol/mol (6.0-6.4%) indicates high risk

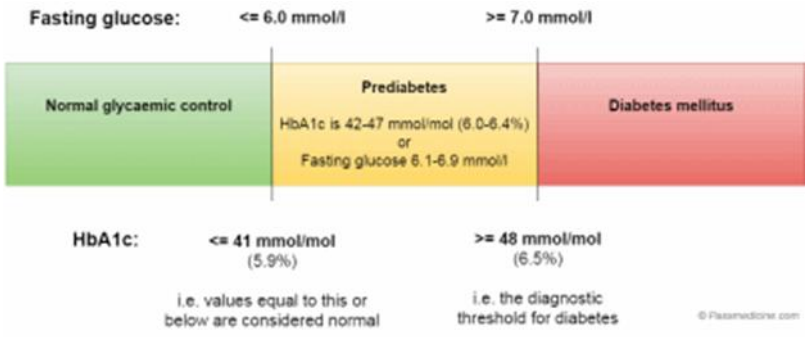


Diagram showing the spectrum of diabetes diagnosis

Management

- lifestyle modification: weight loss, increased exercise, change in diet
- 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'*

Impaired fasting glucose and impaired glucose tolerance

There are two main types of IGR:

- impaired fasting glucose (IFG) - due to hepatic insulin resistance
- impaired glucose tolerance (IGT) - due to muscle insulin resistance
- patients with IGT are more likely to develop T2DM and cardiovascular disease than patients with IFG

Definitions

- 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
- 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

Premature ovarian failure

Premature ovarian failure is defined as the onset of menopausal symptoms and elevated gonadotrophin levels before the age of 40 years. It occurs in around 1 in 100 women.

Causes

- idiopathic - the most common cause
- chemotherapy
- autoimmune
- radiation

Features are similar to those of the normal climacteric but the actual presenting problem may differ

- climacteric symptoms: hot flushes, night sweats
- infertility
- secondary amenorrhoea
- raised FSH, LH levels

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

Prolactin and galactorrhoea

Prolactin is secreted by the anterior pituitary gland with release being controlled by a wide variety of physiological factors. Dopamine acts as the primary prolactin releasing inhibitory factor and hence dopamine agonists such as bromocriptine may be used to control galactorrhoea. It is important to differentiate the causes of galactorrhoea (due to the actions of prolactin on breast tissue) from those of gynaecomastia

Features of excess prolactin

- men: impotence, loss of libido, galactorrhoea
- women: amenorrhoea, galactorrhoea

Causes of raised prolactin

- prolactinoma
- pregnancy
- oestrogens
- physiological: stress, exercise, sleep
- acromegaly: 1/3 of patients
- polycystic ovarian syndrome
- primary hypothyroidism (due to thyrotrophin releasing hormone (TRH) stimulating prolactin release)

Drug causes of raised prolactin

- metoclopramide, domperidone
- phenothiazines
- haloperidol
- very rare: SSRIs, opioids

Pseudohypoparathyroidism

Pseudohypoparathyroidism is caused by target cell insensitivity to parathyroid hormone (PTH) due to a mutation in a G-protein. In type I pseudohypoparathyroidism
there is a complete receptor defect whereas in type II the cell receptor is intact.
Pseudohypoparathyroidism is typically inherited in an autosomal dominant fashion*

Bloods

- PTH: high
- calcium: low
- phosphate: high

Features

- short fourth and fifth metacarpals
- short stature
- cognitive impairment
- obesity
- round face

Investigation

- infusion of PTH followed by measurement of urinary phosphate and cAMP measurement - this can help differentiate between type I (neither phosphate or cAMP levels rise) and II (cAMP rises but phosphate levels do not change)

*it was previously thought to be an X-linked dominant condition

Pseudoxanthoma elasticum

Pseudoxanthoma elasticum is an inherited condition (usually autosomal recessive*) characterised by an abnormality in elastic fibres

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

*there are reports of autosomal dominant inheritance in a minority of cases

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).

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.

Pulmonary surfactant

Surfactant is a mixture of phospholipids, carbohydrates and proteins released by type 2 pneumocytes. The main functioning component is dipalmitoyl phosphatidylcholine (DPPC) which reduces alveolar surface tension.

Basics

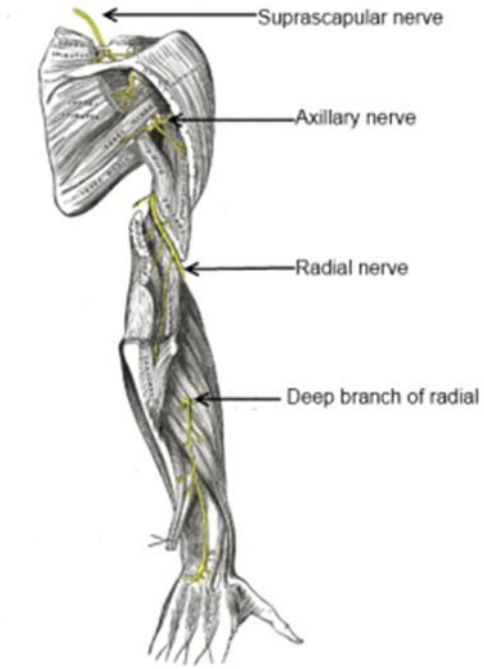
- first detectable around 28 weeks
- as alveoli decrease in size, surfactant concentration is increased, helping prevent the alveoli from collapsing
- reduces the muscular force needed to expand the lungs (i.e. decreases the work of breathing)
- lowers the elastic recoil at low lung volumes and thus helps to prevent the alveoli from collapsing at the end of each expiration

Radial nerve

Continuation of posterior cord of the brachial plexus (root values C5 to T1)

Path

- In the axilla: lies posterior to the axillary artery on subscapularis, latissimus dorsi and teres major.
- Enters the arm between the brachial artery and the long head of triceps (medial to humerus).
- Spirals around the posterior surface of the humerus in the groove for the radial nerve.
- At the distal third of the lateral border of the humerus it then pierces the intermuscular septum and descends in front of the lateral epicondyle.
- At the lateral epicondyle it lies deeply between brachialis and brachioradialis where it then divides into a superficial and deep terminal branch.
- Deep branch crosses the supinator to become the posterior interosseous nerve.



In the image above the relationships of the radial nerve can be appreciated

Regions innervated

Motor (main nerve)	⁾ Triceps ⁾ Anconeus ⁾ Brachioradialis ⁾ Extensor carpi radialis
Motor (posterior interosseous branch)	⁾ Supinator ⁾ Extensor carpi ulnaris ⁾ Extensor digitorum ⁾ Extensor indicis ⁾ Extensor digiti minimi ⁾ Extensor pollicis longus and brevis ⁾ Abductor pollicis longus
Sensory	The area of skin supplying the proximal phalanges on the dorsal aspect of the hand is supplied by the radial nerve (this does not apply to the little finger and part of the ring finger)

Muscular innervation and effect of denervation

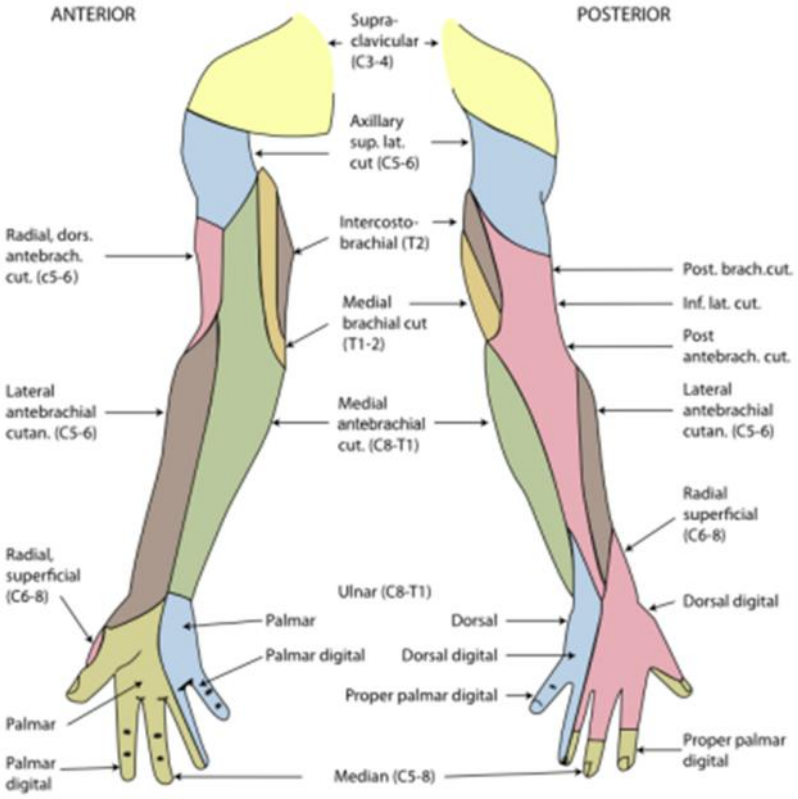
Anatomical location	**Muscle affected**	**Effect of paralysis**
Shoulder	Long head of triceps	Minor effects on shoulder stability in abduction
Arm	Triceps	Loss of elbow extension
Forearm	Supinator Brachioradialis Extensor carpi radialis longus and brevis	Weakening of supination of prone hand and elbow flexion in mid prone position

Patterns of damage

- ⁾ wrist drop
- ⁾ sensory loss to small area between the dorsal aspect of the 1st and 2nd metacarpals

Axillary damage

- as above
- paralysis of triceps



The cutaneous sensation of the upper limb- illustrating the contribution of the radial nerve

Ramsay Hunt syndrome

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

Relative risk

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). The term relative risk ratio is sometimes used instead of relative risk.

To recap

- 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).

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%

Renal anatomy

Each kidney is about 11cm long, 5cm wide and 3cm thick. They are located in a deep gutter alongside the projecting vertebral bodies, on the anterior surface of psoas major. In most cases the left kidney lies approximately 1.5cm higher than the right. The upper pole of both kidneys approximates with the 11th rib (beware pneumothorax during nephrectomy). On the left hand side the hilum is located at the L1 vertebral level and the right kidney at level L1-2. The lower border of the kidneys is usually alongside L3.

Relations

The tables below show the anatomical relations of the kidneys:

Relations	Right Kidney	Left Kidney
Posterior	Quadratus lumborum, diaphragm, psoas major, transversus abdominis	Quadratus lumborum, diaphragm, psoas major, transversus abdominis
Anterior	Hepatic flexure of colon	Stomach, Pancreatic tail
Superior	Liver, adrenal gland	Spleen, adrenal gland

If we consider relations according to whether they are in direct contact or whether there is peritoneum in-between:

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

Fascial covering

Each kidney and suprarenal gland is enclosed within a common layer of investing fascia, derived from the transversalis fascia. It is divided into anterior and posterior layers (Gerotas fascia).

Renal structure

Kidneys are surrounded by an outer cortex and an inner medulla which usually contains between 6 and 10 pyramidal structures. The papilla marks the innermost apex of these. They terminate at the renal pelvis, into the ureter.

Lying in a hollow within the kidney is the renal sinus. This contains:

- 1. Branches of the renal artery
- 2. Tributaries of the renal vein
- 3. Major and minor calyces's
- 4. Fat

Structures at the renal hilum

The renal vein lies most anteriorly, then renal artery (it is an end artery) and the ureter lies most posterior.

Renal transplant: HLA typing and graft failure

The human leucocyte antigen (HLA) system is the name given to the major histocompatibility complex (MHC) in humans. It is coded for on chromosome 6.

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

Graft survival

- 1 year = 90%, 10 years = 60% for cadaveric transplants
- 1 year = 95%, 10 years = 70% for living-donor transplants

Post-op problems

- ATN of graft
- vascular thrombosis
- urine leakage
- UTI

Hyperacute acute rejection (minutes to hours)

- due to pre-existent antibodies against donor HLA type 1 antigens (a type II hypersensitivity reaction)
- rarely seen due to HLA matching

Acute graft failure (< 6 months)

- usually due to mismatched HLA. Cell-mediated (cytotoxic T cells)
- other causes include cytomegalovirus infection
- may be reversible with steroids and immunosuppressants

Causes of chronic graft failure (> 6 months)

- both antibody and cell mediated mechanisms cause fibrosis to the transplanted kidney (chronic allograft nephropathy)
- recurrence of original renal disease (MCGN > IgA > FSGS)

Renin

Renin is secreted by juxtaglomerular cells and hydrolyses angiotensinogen to produce angiotensin I

Factors stimulating renin secretion

- hypotension causing reduced renal perfusion
- hyponatraemia
- sympathetic nerve stimulation
- catecholamines
- erect posture

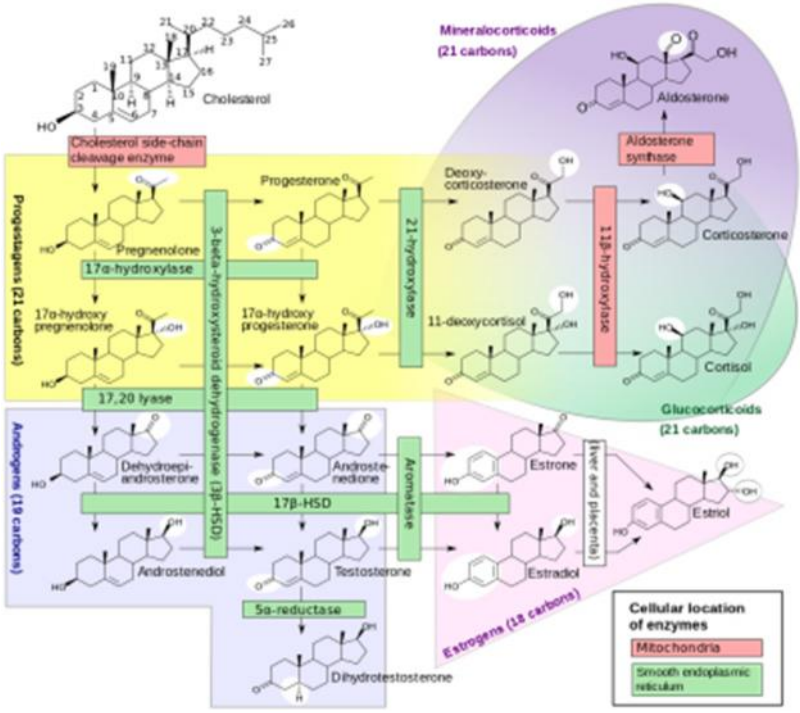
Factors reducing renin secretion

- drugs: beta-blockers, NSAIDs

Renin-angiotensin-aldosterone system

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)



Renin

- an enzyme that is **released by the renal juxtaglomerular cells in response to reduced renal perfusion**
- other factors that stimulate renin secretion include hyponatraemia, sympathetic nerve stimulation
- hydrolyses angiotensinogen to form angiotensin I

Angiotensin II

- angiotensin-converting enzyme (ACE) in the lungs converts angiotensin I → angiotensin II
- angiotensin II has a wide variety of actions:
- causes **vasoconstriction of vascular smooth muscle** leading to raised blood pressure and **vasoconstriction of efferent arteriole of the glomerulus** → increased filtration fraction (FF) to preserve GFR. Remember that FF = GFR / renal plasma flow
- **stimulates thirst** (via the hypothalamus)
- **stimulates aldosterone and ADH** release
- **increases proximal tubule Na^+/H^+** activity

Aldosterone

- released by the zona glomerulosa in response to raised **angiotensin II, potassium, and ACTH levels**
- **causes retention of Na^+** in exchange for K^+/H^+ in distal tubule

Respiratory physiology

Chloride shift

- CO_2 diffuses into RBCs
- $CO_2 + H_2O$ ---- carbonic anhydrase -⟶ $HCO_3^- + H^+$
- H^+ combines with Hb
- HCO_3^- diffuses out of cell,- Cl^- replaces it

Bohr effect

- increasing acidity (or pCO_2) means O_2 binds less well to Hb

Haldane effect

- increase pO_2 means CO_2 binds less well to Hb

Respiratory physiology: control

Control of respiration

- central regulatory centres
- central and peripheral chemoreceptors
- pulmonary receptors

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 pCO_2 & $[H^+]$, lesser extent low pO_2

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

Respiratory physiology: hypoxia

A fall in the partial pressure of oxygen in the blood leads to vasoconstriction of the pulmonary arteries. This allows blood to be diverted to better aerated areas of the lung and improves the efficiency of gaseous exchange

Respiratory physiology: lung compliance

Lung compliance is defined as change in lung volume per unit change in airway pressure

Causes of increased compliance

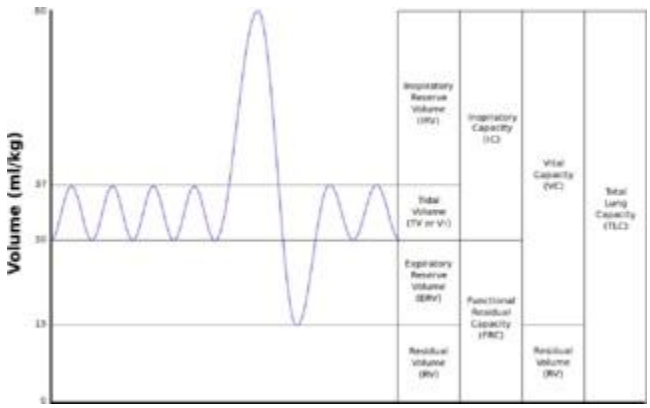
- age
- emphysema - this is due to loss alveolar walls and associated elastic tissue

Causes of decreased compliance

- pulmonary oedema
- pulmonary fibrosis
- pneumonectomy
- kyphosis

Respiratory physiology: lung volumes

The diagram below demonstrates the lung volumes which may be measured:



Tidal volume (TV)

- volume inspired or expired with each breath at rest
- 500ml in males, 350ml in females

Inspiratory reserve volume (IRV) = 2-3 L

- maximum volume of air that can be inspired at the end of a normal tidal inspiration
- inspiratory capacity = TV + IRV

Expiratory reserve volume (ERV) = 750ml

- maximum volume of air that can be expired at the end of a normal tidal expiration

Residual volume (RV) = 1.2L

- volume of air remaining after maximal expiration
- increases with age
- RV = FRC - ERV

Vital capacity (VC) = 5L

- maximum volume of air that can be expired after a maximal inspiration
- 4,500ml in males, 3,500 mls in females
- decreases with age
- VC = inspiratory capacity + ERV

Total lung capacity (TLC) is the sum of the vital capacity + residual volume

Physiological dead space (V_D)

- V_D = tidal volume * ($PaCO_2$ - $PeCO_2$) / $PaCO_2$
- where $PeCO_2$ = expired air CO_2

Screening test statistics

Patients and doctors need to know if a disease or condition is present or absent. Tests can be used to help us decide. Tests generally guide us by indicating how likely it is that the patient has the condition.

In order to interpret test results we need to have a working knowledge of the statistics used to describe them.

Contingency tables (also known as 2 * 2 tables, see below) are used to illustrate and calculate test statistics such as sensitivity. It would be unusual for a medical exam not to feature a question based around screening test statistics. Commit the following table to memory and spend time practicing using it as you will be expected to make calculations using it in your exam.

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

Measure	Formula	Plain english
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

Positive and negative predictive values are prevalence dependent. Likelihood ratios are not prevalence dependent.

Precision

The precision quantifies a tests ability to produce the same measurements with repeated tests.

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

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, IGF, PDGF
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

SIADH: causes

The syndrome of inappropriate ADH secretion (SIADH) is characterised by hyponatraemia secondary to the dilutional effects of excessive water retention.

Causes of SIADH

Category	Examples
Malignancy	• **small cell lung cancer** • also: pancreas, prostate
Neurological	• stroke • subarachnoid haemorrhage • subdural haemorrhage • meningitis/encephalitis/abscess
Infections	• tuberculosis • pneumonia
Drugs	• sulfonylureas* • SSRIs, tricyclics • carbamazepine • vincristine • cyclophosphamide
Other causes	• positive end-expiratory pressure (PEEP) • porphyrias

Management

- correction must be done slowly to avoid precipitating central pontine myelinolysis
- fluid restriction
- demeclocycline: reduces the responsiveness of the collecting tubule cells to ADH
- ADH (vasopressin) receptor antagonists have been developed

*the BNF states this has been reported with glimepiride and glipizide.

Significance tests

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.

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

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).

Two types of errors may occur when testing the null hypothesis

- type I: the null hypothesis is rejected when it is true - 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.
- type II: the null hypothesis is accepted when it is false - 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

	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)

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

Significance tests: types

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

Skewed distributions

Normal (Gaussian) distributions: mean = median = mode

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 '<'

SLE: features

Systemic lupus erythematosus (SLE) is a multisystem, autoimmune disorder. It typically presents in early adulthood and is more common in women and people of Afro-Caribbean origin.

General features

- fatigue
- fever
- mouth ulcers
- lymphadenopathy

Skin

- 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
- non-erosive arthritis

Cardiovascular

- myocarditis

Respiratory

- pleurisy
- fibrosing alveolitis

Renal

- proteinuria
- glomerulonephritis (diffuse proliferative glomerulonephritis is the most common type)

Neuropsychiatric

- anxiety and depression
- psychosis
- seizures

Splenomegaly

Massive splenomegaly

- myelofibrosis
- chronic myeloid leukaemia
- visceral leishmaniasis (kala-azar)
- malaria
- Gaucher's syndrome

Other causes (as above plus)

- portal hypertension e.g. secondary to cirrhosis
- lymphoproliferative disease e.g. CLL, Hodgkin's
- haemolytic anaemia
- infection: hepatitis, glandular fever
- infective endocarditis
- sickle-cell*, thalassaemia
- rheumatoid arthritis (Felty's syndrome)

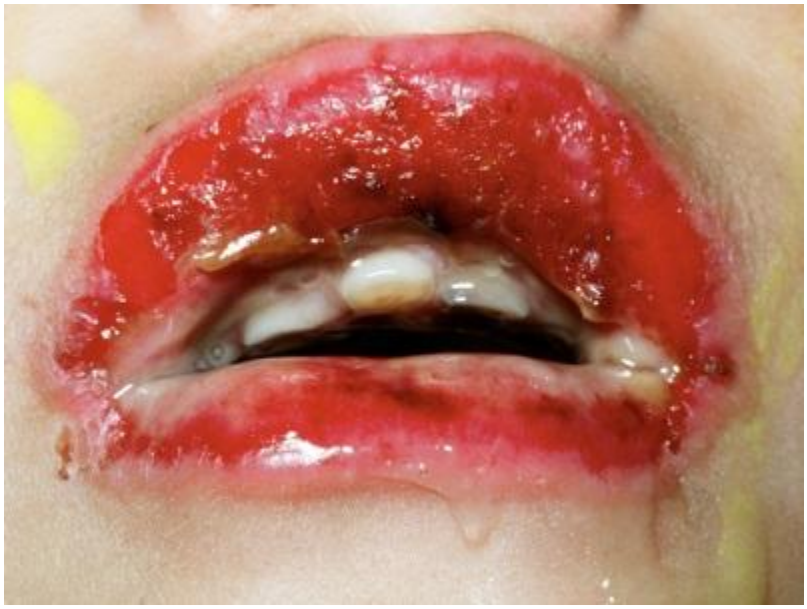
*the majority of adults patients with sickle-cell will have an atrophied spleen due to repeated infarction

Stevens-Johnson syndrome

Stevens-Johnson syndrome severe form of erythema multiforme associated with mucosal involvement and systemic symptoms

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, lamotrigine, carbamazepine, allopurinol, NSAIDs, oral contraceptive pill
- connective tissue disease e.g. SLE
- sarcoidosis
- malignancy

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

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

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.

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

Thiazide diuretics

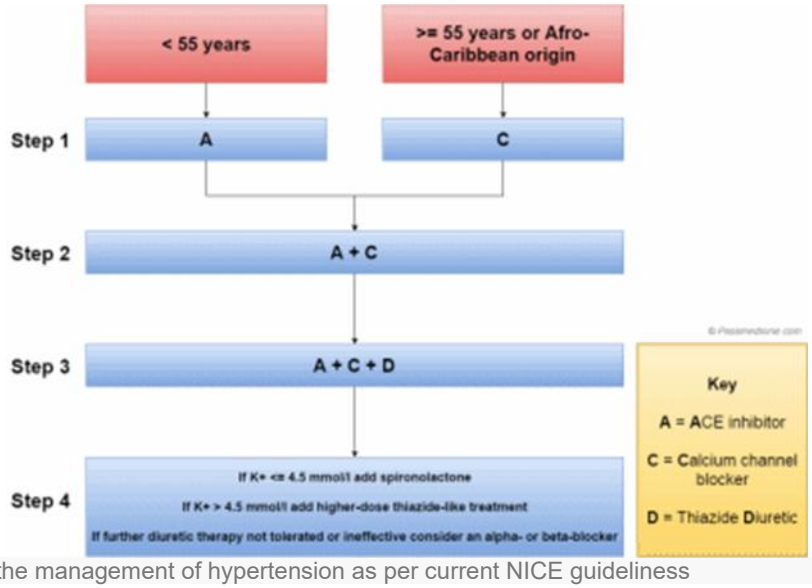
Thiazide diuretics work by inhibiting sodium absorption at the beginning of the distal convoluted tubule (DCT). Potassium is lost as a result of more sodium reaching the collecting ducts. Thiazide diuretics have a role in the treatment of mild heart failure although loop diuretics are better for reducing 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.

Common adverse effects

- dehydration
- postural hypotension
- hyponatraemia, hypokalaemia, hypercalcaemia
- gout
- impaired glucose tolerance
- impotence

Rare adverse effects

- thrombocytopaenia
- agranulocytosis
- photosensitivity rash
- pancreatitis



Flow chart showing the management of hypertension as per current NICE guideliness

Trimethoprim

Trimethoprim is an antibiotic, mainly used in the management of urinary tract infections.

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

Trinucleotide repeat disorders

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)
- spinocerebellar ataxia
- spinobulbar muscular atrophy
- dentatorubral pallidoluysian atrophy

*Friedreich's ataxia is unusual in not demonstrating anticipation

Tumour suppressor genes

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

Tumour suppressor genes - loss of function results in an increased risk of cancer

Oncogenes - gain of function results in an increased risk of cancer

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
- bicuspid aortic valve (15%), coarctation of the aorta (5-10%)
- primary amenorrhoea
- cystic hygroma (often diagnosed prenatally)
- high-arched palate
- short fourth metacarpal
- multiple pigmented naevi
- lymphoedema in neonates (especially feet)

There is also an increased incidence of autoimmune disease (especially autoimmune thyroiditis) and Crohn's disease

Ulnar nerve

Overview

- arises from medial cord of brachial plexus (C8, T1)

Motor to

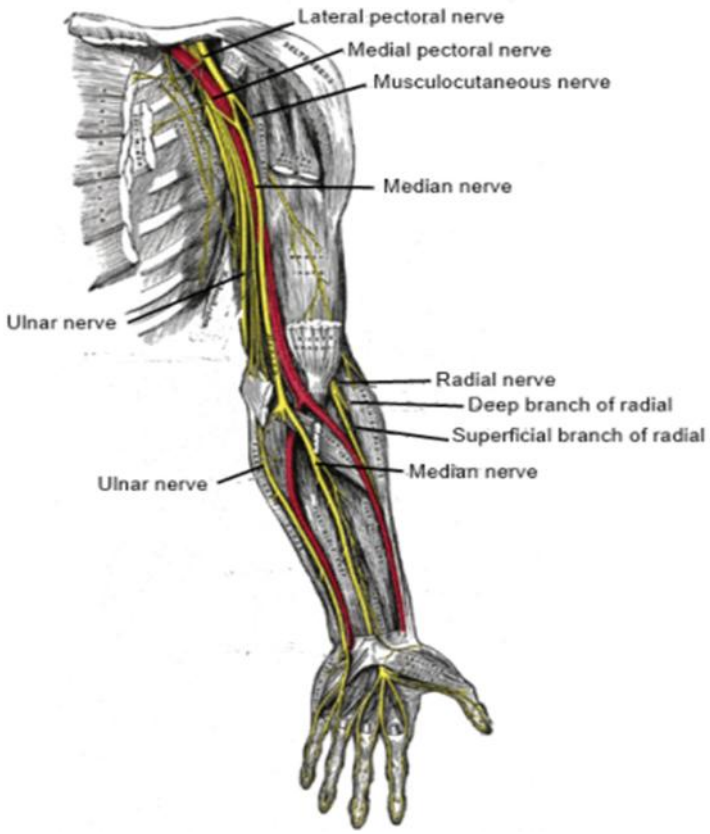
- medial two lumbricals
- aDductor pollicis
- interossei
- hypothenar muscles: abductor digiti minimi, flexor digiti minimi
- flexor carpi ulnaris

Sensory to

- medial 1 1/2 fingers (palmar and dorsal aspects)

Path<

- posteromedial aspect of upper arm to flexor compartment of forearm, then along the ulnar. Passes beneath the flexor carpi ulnaris muscle, then superficially through the flexor retinaculum into the palm of the hand.



Branches

Branch	Supplies
Muscular branch	Flexor carpi ulnaris Medial half of the flexor digitorum profundus
Palmar cutaneous branch (Arises near the middle of the forearm)	Skin on the medial part of the palm
Dorsal cutaneous branch	Dorsal surface of the medial part of the hand
Superficial branch	Cutaneous fibres to the anterior surfaces of the medial one and one-half digits
Deep branch	Hypothenar muscles All the interosseous muscles Third and fourth lumbricals Adductor pollicis Medial head of the flexor pollicis brevis

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

- as above (however, ulnar paradox - clawing is more severe in distal lesions)
- radial deviation of wrist

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 3½ fingers	Wrist lesion → carpal tunnel syndrome

Nerve	Motor	Sensory	Typical mechanism of injury & notes
Ulnar nerve (C8, T1)	Intrinsic hand muscles except LOAF* Wrist flexion	Medial 1½ 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

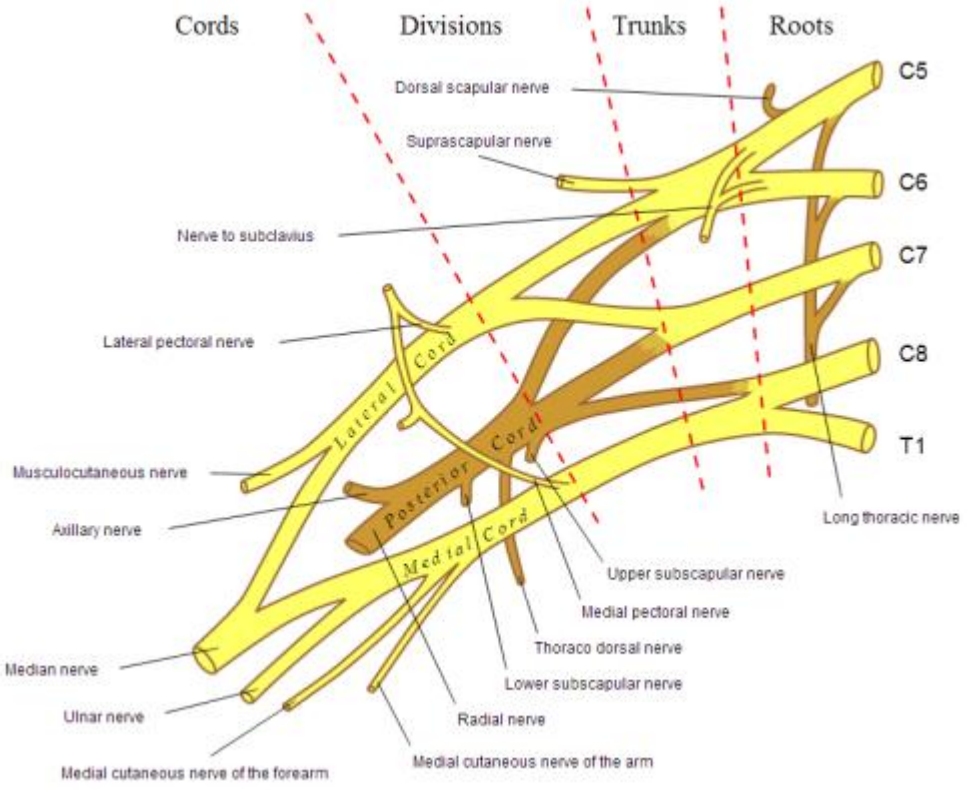


Diagram of the brachial plexus

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

Klumpke injury

- due to damage of the lower trunk of the brachial plexus (C8, T1)
- as above, may be secondary to shoulder dystocia during birth. Also may be caused by a sudden upward jerk of the hand
- associated with Horner's syndrome

*LOAF muscles

- Lateral two lumbricals
- Opponens pollis
- Abductor pollis brevis
- Flexor pollis brevis

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

Vitamin C (ascorbic acid)

Vitamin C is a water soluble vitamin.

Functions

- antioxidant
- collagen synthesis: acts as a cofactor for enzymes that are required for the hydroxylation proline and lysine in the synthesis of collagen
- facilitates iron absorption
- cofactor for norepinephrine synthesis

Vitamin C deficiency (scurvy) leads to defective synthesis of collagen resulting in capillary fragility (bleeding tendency) and poor wound healing

Features vitamin C deficiency

- gingivitis, loose teeth
- poor wound healing
- bleeding from gums, haematuria, epistaxis
- general malaise

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
- increases renal tubular reabsorption and gut absorption of calcium
- increases osteoclastic activity
- increases renal phosphate reabsorption

Consequences of vitamin D deficiency:

- rickets: seen in children
- osteomalacia: seen in adults

Vitamin D-resistant rickets

Vitamin D-resistant rickets is a X-linked dominant condition which 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

Vitamin deficiency

The table below summarises vitamin deficiency states

Vitamin	Chemical name	Deficiency state
A	Retinoids	Night-blindness (nyctalopia)
B1	Thiamine	Beriberi • polyneuropathy, Wernicke-Korsakoff syndrome • heart failure
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
D	Ergocalciferol, cholecalciferol	Rickets, osteomalacia

Vitamin	Chemical name	Deficiency state
E	Tocopherol, tocotrienol	Mild haemolytic anaemia in newborn infants, ataxia, peripheral neuropathy
K	Naphthoquinone	Haemorrhagic disease of the newborn, bleeding diathesis

Wiskott-Aldrich syndrome

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.

Features

- recurrent bacterial infections (e.g. Chest)
- eczema
- thrombocytopaenia
- low IgM levels

X-linked dominant

The following conditions are inherited in a X-linked dominant fashion*:

Alport's syndrome (in around 85% of cases - 10-15% of cases are inherited in an autosomal recessive fashion with rare autosomal dominant variants existing)
Rett syndrome
Vitamin D resistant rickets

*pseudohypoparathyroidism was previously classified as an X-linked dominant condition but has now been shown to be inherited in an autosomal dominant fashion in the majority of cases

X-linked recessive

In X-linked recessive inheritance 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. 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.

Each male child of a heterozygous female carrier has a 50% chance of being affected whilst each female child of a heterozygous female carrier has a 50% chance of being a 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.

X-linked recessive conditions

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

The following diseases have varying patterns of inheritance, with the majority being in an X-linked recessive fashion:

Chronic granulomatous disease (in > 70%)

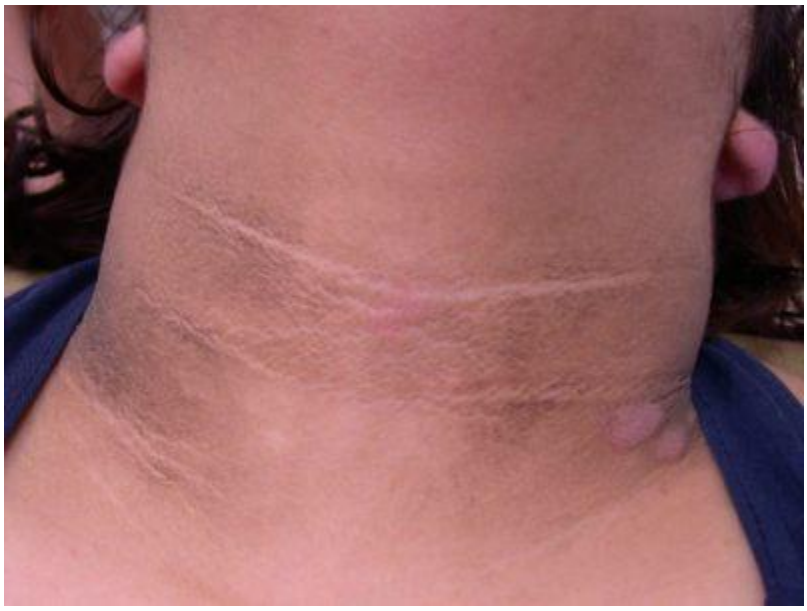
Dermatology

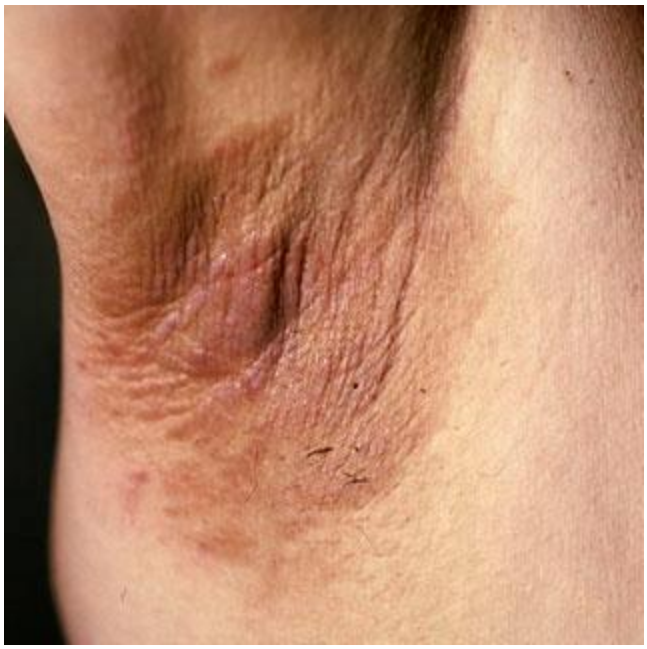
Acanthosis nigricans

Describes symmetrical, brown, velvety plaques that are often found on the neck, axilla and groin

Causes

- gastrointestinal cancer
- diabetes mellitus
- obesity
- polycystic ovarian syndrome
- acromegaly
- Cushing's disease
- hypothyroidism
- familial
- Prader-Willi syndrome
- drugs: oral contraceptive pill, nicotinic acid





Acne rosacea

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

- 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

Acne vulgaris

Acne vulgaris is a common skin disorder which usually occurs in adolescence. It typically affects the face, neck and upper trunk and is 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 resulting in the formation of a keratin plug. This in turn causes obstruction of the pilosebaceous follicle. Activity of sebaceous glands may be controlled by androgen, although levels are often normal in patients with acne
- colonisation by the anaerobic bacterium Propionibacterium acnes
- inflammation

Acne vulgaris: management

Acne vulgaris is a common skin disorder which usually occurs in adolescence. It typically affects the face, neck and upper trunk and is characterised by the obstruction of the pilosebaceous follicles with keratin plugs which results in comedones, inflammation and pustules.

Acne may be classified into mild, moderate or severe:

- mild: 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

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 isotretinoin: only under specialist supervision

There is no role for dietary modification in patients with acne

Actinic keratoses

Actinic, or solar, keratoses (AK) is a common premalignant skin lesion that develops as a consequence of chronic sun exposure

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 options include

- 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

Allergy tests

Skin prick test	**Most commonly used test as easy to perform and inexpensive. 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**
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

Alopecia

Alopecia may be 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*

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

*scarring may develop in untreated tinea capitis if a kerion develops

Alopecia areata

Alopecia areata is a presumed autoimmune condition causing localised, well demarcated patches of hair loss. At the edge of the hair loss, there may be small, broken 'exclamation mark' hairs

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
- topical minoxidil
- phototherapy
- dithranol
- contact immunotherapy
- wigs

Basal cell carcinoma

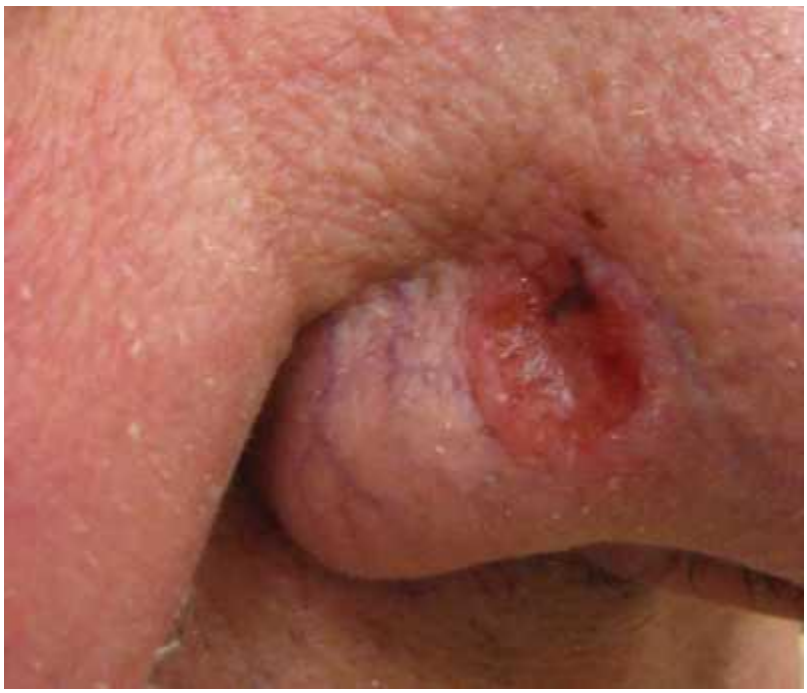
Basal cell carcinoma (BCC) is one of the three main types of skin cancer. Lesions are also known as rodent ulcers and are characterised by slow-growth and local invasion. Metastases are extremely rare. BCC is the most common type of cancer in the Western world.

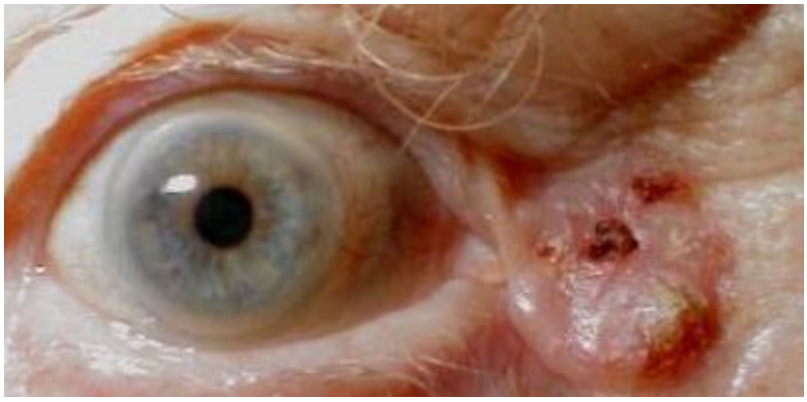
Features

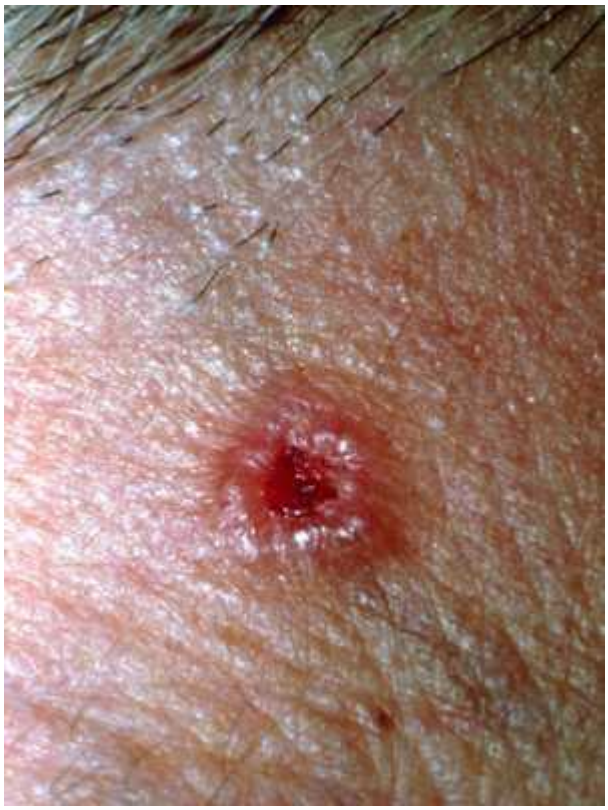
- many types of BCC are described. The most common type is nodular BCC, which is described here
- sun-exposed sites, especially the head and neck account for the majority of lesions
- initially a pearly, flesh-coloured papule with telangiectasia
- may later ulcerate leaving a central 'crater'

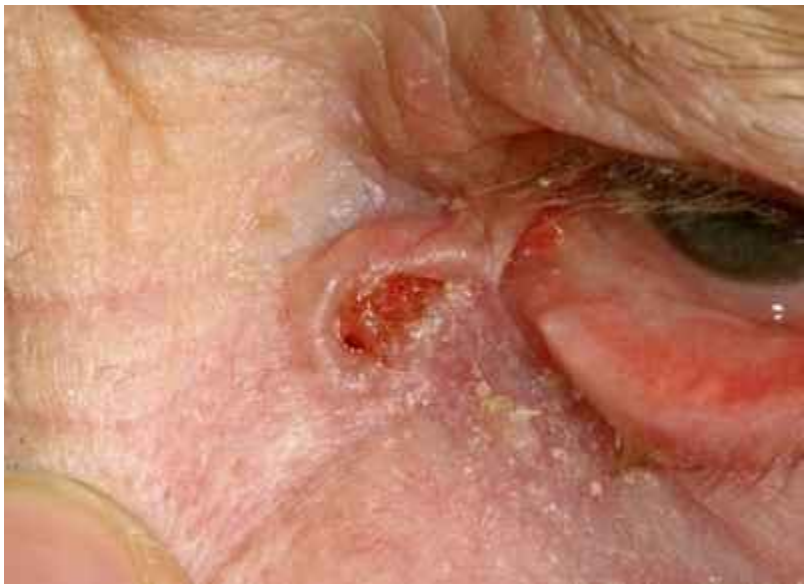
Management options:

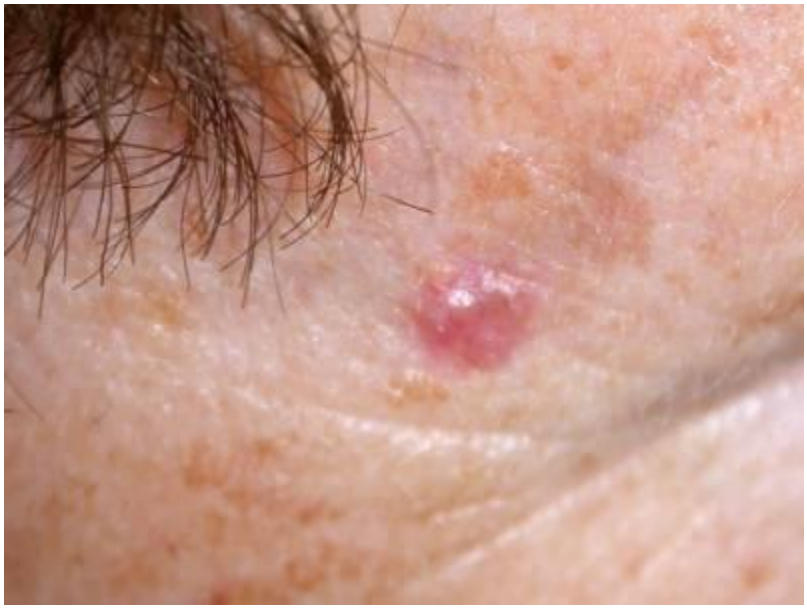
- surgical removal
- curettage
- cryotherapy
- topical cream: imiquimod, fluorouracil
- radiotherapy











Bullous pemphigoid

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

Bullous pemphigoid is more common in elderly patients. Features include

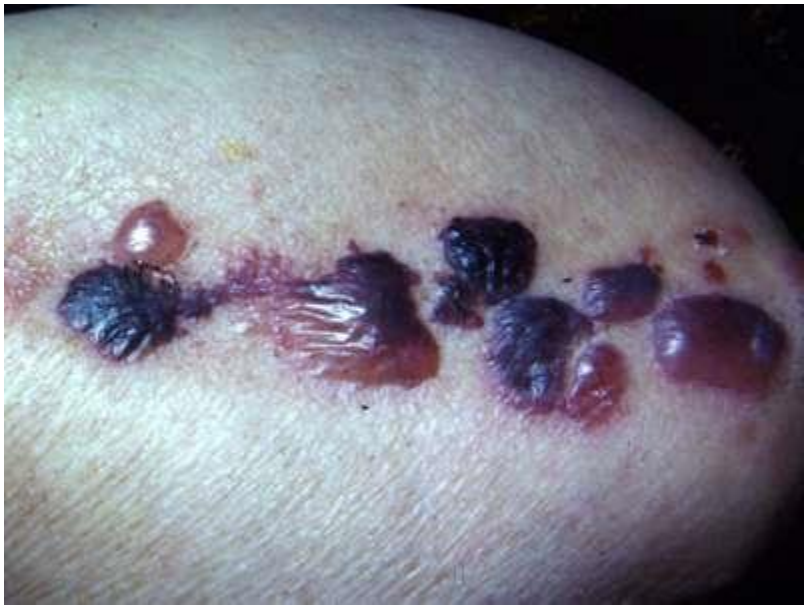
- itchy, tense blisters typically around flexures
- the blisters usually heal without scarring
- mouth is usually spared*

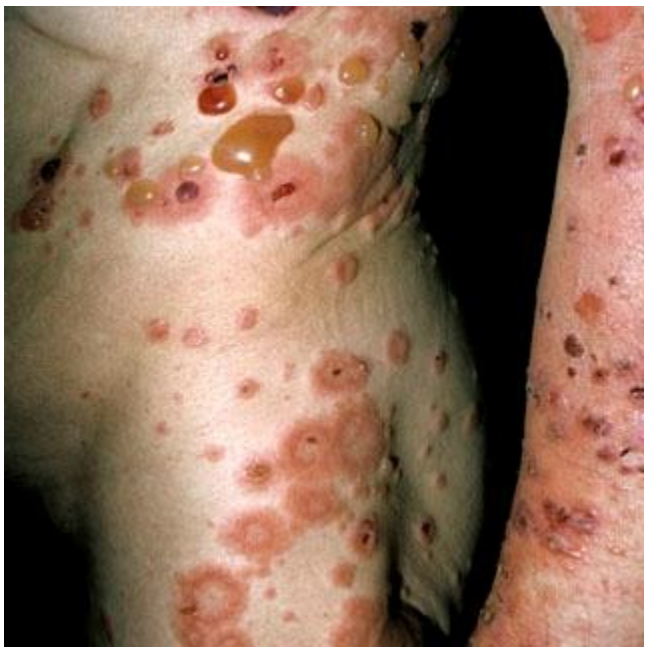
Skin biopsy

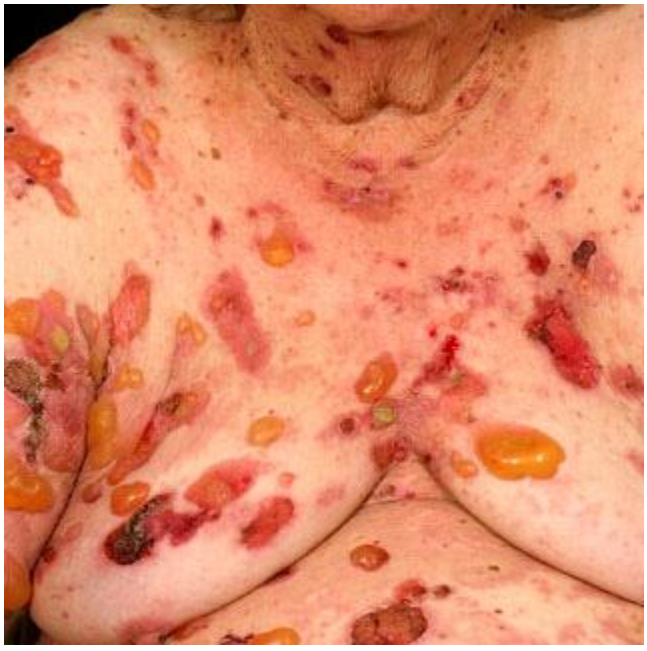
- immunofluorescence shows IgG and C3 at the dermoepidermal junction

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







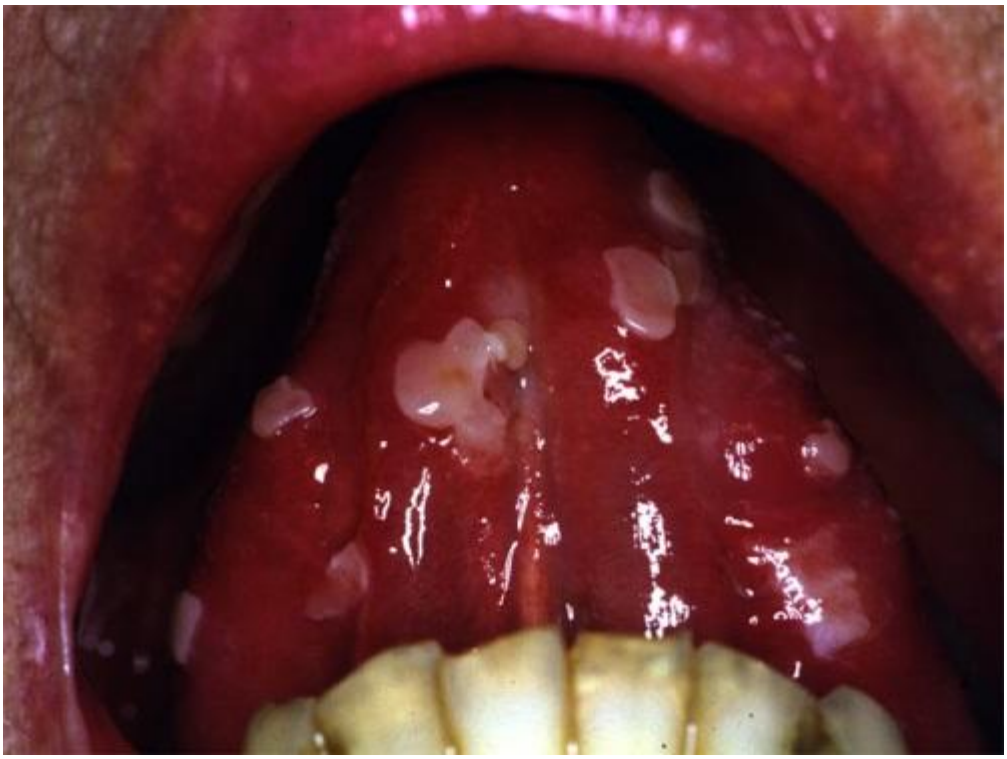
*in reality around 10-50% of patients have a degree of mucosal involvement. It would however be unusual for an exam question to mention mucosal involvement as it is seen as a classic differentiating feature between pemphigoid and pemphigus.

Pemphigus vulgaris

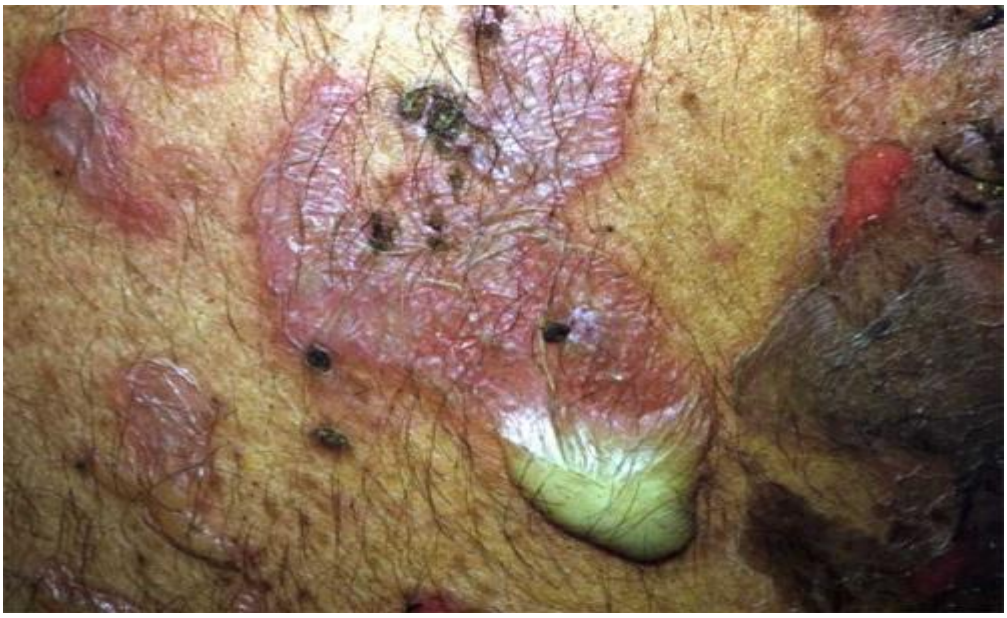
Pemphigus vulgaris is an autoimmune disease caused by antibodies directed against desmoglein 3, a cadherin-type epithelial cell adhesion molecule. It is more common in the Ashkenazi Jewish population

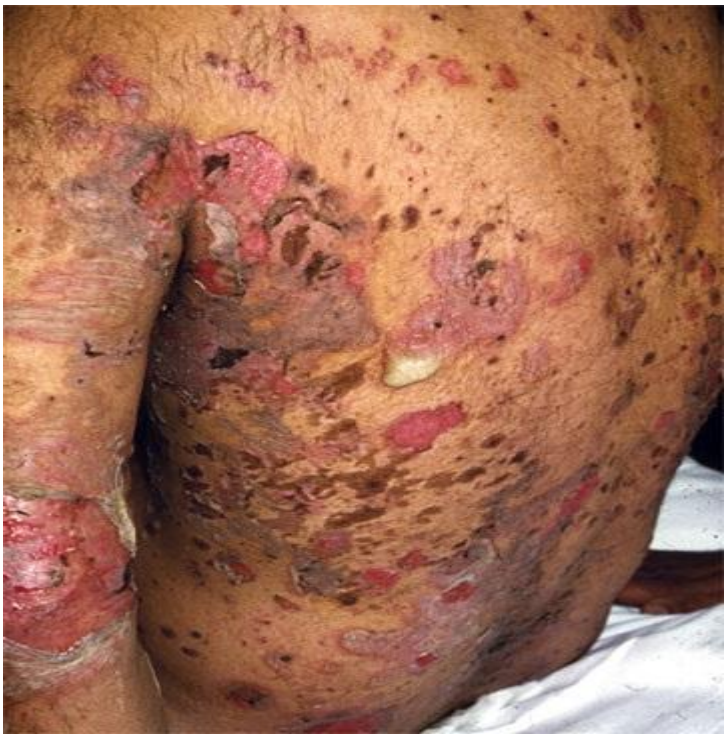
Features

- 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. 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
- acantholysis on biopsy



Mucosal ulceration is common with pemphigus





Management

- steroids
- immunosuppressants

Contact dermatitis

There are two main types of contact dermatitis

- 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
- 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

Dermatitis herpetiformis

Dermatitis herpetiformis is an autoimmune blistering skin disorder associated with coeliac disease. It is caused by deposition of IgA in the dermis.

Features

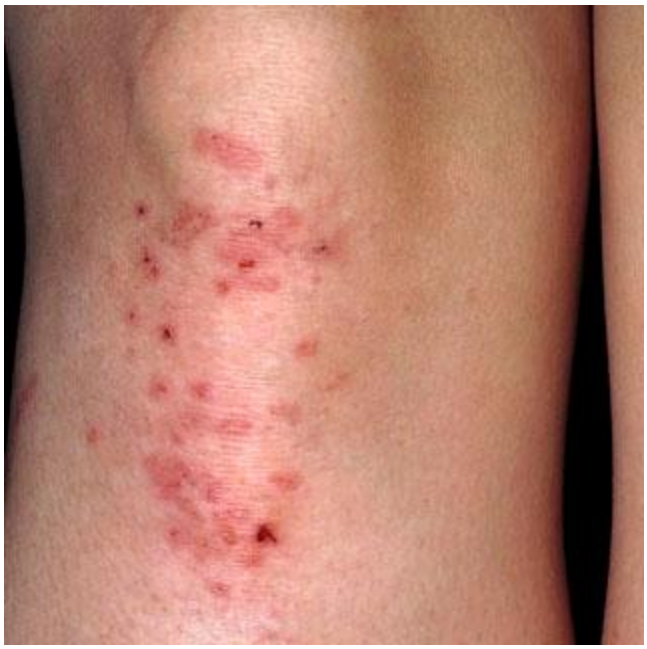
- itchy, vesicular skin lesions on the extensor surfaces (e.g. elbows, knees, buttocks)

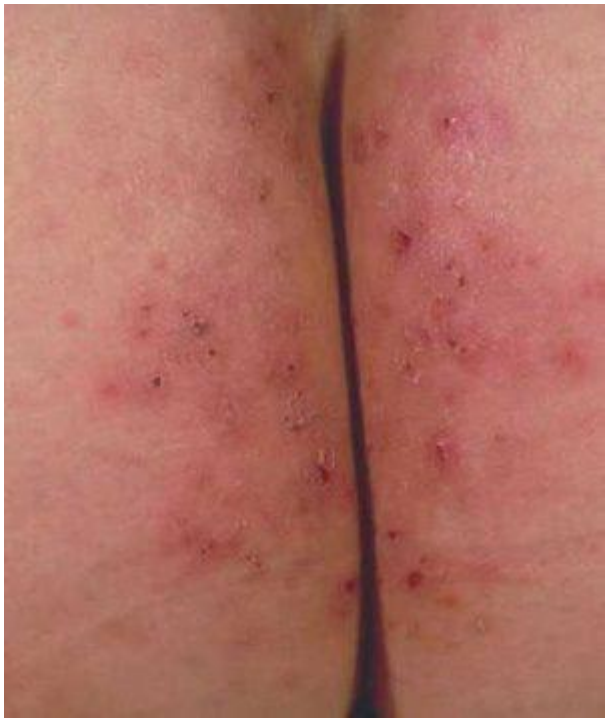
Diagnosis

- skin biopsy: direct immunofluorescence shows deposition of IgA in a granular pattern in the upper dermis

Management

- gluten-free diet
- dapsone





Eczema herpeticum

Eczema herpeticum describes a severe primary infection of the skin by herpes simplex virus 1 or 2. It is more commonly seen in children with atopic eczema. As it is potentially life threatening children should be admitted for IV aciclovir

Eczema: topical steroids

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) Clobetasone butyrate 0.05% (Eumovate)	Fluticasone propionate 0.05% (Cutivate) Betamethasone valerate 0.1% (Betnovate)	Clobetasol 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

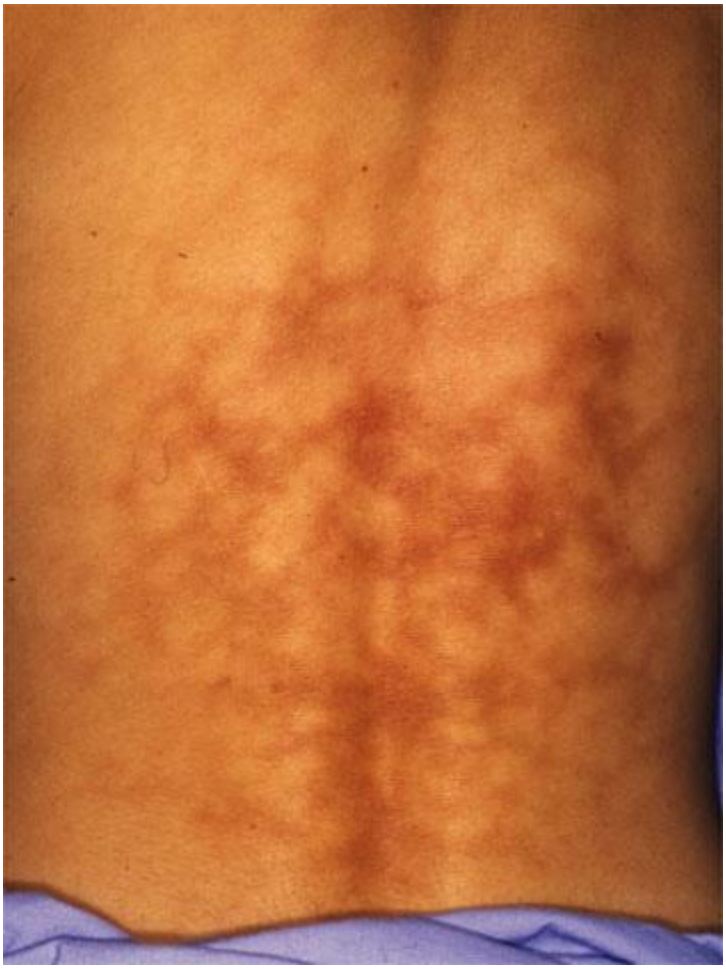
The BNF makes recommendation on the quantity of topical steroids that should be prescribed for an adult for a single daily application for 2 weeks:

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

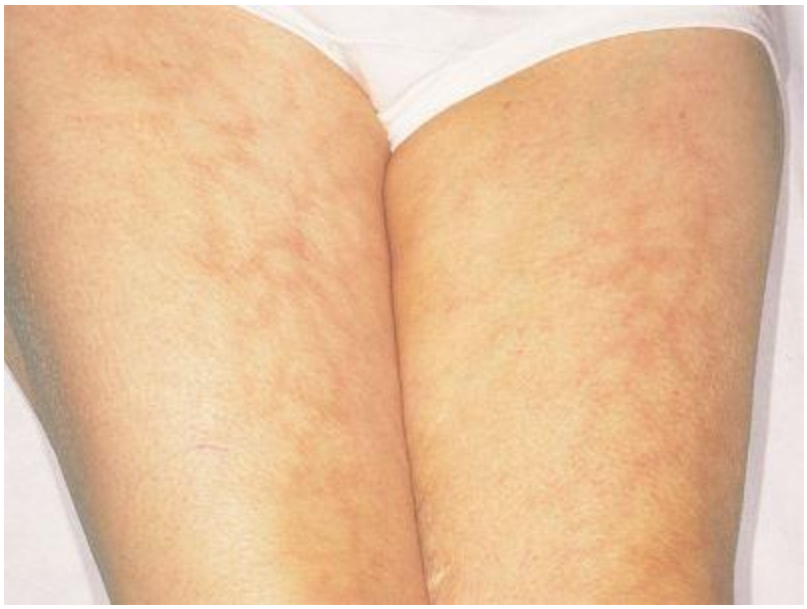
Erythema ab igne

Erythema ab igne is a skin disorder caused by over exposure to infrared radiation. 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.

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

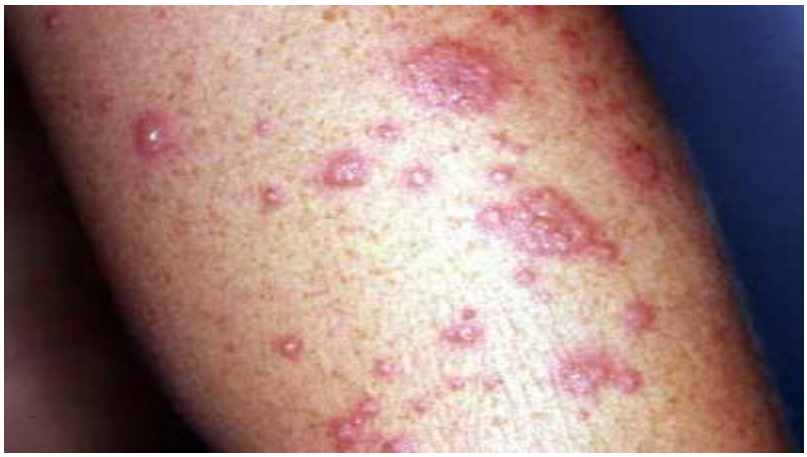
Features

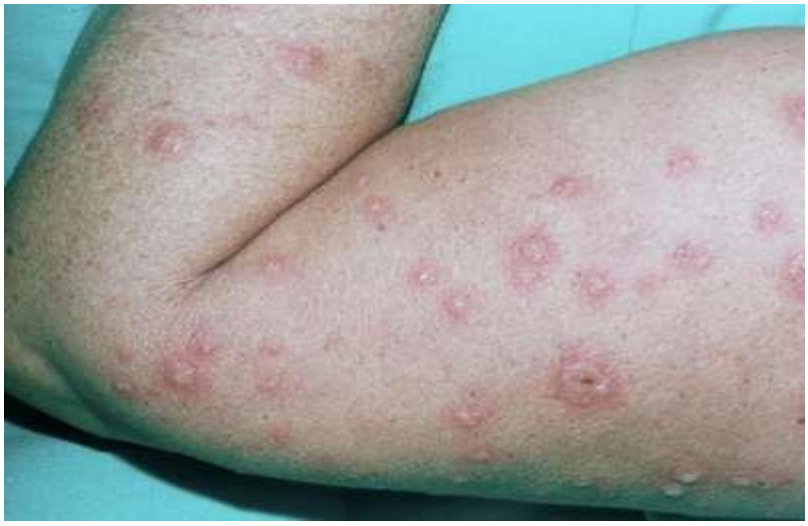
- target lesions
- initially seen on the back of the hands / feet before spreading to the torso
- upper limbs are more commonly affected than the lower limbs
- pruritus is occasionally seen and is usually mild

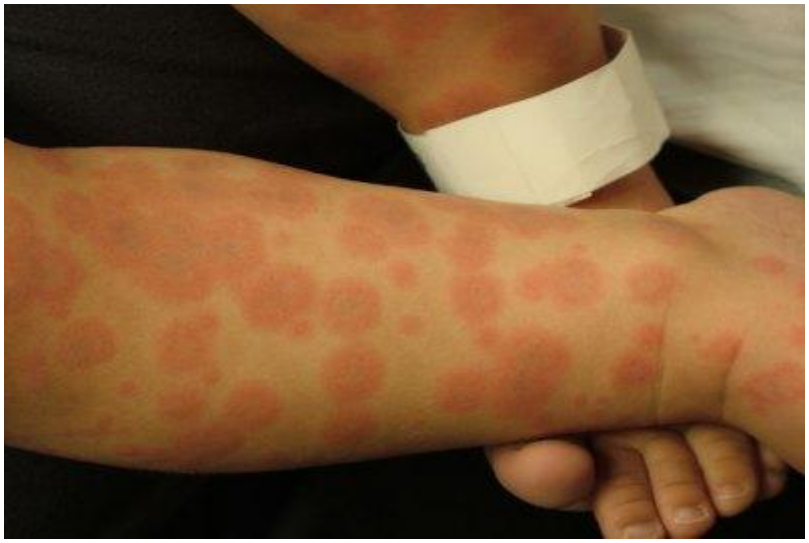
If symptoms are severe and involve blistering and mucosal involvement the term Stevens-Johnson syndrome is used.

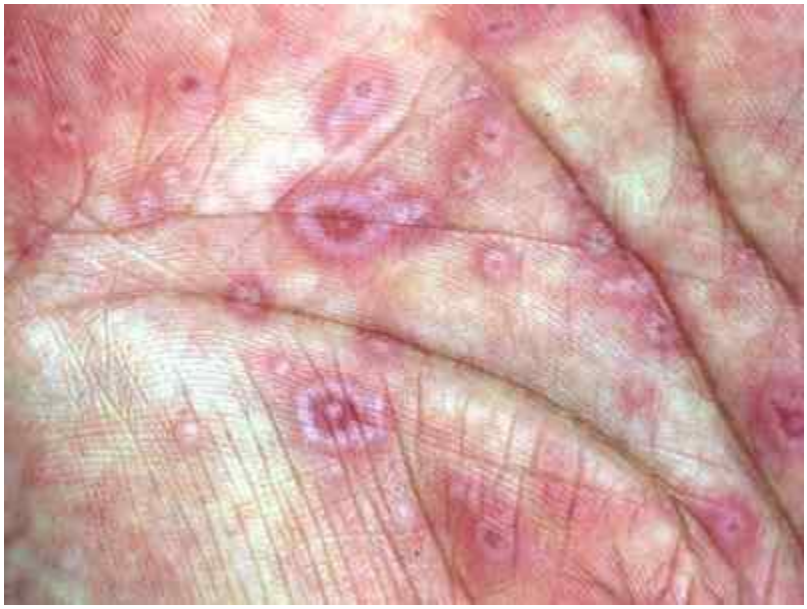
Causes

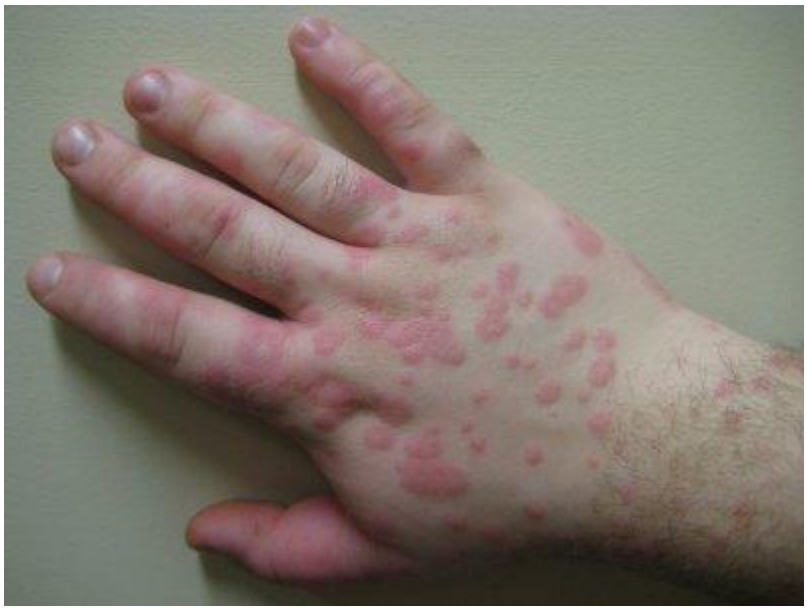
- viruses: herpes simplex virus (the most common cause), Orf*
- idiopathic
- bacteria: Mycoplasma, *Streptococcus*
- drugs: penicillin, sulphonamides, carbamazepine, allopurinol, NSAIDs, oral contraceptive pill, nevirapine
- connective tissue disease e.g. Systemic lupus erythematosus
- sarcoidosis
- malignancy











*Orf is a skin disease of sheep and goats caused by a parapox virus

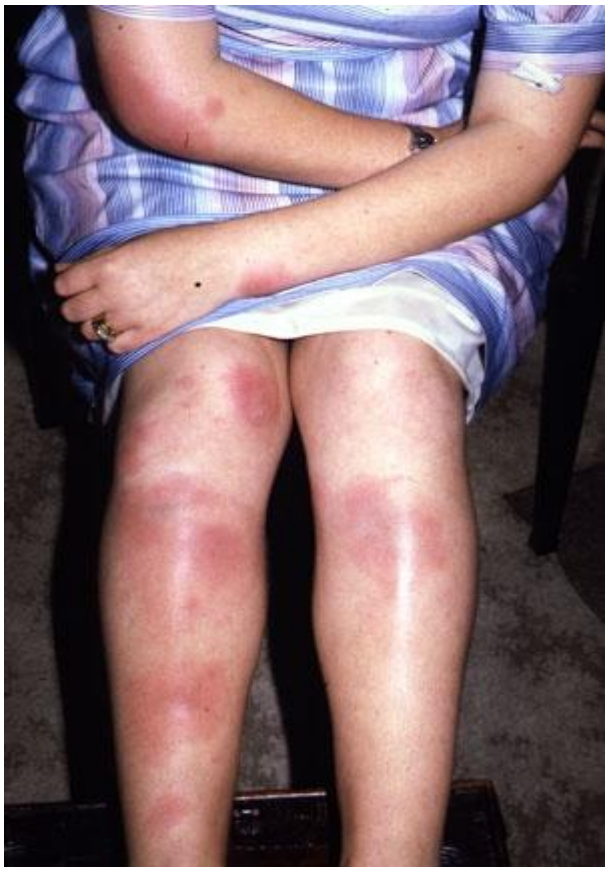
Erythema nodosum

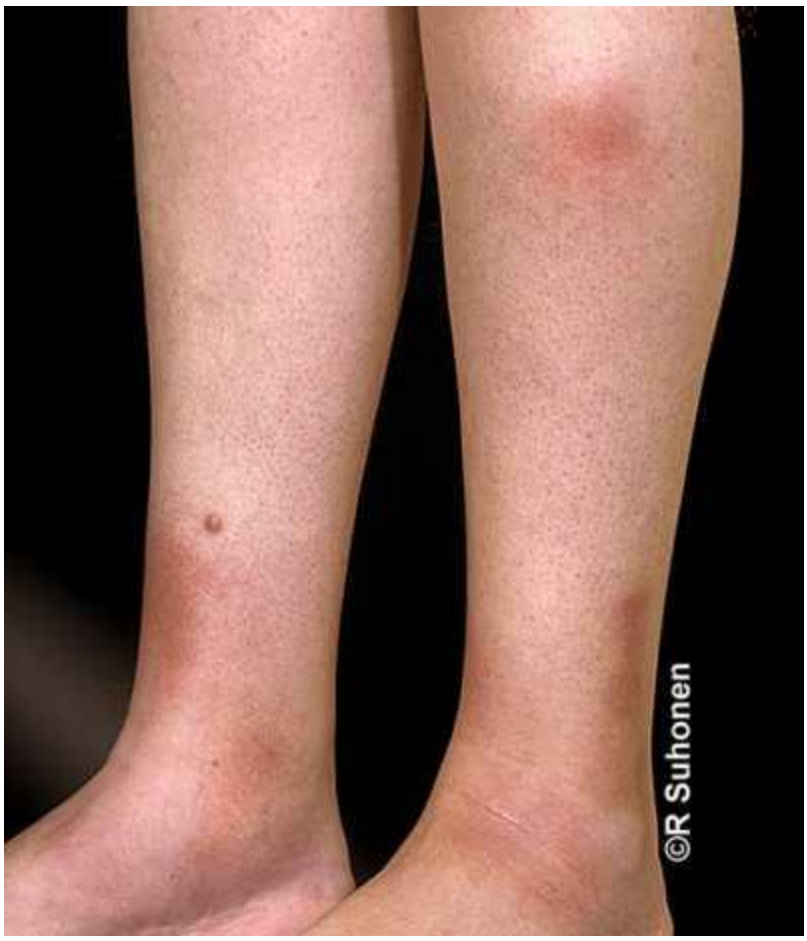
Overview

- inflammation of subcutaneous fat
- 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
- systemic disease: sarcoidosis, inflammatory bowel disease, Behcet's
- malignancy/lymphoma
- drugs: penicillins, sulphonamides, combined oral contraceptive pill
- pregnancy




©R Suhonen

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

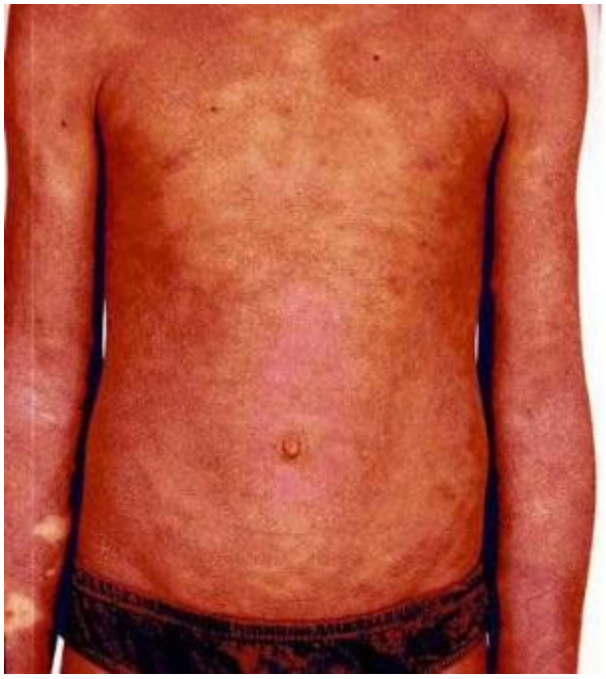
Erythroderma is a term used when more than 95% of the skin is involved in a rash of any kind

Causes of erythroderma

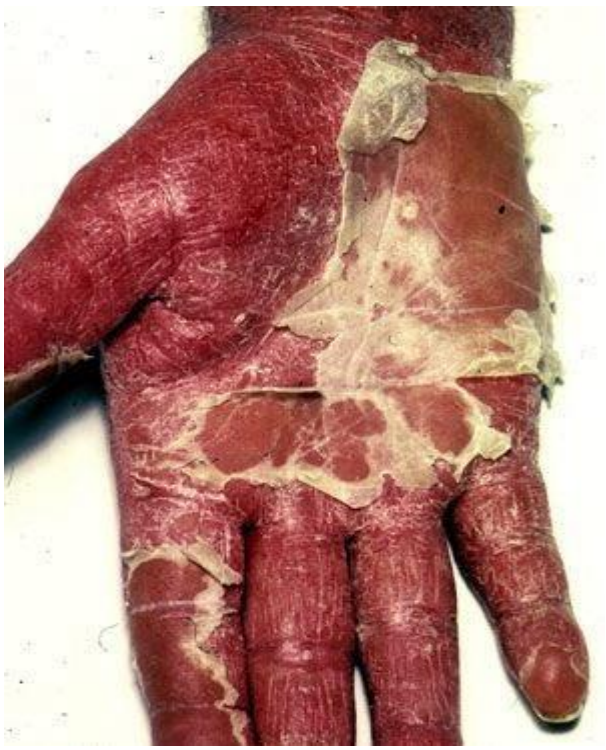
- eczema
- psoriasis
- drugs e.g. gold
- lymphoma, leukaemia
- idiopathic

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

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

Management

- treatment is successful in around 50-80% of people
- diagnosis should be confirmed by microbiology before starting treatment
- dermatophyte infection: oral terbinafine is currently recommended first-line with oral itraconazole as an alternative. Six weeks - 3 months therapy is needed for fingernail infections whilst toenails should be treated for 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

Granuloma annulare

Basics

- 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

A number of associations have been proposed to conditions such as diabetes mellitus but there is only weak evidence for this

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

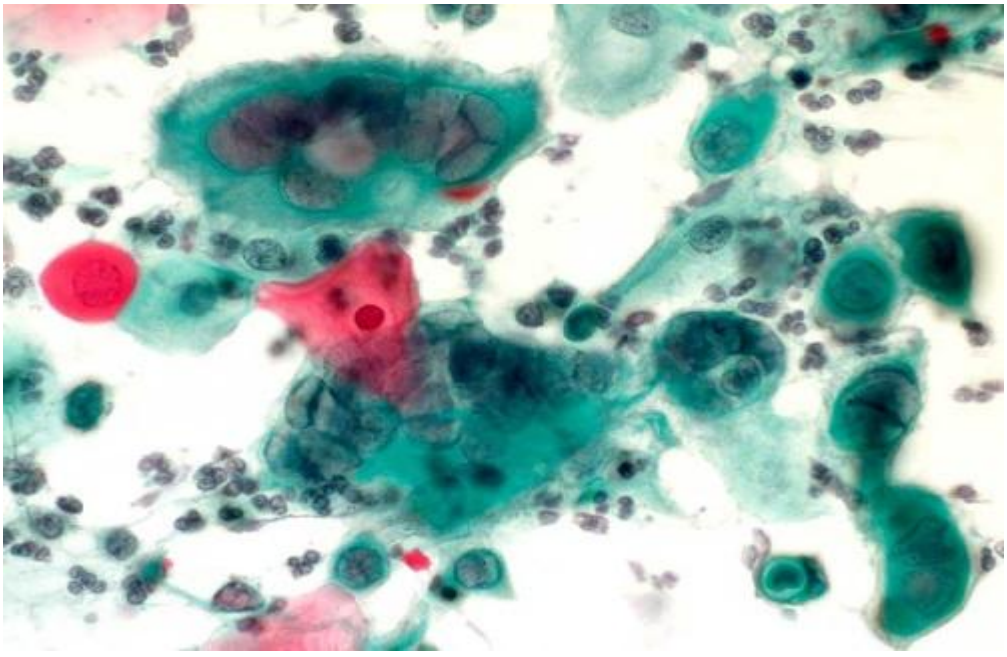
- primary infection: may present with a severe gingivostomatitis
- cold sores
- painful genital ulceration

Management

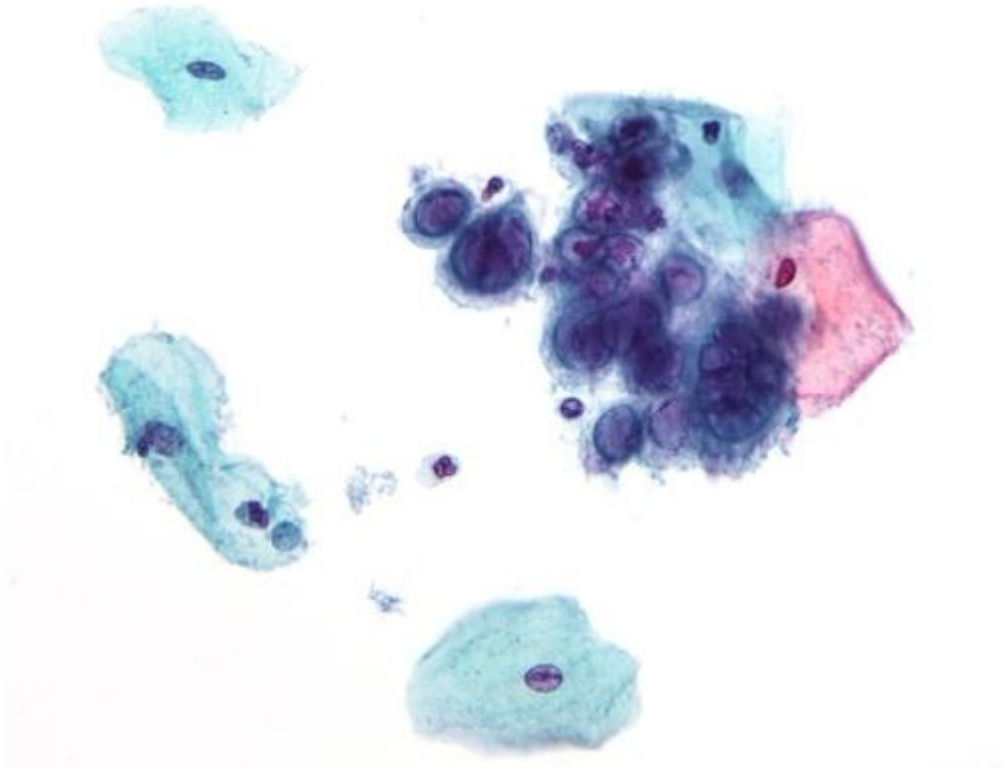
- gingivostomatitis: oral aciclovir, chlorhexidine mouthwash
- cold sores: topical aciclovir although the evidence base for this is modest
- genital herpes: oral aciclovir. Some patients with frequent exacerbations may benefit from longer term aciclovir

Pregnancy

- elective caesarean section at term is advised if a primary attack of herpes occurs during pregnancy at greater than 28 weeks gestation
- women with recurrent herpes who are pregnant should be treated with suppressive therapy and be advised that the risk of transmission to their baby is low



Pap smear. Multinucleated giant cells representing infection by the herpes simplex virus. Note the 3 M's; Multinucleation, Margination of the chromatin, Molding of the nuclei



Further Pap smear showing the cytopathic effect of HSV (multi-nucleation, ground glass & marginated chromatin)

Hirsutism and hypertrichosis

/hirsutism is often used to describe androgen-dependent hair growth in women, with hypertrichosis being used for androgen-independent hair growth

Polycystic ovarian syndrome is the most common causes of hirsutism. Other causes include:

- Cushing's syndrome
- congenital adrenal hyperplasia
- androgen therapy
- obesity: due to peripheral conversion oestrogens to androgens
- adrenal tumour
- androgen secreting ovarian tumour
- drugs: phenytoin

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

Management of hirsutism

- advise weight loss if overweight
- cosmetic techniques such as waxing/bleaching - not available on the NHS
- consider using combined oral contraceptive pills 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

Causes of hypertrichosis

- drugs: minoxidil, ciclosporin, diazoxide
- congenital hypertrichosis lanuginosa, congenital hypertrichosis terminalis
- porphyria cutanea tarda
- anorexia nervosa

Hyperhidrosis

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

Impetigo

Impetigo is a superficial bacterial skin infection usually caused by either *Staphylcoccus aureus* or *Streptococcus pyogenes*. Features

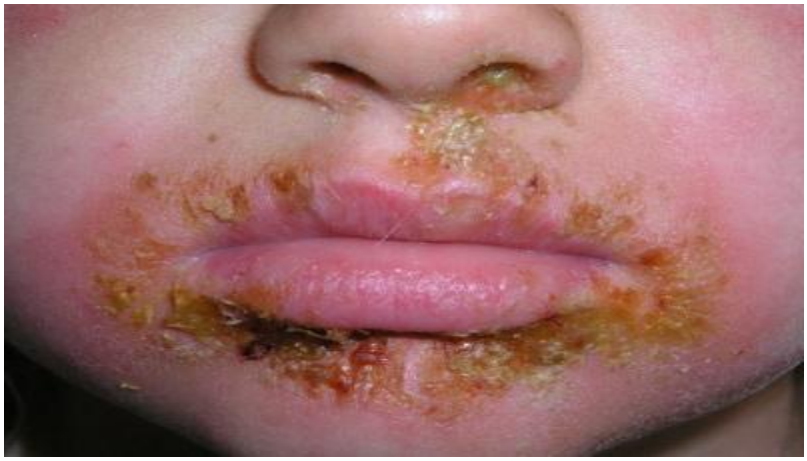
- 'golden', crusted skin lesions typically found around the mouth
- very contagious

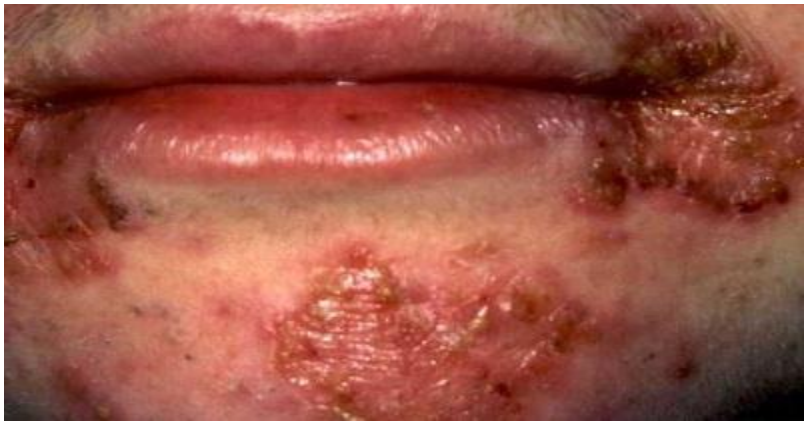
Management
Limited, localised disease

- 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





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

*whilst this is a controversial topic, depression and other psychiatric problems are listed in the BNF

Keloid scars

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

- 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*

Treatment

- early keloids may be treated with intra-lesional steroids e.g. triamcinolone
- excision is sometimes required

*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

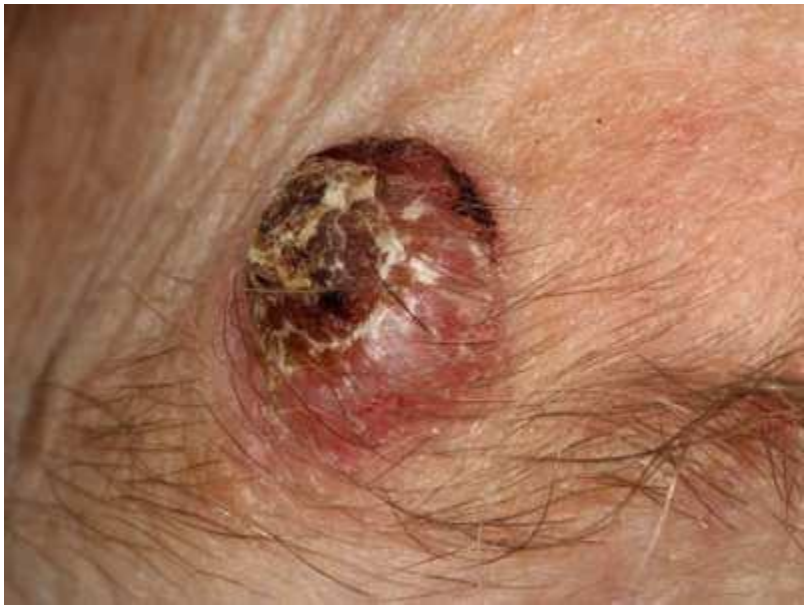
Keratoacanthoma

Keratoacanthoma is a benign epithelial tumour. They are more frequent in middle age and do not become more common in old age (unlike basal cell and squamous cell carcinoma)

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

Spontaneous regression of keratoacanthoma within 3 months is common, often resulting in a scar. Such lesions should however be urgently excised as it is difficult clinically to exclude squamous cell carcinoma. Removal also may prevent scarring.



Koebner phenomenon

The 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

Lentigo maligna

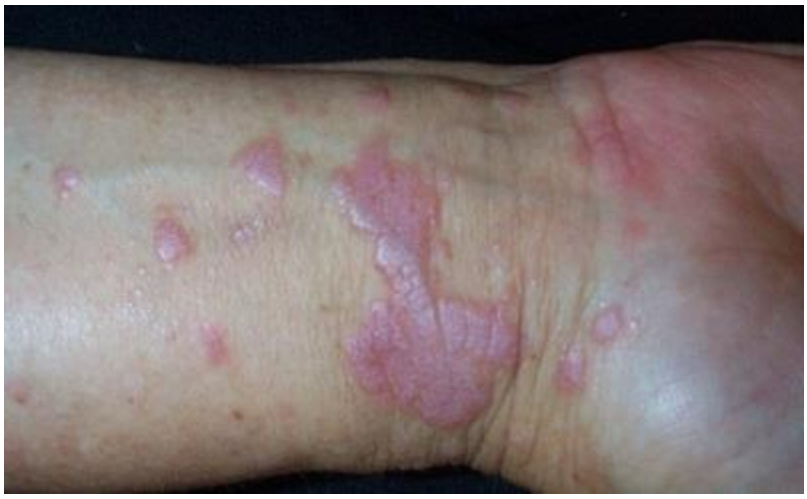
Lentigo maligna is a type of melanoma in-situ. It typically progresses slowly but may at some stage become invasive causing lentigo maligna melanoma.

Lichen planus

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

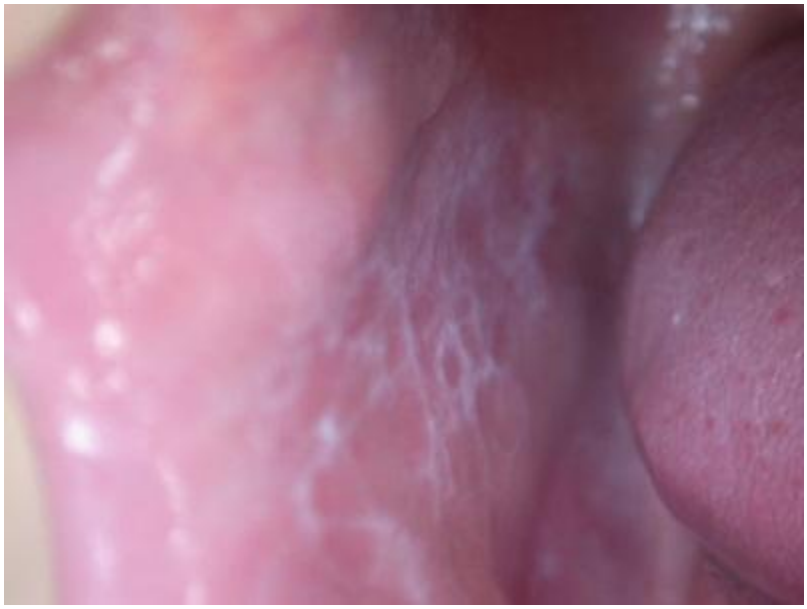


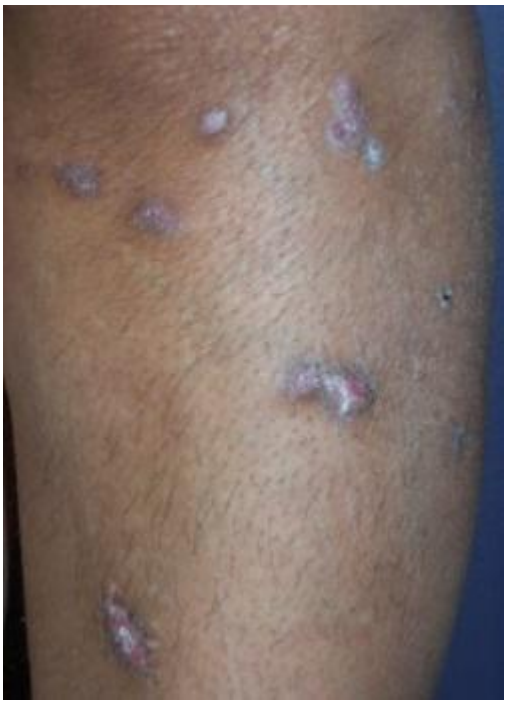
Lichenoid drug eruptions - causes:

- gold
- quinine
- thiazides

Management

- topical steroids are the mainstay of treatment
- extensive lichen planus may require oral steroids or immunosuppression





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

The diagnosis is 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;*

and

- *(v) second-line therapy is to be used.*

Malignant melanoma: prognostic factors

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%

Molluscum contagiosum

Molluscum contagiosum is a common skin infection caused by molluscum contagiosum virus (MCV), a member of the Poxviridae family. Transmission occurs directly by close personal contact, or indirectly via fomites (contaminated surfaces) such as shared towels and flannels. The majority of cases occur in children (often in children with atopic eczema), with the maximum incidence in preschool children aged 1-4 years.

Typically, molluscum contagiosum 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.

Self care advice:

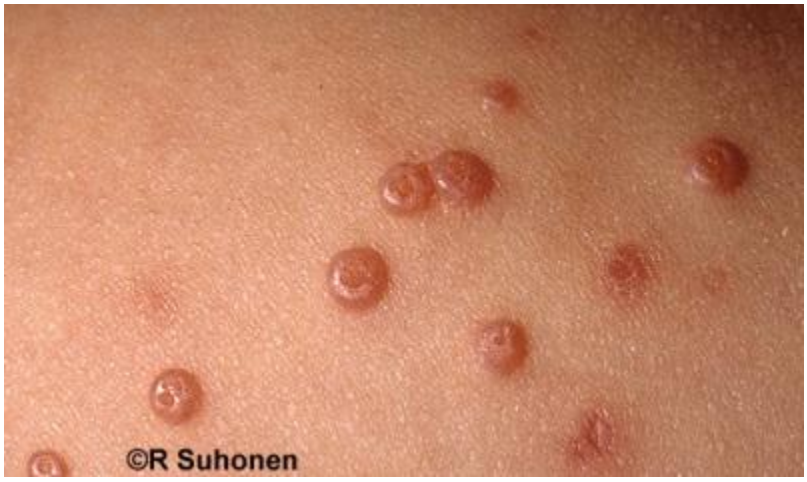
- Reassure people that molluscum contagiosum is a self-limiting condition.
- Spontaneous resolution usually occurs within 18 months
- Explain that lesions are contagious, and it is sensible to avoid sharing towels, clothing, and baths with uninfected people (e.g. siblings)
- Encourage people not to scratch the lesions. If it is problematic, consider treatment to alleviate the itch
- Exclusion from school, gym, or swimming is not necessary

Treatment is not usually recommended. If lesions are troublesome or considered unsightly, use simple trauma or cryotherapy, depending on the parents' wishes and the child's age:

- 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
- 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:

- For people who are HIV-positive with extensive lesions urgent referral to a HIV specialist
- For people with eyelid-margin or ocular lesions and associated red eye urgent referral to an ophthalmologist
- Adults with anogenital lesions should be referred to genito-urinary medicine, for screening for other sexually transmitted infections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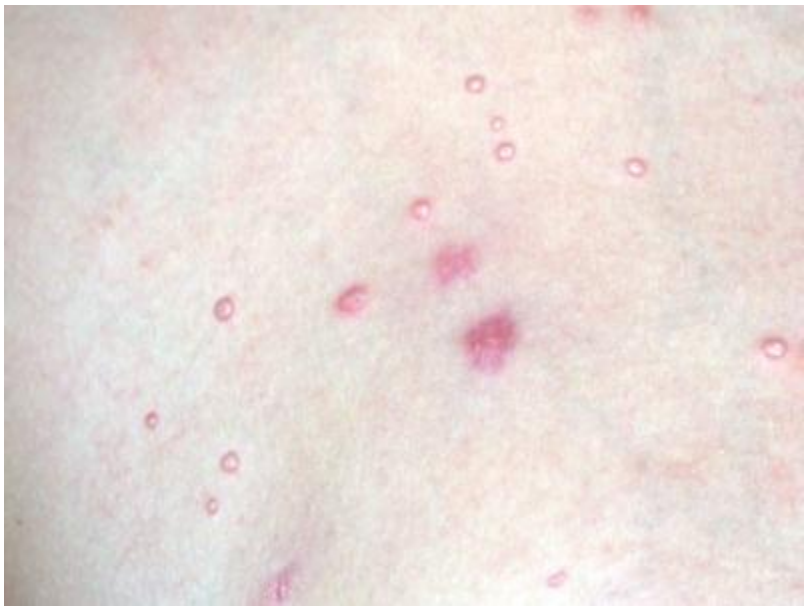


Mycosis fungoides

Mycosis fungoides is a rare form of T-cell lymphoma that affects the skin.

Features

- itchy, red patches which are typically confused with eczema or psoriasis initially
- lesions tend to be of different colours in contrast to eczema/psoriasis where there is greater homogenicity

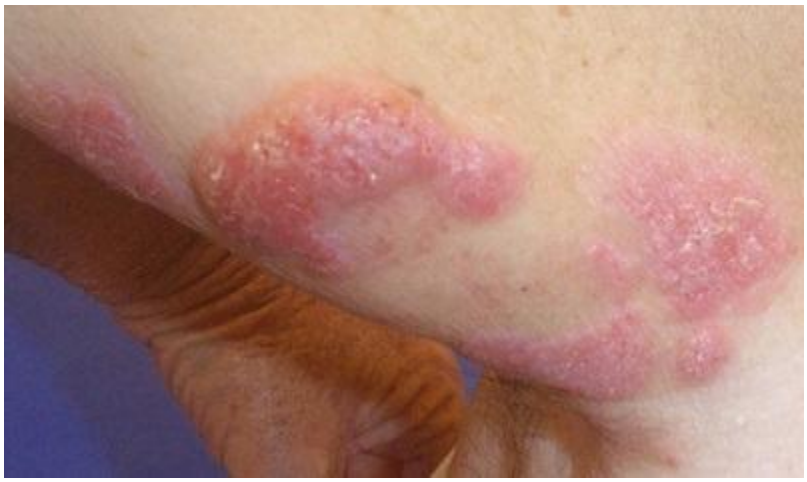
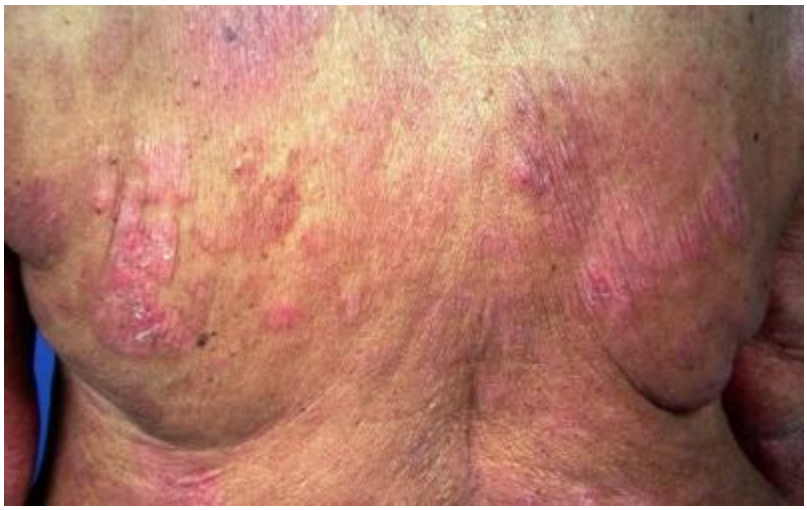


Image showing the plaque stage of mycosis fungoides



Further image showing the plaque stage of mycosis fungoides

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

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, dermatitis
- impaired peripheral circulation e.g. Raynaud's
- systemic disease: hyper- and hypothyroidism

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*
- 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 is 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.

*many ENT doctors disagree with this and feel that concerns about ototoxicity are unfounded

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)

Pellagra

Pellagra is a caused by nicotinic acid (niacin) deficiency. The classical features are the 3 D's - dermatitis, diarrhoea and dementia

Pellagra may occur as a consequence of isoniazid therapy (isoniazid inhibits the conversion of tryptophan to niacin) and it is more common in alcoholics.

Features

- dermatitis (brown scaly rash on sun-exposed sites - termed Casal's necklace if around neck)
- diarrhoea
- dementia, depression
- death if not treated

Pityriasis rosea

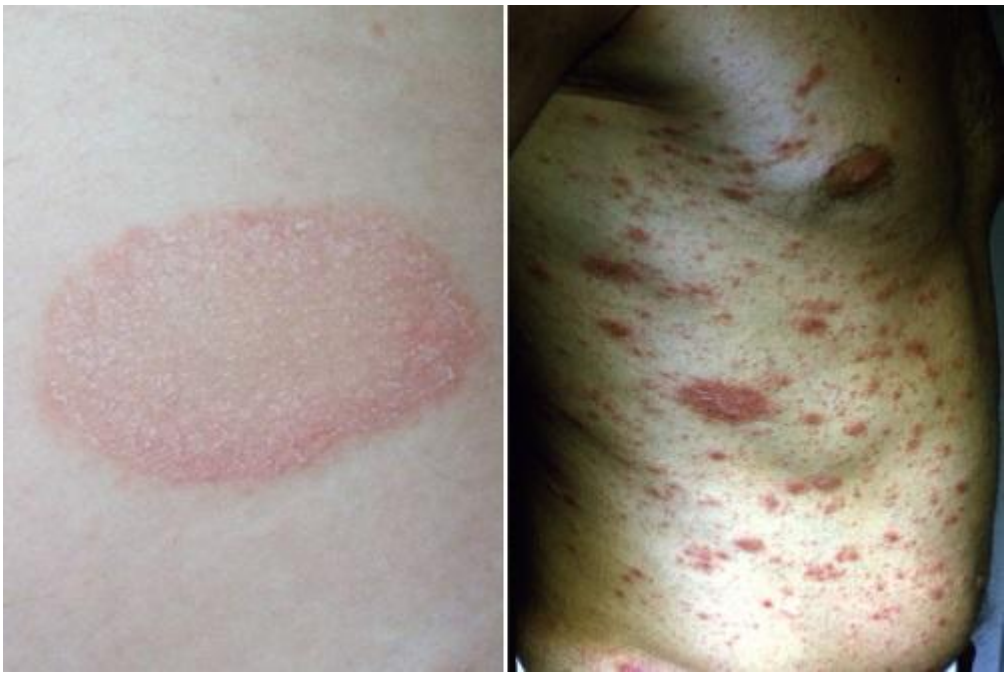
Pityriasis rosea describes an acute, self-limiting rash which tends to affect young adults. The aetiology is not fully understood but is thought that herpes hominis virus 7 (HHV-7) may play a role.

Features

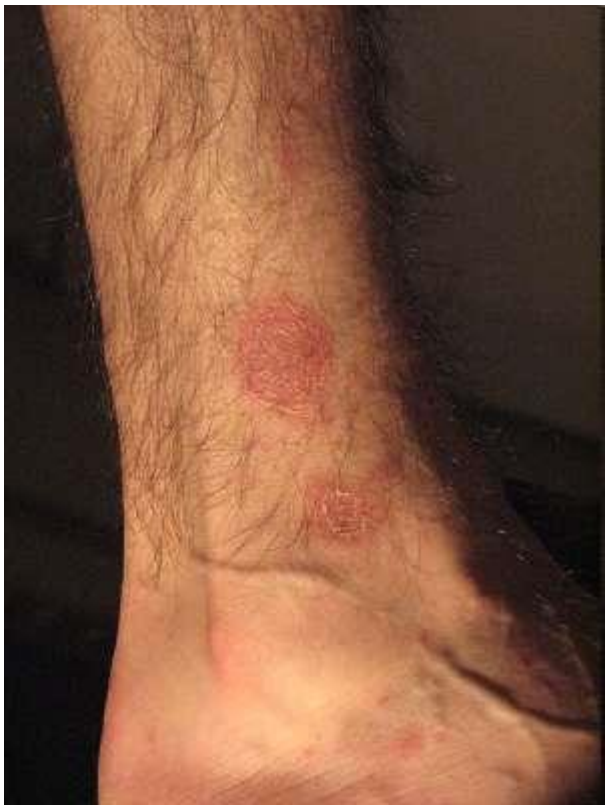
- herald patch (usually on trunk)
- followed by erythematous, oval, scaly patches which follow a characteristic distribution with the longitudinal diameters of the oval lesions running parallel to the line of Langer. This may produce a 'fir-tree' appearance

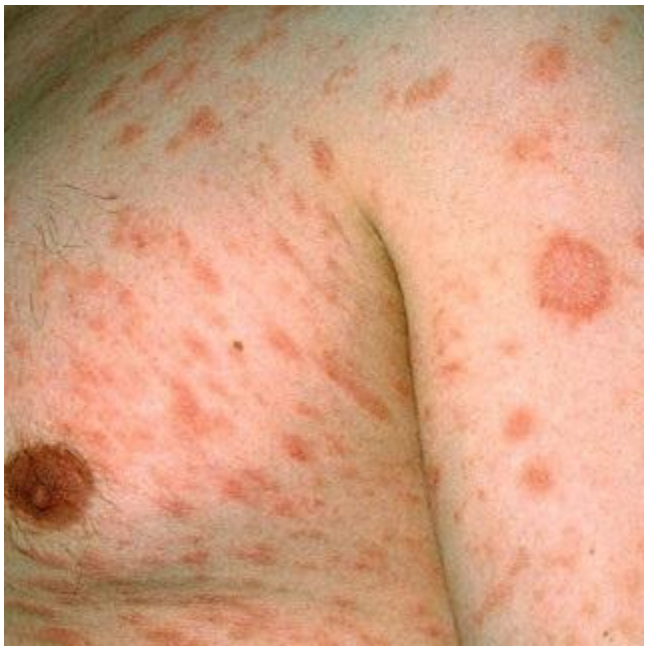
Management

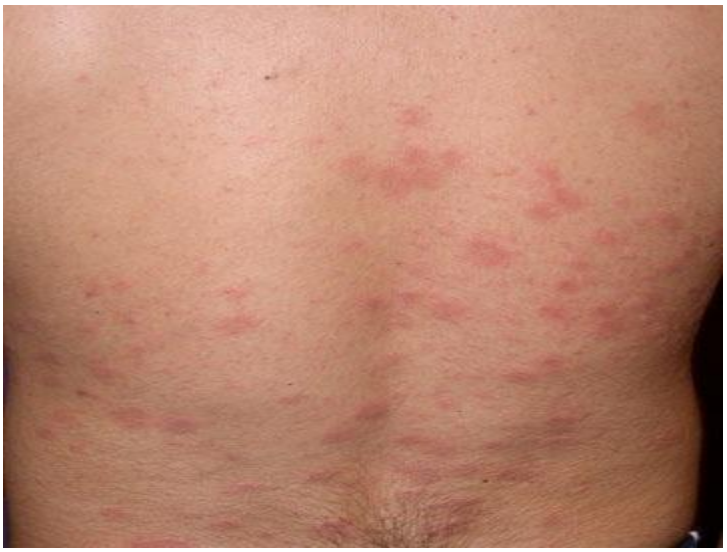
- self-limiting, usually disappears after 4-12 weeks



On the left a typical herald patch is seen. After a few days a more generalised 'fir-tree' rash appears







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

Pityriasis versicolor

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). May be more noticeable following a suntan
- 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
- if extensive disease or failure to respond to topical treatment then consider oral itraconazole

Polycystic ovarian syndrome: management

Polycystic ovarian syndrome (PCOS) is a complex condition of ovarian dysfunction thought to affect between 5-20% of women of reproductive age. Management is complicated and problem based partly because 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.

General

- weight reduction if appropriate
- 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

- a COC pill may be used help manage hirsutism. 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
- if doesn't respond to COC then topical eflornithine may be tried
- spironolactone, flutamide and finasteride may be used under specialist supervision

Infertility

- weight reduction if appropriate
- the management of infertility in patients with PCOS should be supervised by a specialist. There is an ongoing debate as to whether metformin, clomifene or a combination should be used to stimulate ovulation
- a 2007 trial published in the New England Journal of Medicine suggested clomifene was the most effective treatment. There is a potential risk of multiple pregnancies with anti-oestrogen* therapies such as clomifene. The RCOG published an opinion paper in 2008 and concluded that on current evidence metformin is not a first line treatment of choice in the management of PCOS
- metformin is also used, either combined with clomifene or alone, particularly in patients who are obese
- gonadotrophins

*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

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

Porphyria cutanea tarda

Porphyria cutanea tarda is the most common hepatic porphyria. It is due to an inherited defect in uroporphyrinogen decarboxylase or caused by hepatocyte damage e.g. alcohol, hepatitis C, oestrogens

Features

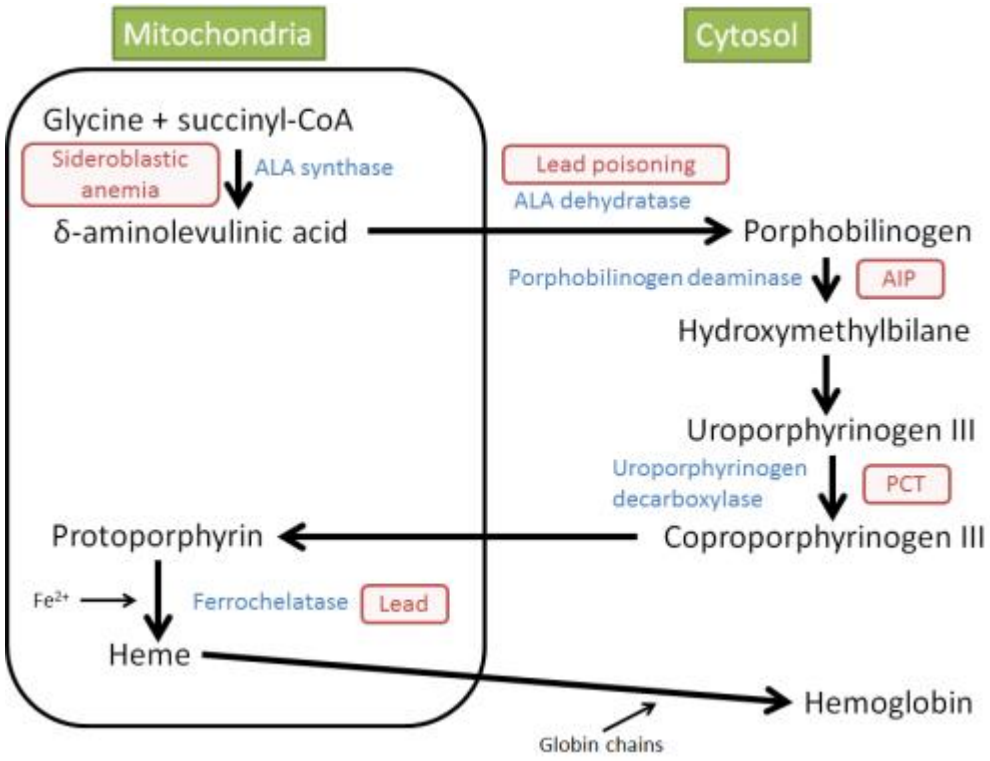
- classically presents with photosensitive rash with blistering and skin fragility on the face and dorsal aspect of hands (most common feature)
- hypertrichosis
- hyperpigmentation

Investigations

- urine: elevated uroporphyrinogen and pink fluorescence of urine under Wood's lamp

Management

- chloroquine
- venesection



Pressure ulcers

The following is based on a 2009 NHS Best Practice Statement. Please see the link for further details. Some selected points are listed below. NICE also published guidelines in 2014.

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

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
- skin disorders: eczema, scabies, psoriasis, pityriasis rosea

Psoriasis

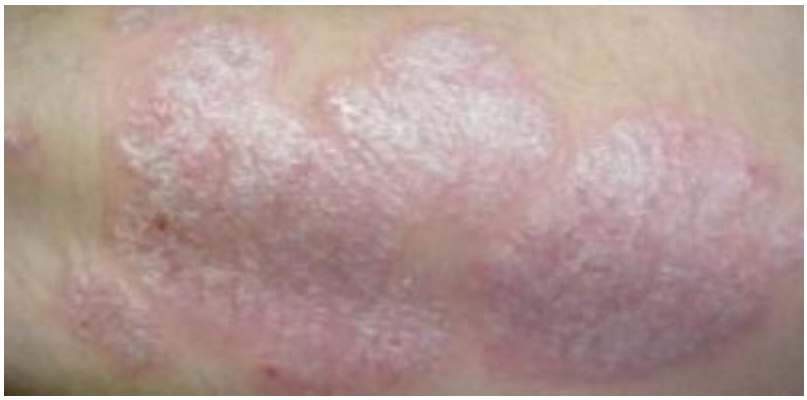
Psoriasis is a common (prevalence around 2%) and chronic skin disorder. It generally presents with red, scaly patches on the skin although it is now recognised that patients with psoriasis are at increased risk of arthritis and cardiovascular disease.

Pathophysiology

- multifactorial and not yet fully understood
- genetic: associated HLA-B13, -B17, and -Cw6. Strong concordance (70%) in identical twins
- immunological: abnormal T cell activity stimulates keratinocyte proliferation. There is increasing evidence this may be mediated by a novel group of T helper cells producing IL-17, designated Th17. These cells seem to be a third T-effector cell subset in addition to Th1 and Th2
- environmental: it is recognised that psoriasis may be worsened (e.g. Skin trauma, stress), triggered (e.g. Streptococcal infection) or improved (e.g. Sunlight) by environmental factors

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

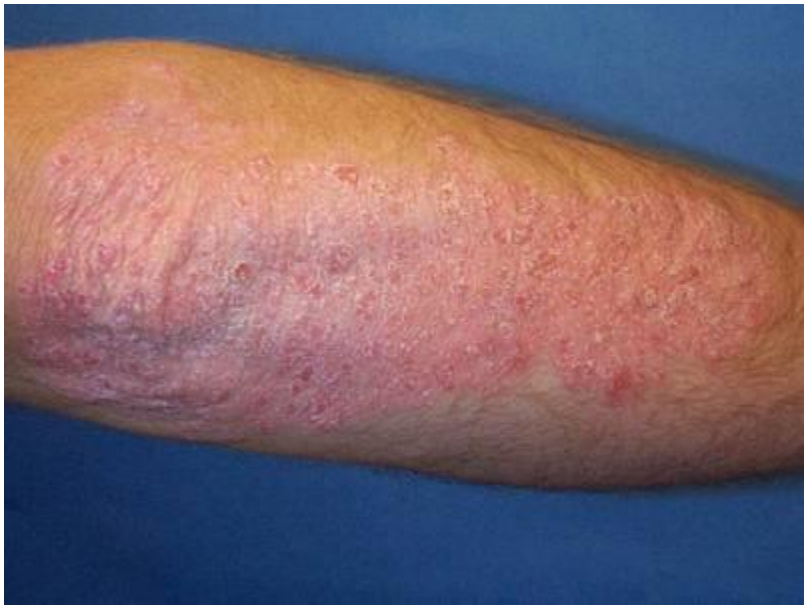


Other features

- nail signs: pitting, onycholysis
- arthritis

Complications

- psoriatic arthropathy (around 10%)
- increased incidence of metabolic syndrome
- increased incidence of cardiovascular disease
- increased incidence of venous thromboembolism
- psychological distress



Psoriasis: exacerbating factors

The following factors may exacerbate psoriasis:

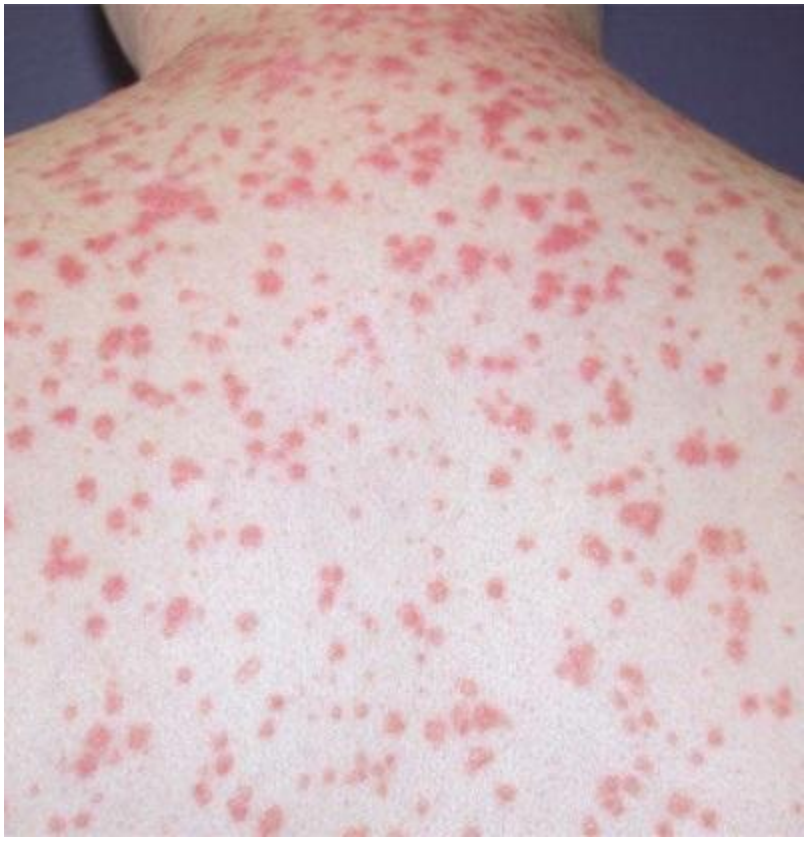
- trauma
- alcohol
- drugs: beta blockers, lithium, antimalarials (chloroquine and hydroxychloroquine), NSAIDs and ACE inhibitors, infliximab
- withdrawal of systemic steroids

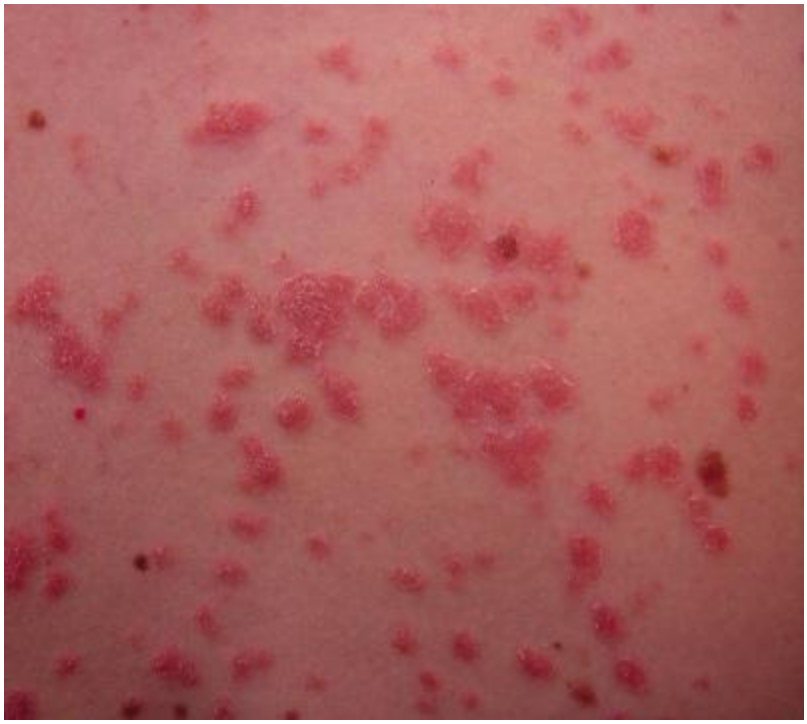
Psoriasis: guttate

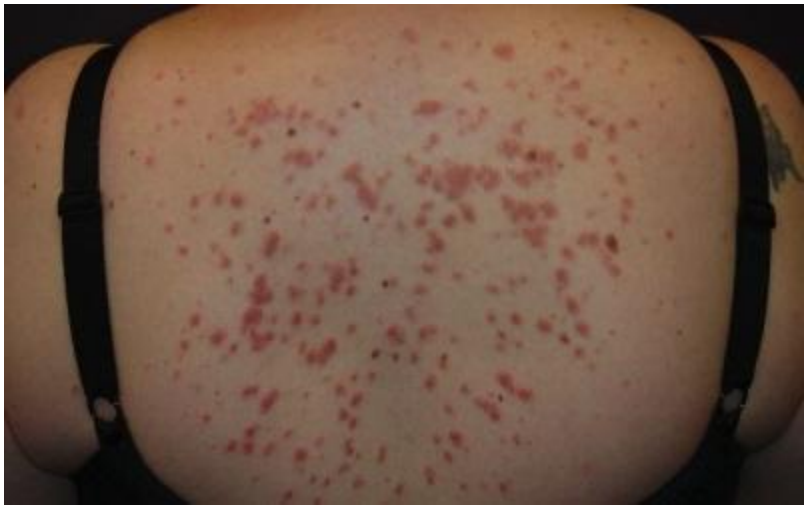
Guttate psoriasis is more common in children and adolescents. It may be precipitated by a streptococcal infection 2-4 weeks prior to the lesions appearing

Features

- tear drop papules on the trunk and limbs







Management

- most cases resolve spontaneously within 2-3 months
- there is no firm evidence to support the use of antibiotics to eradicate streptococcal infection
- topical agents as per psoriasis
- UVB phototherapy
- tonsillectomy may be necessary with recurrent episodes

Differentiating guttate psoriasis and pityriasis rosea

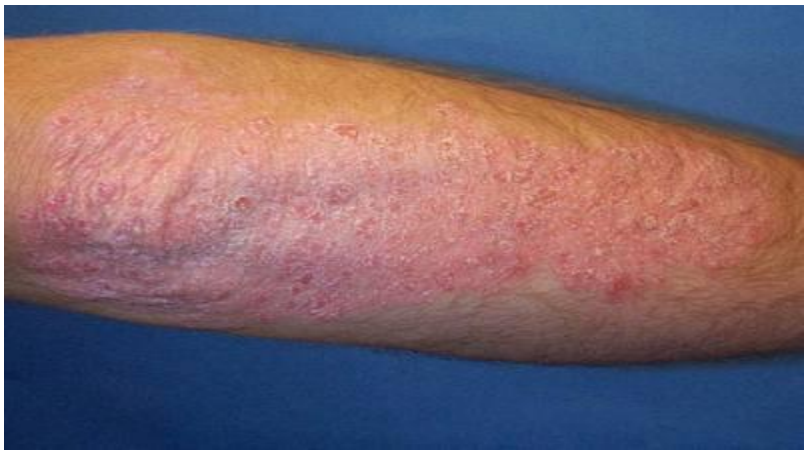
	Guttate psoriasis	Pityriasis rosea
Prodrome	Classically preceded by a streptococcal sore throat 2-4 weeks	Many patients report recent respiratory tract infections but this is not common in questions
Appearance	'Tear drop', scaly papules on the trunk and limbs	Herald patch followed 1-2 weeks later by 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

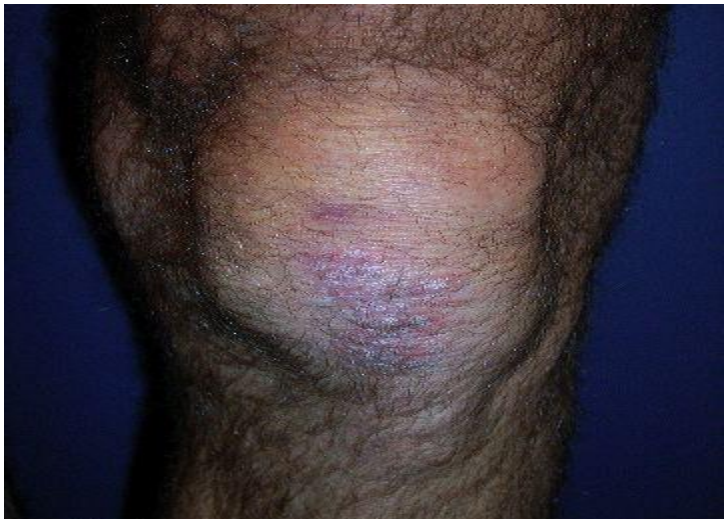
Psoriasis: management

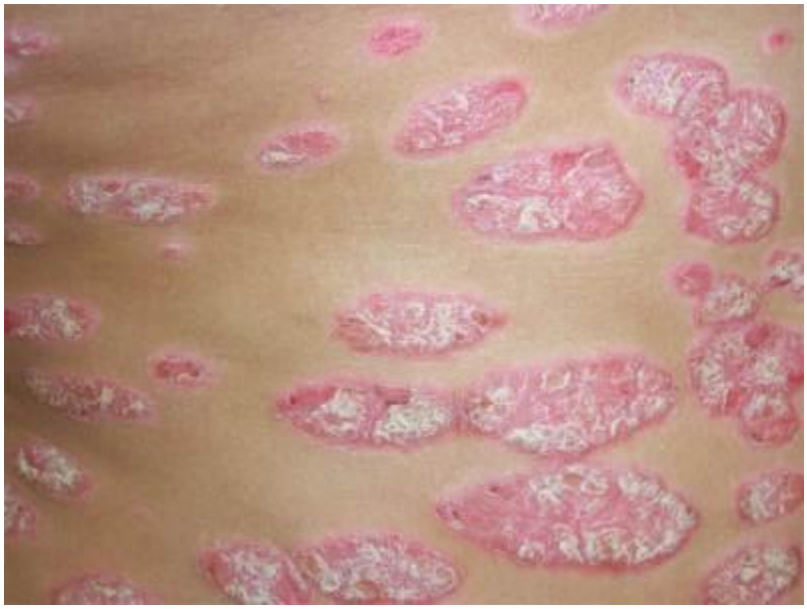
NICE released guidelines in 2012 on the management of psoriasis and psoriatic arthropathy. Please see the link for more details.

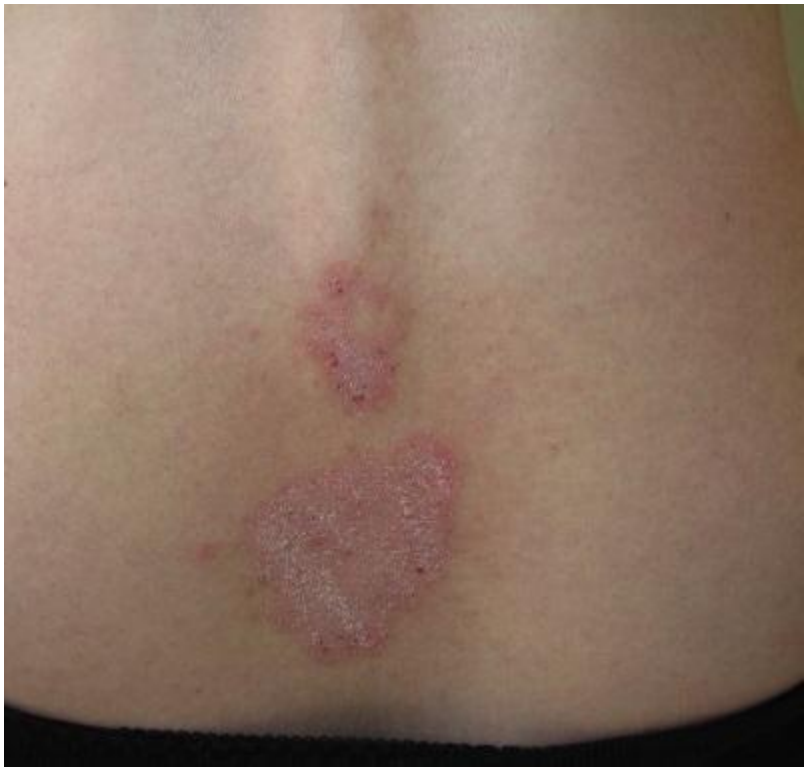
Management of chronic plaque psoriasis

- regular emollients may help to reduce scale loss and reduce pruritus
- first-line: NICE recommend a 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







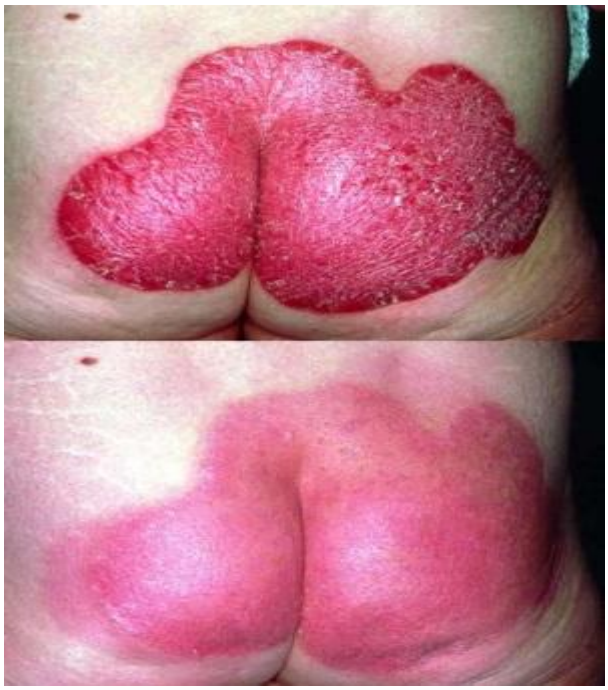


Using topical steroids in psoriasis

- 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

- NICE recommend the use of potent topical corticosteroids used once daily for 4 weeks
- if no improvement after 4 weeks then either use a different formulation of the potent corticosteroid (for example, a shampoo or mousse) and/or a 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

- NICE recommend offering a mild or moderate potency corticosteroid applied once or twice daily for a maximum of 2 weeks

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

- oral methotrexate is used first-line. It is particularly useful if there is associated joint disease
- ciclosporin
- systemic retinoids
- biological agents: infliximab, etanercept and adalimumab
- ustekinumab (IL-12 and IL-23 blocker) is showing promise in early trials

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

Pyoderma gangrenosum

Features

- typically on the lower limbs
- initially small red papule
- later deep, red, necrotic ulcers with a violaceous border
- may be accompanied systemic symptoms e.g. Fever, myalgia

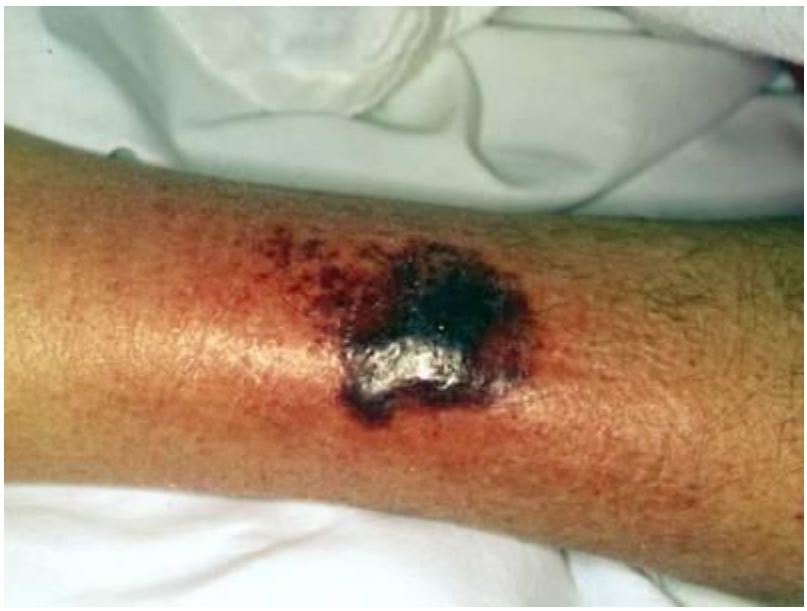
Causes*

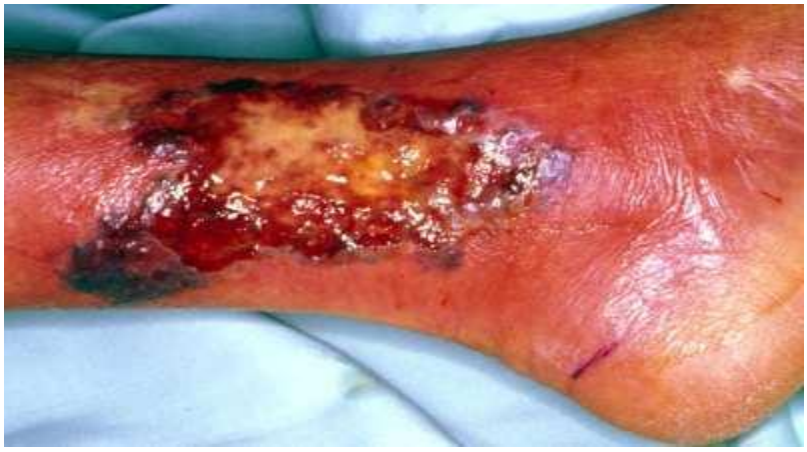
- idiopathic in 50%
- inflammatory bowel disease: ulcerative colitis, Crohn's
- rheumatoid arthritis, SLE
- myeloproliferative disorders
- lymphoma, myeloid leukaemias
- monoclonal gammopathy (IgA)
- primary biliary cirrhosis

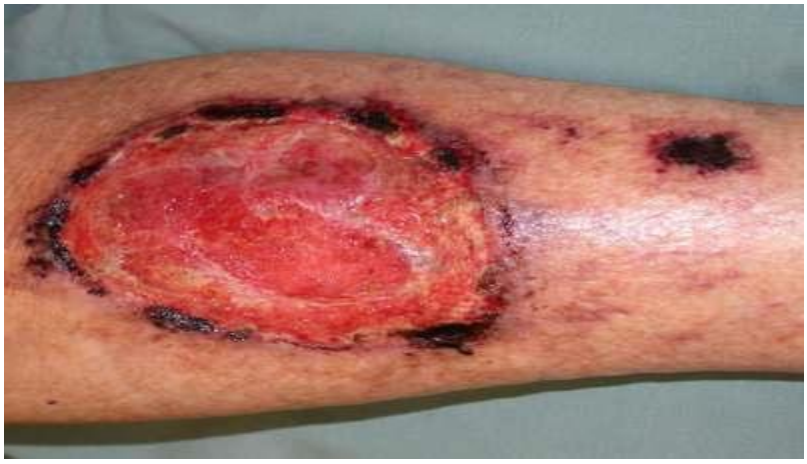
Management

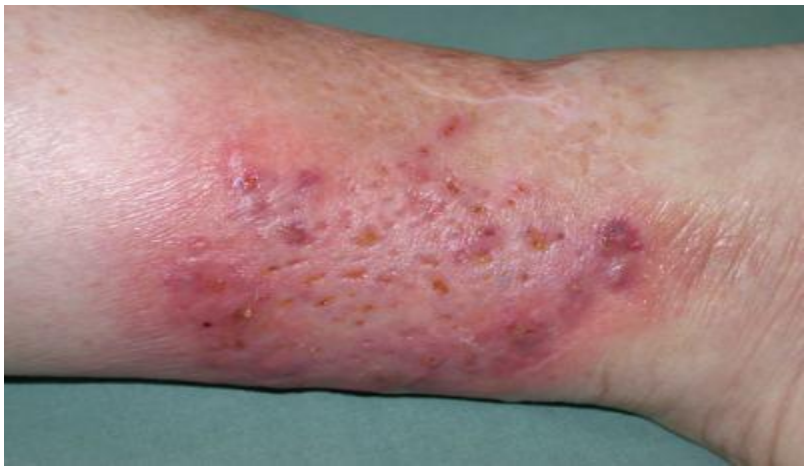
- the potential for rapid progression is high in most patients and most doctors advocate oral steroids as first-line treatment
- other immunosuppressive therapy, for example ciclosporin and infliximab, have a role in difficult cases

*note whilst pyoderma gangrenosum can occur in diabetes mellitus it is rare and is generally not included in a differential of potential causes









Pyogenic granuloma

Pyogenic granuloma is a relatively common benign skin lesion. The name is confusing as they are neither true granulomas nor pyogenic in nature. There are multiple alternative names but perhaps 'eruptive haemangioma' is the most useful.

The cause of pyogenic granuloma is not known but a number of factors are linked:

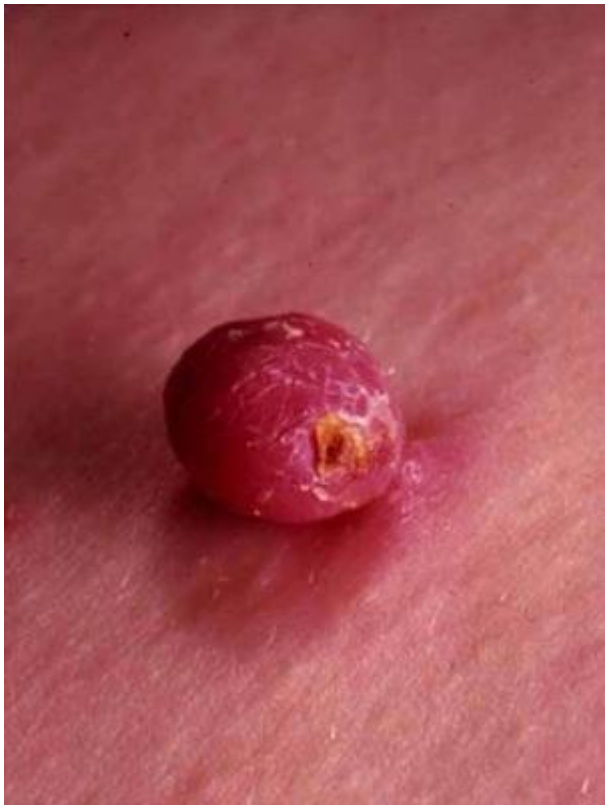
- trauma
- pregnancy
- more common in women and young adults

Features

- most common sites are head/neck, upper trunk and hands. Lesions in the oral mucosa are common in pregnancy
- initially small red/brown spot
- rapidly progress within days to weeks forming raised, red/brown lesions which are often spherical in shape
- the lesions may bleed profusely or ulcerate

Management

- lesions associated with pregnancy often resolve spontaneously post-partum
- other lesions usually persist. Removal methods include curettage and cauterisation, cryotherapy, excision



Sarcoidosis

Sarcoidosis is a multisystem disorder of unknown aetiology characterised by non-caseating granulomas. It is more common in young adults and in people of African descent

Features

- acute: erythema nodosum, bilateral hilar lymphadenopathy, swinging fever, polyarthralgia
- insidious: dyspnoea, non-productive cough, malaise, weight loss
- skin: lupus pernio
- hypercalcaemia: macrophages inside the granulomas cause an increased conversion of vitamin D to its active form (1,25-dihydroxycholecalciferol)

Syndromes associated with sarcoidosis

Lofgren's syndrome is an acute form of the disease characterised by bilateral hilar lymphadenopathy (BHL), erythema nodosum, fever and polyarthralgia. It usually carries an excellent prognosis

In **Mikulicz syndrome*** there is enlargement of the parotid and lacrimal glands due to sarcoidosis, tuberculosis or lymphoma

Heerfordt's syndrome (uveoparotid fever) there is parotid enlargement, fever and uveitis secondary to sarcoidosis

*this term is now considered outdated and unhelpful by many as there is a confusing overlap with Sjogren's syndrome

Seborrhoeic dermatitis in adults

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
- Parkinson's disease

Scalp disease management

- 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

- topical antifungals: e.g. Ketoconazole
- topical steroids: best used for short periods
- difficult to treat - recurrences are common

Sezary syndrome

Sezary syndrome is a type of T-cell cutaenous lymphoma.

Features

- pruritus
- erythroderma typically affecting the palms, soles and face
- atypical T cells
- lymphadenopathy
- hepatosplenomegaly

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

- shiny, painless areas of yellow/red/brown skin typically on the shin
- often associated with surrounding telangiectasia

Infection

- candidiasis
- staphylococcal

Neuropathic ulcers

Vitiligo

Lipoatrophy

Granuloma annulare*

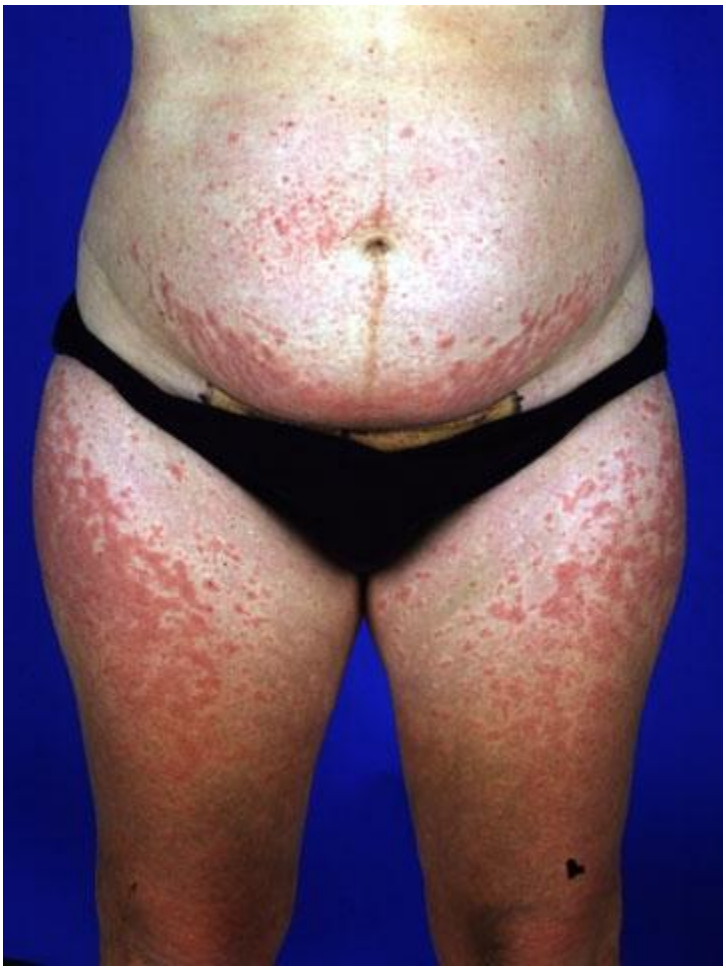
- papular lesions that are often slightly hyperpigmented and depressed centrally

*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

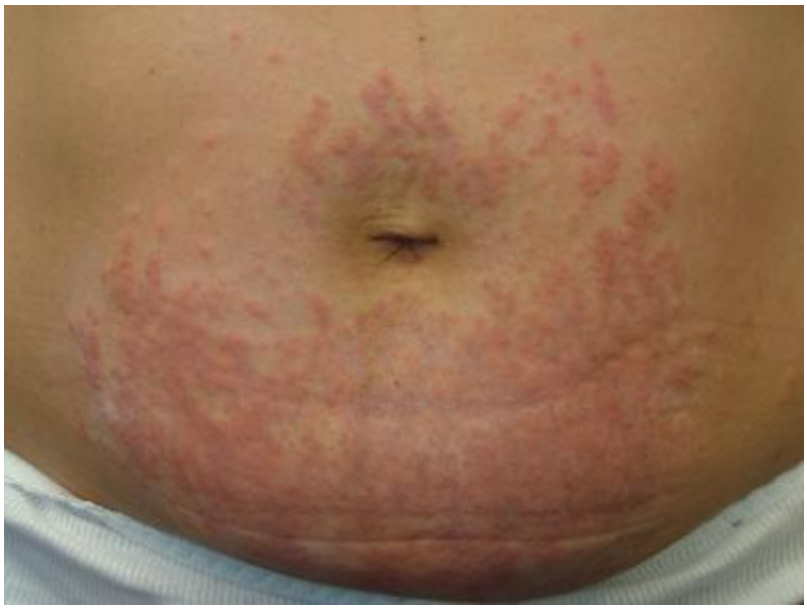
Skin disorders associated with pregnancy

Polymorphic eruption of pregnancy

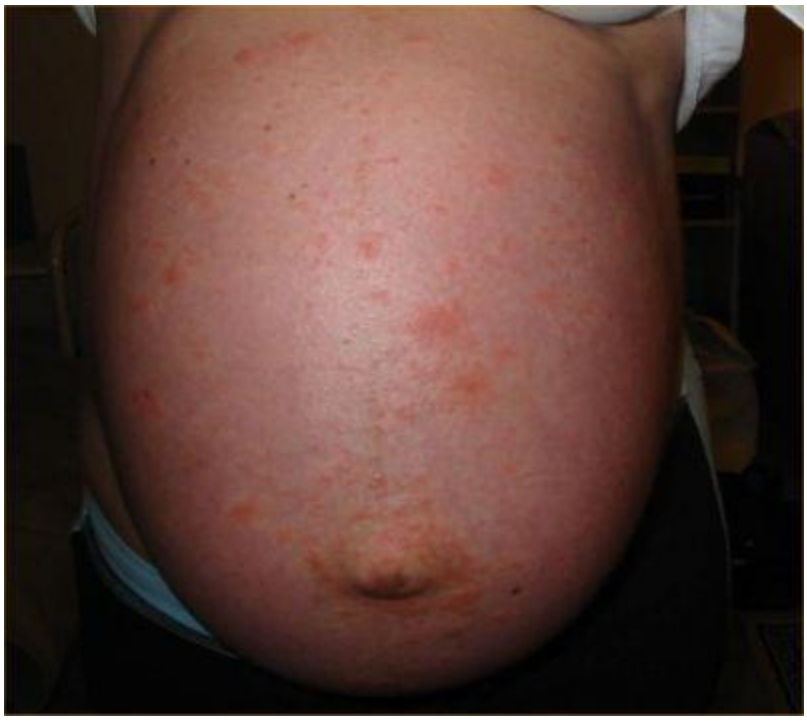
- pruritic condition associated with last trimester
- lesions often first appear in abdominal striae
- management depends on severity: emollients, mild potency topical steroids and oral steroids may be used



Polymorphic eruption of pregnancy



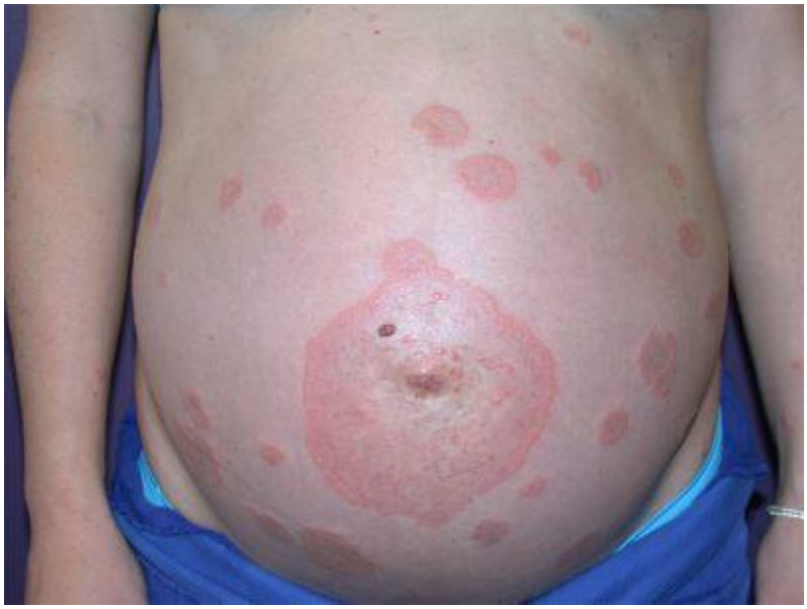
Polymorphic eruption of pregnancy



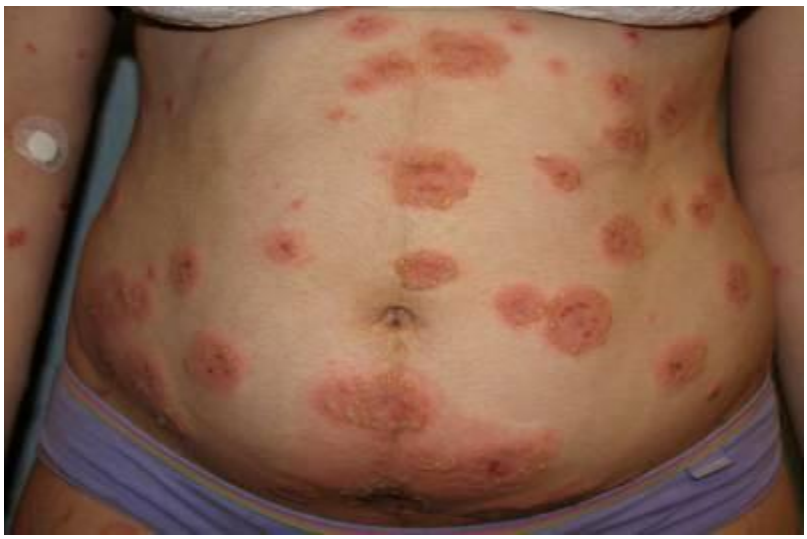
Polymorphic eruption of pregnancy

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

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 is the most common form of cutaneous TB seen in the Indian subcontinent. It generally occurs on the face and is common around the nose and mouth. The initial lesion is an erythematous flat plaque which gradually becomes elevated and may ulcerate later

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

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

- tinea capitis - scalp
- tinea corporis - trunk, legs or arms
- 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
- most common cause is *Trichophyton tonsurans* in the UK and the USA
- may also be caused by *Microsporum canis* acquired from cats or dogs
- diagnosis: lesions due to *Microsporum canis* green fluorescence under Wood's lamp*. However the most useful investigation is scalp scrapings
- management (based on CKS guidelines): oral antifungals: terbinafine for *Trichophyton tonsurans* infections and griseofulvin for *Microsporum* infections. Topical ketoconazole shampoo should be given for the first two weeks to reduce transmission

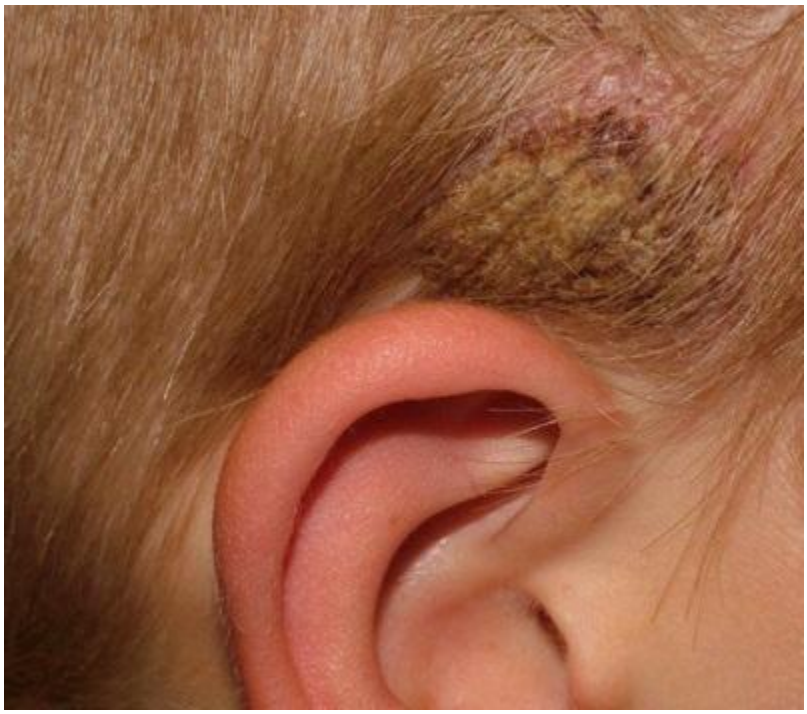


Image showing a kerion

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

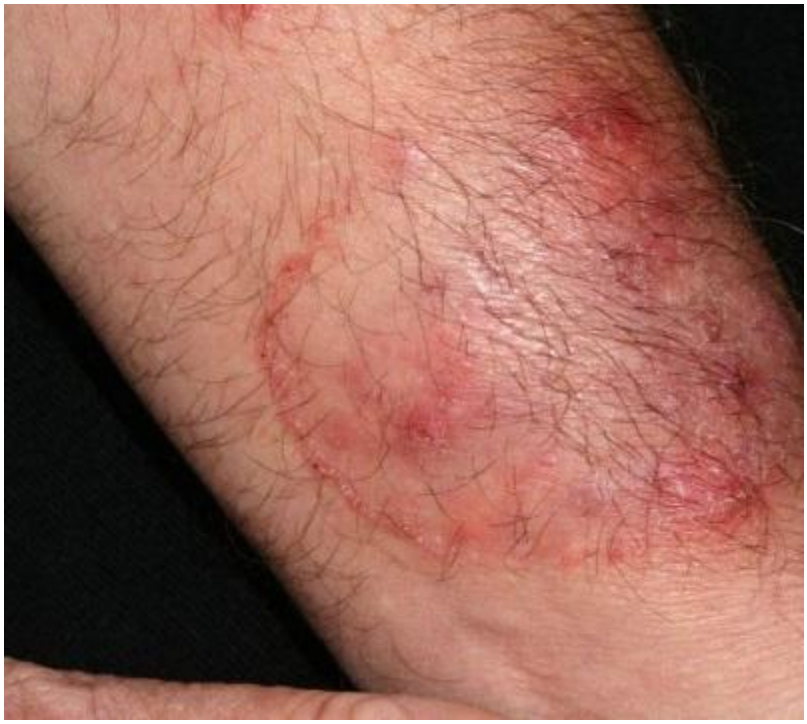


Image showing tinea corporis

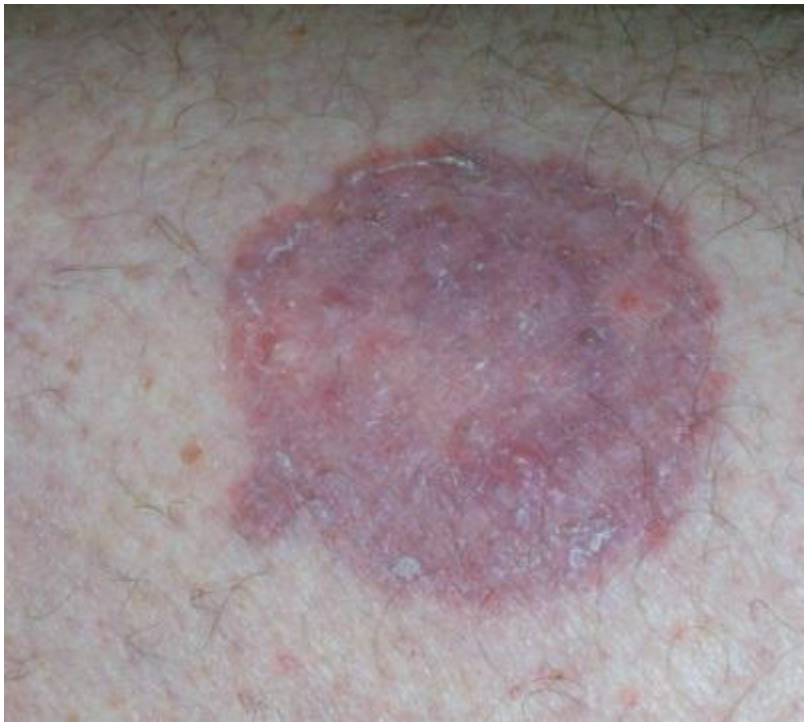


Image showing tinea corporis. Note the well defined border

Tinea pedis (athlete's foot)

- characterised by itchy, peeling skin between the toes
- common in adolescence

*lesions due to *Trichophyton* species do not readily fluoresce under Wood's lamp

Toxic epidermal necrolysis

Toxic epidermal necrolysis (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

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
- 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

Venous ulceration

Venous ulceration is typically seen above 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

- compression bandaging, usually four layer (only treatment shown to be of real benefit)
- 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

Vitiligo

Vitiligo is an autoimmune condition which results in the loss of melanocytes and consequent depigmentation of the skin. It is thought to affect around 1% of the population and symptoms typically develop by the age of 20-30 years.

Features

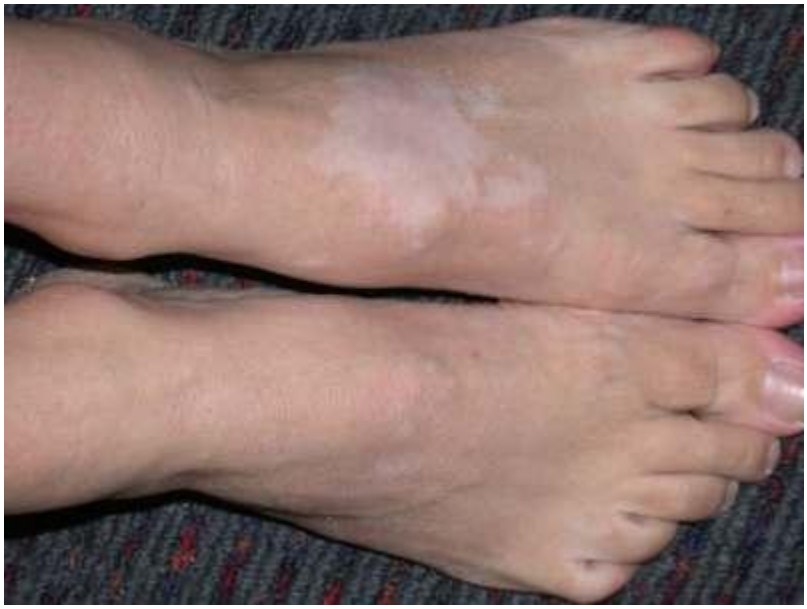
- well demarcated patches of depigmented skin
- the peripheries tend to be most affected
- trauma may precipitate new lesions (Koebner phenomenon)

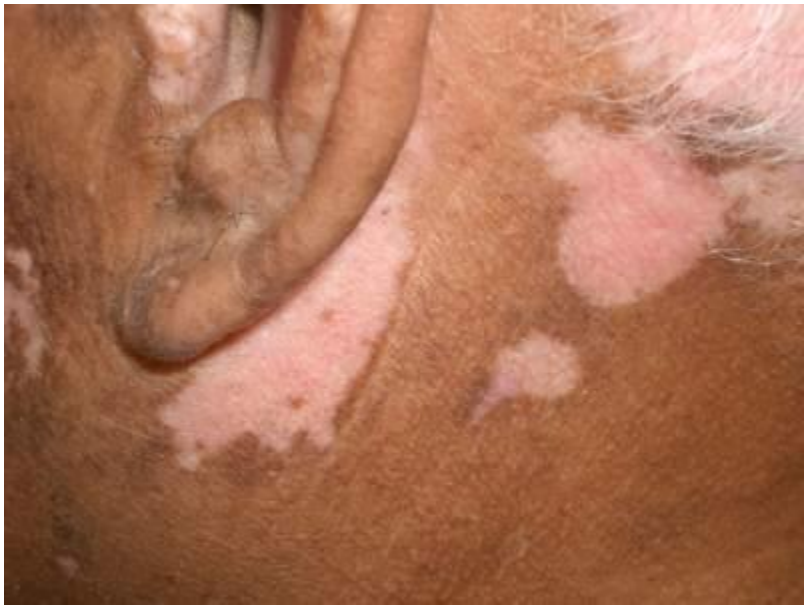
Associated conditions

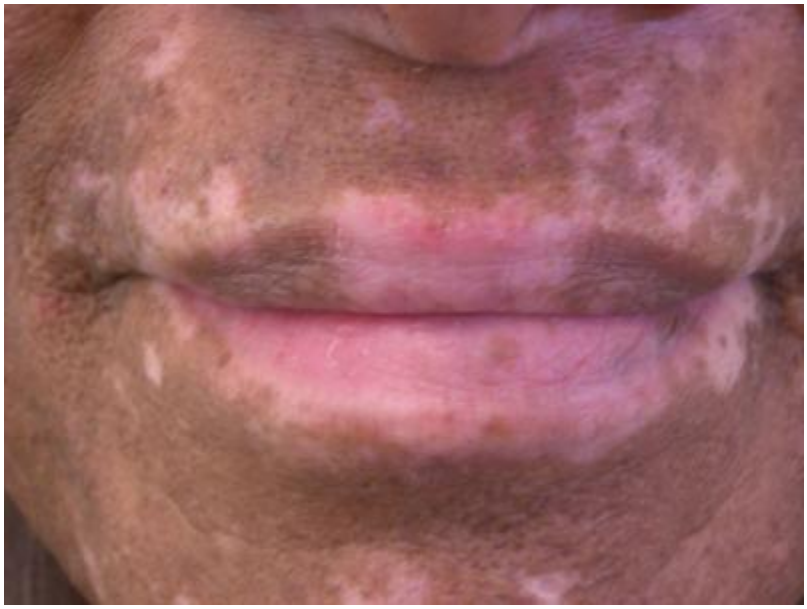
- type 1 diabetes mellitus
- Addison's disease
- autoimmune thyroid disorders
- pernicious anaemia
- alopecia areata

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

Zinc deficiency

Features

- perioral dermatitis: red, crusted lesions
- acrodermatitis
- alopecia
- short stature
- hypogonadism
- hepatosplenomegaly
- geophagia (ingesting clay/soil)
- cognitive impairment

Endocrinology

Acromegaly: features

In acromegaly there is excess growth hormone secondary to a pituitary adenoma in over 95% of cases. A minority of cases are caused by ectopic GHRH or GH production by tumours e.g. pancreatic

Features

- coarse facial appearance, spade-like hands, increase in shoe size
- large tongue, prognathism, interdental spaces
- excessive sweating and oily skin
- features of pituitary tumour: hypopituitarism, headaches, bitemporal hemianopia
- raised prolactin in 1/3 of cases → galactorrhoea
- 6% of patients have MEN-1

Complications

- hypertension
- diabetes (>10%)
- cardiomyopathy
- colorectal cancer

Acromegaly: investigations

Growth hormone (GH) levels vary during the day and are therefore not diagnostic. The definitive test is the oral glucose tolerance (OGTT) with serial GH measurements. Serum IGF-1 may also be used as a screening test and is sometimes used to monitor disease

Oral glucose tolerance test

- in normal patients GH is suppressed to < 2 mu/L with hyperglycaemia
- in acromegaly there is no suppression of GH
- may also demonstrate impaired glucose tolerance which is associated with acromegaly

A pituitary MRI may demonstrate a pituitary tumour

Acromegaly: management

Trans-sphenoidal surgery is first-line treatment for acromegaly in the majority of patients

Dopamine agonists

- for example bromocriptine
- the first effective medical treatment for acromegaly, however now superseded by somatostatin analogues
- effective only in a minority of patients

Somatostatin analogue

- for example octreotide
- effective in 50-70% of patients
- may be used as an adjunct to surgery

Pegvisomant

- GH receptor antagonist - prevents dimerization of the GH receptor
- 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

External irradiation is sometimes used for older patients or following failed surgical/medical treatment

Addison's disease

Autoimmune destruction of the adrenal glands is the commonest cause of primary hypoadrenalism in the UK, accounting for 80% of cases

Features

- lethargy, weakness, anorexia, nausea & vomiting, weight loss, 'salt-craving'
- hyperpigmentation (especially palmar creases), vitiligo, loss of pubic hair in women, hypotension
- crisis: collapse, shock, pyrexia

Other causes of hypoadrenalism

Primary causes

- tuberculosis
- metastases (e.g. bronchial carcinoma)
- meningococcal septicaemia (Waterhouse-Friderichsen syndrome)
- HIV
- antiphospholipid syndrome

Secondary causes

- pituitary disorders (e.g. tumours, irradiation, infiltration)

Exogenous glucocorticoid therapy

Addison's disease: investigations

In a patient with suspected Addison's disease the definite investigation is a ACTH stimulation test (short Synacthen test). Plasma cortisol is measured before and 30 minutes after giving Synacthen 250ug IM. Adrenal autoantibodies such as anti-21-hydroxylase may also be demonstrated.

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

Associated electrolyte abnormalities are seen in around one-third of undiagnosed patients:

- hyperkalaemia
- hyponatraemia
- hypoglycaemia
- metabolic acidosis

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

Management

- hydrocortisone 100 mg im or iv
- 1 litre normal saline infused over 30-60 mins or with dextrose if hypoglycaemic
- 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

Amenorrhoea

Amenorrhoea may be divided into primary (failure to start menses by the age of 16 years) or secondary (cessation of established, regular menstruation for 6 months or longer).

Causes of primary amenorrhoea

- Turner's syndrome
- testicular feminisation
- congenital adrenal hyperplasia
- congenital malformations of the genital tract

Secondary amenorrhoea is defined as when menstruation has previously occurred but has now stopped for at least 6 months.

Causes of secondary amenorrhoea (after excluding pregnancy)

- hypothalamic amenorrhoea (e.g. Stress, excessive exercise)
- polycystic ovarian syndrome (PCOS)
- hyperprolactinaemia
- premature ovarian failure
- thyrotoxicosis*
- 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

*hypothyroidism may also cause amenorrhoea

Androgen insensitivity syndrome

Androgen insensitivity syndrome is an X-linked recessive condition 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
- breast development may occur as a result of conversion of testosterone to oestradiol

Diagnosis

- 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)
- oestrogen therapy

Apparent mineralocorticoid excess

In order to prevent cortisol activation of the mineralocorticoid nuclear receptor and subsequent hyperaldosteronism, 11-hydroxysteroid dehydrogenase type 2 converts cortisol into inactive cortisone at the renal parenchyma.

Apparent mineralocorticoid excess (AME) is often inherited, caused by an autosomal recessive mutation in 11-hydroxysteroid dehydrogenase type 2. However rarely excess liquorice can cause inhibition of 11-hydroxysteroid dehydrogenase type 2 leading to excess cortisol and thus AME.

Autoimmune polyendocrinopathy syndrome

Addison's disease (autoimmune hypoadrenalism) is associated with other endocrine deficiencies in approximately 10% of patients. There are two distinct types of autoimmune polyendocrinopathy syndrome (APS), with type 2 (sometimes referred to as Schmidt's syndrome) being much more common.

APS type 2 has a polygenic inheritance and is linked to HLA DR3/DR4. Patients have Addison's disease plus either:

- type 1 diabetes mellitus
- autoimmune thyroid disease

APS type 1 is occasionally referred to as Multiple Endocrine Deficiency Autoimmune Candidiasis (MEDAC). It is a very rare autosomal recessive disorder caused by mutation of AIRE1 gene on chromosome 21

Features of APS type 1 (2 out of 3 needed)

- chronic mucocutaneous candidiasis (typically first feature as young child)
- Addison's disease
- primary hypoparathyroidism

Vitiligo can occur in both types

Bartter's syndrome

Bartter's syndrome is an inherited cause (usually autosomal recessive) of severe hypokalaemia due to defective chloride absorption at the Na^+ K^+ 2Cl- cotransporter (NKCC2) in the ascending loop of Henle. It should be noted that it is associated with normotension (unlike other endocrine causes of hypokalaemia such as Conn's, Cushing's and Liddle's syndrome which are associated with hypertension).

Loop diuretics work by inhibiting NKCC2 - think of Bartter's syndrome as like taking large doses of furosemide

Features

- usually presents in childhood, e.g. Failure to thrive
- polyuria, polydipsia
- hypokalaemia
- normotension
- weakness

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

- blocks thyroid peroxidase from coupling and iodinating the tyrosine residues on thyroglobulin → reducing thyroid hormone production
- 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

- agranulocytosis
- crosses the placenta, but may be used in low doses during pregnancy

Carcinoid tumours

Carcinoid syndrome

- 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)
- 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
- plasma chromogranin A y

Management

- somatostatin analogues e.g. octreotide
- diarrhoea: cyproheptadine may help

Congenital adrenal hyperplasia: features

21-hydroxylase deficiency features

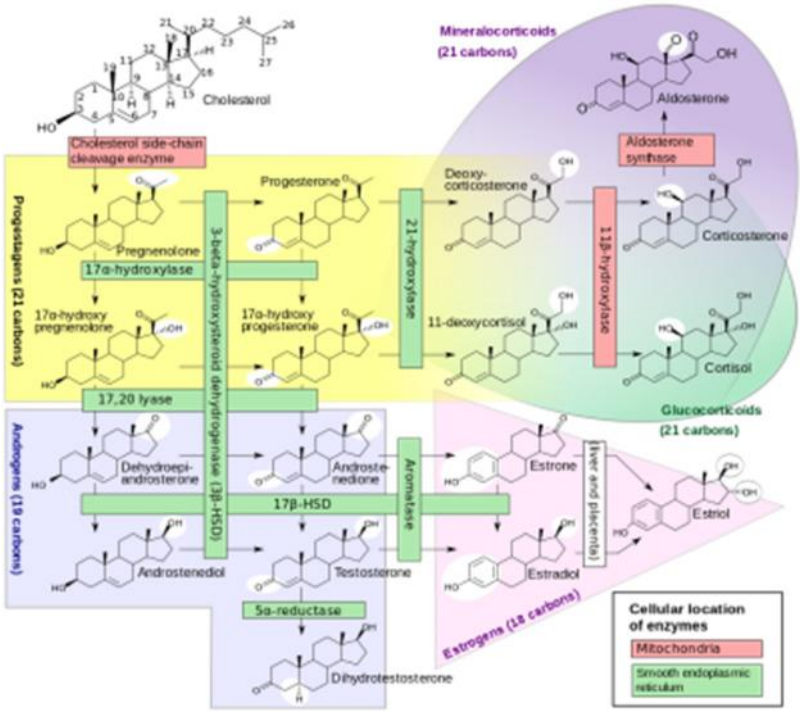
- virilisation of female genitalia
- precocious puberty in males
- 60-70% of patients have a salt-losing crisis at 1-3 wks of age

11-beta hydroxylase deficiency features

- virilisation of female genitalia
- precocious puberty in males
- hypertension
- hypokalaemia

17-hydroxylase deficiency features

- non-virilising in females
- inter-sex in boys
- hypertension



Congenital hypothyroidism

Congenital hypothyroidism affects around 1 in 4000 babies. If not diagnosed and treated within the first four weeks it causes irreversible cognitive impairment

Features

- prolonged neonatal jaundice
- delayed mental & physical milestones
- short stature
- puffy face, macroglossia
- hypotonia

Children are screened at 5-7 days using the heel prick test

Corticosteroids

Corticosteroids are amongst the most commonly prescribed therapies in clinical practice. They are used both systemically (oral or intravenous) or locally (skin creams, inhalers, eye drops, intra-articular). They augment and in some cases replace the natural glucocorticoid and mineralocorticoid activity of endogenous steroids.

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

Selected points on the use of corticosteroids:

- patients on long-term steroids should have their doses doubled during intercurrent illness
- 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

Cushing's syndrome: causes

ACTH dependent causes

- Cushing's disease (80%): pituitary tumour secreting ACTH producing adrenal hyperplasia
- ectopic ACTH production (5-10%): e.g. small cell lung cancer

ACTH independent causes

- iatrogenic: steroids
- adrenal adenoma (5-10%)
- adrenal carcinoma (rare)
- Carney complex: syndrome including cardiac myxoma
- micronodular adrenal dysplasia (very rare)

Pseudo-Cushing's

- mimics Cushing's
- often due to alcohol excess or severe depression
- causes false positive dexamethasone suppression test or 24 hr urinary free cortisol
- insulin stress test may be used to differentiate

Cushing's syndrome: investigations

Investigations are divided into confirming Cushing's syndrome and then localising the lesion. A hypokalaemic metabolic alkalosis may be seen, along with impaired glucose tolerance. Ectopic ACTH secretion (e.g. secondary to small cell lung cancer) is characteristically associated with very low potassium levels. An insulin stress test is used to differentiate between true Cushing's and pseudo-Cushing's

Tests to confirm Cushing's syndrome

The two most commonly used tests are:

- overnight dexamethasone suppression test (most sensitive)
- 24 hr urinary free cortisol

Localisation tests

The first-line localisation is 9am 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

- if pituitary source then cortisol suppressed
- if ectopic/adrenal then no change in cortisol

CRH stimulation

- if pituitary source then cortisol rises
- if ectopic/adrenal then no change in cortisol

Petrosal sinus sampling of ACTH may be needed to differentiate between pituitary and ectopic ACTH secretion

Diabetes mellitus (type 2): diagnosis

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.

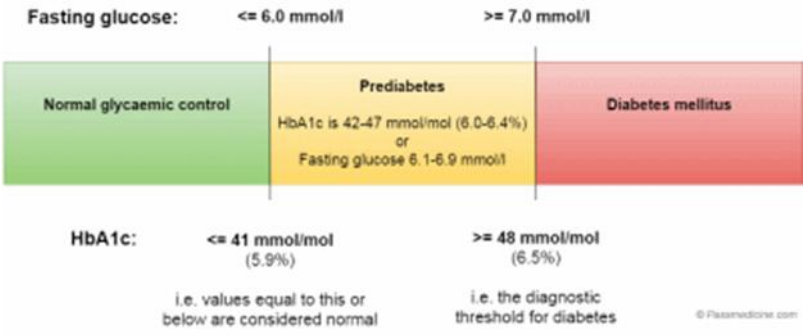


Diagram showing the spectrum of diabetes diagnosis

In 2011 WHO released supplementary guidance on the use of HbA1c on the diagnosis of diabetes:

- a HbA1c of greater than or equal to 48 mmol/mol (6.5%) is diagnostic of diabetes mellitus
- a HbAlc value of less than 48 mmol/mol (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

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

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.'

Diabetes mellitus: a very basic introduction

Diabetes mellitus is one of the most common conditions encountered in clinical practice and represents a significant burden on the health systems of the developed world. It is now estimated that 8% of the total NHS budget is now spent on managing patients with diabetes mellitus.

What is diabetes mellitus?

Diabetes mellitus may be defined as a chronic condition characterised by abnormally raised levels of blood glucose.

Why is the management of diabetes mellitus so important?

Before the advent of insulin therapy untreated type 1 diabetes would usually result in death. Poorly treated type 1 diabetes mellitus can still result in significant morbidity and mortality (as a result of diabetic ketoacidosis). However, the main focus of diabetes management now is reducing the incidence of macrovascular (ischaemic heart disease, stroke) and microvascular (eye, nerve and kidney damage) complications.

Types of diabetes mellitus

There are a number of different types of diabetes mellitus:

Type	Notes
Type 1 diabetes mellitus (T1DM)	Autoimmune disorder where the insulin-producing beta cells of the islets of Langerhans in the pancreas are destroyed by the immune system This results in an absolute deficiency of insulin resulting in raised glucose levels Patients tend to develop T1DM in childhood/early adult life and typically present unwell, possibly in diabetic ketoacidosis

Type	Notes
Type 2 diabetes mellitus (T2DM)	This is the most common cause of diabetes in the developed world. It is caused by a relative deficiency of insulin due to an excess of adipose tissue. In simple terms there isn't enough insulin to 'go around' all the excess fatty tissue, leading to blood glucose creeping up.
Prediabetes	This term is used for 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. They, therefore, require closer monitoring and lifestyle interventions such as weight loss
Gestational diabetes	Some pregnant develop raised glucose levels during pregnancy. This is important to detect as untreated it may lead to adverse outcomes for the mother and baby
Maturity onset diabetes of the young (MODY)	A group of inherited genetic disorders affecting the production of insulin. 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)	The majority of patients with autoimmune-related diabetes present younger in life. There are however a small group of patients who develop such problems later in life. These patients are often misdiagnosed as having T2DM
Other types	Any pathological process which damages the insulin-producing cells of the pancreas may cause diabetes to develop. Examples include chronic pancreatitis and haemochromatosis. Drugs may also cause raised glucose levels. A common example is glucocorticoids which commonly result in raised blood glucose levels

Symptoms and signs

The presentation of diabetes mellitus depends very much on the type:

Type 1 DM	Type 2 DM
Weight loss Polydipsia Polyuria May present with diabetic ketoacidosis - abdominal pain - vomiting - reduced consciousness level	Often picked up incidentally on routine blood tests Polydipsia Polyuria

Remember that the polyuria and polydipsia are due to water being 'dragged' out of the body due to the osmotic effects of excess blood glucose being excreted in the urine (glycosuria).

Investigations

There are 4 main ways to check blood glucose:

- a finger-prick bedside glucose monitor
- a one-off blood glucose. This may either be fasting or non-fasting
- a HbA1c. This measures the amount of glycosylated haemoglobin and represents the average blood glucose over the past 2-3 months
- a glucose tolerance test. In this test, a fasting blood glucose is taken after which a 75g glucose load is taken. After 2 hours a second blood glucose reading is then taken

The diagnostic criteria are determined by WHO.

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.

In 2011 WHO released supplementary guidance on the use of HbA1c for 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

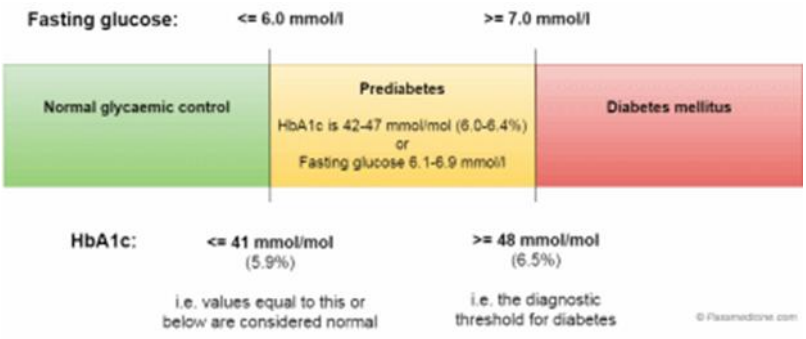


Diagram showing the spectrum of diabetes diagnosis

Management

The principle of managing diabetes mellitus are as follows:

- drug therapy to normalise blood glucose levels
- monitoring for and treating any complications related to diabetes
- modifying any other risk factors for other conditions such as cardiovascular disease

Type 1 diabetes

- patients always require insulin to control the blood sugar levels. This is because there is an absolute deficiency of insulin with no pancreatic tissue left to stimulate with drugs
- different types of insulin are available according to their duration of action

Type 2 diabetes

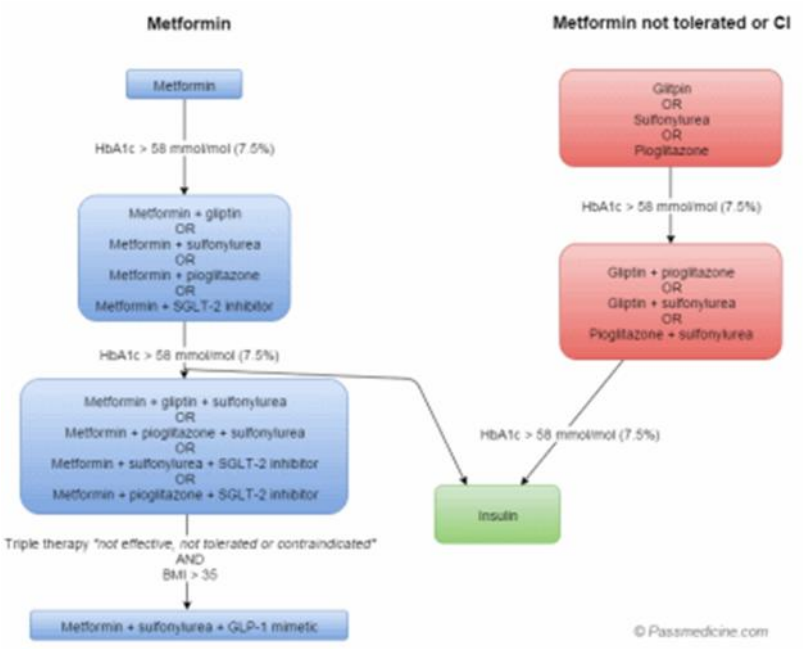
- the majority of patients with type 2 diabetes are controlled using oral medication
- the first-line drug for the vast majority of patients is metformin
- second-line drugs include sulfonylureas, gliptins and pioglitazone. Please see the table below for further information
- if oral medication is not controlling the blood glucose to a sufficient degree then insulin is used

The table below shows some of the main drugs used in the management of diabetes mellitus:

Drug class	Mechanism of action	Route	Main side-effects	Notes
Insulin	Direct replacement for endogenous insulin	Subcutaneous	Hypoglycaemia Weight gain Lipodystrophy	Used in all patients with T1DM and some patients with poorly controlled T2DM Can be classified according to source (analogue, human sequence and porcine) and duration of action (short, immediate, long-acting)
Metformin	Increases insulin sensitivity Decreases hepatic gluconeogenesis	Oral	Gastrointestinal upset Lactic acidosis*	First-line medication in the management of T2DM Cannot be used in patients with an eGFR of < 30 ml/min
Sulfonylureas	Stimulate pancreatic beta cells to secrete insulin	Oral	Hypoglycaemia Weight gain Hyponatraemia	Examples include gliclazide and glimepiride
Thiazolidinediones	Activate PPAR-gamma receptor in adipocytes to promote adipogenesis and fatty acid uptake	Oral	Weight gain Fluid retention	Only currently available thiazolidinedione is pioglitazone

Drug class	Mechanism of action	Route	Main side-effects	Notes
DPP-4 inhibitors (-gliptins)	Increases incretin levels which inhibit glucagon secretion	Oral	Generally well tolerated but increased risk of pancreatitis	
SGLT-2 inhibitors (-gliflozins)	Inhibits reabsorption of glucose in the kidney	Oral	Urinary tract infection	Typically result in weight loss
GLP-1 agonists (-tides)	Incretin mimetic which inhibits glucagon secretion	Subcutaneous	Nausea and vomiting Pancreatitis	Typically result in weight loss

NICE provide guidelines on how drug therapy should be used in T2DM:



*common in exams, much less common in clinical practice

Diabetes mellitus: management of type 2

NICE updated its guidance on the management of type 2 diabetes mellitus (T2DM) in 2015. Key points are listed below:

- 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

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%)

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

This is area which has changed in 2015

- 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%)

Practical examples

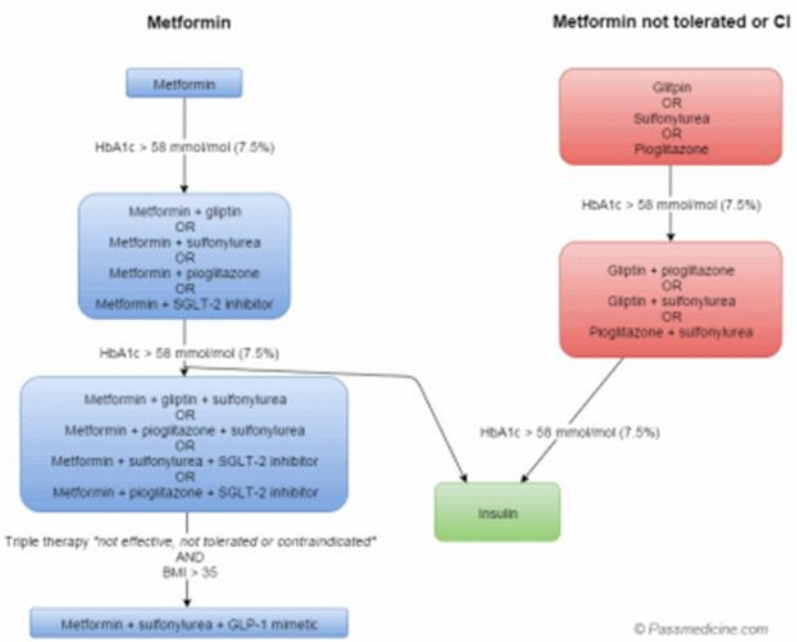
- a patient is newly diagnosed with HbA1c and wants to try lifestyle treatment first. You agree a target of 48 mmol/mol (6.5%)
- you review a patient 6 months after starting metformin. His HbA1c is 51 mmol/mol (6.8%). You increase his metformin from 500mg bd to 500mg tds and reinforce lifestyle factors

Patient already on treatment

Management of T2DM	HbA1c target
Already on one drug, but HbA1c has risen to 58 mmol/mol (7.5%)	53 mmol/mol (7.0%)

Drug treatment

The 2015 NICE guidelines introduced some changes into the management of type 2 diabetes. 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:
- → sulfonylurea
- → gliptin
- → pioglitazone
- → 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 obesityrelated 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

Practical examples

- 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

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

- 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

Risk factor modification

Blood pressure

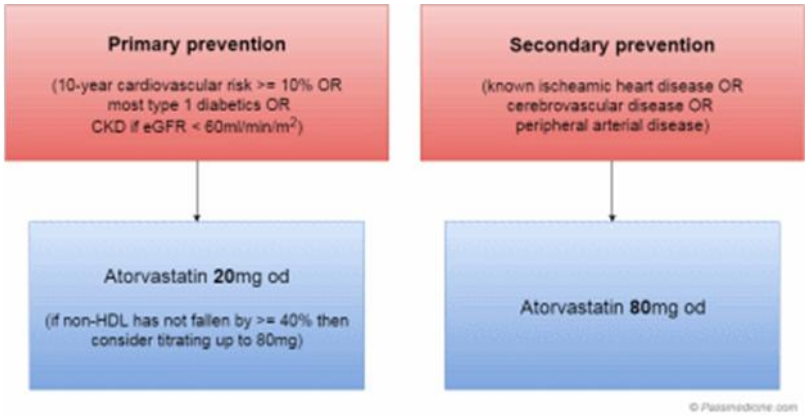
- target is < 140/80 mmHg (or < 130/80 mmHg if end-organ damage is present)
- ACE inhibitors are first-line

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



Graphic showing choice of statin.

*this is a bit confusing because isn't the diagnostic criteria for T2DM HbA1c 48 mmol/mol (6.5%)? So shouldn't all patients be offered metformin at diagnosis? Our interpretation of this is that some patients upon diagnosis will elect to try lifestyle measures, which may reduce their HbA1c below this level. If it then rises to the diagnostic threshold again metformin should be offered

Diabetes mellitus: Ramadan

We know that type 2 diabetes mellitus is more common in people of Asian ethnicity and a significant proportion of those patients in the UK will be Muslim. The BMJ published an excellent and comprehensive review of this issue in 2010[1].

It is important that we can give appropriate advice to Muslim patients to allow them safely observe their fast. This is particularly important from 2014 as Ramadan is due to fall in the long days of the summer months for several years henceforth.

Clearly it is a personal decision whether a patient decides to fast. It may however be worthwhile exploring the fact that people with chronic conditions are exempt from fasting or may be able to delay fasting to the shorter days of the winter months. It is however known that many Muslim patients with diabetes do not class themselves as having a chronic/serious condition which should exempt them from fasting. Around 79% of Muslim patients with type 2 diabetes mellitus fast Ramadan[2].There is an excellent patient information leaflet from Diabetes UK and the Muslim Council of Britain which explores these options in more detail.

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

Diabetes: pathophysiology

Type 1 DM

- autoimmune disease
- antibodies against beta cells of pancreas
- HLA DR4 > HLA DR3
- various antibodies such as islet-associated antigen (IAA) antibody and glutamic acid decarboxylase (GAD) antibody are detected in patients who later go on to develop type 1 DM - their prognostic significance is not yet clear

Diabetic ketoacidosis

Diabetic ketoacidosis may be a complication existing type 1 diabetes mellitus or be the first presentation, accounting for around 6% of cases. Whilst DKA remains a serious condition mortality rates have decreased from 8% to under 1% in the past 20 years.

The most common precipitating factors of DKA are infection, missed insulin doses and myocardial infarction

Features

- abdominal pain
- polyuria, polydipsia, dehydration
- Kussmaul respiration (deep hyperventilation)
- Acetone-smelling breath ('pear drops' smell)

Diagnostic criteria

American Diabetes Association (2009)	Joint British Diabetes Societies (2013)
Key points • glucose > 13.8 mmol/l • pH < 7.30 • serum bicarbonate <18 mmol/l • anion gap > 10 • ketonaemia	Key points • glucose > 11 mmol/l or known diabetes mellitus • pH < 7.3 • bicarbonate < 15 mmol/l • ketones > 3 mmol/l or urine ketones ++ on dipstick

Management

- fluid replacement: most patients with DKA are deplete around 5-8 litres. Isotonic saline is used initially. Please see an example fluid regime below.
- insulin: an intravenous infusion should be started at 0.1 unit/kg/hour. Once blood glucose is < 15 mmol/l an infusion of 5% dextrose should be started
- correction of hypokalaemia

JBDS example of fluid replacement regime for patient with a sSystolic 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
0.9% sodium chloride 1L with potassium chloride	1000ml over next 6 hours

Please note that slower infusion may be indicated in young adults (aged 18-25 years) as they are at greater risk of cerebral oedema.

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

Complications of DKA and its treatment

- gastric stasis
- thromboembolism
- arrhythmias secondary to hyperkalaemia/iatrogenic hypokalaemia
- iatrogenic due to incorrect fluid therapy: cerebral oedema, hypokalaemia, hypoglycaemia
- acute respiratory distress syndrome
- acute kidney injury

Diabetic neuropathy

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
- 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

Gastroparesis

- symptoms include erratic blood glucose control, bloating and vomiting
- management options include metoclopramide, domperidone or erythromycin (prokinetic agents)

Diabetic retinopathy

Diabetic retinopathy is the most common cause of blindness in adults aged 35-65 years-old. Hyperglycaemia is thought to cause increased retinal blood flow and abnormal metabolism in the retinal vessel walls. This precipitates damage to endothelial cells and pericytes

Endothelial dysfunction leads to increased vascular permeability which causes the characteristic exudates seen on fundoscopy. Pericyte dysfunction predisposes to the formation of microaneurysms. Neovasculization is thought to be caused by the production of growth factors in response to retinal ischaemia

In exams you are most likely to be asked about the characteristic features of the various stages/types of diabetic retinopathy. 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

- 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

Maculopathy

- based on location rather than severity, anything is potentially serious
- hard exudates and other 'background' changes on macula
- check visual acuity
- more common in Type II DM

Disorders of sex development

The table below lists the most common disorders of sex development:

Name	Karyotype	Notes
Androgen insensitivity syndrome	46 XY	X-linked recessive condition. Defect in androgen receptor results in end-organ resistance to testosterone causing genotypically male children (46XY) to have a female phenotype. Rudimentary vagina and testes present but no uterus. Testosterone, oestrogen and LH levels are elevated
5-α reductase deficiency	46 XY	Autosomal recessive condition. Results in the inability of males to convert testosterone to dihydrotestosterone (DHT). Individuals have ambiguous genitalia in the newborn period. Hypospadias is common. Virilization at puberty.
Male pseudohermaphroditism	46 XY	Individual has testes but external genitalia are female or ambiguous. may be secondary to androgen insensitivity syndrome
Female pseudohermaphroditism	46 XX	Individual has ovaries but external genitalia are male (virilized) or ambiguous. May be secondary to congenital adrenal hyperplasia
True hermaphroditism	46 XX or 47 XXY	Very rare, both ovarian and testicular tissue are present

DVLA: diabetes mellitus

Until recently people with diabetes who used insulin could not hold a HGV licence. The DVLA changed the rules in October 2011. The following standards need to be met (and also apply to patients using other hypoglycaemic inducing drugs such as sulfonylureas):

- there has not been any severe hypoglycaemic event in the previous 12 months
- the driver has full hypoglycaemic awareness
- the driver must show adequate control of the condition by regular blood glucose monitoring*, at least twice daily and at times relevant to driving
- the driver must demonstrate an understanding of the risks of hypoglycaemia
- here are no other debarring complications of diabetes

From a practical point of view patients on insulin who want to apply for a Group 2 (HGV) licence need to complete a VDIAB1I form.

Other specific points for group 1 drivers:

- 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 and no relevant visual impairment. Drivers are normally contacted by DVLA
- if on tablets or exenatide no need to notify DVLA. If tablets may induce hypoglycaemia (e.g. sulfonylureas) then there must not have been more than one episode of hypoglycaemia requiring the assistance of another person within the preceding 12 months
- if diet controlled alone then no requirement to inform DVLA

*to demonstrate adequate control, the Secretary of State's Honorary Medical Advisory Panel on Diabetes Mellitus has recommended that 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

Dynamic pituitary function tests

A dynamic pituitary function test is used to assess patients with suspected primary pituitary dysfunction

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

*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

Familial hypercholesterolaemia

Familial hypercholesterolaemia (FH) is an autosomal dominant condition that is thought to affect around 1 in 500 people. It results in high levels of LDL-cholesterol which, if untreated, may cause early cardiovascular disease (CVD). FH is caused by mutations in the gene which encodes the LDL-receptor protein.

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:
- for definite FH: tendon xanthoma in patients or 1st or 2nd degree relatives or DNA-based evidence of FH
- 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

- the use of CVD risk estimation using standard tables is not appropriate in FH as they do not accurately reflect the risk of CVD
- referral to a specialist lipid clinic is usually required
- 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

Gitelman's syndrome

Gitelman's syndrome is due to a defect in the thiazide-sensitive Na^+ Cl- transporter in the distal convoluted tubule.

Features

- hypokalaemia
- hypomagnesaemia
- hypocalciuria
- metabolic alkalosis
- normotension

Glycosylated haemoglobin

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. The level of HbA1c therefore is dependant on

- red blood cell lifespan
- average blood glucose concentration

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

HbA1c is generally thought to reflect the blood glucose over the previous '3 months' although there is some evidence it is weighed more strongly to glucose levels of the past 2-4 weeks. NICE recommend *'HbA1c should be checked every 3-6 months until stable, then 6 monthly'.*

The relationship between HbA1c and average blood glucose is complex but has been studied by the Diabetes Control and Complications Trial (DCCT). 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

HBA1c (%)	Average plasma glucose (mmol/l)	IFCC-HbA1c (mmol/mol)
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

Graves' disease: features

Graves' disease is the most common cause of thyrotoxicosis. It is typically seen in women aged 30-50 years.

Features

- typical features of thyrotoxicosis
- specific signs limited to Grave's (see below)

Features seen in Graves' but not in other causes of thyrotoxicosis

- eye signs (30% of patients): exophthalmos, ophthalmoplegia
- pretibial myxoedema
- thyroid acropachy

Autoantibodies

- TSH receptor stimulating antibodies (90%)
- anti-thyroid peroxidase antibodies (75%)

Graves' disease: management

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

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

Block-and-replace

- carbimazole is started at 40mg
- thyroxine is added when the patient is euthyroid
- treatment typically lasts for 6-9 months

The major complication of carbimazole therapy is agranulocytosis

Radioiodine 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
- 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

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
- testicular failure: e.g. mumps
- liver disease
- testicular cancer e.g. seminoma secreting hCG
- ectopic tumour secretion
- hyperthyroidism
- haemodialysis
- drugs: see below

Drug causes of gynaecomastia

- spironolactone (most common drug cause)
- cimetidine
- digoxin
- cannabis
- finasteride
- gonadorelin analogues e.g. Goserelin, buserelin
- oestrogens, anabolic steroids

Very rare drug causes of gynaecomastia

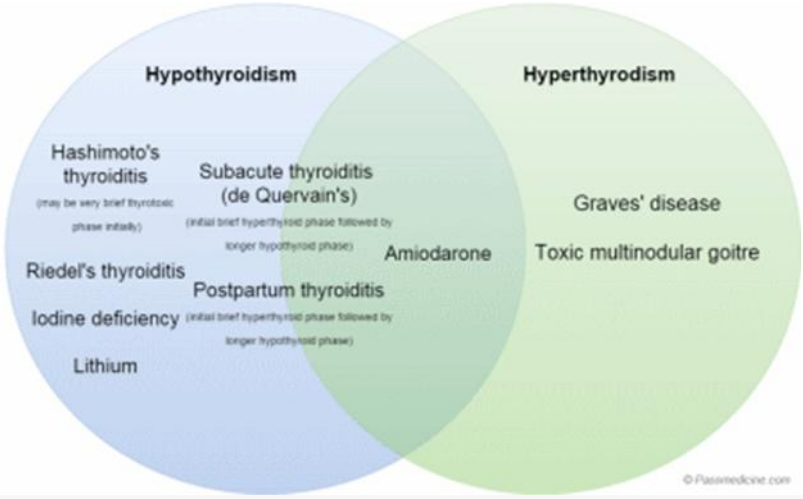
- tricyclics
- isoniazid
- calcium channel blockers
- heroin
- busulfan
- methyldopa

Hashimoto's thyroiditis

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. It is 10 times more common in women

Features

- features of hypothyroidism
- goitre: firm, non-tender
- anti-thyroid peroxidase and also anti-Tg antibodies



Venn diagram showing how different causes of thyroid dysfunction may manifest. Note how many causes of hypothyroidism may have an initial thyrotoxic phase.

Hypercalcaemia: causes

The most common causes of hypercalcaemia are malignancy (bone metastases, myeloma, PTHrP from squamous cell lung cancer) and primary hyperparathyroidism

Other causes include

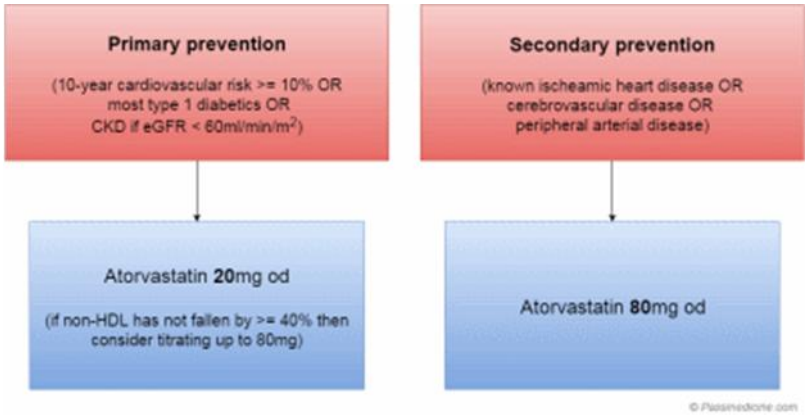
- sarcoidosis*
- vitamin D intoxication
- acromegaly
- thyrotoxicosis
- Milk-alkali syndrome
- drugs: thiazides, calcium containing antacids
- dehydration
- Addison's disease
- Paget's disease of the bone**

*other causes of granulomas may lead to hypercalcaemia e.g. Tuberculosis and histoplasmosis

**usually normal in this condition but hypercalcaemia may occur with prolonged immobilisation

Hyperlipidaemia: management

In 2014 NICE updated their guidelines on lipid modification. This proved highly controversial as it meant that we should be recommending statins to a significant proportion of the population over the age of 60 years. Anyway, the key points of the new guidelines are summarised below.



Graphic showing choice of statin.

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.

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.

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

These are in many ways predictable but NICE make a number of specific points:

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 musclestrengthening 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

- no specific advice is given, overweight patients should be managed in keeping with relevant NICE guidance

Alcohol intake

- again no specific advice, other than the general recommendation that males drink no more than 3-4 units/day and females no more than 2-3 units/day

Smoking cessation

- smokers should be encouraged to quit

Hyperlipidaemia: secondary causes

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

Hyperosmolar hyperglycaemic state

Hyperosmolar hyperglycaemic state (HHS) is confirmed by:

- Dehydration
- Osmolality >320mosmol/kg
- Hyperglycaemia >30 mmol/L with pH >7.3, bicarbonate >15mmolL and no significant ketonenaemia <3mmol/L

Hypoglycaemia

Causes

- insulinoma - increased ratio of proinsulin to insulin
- self-administration of insulin/sulphonylureas
- liver failure
- Addison's disease
- alcohol

Other possible causes in children

- nesidioblastosis - beta cell hyperplasia

Hypoparathyroidism

Primary hypoparathyroidism

- decrease PTH secretion
- e.g. secondary to thyroid surgery*
- 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

- target cells being insensitive to PTH
- due to abnormality in a G protein
- associated with low IQ, short stature, shortened 4th and 5th metacarpals
- low calcium, high phosphate, high PTH
- 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.

Pseudopseudohypoparathyroidism

- similar phenotype to pseudohypoparathyroidism but normal biochemistry

*this may seem an oxymoron, but most medical textbooks classify hypoparathyroidism which is secondary to surgery as being 'primary hypoparathyroidism'

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 hypothyroidism

Hashimoto's thyroiditis

- most common cause
- autoimmune disease, associated with IDDM, Addison's or pernicious anaemia
- may cause transient thyrotoxicosis in the acute phase
- 5-10 times more common in women

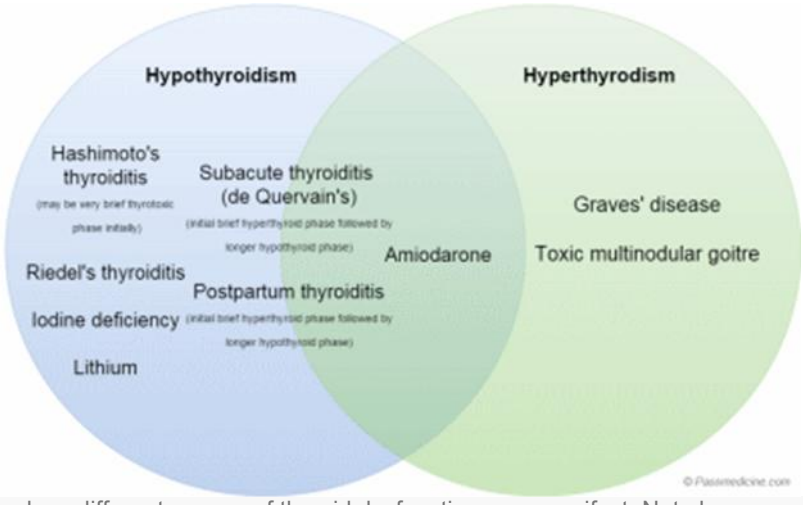
Subacute thyroiditis (de Quervain's)

Riedel thyroiditis

After thyroidectomy or radioiodine treatment

Drug therapy (e.g. lithium, amiodarone or anti-thyroid drugs such as carbimazole)

Dietary iodine deficiency



Venn diagram showing how different causes of thyroid dysfunction may manifest. Note how many causes of hypothyroidism may have an initial thyrotoxic phase.

Secondary hypothyroidism (rare)

From pituitary failure

Other associated conditions

- Down's syndrome
- Turner's syndrome
- coeliac disease

Hypothyroidism: management

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

Side-effects of thyroxine therapy

- hyperthyroidism: due to over treatment
- reduced bone mineral density
- worsening of angina
- atrial fibrillation

Interactions

- iron: absorption of levothyroxine reduced, give at least 2 hours apart

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

Insulinoma

An insulinoma is a neuroendocrine tumour deriving mainly from pancreatic Islets of Langerhans cells

Basics

- most common pancreatic endocrine tumour
- 10% malignant, 10% multiple
- of patients with multiple tumours, 50% have MEN-1

Features

- of hypoglycaemia: typically early in morning or just before meal, e.g. diplopia, weakness etc
- rapid weight gain may be seen
- high insulin, raised proinsulin:insulin ratio
- high C-peptide

Diagnosis

- supervised, prolonged fasting (up to 72 hours)
- CT pancreas

Management

- surgery
- diazoxide and somatostatin if patients are not candidates for surgery

Liddle's syndrome

Liddle's syndrome is a rare autosomal dominant condition that causes hypertension and hypokalaemic alkalosis. It is thought to be caused by disordered sodium channels in the distal tubules leading to increased reabsorption of sodium.

Treatment is with either amiloride or triamterene

Meglitinides

Meglitinides (e.g. repaglinide, nateglinide)

- insulin secretagogues
- like sulfonylureas they bind to an ATP-dependent K^+(K_{ATP}) channel on the cell membrane of pancreatic beta cells
- often used for patients with an erratic lifestyle
- adverse effects include weight gain and hypoglycaemia (less so than sulfonylureas)

Metabolic syndrome

Unfortunately there are a number of competing definitions of the metabolic syndrome around at the present time. It is thought that the key pathophysiological factor is insulin resistance.

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:

- elevated waist circumference: men > 102 cm, women > 88 cm
- elevated triglycerides: > 1.7 mmol/L
- reduced HDL: < 1.03 mmol/L in males and < 1.29 mmol/L in females
- raised blood pressure: > 130/85 mmHg, or active treatment of hypertension
- 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:

- raised triglycerides level: > 1.7 mmol/L, or specific treatment for this lipid abnormality
- reduced HDL cholesterol: < 1.03 mmol/L in males and < 1.29 mmol/L in females, or specific treatment for this lipid abnormality
- raised blood pressure: > 130/85 mm Hg, or active treatment of hypertension
- 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:

- blood pressure: > 140/90 mmHg
- dyslipidaemia: triglycerides: > 1.695 mmol/L and/or high-density lipoprotein cholesterol (HDL-C) < 0.9 mmol/L (male), < 1.0 mmol/L (female)
- central obesity: waist:hip ratio > 0.90 (male), > 0.85 (female), and/or body mass index > 30 kg/m2
- microalbuminuria: urinary albumin excretion ratio > 20 mg/min or albumin:creatinine ratio > 30 mg/g

Other associated features include:

- raised uric acid levels
- non-alcoholic fatty liver disease
- polycystic ovarian syndrome

MODY

Maturity-onset diabetes of the young (MODY) is characterised by the development of type 2 diabetes mellitus in patients < 25 years old. It is typically inherited as an autosomal dominant condition. Over six different genetic mutations have so far been identified as leading to MODY.

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.

MODY 3

- 60% of cases
- due to a defect in the HNF-1 alpha gene

MODY 2

- 20% of cases
- due to a defect in the glucokinase gene

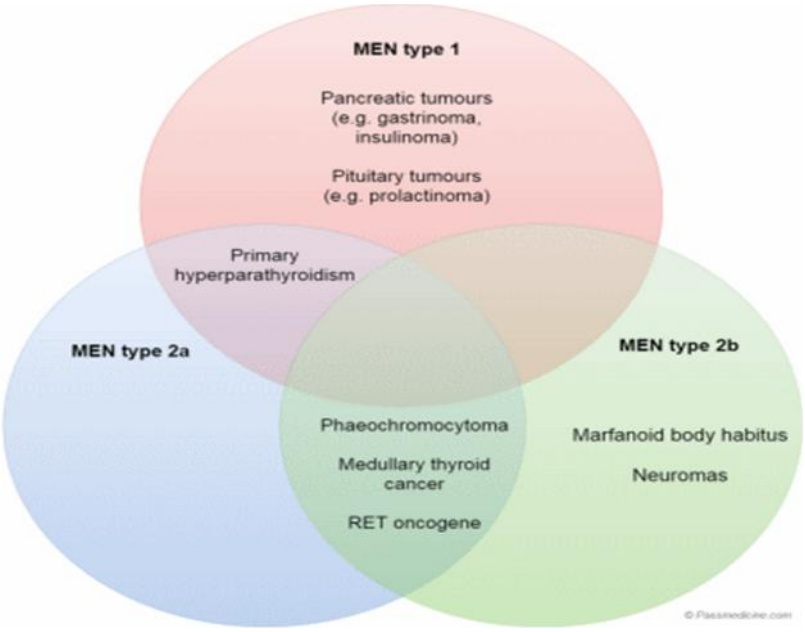
Features of MODY

- typically develops in patients < 25 years
- 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

Multiple endocrine neoplasia

The table below summarises the three main types of multiple endocrine neoplasia (MEN). MEN is inherited as an autosomal dominant disorder.

MEN type I	MEN type IIa	MEN type IIb
3 **P**'s **P**arathyroid (95%): hyperparathyroidism due to parathyroid hyperplasia **P**ituitary (70%) **P**ancreas (50%): e.g. insulinoma, gastrinoma (leading to recurrent peptic ulceration) Also: adrenal and thyroid	Medullary thyroid cancer (70%) 2 **P**'s **P**arathyroid (60%) **P**haeochromocytoma	Medullary thyroid cancer 1 **P** **P**haeochromocytoma Marfanoid body habitus Neuromas
MEN1 gene Most common presentation = hypercalcaemia	RET oncogene	RET oncogene



Venn diagram showing the different types of MEN and their associated features

Neuroblastoma

Neuroblastoma is one of the top five causes of cancer in children, accounting for around 7-8% of childhood malignancies. The tumour arises from neural crest tissue of the adrenal medulla (the most common site) and sympathetic nervous system.

Median age of onset is around 20 months

Features

- abdominal mass
- pallor, weight loss
- bone pain, limp
- hepatomegaly
- paraplegia
- proptosis

Investigation

- raised urinary vanillylmandelic acid (VMA) and homovanillic acid (HVA) levels
- calcification may be seen on abdominal x-ray
- biopsy

Obesity: bariatric surgery

The use of bariatric surgery in the management of obesity has developed significantly over the past decade. 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.

NICE guidelines on bariatric surgery for adults

Consider surgery for people with severe obesity if:

- they have a BMI of 40 kg/m^2 or more, or between 35 kg/m^2 and 40 kg/m^2 and other significant disease (for example, type 2 diabetes mellitus, hypertension) that could be improved if they lost weight
- 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

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)

Obesity: therapeutic options

The management of obesity consists of a step-wise approach:

- conservative: diet, exercise
- medical
- surgical

Orlistat is a pancreatic lipase inhibitor used in the management of obesity. Adverse effects include faecal urgency/incontinence and flatulence. 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, or
- BMI of 30 kg/m^2 or more
- 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, a specific CB1 cannabinoid receptor antagonist, was withdrawn
in October 2008 after the European Medicines Agency warned of serious psychiatric problems including suicide

Paget's disease of the bone

Paget's disease is a disease of increased but uncontrolled bone turnover. It is thought to be primarily a disorder of osteoclasts, with excessive osteoclastic resorption followed by increased osteoblastic activity. Paget's disease is common (UK prevalence 5%) but symptomatic in only 1 in 20 patients

Predisposing factors

- increasing age
- male sex
- northern latitude
- family history

Clinical features - only 5% of patients are symptomatic

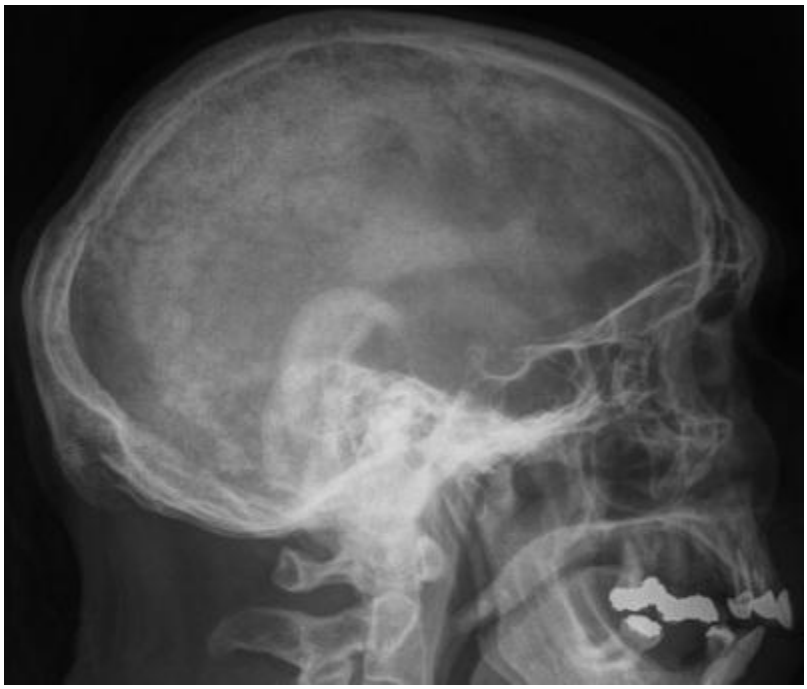
- bone pain (e.g. pelvis, lumbar spine, femur)
- classical, untreated features: bowing of tibia, bossing of skull
- raised alkaline phosphatase (ALP) - calcium* and phosphate are typically normal
- skull x-ray: thickened vault, osteoporosis circumscripta

Indications for treatment include bone pain, skull or long bone deformity, fracture, periarticular Paget's

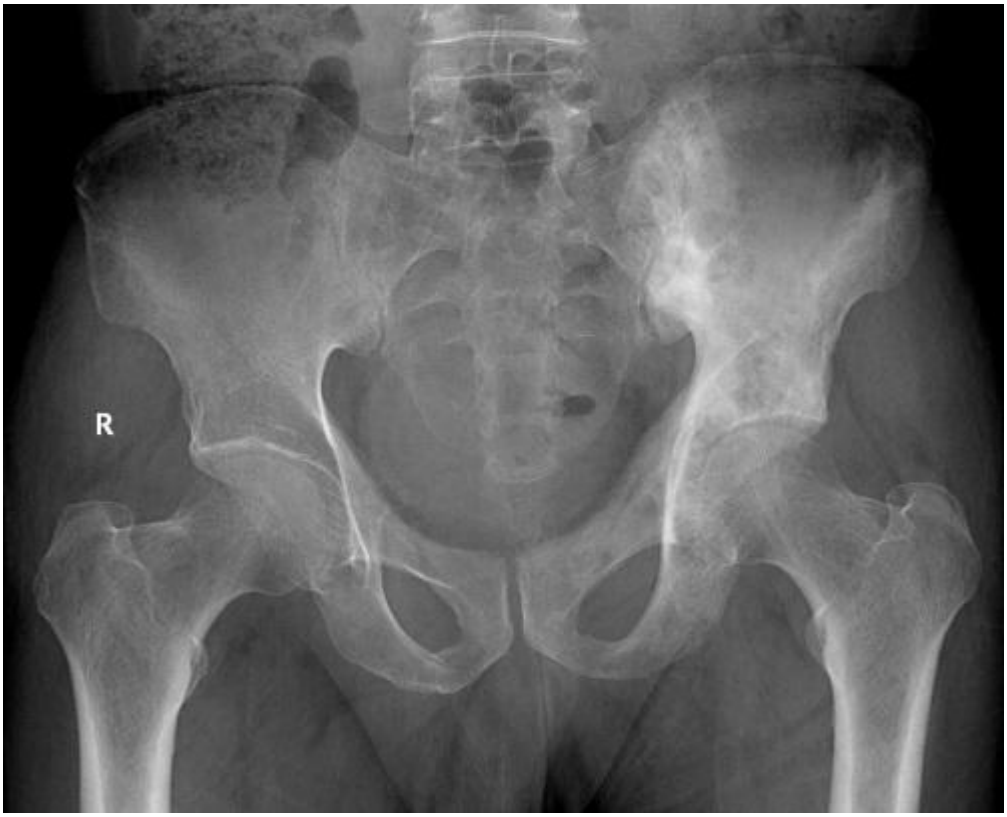
- bisphosphonate (either oral risedronate or IV zoledronate)
- calcitonin is less commonly used now

Complications

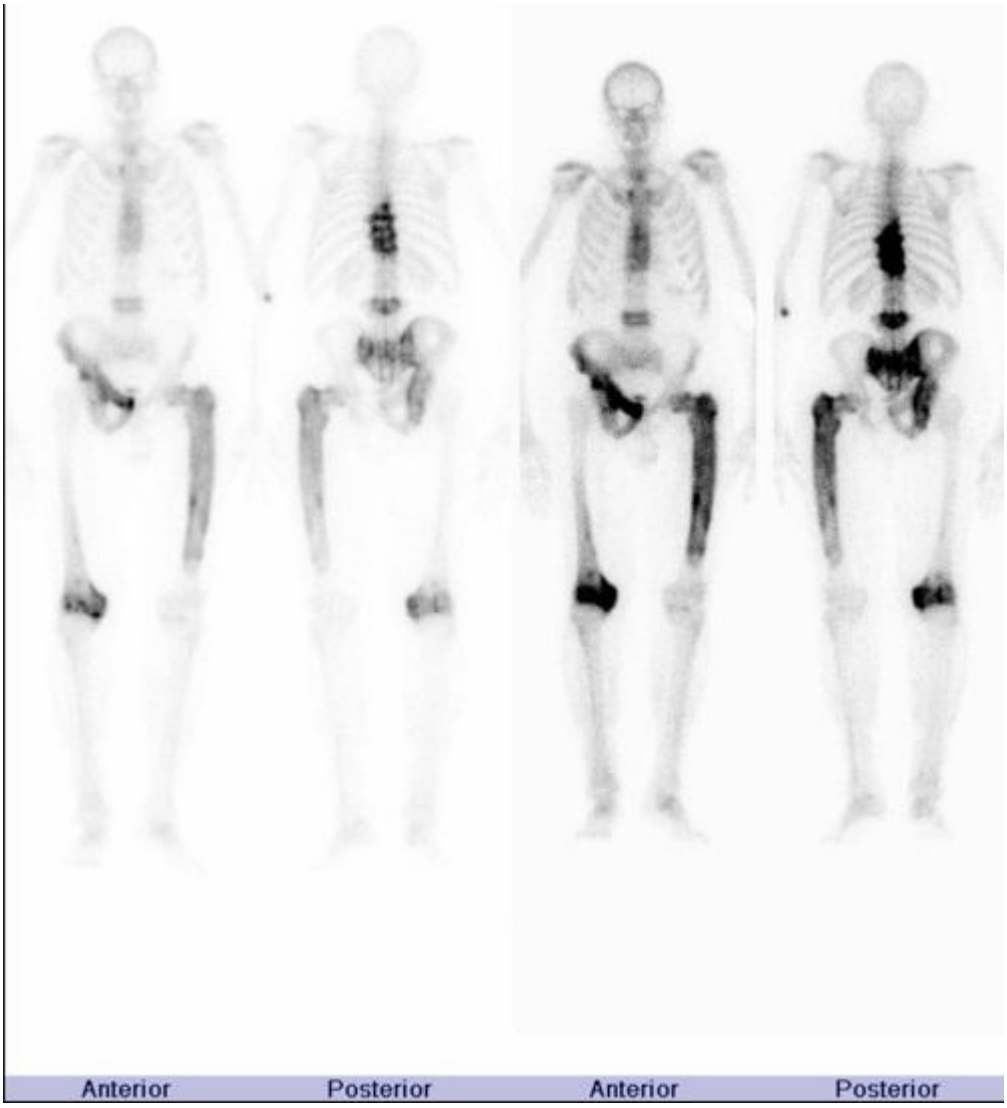
- deafness (cranial nerve entrapment)
- bone sarcoma (1% if affected for > 10 years)
- fractures
- skull thickening
- high-output cardiac failure



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.



Pelvic x-ray from an elderly man with Paget's disease. There is a smooth cortical expansion of the left hemipelvic bones with diffuse increased bone density and coarsening of trabeculae.



Isotope bone scan from a patient with Paget's disease showing a typical distribution in the spine, asymmetrical pelvic disease and proximal long bones.

*usually normal in this condition but hypercalcaemia may occur with prolonged immobilisation

Pendred's syndrome

Pendred is an autosomal recessive genetic disorder that is characterised by bilateral sensorineural deafness, with mild hypothyroidism and a goitre. The patients tend to present with progressive hearing loss and delay in academic progression. Often head trauma tends to make the sensorineural deafness worse, leading to patients having to avoid contact sports.

In Pendred syndrome there is a defect in the organification of iodine, leading to dyshormonogenesis. However thyroid symptoms in pendred syndrome are often mild and patients are often clinically euthyroid, presenting only with a goitre. Thyroid function tests are also often normal, requiring the perchlorate discharge test to aid diagnosis.

The syndrome can be 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 is with thyroid hormone replacement and cochlear implants.

Phaeochromocytoma

Phaeochromocytoma is a rare catecholamine secreting tumour. About 10% are familial and may be associated with MEN type II, neurofibromatosis and 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)
- headaches
- palpitations
- sweating
- anxiety

Tests

- 24 hr urinary collection of metanephrines (sensitivity 97%*)
- this has replaced a 24 hr urinary collection of catecholamines (sensitivity 86%)

Surgery is the definitive management. The patient must first however be stabilized with medical management:

- alpha-blocker (e.g. phenoxybenzamine), given before a
- beta-blocker (e.g. propranolol)

Polycystic ovarian syndrome: features and investigation

Polycystic ovary syndrome (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

- subfertility and infertility
- menstrual disturbances: oligomenorrhea and amenorrhoea
- hirsutism, acne (due to hyperandrogenism)
- obesity
- acanthosis nigricans (due to insulin resistance)

Investigations

- pelvic ultrasound: multiple cysts on the ovaries
- FSH, LH, prolactin, TSH, and testosterone are useful investigations: raised LH:FSH ratio is a 'classical' feature but is no longer thought to be useful in diagnosis. Prolactin may be normal or mildly elevated. Testosterone may be normal or mildly elevated - however, if markedly raised consider other causes
- check for impaired glucose tolerance

Pregnancy: diabetes mellitus

Diabetes mellitus may be a pre-existing problem or develop during pregnancy, gestational diabetes. It complicates around 1 in 40 pregnancies. NICE updated the guidance in 2015

Risk factors for gestational diabetes

- BMI of > 30 kg/m²
- previous macrosomic baby weighing 4.5 kg or above
- previous gestational diabetes
- first-degree relative with diabetes
- family origin with a high prevalence of diabetes (South Asian, black Caribbean and Middle Eastern)

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

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

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 selfmonitoring of blood glucose
- advice about diet (including eating foods with a low glycaemic index) and exercise should be given
- if the fasting plasma glucose level is < 7 mmol//l a 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
- 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
- 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

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

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

Pregnancy: thyroid problems

In pregnancy there is an increase in the levels of thyroxine-binding globulin (TBG). This causes an increase in the levels of total thyroxine but does not affect the free thyroxine level

Thyrotoxicosis

Untreated thyrotoxicosis increases the risk of fetal loss, maternal heart failure and premature labour

Graves' disease is the most common cause of thyrotoxicosis in pregnancy. It is also recognised that activation of the TSH receptor by HCG may also occur - often termed transient gestational hyperthyroidism. HCG levels will fall in second and third trimester

Management

- propylthiouracil has traditionally been the antithyroid drug of choice. This approach was supported by the 2007 Endocrine Society consensus guidelines
- 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
- block-and-replace regimes should not be used in pregnancy
- radioiodine therapy is contraindicated

Hypothyroidism

Key points

- thyroxine is safe during pregnancy
- serum thyroid stimulating hormone measured in each trimester and 6-8 weeks post-partum
- some women require an increased dose of thyroxine during pregnancy
- breast feeding is safe whilst on thyroxine

Primary hyperparathyroidism

In exams, primary hyperparathyroidism is stereotypically seen in elderly females with an unquenchable thirst and an inappropriately normal or raised parathyroid hormone level. It is most commonly due to a solitary adenoma

Causes of primary hyperparathyroidism

- 80%: solitary adenoma
- 15%: hyperplasia
- 4%: multiple adenoma
- 1%: carcinoma

Features - 'bones, stones, abdominal groans and psychic moans'

- polydipsia, polyuria
- peptic ulceration/constipation/pancreatitis
- bone pain/fracture
- renal stones
- depression
- hypertension

Associations

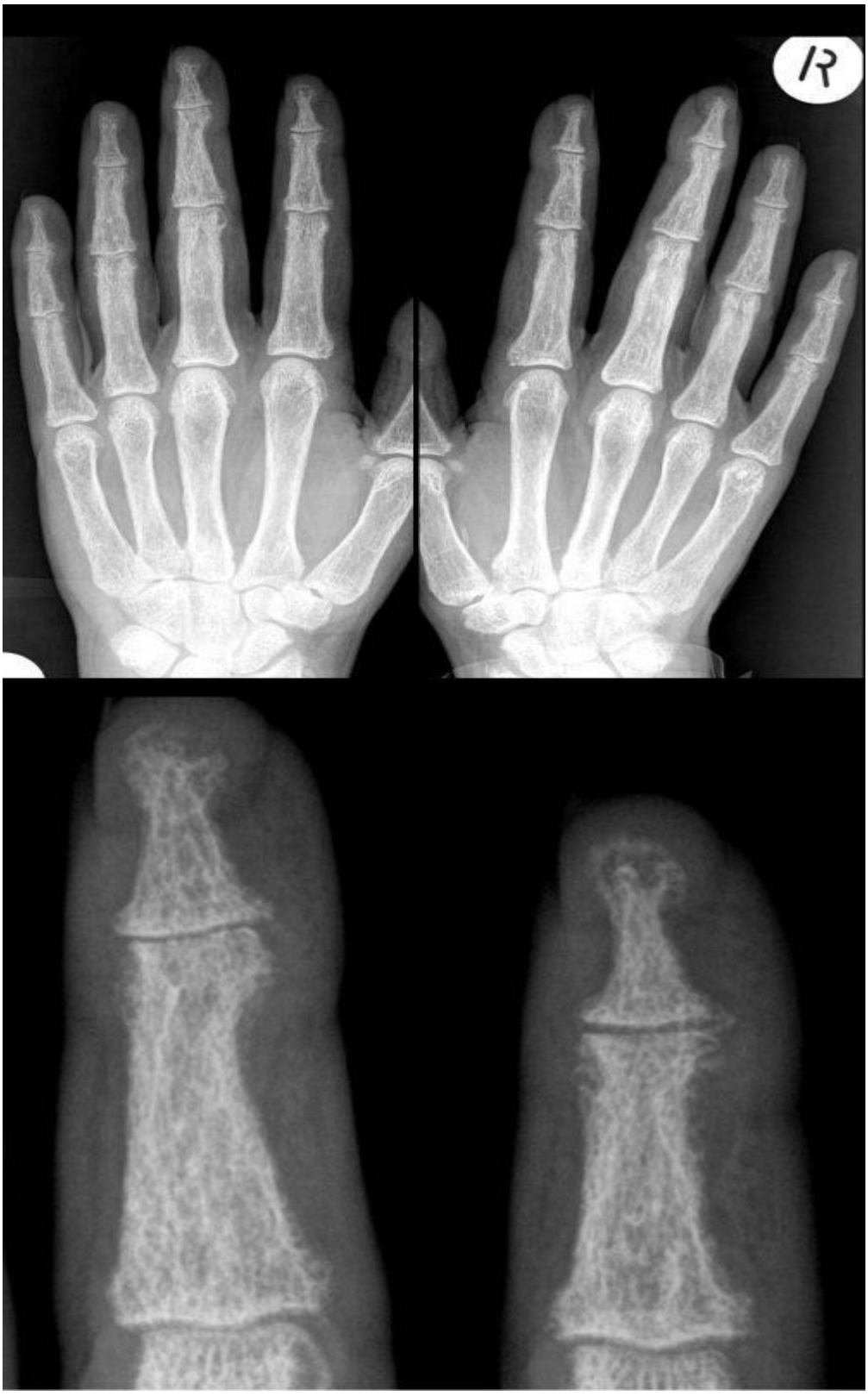
- hypertension
- multiple endocrine neoplasia: MEN I and II

Investigations

- raised calcium, low phosphate
- PTH may be raised or normal
- technetium-MIBI subtraction scan

Treatment

- total parathyroidectomy



Bilateral hand radiographs in a middle-aged woman demonstrating generalised osteopenia, erosion of the terminal phalangeal tufts (acro-osteolysis) and subperiosteal resorption of bone particularly the radial aspects of the 2nd and 3rd middle phalanges. These changes are consistent with a diagnosis of hyperparathyroidism.

Remnant hyperlipidaemia

Overview

- rare cause of mixed hyperlipidaemia (raised cholesterol and triglyceride levels)
- also known as Fredrickson type III hyperlipidaemia, broad-beta disease and dysbetalipoproteinaemia
- associated with apo-e2 homozygosity
- high incidence of ischaemic heart disease and peripheral vascular disease
- thought to be caused by impaired removal of intermediate density lipoprotein from the circulation by the liver

Features

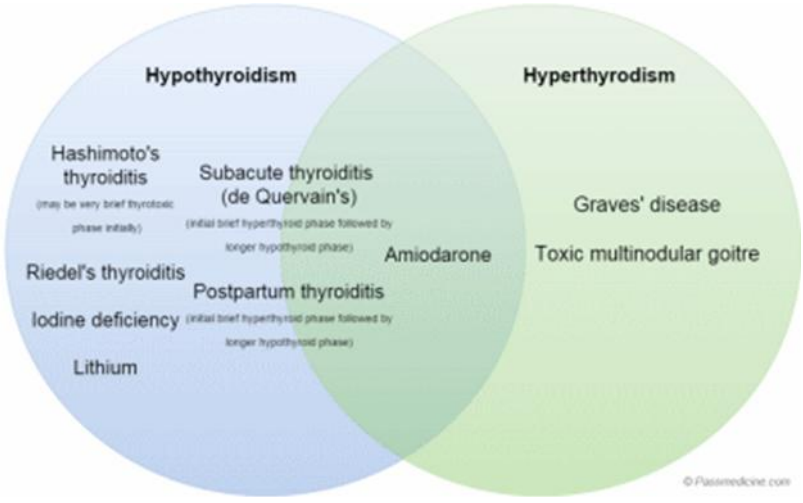
- yellow palmar creases
- palmer xanthomas
- tuberous xanthomas

Management

- fibrates are first line treatment

Riedel's thyroiditis

Riedel's thyroiditis is a rare cause of hypothyroidism characterised by dense fibrous tissue replacing the normal thyroid parenchyma. On examination a hard, fixed, painless goitre is noted. It is usually seen in middle-aged women. It is associated with retroperitoneal fibrosis.



Venn diagram showing how different causes of thyroid dysfunction may manifest. Note how many causes of hypothyroidism may have an initial thyrotoxic phase.

SGLT2 inhibitors

SGLT2 inhibitors reversibly inhibit sodium-glucose co-transporter 2 (SGLT2) in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion.

Examples include canagliflozin, dapagliflozin and empagliflozin

Important adverse effects include

- genital infection (secondary to glycosuria)
- diabetic ketoacidosis

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).

Changes are reversible upon recovery from the systemic illness.

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
- thyroid acropachy: clubbing
- scalp hair thinning
- increased sweating

Pruritus can occur in both hyper- and hypothyroidism

Subacute (De Quervain's) thyroiditis

Subacute thyroiditis (also known as De Quervain's thyroiditis and subacute granulomatous thyroiditis) is thought to occur following viral infection and typically presents with hyperthyroidism.

There are typically 4 phases;

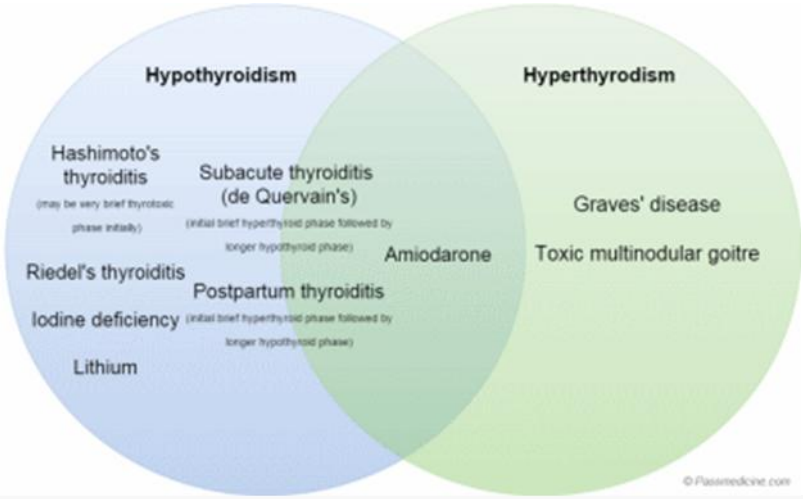
- phase 1 (lasts 3-6 weeks): hyperthyroidism, painful goitre, raised ESR
- phase 2 (1-3 weeks): euthyroid
- phase 3 (weeks - months): hypothyroidism
- phase 4: thyroid structure and function goes back to normal

Investigations

- globally reduced uptake on iodine-131 scan

Management

- usually self-limiting - most patients do not require treatment
- thyroid pain may respond to aspirin or other NSAIDs
- in more severe cases steroids are used, particularly if hypothyroidism develops



Venn diagram showing how different causes of thyroid dysfunction may manifest. Note how many causes of hypothyroidism may have an initial thyrotoxic phase.

Subclinical hyperthyroidism

Subclinical hyperthyroidism is an entity which is gaining increasing recognition. 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

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

Sulfonylureas

Sulfonylureas are oral hypoglycaemic drugs used in the management of type 2 diabetes mellitus. They work by increasing pancreatic insulin secretion and hence are only effective if functional B-cells are present. On a molecular level they bind to an ATP-dependent K^+(K_{ATP}) channel on the cell membrane of pancreatic beta cells.

Common adverse effects

- hypoglycaemic episodes (more common with long acting preparations such as chlorpropamide)
- weight gain

Rarer adverse effects

- syndrome of inappropriate ADH secretion
- bone marrow suppression
- liver damage (cholestatic)
- peripheral neuropathy

Sulfonylureas should be avoided in breast feeding and pregnancy

Thiazolidinediones

Thiazolidinediones are a class of agents used in the treatment of type 2 diabetes mellitus. They are agonists to the PPAR-gamma receptor and reduce peripheral insulin resistance. Rosiglitazone was withdrawn in 2010 following concerns about the cardiovascular side-effect profile.

The PPAR-gamma receptor is an intracellular nuclear receptor. It's natural ligands are free fatty acids and it is thought to control adipocyte differentiation and function.

Adverse effects

- weight gain
- liver impairment: monitor LFTs
- fluid retention - therefore contraindicated in heart failure. The risk of fluid retention is increased if the patient also takes insulin
- recent studies have indicated an increased risk of fractures
- bladder cancer: recent studies have shown an increased risk of bladder cancer in patients taking pioglitazone (hazard ratio 2.64)

Thyroid cancer

Features of hyperthyroidism or hypothyroidism are not commonly seen in patients with thyroid malignancies as they rarely secrete thyroid hormones

Main points

Type	Percentage	
Papillary	70%	Often young females - excellent prognosis
Follicular	20%	
Medullary	5%	Cancer of parafollicular (C) cells, secrete calcitonin, part of MEN-2
Anaplastic	1%	Not responsive to treatment, can cause pressure symptoms
Lymphoma	Rare	Associated with Hashimoto's

Management of papillary and follicular cancer

- total thyroidectomy
- followed by radioiodine (I-131) to kill residual cells
- yearly thyroglobulin levels to detect early recurrent disease

Further information

Type	Notes
Papillary carcinoma	• Usually contain a mixture of papillary and colloidal filled follicles • Histologically tumour has papillary projections and pale empty nuclei • Seldom encapsulated • Lymph node metastasis predominate • Haematogenous metastasis rare
Follicular adenoma	• Usually present as a solitary thyroid nodule • Malignancy can only be excluded on formal histological assessment
Follicular carcinoma	• May appear macroscopically encapsulated, microscopically capsular invasion is seen. Without this finding the lesion is a follicular adenoma. • Vascular invasion predominates • Multifocal disease raree
Medullary carcinoma	• C cells derived from neural crest and not thyroid tissue • Serum calcitonin levels often raised • Familial genetic disease accounts for up to 20% cases • Both lymphatic and haematogenous metastasis are recognised, nodal disease is associated with a very poor prognosis.
Anaplastic carcinoma	• Most common in elderly females • Local invasion is a common feature • Treatment is by resection where possible, palliation may be achieved through isthmusectomy and radiotherapy. Chemotherapy is ineffective.

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 maintain normal circulating levels of the hormone, in this case thyroxine and triiodothyronine.

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

Whilst there are a number of causes thyrotoxicosis the vast majority are primary in nature. Congenital thyrotoxicosis is not seen and secondary hyperthyroidism is rare, account for less than 1% of cases.

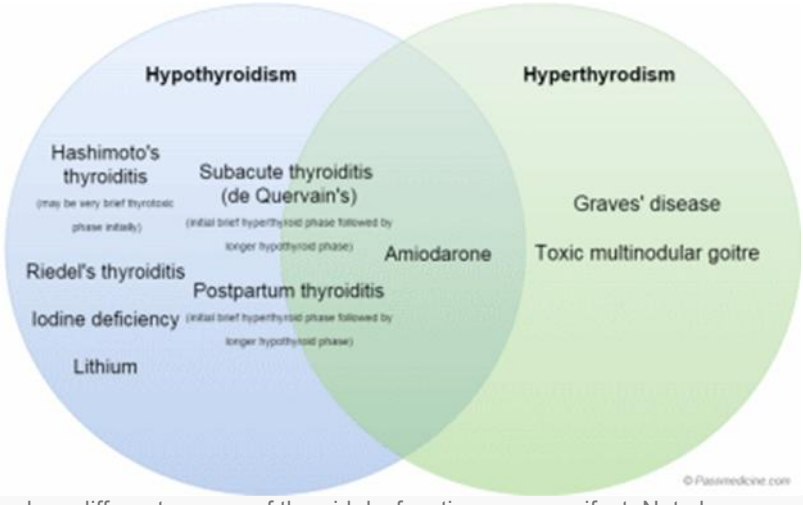
What causes thyroid problems?

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** **Lethargy** **Cold intolerance**	**Weight loss** 'Manic', restlessness Heat intolerance
Cardiac	-	**Palpitations**, may even provoke arrhythmias e.g. atrial fibrillation
Skin	Dry (anhydrosis), cold, yellowish skin Non-pitting oedema (e.g. hands, face) Dry, coarse scalp hair, loss of lateral aspect of eyebrows	Increased sweating Pretibial myxoedema: erythematous, oedematous lesions above the lateral malleoli Thyroid acropachy: clubbing

Feature	Hypothyroidism	Thyrotoxicosis
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
- 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

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
- 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

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

Thyroid eye disease

Thyroid eye disease affects between 25-50% of patients with Graves' disease.

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

Prevention

- smoking is the most important modifiable risk factor for the development of thyroid eye disease
- radioiodine treatment may increase the inflammatory symptoms seen in thyroid eye disease. In a recent study of patients with Graves' disease around 15% developed, or had worsening of, eye disease. Prednisolone may help reduce the risk

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 may be needed to help prevent corneal inflammation caused by exposure
- steroids
- radiotherapy
- surgery

Monitoring patients with established thyroid eye disease

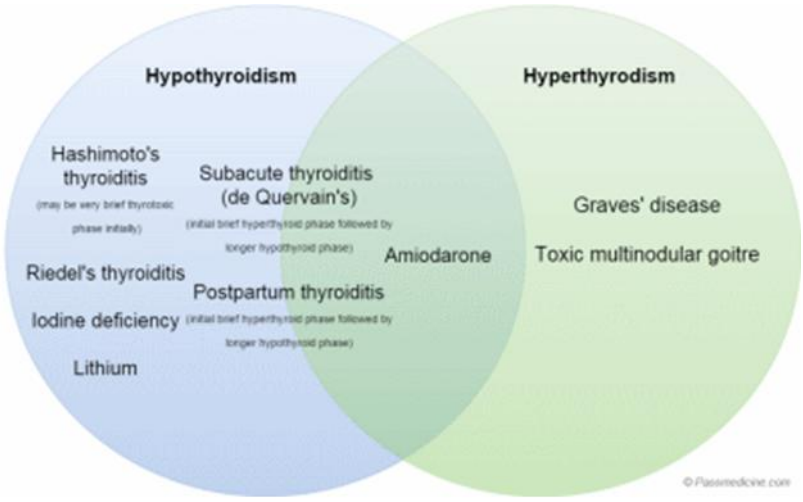
For patients with established thyroid eye disease the following symptoms/signs should indicate the need for urgent review by an ophthalmologist (see EUGOGO guidelines):

- unexplained deterioration in vision
- awareness of change in intensity or quality of colour vision in one or both eyes
- history of eye suddenly 'popping out' (globe subluxation)
- obvious corneal opacity
- cornea still visible when the eyelids are closed
- disc swelling

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	



Venn diagram showing how different causes of thyroid dysfunction may manifest. Note how many causes of hypothyroidism may have an initial thyrotoxic phase.

*now referred to as non-thyroidal illness
**TSH may be normal in some cases

Thyroid storm

Thyroid storm is a rare but life-threatening complication of thyrotoxicosis. 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

Clinical features include:

- fever > 38.5ºC
- tachycardia
- confusion and agitation
- nausea and vomiting
- hypertension
- heart failure
- abnormal liver function test

Management

- symptomatic treatment e.g. paracetamol
- treatment of underlying precipitating event
- propranolol
- anti-thyroid drugs: e.g. methimazole or propylthiouracil
- Lugol's iodine
- dexamethasone - e.g. 4mg IV qds - blocks the conversion of T4 to T3

Thyrotoxicosis

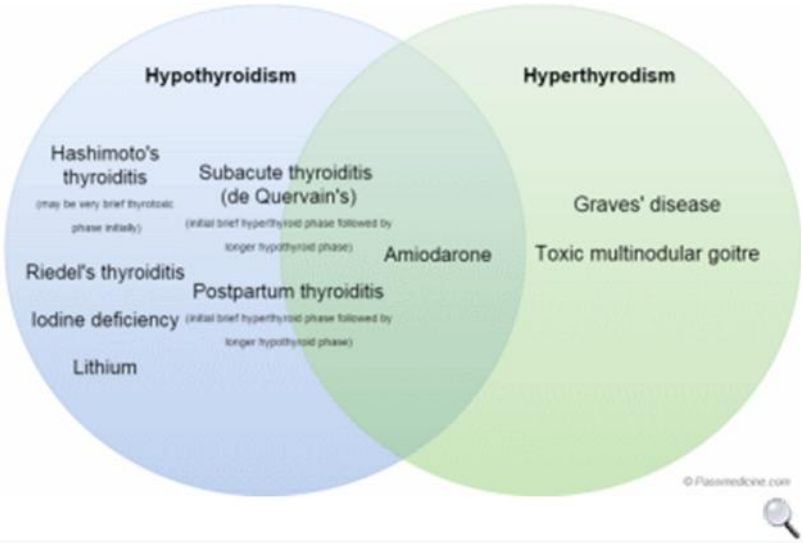
Graves' disease accounts for around 50-60% of cases of thyrotoxicosis.

Causes

- Graves' disease
- toxic nodular goitre
- acute phase of subacute (de Quervain's) thyroiditis
- acute phase of post-partum thyroiditis
- acute phase of Hashimoto's thyroiditis (later results in hypothyroidism)
- amiodarone therapy

Investigation

- TSH down, T4 and T3 up
- thyroid autoantibodies
- other investigations are not routinely done but includes isotope scanning



Venn diagram showing how different causes of thyroid dysfunction may manifest. Note how many causes of hypothyroidism may have an initial thyrotoxic phase.

Toxic multinodular goitre

Toxic multinodular goitre describes a thyroid gland that contains a number of :

Nuclear scintigraphy reveals patchy uptake

The treatment of choice is radioiodine therapy

Water deprivation test

Method

- prevent patient drinking water
- ask patient to empty bladder
- hourly urine and plasma osmolalities

	Starting plasma osm.	**Final urine osm.**	**Urine osm. post-DDAVP**
Normal	Normal	> 600	> 600
Psychogenic polydipsia	Low	> 400	> 400
Cranial DI	High	< 300	> 600
Nephrogenic DI	High	< 300	< 300

Gastroenterology

Abdominal pain

The table below gives characteristic exam question features for conditions causing abdominal pain. Unusual and 'medical' causes of abdominal pain should also be remembered:

- myocardial infarction
- diabetic ketoacidosis
- pneumonia
- acute intermittent porphyria
- lead poisoning

Condition	Characteristic exam feature
Peptic ulcer disease	Duodenal ulcers: more common than gastric ulcers, epigastric pain relieved by eating Gastric ulcers: epigastric pain worsened by eating Features of upper gastrointestinal haemorrhage may be seen (haematemesis, melena etc)
Appendicitis	Pain initial in the central abdomen before localising to the right iliac fossa Anorexia is common Tachycardia, low-grade pyrexia, tenderness in RIF Rovsing's sign: more pain in RIF than LIF when palpating LIF
Acute pancreatitis	Usually due to alcohol or gallstones Severe epigastric pain Vomiting is common Examination may reveal tenderness, ileus and low-grade fever Periumbilical discolouration (Cullen's sign) and flank discolouration (Grey-Turner's sign) is described but rare

Condition	Characteristic exam feature
Biliary colic	Pain in the RUQ radiating to the back and interscapular region, may be following a fatty meal. Slight misnomer as the pain may persist for hours Obstructive jaundice may cause pale stools and dark urine It is sometimes taught that patients are female, forties, fat and fair although this is obviously a generalisation
Acute cholecystitis	History of gallstones symptoms (see above) Continuous RUQ pain Fever, raised inflammatory markers and white cells Murphy's sign positive (arrest of inspiration on palpation of the RUQ)
Diverticulitis	Colicky pain typically in the LLQ Fever, raised inflammatory markers and white cells
Abdominal aortic aneurysm	Severe central abdominal pain radiating to the back Presentation may be catastrophic (e.g. Sudden collapse) or sub-acute (persistent severe central abdominal pain with developing shock) Patients may have a history of cardiovascular disease
Intestinal obstruction	History of malignancy/previous operations Vomiting Not opened bowels recently 'Tinkling' bowel sounds

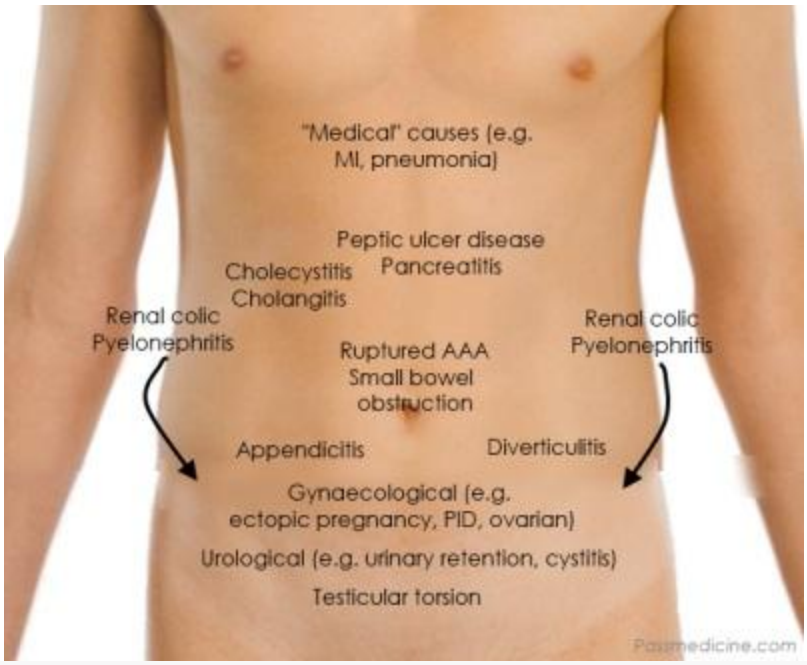


Diagram showing stereotypical areas where particular conditions present. The diagram is not exhaustive and only lists the more common conditions seen in clinical practice. Note how pain from renal causes such as renal/ureteric colic and pyelonephritis may radiate and move from the loins towards the suprapubic area.

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. Achalasia typically presents in middle-age and is equally common in men and women.

Clinical features

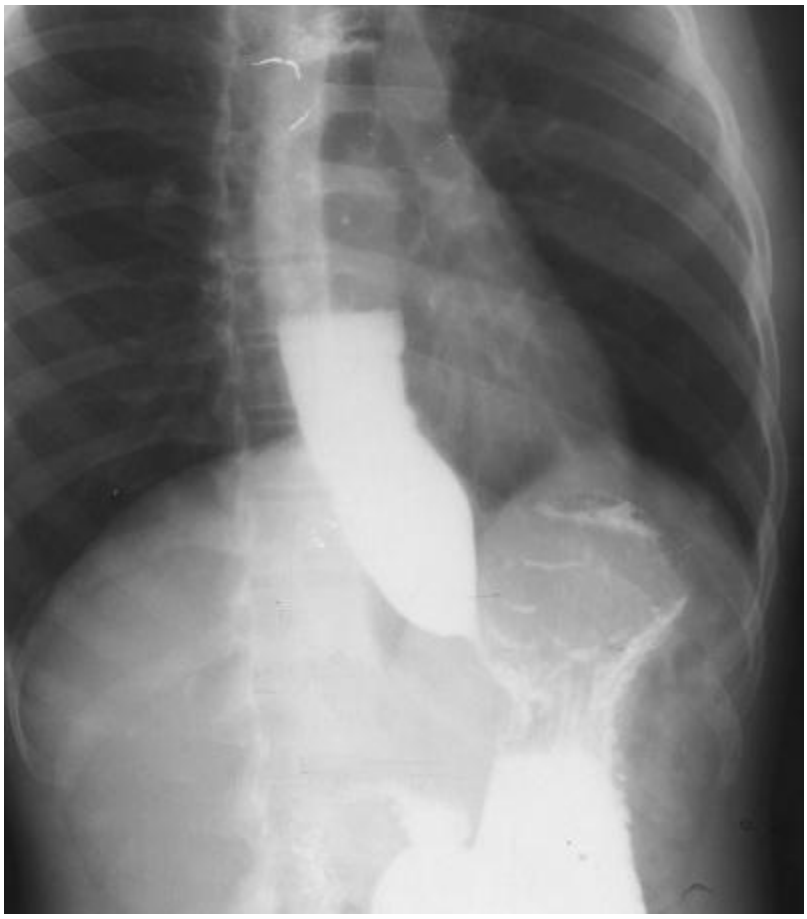
- dysphagia of BOTH liquids and solids
- typically variation in severity of symptoms
- heartburn
- regurgitation of food - may lead to cough, aspiration pneumonia etc
- malignant change in small number of patients

Investigations

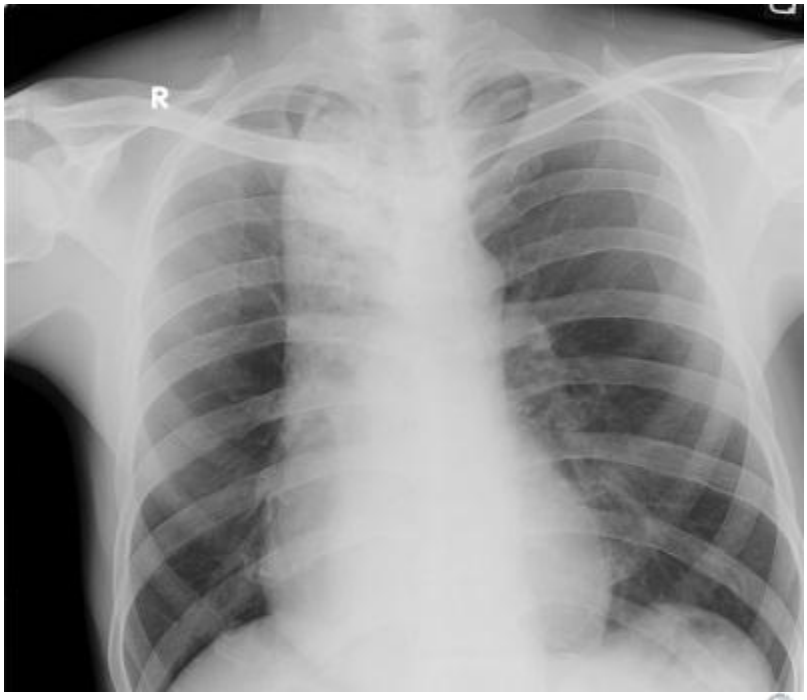
- manometry: excessive LOS tone which doesn't relax on swallowing - considered most important diagnostic test
- barium swallow shows grossly expanded oesophagus, fluid level, 'bird's beak' appearance
- CXR: wide mediastinum, fluid level

Treatment

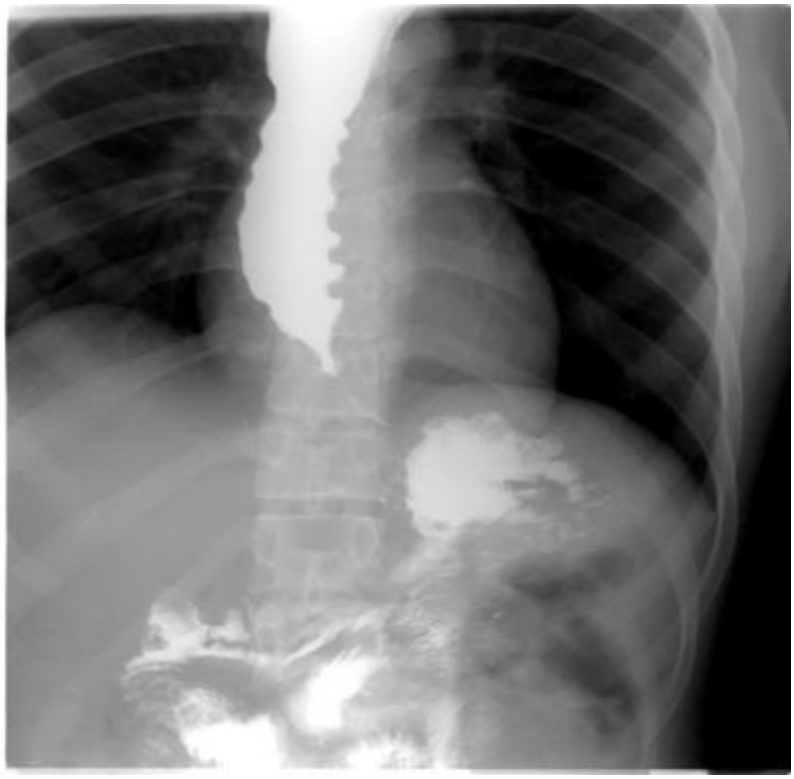
- intra-sphincteric injection of botulinum toxin
- Heller cardiomyotomy
- balloon dilation
- drug therapy has a role but is limited by side-effects



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

Acute appendicitis

History

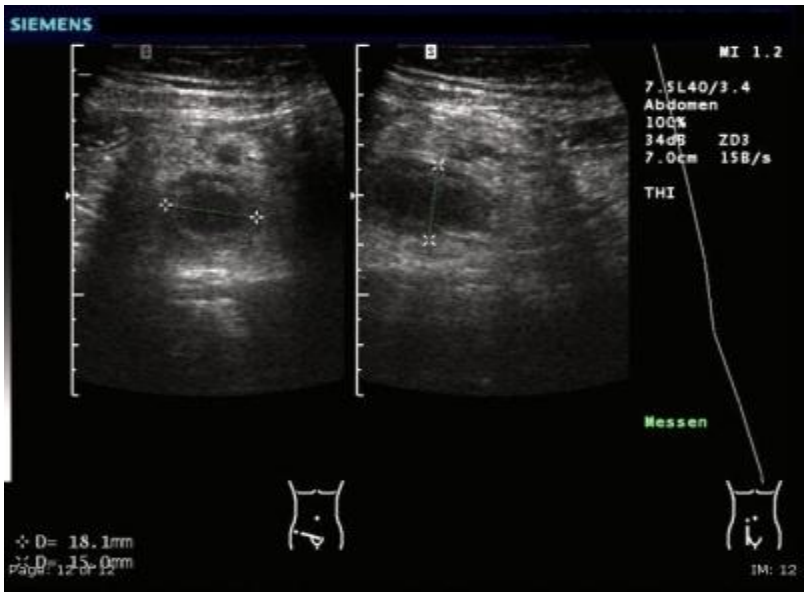
- peri-umbilical abdominal pain (visceral stretching of appendix lumen and appendix is mid gut structure) radiating to the right iliac fossa due to localised parietal peritoneal inflammation
- vomit once or twice but marked and persistent vomiting is unusual
- diarrhoea is rare. However, pelvic appendicitis may cause localised rectal irritation of some loose stools. A pelvic abscess may also cause diarrhoea
- mild pyrexia is common - temperature is usually 37.5-38°C. Higher temperatures are more typical of conditions like mesenteric adenitis
- anorexia is very common. It is very unusual for patients with appendicitis to be hungry
- around 50% of patients have the typical symptoms of anorexia, peri-umbilical pain and nausea followed by more localised right lower quadrant pain

Examination

- generalised peritonitis if perforation has occurred or localised peritonism
- retrocaecal appendicitis may have relatively few signs
- digital rectal examination may reveal boggy sensation if pelvic abscess is present, or even tenderness with a pelvic appendix

Diagnosis

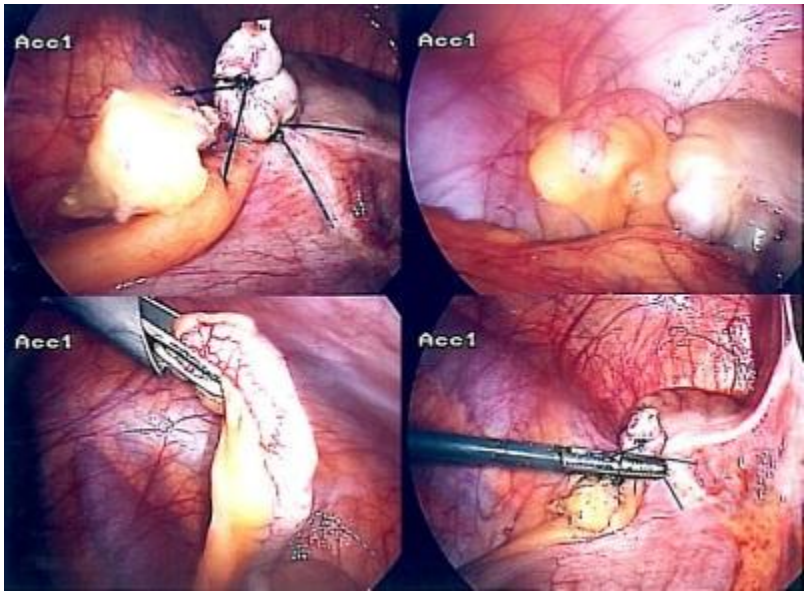
- typically raised inflammatory markers coupled with compatible history and examination findings should be enough to justify appendicectomy.
- urine analysis may show mild leucocytosis but no nitrites.
- ultrasound is useful in females where pelvic organ pathology is suspected. Although it is not always possible to visualise the appendix on ultrasound, the presence of free fluid (always pathological in males) should raise suspicion.



Ultrasound examination may show evidence of lumenal obstruction and thickening of the appendiceal wall as shown below

Management

- appendicectomy which can be performed via either an open or laparoscopic approach.
- administration of metronidazole reduces wound infection rates.
- patients with perforated appendicitis require copious abdominal lavage.
- patients without peritonitis who have an appendix mass should receive broad spectrum antibiotics and consideration given to performing an interval appendicectomy.
- be wary in the older patients who may have either an underlying caecal malignancy or perforated sigmoid diverticular disease.



Laparoscopic appendicectomy is becoming increasing popular as demonstrated below

Acute pancreatitis: features

Rare features associated with pancreatitis include:

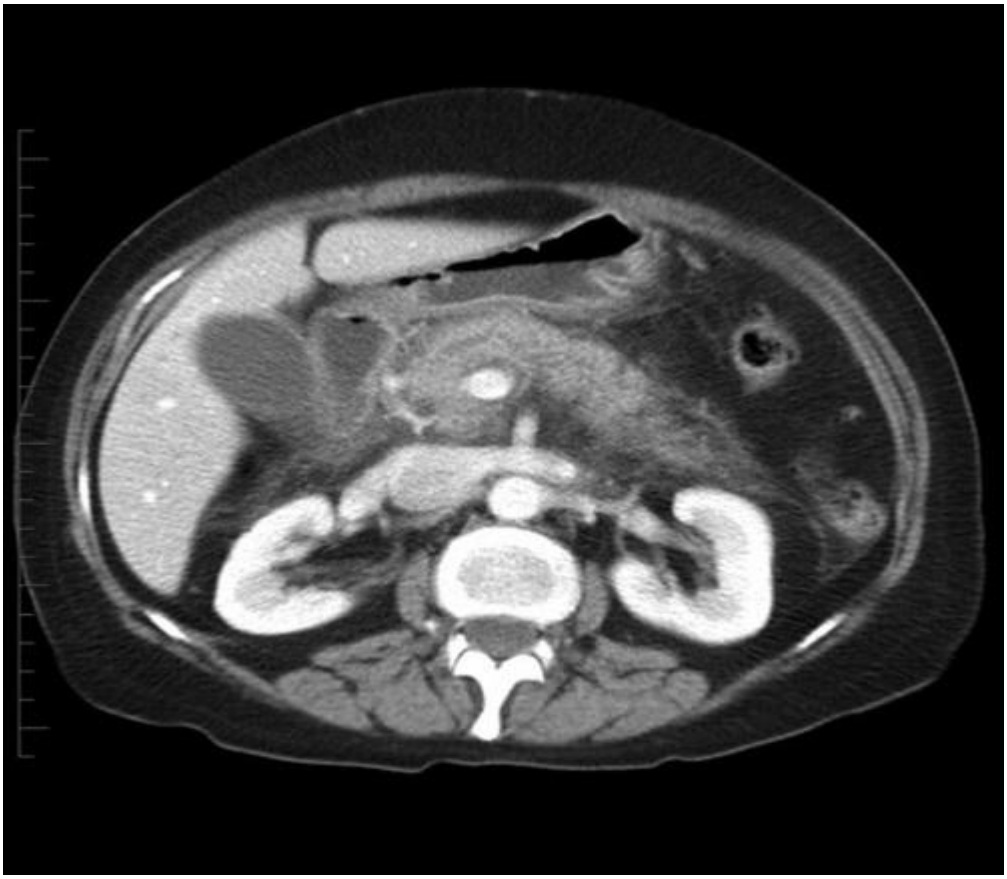
- ischaemic (Purtscher) retinopathy - may cause temporary or permanent blindness

Acute pancreatitis: causes

The vast majority of cases in the UK are caused by gallstones and alcohol

Popular mnemonic is **GET SMASHED**

- **G**allstones
- **E**thanol
- **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
- **D**rugs (azathioprine, mesalazine*, didanosine, bendroflumethiazide, furosemide, pentamidine, steroids, sodium valproate)



CT from a patient with acute pancreatitis. Note the diffuse parenchymal enlargement with oedema and indistinct margins.

*pancreatitis is 7 times more common in patients taking mesalazine than sulfasalazine

Acute upper gastrointestinal bleeding

NICE published guidelines in 2012 on the management of acute upper gastrointestinal bleeding which is most commonly due to either peptic ulcer disease or oesophageal varices. Some of the key points are detailed below.

Risk assessment

- use the Blatchford score at first assessment, and
- the full Rockall score after endoscopy

Blatchford score

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 • 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

Resuscitation

- ABC, wide-bore intravenous access * 2
- 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

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
- 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

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

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

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
- mesalazine is still however associated with side-effects such as GI upset, headache, agranulocytosis, pancreatitis*, interstitial nephritis

Olsalazine

- two molecules of 5-ASA linked by a diazo bond, which is broken by colonic bacteria

*pancreatitis is 7 times more common in patients taking mesalazine than sulfasalazine

Amoebiasis

Amoebiasis is caused by *Entamoeba histolytica* (an amoeboid protozoan) and spread by the faecal-oral route. It is estimated that 10% of the world's population is chronically infected. Infection can be asymptomatic, cause mild diarrhoea or severe amoebic dysentery. Amoebiasis also causes liver and colonic abscesses

Amoebic dysentery

- profuse, bloody diarrhoea
- stool microscopy may show trophozoites
- treatment is with metronidazole

Amoebic liver abscess

- usually a single mass in the right lobe (may be multiple)
- features: fever, RUQ pain
- serology positive in > 90%

Anal fissure

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

Risk factors

- constipation
- inflammatory bowel disease
- sexually transmitted infections e.g. HIV, syphilis, herpes

Features

- painful, bright red, rectal bleeding

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

Ascending cholangitis

Ascending cholangitis is a bacterial infection of the biliary tree. The most common predisposing factor is gallstones.

Charcot's triad of right upper quadrant (RUQ) pain, fever and jaundice occurs in about 20-50% of patients

- fever is the most common feature, seen in 90% of patients
- RUQ pain 70%
- jaundice 60%
- hypotension and confusion are also common

Management

- intravenous antibiotics
- endoscopic retrograde cholangiopancreatography (ERCP) after 24-48 hours to relieve any obstruction

Autoimmune hepatitis

Autoimmune hepatitis is condition of unknown aetiology which is most commonly seen in young females. Recognised associations include other autoimmune disorders, hypergammaglobulinaemia and HLA B8, DR3. 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)
- ANA/SMA/LKM1 antibodies, raised IgG levels
- liver biopsy: inflammation extending beyond limiting plate 'piecemeal necrosis', bridging necrosis

Management

- steroids, other immunosuppressants e.g. azathioprine
- liver transplantation

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

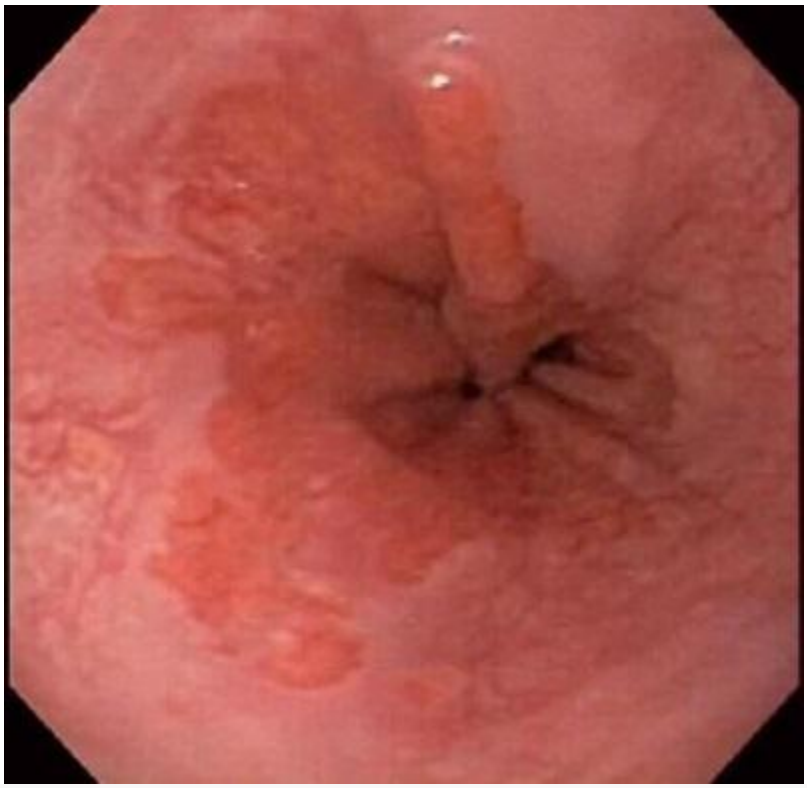
In practice many clinicians give an empirical course of antibiotics as a trial

Barrett's oesophagus

Barrett's refers to the metaplasia of the lower oesophageal mucosa, with the usual squamous epithelium being replaced by columnar epithelium. There is an increased risk of oesophageal adenocarcinoma, estimated at 50-100 fold.

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)



Endoscopy image showing a short segment of Barrett's oesophagus

Management

- endoscopic surveillance with biopsies
- high-dose proton pump inhibitor: 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

Bile-acid malabsorption

Bile-acid malabsorption is a cause of chronic diarrhoea. This may be primary, due to an excessive production of bile acid, or secondary to an underlying gastrointestinal disorder causing reduced bile acid absorption. Secondary causes are often seen in patients with ileal disease, such as with Crohn's.

Other secondary causes include:

- cholecystectomy
- coeliac disease
- small intestinal bacterial overgrowth

Investigation

- the test of choice is **SeHCAT**
- nuclear medicine test using a gamma-emitting selenium molecule in selenium homocholic acid taurine or tauroselcholic acid (SeHCAT)
- scans are done 7 days apart to assess the retention/loss of radiolabelled ^{75}SeHCAT

Management

- bile acid sequestrants e.g. cholestyramine

Budd-Chiari syndrome

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

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 (µmol/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

Chronic pancreatitis

Chronic pancreatitis is an inflammatory condition which can ultimately affect both the exocrine and endocrine functions of the pancreas. Around 80% of cases are due to alcohol excess with up to 20% of cases being unexplained

Features

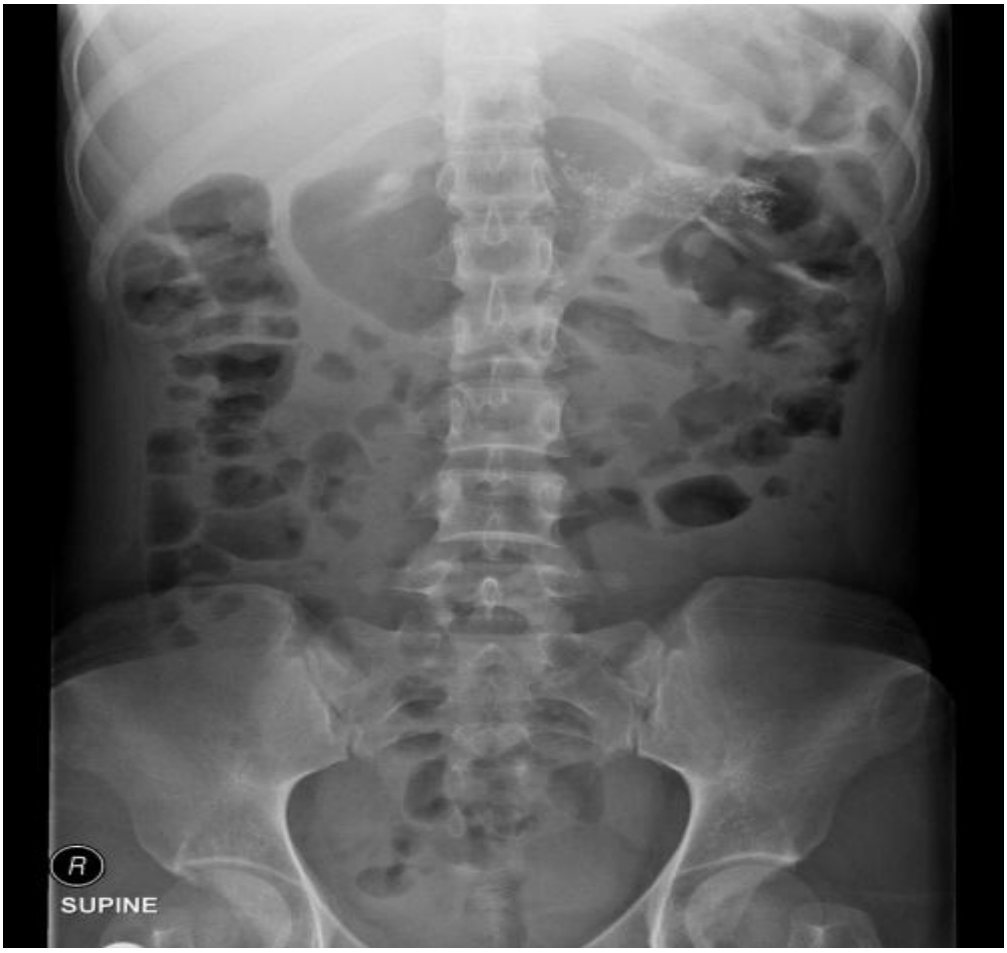
- pain is typically worse 15 to 30 minutes following a meal
- steatorrhoea: symptoms of pancreatic insufficiency usually develop between 5 and 25 years after the onset of pain
- diabetes mellitus develops in the majority of patients. It typically occurs more than 20 years after symptom begin

Investigation

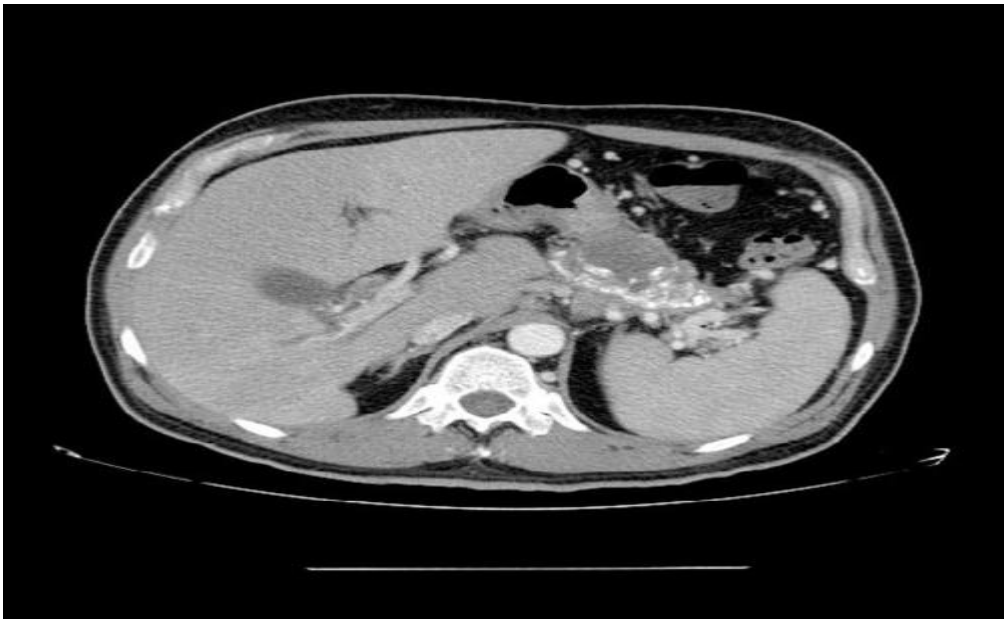
- abdominal x-ray shows pancreatic calcification in 30% of cases
- CT is more sensitive at detecting pancreatic calcification. Sensitivity is 80%, specificity is 85%
- functional tests: faecal elastase may be used to assess exocrine function if imaging inconclusive

Management

- pancreatic enzyme supplements
- analgesia
- antioxidants: limited evidence base - one study suggests benefit in early disease



Multiple small calcific foci projected in the pancreas consistent with chronic pancreatitis



CT showing an irregular shaped pancreas with the typical calcification of chronic pancreatitis

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*.

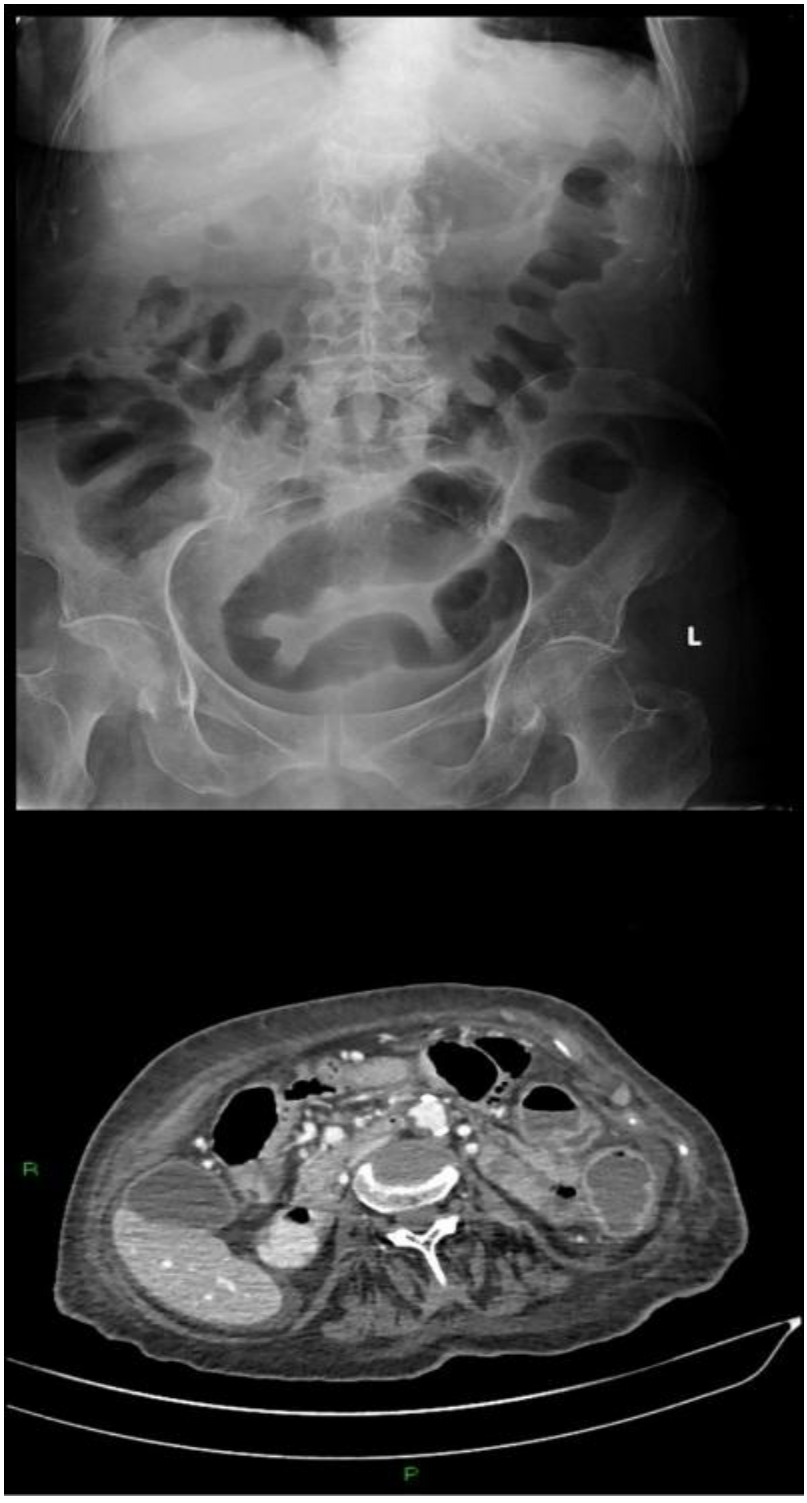
Features

- 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

Management

- first-line therapy is oral metronidazole for 10-14 days
- if severe or not responding to metronidazole then oral vancomycin may be used
- for life-threatening infections a combination of oral vancomycin and intravenous metronidazole should be used



Elderly lady with infectious colitis secondary to *Clostridium difficile*. On the abdominal film note the loss of bowel wall architecture and thumb-printing consistent with colitis. The CT from the same patient is enhanced by oral contrast. There is moderate free fluid in pelvis and peritoneum. The colon is oedematous throughout with enhancing walls, but of normal calibre. The sigmoid colon is smooth and featureless. Small bowel, liver, spleen, kidneys, adrenals and pancreas are normal.

Coeliac disease

Coeliac disease is caused by sensitivity to the protein gluten. Repeated exposure leads to villous atrophy which in turn causes 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-DQ8 (80%).

In 2009 NICE issued guidelines on the investigation of coeliac disease. They 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

Complications

- anaemia: iron, folate and vitamin B12 deficiency (folate deficiency is more common than vitamin B12 deficiency in coeliac disease)
- hyposplenism
- osteoporosis, osteomalacia
- lactose intolerance
- enteropathy-associated T-cell lymphoma of small intestine
- subfertility, unfavourable pregnancy outcomes
- rare: oesophageal cancer, other malignancies

Coeliac disease: investigation

Coeliac disease is caused by sensitivity to the protein gluten. Repeated exposure leads to villous atrophy which in turn causes malabsorption. Conditions associated with coeliac disease include dermatitis herpetiformis (a vesicular, pruritic skin eruption) and autoimmune disorders (type 1 diabetes mellitus and autoimmune hepatitis).

Diagnosis is made by a combination of immunology and jejunal biopsy. Villous atrophy and immunology normally reverses on a gluten-free diet.

NICE issued guidelines on the investigation of coeliac disease in 2009. 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.

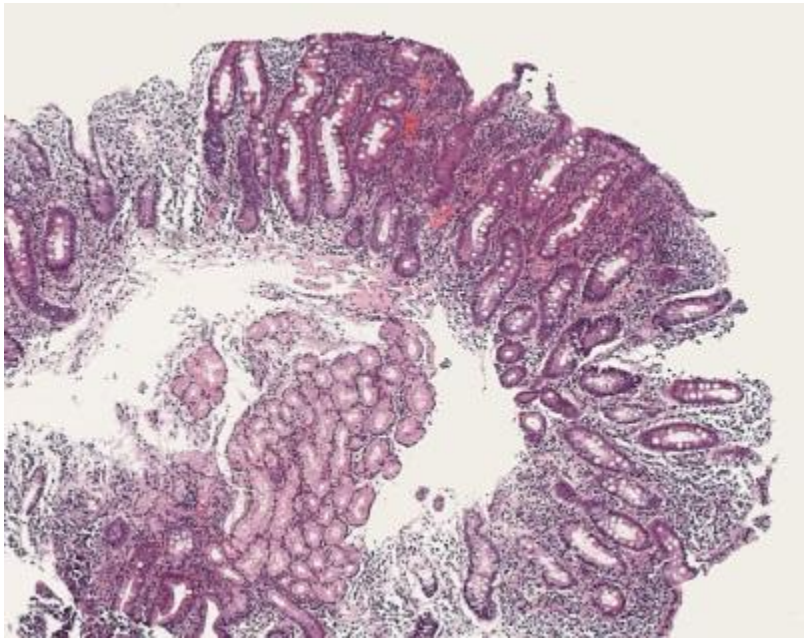
Immunology

- tissue transglutaminase (TTG) antibodies (IgA) are first-choice according to NICE
- endomyseal antibody (IgA)
- anti-gliadin antibody (IgA or IgG) tests are not recommended by NICE
- anti-casein antibodies are also found in some patients

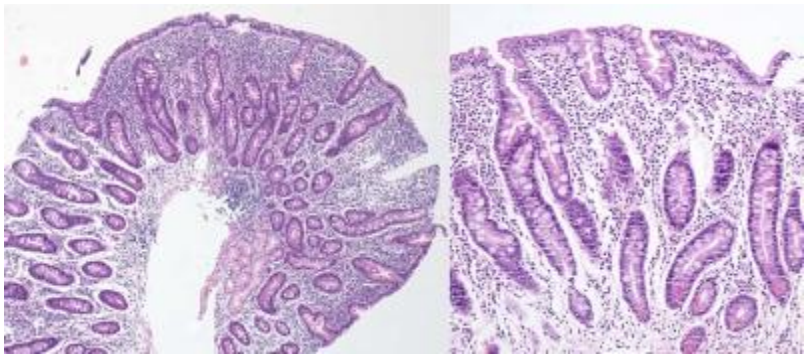
Jejunal biopsy

- villous atrophy
- crypt hyperplasia
- increase in intraepithelial lymphocytes
- lamina propria infiltration with lymphocytes

Rectal gluten challenge has been described but is not widely used



Duodenal biopsy from a patient with coeliac disease. Complete atrophy of the villi with flat mucosa and marked crypt hyperplasia. Intraepithelial lymphocytosis. Dense mixed inflammatory infiltrate in the lamina propria.



Duodenal biopsy from a patient with coeliac disease. Flat mucosa with hyperplastic crypts and dense cellular infiltrate in the lamina propria. Increased number of intraepithelial lymphocytes and vacuolated superficial epithelial cell vacuolated superficial epithelial cells. Higher magnification image on the right.

Coeliac disease: management

The management of coeliac disease involves a **gluten-free diet**. Gluten containing cereals include:

- wheat: bread, pasta, pastry
- barley*: beer
- rye
- oats**

Some notable foods which are gluten-free include:

- rice
- potatoes
- corn (maize)

Tissue transglutaminase antibodies may be checked to check compliance with a gluten free diet.

Patients with coeliac disease often have a degree of **functional hyposplenism**. For this reason all patients with coeliac disease are offered the pneumococcal vaccine. Currrent guidelines suggest giving the influenza vaccine on an individual basis.

*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
**some patients with coeliac disease appear able to tolerate oats

Colorectal cancer: genetics

It is currently thought there are three types of colon cancer:

- sporadic (95%)
- hereditary non-polyposis colorectal carcinoma (HNPCC, 5%)
- familial adenomatous polyposis (FAP, <1%)

Studies have shown that sporadic colon cancer may be due to a series of genetic mutations. For example, more than half of colon cancers show allelic loss of the APC gene. It is believed a further series of gene abnormalities e.g. activation of the K-ras oncogene, deletion of p53 and DCC tumour suppressor genes lead to invasive carcinoma

HNPCC, an autosomal dominant condition, is the 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. Currently seven mutations have been identified, which affect genes involved in DNA mismatch repair leading to microsatellite instability. The most common genes involved are:

- MSH2 (60% of cases)
- 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

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. 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

Crohn's disease

Crohn's disease is a form of inflammatory bowel disease. It commonly affects the terminal ileum and colon but may be seen anywhere from the mouth to anus.

Pathology

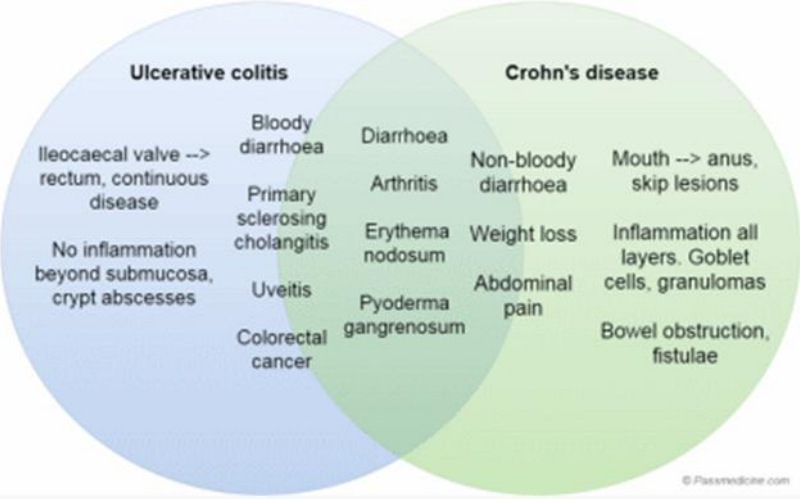
- cause is unknown but there is a strong genetic susceptibility
- inflammation occurs in all layers, down to the serosa. This is why patients with Crohn's are prone to strictures, fistulas and adhesions

Crohn's disease typically presents in late adolescence or early adulthood. Features include:

- 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 diarrhoea
- abdominal pain: the most prominent symptom in children
- perianal disease: e.g. Skin tags or ulcers
- extra-intestinal features are more common in patients with colitis or perianal disease

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	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
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



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: investigation

Crohn's disease is a form of inflammatory bowel disease. It commonly affects the terminal ileum and colon but may be seen anywhere from the mouth to anus

Bloods

- C-reactive protein correlates well with disease activity

Endoscopy

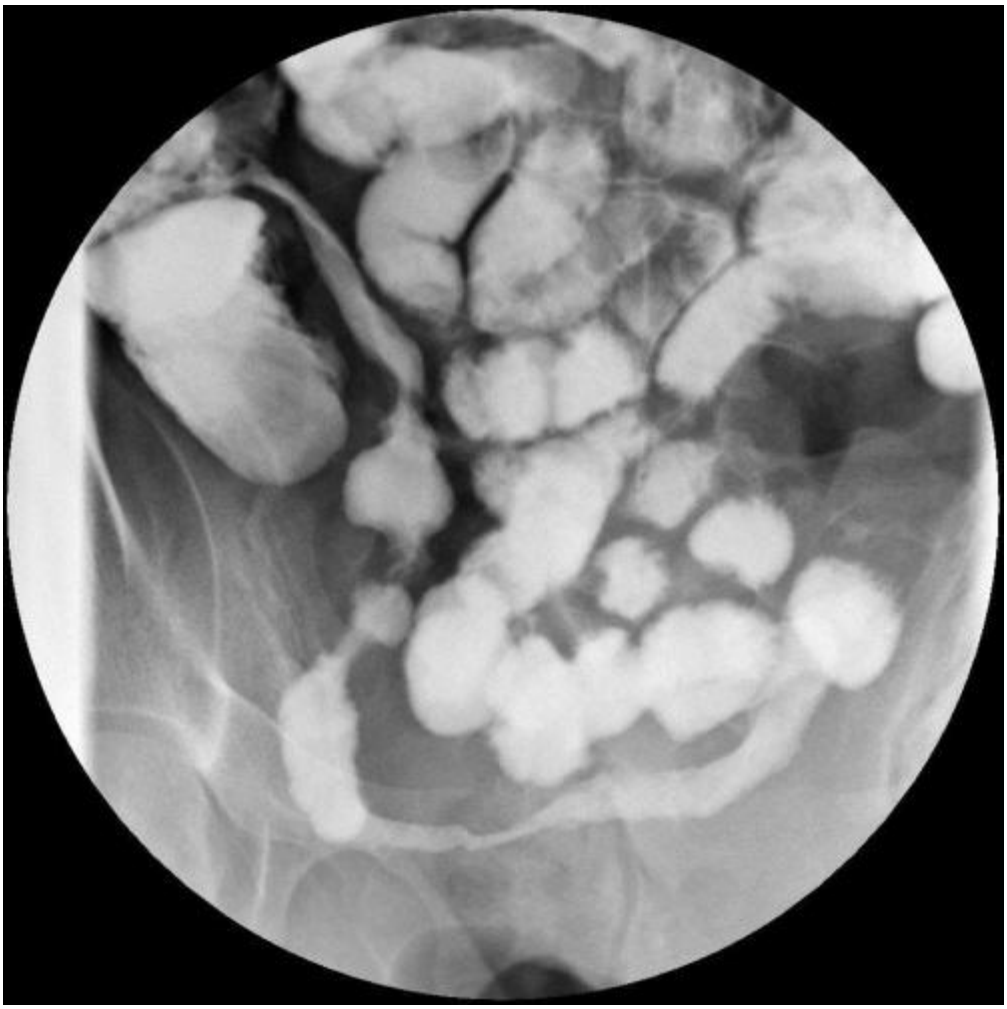
- colonoscopy is the investigation of choice
- features suggest of Crohn's include deep ulcers, skip lesions

Histology

- inflammation in all layers from mucosa to serosa
- goblet cells
- granulomas

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'.

Crohn's disease: management

Crohn's disease is a form of inflammatory bowel disease. It commonly affects the terminal ileum and colon but may be seen anywhere from the mouth to anus. NICE published guidelines on the management of Crohn's disease in 2012.

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

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

- as above, stopping smoking is a priority (remember: smoking makes Crohn's worse, but may help ulcerative colitis)
- azathioprine or mercaptopurine is used first-line to maintain remission
- methotrexate is used second-line
- 5-ASA drugs (e.g. mesalazine) should be considered if a patient has had previous surgery

Surgery

- around 80% of patients with Crohn's disease will eventually have surgery
- see below for further detail

Surgical interventions in Crohn's disease

The commonest disease pattern in Crohn's is stricturing terminal ileal disease and this often culminates in an ileocaecal resection. Other procedures performed include segmental small bowel resections and stricturoplasty. Colonic involvement in patients with Crohn's is not common and, where found, distribution is often segmental. However, despite this distribution segmental resections of the colon in patients with Crohn's disease are generally not advocated because the recurrence rate in the remaining colon is extremely high, as a result, the standard options of colonic surgery in Crohn's patients are generally; sub total colectomy, panproctocolectomy and staged sub total colectomy and proctectomy. Restorative procedures such as ileoanal pouch have no role in therapy.

Crohn's disease is notorious for the developmental of intestinal fistulae; these may form between the rectum and skin (perianal) or the small bowel and skin. Fistulation between loops of bowel may also occur and result in bacterial overgrowth and malabsorption. Management of enterocutaneous fistulae involves controlling sepsis, optimising nutrition, imaging the disease and planning definitive surgical management.

*assess thiopurine methyltransferase (TPMT) activity before offering azathioprine or mercaptopurine

Diphtheria

Diphtheria is caused by the Gram positive bacterium *Corynebacterium diphtheriae*

Pathophysiology

- releases an exotoxin encoded by a β-prophage
- exotoxin inhibits protein synthesis by catalyzing ADP-ribosylation of elongation factor EF-2

Diphtheria toxin commonly causes a 'diphtheric membrane' on tonsils caused by necrotic mucosal cells. Systemic distribution may produce necrosis of myocardial, neural and renal tissue

Possible presentations

- recent visitors to Eastern Europe/Russia/Asia
- sore throat with a 'diphtheric membrane' - see above
- bulky cervical lymphadenopathy
- neuritis e.g. cranial nerves
- heart block

Diverticulosis

Diverticulosis is an extremely common disorder characterised by multiple outpouchings of the bowel wall, most commonly in the sigmoid colon. Strictly speaking the term diverticular disease is reserved for patients who are symptomatic - diverticulosis is the more accurate term for diverticula being present.

Diverticulosis can present in a number of ways:

- painful diverticular disease: altered bowel habit, colicky left sided abdominal pain. A high fibre diet is usually recommended to minimise symptoms
- diverticulitis: see below for more details

Diverticulitis

One of the diverticular become infected. The classical presentation is:

- left iliac fossa pain and tenderness
- anorexia, nausea and vomiting
- diarrhoea
- features of infection (pyrexia, raised WBC and CRP)

Management:

- mild attacks can be treated with oral antibiotics
- more significant episodes are managed in hospital. Patients are made nil by mouth, intravenous fluids and intravenous antibiotics (typical a cephalosporin + metronidazole) are given

Complications of diverticulitis include:

- abscess formation
- peritonitis
- obstruction
- perforation

Drug-induced liver disease

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 picture:

- paracetamol
- sodium valproate, phenytoin
- MAOIs
- halothane
- anti-tuberculosis: isoniazid, rifampicin, pyrazinamide
- statins
- alcohol
- amiodarone
- methyldopa
- nitrofurantoin

The following drugs tend to cause cholestasis (+/- hepatitis):

- oral contraceptive pill
- antibiotics: flucloxacillin, co-amoxiclav, erythromycin*
- anabolic steroids, testosterones
- phenothiazines: chlorpromazine, prochlorperazine
- sulphonylureas
- fibrates
- rare reported causes: nifedipine

Liver cirrhosis

- methotrexate
- methyldopa
- amiodarone

*risk may be reduced with erythromycin stearate

Drugs causing dyspepsia

Causes

- NSAIDs
- bisphosphonates
- steroids

The following drugs may cause reflux by reducing lower oesophageal sphincter (LOS) pressure

- calcium channel blockers*
- nitrates*
- theophyllines

*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.

Dubin-Johnson syndrome

Dubin-Johnson syndrome is a 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

Dyspepsia

The 2015 NICE guidelines 'Suspected cancer: recognition and referral' further updated the advice on who needs urgent referral for an endoscopy (i.e. within 2 weeks). The list below combines the advice for oesophageal and stomach cancer, with the bold added by the author, not NICE.

Urgent

All patient who've got **dysphagia**

All patient who've got an **upper abdominal mass** consistent with stomach cancer

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*

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

Dysphagia

The table below gives characteristic exam question features for conditions causing dysphagia:

Causes	Notes
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 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

Causes	Notes
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

Causes of dysphagia - by classification

As with many conditions, it's often useful to think about causes of a symptom in a structured way:

Classification	Examples
Extrinsic	⁾ Mediastinal masses ⁾ Cervical spondylosis
Oesophageal wall	⁾ Achalasia ⁾ Diffuse oesophageal spasm ⁾ Hypertensive lower oesophageal sphincter
Intrinsic	⁾ Tumours ⁾ Strictures ⁾ Oesophageal web ⁾ Schatzki rings
Neurological	⁾ CVA ⁾ Parkinson's disease ⁾ Multiple Sclerosis ⁾ Brainstem pathology ⁾ Myasthenia Gravis

Investigation

All patients require an upper GI endoscopy unless there are compelling reasons for this not to be performed. Motility disorders may be best appreciated by undertaking fluoroscopic swallowing studies.

A full blood count should be performed.

Ambulatory oesophageal pH and manometry studies will be required to evaluate conditions such as achalasia and patients with GORD being considered for fundoplication surgery.

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 superantigens 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

Organism	Toxin	Notes
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

Organism	Toxin	Notes
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*.

Gallstones

Up to 24% of women and 12% of men may have gallstones. Of these up to 30% may develop local infection and cholecystitis. In patients subjected to surgery, 12% will have stones contained within the common bile duct. The majority of gallstones are of a mixed composition (50%) with pure cholesterol stones accounting for 20% of cases.

The aetiology of CBD stones differs in the world, in the West most CBD stones are the result of migration. In the East, a far higher proportion arise in the CBD de novo.

The classical symptoms are of colicky right upper quadrant pain that occurs postprandially. The symptoms are usually worst following a fatty meal when cholecystokinin levels are highest and gallbladder contraction is maximal.

Investigation

In almost all suspected cases the standard diagnostic workup consists of abdominal ultrasound and liver function tests. Of patients who have stones within the bile duct, 60% will have at least one abnormal result on LFT's. Ultrasound is an important test, but is operator dependent and therefore may occasionally need to be repeated if a negative result is at odds with the clinical picture. Where stones are suspected in the bile duct the options lie between magnetic resonance cholangiography and intraoperative imaging. The choice between these two options is determined by the skills and experience of the surgeon. The advantages of intraoperative imaging are less useful in making therapeutic decisions if the operator is unhappy about proceeding the bile duct exploration, and in such circumstances, preoperative MRCP is probably a better option.

Specific gallstone and gallbladder related disease

Disease	Features	Management
Biliary colic	Colicky abdominal pain, worse postprandially, worse after fatty foods	If imaging shows gallstones and history compatible then laparoscopic cholecystectomy
Acute cholecystitis	Right upper quadrant pain Fever Murphys sign on examination Occasionally mildly deranged LFT's (especially if Mirizzi syndrome)	Imaging (USS) and cholecystectomy (ideally within 48 hours of presentation) (2)

Disease	Features	Management
Gallbladder abscess	Usually prodromal illness and right upper quadrant pain Swinging pyrexia Patient may be systemically unwell Generalised peritonism not present	Imaging with USS +/- CT Scanning Ideally, surgery although subtotal cholecystectomy may be needed if Calot's triangle is hostile In unfit patients, percutaneous drainage may be considered
Cholangitis	Patient severely septic and unwell Jaundice Right upper quadrant pain	Fluid resuscitation Broad-spectrum intravenous antibiotics Correct any coagulopathy Early ERCP
Gallstone ileus	Patients may have a history of previous cholecystitis and known gallstones Small bowel obstruction (may be intermittent)	Laparotomy and removal of the gallstone from small bowel, the enterotomy must be made proximal to the site of obstruction and not at the site of obstruction. The fistula between the gallbladder and duodenum should not be interfered with.
Acalculous cholecystitis	Patients with intercurrent illness (e.g. diabetes, organ failure) Patient of systemically unwell Gallbladder inflammation in absence of stones High fever	If patient fit then cholecystectomy, if unfit then percutaneous cholecystostomy

Treatment

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.

Patients with asymptomatic gallstones rarely develop symptoms related to them (less than 2% per year) and may, therefore, be managed expectantly. In almost all cases of symptomatic gallstones the treatment of choice is cholecystectomy performed via the laparoscopic route. In the very frail patient, there is sometimes a role for the selective use of ultrasound guided cholecystostomy.

During the course of the procedure, some surgeons will routinely perform either intraoperative cholangiography to either confirm anatomy or to exclude CBD stones. The latter may be more easily achieved by use of laparoscopic ultrasound. If stones are found then the options lie between early ERCP in the day or so following surgery or immediate surgical exploration of the bile duct. When performed via the trans cystic route this adds little in the way of morbidity and certainly results in faster recovery. Where transcystic exploration fails the alternative strategy is that of formal choledochotomy. The exploration of a small duct is challenging and ducts of less than 8mm should not be explored. Small stones that measure less than 5mm may be safely left and most will pass spontaneously.

Risks of ERCP(1)

- Bleeding 0.9% (rises to 1.5% if sphincterotomy performed)
- Duodenal perforation 0.4%
- Cholangitis 1.1%
- Pancreatitis 1.5%

Gastric MALT lymphoma

Overview

- associated with *H. pylori* infection in 95% of cases
- good prognosis
- if low grade then 80% respond to *H. pylori* eradication

Features

- paraproteinaemia may be present

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)
- jaundice may only be seen during an intercurrent illness

Investigation and management

- investigation: rise in bilirubin following prolonged fasting or IV nicotinic acid
- no treatment required

*the exact mode of inheritance is still a matter of debate

GORD: investigation

Overview

- poor correlation between symptoms and endoscopy appearance

Indications for upper GI endoscopy:

- age > 55 years
- symptoms > 4 weeks or persistent symptoms despite treatment
- dysphagia
- relapsing symptoms
- weight loss

If endoscopy is negative consider 24-hr oesophageal pH monitoring (the gold standard test for diagnosis)

Haemochromatosis: features

Haemochromatosis is an autosomal recessive disorder of iron absorption and metabolism resulting in iron accumulation. It is caused by inheritance of mutations in the HFE gene on both copies of chromosome 6*. It is often asymptomatic in early disease and initial symptoms often non-specific e.g. lethargy and arthralgia

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

Presenting features

- early symptoms include fatigue, erectile dysfunction and arthralgia (often of the hands)
- '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)

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

*there are rare cases of families with classic features of genetic haemochromatosis but no mutation in the HFE gene
**whilst elevated liver function tests and hepatomegaly may be reversible, cirrhosis is not

Haemochromatosis: investigation

Haemochromatosis is an autosomal recessive disorder of iron absorption and metabolism resulting in iron accumulation. It is caused by inheritance of mutations in the HFE gene on both copies of chromosome 6*.

There is continued debate about 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

- molecular genetic testing for the C282Y and H63D mutations
- liver biopsy: Perl's stain

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
- low TIBC

Monitoring adequacy of venesection

- transferrin saturation should be kept below 50% and the serum ferritin concentration below 50 ug/l

Joint x-rays characteristically show chondrocalcinosis

*there are rare cases of families with classic features of genetic haemochromatosis but no mutation in the HFE gene

Helicobacter pylori

Helicobacter pylori is a Gram negative bacteria associated with a variety of gastrointestinal problems, principally peptic ulcer disease

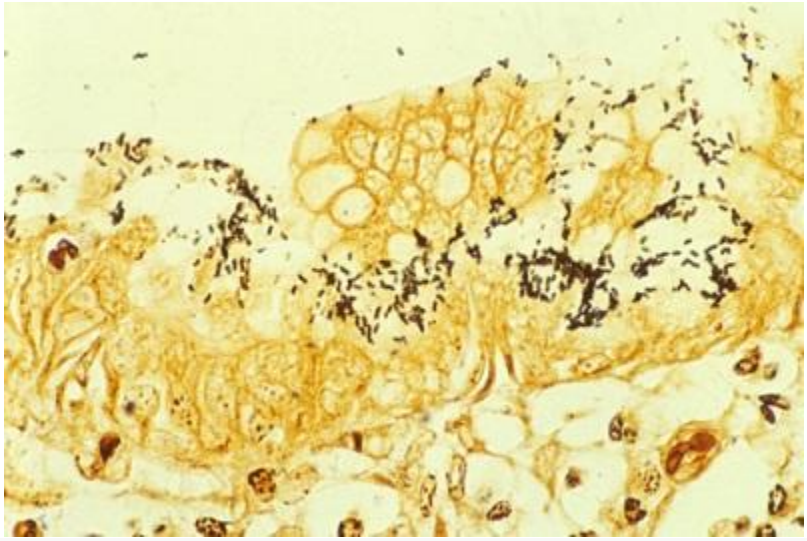
Associations

- 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

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

Management - eradication may be achieved with a 7 day course of

- a proton pump inhibitor + amoxicillin + clarithromycin, or
- a proton pump inhibitor + metronidazole + clarithromycin



H. pylori colonized on the surface of regenerative epithelium (silver stain)

Helicobacter pylori: tests

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%

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%

Serum antibody

- remains positive after eradication
- sensitivity 85%, specificity 80%

Culture of gastric biopsy

- provide information on antibiotic sensitivity
- sensitivity 70%, specificity 100%

Gastric biopsy

- histological evaluation alone, no culture
- sensitivity 95-99%, specificity 95-99%

Stool antigen test

- sensitivity 90%, specificity 95%

Hepatitis C

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. 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

Transmission

- the risk of transmission during a needle stick injury is about 2%
- the vertical transmission rate from mother to child is about 6%. The risk is higher if there is coexistent HIV
- breast feeding is not contraindicated in mothers with hepatitis C
- the risk of transmitting the virus during sexual intercourse is probably less than 5%

Features

- after exposure to the hepatitis C virus less than 20% of patients develop an acute hepatitis

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

- treatment depends on genotype
- currently a combination of pegylated interferon-alpha, ribavirin and a a protease inhibitor (e.g. boceprevir, simeprevir and telaprevir) is used
- cure rates are now approaching 90%, including for some strains which have been previously difficult to treat
- the aim of treatment is sustained virological response (SVR), defined as undetectable

serum HCV RNA six months after the end of therapy

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

Hepatitis D

Hepatitis D is a single stranded RNA virus that is transmitted parenterally. 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.

Hepatobiliary disease and related disorders

The table below gives characteristic exam question features for conditions causing hepatobiliary disease and related disorders:

Condition	Features
Viral hepatitis	Common symptoms include: • nausea and vomiting, anorexia • myalgia • lethargy • right upper quadrant (RUQ) pain Questions may point to risk factors such as foreign travel or intravenous drug use.
Congestive hepatomegaly	The liver only usually causes pain if stretched. One common way this can occur is as a consequence of congestive heart failure. In severe cases cirrhosis may occur.
Biliary colic	RUQ pain, intermittent, usually begins abruptly and subsides gradually. Attacks often occur after eating. Nausea is common. It is sometimes taught that patients are female, forties, fat and fair although this is obviously a generalisation.
Acute cholecystitis	Pain similar to biliary colic but more severe and persistent. The pain may radiate to the back or right shoulder. The patient may be pyrexial and Murphy's sign positive (arrest of inspiration on palpation of the RUQ)
Ascending cholangitis	An infection of the bile ducts commonly secondary to gallstones. Classically presents with a triad of: • fever (rigors are common) • RUQ pain • jaundice

Condition	Features
Gallstone ileus	This describes small bowel obstruction secondary to an impacted gallstone. It may develop if a fistula forms between a gangrenous gallbladder and the duodenum. Abdominal pain, distension and vomiting are seen.
Cholangiocarcinoma	Persistent biliary colic symptoms, associated with anorexia, jaundice and weight loss. A palpable mass in the right upper quadrant (Courvoisier sign), periumbilical lymphadenopathy (Sister Mary Joseph nodes) and left supraclavicular adenopathy (Virchow node) may be seen
Acute pancreatitis	Usually due to alcohol or gallstones Severe epigastric pain Vomiting is common Examination may reveal tenderness, ileus and low-grade fever Periumbilical discolouration (Cullen's sign) and flank discolouration (Grey-Turner's sign) is described but rare
Pancreatic cancer	Painless jaundice is the classical presentation of pancreatic cancer. However pain is actually a relatively common presenting symptom of pancreatic cancer. Anorexia and weight loss are common
Amoebic liver abscess	Typical symptoms are malaise, anorexia and weight loss. The associated RUQ pain tends to be mild and jaundice is uncommon.

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

Hepatorenal syndrome: management

The management of hepatorenal syndrome (HRS) is notoriously difficult. The ideal treatment is liver transplantation but patients are often too unwell to have surgery and there is a shortage of donors

The most accepted theory regarding the pathophysiology of HRS is that vasoactive mediators cause **splanchnic vasodilation** which in turn reduces the systemic vascular resistance. This results in 'underfilling' of the kidneys. This is sensed by the juxtaglomerular apparatus which then activates the renin-angiotensin-aldosterone system, causing renal vasoconstriction which is not enough to counterbalance the effects of the splanchnic vasodilation.

Hepatorenal syndrome has been categorized into two types:

Type 1 HRS	**Type 2 HRS**
Rapidly progressive Doubling of serum creatinine to > 221 µmol/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

Management options

- vasopressin analogues, for example terlipressin, have a growing evidence base supporting their use. They work by causing vasoconstriction of the splanchnic circulation
- volume expansion with 20% albumin
- transjugular intrahepatic portosystemic shunt

Hirschsprung's disease

Hirschsprung's disease is caused by an aganglionic segment of bowel due to a developmental failure of the parasympathetic Auerbach and Meissner plexuses. Although rare (occurring in 1 in 5,000 births) it is an important differential diagnosis in childhood constipation

Possible presentations

- neonatal period e.g. failure or delay to pass meconium
- older children: constipation, abdominal distension

Associations

- 3 times more common in males
- Down's syndrome

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

IBD: histology

This histological differences between ulcerative colitis and Crohn's are summarised below:

Ulcerative colitis

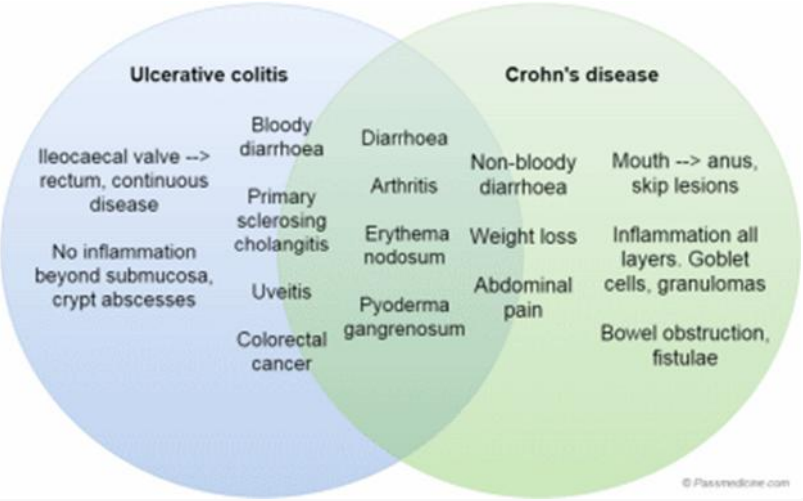
- inflammation in mucosa and submucosa only (unless fulminant disease)
- widespread ulceration with preservation of adjacent mucosa which has the appearance of polyps ('pseudopolyps')
- inflammatory cell infiltrate in lamina propria
- crypt abscesses
- depletion of goblet cells and mucin from gland epithelium
- granulomas are infrequent

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

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.



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

There are however some key differences which are highlighted in table below:

	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

	Crohn's disease (CD)	Ulcerative colitis (UC)
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	Barium enema - loss of haustrations - superficial ulceration, 'pseudopolyps'

	Crohn's disease (CD)	Ulcerative colitis (UC)
	• strictures: 'Kantor's string sign' • proximal bowel dilation • 'rose thorn' ulcers • fistulae	• long standing disease: colon is narrow and short -'drainpipe colon'

*impaired bile acid rebsorption increases the loss calcium in the bile. Calcium normally binds oxalate.

Inherited causes of jaundice

There are 4 inherited causes of jaundice you need to be aware of: Gilbert's syndrome, Crigler-Najjar syndrome, Dubin-Johnson syndrome and Rotor's syndrome. It is important for the exam to be able to classify them according to whether they cause conjugated or unconjugated hyperbilirubinaemia:

Unconjugated hyperbilirubinaemia	Conjugated hyperbilirubinaemia
Gilbert's syndrome Crigler-Najjar syndrome	Dubin-Johnson syndrome Rotor syndrome

Important points for the exam:

Gilbert's syndrome

- autosomal recessive
- UDP-glucuronyl transferase deficiency causing defective conjugation
- benign

Crigler-Najjar syndrome, type 1

- autosomal recessive
- absolute deficiency of UDP-glucuronosyl transferase
- do not survive to adulthood

Crigler-Najjar syndrome, type 2

- slightly more common than type 1 and less severe
- may improve with phenobarbital

Dubin-Johnson syndrome

- autosomal recessive. Relatively common in Iranian Jews
- mutation in the canalicular multidrug resistance protein 2 (MRP2) results in defective hepatic excretion of bilirubin
- results in a grossly black liver
- benign

Rotor syndrome

- autosomal recessive
- defect in the hepatic uptake and storage of bilirubin
- benign

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

Irritable bowel syndrome: diagnosis

NICE published clinical guidelines on the diagnosis and management of irritable bowel syndrome (IBS) in 2008

The diagnosis of IBS should be considered if the patient has had the following for at least 6 months:

- abdominal pain, and/or
- bloating, and/or
- 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:

- altered stool passage (straining, urgency, incomplete evacuation)
- abdominal bloating (more common in women than men), distension, tension or hardness
- symptoms made worse by eating
- passage of mucus

Features such as lethargy, nausea, backache and bladder symptoms may also support the diagnosis

Red flag features should be enquired about:

- rectal bleeding
- unexplained/unintentional weight loss
- family history of bowel or ovarian cancer
- onset after 60 years of age

Suggested primary care investigations are:

- full blood count
- ESR/CRP
- coeliac disease screen (tissue transglutaminase antibodies)

Irritable bowel syndrome: management

The management of irritable bowel syndrome (IBS) is often difficult and varies considerably between patients. NICE updated it's guidelines in 2015.

First-line pharmacological treatment - according to predominant symptom

- pain: antispasmodic agents
- constipation: laxatives but avoid lactulose
- diarrhoea: loperamide is first-line

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, wholemeal 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).

Ischaemic hepatitis

Ischaemic hepatitis is a diffuse hepatic injury resulting from acute hypoperfusion (sometimes known as 'shock liver'). It is not an inflammatory process. It is diagnosed in the presence of an inciting event (in this case a 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.

Jejunal villous atrophy

Whilst coeliac disease is the classic cause of jejunal villous atrophy there are a number of other causes you need to be aware of

Causes

- coeliac disease
- tropical sprue
- hypogammaglobulinaemia
- gastrointestinal lymphoma
- Whipple's disease
- cow's milk intolerance

Liver biopsy

Contraindications to percutaneous liver biopsy

- deranged clotting (e.g. INR > 1.4)
- low platelets (e.g. < 60 * 10^9/l)
- anaemia
- extrahepatic biliary obstruction
- hydatid cyst
- haemoangioma
- uncooperative patient
- ascites

Malabsorption

Malabsorption is characterised by diarrhoea, steatorrhoea and weight loss. Causes may be broadly divided into intestinal (e.g. villous atrophy), pancreatic (deficiency of pancreatic enzyme production or secretion) and 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)
- short bowel syndrome
- lymphoma

Malnutrition

Malnutrition is an important consequence of and contributor to chronic disease. It is clearly a complex and multifactorial problem that can be difficult to manage but there are a number of key points to remember for the exam.

NICE define malnutrition as the following:

- a Body Mass Index (BMI) of less than 18.5; or
- unintentional weight loss greater than 10% within the last 3-6 months; or
- 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). A link is provided to a copy of the MUST score algorithm.

- 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
- 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

Meckel's diverticulum

Meckel's diverticulum is a congenital diverticulum of the small intestine. It is a remnant of the omphalomesenteric duct (also called the vitellointestinal duct) and contains ectopic ileal, gastric or pancreatic mucosa

Rule of 2's

- occurs in 2% of the population
- is 2 feet from the ileocaecal valve
- is 2 inches long

Presentation (usually asymptomatic)

- abdominal pain mimicking appendicitis
- rectal bleeding
- intestinal obstruction: secondary to an omphalomesenteric band (most commonly), volvulus and intussusception

Management

- removal if narrow neck or symptomatic. Options are between wedge excision or formal small bowel resection and anastomosis.

Pathophysiology

- normally, in the foetus, there is an attachment between the vitellointestinal duct and the yolk sac.This disappears at 6 weeks gestation
- the tip is free in the majority of cases
- associated with enterocystomas, umbilical sinuses, and omphaloileal fistulas.
- arterial supply: omphalomesenteric artery.
- typically lined by ileal mucosa but ectopic gastric mucosa can occur, with the risk of peptic ulceration. Pancreatic and jejunal mucosa can also occur

Melanosis coli

Melanosis coli is a disorder of pigmentation of the bowel wall. Histology demonstrates pigment-laden macrophages

It is associated with laxative abuse, especially anthraquinone compounds such as senna

Mesenteric ischaemia

Mesenteric ischaemia is primarily caused by arterial embolism resulting in infarction of the colon. It is more likely to 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.

Predisposing factors

- increasing age
- atrial fibrillation
- other causes of emboli: endocarditis
- cardiovascular disease risk factors: smoking, hypertension, diabetes
- cocaine: ischaemic colitis is sometimes seen in young patients following cocaine use

Features

- abdominal pain
- rectal bleeding
- diarrhoea
- fever
- bloods typically show an elevated WBC associated with acidosis

Management

- supportive care
- laparotomy and bowel resection

Metoclopramide

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
- hyperprolactinaemia
- tardive dyskinesia
- parkinsonism

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) is a term used to describe liver changes similar to those seen in alcoholic hepatitis in the absence of a history of alcohol abuse. It is relatively common and thought 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

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)

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

Oesophageal varices

Acute treatment of variceal haemorrhage

- 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. It has been shown to be of benefit in initial haemostasis and preventing rebleeding. 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
- 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

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 which typically occur at 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

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
- migratory thrombophlebitis (Trousseau sign) is more common than with other cancers

Investigation

- ultrasound has a sensitivity of around 60-90%
- high resolution CT scanning is the investigation of choice if the diagnosis is suspected

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

Pancreatic cancer: features and investigation

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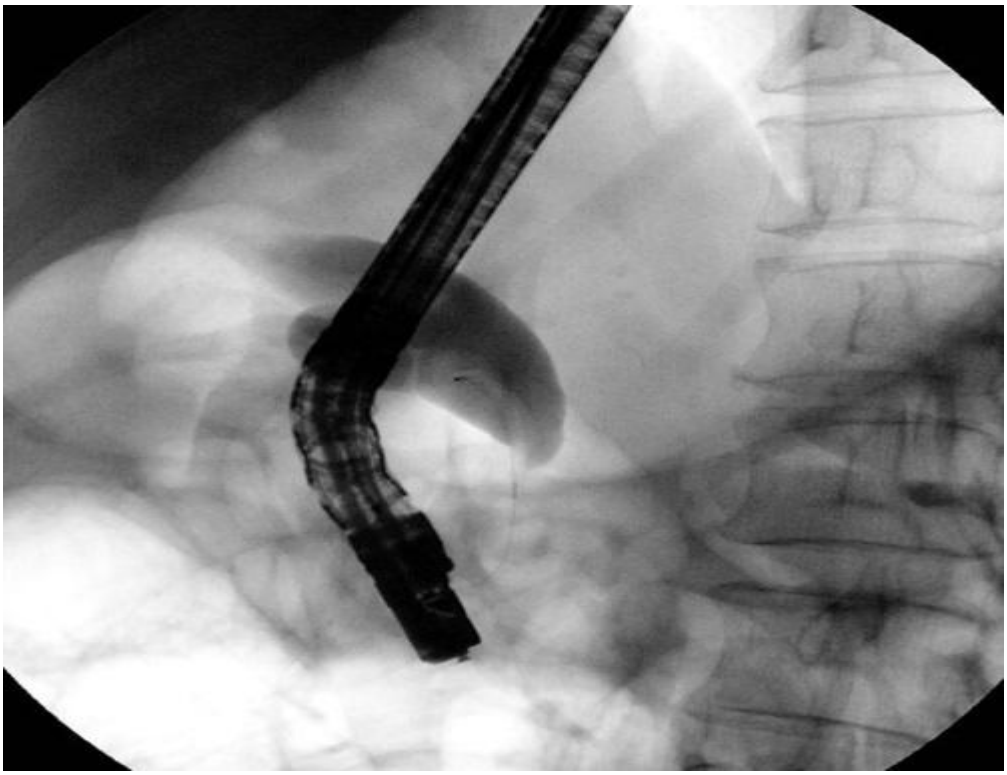


ERCP showing invasive ductal adenocarcinoma. Note the dilation of the common bile duct due to the pancreatic lesion

Pernicious anaemia: investigation

Investigation

- anti gastric parietal cell antibodies in 90% (but low specificity)
- anti intrinsic factor antibodies in 50% (specific for pernicious anaemia)
- macrocytic anaemia
- 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

Schilling test

- radiolabelled B12 given on two occasions
- first on its own
- second with oral IF
- urine B12 levels measured

Peutz-Jeghers syndrome

Peutz-Jeghers syndrome is an autosomal dominant condition characterised by numerous hamartomatous polyps in the gastrointestinal tract. It is also associated with 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.

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

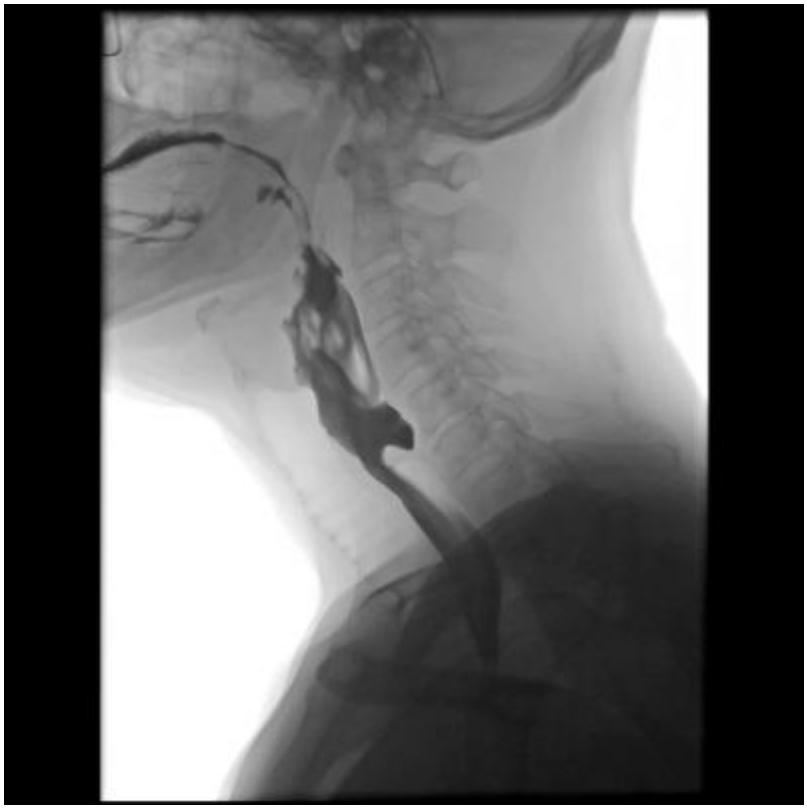
- conservative unless complications develop

Pharyngeal pouch

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. It is more common in older patients and is 5 times more common in men

Features

- dysphagia
- regurgitation
- aspiration
- neck swelling which gurgles on palpation
- halitosis



Still image taken from a barium swallow with fluoroscopy. During swallowing an outpouching of the posterior hypopharyngeal wall is visualised at the level C5-C6, right above the upper oesophageal sphincter

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 is often difficult, but often involves a low-fat diet and the introduction of 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. Antibiotics and pancreatic enzyme replacements play no part in management.

Pregnancy: jaundice

Intrahepatic cholestasis of pregnancy

Intrahepatic cholestasis of pregnancy (also known as obstetric cholestasis) occurs in around 1% of pregnancies and is generally seen in the third trimester. It is the most common liver disease of pregnancy.

Features

- pruritus, often in the palms and soles
- no rash (although skin changes may be seen due to scratching)
- raised bilirubin

Management

- ursodeoxycholic acid is used for symptomatic relief
- women are typically induced at 37 weeks

Complications include an increased rate of stillbirth. It is not generally associated with increased maternal morbidity

Acute fatty liver of pregnancy

Acute fatty liver of pregnancy is rare complication which may occur in the third trimester or the period immediately following delivery.

Features

- abdominal pain
- nausea & vomiting
- headache
- jaundice
- hypoglycaemia
- severe disease may result in pre-eclampsia

Investigations

- ALT is typically elevated e.g. 500 u/l

Management

- support care
- once stabilised delivery is the definitive management

Gilbert's, Dubin-Johnson syndrome, may be exacerbated during pregnancy

HELLP

- Haemolysis, Elevated Liver enzymes, Low Platelets

Primary biliary cirrhosis

Primary biliary cirrhosis (now increasingly referred to as primary biliary cholangitis) is a chronic liver disorder typically seen in middle-aged females (female:male ratio of 9:1). The aetiology is not fully understood although it is thought to be an autoimmune condition. Interlobular bile ducts become damaged by a chronic inflammatory process causing progressive cholestasis which may eventually progress to cirrhosis. The classic presentation is itching in a middle-aged woman

Associations

- Sjogren's syndrome (seen in up to 80% of patients)
- rheumatoid arthritis
- systemic sclerosis
- thyroid disease

Diagnosis

- anti-mitochondrial antibodies (AMA) M2 subtype are present in 98% of patients and are highly specific
- smooth muscle antibodies in 30% of patients
- raised serum IgM

Management

- pruritus: cholestyramine
- fat-soluble vitamin supplementation
- ursodeoxycholic acid
- liver transplantation e.g. if bilirubin > 100 (PBC is a major indication) - recurrence in graft can occur but is not usually a problem

Primary biliary cirrhosis: features

Primary biliary cirrhosis (now increasingly referred to as primary biliary cholangitis) is a chronic liver disorder typically seen in middle-aged females (female:male ratio of 9:1). The aetiology is not fully understood although it is thought to be an autoimmune condition. Interlobular bile ducts become damaged by a chronic inflammatory process causing progressive cholestasis, which may eventually progress to cirrhosis. The classic presentation is itching in a middle-aged woman

Clinical features

- 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
- late: may progress to liver failure

Complications

- malabsorption: osteomalacia, coagulopathy
- sicca syndrome occurs in 70% of cases
- portal hypertension: ascites, variceal haemorrhage
- hepatocellular cancer (20-fold increased risk)

Primary sclerosing cholangitis

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

- cholestasis: jaundice and pruritus
- right upper quadrant pain
- fatigue

Investigation

- ERCP is the standard diagnostic tool, showing multiple biliary strictures giving a 'beaded' appearance
- ANCA may be positive
- 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

Proton pump inhibitors

Proton pump inhibitors (PPI) are a group of drugs which profoundly reduce acid secretion in the stomach. They irreversibly blocking the hydrogen/potassium adenosine triphosphatase enzyme system (the H^+/K^+ ATPase) of the gastric parietal cell

Examples include omeprazole and lansoprazole

Pyloric stenosis

Pyloric stenosis typically presents in the second to fourth weeks of life with vomiting, although rarely may present later at up to four months. It is caused by hypertrophy of the circular muscles of the pylorus

Epidemiology

- incidence of 4 per 1,000 live births
- 4 times more common in males
- 10-15% of infants have a positive family history
- first-borns are more commonly affected

Features

- 'projectile' vomiting, typically 30 minutes after a feed
- constipation and dehydration may also be present
- a palpable mass may be present in the upper abdomen
- hypochloraemic, hypokalaemic alkalosis due to persistent vomiting

Diagnosis is most commonly made by ultrasound

Management is with Ramstedt pyloromyotomy

Refeeding syndrome

Refeeding syndrome describes the metabolic abnormalities which occur on feeding a person following a period of starvation. The metabolic consequences include:

- hypophosphataemia
- hypokalaemia
- hypomagnesaemia
- abnormal fluid balance

These abnormalities can lead to organ failure.

Prevention

NICE produced guidelines in 2006 on nutritional support. Refeeding syndrome may avoided by identifying patients at a high-risk of developing refeeding syndrome:

Patients are considered high-risk if one or more of the following:

- BMI < 16 kg/m^2
- unintentional weight loss >15% over 3-6 months
- little nutritional intake > 10 days
- hypokalaemia, hypophosphataemia or hypomagnesaemia prior to feeding (unless high)

If two or more of the following:

- BMI < 18.5 kg/m^2
- unintentional weight loss > 10% over 3-6 months
- little nutritional intake > 5 days
- history of: alcohol abuse, drug therapy including insulin, chemotherapy, diuretics and antacids

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.

Skin disorders associated with malignancy

Paraneoplastic syndromes associated with internal malignancies:

Skin disorder	Associated malignancies
Acanthosis nigricans	Gastric cancer
Acquired ichthyosis	Lymphoma
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

Small bowel bacterial overgrowth syndrome

Small bowel bacterial overgrowth syndrome (SBBOS) is a disorder characterised by excessive amounts of bacteria in the small bowel resulting in gastrointestinal symptoms.

Risk factors for SBBOS

- neonates with congenital gastrointestinal abnormalities
- scleroderma
- diabetes mellitus

It should be noted that many of the features overlap with irritable bowel syndrome:

- chronic diarrhoea
- bloating, flatulence
- abdominal pain

Diagnosis

- hydrogen breath test

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.

Spironolactone

Spironolactone is an aldosterone antagonist which acts in the cortical 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

Adverse effects

- hyperkalaemia
- gynaecomastia

RALES

- NYHA III + IV, patients already taking ACE inhibitor
- low dose spironolactone reduces all cause mortality

Spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis (SBP) is a form of peritonitis usually seen in patients with ascites secondary to liver cirrhosis.

Diagnosis

- paracentesis: neutrophil count > 250 cells/ul

Management

- intravenous cefotaxime is usually given

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

Alcoholic liver disease is a marker of poor prognosis in SBP.

Total parenteral nutrition

- Commonly used in nutritionally compromised surgical patients
- Bags contain combinations of glucose, lipids and essential electrolytes, the exact composition is determined by the patients nutritional requirements.
- Although it may be infused peripherally, this may result in thrombophlebitis.
- Longer term infusions should be administered into a central vein (preferably via a PICC line).
- Complications are related to sepsis, re-feeding syndromes and hepatic dysfunction.

Ulcerative colitis

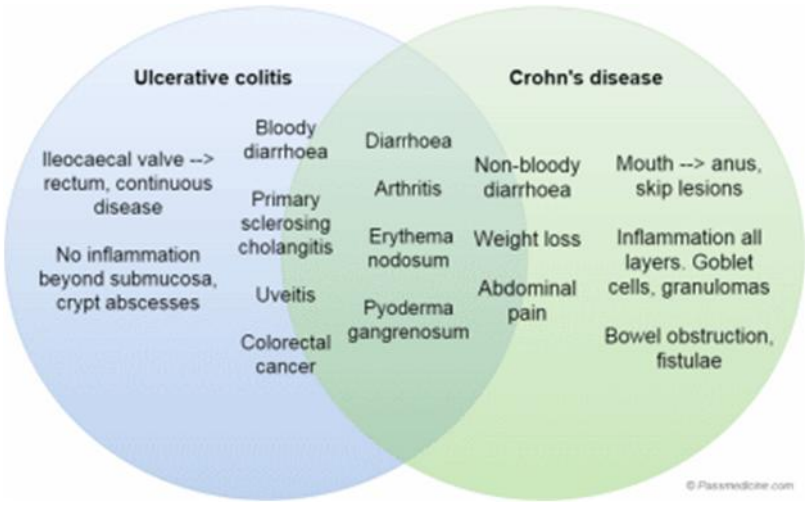
Ulcerative colitis (UC) is a form of inflammatory bowel disease. Inflammation always starts at rectum (hence it is the most common site for UC), never spreads beyond ileocaecal valve and is continuous. The peak incidence of ulcerative colitis is in people aged 15-25 years and in those aged 55-65 years.

The initial presentation is usually following insidious and intermittent symptoms. Features include:

- bloody diarrhoea
- urgency
- tenesmus
- abdominal pain, particularly in the left lower quadrant
- extra-intestinal features (see below)

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	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
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



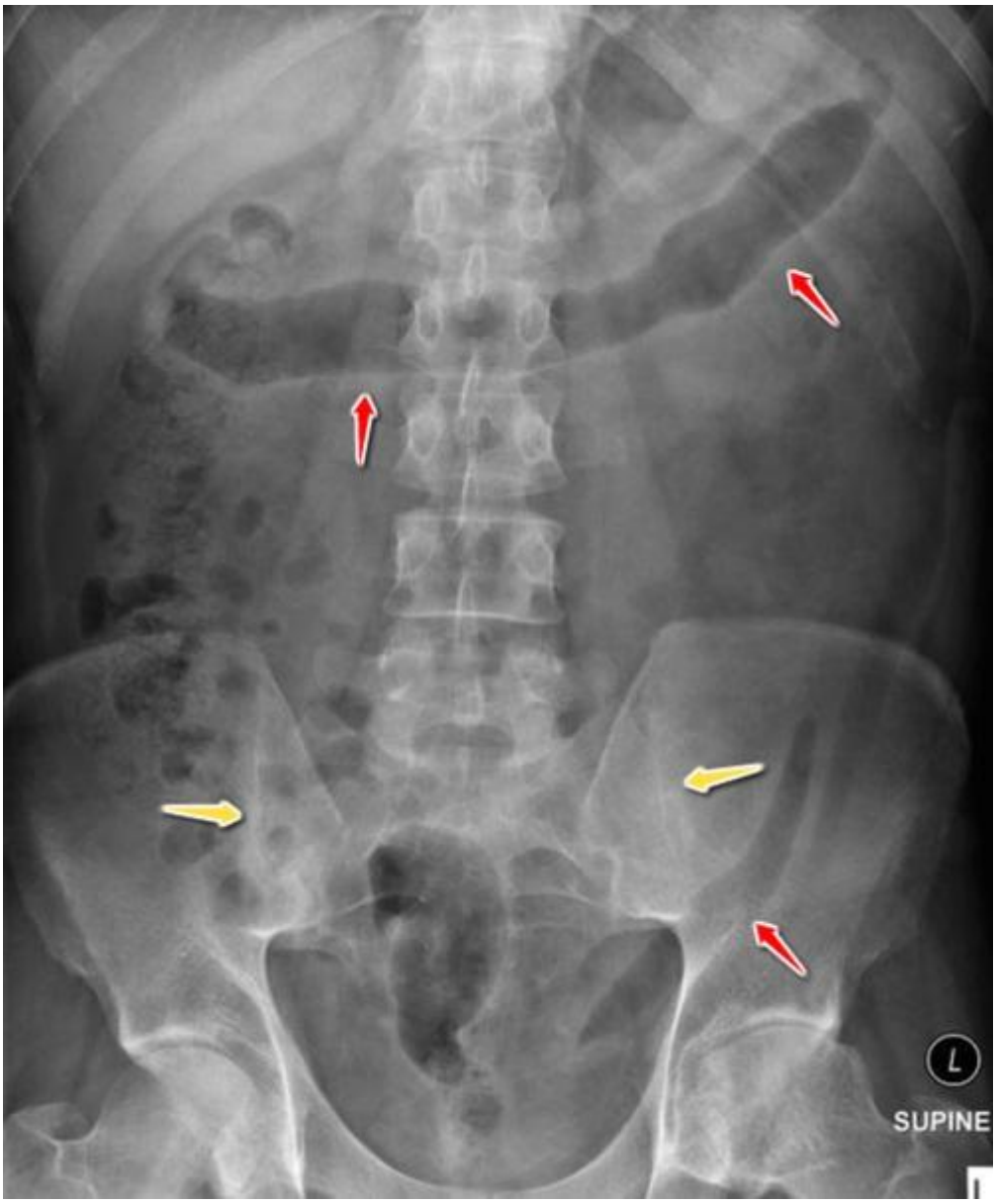
Venn diagram showing shared features and differences between ulcerative colitis and Crohn's disease. Note that whilst some features are present in both, some are much more common in one of the conditions, for example colorectal cancer in ulcerative colitis

Pathology

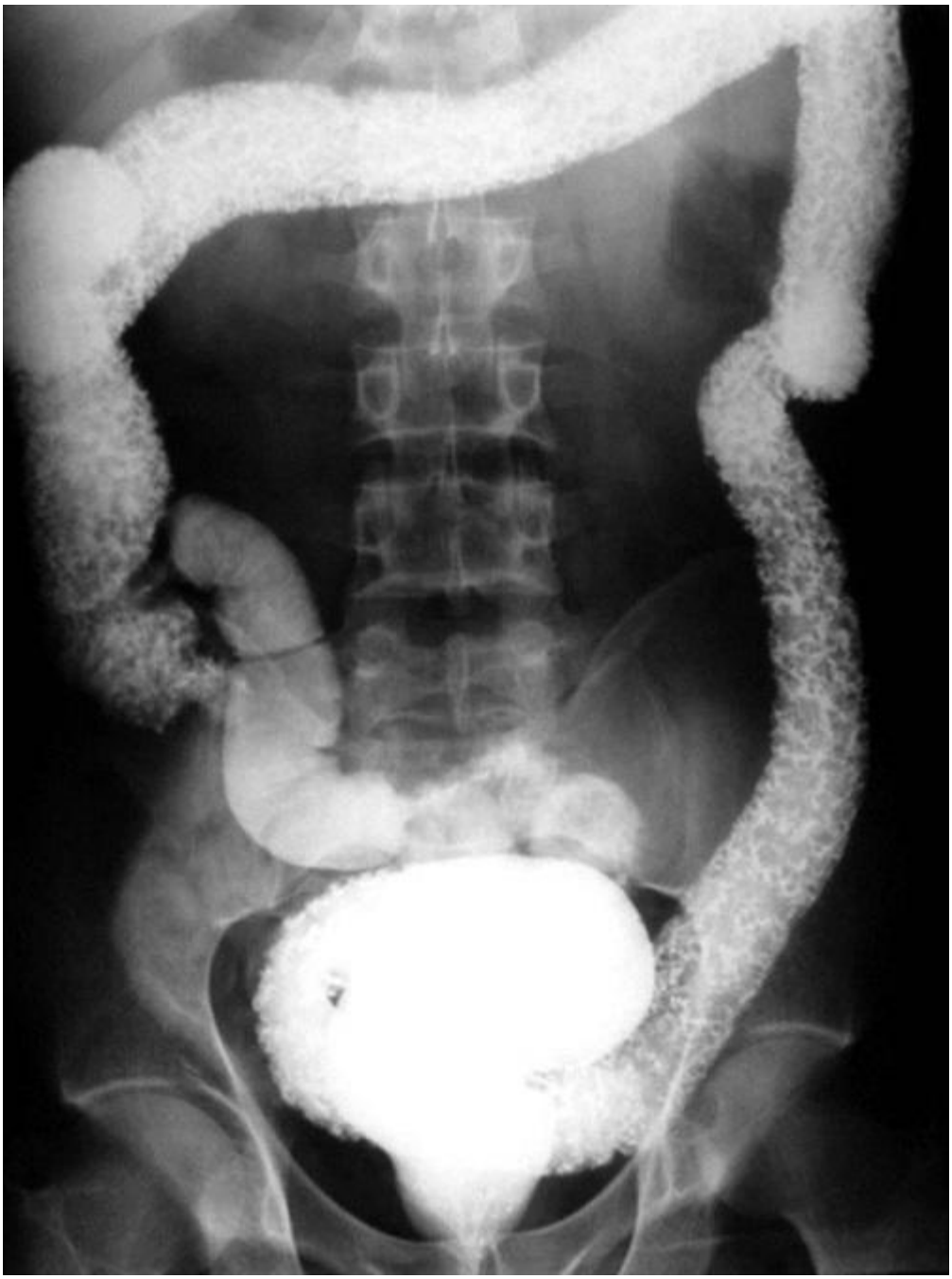
- red, raw mucosa, bleeds easily
- no inflammation beyond submucosa (unless fulminant disease)
- widespread ulceration with preservation of adjacent mucosa which has the appearance of polyps ('pseudopolyps')
- inflammatory cell infiltrate in lamina propria
- neutrophils migrate through the walls of glands 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.



Barium enema from a patient with ulcerative colitis. The whole colon, without skips is affected by an irregular mucosa with loss of normal haustral markings.

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 in inflammatory bowel disease patients should be decided following risk stratification.

Lower risk

5 year follow up colonoscopy

- Extensive colitis with no active endoscopic/histological inflammation
- OR left sided colitis
- OR Crohn's colitis of <50% colon

Intermediate risk

3 year colonoscopy

- Extensive colitis with mild active endoscopy/histological inflammation
- OR 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
- OR stricture in past 5 years
- OR dysplasia in past 5 years declining surgery
- OR primary sclerosing cholangitis / transplant for primary sclerosing cholangitis
- OR family history of colorectal cancer in first degree relatives aged <50 years

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

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.

The vast majority are asymptomatic. Possible features:

- non-specific lower gastrointestinal symptoms
- secretory diarrhoea may occur
- microcytic anaemia
- hypokalaemia

VIPoma

VIP (vasoactive intestinal peptide)

- source: small intestine, pancreas
- stimulation: neural
- actions: stimulates secretion by pancreas and intestines, inhibits acid and pepsinogen secretion

VIPoma

- 90% arise from pancreas
- large volume diarrhoea
- weight loss
- dehydration
- hypokalaemia, hypochlorhydia

Whipple's disease

Whipple's disease is a rare multi-system disorder caused by *Tropheryma whippelii* infection. It is more common in those who are HLA-B27 positive and in middle-aged men

Features

- malabsorption: diarrhoea, weight loss
- large-joint arthralgia
- lymphadenopathy
- skin: hyperpigmentation and photosensitivity
- pleurisy, pericarditis
- neurological symptoms (rare): ophthalmoplegia, dementia, seizures, ataxia, myoclonus

Investigation

- jejunal biopsy shows deposition of macrophages containing Periodic acid-Schiff (PAS) granules

Management

- guidelines vary: oral co-trimoxazole for a year is thought to have the lowest relapse rate, sometimes preceded by a course of IV penicillin

Wilson's disease

Wilson's disease is an autosomal recessive disorder characterised by excessive copper deposition in the tissues. Metabolic abnormalities include increased copper absorption from the small intestine and decreased hepatic copper excretion. Wilson's disease is caused by a defect in the ATP7B gene located on chromosome 13.

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

Features result from excessive copper deposition in the tissues, especially the brain, liver and cornea:

- liver: hepatitis, cirrhosis
- neurological: basal ganglia degeneration, speech and behavioural problems are often the first manifestations. Also: asterixis, chorea, dementia
- Kayser-Fleischer rings
- renal tubular acidosis (esp. Fanconi syndrome)
- haemolysis
- blue nails

Diagnosis

- reduced serum caeruloplasmin
- reduced serum copper (counter-intuitive, but 95% of plasma copper is carried by ceruloplasmin)
- increased 24hr urinary copper excretion

Management

- penicillamine (chelates copper) has been the traditional first-line treatment
- trientine hydrochloride is an alternative chelating agent which may become first-line treatment in the future
- tetrathiomolybdate is a newer agent that is currently under investigation

Zollinger-Ellison syndrome

Zollinger-Ellison syndrome is condition characterised by excessive levels of gastrin, usually from a gastrin secreting tumour usually of the duodenum or pancreas. Around 30% occur as part of MEN type I syndrome

Features

- multiple gastroduodenal ulcers
- diarrhoea
- malabsorption

Diagnosis

- fasting gastrin levels: the single best screen test
- secretin stimulation test

Infectious diseases and STIs

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

Animal bites

The majority of bites seen in everyday practice involve dogs and cats. 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

Anthrax

Anthrax is caused by *Bacillus anthracis*, a Gram positive rod. It is spread by infected carcasses. It is also known as Woolsorters' disease. *Bacillus anthracis* produces a tripartite protein toxin

- protective antigen
- oedema factor: a bacterial adenylate cyclase which increases cAMP
- lethal factor: toxic to macrophages

Features

- causes painless black eschar (cutaneous 'malignant pustule', but no pus)
- typically painless and non-tender
- may cause marked oedema
- anthrax can cause gastrointestinal bleeding

Management

- 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

Antibiotics: anaerobic activity

The following antibiotics have anti-anaerobic activity

- penicillins
- cephalosporins (except ceftazidime)
- erythromycin
- metronidazole
- tetracycline

The following antibiotics do not have anti-anaerobic activity

- gentamicin
- ciprofloxacin
- ceftazidime

Antibiotics: bactericidal vs. bacteriostatic

Bactericidal antibiotics

- penicillins
- cephalosporins
- aminoglycosides
- nitrofurantoin
- metronidazole
- quinolones
- rifampicin
- isoniazid

Bacteriostatic antibiotics

- chloramphenicol
- macrolides
- tetracyclines
- sulphonamides
- trimethoprim

Bacterial vaginosis

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.

Whilst BV is not a sexually transmitted infection it is seen almost exclusively in sexually active women.

Features

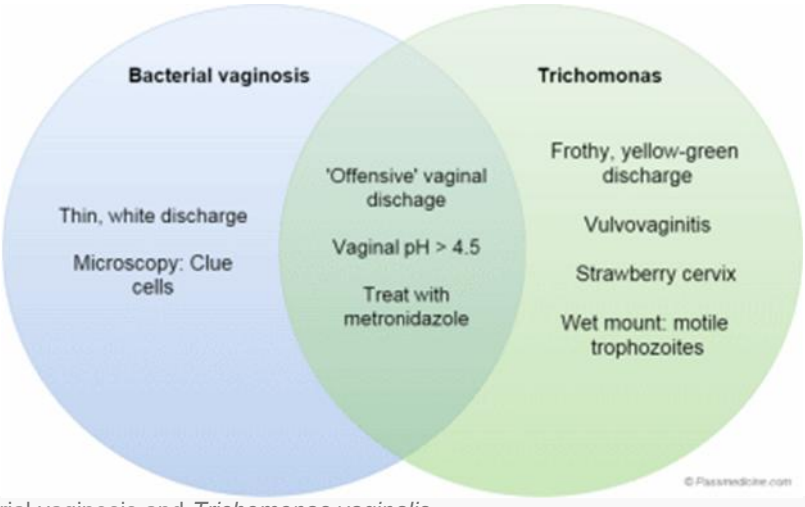
- vaginal discharge: 'fishy', offensive
- asymptomatic in 50%

Amsel's criteria for diagnosis of BV - 3 of the following 4 points should be present

- thin, white homogenous discharge
- clue cells on microscopy: stippled vaginal epithelial cells
- vaginal pH > 4.5
- positive whiff test (addition of potassium hydroxide results in fishy odour)

Management

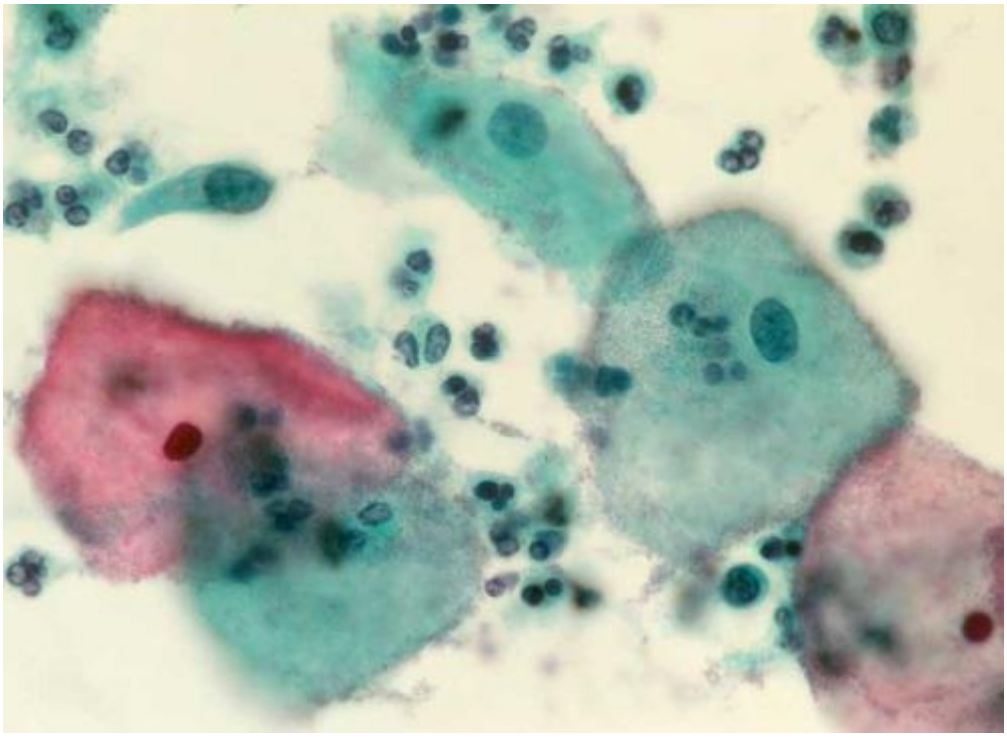
- oral metronidazole for 5-7 days
- 70-80% initial cure rate
- relapse rate > 50% within 3 months
- the BNF suggests topical metronidazole or topical clindamycin as alternatives



Comparison of bacterial vaginosis and *Trichomonas vaginalis*

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



Clue cells - epithelial cells develop a stippled appearance due to being covered with bacteria

Brucellosis

Brucellosis is a zoonosis more common in the Middle East and in farmers. Four major species cause infection in humans: B melitensis (sheep), B abortus (cattle), B canis and B suis (pigs). Brucellosis has an incubation period 2 - 6 weeks

Features

- non-specific: fever, malaise
- hepatosplenomegaly
- sacroilitis: spinal tenderness may be seen
- complications: osteomyelitis, infective endocarditis, meningoencephalitis, orchitis
- leukopenia often seen

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

Management

- doxycycline and streptomycin

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 and has an incubation period of 1-6 days.

Features

- prodrome: headache malaise
- diarrhoea: often bloody
- abdominal pain

Management

- usually self-limiting
- 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

Cat scratch disease

Cat scratch disease is generally caused by the Gram negative rod *Bartonella henselae*

Features

- fever
- history of a cat scratch
- regional lymphadenopathy
- headache, malaise

Cellulitis

Cellulitis is a term used to describe an inflammation of the skin and subcutaneous tissues, typically due to infection by *Streptococcus pyogenes* or *Staphylcoccus aureus*.

Features

- commonly occurs on the shins
- erythema, pain, swelling
- there may be some associated systemic upset such as fever

Criteria for admission

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 compromize
IV	The person has sepsis syndrome or a severe life-threatening infection such as necrotizing fasciitis

They recommend the following that we admit for intravenous antibiotics the following patients:

- Has Eron Class III or Class IV cellulitis.
- Has severe or rapidly deteriorating cellulitis (for example extensive areas of skin).
- Is very young (under 1 year of age) or frail.
- Is immunocompromized.
- Has significant lymphoedema.
- Has facial cellulitis (unless very mild) or periorbital cellulitis.

The following is recommend regarding 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 - check local guidelines.

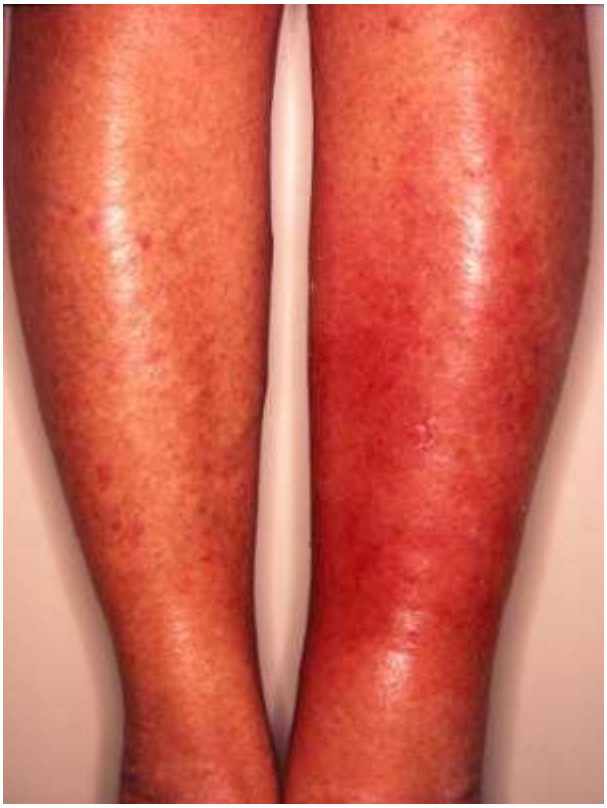
Other patients can be treated with oral antibiotics.

Management

The BNF recommends flucloxacillin as first-line treatment for mild/moderate cellulitis. Clarithromycin or clindamycin is recommend in patients allergic to penicillin.

Many local protocols now suggest the use of oral clindamycin in patients who have failed to respond to flucloxacillin.

Severe cellulitis should be treated with intravenous benzylpenicillin + flucloxacillin.



Chickenpox

Chickenpox is caused by primary infection with varicella zoster virus. Shingles is reactivation of dormant virus in dorsal root ganglion

Chickenpox is highly infectious

- 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

Clinical features (tend to be more severe in older children/adults)

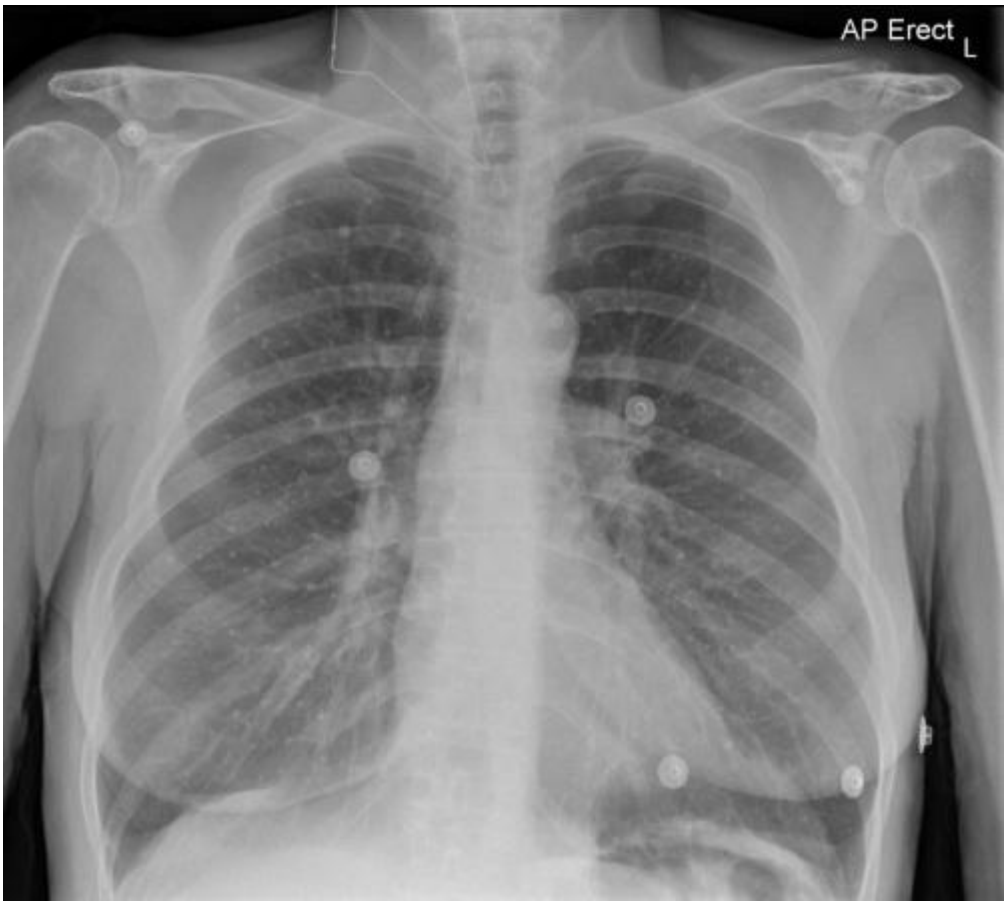
- fever initially
- itchy, rash starting on head/trunk before spreading. Initially macular then papular then vesicular
- systemic upset is usually mild

Management is supportive

- keep cool, trim nails
- calamine lotion
- school exclusion: the 2016 Public Health England guidelines reverted to the traditional advice to exclude children **until all vesicles have crusted over**, rather than 5 days post onset of rash, which had been advocated over recent years
- immunocompromised patients and newborns with peripartum exposure should receive varicella zoster immunoglobulin (VZIG). If chickenpox develops then IV aciclovir should be considered

A common complication is secondary bacterial infection of the lesions. Rare complications include

- pneumonia
- encephalitis (cerebellar involvement may be seen)
- disseminated haemorrhagic chickenpox
- arthritis, nephritis and pancreatitis may very rarely be seen



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 is caused by primary infection with varicella zoster virus. Shingles is reactivation of dormant virus in dorsal root ganglion. In pregnancy there is a risk to both the mother and also the fetus, a syndrome now termed fetal varicella syndrome

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

Chikungunya

Alphavirus disease caused by infected mosquitoes. Areas affected are Africa, Asia and Indian subcontinent but in recent years there has been seen in a few cases in Southern Europe. Tanzania had the first reported case.

Symptoms: Prominent symptoms are severe joint pain and abrupt onset of high fever. Other symptoms include general flu-like illness of muscle ache, headache, and fatigue. The disease shares its symptoms with dengue but tends to have more joint pain which can be debilitating. A rash may develop as with other viral illness and swelling of the joints in not uncommon.

Treatment: Relief of symptoms. No specific treatment.

Chlamydia

Chlamydia is the most prevalent sexually transmitted infection in the UK and is caused by *Chlamydia trachomatis*, an obligate intracellular pathogen. Approximately 1 in 10 young women in the UK have *Chlamydia*. The incubation period is around 7-21 days, although it should be remembered a large percentage of cases are asymptomatic

Features

- asymptomatic in around 70% of women and 50% of men
- women: cervicitis (discharge, bleeding), dysuria
- men: urethral discharge, dysuria

Potential complications

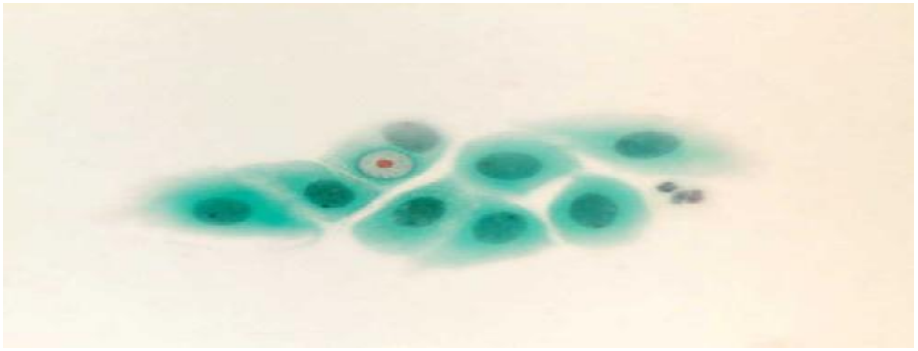
- epididymitis
- pelvic inflammatory disease
- endometritis
- increased incidence of ectopic pregnancies
- infertility
- reactive arthritis
- perihepatitis (Fitz-Hugh-Curtis syndrome)

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



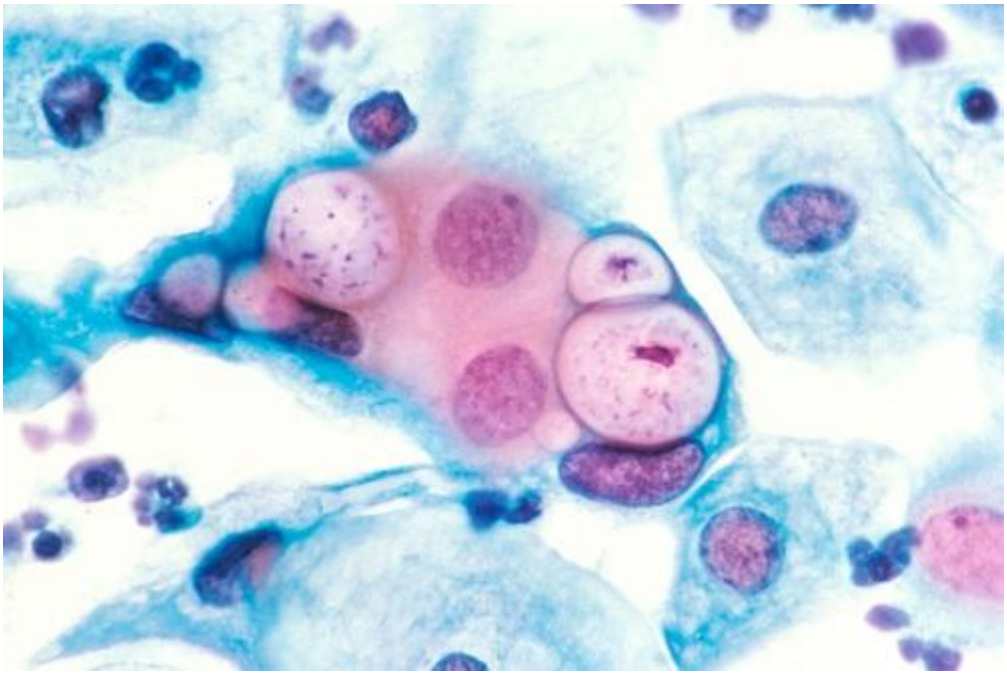
Pap smear demonstrating infected endocervical cells. Red inclusion bodies are typical

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 azithromycin, erythromycin or amoxicillin may be used. The SIGN guidelines suggest azithromycin 1g stat is the drug of choice '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 urethral symptoms: all contacts since, and in the four weeks prior to, the onset

of symptoms

- 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)



Another Pap smear demonstrating infected endocervical cells. Stained with H&E

Cholera

Overview

- caused by Vibro cholerae - Gram negative bacteria

Features

- profuse 'rice water' diarrhoea
- dehydration
- hypoglycaemia

Management

- oral rehydration therapy
- antibiotics: doxycycline, ciprofloxacin

Classification of bacteria

Remember:

- Gram positive cocci = staphylococci + streptococci (including enterococci)
- Gram negative cocci = *Neisseria meningitidis* + *Neisseria gonorrhoeae*, also *Moraxella*

Therefore, only a small list of Gram positive rods (bacilli) need to be memorised to categorise all bacteria - mnemonic = ABCD L

- *Actinomyces*
- *Bacillus anthracis* (anthrax)
- *Clostridium*
- Diphtheria: *Corynebacterium diphtheriae*
- *Listeria monocytogenes*

Remaining organisms are Gram negative rods

Congenital infections

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

Dengue fever

Dengue fever is a viral infection which can progress to viral haemorrhagic fever (also yellow fever, Lassa fever, Ebola)

Basics

- transmitted by the Aedes aegyti mosquito
- incubation period of 7 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
- pleuritic pain
- facial flushing (dengue)
- maculopapular rash

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

Epstein-Barr virus: associated conditions

Malignancies associated with EBV infection

- Burkitt's lymphoma*
- Hodgkin's lymphoma
- nasopharyngeal carcinoma
- HIV-associated central nervous system lymphomas

The non-malignant condition hairy leukoplakia is also associated with EBV infection.

*EBV is currently thought to be associated with both African and sporadic Burkitt's

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:

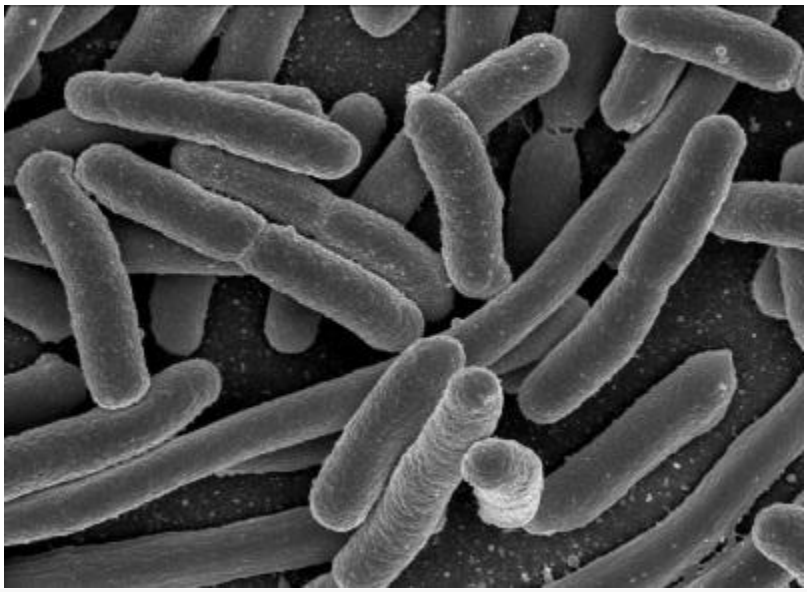
- diarrhoeal illnesses
- UTIs
- neonatal meningitis

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.



Scanning electron micrograph of *Escherichia coli*, grown in culture and adhered to a cover slip. Credit: NIAID

Gastroenteritis

Gastroenteritis may either occur whilst at home or whilst travelling abroad (travellers' diarrhoea)

Travellers' diarrhoea may be 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*

Another pattern of illness is 'acute food poisoning'. This describes the sudden onset of nausea, vomiting and diarrhoea after the ingestion of a toxin. Acute food poisoning is typically caused by *Staphylococcus aureus*, *Bacillus cereus* or *Clostridium perfringens*.

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	A flu-like prodrome is usually followed by crampy abdominal pains, fever and diarrhoea which may be bloody Complications include Guillain-Barre syndrome
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

*vomiting subtype, the diarrhoeal illness has an incubation period of 6-14 hours

Genital warts

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.

Features

- small (2 - 5 mm) fleshy protuberances which are slightly pigmented
- may bleed or itch

Management

- topical podophyllum or cryotherapy are commonly used as first-line treatments depending on the location and type of lesion. Multiple, non-keratinised warts are generally best treated with topical agents whereas solitary, keratinised warts respond better to cryotherapy
- imiquimod is a topical cream which is generally used second line
- 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

Giardiasis

Giardiasis is caused by the flagellate protozoan *Giardia lamblia*. It is spread by the faeco-oral route

Features

- often asymptomatic
- lethargy, bloating, abdominal pain
- non-bloody diarrhoea
- chronic diarrhoea, malabsorption and lactose intolerance can occur
- stool microscopy for trophozoite and cysts are classically negative, therefore duodenal fluid aspirates or 'string tests' (fluid absorbed onto swallowed string) are sometimes needed

Treatment is with metronidazole

Gonorrhoea

Gonorrhoea is caused by the Gram negative diplococcus *Neisseria gonorrhoeae*. 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

Features

- males: urethral discharge, dysuria
- females: cervicitis e.g. leading to vaginal discharge
- rectal and pharyngeal infection is usually asymptomatic

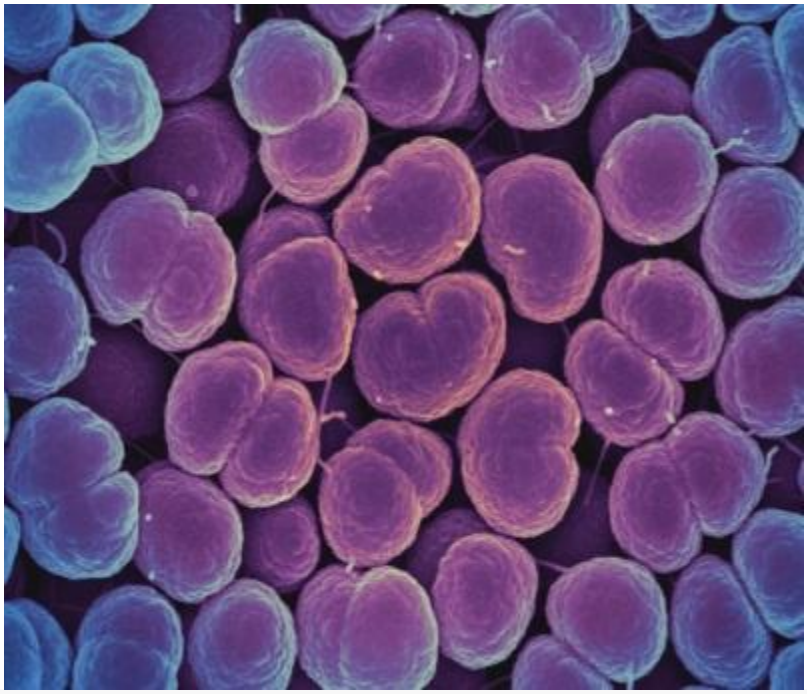
Microbiology

- immunisation is not possible and 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)

Local complications that may develop include urethral strictures, epididymitis and salpingitis (hence may lead to infertility). Disseminated infection may occur - see below

Management

- ciprofloxacin used to be the treatment of choice. However, there is increased resistance to ciprofloxacin and therefore cephalosporins are now used
- 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. This combination can be used in pregnant women as well
- if ceftriaxone is refused or contraindicated other options include cefixime 400mg PO (single dose)



Colorized scanning electron micrograph of *Neisseria gonorrhoeae*. Credit: NIAID

Disseminated gonococcal infection (DGI) and gonococcal arthritis may also occur, with gonococcal infection being the most common cause of septic arthritis in young adults. The pathophysiology of DGI is not fully understood but is thought to be due to haematogenous spread from mucosal infection (e.g. Asymptomatic genital infection). Initially there may be a classic triad of symptoms: tenosynovitis, migratory polyarthritis and dermatitis. Later complications include septic arthritis, endocarditis and perihepatitis (Fitz-Hugh-Curtis syndrome)

Key features of disseminated gonococcal infection

- tenosynovitis
- migratory polyarthritis
- dermatitis (lesions can be maculopapular or vesicular)

H1N1 influenza pandemic

The 2009 H1N1 influenza (swine flu) outbreak was first observed in Mexico in early 2009. In June 2009, the WHO declared the outbreak to be a pandemic.

H1N1

The H1N1 virus is a subtype of the influenza A virus and the most common cause of flu in humans. The 2009 pandemic was caused by a new strain of the H1N1 virus.

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 are two main treatments currently available:

Oseltamivir (Tamiflu)

- oral medication
- a neuraminidase inhibitor which prevents new viral particles from being released by infected cells
- common side-effects include nausea, vomiting, diarrhoea and headaches

Zanamivir (Relenza)

- inhaled medication*
- also a neuraminidase inhibitor
- may induce bronchospasm in asthmatics

*intravenous preparations are available for patients who are acutely unwell

Hepatitis B

Hepatitis B is a double-stranded DNA hepadnavirus and is spread through exposure to infected blood or body fluids, including vertical transmission from mother to child. The incubation period is 6-20 weeks.

The features of hepatitis B include fever, jaundice and elevated liver transaminases.

Complications of hepatitis B infection

- chronic hepatitis (5-10%)
- fulminant liver failure (1%)
- hepatocellular carcinoma
- glomerulonephritis
- polyarteritis nodosa
- cryoglobulinaemia

Immunisation against hepatitis B (please see the Greenbook link for more details)

- contains HBsAg adsorbed onto aluminium hydroxide adjuvant and is prepared from yeast cells using recombinant DNA technology
- most schedules give 3 doses of the vaccine with a recommendation for a 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
- around 10-15% of adults fail to respond or respond poorly to 3 doses of the vaccine. Risk factors include age over 40 years, obesity, smoking, alcohol excess and immunosuppression
- 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 levels should be checked 1-4 months after primary immunisation
- the table below shows how to interpret anti-HBs levels:

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

Management of hepatitis B

- pegylated interferon-alpha used to be the only treatment available. It reduces viral replication in up to 30% of chronic carriers. A 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
- whilst NICE still advocate the use of pegylated interferon firstl-line other antiviral medications are increasingly used with an aim to suppress viral replication (not in a dissimilar way to treating HIV patients)
- examples include tenofovir and entecavir

Hepatitis B and pregnancy

Basics

- all pregnant women are offered screening for hepatitis B
- 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
- studies are currently evaluating the role of oral antiviral treatment (e.g. Lamivudine) in the latter part of pregnancy
- there is little evidence to suggest caesarean section reduces vertical transmission rates
- hepatitis B cannot be transmitted via breastfeeding (in contrast to HIV)

Hepatitis B serology

Interpreting hepatitis B serology is a dying art form which still occurs at regular intervals in medical exams. 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
- HBsAg normally implies acute disease (present for 1-6 months)
- if HBsAg is present for > 6 months then this implies chronic disease (i.e. Infective)
- 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. IgG anti-HBc persists
- HbeAg results from breakdown of core antigen from infected liver cells as is therefore a marker of infectivity

Example results

- 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

HBsAg = ongoing infection, either acute or chronic if present > 6 months

anti-HB**c** = **c**aught, i.e. negative if immunized

Hepatitis E

Overview

- 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, but carries a significant mortality (about 20%) during pregnancy
- does not cause chronic disease or an increased risk of hepatocellular cancer
- a vaccine is currently in development*, but is not yet in widespread use

HIV and pregnancy

With the increased incidence of HIV infection amongst the heterosexual population there are an increasing number of HIV positive women giving birth in the UK. 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.

Guidelines regularly change on this subject and most recent guidelines can be found using the links provided.

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

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: 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

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*

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

*nitazoxanide is licensed in the US for immunocompetent patients

HIV: immunisation

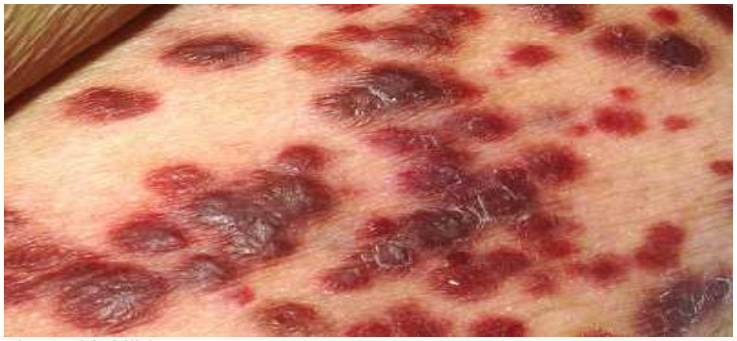
The Department of Health 'Greenbook' on immunisation defers to the British HIV Association for guidelines relating to immunisation of HIV-infected adults

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)	Measles, Mumps, Rubella (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)
- presents as purple papules or plaques on the skin or mucosa (e.g. gastrointestinal and respiratory tract)
- skin lesions may later ulcerate
- respiratory involvement may cause massive haemoptysis and pleural effusion
- radiotherapy + resection



Kaposi's sarcoma in a patient with HIV

HIV: Mycobacterium avium complex

Mycobacterium avium complex (MAC) is an atypical mycobacterial infection seen in HIV patients. It is caused by both Mycobacterium avium and Mycobacterium intracellulare, and is often referred to as Mycobacterium avium-intracellulare (MAI). Over 95% of MAC infections in patients with HIV are caused by Mycobacterium avium. MAC is generally seen when the CD4 count is less than 50 cells/mm^3

Features

- fever, sweats
- abdominal: pain, diarrhoea
- lung: dyspnoea, cough
- anaemia
- lymphadenopathy
- hepatomegaly/deranged LFTs

Diagnosis

- blood cultures
- bone marrow aspirate

Prophylaxis

- clarithromycin or azithromycin when CD4 is less than 100 cells/mm^3

Management

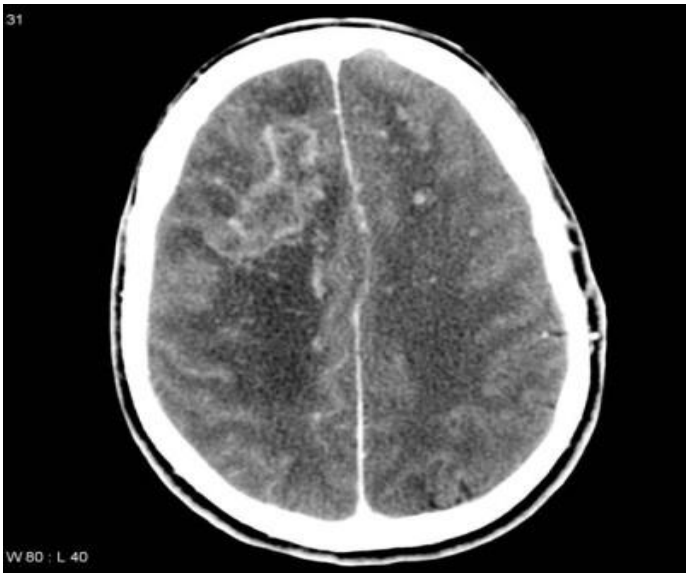
- rifampicin + ethambutol + clarithromycin

HIV: neurocomplications

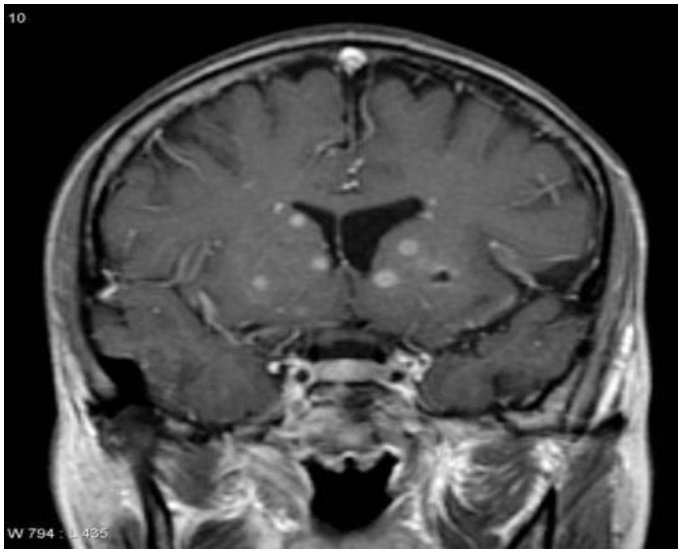
Focal neurological lesions

Toxoplasmosis

- accounts for around 50% of cerebral lesions in patients with HIV
- constitutional symptoms, headache, confusion, drowsiness
- CT: usually single or multiple ring enhancing lesions, mass effect may be seen
- management: sulfadiazine and pyrimethamine



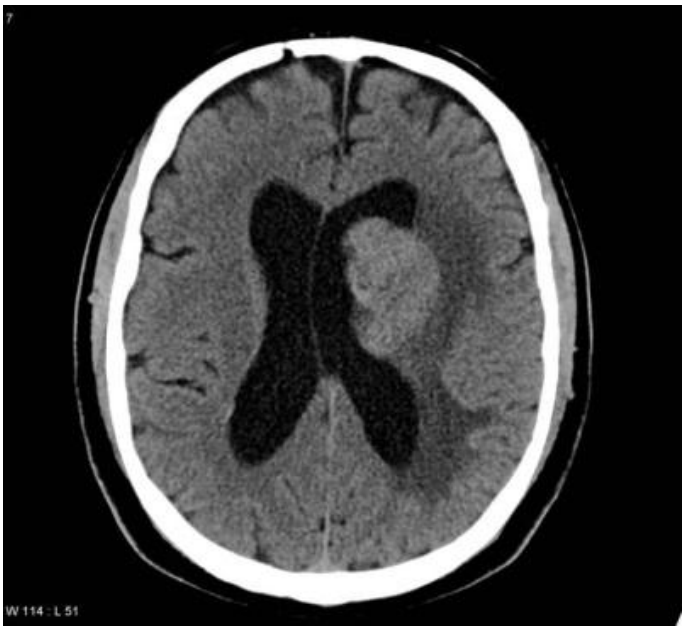
Cerebral toxoplasmosis: CT scan with contrast showing multiple ring enhancing lesions



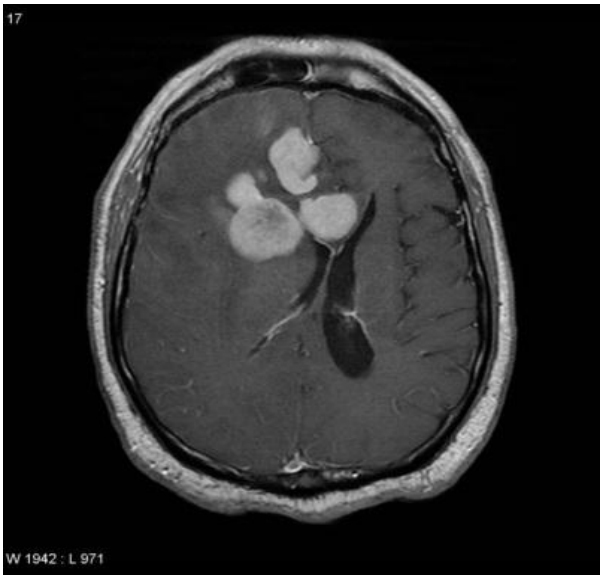
Cerebral toxoplasmosis: MRI (T1 C+) demonstrates multiple small peripherally enhancing nodules located predominantly in the basal ganglia as well as the central portions of the cerebellar hemispheres. Only a small amount of surrounding oedema is present.

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. It is clearly important given the vastly different treatment strategies. The table below gives some general differences. Please see the Radiopaedia link for more details.

Toxoplasmosis	Lymphoma
Multiple lesions Ring or nodular enhancement Thallium SPECT negative	Single lesion Solid (homogenous) enhancement Thallium SPECT positive

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
- 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

Progressive multifocal leukoencephalopathy (PML)

- widespread demyelination
- due to infection of oligodendrocytes by JC virus (a polyoma DNA virus)
- symptoms, subacute onset : behavioural changes, speech, motor, visual impairment
- CT: single or multiple lesions, no mass effect, don't usually enhance. MRI is better - high-signal demyelinating white matter lesions are seen

AIDS dementia complex

- caused by HIV virus itself
- symptoms: behavioural changes, motor impairment
- CT: cortical and subcortical atrophy

HIV: opportunistic infections and other disorders

The table below shows the infections and other disorders that may be encountered by patients with HIV according to the CD4 count.

CD4 count 200 - 500 cells/mm³

Disorder	Notes
Oral thrush	Secondary to *Candida albicans*
Shingles	Secondary to herpes zoster
Hairy leukoplakia	Secondary to EBV
Kaposi sarcoma	Secondary to HHV-8

CD4 count 100 - 200 cells/mm³

Disorder	Notes
Cryptosporidiosis	Whilst patients with a CD4 count of 200-500 may develop cryptosporidiosis the disease is usually self-limiting and similar to that in immunocompetent hosts
Cerebral toxoplasmosis	
Progressive multifocal leukoencephalopathy	Secondary to the JC virus
Pneumocystis jirovecii pneumonia	
HIV dementia	

CD4 count 50 - 100 cells/mm³

Disorder	Notes
Aspergillosis	Secondary to *Aspergillus fumigatus*
Oesophageal candidiasis	Secondary to *Candida albicans*
Cryptococcal meningitis	
Primary CNS lymphoma	Secondary to EBV

CD4 count < 50 cells/mm³

Disorder	Notes
Cytomegalovirus retinitis	Affects around 30-40% of patients with CD4 < 50 cells/mm³
Mycobacterium avium-intracellulare infection	

HIV: *Pneumocystis jiroveci* pneumonia

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
- PCP is the most common opportunistic infection in AIDS
- all patients with a CD4 count < 200/mm³ should receive PCP prophylaxis

Features

- dyspnoea
- dry cough
- fever
- very few chest signs

Pneumothorax is a common complication of PCP.

Extrapulmonary manifestations are rare (1-2% of cases), may cause

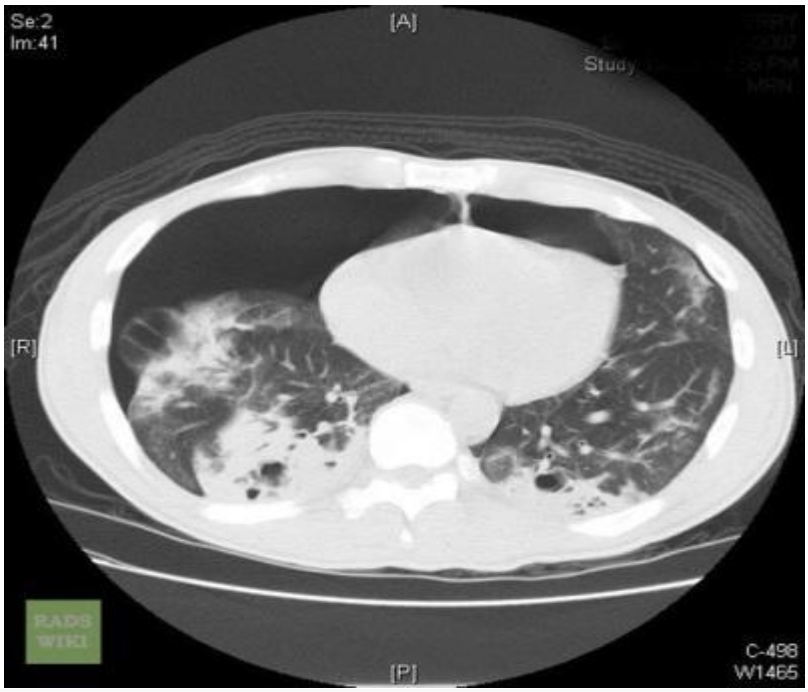
- hepatosplenomegaly
- lymphadenopathy
- choroid lesions

Investigation

- CXR: typically shows bilateral interstitial pulmonary infiltrates but can present with other x-ray findings e.g. lobar consolidation. May be normal
- exercise-induced desaturation
- sputum often fails to show PCP, bronchoalveolar lavage (BAL) often needed to demonstrate PCP (silver stain shows characteristic cysts)

Management

- co-trimoxazole
- IV pentamidine in severe cases
- steroids if hypoxic (if pO2 < 9.3kPa then steroids reduce risk of respiratory failure by 50% and death by a third)



CT scan showing a large pneumothorax developing in a patient with *Pneumocystis jiroveci* pneumonia

HIV: seroconversion

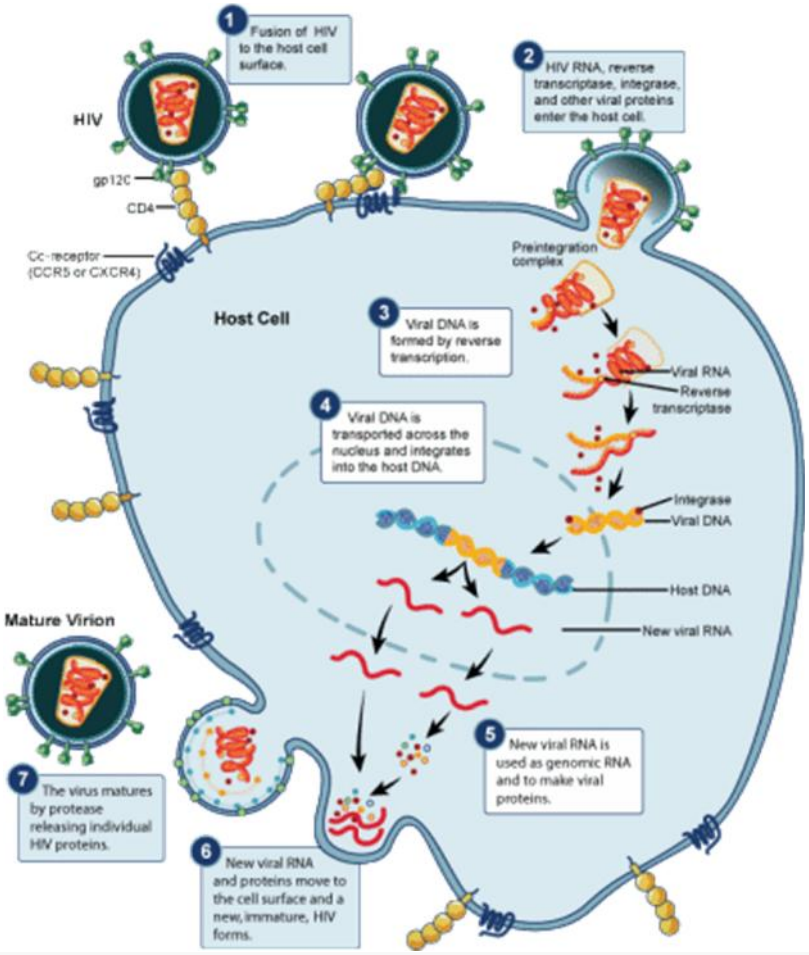
HIV seroconversion is symptomatic in 60-80% of patients and typically presents as a glandular fever type illness. Increased symptomatic severity is associated with poorer long term prognosis. It typically occurs 3-12 weeks after infection

Features

- sore throat
- lymphadenopathy
- malaise, myalgia, arthralgia
- diarrhoea
- maculopapular rash
- mouth ulcers
- rarely meningoencephalitis

Diagnosis

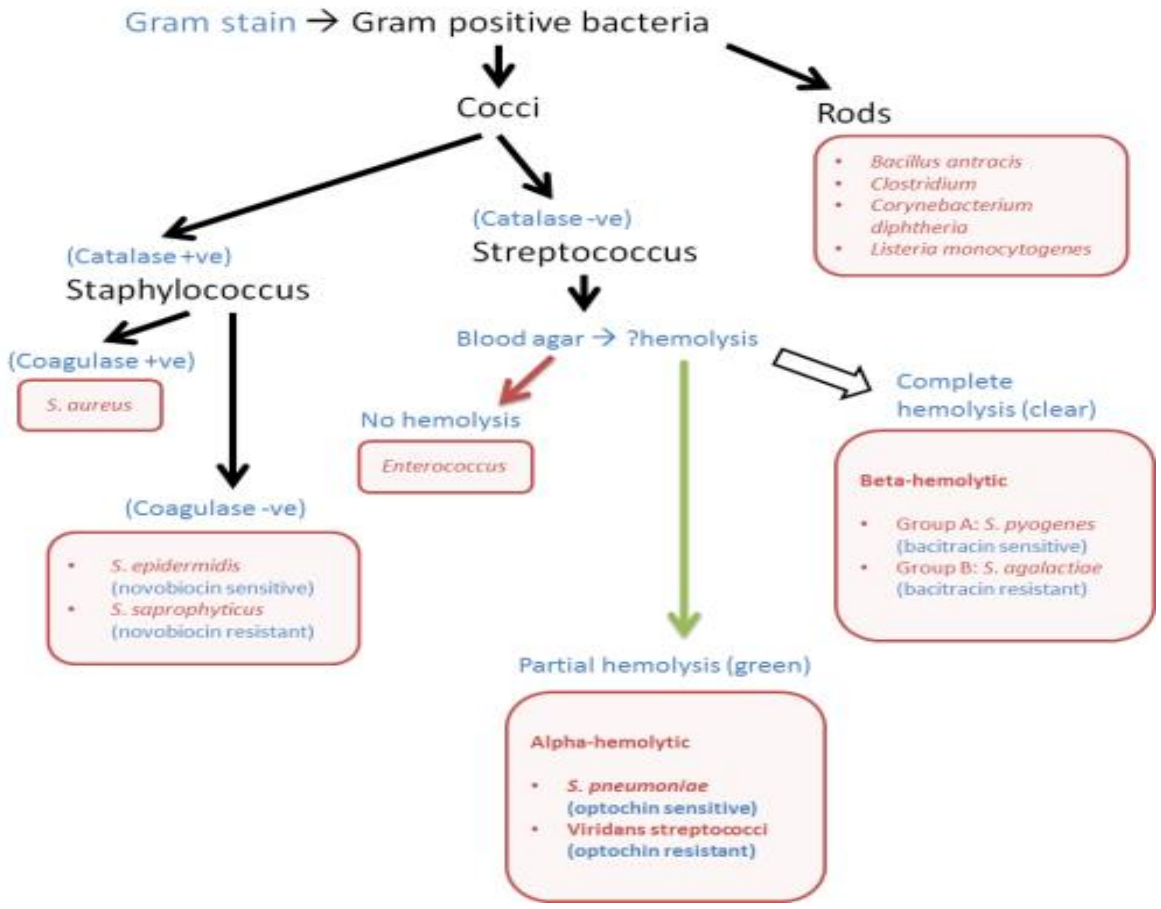
- antibodies to HIV may not be present
- HIV PCR and p24 antigen tests can confirm diagnosis



An illustration model of the HIV Replication Cycle. Each step of the cycle is numbered and concisely described. Credit: NIAID

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
- complete haemolysis (clear): β-haemolytic
- no haemolysis: γ-haemolytic

α-haemolytic streptococci

- optochin sensitive: *S. pneumoniae*
- optochin resistant: Viridans streptococci

β-haemolytic streptococci

- bacitracin sensitive: Group A: *S. pyogenes*
- bacitracin resistant: Group B: *S. agalactiae*

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

- meningococcus
- diphtheria
- influenza
- scarlet fever

1 - 2 weeks

- malaria
- dengue fever
- typhoid
- measles

2 - 3 weeks

- mumps
- rubella
- chickenpox

Longer than 3 weeks

- infectious mononucleosis
- cytomegalovirus
- viral hepatitis
- HIV

Infectious mononucleosis

Infectious mononucleosis (glandular fever) is caused by the Epstein-Barr virus (also known as human herpesvirus 4, HHV-4). It is most common in adolescents and young adults.

Features

- sore throat
- lymphadenopathy
- pyrexia
- malaise, anorexia, headache
- palatal petechiae
- splenomegaly - occurs in around 50% of patients and may rarely predispose to splenic rupture
- hepatitis
- presence of 50% lymphocytes with at least 10% atypical lymphocytes
- 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

Diagnosis

- heterophil antibody test (Monospot test) - NICE guidelines suggest FBC and Monospot in the second week of the illness to confirm a diagnosis of glandular fever.

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

Infective endocarditis: prognosis and management

Poor prognostic factors

- Staph aureus infection (see below)
- prosthetic valve (especially 'early', acquired during surgery)
- culture negative endocarditis
- low complement levels

Mortality according to organism

- staphylococci - 30%
- bowel organisms - 15%
- streptococci - 5%

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
Endocarditis caused by less sensitive streptococci	Benzylpenicillin + low-dose gentamicin If penicillin allergic • vancomycin + low-dose gentamicin

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

Leishmaniasis

Leishmaniasis is caused by the intracellular protozoa Leishmania, usually being spread by sand flies. Cutaneous, mucocutaneous leishmaniasis and visceral forms are seen

Cutaneous leishmaniasis

- caused by *Leishmania tropica* or *Leishmania mexicana*
- crusted lesion at site of bite
- may be underlying ulcer

Mucocutaneous leishmaniasis

- caused by *Leishmania braziliensis*
- skin lesions may spread to involve mucosae of nose, pharynx etc

Visceral leishmaniasis (kala-azar)

- mostly caused by *Leishmania donovani*
- occurs in the Mediterranean, Asia, South America, Africa
- fever, sweats, rigors
- massive splenomegaly. hepatomegaly
- poor appetite*, weight loss
- grey skin - 'kala-azar' means black sickness
- pancytopaenia secondary to hypersplenism

*occasionally patients may report increased appetite with paradoxical weight loss

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

Leptospirosis

Also known as Weil's disease*, 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 hepatorenal failure

Features

- fever
- flu-like symptoms
- renal failure (seen in 50% of patients)
- jaundice
- subconjunctival haemorrhage
- headache, may herald the onset of meningitis

Management

- high-dose benzylpenicillin or doxycycline

*the term Weil's disease is sometimes reserved for the most severe 10% of cases that are associated with jaundice

Linezolid

Linezolid is a type of oxazolidonone antibiotic which has been introduced in recent years. It inhibits bacterial protein synthesis by stopping formation of the 70s initiation complex and is bacteriostatic nature

Spectrum, highly active against Gram positive organisms including:

- MRSA (Methicillin-resistant *Staphylococcus aureus*)
- VRE (Vancomycin-resistant enterococcus)
- GISA (Glycopeptide Intermediate *Staphylococcus aureus*)

Adverse effects

- thrombocytopenia (reversible on stopping)
- monoamine oxidase inhibitor: avoid tyramine containing foods

Listeria

Listeria monocytogenes is a Gram positive bacillus which 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.

Features - can present in a variety of ways

- diarrhoea, flu-like illness
- pneumonia , meningoencephalitis
- ataxia and seizures

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

Lyme disease

Lyme disease is caused by the spirochaete *Borrelia burgdorferi* and is spread by ticks

Features

- early: erythema chronicum migrans + systemic features (fever, arthralgia)
- CVS: heart block, myocarditis
- neuro: cranial nerve palsies, meningitis

Investigation

- serology: antibodies to *Borrelia burgdorferi*

Management

- 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)

Lyme disease: features

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'. Oc curs in 70% of patients)
- systemic symptoms: malaise, fever, arthralgia

Later features

- CVS: heart block, myocarditis
- neurological: cranial nerve palsies, meningitis
- polyarthritis

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

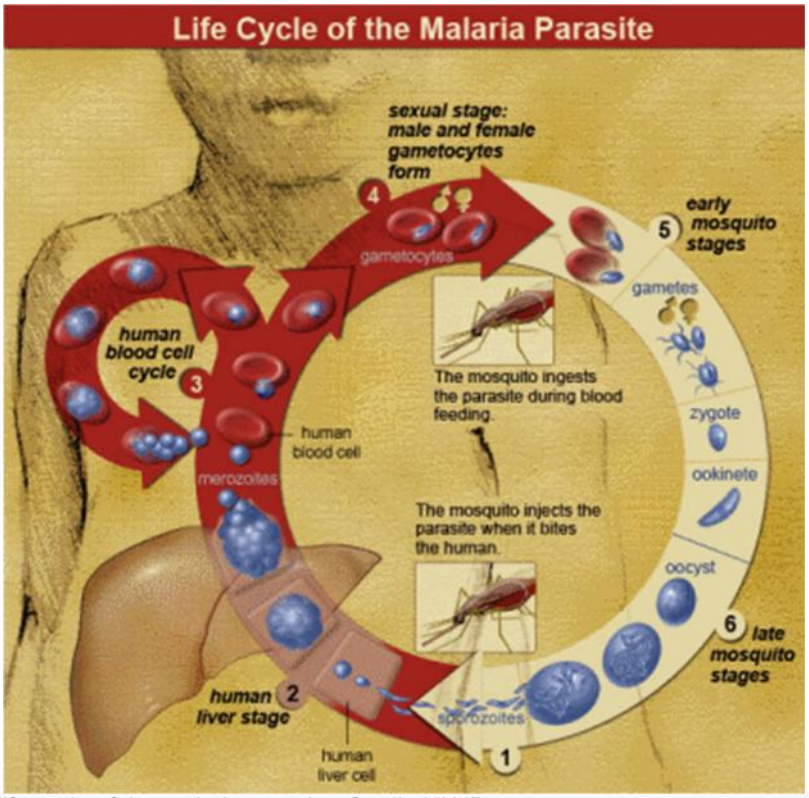
Malaria is a disease caused by *Plasmodium* protozoa which is spread by the female Anopheles mosquito. There are four different species which cause disease in man:

- *Plasmodium falciparum*
- *Plasmodium vivax*
- *Plasmodium ovale*
- *Plasmodium malariae*

Plasmodium falciparum causes nearly all episodes of severe malaria. The other three types, of which *Plasmodium vivax* is the most common, cause 'benign' malaria

The protection from malaria that sickle-cell trait offers is well documented. Other protective factors include

- G6PD deficiency
- HLA-B53
- absence of Duffy antigens



An illustration of the life cycle of the malaria parasite. Credit: NIAID

Malaria: Falciparum

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)
- 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
- intravenous artesunate is now recommended by WHO in preference to intravenous quinine
- if parasite count > 10% then exchange transfusion should be considered
- shock may indicate coexistent bacterial septicaemia - malaria rarely causes haemodynamic collapse

Malaria: non-falciparum

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

Features

- general features of malaria: fever, headache, splenomegaly
- *Plasmodium vivax/ovale*: cyclical fever every 48 hours. *Plasmodium malariae*: cyclical fever every 72 hours
- *Plasmodium malariae*: is associated with nephrotic syndrome

Ovale and vivax malaria have a hypnozoite stage and may therefore relapse following treatment.

Treatment

- in areas which are known to be chloroquine-sensitive then WHO recommend either an artemisinin-based combination therapy (ACT) or chloroquine
- in areas which are known to be chloroquine-resistant an ACT should be used
- ACTs should be avoided in pregnant women
- patients with ovale or vivax malaria should be given primaquine following acute treatment with chloroquine to destroy liver hypnozoites and prevent relapse

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.

Up-to-date charts with recommended regimes for malarial zones should be consulted prior to prescribing

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

Drug	Side-effects + notes	Time to begin before travel	Time to end after travel
Proguanil (Paludrine)		1 week	4 weeks
Proguanil + chloroquine	See above	1 week	4 weeks

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

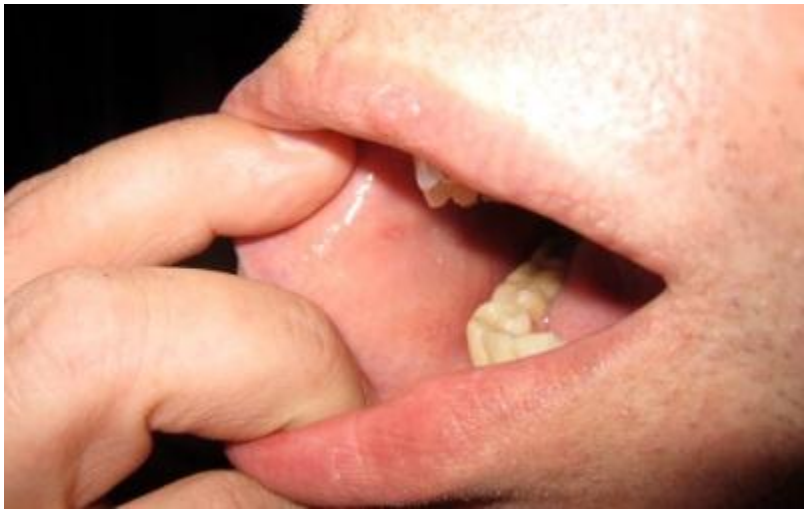
Measles

Overview

- RNA paramyxovirus
- spread by droplets
- infective from prodrome until 4 days after rash starts
- incubation period = 10-14 days

Features

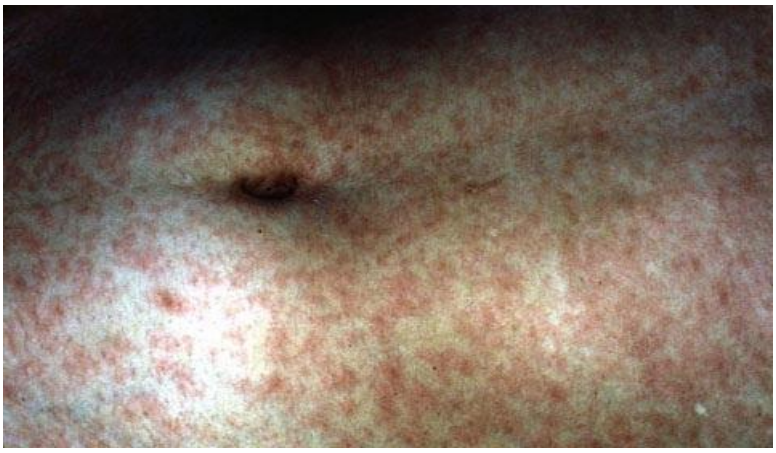
- prodrome: irritable, conjunctivitis, fever
- Koplik spots (before rash): white spots ('grain of salt') on buccal mucosa
- rash: starts behind ears then to whole body, discrete maculopapular rash becoming blotchy & confluent



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

Meningitis: causes

0 - 3 months

- Group B *Streptococcus* (most common cause in neonates)
- *E. coli*
- *Listeria monocytogenes*

3 months - 6 years

- *Neisseria meningitidis*
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*

6 years - 60 years

- *Neisseria meningitidis*
- *Streptococcus pneumoniae*

> 60 years

- *Streptococcus pneumoniae*
- *Neisseria meningitidis*
- *Listeria monocytogenes*

Immunosuppressed

- *Listeria monocytogenes*

Meningitis: CSF analysis

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/mm^3	15 - 1,000 lymphocytes/mm^3	10 - 1,000 lymphocytes/mm^3

The Ziehl-Neelsen stain is only 20% sensitive in the detection of tuberculous meningitis and therefore PCR is sometimes used (sensitivity = 75%)

*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

Meningitis: management

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

Management
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.

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.

Management of contacts

- prophylaxis needs to be offered to household and close contacts of patients affected with meningococcal meningitis
- oral ciprofloxacin or rifampicin or may be used. 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
- 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 meninigitis 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. Please see the link for more details

Meningococcal septicaemia: investigations

Meningococcal septicaemia is a frightening condition for patients, parents and doctors. 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. Much of the following is based on the 2010 NICE guidelines (please see link).

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

MRSA

Methicillin-resistant *Staphylococcus aureus* (MRSA) was one of the first organisms which highlighted the dangers of hospital-acquired infections.

Who should be screened for MRSA?

- all patients awaiting elective admissions (exceptions include day patients having terminations of pregnancy and ophthalmic surgery. Patients admitted to mental health trusts are also excluded)
- from 2011 all emergency admissions will be screened

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

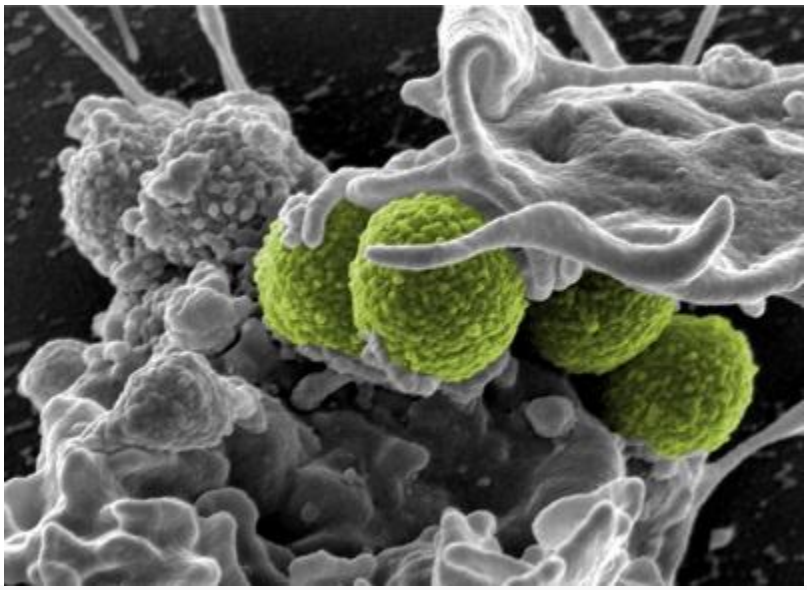
The following antibiotics are commonly used in the treatment of MRSA infections:

- vancomycin
- teicoplanin
- linezolid

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



Interaction of MRSA (green bacteria) with a human white cell. The bacteria shown is strain MRSA252, a leading cause of hospital-associated infections in the United States and United Kingdom. Credit: NIAID

Necrotising fasciitis

Necrotising fasciitis is a medical emergency that is difficult to recognise in the early stages

It can be classified 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*

Features

- acute onset
- painful, erythematous lesion develops
- extremely tender over infected tissue

Management

- urgent surgical referral debridement
- intravenous antibiotics

Nematodes

Ancylostoma braziliense

- most common cause of cutaneous larva migrans
- common in Central and Southern America

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

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

Osteomyelitis

Osteomyelitis describes an infection of the bone.

Staph. aureus is the most common cause except in patients with sickle-cell anaemia where *Salmonella* species predominate.

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%

Management

- flucloxacillin for 6 weeks
- clindamycin if penicillin-allergic

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
- 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

Post-exposure prophylaxis

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 whilst those in the process of being vaccinated should have an accelerated course of HBV vaccine

Hepatitis C

- monthly PCR - if seroconversion then interferon +/- ribavirin

HIV

- a combination of oral antiretrovirals (e.g. Tenofovir, emtricitabine, lopinavir and ritonavir) as soon as possible (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 needlestick injury

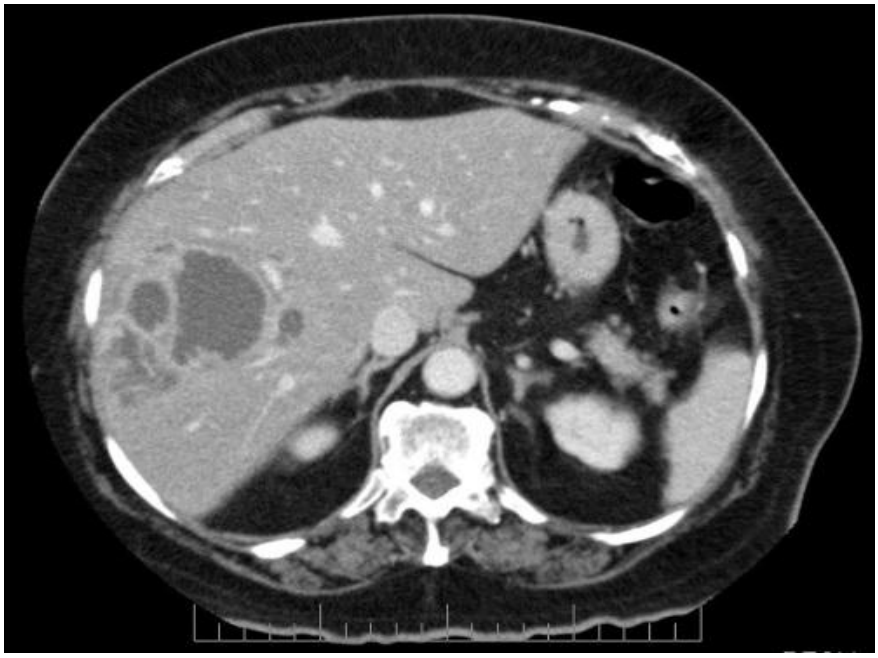
Hepatitis B	**20-30%**
Hepatitis C	0.5-2%
HIV	0.3%

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



CT showing a pyogenic liver abscess in the right lobe of the liver.

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

Rabies

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

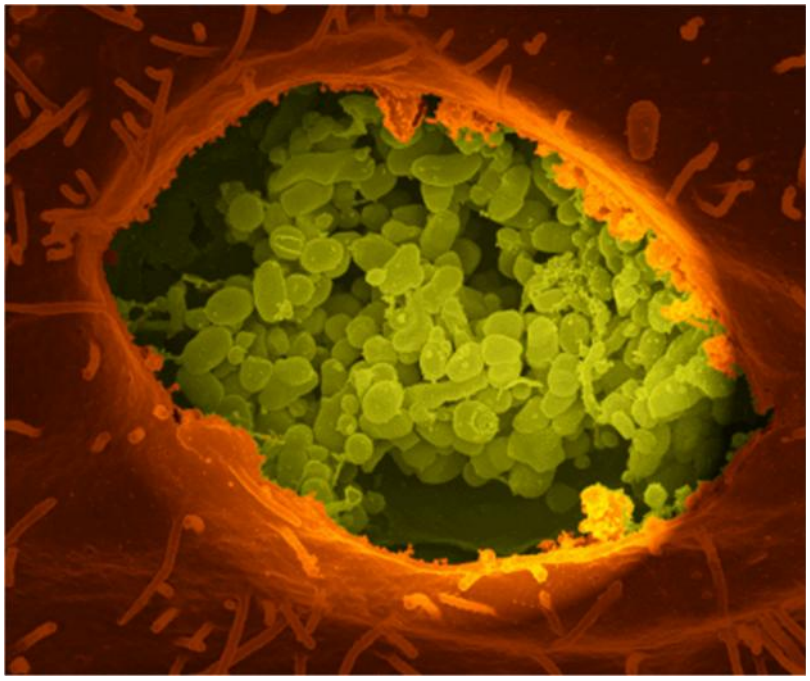
There is now considered to be 'no risk' of developing rabies following an animal bite in the UK and the majority of developed countries. Following an animal bite in at risk countries:

- 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

Rickettsiae

Rickettsiae are Gram-negative obligate intracellular parasites. Types of rickettsiae cause a variety of diseases that are typically characterised by fever, headache and rash. A notable exception is Q fever (cause by *Coxiella burnetti* which causes pneumonia but no rash. The Weil-Felix reaction is positive except in Q fever. Rickettsial diseases are all treated with tetracyclines.

Disease	Cause	Vector	Notes
Rocky Mountain spotted fever	*Rickettsia ricketsii*	Tick	Headache and fever are common Rash starts on the peripheries (wrist, ankles) before spreading centrally. It is initially maculopapular before becoming vasculitic Endemic to east coast of US
Q fever	*Coxiella burnetti*	No vector	No rash but causes pneumonia
Endemic typhus	*Rickettsia typhi*	Flea	Rash starts centrally then spreads to the peripheries
Epidemic typhus	*Rickettsia prowazekii*	Human body louse	
Ehrlichliosis	*Ehrlichia*	Tick	



A dry fracture of a Vero cell exposing the contents of a vacuole where *Coxiella burnetti* are busy growing. Note the intracellular nature of the organism. Credit: NIAID

Salmonella

The *Salmonella* group contains many members, most of which cause diarrhoeal diseases. They are aerobic, Gram negative rods which are not normally present as commensals in the gut.

Typhoid and paratyphoid are caused by *Salmonella typhi* and *Salmonella paratyphi* (types A, B & C) respectively. They are often termed enteric fevers, producing systemic symptoms such as headache, fever, arthralgia

Features

- initially systemic upset as above
- relative bradycardia
- abdominal pain, distension
- constipation: although *Salmonella* is a recognised cause of diarrhoea, constipation is more common in typhoid
- rose spots: present on the trunk in 40% of patients, and are more common in paratyphoid

Possible complications include

- 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)

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
- linear burrows on the side of fingers, interdigital webs and flexor aspects of the wrist
- 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)

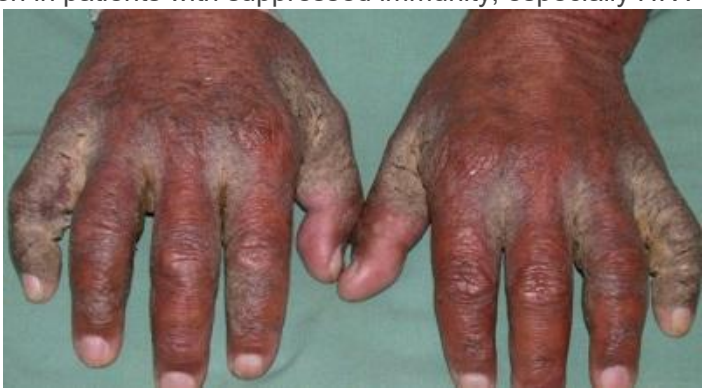
- avoid close physical contact with others until treatment is complete
- all household and close physical contacts should be treated at the same time, even if asymptomatic
- launder, iron or tumble dry clothing, bedding, towels, etc., on the first day of treatment to kill off mites.

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

Schistosomiasis

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

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

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

Surgical aspects

Indications

- Trauma: 1/4 are iatrogenic
- Spontaneous rupture: EBV
- Hypersplenism: hereditary spherocytosis or elliptocytosis etc
- Malignancy: lymphoma or leukaemia
- Splenic cysts, hydatid cysts, splenic abscesses

Splenectomy following trauma

- GA
- Long midline incision
- If time permits insert a self retaining retractor (e.g. Balfour/ omnitract)
- Large amount of free blood is usually present. Pack all 4 quadrants of the abdomen. Allow the anaesthetist to 'catch up'
- Remove the packs and assess the viability of the spleen. Hilar injuries and extensive parenchymal lacerations will usually require splenectomy.
- Divide the short gastric vessels and ligate them.
- Clamp the splenic artery and vein. Two clamps on the patient side are better and allow for double ligation and serve as a safety net if your assistant does not release the clamp smoothly.
- Be careful not to damage the tail of the pancreas, if you do then this will need to be formally removed and the pancreatic duct closed.
- Wash out the abdomen and place a tube drain to the splenic bed.
- Some surgeons implant a portion of spleen into the omentum, whether you decide to do this is a matter of personal choice.
- Postoperatively the patient will require prophylactic penicillin V and pneumococcal vaccine.

Elective splenectomy

- Elective splenectomy is a very different operation from that performed in the emergency setting. The spleen is often large (sometimes massive)
- Most cases can be performed laparoscopically. The spleen will often be macerated inside a specimen bag to facilitate extraction.

Complications

- Haemorrhage (may be early and either from short gastrics or splenic hilar vessels
- Pancreatic fistula (from iatrogenic damage to pancreatic tail)
- Thrombocytosis: prophylactic aspirin
- Encapsulated bacteria infection e.g. *Strep. pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis*

Post-splenectomy changes

- Platelets will rise first (therefore in ITP should be given after splenic artery clamped)
- Blood film will change over following weeks, Howell-Jolly bodies will appear
- Other blood film changes include target cells and Pappenheimer bodies
- Increased risk of post-splenectomy sepsis, therefore prophylactic antibiotics and pneumococcal vaccine should be given.

Post-splenectomy sepsis

- Typically occurs with encapsulated organisms
- Opsonisation occurs but then not recognised

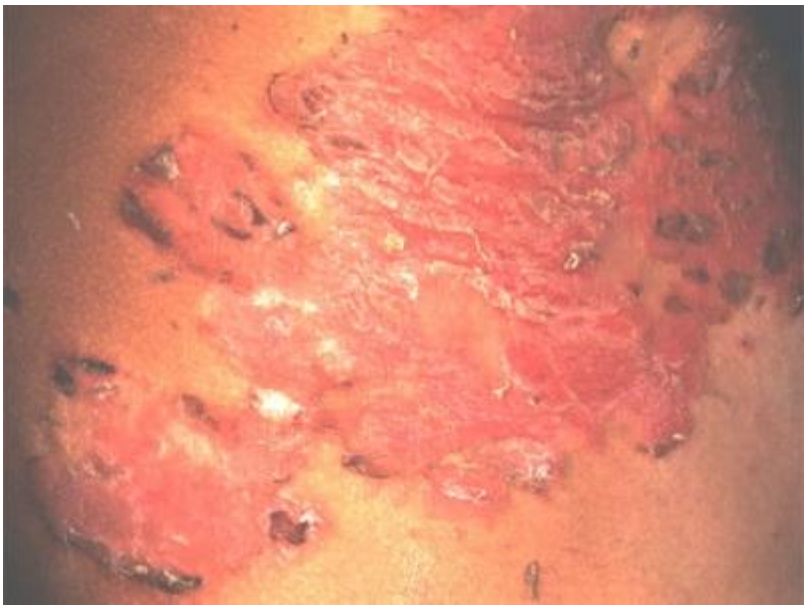
*usually from dog bites

Staphylococcal toxic shock syndrome

Staphylococcal toxic shock syndrome describes a severe systemic reaction to staphylococcal exotoxins. It came to prominence in the early 1980's following a series of cases related to infected tampons

Centers for Disease Control and Prevention diagnostic criteria

- fever: temperature > 38.9ºC
- 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)



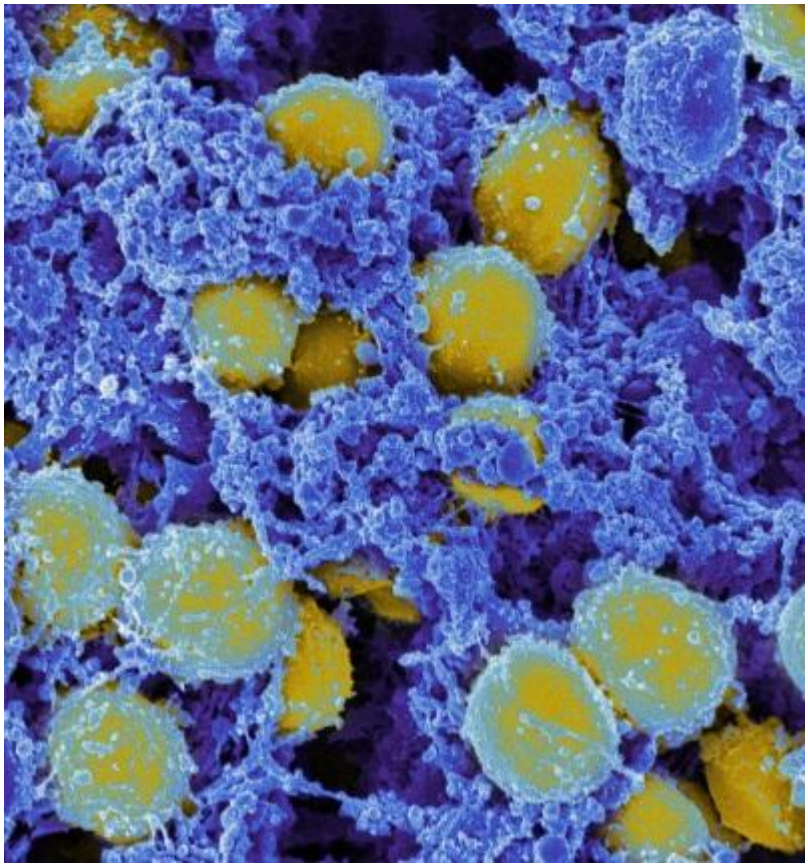
Staphylococci

Staphylococci are a common type of bacteria which are often found normal commensal organisms but may also cause invasive disease. Some basic facts include:

- Gram-positive cocci
- facultative anaerobes
- produce catalase

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



Scanning electromicrograph of Staphylococcus aureus bacteria. Credit: NIAID

STI: ulcers

Genital herpes is most often caused by the herpes simplex virus (HSV) type 2 (cold sores are usually due to HSV type 1). Primary attacks are often severe and associated with fever whilst subsequent attacks are generally less severe and localised to one site

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

Chancroid is a tropical disease caused by *Haemophilus ducreyi*. It causes painful genital ulcers associated with unilateral, painful inguinal lymph node enlargement. The ulcers typically have a sharply defined, ragged, undermined border.

Lymphogranuloma venereum (LGV) is caused by *Chlamydia trachomatis*. Typically infection comprises of three stages

- stage 1: small painless pustule which later forms an ulcer
- stage 2: painful inguinal lymphadenopathy
- stage 3: proctocolitis

LGV is treated using doxycycline.

Other causes of genital ulcers

- Behcet's disease
- carcinoma
- granuloma inguinale: *Klebsiella granulomatis**

*previously called *Calymmatobacterium granulomatis*

Streptococci

Streptococci are gram-positive cocci. They may be divided into alpha and beta haemolytic types

Alpha haemolytic streptococci (partial haemolysis)

The most important alpha haemolytic *Streptococcus* is *Streptococcus pneumoniae* (pneumococcus). Pneumococcus is a common cause of pneumonia, meningitis and otitis media. 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

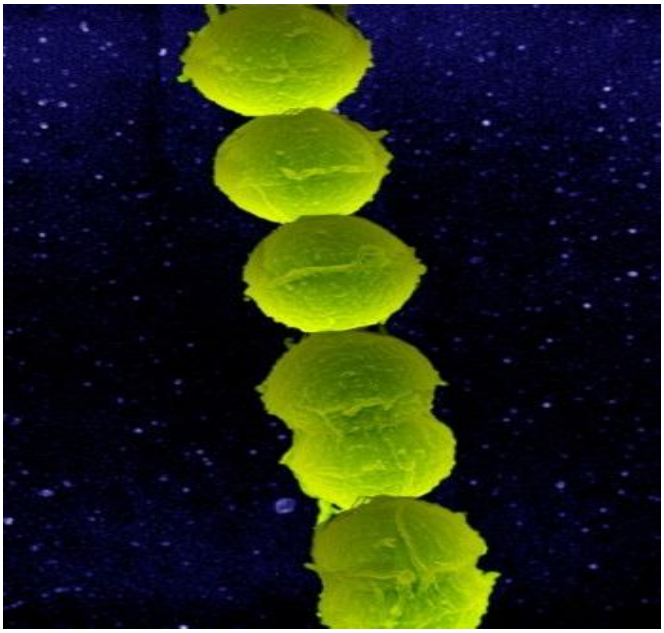
- most important organism is *Streptococcus pyogenes*
- responsible for erysipelas, impetigo, cellulitis, type 2 necrotizing fasciitis and pharyngitis/tonsillitis
- immunological reactions can cause rheumatic fever or post-streptococcal glomerulonephritis
- erythrogenic toxins cause scarlet fever

Group B

- *Streptococcus agalactiae* may lead to neonatal meningitis and septicaemia

Group D

- *Enterococcus*



Group B streptococcus bacteria. Credit: NIAID

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

Syphilis

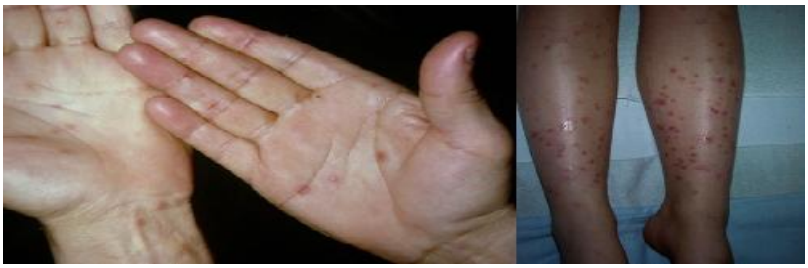
Syphilis is a sexually transmitted infection caused by the spirochaete *Treponema pallidum*. Infection is characterised by primary, secondary and tertiary stages. The incubation period is between 9-90 days

Primary features

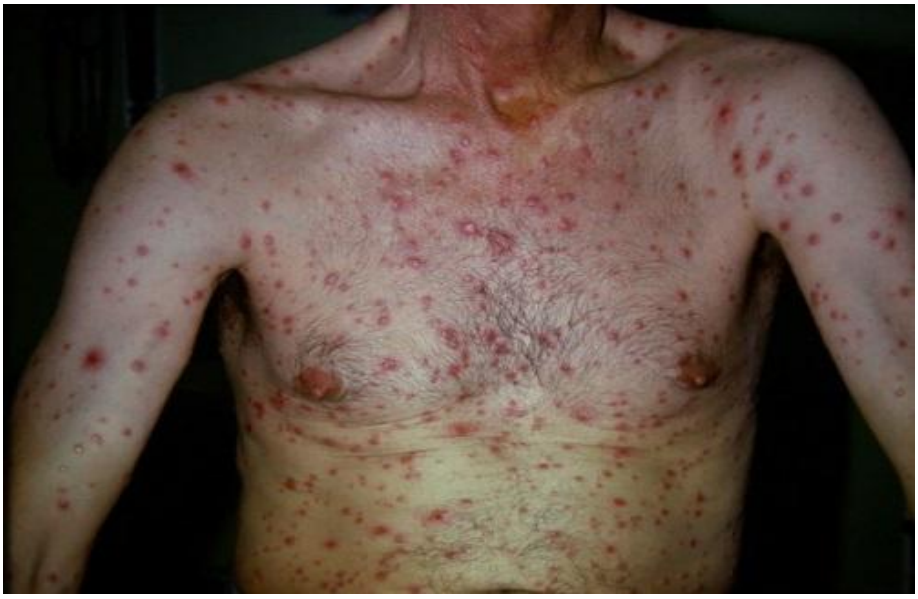
- chancre - painless ulcer at the site of sexual contact
- local non-tender lymphadenopathy
- often not seen in women (the lesion may be on the cervix)

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

- gummas (granulomatous lesions of the skin and bones)
- 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

Syphilis: investigation

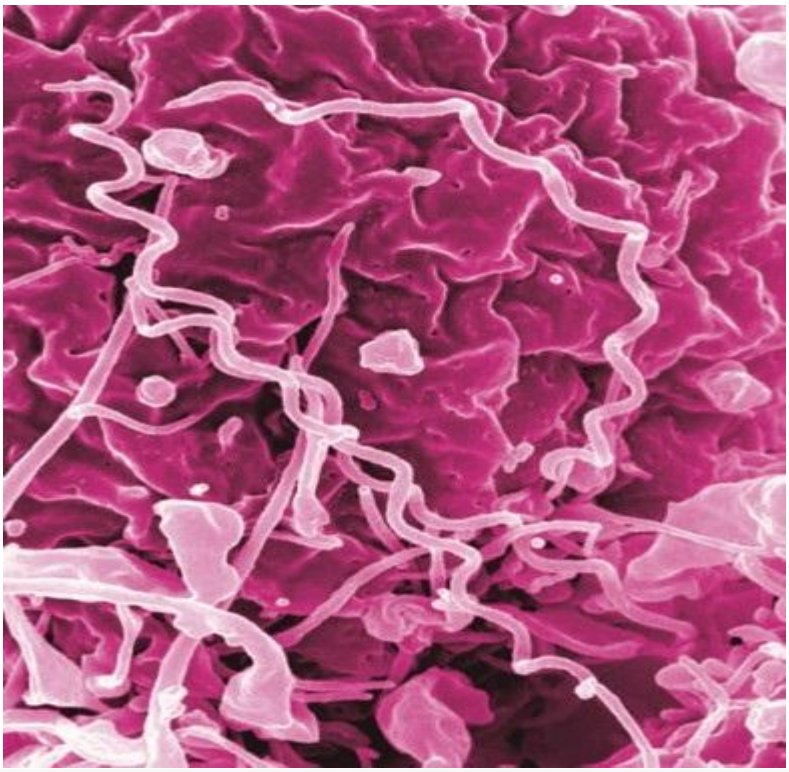
Treponema pallidum is a very sensitive organism and cannot be grown on artificial media. The diagnosis is therefore usually based on clinical features, serology and microscopic examination of infected tissue

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

Treponemal specific antibody tests
- example: TPHA (*Treponema pallidum* HaemAgglutination test)
- remains positive after treatment

Causes of false positive cardiolipin tests
- pregnancy
- SLE, anti-phospholipid syndrome
- TB
- leprosy
- malaria
- HIV



Treponema pallidum, the bacteria that cause syphilis. Note the spiral shape of the organism. Credit: NIAID

Syphilis: management

Management

- benzylpenicillin
- alternatives: doxycycline
- the Jarisch-Herxheimer reaction is sometimes seen following treatment. Fever, rash, tachycardia after first dose of antibiotic. It is thought to be due to the release of endotoxins following bacterial death and typically occurs within a few hours of treatment.

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)
- 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. Tetanospasmin prevents release of GABA

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)
- 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.

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

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

Toxoplasmosis

Toxoplasma gondii is a 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. The usual animal reservoir is the cat, although other animals such as rats carry the disease.

Most infections are asymptomatic. Symptomatic patients usually have a self-limiting infection, often having clinical features resembling infectious mononucleosis (fever, malaise, lymphadenopathy). Other less common manifestations include meningioencephalitis and myocarditis.

Investigation

- antibody test
- Sabin-Feldman dye test

Treatment is usually reserved for those with severe infections or patients who are immunosuppressed

- pyrimethamine plus sulphadiazine for at least 6 weeks

Congenital toxoplasmosis is due to transplacental spread from the mother. It causes a variety of effects to the unborn child including microcephaly, hydrocephalus, cerebral calcification and choroidoretinitis.

Trypanosomiasis

Two main form of this protozoal disease are recognised - African trypanosomiasis (sleeping sickness) and American trypanosomiasis (Chagas' disease)

Two forms of **African trypanosomiasis**, or **sleeping sickness**, are seen - *Trypanosoma gambiense* in West Africa and *Trypanosoma rhodesiense* in East Africa. Both types are spread by the tsetse fly. *Trypanosoma rhodesiense* tends to follow a more acute course. 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

Management

- early disease: IV pentamidine or suramin
- later disease or central nervous system involvement: IV melarsoprol

American trypanosomiasis, or **Chagas' disease**, is caused by the protozoan *Trypanosoma cruzi*. The vast majority of patients (95%) are asymptomatic in the acute phase although a chagoma (an erythematous nodule at site of infection) and periorbital oedema are sometimes seen. Chronic Chagas' disease mainly affects the heart and gastrointestinal tract

- myocarditis may lead to dilated cardiomyopathy (with apical atophy) and arrhythmias
- gastrointestinal features includes megaoesophagus and megacolon causing dysphagia and constipation

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: diagnosis

In adults induction of sputum or bronchoscopy and lavage may be used in patients who cannot produce sputum

In children who are unable to cough up sputum, the gold standard is gastric washings for M tuberculosis culture

Urinary tract infection in adults: management

Lower urinary tract infections

Non-pregnant women

- local antibiotic guidelines should be followed if available
- 2012 SIGN guidelines recommend trimethoprim or nitrofurantoin for 3 days

Pregnant women with symptomatic bacteriuria should be treated with an antibiotic for 7 days. A urine culture should be sent. For asymptomatic pregnant women:

- a urine culture should be performed routinely at the first antenatal visit
- if positive, a second urine culture should be sent to confirm the presence of bacteriuria
- SIGN recommend to treat asymptomatic bacteriuria detected during pregnancy with an antibiotic
- a 7 day course of antibiotics should be given
- a further urine culture should be sent following completion of treatment as a test of cure

Acute pyelonephritis

For patients with sign of acute pyelonephritis hospital admission should be considered

- local antibiotic guidelines should be followed if available
- the BNF currently recommends a broad-spectrum cephalosporin or a quinolone (for non-pregnant women) for 10-14 days

Vaccinations

It is important to be aware of vaccines which are of the live-attenuated type as these may pose a risk to immunocompromised patients. The main types of vaccine are as follows:

Live attenuated

- BCG
- measles, mumps, rubella (MMR)
- influenza (intranasal)
- oral rotavirus
- oral polio
- yellow fever
- oral typhoid*

Inactivated preparations

- rabies
- influenza (intramuscular)

Detoxified exotoxins

- tetanus

Extracts of the organism/virus (sometimes termed fragment)**

- 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

*whole cell typhoid vaccine is no longer used in the UK

**may also be produced using recombinant DNA technology

Vaginal discharge

Vaginal discharge is a common presenting symptom and is not always pathological

Common causes

- physiological
- *Candida*
- *Trichomonas vaginalis*
- bacterial vaginosis

Less common causes

- *Gonorrhoea*
- *Chlamydia* can cause a vaginal discharge although this is rarely the presenting symptoms
- ectropion
- foreign body
- cervical cancer

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

Vancomycin

Vancomycin is a glycopeptide antibiotic used in the treatment of Gram positive infections, particularly methicillin-resistant Staphylococcus aureus (MRSA).

Mechanism of action

- inhibits cell wall formation by binding to D-Ala-D-Ala moieties, preventing polymerization of peptidoglycans

Mechanism of resistance

- alteration to the terminal amino acid residues of the NAM/NAG-peptide subunits (normally D-alanyl-D-alanine) to which the antibiotic binds

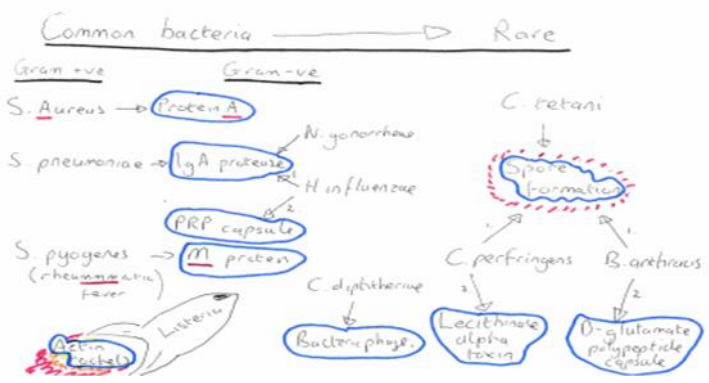
Adverse effects

- nephrotoxicity
- ototoxicity
- thrombophlebitis
- red man syndrome; occurs on rapid infusion of vancomycin

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*



Zika virus

Zika is a mosquito-borne infection caused by Zika virus, a member of the genus flavivirus and family Flaviviridae. It was first isolated from a monkey in the Zika forest in Uganda in 1947.

Transmission is usually via the bite of an infected Aedes mosquito, although a small number of cases of sexual transmission have been reported. There is increasing evidence of transmission via the placenta from mother to fetus.

The majority of people infected with Zika virus have no symptoms. For those with symptoms, Zika virus tends to cause a mild, short-lived (2 to 7 days) febrile disease. Signs and symptoms suggestive of Zika virus infection may include a combination of the following:

- fever
- rash
- arthralgia/arthritis
- conjunctivitis
- myalgia
- headache
- retro-orbital pain
- pruritus

Serious complications in adults are not common, although the virus has been associated with Guillain-Barre syndrome. Scientific consensus however has linked Zika with microcephaly and other congenital abnormalities, which has led the World Health Organisation (WHO) to declare a Public Health Emergency of International Concern (PHEIC).

Advice for travellers

There is currently no vaccine or drug to prevent Zika infection. Prevention revolves around avoiding mosquito bites (Aedes mosquitoes usually bite during the day) by using mosquito repellent and cover up clothing. Pregnant women are advised to avoid non-essential travel to Zika prevalent areas until after pregnancy.

Nephrology

Acute kidney injury: acute tubular necrosis vs. prerenal uraemia

Prerenal uraemia - kidneys hold on to sodium to preserve volume

	Pre-renal uraemia	**Acute tubular necrosis**
Urine sodium	< 20 mmol/L	> 30 mmol/L
Fractional sodium excretion*	< 1%	> 1%
Fractional urea excretion**	< 35%	>35%
Urine:plasma osmolality	> 1.5	< 1.1
Urine:plasma urea	> 10:1	< 8:1
Specific gravity	> 1020	< 1010
Urine	'bland' sediment	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

Acute vs. chronic renal failure

Best way to differentiate is renal ultrasound - most patients with CRF have bilateral small kidneys

Exceptions

- autosomal dominant polycystic kidney disease
- diabetic nephropathy
- amyloidosis
- HIV-associated nephropathy

Other features suggesting CRF rather than ARF

- hypocalcaemia (due to lack of vitamin D)

ADPKD

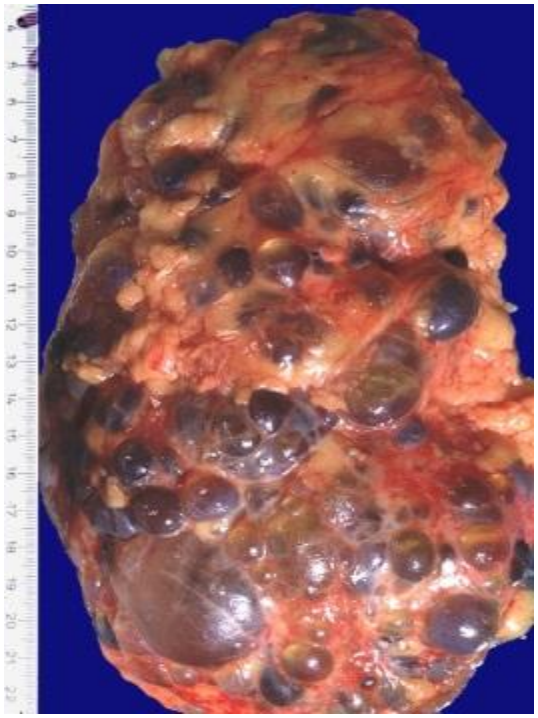
Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited cause of kidney disease, affecting 1 in 1,000 Caucasians. Two disease loci have been identified, PKD1 and PKD2, which code for polycystin-1 and polycystin-2 respectively

ADPKD type 1	**ADPKD type 2**
85% of cases	15% of cases
Chromosome 16	Chromosome 4
Presents with renal failure earlier	

The screening investigation for relatives is abdominal ultrasound:

Ultrasound diagnostic criteria (in patients with positive family history)

- two cysts, unilateral or bilateral, if aged < 30 years
- two cysts in both kidneys if aged 30-59 years
- four cysts in both kidneys if aged > 60 years



Extensive cysts are seen in an enlarged kidney

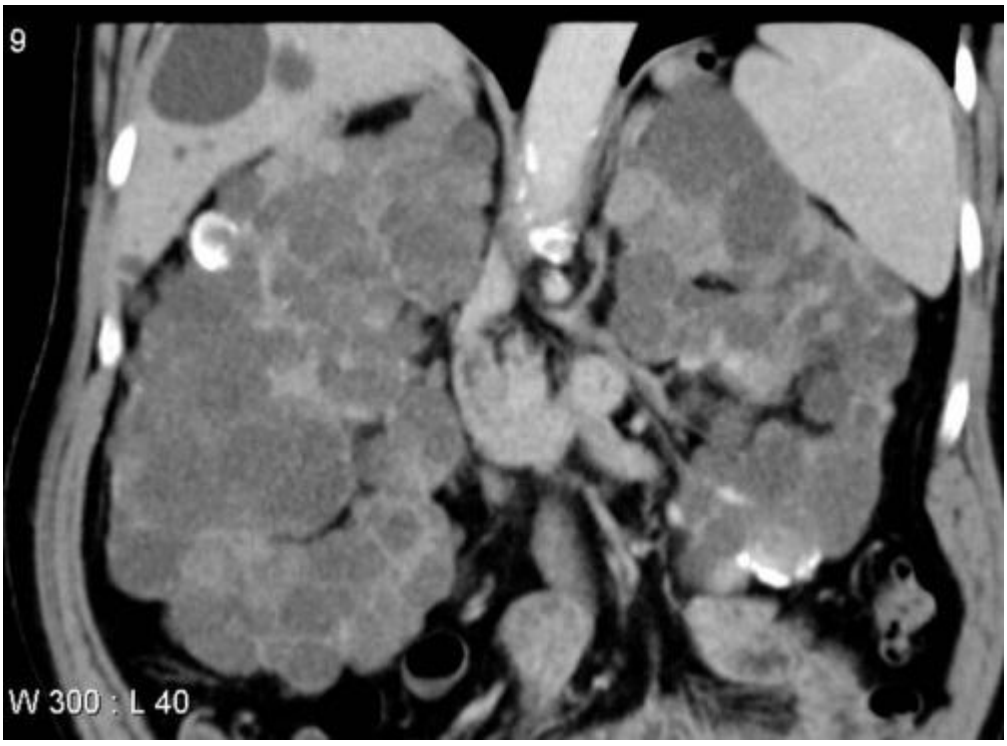
ADPKD: features

Features

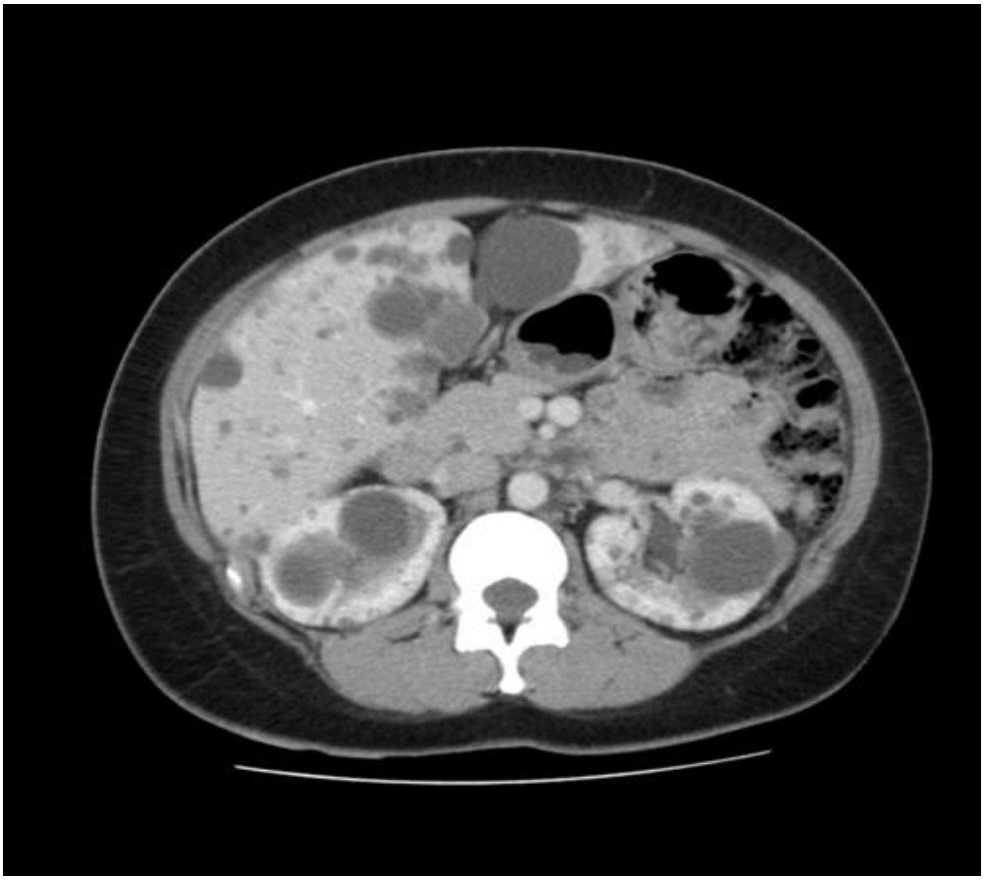
- hypertension
- recurrent UTIs
- abdominal pain
- renal stones
- haematuria
- chronic kidney disease

Extra-renal manifestations

- liver cysts (70%)
- berry aneurysms (8%)
- cardiovascular system: mitral valve prolapse, mitral/tricuspid incompetence, aortic root dilation, aortic dissection
- cysts in other organs: pancreas, spleen; very rarely: thyroid, oesophagus, ovary



CT of the abdomen demonstrates both kidneys to be markedly enlarged by innumerable cysts ranging in size from a few millimeters to multiple centimeters with cysts also present in the liver



CT showing multiple cysts of varying sizes in the liver, and bilateral kidneys with little remaining normal renal parenchyma.

Alport's syndrome

Alport's syndrome is usually inherited in an X-linked dominant pattern*. It is due to a defect in the gene which codes for type IV collagen resulting in an abnormal glomerular-basement membrane (GBM). The disease is more severe in males with females rarely developing renal failure

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

Alport's syndrome usually presents in childhood. The following features may be seen:

- microscopic haematuria
- progressive renal failure
- bilateral sensorineural deafness
- lenticonus: protrusion of the lens surface into the anterior chamber
- retinitis pigmentosa
- renal biopsy: splitting of lamina densa seen on electron microscopy

*in around 85% of cases - 10-15% of cases are inherited in an autosomal recessive fashion with rare autosomal dominant variants existing

Amyloidosis

Overview

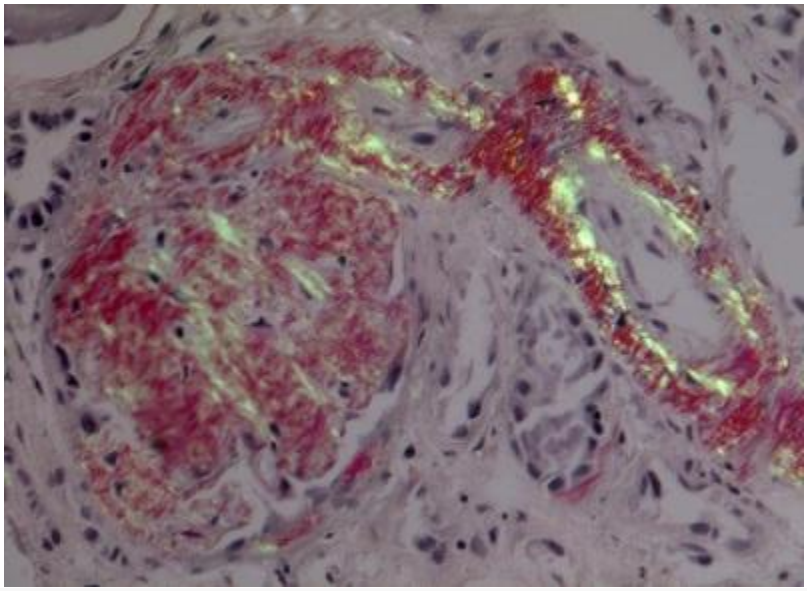
- amyloidosis is a term which describes the extracellular deposition of an insoluble fibrillar protein termed amyloid
- amyloid is derived from many different precursor proteins
- in addition to the fibrillar component, amyloid also contains a non-fibrillary protein called amyloid-P component, derived from the acute phase protein serum amyloid P
- other non-fibrillary components include apolipoprotein E and heparan sulphate proteoglycans
- the accumulation of amyloid fibrils leads to tissue/organ dysfunction

Classification

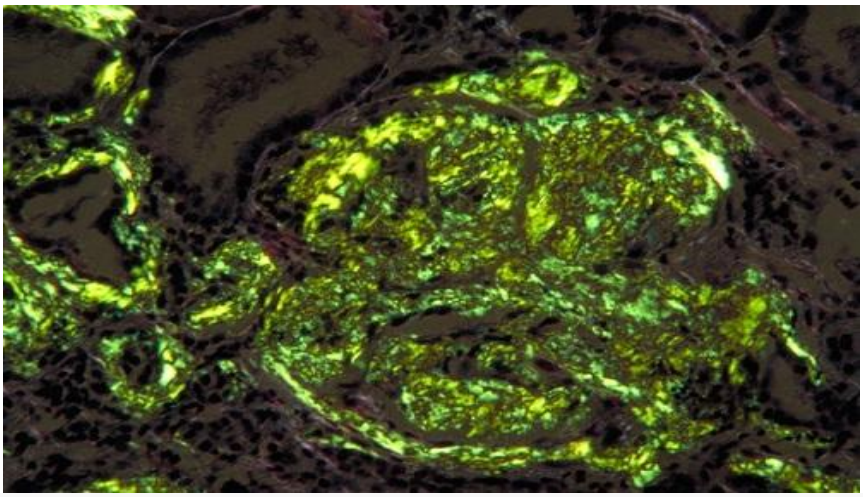
- systemic or localized
- further characterised by precursor protein (e.g. AL in myeloma - A for Amyloid, L for immunoglobulin Light chain fragments)

Diagnosis

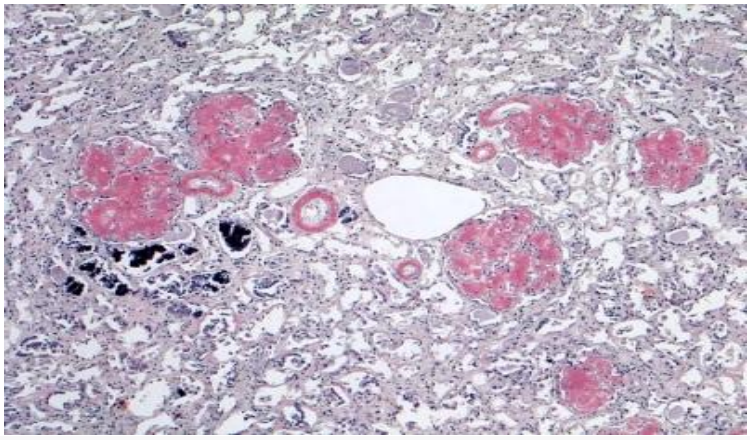
- Congo red staining: apple-green birefringence
- serum amyloid precursor (SAP) scan
- biopsy of rectal tissue



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

Amyloidosis: types

AL amyloid

- L for immunoglobulin Light chain fragment
- due to myeloma, Waldenstrom's, MGUS
- features include: cardiac and neurological involvement, macroglossia, periorbital eccymoses

AA amyloid

- A for precursor serum amyloid A protein, an acute phase reactant
- seen in chronic infection/inflammation
- e.g. TB, bronchiectasis, rheumatoid arthritis
- features: renal involvement most common feature

Beta-2 microglobulin amyloidosis

- precursor protein is beta-2 microglobulin, part of the major histocompatibility complex
- associated with patients on renal dialysis

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 which encodes fibrocystin, a protein important for normal renal tubule development.

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.

Cholesterol embolisation

Overview

- cholesterol emboli may break off causing renal disease
- seen more commonly in arteriopaths, abdominal aortic aneurysms

Features

- eosinophilia
- purpura
- renal failure
- livedo reticularis

Chronic kidney disease: causes

Common causes of chronic kidney disease

- diabetic nephropathy
- chronic glomerulonephritis
- chronic pyelonephritis
- hypertension
- adult polycystic kidney disease

Chronic kidney disease: eGFR and classification

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:

- serum creatinine
- age
- gender
- ethnicity

Factors which may affect the result

- pregnancy
- muscle mass (e.g. amputees, body-builders)
- eating red meat 12 hours prior to the sample being taken

CKD may be classified according to GFR:

CKD stage	**GFR range**
1	Greater than 90 ml/min, with some sign of kidney damage on other tests (if all the kidney tests* are normal, there is no CKD)
2	60-90 ml/min with some sign of kidney damage (if kidney tests* are normal, there is no CKD)
3a	45-59 ml/min, a moderate reduction in kidney function
3b	30-44 ml/min, a moderate reduction in kidney function
4	15-29 ml/min, a severe reduction in kidney function
5	Less than 15 ml/min, established kidney failure - dialysis or a kidney transplant may be needed

*i.e. normal U&Es and no proteinuria

Chronic kidney disease: hypertension

The majority of patients with chronic kidney disease (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*. 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

*the NKF K/DOQI guidelines suggest a lower cut-off of less than 30 ml/min

Chronic kidney disease: 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

Approximate equivalent values

ACR (mg/mmol)	PCR (mg/mmol)	Urinary protein excretion (g/24 h)
30	50	0.5
70	100	1

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 between 3 mg/mmol and 70 mg/mmol, this should be confirmed by a subsequent early morning sample. If the initial ACR is 70 mg/mmol or more, a repeat sample need not be tested.

Interpreting the ACR results

- the NICE guidelines state 'regard a confirmed ACR of 3 mg/mmol or more as clinically important proteinuria'

NICE recommendations for referral to a nephrologist:

- a urinary albumin:creatinine ratio (ACR) of 70 mg/mmol or more, unless known to be caused by diabetes and already appropriately treated
- a urinary ACR of 30 mg/mmol or more, together with persistent haematuria (two out of three dipstick tests show 1+ or more of blood) after exclusion of a urinary tract infection
- consider referral to a nephrologist for people with an ACR between 3-29 mg/mmol who have persistent haematuria and other risk factors such as a declining eGFR, or cardiovascular disease

Frequency of monitoring eGFR (number of times per year by eGFR and ACR categories) for people with or at risk of CKD

eGFR categories (mL/min/1.73 m2)	**ACR categories (mg/mmol)**		
	A1 (< 3) Normal to mildly increased	A2 (3-30) Moderately increased	A3 (> 30) Severely increased
G1 >=90 Normal and high	=< 1	1	>= 1
G2 60-89 Mild reduction related to normal range for a young adult	=< 1	1	>= 1
G3a 45-59 Mild to moderate reduction	1	1	2
G3b 30-44 Moderate to severe reduction	=< 2	2	>= 2
G4 15-29 Severe reduction	2	2	3
G5 <15 Kidney failure	4	>=4	>=4

Cytomegalovirus

Cytomegalovirus (CMV) is one of the herpes viruses. 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.

Pathophysiology

- infected cells have a 'Owl's eye' appearance due to intranuclear inclusion bodies

Patterns of disease

Congenital CMV infection

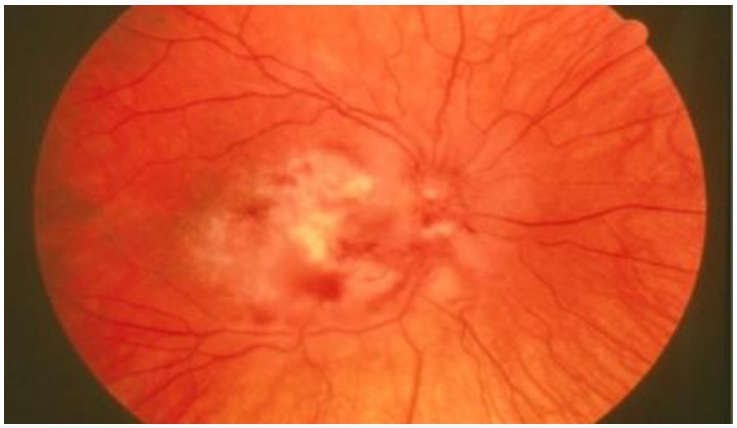
- features include growth retardation, pinpoint petechial 'blueberry muffin' skin lesions, microcephaly, sensorineural deafness, encephalitiis (seizures) and hepatosplenomegaly

CMV mononucleosis

- infectious mononucelosis-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



Fundus photograph showing CMV retinitis. Credit: National Eye Institute, National Institutes of Health

CMV encephalopathy

- seen in patients with HIV who have low CD4 counts

CMV pneumonitis

CMV colitis

Diabetic nephropathy: stages

Diabetic nephropathy may be classified as occurring in five stages*:

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

Erythropoietin

Erythropoietin is a haematopoietic growth factor that stimulates the production of erythrocytes. The main uses of erythropoietin are to treat the anaemia associated with chronic kidney disease and that associated with cytotoxic therapy.

Side-effects of erythropoietin

- accelerated hypertension potentially leading to encephalopathy and seizures (blood pressure increases in 25% of patients)
- bone aches
- flu-like symptoms
- skin rashes, urticaria
- pure red cell aplasia* (due to antibodies against erythropoietin)
- raised PCV increases risk of thrombosis (e.g. Fistula)
- iron deficiency 2nd to increased erythropoiesis

There are a number of reasons why patients may fail to respond to erythropoietin therapy:

- iron deficiency
- inadequate dose
- concurrent infection/inflammation
- hyperparathyroid bone disease
- aluminium toxicity

*the risk is greatly reduced with darbepoetin

Fanconi syndrome

Fanconi syndrome describes a generalised disorder of renal tubular transport in the proximal convoluted tubule resulting in:

- type 2 (proximal) renal tubular acidosis
- polyuria
- aminoaciduria
- glycosuria
- phosphaturia
- osteomalacia

Causes

- cystinosis (most common cause in children)
- Sjogren's syndrome
- multiple myeloma
- nephrotic syndrome
- Wilson's disease

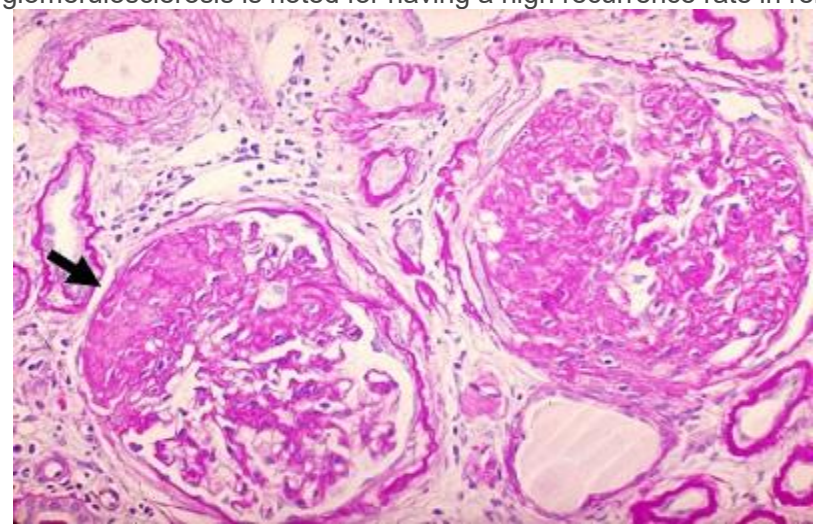
Focal segmental glomerulosclerosis

Focal segmental glomerulosclerosis is cause of nephrotic syndrome and chronic kidney disease. It generally presents in young adults.

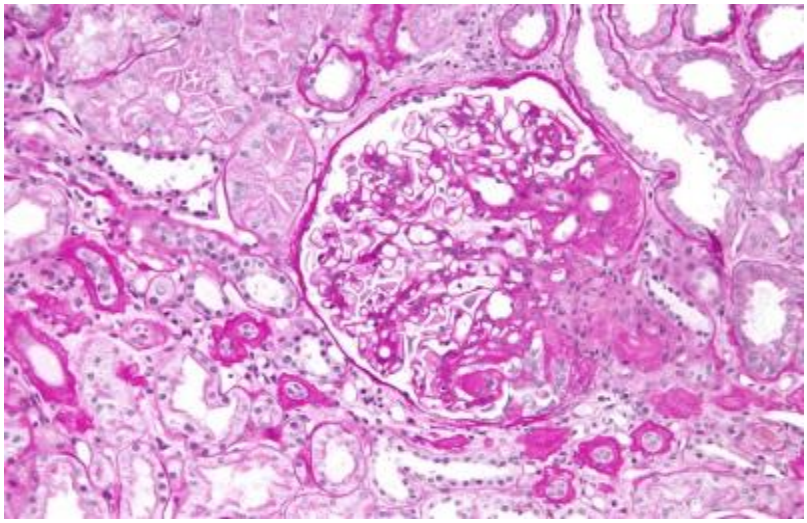
Causes

- idiopathic
- secondary to other renal pathology e.g. IgA nephropathy, reflux nephropathy
- HIV
- heroin
- Alport's syndrome
- sickle-cell

Focal segmental glomerulosclerosis is noted for having a high recurrence rate in renal transplants.



Sclerosis of the glomerulus is seen next to Bowman's capsule



Sclerosis is seen in the perihilar region of the glomerulus

Glomerulonephritides

Knowing a few key facts is the best way to approach the difficult subject of glomerulonephritis:

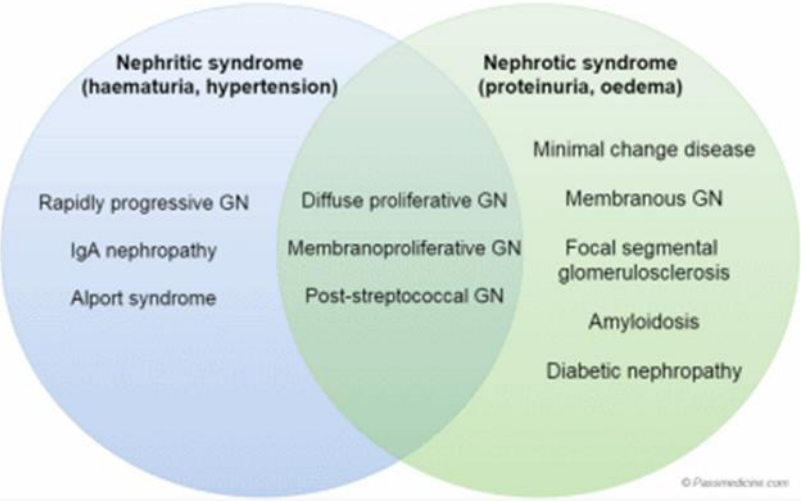


Diagram showing the glomerulonephritides and how they typically present

Typically presents with nephritic syndrome (haematuria, hypertension)

Rapidly progressive glomerulonephritis - aka crescentic glomerulonephritis

- rapid onset, often presenting as acute kidney injury
- causes include Goodpasture's, ANCA positive vasculitis

IgA nephropathy - aka Berger's disease, mesangioproliferative GN

- typically young adult with haematuria following an URTI

Mixed nephritic/nephrotic presentation

Diffuse proliferative glomerulonephritis

- classical post-streptococcal glomerulonephritis in child
- presents as nephritic syndrome / acute kidney injury
- most common form of renal disease in SLE

Membranoproliferative glomerulonephritis (mesangiocapillary)

- type 1: cryoglobulinaemia, hepatitis C
- type 2: partial lipodystrophy

Typically presents with nephrotic syndrome (proteinuria, oedema)

Minimal change disease

- typically a child with nephrotic syndrome (accounts for 80%)
- causes: Hodgkin's, NSAIDs
- good response to steroids

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

Focal segmental glomerulosclerosis

- may be idiopathic or secondary to HIV, heroin
- presentation: proteinuria / nephrotic syndrome / chronic kidney disease

Glomerulonephritis and low complement

Disorders associated with glomerulonephritis and low serum complement levels

- post-streptococcal glomerulonephritis
- subacute bacterial endocarditis
- systemic lupus erythematosus
- mesangiocapillary glomerulonephritis

Goodpasture's syndrome

Goodpasture's syndrome is rare condition associated with both pulmonary haemorrhage and rapidly progressive glomerulonephritis. It is caused by anti-glomerular basement membrane (anti-GBM) antibodies against type IV collagen. Goodpasture's syndrome is more common in men (sex ratio 2:1) and has a bimodal age distribution (peaks in 20-30 and 60-70 age bracket). It is associated with HLA DR2.

Features

- pulmonary haemorrhage
- followed by rapidly progressive glomerulonephritis

Factors which increase likelihood of pulmonary haemorrhage

- smoking
- lower respiratory tract infection
- pulmonary oedema
- inhalation of hydrocarbons
- young males

Investigations

- renal biopsy: linear IgG deposits along basement membrane
- raised transfer factor secondary to pulmonary haemorrhages

Management

- plasma exchange (plasmapheresis)
- steroids
- cyclophosphamide

Haematuria

The management of patients with haematuria is often difficult due to the absence of widely followed guidelines. It is sometimes unclear whether patients are best managed in primary care, by urologists or by nephrologists.

The terminology surrounding haematuria is changing. Microscopic or dipstick positive haematuria is increasingly termed non-visible haematuria whilst macroscopic haematuria is termed visible haematuria. Non-visible 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

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
- 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

NICE urgent cancer referral guidelines were updated in 2015.

Urgent referral (i.e. within 2 weeks)

Aged >= 45 years AND:

- unexplained visible haematuria without urinary tract infection, or
- visible haematuria that persists or recurs after successful treatment of urinary tract infection

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 >= 60 years with recurrent or persistent unexplained urinary tract infection

Since the investigation (or not) of non-visible haematuria is such as a common dilemma a number of guidelines have been published. They generally agree with NICE guidance, of note:

- 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

Haemolytic uraemic syndrome

Haemolytic uraemic syndrome is generally seen in young children and produces a triad of:

- acute renal failure
- microangiopathic haemolytic anaemia
- thrombocytopenia

Causes

- post-dysentery - classically E coli 0157:H7 ('verotoxigenic', 'enterohaemorrhagic')
- tumours
- pregnancy
- ciclosporin, the Pill
- systemic lupus erythematosus
- HIV

Investigations

- full blood count: anaemia, thrombocytopaenia, fragmented blood film
- U&E: acute renal failure
- stool culture

Management

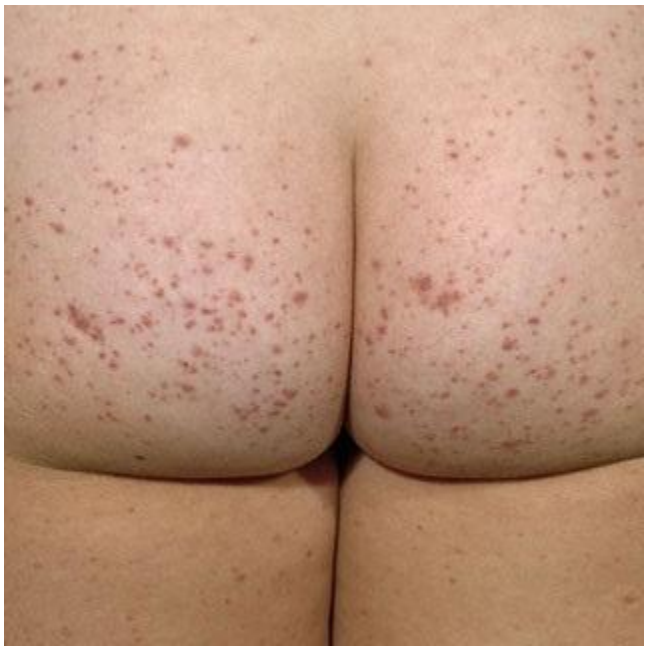
- treatment is supportive e.g. Fluids, blood transfusion and dialysis if required
- there is no role for antibiotics, despite the preceding diarrhoeal illness in many patients
- the indications for plasma exchange in HUS are complicated. As a general rule plasma exchange is reserved for severe cases of HUS not associated with diarrhoea

Henoch-Schonlein purpura

Henoch-Schonlein purpura (HSP) is an IgA mediated small vessel vasculitis. There is a degree of overlap with IgA nephropathy (Berger's disease). HSP is usually seen in children following an infection.

Features

- palpable purpuric rash (with localized oedema) over buttocks and extensor surfaces of arms and legs
- abdominal pain
- polyarthritis
- features of IgA nephropathy may occur e.g. haematuria, renal failure

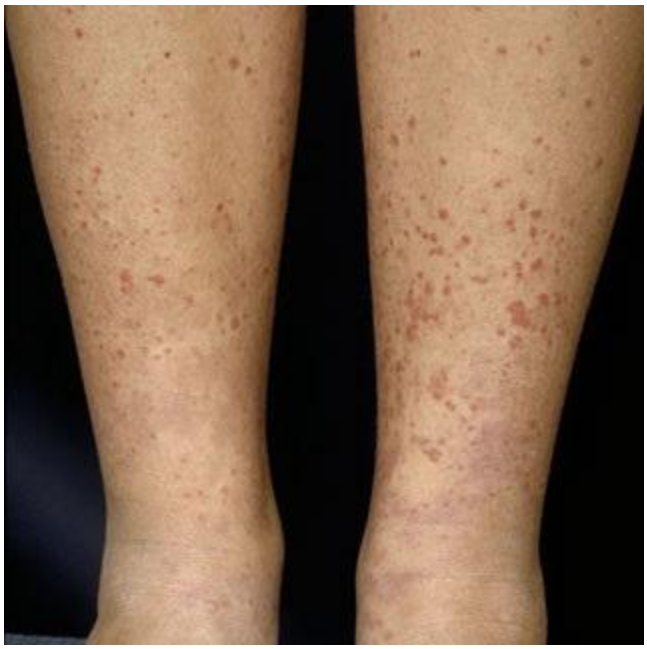


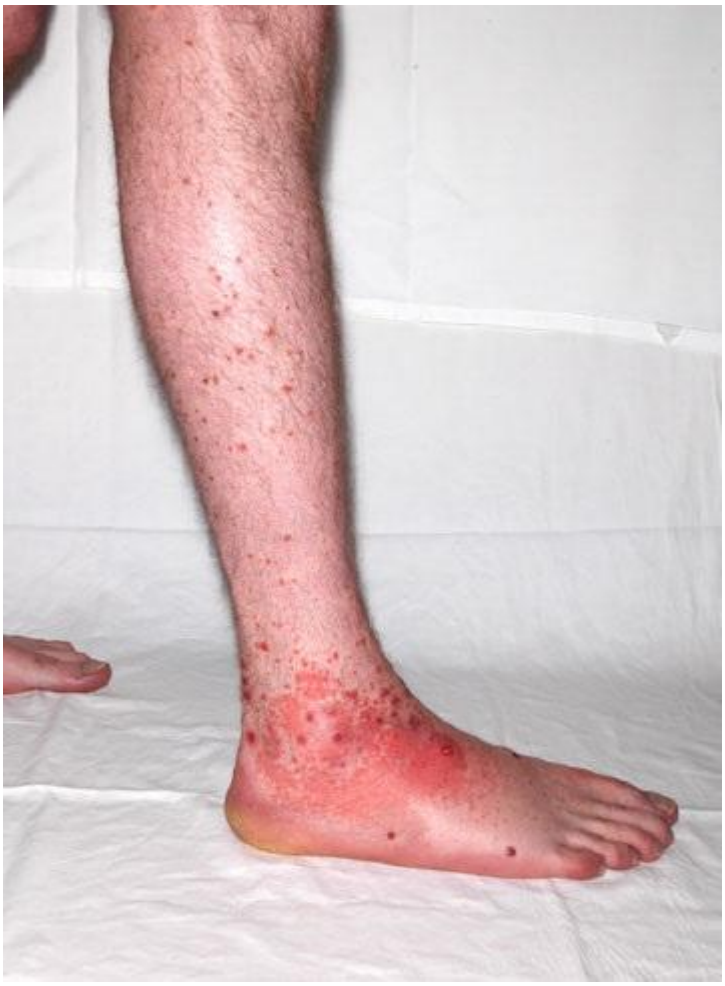
Treatment

- analgesia for arthralgia
- treatment of nephropathy is generally supportive. There is inconsistent evidence for the use of steroids and immunosuppressants

Prognosis

- usually excellent, HSP is a self-limiting condition, especially in children without renal involvement
- around 1/3rd of patients have a relapse





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
- elevated urea and creatinine
- normotension

Hyperkalaemia: management

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). Management may be categorised by the aims of treatment

Stabilisation of the cardiac membrane

- intravenous calcium gluconate

Short-term shift in potassium from extracellular to intracellular fluid compartment

- combined insulin/dextrose infusion
- nebulised salbutamol

Removal of potassium from the body

- calcium resonium (orally or enema)
- loop diuretics
- dialysis

Hypokalaemia and 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

Hypokalaemia with hypertension

- Cushing's syndrome
- Conn's syndrome (primary hyperaldosteronism)
- Liddle's syndrome
- 11-beta hydroxylase deficiency*

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

*21-hydroxylase deficiency, which accounts for 90% of congenital adrenal hyperplasia cases, is not associated with hypertension

**type 4 renal tubular acidosis is associated with hyperkalaemia

IgA nephropathy

Basics

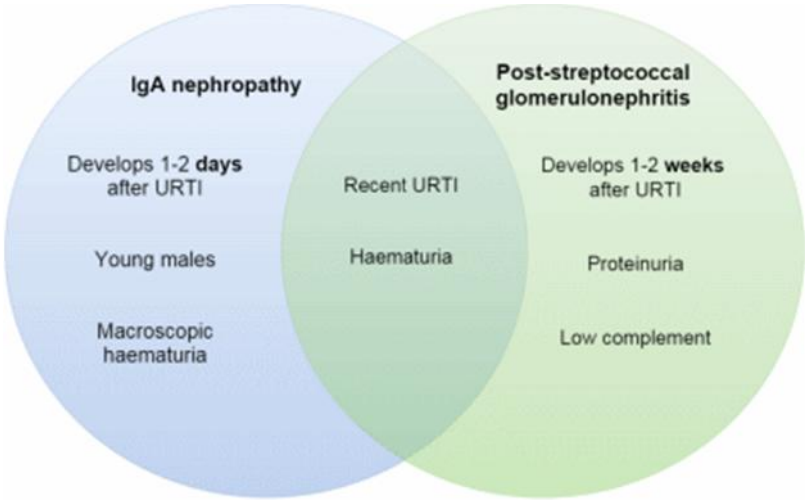
- also called Berger's disease or mesangioproliferative glomerulonephritis
- commonest cause of glomerulonephritis worldwide
- thought to be caused by mesangial deposition of IgA immune complexes
- there is considerable pathological overlap with Henoch-Schonlein purpura (HSP)
- histology: mesangial hypercellularity, positive immunofluorescence for IgA & C3

Presentations

- young male, recurrent episodes of macroscopic haematuria
- typically associated with mucosal infections e.g., URTI
- nephrotic range proteinuria is rare
- renal failure

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



Associated conditions

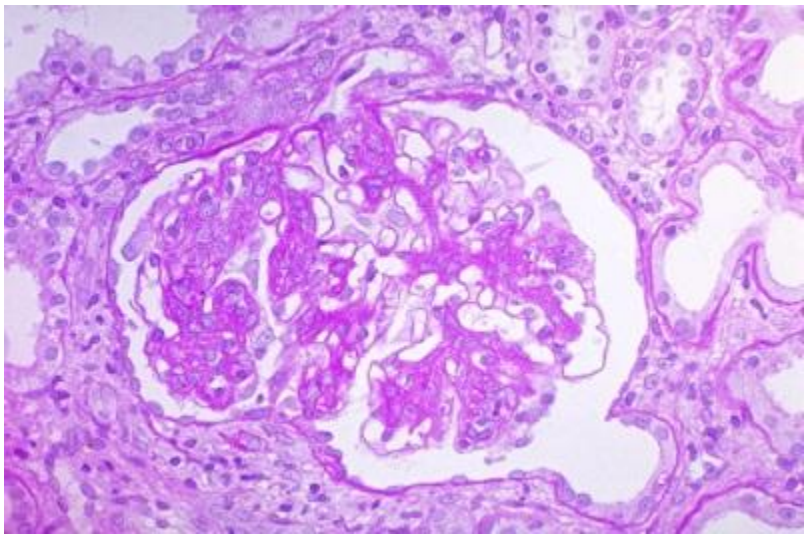
- alcoholic cirrhosis
- coeliac disease/dermatitis herpetiformis
- Henoch-Schonlein purpura

Management

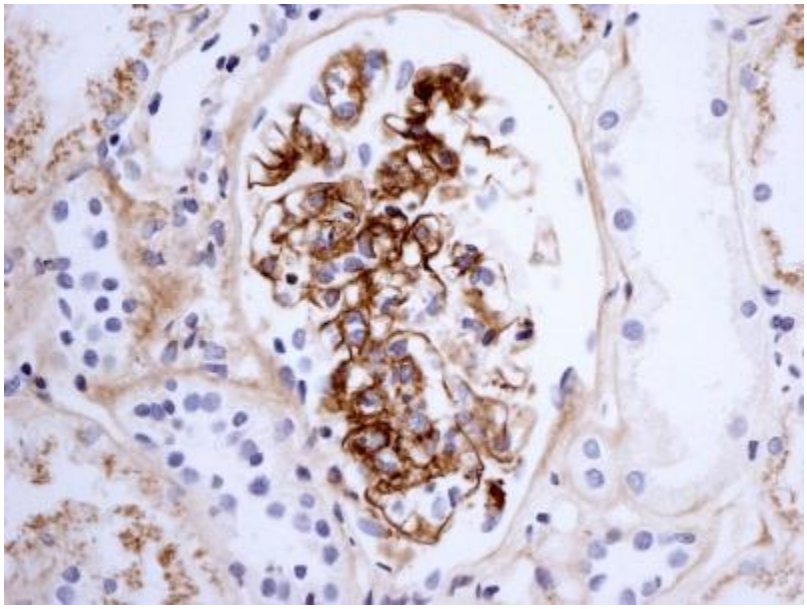
- steroids/immunosuppressants not be shown to be useful

Prognosis

- 25% of patients develop ESRF
- markers of good prognosis: frank haematuria
- markers of poor prognosis: male gender, proteinuria (especially > 2 g/day), hypertension, smoking, hyperlipidaemia, ACE genotype DD



Proliferation and hypercellularity of the mesangium is seen in the glomerulus



Immunostaining for IgA in a patient with HSP

Membranoproliferative glomerulonephritis

Overview

- also known as mesangiocapillary glomerulonephritis
- may present as nephrotic syndrome, haematuria or proteinuria
- poor prognosis

Type 1

- accounts for 90% of cases
- subendothelial immune deposits of electron dense material resulting in a 'tram-track' appearance
- cause: cryoglobulinaemia, hepatitis C

Type 2 - 'dense deposit disease'

- causes: partial lipodystrophy, factor H deficiency
- reduced serum complement
- C3b nephritic factor (an antibody against C3bBb) found in 70%

Type 3

- causes: hepatitis B and C

Management

- steroids may be effective

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.

Renal biopsy demonstrates:

- electron microscopy: the basement membrane is thickened with subepithelial electron dense deposits. This creates a 'spike and dome' appearance

Causes

- idiopathic
- infections: hepatitis B, malaria, syphilis
- malignancy: lung cancer, lymphoma, leukaemia
- drugs: gold, penicillamine, NSAIDs
- autoimmune diseases: systemic lupus erythematosus (class V disease), thyroiditis, rheumatoid

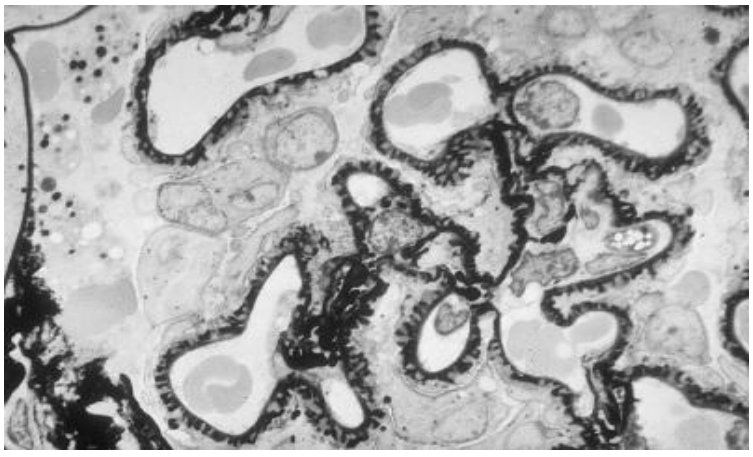
Prognosis - rule of thirds

- 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

- immunosuppression: corticosteroids alone have not been shown to be effective. A combination of corticosteroid + another agent such as chlorambucil is often used
- blood pressure control: ACE inhibitors have been shown to reduce proteinuria
- consider anticoagulation



Silver-stained section showing thickened basement membrane, subepithelial spikes

Minimal change disease

Minimal change disease nearly always presents as nephrotic syndrome, accounting for 75% of cases in children and 25% in adults.

The majority of cases are idiopathic, but in around 10-20% a cause is found:

- drugs: NSAIDs, rifampicin
- Hodgkin's lymphoma, thymoma
- infectious mononucleosis

Pathophysiology

- 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
- highly selective proteinuria*
- renal biopsy: electron microscopy shows fusion of podocytes

Management

- majority of cases (80%) are steroid responsive
- cyclophosphamide is the next step for steroid resistant cases

Prognosis is overall good, although relapse is common. Roughly:

- 1/3 have just one episode
- 1/3 have infrequent relapses
- 1/3 have frequent relapses which stop before adulthood

*only intermediate-sized proteins such as albumin and transferrin leak through the glomerulus

Nephrotic syndrome

Triad of:

- 1. Proteinuria (> 3g/24hr) causing
- 2. Hypoalbuminaemia (< 30g/L) and
- 3. Oedema

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.

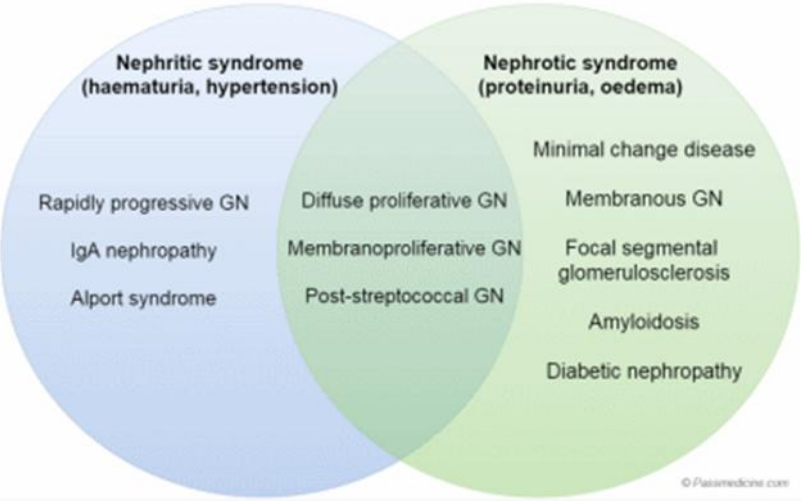


Diagram showing the glomerulonephritides and how they typically present

Nephrotic syndrome: causes

Primary glomerulonephritis accounts for around 80% of cases

- minimal change glomerulonephritis (causes 80% in children, 30% in adults)
- membranous glomerulonephritis
- focal segmental glomerulosclerosis
- membranoproliferative glomerulonephritis

Systemic disease (about 20%)

- diabetes mellitus
- systemic lupus erythematosus
- amyloidosis

Drugs

- gold (sodium aurothiomalate), penicillamine

Others

- congenital
- neoplasia: carcinoma, lymphoma, leukaemia, myeloma
- infection: bacterial endocarditis, hepatitis B, malaria

Nephrotic syndrome: complications

Complications

- increased risk of infection due to urinary immunoglobulin loss
- increased risk of thromboembolism related to loss of antithrombin III and plasminogen in the urine
- hyperlipidaemia
- hypocalcaemia (vitamin D and binding protein lost in urine)
- acute renal failure

Nephrotoxicity due to contrast media

Contrast media nephrotoxicity may be defined as a 25% increase in creatinine occurring within 3 days of the intravascular administration of contrast media.

Risk factors include

- known renal impairment (especially diabetic nephropathy)
- age > 70 years
- dehydration
- cardiac failure
- the use of nephrotoxic drugs such as NSAIDs

Prevention

- 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
- 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

Papillary necrosis

Causes

- chronic analgesia use
- sickle cell disease
- TB
- acute pyelonephritis
- diabetes mellitus

Features

- fever, loin pain, haematuria
- IVU - papillary necrosis with renal scarring - 'cup & spill'

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

- peritonitis: coagulase-negative staphylococci such as *Staphylococcus epidermidis* is the most common cause. *Staphylococcus aureus* is another common cause
- sclerosing peritonitis

Plasma exchange

Indications for plasma exchange (also known as plasmapheresis)

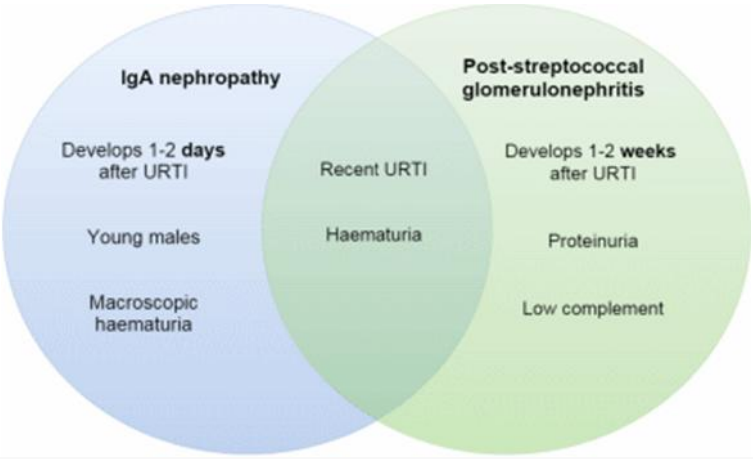
- Guillain-Barre syndrome
- myasthenia gravis
- Goodpasture's syndrome
- ANCA positive vasculitis e.g. Wegener's, Churg-Strauss
- TTP/HUS
- cryoglobulinaemia
- hyperviscosity syndrome e.g. secondary to myeloma

Post-streptococcal glomerulonephritis

Post-streptococcal glomerulonephritis typically occurs 7-14 days following a group A beta-haemolytic *Streptococcus* infection (usually *Streptococcus pyogenes*). It is caused by immune complex (IgG, IgM and C3) deposition in the glomeruli. Young children most commonly affected.

Features

- general: headache, malaise
- haematuria
- proteinuria
- hypertension
- low C3
- raised ASO titre

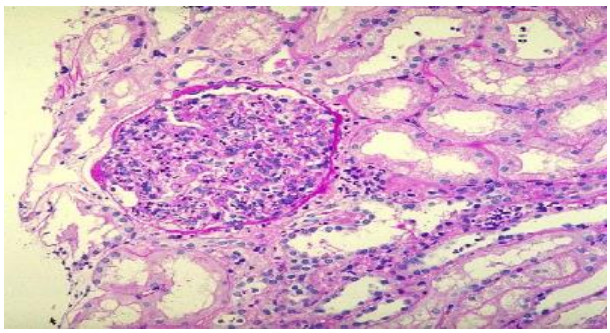


IgA nephropathy and post-streptococcal glomerulonephritis are often confused as they both can cause renal disease following an URTI

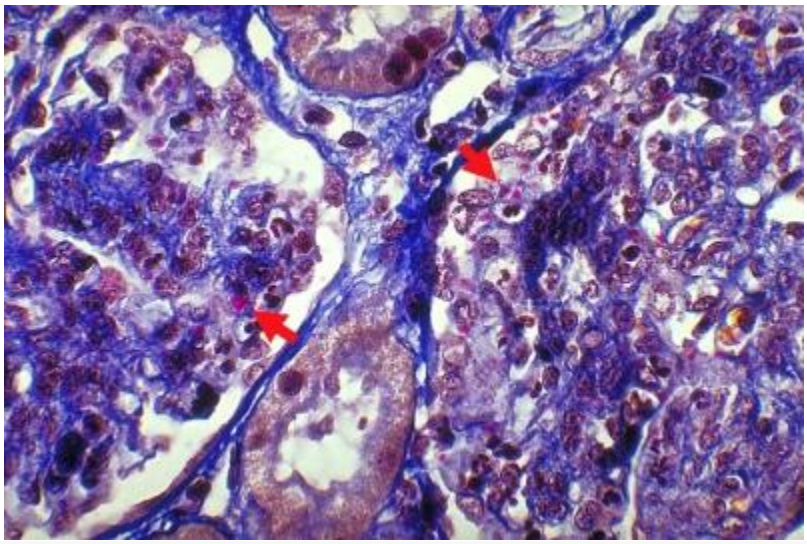
Renal biopsy features

- post-streptococcal glomerulonephritis causes acute, diffuse proliferative glomerulonephritis
- endothelial proliferation with neutrophils
- electron microscopy: subepithelial 'humps' caused by lumpy immune complex deposits
- immunofluorescence: granular or 'starry sky' appearance

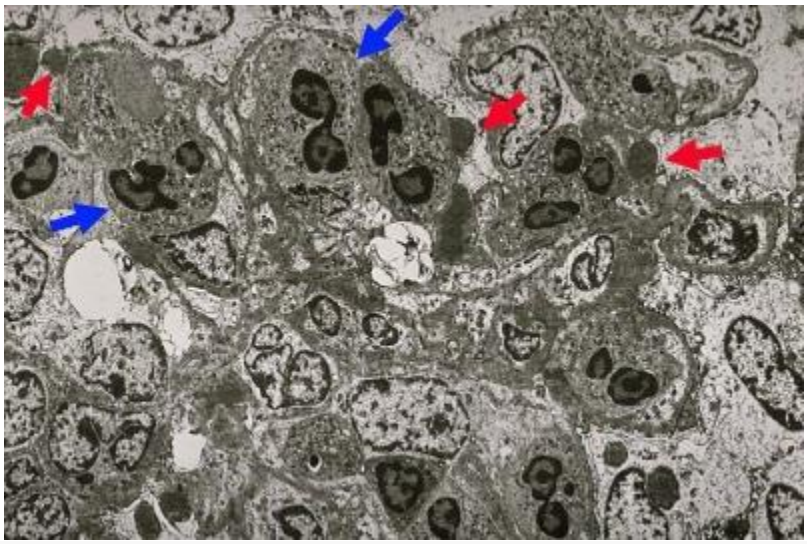
Carries a good prognosis



Proliferation of endothelium and mesangium with recruitment of neutrophils. Tubules are normal



Subepithelial humps on the outside of the basal membrane



Electron microscopy. Numerous neutrophils (blue arrows) and subepithelial humps (red arrows)

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
- 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

Drugs relatively safe - can sometimes use normal dose depending on the degree of chronic kidney disease

- antibiotics: erythromycin, rifampicin
- diazepam
- warfarin

Primary hyperaldosteronism

Primary hyperaldosteronism was previously thought to be most commonly caused by an adrenal adenoma, termed Conn's syndrome. However, recent studies have shown that bilateral idiopathic adrenal hyperplasia is the cause in up to 70% of cases. Differentiating between the two is important as this determines treatment. Adrenal carcinoma is an extremely rare cause of primary hyperaldosteronism

Features

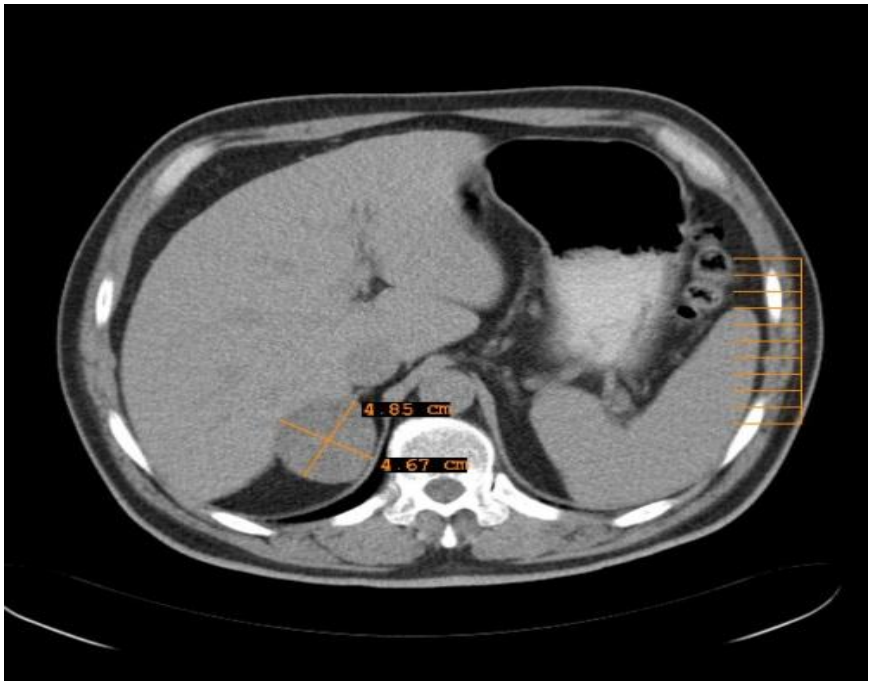
- hypertension
- hypokalaemia (e.g. muscle weakness)
- alkalosis

Investigations

- high serum aldosterone
- low serum renin
- high-resolution CT abdomen
- adrenal vein sampling

Management

- adrenal adenoma: surgery
- bilateral adrenocortical hyperplasia: aldosterone antagonist e.g. spironolactone



CT abdomen showing a right-sided adrenal adenoma in a patient who presented with hypertension and hypokalaemia. The adenoma can be seen 'next to' or 'below' the liver.

Renal cell cancer

Renal cell cancer is also known as hypernephroma and accounts for 85% of primary renal neoplasms. It arises from proximal renal tubular epithelium

Associations*

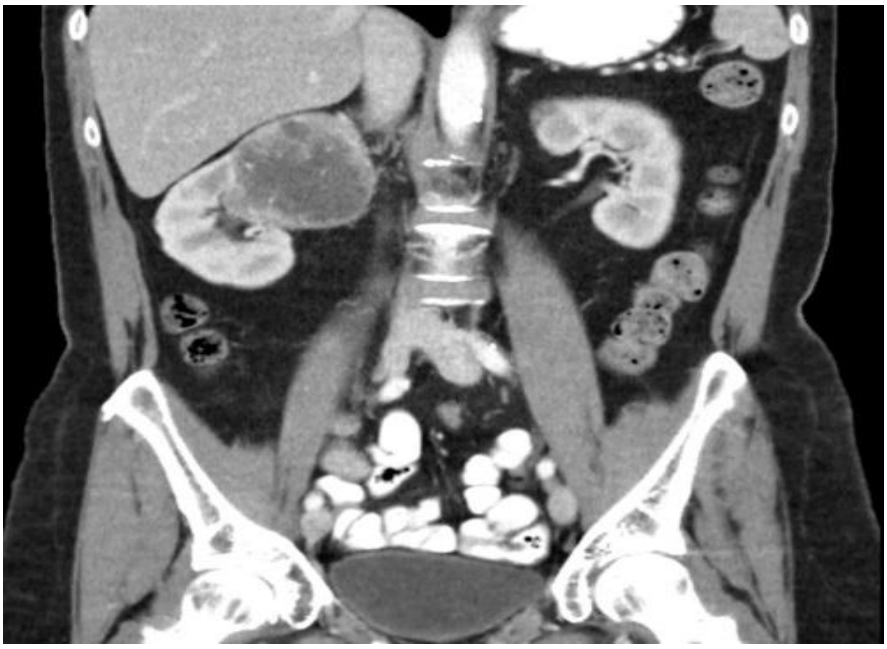
- more common in middle-aged men
- smoking
- von Hippel-Lindau syndrome
- tuberous sclerosis

Features

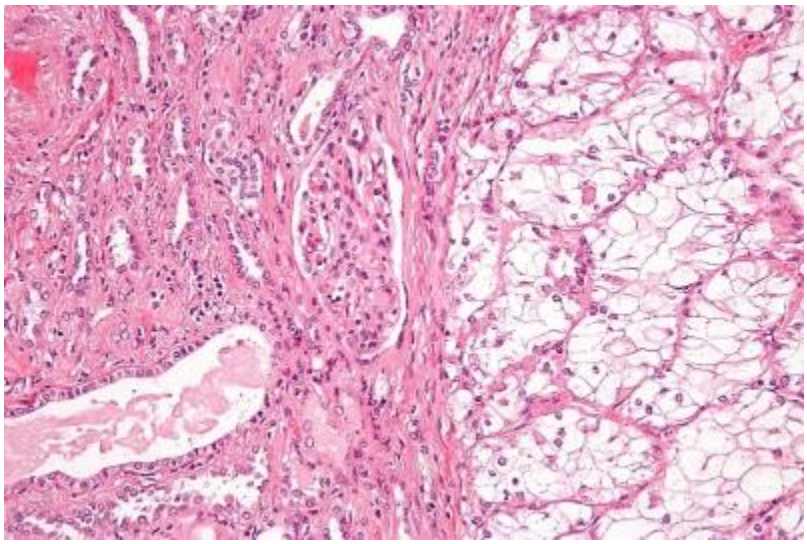
- classical triad: haematuria, loin pain, abdominal mass
- pyrexia of unknown origin
- left varicocele (due to occlusion of left testicular vein)
- endocrine effects: may secrete erythropoietin (polycythaemia), parathyroid hormone (hypercalcaemia), renin, ACTH
- 25% have metastases at presentation

Management

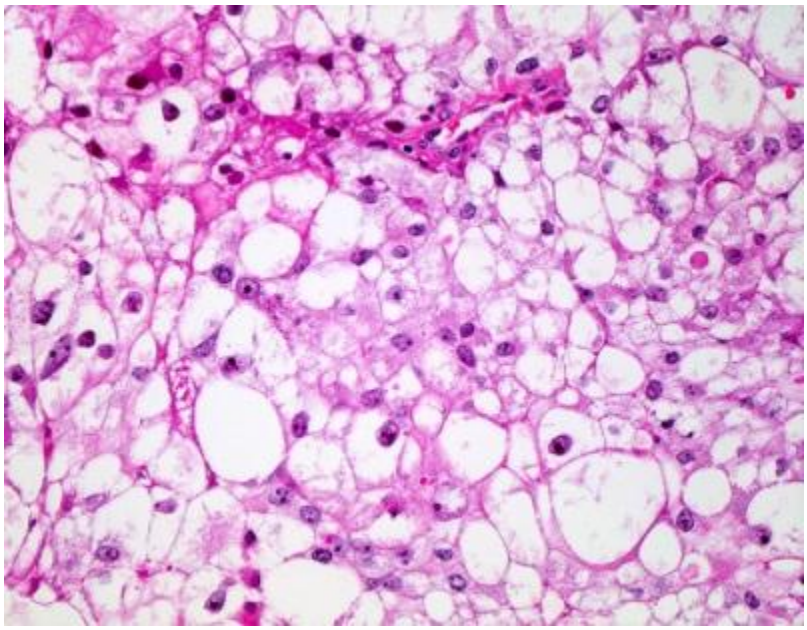
- for confined disease a partial or total nephrectomy depending on the tumour size
- alpha-interferon and interleukin-2 have been used to reduce tumour size and also treat patients with metatases
- receptor tyrosine kinase inhibitors (e.g. sorafenib, sunitinib) have been shown to have superior efficacy compared to interferon-alpha



Coronal CT scan of a middle-aged woman with renal cell cancer. Note the heterogeneously enhancing mass at the upper pole of the right kidney



Left: normal kidney. Right: 'clear-cell' pattern of renal cell carcinoma



'Clear-cell' pattern of renal cell carcinoma - clear cytoplasm, small nuclei

*incidence of renal cell cancer is only slightly increased in patients with autosomal dominant polycystic kidney disease

Renal papillary necrosis

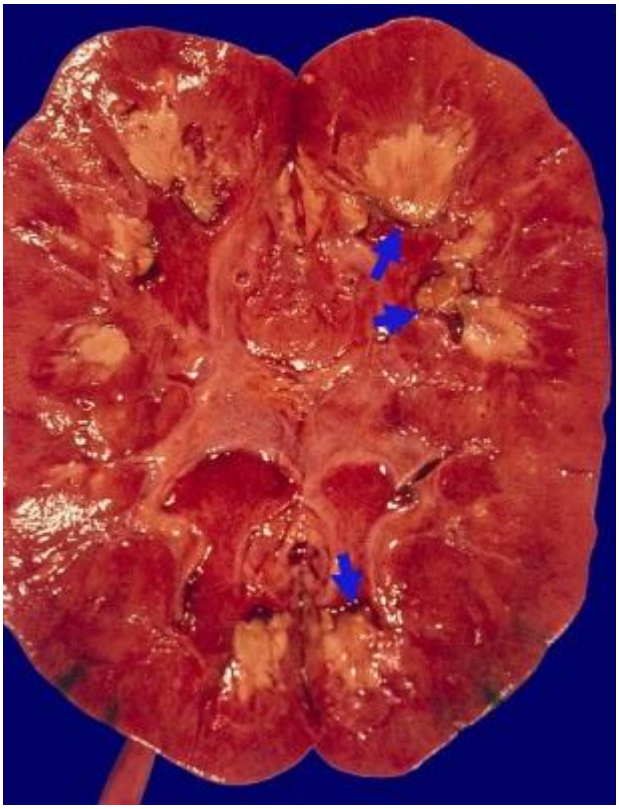
Renal papillary necrosis describes the coagulative necrosis of the renal papillae due to a variety of causes.

Features

- visible haematuria
- loin pain
- proteinuria

Causes

- severe acute pyelonephritis
- diabetic nephropathy
- obstructive nephropathy
- analgesic nephropathy: phenacetin was the classic cause but this has now been withdrawn
- sickle cell anaemia



Renal papillary necrosis secondary to acute pyelonephritis. Note the pale areas highlighted by the blue arrows

Renal stones: imaging

The table below summarises the appearance of different types of renal stone on x-ray

Type	Frequency	Radiograph appearance
Calcium oxalate	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

*stag-horn calculi 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). Ureaplasma urealyticum and Proteus infections predispose to their formation

Renal stones: management

Initial management of renal colic

Medication

- the British Association of Urological Surgeons (BAUS) recommend diclofenac (intramuscular/oral) as the analgesia of choice for renal colic*
- BAUS also endorse the widespread use of alpha-adrenergic blockers to aid ureteric stone passage

Imaging

- BAUS guidelines recommend ultrasound as the initial imaging modality of choice. The sensitivity of ultrasound for stones is around 45% and specificity is around 90%. Complications such as hydronephrosis can also be quickly identified
- following an ultrasound, BAUS recommend a non-contrast CT (NCCT) to confirm the diagnosis. 99% of stones are identifiable on NCCT. Some GPs now have direct access to NCCT

Stones < 5 mm will usually pass spontaneously. Lithotripsy and nephrolithotomy may be for severe cases.

Management of renal stones

Most renal stones measuring less than 5mm in maximum diameter will typically pass within 4 weeks of symptom onset. More intensive and urgent treatment is indicated in the presence of ureteric obstruction, renal developmental abnormality such as horseshoe kidney and previous renal transplant. Ureteric obstruction due to stones together with infection is a surgical emergency and the system must be decompressed. Options include nephrostomy tube placement, insertion of ureteric catheters and ureteric stent placement.

In the non emergency setting the preferred options for treatment of stone disease include extra corporeal shock wave lithotripsy, percutaneous nephrolithotomy, ureteroscopy, open surgery remains an option for selected cases. However, minimally invasive options are the most popular first line treatment.

Shock wave lithotripsy

- A shock wave is generated external to the patient, internally cavitation bubbles and mechanical stress lead to stone fragmentation. The passage of shock waves can result in the development of solid organ injury. Fragmentation of larger stones may result in the development of ureteric obstruction. The procedure is uncomfortable for patients and analgesia is required during the procedure and afterwards.

Ureteroscopy

- A ureteroscope is passed retrograde through the ureter and into the renal pelvis. It is indicated in individuals (e.g. pregnant females) where lithotripsy is contraindicated and in complex stone disease. In most cases a stent is left in situ for 4 weeks after the procedure.

Percutaneous nephrolithotomy

- In this procedure access is gained to the renal collecting system. Once access is achieved, intra corporeal lithotripsy or stone fragmentation is performed and stone fragments removed.

Therapeutic selection

Disease	Option
Stone burden of less than 2cm in aggregate	Lithotripsy
Stone burden of less than 2cm in pregnant females	Ureteroscopy
Complex renal calculi and staghorn calculi	Percutaneous nephrolithotomy
Ureteric calculi less than 5mm	Manage expectantly

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
- 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)

Oxalate stones

- cholestyramine reduces urinary oxalate secretion
- pyridoxine reduces urinary oxalate secretion

Uric acid stones

- allopurinol
- urinary alkalinization e.g. oral bicarbonate

*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

Renal stones: risk factors

Risk factors

- dehydration
- hypercalciuria, hyperparathyroidism, hypercalcaemia
- cystinuria
- high dietary oxalate
- renal tubular acidosis
- medullary sponge kidney, polycystic kidney disease
- beryllium or cadmium exposure

Risk factors for urate stones

- gout
- ileostomy: loss of bicarbonate and fluid results in acidic urine, causing the precipitation of uric acid

Drug causes

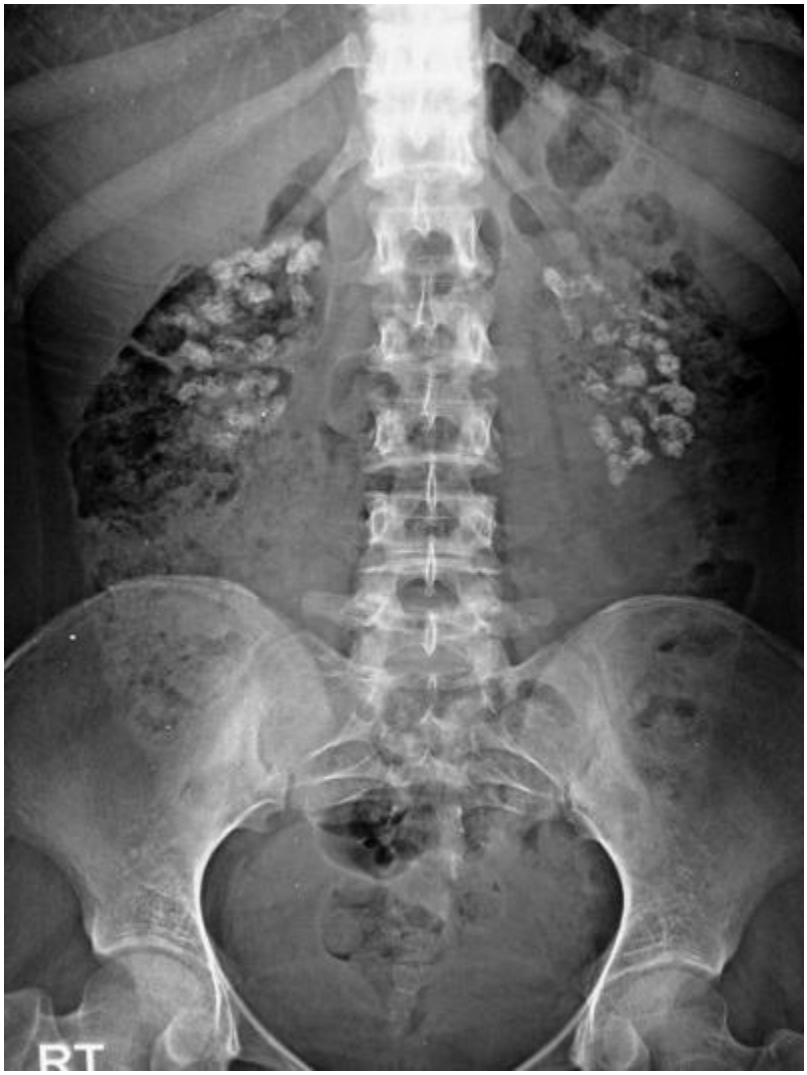
- drugs that promote calcium stones: loop diuretics, steroids, acetazolamide, theophylline
- thiazides can prevent calcium stones (increase distal tubular calcium resorption)

Renal tubular acidosis

All three types of renal tubular acidosis (RTA) are associated with hyperchloraemic metabolic acidosis (normal anion gap)

Type 1 RTA (distal)

- inability to generate acid urine (secrete H+) in distal tubule
- causes hypokalaemia
- complications include nephrocalcinosis and renal stones
- causes include idiopathic, RA, SLE, Sjogren's, amphotericin B toxicity, analgesic nephropathy



Abdominal x-ray showing nephrocalcinosis - a classical finding in type 1 RTA

Type 2 RTA (proximal)

- decreased HCO3- reabsorption in proximal tubule
- causes hypokalaemia
- complications include osteomalacia
- causes include idiopathic, as part of Fanconi syndrome, Wilson's disease, cystinosis, outdated tetracyclines

Type 4 RTA (hyperkalaemic)

- reduction in aldosterone leads in turn to a reduction in proximal tubular ammonium excretion
- causes hyperkalaemia
- causes include hypoaldosteronism, diabetes

Renal vascular disease

Renal vascular disease is most commonly due to atherosclerosis (> 95% of patients). It is associated with risk factors such as smoking and hypertension that cause atheroma elsewhere in the body. It may present as hypertension, chronic renal failure or 'flash' pulmonary oedema. 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

Investigation

- MR angiography is now the investigation of choice
- CT angiography
- conventional renal angiography is less commonly performed used nowadays, but may still have a role when planning surgery

Retroperitoneal fibrosis

Lower back/flank pain is the most common presenting feature. Fever and lower limb oedema is also seen in some patients.

Associations

- Riedel's thyroiditis
- previous radiotherapy
- sarcoidosis
- inflammatory abdominal aortic aneurysm
- drugs: methysergide

Rhabdomyolysis

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

Features

- acute renal failure with disproportionately raised creatinine
- elevated CK
- myoglobinuria
- hypocalcaemia (myoglobin binds calcium)
- elevated phosphate (released from myocytes)

Causes

- seizure
- collapse/coma (e.g. elderly patients collapses at home, found 8 hours later)
- ecstasy
- crush injury
- McArdle's syndrome
- drugs: statins

Management

- IV fluids to maintain good urine output
- urinary alkalinization is sometimes used

Sterile pyuria

Causes

- partially treated UTI
- urethritis e.g. *Chlamydia*
- renal tuberculosis
- renal stones
- appendicitis
- bladder/renal cell cancer
- adult polycystic kidney disease
- analgesic nephropathy

Thin basement membrane disease

An inherited disorder of type IV collagen that causes thinning of the basement membrane. It may affect up to 5% of the population and about 30% patients report a family history of haematuria. Diagnosis is usually based on the history of persistent haematuria, normal kidney function and family history of haematuria without kidney failure. It is generally a benign disorder and biopsy is rarely indicated.

Thrombotic thrombocytopenic purpura

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
- overlaps with haemolytic uraemic syndrome (HUS)

Features

- rare, typically adult females
- fever
- fluctuating neuro signs (microemboli)
- microangiopathic haemolytic anaemia
- thrombocytopenia
- renal failure

Causes

- post-infection e.g. urinary, gastrointestinal
- pregnancy
- drugs: ciclosporin, oral contraceptive pill, penicillin, clopidogrel, aciclovir
- tumours
- SLE
- HIV

Wilms' tumour

Wilms' nephroblastoma is one of the most common childhood malignancies. It typically presents in children under 5 years of age, with a median age of 3 years old.

Features

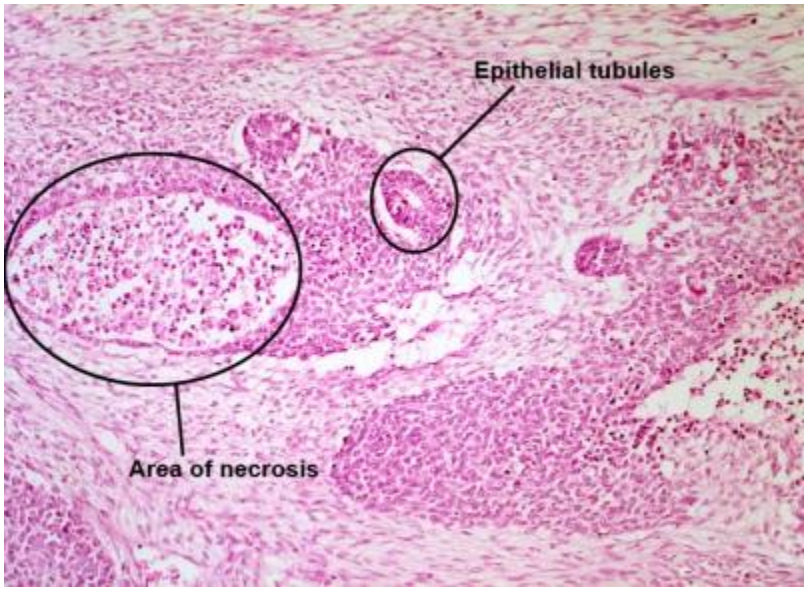
- abdominal mass (most common presenting feature)
- painless haematuria
- flank pain
- other features: anorexia, fever
- unilateral in 95% of cases
- metastases are found in 20% of patients (most commonly lung)

Associations

- Beckwith-Wiedemann syndrome
- as part of WAGR syndrome with Aniridia, Genitourinary malformations, mental Retardation
- hemihypertrophy
- around one-third of cases are associated with a loss-of-function mutation in the WT1 gene on chromosome 11

Management

- nephrectomy
- chemotherapy
- radiotherapy if advanced disease
- prognosis: good, 80% cure rate



Histological features include epithelial tubules, areas of necrosis, immature glomerular structures, stroma with spindle cells and small cell blastomatous tissues resembling the metanephric blastema

Neurology

Absence seizures

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

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

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

- subacute combined degeneration of the cord
- motor neuron disease
- Friedreich's ataxia
- syringomyelia
- taboparesis (syphilis)
- conus medullaris lesion

Acoustic neuroma

Acoustic neuromas (more correctly called vestibular schwannomas) account for approximately five percent of intracranial tumours and 90 percent of cerebellopontine angle

Features can be predicted by the affected cranial nerves

- cranial nerve VIII: hearing loss, vertigo, tinnitus
- cranial nerve V: absent corneal reflex
- cranial nerve VII: facial palsy

Bilateral acoustic neuromas are seen in neurofibromatosis type 2

MRI of the cerebellopontine angle is the investigation of choice

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

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

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.

Alzheimer's disease

Alzheimer's disease is a progressive degenerative disease of the brain accounting for the majority of dementia seen in the UK

Genetics

- most cases are sporadic
- 5% of cases are inherited as an autosomal dominant trait
- mutations in the amyloid precursor protein (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

Pathological changes

- 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

Neurofibrillary tangles

- paired helical filaments are partly made from a protein called tau
- in AD are tau proteins are excessively phosphorylated

Management

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

Anderson-Fabry disease

Overview

- X-linked recessive
- deficiency of alpha-galactosidase A

Features

- burning pain/paraesthesia in childhood
- angiokeratomas
- lens opacities
- proteinuria
- early cardiovascular disease

Aphasia

The table below lists the major types of aphasia. Remember that dysarthria is different and refers to a motor speech disorder.

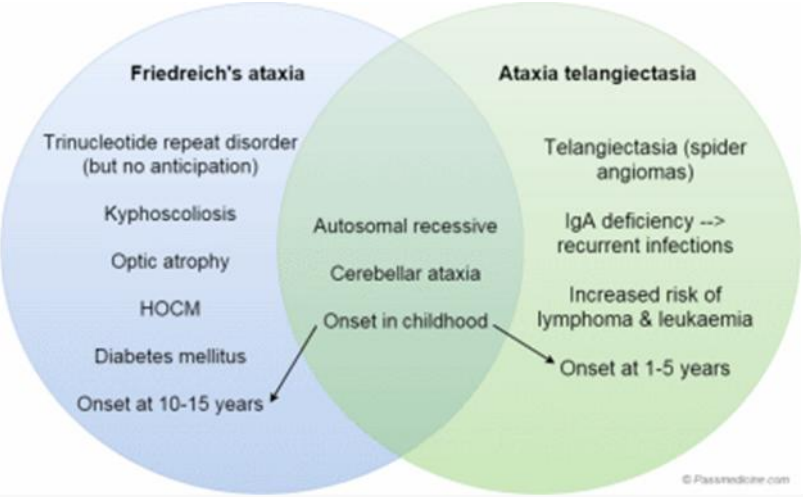
Type of aphasia	Notes
Wernicke's (receptive) aphasia	Due to a lesion of the superior temporal gyrus This area 'forms' the speech before 'sending it' to Broca's area. Lesions result in sentences that make no sense, word substitution and neologisms but speech remains fluent Comprehension is impaired
Broca's (expressive) aphasia	Due to a lesion of the inferior frontal gyrus Speech is non-fluent, laboured, and halting Comprehension is normal
Conduction aphasia	Classically due to a stroke affecting the arcuate fasiculus - the connection between Wernicke's and Broca's area Speech is fluent but repetition is poor. Aware of the errors they are making Comprehension is normal
Global aphasia	Large lesion affecting all 3 of the above areas resulting in severe expressive and receptive aphasia

Ataxic telangiectasia

Ataxic telangiectasia is an 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.

Features

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



Comparison of Friedreich's ataxia and ataxic telangiectasia. Note in particular how ataxic telangiectasia tends to present much earlier, often at the age of 1-2 years

Atrial septal defects

Atrial septal defects (ASDs) are the most likely congenital heart defect to be found in adulthood. They carry a significant mortality, with 50% of patients being dead at 50 years. Two types of ASDs are recognised, ostium secundum and ostium primum. Ostium secundum are the most common

Features

- ejection systolic murmur, fixed splitting of S2
- embolism may pass from venous system to left side of heart causing a stroke

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
- ECG: RBBB with LAD, prolonged PR interval

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

Bell's palsy

Bell's palsy may be defined as an acute, unilateral, idiopathic, facial nerve paralysis. The aetiology is unknown although the role of the herpes simplex virus has been investigated previously. The peak incidence is 20-40 years and the condition is more common in pregnant women.

Features

- lower motor neuron facial nerve palsy - forehead affected*
- patients may also notice post-auricular pain (may precede paralysis), altered taste, dry eyes, hyperacusis

Management

- in the past a variety of treatment options have been proposed including no treatment, prednisolone only and a combination of aciclovir and prednisolone
- following a National Institute for Health randomised controlled trial it is now recommended that 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

*upper motor neuron lesion 'spares' upper face

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 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

BPPV has a good prognosis and usually resolves spontaneously after a few weeks to months. 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.

Brain lesions

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

Gross anatomy

Parietal lobe lesions

- sensory inattention
- apraxias
- astereognosis (tactile agnosia)
- inferior homonymous quadrantanopia
- Gerstmann's syndrome (lesion of dominant parietal): alexia, acalculia, finger agnosia and right-left disorientation

Occipital lobe lesions

- homonymous hemianopia (with macula sparing)
- cortical blindness
- visual agnosia

Temporal lobe lesion

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

Frontal lobes lesions

- 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
- inability to generate a list

Cerebellum lesions

- midline lesions: gait and truncal ataxia
- hemisphere lesions: intention tremor, past pointing, dysdiadokinesis, nystagmus

More specific areas

Area	Associated conditions
Medial thalamus and mammillary bodies of the hypothalamus	Wernicke and Korsakoff 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, hyperphagia, visual agnosia

Carbamazepine

Carbamazepine is chemically similar to the tricyclic antidepressant drugs. It is 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
- dizziness and ataxia
- drowsiness
- headache
- visual disturbances (especially diplopia)
- Steven-Johnson syndrome
- leucopenia and agranulocytosis
- syndrome of inappropriate ADH secretion

Cataplexy

Cataplexy describes the sudden and transient loss of muscular tone caused by strong emotion (e.g. laughter, being frightened). Around two-thirds of patients with narcolepsy have cataplexy.

Features range from buckling knees to collapse.

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

Cerebrospinal fluid: raised lymphocytes

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

Cerebrospinal fluid: raised protein

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- glucose = > 2/3 blood glucose
- cells: red cells = 0, white cells < 5/mm³

The following conditions are associated with raised protein levels

- Guillain-Barre syndrome
- tuberculous, fungal and bacterial meningitis
- Froin's syndrome*
- viral encephalitis

*describes an increase in CSF protein below a spinal canal blockage (e.g. tumour, disc, infection)

Chorea

Chorea describes involuntary, rapid, jerky movements which often move from one part of the body to another. 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

- Huntington's disease, Wilson's disease, ataxic telangiectasia
- SLE, anti-phospholipid syndrome
- rheumatic fever: Sydenham's chorea
- drugs: oral contraceptive pill, L-dopa, antipsychotics
- neuroacanthocytosis
- pregnancy: chorea gravidarum
- thyrotoxicosis
- polycythaemia rubra vera
- carbon monoxide poisoning
- cerebrovascular disease

Cluster headache

Cluster headaches* are more common in men (5:1) and smokers.

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)
- 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
- prophylaxis: verapamil, prednisolone
- NICE recommend seeking specialist advice from a neurologist if a patient develops cluster headaches with respect to neuroimaging

*some neurologists use the term trigeminal autonomic cephalgia to group a number of conditions including cluster headache, paroxysmal hemicrania and short-lived unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT). It is recommended such patients are referred for specialist assessment as specific treatment may be required, for example it is known paroxysmal hemicrania responds very well to indomethacin

Cranial nerves

The table below lists the major characteristics of the 12 cranial nerves:

Nerve	Functions	Clinical	Pathway/foramen
I (Olfactory)	Smell		Cribriform plate
II (Optic)	Sight		Optic canal
III (Oculomotor)	Eye movement (MR, IO, SR, IR) Pupil constriction Accomodation Eyelid opening	Palsy results in • ptosis • 'down and out' eye • dilated, fixed pupil	Superior orbital fissure (SOF)
IV (Trochlear)	Eye movement (SO)	Palsy results in defective downward gaze → vertical diplopia	SOF
V (Trigeminal)	Facial sensation Mastication	Lesions may cause: • trigeminal neuralgia • loss of corneal reflex (afferent) • loss of facial sensation • paralysis of mastication muscles • deviation of jaw to weak side	V_1: SOF, V_2: Foramen rotundum, V_3: Foramen ovale

Nerve	Functions	Clinical	Pathway/foramen
VI (Abducens)	Eye movement (LR)	Palsy results in defective abduction → horizontal diplopia	SOF
VII (Facial)	Facial movement Taste (anterior 2/3rds of tongue) Lacrimation Salivation	Lesions may result in: ⁾ flaccid paralysis of upper + lower face ⁾ loss of corneal reflex (efferent) ⁾ loss of taste ⁾ hyperacusis	Internal auditory meatus
VIII (Vestibulocochlear)	Hearing, balance	Hearing loss Vertigo, nystagmus Acoustic neuromas are Schwann cell tumours of the cochlear nerve	Internal auditory meatus
IX (Glossopharyngeal)	Taste (posterior 1/3rd of tongue) Salivation Swallowing Mediates input from carotid body & sinus	Lesions may result in; ⁾ hypersensitive carotid sinus reflex ⁾ loss of gag reflex (afferent)	Jugular foramen

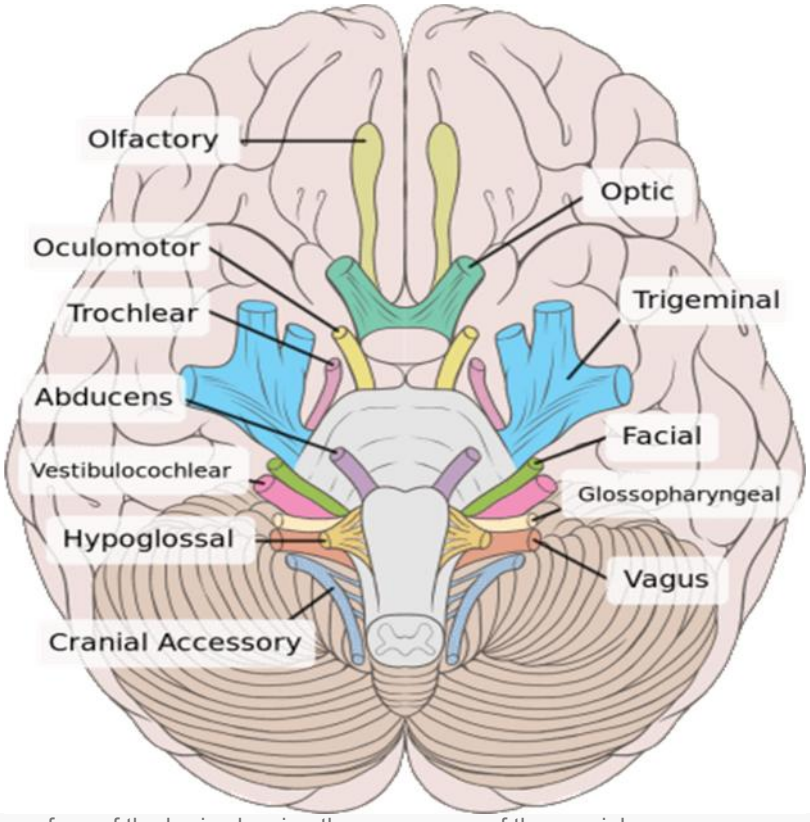
Nerve	Functions	Clinical	Pathway/foramen
X (Vagus)	Phonation Swallowing Innervates viscera	Lesions may result in; ⦚ uvula deviates away from site of lesion ⦚ loss of gag reflex (efferent)	Jugular foramen
XI (Accessory)	Head and shoulder movement	Lesions may result in; ⦚ weakness turning head to contralateral side	Jugular foramen
XII (Hypoglossal)	Tongue movement	Tongue deviates towards side of lesion	Hypoglossal canal

Some cranial nerves are motor, some sensory and some are both. The most useful mnemonic is given below.

CN I ----------→XII

Some **S**ay **M**arry **M**oney **B**ut **M**y **B**rother **S**ays **B**ig **B**rains **M**atter **M**ost

S = Sensory, **M** = Motor, **B** = Both



View from the inferior surface of the brain showing the emergence of the cranial nerves

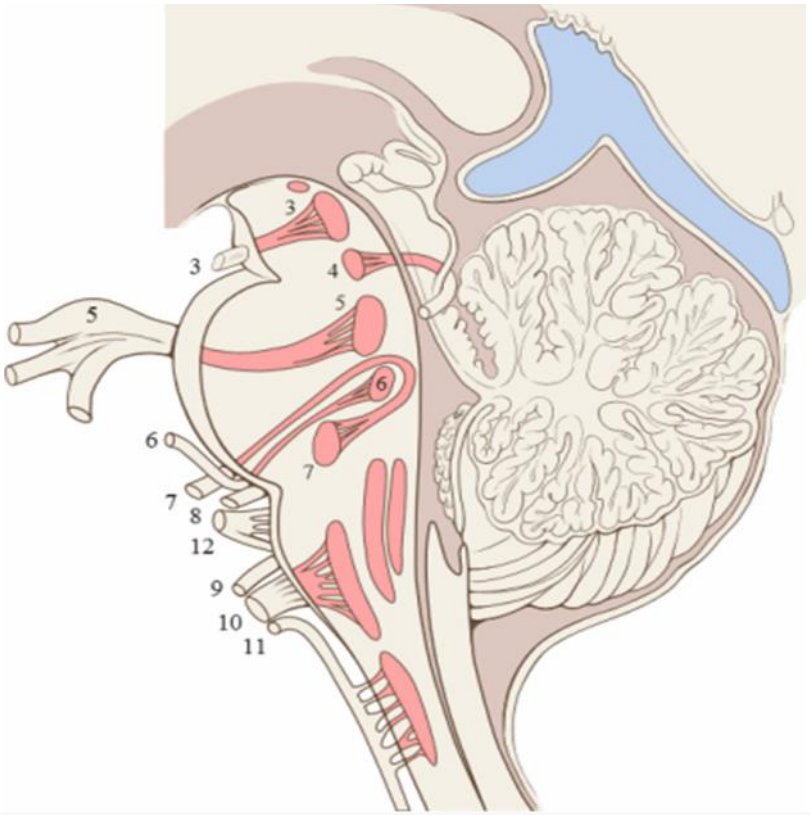


Diagram showing the nuclei of the cranial nerves in the brainstem

Cranial nerve reflexes

Reflex	Afferent limb	Efferent limb
Corneal	Ophthalmic nerve (V_1)	Facial nerve (VII)
Jaw jerk	Mandibular nerve (V_3)	Mandibular nerve (V_3)
Gag	Glossopharyngeal nerve (IX)	Vagal nerve (X)
Carotid sinus	Glossopharyngeal nerve (IX)	Vagal nerve (X)
Pupillary light	Optic nerve (II)	Oculomotor nerve (III)
Lacrimation	Ophthalmic nerve (V_1)	Facial nerve (VII)

Creutzfeldt-Jakob disease

Creutzfeldt-Jakob disease (CJD) is rapidly progressive neurological condition caused by prion proteins. These proteins induce the formation of amyloid folds resulting in tightly packed beta-pleated sheets resistant to proteases.

Features

- dementia (rapid onset)
- myoclonus

Investigation

- CSF is usually normal
- EEG: biphasic, high amplitude sharp waves (only in sporadic CJD)
- MRI: hyperintense signals in the basal ganglia and thalamus

Sporadic CJD

- accounts for 85% of cases
- 10-15% of cases are familial
- mean age of onset is 65 years

New variant CJD

- younger patients (average age of onset = 25 years)
- psychological symptoms such as anxiety, withdrawal and dysphonia are the most common presenting features
- the 'prion protein' is encoded on chromosome 20 - it's role is not yet 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
- median survival = 13 months

Other prion diseases

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

Degenerative cervical myelopathy

Degenerative cervical myelopathy (DCM) has a number of risk factors, which include smoking due to its effects on the intervertebral discs, genetics and occupation - those exposing patients to high axial loading [1].

The presentation of DCM is very variable. Early symptoms are often subtle and can vary in severity day to day, making the disease difficult to detect initially. However as a progressive condition, worsening, deteriorating or new symptoms should be a warning sign.

DCM symptoms can include any combination of [1]:

- Pain (affecting the neck, upper or lower limbs)
- Loss of motor function (loss of digital dexterity, preventing simple tasks such as holding a fork or doing up their shirt buttons, arm or leg weakness/stiffness leading to impaired gait and imbalance
- Loss of sensory function causing numbness
- Loss of autonomic function (urinary or faecal incontinence and/or impotence) - these can occur and do not necessarily suggest cauda equina syndrome in the absence of other hallmarks of that condition

The most common symptoms at presentation of DCM are unknown, but in one series 50% of patients were initially incorrectly diagnosed and sometimes treated for carpal tunnel syndrome [2].

An MRI of the cervical spine is the gold standard test where cervical myelopathy is suspected. It may reveal disc degeneration and ligament hypertrophy, with accompanying cord signal change.

All patients with degenerative cervical myelopathy should be urgently referred for assessment by specialist spinal services (neurosurgery or orthopaedic spinal surgery). This is due to the importance of early treatment. The timing of surgery is important, as any existing spinal cord damage can be permanent. Early treatment (within 6 months of diagnosis) offers the best chance of a full recovery but at present, most patients are presenting too late. In one study, patients averaged over 5 appointments before diagnosis, representing >2 years.

Currently, decompressive surgery is the only effective treatment. It has been shown to prevent disease progression. Close observation is an option for mild stable disease, but anything progressive or more severe requires surgery to prevent further deterioration. Physiotherapy should only be initiated by specialist services, as manipulation can cause more spinal cord damage.

Dementia

Dementia is thought to affect over 700,000 people in the UK and accounts for a large amount of health and social care spending. The most common cause of dementia in the UK is Alzheimer's disease followed by vascular and Lewy body dementia. These conditions may coexist.

Features

- diagnosis can be difficult and is often delayed
- assessment tools include the Abbreviated mental test score (AMTS), 6-Item cognitive impairment test (6CIT), General practitioner assessment of cognition (GPCOG) and the mini-mental state examination (MMSE) is widely used. A MMSE score of 24 or less out of 30 suggests dementia

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

*in the 2011 NICE guidelines structural imaging was said to be essential in the investigation of dementia

Dementia: causes

Common causes

- Alzheimer's disease
- cerebrovascular disease: multi-infarct dementia (c. 10-20%)
- 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

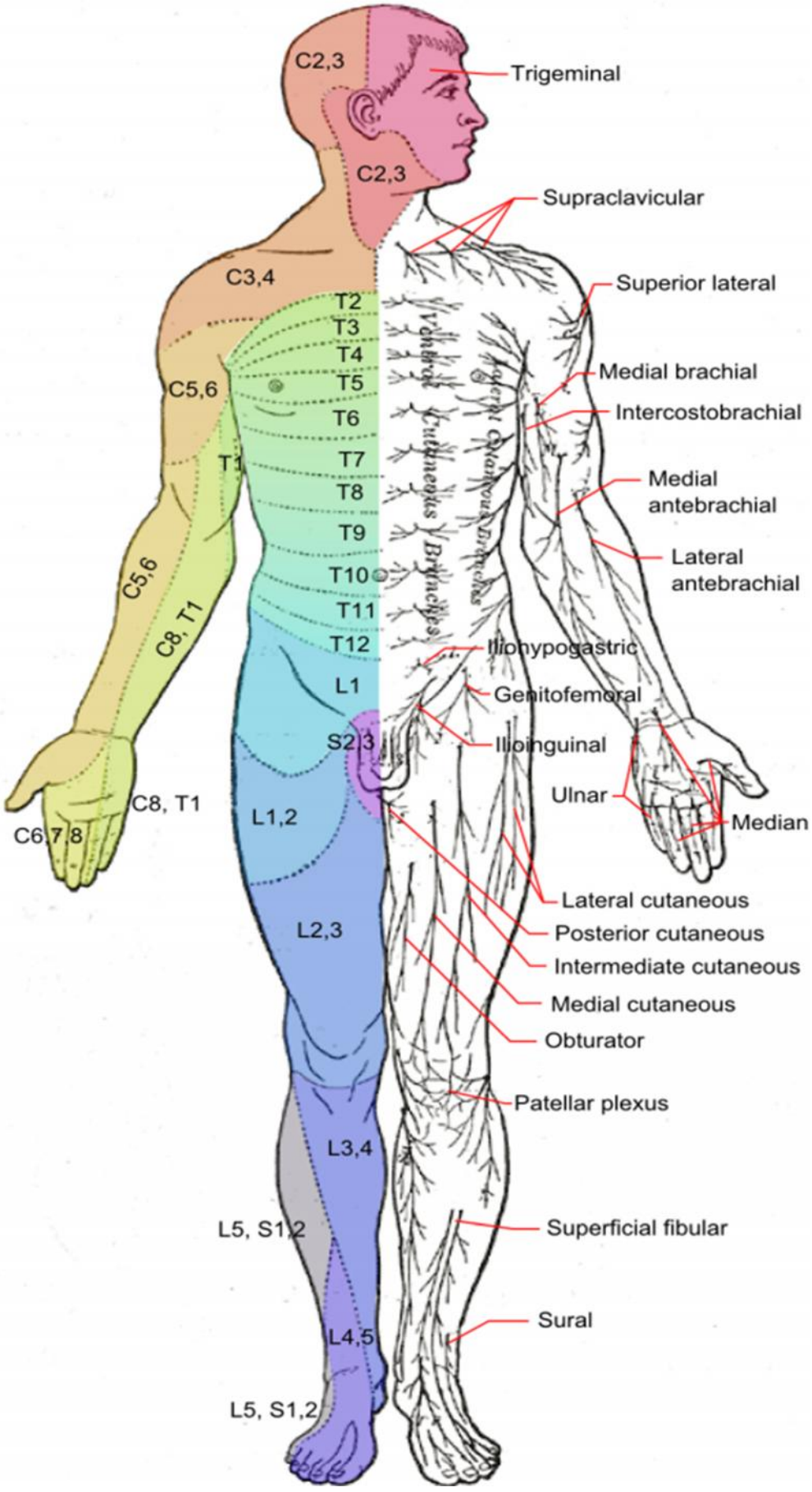
- hypothyroidism, Addison's
- B12/folate/thiamine deficiency
- syphilis
- brain tumour
- normal pressure hydrocephalus
- subdural haematoma
- depression
- chronic drug use e.g. Alcohol, barbiturates

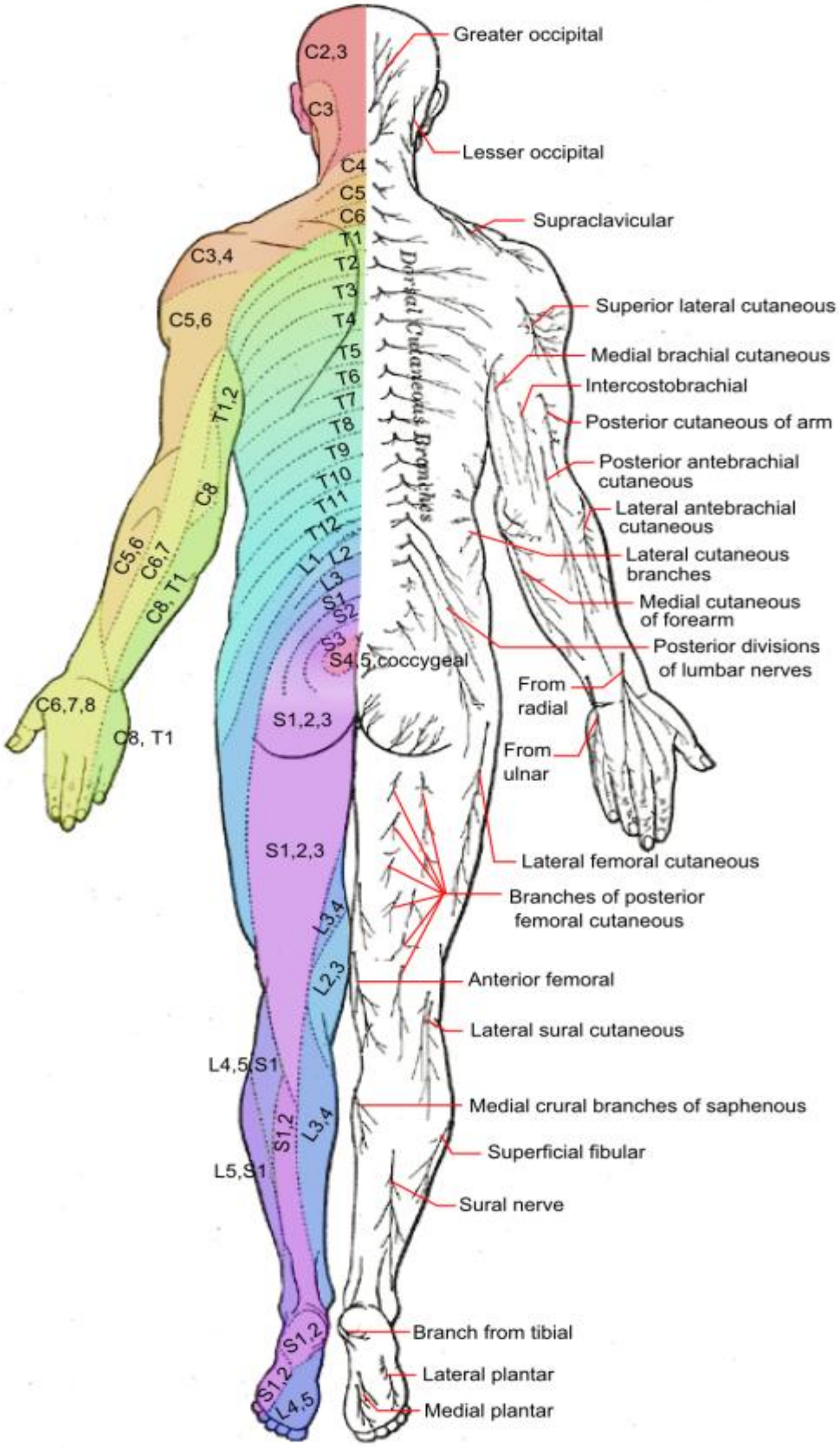
Dermatomes

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	
C8	Ring + little finger	
T4	Nipples	T4 at the Teat Pore
T5	Inframammary fold	
T7	Xiphoid process	
T10	Umbilicus	BellybuT-TEN

Nerve root	Landmark	Mnemonics
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
S1	Lateral foot, small toe	S1 = the smallest one
S2, S3	Genitalia	


C2,3
Trigeminal
C2,3
Supraclavicular
C3,4
Superior lateral
T2
T3
T4
T5
T6
T7
T8
T9
T10
T11
T12
L1
S2,3
L1,2
L2,3
L3,4
L5, S1,2
L4,5
L5, S1,2
C5,6
T1
C5,6
C8, T1
C8, T1
C6,7,8
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
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L1
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S3
S4,5,coccygeal
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

Diabetes insipidus

Diabetes insipidus (DI) is a condition characterised by either a deficiency of antidiuretic hormone, ADH, (cranial DI) or an insensitivity to antidiuretic hormone (nephrogenic DI).

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: the more common form affects the vasopression (ADH) receptor, the less common form results from a mutation in the gene that encodes the aquaporin 2 channel
- electrolytes: hypercalcaemia, hypokalaemia
- drugs: demeclocycline, lithium
- tubulo-interstitial disease: obstruction, sickle-cell, pyelonephritis

Features

- polyuria
- polydipsia

Investigation

- high plasma osmolality, low urine osmolality
- water deprivation test

Drugs causing peripheral neuropathy

Drugs causing a peripheral neuropathy

- antibiotics: nitrofurantoin, metronidazole
- amiodarone
- isoniazid
- vincristine

DVLA: neurological disorders

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*. 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, may not need to inform DVLA if no residual neurological deficit
- multiple TIAs over short period of times: 3 months off driving and inform DVLA
- craniotomy e.g. For meningioma: 1 year off driving**
- 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

*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

**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

Eclampsia

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

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)

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
- partial seizures progressing to generalised seizures

Partial - focal features depending on location

- simple (no disturbance of consciousness or awareness)
- complex (consciousness is disturbed)
- temporal lobe → aura, déjà vu, jamais vu; motor → Jacksonian

Epilepsy: pregnancy and breast feeding

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: associated with neural tube defects
- carbamazepine: often considered the least teratogenic of the older antiepileptics
- phenytoin: associated with cleft palate
- lamotrigine: studies to date suggest 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

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

Sodium valproate

The November 2013 issue of the Drug Safety Update also carried a warning about new evidence

showing a significant risk of neurodevelopmental delay in children following maternal use of sodium valproate.

The update concludes that sodium valproate should not be used during pregnancy and in women of childbearing age unless clearly necessary. Women of childbearing age should not start treatment without specialist neurological or psychiatric advice.

Epilepsy: treatment

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

Myoclonic seizures

- sodium valproate
- second line: clonazepam, lamotrigine

Partial seizures

- carbamazepine or lamotrigine
- second line: sodium valproate

*carbamazepine may actually exacerbate absence seizure

Essential tremor

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

Ethosuximide

Ethosuximide is an antiepileptic that is particularly indicated in patients with absence seizures

Mechanism of action

- blocks T-type calcium channels in thalamic neurons

Facial nerve

Supply - 'face, ear, taste, tear'

- face: muscles of facial expression
- ear: nerve to stapedius
- taste: supplies anterior two-thirds of tongue
- tear: parasympathetic fibres to lacrimal glands, also salivary glands

Causes of bilateral facial nerve palsy

- sarcoidosis
- Guillain-Barre syndrome
- polio, 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*** **diabetes mellitus**	**stroke**

LMN vs. UMN

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

*may also cause an UMN palsy

Friedreich's ataxia

Friedreich's ataxia is the most common of the early-onset hereditary ataxias. It is an 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.

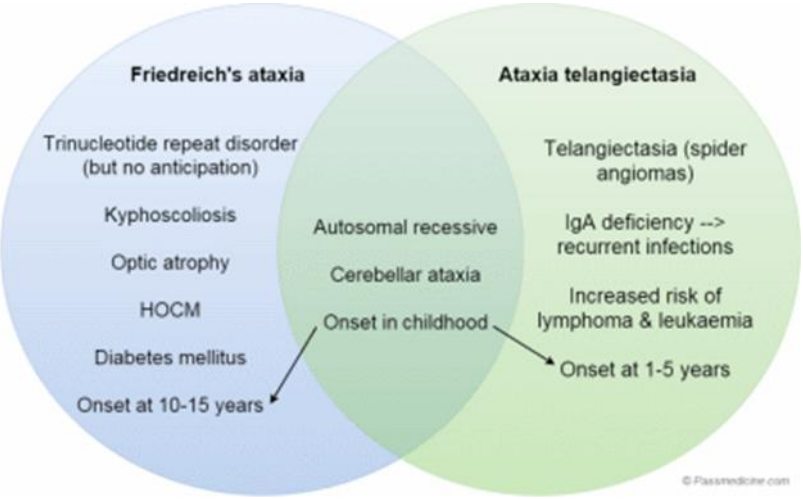
The typical age of onset is 10-15 years old. Gait ataxia and kyphoscoliosis are the most common presenting features.

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



Comparison of Friedreich's ataxia and ataxic telangiectasia. Note in particular how ataxic telangiectasia tends to present much earlier, often at the age of 1-2 years

Frontotemporal lobar degeneration

Frontotemporal lobar degeneration (FTLD) is the third most common type of cortical dementia after Alzheimer's and Lewy body dementia.

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 and is 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.

Guillain-Barre syndrome

Guillain-Barre syndrome describes an immune mediated demyelination of the peripheral nervous system often triggered by an infection (classically *Campylobacterjejuni*)

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

- 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

Guillain-Barre syndrome: features

Guillain-Barre syndrome describes an immune mediated demyelination of the peripheral nervous system often triggered by an infection (classically *Campylobacter jejuni*).

The characteristic features of Guillain-Barre syndrome is 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. 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

Less common findings

- papilloedema: thought to be secondary to reduced CSF resorption

Guillain-Barre syndrome: management

Guillain-Barre syndrome describes an immune mediated demyelination of the peripheral nervous system often triggered by an infection (classically *Campylobacter jejuni*).

Management

- plasma exchange
- IV immunoglobulins (IVIG): as effective as plasma exchange. No benefit in combining both treatments. IVIG may be easier to administer and tends to have fewer side-effects
- steroids and immunosuppressants have not been shown to be beneficial
- FVC regularly to monitor respiratory function

Prognosis

- 20% suffer permanent disability, 5% die

Guillain-Barre syndrome: prognosis

Guillain-Barre syndrome (GBS) describes an immune mediated demyelination of the peripheral nervous system often triggered by an infection (classically *Campylobacterjejuni*)

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

Head injury: NICE guidance on investigation

NICE has strict and clear guidance regarding which adult patients are safe to discharge and which need further CT head imaging. The latter group are also divided into two further cohorts, those who require an immediate CT head and those requiring CT head within 8 hours of injury:

CT head immediately

- 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 who have sustained a head injury with no other indications for a CT head scan, perform a CT head scan within 8 hours of the injury.

Head injury: types of traumatic brain injury

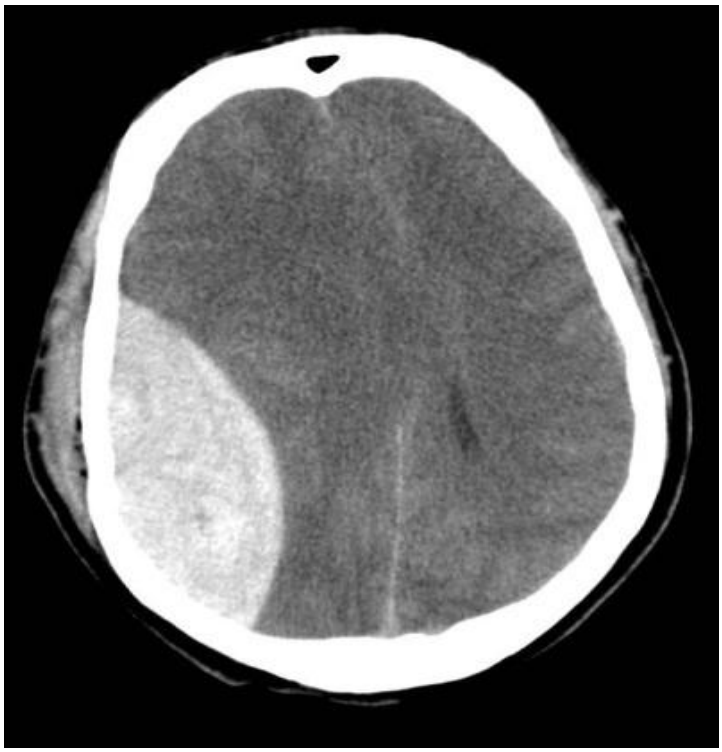
Basics

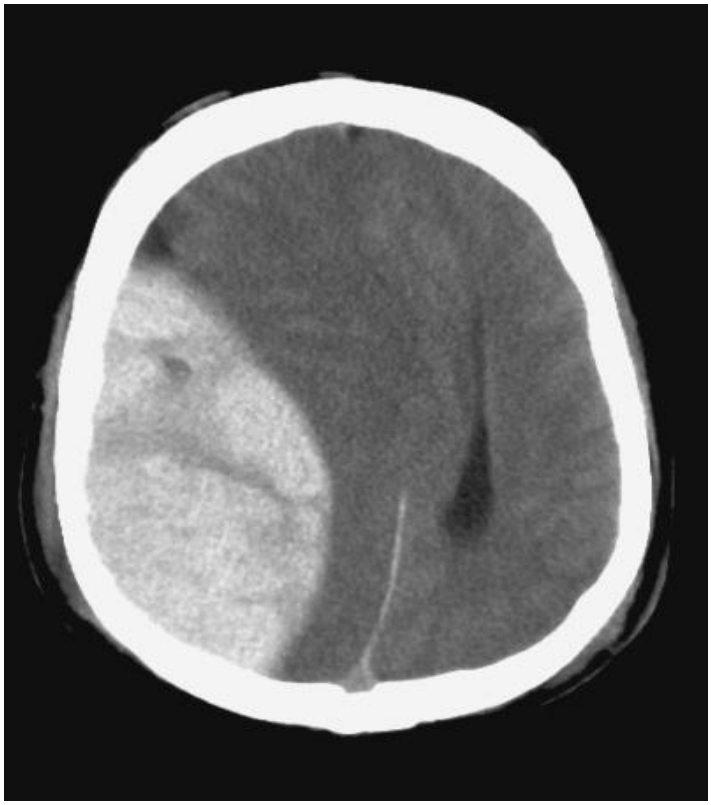
- primary brain injury may be focal (contusion/haematoma) or diffuse (diffuse axonal injury)
- diffuse axonal injury occurs as a result of mechanical shearing following deceleration, causing disruption and tearing of axons
- intra-cranial haematomas can be extradural, subdural or intracerebral, while 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

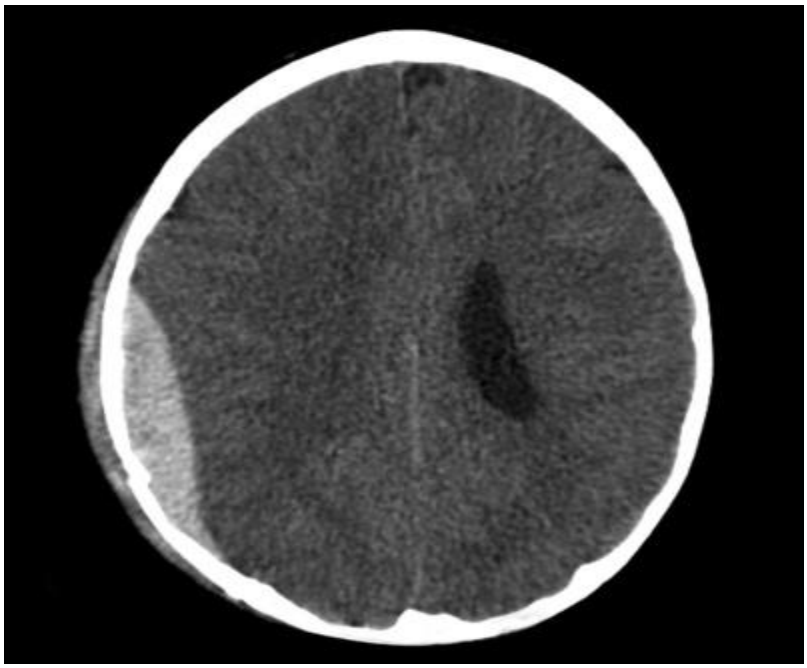
Type of injury	Notes
Extradural (epidural) haematoma	Bleeding into the space between the dura mater and the skull. Often results from acceleration-deceleration trauma or a blow to the side of the head. The majority of epidural haematomas occur in the temporal region where skull fractures cause a rupture of the middle meningeal artery. Features - features of raised intracranial pressure - some patients may exhibit a lucid interval
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

Image gallery

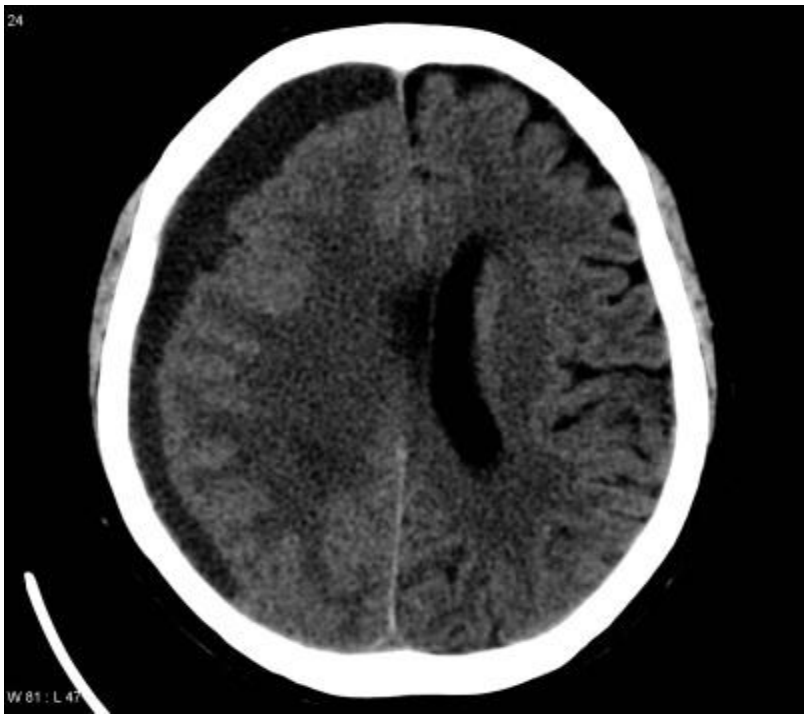
Extradural (epidural) haematoma:

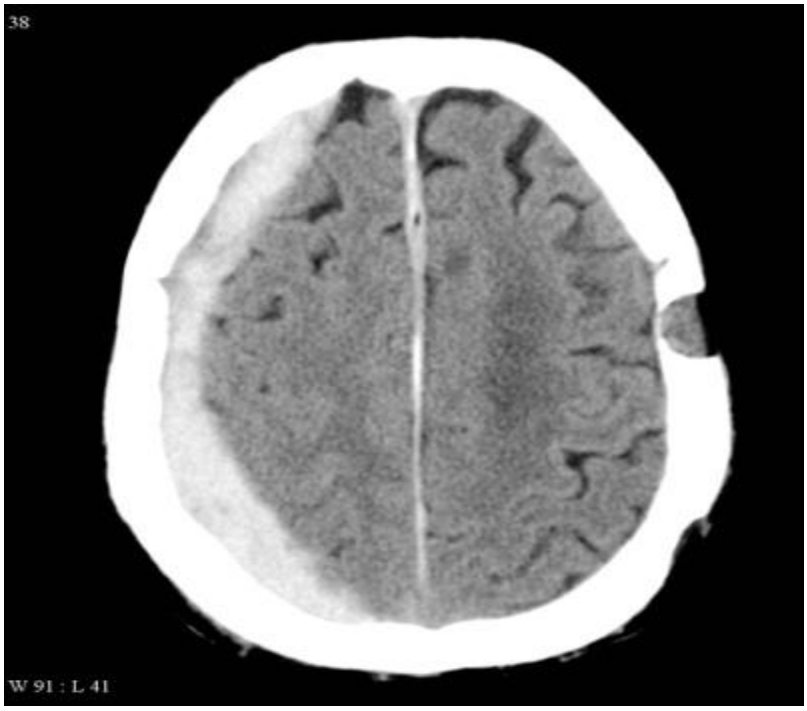




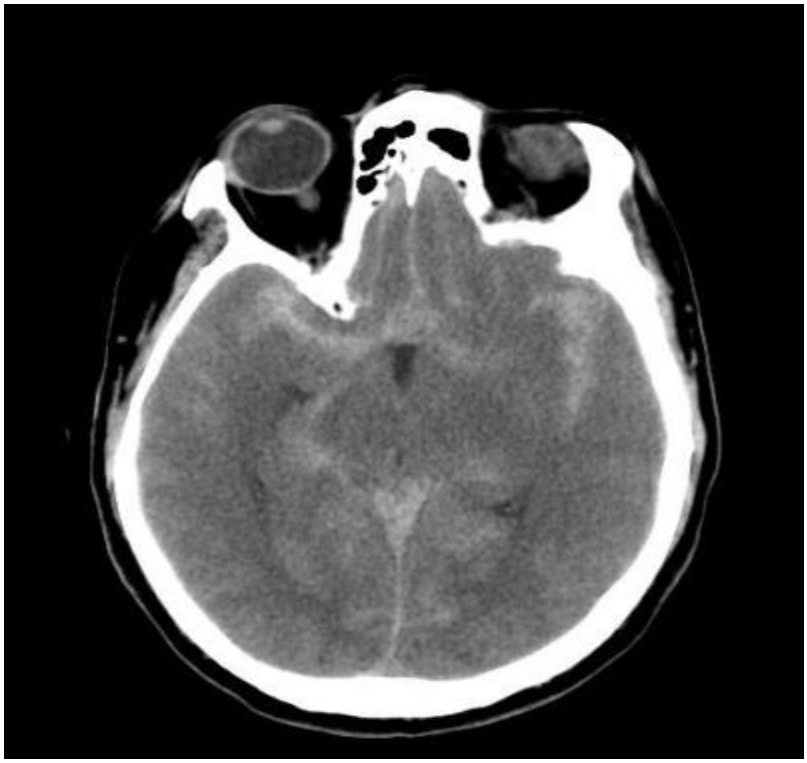


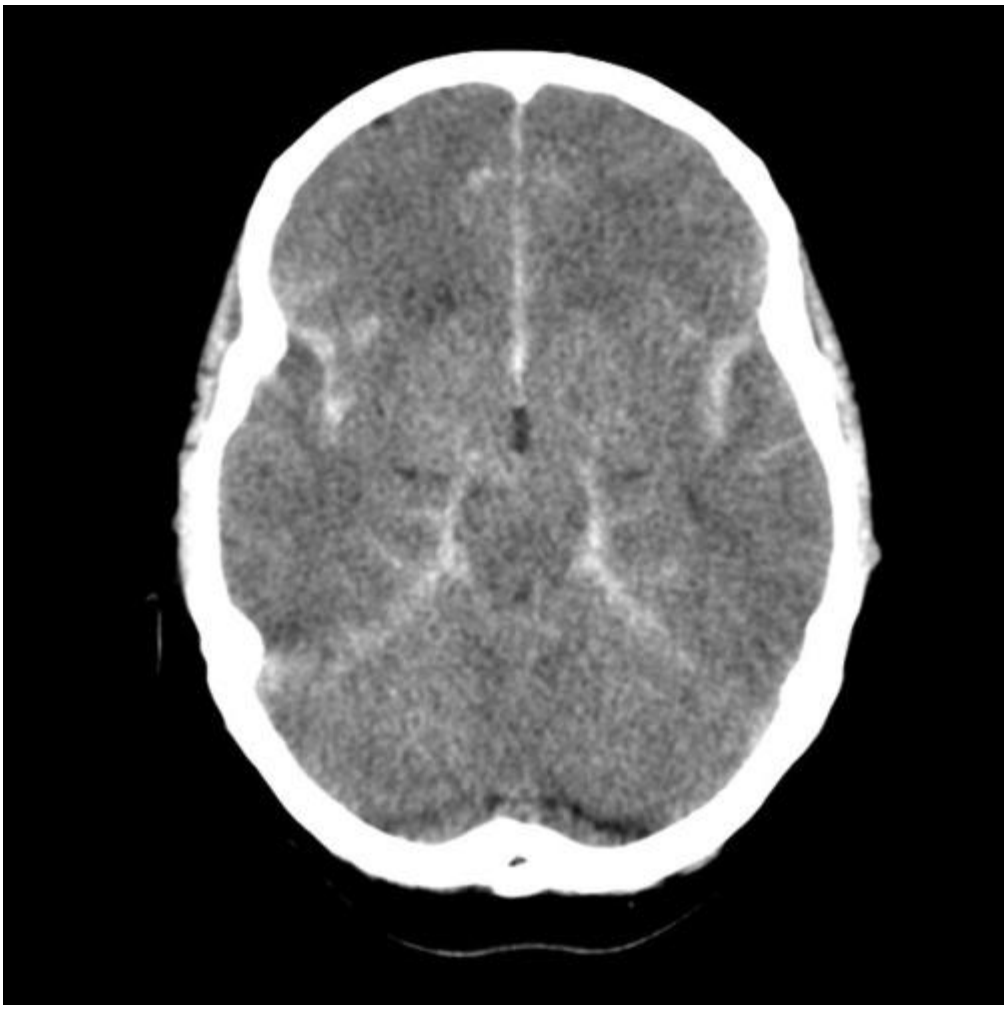
Subdural haematoma:





Subarachnoid haemorrhage:





Headache

Headache accounts for a large proportion of medical consultations. The table below summarises the main characteristics of common or important causes:

Migraine	**Recurrent, severe headache which is usually unilateral and throbbing in nature** **May be be associated with aura, nausea and photosensitivity** **Aggravated by, or causes avoidance of, routine activities of daily living. Patients often describe 'going to bed'.** **In women may be associated with menstruation**
Tension headache	Recurrent, non-disabling, bilateral headache, often described as a 'tight-band' Not aggravated by routine activities of daily living
Cluster headache*	Pain typical occurs once or twice a day, each episode lasting 15 mins - 2 hours with clusters typically lasting 4-12 weeks Intense pain around one eye (recurrent attacks 'always' affect same side) Patient is restless during an attack Accompanied by redness, lacrimation, lid swelling More common in men and smokers
Temporal arteritis	Typically patient > 60 years old Usually rapid onset (e.g. < 1 month) of unilateral headache Jaw claudication (65%) Tender, palpable temporal artery Raised ESR
Medication overuse headache	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

Other causes of headache

Acute single episode

- meningitis
- encephalitis
- subarachnoid haemorrhage
- head injury
- sinusitis
- glaucoma (acute closed-angle)
- tropical illness e.g. Malaria

Chronic headache

- chronically raised ICP
- Paget's disease
- psychological

*some neurologists use the term trigeminal autonomic cephalgia to group a number of conditions including cluster headache, paroxysmal hemicrania and short-lived unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT). It is recommended such patients are referred for specialist assessment as specific treatment may be required, for example it is known paroxysmal hemicrania responds very well to indomethacin

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)	Threadworm infestation is asymptomatic in around 90% of cases, possible features include perianal itching, particularly at night; girls may have vulval symptoms 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	-bendazoles
Ancylostoma duodenale, *Necator americanus*(hookworms)	Larvae penetrate skin of feet; gastrointestinal infection → anaemia Thin-shelled ova	-bendazoles

Worm	Notes	Treatment
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

Worm	Notes	Treatment
Ascaris lumbricoides(giant roundworm)	Eggs are visible in faeces May cause intestinal obstruction and occasional migrate to lung (Loffler's syndrome)	-bendazoles

Cestodes (tapeworms)

Worm	Notes	Treatment
Echinococcus granulosus	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

Hemiballism

Hemiballism occurs following damage to the subthalamic nucleus. 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

Symptoms may decrease whilst the patient is asleep.

Antidopaminergic agents (e.g. Haloperidol) are the mainstay of treatment

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

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

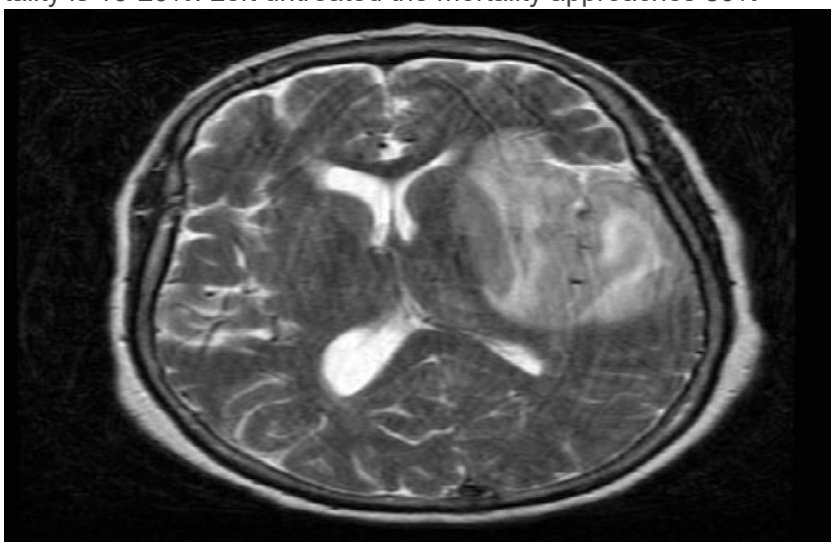
Investigation

- CSF: lymphocytosis, elevated protein
- PCR for HSV
- CT: medial temporal and inferior frontal changes (e.g. petechial haemorrhages) - normal in one-third of patients
- MRI is better
- EEG pattern: lateralised periodic discharges at 2 Hz

Treatment

- intravenous aciclovir

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.

Hodgkin's lymphoma: histological classification and prognosis

Hodgkin's lymphoma is a malignant proliferation of lymphocytes characterised by the presence of the Reed-Sternberg cell. It has a bimodal age distributions being most common in the third and seventh decades

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	A*round 5%	Best prognosis	
Lymphocyte depleted	Rare	Worst prognosis	

'B' symptoms also imply a poor prognosis

- weight loss > 10% in last 6 months
- fever > 38ºC
- 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/µl or < 8%
- male
- albumin < 40 g/l
- white blood count > 15,000/µl

*Reed-Sternberg cells with nuclei surrounded by a clear space

Horner's syndrome

Features

- miosis (small pupil)
- ptosis
- enophthalmos* (sunken eye)
- anhidrosis (loss of sweating one side)

Distinguishing between causes

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

Central lesions	**Pre-ganglionic lesions**	**Post-ganglionic lesions**
Anhidrosis of the face, arm and trunk	Anhidrosis of the face	No anhidrosis
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

*in reality the appearance is due to a narrow palpebral aperture rather than true enophthalmos

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

- HSMN type I: primarily due to demyelinating pathology
- 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

Huntington's disease

Huntington's disease is an inherited neurodegenerative condition. It is a progressive and incurable condition that typically results in death 20 years after the initial symptoms develop.

Genetics

- autosomal dominant
- 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 chromosome 4

Features typical develop after 35 years of age

- chorea
- personality changes (e.g. irritability, apathy, depression) and intellectual impairment
- dystonia
- saccadic eye movements

Idiopathic intracranial hypertension

Idiopathic intracranial hypertension (also known as pseudotumour cerebri and formerly benign intracranial hypertension) is a condition classically seen in young, overweight females.

Features

- headache
- blurred vision
- papilloedema (usually present)
- enlarged blind spot
- sixth nerve palsy may be present

Risk factors

- obesity
- female sex
- pregnancy
- drugs*: oral contraceptive pill, steroids, tetracycline, vitamin A, lithium

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: optic nerve sheath decompression and fenestration may be needed to prevent damage to the optic nerve. A lumboperitoneal or ventriculoperitoneal shunt may also be performed to reduce intracranial pressure

*if intracranial hypertension is thought to occur secondary to a known causes (e.g. Medication) then it is of course not idiopathic

Intracranial venous thrombosis

Overview

- can cause cerebral infarction, much lesson common than arterial causes
- 50% of patients have isolated sagittal sinus thromboses - the remainder have coexistent lateral sinus thromboses and cavernous sinus thromboses

Features

- headache (may be sudden onset)
- nausea & vomiting

Sagittal sinus thrombosis

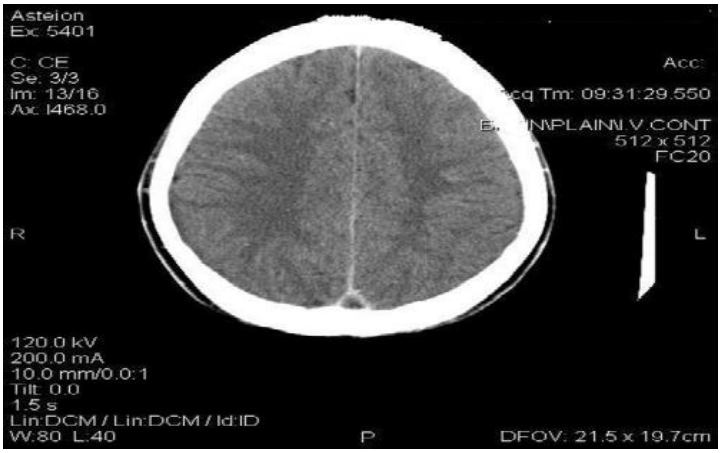
- may present with seizures and hemiplegia
- parasagittal biparietal or bifrontal haemorrhagic infarctions are sometimes seen

Cavernous sinus thrombosis

- other causes of cavernous sinus syndrome: local infection (e.g. sinusitis), neoplasia, trauma
- periorbital oedema
- ophthalmoplegia: 6th nerve damage typically occurs before 3rd & 4th
- trigeminal nerve involvement may lead to hyperaesthesia of upper face and eye pain
- central retinal vein thrombosis

Lateral sinus thrombosis

- 6th and 7th cranial nerve palsies



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

Lambert-Eaton syndrome

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)
- hyporeflexia
- autonomic symptoms: dry mouth, impotence, difficultly micturating
- ophthalmoplegia and ptosis not commonly a feature (unlike in myasthenia gravis)

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

*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

Lateral medullary syndrome

Lateral medullary syndrome, also known as Wallenberg's syndrome, occurs following occlusion of the posterior inferior cerebellar artery

Cerebellar features

- ataxia
- nystagmus

Brainstem features

- ipsilateral: dysphagia, facial numbness, cranial nerve palsy e.g. Horner's
- contralateral: limb sensory loss

Levodopa

Overview

- usually combined with a decarboxylase inhibitor (e.g. carbidopa or benserazide) to prevent peripheral metabolism of L-dopa to dopamine
- reduced effectiveness with time (usually by 2 years)
- no use in neuroleptic induced parkinsonism

Adverse effects

- dyskinesia
- 'on-off' effect
- postural hypotension
- cardiac arrhythmias
- nausea & vomiting
- psychosis
- reddish discolouration of urine upon standing

Lewy body dementia

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

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

Features

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

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-iodophenyl)-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%

Medication overuse headache

Medication overuse headache is one of the most common causes of chronic daily headache. It 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

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. Meniere's disease 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

Meralgia paraesthetica

Basics

- caused by compression of lateral cutaneous nerve of thigh
- typically burning sensation over antero-lateral aspect of thigh

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)

*In children, attacks may be shorter-lasting, headache is more commonly bilateral, and gastrointestinal disturbance is more prominent.

Migraine with aura (seen in around 25% of migraine patients) tends to be easier to diagnose with a

typical aura being progressive in nature and may occur hours prior to the headache. Typical aura include a transient hemianopic disturbance or a spreading scintillating scotoma ('jagged crescent'). Sensory symptoms may also occur

If we compare these guidelines to the **NICE criteria** the following points are noted:

- NICE suggests migraines may be unilateral or bilateral
- NICE also give more detail about typical auras:

Auras may occur with or without headache and:

- 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.

Migraine: pregnancy, contraception and other hormonal factors

SIGN produced guidelines in 2008 on the management of migraine, the following is selected highlights:

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

Miosis

Causes of miosis (small pupil)

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

Drugs causes

- opiates
- parasympathomimetics: pilocarpine
- organophosphate toxicity

Motor neuron disease: features

Motor neuron disease is a neurological condition of unknown cause which can present with both upper and lower motor neuron signs. It rarely presents before 40 years and various patterns of disease are recognised including amyotrophic lateral sclerosis, progressive muscular atrophy and bulbar palsy

There are a number of clues which point towards a diagnosis of motor neuron disease:

- fasciculation
- the absence of sensory signs/symptoms*
- the mixture of lower motor neurone and upper motor neurone signs
- 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

The diagnosis of motor neuron disease is clinical, but nerve conduction studies will show normal motor conduction and can help exclude a neuropathy. Electromyography shows a reduced number of action potentials with an increased amplitude. MRI is usually performed to exclude the differential diagnosis of cervical cord compression and myelopathy

*vague sensory symptoms may occur early in the disease (e.g. limb pain) but 'never' sensory signs

Motor neuron disease: types

Motor neuron disease is a neurological condition of unknown cause which can present with both upper and lower motor neuron signs. It rarely presents before 40 years and various patterns of disease are recognised including amyotrophic lateral sclerosis, primary lateral sclerosis, progressive muscular atrophy and progressive bulbar palsy. In some patients however, there is a combination of clinical patterns

Amyotrophic lateral sclerosis (50% of patients)

- typically LMN signs in arms and UMN signs in legs
- in familial cases the gene responsible lies on chromosome 21 and codes for superoxide dismutase

Primary lateral sclerosis

- UMN signs only

Progressive muscular atrophy

- LMN signs only
- affects distal muscles before proximal
- carries best prognosis

Progressive bulbar palsy

- palsy of the tongue, muscles of chewing/swallowing and facial muscles due to loss of function of brainstem motor nuclei
- carries worst prognosis

Motor neuron disease: management

Motor neuron disease is a neurological condition of unknown cause which can present with both upper and lower motor neuron signs. It rarely presents before 40 years and various patterns of disease are recognised including amyotrophic lateral sclerosis, progressive muscular atrophy and bulbar palsy

Riluzole

- prevents stimulation of glutamate receptors
- used mainly in amyotrophic lateral sclerosis
- prolongs life by about 3 months

Respiratory care

- non-invasive ventilation (usually BIPAP) is used at night
- studies have shown a survival benefit of around 7 months

Prognosis

- poor: 50% of patients die within 3 years

Multiple sclerosis: features

Patient's with multiple sclerosis (MS) may present with non-specific features, for example around 75% of patients have significant lethargy.

Visual

- optic neuritis: common presenting feature
- 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

Motor

- 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

Multiple sclerosis: prognostic features

Good prognosis features

- female sex
- young age of onset (i.e. 20s or 30s)
- relapsing-remitting disease
- sensory symptoms only
- long interval between first two relapses
- complete recovery between relapses

Ways of remembering prognostic features

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

Multiple sclerosis: management

Treatment in multiple sclerosis is focused at reducing the frequency and duration of relapses. There is no cure.

Acute relapse

High dose steroids (e.g. oral or IV methylprednisolone) may be given for 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

Other drugs used in the management of multiple sclerosis include:

- glatiramer acetate: immunomodulating drug - acts as an 'immune decoy'
- 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
- fingolimod: sphingosine 1-phosphate receptor modulator, prevents lymphocytes from leaving lymph nodes. An oral formulation is available

Some specific problems

Fatigue

- once other problems (e.g. anaemia, thyroid or depression) have been excluded NICE recommend a trial of amantadine
- other options include mindfulness training and CBT

Spasticity

- baclofen and gabapentin are first-line. Other options include diazepam, dantrolene and tizanidine
- physiotherapy is important
- cannabis and botox are undergoing evalulation

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

Oscillopsia (visual fields apper to oscillate)

- gabapentin is first-line

Multiple system atrophy

Shy-Drager syndrome is a type of multiple system atrophy

Features

- parkinsonism
- autonomic disturbance (atonic bladder, postural hypotension)
- cerebellar signs

Myasthenia gravis

Myasthenia gravis is an autoimmune disorder resulting in insufficient functioning acetylcholine receptors. Antibodies to acetylcholine receptors are seen in 85-90% of cases*. Myasthenia is more common in women (2:1)

The key feature is muscle fatigability - muscles become progressively weaker during periods of activity and slowly improve after periods of rest:

- extraocular muscle weakness: diplopia
- proximal muscle weakness: face, neck, limb girdle
- ptosis
- dysphagia

Associations

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

Investigations

- single fibre electromyography: high sensitivity (92-100%)
- CT thorax to exclude thymoma
- CK normal
- autoantibodies: around 85-90% of patients have antibodies to acetylcholine receptors. In the remaining patients, about about 40% are positive for anti-muscle-specific tyrosine kinase antibodies
- Tensilon test: IV edrophonium reduces muscle weakness temporarily - not commonly used anymore due to the risk of cardiac arrhythmia

Management

- long-acting anticholinesterase e.g. pyridostigmine
- immunosuppression: prednisolone initially
- thymectomy

Management of myasthenic crisis

- plasmapheresis
- intravenous immunoglobulins

*antibodies are less commonly seen in disease limited to the ocular muscles

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
- quinidine, procainamide
- beta-blockers
- lithium
- phenytoin
- antibiotics: gentamicin, macrolides, quinolones, tetracyclines

Myotonic dystrophy

Myotonic dystrophy (also called dystrophia myotonica) is an inherited myopathy with features developing at around 20-30 years old. It affects skeletal, cardiac and smooth muscle. There are two main types of myotonic dystrophy, DM1 and DM2.

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
- bilateral ptosis
- cataracts
- dysarthria

Other features

- myotonia (tonic spasm of muscle)
- weakness of arms and legs (distal initially)
- mild mental impairment
- diabetes mellitus
- testicular atrophy
- cardiac involvement: heart block, cardiomyopathy
- dysphagia

Nerve conduction studies

Nerve conduction studies (NCS) are useful in determining between axonal and demyelinating pathology

Axonal

- normal conduction velocity
- reduced amplitude

Demyelinating

- reduced conduction velocity
- normal amplitude

Neuromyelitis optica

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[1]. It 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[2]:

- 1. Spinal cord lesion involving 3 or more spinal levels
- 2. Initially normal MRI brain
- 3. Aquaporin 4 positive serum antibody

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

NICE updated their guidance on the management of neuropathic pain in 2013:

- first-line treatment*: amitriptyline, duloxetine, gabapentin or 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

*please note that for some specific conditions the guidance may vary. For example carbamazepine is used first-line for trigeminal neuralgia

Normal pressure hydrocephalus

Normal pressure hydrocephalus is a reversible cause of dementia seen in elderly patients. It is thought to be secondary to reduced CSF absorption at the arachnoid villi. These changes may be secondary to head injury, subarachnoid haemorrhage or meningitis.

A classical triad of features is seen

- urinary incontinence
- dementia and bradyphrenia
- gait abnormality (may be similar to Parkinson's disease)

It is thought around 60% of patients will have all 3 features at the time of diagnosis. Symptoms typically develop over a few months.

Imaging

- hydrocephalus with an enlarged fourth ventricle
- in addition to the ventriculomegaly there is typically an absence of substantial sulcal atrophy

Management

- ventriculoperitoneal shunting
- around 10% of patients who have shunts experience significant complications such as seizures, infection and intracerebral haemorrhages

Nystagmus

Upbeat nystagmus

- cerebellar vermis lesions

Downbeat nystagmus - foramen magnum lesions

- Arnold-Chiari malformation

Horizontal optokinetic nystagmus, a normal (physiological) form of nystagmus

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

Parkinson's disease: features

Parkinson's disease is a progressive neurodegenerative condition caused by degeneration of dopaminergic neurons in the substantia nigra.. This results in a classic triad of features: bradykinesia, tremor and rigidity. The symptoms of Parkinson's disease are characteristically asymmetrical.

Epidemiology

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

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

Rigidity

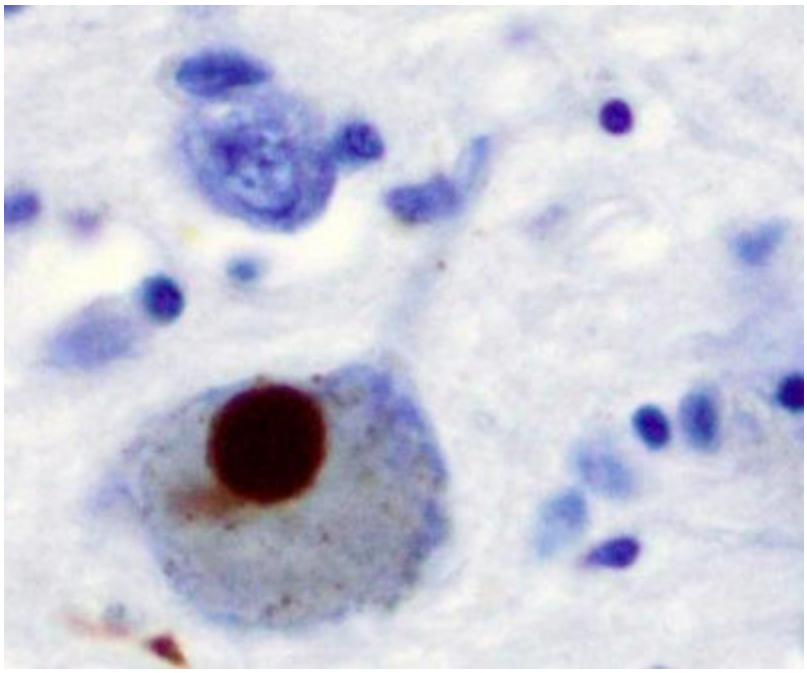
- lead pipe
- cogwheel: due to superimposed tremor

Other characteristic features

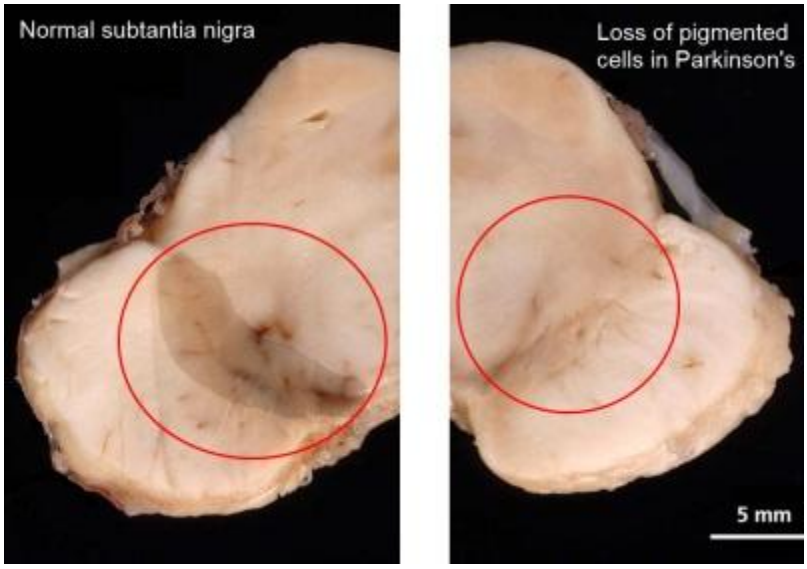
- mask-like facies
- flexed posture
- micrographia
- drooling of saliva
- psychiatric features: depression is the most common feature (affects about 40%); dementia, psychosis and sleep disturbances may also occur
- impaired olfaction
- REM sleep behaviour disorder

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.

Parkinson's disease: management

Currently accepted practice in the management of patients with Parkinson's disease (PD) is to delay treatment until the onset of disabling symptoms and then to introduce a dopamine receptor agonist. If the patient is elderly, levodopa is sometimes used as an initial treatment.

Dopamine receptor agonists

- e.g. Bromocriptine, ropinirole, cabergoline, 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 echocardiogram, ESR, creatinine and chest x-ray should be obtained prior to treatment and patients should be closely monitored
- patients should be warned about the potential for dopamine receptor agonists to cause impulse control disorders and excessive daytime somnolence
- more likely than levodopa to cause hallucinations in older patients. Nasal congestion and postural hypotension are also seen in some patients

Levodopa

- usually combined with a decarboxylase inhibitor (e.g. carbidopa or benserazide) to prevent peripheral metabolism of levodopa to dopamine
- reduced effectiveness with time (usually by 2 years)
- unwanted effects: dyskinesia (involuntary writhing movements), 'on-off' effect, dry mouth, anorexia, palpitations, postural hypotension, psychosis, drowsiness
- no use in neuroleptic induced parkinsonism

MAO-B (Monoamine Oxidase-B) inhibitors

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

Amantadine

- mechanism is not fully understood, probably increases dopamine release and inhibits its uptake at dopaminergic synapses
- side-effects include ataxia, slurred speech, confusion, dizziness and livedo reticularis

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
- 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)

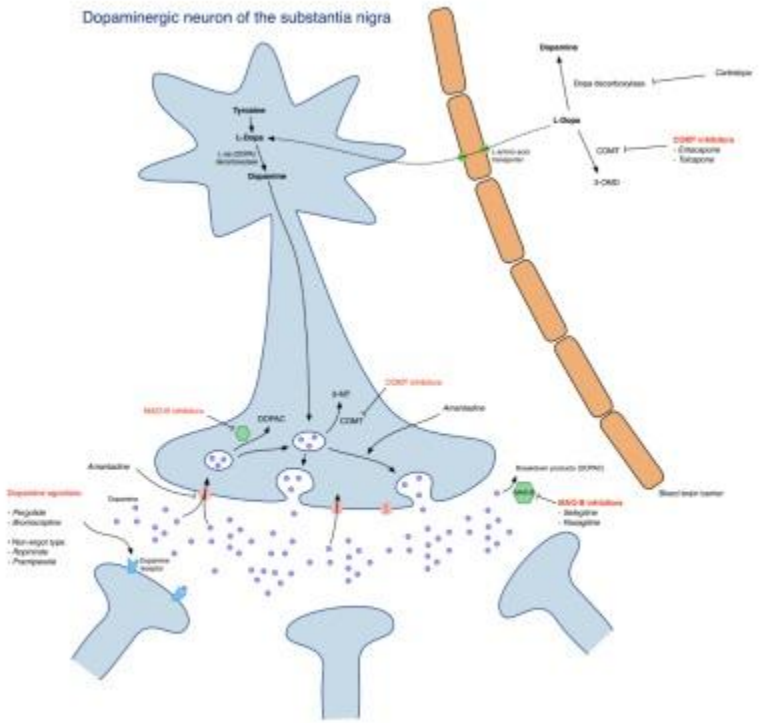


Diagram showing the mechanism of action of Parkinson's drugs

*pergolide was withdrawn from the US market in March 2007 due to concern regarding increased incidence of valvular dysfunction

Parkinsonism

Causes of Parkinsonism

- Parkinson's disease
- drug-induced e.g. antipsychotics, metoclopramide - see below
- progressive supranuclear 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

Peripheral neuropathy

Peripheral neuropathy may be divided into conditions which predominately cause a motor or sensory loss

Predominately motor loss

- Guillain-Barre syndrome
- porphyria
- lead poisoning
- hereditary sensorimotor neuropathies (HSMN) - Charcot-Marie-Tooth
- chronic inflammatory demyelinating polyneuropathy (CIDP)
- diphtheria

Predominately sensory loss

- diabetes
- uraemia
- leprosy
- alcoholism
- vitamin B12 deficiency
- amyloidosis

Alcoholic neuropathy

- secondary to both direct toxic effects and reduced absorption of B vitamins
- sensory symptoms typically present prior to motor symptoms

Vitamin B12 deficiency

- subacute combined degeneration of spinal cord
- dorsal column usually affected first (joint position, vibration) prior to distal paraesthesia

Peripheral neuropathy: demyelinating vs. axonal

Demyelinating pathology

- Guillain-Barre syndrome
- chronic inflammatory demyelinating polyneuropathy (CIDP)
- amiodarone
- hereditary sensorimotor neuropathies (HSMN) type I
- paraprotein neuropathy

Axonal pathology

- alcohol
- diabetes mellitus*
- vasculitis
- vitamin B12 deficiency*
- hereditary sensorimotor neuropathies (HSMN) type II

* may also cause a demyelinating picture

Pituitary apoplexy

Sudden enlargement of pituitary tumour secondary to haemorrhage or infarction

Features

- sudden onset headache similar to that seen in subarachnoid haemorrhage
- vomiting
- neck stiffness
- visual field defects: classically bitemporal superior quadrantic defect
- extraocular nerve palsies
- features of pituitary insufficiency e.g. Hypotension secondary to hypoadrenalism

Post-lumbar puncture headache

Headache following lumbar puncture (LP) occurs in approximately one-third of patients. The pathophysiology of is unclear but may relate to a 'leak' of CSF following dural puncture. Post-LP headaches are more common in young females with a low body mass index

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	Increased volume of CSF removed Bed rest following procedure Increased fluid intake post procedure Opening pressure of CSF Position of patient

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

Progressive supranuclear palsy

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

Management

- poor response to L-dopa

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

Restless legs syndrome

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
- uraemia
- diabetes mellitus
- pregnancy

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

Management

- simple measures: walking, stretching, massaging affected limbs
- treat any iron deficiency
- dopamine agonists are first-line treatment (e.g. Pramipexole, ropinirole)
- benzodiazepines
- gabapentin

Reye's syndrome

Reye's syndrome is a severe, progressive encephalopathy affecting children that is accompanied by 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

Although the prognosis has improved over recent years there is still a mortality rate of 15-25%.

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

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
- transverse myelitis e.g. HIV
- syringomyelia
- hereditary spastic paraplegia
- osteoarthritis of the cervical spine

Spinal cord compression

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

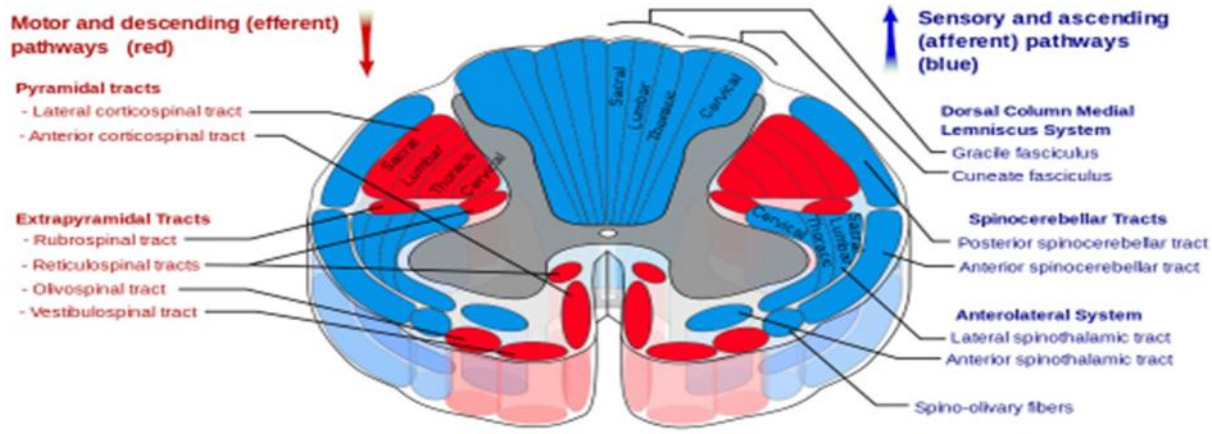
- back pain - the earliest and most common symptom - may be worse on lying down and coughing
- lower limb weakness
- sensory changes: sensory loss and numbness
- neurological signs depend on the level of the lesion. Lesions above L1 usually result in upper motor neuron signs in the legs and a sensory 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

Management

- high-dose oral dexamethasone
- urgent oncological assessment for consideration of radiotherapy or surgery

Spinal cord lesions

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



Motor lesions

Amyotrophic lateral sclerosis (motor neuron disease)

- affects both upper (corticospinal tracts) and lower motor neurons
- results in a combination of upper and lower motor neuron signs

Poliomyelitis

- affects anterior horns resulting in lower motor neuron signs

Combined motor and sensory lesions

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

Disorder	Tracts affected	Clinical notes
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) In addition cerebellar ataxia → other features e.g. intention tremor
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

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
Posterior cerebral artery	Contralateral homonymous hemianopia with macular sparing Visual agnosia
Weber's syndrome (branches of the posterior cerebral artery that supply the midbrain)	Ipsilateral CN III palsy Contralateral weakness of upper and lower extremity
Posterior inferior cerebellar artery (lateral medullary syndrome, Wallenberg syndrome)	Ipsilateral: facial pain and temperature loss Contralateral: limb/torso pain and temperature loss Ataxia, nystagmus

Site of the lesion	Associated effects
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

Lacunar strokes

- 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

Stroke: management

The Royal College of Physicians (RCP) published guidelines on the diagnosis and management of patients following a stroke in 2004. NICE also issued stroke guidelines in 2008, although they modified their guidance with respect to antiplatelet therapy in 2010.

Selected points relating to the management of acute stroke include:

- 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
- with regards to atrial fibrillation, the RCP state: 'anticoagulants should not be started until brain imaging has excluded haemorrhage, and usually not until 14 days have passed from the onset of an ischaemic stroke'
- if the cholesterol is > 3.5 mmol/l patients should be commenced on a statin. Many physicians will delay treatment until after at least 48 hours due to the risk of haemorrhagic transformation

Thrombolysis

Thrombolysis should only be given if:

- it is administered within 4.5 hours of onset of stroke symptoms (unless as part of a clinical trial)
- haemorrhage has been definitively excluded (i.e. Imaging has been performed)

Alteplase is currently recommended by NICE.

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 - Lumbar puncture in preceding 7 days - Gastrointestinal haemorrhage in preceding 3 weeks - Active bleeding - Pregnancy - 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

Secondary prevention

NICE also published a technology appraisal in 2010 on the use of clopidogrel and dipyridamole

Recommendations from NICE include:

- clopidogrel is now recommended by NICE ahead of combination use of aspirin plus modified release (MR) dipyridamole in people who have had an ischaemic stroke
- 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

With regards to carotid artery endarterectomy:

- recommend if patient has suffered stroke or TIA in the carotid territory and are not severely disabled
- should only be considered if carotid stenosis > 70% according ECST** criteria or > 50% according to NASCET*** criteria

*the 2009 Controlling hypertension and hypotension immediately post-stroke (CHHIPS) trial may change thinking on this but guidelines have yet to change to reflect this
**European Carotid Surgery Trialists' Collaborative Group
***North American Symptomatic Carotid Endarterectomy Trial

Stroke: types

The **Oxford Stroke Classification** (also known as the Bamford Classification) classifies strokes based on the initial symptoms. A summary is as follows:

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:
- 1. unilateral weakness (and/or sensory deficit) of face and arm, arm and leg or all three.
- 2. pure sensory stroke.
- 3. ataxic hemiparesis

Posterior circulation infarcts (POCI, c. 25%)

- involves vertebrobasilar arteries
- presents with 1 of the following:
- 1. cerebellar or brainstem syndromes
- 2. loss of consciousness
- 3. isolated homonymous hemianopia

Other recognised patterns of stroke:

Lateral medullary syndrome (posterior inferior cerebellar artery)

- aka Wallenberg's syndrome
- ipsilateral: ataxia, nystagmus, dysphagia, facial numbness, cranial nerve palsy e.g. Horner's
- contralateral: limb sensory loss

Weber's syndrome

- ipsilateral III palsy
- contralateral weakness

Subarachnoid haemorrhage

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
- trauma
- tumours

Investigations

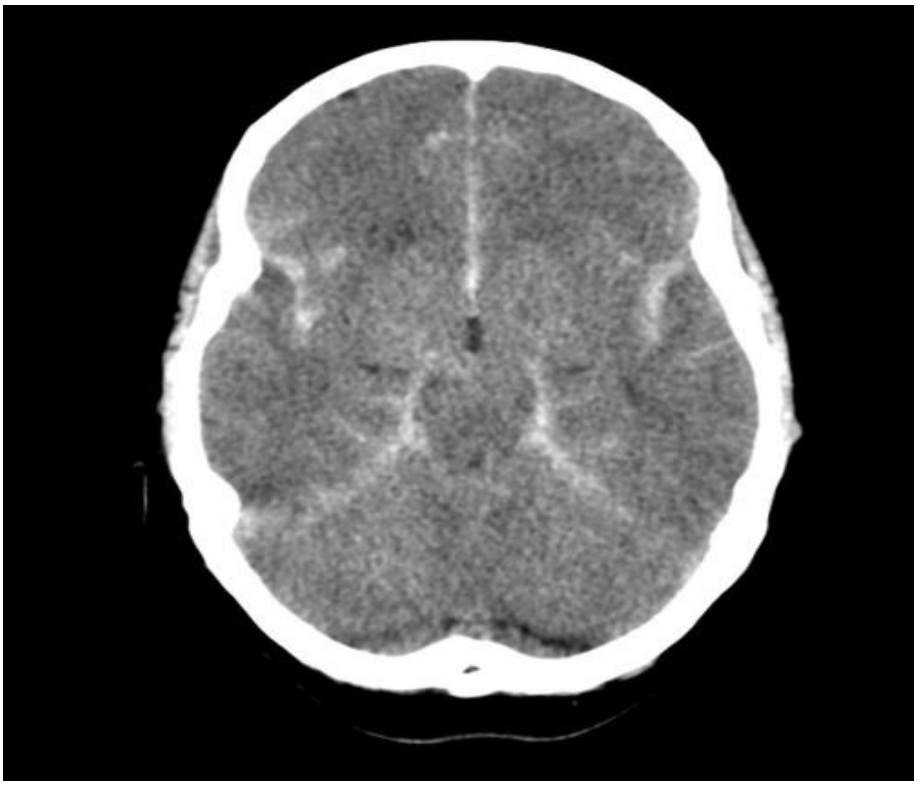
- CT: negative in 5%
- lumbar puncture: done after 12 hrs (allowing time for xanthochromia to develop)

Complications

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

Management

- neurosurgical opinion: no clear evidence over early surgical intervention against delayed intervention
- 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*



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.

*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

Subdural haemorrhage

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

Features

- headache
- classically fluctuating conscious level
- raised ICP

Treatment

- needs neurosurgical review ? burr hole

Syringomyelia

Overview

- development of cavity (syrinx) within the spinal cord
- if extends into medulla then termed syringobulbia
- strongly associated with the Arnold-Chiari malformation

Features

- maybe asymmetrical initially
- slowly progressives, possibly over years
- motor: wasting and weakness of arms
- sensory: spinothalamic sensory loss (pain and temperature)
- loss of reflexes, bilateral upgoing plantars
- also seen: Horner's syndrome

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* 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

Other causes include

- impacted ear wax
- chronic suppurative otitis media

*10% of patients may have a 'flamingo tinge', caused by hyperaemia

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)

Transient ischaemic attack

NICE issued updated guidelines relating to stroke and transient ischaemic attack (TIA) in 2008. They advocated the use of the ABCD2 prognostic score for risk stratifying patients who've had a suspected TIA:

	Criteria	Points
A	**A**ge >= 60 years	1
B	**B**lood pressure >= 140/90 mmHg	1
C	**C**linical 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

This gives a total score ranging from 0 to 7. People who have had a suspected TIA who are at a higher risk of stroke (that is, with an ABCD2 score of 4 or above) 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:

- 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.

Antithrombotic therapy

- clopidogrel is recommended first-line (as for patients who've had a stroke)
- aspirin + dipyridamole should be given to patients who cannot tolerate clopidogrel
- these recommendations follow the 2012 Royal College of Physicians National clinical guideline for stroke. Please see the link for more details (section 5.5)
- these guidelines may change following the CHANCE study (NEJM 2013;369:11). This study looked at giving high-risk TIA patients aspirin + clopidogrel for the first 90 days compared to aspirin alone. 11.7% of aspirin only patients had a stroke over 90 days compared to 8.2% of dual antiplatelet patients

With regards to carotid artery endarterectomy:

- recommend if patient has suffered stroke or TIA in the carotid territory and are not severely disabled
- should only be considered if carotid stenosis > 70% according ECST* criteria or > 50% according to NASCET** criteria

*European Carotid Surgery Trialists' Collaborative Group
**North American Symptomatic Carotid Endarterectomy Trial

Trigeminal neuralgia

Trigeminal neuralgia is a pain syndrome characterised by severe unilateral pain. The vast majority of cases are idiopathic but compression of the trigeminal roots by tumours or vascular problems may occur

The International Headache Society defines trigeminal neuralgia as:

- a 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

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

Tuberous sclerosis

Tuberous sclerosis (TS) is a genetic condition of autosomal dominant inheritance. Like neurofibromatosis, the majority of features seen in TS are neuro-cutaneous

Cutaneous features

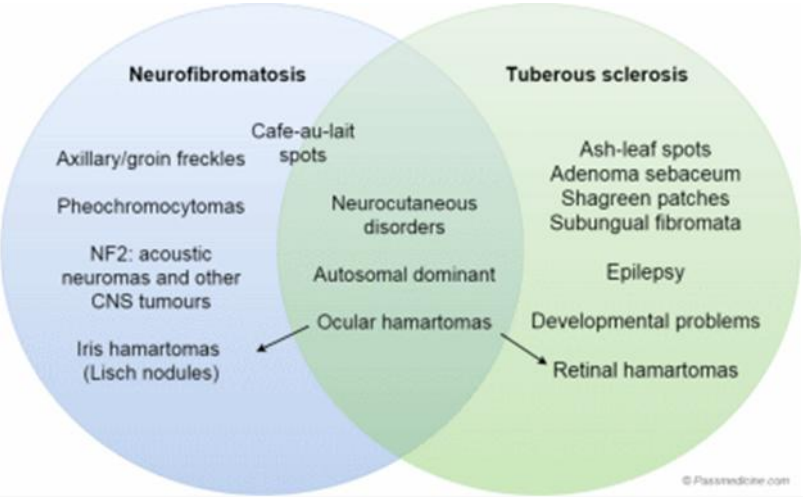
- depigmented 'ash-leaf' spots which fluoresce under UV light
- roughened patches of skin over lumbar spine (Shagreen patches)
- adenoma sebaceum (angiofibromas): butterfly distribution over nose
- fibromata beneath nails (subungual fibromata)
- café-au-lait spots* may be seen

Neurological features

- developmental delay
- epilepsy (infantile spasms or partial)
- intellectual impairment

Also

- retinal hamartomas: dense white areas on retina (phakomata)
- rhabdomyomas of the heart
- gliomatous changes can occur in the brain lesions
- polycystic kidneys, renal angiomyolipomata
- lymphangioleiomyomatosis: multiple lung cysts



Comparison of neurofibromatosis and tuberous sclerosis. Note that whilst they are both autosomal dominant neurocutaneous disorders there is little overlap otherwise

*these of course are more commonly associated with neurofibromatosis. However a 1998 study of 106 children with TS found café-au-lait spots in 28% of patients

Vigabatrin

Key points

- 40% of patients develop visual field defects, which may be irreversible
- visual fields should be checked every 6 months

Visual field defects

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

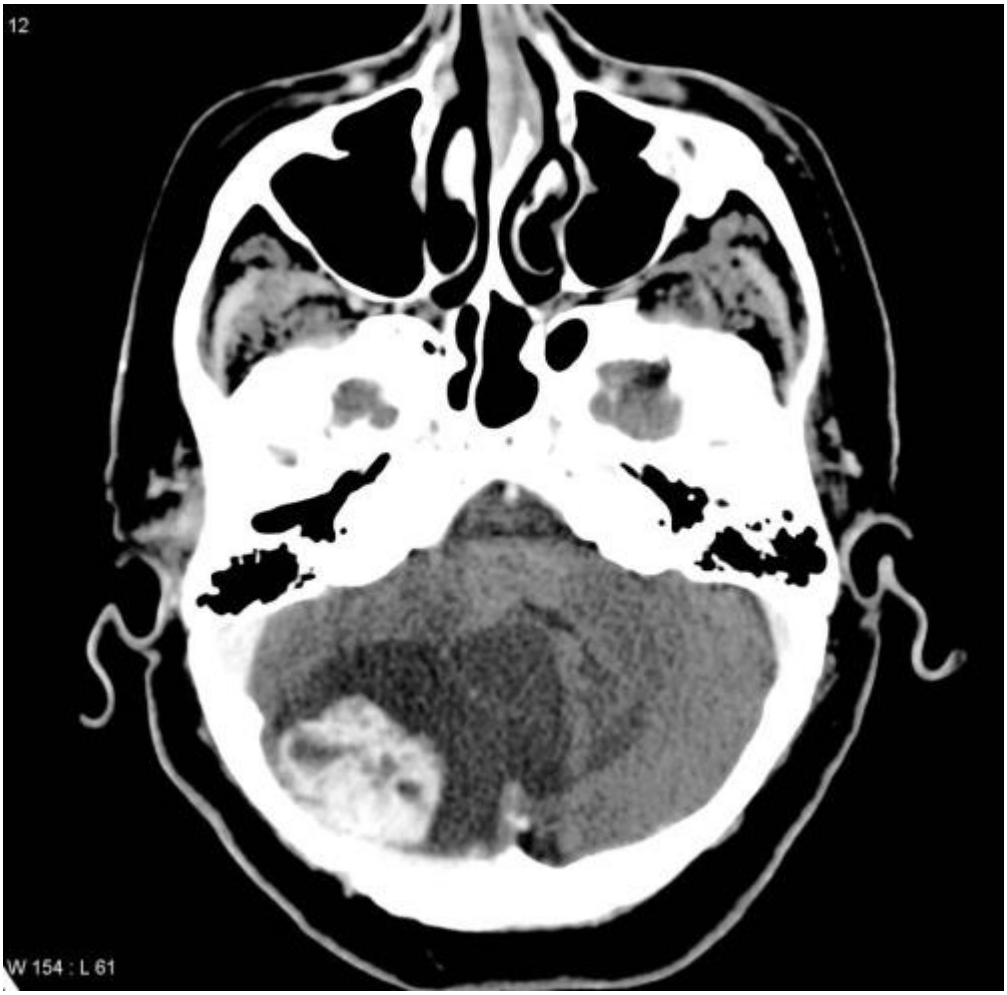
*this is very much the 'exam answer'. Actual studies suggest that the majority of quadrantanopias are caused by occipital lobe lesions. Please see the following link for more details.

Von Hippel-Lindau syndrome

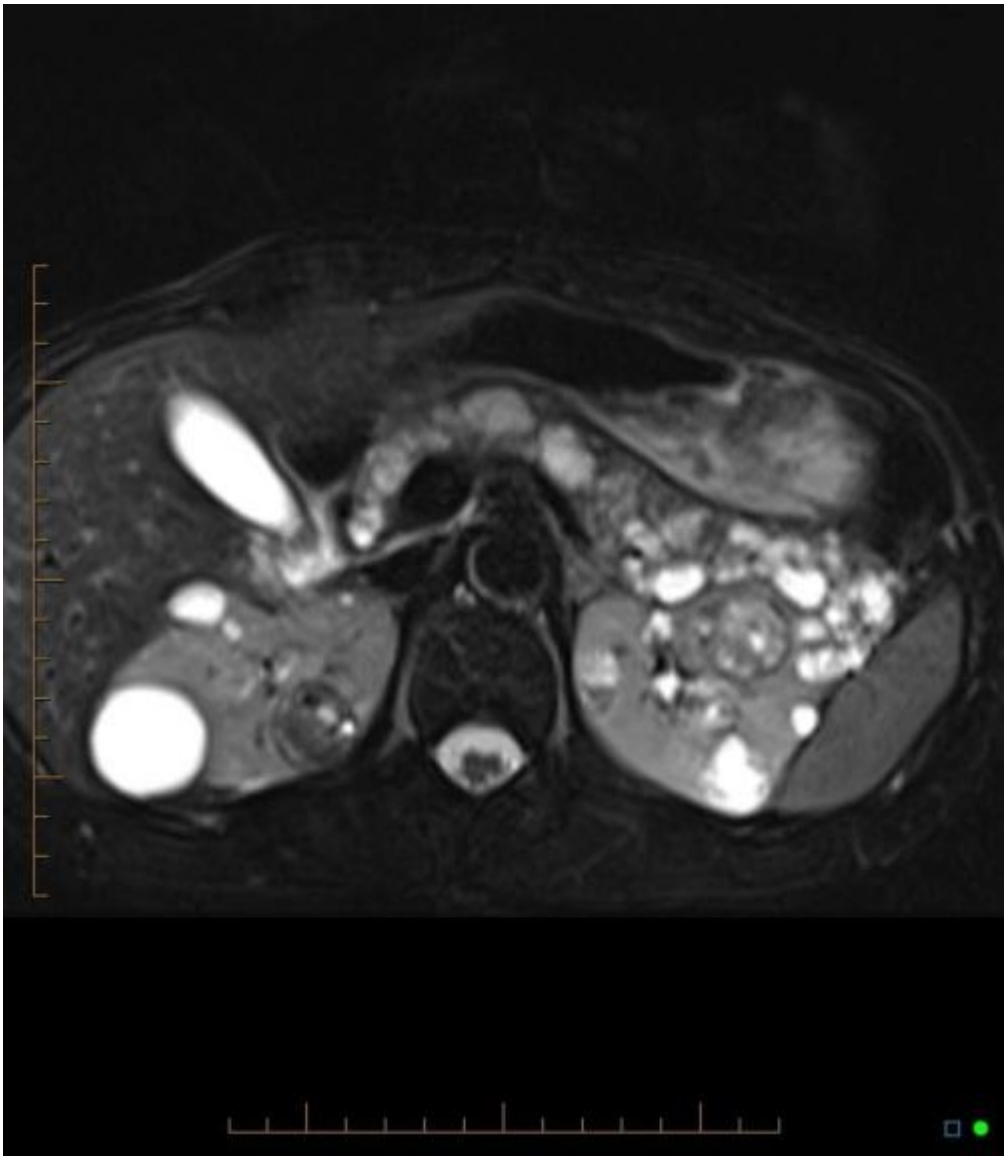
Von Hippel-Lindau (VHL) syndrome is an autosomal dominant condition predisposing to neoplasia. It is due to an abnormality in the VHL gene located on short arm of chromosome 3

Features

- cerebellar haemangiomas
- retinal haemangiomas: vitreous haemorrhage
- renal cysts (premalignant)
- phaeochromocytoma
- extra-renal cysts: epididymal, pancreatic, hepatic
- endolymphatic sac tumours



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.

Ophthalmology

Acute angle closure glaucoma

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
- lens growth associated with age

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
- corneal oedema results in dull or hazy cornea
- systemic upset may be seen, such as nausea and vomiting and even abdominal pain

Management

- urgent referral to an ophthalmologist
- management options include reducing aqueous secretions with acetazolamide and inducing pupillary constriction with topical pilocarpine

Age related 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.

Traditionally two forms of macular degeneration are seen:

- dry (geographic atrophy) macular degeneration: characterised by drusen - yellow round spots in Bruch's membrane
- 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

- 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. Straight lines may appear crooked or wavy
- 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

- NICE guidance suggests referring patients with suspected macular degeneration for ophthalmological assessment within 1 week
- 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

Dry macular degeneration - no current medical treatments

Wet macular degeneration

- photocoagulation
- photodynamic therapy
- anti-vascular endothelial growth factor (anti-VEGF) treatments: intravitreal ranibizumab

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

- pseudoxanthoma elasticum
- Ehler-Danlos syndrome
- Paget's disease
- sickle-cell anaemia
- acromegaly

Anterior uveitis

Anterior uveitis is one of the important differentials of a red eye. It is also referred to as iritis.

Features

- acute onset
- ocular discomfort & pain (may increase with use)
- pupil may be irregular and small
- photophobia (often intense)
- blurred vision
- red eyes
- lacrimation
- ciliary flush
- hypopyon; describes pus and inflammatory cells in the anterior chamber, often resulting in a visible fluid level
- visual acuity initially normal → impaired

Associated conditions

- ankylosing spondylitis
- reactive arthritis
- ulcerative colitis, Crohn's disease
- Behcet's disease

Management

- urgent review by ophthalmology
- cycloplegics (dilates the pupil which helps to relieve pain and photophobia) e.g. Atropine, cyclopentolate
- steroid eye drops

Argyll-Robertson pupil

Argyll-Robertson pupil is one of the classic pupillary syndrome. It is sometimes seen in neurosyphilis and is often said to be 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

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*
- artificial tears may be given for symptom relief in people with dry eyes or an abnormal tear film

*an alternative is sodium bicarbonate, a teaspoonful in a cup of cooled water that has recently been boiled

Cataracts

Majority

- age related
- UV light

Systemic

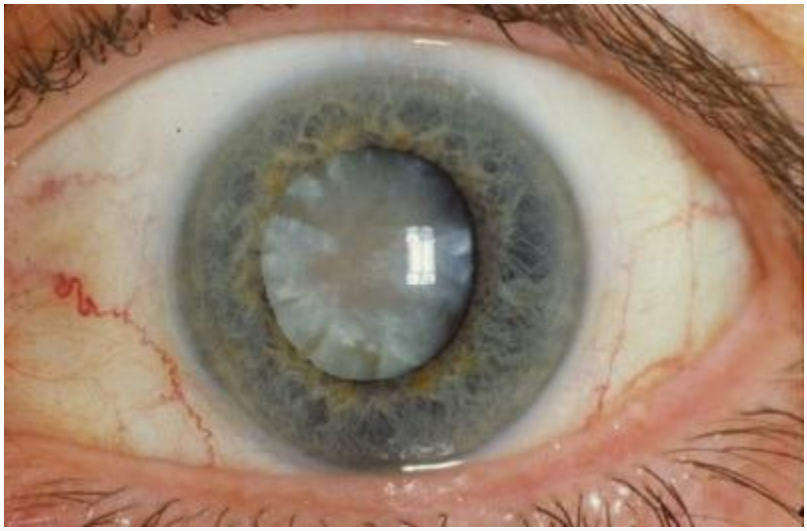
- diabetes mellitus
- steroids
- infection (congenital rubella)
- metabolic (hypocalcaemia, galactosaemia)
- myotonic dystrophy, Down's syndrome

Ocular

- trauma
- uveitis
- high myopia
- topical steroids

Classification

- Nuclear: change lens refractive index, common in old age
- Polar: localized, commonly inherited, lie in the visual axis
- Subcapsular: due to steroid use, just deep to the lens capsule, in the visual axis
- Dot opacities: common in normal lenses, also seen in diabetes and myotonic dystrophy



A hypermature age-related cortico-nuclear cataract with a brunescent (brown) nucleus. Credit National Eye Institute, National Institutes of Health.

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. This must occur in the absence of any other significant neuropsychiatric disturbance.

Risk factors include:

- Advanced age
- Peripheral visual impairment
- Social isolation
- Sensory deprivation
- Early cognitive impairment

CBS is equally distributed between sexes and does not show any familial predisposition. The most common ophthalmological conditions associated with this syndrome are age-related macular degeneration, followed by glaucoma and cataract.

Well-formed complex visual hallucinations are thought to occur in 10-30 percent of individuals with severe visual impairment. Prevalence of CBS in visually impaired people is thought to be between 11 and 15 percent.

Around a third find the hallucinations themselves an unpleasant or disturbing experience. 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).

Cox (2014) Negative outcome Charles Bonnet Syndrome. Br J Ophthalmol.

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

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

Holmes-Adie pupil

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
- once the pupil has constricted it remains small for an abnormally long time
- slowly reactive to accommodation but very poorly (if at all) to light

Holmes-Adie syndrome

- association of Holmes-Adie pupil with absent ankle/knee reflexes

Homocystinuria

Homocystinuria is a rare autosomal recessive disease caused by deficiency of cystathionine beta synthase. This results in an accumulation of homocysteine which is then oxidized to homocystine.

Features

- often patients have fine, fair hair
- musculoskeletal: may be similar to Marfan's - arachnodactyly etc
- neurological patients may have learning difficulties, seizures
- ocular: downwards (inferonasal) dislocation of lens
- increased risk of arterial and venous thromboembolism
- also malar flush, livedo reticularis

Diagnosis is made by the cyanide-nitroprusside test, which is also positive in cystinuria

Treatment is vitamin B6 (pyridoxine) supplements

Keratitis

Keratitis describes inflammation of the cornea. There are a variety of causes:

Features

- red eye: pain and erythema
- photophobia
- foreign body, gritty sensation
- hypopyon may be seen

Infective

- viral: herpes simplex keratitis
- bacterial: typically *Staphylococcus aureus*. *Pseudomonas aeruginosa* is seen in contact lens wearers
- 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)

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 is with 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

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, cocaine
- anticholinergic drugs: tricyclic antidepressants

Optic atrophy

Optic atrophy is seen as pale, well demarcated disc on fundoscopy. It is usually bilateral and causes a gradual loss of vision*. 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
- DIDMOAD - the association of cranial Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness (also known as Wolfram's syndrome)

*strictly speaking optic atrophy is a descriptive term, it is the optic neuropathy that results in visual loss

Optic neuritis

Causes

- multiple sclerosis
- diabetes
- syphilis

Features

- unilateral decrease in visual acuity over hours or days
- poor discrimination of colours, 'red desaturation'
- pain worse on eye movement
- relative afferent pupillary defect
- central scotoma

Management

- high-dose steroids
- recovery usually takes 4-6 weeks

Prognosis

- MRI: if > 3 white-matter lesions, 5-year risk of developing multiple sclerosis is c. 50%

Primary open-angle glaucoma

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

Primary open-angle glaucoma (POAG, also referred to as chronic simple glaucoma) is present in around 2% of people older than 40 years. Other than age, risk factors include:

- family history
- black patients
- myopia
- hypertension
- diabetes mellitus

POAG may present insidiously and for this reason is often detected during routine optometry appointments. Features may include

- peripheral visual field loss - nasal scotomas progressing to 'tunnel vision'
- decreased visual acuity
- optic disc cupping

Primary open-angle glaucoma: management

The majority of patients with primary open-angle glaucoma are managed with eye drops. These aim to lower intra-ocular pressure which in turn has been shown to prevent progressive loss of visual field.

Medication	Mode of action	Notes
Prostaglandin analogues (e.g. Latanoprost)	Increases uveoscleral outflow	Once daily administration Adverse effects include 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

Surgery in the form of a trabeculectomy may be considered in refractory cases.

Red eye

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

Scleritis

- severe pain (may be worse on movement) and tenderness
- may be underlying autoimmune disease e.g. rheumatoid arthritis

Conjunctivitis

- purulent discharge if bacterial, clear discharge if viral

Subconjunctival haemorrhage

- history of trauma or coughing bouts

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

Retinitis pigmentosa

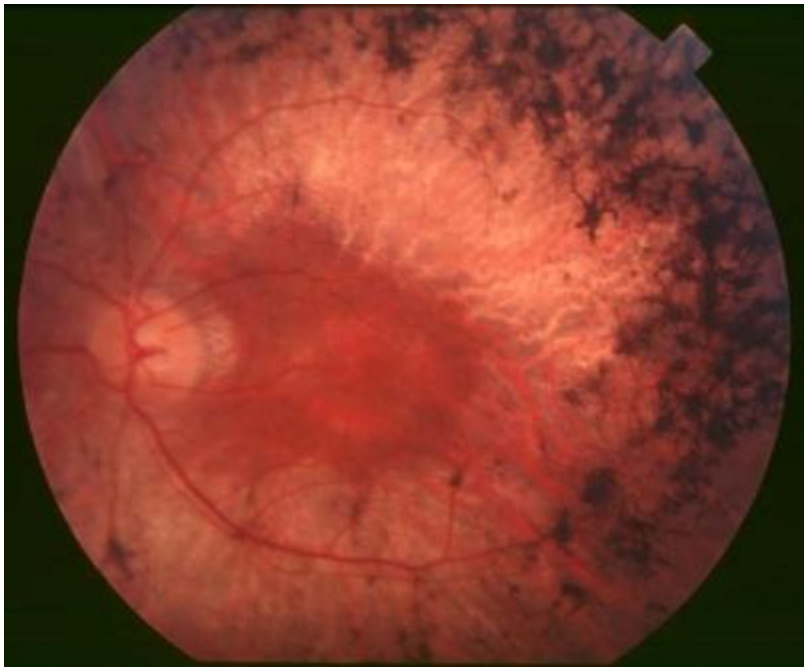
Retinitis pigmentosa primarily affects the peripheral retina resulting in tunnel vision

Features

- night blindness is often the initial sign
- tunnel vision due to loss of the peripheral retina (occasionally referred to as funnel 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



Fundus showing changes secondary to retinitis pigmentosa

Rheumatoid arthritis: ocular manifestations

Ocular manifestations of rheumatoid arthritis are common, with 25% of patients having eye problems

Ocular manifestations

- keratoconjunctivitis sicca (most common)
- episcleritis (erythema)
- scleritis (erythema and pain)
- corneal ulceration
- keratitis

Iatrogenic

- steroid-induced cataracts
- chloroquine retinopathy

Sudden painless loss of vision

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

- incidence increases with age, more common than arterial occlusion
- causes: glaucoma, polycythaemia, hypertension
- severe retinal haemorrhages are usually seen on fundoscopy

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

Vitreous haemorrhage

- causes: diabetes, bleeding disorders
- 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	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 Moderate bleeds may be described as numerous dark spots Small bleeds may cause floaters

Third nerve palsy

Features

- eye is deviated 'down and out'
- ptosis
- pupil may be dilated (sometimes called a 'surgical' third nerve palsy)

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

*this term is usually associated with sixth nerve palsies but it may be used for a variety of neurological presentations

Tunnel vision

Tunnel vision is the concentric diminution of the visual fields

Causes

- papilloedema
- glaucoma
- retinitis pigmentosa
- choroidoretinitis
- optic atrophy secondary to tabes dorsalis
- hysteria

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 ophthalmoplegia/nystagmus, ataxia and confusion may occur. 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

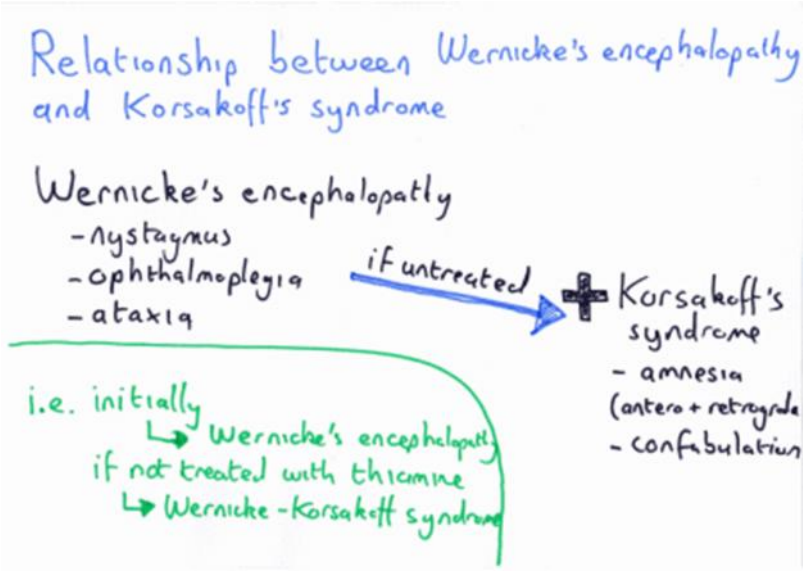
Investigations

- decreased red cell transketolase
- MRI

Treatment is with urgent replacement of thiamine

Relationship with Korsakoff 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.



Psychiatry

Alcohol withdrawal

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

Management

- benzodiazepines
- carbamazepine also effective in treatment of alcohol withdrawal
- phenytoin is said not to be as effective in the treatment of alcohol withdrawal seizures

Anorexia nervosa

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

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

The prognosis of patients with anorexia nervosa remains poor. Up to 10% of patients will eventually die because of the disorder.

Anorexia nervosa: features

Anorexia nervosa is associated with a number of characteristic clinical signs and physiological abnormalities which are summarised below

Features

- reduced body mass index
- bradycardia
- hypotension
- enlarged salivary glands

Physiological abnormalities

- hypokalaemia
- low FSH, LH, oestrogens and testosterone
- raised cortisol and growth hormone
- impaired glucose tolerance
- hypercholesterolaemia
- hypercarotinaemia
- low T3

Aphonia

Aphonia describes the inability to speak. Causes include:

- recurrent laryngeal nerve palsy (e.g. Post-thyroidectomy)
- psychogenic

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)

Bulimia nervosa

Bulimia nervosa is a type of eating disorder characterised by episodes of binge eating followed by intentional vomiting

Management

- referral for specialist care is appropriate in all cases
- cognitive behaviour therapy (CBT) is currently consider first-line treatment
- interpersonal psychotherapy is also used but takes much longer than CBT
- pharmacological treatments have a limited role - a trial of high-dose fluoxetine is currently licensed for bulimia but long-term data is lacking

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

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.

De Clerambault's syndrome

De Clerambault'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.

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

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

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. However, having some understanding of the potential stages a person may go through whilst grieving can help determine whether a patient is having a 'normal' grief reaction or is developing a more significant problem.

One of the most popular models of grief divides it into 5 stages.

- 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
- Anger: this is commonly directed against other family members and medical professionals
- Bargaining
- Depression
- Acceptance

It should be noted that many patients will not go through all 5 stages.

Abnormal, or atypical, grief reactions are more likely to occur in women and if the death is sudden and unexpected. Other risk factors include a problematic relationship before death or 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

Hypomania vs. mania

The presence of psychotic symptoms differentiates mania from hypomania

Psychotic symptoms

- delusions of grandeur
- auditory hallucinations

The following symptoms are common to both hypomania and mania

Mood

- predominately elevated
- irritable

Speech and thought

- pressured
- flight of ideas
- poor attention

Behaviour

- insomnia
- loss of inhibitions: sexual promiscuity, overspending, risk-taking
- increased appetite

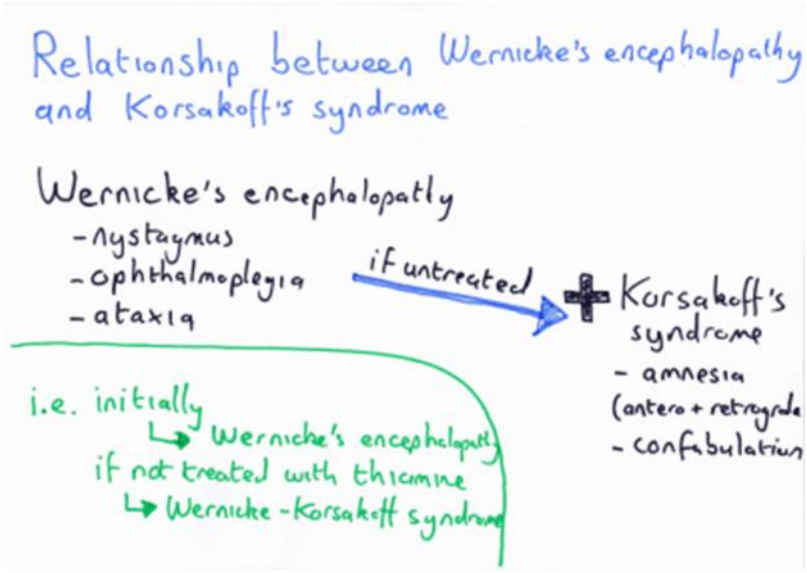
Korsakoff's syndrome

Overview

- marked memory disorder often seen in alcoholics
- thiamine deficiency causes damage and haemorrhage to the mammillary bodies of the hypothalamus and the medial thalamus
- in often follows on from untreated Wernicke's encephalopathy

Features

- anterograde amnesia: inability to acquire new memories
- retrograde amnesia
- confabulation



Othello's syndrome

Othello's syndrome is pathological jealousy where a person is convinced their partner is cheating on them without any real proof. This is accompanied by socially unacceptable behaviour linked to these claims.

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) 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 doe 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

Disorder	Features
	) 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) 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

Disorder	Features
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
Schizotypal	⟩ Ideas of reference (differ from delusions in that some insight is retained) ⟩ Odd beliefs and magical thinking ⟩ Unusual perceptual disturbances

Disorder	Features
	• Paranoid ideation and suspiciousness • Odd, eccentric behaviour • Lack of close friends other than family members • Inappropriate affect • Odd speech without being incoherent

Post-concussion syndrome

Post-concussion syndrome is seen after even minor head trauma

Typical features include

- headache
- fatigue
- anxiety/depression
- dizziness

Post-partum mental health problems

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

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

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

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: 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*:

- 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
- negative symptoms: incongruity/blunting of affect, anhedonia (inability to derive pleasure), alogia (poverty of speech), avolition (poor motivation)

*occasionally referred to as thought alienation

Schizophrenia: 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

NICE published guidelines on the management of schizophrenia in 2009.

Key points:

- 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)

Seasonal affective disorder

Seasonal affective disorder (SAD) describes depression which occurs predominately around the winter months. SAD should be treated the same way as depression, therefore as per the NICE guidelines for mild depression, you would begin with psychological therapies and follow up with the patient in 2 weeks to ensure that there has been no deterioration. Following this an SSRI can be given if needed. In seasonal affective disorder, you should not give the patient sleeping tablets as this can make the symptoms worse. Finally, the evidence for light therapy is limited and as such it is not routinely recommended.

Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are considered first-line treatment for the majority of patients with depression.

- citalopram (although see below re: 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
- 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 for increased anxiety and agitation after starting a SSRI
- fluoxetine and paroxetine have a higher propensity for drug interactions

Citalopram and the QT interval

- the Medicines and Healthcare products Regulatory Agency (MHRA) released a warning on the use of citalopram in 2011
- it advised that 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

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.

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.

Discontinuation symptoms

- increased mood change
- restlessness
- difficulty sleeping
- unsteadiness
- sweating
- gastrointestinal symptoms: pain, cramping, diarrhoea, vomiting
- paraesthesia

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

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

Tricyclic antidepressants

Tricyclic antidepressants (TCAs) are used less commonly now for depression due to their side-effects and toxicity in overdose. They are however used widely in the treatment of neuropathic pain, where smaller doses are typically required.

Common side-effects

- drowsiness
- dry mouth
- blurred vision
- constipation
- urinary retention

Choice of tricyclic

- low-dose amitriptyline is commonly used in the management of neuropathic pain and the prophylaxis of headache (both tension and migraine)
- lofepramine has a lower incidence of toxicity in overdose
- amitriptyline and dosulepin (dothiepin) are considered the most dangerous in overdose

More sedative	Less sedative
Amitriptyline Clomipramine Dosulepin Trazodone*	Imipramine Lofepramine Nortriptyline

*trazodone is technically a 'tricyclic-related antidepressant'

Unexplained symptoms

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

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

Respiratory medicine

Allergic bronchopulmonary aspergillosis

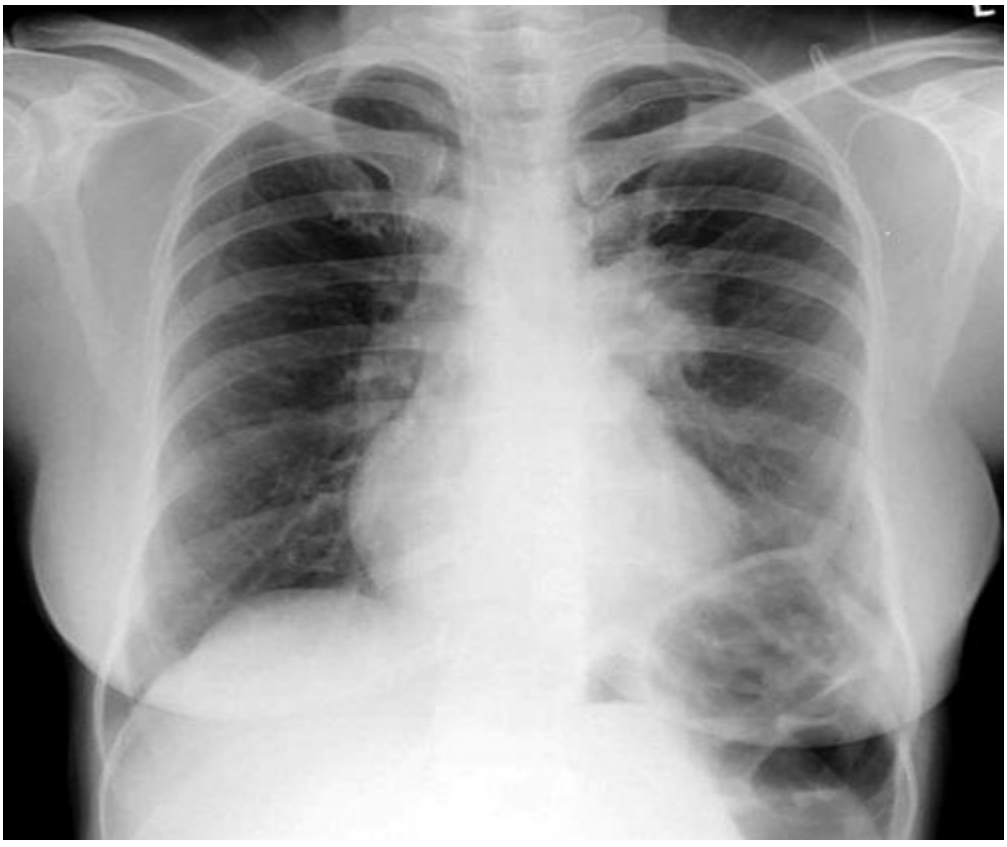
Allergic bronchopulmonary aspergillosis results from an allergy to Aspergillus spores. In the exam questions often give a history of bronchiectasis and eosinophilia.

Features

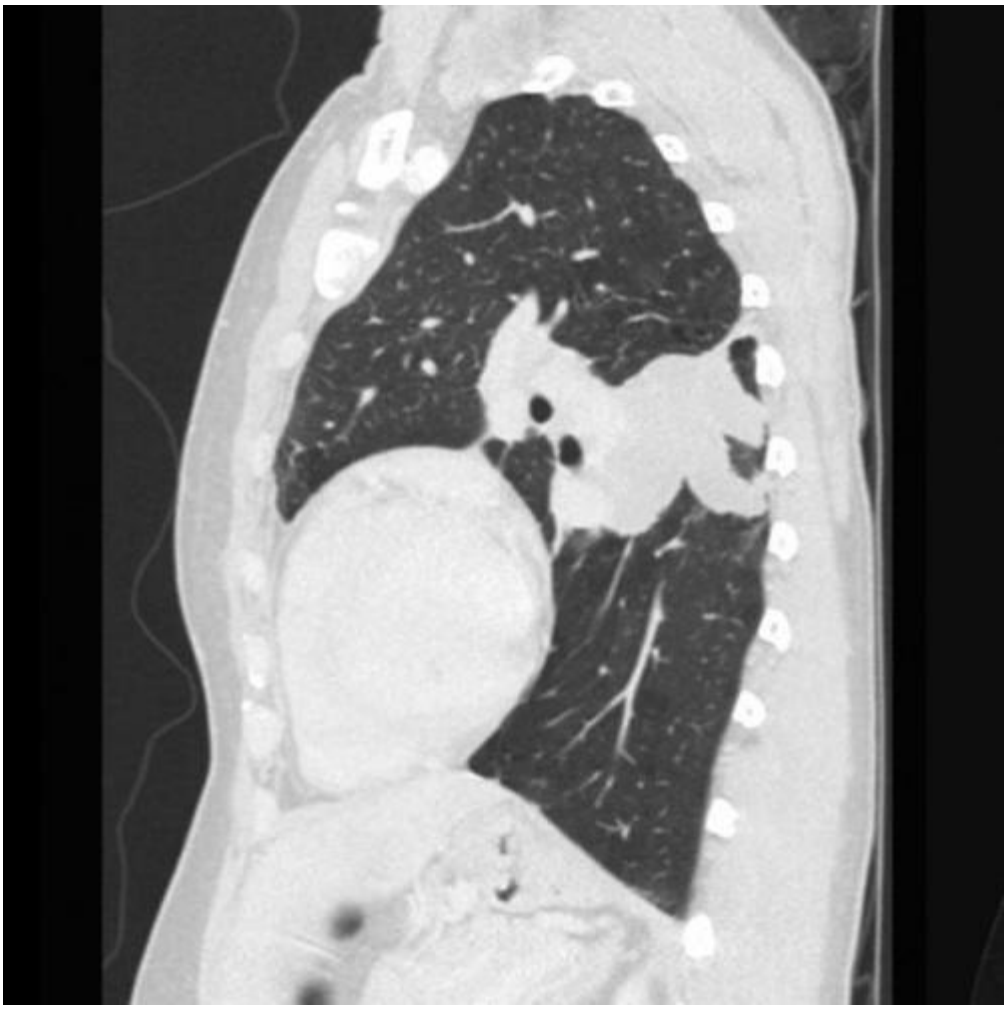
- bronchoconstriction: wheeze, cough, dyspnoea
- bronchiectasis (proximal)

Investigations

- eosinophilia
- flitting CXR changes
- positive radioallergosorbent (RAST) test to Aspergillus
- positive IgG precipitins (not as positive as in aspergilloma)
- raised IgE



Chest x-ray of a 40-year-old woman with ABPA demonstrating a mass overlying the left hilum. In the right upper parahilar region a few ring shadow / tram track opacities are also noted, suggestive of bronchiectasis



CT scan from the same patient. CT reveals a branching lesion in the superior segment of the left lower lobe with classic finger in glove appearance which represents of mucous filling dilated bronchi (i.e. bronchocoeles). Bronchocoeles are a common feature of allergic bronchopulmonary aspergillosis (ABPA)

Management

- steroids
- itraconazole is sometimes introduced as a second line agent

Alpha-1 antitrypsin deficiency

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 role of A1AT is to protect cells from enzymes such as neutrophil elastase.

Genetics

- located on chromosome 14
- inherited in an autosomal recessive / co-dominant fashion*
- alleles classified by their electrophoretic mobility - M for normal, S for slow, and Z for very slow
- normal = PiMM
- homozygous PiSS (50% normal A1AT levels)
- homozygous PiZZ (10% normal A1AT levels)

Features

- patients who manifest disease usually have PiZZ genotype
- lungs: panacinar emphysema, most marked in lower lobes
- liver: cirrhosis and hepatocellular carcinoma in adults, cholestasis in children

Investigations

- A1AT concentrations

Management

- no smoking
- supportive: bronchodilators, physiotherapy
- intravenous alpha1-antitrypsin protein concentrates
- surgery: volume reduction surgery, lung transplantation

*trusted sources are split on which is a more accurate description

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)

Urinary tract

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

Skin

Condition	Recommended treatment
Impetigo	Topical fusidic acid, oral flucloxacillin or erythromycin if widespread
Cellulitis	Flucloxacillin (clarithromycin or clindomycin if penicillin-allergic)
Erysipelas	Phenoxymethylpenicillin (erythromycin if penicillin-allergic)
Animal or human bite	Co-amoxiclav (doxycycline + metronidazole if penicillin-allergic)
Mastitis during breast-feeding	Flucloxacillin

Ear, nose & throat

Condition	Recommended treatment
Throat infections	Phenoxymethylpenicillin (erythromycin alone if penicillin-allergic)
Sinusitis	Amoxicillin or doxycycline or erythromycin
Otitis media	Amoxicillin (erythromycin if penicillin-allergic)
Otitis externa*	Flucloxacillin (erythromycin if penicillin-allergic)
Periapical or periodontal abscess	Amoxicillin

Condition	Recommended treatment
Gingivitis: acute necrotising ulcerative	Metronidazole

Genital system

Condition	Recommended treatment
Gonorrhoea	Intramuscular ceftriaxone + oral azithromycin
Chlamydia	Doxycycline or azithromycin
Pelvic inflammatory disease	Oral ofloxacin + oral metronidazole or intramuscular ceftriaxone + oral doxycycline + oral metronidazole
Syphilis	Benzathine benzylpenicillin or doxycycline or erythromycin
Bacterial vaginosis	Oral or topical metronidazole or topical clindamycin

Gastrointestinal

Condition	Recommended treatment
Clostridium difficile	First episode: metronidazole Second or subsequent episode of infection: vancomycin
Campylobacter enteritis	Clarithromycin
Salmonella (non-typhoid)	Ciprofloxacin
Shigellosis	Ciprofloxacin

*a combined topical antibiotic and corticosteroid is generally used for mild/moderate cases of otitis externa

ARDS

Basics

- acute respiratory distress syndrome
- caused by increased permeability of alveolar capillaries leading to fluid accumulation in alveoli i.e. non-cardiogenic pulmonary oedema

Criteria (American-European Consensus Conference)

- acute onset
- bilateral infiltrates on CXR
- non-cardiogenic (pulmonary artery wedge pressure needed if doubt)
- pO2/FiO2 < 200 mmHg

Causes

- infection: sepsis, pneumonia
- massive blood transfusion
- trauma
- smoke inhalation
- pancreatitis
- cardio-pulmonary bypass

Asbestos and the lung

Asbestos can cause a variety of lung disease from benign pleural plaques to mesothelioma.

Pleural plaques

Pleural plaques are benign and do not undergo malignant change. They are the most common form of asbestos related lung disease and generally occur after a latent period of 20-40 years.

Pleural thickening

Asbestos exposure may cause diffuse pleural thickening in a similar pattern to that seen following an empyema or haemothorax. The underlying pathophysiology is not fully understood.

Asbestosis

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. The latent period is typically 15-30 years. 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.

Mesothelioma

Mesothelioma is a malignant disease of the pleura. Crocidolite (blue) asbestos is the most dangerous form.

Possible features

- progressive shortness-of-breath
- chest pain
- pleural effusion

Patients are usually offered palliative chemotherapy and there is also a limited role for surgery and radiotherapy. Unfortunately the prognosis is very poor, with a median survival from diagnosis of 8-14 months.

Lung cancer

Asbestos exposure is a risk factor for lung cancer and also has a synergistic effect with cigarette smoke.

Aspergilloma

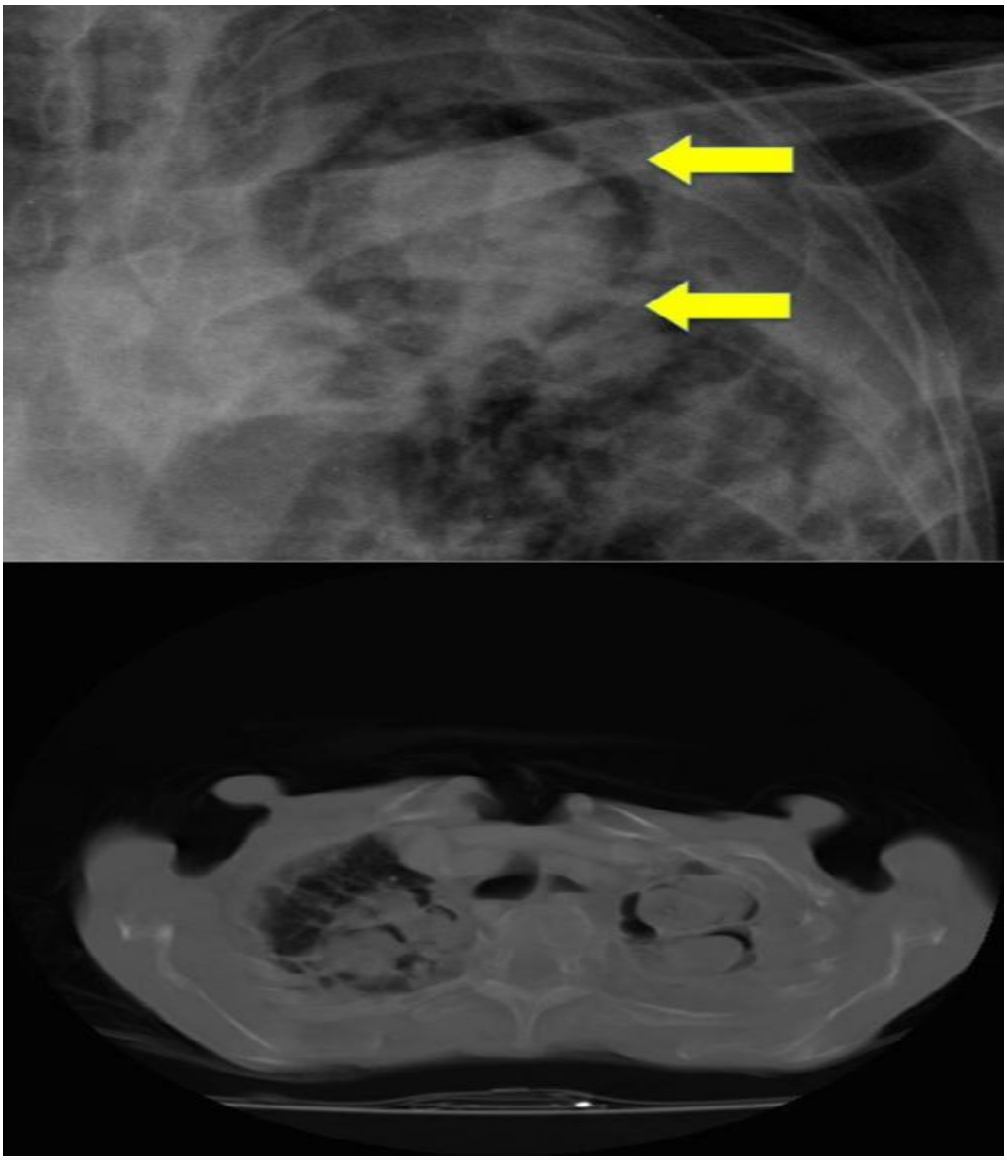
An aspergilloma is a mycetoma (mass-like fungus ball) which often colonises an existing lung cavity (e.g. secondary to tuberculosis, lung cancer or cystic fibrosis)

Usually asymptomatic but features may include

- cough
- haemoptysis (may be severe)

Investigations

- chest x-ray containing a rounded opacity
- high titres Aspergillus precipitins



Aspergilloma in a patient with cavities secondary to previous tuberculosis infection. The close-up CXR and CT scan from the same patient demonstrate a rounded soft tissue attenuating masses located in a surrounding cavity.

Asthma: acute severe

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% Silent chest, cyanosis or feeble 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.

British Thoracic Society guidelines

- magnesium sulphate recommended as next step for patients who are not responding (e.g. 1.2 - 2g IV over 20 mins)
- little evidence to support use of IV aminophylline (although still mentioned in management plans)
- if no response consider IV salbutamol

Asthma: diagnosis

The British Thoracic Society (BTS) updated their asthma guidelines in 2016 resulting in some significant changes in how asthma is diagnosed and managed.

The diagnosis of asthma remains clinical, based on a combination of history, examination and investigation results. **There is no one definitive test and the combination of findings results in a high, intermediate or low probability of asthma**.

There are a number of respiratory symptoms which should make you consider asthma as a diagnosis. The guidelines remind us that the predictive value of individual symptoms or signs is poor.

- wheeze
- cough
- breathlessness
- chest tightness

Once a diagnosis is being considered, a combination of history, examination and investigation results should be used to determine whether a patient has a high, intermediate or low probability of asthma. Factors which should be considered include:

- **recurrent episodes of symptoms**: may be triggered by viral infection, allergen exposure, NSAIDs/beta-blockers and/or exacerbated by exercise, cold air and emotion/laughter in children
- **recorded observation of wheeze**: due to varying use of language this usually means wheeze documented by a clinician
- **symptom variability**: asthma is generally worse at night or early in the morning
- **personal history of atopy**: e.g. eczema/allergic rhinitis
- **absence of symptoms of alternative diagnosis**: e.g. COPD, dysfunctional breathing or obesity*
- **historical record of variable peak flows or FEV_1**

At this point, **the guidelines do not make specific recommendations about who is considered to have a high, medium or low probability of asthma**. It is now recommended that we make a clinical judgement about likelihood, which probably better reflects day-to-day practice.

If a patient has a **high** probability of asthma:

- treatment should be initiated (typically 6 weeks of inhaled corticosteroid)
- an assessment should be made about whether the patient has responded to treatment using either a validated scoring system or lung functions tests (FEV_1at clinic visits or by domiciliary serial peak flows)
- a good response to treatment is clearly supportive of an asthma diagnosis, a poor response should prompt tests for airway obstruction with spirometry and bronchodilator reversibility

If a patient has a **intermediate** probability of asthma:

- tests for airway obstruction with spirometry and bronchodilator reversibility should be undertaken
- if a child is too young to perform spirometry the BTS recommend we consider watchful waiting if the child is asymptomatic, or offer a carefully monitored trial of treatment if the child is symptomatic

If a patient has a **low** probability of asthma:

- investigations should continue looking for alternative causes of the presenting symptoms
- if other diagnoses considered unlikely then investigations for asthma should be arranged, including spirometry and bronchodilator reversibility

Reasons for referring to secondary care include:

- if the diagnosis remains unclear despite investigations
- suspected occupational asthma
- poor response to treatment
- a severe or life-threatening asthma attack
- there are other 'red-flags' which may indicate more severe disease or alternative diagnosis such as systemic features (weight loss, fever etc), failure to thrive in children, focal signs, chronic sputum production etc. Please see the guidelines for the full list

Once a diagnosis of asthma has been made all patients (or parents/carers) should be offered self-management education including a written personalised asthma action plan

- in adults, these may be based on symptoms/peak flows whereas in children symptom-based plans are preferred

*in the extended guidelines the BTS state some of the symptoms/factors which may point to an alternative diagnosis. Please see the guidelines for the full list:

Clinical clue	Possible diagnosis
Predominant cough without lung function abnormalities	Chronic cough syndromes; pertussis
Prominent dizziness, light-headedness, peripheral tingling	Dysfunctional breathing
Recurrent severe asthma attacks without objective confirmatory evidence	Vocal cord dysfunction
Predominant nasal symptoms without lung function abnormalities	Rhinitis
Postural and food-related symptoms, predominant cough	Gastro-oesophageal reflux
Orthopnoea, paroxysmal nocturnal dyspnoea, peripheral oedema, preexisting cardiac disease	Cardiac failure
Crackles on auscultation	Pulmonary fibrosis
Significant smoking history (ie, >30 pack-years), age of onset >35 years	COPD
Chronic productive cough in the absence of wheeze or breathlessness	Bronchiectasis; inhaled foreign body; obliterative bronchioitis; large airway stenosis
New onset in smoker, systemic symptoms, weight loss, haemoptysis	Lung cancer; sarcoidosis

Asthma: management in adults

The British Thoracic Society (BTS) updated their asthma guidelines in 2016 resulting in some significant changes in how asthma is diagnosed and managed. In terms of management, some of the key changes include:

- the previous numbered steps have been abandoned
- all patients should receive an inhaled corticosteroid, right from the point of assessment in patients with suspected asthma
- a combined inhaled corticosteroid/long-acting beta agonist (ICS/LABA) is recommended instead of separate inhalers to increase compliance
- a long-acting muscarinic antagonist (LAMA) is an options for patient who haven't responded to a combined ICS/LABA inhaler

In terms of management, the BTS suggest the following approach:

- 1. Start treatment at the level most appropriate to initial severity
- 2. Achieve early control
- 3. Maintain control by increasing treatment as necessary and decreasing treatment when control is good

The previous steps 1-5 of asthma management have been abandoned. Previously 'Step 1' of asthma management was the use of a short-acting beta agonist (SABA) as required. This is no longer suggested as the initial first step. Instead, **all patients from the 'diagnosis and assessment' onwards should use a SABA as required**. Having to use a SABA more than **3 times per week** is considered a sign that further add-on therapy is needed.

Initial step

It is now recommended that a low-dose inhaled corticosteroid (ICS) is started in all patients with a diagnosis, or suspected diagnosis, of asthma, right from the 'diagnosis and assessment' period prior to a formal diagnosis being made. **The first step of asthma management is now a low-dose inhaled corticosteroid in combination with a short-acting beta agonist**.

Next step.

The **a long-acting beta agonist (LABA)**. This should ideally be in the form of a **combination inhaler**.

Next step..

If poor control remains the next step depends on the response to the LABA:

- no response to LABA - stop LABA and increase dose of ICS to medium-dose
- response to LABA - continue LABA and increase ICS to medium-dose. An alternative to this is to continue on the current treatment but consider a trial of a leukotriene receptor antagonist, SR theophylline or a long-acting muscarinic antagonist (LAMA)

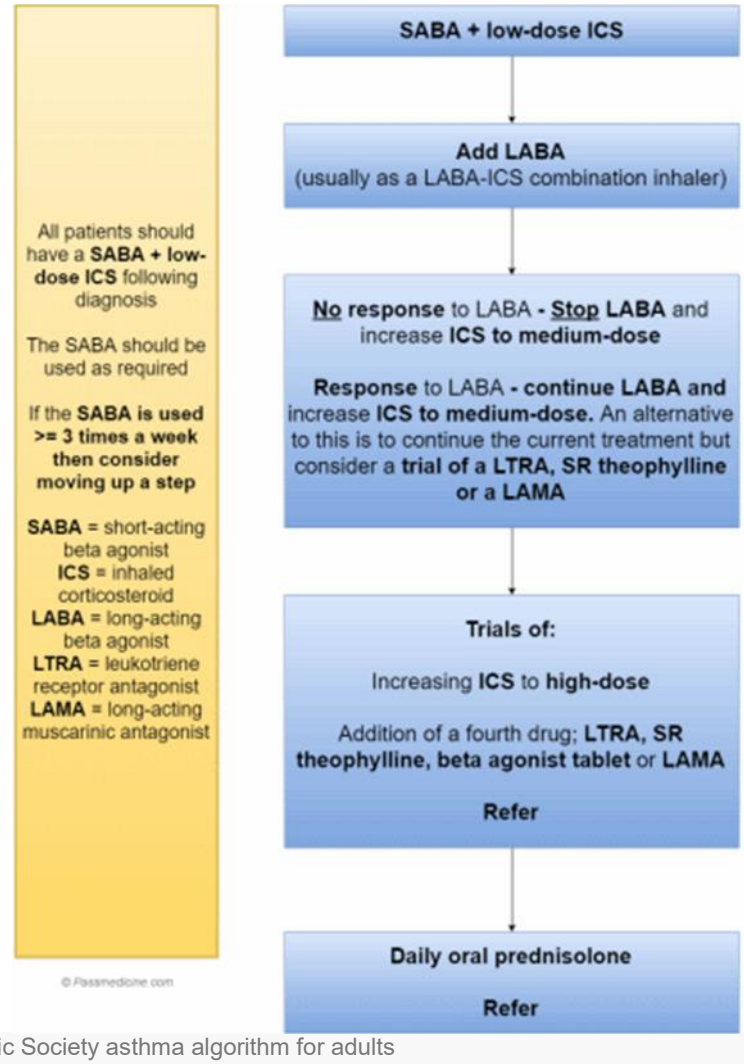
Next step...

Consider trials of either:

- increasing the ICS to high-dose, OR
- the addition of a fourth drug (e.g. a leukotriene receptor antagonist, SR theophylline, a LAMA or an oral beta-agonist tablet)
- patient should be referred to specialist care at this point

Next step....

The consideration of regular oral steroids at the lowest dose providing adequate daily control.



2016 British Thoracic Society asthma algorithm for adults

Table showing examples of inhaled corticosteroid doses

Low	Medium	High
Beclometasone dipropionate • Clenil - 100 mcg two puffs bd • Qvar - 50 mcg two puffs bd Fluticasone propionate • Flixotide - 50 mcg two puffs bd	Beclometasone dipropionate • Clenil - 200 mcg two puffs bd • Qvar - 100 mcg two puffs bd Fluticasone propionate • Flixotide - 125 mcg two puffs bd	Beclometasone dipropionate • Clenil - 250 mcg two-four puffs bd • Qvar - 100 mcg four puffs bd Fluticasone propionate • Flixotide - 250 mcg two puffs bd

Asthma: occupational

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.

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
- platinum salts
- soldering flux resin
- glutaraldehyde
- flour
- epoxy resins
- proteolytic enzymes

Serial measurements of peak expiratory flow are recommended at work and away from work.

Referral should be made to a respiratory specialist for patients with suspected occupational asthma.

Bilateral hilar lymphadenopathy

The most common causes of bilateral hilar lymphadenopathy are sarcoidosis and tuberculosis

Other causes include:

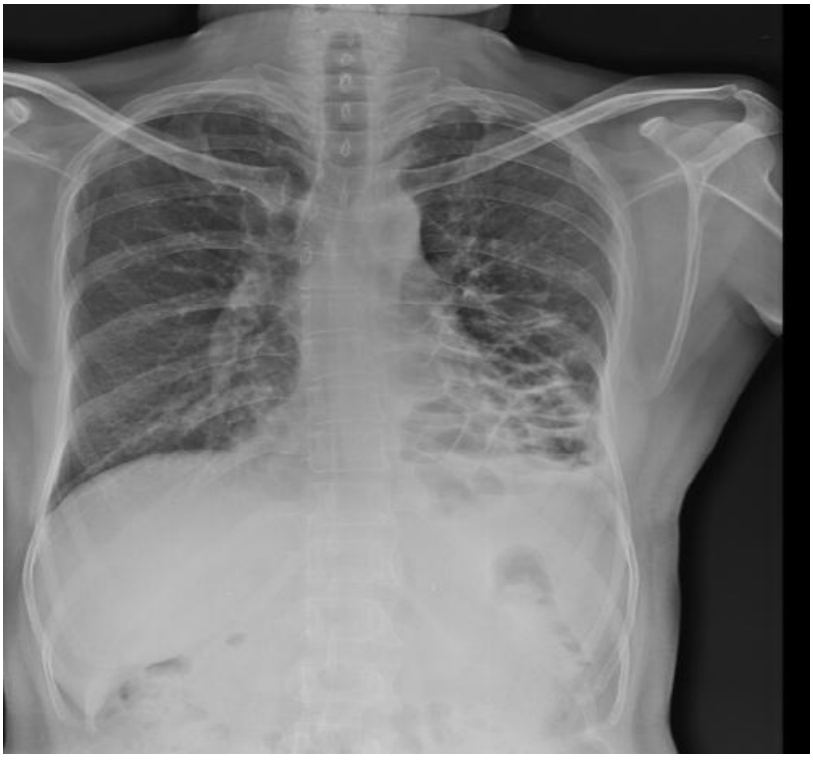
- lymphoma/other malignancy
- pneumoconiosis e.g. berylliosis
- fungi e.g. histoplasmosis, coccidioidomycosis

Bronchiectasis: causes

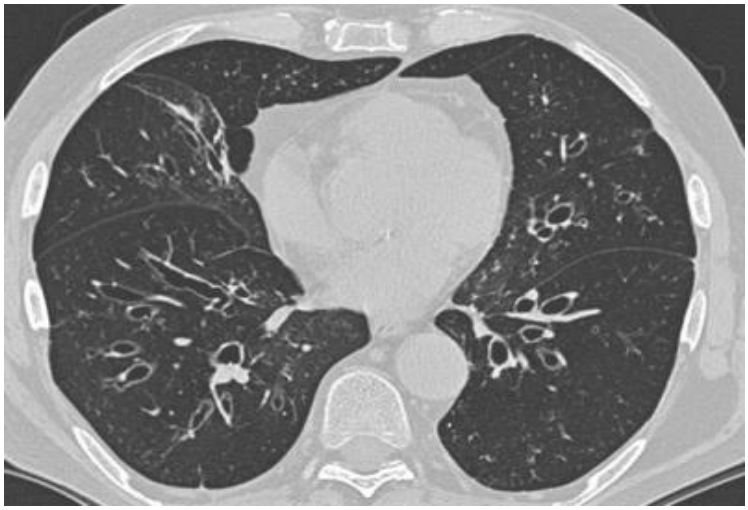
Bronchiectasis describes a permanent dilatation of the airways secondary to chronic infection or inflammation. There are a wide variety of causes are listed below:

Causes

- post-infective: tuberculosis, measles, pertussis, pneumonia
- cystic fibrosis
- bronchial obstruction e.g. lung cancer/foreign body
- immune deficiency: selective IgA, hypogammaglobulinaemia
- allergic bronchopulmonary aspergillosis (ABPA)
- ciliary dyskinetic syndromes: Kartagener's syndrome, Young's syndrome
- yellow nail syndrome



Chest x-ray showing tramlines, most prominent in the left lower zone



CT chest showing widespread tram-track and signet ring signs

Bronchiectasis: management

Bronchiectasis describes a permanent dilatation of the airways secondary to chronic infection or inflammation. 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
- surgery in selected cases (e.g. Localised disease)

Most common organisms isolated from patients with bronchiectasis:

- *Haemophilus influenzae* (most common)
- *Pseudomonas aeruginosa*
- Klebsiella spp.
- *Streptococcus pneumoniae*

Chest x-ray: cavitating lung lesion

Differential

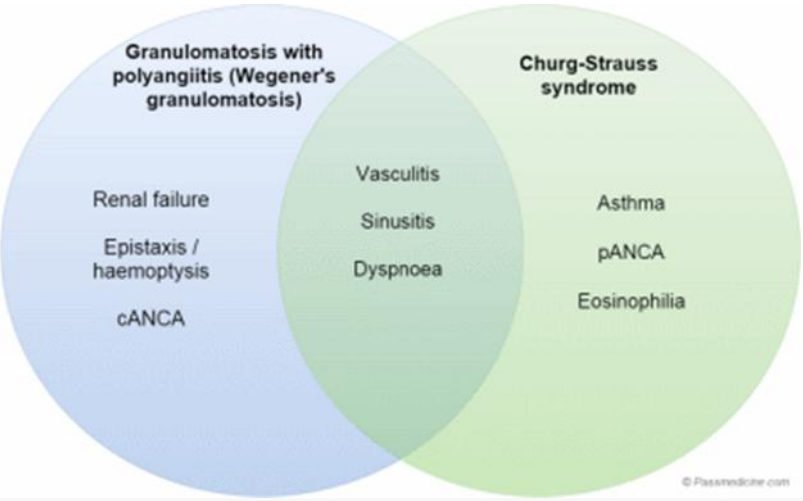
- abscess (Staph aureus, Klebsiella and *Pseudomonas*)
- squamous cell lung cancer
- tuberculosis
- Wegener's granulomatosis
- pulmonary embolism
- rheumatoid arthritis
- aspergillosis, histoplasmosis, coccidioidomycosis

Churg-Strauss syndrome

Churg-Strauss syndrome is an ANCA associated small-medium vessel vasculitis.

Features

- asthma
- blood eosinophilia (e.g. > 10%)
- paranasal sinusitis
- mononeuritis multiplex
- pANCA positive in 60%



Comparison of granulomatosis with polyangiitis and Churg-Strauss syndrome

Leukotriene receptor antagonists may precipitate the disease

COPD: 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

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

Measuring peak expiratory flow is of limited value in COPD, as it may underestimate the degree of airflow obstruction.

*note that the grading system has changed following the 2010 NICE guidelines. If the FEV1 is greater than 80% predicted but the post-bronchodilator FEV1/FVC is < 0.7 then this is classified as Stage 1 - mild

**symptoms should be present to diagnose COPD in these patients

COPD: long-term oxygen therapy

The 2010 NICE guidelines on COPD clearly define which patients should be assessed for and offered long-term oxygen therapy (LTOT). Patients who receive LTOT should breathe supplementary oxygen for at least 15 hours a day. Oxygen concentrators are used to provide a fixed supply for LTOT.

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

Assessment is done by measuring arterial blood gases on 2 occasions at least 3 weeks apart in patients with stable COPD on optimal management.

Offer LTOT 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

COPD: management of acute exacerbations

The most common bacterial organisms that cause infective exacerbations of COPD are:

- *Haemophilus influenzae* (most common cause)
- *Streptococcus pneumoniae*
- *Moraxella catarrhalis*

Respiratory viruses account for around 30% of exacerbations, with the human rhinovirus being the most important pathogen.

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
- 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'

COPD: stable management

NICE updated it's guidelines on the management of chronic obstructive pulmonary disease (COPD) in 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

Cryptogenic organizing pneumonia

Cryptogenic organizing pneumonia (COP) is a diffuse interstitial lung disease that affects the distal bronchioles, respiratory bronchioles, alveolar ducts and alveolar walls. It affects 6-7 people per 100,000. The aetiology is unknown.

Males and females are equally affected and tend to present in the 5th or 6th decade of life and is not associated with smoking. Patients typically present with a cough, shortness of breath, fever and malaise. Symptoms can be present for weeks or months. There is often a history of non-response to antibiotics. Haemoptysis is rare. Clinical examination is often normal but inspiratory crackles can be heard. Wheeze and clubbing are rare.

Bloods show a leukocytosis and an elevated ESR and CRP. Imaging typically shows bilateral patchy or diffuse consolidative or ground glass opacities. Lung function tests are most commonly restrictive but can be obstructive or normal. The transfer factor is reduced.

Diagnosis is clinical. Treatment is watch and wait if mild or high dose oral steroids if severe.

Cystic fibrosis: diagnosis

Sweat test

- patient's with CF have abnormally high sweat chloride
- normal value < 40 mEq/l, CF indicated by > 60 mEq/l

Causes of false positive sweat test

- malnutrition
- adrenal insufficiency
- glycogen storage diseases
- nephrogenic diabetes insipidus
- hypothyroidism, hypoparathyroidism
- G6PD
- ectodermal dysplasia

Cystic fibrosis: features

Presenting features

- neonatal period (around 20%): meconium ileus, less commonly prolonged jaundice
- recurrent chest infections (40%)
- malabsorption (30%): steatorrhoea, failure to thrive
- other features (10%): liver disease

Other features of cystic fibrosis

- short stature
- diabetes mellitus
- delayed puberty
- rectal prolapse (due to bulky stools)
- nasal polyps
- male infertility, female subfertility

Cystic fibrosis: management

Management of cystic fibrosis involves a multidisciplinary approach

Key points

- regular (at least twice daily) chest physiotherapy and postural drainage. Parents are usually taught to do this. Deep breathing exercises are also useful
- high calorie diet, including high fat intake*
- vitamin supplementation
- pancreatic enzyme supplements taken with meals
- heart and lung transplant

*this is now the standard recommendation - previously high calorie, low-fat diets have been recommended to reduce the amount of steatorrhoea

Extrinsic allergic alveolitis

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.

Examples

- bird fanciers' lung: avian proteins
- farmers lung: spores of *Saccharopolyspora rectivirgula* (formerly *Micropolyspora faeni*)
- malt workers' lung: *Aspergillus clavatus*
- mushroom workers' lung: thermophilic actinomycetes*

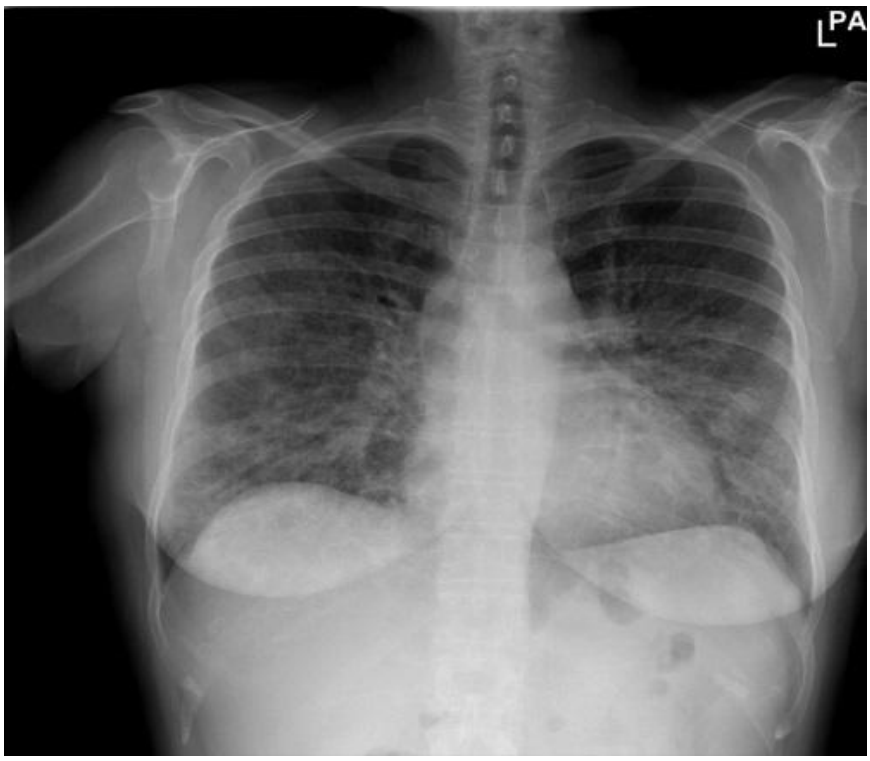
Presentation

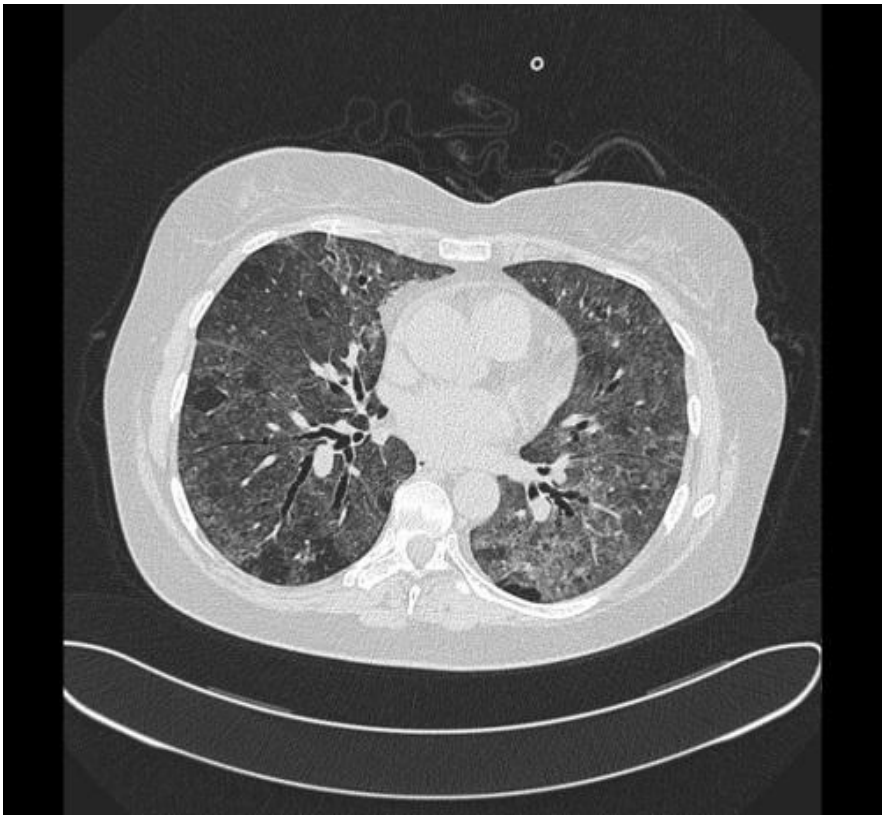
- acute: occur 4-8 hrs after exposure, SOB, dry cough, fever
- chronic

Investigation

- chest x-ray: upper/mid-zone fibrosis
- bronchoalveolar lavage: lymphocytosis
- blood: NO eosinophilia

*here the terminology is slightly confusing as thermophilic actinomycetes is an umbrella term covering strains such as *Micropolyspora faeni*





Chest x-ray and CT scan from a middle-aged woman who presented with dyspnoea. The CT demonstrates multuple centrilobular ground glass nodules consistent with hypersensitivity pneumonitis

Fitness to fly

The Civil Aviation Authority (CAA) has issued guidelines on air travel for people with medical conditions; please see the link provided.

Cardiovascular disease

- unstable angina, uncontrolled hypertension, uncontrolled cardiac arrhythmia, decompensated heart failure, severe symptomatic valvular disease: should not fly
- uncomplicated myocardial infarction: may fly after 7-10 days
- complicated myocardial infarction: after 4-6 weeks
- coronary artery bypass graft: after 10-14 days
- percutaneous coronary intervention: after 5 days

Respiratory disease

- pneumonia: should be 'clinically improved with no residual infection'
- pneumothorax: absolute contraindication, the CAA suggest patients may travel 2 weeks after successful drainage if there is no residual air. The British Thoracic Society used to recommend not travelling by air for a period of 6 weeks but this has now been changed to 1 week post check x-ray

Pregnancy

- most airlines do not allow travel after 36 weeks for a single pregnancy and after 32 weeks for a multiple pregnancy
- most airlines require a certificate after 28 weeks confirming that the pregnancy is progressing normally

Surgery

- travel should be avoided for 10 days following abdominal surgery
- laparoscopic surgery: after 24 hours
- colonoscopy: after 24 hours
- following the application of a plaster cast, the majority of airlines restrict flying for 24 hours on flights of less than 2 hours or 48 hours for longer flights

Haematological disorders

- patients with a haemoglobin of greater than 8 g/dl may travel without problems (assuming there is no coexisting condition such as cardiovascular or respiratory disease)

Flow volume loop

A normal flow volume loop is often described as a 'triangle on top of a semi circle'

Flow volume loops are the most suitable way of assessing compression of the upper airway

Idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF, previously termed cryptogenic fibrosing alveolitis) is a chronic lung condition characterised by progressive fibrosis of the interstitium of the lungs. Whilst there are many causes of lung fibrosis (e.g. medications, connective tissue disease, asbestos) the term IPF is reserved when no underlying cause exists.

IPF is typically seen in patients aged 50-70 years and is twice as common in men.

Features

- progressive exertional dyspnoea
- bibasal crackles on auscultation
- dry cough
- clubbing

Diagnosis

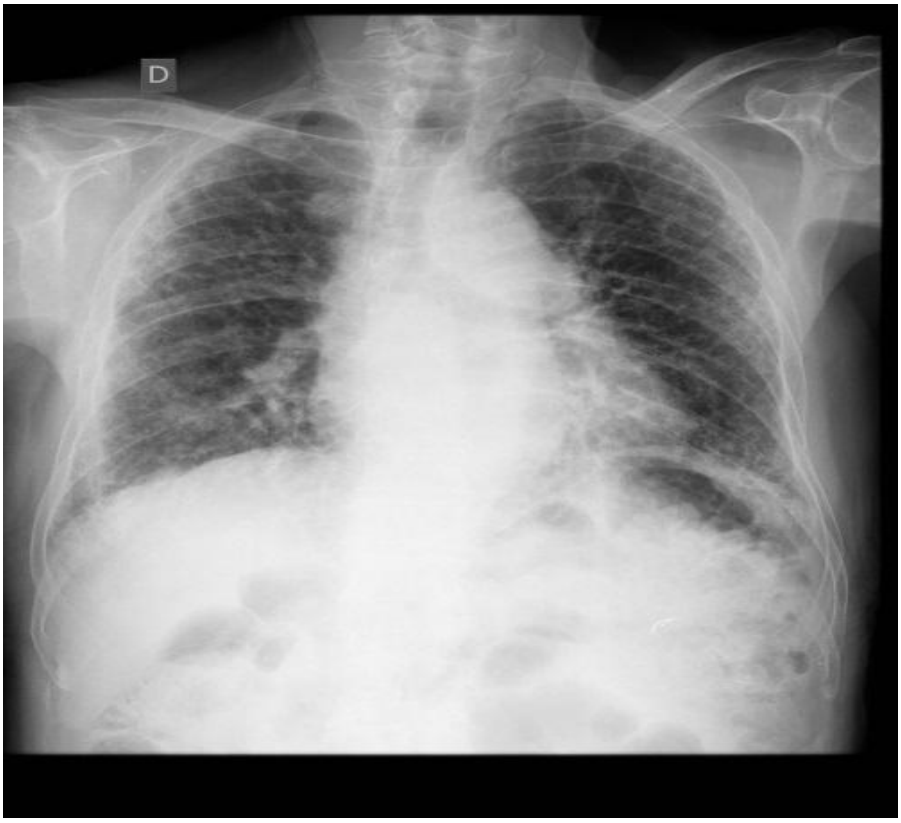
- spirometry: classically a restrictive picture (FEV1 normal/decreased, FVC decreased, FEV1/FVC increased)
- impaired gas exchange: reduced transfer factor (TLCO)
- imaging: bilateral interstitial shadowing (typically small, irregular, peripheral opacities - 'ground-glass' - later progressing to 'honeycombing') 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
- 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

Management

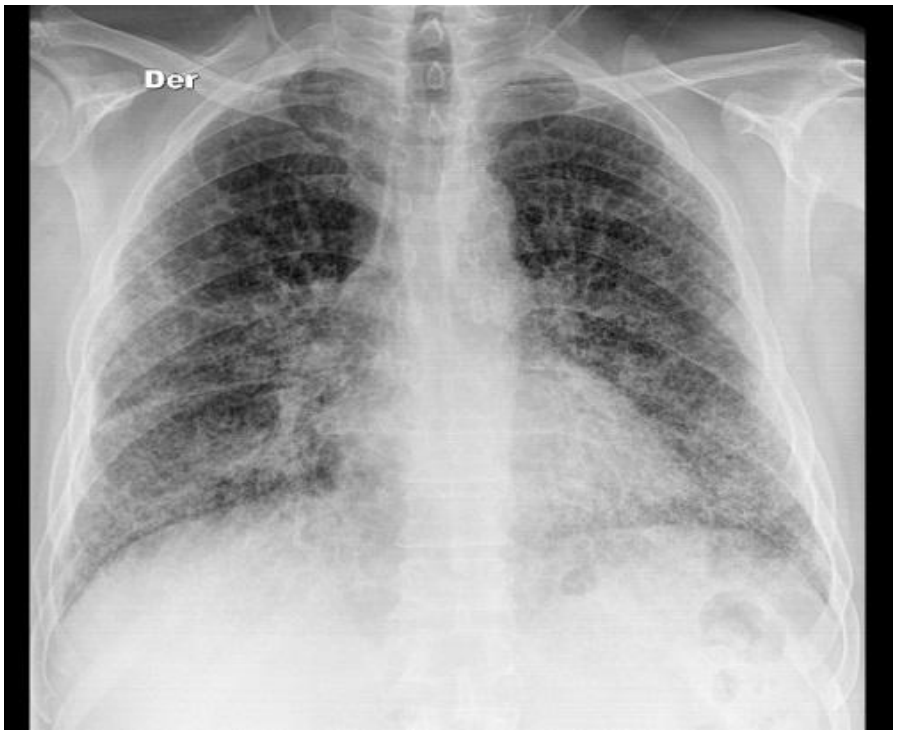
- pulmonary rehabilitation
- very few medications have been shown to give any benefit in IPF. There is some evidence that pirfenidone (an antifibrotic agent) may be useful in selected patients (see NICE guidelines)
- many patients will require supplementary oxygen and eventually a lung transplant

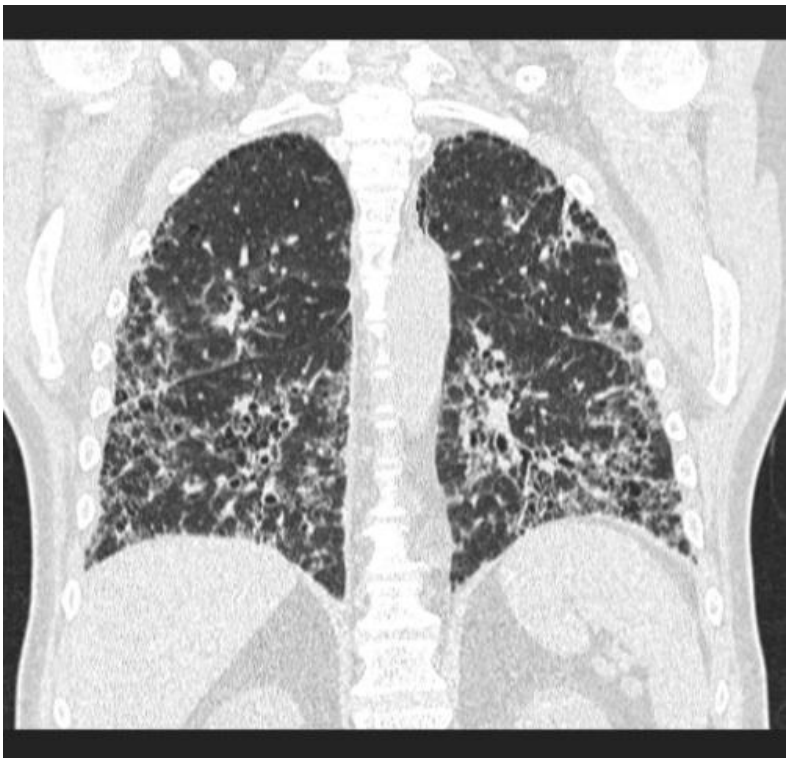
Prognosis

- poor, average life expectancy is around 3-4 years

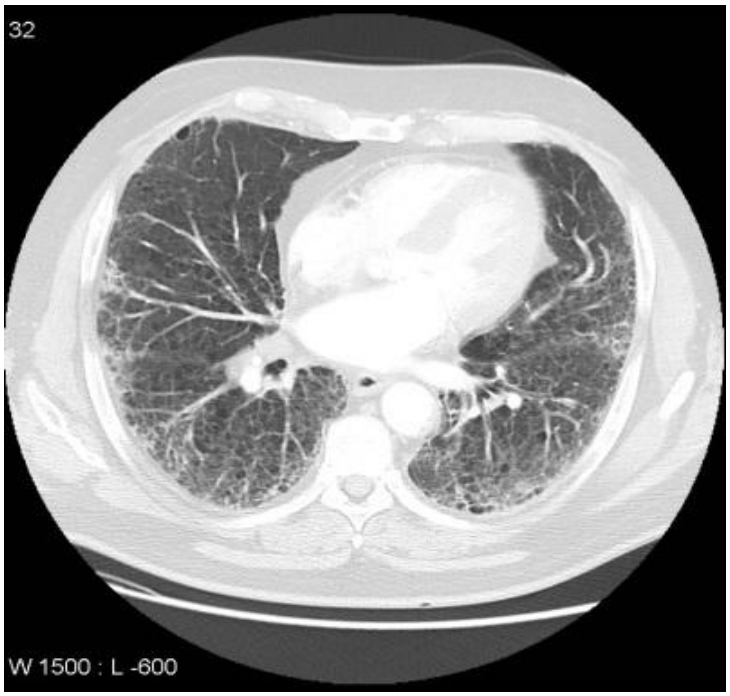


Chest X-ray shows sub-pleural reticular opacities that increase from the apex to the bases of the lungs





Chest X-ray and CT scan from a patient who presented with dyspnoea. The x-ray shows reitcular opacities predominantly in the bases. In addition the CT demonstrates honeycombing and traction bronchiectasis



CT scan showing advanced pulmonary fibrosis including 'honeycombing'

Kartagener's syndrome

Kartagener's syndrome (also known as primary ciliary dyskinesia) was first described in 1933 and most frequently occurs in examinations due to its association with dextrocardia (e.g. 'quiet heart sounds', 'small volume complexes in lateral leads')

Pathogenesis

- dynein arm defect results in immotile cilia

Features

- dextrocardia or complete situs inversus
- bronchiectasis
- recurrent sinusitis
- subfertility (secondary to diminished sperm motility and defective ciliary action in the fallopian tubes)

Legionella

Legionnaire's disease is caused by the intracellular bacterium *Legionella pneumophilia*. It is typically colonizes water tanks and hence questions may hint at air-conditioning systems or foreign holidays. Person-to-person transmission is not seen

Features

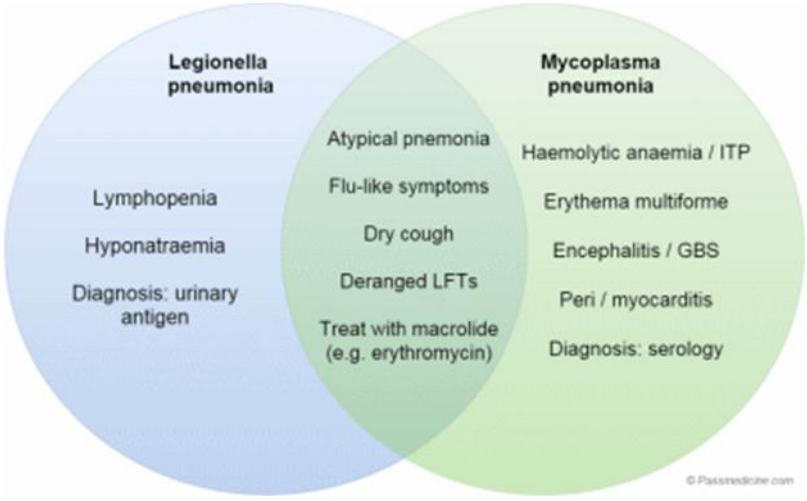
- flu-like symptoms including fever (present in > 95% of patients)
- dry cough
- relative bradycardia
- confusion
- lymphopaenia
- hyponatraemia
- deranged liver function tests
- pleural effusion: seen in around 30% of patients

Diagnosis

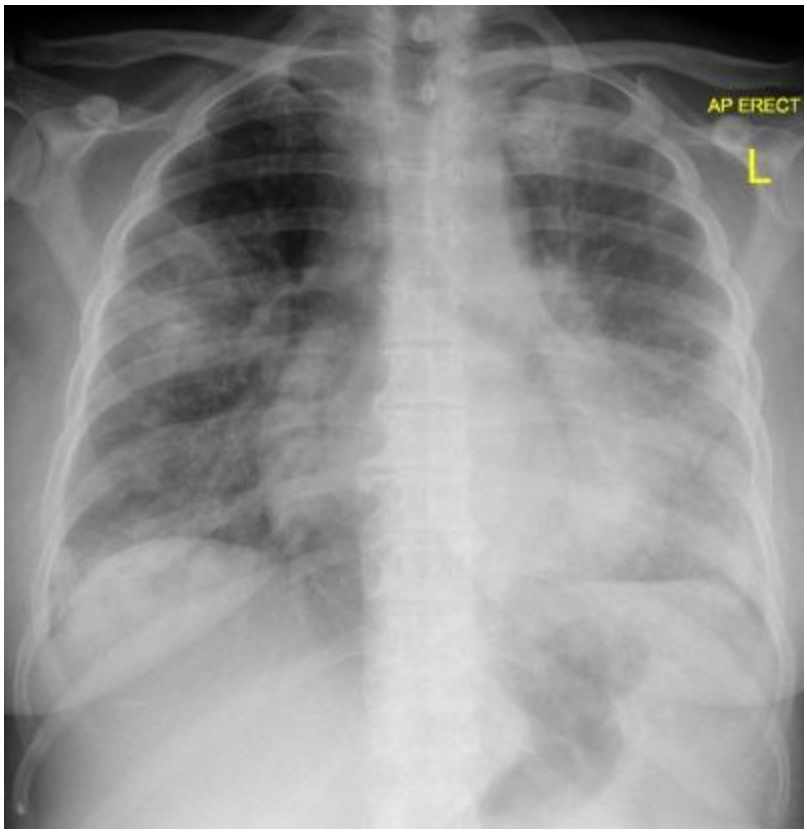
- urinary antigen

Management

- treat with erythromycin



Comparison of Legionella and Mycoplasma pneumonia



Chest x-ray features of legionella pnuemonia are non-specific but includes a mid-to-lower zone predominance of patchy consolidation. Pleural effusions are seen in around 30%.

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.

Lung cancer: carcinoid

The vast majority of bronchial adenomas are carcinoid tumours, arising from the amine precursor uptake and decarboxylation (APUD) system, like small cell tumours. Lung carcinoid accounts 1% of lung tumours and for 10% of carcinoid tumours. The term bronchial adenoma is being phased out.

Lung carcinoid

- typical age = 40-50 years
- smoking not risk factor
- slow growing: e.g. long history of cough, recurrent haemoptysis
- often centrally located and not seen on CXR
- 'cherry red ball' often seen on bronchoscopy
- carcinoid syndrome itself is rare (associated with liver metastases)

Management

- surgical resection
- if no metastases then 90% survival at 5 years

Lung cancer: non-small cell

There are three main subtypes of non-small cell lung cancer:

Squamous cell cancer

- typically central
- associated with parathyroid hormone-related protein (PTHrP) secretion → hypercalcaemia
- strongly associated with finger clubbing
- hypertrophic pulmonary osteoarthropathy (HPOA)

Adenocarcinoma

- typically peripheral
- most common type of lung cancer in non-smokers, although the majority of patients who develop lung adenocarcinoma are smokers

Large cell lung carcinoma

- typically peripheral
- anaplastic, poorly differentiated tumours with a poor prognosis
- may secrete β-hCG

Lung cancer: non-small cell management

Management

- only 20% suitable for surgery
- mediastinoscopy performed prior to surgery as CT does not always show mediastinal lymph node involvement
- curative or palliative radiotherapy
- poor response to chemotherapy

Surgery contraindications

- assess general health
- stage IIIb or IV (i.e. metastases present)
- FEV1 < 1.5 litres is considered a general cut-off point*
- malignant pleural effusion
- tumour near hilum
- vocal cord paralysis
- SVC obstruction

* However if FEV1 < 1.5 for lobectomy or < 2.0 for pneumonectomy then some authorities advocate further lung function tests as operations may still go ahead based on the results

Lung cancer: paraneoplastic features

Small cell

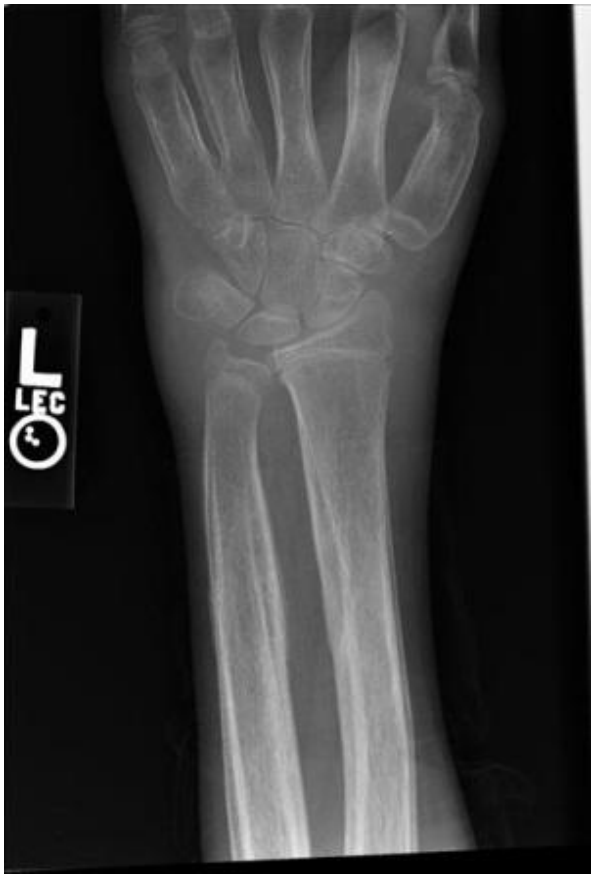
- ADH
- ACTH - not typical, hypertension, hyperglycaemia, hypokalaemia, alkalosis and muscle weakness are more common than buffalo hump etc
- Lambert-Eaton syndrome

Squamous cell

- parathyroid hormone-related protein (PTH-rp) secretion causing hypercalcaemia
- clubbing
- hypertrophic pulmonary osteoarthropathy (HPOA)
- hyperthyroidism due to ectopic TSH

Adenocarcinoma

- gynaecomastia



Hypertrophic pulmonary osteoarthropathy is a proliferative periostisis involving that typically involves the long bones. It is often painful.

Lung cancer: risk factors

Smoking

- increases risk of lung ca by a factor of 10

Other factors

- asbestos - increases risk of lung ca by a factor of 5
- arsenic
- radon
- nickel
- chromate
- aromatic hydrocarbon
- cryptogenic fibrosing alveolitis

Factors that are NOT related

- coal dust

Smoking and asbestos are synergistic, i.e. a smoker with asbestos exposure has a 10 * 5 = 50 times increased risk

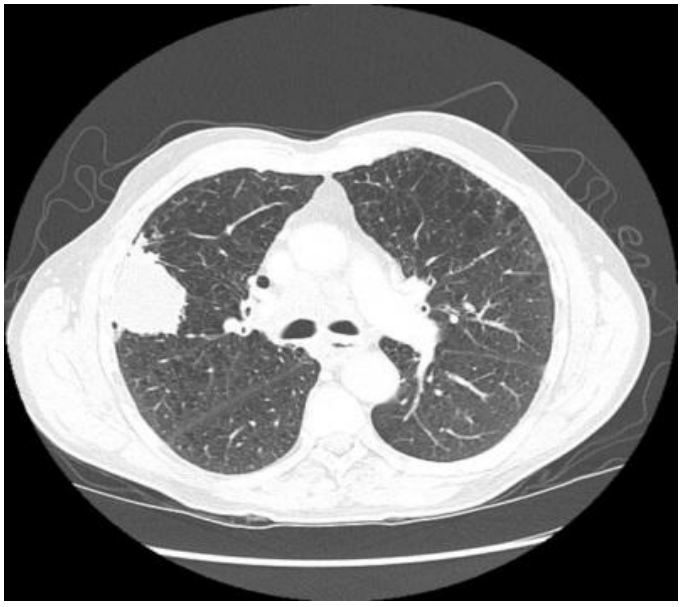
Lung cancer: small cell

Features

- usually central
- arise from APUD* cells
- associated with ectopic ADH, ACTH secretion
- ADH → hyponatraemia
- ACTH → Cushing's syndrome
- ACTH secretion can cause bilateral adrenal hyperplasia, the high levels of cortisol can lead to hypokalaemic alkalosis
- Lambert-Eaton syndrome: antibodies to voltage gated calcium channels causing myasthenic like syndrome

Management

- usually metastatic disease by time of diagnosis
- patients with very early stage disease (T1-2a, N0, M0) are now considered for surgery. NICE support this approach in their 2011 guidelines
- however, most patients with limited disease receive a combination of chemotherapy and radiotherapy
- patients with more extensive disease are offered palliative chemotherapy



CT scan showing small cell lung cancer with multiple pulmonary nodules and extensive mediastinal nodal metastases.

*an acronym for

- Amine - high amine content
- Precursor Uptake - high uptake of amine precursors
- Decarboxylase - high content of the enzyme decarboxylase

Lung fibrosis

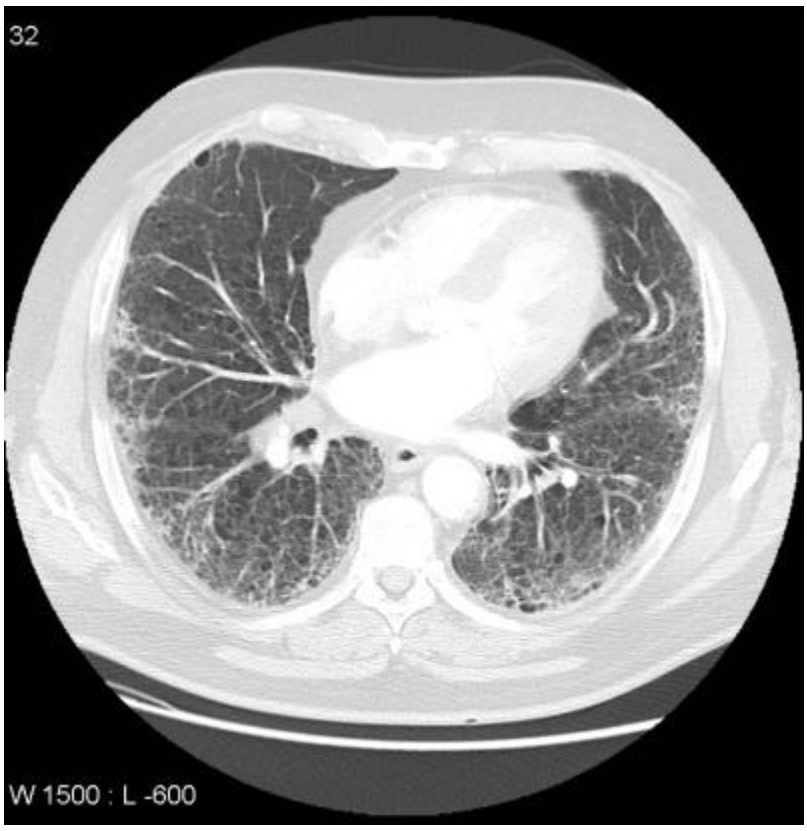
It is important in the exam to be able to differentiate between conditions causing predominately upper or lower zone fibrosis. It should be noted that the more common causes (idiopathic pulmonary fibrosis, drugs) tend to affect the lower zones

Fibrosis predominately affecting the upper zones

- hypersensitivity pneumonitis (also known as extrinsic allergic alveolitis)
- coal worker's pneumoconiosis/progressive massive fibrosis
- silicosis
- sarcoidosis
- ankylosing spondylitis (rare)
- histiocytosis
- tuberculosis

Fibrosis predominately affecting the lower zones

- idiopathic pulmonary fibrosis
- most connective tissue disorders (except ankylosing spondylitis)
- drug-induced: amiodarone, bleomycin, methotrexate
- asbestosis



CT scan showing advanced pulmonary fibrosis including 'honeycombing'

Mesothelioma

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

Basics

- Malignancy of mesothelial cells of pleura
- Metastases to contralateral lung and peritoneum
- Right lung affected more often than left

Investigation/diagnosis

- suspicion is normally raised by a chest x-ray showing either a pleural effusion or pleural thickening
- 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)
- local anaesthetic thoracoscopy is increasingly used to investigate cytology negative exudative effusions as it has a high diagnostic yield (around 95%)
- if an area of pleural nodularity is seen on CT then an image-guided pleural biopsy may be used

Management

- Symptomatic
- Industrial compensation
- Chemotherapy, Surgery if operable
- Prognosis poor, median survival 12 months

Mycoplasma pneumoniae

Mycoplasma pneumoniae is a cause of atypical pneumonia which often affects younger patients. It is associated with a number of characteristic complications such as erythema multiforme and cold autoimmune haemolytic anaemia. Epidemics of *Mycoplasma pneumoniae* classically occur every 4 years. 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 disease typically has a prolonged and gradual onset
- flu-like symptoms classically precede a dry cough
- bilateral consolidation on x-ray
- complications may occur as below

Complications

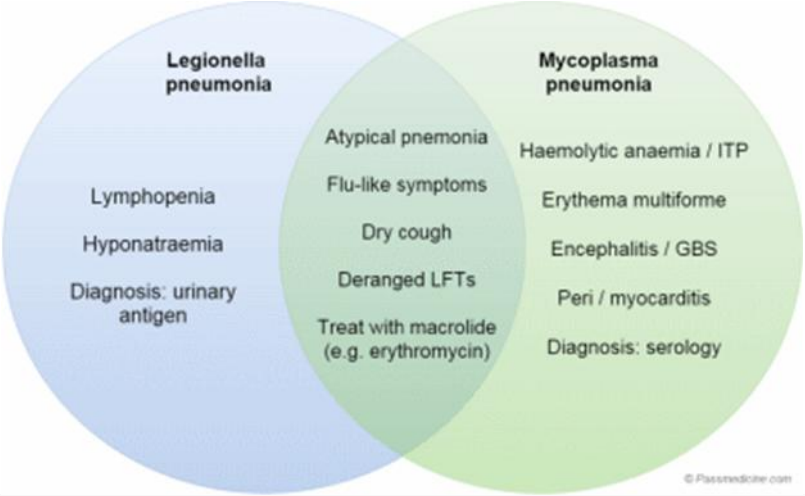
- cold agglutins (IgM) may cause an haemolytic anaemia, thrombocytopenia
- erythema multiforme, erythema nodosum
- meningoencephalitis, Guillain-Barre syndrome
- bullous myringitis: painful vesicles on the tympanic membrane
- pericarditis/myocarditis
- gastrointestinal: hepatitis, pancreatitis
- renal: acute glomerulonephritis

Investigations

- diagnosis is generally by Mycoplasma serology
- positive cold agglutination test

Management

- erythromycin/clarithromycin
- tetracyclines such as doxycycline are an alternative



Comparison of Legionella and Mycoplasma pneumonia

Non-invasive ventilation

The British Thoracic Society (BTS) published guidelines in 2002 on the use of non-invasive ventilation in acute respiratory failure. Following these the Royal College of Physicians published guidelines in 2008.

Non-invasive ventilation - key indications

- COPD with respiratory acidosis pH 7.25-7.35
- 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

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

Obstructive sleep apnoea/hypopnoea syndrome

Predisposing factors

- obesity
- macroglossia: acromegaly, hypothyroidism, amyloidosis
- large tonsils
- Marfan's syndrome

Consequence

- daytime somnolence
- hypertension

SIGN guidelines for the diagnosis and management of patients with OSAHS were published in 2003

Assessment of sleepiness

- Epworth Sleepiness Scale - questionnaire completed by patient +/- partner
- Multiple Sleep Latency Test (MSLT) - measures the time to fall asleep in a dark room (using EEG criteria)

Diagnostic tests

- sleep studies - ranging from monitoring of pulse oximetry at night to full polysomnography where a wide variety of physiological factors are measured including EEG, respiratory airflow, thoraco-abdominal movement, snoring and pulse oximetry

Management

- weight loss
- CPAP is first line for moderate or severe OSAHS
- intra-oral devices (e.g. mandibular advancement) may be used if CPAP is not tolerated or for patients with mild OSAHS where there is no daytime sleepiness
- limited evidence to support use of pharmacological agents

Oxygen therapy

The British Thoracic Society published guidelines on emergency oxygen therapy in 2008. The following selected points are taken from the guidelines. Please see the link provided for the full guideline.

In patients who are critically ill (anaphylaxis, shock etc) oxygen should initially be given via a reservoir mask at 15 l/min. Hypoxia kills. The BTS guidelines specifically exclude certain conditions where the patient is acutely unwell (e.g. myocardial infarction) but stable.

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

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

Pleural effusion

Exudate (> 30g/L protein)

- infection: pneumonia, TB, subphrenic abscess
- connective tissue disease: RA, SLE
- neoplasia: lung cancer, mesothelioma, metastases
- pancreatitis
- pulmonary embolism
- Dressler's syndrome
- yellow nail syndrome

Transudate (< 30g/L protein)

- heart failure
- hypoalbuminaemia (liver disease, nephrotic syndrome, malabsorption)
- hypothyroidism
- Meigs' syndrome

Pleural effusion: investigation

The British Thoracic Society (BTS) produced guidelines in 2010 covering the investigation of patients with a pleural effusion.

Imaging

- posterioranterior (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

Pleural aspiration

- as above, 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 was developed in 1972 to help 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 chest tube should be placed

Other characteristic pleural fluid findings:

- low glucose: rheumatoid arthritis, tuberculosis
- raised amylase: pancreatitis, oesophageal perforation
- heavy blood staining: mesothelioma, pulmonary embolism, tuberculosis

Pneumonia: community-acquired

Community acquired pneumonia (CAP) may be caused by the following infectious agents:

- *Streptococcus pneumoniae* (accounts for around 80% of cases)
- *Haemophilus influenzae*
- *Staphylococcus aureus*: commonly after the 'flu
- atypical pneumonias (e.g. Due to *Mycoplasma pneumoniae*)
- viruses

Klebsiella pneumoniae is classically in alcoholics

Streptococcus pneumoniae **(pneumococcus)** is the most common cause of community-acquired pneumonia

Characteristic features of pneumococcal pneumonia

- rapid onset
- high fever
- pleuritic chest pain
- herpes labialis

Management

CURB-65 criteria of severe pneumonia

- Confusion (abbreviated mental test score <= 8/10)
- Urea > 7 mmol/L
- Respiratory rate >= 30 / min
- BP: systolic <= 90 or diastolic <= 60 mmHg
- age >= 65 years

Patients with 3 or more (out of 5) of the above criteria are regarded as having a severe pneumonia

The British Thoracic Society published guidelines in 2009:

- low or moderate severity CAP: oral amoxicillin. A macrolide should be added for patients admitted to hospital
- high severity CAP: intravenous co-amoxiclav + clarithromycin OR cefuroxime + clarithromycin OR cefotaxime + clarithromycin
- 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

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

Patients with a CURB-65 score of 0 should be managed in the community.

Patients with a CURB-65 score of 1 should have their $Sa0_2$ assessed which should be >92% to be safely managed in the community and a CXR performed. If the CXR shows bilateral/multilobar shadowing hospital admission is advised.

Patients with a CURB-65 score of 2 or more should be managed in hospital as this represents a severe community acquired pneumonia.

The CURB-65 score also 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.

Other factors associated with a poor prognosis include:

- presence of coexisting disease
- hypoxaemia (pO2 < 8 kPa) independent of FiO2

Pneumothorax

The British Thoracic Society (BTS) published updated guidelines for the management of spontaneous pneumothorax in 2010. A pneumothorax is termed primary if there is no underlying lung disease and secondary if there is

Primary pneumothorax

Recommendations include:

- 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 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

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.
- otherwise aspiration should be attempted if the rim of air is between 1-2cm. If aspiration fails (i.e. pneumothorax is still greater then 1cm) a chest drain should be inserted. All patients should be admitted for at least 24 hours
- if the pneumothorax is less the 1cm then the BTS guidelines suggest giving oxygen and admitting for 24 hours
- regarding scuba diving, the 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.'*

Iatrogenic pneumothorax

Recommendations include:

- 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

Pregnancy: DVT/PE investigation

Guidelines were updated in 2015 by the Royal College of Obstetricians. Key points include:

- ECG and chest x-ray should be performed in all patients

- compression duplex Doppler should be performed if the chest x-ray is normal - this may provide indirect evidence of a pulmonary embolism and negate the need for further radiation exposure

- the decision to perform a V/Q or CTPA should be taken at a local level after discussion with the patient and radiologist

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.

Pulmonary arterial hypertension: causes and classification

Pulmonary arterial hypertension (PAH) may be defined as a sustained elevation in mean pulmonary arterial pressure of greater than 25 mmHg at rest or 30 mmHg after exercise. PAH has recently been reclassified by the WHO:

Group 1: Pulmonary arterial hypertension (PAH)
- idiopathic*
- familial
- associated conditions: collagen vascular disease, congenital heart disease with systemic to pulmonary shunts, HIV**, drugs and toxins, 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

*previously termed primary pulmonary hypertension
**the mechanism by which HIV infection produces pulmonary hypertension remains unknown

Pulmonary embolism: investigation

We know from experience that few patients (around 10%) present with the medical student textbook triad of pleuritic chest pain, dyspnoea and haemoptysis. Pulmonary embolism can be difficult to diagnose as it can present with virtually any cardiorespiratory symptom/sign depending on it's location and size.

So which features make pulmonary embolism *more* likely?

The PIOPED study[1] in 2007 looked at the frequency of different symptoms and signs in patients who were diagnosed with pulmonary embolism.

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%

It is interesting to note that the Well's criteria for diagnosing a PE use tachycardia rather than tachypnoea.

2012 NICE guidelines

All patients with symptoms or signs suggestive of a PE should have a history taken, examination performed and a chest x-ray to exclude other pathology.

If a PE is still suspected a two-level PE Wells score should be performed:

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

Clinical feature	Points
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

If a PE is 'likely' (more than 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.

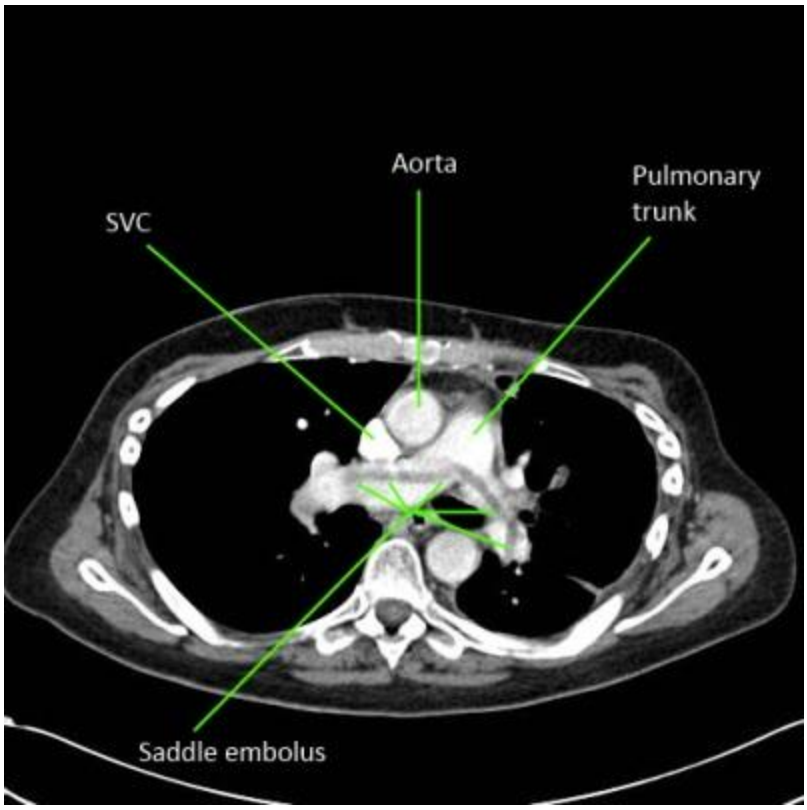
If a PE is 'unlikely' (4 points or less) arranged a D-dimer test. If this is positive arrange an immediate computed tomography pulmonary angiogram (CTPA). If there is a delay in getting the CTPA then give low-molecular weight heparin until the scan is performed.

If the patient has an allergy to contrast media or renal impairment a V/Q scan should be used instead of a CTPA.

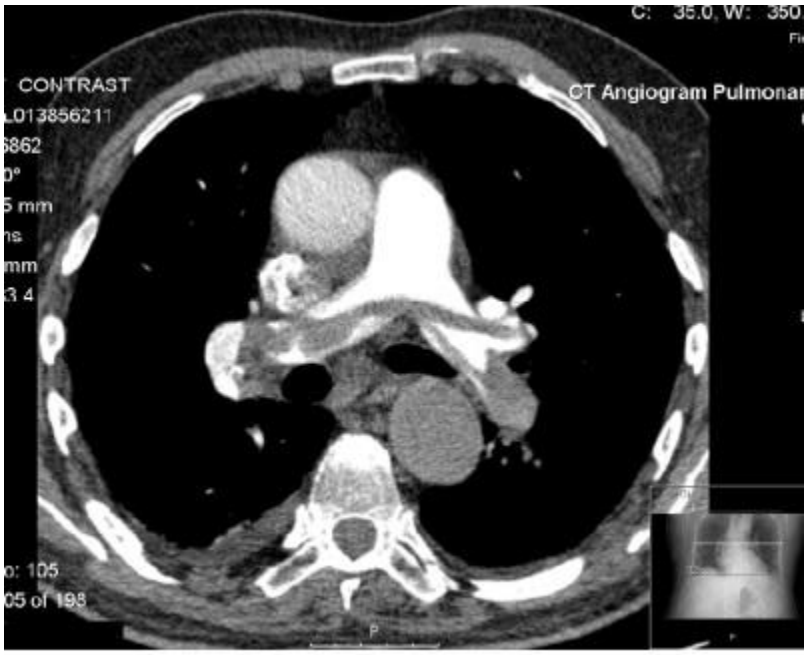
CTPA or V/Q scan?

The consensus view from the British Thoracic Society and NICE guidelines is as follows:

- computed tomographic pulmonary angiography (CTPA) is now the recommended initial lung-imaging modality for non-massive PE. Advantages compared to V/Q scans include speed, easier to perform out-of-hours, a reduced need for further imaging and the possibility of providing an alternative diagnosis if PE is excluded
- if the CTPA is negative then patients do not need further investigations or treatment for PE
- ventilation-perfusion scanning may be used initially if appropriate facilities exist, the chest x-ray is normal, and there is no significant symptomatic concurrent cardiopulmonary disease



Labelled CTPA showing a large saddle embolus



Further CTPA again showing a saddle embolus

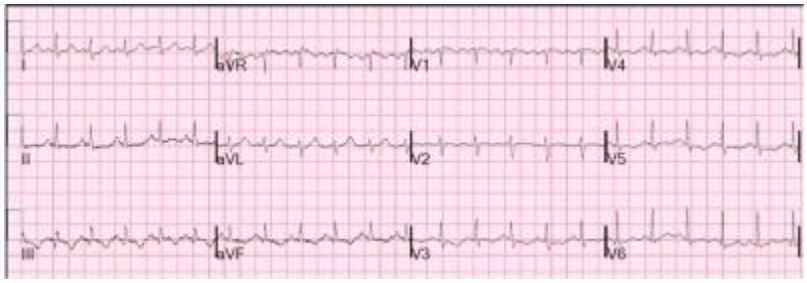
Some other points

D-dimers

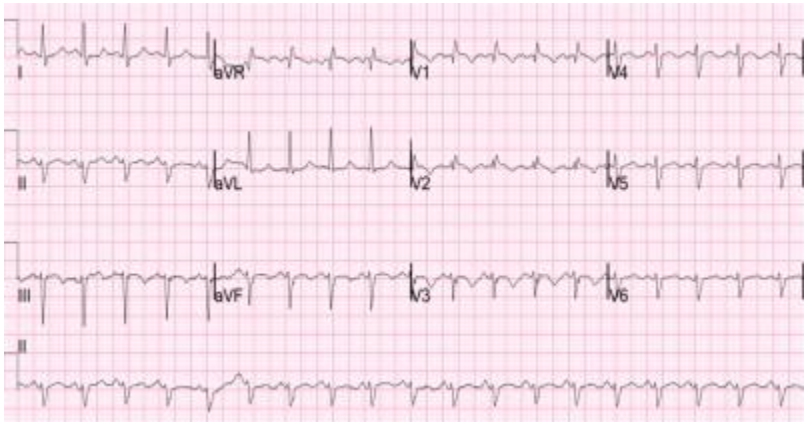
- sensitivity = 95-98%, but poor specificity

ECG

- the classic ECG changes seen in PE are a large S wave in lead I, a large Q wave in lead III and an inverted T wave in lead III - 'S1Q3T3'. However this change is seen in no more than 20% of patients
- right bundle branch block and right axis deviation are also associated with PE
- sinus tachycardia may also be seen



ECG from a patient with a PE. Shows a sinus tachycardia and a partial S1Q3T3 - the S wave is not particularly convincing.



ECG of a patient with a PE. It shows some of the ECG features that may be associated with PE (sinus tachycardia, S1, T3 and T wave inversion in the precordial leads). Other features such as the left axis deviation are atypical.

V/Q scan

- sensitivity = 98%; specificity = 40% - high negative predictive value, i.e. if normal virtually excludes PE
- other causes of mismatch in V/Q include old pulmonary embolisms, AV malformations, vasculitis, previous radiotherapy
- COPD gives matched defects

CTPA

- peripheral emboli affecting subsegmental arteries may be missed

Pulmonary angiography

- the gold standard
- significant complication rate compared to other investigations

Pulmonary embolism: management

The NICE guidelines of 2012 provided some clarity on how long patients should be anticoagulated for after a pulmonary embolism (PE). Selected points are listed below.

Low molecular weight heparin (LMWH) or fondaparinux should be given initially after a PE is diagnosed. An exception to this is for patients with a massive PE where thrombolysis is being considered. In such a situation unfractionated heparin should be used.

- 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 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) it may imply the patient has a tendency to thrombosis and should be given treatment longer than the norm of 3 months
- for patients with active cancer NICE recommend using LMWH for 6 months

Thrombolysis

- thrombolysis is now recommended as the first-line treatment for massive PE where there is circulatory failure (e.g. hypotension). Other invasive approaches should be considered where appropriate facilities exist

Pulmonary 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

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

Tropical pulmonary eosinophilia

- associated with *Wuchereria bancrofti* infection

Pulmonary function tests

Pulmonary function tests can be used to determine whether a respiratory disease is obstructive or restrictive. The table below summarises the main findings and gives some example conditions:

Obstructive lung disease	**Restrictive lung disease**
FEV1 - significantly reduced FVC - reduced or normal FEV1% (FEV1/FVC) - reduced	FEV1 - reduced FVC - significantly reduced FEV1% (FEV1/FVC) - normal or increased
Asthma COPD Bronchiectasis Bronchiolitis obliterans	Pulmonary fibrosis Asbestosis Sarcoidosis Acute respiratory distress syndrome Infant respiratory distress syndrome Kyphoscoliosis Neuromuscular disorders

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

Respiratory alkalosis

Common causes

- anxiety leading to hyperventilation
- pulmonary embolism
- salicylate poisoning*
- CNS disorders: stroke, subarachnoid haemorrhage, encephalitis
- altitude
- pregnancy

*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

Respiratory pathogens

The table below lists the more common respiratory pathogens:

Pathogen	Associated condition
Respiratory syncytial virus	Bronchiolitis
Parainfluenza virus	Croup
Rhinovirus	Common cold
Influenza virus	Flu
Streptococcuspneumoniae	The most common cause of community-acquired pneumonia
Haemophilus influenzae	Community-acquired pneumonia Most common cause of bronchiectasis exacerbations Acute epiglottitis
Staphylococcusaureus	Pneumonia, particularly following influenza
Mycoplasma pneumoniae	Atypical pneumonia Flu-like symptoms classically precede a dry cough. Complications include haemolytic anaemia and erythema multiforme
Legionella pneumophilia	Atypical pneumonia Classically spread by air-conditioning systems, causes dry cough. Lymphopenia, deranged liver function tests and hyponatraemia may be seen

Pathogen	Associated condition
Pneumocystis jiroveci	Common cause of pneumonia in HIV patients. Typically patients have few chest signs and develop exertional dyspnoea
Mycobacterium tuberculosis	Causes tuberculosis. A wide range of presentations from asymptomatic to disseminated disease are possible. Cough, night sweats and weight loss may be seen

Rheumatoid arthritis: respiratory manifestations

A variety of respiratory problems may be seen in patients with rheumatoid arthritis:

- pulmonary fibrosis
- pleural effusion
- pulmonary nodules
- bronchiolitis obliterans
- complications of drug therapy e.g. methotrexate pneumonitis
- pleurisy
- Caplan's syndrome - massive fibrotic nodules with occupational coal dust exposure
- infection (possibly atypical) secondary to immunosuppression

Sarcoidosis: investigation

There is no one diagnostic test for sarcoidosis and hence diagnosis is still largely clinical. ACE levels 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. Routine bloods may show hypercalcaemia (seen in 10% if patients) and a raised ESR

A chest x-ray may show the following changes:

- stage 0 = normal
- stage 1 = bilateral hilar lymphadenopathy (BHL)
- stage 2 = BHL + interstitial infiltrates
- stage 3 = diffuse interstitial infiltrates only
- stage 4 = diffuse fibrosis

Other investigations*

- spirometry: may show a restrictive defect
- tissue biopsy: non-caseating granulomas
- gallium-67 scan - not used routinely

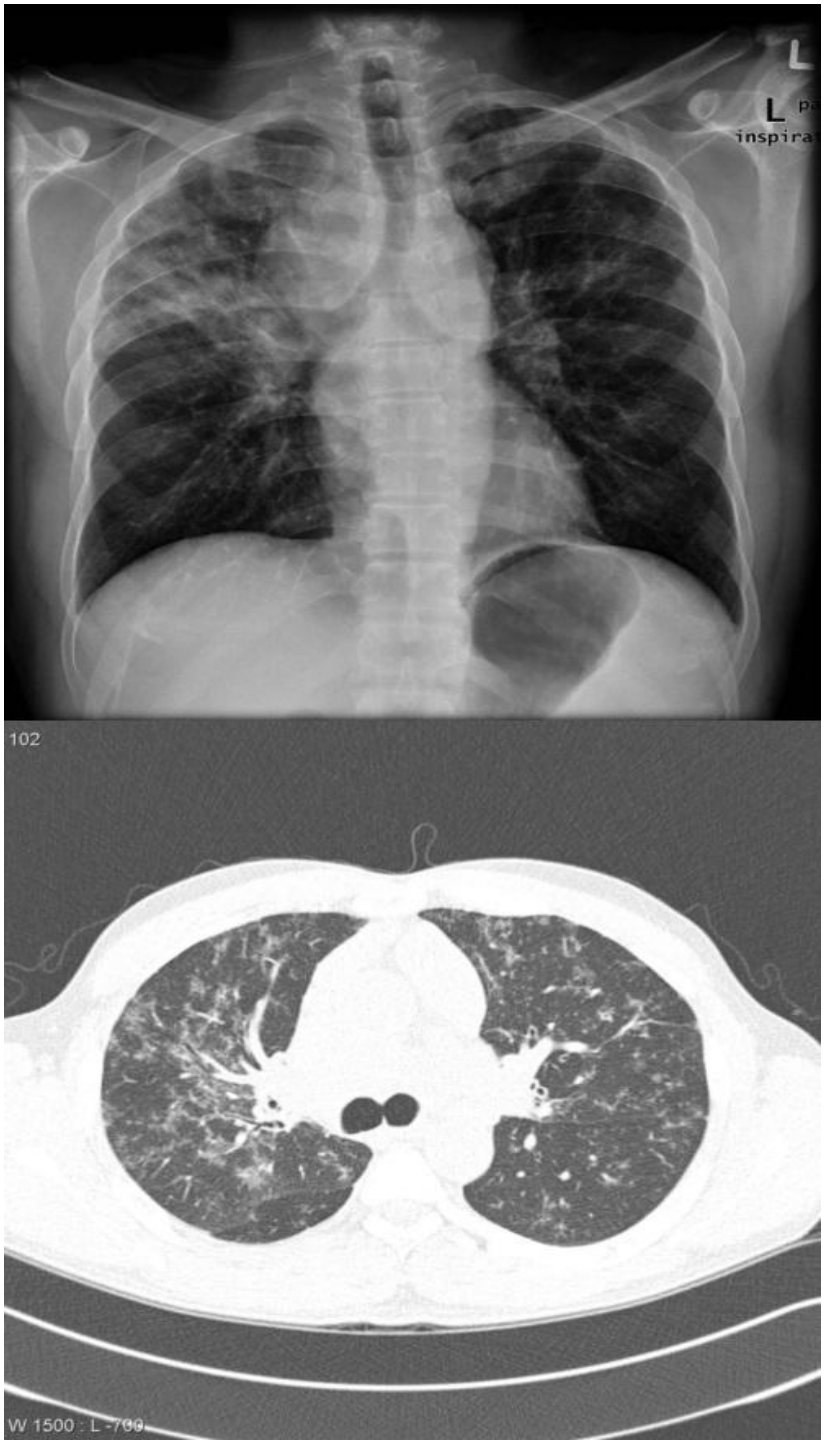
*the Kveim test (where part of the spleen from a patient with known sarcoidosis is injected under the skin) is no longer performed due to concerns about cross-infection

Sarcoidosis: management

Sarcoidosis is a multisystem disorder of unknown aetiology characterised by non-caseating granulomas. It is more common in young adults and in people of African descent.

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
- eye, heart or neuro involvement



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.

Silicosis

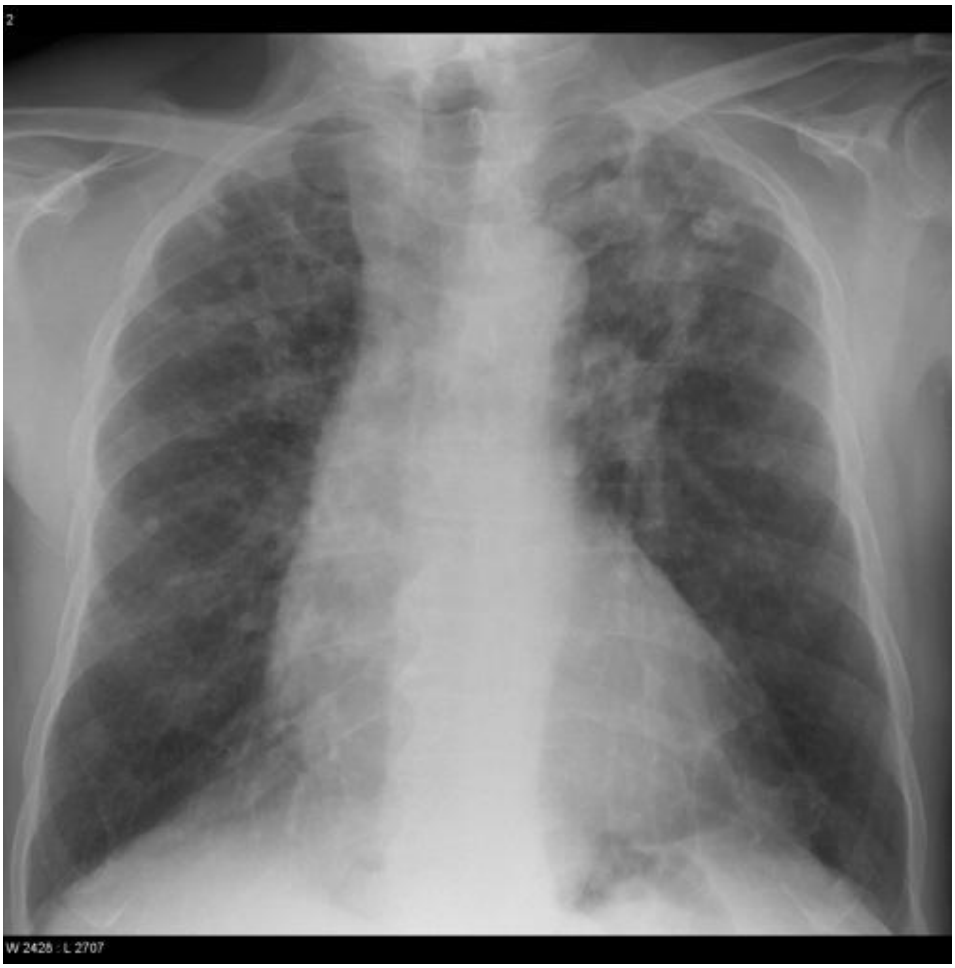
Silicosis is a fibrosing lung disease caused by the inhalation of fine particles of crystalline silicon dioxide (silica). It is a risk factor for developing TB (silica is toxic to macrophages).

Occupations at risk of silicosis

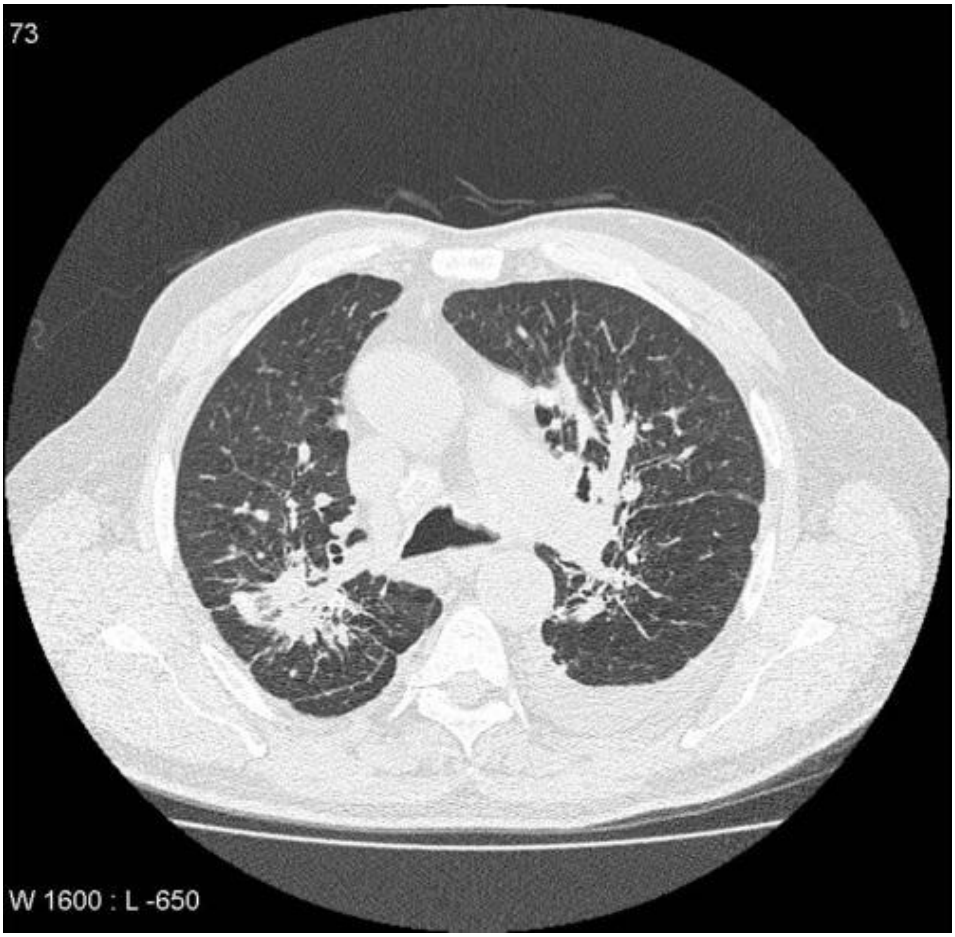
- mining
- slate works
- foundries
- potteries

Features

- fibrosing lung disease
- 'egg-shell' calcification of the hilar lymph nodes



Chest x-ray from a patient with silicosis. Note the bilateral diffuse upper lobe reticular shadowing superimposed with occasional scattered mass like opacities. These features are in keeping with silicosis and progressive massive fibrosis (PMF)



CT scan from a patient with silicosis showing upper zone predominant mass-like scarring with calcification and volume loss. Hilar and mediastinal lymph node calcification also noted. No cavitary changes are seen. There is a left pleural effusion.

Transfer factor

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)

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** **male gender, exercise**	**pulmonary fibrosis** **pneumonia** **pulmonary emboli** **pulmonary oedema** **emphysema** **anaemia** **low cardiac output**

KCO also tends to increase with age. Some conditions may cause an increased KCO with a normal or reduced TLCO

- pneumonectomy/lobectomy
- scoliosis/kyphosis
- neuromuscular weakness
- ankylosis of costovertebral joints e.g. ankylosing spondylitis

Tuberculosis: drug therapy

The standard therapy for treating **active tuberculosis** is:

Initial phase - first 2 months (RIPE)

- Rifampicin
- Isoniazid
- Pyrazinamide
- 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)

Continuation phase - next 4 months

- Rifampicin
- Isoniazid

The treatment for **latent tuberculosis** is isoniazid alone for 6 months

Patients with **meningeal tuberculosis** are treated for a prolonged period (at least 12 months) with the addition of steroids

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: screening

The Mantoux test is the main technique used to screen for latent tuberculosis. 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)

Mantoux test

- 0.1 ml of 1:1,000 purified protein derivative (PPD) injected intradermally
- result read 2-3 days later

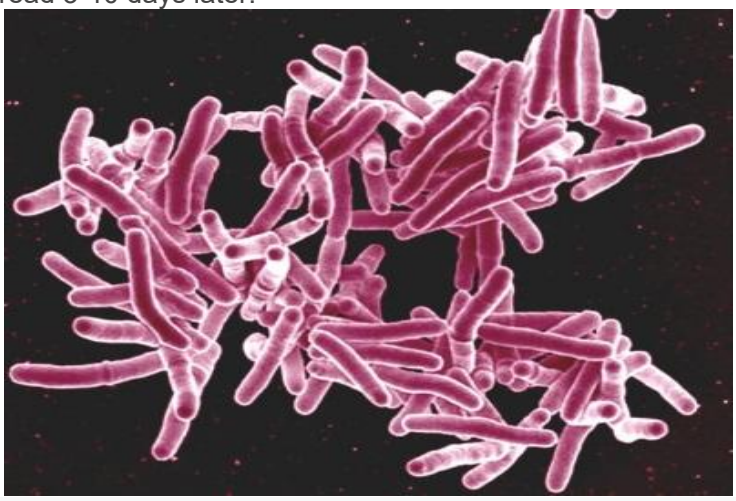
Diameter of induration	Positivity	Interpretation
< 6mm	Negative - no significant hypersensitivity to tuberculin protein	Previously unvaccinated individuals may be given the BCG
6 - 15mm	Positive - hypersensitive to tuberculin protein	Should not be given BCG. May be due to previous TB infection or BCG
> 15mm	Strongly positive - strongly hypersensitive to tuberculin protein	Suggests tuberculosis infection.

False negative tests may be caused by:

- miliary TB
- sarcoidosis
- HIV
- lymphoma
- very young age (e.g. < 6 months)

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.



Scanning electron micrograph of Mycobacterium tuberculosis bacteria, which cause TB. Credit: NIAID

Rheumatology

Adhesive capsulitis

Adhesive capsulitis (frozen shoulder) is a common cause of shoulder pain. It is most common in middle-aged females. The aetiology of frozen shoulder is not fully understood.

Associations

- diabetes mellitus: up to 20% of diabetics may have an episode of frozen shoulder

Features typically develop over days

- external rotation is affected more than internal rotation or abduction
- both active and passive movement are affected
- patients typically have a painful freezing phase, an adhesive phase and a recovery phase
- bilateral in up to 20% of patients
- the episode typically lasts between 6 months and 2 years

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

Ankle injury: Ottawa rules

The Ottawa Rules with 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:

- 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)
- 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)
- 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

Alkaptonuria

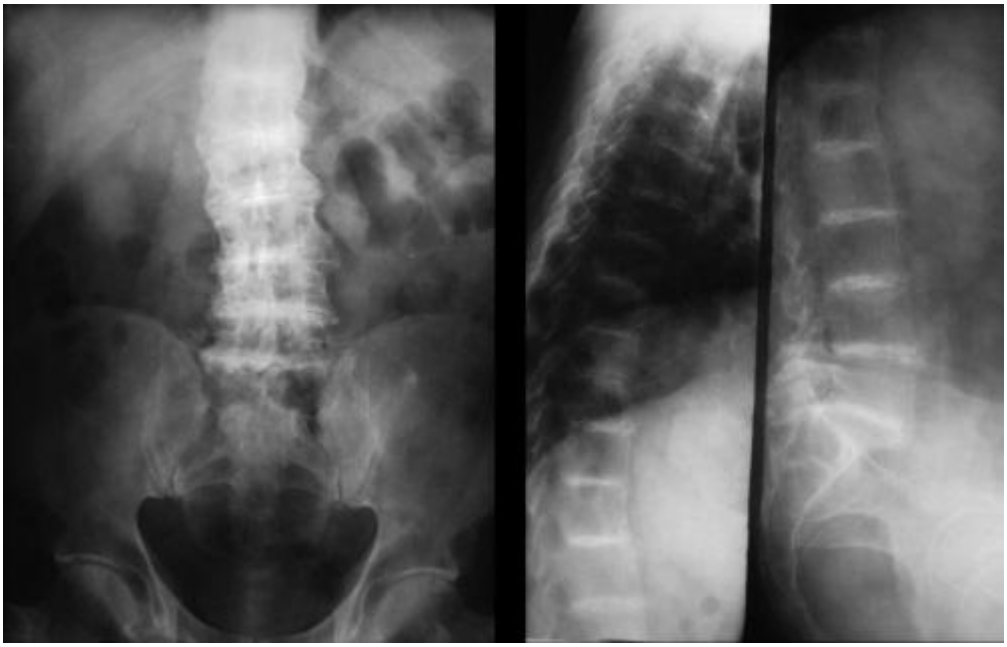
Alkaptonuria (ochronosis) is a rare autosomal recessive disorder of phenylalanine and tyrosine metabolism caused by a lack of the enzyme homogentisic dioxygenase (HGD) which results in a build-up of toxic homogentisic acid. The kidneys filter the homogentisic acid (hence black urine) but eventually it accumulates in cartilage and other tissues.

Alkaptonuria is generally a benign and often asymptomatic condition. Possible features include:

- pigmented sclera
- urine turns black if left exposed to the air
- intervertebral disc calcification may result in back pain
- renal stones

Treatment

- high-dose vitamin C
- dietary restriction of phenylalanine and tyrosine



Multi-level intervertebral disc calcification with disc space narrowing

Ankylosing spondylitis: features

Ankylosing spondylitis is a HLA-B27 associated spondyloarthropathy. It typically presents in males (sex ratio 3:1) aged 20-30 years old.
Features

- typically a young man who presents with lower back pain and stiffness of insidious onset
- stiffness is usually worse in the morning and improves with exercise
- the patient may experience pain at night which improves on getting up

Clinical examination

- reduced lateral flexion
- reduced forward flexion - Schober's test - a line is drawn 10 cm above and 5 cm below the back dimples (dimples of Venus). The distance between the two lines should increase by more than 5 cm when the patient bends as far forward as possible
- reduced chest expansion

Other features - the 'A's

- Apical fibrosis
- Anterior uveitis
- Aortic regurgitation
- Achilles tendonitis
- AV node block
- Amyloidosis
- and cauda equina syndrome
- peripheral arthritis (25%, more common if female)

Ankylosing spondylitis: investigation and management

Ankylosing spondylitis is a HLA-B27 associated spondyloarthropathy. It typically presents in males (sex ratio 3:1) aged 20-30 years old.

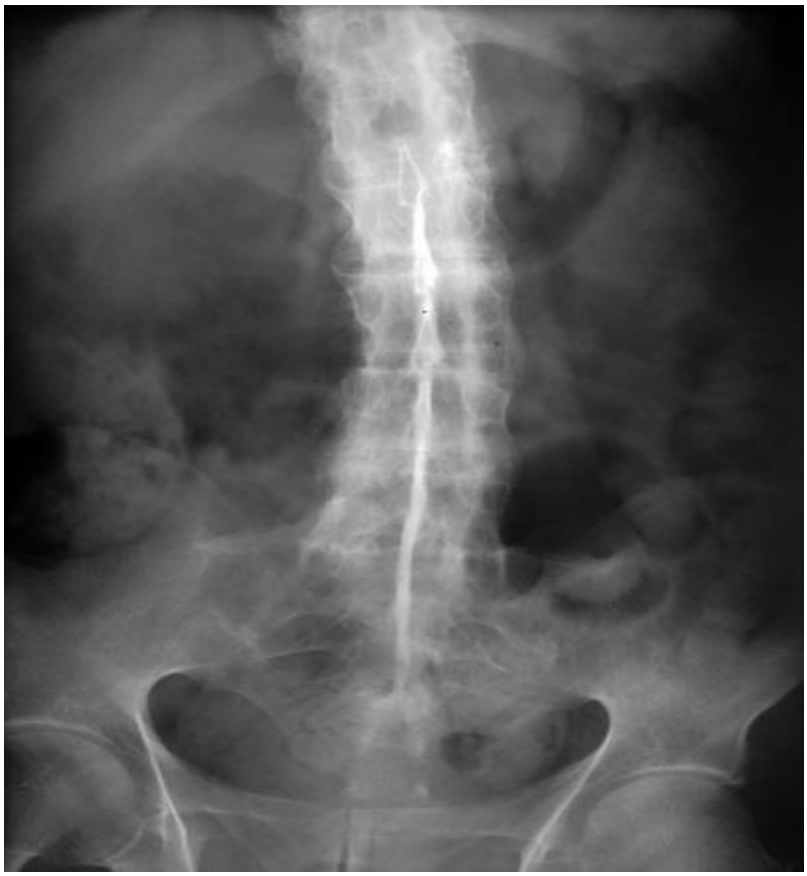
Investigation

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 as it is positive in:

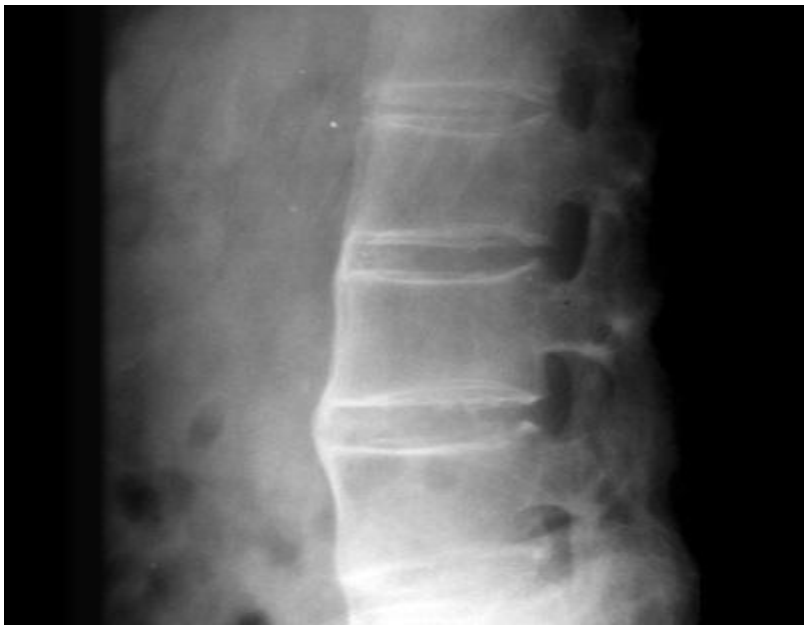
- 90% of patients with ankylosing spondylitis
- 10% of normal patients

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:

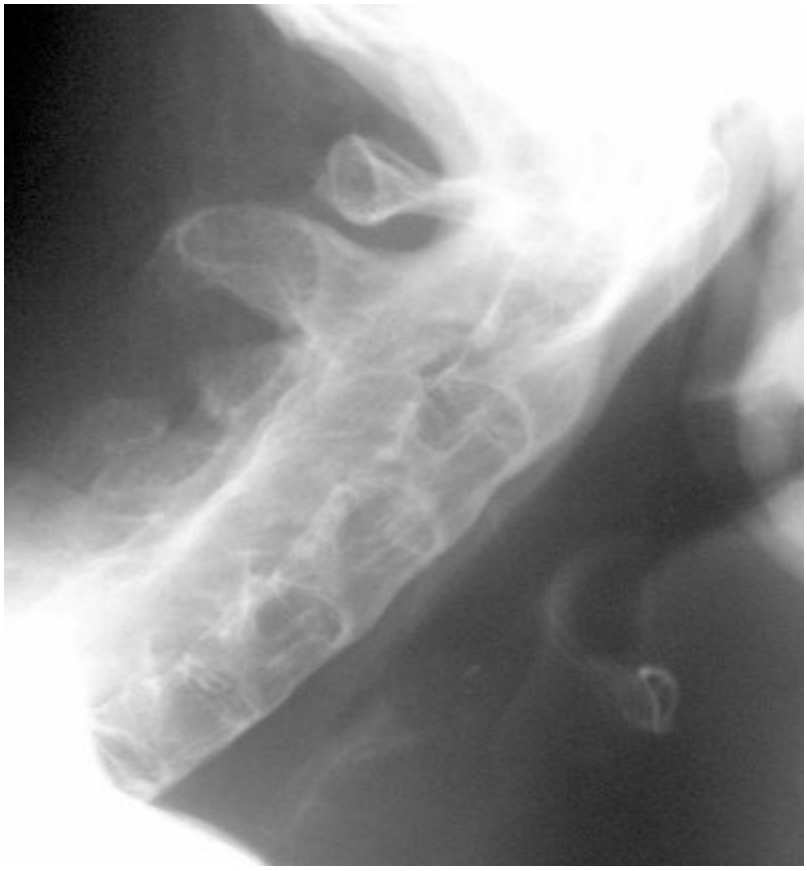
- sacroilitis: subchondral erosions, sclerosis
- squaring of lumbar vertebrae
- 'bamboo spine' (late & uncommon)
- syndesmophytes: due to ossification of outer fibers of annulus fibrosus
- chest x-ray: apical fibrosis



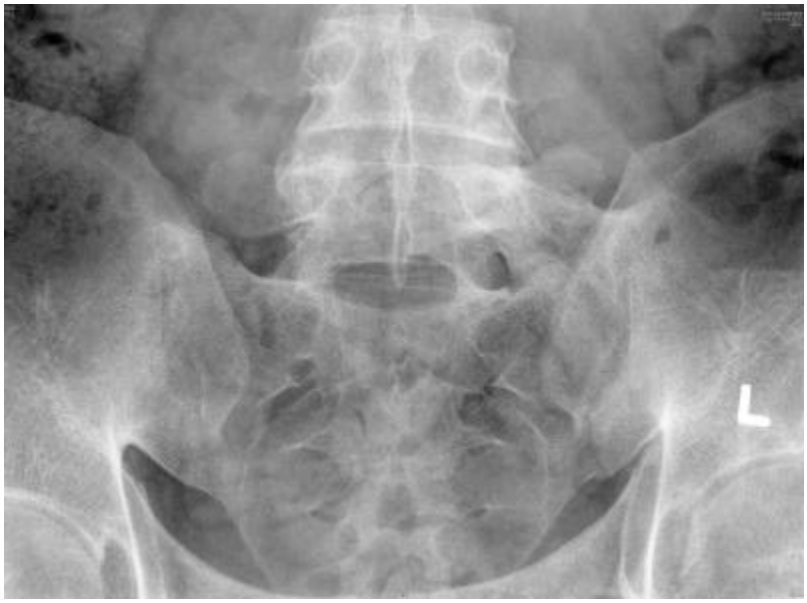
40-year-old male. There is typical appearance of bamboo spine with a single central radiodense line related to ossification of supraspinous and interspinous ligaments which is called dagger sign. Ankylosing is detectable in both sacroiliac joints



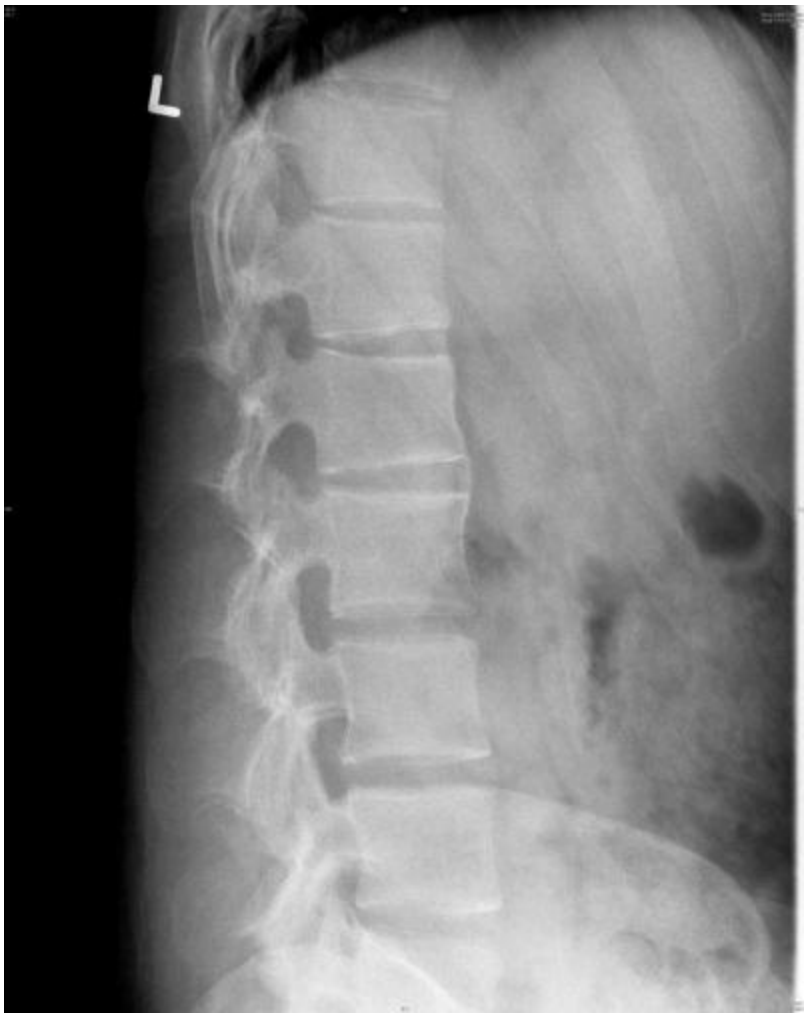
Ankylosing spondylitis with well formed syndesmophytes



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

Spirometry may show a restrictive defect due to a combination of pulmonary fibrosis, kyphosis and ankylosis of the costovertebral joints.

Management

The following is partly based on the 2010 EULAR guidelines (please see the link for more details):

- encourage regular exercise such as swimming
- physiotherapy
- NSAIDs are the first-line treatment
- the disease-modifying drugs which are used to treat rheumatoid arthritis (such as sulphasalazine) are only really useful if there is peripheral joint involvement
- the 2010 EULAR guidelines suggest: *'Anti-TNF therapy should be given to patients with persistently high disease activity despite conventional treatments'*
- research is ongoing to see whether anti-TNF therapies such as etanercept and adalimumab should be used earlier in the course of the disease

Azathioprine

Azathioprine is metabolised to the active compound mercaptopurine, a purine analogue that inhibits purine synthesis. A thiopurine methyltransferase (TPMT) test may be needed to look for individuals prone to azathioprine toxicity.

Adverse effects include

- bone marrow depression
- nausea/vomiting
- pancreatitis

A significant interaction may occur with allopurinol and hence lower doses of azathioprine should be used.

Behcet's syndrome

Behcet's syndrome is a complex multisystem disorder associated with presumed autoimmune mediated inflammation of the arteries and veins. The precise aetiology has yet to be elucidated however. The classic triad of symptoms are oral ulcers, genital ulcers and anterior uveitis

Epidemiology

- more common in the eastern Mediterranean (e.g. Turkey)
- more common in men (complicated gender distribution which varies according to country. Overall, Behcet's is considered to be more common and more severe in men)
- tends to affect young adults (e.g. 20 - 40 years old)
- associated with HLA B5* and MICA6 allele
- around 30% of patients have a positive family history

Features

- classically: 1) oral ulcers 2) genital ulcers 3) anterior uveitis
- thrombophlebitis
- arthritis
- neurological involvement (e.g. aseptic meningitis)
- GI: abdo pain, diarrhoea, colitis
- erythema nodosum, DVT

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)

*more specifically HLA B51, a split antigen of HLA B5

Bisphosphonates

Bisphosphonates are analogues of pyrophosphate, a molecule which decreases demineralisation in bone. They inhibit osteoclasts by reducing recruitment and promoting apoptosis.

Clinical uses

- prevention and treatment of osteoporosis
- hypercalcaemia
- Paget's disease
- pain from bone metatases

Adverse effects

- oesophageal reactions: oesophagitis, oesophageal ulcers (especially alendronate)
- osteonecrosis of the jaw
- 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'

The duration of bisphosphonate treatment varies according to the level of risk. Some authorities recommend stopping bisphosphonates at 5 years if the following apply:

- patient is < 75-years-old
- femoral neck T-score of > -2.5
- low risk according to FRAX/NOGG

Bone disorders: lab values

Disorder	Calcium	Phosphate	ALP	PTH
Osteoporosis	Normal	Normal	Normal	Normal
Osteomalacia	Decreased	Decreased	Increased	Increased
Primary hyperparathyroidism (→ osteitis fibrosa cystica)	Increased	Decreased	Increased	Increased
Chronic kidney disease (→ secondary hyperparathyroidism)	Decreased	Increased	Increased	Increased
Paget's disease	Normal	Normal	Increased	Normal
Osteopetrosis	Normal	Normal	Normal	Normal

Bone tumours

Benign tumours

Tumour	Notes
Osteoma	• benign 'overgrowth' of bone, most typically occuring on the skull • associated with Gardner's syndrome (a variant of familial adenomatous polyposis, FAP)
Osteochondroma (exotosis)	• most common benign bone tumour • more in males, usually diagnosed in patients aged < 20 years • cartilage-capped bony projection on the external surface of a bone
Giant cell tumour	• tumour of multinucleated giant cells within a fibrous stroma • peak incidence: 20-40 years • occurs most frequently in the epiphyses of long bones • X-ray shows a 'double bubble' or 'soap bubble' appearance

Malignant tumours

Tumour	Notes
Osteosarcoma	• most common primary malignant bone tumour • seen mainly in children and adolescents • occurs most frequently in the metaphyseal region of long bones prior to epiphyseal closure, with 40% occuring in the femur, 20% in the tibia, and 10% in the humerus • x-ray shows Codman triangle (from periosteal elevation) and 'sunburst' pattern • mutation of the Rb gene significantly increases risk of osteosarcoma (hence association with retinoblastoma) • other predisposing factors include Paget's disease of the bone and radiotherapy
Ewing's sarcoma	• small round blue cell tumour • seen mainly in children and adolescents • occurs most frequently in the pelvis and long bones. Tends to cause severe pain • associated with t(11;22) translocation which results in an EWS-FLI1 gene product • x-ray shows 'onion skin' appearance
Chondrosarcoma	• malignant tumour of cartilage • most commonly affects the axial skeleton • more common in middle-age

Carpal tunnel syndrome

Carpal tunnel syndrome is caused by compression of median nerve in the carpal tunnel.

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 hypothenar)
- Tinel's sign: tapping causes paraesthesia
- Phalen's sign: flexion of wrist causes symptoms

Causes

- idiopathic
- pregnancy
- oedema e.g. heart failure
- lunate fracture
- rheumatoid arthritis

Electrophysiology

- motor + sensory: prolongation of the action potential

Treatment

- corticosteroid injection
- wrist splints at night
- surgical decompression (flexor retinaculum division)

Chronic fatigue syndrome

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
- 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

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*, coeliac screening and also urinalysis

Management

- cognitive behaviour therapy - very effective, number needed to treat = 2
- graded exercise therapy - a formal supervised program, not advice to go to the gym
- 'pacing' - organising activities to avoid tiring
- low-dose amitriptyline may be useful for poor sleep
- referral to a pain management clinic if pain is a predominant feature

Better prognosis in children

*children and young people only

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
- type II (25%): mixed monoclonal and polyclonal: usually with rheumatoid factor (RF)
- type III (50%): polyclonal: usually with RF

Type I

- monoclonal - IgG or IgM
- associations: multiple myeloma, Waldenström macroglobulinaemia

Type II

- mixed monoclonal and polyclonal: usually with RF
- associations: hepatitis C, RA, Sjogren's, lymphoma

Type III

- polyclonal: usually with RF
- associations: rheumatoid arthritis, 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

Dactylitis

Dactylitis describes the inflammation of a digit (finger or toe).

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

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: with the thumb is flexed across the palm of the hand, pain is reproduced by movement of the wrist into flexion and ulnar deviation

Management

- analgesia
- steroid injection
- immobilisation with a thumb splint (spica) may be effective
- surgical treatment is sometimes required

Dermatomyositis

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

Skin features

- photosensitive
- macular rash over back and shoulder
- heliotrope rash in the periorbital region
- Gottron's papules - roughened red papules over extensor surfaces of fingers
- nail fold capillary dilatation

Other features

- proximal muscle weakness +/- tenderness
- Raynaud's
- respiratory muscle weakness
- interstitial lung disease: e.g. Fibrosing alveolitis or organising pneumonia
- dysphagia, dysphonia

Dermatomyositis: investigations and management

Investigations

- elevated creatine kinase
- EMG
- muscle biopsy
- 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

Management

- prednisolone

Discoid lupus erythematous

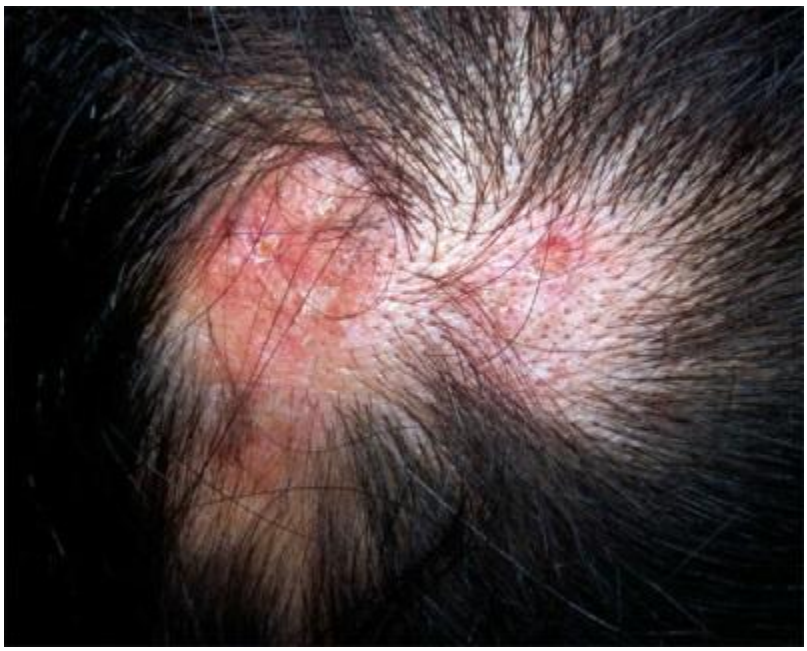
Discoid lupus erythematosus is a benign disorder generally seen in younger females. It very rarely progresses to systemic lupus erythematosus (in less than 5% of cases). Discoid lupus erythematosus is characterised by follicular keratin plugs and is thought to be autoimmune in aetiology

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

Management

- topical steroid cream
- oral antimalarials may be used second-line e.g. hydroxychloroquine
- avoid sun exposure



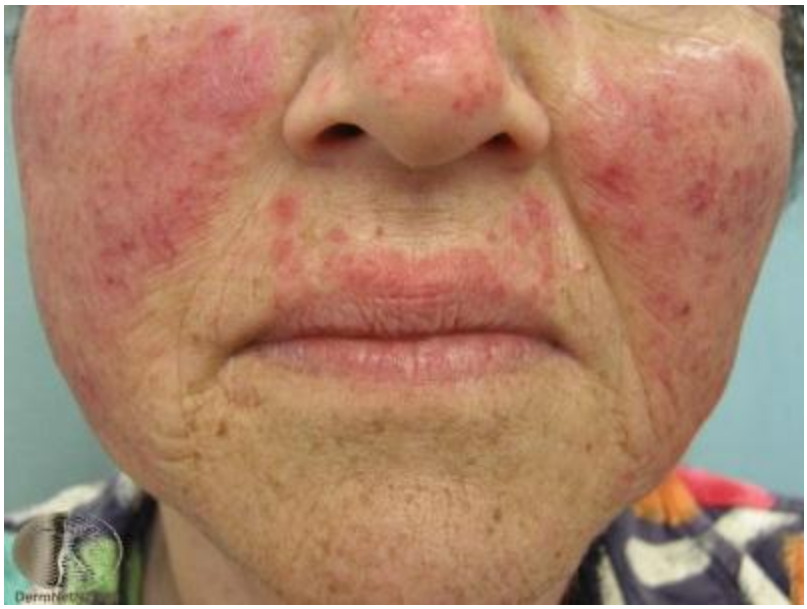
Discoid lupus erythematous affecting the scalp

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.

Features

- arthralgia
- myalgia
- skin (e.g. malar rash) and pulmonary involvement (e.g. pleurisy) are common
- ANA positive in 100%, dsDNA negative
- anti-histone antibodies are found in 80-90%
- anti-Ro, anti-Smith positive in around 5%



A woman with drug-induced lupus

Most common causes

- procainamide
- hydralazine

Less common causes

- isoniazid
- minocycline
- phenytoin

Ehler-Danlos syndrome

Ehler-Danlos syndrome is an autosomal dominant connective tissue disorder that mostly affects type III collagen. This results in the tissue being more elastic than normal leading to joint hypermobility and increased elasticity of the skin.

Features and complications

- elastic, fragile skin
- joint hypermobility: recurrent joint dislocation
- easy bruising
- aortic regurgitation, mitral valve prolapse and aortic dissection
- subarachnoid haemorrhage
- angioid retinal streaks

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**
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

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**
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.

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

Familial Mediterranean Fever

Familial Mediterranean Fever (FMF, also known as recurrent polyserositis) is an autosomal recessive disorder which typically presents by the second decade. It is more common in people of Turkish, Armenian and Arabic descent

Features - attacks typically last 1-3 days

- pyrexia
- abdominal pain (due to peritonitis)
- pleurisy
- pericarditis
- arthritis
- erysipeloid rash on lower limbs

Management

- colchicine may help

Gout: drug causes

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)

Drug causes

- thiazides, furosemide
- alcohol
- cytotoxic agents
- pyrazinamide

Gout: features

Gout is a form of inflammatory arthritis. Patients typically have episodes lasting several days when their gout flares and are often symptom free between episodes. The acute episodes typically develop maximal intensity with 12 hours/ The main features it presents with are:

- pain: this is often very significant
- swelling
- erythema

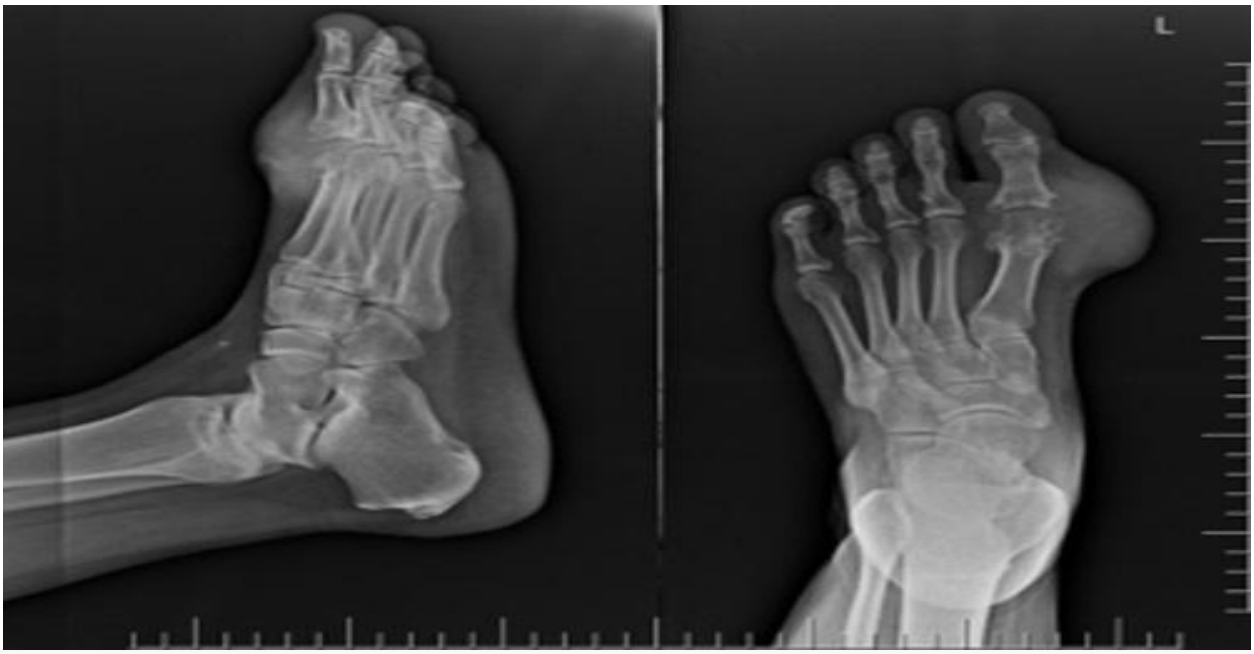
Around 50% of first presentations affect the 1st metatarsophalangeal (MTP) joint. Attacks of gout affecting this area where historically called podogra. Other commonly affected joints include:

- ankle
- wrist
- knee

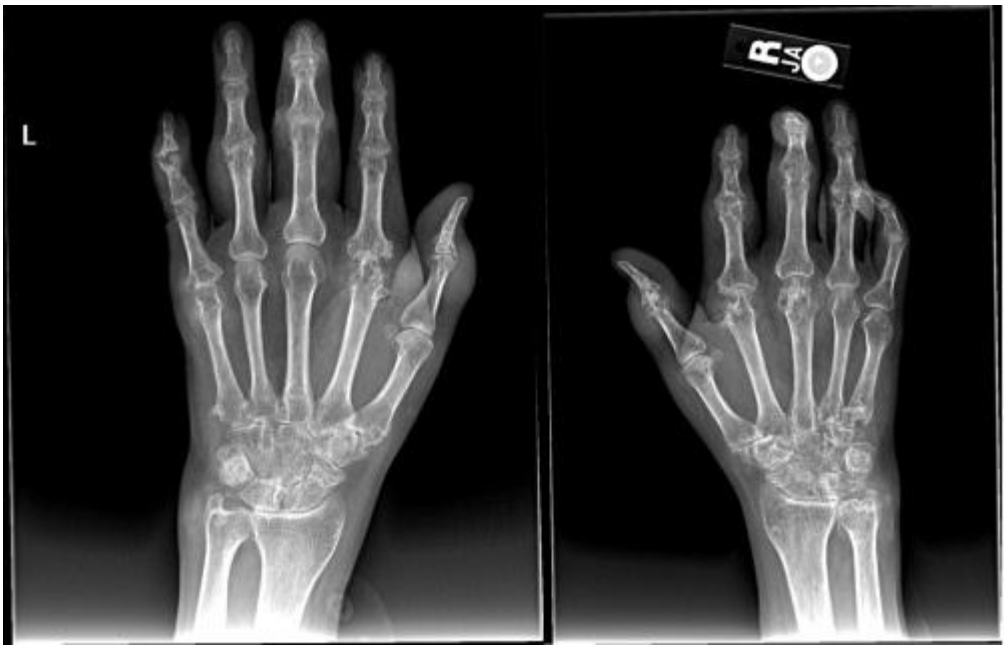
If untreated repeated acute episodes of gout can damage the joints resulting in a more chronic joint problem.

Radiological features of gout include:

- joint effusion is an early sign
- well-defined 'punched-out' erosions with sclerotic margins ina juxta-articular distribution, often with overhanging edges
- relative preservation of joint space until late disease
- eccentric erosions
- no periarticular osteopaenia (in contrast to rheumatoid arthritis)
- soft tissue tophi may be seen



X ray of a patient with gout affecting his feet. It demonstrates juxta-articular erosive changes around the 1st MTP joint with overhanging edges and associated with a moderate soft tissue swelling. The joint space is maintained.



X-ray of a patient with gout affecting his hands. There are multiple periarticular erosions bilaterally with adjacent large soft tissue masses and relatively preserved joint spaces. In the right hand, these findings are most prominent at the 1st interphalangeal, 2nd-4th proximal interphalangeal, 1st-3rd metacarpohalangeal and carpometacarpal joints. In the left hand, the findings are most prominent at the ulnar styloid, scapholunate joint, first and fifth carpometacarpal joints, second and fifth metacarpophalangeal joints and 1st interphalangeal joint.

Gout: predisposing factors

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)

Decreased excretion of uric acid

- drugs*: diuretics
- chronic kidney disease
- lead toxicity

Increased production of uric acid

- myeloproliferative/lymphoproliferative disorder
- cytotoxic drugs
- severe psoriasis

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, self-mutilation

*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

Gout: management

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 > 450 µmol/l)

Acute management

- NSAIDs
- intra-articular steroid injection
- colchicine* has a slower onset of action. The main side-effect is diarrhoea
- oral steroids may be considered if NSAIDs and colchicine are contraindicated. A dose of prednisolone 15mg/day is usually used
- if the patient is already taking allopurinol it should be continued

Allopurinol prophylaxis - see indications below

- 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
- NSAID or colchicine cover should be used when starting allopurinol

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
- prophylaxis if on cytotoxics or diuretics

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

Other points

- losartan has a specific uricosuric action and may be particularly suitable for the many patients who have coexistant hypertension
- calcium channel blockers also decrease 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

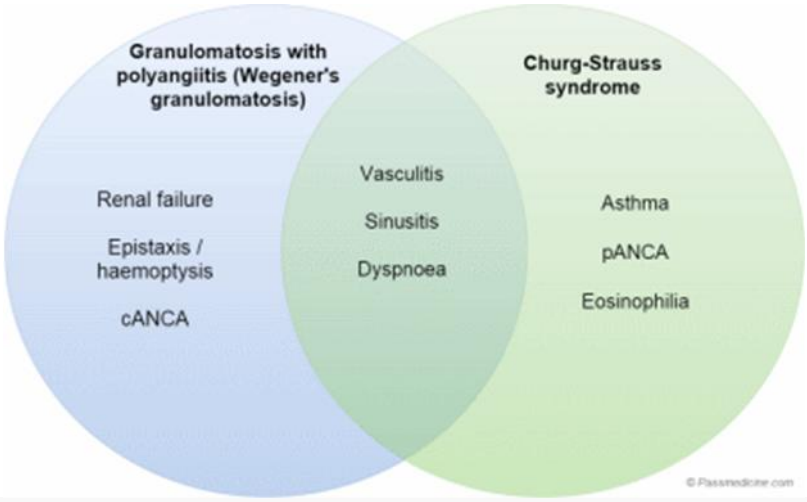
*inhibits microtubule polymerization by binding to tubulin, interfering with mitosis. Also inhibits neutrophil motility and activity
**patients with Lesch-Nyhan syndrome often take allopurinol for life

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.

Features

- upper respiratory tract: epistaxis, sinusitis, nasal crusting
- lower respiratory tract: dyspnoea, haemoptysis
- rapidly progressive glomerulonephritis ('pauci-immune', 80% of patients)
- saddle-shape nose deformity
- also: vasculitic rash, eye involvement (e.g. proptosis), cranial nerve lesions



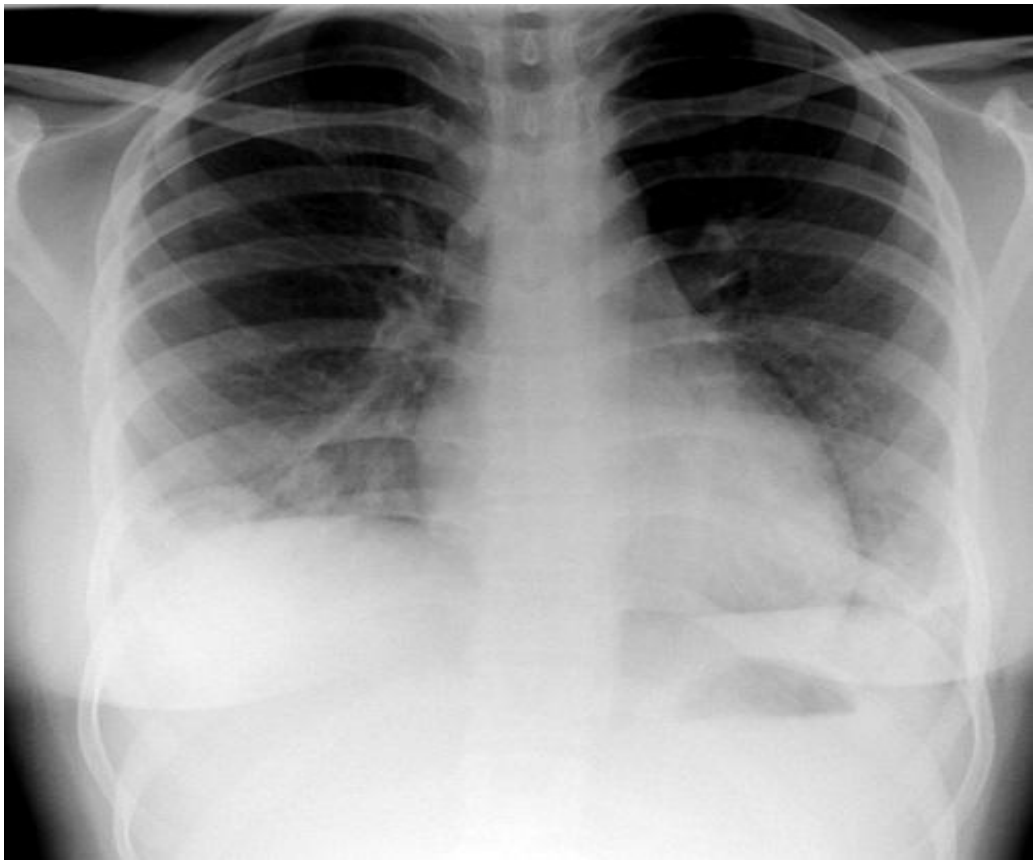
Comparison of granulomatosis with polyangiitis and Churg-Strauss syndrome

Investigations

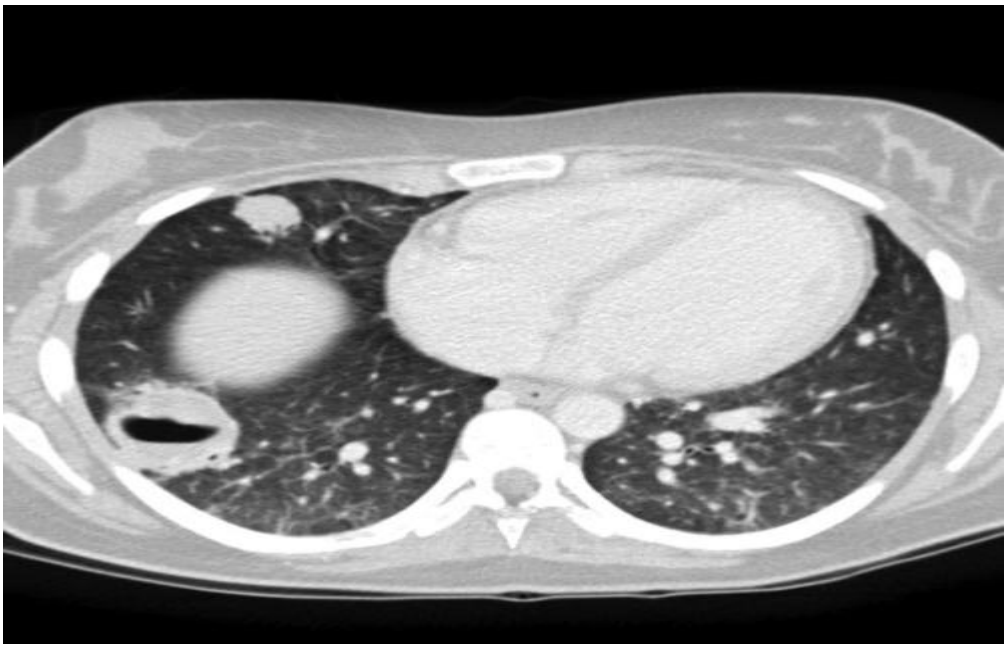
- cANCA positive in > 90%, pANCA positive in 25%
- chest x-ray: wide variety of presentations, including cavitating lesions
- renal biopsy: epithelial crescents in Bowman's capsule

Management

- steroids
- cyclophosphamide (90% response)
- plasma exchange
- median survival = 8-9 years



Chest x-ray from a young male patient with granulomatosis with polyangiitis. Whilst the changes are subtle it demonstrates a number of ill-defined nodules the largest of which projects over the dome of the right hemidiaphragm. This nodule appears to have a central lucency suggesting cavitation



CT of the same patient showing the changes in a much more obvious way, confirming the presence of at least 2 nodules, the larger of the two having a large central cavity and and air-fluid level

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

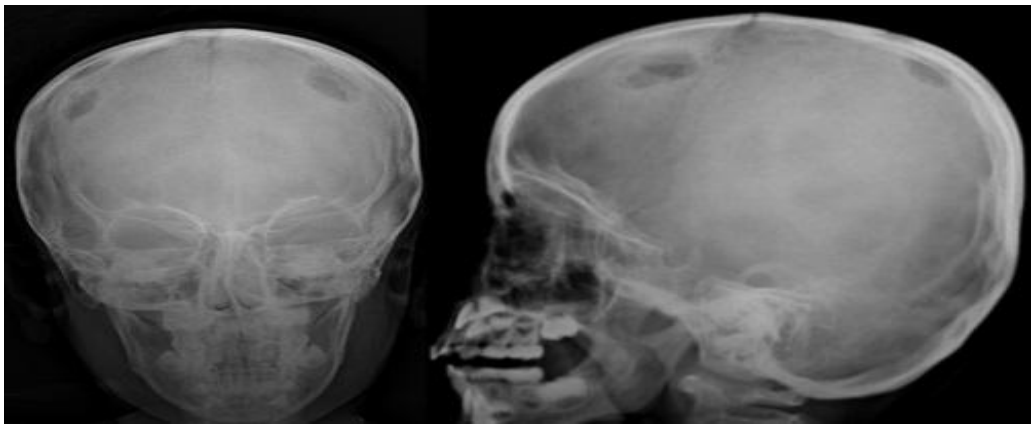
Condition	Features
Pubic symphysis dysfunction	Common in pregnancy Ligament laxity increases in response to hormonal changes of pregnancy Pain over the pubic symphysis with radiation to the groins and the medial aspects of the thighs. A waddling gait may be seen
Transient idiopathic osteoporosis	An uncommon 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

Langerhans cell histiocytosis

Langerhans cell histiocytosis is a rare condition associated with the abnormal proliferation of histiocytes. It typically presents in childhood with bony lesions.

Features

- bone pain, typically in the skull or proximal femur
- cutaneous nodules
- recurrent otitis media/mastoiditis
- tennis racket-shaped Birbeck granules on electromicroscopy



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.

Lateral epicondylitis

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

McArdle's disease

Overview

- autosomal recessive type V glycogen storage disease
- caused by myophosphorylase deficiency
- this causes decreased muscle glycogenolysis

Features

- muscle pain and stiffness following exercise
- muscle cramps
- myoglobinuria
- low lactate levels during exercise

Methotrexate

Methotrexate is an antimetabolite which inhibits dihydrofolate reductase, an enzyme essential for the synthesis of purines and pyrimidines

Indications

- rheumatoid arthritis
- psoriasis
- acute lymphoblastic leukaemia

Adverse effects

- mucositis
- myelosuppression
- pneumonitis
- pulmonary fibrosis
- liver cirrhosis

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 a drug with a high potential for patient harm. It is therefore important that you are familiar with guidelines relating to its use
- 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 weekly (source: BNF)
- only one strength of methotrexate tablet should be prescribed (usually 2.5 mg)
- avoid prescribing trimethoprim or cotrimoxazole concurrently - increases risk of marrow aplasia

Mixed connective tissue disease

Features of SLE, systemic sclerosis and polymyositis

Anti-RNP positive

Myopathies

Features

- symmetrical muscle weakness (proximal > distal)
- common problems are rising from chair or getting out of bath
- sensation normal, reflexes normal, no fasciculation

Causes

- inflammatory: polymyositis
- inherited: Duchenne/Becker muscular dystrophy, myotonic dystrophy
- endocrine: Cushing's, thyrotoxicosis
- alcohol

Osteoarthritis: management

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, 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

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: causes

Advancing age and female sex and significant risk factors for osteoporosis. Prevalence of osteoporosis increases from 2% at 50 years to more than 25% at 80 years in women.

There are many other risk factors and secondary causes of osteoporosis. We'll start by looking at the most 'important' ones - these 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
- low body mass index
- current smoking

Other risk factors

- sedentary lifestyle
- premature menopause
- 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

Medications that may worsen osteoporosis (other than glucocorticoids):

- SSRIs
- antiepileptics
- proton pump inhibitors
- glitazones
- long term heparin therapy
- aromatase inhibitors e.g. anastrozole

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

Osteoporosis: DEXA scan

Basics

- T score: based on bone mass of young reference population
- 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

T score

- > -1.0 = normal
- -1.0 to -2.5 = osteopaenia
- < -2.5 = osteoporosis

Osteoporosis: glucocorticoid-induced

We know that one of the most important risk factors for osteoporosis is the use of corticosteroids. As these drugs are so widely used in clinical practice it is important we manage this risk appropriately.

The most widely followed guidelines are based around the 2002 Royal College of Physicians (RCP) 'Glucocorticoid-induced osteoporosis: A concise guide to prevention and treatment'.

The risk of osteoporosis is thought to rise significantly once a patient is taking the equivalent of prednisolone 7.5mg a day for 3 or more months. It is important to note that we should manage patients 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 essentially divide patients into two groups.

1. Patients over the age of 65 years or those who've previously had a fragility fracture should be offered bone protection.

2. Patients under the age of 65 years should be offered a bone density scan, with further management dependent:

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

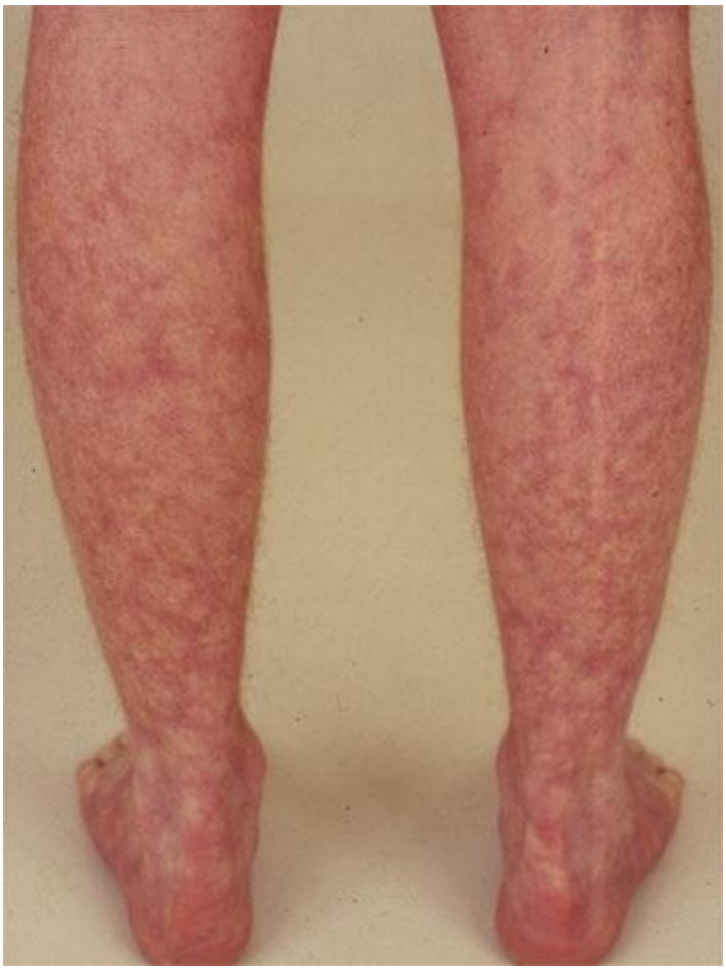
The first-line treatment is alendronate. Patients should also be calcium and vitamin D replete.

Polyarteritis nodosa

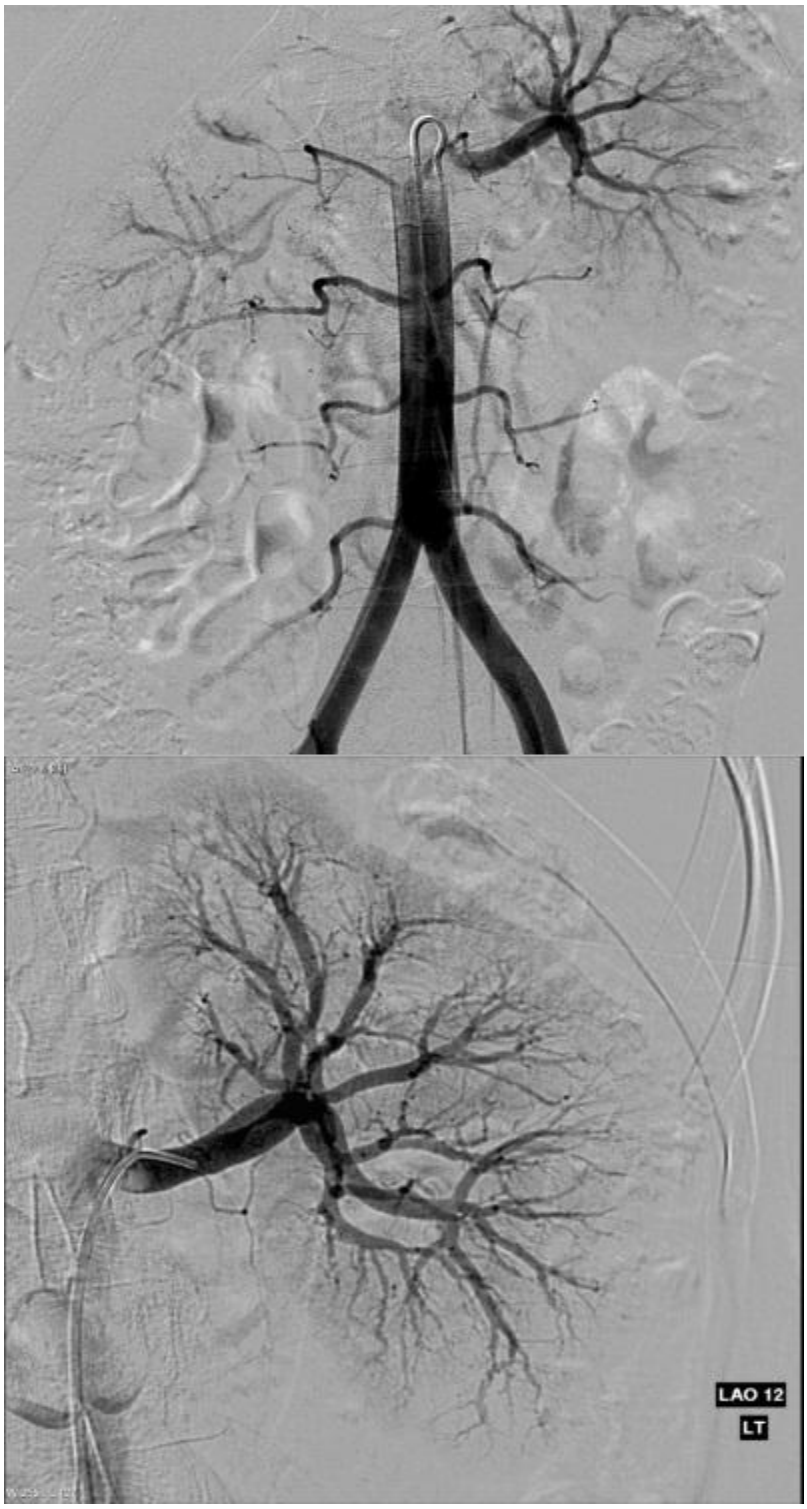
Polyarteritis nodosa (PAN) is a vasculitis affecting medium-sized arteries with necrotizing inflammation leading to aneurysm formation. PAN is more common in middle-aged men and is associated with hepatitis B infection

Features

- fever, malaise, arthralgia
- weight loss
- hypertension
- mononeuritis multiplex, sensorimotor polyneuropathy
- testicular pain
- livedo reticularis
- haematuria, renal failure
- perinuclear-antineutrophil cytoplasmic antibodies (ANCA) are found in around 20% of patients with 'classic' PAN
- hepatitis B serology positive in 30% of patients



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.

Polyarthritis

Differential diagnosis

- rheumatoid arthritis
- SLE
- seronegative spondyloarthropathies
- Henoch-Schonlein purpura
- sarcoidosis
- tuberculosis
- pseudogout
- viral infection: EBV, HIV, hepatitis, mumps, rubella

Polymyalgia rheumatica

Pathophysiology

- overlaps with temporal 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

Features

- typically patient > 60 years old
- usually rapid onset (e.g. < 1 month)
- aching, morning stiffness in proximal limb muscles (not weakness)
- also mild polyarthralgia, lethargy, depression, low-grade fever, anorexia, night sweats

Investigations

- ESR > 40 mm/hr
- note CK and EMG normal
- reduced CD8+ T cells

Treatment

- prednisolone e.g. 15mg/od - dramatic response

Polymyositis

Overview

- inflammatory disorder causing symmetrical, proximal muscle weakness
- thought to be a T-cellmediated cytotoxic process directed against muscle fibres
- may be idiopathic or associated with connective tissue disorders
- associated with malignancy
- 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

Features

- proximal muscle weakness +/- tenderness
- Raynaud's
- respiratory muscle weakness
- interstitial lung disease: e.g. fibrosing alveolitis or organising pneumonia
- dysphagia, dysphonia

Investigations

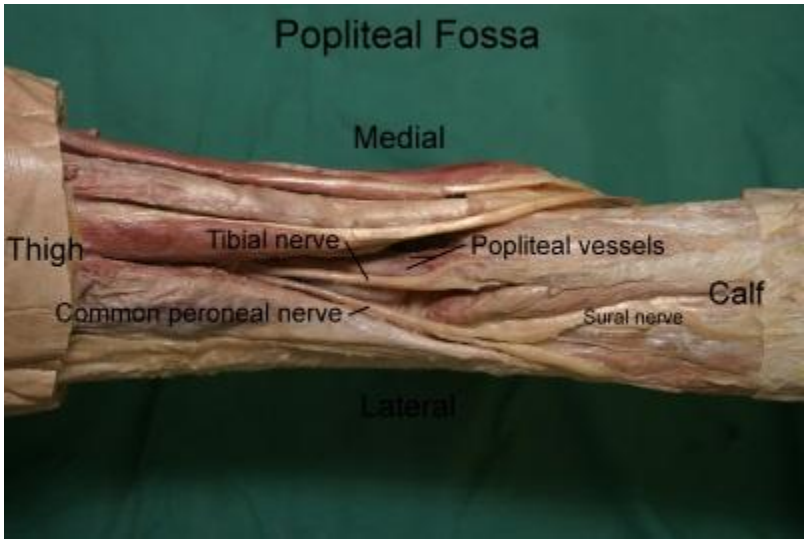
- elevated creatine kinase
- EMG
- muscle biopsy
- anti-Jo-1 antibodies are seen in pattern of disease associated with lung involvement, Raynaud's and fever

Popliteal fossa

Boundaries of the popliteal fossa

Laterally	Biceps femoris above, lateral head of gastrocnemius and plantaris below
Medially	Semimembranosus and semitendinosus above, medial head of gastrocnemius below
Floor	Popliteal surface of the femur, posterior ligament of knee joint and popliteus muscle
Roof	Superficial and deep fascia

Image showing the popliteal fossa



Contents

- Popliteal artery and vein
- Small saphenous vein
- Common peroneal nerve
- Tibial nerve
- Posterior cutaneous nerve of the thigh
- Genicular branch of the obturator nerve
- Lymph nodes

Pseudogout

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: weakly-positively birefringent rhomboid shaped crystals
- x-ray: chondrocalcinosis

Management

- aspiration of joint fluid, to exclude septic arthritis
- NSAIDs or intra-articular, intra-muscular or oral steroids as for gout

Psoriatic arthropathy

Psoriatic arthropathy correlates poorly with cutaneous psoriasis and often precedes the development of skin lesions. Around 10-20% percent of patients with skin lesions develop an arthropathy with males and females being equally affected

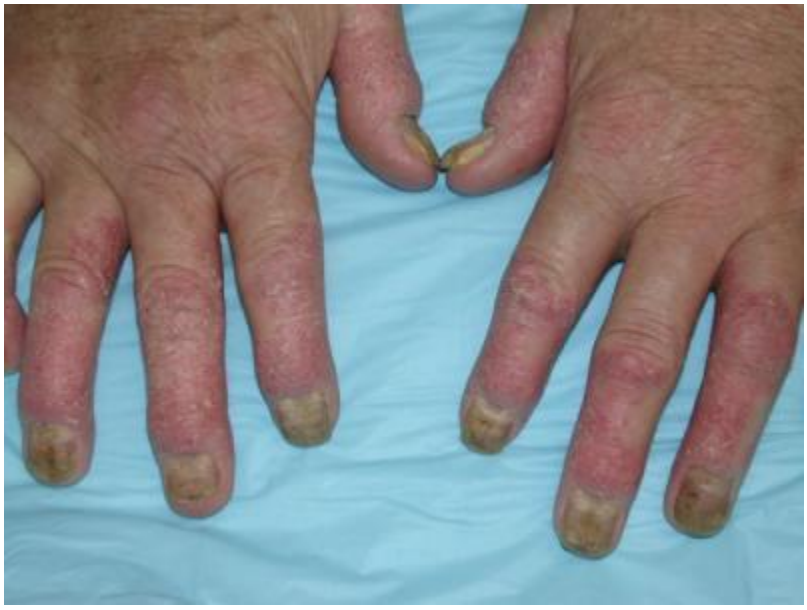
Types*

- rheumatoid-like polyarthritis: (30-40%, most common type)
- asymmetrical oligoarthritis: typically affects hands and feet (20-30%)
- sacroilitis
- DIP joint disease (10%)
- arthritis mutilans (severe deformity fingers/hand, 'telescoping fingers')

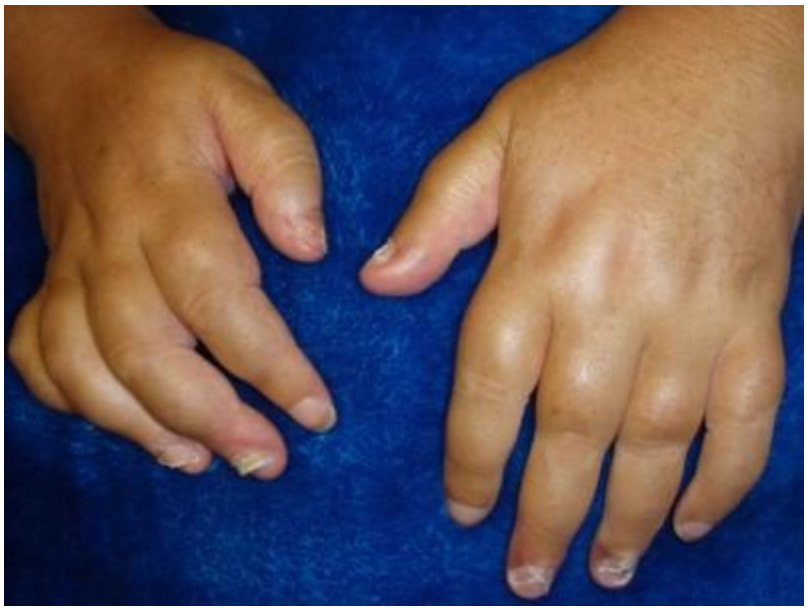
Management

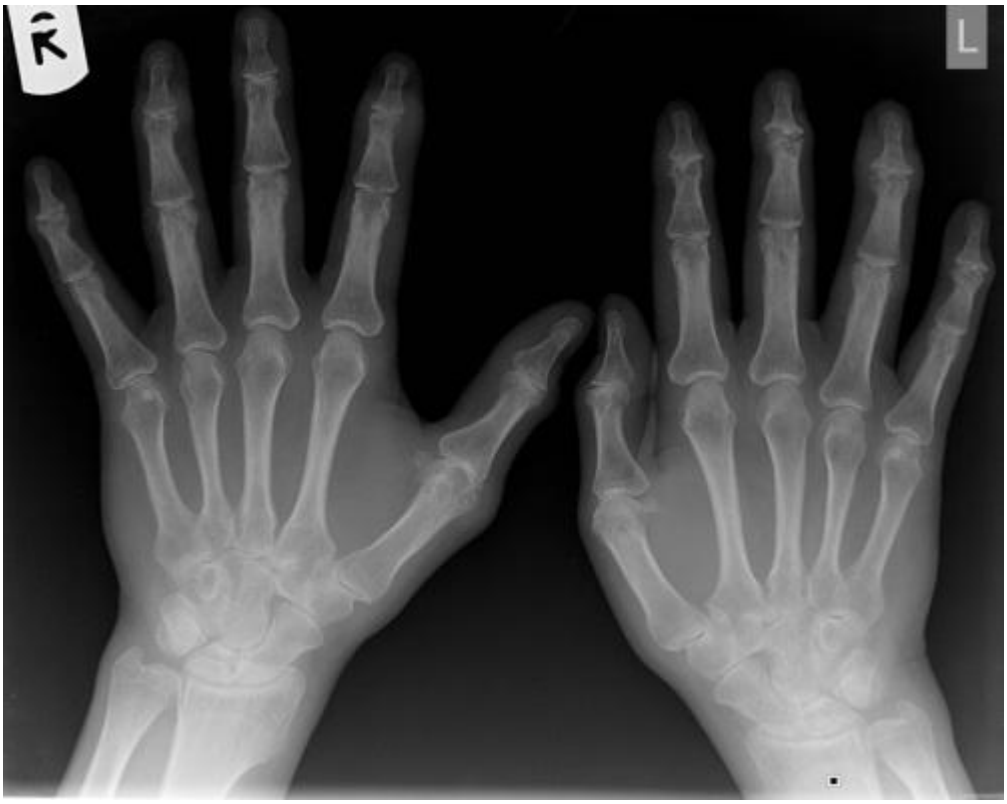
- treat as rheumatoid arthritis
- but better prognosis

*Until recently it was thought asymmetrical oligoarthritis was the most common type, based on data from the original 1973 Moll and Wright paper. Please see the link for a comparison of more recent studies

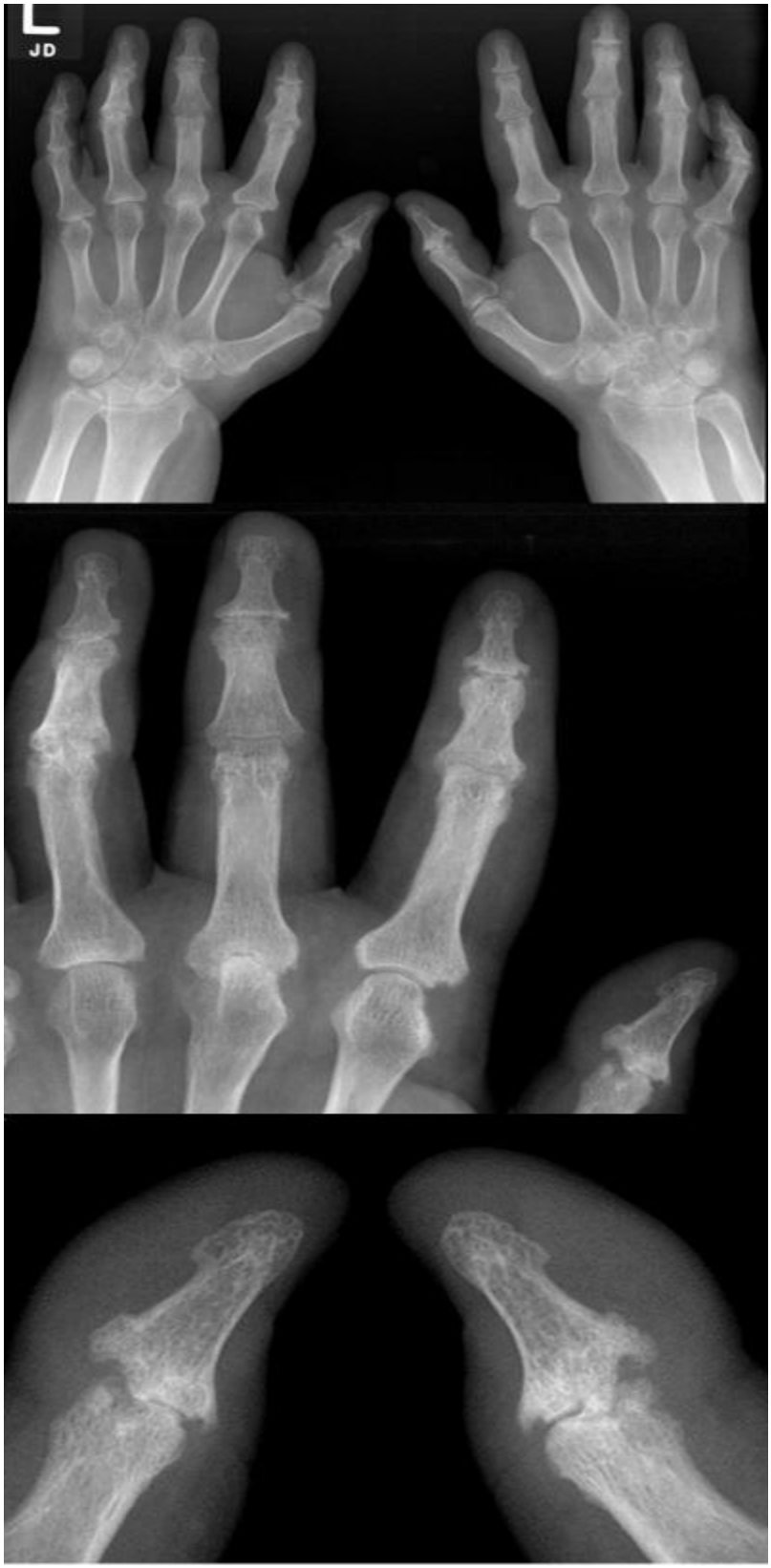


Notice the nail changes on this image as well





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.



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.

Raynaud's

Raynaud's phenomena may be primary (Raynaud's disease) or secondary (Raynaud's phenomenon)

Raynaud's disease typically presents in young women (e.g. 30 years old) with symmetrical attacks

Factors suggesting underlying connective tissue disease

- onset after 40 years
- 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

Secondary causes

- connective tissue disorders: scleroderma (most common), rheumatoid arthritis, SLE
- leukaemia
- type I cryoglobulinaemia, cold agglutinins
- use of vibrating tools
- drugs: oral contraceptive pill, ergot
- cervical rib

Management

- first-line: calcium channel blockers e.g. nifedipine
- IV prostacyclin infusions: effects may last several weeks/months

Reactive arthritis

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).

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'

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*

Management

- symptomatic: analgesia, NSAIDS, intra-articular steroids
- sulfasalazine and methotrexate are sometimes used for persistent disease
- symptoms rarely last more than 12 months

Reactive arthritis: features

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).

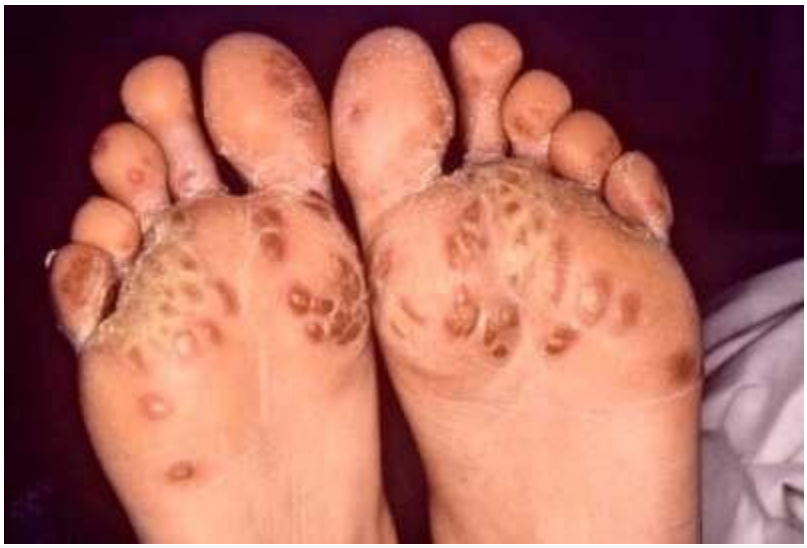
Reactive arthritis is defined as an arthritis that develops following an infection where the organism cannot be recovered from the joint.

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
- 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)

Around 25% of patients have recurrent episodes whilst 10% of patients develop chronic disease

'Can't see, pee or climb a tree'



Keratoderma blenorrhagica

Rheumatoid arthritis: epidemiology

Epidemiology

- peak onset = 30-50 years, although occurs in all age groups
- F:M ratio = 3:1
- prevalence = 1%
- some ethnic differences e.g. high in Native Americans
- associated with HLA-DR4 (especially Felty's syndrome)

Rheumatoid arthritis: presentation

Typical features

- swollen, painful joints in hands and feet
- stiffness worse in the morning
- gradually gets worse with larger joints becoming involved
- presentation usually insidiously develops over a few months
- positive 'squeeze test' - discomfort on squeezing across the metacarpal or metatarsal joints

Other presentations:

- acute onset with marked systemic disturbance
- relapsing/remitting monoarthritis of different large joints (palindromic rheumatism)

Rheumatoid arthritis: x-ray changes

Early x-ray findings

- loss of joint space
- juxta-articular osteoporosis
- soft-tissue swelling

Late x-ray findings

- periarticular erosions
- subluxation

Rheumatoid arthritis: diagnosis

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)

Key

- RF = rheumatoid factor
- ACPA = anti-cyclic citrullinated peptide antibody

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
	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

Rheumatoid arthritis: antibodies

Rheumatoid factor

Rheumatoid factor (RF) is a circulating antibody (usually IgM) which reacts with the Fc portion of the patients own IgG

RF can be detected by either

- Rose-Waaler test: sheep red cell agglutination
- Latex agglutination test (less specific)

RF is positive in 70-80% of patients with rheumatoid arthritis, high titre levels are associated with severe progressive disease (but NOT a marker of disease activity)

Other conditions associated with a positive RF include:

- Sjogren's syndrome (around 100%)
- Felty's syndrome (around 100%)
- infective endocarditis (= 50%)
- SLE (= 20-30%)
- systemic sclerosis (= 30%)
- general population (= 5%)
- rarely: TB, HBV, EBV, leprosy

Anti-cyclic citrullinated peptide antibody
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 a sensitivity similar to rheumatoid factor (70-80%, see below) with a much higher specificity of 90-95%.

NICE recommends that patients with suspected rheumatoid arthritis who are rheumatoid factor negative should be test for anti-CCP antibodies.

- hypoxanthine-guanine phosphoribosyl transferase (HGPRTase) deficiency
- x-linked recessive therefore only seen in boys
- features: gout, renal failure, neurological deficits, learning difficulties, self-mutilation

*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

Rheumatoid arthritis: prognostic features

A number of features have been shown to predict a poor prognosis in patients with rheumatoid arthritis, as listed below
Poor prognostic features

- rheumatoid factor positive
- poor functional status at presentation
- HLA DR4
- X-ray: early erosions (e.g. after < 2 years)
- extra articular features e.g. nodules
- insidious onset
- anti-CCP antibodies

In terms of gender there seems to be a split in what the established sources state is associated with a poor prognosis. However both the American College of Rheumatology and the recent NICE guidelines (which looked at a huge number of prognosis studies) seem to conclude that female gender is associated with a poor prognosis.

Rheumatoid arthritis: complications

A wide variety of extra-articular complications occur in patients with rheumatoid arthritis (RA):

- respiratory: pulmonary fibrosis, pleural effusion, pulmonary nodules, bronchiolitis obliterans, methotrexate pneumonitis, pleurisy
- ocular: keratoconjunctivitis sicca (most common), episcleritis, scleritis, corneal ulceration, keratitis, steroid-induced cataracts, chloroquine retinopathy
- osteoporosis
- ischaemic heart disease: RA carries a similar risk to type 2 diabetes mellitus
- increased risk of infections
- depression

Less common

- Felty's syndrome (RA + splenomegaly + low white cell count)
- amyloidosis

Rheumatoid arthritis: management

The management of rheumatoid arthritis (RA) has been revolutionised by the introduction of disease-modifying therapies in the past decade. NICE has issued a number of technology appraisals on the newer agents and released general guidelines in 2009.

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.

Initial therapy

- in the 2009 NICE guidelines it is recommend that patients with newly diagnosed active RA start a combination of DMARDs (including methotrexate and at least one other DMARD, plus short-term glucocorticoids)

DMARDs

- methotrexate is the most widely used DMARD. Monitoring of FBC & LFTs is essential due to the risk of myelosuppression and liver cirrhosis. Other important side-effects include pneumonitis
- sulfasalazine
- leflunomide
- hydroxychloroquine

TNF-inhibitors

- the current indication for a TNF-inhibitor is an inadequate response to at least two DMARDs including methotrexate
- etanercept: recombinant human protein, acts as a decoy receptor for TNF-α, subcutaneous administration, can cause demyelination, risks include reactivation of tuberculosis
- infliximab: monoclonal antibody, binds to TNF-α and prevents it from binding with TNF receptors, intravenous administration, risks include reactivation of tuberculosis
- adalimumab: monoclonal antibody, subcutaneous administration

Rituximab

- anti-CD20 monoclonal antibody, results in B-cell depletion
- two 1g intravenous infusions are given two weeks apart
- infusion reactions are common

Abatacept

- fusion protein that modulates a key signal required for activation of T lymphocytes
- leads to decreased T-cell proliferation and cytokine production
- given as an infusion
- not currently recommend by NICE

Rheumatoid arthritis: pregnancy

Rheumatoid arthritis (RA) typically develops in women of a reproductive age. Issues surrounding conception are therefore commonly encountered. There are no current published guidelines regarding how patients considering conception should be managed although expert reviews are largely in agreement.

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
- methotrexate is not safe in pregnancy and needs to be stopped at least 3 months before conception
- leflunomide is not safe in pregnancy
- sulfasalazine and hydroxychloroquine are considered safe in pregnancy
- interestingly studies looking at pregnancy outcomes in patients treated with TNF-α blockers do not show any significant increase in adverse outcomes. It should be noted however that many of the patients included in the study stopped taking TNF-α blockers when they found out they were pregnant
- low-dose corticosteroids may be used in pregnancy to control symptoms
- 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
- patients should be referred to an obstetric anaesthetist due to the risk of atlanto-axial subluxation

Rotator cuff muscles

SItS - small t for teres minor

Supraspinatus
Infraspinatus
teres minor
Subscapularis

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

Sarcoidosis: prognostic features

Sarcoidosis is a multisystem disorder of unknown aetiology characterised by non-caseating granulomas. It is more common in young adults and in people of African descent. Sarcoidosis remits without treatment in approximately two-thirds of people

Factors associated with poor prognosis

- insidious onset, symptoms > 6 months
- absence of erythema nodosum
- extrapulmonary manifestations: e.g. lupus pernio, splenomegaly
- CXR: stage III-IV features
- black people

Septic arthritis

Overview

- most common organism overall is *Staphylococcus aureus*
- in young adults who are sexually active *Neisseria gonorrhoeae* should also be considered

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)
- needle aspiration should be used to decompress the joint
- arthroscopic lavage may be required

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)

Systemic lupus erythematosus

Epidemiology

- much more common in females (F:M = 9:1)
- more common in Afro-Caribbeans* and Asian communities
- 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

*It is said the incidence in black Africans is much lower than in black Americans - the reasons for this are unclear

SLE: investigations

Immunology

- 99% are ANA positive
- 20% are rheumatoid factor positive
- anti-dsDNA: highly specific (> 99%), but less sensitive (70%)
- anti-Smith: most specific (> 99%), sensitivity (30%)
- also: anti-U1 RNP, SS-A (anti-Ro) and SS-B (anti-La)

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)

SLE: pregnancy

Overview

- 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

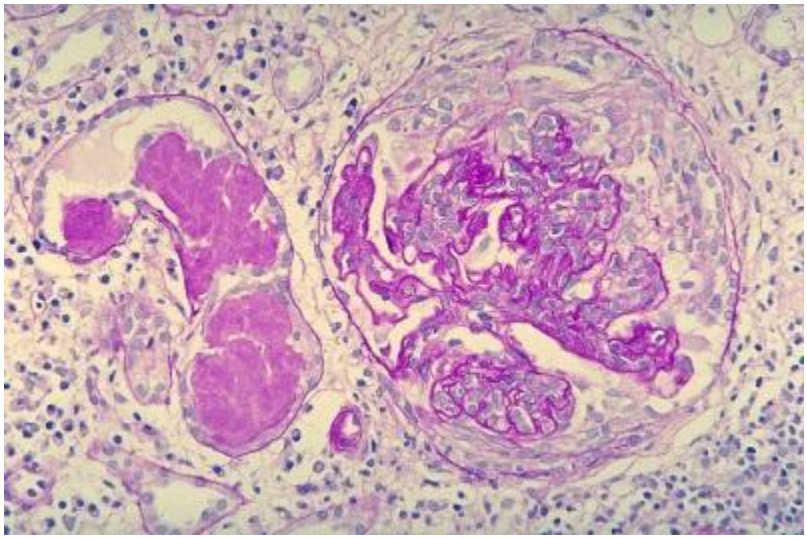
SLE: renal complications

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

Class IV (diffuse proliferative glomerulonephritis) is the most common and severe form. Renal biopsy characteristically shows the following findings:

- glomeruli shows endothelial and mesangial proliferation, 'wire-loop' appearance
- if severe, the capillary wall may be thickened secondary to immune complex deposition
- electron microscopy shows subendothelial immune complex deposits
- granular appearance on immunofluorescence



Diffuse proliferative SLE. Proliferation of endothelial and mesangial cells. The thickening of the capillary wall results in a 'wire-loop' appearance. Some crescents are present.

Management

- treat hypertension
- corticosteroids if clinical evidence of disease
- immunosuppressants e.g. azathiopine/cyclophosphamide

Still's disease in adults

Adult Still's disease

- typically affects 16-35 year olds

Features

- arthralgia
- elevated serum ferritin
- rash: salmon-pink, maculopapular
- pyrexia
- lymphadenopathy
- rheumatoid factor (RF) and anti-nuclear antibody (ANA) negative

Temporal arteritis

Temporal arteritis is large vessel vasculitis which overlaps with polymyalgia rheumatica (PMR). Histology shows changes which characteristically 'skips' certain sections of affected artery whilst damaging others.

Features

- typically patient > 60 years old
- usually rapid onset (e.g. < 1 month)
- headache (found in 85%)
- jaw claudication (65%)
- visual disturbances secondary to anterior ischemic optic neuropathy
- 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
- temporal artery biopsy: skip lesions may be present
- 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

Systemic sclerosis

Systemic sclerosis is a condition of unknown aetiology characterised by hardened, sclerotic skin and other connective tissues. It is four times more common in females

There are three patterns of disease:

Limited cutaneous systemic sclerosis

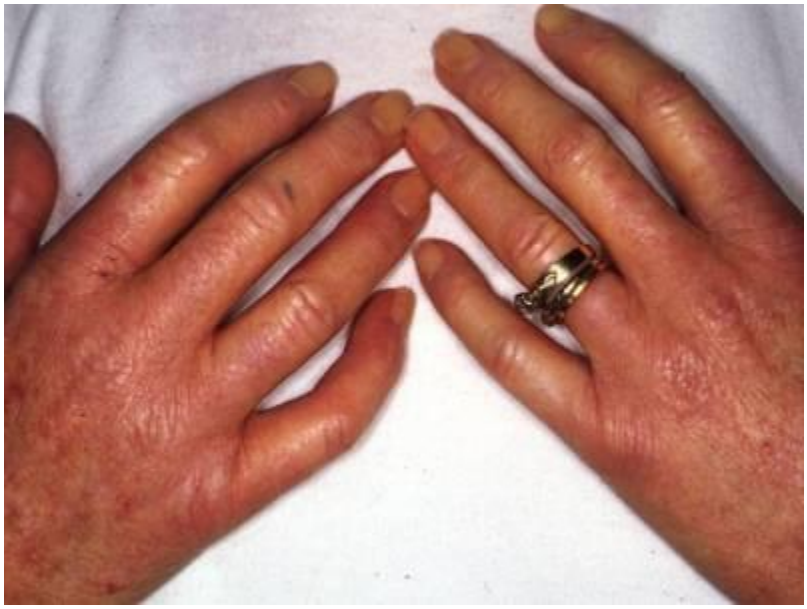
- Raynaud's may be first sign
- scleroderma affects face and distal limbs predominately
- associated with anti-centromere antibodies
- a subtype of limited systemic sclerosis is CREST syndrome: Calcinosis, Raynaud's phenomenon, oEsophageal dysmotility, Sclerodactyly, Telangiectasia

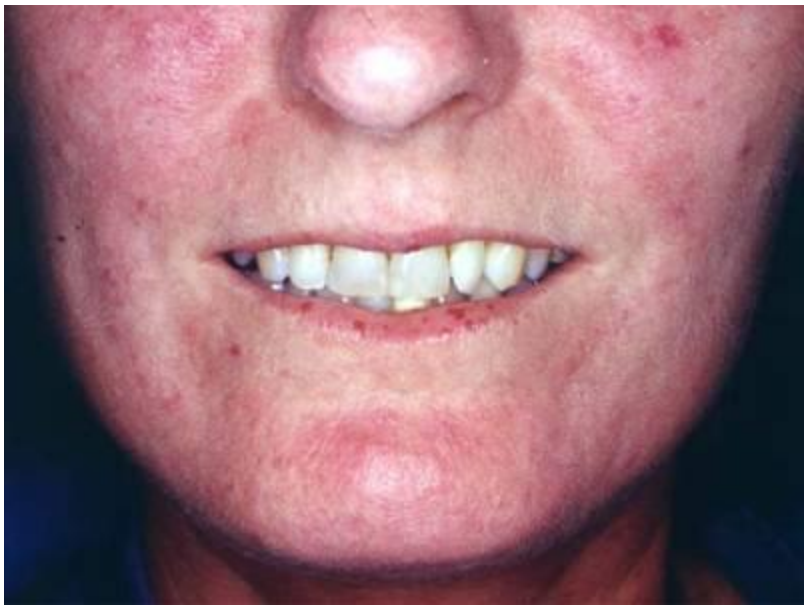
Diffuse cutaneous systemic sclerosis

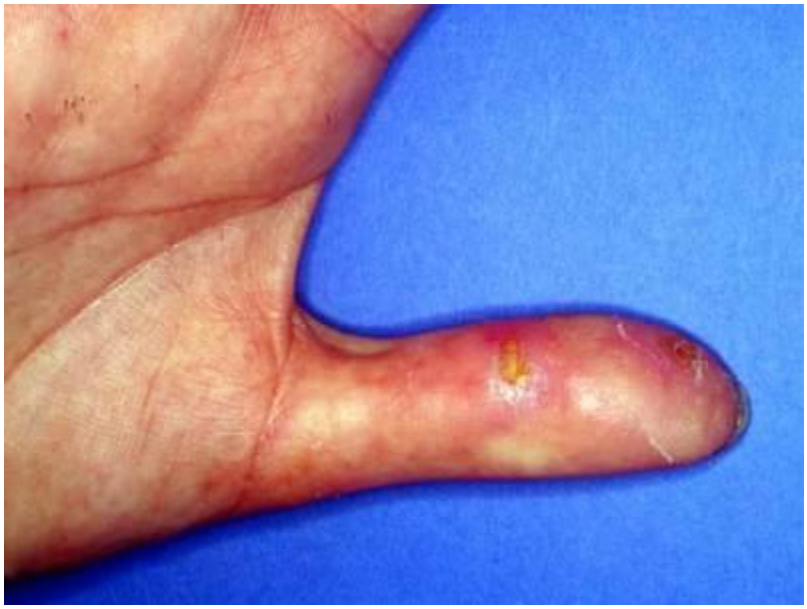
- scleroderma affects trunk and proximal limbs predominately
- associated with scl-70 antibodies
- hypertension, lung fibrosis and renal involvement seen
- poor prognosis

Scleroderma (without internal organ involvement)

- tightening and fibrosis of skin
- may be manifest as plaques (morphoea) or linear







Antibodies

- ANA positive in 90%
- RF positive in 30%
- anti-scl-70 antibodies associated with diffuse cutaneous systemic sclerosis
- anti-centromere antibodies associated with limited cutaneous systemic sclerosis

Tuberculosis

Tuberculosis (TB) is an infection caused by *Mycobacterium tuberculosis* that most commonly affects the lungs. Understanding the pathophysiology of TB can be difficult - the key 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 immunocompotent people the intially lesion usually heals by fibrosis. Those who are immunocompromised may develop disseminated disease (miliary tuberculosis).

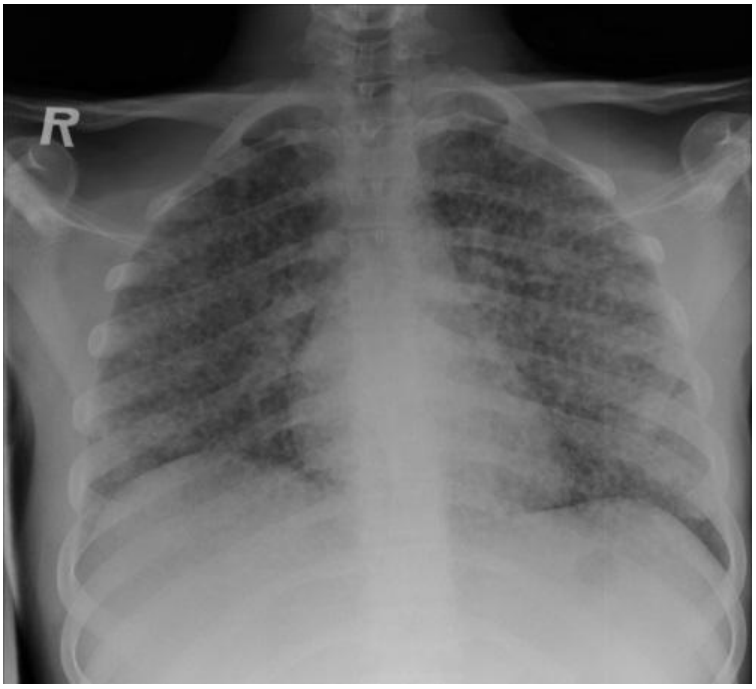
Secondary (post-primary) tuberculosis

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:

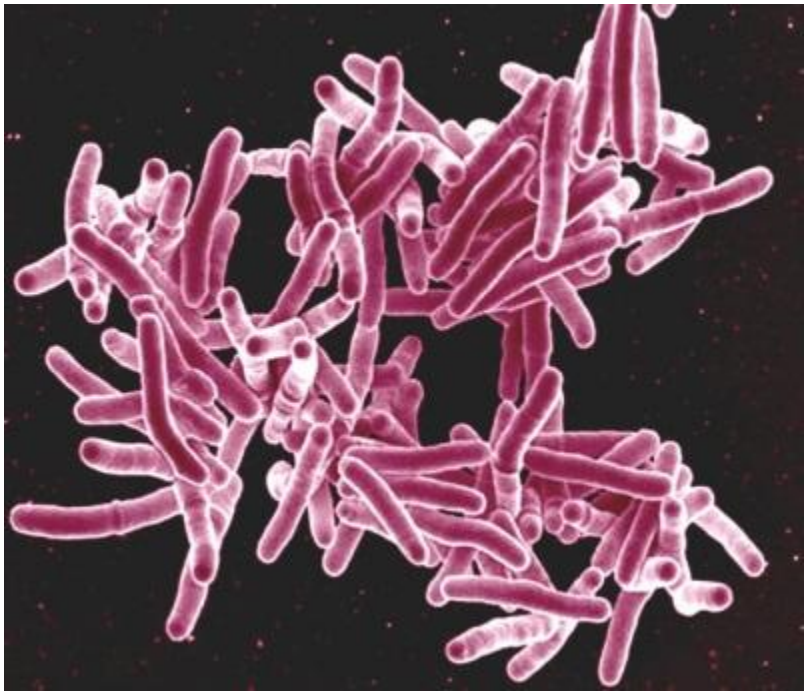
- immunosuppressive drugs including steroids
- HIV
- malnutrition

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



Miliary tuberculosis



Scanning electron micrograph of Mycobacterium tuberculosis bacteria, which cause TB. Credit: NIAID

Tumour necrosis factor

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 costimulator 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)

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

Vitamin D supplementation

Vitamin D supplementation has been a hot topic for a number of years now. The muddied waters are now slightly clearer following the release of the following:

- 2012: letter by the Chief Medical Officer regarding vitamin D supplementation
- 2013: National Osteoporosis Society (NOS) release UK Vitamin D guideline

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 key message is that not many people warrant a vitamin D test. 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

Patients with osteoporosis should always be given calcium/vitamin D supplements so testing is not considered necessary. People who are at higher risk of vitamin D deficiency (see above) should be treated anyway so again testing is not necessary.

Key Points

Wilson's disease - serum caeruloplasmin is **decreased**

'Fasciculations' - think motor neuron disease

24hr oesophageal pH monitoring is gold standard investigation in GORD

AIP - porphobilinogen de**A**minase; P**C**T - uroporphyrinogen de**C**arboxylase

Chorea is caused by damage to the basal ganglia, in particular the **C**audate nucleus

Drusen = **D**ry macular degeneration

Dystrophia myotonica - **D**M1

- **d**istal weakness initially
- autosomal **d**ominant
- **d**iabetes
- **d**ysarthria

Goodpasture's syndrome

- Ig**G** deposits on renal biopsy
- anti-**G**BM antibodies

Legionella pneumophilia is best diagnosed by the **urinary antigen** test

PHaeochromocytoma - give **PH**enoxybenzamine before beta-blockers

Schistosomiasis is a risk factor for **S**quamous cell bladder cancer

Stag-horn calculi

- composed of **S**truvite (ammonium magnesium phosphate, triple phosphate)
- form in alkaline urine (ammonia producing bacteria such as Ureaplasma urealyticum and Proteus therefore predispose)

TNF-α inhibitors may reactivate **T**B
Streptococcus pneumoniae is associated with cold sores
Chlamydia - treat with azithromycin or doxycycline
E. coli is the most common cause of travellers' diarrhoea
H. pylori eradication: - PPI + amoxicillin + clarithromycin, or - PPI + metronidazole + clarithromycin
Saccharopolyspora rectivirgula causes farmer's lung, a type of EAA
Streptococcus bovis endocarditis is associated with colorectal cancer
ACE inhibitors have reduced efficacy in black patients and are therefore not used first-line
ADPKD type 1 = chromosome 16 = 85% of cases
ADPKD type 2 = chromosome 4 = 15% of cases
ATN or prerenal uraemia? In prerenal uraemia think of the kidneys holding on to sodium to preserve volume
Absence seizures - good prognosis: 90-95% become seizure free in adolescence
Absolute risk reduction = (Control event rate) - (Experimental event rate)
Acne rosacea treatment: - mild/moderate: topical metronidazole - severe/resistant: oral tetracycline
Acromegaly: increased sweating is caused by sweat gland hypertrophy
Activated protein C resistance (Factor V Leiden) is the most common inherited thrombophilia
Acute angle closure glaucoma is associated with hypermetropia, where as primary open-angle glaucoma is associated with myopia
Acute myeloid leukaemia - good prognosis: t(15;17)
Acute myeloid leukaemia - poor prognosis: deletion of chromosome 5 or 7
Acute promyelocytic leukaemia - t(15;17)
Addison's disease is associated with a metabolic acidosis

Adenosine - dipyridamole enhances effect - aminophylline reduces effect
Adrenal cortex mnemonic: GFR - ACD
Adrenaline induced ischaemia - phentolamine
Alcohol withdrawal - symptoms: 6-12 hours - seizures: 36 hours - delirium tremens: 72 hours
Allopurinol inhibits xanthine oxidase
Alpha-1 antitrypsin deficiency - autosomal recessive / co-dominant
Alport's syndrome - X-linked dominant (in the majority)
Alport's syndrome - type IV collagen defect
Amiodarone - MOA: blocks potassium channels
Amylase: breaks starch down to sugars
Anal fissure - topical glyceryl trinitrate
Anaphylaxis - serum tryptase levels rise following an acute episode
Anaphylaxis = type I hypersensitivity reaction
Anaplastic thyroid cancer - aggressive, difficult to treat and often causes pressure symptoms
Angiodysplasia is associated with aortic stenosis
Animal bite - co-amoxiclav
Ankylosing spondylitis - x-ray findings: subchondral erosions, sclerosis and squaring of lumbar vertebrae

Ankylosing spondylitis features - the 'A's

- Apical fibrosis
- Anterior uveitis
- Aortic regurgitation
- Achilles tendonitis
- AV node block
- Amyloidosis

Anorexia features

- most things low
- **G**'s and **C**'s raised: **g**rowth hormone, **g**lucose, salivary **g**lands, **c**ortisol, **c**holesterol, **c**arotinaemia

Anti-cyclic citrullinated peptide antibodies are associated with rheumatoid arthritis

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

Anti-ribonuclear protein (anti-RNP) = mixed connective tissue disease

Antibiotic prophylaxis reduces mortality in cirrhotic patients with gastrointestinal bleeding

Anticipation in trinucleotide repeat disorders = **earlier onset** in successive generations

Antidiuretic hormone (ADH) - site of action = collecting ducts

Antiphospholipid syndrome in pregnancy: aspirin + LMWH

Antiphospholipid syndrome: (paradoxically) prolonged APTT + low platelets

Antiphospholipid syndrome: arterial/venous thrombosis, miscarriage, livedo reticularis

Antiplatelets

- TIA: clopidogrel
- ischaemic stroke: clopidogrel

Antipsychotics in the elderly - increased risk of stroke and VTE

Aortic dissection

- type A - ascending aorta - control BP(IV labetalol) + surgery
- type B - descending aorta - control BP(IV labetalol)

Aortic stenosis - S4 is a marker of severity

Aortic stenosis - most common cause:

- younger patients < 65 years: bicuspid aortic valve
- older patients > 65 years: calcification

Aortic stenosis management: AVR if symptomatic, otherwise cut-off is gradient of 40 mmHg

Aspergillus clavatus causes malt workers' lung, a type of EAA

Aspirin is a common cause of urticaria

Asthma - intermediate probability - do spirometry first-line

Asthma diagnosis - if high probability of asthma - start treatment

Asymmetrical symptoms suggests idiopathic Parkinson's

Atrial fibrillation - cardioversion: amiodarone + flecainide

Atrial fibrillation: rate control - beta blockers preferable to digoxin

Atrial myxoma - commonest site = left atrium

Atrial natriuretic peptide - powerful vasodilator

Atypical antipsychotics commonly cause weight gain

Atypical lymphocytes - ?glandular fever

Autosomal recessive conditions are 'metabolic' - exceptions: inherited ataxias

Autosomal dominant conditions are 'structural' - exceptions: hyperlipidaemia type II, hypokalaemic periodic paralysis

Azathioprine - check thiopurine methyltransferase deficiency (TPMT) before treatment

B-type natriuretic peptide is mainly secreted by the ventricular myocardium

BNP - actions:

- vasodilator
- diuretic and natriuretic
- suppresses both sympathetic tone and the renin-angiotensin-aldosterone system

Bacterial vaginosis - overgrowth of predominately *Gardnerella vaginalis*

Bacterial vaginosis: oral metronidazole

Bartter's syndrome is associated with normotension
Bendroflumethiazide - mechanism of hypokalaemia: - increased sodium reaching the collecting ducts - activation of the renin-angiotensin-aldosterone
Bendroflumethiazide - site of action = proximal part of the distal convoluted tubules
Benzodiazepines enhance the effect of GABA, the main inhibitory neurotransmitter
Beta-blocker overdose management: atropine + glucagon
Bilateral idiopathic adrenal hyperplasia is the most common cause of primary hyperaldosteronism
Bisphosphonates can cause a variety of oesophageal problems
Bisphosphonates inhibit osteoclasts
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
Blisters/bullae - no mucosal involvement (in exams at least*): bullous pemphigoid - mucosal involvement: pemphigus vulgaris
Blood pressure target (based on clinic readings) for patients < 80 years - 140/90 mmHg
Bosentan - endothelin-1 receptor antagonist
Breakthrough dose = 1/6th of daily morphine dose
Breast feeding is acceptable with nearly all anti-epileptic drugs
Bronchiectasis: most common organism = *Haemophilus influenzae*

Brush border enzymes:

- maltase: glucose + glucose
- sucrase: glucose + fructose
- lactase: glucose + galactose

Bupropion: contraindicated in epilepsy

Burkitt's lymphoma - c-myc gene translocation

Burkitt's lymphoma is a common cause of tumour lysis syndrome

Burning thigh pain - ? meralgia paraesthetica - lateral cutaneous nerve of thigh compression

CKD on haemodialysis - most likely cause of death is IHD

CKD: only diagnose stages 1 & 2 if supporting evidence to accompany eGFR

CLL - immunophenotyping is investigation of choice

CLL - treatment: Fludarabine, Cyclophosphamide and Rituximab (FCR)

CLL is caused by a monoclonal proliferation of B-cell lymphocytes

CML - Philadelphia chromosome - t(9:22)

COPD - LTOT if 2 measurements of pO2 < 7.3 kPa

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

CT head showing temporal lobe changes - think herpes simplex encephalitis

CTPA is the first line investigation for PE according to current BTS guidelines

Calcium channel blockers - side-effects: headache, flushing, ankle oedema

Calcium channel blockers are now preferred to thiazides in the treatment of hypertension

Cancer patients with VTE - 6 months of LMWH

Carbon monoxide poisoning - most common feature = headache

Case-control studies - odds ratio

Cat scratch disease - caused by *Bartonella henselae*

Causes of raised **p**rolactin - the **p**'s

- **p**regnancy
- **p**rolactinoma
- **p**hysiological
- **p**olycystic ovarian syndrome
- **p**rimary hypothyroidism
- **p**henothiazines, metoclo**p**ramide, dom**p**eridone

Causes of villous atrophy (other than coeliacs): tropical sprue, Whipple's, lymphoma, hypogammaglobulinaemia

Central retinal vein occlusion - sudden painless loss of vision, severe retinal haemorrhages on fundoscopy

Cephalosporins are now the treatment of choice for Gonorrhoea

Cephalosporins, not just clindamycin, are strongly linked to *Clostridium difficile*

Cetuximab - monoclonal antibody against the epidermal growth factor receptor

Chickenpox exposure in pregnancy - first step is to check antibodies

Chickenpox exposure when pregnant - if not immune give VZIG

Chronic myeloid leukaemia - imatinib = tyrosine kinase inhibitor

Ciclosporin + tacrolimus - MOA: inhibit calcineurin thus decreasing IL-2

Ciclosporin - decreases IL-2 release by inhibiting calcineurin

Ciclosporin side-effects: everything is increased - fluid, BP, K^+, hair, gums, glucose

Ciprofloxacin - tendinopathy

Cisplatin is associated with hypomagnesaemia

Cisplatin may cause peripheral neuropathy

Clopidogrel inhibits ADP binding to platelet receptors

Clozapine is no longer used first-line due to the risk of agranulocytosis

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

Coeliac disease - tissue transglutaminase antibodies first-line test

Cohort studies - relative risk

Collapse + ARF → rhabdomyolysis - treat with IV fluids
Colorectal cancer screening - PPV of FOB = 5 - 15%
Combined B- and T-cell disorders: SCID WAS ataxic (SCID, Wiskott-Aldrich syndrome, ataxic telangiectasia)
Complete heart block causes a variable intensity of S1
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
Congenital heart disease - cyanotic: TGA most common at birth, Fallot's most common overall - acyanotic: VSD most common cause
Congenital rubella - sensorineural deafness - congenital cataracts
Congenital toxoplasmosis - cerebral calcification - chorioretinitis
Contraindications to lung cancer surgery include SVC obstruction, FEV < 1.5, MALIGNANT pleural effusion, and vocal cord paralysis
Cushing's syndrome - hypokalaemic metabolic alkalosis
Cyclophosphamide - haemorrhagic cystitis - prevent with mesna
Cytomegalovirus is the most common and important viral infection in solid organ transplant recipients
DVLA advice following angioplasty - cannot drive for 1 week
DVLA advice post CVA: cannot drive for 1 month
DVLA advice post MI - cannot drive for 4 weeks
DVLA advice post multipler TIAs: cannot drive for 3 months

Deletion of chromosome 15

- **P**rader-Willi - **p**aternal
- Angel**m**an syndrome - **m**aternal

Dentistry in warfarinised patients - check INR 72 hours before procedure, proceed if INR < 4.0

Dermatitis herpetiformis - caused by IgA deposition in the dermis

Dermatomyositis antibodies: ANA most common, anti-Mi-2 most specific

Dermatophyte nail infections - use oral terbinafine

Desmopressiin - induces release of von Willebrand's factor from endothelial cells

Deterioration in patient with hepatitis B - ? hepatocellular carcinoma

DiGeorge syndrome - a T-cell disorder

Diabetes diagnosis: fasting > 7.0, random > 11.1 - if asymptomatic need two readings

Diabetes mellitus - HbA1c of 6.5% or greater is now diagnostic (WHO 2011)

Diarrhoea + hypokalaemia → villous adenoma

Diarrhoea - biospy shows pigment laden macrophages = laxative abuse

Diffuse proliferative glomerulonephritis is the most common and severe form of renal disease in SLE patients

Diffuse proliferative glomerulonephritis, causes:

- post-streptococcal
- SLE

Digoxin - inhibits the Na^+/K^+ ATPase pump

Dipyridamole is a non-specific phosphodiesterase inhibitor and decreases cellular uptake of adenosine

Discoid lupus erythematous - topical steroids → oral hydroxychloroquine

Disproportionate microcytic anaemia - think beta-thalassaemia trait

Dosulepin - avoid as dangerous in overdose

Drug metabolism

- phase I: oxidation, reduction, hydrolysis
- phase II: conjugation

Dry skin is the most common side-effect of isotretinoin

During Ramadan, one-third of the normal metformin dose should be taken before sunrise and two-thirds should be taken after sunset

Dysphagia affecting both solids and liquids from the start - think achalasia

EBV: associated malignancies:

- Burkitt's lymphoma
- Hodgkin's lymphoma
- nasopharyngeal carcinoma

Eclampsia - give magnesium sulphate first-line

Endometrial cancer is the second most common association of HNPCC after colorectal cancer

Epidermis - 5 layers - bottom layer = stratum germinativum which gives rise to keratinocytes and contains melanocytes

Epidural haematoma - lucid interval

Epilepsy + pregnancy = 5mg folic acid

Epilepsy medication: first-line

- generalised seizure: sodium valproate
- partial seizure: carbamazepine

Episodic eye pain, lacrimation, nasal stuffiness occurring daily - cluster headache

Erythema nodosum is associated with a good prognosis in sarcoidosis

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

Ethylene glycol toxicity management - fomepizole. Also ethanol / haemodialysis

Exenatide = Glucagon-like peptide-1 (GLP-1) mimetic

Exenatide causes vomiting

FVC is used to monitor respiratory function in Guillain-Barre syndrome
Factor V Leiden mutation results in activated protein C resistance
Finasteride treatment of BPH may take 6 months before results are seen
Flash pulmonary oedema, U&Es worse on ACE inhibitor, asymmetrical kidneys → renal artery stenosis - do MR angiography
Flashes and floaters - vitreous/retinal detachment
Flexural psoriasis - topical steroid
Flow volume loop is the investigation of choice for upper airway compression
Flucloxacillin + co-amoxiclav are well recognised causes of cholestasis
Fluctuating confusion/consciousness? - subdural haematoma
Fluctuating consciousness = subdural haemorrhage
Flushing, diarrhoea, bronchospasm, tricuspid stenosis, pellagra → carcinoid with liver mets - diagnosis: urinary 5-HIAA
Foam cells are fat-laden macrophages
Fomepizole - used in ethylene glycol and methanol poisoning - competitive inhibitor of alcohol dehydrogenase
Funnel plots - show publication bias in meta-analyses
Gallop rhythm (S3) is an early sign of LVF
Gastric MALT lymphoma - eradicate *H. pylori*
Gastric adenocarcinoma - signet ring cells
Genital ulcers - painful: herpes much more common than chancroid - painless: syphilis more common than lymphogranuloma venereum + granuloma inguinale
Genital wart treatment - multiple, non-keratinised warts: topical podophyllum - solitary, keratinised warts: cryotherapy
Genital warts - 90% are caused by HPV 6 & 11

Gingival hyperplasia: phenytoin, ciclosporin, calcium channel blockers and AML
Gitelman's syndrome: normotension with hypokalaemia
Give 50% of normal energy intake in starved patients (> 5 days) to avoid refeeding syndrome
Gliptins = Dipeptidyl peptidase-4 (DPP-4) inhibitors
Glitazones are agonists of PPAR-gamma receptors, reducing peripheral insulin resistance
Gout: start allopurinol if >= 2 attacks in 12 month period
Graves' disease is the most common cause of thyrotoxicosis
HIV - multiple ring enhancing lesions = toxoplasmosis
HIV drugs, rule of thumb: • NRTIs end in 'ine' • Pis: end in 'vir' • NNRTIs: nevirapine, efavirenz
HIV: anti-retrovirals - P450 interaction • nevirapine (a NNRTI): induces P450 • protease inhibitors: inhibits P450
HOCM - drugs to avoid: nitrates, ACE-inhibitors, inotropes
HOCM - poor prognostic factor on echo = septal wall thickness of > 3cm
HOCM is the most common cause of sudden cardiac death in the young
HRT: adding a progestogen increases the risk of breast cancer
HRT: unopposed oestrogen increases risk of endometrial cancer
HUS or TTP? Neuro signs point towards TTP
Haemochromatosis is autosomal recessive
Haemochromatosis is more common than cystic fibrosis
Haemolytic uraemic syndrome - classically caused by E coli 0157:H7
Hashimoto's thyroiditis = hypothyroidism + goitre + anti-TPO
Hashimoto's thyroiditis is associated with thyroid lymphoma

Hemiballism is caused by damage to the subthalamic nucleus

Heparin-induced thrombocytopaenia - antibodies form against complexes of platelet factor 4 (PF4) and heparin

Hepatitis C - 80-85% become chronically infected

Hepatocellular carcinoma

- hepatitis B most common cause worldwide
- hepatitis C most common cause in Europe

Hepatorenal syndrome is primarily caused by splanchnic vasodilation

Hereditary angioedema - C1-INH deficiency

Hereditary angioedema - C4 is the best screening test inbetween attacks

Hereditary haemorrhagic telangiectasia - autosomal dominant

Hiccups in palliative care - chlorpromazine or haloperidol

Hodgkin's lymphoma - best prognosis = lymphocyte predominant

Hodgkin's lymphoma - most common type = nodular sclerosing

Holmes ADIe = DIlated pupil, females, absent leg reflexes

Homocystinuria - give vitamin B6 (pyridoxine)

Homocystinuria is caused by a deficiency of cystathionine beta synthase

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

Hypercalcaemia, renal failure, high total protein = myeloma

Hypercholesterolaemia rather than hypertriglyceridaemia: nephrotic syndrome, cholestasis, hypothyroidism

Hypertension - NICE now recommend ambulatory blood pressure monitoring to aid diagnosis

Hypertension - step 4

- $K^+ < 4.5$ then spironolactone
- $K^+ > 4.5$ then higher-dose thiazide-like diuretic

Hypertension in diabetics - ACE-inhibitors are first-line regardless of age
Hypertension should not be treated in the initial period following a stroke
Hypocalcaemia: Trousseau's sign is more sensitive and specific than Chvostek's sign
Hypokalaemia - U waves on ECG
ICD means loss of HGV licence, regardless of the circumstances
ITP - give oral prednisolone
IgD is involved in the activation of B-cells
IgM paraproteinaemia - ?Waldenstrom's macroglobulinaemia
Impetigo - topical fusidic acid → oral flucloxacillin / topical retapamulin
In the primary prevention of CVD using statins aim for a reduction in non-HDL cholesterol of > 40%
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
Infective endocarditis - streptococcal infection carries a good prognosis
Infective endocarditis - strongest risk factor is previous episode of infective endocarditis
Inferior MI - right coronary artery lesion
Infertility in PCOS - clomifene is superior to metformin
Insoluble sources of fibre such as bran and wholemeal should be avoided in IBS
Insulinoma is diagnosed with supervised prolonged fasting
Iron reduces the absorption of thyroxine
Isocyanates are the most common cause of occupational asthma
Isoniazid **inhibits** the P450 system
Isoniazid causes peripheral neuropathy

Isotretinoin adverse effects

- teratogenicity - females MUST be taking contraception
- low mood
- dry eyes and lips
- raised triglycerides
- hair thinning
- nose bleeds

JVP: **C** wave - **c**losure of the tricuspid valve

JVP: giant v waves in tricuspid regurgitation

JVP: x descent = fall in atrial pressure during ventricular systole

JVP: y descent = opening of tricuspid valve

Kaposi's sarcoma - caused by HHV-8 (human herpes virus 8)

Kearns-Sayre syndrome

- mitochondrial inheritance
- onset < 20-years-old
- external ophthalmoplegia
- retinitis pigmentosa

Keloid scars - more common in young, black, male adults

Keloid scars are most common on the sternum

Klinefelter's - LH & FSH raised
Kallman's - LH & FSH low-normal

Klinefelter's? - do a karyotype

L5 lesion features = loss of foot/big toe dorsiflexion + sensory loss dorsum of the foot

LH surge causes ovulation

Labetalol is first-line for pregnancy-induced hypertension

Lateral epicondylitis: worse on resisted wrist extension/suppination whilst elbow extended

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

Leptin is secreted by adipose tissue

Leptospirosis - give penicillin or doxycycline

Lichen

- **p**lanus: **p**urple, **p**ruritic, **p**apular, **p**olygonal rash on flexor surfaces. Wickham's striae over surface. Oral involvement common
- sclerosus: itchy white spots typically seen on the vulva of elderly women

Liddle's syndrome: hypokalaemia + hypertension

Likelihood ratio for a positive test result = sensitivity / (1 - specificity)

Limited (**central**) systemic sclerosis = anti-**centro**mere antibodies

Lithium: fine tremor in chronic treatment, coarse tremor in acute toxicity

Live attenuated vaccines

- BCG
- MMR
- oral polio
- yellow fever
- oral typhoid

Lofepramine - the safest TCA in overdosage

Long QT syndrome - usually due to loss-of-function/blockage of K+ channels

Loss of corneal reflex - think acoustic neuroma

Lung adenocarcinoma

- most common type in non-smokers
- peripheral lesion

Macular degeneration - smoking is risk factor

Magnesium sulphate - monitor reflexes + respiratory rate

Main indication for HRT: control of vasomotor symptoms

Man returns from trip abroad with maculopapular rash and flu-like illness - think HIV seroconversion

Management of venous ulceration - compression bandaging

Massive PE + hypotension - thrombolyse

Mechanical valves - target INR:

- aortic: 3.0
- mitral: 3.5

Medication overuse headache

- simple analgesia + triptans: stop abruptly
- opioid analgesia: withdraw gradually

Meglitinides - stimulate insulin release - good for erratic lifestyle

Melanoma: the invasion depth of the tumour is the single most important prognostic factor

Membranoproliferative glomerulonephritis (mesangiocapillary)

- type 1: cryoglobulinaemia, hepatitis C
- type 2: partial lipodystrophy

Mesangiocapillary glomerulonephritis (membranoproliferative)

- type 1: cryoglobulinaemia, hepatitis C
- type 2: partial lipodystrophy

Metastatic bone pain may respond to NSAIDs, bisphosphonates or radiotherapy

Metformin should be titrated slowly, leave at least 1 week before increasing dose

Methadone is a common cause of QT prolongation

Methaemoglobinaemia = oxidation of Fe2+ in haemoglobin to Fe3+

Migraine

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

Miller Fisher syndrome - areflexia, ataxia, ophthalmoplegia

Minimal change glomerulonephritis - prednisolone

Mitochondrial diseases follow a maternal inheritance pattern

Molecular biology techniques

- SNOW (**S**outh - **NO**rth - **W**est)
- DROP (**D**NA - **R**NA - **P**rotein)

Most common cause of endocarditis:

- *Staphylococcus aureus*
- *Staphylococcus epidermidis* if < 2 months post valve surgery

Most common organism found in central line infections - *Staphylococcus epidermidis*

Motion sickness - hyoscine > cyclizine > promethazine

Motor neuron disease - riluzole

Motor neuron disease - treatment: NIV is better than riluzole

Mucocutaneous ulceration following travel? - *Leishmania brasiliensis*

Mumps meningitis is associated with a low CSF glucose

Mycoplasma pneumonia if allergic/intolerant to macrolides - doxycycline

Mycoplasma? - serology is diagnostic

Myelofibrosis - most common presenting symptom - lethargy

Myoglobin rises first following a myocardial infarction

NICE recommend avoiding lactulose in the management of IBS

NICE recommend co-prescribing a PPI with NSAIDs in all patients with osteoarthritis

NNT = 1 / Absolute Risk Reduction

Nephrotic syndrome - malignancies cause membranous glomerulonephritis

Nephrotic syndrome in children / young adults - minimal change glomerulonephritis

Neuroimaging is required to diagnose dementia

Nicotinic acid increases HDL levels

Nitric oxide - vasodilation + inhibits platelet aggregation

Normal pO2 but decreased oxygen saturation is characteristic of methaemoglobinaemia

Obese T2DM with abnormal LFTs - ? non-alcoholic fatty liver disease

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

Obesity - NICE bariatric referral cut-offs

- with risk factors (T2DM, BP etc): > 35 kg/m^2
- no risk factors: > 40 kg/m^2

Obesity hormones

- **L**eptin **L**owers appetite
- **G**hrelin **G**ains appetite

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

Oesophageal adenocarcinoma is associated with GORD or Barrett's

Optic neuritis is common in patients taking ethambutol

Oral ulcers + genital ulcers + anterior uveitis = Behcet's

Osteoarthritis - paracetamol + topical NSAIDs (if knee/hand) first-line

Osteomalacia

- low: calcium, phosphate
- raised: alkaline phosphatase

Osteomyelitis: MRI is the imaging modality of choice

Osteoporosis in a man - check testosterone

Oxygen dissociation curve

- shifts **L**eft - **L**ower oxygen delivery - **L**ower acidity, temp, 2-3 DPG - also HbF, carboxy/methaemoglobin
- shifts **R**ight - **R**aised oxygen delivery - **R**aised acidity, temp, 2-3 DPG

PCI - patients with drug-eluting stents require a longer duration of clopidogrel therapy

PCI: stent thrombosis - withdrawal of antiplatelets biggest risk factor

Paget's disease - old man, bone pain, raised ALP

Painful third nerve palsy = posterior communicating artery aneurysm
Paradoxical embolus - PFO most common cause - do TOE
Paraneoplastic features of lung cancer - squamous cell: PTHrp, clubbing, HPOA - small cell: ADH, ACTH, Lambert-Eaton syndrome
Parkinson's disease - most common psychiatric problem is depression
Paroxetine - higher incidence of discontinuation symptoms
Patent ductus arteriosus - collapsing pulse
Patients cannot drive for 6 months following a seizure
Patients on insulin may now hold a HGV licence if they meet strict DVLA criteria
Patients on long-term steroids should have their doses doubled during intercurrent illness
Patients with Sjogren's syndrome have an increased risk of lymphoid malignancies
Patients with established CVD should take atorvastatin 80mg on
Peutz-Jeghers syndrome - autosomal dominant
Phaeochromocytoma: do 24 hr urinary metanephrines, not catecholamines
Philadelphia translocation, t(9;22) - good prognosis in CML, poor prognosis in AML + ALL
Pneumocystis jiroveci pneumonia - pneumothorax is a common complication
Pneumonia in an alcoholic - Klebsiella
Polycystic ovarian syndrome - ovarian cysts are the most consistent feature
Polycythaemia rubra vera - JAK2 mutation
Polycythaemia rubra vera - around 5-15% progress to myelofibrosis or AML
Polycythaemia rubra vera is associated with a low ESR
Polymorphic eruption of pregnancy is not associated with blistering

Porphyria cutanea tarda

- blistering photosensitive rash
- hypertrichosis
- hyperpigmentation

Positive predictive value = TP / (TP + FP)

Post-exposure prophylaxis for HIV: oral antiretroviral therapy for 4 weeks

Post-natal depression is seen in around 10% of women

Power = 1 - the probability of a type II error

Preceding influenza predisposes to *Staphylococcus aureus* pneumonia

Primary biliary cirrhosis - the **M** rule

- Ig**M**
- anti-**M**itochondrial antibodies, **M**2 subtype
- **M**iddle aged females

Primary percutaneous coronary intervention is the gold-standard treatment for ST-elevation myocardial infarction

Prinzmetal angina - treatment = dihydropyridine calcium channel blocker

Progressive supranuclear palsy: parkinsonism, impairment of vertical gaze

Prolactin - under continuous inhibition

Prosthetic heart valves - antithrombotic therapy:

- bioprosthetic: aspirin
- mechanical: warfarin + aspirin

Prosthetic heart valves - mechanical valves last longer and tend to be given to younger patients

Pseudogout - positively birefringent rhomboid shaped crystals

Psoriasis: common triggers are beta-blockers and lithium

Pulmonary arteries vasoconstrict in the presence of hypoxia

Pulmonary embolism - CTPA is first-line investigation

Pulmonary embolism - normal CXR

Pulmonary surfactant - main constituent is **dipalmitoyl phosphatidylcholine (DPPC)**

Pulsus alternans - seen in left ventricular failure

QT interval: Time between the start of the Q wave and the end of the T wave

Rabies - following possible exposure give immunglobulin + vaccination

Rapidly progressive glomerulonephritis, causes:

- Goodpasture's
- ANCA positive vasculitis

Rasburicase - a recombinant version of urate oxidase, an enzyme that metabolizes uric acid to allantoin

Raynaud's disease (i.e. primary) presents in young women with bilateral symptoms

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

Red eye - glaucoma or uveitis?

- glaucoma: severe pain, haloes, 'semi-dilated' pupil
- uveitis: small, fixed oval pupil, ciliary flush

Refeeding syndrome causes hypophosphataemia

Relative risk = EER / CER

Relative risk reduction = (EER - CER) / CER

Renal stones on x-ray

- cystine stones: semi-opaque
- urate + xanthine stones: radio-lucent

Renal transplant + infection ?CMV

Renal transplant HLA matching - DR is the most important

Renal tubular acidosis causes a normal anion gap

Restless leg syndrome - management includes dopamine agonists such as ropinirole

Restrictive cardiomyopathy: amyloid (most common), haemochromatosis, Loffler's syndrome, sarcoidosis, scleroderma

Retinitis pigmentosa - night blindness + tunnel vision

Rheumatoid arthritis - HLA DR4

Rheumatoid arthritis - TNF is key in pathophysiology

Rheumatoid arthritis: patients have an increased risk of IHD

Rheumatoid factor is an IgM antibody against IgG

Rituximab - monoclonal antibody against CD20

Ropinirole - dopamine receptor agonist

SIADH - drug causes: carbamazepine, sulfonylureas, SSRIs, tricyclics

SLE - antibodies associated with congenital heart block = anti-Ro

SLE: ANA is 99% sensitive - anti-Sm & anti-dsDNA are 99% specific

SLE: C3 & C4 low

SSRI + NSAID = GI bleeding risk - give a PPI

Sarcoidosis CXR

- 1 = BHL
- 2 = BHL + infiltrates
- 3 = infiltrates
- 4 = fibrosis

Scabies - permethrin treatment: all skin including scalp + leave for 12 hours + retreat in 7 days

Schistosoma **haem**atobium causes **haem**aturia

Scleritis is painful, episcleritis is not painful

Screening for haemochromatosis

- general population: transferrin saturation > ferritin
- family members: HFE genetic testing

SeHCAT is the investigation of choice for bile acid malabsorption

Seborrhoeic dermatitis - first-line treatment is topical ketoconazole

Second heart sound (S2) - loud: hypertension - soft: AS - fixed split: ASD - reversed split: LBBB
Septic arthritis - most common organism: *Staphylococcus aureus*
Septic arthritis: IV flucloxacillin
Serial peak flow measurements at work and at home are used to detect occupational asthma
Severe falciparum malaria - intravenous artesunate
Severe hepatitis in a pregnant woman - think hepatitis E
Severe pre-eclampsia - restrict fluids
Shoulder abduction - deltoid muscle - axillary nerve (C5,C6)
Skewed distributions - alphabetical order: mean - median - mode - '>' for positive, '<' for negative
Sleep apnoea causes include obesity and macroglossia
Small cell lung cancer accounts 50-75% of case of ectopic ACTH
Spontaneous bacterial peritonitis - intravenous cefotaxime
Standard error of the mean = standard deviation / square root (number of patients)
Statins + erythromycin/clarithromycin - an important and common interaction
Statins inhibit HMG-CoA reductase, the rate-limiting enzyme in hepatic cholesterol synthesis
Stroke thrombolysis - only consider if less than 4.5 hours and haemorrhage excluded
Sudden death, unusual collapse in young person - ? HOCM
Supportive therapy is the mainstay of treatment in Cryptosporidium diarrhoea
Symptom control in non-CF bronchiectasis - inspiratory muscle training + postural drainage
Syringomyelia - spinothalamic sensory loss (pain and temperature)

TTP - plasma exchange is first-line
Tachycardia with a rate of 150/min ?atrial flutter
Taxanes (e.g. Docetaxel) prevent microtubule disassembly
Tear-drop poikilocytes = myelofibrosis
Terlipressin - method of action = constriction of the splanchnic vessels
The PTH level in primary hyperparathyroidism may be normal
The diagnostic test for acromegaly is an oral glucose tolerance with growth hormone measurements
The gold standard test for achalasia is oesophageal manometry
The majority of patients with sarcoidosis get better without treatment
The overnight dexamethasone suppression test is the best test to diagnosis Cushing's syndrome
The short synacthen test is the best test to diagnose Addison's disease
The sulfamethoxazole in co-trimoxazole causes haemolysis in G6PD, not the trimethoprim
The vast majority of gout is due to decreased renal excretion of uric acid
Thiazides cause hypercalcaemia
Thyrotoxicosis with tender goitre = subacute (De Quervain's) thyroiditis
Ticagrelor has a similar mechanism of action to clopidogrel - inhibits ADP binding to platelet receptors
Topical steroids - moderate: Clobetasone butyrate 0.05% - potent: Betamethasone valerate 0.1% - very potent: Clobetasol propionate 0.05%
Transfer factor - raised: asthma, haemorrhage, left-to-right shunts, polycythaemia - low: everything else
Trastuzumab (Herceptin) - cardiac toxicity is common
Trastuzumab (Herceptin) - monoclonal antibody that acts on the HER2/neu receptor
Treatment of acute glaucoma - acetazolamide + pilocarpine

Tricyclic overdose - give IV bicarbonate
Trigeminal neuralgia - carbamazepine is first-line
Trimethoprim may cause pantcytopaenia
Turner's syndrome - most common cardiac defect is bicuspid aortic valve
URTI symptoms + amoxicillin → rash ?glandular fever
Ulcerative colitis - the rectum is the most common site affected
Ultrasound is the screening test for adult polycystic kidney disease
Unexplained symptoms - **S**omatisation = **S**ymptoms - hypo**C**hondria = **C**ancer
Urea breath test - no antibiotics in past 4 weeks, no antisecretory drugs (e.g. PPI) in past 2 weeks
Urethritis + arthritis + conjunctivitis = reactive arthritis
Urinary histamine is used to diagnose systemic mastocytosis
Urinary incontinence + gait abnormality + dementia = normal pressure hydrocephalus
V for Vigabatrin - V for Visual field defects
Venous thromoboembolism - length of warfarin treatment - provoked (e.g. recent surgery): 3 months - unprovoked: 6 months
Ventricular tachycardia - verapamil is contraindicated
Viagra? - contraindicated by nitrates and nicorandil
Vincristine - peripheral neuropathy
Visual changes secondary to drugs - blue vision: Viagra ('the blue pill') - yellow-green vision: digoxin

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

Vitamin B12 is actively absorbed in the terminal ileum

Warfarin - clotting factors affected mnemonic - 1972 (**1**0, **9**, **7**, **2**)

Waterlow score - used to identify patients at risk of pressure sores

Whipple's disease: jejunal biopsy shows deposition of macrophages containing Periodic acid-Schiff (PAS) granules

Wilson's disease - autosomal recessive

Wiskott-Aldrich syndrome

- recurrent bacterial infections (e.g. Chest)
- eczema
- thrombocytopaenia

Women with pulmonary hypertension should avoid becoming pregnant due to very high mortality levels

X-linked conditions: Duchenne/Becker, haemophilia, G6PD

X-linked recessive conditions - no male-to-male transmission

X-linked recessive conditions - there is no male-to-male transmission. Affected males can only have unaffected sons and carrier daughters.

Young man with AF, no TIA or risk factors, no treatment is now preferred to aspirin

Zero-order (saturation) kinetics

- phenytoin
- alcohol

Zollinger-Ellison syndrome: epigastric pain and diarrhoea

cANCA = granulomatosis with polyangiitis; pANCA = Churg-Strauss + others

eGFR variables - CAGE - **C**reatinine, **A**ge, **G**ender, **E**thnicity