Medicine

Cardiology

ECG Interpretation

1. Rate

- Normal: 60-100
- **Regular Rhythm:** 300 divided by the number of boxes in 1 R-R interval
- **Irregular Rhythm:** Number of QRS complexes in the rhythm strip x 6

2. Rhythm

- Regular
- Regularly Irregular
  - Sinus arrhythmia: R-R varies slightly with respiration, common in young
  - Varying block: multiple rates which are multiples of each other
- Irregularly irregular

3. Axis

- Normal: -30° - +90°, leads I & II positive
- **RAD:** Lead I negative & lead III most positive
- **LAD:** Lead II negative & lead I most positive

4. P Waves

- Present? If absent, examine baseline:
  - Sawtooth (Atrial flutter)
  - Chaotic (Atrial fibrillation)
  - Flat (no atrial activity)
- Followed by QRS?
- Shape?
  - **P Mitrale:** Bifid P waves (LA hypertrophy)
    - Hypertension, AS, MR, MS
  - **P Pulmonale:** Peaked P waves (RA hypertrophy)
    - Pulmonary hypertension/cor pulmonale

5. PR Intervals

- From beginning of P wave to beginning of QRS
- Normal: 120-200ms (3-5 small boxes)
- Shortened: Accessory pathway (WPW), HOCM
- Prolonged: Heart block
- Depressed: Pericarditis

6. QRS Complex

Width

- **Narrow complex** (normal): < 120ms, impulse spreading through bundle of His & Purkinje fibres
- **Broad complex:** > 120ms, impulse spreading through myocardium (ventricular ectopic/BBB)

Height

- **Small complex:** < 5mm in limb leads/10mm in chest leads
- **Tall complex:** Determined by Sokolow-Lyon index/Cornel index, may indicate VH

Morphology

- Any positive deflection is an R wave
- Negative deflection before an R wave is a Q wave
  - Normal in I, AVL, V5, V6
  - **Pathological Q Wave:** > 25% height of ensuing R wave/ > 2mm tall & 40ms long
  - May indicate previous MI (develop within a few hours)
- Negative deflection after an R wave is an S wave
- Transition from S > R to R > S should occur at V3/V4
  - **Poor progression**: S > R at V5
- J point is where QRS complex joins ST segment
  - **High take-off/benign early repolarisation**: J point & therefore ST segment is elevated in multiple territories
    - Common under 50
    - T wave also raised
    - Does not evolve

7. ST Segment

- **Elevation** is significant if > 1mm in 2+ contiguous limb leads/> 2mm in 2+ contiguous chest leads
  - Acute full thickness infarction
  - Pericarditis (saddle-shaped)
  - Ventricular aneurysm
- **Depression** is significant if >0.5mm in 2+ contiguous leads
  - Ischaemia

8. QT Interval

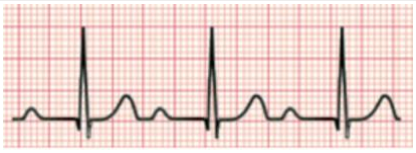
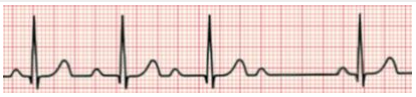
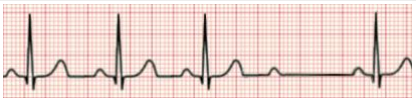
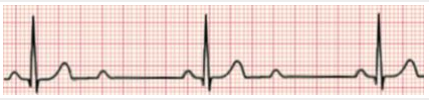
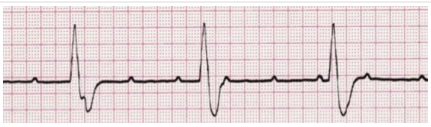
- Start of QRS to end of T wave
- Normal QTc 380-420ms
- Barrett's formula: QTc = QT/√R-R
- **Long QTc**: Toxins (macrolides, Ia/III antiarrhythmics, TCAs, antihistamines), inherited, ischaemia, myocarditis, mitral prolapse, electrolytes (↓Mg, K, Ca, temp)
- **Short QTc:** Digoxin, beta blockers, phenytoin

9. T Wave

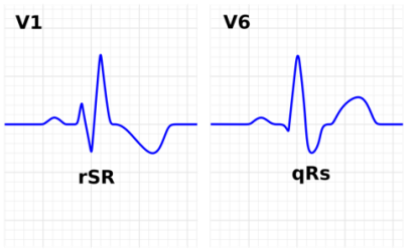
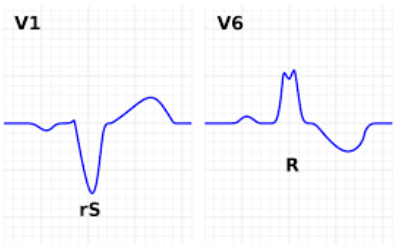
- **Tall:** > 5mm in limb leads/10mm in chest leads
  - Hyperkalaemia (tented)
  - Hyperacute MI
- **Inverted:** Normal in V1 & normal variant in III
  - Ischaemia
  - BBB (V4-6 in LBBB and V1-V3 in RBBB)
  - Pulmonary embolism
  - Left ventricular hypertrophy (in the lateral leads)
  - Hypertrophic cardiomyopathy (widespread)
  - General illness
- **Biphasic**: ischaemia/hypokalaemia
- **Flattened:** ischaemia/hypokalaemia

Specific ECG Abnormalities

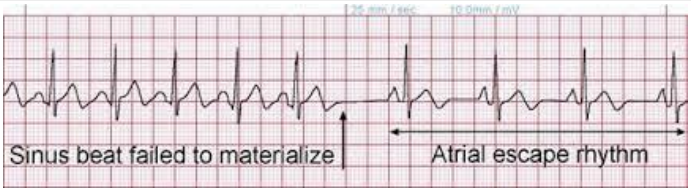
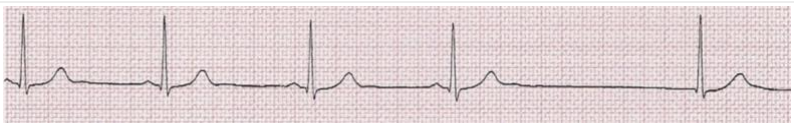
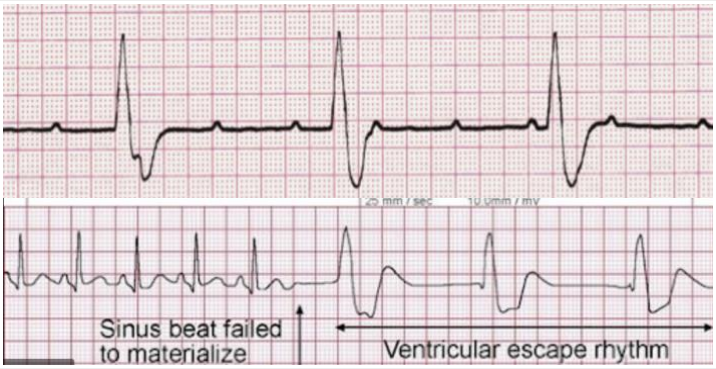
Heart Block/AV Block

	Features	ECG	Causes
1st Degree Heart Block	PR > 200ms & unchanging No missed beats		Normal variant Athletes Sick sinus syndrome IHD (especially inferior MI) Acute myocarditis Drugs (BBs, digoxin)
2nd Degree Heart Block - Wenckebach/Mobitz I	Progressive PR lengthening Reset by 1 non-conducted PR		
2nd Degree Heart Block - Mobitz II	Constant PR QRS missed at regular intervals		
Mobitz II with 2:1 block	May progress to complete heart block		
Complete/3rd Degree Heart Block	P waves and QRS complexes dissociated May be bradycardic with haemodynamic compromise QRS complexes can be narrow (junctional escape) or broad (ventricular escape)		IHD (especially inferior MI) Idiopathic (fibrosis) Congenital Aortic valve calcification Cardiac surgery/trauma Infiltration (abscess/granuloma/tumour/parasite)

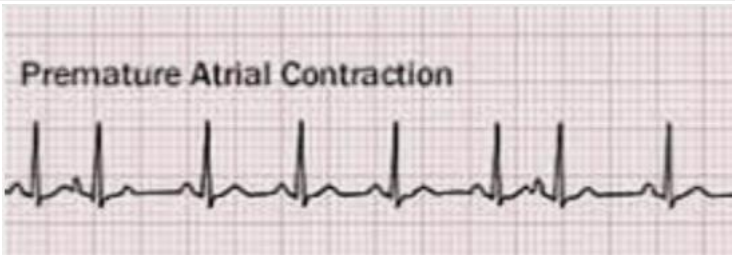
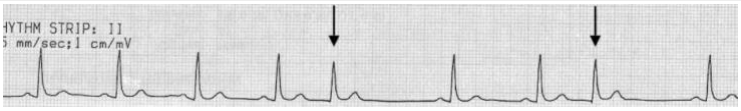
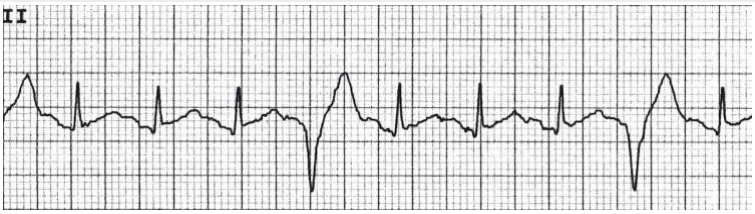
Branch Blocks

	Features	ECG	Causes
Right BBB	QRS > 120ms RSR with dominant R in V1 T wave inversion in V1-V3/4 Slurred S wave in V6		Inferior MI Normal variant Congenital - ASD/VSD/Fallot Hypertrophy - pulmonary embolism/cor pulmonale
Left BBB	QRS > 120ms Dominant S in V1 Notched "M" pattern in V5/V6 T wave inversion in I, aVL, V5-V6		Fibrosis (idiopathic) LVH – AS, HTN IHD – inferior MI Cardiomyopathy
Bifascicular Block	RBBB + LAD		RBBB + left anterior hemiblock
Trifascicular Block	Bifascicular block + 1st degree heart block May need pacing		

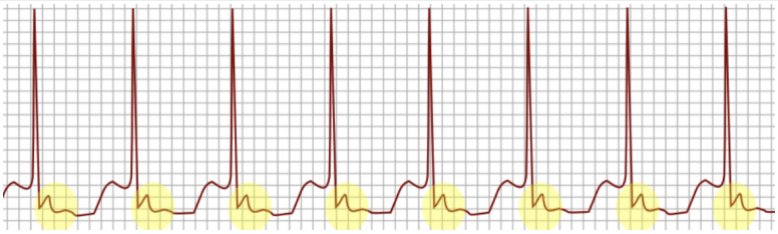
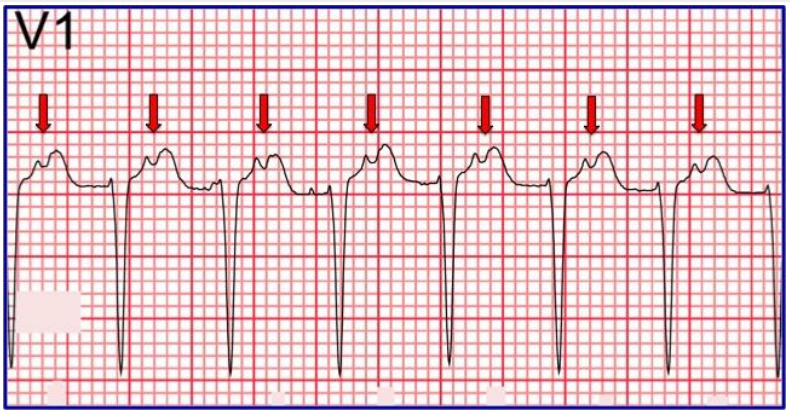
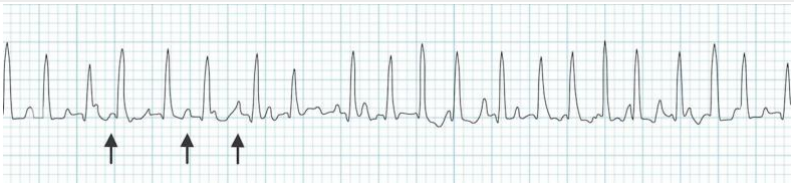
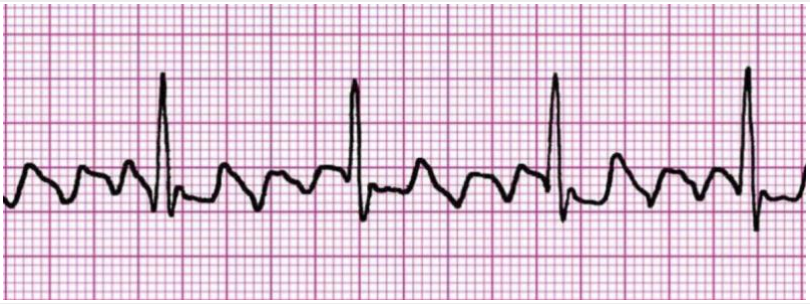
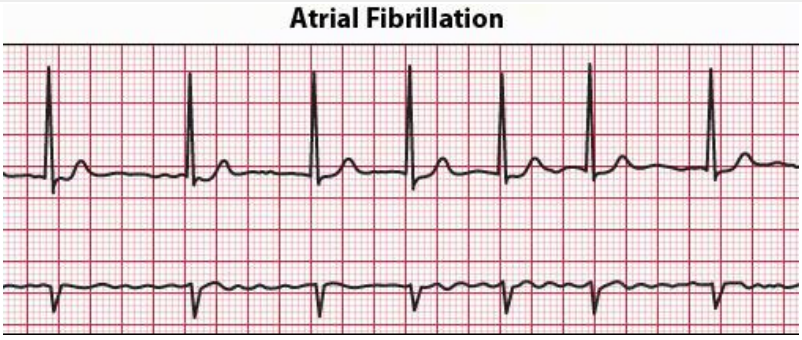
Escape Rhythms

	Features	ECG
Atrial Escape	Failure of SA node to depolarise followed by abnormal P wave after a pause Narrow QRS 60-80bpm	
Junctional Escape	Failure of SA node to depolarise No P wave Normal QRS 40-60bpm	
Ventricular Escape	Can be a result of 3rd degree block (regular P waves) or SA node failure (no P waves) Wide WRS 20bpm	

Extrasystoles/Premature Beats

	Features	ECG
Atrial Extrasystole/Premature Atrial Complex	Abnormal P wave Normal QRS	
Junctional Extrasystole/Premature Junctional Complex	P wave buried in/immediately before/after QRS Normal QRS	
Ventricular Extrasystole/Premature Ventricular Complex	No P wave Wide QRS Abnormal T wave	

Narrow Complex/Supraventricular Tachycardias

	Features	ECG
AV Nodal Re-entrant Tachycardia	P wave absent/immediately before/after QRS Normal QRS Most common regular SVT Reentrant circuit within or next to AV node	
AVRT	P wave usually visible between complexes QRS may be narrow/wide Accessory conduction bundle	
Atrial Tachycardia	Abnormal P wave Normal QRS Rate > 150bpm Ectopic atrial focus Can be multifocal (multiple P wave morphologies)	
Atrial Flutter	Sawtooth baseline with atria contracting at 300bpm AV block (2:1, 3:1, 4:1) Normal QRS	
Atrial Fibrillation	No P waves, chaotic baselines Irregularly irregular QRS rhythm	

Stable Angina

Causes

- Atherosclerosis (majority)
- Anaemia
- Aortic stenosis
- Tachyarrhythmias
- Arteritis

Risk Factors (as for all CVD)

Non-modifiable

- Age
- Male sex
- Family history of MI < 55yrs
- Genetic hyperlipidaemia

Modifiable

- Smoking
- Alcohol consumption
- Poor diet (high sugar and trans-fat & reduced fruit, vegetables, & omega 3 consumption)
- Low exercise
- Obesity
- Poor sleep/OSA
- Stress

Medical Co-morbidities

- Diabetes
- Hypertension
- Chronic Kidney Disease
- Inflammatory conditions (eg RA)
- Atypical antipsychotics

Presentation

1. Constricting pain in front of chest/neck/ shoulders/jaw/arms
2. Precipitated by physical exertion
3. Relieved by rest/GTN spray in ~ 5 minutes

- **Typical angina:** all 3 features
- **Atypical angina:** 2 features
- **Non-anginal chest pain:** 1 or none

Investigations

Diagnostic

- 1st line: CT coronary angiography
- 2nd line: non-invasive functional imaging
- 3rd line: invasive coronary angiography

Baseline

- ECG
- FBC, U+Es (prior to ACEi), LFTs (prior to statins), TFTs
- Lipid profile
- HbA1C & fasting glucose

General Management

- **R**efer to cardiology
- **A**dvise diagnosis, management, lifestyle optimisation, when to call an ambulance
- **M**edical management
- **P**rocedural management

Medical Management

Immediate Symptomatic Relief

- GTN spray PRN
- Take again after 5 minutes if needed, call ambulance if no relief 5 minutes after second dose

Long-Term Symptomatic Relief

- **1st-line:** Beta-blocker OR non-dihydropyridine CCB
- **2nd-line:** Beta-blocker & dihydropyridine CCB
  - Don't combine BB with non-dihydropyridine
- **Alternatives:** (only to be added while awaiting PCI/CABG)
  - Isosorbide mononitrate
  - Ivabradine
  - Nicorandil
  - Ranolazine

Secondary CVD Prevention

- Aspirin 75mg
- Atorvastatin 80mg
- ACE inhibitor
- Beta-blocker (already on for symptomatic relief)

Procedural Management

Percutaneous Coronary Intervention (Stenting)

- **Indications**
  - Poor response to drug treatment
- **Complications**
  - Re-stenosis (20-30% at 6 months)
    - Clopidogrel reduces risk: 1 month with bare metal stent, 1 year with drug-eluting stent
  - Emergency CABG
  - MI (< 2%)
  - Death (< 0.5%)

Coronary Artery Bypass Graft

- **Indications**
  - Left main stem disease
  - Triple vessel disease
  - Refractory angina
  - Unsuccessful PCI
- **Complications**
  - MI
  - Stroke
  - Tamponade/haemothorax
  - Postperfusion syndrome
  - Post-op AF
  - Nonunion of sternum
  - Graft stenosis

Acute Coronary Syndrome Presentation & Investigation

Causes

- Unstable Angina
- NSTEMI
- STEMI

Presentation

Symptoms

- Acute central constricting chest pain > 20 min
  - Does not resolve with rest/GTN spray
  - Radiates to jaw/arm (classically left, can be right)
- Nausea & vomiting
- Sweating
- Palpitations
- Dyspnoea
- Sense of doom

Silent MI (elderly/diabetes)

- Syncope
- Delirium
- Post-op oliguria/hypotension

Signs

- Pallor/sweating
- Pulse & BP high OR low
- 4th heart sound
- LVF signs

Differential

- Angina
- Carditis
- Aortic dissection
- PE
- Pneumothorax
- Pneumonia
- Costochondritis
- GI
- Anxiety

Types of MI

1. Typical MI due to acute coronary event
2. Ischaemia secondary to increased demand/reduced oxygen supply (severe anaemia/tachycardia/hypotension)
3. Sudden cardiac death/arrest suggestive of an ischaemic event
4. Iatrogenic MI associated with PCI/CABG

Investigations

ECG

- Significant ST elevation OR new LBBB in the context of ACS diagnoses a STEMI
- **Other STEMI changes**
  - Hyperacute T waves
  - Pathological Q waves (full thickness infarct)
  - T wave inversion (late)
- **NSTEMI changes**
  - ST depression
  - T wave inversion
  - Pathological Q waves

Artery	Heart Area	ECG Leads
Left Coronary Artery	Anterolateral	I, aVL, V3-6
LAD	Anterior	V1-4
Circumflex	Lateral	I, aVL, V5-6
Right Coronary Artery	Inferior	II, III, aVF

Troponin

- Serial (baseline + 6 + 12 hours)
- Rise indicates myocyte damage/death
- Other causes:
  - CKD
  - Sepsis
  - Myocarditis
  - Aortic dissection
  - PE

Others

- Investigations as per stable angina (baseline bloods + CT coronary angiogram)
- CXR
  - Cardiomegaly
  - Pulmonary oedema
  - Widened mediastinum (aortic rupture/dissection)
- Echo to assess functional damage

Diagnosis

STEMI

- Typical clinical features + ST elevation/new LBBB + positive troponin

NSTEMI

- Typical clinical features + no ST elevation/new LBBB + positive troponin

Unstable Angina

- Typical clinical features + no ST elevation/new LBBB + negative troponin

Management of Acute Coronary Syndromes

Initial Common Drug Therapy

- Aspirin 300mg
- Another antiplatelet
  - Ticagrelor
  - Prasugrel
  - Clopidogrel (if already on DOAC)
- Oxygen if SpO2 < 94%
- Morphine if severe pain only (± metoclopramide)
  - Routine morphine may be associated with adverse outcomes
- Nitrates
  - Sublingual or IV
  - Caution if patient is hypotensive, keep SBP > 90mmHg
  - Contraindicated in RV infarct/sildenafil use

STEMI Management

Percutaneous Coronary Intervention

- Management of choice if within 12hrs
  - Should still be considered if presenting after 12hrs with signs of ongoing ischaemia
- Requires dual antiplatelet therapy in advance
  - Prasugrel (clopidogrel if patient takes an oral anticoagulant) in addition to aspirin
- UFH with GPI bailout during PCI if radial access, bivalirudin with GPI bailout if femoral access
- **Complications**
  - Bleeding
  - Emboli
  - Arrhythmias

Thrombolysis

- Indicated when primary PCI is not available until > 120 minutes after the time when thrombolysis can be given
- Contraindicated 24hrs after beginning of symptoms
- If ECG changes have not resolved after 60-90 minutes, PCI should be considered
- Patients are given antithrombin drug (eg LMWH) as well as fibrinolytic agent:
  - Streptokinase
  - Alteplase
  - Tenecteplase
- **Contraindications**
  - **A**ortic dissection
  - **G**I bleeding
  - **A**llergic reaction in the past
  - **I**atrogenic (recent surgery)
  - **N**euro: AVM/neoplasm/past CVA
  - **S**evere HTN
  - **T**rauma, including CPR
- **Complications**
  - Bleeding
  - Stroke
  - Arrhythmia
  - Allergic reaction

NSTEMI Management

- Fondaparinux for patients not at high risk of bleeding

Primary PCI in NSTEMI

- Immediate: Haemodynamically unstable
- Within 72hrs: GRACE score risk assessment > 3%

Conservative Management

- Further antiplatelet ('dual antiplatelet therapy', i.e. aspirin + another drug)
  - If the patient is not at a high risk of bleeding: ticagrelor
  - If the patient is at a high risk of bleeding: clopidogrel

Secondary Prevention

Medical

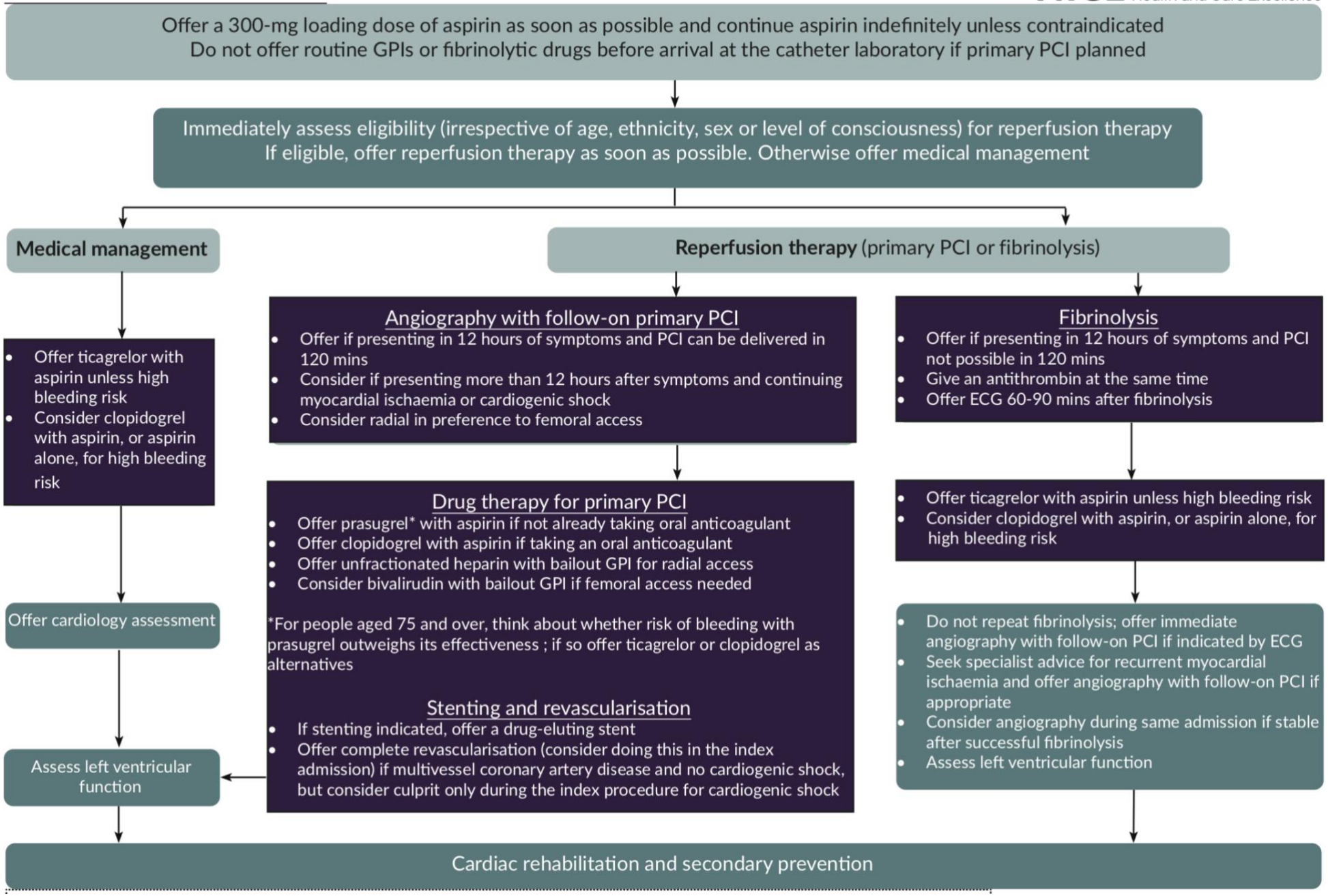
- Aspirin 75mg
- Another antiplatelet (clopidogrel/ticagrelor for up to 12 months)
- Atorvastatin 80mg
- ACE inhibitor
- Atenolol/other beta blocker
- Aldosterone antagonist if clinical evidence of heart failure

Lifestyle

- Stop smoking
- Reduce alcohol consumption
- Mediterranean diet
- Cardiac rehabilitation
- Optimise treatment of comorbidities

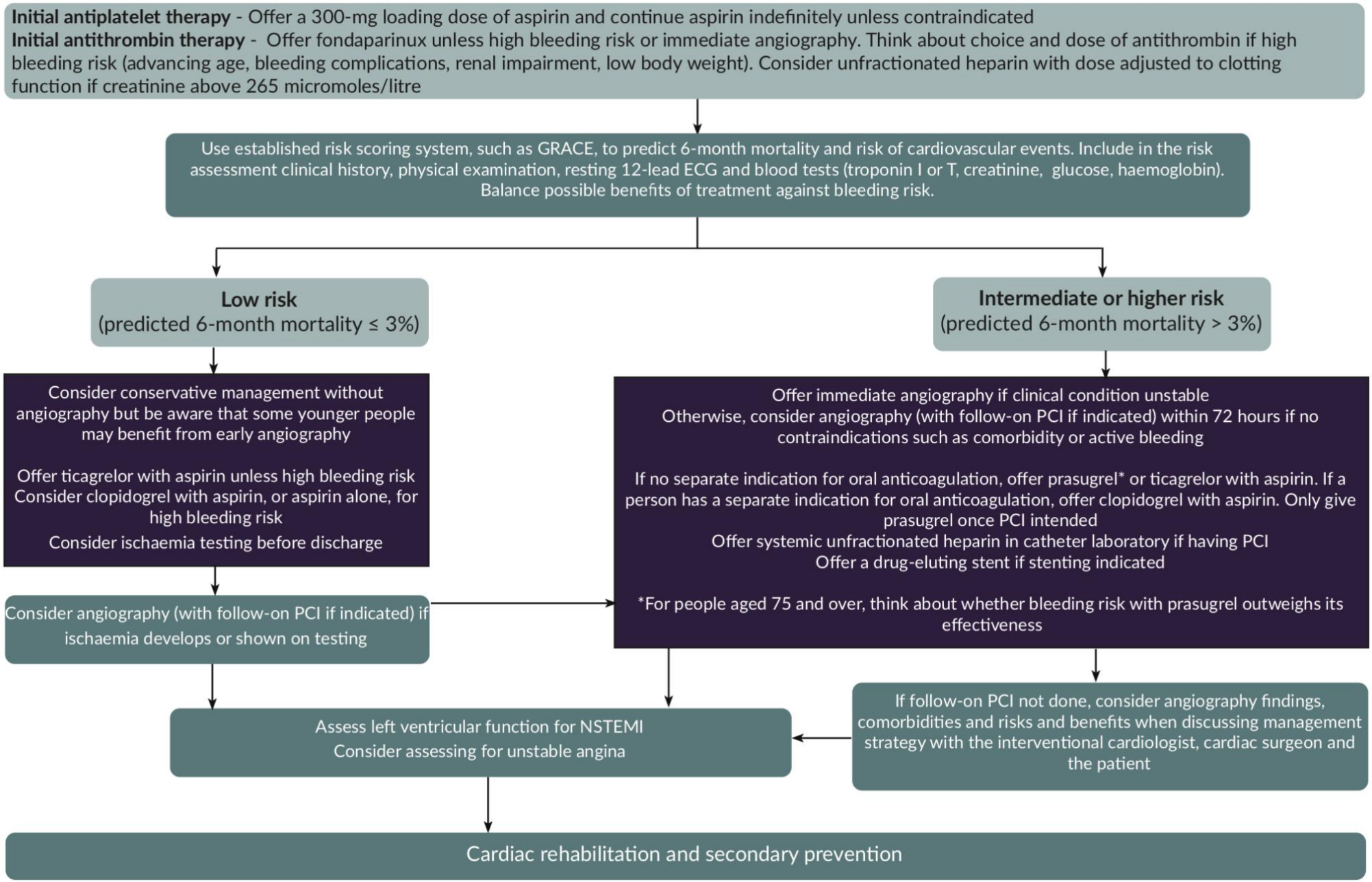
STEMI: early management

NICE National Institute for Health and Care Excellence



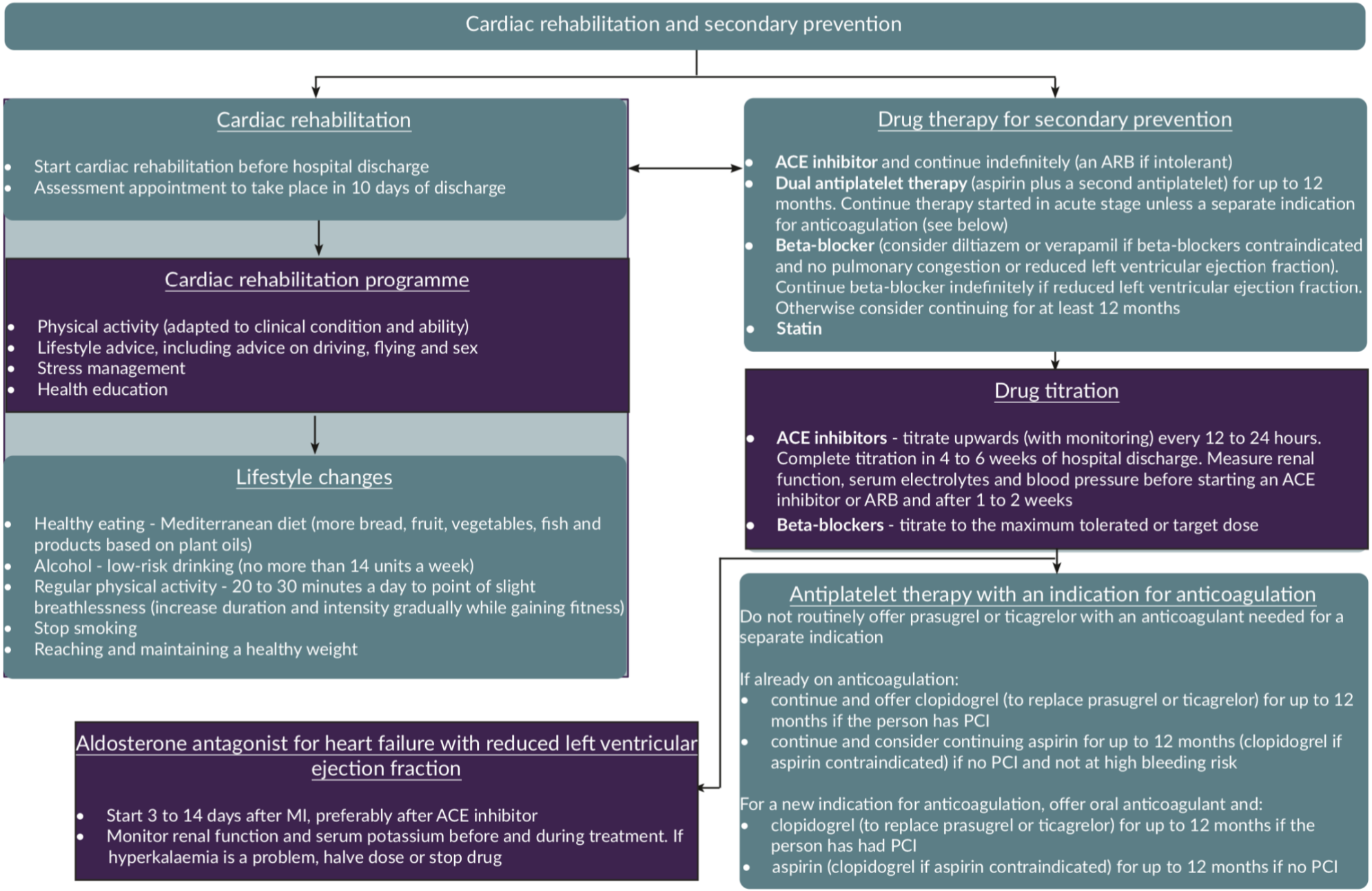
NSTEMI/unstable angina: early management

NICE National Institute for Health and Care Excellence



Cardiac rehabilitation and secondary prevention

NICE National Institute for Health and Care Excellence



MI Complications

Death

- Occurs due to acute LVF, cardiac arrest, or cardiogenic shock

Heart Failure

Left Ventricular Failure

- Can be severe acutely (pulmonary oedema) or clinically milder chronic heart failure following an MI

Right Ventricular Failure

- Occurs with right ventricular infarction
- Avoid vasodilators & diuretics, inotropes may be required

Arrhythmias

Tachy

- Most types are possible
- **AF/Flutter:** DC cardioversion if unstable, medical cardioversion otherwise
- **Frequent PVC:** Common, no specific treatment
- **VT:** DC cardioversion if unstable, medical cardioversion otherwise. May need pacing
- **VF:** DC shock
  - < 48hrs: occurs due to reperfusion with good prognosis
  - > 48hrs: indicated extensive cardiac damage

Brady

- Sinus bradycardia common in inferior MI, may be atropine resistant (due to nodal infarction)
- All degrees of heart block & branch block are possible
- 1st degree block should be monitored as it commonly progresses
- Mobitz II & above should be paced
- Trifascicular/bifascicular block should be paced
- Ventricular bradycardia suggests SA & AV node damage

Pericarditis

Presentation

- Early
- Mild fever & central pain relieved by sitting forward
- Pericardial friction rub

ECG

- Saddle-shaped ST elevation ± PR depression

Management

- NSAIDs
- Echo to exclude effusion

Embolism

- Left ventricular mural thrombosis
- Anticoagulation (warfarin) for 3 months should be considered after large anterior MI

Rupture

LV Free Wall

- Cardiac tamponade
- **Beck's Triad:**
  - Hypotension
  - Raised JVP
  - Muffled heart sounds

Papillary Muscle/Chordae

- Mitral regurgitation
- Pansystolic murmur & pulmonary oedema

Septum

- Post-MI VSD
- Pansystolic murmur, raised JVP & heart failure

Ventricular Aneurysm

Presentation

- 4-6wks
- LVF
- Angina
- Recurrent VT
- Systemic emboli

ECG

- Persistent ST elevation

Management

- Anticoagulate & consider excision

Dressler Syndrome

- Pleuro-pericarditis due to antibodies against myocyte sarcolemma

Presentation

- 2-6wks
- Recurrent pericarditis & pleural effusions
- Fever
- Anaemia
- Raised ESR

Management

- NSAIDs
- Steroids if severe

Acute Left Ventricular Failure

- Acute inability of left ventricle to adequately pump blood resulting in pulmonary congestion & oedema

Triggers

- Iatrogenic (excess fluids, particular in an older patient with impaired LV function)
- MI
- Sepsis
- Arrhythmias
- Hypertensive emergency
- Mechanical (valve leak, VSD, ventricular aneurysm)
- Pulmonary embolism

Presentation

Symptoms

- Acute onset shortness of breath
- Cough productive of frothy white/pink sputum

Signs

- Increased resp rate
- Decreased SpO2
- Tachycardia
- 3rd heart sound
- Bilateral basal crackles
- Hypotension/cardiogenic shock in severe cases

Underlying Causes

- Chest pain (MI)
- Fever (sepsis)
- Palpitations (arrhythmias)

Concurrent RV Failure

- Raised JVP
- Peripheral oedema

Investigations

- ECG to look for arrhythmias
- ABG (type I respiratory failure)
- Bloods: routine + BNP, troponin

NT-proBNP

- Released by overstretched ventricles
- Sensitive but not specific, also elevated in:
  - Tachycardia
  - Sepsis
  - PE
  - Renal impairment
  - COPD

Echocardiography

- Measurement of ejection fraction (EF): > 50% normal

CXR

- Cardiomegaly
- "Bat-wing" oedema
- Bilateral pleural effusion
- Kerley-B lines & fluid in interlobar fissures
- Upper lobe diversion

Management of LVF with Pulmonary Oedema

- Don't wait for investigations if clinical diagnosis is obvious & patient is unstable

1. Stop fluids
2. Sit up
3. Oxygen
   - If SpO2 < 94%
   - Caution in patients with COPD
4. Furosemide 40-80mg IV
5. Nitrates if SBP > 90mmHg
   - GTN sublingual
   - ISMN IV infusion

If worsening

6. More furosemide/increase nitrate infusion
7. CPAP/invasive ventilation
8. If SBP < 90mmHg, manage as cardiogenic shock

Continuing Management

- Daily weights
- DVT prophylaxis
- Repeat & monitor CXR & bloods
- ACE inhibitor & BB for heart failure (± spironolactone)
- Manage arrhythmias if present

Chronic Heart Failure

Framingham Criteria

- 2 major or 1 major + 2 minor

Major	Minor
• PND • Hepatojugular reflux • Neck vein distension • S3 • Bilateral basal crackles • Cardiomegaly • Acute pulmonary oedema • CVP > 16cmH2O • Weight loss > 4.5kg in 5 days of treatment	• Bilateral ankle oedema • Extertional dyspnoea • HR > 120 • Nocturnal cough • Hepatomegaly • Pleural effusion • 30% reduction in vital capacity

NYHA Dyspnoea Classification

1. No limitation of activity
2. Comfortable at rest & dyspnoea on ordinary activity
3. Marked limitation of ordinary activity
4. Dyspnoea at rest, discomfort with any activity

Investigations

NT-proBNP

- Released by overstretched ventricles
- Sensitive but not specific, also elevated in:
  - Tachycardia
  - Sepsis
  - PE
  - Renal impairment
  - COPD
- < 100 excludes heart failure
- Mortality increases with BNP

Other Bloods

- FBC, U+E, TFTs, glucose, lipids

CXR

- Alveolar oedema
- Kerley B lines
- Cardiomegaly
- Upper lobe diversion
- Effusions
- Fluid in fissures

ECG

- Ischaemia/arrhythmia/hypertrophy

Echo

- Ejection fraction
  - HFrEF: > 50%, Typically occurs due to myocyte loss
  - HFpEF: < 40%, Typically occurs due to chronic comorbidities (HTN, DM, etc)
- Focal/global hypokinesia
- Hypertrophy
- Valve lesions
- Intracardiac shunt

General Management

- Refer (urgent if BNP > 2,000ng/L)

Cardiovascular Risk

- Stop smoking
- Reduce salt intake
- Optimise weight
- Exercise/rehab
- Medical – statin

Manage Underlying Cause/Precipitants

- Valve disease – surgery if severe
- Arrhythmias
- Ischaemia

Vaccines

- Yearly flu & pneumococcal

Medical Management

First Line

- ACE inhibitor/ARB + Beta-blocker
  - Started one at a time
  - Only affect mortality in HFrEF
- Loop diuretic
  - Addresses symptoms of fluid overload only, no effects on mortality

Second Line

- Add aldosterone antagonist
  - Monitor electrolytes

Third Line (specialist)

- Sacubitril-valsartan
  - If EF < 35%
  - ACEi/ARB washout period needed
- SGLT-2 inhibitor
  - If T2DM
- Ivabradine
  - If sinus rhythm, > 75bpm, EF < 35%
- Digoxin
  - Symptomatic only
  - Strongly indicated in co-existing AF
- Hydralazine + nitrate
  - Especially in patients of African/Caribbean descent

Invasive Options

- Cardiac resynchronisation
  - Indicated if wide QRS on ECG
- Intra-aortic balloon counterpulsation
- LVAD
- Heart transplant

Hypertension

Stages

- **Stage 1:** clinic BP > 140/90 or home BP > 135/85
- **Stage 2:** clinic BP > 160/100 or home BP > 155/95
- **Stage 3:** clinic BP > 180/110
- **Malignant:** BP > 180/110 with papilloedema/retinal haemorrhage
- **Isolated Systolic HTN:** SBP > 140, DBP < 90

Causes

Primary/Essential

- 95% of cases

Secondary

- Renal disease (most common)
  - Renal artery stenosis
  - Glomerulonephritis
  - PKD
- Obesity
- Pregnancy (PIH/PET)
- Endocrine
  - Conn's
  - Cushing's
  - Thyrotoxicosis
  - Acromegaly
  - Phaeochromocytoma
- Drugs
  - Cocaine
  - NSAIDs
  - OCP
- Neurogenic
  - Raised ICP
  - Diffuse axonal injury
  - Spinal section
- Fluid overload
- Coarctation of the aorta

End-Organ Damage

Cardiac

- Ischaemic heart disease
- Heart failure
- Valvular regurgitation

Vascular

- Atherosclerosis
- Aneurysm (aortic)
- Dissection (aortic)

Neuro

- CVA
- Encephalopathy with malignant hypertension

Eyes

- Hypertensive retinopathy

Kidneys

- Hypertensive nephropathy – CKD with proteinuria

Management

General

- Increase exercise
- Decrease smoking, alcohol, salt, caffeine

Indications for Pharmacological Management

- All patients with stage 2 hypertension
- All patients under 80 with stage 1 hypertension and 1+ of:
  - QRISK Score > 10%
  - Diabetes
  - Renal disease
  - Cardiovascular disease
  - End-organ damage

Pharmacological Management

1. **< 55 & white/diabetic:** ACEi/ARB | **> 55/black:** CCB
2. ACEi/ARB + CCB/Thiazide
3. ACEi/ARB + CCB + Thiazide
4. If potassium is < 4.5mmol/L, add aldosterone antagonist.
   If potassium is > 4.5mmol/L, add alpha or beta blocker
5. Refer if still not meeting targets

Treatment Targets

Age	Systolic Target	Diastolic Target
< 80 years	< 140	< 90
> 80 years	< 150	< 90

Atrial Fibrillation

Presentation
- Palpitations
- Shortness of breath
- Syncope
- Angina
- **Irregularly irregular pulse**
  - Other causes are:
    - Ventricular ectopics
    - Multifocal atrial ectopics
    - Sinus arrhythmia
- Signs of associated disease
  - Hyperthyroidism
  - Sepsis
  - Stroke

Causes
- Mitral valve pathology
- Ischaemic heart disease
- Thyrotoxicosis
- Hypertension
- Sepsis

Classification
Valves
- **Valvular AF** is associated with underlying severe mitral stenosis/mechanical valve
- **Non-valvular AF** is associated with no or other valve disease (mitral regurgitation/aortic stenosis)

Onset/Duration
- **First detected episode** is the first classification
- **Recurrent episodes** occur more than 2 times
  - **Paroxysmal AF** is self-resolving withing 7 days
  - **Persistent AF** lasts > 7 days
- **Permanent AF** is resistant to cardioversion or the decision has been made not to cardiovert

Investigations
ECG
- Irregularly irregular R-R intervals with no P waves & chaotic baseline

Echo
- Underlying structural abnormality

Bloods
- U+E, TFTs, troponin

Indications for Long Term Rhythm vs Rate Control
- High cardiovascular risk
  - Previous event, HTN, DM, LVH, etc
- Failure of rate control
- Symptoms despite adequate rate control
- Heart failure
- Age < 65

Acute Management
- Emergency electrical cardioversion if haemodynamically unstable, without waiting to beanticoagulated

Haemodynamically Stable & Presenting Within 48hrs
- Pharmacological cardioversion
  - Flecainide if no structural heart disease
  - Amiodarone
- Electrical cardioversion

Haemodynamically Stable & Presenting After 48hrs
- Delay cardioversion until 3 weeks of anticoagulation
  - Offer rate control during this time
- Alternatively, perform transoesophageal echo to rule out left atrial appendage thrombus

Long Term Rate Control
- To be offered to all patients except:
  - AF with a reversible cause
  - Heart failure primarily caused by AF
  - New-onset AF
  - Rhythm control strategy more suited based on clinical judgement

Monotherapy
- Beta-blocker or non-dihydropyridine CCB 1st line
  - Avoid CCB in heart failure
- Digoxin considered in:
  - Individuals with little-no physical exercise
  - BBs & CCBs contraindicated/not tolerated/preferred

Combination Therapy (if monotherapy insufficient)
- 2 of:
  - Beta-blocker
  - Diltiazem
  - Digoxin

Long Term Rhythm Control
- Beta-blocker 1st line
- Dronedarone 2nd line

"Pill-in-pocket"
- Individuals with paroxysmal AF who:
  - Have no history of LV/valvular dysfunction/IHD
  - Have infrequent episodes
  - Have SBP > 100mmHg & resting HR > 70bpm
  - Can understand when & how to take medication
- Flecainide

Cardioversion
- Amiodarone taken 4 weeks before until up to 12 months after electrical cardioversion

Left Atrial Ablation
- Consider when drug treatment is not effective/suitable/tolerated or if other cardiac surgery is going ahead

Anticoagulation in Atrial Fibrillation

- Patients without anticoagulation have a roughly 5% (depending on CHADS-VASc) risk of stroke each year
- Patients with anticoagulation have a 1-2% risk of stroke each year
- **No longer any role for aspirin in stroke prevention in AF**

Indications for Anticoagulation

- Any patient with AF & a CHADS-VASc score of 2 or more (taking into account bleeding risk)
- Any male patient with AF & a CHADS-VASc score of 1 or more (taking into account bleeding risk)

DOAC vs Warfarin

	DOAC	Warfarin
Advantages	• **Typically 1st line in non-valvular AF** No monitoring • Fewer interaction problems • Equal/slightly better stroke prevention • Equal/slightly better bleeding risk	• **Only option in valvular AF** • Monitoring can be beneficial in high-risk patients • Reversible • Cheap
Disadvantages	• Expensive due to patent – apixaban will be off patent in 2022 • No reversal (andexanet alfa but not very established)	• Monitoring required

CHA_2DS_2-VASc Score

C	Congestive HF	1
H	Hypertension (including treated)	1
A_2	Age > 75	2
	Age 65-74	1
D	Diabetes	1
S_2	Prior stroke/TIA	2
V	Vascular disease (peripheral/IHD)	1
S	Sex (Female)	1

HASBLED Score

H	Hypertension (uncontrolled, < 160mmHg)	1
A	Abnormal renal function (dialysis/creatinine > 200)	1
	Abnormal liver function (cirrhosis/bilirubin > 2x normal, ALT/AST/ALP > 3x normal)	1
S	Stroke history	1
B	History of bleeding tendency	1
L	Labile INR, TTR < 60%	1
E	Eldery (> 65)	2
D	Drugs predisposing to bleeding	1
	Alcohol use (> 8 units/week)	1

Rationale

- No strict guidelines on how to use
- Score of 3+ indicates high risk of bleeding defined as:
  - Intracranial haemorrhage
  - Hospitalisation
  - Haemoglobin decrease of > 2g/dL
  - Transfusion

Management of a High INR

Major Bleeding

- Stop warfarin
- IV vitamin K 5mg
- PCC/FFP

Minor Bleeding

- **INR > 8**
  - Stop warfarin
  - IV vitamin K 1-3mg, repeat after 24hrs if INR still high
  - Restart warfarin when INR < 5
- **INR 5-8**
  - Stop warfarin
  - IV vitamin K 1-3mg
  - Restart warfarin when INR < 5

No Bleeding

- **INR > 8**
  - Stop warfarin
  - PO vitamin K 1-5mg (using IV preparation), repeat after 24hrs if INR still high
  - Restart warfarin when INR < 5
- **INR 5-8**
  - Withhold 1-2 doses
  - Restart with a lower dose

Aortic Stenosis

Causes

- Senile calcification (most common > 65)
- Bicuspid aortic valve (most common < 65)
- William's syndrome (supravalvular AS)
- Post-rheumatic fever
- Subvalvular (HOCM)

Presentation

- **Triad** of chest pain, dyspnoea & syncope
- Arrhythmias
- Systemic emboli (infective endocarditis)
- Sudden death
- **Murmur**
  - Ejection systolic murmur ± ejection click
  - Loudest in aortic area (2nd intercostal space, right sternal border)
  - Radiates to carotids
  - Decreases with Valsalva manoeuvre

Features of Severe AS

- Narrow pulse pressure
- Slow rising pulse
- Delayed ESM
- Soft/absent S2
- S4
- Thrill
- Left ventricular failure

Aortic Sclerosis

- Important differential
- Valve thickening with no pressure gradient
- Turbulent flow causes murmur which does not radiate and is associated with normal pulse

Investigations

Bloods

- FBC, U+E, lipids, glucose

ECG

- LVH, P mitrale, LAD, poor R wave progression
- LBBB/AV block – may need pacing

CXR

- Calcified aortic valve, especially on lateral films
- Signs of LVH/heart failure
- Post-stenotic dilatation of ascending aorta

Echo & Doppler

- Diagnostic

	Jet Velocity (m/s)	Valve Area (cm^2)	Mean gradient (mmHg)
Normal	< 2.0	3.0 – 4.0	< 5mmHg
Mild AS	2.0 – 2.9	> 1.5	< 20mmHg
Moderate AS	3.0 – 3.9	1.0 – 1.5	20 – 39mmHg
Severe AS	> 4.0	< 1.0	> 40mmHg

Catheterisation

- Indicated in severe AS to directly assess gradient, function, & coronaries

Exercise Stress Test

- Useful to assess exercise capacity in asymptomatic patients
- Contraindicated in severe AS

Medical Management

- Optimise cardiovascular risk
- Treat angina (BBs) & heart failure (ACEi & diuretics)
- Monitor with regular echo

Surgical Management

Indications

- Severe symptomatic AS
- Severe asymptomatic AS with ejection fraction < 50%
- Severe asymptomatic AS undergoing other cardiac surgery

Types

- Mechanical valves have a lifetime > 20 years but require lifelong anticoagulation (INR 2.5-3.5)
- Bioprosthetic valves have a lifetime of 10 years and do not require long term anticoagulation

TAVI

- Used in older patients not fit for open surgery
- Long term data lacking
- Typically bioprosthetic

Prognosis (without surgery)

- Angina/syncope: 2-3 years
- LVF: 1-2 years

Aortic Regurgitation

Causes

Valve Disease

- Rheumatic fever
- Infective endocarditis
- Connective tissue disease (RA/SLE)
- Bicuspid aortic valve

Aortic Root Disease

- Aortic dissection
- Spondyloarthropathies
- Hypertension
- Syphilis
- Marfan's/Ehlers Danlos syndromes

Features

Symptoms

- Symptoms of heart failure (dyspnoea, orthopnoea, PND)

Murmur

- Early soft diastolic
- Increased by handgrip manoeuvre
- **Austin-Flint Murmur**
  - May be seen in severe AR
  - Mid-diastolic rumbling murmur heard at apex
  - Caused by regurgitation streams forcing partial closure of mitral valve leaflets

Other Signs

- Collapsing pulse and wide pulse pressure
- **Quincke's sign:** nailbed pulsation
- **De Musset's sign:** head pulsation
- **De Roziez's sign:** Femoral artery compressed with finger gives:
  - Systolic murmur 2cm distal
  - Diastolic murmur 2cm proximal

Investigations

ECG

- LVH

Echo

- Diagnostic

CXR

- Cardiomegaly
- Dilated ascending aorta
- Pulmonary oedema

Cardiac Catheterisation

- Assesses ventricular function, valve root anatomy, other valves, etc

Management

- Reduction of blood pressure
- Monitoring every 6-12 months

Indications for Surgery

- Enlarged ascending aorta
- Increasing symptoms
- Decreased LV function/increased dilatation
- Infective endocarditis refractory to medical treatment

Mitral Stenosis

Causes

- **Rheumatic fever**
- Others (rare)
  - Mucopolysaccharidoses
  - Malignant carcinoid
  - Endocardial fibroelastosis
  - Congenital
  - Prosthetic valve

Features

Symptoms

- Pulmonary hypertension
  - Dyspnoea
- Enlarged left atrium
  - Hoarseness
  - Dysphagia
- Chest pain
- Palpitations
- Systemic emboli
- Infective endocarditis

Murmur

- Mid-late diastolic
- Best heard in expiration
- Loud S1 and opening snap

Other Signs

- Low pulse volume
- Malar flush
- Atrial fibrillation

Severe MS

- Increasing length of murmur
- Opening snap closer to S2

Investigations

ECG

- RVH, AF, P mitrale

Echo

- Diagnostic
- Severe stenosis if valve area is <1cm/m^2 of body surface are

CXR

- Left atrial enlargement
  - Double shadow in right cardiac silhouette
- Pulmonary oedema
- Calcified mitral valve

Management

Medical

- Manage AF if present
- Diuretics to reduce preload

Interventional

- Balloon valvuloplasty (if pliable, non-calcified valve)/open mitral valvulotomy/valve replacement

Mitral Regurgitation

Causes

- Functional (LV dilatation)
- Annular calcification (age-associated)
- Post MI
- Mitral prolapse
- Rheumatic fever
- Infective endocarditis

Features

Symptoms

- Mostly asymptomatic
- LVF (fatigue, dyspnoea)
- Arrhythmias

Murmur

- Pansystolic blowing murmur radiating to axilla
- Quiet S1, split S2

Other Signs

- Displaced apex beat (LVD)

Investigations

ECG

- AF, P mitrale,

Echo

- Diagnostic

CXR

- Enlarged LA & LV
- Mitral calcification
- Pulmonary oedema

Management

Medical

- **Acute cases:** nitrates, diuretics, inotropes, intra-aortic balloon pump
- **Heart failure:** ACEi, BB, spironolactone

Interventional

- Surgical repair/replacement for severe or worsening cases

Mitral Prolapse

- Present in 5-10% of population

Associations

- Congenital heart disease
- Cardiomyopathy
- Turner Syndrome
- Fragile X syndrome
- Marfan's/Ehlers Danlos syndrome
- Osteogenesis imperfecta
- WPW
- Long QT syndrome
- Polycystic kidney disease

Features

Symptoms

- Usually asymptomatic
- May develop chest pain/palpitations

Signs

- Mid-systolic click ± late systolic murmur

Complications

- Mitral regurgitation
- Cerebral emboli
- Arrhythmias
- Sudden death

Investigations

Echo

- Diagnostic

Management

- Beta blockers may help chest pain/palpitations
- Surgery if severe MR

Right Heart Valve Disease

Tricuspid Regurgitation

Causes

- Functional, rheumatic fever, infective endocarditis, Ebstein's anomaly

Symptoms

- Fatigue, hepatic pain on exertion, ascites, odemea

Signs

- Giant V waves with prominent Y descent in JVP
- Pansystolic murmur, right ventricular heave, hepatomegaly, jaundice, ascites

Management

- Diuretics
- Surgery if severe (10% 30 day mortality)
- 50% 5 year mortality for TR due to myocardial dysfunction/dilatation

Tricuspid Stenosis

Causes

- Rheumatic fever, almost always with mitral/aortic disease
- Also infective endocarditis, congenital

Symptoms

- Fatigue, ascites, oedema

Signs

- Giant A wave with prominent Y descent in JVP
- Early systolic murmur at left sternal edge with opening snap

Management

- Diuretics
- Surgical repair

Pulmonic Regurgitation

Causes

- Pulmonary hypertension

Signs

- Decrescendo murmur in early diastole at left sternal edge
  - Known as Graham Steell murmur is associated with mitral stenosis and pulmonary hypertension

Pulmonic Stenosis

Causes

- Congenital (Turner, Williams, Noonan, tetralogy of Fallot, rubella), rheumatic fever, carcinoid syndrome

Symptoms

- Dyspnoea, fatigue, oedema, ascites

Signs

- Dysmorphia of congenital cause
- Prominent A wave
- Systolic ejection murmur radiating to left shoulder

Management

- Pulmonic valvuloplasty/valvulotomy

Prosthetic Heart Valves

	Bioprosthetic	Mechanical

Types	• Bovine
	• Porcine
		• Ball and cage
		  – No longer used due to thrombus risk
		• Tilting disc
		• St Jude/Bileaflet
		  – Most common now, lowest thrombus risk

Lifespan	• ~10 years, used in older patients
	  – > 65 for aortic
	  – > 70 for mitral
		• Low failure rate

Thromboprophylaxis	• May not be needed long term
	• Warfarin for ~3 months and lifelong aspirin
		• Lifelong anticoagulation required
		• Warfarin, INR targets:
		  – Aortic 3.0
		  – Mitral 3.5
		• Aspirin added if there is an additional indication (eg IHD)

Other complications/features	• Infective endocarditis risk 2.5% (1.5% with a TAVI) • 15% mortality • Prophylactic antibiotics no longer recommended for routine dental procedures etc	

		• Haemolysis
		• Added heart sounds
		  – S1 click for metallic mitral valve
		  – S2 click for metallic aortic valve

TAVI

- Transcatheter aortic valve implantation
- Outcomes not well known yet
- Open surgery still preferred for young fit patients
- Bioprosthetic valve, long term warfarin not usually required

Infective Endocarditis

- Infection of the endocardium including heart valves
- Any fever with a new murmur or fever lasting >1 week in an individual at risk for IE must be investigated promptly

Risk Factors

Acute IE	Subacute IE
• Skin breaches (wounds, IV lines, etc) • Immunosuppression • Renal disease • Diabetes mellitus	• Abnormal valves • Aortic/mitral disease • Coarctation/PDA/VSD • Prosthetic valves – Early (within 60 days) (caused by S. epidermidis, poor prognosis) or late • IV drug use - tricuspid

Causes

Common

- Viridans strep
- Staph aureus
- Strep bovis
  - Associated with colon cancer, ?endoscopy
- Enterococci
- Coxiella burnetti

Rare

- HACEK
- Chlamydia
- Fungi
- SLE, malignancy

Features

Septic

- Fever, rigors, night sweats
- Malaise
- Splenomegaly
- Anaemia
- Clubbing

Cardiac Lesions

- New/changed murmur
- Valve regurgitation/obstruction precipitating HF
- Prolonged PR interval/complete heart block

Immune Phenomena

- Glomerulonephritis/AKI
- Roth spots
  - Retinal haemorrhages with pale centre
- Splinter haemorrhages
- Osler's nodes
  - Painful lesions in pulp of fingers/toes

Embolic Phenomena

- Janeway lesions
  - Painless palmar/plantar macules
- Abscesses in any organ

Investigations

Bloods

- **Cultures:** 3 at different times from different sites at peak of fever
- Normochromic normocytic anaemia, neutrophilia
- Raised ESR/CRP
- Rheumatoid factor positive
- U+E, Mg2+, LFT

Urinalysis

- For microscopic haematuria

CXR

- Cardiomegaly/pulmonary oedema

ECG

- To monitor for heartblock

Echo

- To visualise valvular lesions/aortic root abscess etc
- TOE more sensitive

CT

- For systemic abscesses

Modified Duke Criteria

- 2 major/1 major + 3 minor/5 minor

Major Criteria

- Positive cultures
  - 2 cultures positive for typical organisms
  - Persistent bacteraemia from cultures >12hrs apart
  - Positive serology for C. burnetti/Bartonella/C. psitacci
- Endocardial involvement
  - New valvular regurgitation
  - Positive echo features
    - Oscillating structures
    - Abscess
    - Prosthetic valve dehiscence

Minor Criteria

- Predisposition
  - Cardiac lesion
  - IVDU
- Fever > 38°C
- Vascular phenomena
- Immunological phenomena
- Positive culture not meeting major criteria

Infective Endocarditis Ctd

Management

- Start blind antibiotic therapy immediately after cultures are taken
- Minimum 4-6 weeks based on microbiology & C&S results

	Native Valve	Prosthetic Valve
Blind/Empiric	Amoxicillin 2g q4h IV + Flucloxacillin 2g q4h IV + Gentamicin 3mg/kg q4hr IV	Vancomycin 25mg/kg (max 2g) loading dose then 15mg/kg q12hr IV + Gentamycin 3mg/kg q24hr IV + Rifampicin 300-600mg q12hr PO/IV After 3-5 days/bacteraemia cleared
	Penicillin allergy	
	Vancomycin 25mg/kg (max 2g) loading dose then 15mg/kg q12hr IV + Gentamycin 3mg/kg q24hr IV	
MRSA/CNS suspected	Vancomycin 25mg/kg (max 2g) loading dose then 15mg/kg q12hr IV + Gentamycin 3mg/kg q24hr IV	

Indications for Surgery:

- Severe valvular incompetence
- Aortic abscess (may be indicated by lengthening PR interval)
- Resistant/fungal infections
- Cardiac failure refractory to standard treatment
- Recurrent emboli after antibiotic therapy

Prognosis

- 50% require surgery
- 20% in hospital mortality
  - Staphylococci 30%
  - Bowel organisms 15%
  - Streptococci 5%
- 15% recurrence at 2 years

Prophylaxis

- No longer recommended during routine procedures
- If given an antibiotic for other reasons, it should cover IE organisms

Acute Myocarditis

- Inflammation of myocardium often associated with simultaneous pericarditis

Causes

- **Idiopathic:** 50% of cases
- **Viral:** Coxsackie B, HIV, entero, adeno, EBV, CMV, mumps, HHV-6, rubeola
- **Bacterial:** Staph, Strep, Clostridia, diphteria, TB, meningococcus, mycoplasma
- **Spirochetes:** Leptospirosis, syphilis, Lyme disease
- **Protozoa:** Chagas', Leishmania, toxoplasmosis
- **Drugs:** Cyclophosphamide, trastuzumab, penicillin, chloramphenicol
- **Toxins:** Cocaine, lithium, alcohol, lead, arsenic
- **Immunological:** SLE, sarcoid, Kawasaki, scleroderma, heart transplant rejection

Features

- Typically acute presentation in a younger patient
- Chest pain
- Dyspnoea
- Palpitations

Investigations

Bloods

- Raised ESR & CRP
- Raised troponin
- Raised BNP

ECG

- Tachycardia
- ST elevation & T wave inversion

Management

- Treat underlying cause if present
- Treat arrhythmias/heart failure
- Avoid exercise

Complications

- Heart failure
- Arrhythmia
- Sudden death
- Dilated cardiomyopathy

Prognosis

- 50% recovery within 4 weeks
- 12-25% will develop dilated cardiomyopathy and severe heart failure (can occur years after recovery)

Acute Pericarditis

Causes

- **Idiopathic**
- **Viruses:** coxsackie, echovirus, EBV, CMV, adeno, mumps, varicella, HIV
- **Bacteria:** TB (commonest worldwide), Lyme disease, Q fever, pneumonia, rheumatic fever
- **Fungi/parasites:** Rare except in immunocompromised
- **Autoimmune:** systemic autoimmune disease (SLE/RA/vasculitis/IBD/sarcoid/amyloid), Dressler's syndrome
- **Drugs:** Procainamide, hydralazine, penicillin, isoniazid
- **Metabolic:** uraemia, hypothyroidism, anorexia nervosa
- **Others:** trauma, surgery, malignancy, radiotherapy, CHF

Features

- Central chest pain
  - Worse on inspiration/lying flat
  - Relieved by leaning forward
- Friction rub
- Fever
- Tachycardia & tachypnoea

Investigations

Bloods

- Inflammatory markers/cardiac enzymes may be raised

ECG

- Global/widespread changes
- Saddle-shaped ST elevation
- PR depression most specific for pericarditis

Echo

- Check for pericardial effusion

CXR

- Check for cardiomegaly (pericardial effusion)

Management

- NSAIDs with gastric protection for 1-2 weeks
- Add colchicine 500mg OD/BD for 3 months to reduce recurrence risk
- Immune causes/non-resolving: steroids (may increase recurrence risk)

Constrictive Pericarditis

Causes

- Any cause of acute pericarditis, particularly TB

Features

- Dyspnoea
- Right heart failure
  - Elevated JVP, ascites, hepatomegaly, oedema
- JVP shows prominent x and y descent
- Pericardial knock (loud S3)
- Kussmaul's sign
  - Raised JVP during inspiration

Investigations

CXR

- Small heart with calcified pericardium

MRI

- Helps differentiate from restrictive cardiomyopathy

Management

- Surgical excision, medical treatment of heart failure

Pericardial Effusion

- Accumulation of pericardial fluid (normal 10-50ml)

Causes

- Pericarditis
- Myocardial rupture
- Aortic dissection
- Empyema
- Malignancy

Features

- Dyspnoea
- Chest pain
- Hiccoughs (phrenic nerve compression)
- Muffled heart sounds
- Bronchial breathing over left base

Investigations

ECG

- Low voltage QRS complexes
- Electrical alternans

Echo

- Anechoic zone surrounding heart

CXR

- Large globular heart (if effusion is > 300ml)

Cardiac Tamponade

- Accumulation of pericardial fluid under pressure
- Reduces ventricular filling & cardiac output, can quickly lead to cardiac arrest

Features

Beck's Triad

- Hypotension
- Raised JVP
- Muffled heart sounds

Others

- Dyspnoea
- Tachycardia
- Absent Y descent on JVP
- Pulsus paradoxus
- Kussmaul's sign

Investigations

Echo (Diagnostic)

- Anechoic zone around heart (> 2cm or > 1cm if acute)

ECG

- Low voltage QRS complexes
- Electrical alternans

Management

- Senior help
- Urgent drainage of fluid
- Send fluid for culture, ZN stain, & cytology

Genetic Cardiomyopathies

Hypertrophic Obstructed Cardiomyopathy

- Autosomal dominant disorder present in 1/500 people
- Most common cause of sudden cardiac death in the young

Pathophysiology

- Defect in gene for B-myosin heavy chain or myosin binding protein C
- LV hypertrophy causing decreased compliance and cardiac output ± outflow obstruction (subaortic hypertrophy of ventricular septum)
- Myofibrillar hypertrophy with myocyte hypertrophy and fibrosis on biopsy

Features

- Often asymptomatic
- Exertional dyspnoea/angina
- Syncope
  - Functional aortic stenosis from outflow obstruction
- Arrhythmias
  - Sudden death due to ventricular arrythmia
- Jerky pulse, large A waves, double apex beat
- Ejection systolic murmur
  - Increased with Valsalva manoeuvre
- Mitral regurgitation due to impaired valve closure

Associations

- Friedrich's ataxia
- WPW

Investigations

- **Echo**
  - Mitral regurgitation
  - Systolic anterior motion of anterior mitral valve leaflet
  - Asymmetric hypertrophy
- **ECG**
  - LVH
  - Deep Q waves
  - Atrial fibrillation occasionally
  - Non-specific ST segment and T wave changes

Management

- Amiodarone
- Beta-blocker/verapamil
- Cardioverter defibrillator (ICD)
- Dual chamber pacemaker
- **Avoid:**
  - Nitrates
  - ACE inhibitors
  - Inotropes

Arrhythmogenic Right Ventricular Dysplasia

- Second most common cause of sudden cardiac death in the young

Pathophysiology

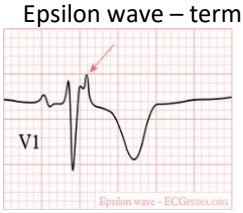
- Autosomal dominant inheritance with variable expression
- Right ventricular myocardium is replaced with fatty and fibrofatty tissue
- 50% of patients have defects in genes encoding for desmosome components

Features

- Palpitations
- Syncope
- Sudden death

Investigations

- **Echo**
  - Subtle in early stages
  - Enlarged hypokinetic right ventricle with thin free wall
- **ECG**
  - Abnormalities seen in V1-V3
  - T wave inversion
  - Epsilon wave – terminal notch in QRS complex



- **MRI**
  - Fibrofatty tissue

Management

- Antiarrhythmics (sotalol most common)
- Catheter ablation to prevent ventricular tachycardia
- ICD

Naxos Disease

- AR variant of ARVD consisting of ARVD, palmoplantar keratosis and woolly hair

Mixed Cardiomyopathies

Dilated Cardiomyopathy

- 90% of cardiomyopathies

Causes

- Idiopathic (most common)
- Myocarditis
- IHD
- Peripartum
- Hypertension
- Iatrogenic (eg doxorubicin)
- Substance abuse
- Inherited
  - Predisposition to DCM in 1/3
  - Muscular dystrophies
- Infiltrative
  - Haemochromatosis
  - Sarcoidosis
- Nutritional
  - Wet beri-beri

Pathophysiology

- Eccentric hypertrophy
- Dilated chambers leads to systolic dysfunction

Features

- Heart failure
- Tricuspid/mitral regurgitation
- S3
- Balloon appearance of heart on CXR

Management

- Bed rest
- Diuretics, Beta-blockers, ACE-inhibitors, anticoagulation
- Biventricular pacemaker/LVAD
- Transplantation

Mortality

- ~40% in 2 years

Restrictive Cardiomyopathy

Causes

- Idiopathic
- Amyloid/sarcoid/scleroderma
- Haemochromatosis
- Loeffler's pericarditis

Features

- RHF (oedema, ascites, hepatomegaly)
- Raised JVP with prominent X and Y descents

Investigations

- Echo
- ECG
- MRI

Management

- Treat underlying cause

Acquired Cardiomyopathies

Peripartum Cardiomyopathy

- Typically develops between last month of pregnancy and 5 months postpartum
- Dilated cardiomyopathy
- More common in older women, increased parity, multiple gestations

Takotsubo Cardiomyopathy

- Transient cardiomyopathy usually triggered by stress

Pathophysiology

- Ballooning of the apex caused by hypokinesis of the mid and apical segments of the myocardium with normal contraction of the basal segments

Features

- Chest pain
- Heart failure
- ST elevation
- Normal coronary angiogram

Management

- Supportive, most patients will recover

Respiratory Medicine

Respiratory Failure

Type 1 Respiratory Failure

- PaO2 < 8kPa with a normal or low PaCO2
- V/Q mismatch and failure of diffusion (because CO2 diffuses easier than O2)

Causes

- Pneumonia
- Pulmonary embolism
- Pulmonary oedema
- Emphysema
- Pulmonary fibrosis
- ARDS

Type 2 Respiratory Failure

- PaO2 < 8kPa and PaCO2 > 6kPa
- Alveolar hypoventilation

Causes

- **Pulmonary disease**
  - COPD
  - Asthma
  - Pneumonia
  - End stage pulmonary fibrosis
- **Reduced respiratory drive**
  - Sedative drugs
  - CNS mass/trauma
- **Neuromuscular disease**
  - Myasthenia gravis
  - Guillain-Barré syndrome
  - Cervical cord lesion
  - Diaphragmatic paralysis
- **Chest wall disease**
  - Flail chest
  - Kyphoscoliosis

Features

- Underlying cause plus:

Hypoxia

- Dyspnoea
- Restlessness
- Agitation
- Confusion
- Central cyanosis
- Polycythaemia/pulmonary hypertension/cor pulmonale if chronic

Hypercapnia

- Headache
- Peripheral vasodilation
- Tachycardia
- Bounding pulse
- Tremor/flap
- Papilloedema
- Reduced LOC/coma

Investigations

- FBC, CRP, U+E, ABG
- CXR
- Sputum & blood cultures if febrile
- Spirometry

Management

- Treat underlying cause

Type 1

- Give oxygen to target SpO2 of 94-98%
- Assisted ventilation if PaO2 < 8kPa despite 60% O2

Type 2

- Start oxygen at 24%
- Recheck ABG after ~20mins
  - If PaCO2 is steady or lower, increase to 28%
  - If PaCO2 has increased by > 1.5kPa, consider NIPPV
- Consider intubation if this fails

COPD

- Persistent respiratory symptoms & airflow limitation due to airway/alveolar abnormalities usually caused by exposure to noxious particles/gases.
- **Chronic Bronchitis**: productive cough for 3 months in each of 2 successive years with other causes of chronic cough excluded
- **Emphysema:** abnormal permanent enlargement of airspaces distal to the terminal bronchioles & destruction of the airspace walls

Risk Factors

- **Smoking**
- **Alpha-1 anti-trypsin deficiency**
- Atopy/asthma
- Occupational exposure (cadmium, cement, cotton, coal)

Presentation

Symptoms

- Cough, often productive
- Dyspnoea
- Wheeze
- Cor pulmonale in severe cases

Signs

- Hyperinflation
  - Hyperresonance on percussion
  - Distant heart sounds
  - Increased AP chest diameter
  - Flatted diaphragm with little movement (found on percussion)
- Decreased breath sounds
- Wheeze
- Basal crackles
- Signs of respiratory distress
  - Accessory muscles
  - Cyanosis
  - Asterixis (hypercapnia)
- **NOT CLUBBING**

mMRC Dyspnoea Scale

1	Dyspnoea only on vigorous exertion
2	Dyspnoea on hurrying/walking up stairs
3	Walks slower than contemporaries/has to stop for breath at own pace
4	Stops for breath after < 100m/few minutes
5	Too breathless to leave the house/breathless when dressing or undressing

Investigations

- Spirometry
  - Post bronchodilator FEV1/FVC ratio < 0.7
- Chest x-ray
  - Hyperinflation
  - Bullae
  - Flat hemidiaphragm
  - Exclude lung cancer
- Full blood count
  - Exclude secondary polycythaemia
  - Eosinophilia suggests steroid responsiveness
- BMI calculation

COPD GOLD

Airflow Limitation Severity (FEV1 % of predicted)

GOLD 1	Mild	> 80%
GOLD 2	Moderate	50 – 79%
GOLD 3	Severe	30 – 49%
GOLD 4	Very Severe	< 30%

Assessment of Symptoms & Exacerbation Risk

Exacerbation History	mMRC Scale 0-1	mMRC Scale 2+
2+ or 1+ leading to hospital admission	C	D
0 or 1 (not leading to hospital admission)	A	B

Asthmatic/Steroid Responsive Features

- Any previous, secure diagnosis of asthma/atopy
- High blood eosinophil count
- Substantial variation in FEV1 over time
- Substantial diurnal variation in PEFR (at least 20%)

General Management of Stable COPD

- Smoking cessation
  - Advice
  - NRT
  - Varenicline/bupropion
- Annual influenza vaccine
- Once-off pneumococcal vaccine
- Pulmonary rehab if patient views themself as debilitated (usually mMRC grade 3)

Bronchodilators in Stable COPD

- NICE recommends combined inhalers where possible

1. SABA or SAMA

No Asthmatic/Steroid Responsive Features Present	Asthmatic/Steroid Responsive Features Present
2. Add LABA + LAMA – If taking SAMA at step 1, switch it to a SABA	**2.** Add LABA + ICS

3. Triple therapy with LAMA, LABA, + ICS
- If taking SAMA at step 1, switch it to a SABA

Other Management

Oral Theophylline

- Only if inhaled agents are trialled and failed/not suitable

Prophylactic Antibiotics

- Azithromycin in select patients only
- Patients who do not smoke, have optimised treatment and continue to have exacerbations (COPD D)
- CT thorax (to exclude bronchiectasis), sputum culture (to exclude atypicals), ECG (to exclude long QT), LFTs

Mucolytics

- Trialled in chronic productive cough & continued if improvement

Col Pulmonale

- Loop diuretic & consider LTOT

LTOT in COPD (NICE)

Indications for Assessment

- Severe/very severe airflow obstruction
- Cyanosis
- Polycythaemia
- Peripheral oedema
- Raised JVP
- SpO2 < 92% on room air

Assessment

- ABGs on 2 occasions at least 3 weeks apart in patients with stable COPD on optimum management

LTOT Criteria

- pO2 < 7.3kPa
- PO2 7.3 – 8kPa plus 1 of:
  - Secondary polycythaemia
  - Peripheral oedema
  - Pulmonary hypertension

Smoking

- Do not offer LTOT to patients who continue to smoke despite cessation advice & treatment & referral to specialist quitting services

Risk Assessment

- Risk of falls (tripping over equipment)
- Risk of burns & fires
  - Increased risk for those living with someone who smokes, including e-cigarettes

Acute Exacerbation of COPD

- Acute & sustained worsening of symptoms of COPD

Causes

- 70% are caused by respiratory infections, most of which are viral

Bacterial Causes:

- Haemophilus influenzae
- Moraxella catarrhalis
- Streptococcus pneumoniae
- Pseudomonas aeruginosa

Risk Factors

- Older age
- Productive cough
- Longer duration of COPD
- History of antibiotic therapy
- COPD-related hospitalisation in the previous year
- Theophylline therapy
- Medical comorbidities

Presentation

- Increase in dyspnoea, cough, & wheeze
- Increased sputum volume (may be purulent if bacterial infection)
- Hypoxia
- Confusion

Investigations

- FBC, U+E
- CXR
- ABG
- ECG (exclude comorbidities)
- Theophylline level if applicable
- Sputum culture only if sputum is purulent
- Blood culture only if patient is pyrexic

Management

- Increase frequency of inhalers, consider nebuliser
- Prednisolone 30mg for 5 days

Antibiotics

- Only if there is purulent sputum or signs of pneumonia
  - Amoxicillin/clarithromycin/doxycycline

Chronic Asthma

- Chronic inflammatory disease of the airways caused by type I hypersensitivity to a variety of triggers resulting in reversible bronchospasm & airway obstruction

Risk Factors

- Personal/family history of atopy
  - Allergic rhinitis (hay fever)
  - Atopic dermatitis (eczema)
- Antenatal factors
  - Maternal smoking
  - Viral (especially RSV) infection during pregnancy
- Low birth weight
- Not being breastfed
- Exposure to high concentrations of allergens (eg dust mites)/second hand smoke/air pollution
- Hygiene hypothesis: reduced exposure to infections in childhood increases adult risk of asthma

Presentation

Symptoms

- Cough
- Wheeze
- Dyspnoea
- Occur in response to typical **triggers:**
  - Inhaled allergens (dust, pollen)
  - Exercise
  - Cold air
  - Stress/anxiety
- **Diurnal variation** with cough typically worse at night

Signs

- Widespread polyphonic wheeze
- Hyperinflation
- Reduced air entry
- Reduced PEFR
- Nasal poyps
- Signs of steroid use
- **NOT CLUBBING**

Diagnosis

- Symptoms of asthma + one of
  - FeNO level of 40+ppb with either positive bronchodilator reversibility, positive peak flow variability or bronchial hyperreactivity
  - FeNO level of 25-39ppb and a positive bronchial challenge test
  - Positive bronchodilator reversibility & positive peak flow variability irrespective of FeNO level

Occupational Asthma

- Symptoms associated with working days and subside at weekends/on holidays
- Specialist referral

Investigations

Objective Asthma Investigations

Test	Positive Result
FeNO	40ppb or more
Obstructive Spirometry	FEV1/FVC ration < 0.7
Bronchodilator reversibility	Improvement of FEV1 of 12% or more & 200ml or more
Peak flow variability (diary)	Variability over 20%
Direct bronchial challenge with methacholine /histamine	*Provocative concentration of methacholine causing 20% fall in FEV1* (PC20) of 8mg/ml or less

Others

- **Bloods**
  - FBC (eosinophilia)
  - IgE
  - Aspergillus serology
- **CXR**
  - Hyperinflation

Management

General

- Inhaler technique
- Avoid triggers
- Monitor peak flow diary (2-4/d)
- Education: liaison with specialist nurse, acute attack action plan, advise exercise
- Annual influenza vaccine

Drug Ladder (GINA) – Option 1

Step	Reliever	Maintenance	Additional
1	PRN low dose MART		
2			LTRA
3		Low-dose MART	LTRA
4	PRN medium dose MART	Medium dose MART	LTRA
5		Add LAMA Consider high dose MART	LTRA Refer

Drug Ladder (GINA) – Option 2

Step	Reliever	Maintenance	Additional
1	PRN SABA		
2		Low dose ICS	LTRA
3		Low dose ICS-LABA	LTRA
4		Medium/high dose ICS-LABA	LTRA
5		Add LAMA Consider high dose ICS-LABA	LTRA Refer

*MART

- Maintenance and reliever therapy
- ICS and LABA in single inhaler
  - LABA must have a fast acting component (formoterol)

Acute Asthma

- Worsening dyspnoea, wheeze, & cough that is not responding to salbutamol in patient with chronic asthma

Features & Severity

Moderate	Severe	Life-threatening	Near-fatal
PEFR 50-75% best/predicted Speech normal RR < 25/min Pulse < 110bpm	PEFR 33-50% best/predicted Can't complete sentences RR > 25/min Pulse > 110bpm	PEFR < 33% best/predicted Oxygen sats < 92% Silent chest, cyanosis, or weak respiratory effort Bradycardia, dysrhythmia, or hypotension Exhaustion, confusion, or coma Normal pCO2	Raised pCO2 Requiring mechanical ventilation with raised inflation pressure

Investigations

- ABG if SpO2 is < 92%
- CXR only if:
  - Life-threatening asthma
  - Suspected pneumothorax
  - Failure to respond to treatment

Admission Criteria

- Life-threatening attack
- Severe attack not responding to initial treatment
- Previous near-fatal attack
- Pregnancy
- Attack despite oral corticosteroids
- Presentation at night

Discharge Criteria

- Stable on discharge meds (no nebulisers or oxygen) for 12-24 hours
- Inhaler technique checked
- PEFR > 75% best/predicted with diurnal variability < 20%

Immediate Management

Oxygen

- 15L via NRB, titrated to maintain SpO2 94-98%

Salbutamol

- Can be given via MDI in moderate/severe attacks
- Given via nebuliser in life-threatening/near-fatal attacks
  - 5mg nebulised with oxygen (or terbutaline 10mg)

Corticosteroid

- Hydrocortisone 100mg IV or prednisolone 50mg orally

Ipratropium Bromide

- 0.5mg given via nebuliser in severe and above attacks or in attacks not responding to earlier treatment

Magnesium Sulfate

- 2g IVI over 20 minutes in severe and above attacks or in attacks not responding to earlier treatment

Improving

- Salbutamol (+ ipratropium if started) every 4-6 hours
- Continue steroids (pred 50mg) for 5 days
- Monitor SpO2 (94-98%) and PEFR (aiming for > 75% best/predicted)

Not Improving

- Senior help
- Nebulised salbutamol 5mg every 15-30 minutes OR IVI 10mg/hr
  - Monitor ECG
- Nebulised ipratropium 0.5mg every 6 hours
- Aminophylline
  - 5mg/kg IVI over 20mins loading does **unless already on theophylline**
  - Continue at 0.5mg/kg/hr
  - Monitor levels
- ICU & invasive ventilation if needed

Bacterial Pneumonia

- Inflammation of the alveoli caused by bacterial infection (most common infective pneumonia in adults)

Microbiology

Streptococcus pneumoniae	50-80% of cases Vaccine available Associated with rapid onset, high fever & herpes labialis
Haemophilus influenzae	Up to 20% of cases Common in patients with COPD
Staphylococcus aureus	Common following influenza
Mycoplasma pneumoniae	Atypical pneumonia
Legionella pneumophila	Atypical pneumonia Classically secondary to infected air conditioners
Klebsiella pneumoniae	Common in alcoholics
Pneumocystis jirovecii	Typically seen in HIV

Classification

Community Acquired Pneumonia (CAP)

- Developed outside hospital or within 48 hours of hospital admission

Hospital Acquired Pneumonia (HAP)

- Developed more than 48 hours after hospital admission

Features

Symptoms

- Cough with green/purulent sputum/haemoptysis
- Dyspnoea
- Chest pain (may be pleuritic)
- Delirium
- Fever/sepsis

Signs

- Tachypnoea, tachycardia, fever, hypotension
- Hypoxia
- Bronchial breath sounds
- Focal course crackles
- Focal dullness to percussion

Investigations

CXR

- Classical finding is lobar consolidation

Bloods

- **FBC** may show neutrophilia in bacterial infection
- **CRP** raised due to infection, monitor response to treatment
- **U&Es** for hydration, renal function & CURB-65

ABG

- Indicated if there is reduced oxygen saturations or pre-existing respiratory disease

Others

- Sputum/blood cultures and pneumococcal/legionella urinary antigen tests for moderate/severe cases

CURB-65

- Risk stratification score for community acquired pneumonia

C	Confusion (AMT score < 8/10)
U	Urea > 7mmol/L
R	Resp rate > 30/min
B	Blood pressure < 90 systolic/< 60 diastolic
65	Age ≥ 65

Scores

- **0-1:** Low (3%) mortality risk, manage at home
- **2:** Medium (3-15%) mortality risk, manage in hospital
- **3+:** High (>15%) mortality risk, consider ICU assessment

Management

Antibiotics

Severity	1st Line Empirical	Penicillin Allergy	Days
CURB 0-1	Amoxicillin Co-amoxiclav/clarithro/doxy if recent abx	Clarithromycin	5
CURB 2	Co-amoxiclav + clarithromycin	Doxycycline /levofloxacin	7-10
CURB 3		Cefuroxime + clarithromycin /doxycycline /levofloxacin	
CURB 4-5	Ceftriaxone + clarithromycin Co-amox + clarithromycin for oral stepdown	Levofloxacin + vancomycin	
HAP	Pipericillin-Tazobactam IV Add vancomycin if MRSA suspected	Ceftazidime + vancomycin	7

- All durations can be extended if clinical improvement is delayed
- Antibiotics can be tailored to culture sensitivities when available

Others

- Oxygen if hypoxaemic
- IV fluids if hypotensive/dehydrated

Complications

- Respiratory failure
- Sepsis
- Atrial fibrillation
- Pleural effusion
- Pleural empyema
- Lung abscess
- Pericarditis/myocarditis

Aspiration Pneumonia

- Alveolar inflammation caused by inhalation of foreign (usually oral or gastric) material.
- Acidity of inhaled material causes chemical pneumonia in addition to introduced infection
- Most commonly affects right middle and lower lobes due to anatomy of right main bronchus (wider and more vertical)

Risk Factors/Causes

- Difficulty swallowing
  - Stroke
  - MS
  - Intoxication
- Poor dental hygiene
- Prolonged hospitalisation/surgical procedures
- Impaired consciousness
- Impaired mucociliary clearance

Microbiology

- Most commonly aerobes
  - Streptococcus pneumoniae
  - Staphylococcus aureus
  - Haemophilus influenzae
  - Pseudomonas aeruginosa

Managements

- Antibiotics as per pneumonia ± metronidazole

Pneumocystis Pneumonia

- Pneumocystis jirovecii is an opportunistic fungus and is the most common opportunistic infection in AIDs

Features

- Dyspnoea
- Dry cough
- Fever
- Very few chest signs

Investigations

CXR

- Typically shows bilateral interstitial pulmonary infiltrates
- May show pneumothorax

BAL

- Silver stain shows characteristic cysts

Other

- Exercise induced desaturations

Management

- Co-trimoxazole/IV pentamidine for 2-3 weeks
- Steroids if respiratory failure

Prophylaxis

- Co-trimoxazole for patients with CD4 count < 200

Atypical Pneumonias

Mycoplasma pneumoniae

Features

- Flu like symptoms followed by dry cough

Investigations

- **CXR**
  - Reticular nodular shadowing or patchy consolidation of one lower lobe
- **Sputum PCR/Serology**
  - Diagnostic

Complications

- Cold AIHA
- Erythema multiforme/Stevens-Johnson syndrome
- Meningoencephalitis
- Guillain-Barré syndrome

Management

- Clarithromycin/doxycycline/fluoroquinolone

Legionella Pneumophila

- Colonises water tanks <60° causing outbreaks

Features

- Flu-like symptoms followed by dry cough & dyspnoea
- Extrapulmonary features:
  - Anorexia
  - Diarrhoea & vomiting
  - Hepatitis
  - Renal failure
  - Confusion
  - Coma

Investigations

- **Bloods**
  - Lymphopenia
  - Hyponatraemia
  - Deranged LFTs
- **CXR**
  - Bi-basal consolidation
- **Urine**
  - Urinalysis may show haematuria
  - Urine PCR is diagnostic

Management

- Fluoroquinolone/clarithromycin
- 10% mortality

Chlamydophila

- Chlamydophila pneumonia spreads person-person and causes pharyngitis & otitis followed by pneumonia
- Chlamydophila psittaci is spread by infected birds and causes flu-like symptoms and pneumonia

Investigations

- Serology/PCR of invasive samples

Management

- Doxyxcycline/clarithromycin

Viral Pneumonia

- Caused by influenza, H1N1, COVID, SARS, CMV, etc
- Supportive care with public health notification and isolation if necessary

Lung Abscess

- Cavitating area of suppurative inflammation/infection within the lung

Causes

- Non-resolved pneumonia
- Aspiration
  - Alcoholism
  - Oesophageal obstruction
  - Neurological
- Bronchial obstruction
  - Tumour
  - Foreign body
- Lung infarction
- Septic emboli
  - Right heart endocarditis
  - Sepsis
  - IVDU
- Subphrenic/hepatic abscess

Features

Symptoms

- Swinging fever
- Cough with purulent sputum
- Haemoptysis
- Dyspnoea
- Pleuritic pain
- Malaise
- Weight loss

Signs

- Focal crepitations
- Finger clubbing

Investigations

Bloods

- FBC shows anaemia & neutrophilia
- Raised inflammatory markers
- Blood cultures

Sputum

- Culture & microscopy

Imaging

- CXR/CT shows walled off cavity with fluid level
- CT can check for obstruction

Bronchoscopy

- Specimens for culture

Management

- Antibiotics as per sensitivities
- Postural drainage
- Surgical excision/drainage may be required

Bronchiectasis

- Chronic inflammation and dilatation of airways

Causes

Post-infective

- TB, measles, pertussis, pneumonia

Congenital

- Cystic fibrosis
- Ciliary dyskinesia (Kartagener's, Young)

Immunodeficiency

- Selective IgA deficiency
- Hypogammaglobinaemia

Obstruction

- Tumour
- Foreign body

Others

- Allergic bronchopulmonary aspergillosis
- Rheumatoid arthritis
- Ulcerative colitis

Organisms

- Haemophilus (most common)
- Pseudomonas
- Klebsiella
- Strep pneumoniae

Features

Symptoms

- Cough with large volumes of purulent sputum
- Intermittent haemoptysis

Signs

- Finger clubbing
- Coarse inspiratory crackles
- Wheeze

Investigations

Sputum

- Culture & sensitivities

Imaging

- CT/CXR shows tram track sign of dilated airways
- CT shows signet ring sign and extent of airway disease

Bronchoscopy

- To identify site of haemoptysis

Others

- Serum immunoglobulins & aspergillus precipitins

Management

General

- Postural drainage & airway clearance techniques
- Management of treatable causes (ABPA, immunodeficiency)
- Immunisations

Antibiotics

- Management of exacerbations according to sensitivities
- Long term antibiotics if > 3 exacerbations per year

Bronchodilators

- Eg nebulised salbutamol – useful if co-existing asthma/COPD/ABPA etc

Surgery

- Localised disease or massive haemoptysis

Allergic Bronchopulmonary Aspergillosis

- Allergy to ubiquitous Aspergillus spores

Features

- Bronchoconstriction
  - Dyspnoea, wheeze, cough
  - May have a label of asthma
- Proximal bronchiectasis

Investigations

Bloods

- Eosinophilia
- Raised IgE

CXR

- Bronchiectasis
- Bronchocoeles

Specific Tests

- Positive RAST test to aspergillus
- Positive IgG precipitins

Management

- Steroids
- Itraconazole may be used second line

Aspergilloma

- Mycetoma (fungal mass) colonising pre-existing lung cavity from lung cancer, TB, CF, etc

Features

- May be asymptomatic
- Cough
- Haemoptysis (can be massive)

Investigations

- CXR: rounded opacity with crescent sign
- Strongly positive IgG precipitins

Management

- Excision for solitary lesions or for massive haemoptysis

Invasive Aspergillosis

- Systemic Aspergillus infection
- Large cause of mortality in immunocompromised
- Aflatoxins (especially from A. flavus) lead to cirrhosis & HCC

Risk Factors

- HIV
- Leukaemia
- Post broad spectrum antibiotics

Investigations

- Consolidation & abscesses on CXR
- Positive IgG precipitins
- Sputum/BAL MCS

Management

- Voriconazole/amphotericin
- 30% mortality

Tuberculosis

- Infection with Mycobacterium tuberculosis – lung is the most common site
- Spread by respiratory droplets

Stages

Primary infection

- Formation of a small lung lesion called a Ghon focus (Ghon complex in association with hilar lymphadenopathy)
- Walled off by fibrosis in most immunocompetent individuals

Latent TB

- Infection without disease due to persistent immune containment
- Blood/skin tests are positive, sputum is negative
- Patient is asymptomatic and not contagious
- 5-10% lifetime reactivation risk
- ~ 1 third of the world population

Active TB

- Failure of the immune system to contain infection
- May arise from primary infection or re-activation of latent TB
- Sputum positive
- Patient symptomatic and contagious
- Risk factors for re-activation:
  - Infection < 2 years
  - HIV
  - Organ transplantation
  - Immunosuppression (including steroids)
  - Silicosis
  - Illicit drug use
  - Low socio-economic status
  - Haemodialysis

Features

Systemic

- Low grade fever
- Anorexia & weight loss
- Night sweats
- Clubbing
- Erythema nodosum

Pulmonary

- Cough (dry then productive)
- Pleurisy
- Haemoptysis
- Pleural effusion

Extrapulmonary

- **Tuberculous lymphadenitis:** painless cervical/supraclavicular lymphadenopathy
- **Spinal (Pott's disease):** vertebral collapse, bone pain & tenderness, neurological signs
- **CNS:** headache, meningism, focal deficits, mass effect
- **Cardiac:** pericardial disease
- **Skin:** Lupus vulgaris
- **Gastrointestinal:** Ileocaecal disease, colicky pain, vomiting, obstruction
- **Genitourinary:** dysuria, frequency, loin pain, haematuria, sterile pyuria, strictures

Investigations

Latent TB

- Neither test can exclude or confirm active disease
- **Mantoux test (Tuberculin skin testing)**
  - 1ml of purified protein derivative injected intradermally and read 2-3 days later
  - Positive if skin induration is > 15mm with no risk factors/5mm with risk factors
  - Positive if BCG vaccinated
- **Interferon Gamma Release Assay**
  - Measures response of T-cells to TB antigen exposure
  - Greater specificity if TB vaccinated

Active Pulmonary TB

- **CXR**
  - Cavitating fibronodular opacities typically in apices
  - Bilateral hilar lymphadenopathy
  - Miliary TB: "millet seed" appearance
    - Associated with haematogenous spread of primary disease in immunocompromised individuals
- **Sputum Smear**
  - Fast and cheap
  - 3 specimens needed
  - Stained for Acid-Fast Bacilli (AFB) – all mycobacteria are positive
  - 50-80% sensitive
- **Sputum Culture**
  - Gold standard - more sensitive and can assess sensitivities
  - Takes 1-3 weeks in liquid media, longer in solid media
- **Nucleic Acid Amplification Tests**
  - Performed on sputum samples
  - Rapid diagnosis (< 24hrs)
  - Can detect drug resistances

Extrapulmonary Disease

- AFB stain on any biopsies/aspirations
- NAAT on any sterile body fluid

Other

- HIV test

TB Management

Active TB

	Initial 2 months	Further 4 months	Side effects
Rifampicin	✓	✓	Enzyme induction: care with warfarin, oestrogens, phenytoin, etc Hepatitis Body secretions turned orange-red – can cause contact lens staining
Isoniazid	✓	✓	Inhibits formation of vitamin B6 (pyridoxine) causing peripheral neuropathy (prevent by supplementing pyridoxine) Hepatitis Agranulocytosis Enzyme induction
Pyrazinamide	✓		Hyperuricaemia & gout Arthralgia & myalgia Hepatitis
Ethambutol	✓		Optic neuritis – check acuity before and during treatment

Drug Resistant TB

Classification

- Drug resistant: resistant to any above drug
- Multi-drug resistant: resistant to rifampicin and isoniazid
- Extensively drug resistant: resistant to rifampicin, isoniazid, one injectable agent (eg amikacin, capreomycin) and one fluoroquinolone

Risk Factors

- Previous TB treatment
- Contact with drug resistant TB
- Birth/residence in high risk country

Management

- Expert input
- Treatment with at least 6 agents to which it is sensitive

Latent TB

- Balance of risk of reactivation and side effects of treatment
- Offer to all who are at increased risk of reactivation
- 3 months of rifampicin & isoniazid or 6 months of isoniazid

Extrapulmonary Disease

CNS & Spinal

- Extend continuation phase to 10 months
- Adjunctive high dose steroids in initial treatment phase

Pericardial

- Adjunctive high dose steroids in initial treatment phase

Interstitial Lung Disease

- Umbrella term for diseases which diffusely affect the lung parenchyma with chronic inflammation and interstitial fibrosis

Common Clinical Features

- Exertional dyspnoea
- Non-productive cough
- Fine end-inspiratory crepitations
- Restrictive spirometry pattern

Classification

Non-Idiopathic						Idiopathic
Iatrogenic	Occupational/ EAA	CT Disease	Granulomatous	Infective	Other	IPF Non-specific interstitial pneumonias
Drugs (HSP) • Amiodarone • Nitrofurantoin • Methotrexate • Bleomycin Radiation	Asbestos Silicosis EAA	Rheumatoid arthritis SLE Systemic sclerosis Sjogren's syndrome Poly/dermatomyositis	Sarcoidosis TB Berylliosis (EAA)	TB Viral Post-infective	GORD UC RTA	

Extrinsic Allergic Alveolitis

- Lung damage caused by type III hypersensitivity to a variety of inhaled pathogens

Causes

- Bird-fancier's/pigeon-fancier's lung (protein in bird droppings)
- Farmer's lung (*Saccharopolyspora rectivirgula* spores)
- Mushroom worker's lung (thermophilic actinomycetes)
- Malt worker's lung (*Aspergillus clavatus*)

Features

Acute (4-6 hours after exposure)

- Fever, rigors, malaise
- Dry cough
- Dyspnoea
- Fine bi-basal crackles

Chronic

- Increasing dyspnoea
- Weight loss
- Finger clubbing
- Type 1 respiratory failure
- Cor pulmonale

Investigations

Bloods

- Neutrophilia
- NO eosinophilia
- Raised ESR
- Assays for specific IgG antibodies

Imaging

- Upper/mid zone fibrosis
- Honeycomb lung
- Extensive fibrosis & ground glass appearance on CT

BAL

- Lymphocytes & mast cells

Management

- Removal & avoidance of pathogens (face masks can be effective)
- Long term steroids

Idiopathic Pulmonary Fibrosis

- Chronic progressive interstitial fibrosis with no known underlying cause, commonest cause of ILD
- Typically occurs aged 50-70, twice as common in men
- Average survival is ~ 4 years

Features

- Progressive dyspnoea
- Dry cough
- Bibasal fine end-inspiratory crepitations
- Clubbing

Complications

- Respiratory failure
- Increased risk of lung cancer

Investigations

Bloods

- ABG shows type 1 (2 if severe) respiratory failure
- Raised CRP & immunoglobulins
- ANA positive in 30%, RF positive in 10%

Imaging

- Decreased lung volume
- Reticular subpleural shadowing increasing from apices to bases
- Honeycomb lung
- CT is more sensitive and essential for diagnosis

BAL

- Raised lymphocytes indicate better prognosis
- Raised neutrophils/eosinophils indicate worse prognosis

Spirometry

- Restrictive pattern

Biopsy

- Not always needed
- Histology shows "usual interstitial pneumonia"

Management

- Pulmonary rehab & palliative care
- Consideration for lung transplant
- Anti-fibrotic (pirfenidone) in select patients
- High dose steroids should not be used

Granulomatosis with Polyangiitis

- AKA Wegener's granulomatosis
- Autoimmune necrotising granulomatous vasculitis affecting upper & lower respiratory tract & kidneys

Features

URT

- Epistaxis
- Chronic sinusitis
- Saddle-nose deformity
- Nasal crusting

LRT

- Cough
- Dyspnoea
- Haemoptysis
- Pleurisy

Renal

- Pauci-immune RPGN in 80% of patients
  - Haematuria & proteinuria

Others

- Skin lesions: palpable purpura
- Ocular lesions: conjunctivitis, keratitis, uveitis
- Cranial nerve lesions

Investigations

- cANCA (PR3) positive in 90%, pANCA (MPO) positive in 25%
- CXR can show a wide variety of lesions
  - Bilateral nodular lesions
  - Cavitation
- Renal biopsy showing epithelial crescents

Management

- Steroids
- Cyclophosphamide
- Plasma exchange
- Median survival 8-9 years

Eosinophilic Granulomatosis with Polyangiitis

- AKA Churg-Strauss syndrome
- Small-medium vessel vasculitis
- May be precipitated by montelukast

Features

- Late onset asthma
- Paranasal sinusitis
- Mononeuritis multiplex
- RPGN
- Palpable skin purpura
- GIT bleeding

Investigations

- Eosinophilia
- pANCA (MPO) positive in 60%

Sarcoidosis

- Multisystem disorder of unknown cause characterised by non-caseating granulomas

Epidemiology

- 20-40 years
- F>M
- Afro Caribbean
- HLA-DRB1 & DQB1 alleles

Features

- Presents incidentally on CXR in 20-40%

Systemic	Fever Anorexia & weight loss Lymphadenopathy Hepatosplenomegaly
Pulmonary	Dry cough Progressive dyspnoea & decreased exercise tolerance Chest pain Progressive symptoms and lung function deterioration in 10-20%
URT	Otitis & sinusitis
MSK	Polyarthralgia Dactylitis
Neuro	Peripheral & cranial polyneuropathies (eg Bell's palsy) Meningitis/transverse myelitis Space occupying lesion
Endocrine	Pituitary dysfunction (eg amenorrhoea) Hypercalcaemia (leads to renal stones, nephrocalcinosis, diabetes insipidus)
Ophthalmic	Uveitis Keratoconjunctivitis Sjogren's
Cardiac	Restrictive cardiomyopathy Pericardial effusion
Hepatic	Hepatomegaly with cholestatic LFTs
Skin	Erythema nodosum Lupus pernio

Specific Syndromes

Lofgren's Syndrome

- Acute form with BHL, erythema nodosum, fever, polyarthralgia
- Good prognosis

Heerfordt's Syndrome

- Parotid enlargement, uveitis, fever

Investigations

Bloods

- Raised inflammatory markers
- Lymphopenia
- Raised LFTs (cholestatic)
- Raised immunoglobulins
- Raised serum ACE in 60% (non-specific)
- Hypercalcaemia

Imaging

- CXR abnormal in 90%

Stage 1	BHL
Stage 2	BHL + peripheral pulmonary infiltrates
Stage 3	Peripheral infiltrates without BHL
Stage 4	Progressive pulmonary fibrosis Bulla formation (honeycombing) Pleural involvement

- CT/MRI may be useful in assessing extent of pulmonary disease or diagnosis neurological disease
- Ultrasound may demonstrate nephrocalcinosis or hepatosplenomegaly
- Bone X-rays can show punched out lesions in terminal phalanges

Tissue Biopsy

- Taken from affected organ (lung, liver, skin, lacrimal glands, lymph nodes)
- Non-caseating granulomas are diagnostic

Spirometry

- Restrictive pattern
- Decreased transfer factor

BAL

- Increased lymphocytes in active disease
- Increased neutrophils in fibrosis

Management

- BHL alone needs no treatment

Acute Sarcoidosis/Lofgren's

- Bed rest & NSAIDs

Steroids

- Indicated by:
  - Hypercalcaemia
  - Stage 2+ lung disease with symptoms
  - Eye, heart, or neuro involvement
- Prednisolone 40mg/24hrs for 4-6 weeks, then a reducing dose for ~ 1 year

Other

- IV methylprednisolone or immunosuppression (MTX/HCQ/ciclosporin/cyclophosphamide) in severe illness
- Anti-TNF in refractory cases
- Lung transplantation in severe refractory cases

Prognosis

- 60% with thoracic disease resolve over 2 years
- 20% respond to steroid therapy
- Remainder are unlikely to improve

Acute Respiratory Distress Syndrome

- Non-cardiogenic pulmonary oedema caused by increased permeability of alveolar capillaries and alveolar fluid accumulation
- Often accompanied by multi-organ failure
- 40% mortality

Causes

Pulmonary

- Pneumonia
- Gastric aspiration
- Smoke inhalation
- Vasculitis
- Contusion

Others

- Shock
- Sepsis
- Haemorrhage/massive transfusion
- DIC
- Acute pancreatitis
- Acute liver failure
- Head injury
- Malaria
- Fat embolism
- Burns
- Obstetric complications
- Drugs (aspirin, heroin, paraquat)

Features

- Acute onset & severe
- Tachypnoea & tachycardia
- Dyspnoea
- Cyanosis
- Low SpO2
- Bilateral fine inspiratory crackles

Diagnosis

Investigations

- FBC, CRP, U+E, LFT, amylase, clotting, cultures
- ABG
- CXR
- Pulmonary artery catheter if clinically uncertain whether heart failure

American-European Consensus Conference Criteria (all 4)

1. Acute onset (w/i 1 week of known cause)
2. Bilateral infiltrate on CXR
3. Non-cardiogenic (clinical or PCWP < 19mmHg)
4. PaO2:FiO2 < 200

Management

- Usually in ICU

Respiratory Support

- NIPPV with 40-60% oxygen may be sufficient but invasive ventilation is often necessary
  - Indicated by PaO2 <8.3kPa despite 60% O2 or PaCO2 > 6kPa
- Low tidal volumes with low-moderate PEEP improve outcomes due to pneumothorax risk with poor lung compliance

Circulatory Support

- Invasive haemodynamic monitoring
- Conservative fluid management with pressors/vasodilator to maintain oxygen delivery
- Haemofiltration may be necessary for a negative fluid balance

Others

- Treat any underlying cause e.g. sepsis
- Nutritional support

Pulmonary Embolism

- Typically caused by thromboembolism from venous circulation (DVT)
- More rarely: RV thrombus post MI, septic emboli in right sided infective endocarditis, fat/air/amniotic fluid embolism, neoplastic emboli

Risk Factors

- Recent surgery
  - Especially abdominal/pelvic or hip/knee replacements
- Thrombophilia (eg anti-phospholipid syndrome)
- Leg fracture
- Prolonged immobility
- Malignancy
- Pregnancy/postpartum
- COCP/HRT
- Previous PE

Features

Symptoms	Signs
Classic triad (10%):	Tachycardia
Dyspnoea	Tachypnoea
Pleuritic pain	Fever
Haemoptysis	Crackles

Investigation/Diagnosis

Wells Score

Clinical suspicion of DVT	3
Alternative diagnosis is less likely than PE	3
Tachycardia > 100	1.5
Immobilisation > 3 days or surgery in the last 4 weeks	1.5
Previous DVT/PE	1.5
Haemoptysis	1
Malignancy (being treated/treated in last 6 months/palliative)	1

Score > 4	Score < 4
Do immediate CTPA Start empirical DOAC if CTPA not immediately available	Do D-dimers If positive, do CTPA If negative, consider alternative diagnosis
CTPA positive	**CTPA negative**
Diagnosed PE	Consider proximal leg vein ultrasound for DVT

CTPA

- Shows filling defects in pulmonary arteries
- Peripheral emboli affecting subsegmental arteries may be missed

V/Q Scan

- Previous investigation of choice
- May still be preferred in renal impairment or pregnancy (debated, more risk to fetus but less risk to mother)

CXR

- Recommended to exclude other pathology but usually normal

ECG

- Classic change is "S1Q3T3", seen in ~20%
  - Large S wave in I
  - Large/pathological Q wave in III
  - Inverted T wave in III
- RBBB/RAD/sinus tachycardia may also be seen
- Sinus tachycardia is the most common finding

Management

Haemodynamically Unstable → Thrombolysis

Haemodynamically Stable → Anticoagulation

Thrombolysis

- Eg Alteplase 10mg IV bolus followed by 90mg over 2 hours
- **Contraindications**
  - Active internal bleeding
  - Recent haemorrhage/trauma/surgery
  - Coagulation disoders
  - Intracranial neoplasm
  - Stroke in last 3 months
  - Aortic dissection
  - Recent head injury
  - Severe hypertension
- **Complications**
  - Haemorrhage
  - Hypotension (more common with streptokinase)
  - Allergic reactions to streptokinase

Anticoagulation

- As of 2020 NICE recommend a DOAC once PE is suspected and continued if PE is confirmed
- If apixaban/rivaroxaban are not suitable, LMWH followed by edoxaban/dabigatran or followed by warfarin should be used
- In severe renal impairment LMWH/UFH/LMWH then warfarin can be used
- If the patient has triple positive anti-phospholipid syndrome, LMWH followed by warfarin should be used
- **Duration of treatment:**
  - 3 months if provoked (eg by immobility/surgery etc)
  - 6 months if unprovoked/cause cannot be removed
    - Consider investigating for possible malignancy/thrombophilia
- Outpatient treatment can be offered if stable with no comorbidities

Others

- IVC filters may be surgically implanted in individuals who have recurrent PEs despite adequate anticoagulation/anticoagulation is not possible
  - Weak evidence base

Prevention

- Prophylactic heparin is given to all immobile inpatients
- HRT and COCP should be stopped before surgeries

Pleural Effusion

- Collection of fluid in the pleural cavity

Causes

Transudative (< 30g/L of protein)	Exudative (> 30g/L of protein)

Heart failure (most common transudative cause)
Hypoalbuminaemia
  Liver failure
  Nephrotic syndrome
  Malabsorption
Hypothyroidism
Meig's syndrome
	Infection
	  Pneumonia (most common exudative cause)
	  TB
	  Subphrenic abscess
	Connective tissue disease
	  SLE
	  RA
	Malignancy
	  Lung
	  Mesothelioma
	  Metastases
	Pancreatitis
	PE
	Dressler's syndrome
	Yellow nail syndrome

Features

Symptoms

- Dyspnoea
- Pleuritic pain
- Dry cough

Signs

- Decreased expansion, focal dullness to percussion, & reduced breath sound on affected side
- Bronchial breathing above effusion
- Tracheal deviation in large effusions
- Signs of associated disease (malignancy, heart failure, liver failure, SLE)

Investigations

CXR

- Small effusions blunt costophrenic angles
- Larger effusions show dense shadows with concave upper borders

Ultrasound

- Recommended for diagnostic tap

Diagnostic Tap

- Using 21g needle and 50ml syringe
- Sited with ultrasound (traditionally 1-2 levels below top of effusion as percussed)
- Fluid should be sent for pH, protein, glucose, LDH, amylase, immunology, microbiology, cytology

CT Thorax

- Increasingly used to diagnose underlying cause, especially in exudative cases

Pleural Fluid Analysis Interpretation

Gross Appearance	
Clear/straw coloured	Transudate or exudate
Turbid/purulent	Empyema
Haemorrhagic	Trauma/malignancy/pulmonary infarction
Cytology	
Neutrophils ++	Parapneumonic effusion/PE
Lymphocytes ++	Malignancy/TB/RA/SLE/sarcoid
Mesothelial cells ++	Pulmonary infarction
Abnormal mesothelial cells	Mesothelioma
Chemistry	
Protein < 25g/L	Transudative
Protein > 35g/L	Exudative
Protein 25-35g/L	Use Light's criteria
Glucose < 3.3mmol/L	Empyema/malignancy/TB /RA/SLE
pH < 7.2	
LDH pleural: serum >0.6	
Raised amylase	Pancreatitis/oesophageal rupture
Immunology	
Rheumatoid factor	RA
Antinuclear antibody	SLE
Low complement	RA/SLE/malignancy/infection

Light's Criteria

- If any of the following are present, effusion is likely to be exudative:
  - Pleural fluid:serum protein > 0.5
  - Pleural fluid:serum LDH > 0.6
  - Pleural fluid LDH more than 2/3 the ULN for serum LDH
- Apply if pleural fluid protein level is between 25-35g/L

Management

- Treat underlying cause

Drainage

- If symptomatic
- Aspiration as per diagnostic tap (repeated if necessary) or chest drain insertion
- Chest drain indicated if infection is suspected
  - Turbid/cloudy fluid or pH < 7.2

Recurrent Effusions

- Recurrent aspiration
- Thorascopic mechanical pleurodesis is effective for recurrent malignant effusions
- Indwelling pleural catheter

Pneumothorax

- Air in the pleural cavity

Causes/Risk Factors

Spontaneous

- Typically in tall thin young males, due to rupture of subpleural bulla

Pre-existing Pulmonary Disease

- COPD
- Asthma
- CF
- Lung Ca
- PCP

Connective Tissue Disease

- Marfan's syndrome
- Rheumatoid arthritis

Iatrogenic

- Non-invasive or invasive ventilation
- Subclavian CVP line insertion
- Biopsies

Catamenial

- Occurring in women in association with menstrual period, due to pleural endometriosis

Traumatic

- Chest wall injuries
- Risk of tension pneumothorax

Features

- Sudden onset
- Dyspnoea
- Pleuritic pain
- Tachycardia & tachypnoea
- Sudden deterioration in those with pre-existing lung disease
- Reduced saturations in those being ventilated
- Reduced expansion, hyperresonance to percussion and reduced breath sides on same side
- Tracheal deviation away in tension pneumothorax

Investigations

CXR

- Only if tension pneumothorax is not suspected
- Expiratory film: look for peripheral areas with no lung markings
- Care not to mistake large bulla for pneumothorax

ABG

- If hypoxic

Management

Primary/Spontaneous

- If not short of breath and air rim is < 2cm, discharge
  - Otherwise, attempt aspiration
  - If this fails (still SOB/> 2cm), insert chest drain

Secondary

- If air rim is < 1cm, admit for oxygen and observation for 24 hours
- If air rim is 1-2cm, aspiration should be attempted
  - If this fails, insert a chest drain
- If air rim is > 2cm or patient is short of breath, insert a chest drain

Iatrogenic

- Higher chance of resolution and lower chance of recurrence, majority need only observation
- Aspiration preferred if treatment is needed
- Ventilated patients need chest drains

Discharge Advice

Smoking

- Cessation strongly advised
  - Lifetime risk in healthy smoking males is 10%
  - Lifetime risk in non-smoking males is 0.1%

Flying

- Absolutely contraindicated until 2 weeks after successful drainage/1 week after confirmation of resolution on CXR

Scuba Diving

- Absolutely contraindicated unless patient has had surgical bilateral pleurectomy and has normal post-operative lung function tests and CXR

Tension Pneumothorax

- Occurs following trauma: lung parenchymal/chest wall flap creates functional one way valve leading to build up of air under pressure in pleural cavity
- Can cause mediastinal displacement and cardiorespiratory arrest rapidly

Features

- Tachycardia, tachypnoea, circulatory compromise
- Chest pain & signs of trauma
- Distended neck veins
- Tracheal deviation away from affected side
- Hyperresonant percussion & reduced air entry on affected side

Management

- Immediate needle decompression
  - 14-16g syringe, partially filled with saline and with plunger removed, inserted into **2nd intercostal space on midclavicular line** of affected side
  - Alternatively, 4th or 5th intercostal space between anterior axillary and midaxillary line
- CXR can be performed after
- Insert chest drain after needle decompression

Obstructive Sleep Apnoea

- Partial pharyngeal airway collapse during sleep leading to apnoeic episode terminated by partial waking

Predisposing Factors

- Male sex
- Obesity
- Macroglossia
  - Acromegaly
  - Hypothyroidism
  - Amyloidosis
- Large tonsils
- Marfan's syndrome

Features

- Loud snoring
- Excessive daytime sleepiness
- Poor sleep quality
- Morning headache
- Decreased libido
- Decreased cognitive performance

Complications

- Pulmonary hypertension
- Type II respiratory failure
- Hypertension

Assessment

- Epworth Sleepiness Scale to be completed by patient ± partner

Polysomnography

- Pulse oximetry, EEG, respiratory airflow, thoraco-abdominal movement, & snoring measured during a night of sleep
- Measures episodes of apnoea/hypopnoea
  - 15 or more episodes per hour is considered significant sleep apnoea

Management

- Weight loss
- Nocturnal CPAP for moderate to severe disease
- Mandibular advancement device for mild disease or when CPAP is not tolerated
- Surgery (eg removal of tonsils/nasal polyps) may be indicated

Cor Pulmonale

- Right heart failure caused by chronic pulmonary hypertension
- 50% mortality in 5 years

Causes

Lung Disease

- COPD
- Bronchiectasis
- Pulmonary fibrosis
- Severe chronic asthma
- Lung resection

Pulmonary Vascular Disease

- Pulmonary emboli
- Pulmonary vasculitis
- Primary pulmonary hypertension
- ARDS
- Sickle cell disease
- Parasite infestation

Musculoskeletal

- Kyphoscoliosis

Neuromuscular

- Myasthenia gravis
- Poliomyelitis
- Motor neuron disease

Hypoventilation

- OSA

Cerebrovascular Disease

Features

- Dyspnoea
- Fatigue
- Syncope
- Cyanosis
- Tachycardia
- Tricuspid regurgitation (pansystolic murmur)
- RV heave

Investigations

Bloods

- Polycythaemia
- Hypoxia ± hypercapnia on ABG

CXR

- Enlarged right atrium & ventricle and prominent pulmonary arteries

ECG

- P pulmonale
- RAD & RVH

Management

- Treat underlying cause
- Treat respiratory failure
  - Oxygen in the acute setting
  - Assessment for LTOT
- Treat cardiac failure
  - Diuretics
  - Spironolactone
- Venesection if haematocrit > 55%
- Assess for heart-lung transplant in young patients

Lung Cancer (Bronchial Carcinoma)

Type	%	Aetiology/Histology	Location	Specific Features	Paraneoplastic Features
Small Cell (SCLC)	20	Endocrine (Kulchitsky) cells	Usually central but mostly disseminated at presentation	Poor prognosis	SIADH & hyponatraemia Ectopic ACTH secretion leading to Cushing's syndrome Hypoglycaemia, hyperkalaemia, alkalosis, muscle weakness Lambert-Eaton myasthenic syndrome Limbic Encephalitis
Squamous Cell Carcinoma	30		Typically central	Strongly associated with finger clubbing & HPOA	PTHrP secretion leading to hypercalcaemia Ectopic TSH secretion leading to hyperthyroidism HPOA
Adenocarcinoma	35	Most common in non-smokers (but most diagnosed are smokers)	Typically peripheral		Gynaecomastia HPOA
Large Cell	10	Anaplastic poorly differentiated cells	Typically peripheral	Poor prognosis	BhCG secretion

Symptoms	Signs	Extrapulmonary Manifestations
Persistent cough Haemoptysis Chest pain Weight loss/anorexia/lethargy Slow resolving pneumonia Hoarseness/Horner's syndrome (Pancoast tumour)	Focal monophonic wheeze Signs of collapse/consolidation/effusion	Cachexia Finger clubbing Hypertrophic pulmonary osteoarthropathy (wrist pain) Supraclavicular/axillary lymphadenopathy Superior vena cava syndrome (Pemberton's sign) Paraneoplastic syndromes as above

Risk Factors

- **Smoking**
  - Associated with 90% of lung cancers
- Passive smoking
- Asbestos exposure
- Radon exposure
- Chromium, arsenic, iron oxides

Investigations

CXR

- Often first investigation performed
- May show nodule, hilar enlargement, lobar collapse, consolidation, effusion, bony secondaries, or appear normal (10%)

CT Thorax

- Investigation of choice

Bronchoscopy

- Used to obtain biopsy ± endobronchial ultrasound guidance (biopsy may also be obtained percutaneously)

PET-CT

- Used for staging

Bloods

- Thrombocytosis may be seen

Lung Functions Tests

- To assess fitness for treatment

Sputum Cytology

Staging

Tumour

Tx: Malignant cells in bronchial secretions only
Tis: CIS (rare)
T0: None
T1: Tumour < 3cm, lobar or distant airway
T2: > 3cm in size & > 2cm from carina/pleura
T3: < 2cm from carina or involving chest wall/diaphragm
T4: Involving mediastinum/malignant effusion present

Nodes

N0: None
N1: Peribronchial/ipsilateral hilum
N2: Ipsilateral mediastinum
N3: Contralateral hilum/mediastinum/supraclavicular

Metastases

M0: None
M1a: Nodule in other lung/pleural lesion/malignant effusion
M1b: Distant mets

Overall Stage

I	II	IIIa	IIIb	IV
Up to T2 N0 M0	T1/2 N1 T3 N0	T3 N1 T1-3 N2	T1-4 N3 T4 N0-2	M1

Lung Cancer Management

- MDT decisions

NSCLC

- Surgery (lobectomy) is treatment of choice but only 20% of patients are suitable
- Contraindicated by:
  - Poor general health/fitness
  - FEV1 < 1.5L
  - Metastatic disease
  - Malignant pleural effusion
  - Tumour new hilum
  - Vocal cord paralysis
  - SVC obstruction
- Radical radiotherapy is used in stages I-III
- Palliative chemoradiotherapy is used in more advanced disease
  - Platinum based agents and epidermal growth factor monoclonal antibodies (cetuximab)

SCLC

- Surgery for early stage disease (stage I)
- Chemoradiotherapy used if patient is well enough

Palliative Measures

- Targeted radiotherapy for SVC obstruction/haemoptysis/bone mets/cerebral mets
- Endobronchial therapy (stenting, cryotherapy, brachytherapy)
- Pleural drainage/pleurodesis for recurrent pleural effusions
- Analgesia, steroids, anti-emetics, bronchodilators, antidepressants

Prognosis

NSCLC

- 50% 2 year survival without spread
- 10% 2 year survival with spread

SCLC

- Median survival 3 months if untreated
- Median survival 1-1.5 years if treated

Asbestos & The Lung

- Cause of a wide variety of lung/pleural pathologies

Pleural Plaques

- Most common asbestos-related lung disease
- Do not undergo malignant change
- Occur up to 40 years after exposure

Pleural Thickening

- Asbestos can cause diffuse pleural thickening
- Similar to that occurring following empyema/haemothorax

Asbestosis

- Lower-lobe fibrosis occurring 15-30 years after exposure
- Severity related to length of exposure
- Conservative/supportive treatment only

Lung Cancer

Bronchial Carcinoma

- Asbestos is a risk factor and is synergistic with smoking

Malignant Mesothelioma

- Mainly occurs following asbestos exposure (~ 45 years later)
- Crocidolite (blue) asbestos is the most dangerous
- Not exposure dependent, a single exposure is enough
- 90% report asbestos exposure, 20% have co-existing asbestosis

Malignant Mesothelioma

- Tumour mainly occurring in the pleura and rarely the peritoneum/other mesothelial tissues

Features

- Dyspnoea
- Weight loss
- Chest wall pain
- Clubbing
- Painless pleural effusion
- History of asbestos exposure in 90%, asbestosis in 20%
- Metastasis occurs to other pleura and peritoneum
- Right lung affected more than left
- Often diagnosed post-mortem

Investigations

Imaging

- CXR/CT shows pleural effusion/thickening/nodularity

Pleural Fluid

- Exudative effusion
- Blood or abnormal mesothelial cells

Thoracoscopy

- 95% sensitive in cytology negative exudative effusions

Biopsy

- Usually image-guided pleural biopsy

Management

- Very poor prognosis (< 2 years)
- Palliative chemotherapy can improve survival
- Pleurodesis/indwelling pleural catheter improves QOL

Cystic Fibrosis

- Autosomal recessive condition caused by a defective chloride channel leading to hyperviscous secretions
- 1/25 are carriers

Features

Neonatal

- Failure to thrive
- Meconium ileus
- Rectal prolapse

Older Children/Adults

Respiratory	Gastrointestinal	Other
Cough	Pancreatic insufficiency (Malabsorption, steatorrhoea, diabetes)	Male infertility (congenital absence of vas deferens)
Wheeze		
Bronchiectasis	Distal intestinal obstruction	Female subfertility (ciliary dysmotility)
Recurrent infections	Gallstones	Nasal polyps
Staph aureus	Cirrhosis	Arthritis
Pseudomonas aeruginosa		Osteoporosis
Burkholderia cepacia		Vasculitis
Aspergillus		HPOA
Pneumothorax		Finger clubbing
Haemoptysis		
Cor pulmonale		

Diagnosis

- Screened for in bloodspot
- Sweat test
  - Sweat stimulated by electrodes and pilocarpine
  - Positive result: chloride > 60mEq/L

Management

Chest

- Twice daily chest physio & postural drainage
- Antibiotics for infections & prophylactically
- Sputum/washout cultures
  - Pseudomonas colonisation is a poor prognostic factor
- Mucolytics (nebulised DNase/ hypertonic saline)
- Bronchodilators
- Annual CXR review
- Advanced disease:
  - Oxygen
  - Diuretics for cor pulmonale
  - Transplant consideration
    - Contraindicated in Burkholderia colonisation

Gastrointestinal

- Pancreatic enzyme replacement
- Fat soluble vitamin supplementation
- Ursedeoxycholic acid for liver dysfunction
- Consider liver transplant in cirrhosis

Others

- Screening and treatment for diabetes (annual OGTT from 12)
- Screening and treatment for osteoporosis
- Fertility counselling and treatment

Mutation-Specific Therapies

- Orkambi is a combination of Lumacaftor & Ivacaftor
- Treats CF which is homozygous for delta F508 mutation
- Lumacaftor increases transportation of CFTR to cell surface
- Ivacaftor potentiates CFTR at the cell surface

Metabolic Medicine

Hydration & Fluids

Dehydration & Fluid Overload

Dehydration	Fluid Overload
Symptoms/Signs	
Dry mucous membranes Loss of skin turgor Cool peripheries Prolonged CRT Postural BP drop before sustained hypotension Sunken eyes Severe: oliguria, tachycardia, hypotension, delirium	Dyspnoea Tachypnoea Frothy cough Sacral/ankle pitting oedema Bilateral basal crepitations
Investigations	
Raised urea disproportionate to creatinine Raised albumin concentration (useful to track changes) Raised haematocrit	Pulmonary oedema on CXR
Aetiology	
GI losses • Vomiting, diarrhoea **Renal losses** • Diabetes mellitus, diuretic therapy, diabetes insipidus **Skin losses** • Hot environment, fever, burns, exudative skin lesions **3rd space sequestration** • Ascites, hip fracture	Renal failure Excessive fluid therapy

Maintenance Fluid & Electrolyte Requirements

Water
- 25-30ml/kg/day
  - Usually 2-2.5L/day

Electrolytes
- 1/mmol/kg/day of sodium, potassium & chloride

Glucose
- 50-100g/day

Calculating Volume Deficit
- The only way to know for certain is to have an accurate pre- & post-deficit weight
- Parameters can be monitored to assess efficacy of fluid replacement:
  - Clinical signs (BP, JVP)
  - Urine output
    - Should be > 0.5ml/kg/hour
  - Urine sodium concentration
    - If < 15mmol/L, fluid deficit is still being sensed by the kidneys

IV Fluid Types

	Na^+	Cl^-	K^+	$HCO3^-$	Glucose
Plasma	135-145	98-105	3.5-5	22-28	-
Normal Saline	154	154	-	-	-
5% Glucose	-	-	-	-	50g
Glucose with 1/5 normal saline	30	30	-	-	40g
Hartmann's	131	111	5	29	-

Normal (0.9%) Saline
- Isotonic with plasma
- Rapidly equilibrates in extracellular space and enters intravascular space more slowly
  - **Therefore ideal for fluid resuscitation**
- Can be used for maintenance
- Excess use carries risk of hyperchloraemic metabolic acidosis
- Hypertonic & hypotonic saline available for specialist use

5% Glucose (Dextrose)
- Isotonic with saline but contains very little actual energy
- Glucose is rapidly metabolised by liver leaving only water which rapidly distributes through the whole body space
  - **Therefore useless for fluid resuscitation**
- Can be used for maintenance
- Excess use carries risk of fluid overload & hyponatraemia

Colloids
- Remain in intravascular space for longer than other fluids
  - **Therefore good for fluid resuscitation**
- Not useful for maintenance
- Can cause anaphylaxis

Glucose with 1/5 Normal Saline
- Contains right amount of Na & Cl if given 10-hourly
- Commonly used in paediatrics

Hartmann's Solution
- More "physiological" alternative to normal saline

Potassium in IV Fluids
- Can be added to 5% glucose/normal saline/glucose with saline
- Higher amounts required in GI losses
- Maximum concentration of 40mmol/L (outside of specialist prescription) at a maximum rate of 20mmol/hr with cardiac monitoring
- High concentrations risk arrhythmias/asystole and thrombophlebitis
  - Concentrations above 40mmol/L must be given via CVC
  - Concentrations above 10mmol/L require ECG monitoring

IV Fluids – Special Cases

Acute Blood Loss
- Resuscitate with normal saline or colloid until blood is available

Children
- Glucose with saline for maintenance
- In 24 hours:
  - 100ml/kg for first 10kg
  - 50ml/kg for second 10kg
  - 20ml/kg thereafter

Elderly
- Smaller resuscitation boluses due to risk of fluid overload

GI Losses
- Potassium needs replacement

Heart Failure
- Use with care to avoid fluid overload

Liver Failure
- Patients have a raised total body sodium so normal saline should be avoided

Acute Pancreatitis
- Aggressive resuscitation required due to large amounts of 3rd space sequestration

Low Urine Output
- Aim for > 1ml/kg/hr: give 500ml (250ml in elderly/HF) boluses over 1 hours and recheck
- Exclude retention (if not catheterised) and blocked catheter

Post-operative
- Calculate & account for intra-operative losses and losses from drain etc

Shock
- Resuscitate with NS or colloid via large-bore cannulae

Transpiration Losses
- Fever, burns, etc
- May require aggressive resuscitation

Acid-Base Balance

Assessment

pH
- < 7.35: acidosis
- > 7.45: alkalosis

CO_2
- Normal range 4.7-6kPa
- CO2 is acidic
- If CO2 is in agreement with the pH, the problem is respiratory
  - High CO2 in acidosis, low CO2 in alkalosis
- If CO2 goes against the pH, it is a compensatory change
  - High CO2 in alkalosis, low CO2 in acidosis

HCO_3^-
- Normal range 22-28mmol/L
- HCO3- is basic
- If HCO3- is in agreement with pH, the problem is metabolic
  - High HCO3- in alkalosis, low HCO3- in acidosis
- If HCO3- goes against the pH, it is a compensatory change
  - High HCO3- in acidosis, low HCO3- in alkalosis

Anion Gap
- Difference between plasma cations (Na + K) and anions (Cl + HCO3-)
- Normal range 12-20mmol/L
- Alternatively potassium can be left out (normal range is then 8-16mmol/L)

Metabolic Acidosis Causes

Raised Anion Gap
- Lactic acid (shock, ischaemia, infection)
- Urate (renal failure)
- Ketones (diabetes, alcohol)
- Drugs (salicylates, biguanides, ethylene glycol, methanol)
- 5-oxoproline: chronic paracetamol use

Normal Anion Gap/Hyperchloraemic
- Renal tubular acidosis
- Diarrhoea
- Drugs (acetazolamide)
- Addison's Disease
- Pancreatic fistula
- Ammonium chloride ingestion/injection

Metabolic Alkalosis Causes
- Vomiting
- Potassium depletion (diuretics)
- Burns
- Ingestion of base

Respiratory Acidosis Causes
- Type 2 respiratory failure, most commonly COPD

Respiratory Alkalosis Causes
- Hyperventilation
- CNS causes: stroke, SAH, meningitis
- Others: mild-moderate asthma, anxiety, altitude, fever, pregnancy, PE, salicylate

Hyponatraemia

- Needs to be evaluated in the context of fluid status as total sodium may not actually be depleted
- Acute (< 48 hours onset) or chronic (> 48 hours onset)

Severity

- Mild: 130-134mmol/L
- Moderate: 120-129mmol/L
- Severe: < 120mmol/L

Causes

Hypovolaemic

- Diuretic stage of renal failure
- Diuretics
- Addisonian crisis

Euvolaemic

- SIADH
- Iatrogenic, especially with excess 5% glucose

Hypervolaemic

- Heart failure
- Liver failure
- Nephrotic syndrome

Features

Early

- Anorexia
- Nausea & vomiting
- Malaise
- Headache
- Dizziness

Late

- Confusion
- Weakness & muscle cramps
- Coma
- Seizures
- Respiratory arrest

Management

- Exclude artefactual result & look for drug causes of hyponatraemia

Chronic Hyponatraemia Without Severe Symptoms

- **Hypovolaemic Cause:**
  - Normal saline, often given as trial
    - If serum sodium rises, supports diagnosis of hypovolaemic hyponatraemia
    - If serum sodium decreases, alternative diagnosis such as SIADH is more likely
- **Euvolaemic Cause**
  - Fluid restrict up to 500-1000ml/day
  - Consider medications:
    - Domeclocycline
    - Vaptans
- **Hypervolaemic Cause**
  - Fluid restrict up to 500-1000ml/day
  - Consider loop diuretic/vaptans

Acute/Severe Symptoms

- Close monitoring in HDU/ICU setting
- Hypertonic saline can be used

Hypernatraemia

Causes

- Dehydration
- Osmotic diuresis (eg HONKC)
- Diabetes insipidus
- Excess IV saline
- Primary aldosteronism

Features

Signs/Symptoms

- Lethargy
- Thirst
- Weakness
- Irritability
- Confusion
- Coma
- Seizures

Investigations

- Raised sodium (> 145mmom/L)
- Raised urea, albumin & HCT as per dehydration

Management

- Oral water if possible
- IV glucose 5% slowly if oral water not possible
  - Slow, 1L/6hours
  - Guided by urine output & sodium levels
- IV normal saline can be given in hypovolaemia as it causes less marked fluid shifts and is hypotonic in hypernatraemic patients

Complications of Sodium Correction

Central Pontine Myelinolysis/Osmotic Demyelination Syndrome

- Occurs due to over-correction of severe hyponatraemia
- To avoid, sodium levels should be raised by no more than 4-6mmol/L/24hrs
- Symptoms occur after 2 days & are usually irreversible
  - Dysarthria
  - Dysphagia
  - Quadriparesis
  - Seizures
  - Confusion
  - Coma
  - Locked-in syndrome

Cerebral Oedema

- Can be caused by overly rapid correction of dehydration/hypernatraemia
- Results in seizures, coma, & death
- Correct sodium at rate of less than 0.5mmol/L/hr

Hypokalaemia

- Serum potassium < 3.5mmol/L

Causes

GI Losses

- Vomiting
- Diarrhoea
- Pyloric stenosis
- Rectal villous adenoma
- Fistula

Renal Losses

- Renal tubular failure

Endocrine

- Cushing's syndrome
- Conn's syndrome

Drugs

- Diuretics (thiazide, loop, acetazolamide)

Others

- Liquorice
- Alkalosis
- Magnesium deficiency
  - Hypokalaemia difficult to treat until magnesium is normalised

Features

Symptoms

- Muscle weakness
- Cramps
- Palpitations & light-headedness
- Constipation
- Hypokalaemic periodic paralysis
  - Muscle weakness lasting up to 72hrs

Signs

- Hypotonia
- Hyporeflexia
- Tetany

ECG

- Small/inverted T waves
- Prominent U waves
- Prolonged PR interval
- ST segment depression

Management

Mild (> 2.5mmol/L, no symptoms)

- Oral potassium supplementation (> 80mmol/24hrs)
- Recheck after 3 days
- Consider replacing loop/thiazide diuretics

Severe (< 2.5mmol/L or symptoms)

- IV potassium correction
  - Never more than 40mmol/L
  - Never more than 20mmol/hr
  - Cardiac monitoring required

Hyperkalaemia

- Serum potassium > 5.5mmol/L

Causes

Increased Intake

- Excessive potassium infusion
- Replacement salts containing potassium
- High potassium foods

Extracellular Shift

- Burns
- DKA
- Metabolic acidosis
- Rhabdomyolysis

Renal Retention

- AKI/oliguric renal failure

Endocrine

- Addison's disease/adrenal failure

Drugs

- Potassium sparing diuretics
- ACE inhibitors/ARBs
- Suxamethonium
- Beta blockers
- Heparin

Artefactual Result

- Haemolysis
  - Difficult venepuncture
  - Patient's clenched fist
  - Delayed processing
- Potassium EDTA contamination from haematology bottle (do biochemistry before haematology)
- Thrombocytosis

Features

Symptoms

- Chest pain
- Palpitations
- Weakness
- Light-headedness

Signs

- Irregular tachycardia

ECG

- Tall tented T waves
- Small P waves
- Widened QRS complexes becoming sinusoidal
- Ventricular tachycardia

Management

Non-Urgent (< 6.5mmol/L, no ECG changes)

- Treat underlying cause
- Review medications
- Calcium Resonium can prevent potassium absorption from the gut and lower levels over a few days

Urgent (> 6.5mmol/L or myocardial excitability)

- 10ml 10% calcium chloride/30ml 10% calcium gluconate over 5-10 minutes in large vein, repeated as per ECG if necessary
- 10u insulin in 25g glucose
- 10-20mg nebulised salbutamol (10mg in IHD, none in tachyarrhythmias)
- Definitive correction by removal of cause or RRT

Hypocalcaemia

- Total serum calcium < 2.2 mmol/L or serum ionised calcium <1.17mmol/L

Causes

With Raised Phosphate

- CKD
- Hypoparathyroidism
- Pseudohypoparathyroidism
- Acute rhabdomyolysis
- Hypomagnesaemia

With Low/Normal Phosphate

- Vitamin D deficiency
- Osteomalacia
- Acute pancreatitis
- Overhydration
- Respiratory alkalosis (reduced ionised calcium)

Features

S	Spasms – Trousseau's sign: BP cuff causes carpopedal spasm – Chvostek's sign: tapping over parotid causes facial twitching
P	Perioral paraesthesia
A	Anxiety/irritability
S	Seizures
M	Muscle tone (smooth) increased – Colic – Wheeze – Dysphagia
O	Orientation impaired, confusion
D	Dermatitis
I	Impetigo herpetiformis
C	Choreoathetosis Cataract Cardiomyopathy (long QT interval)

Management

Mild Symptoms

- Calcium 5mmol/6hr PO with daily calcium levels

Severe Symptoms

- 10ml of 10% calcium gluconate over 10 minutes
- Repeat as necessary with ECG monitoring
- Correct respiratory alkalosis

Hypercalcaemia

- Total serum calcium > 2.6mmolL

Causes

- Main distinction is hyperparathyroidism vs malignancy

Albumin ↑	Urea ↑		Dehydration
	Urea ↕		Cuffed specimen
Albumin ↓/↔	Phosphate ↓/↔		**Primary hyperparathyroidism** Tertiary hyperparathyroidism **PTHrP (paraneoplastic)**
	Phosphate ↑/↔	ALP ↑	**Bone metastases** Sarcoidosis Thyrotoxicosis Lithium
		ALP ↕	**Myeloma** Vitamin D excess Sarcoidosis Raised bicarb Familial hypocalciuric hypercalcaemia

Features

- "Bones, stones, moans, & groans"

Musculoskeletal

- Bone pain & cortical thinning due to underlying cause

Renal

- Renal stones
- Renal failure
- Nephrogenic diabetes insipidus (polyuria & polydipsia)

Neuropsychiatric

- Depression
- Confusion

Gastrointestinal

- Constipation
- Abdominal pain
- Vomiting
- Anorexia & weight loss

Cardiovascular

- Hypertension
- **ECG:** Decreased QT interval

Investigations

Bloods

- FBC, U+E, bone profile, ABG, protein electrophoresis

Imaging

- CXR, radioisotope bone scan

Others

- 24 hour urinary calcium excretion

Management

- Diagnose & treat underlying cause

If > 3.5mmol/L and symptomatic:

1. Correct dehydration (normal saline)
2. Bisphosphonates
   - Zoledronic acid 4mg in 100ml over 15 minutes
3. Further management as per underlying cause

Hypomagnesaemia

Causes
- Diuretics
- Severe diarrhoea
- DKA
- Hypokalaemia, hypocalcaemia, hypophosphataemia
- Alcohol abuse
- TPN

Features
- Paraesthesia
- Ataxia
- Seizures
- Tetany
- Arrhythmias
- Exacerbation/precipitation of digoxin toxicity

Management
- PO or IV magnesium salts if needed
  - Eg MgSO4 8mg IV over 3mins to 2 hours depending on severity

Hypermagnesaemia
- Rarely requires treatment

Causes
- Renal failure
- Iatrogenic (eg excessive antacids)

Features
- Only if severe
- Bradycardia
- Hypotension
- Hyporeflexia
- Respiratory depression
- Coma

Hypophosphataemia
- Common, rarely significant

Causes
- Alcohol withdrawal
- Acute liver failure
- Refeeding syndrome
- Osteomalacia
- Primary hyperparathyroidism
- Severe DKA

Features
- Muscle weakness/rhabdomyolysis
- Haemolysis
- White cell & platelet dysfunction
- Arrhythmias & cardiac arrest

Management
- Oral or parenteral supplementation
- Don’t give IV phosphate in hypercalcaemia or oliguria

Hyperphosphataemia

Causes
- Chronic kidney disease
- Tumour lysis syndrome

Management
- Phosphate binders with meals

Zinc Deficiency

Causes
- TPN
- Poor diet
  - Too few cereals/dairy products
  - Anorexia
  - Alcoholism
- Rare genetic defects

Features
- Alopecia
- Dermatitis
  - Particularly around nostrils/corners of mouth
- Night blindness
- Diarrhoea

Diagnosis
- Trial of therapeutic zinc
  - Plasma levels unreliable, low results possible outside of deficiency (eg infection, trauma)

Hyperuricaemia

Causes

Increased Synthesis/Cell Turnover

- Lesch-Nyhan syndrome
- Myeloproliferative disorders (tumour lysis syndrome)
- Purine rich diet
- Exercise
- Psoriasis
- Cytotoxics

Decreased Excretion

- Primary gout
- Chronic renal failure
- Pre-eclampsia
- Alcohol
- Lead nephropathy
- Drugs: loop/thiazide diuretics, pyrazinamide

Others

- Associated with hyperlipidaemia/hypertension /metabolic syndrome

Complications

- Gout
- Renal failure (crystal nephropathy)
- Urate renal stones

Management

- Treatment depends on complication
- Allopurinol (xanthine oxidase inhibitor) and rasburicase (recombinant xanthine oxidase) are used to prevent tumour lysis syndrome/treat gout/prevent urate renal stone

Hyperlipidaemia

- Excess levels of blood cholesterol which is a major risk factor for cardiovascular disease

Causes

Primary

- Common primary hyperlipidaemia (70%, increase in LDL only)
- Familial hyperlipidaemias

Secondary

- **Predominantly hypertriglyceridaemia:**
  - Diabetes
  - Obesity
  - Alcohol
  - CKD
  - Liver disease
  - Drugs: thiazides, non-selective beta blockers, unopposed oestrogen
- **Predominantly hypercholesterolaemia:**
  - Nephrotic syndrome
  - Cholestasis
  - Hypothyroidism

Screening

- Fasting lipid profile for those who are at:

Increased risk of hyperlipidaemia

- Family history
- Corneal arcus
- Xanthomata or xanthelasmata

Increased risk of CVD

- Known CVD
- Family history of CVD < 60
- DM/impaired glucose tolerance
- Hypertension
- Smoking
- High BMI

Management

Primary Prevention

- Atorvastatin 20mg for:
  - Anyone with QRISK score > 10%
  - Patients with diabetes
  - Patients with CKD
- Repeat lipid profile at 3 months
  - Aim for non-HDL decrease of 40%
  - Discuss lifestyle, concordance, & consider increasing dose to 80mg if this fails

Secondary Prevention

- Atorvastatin 80mg for any patient with CVD in the absence of contraindications

Ezetimibe

- Cholesterol inhibitor
- Recommended as adjunctive therapy when statin fails to meet lipid targets or first line therapy when a statin is contraindicated

Familial Hyperlipidaemia

- Heterogenous group of genetic disorders resulting in hyperlipidaemia and massively increased cardiovascular risk at a younger age
- Familial hypercholesterolaemia is the most common form – AD mutations in LDL receptor gene

Diagnosis

Simon Boone Criteria

- TC > 7.5mmol/L & LDL-C > 4.9mmol/L in adults or TC > 6.7mmol/L & LDL-c > 4.0mmol/L in children plus:
- **Definite:** Tendon xanthoma in 1st/2nd degree relative or genetic evidence
- **Possible:** MI under 50 in 2nd degree relative/MI under 60 in 1st degree relative/family history of raised cholesterol levels

Screening

- Any above criteria
- Screening for all first degree relatives (including children, should be done before 10 years old)

Management

- No use for QRISK score, treat as soon as diagnosed
- Manage as per secondary prevention

Endocrinology

Diabetes Mellitus

- Chronic conditions characterised by hyperglycaemia resulting from a lack of, or reduced sensitivity to, endogenous insulin

Types of DM

Type 1 Diabetes Mellitus

- Insulin deficiency caused by autoimmune destruction of the insulin secreting beta cells in the pancreatic islets of Langerhans
- Associated with other autoimmune diseases (90% HLA-DR3 ± DR4)
- Typically presents in childhood/adolescence/early adulthood as a subacute (weeks) course of polyuria, polydipsia & weight loss ± DKA
- 30% concordance in identical twins
- **Latent Autoimmune Diabetes of Adults** is a form of T1DM that affects older adults with a slower progression to insulin deficiency

Type 2 Diabetes Mellitus

- Slow progression of decreased insulin secretion and increased peripheral insulin resistance, associated with age, obesity, lack of exercise, alcohol intake, males, and Asian ethnicity
- Majority are over 40 but cases are seen as young as teenagers with increasing levels of obesity
- Typically asymptomatic and found on screening, or first presents with established complications
- 80% concordance in identical twins
- **Maturity Onset Diabetes of the Young** is a rare autosomal dominant inherited form of T2DM affecting younger patients

Prediabetes

- Refers to raised glucose levels not meeting the diagnostic levels for diabetes. These individuals are more likely to later develop T2DM
- **Impaired Fasting Glucose:** 6.1-7mmol/L
- **Impaired Glucose Tolerance:** OGTT 7.8-11.1mmol/L

Gestational Diabetes

- Impaired glucose tolerance during pregnancy
- Defined by lower glucose levels than other types as these levels are harmful to the developing fetus
  - Fasting > 5.1mmol/L
  - OGTT > 8.5mmol/L

Others

- Pancreatic failure
  - Pancreatitis, surgery, haemochromatosis, cystic fibrosis
- Endocrine
  - Cushing's syndrome, acromegaly, phaeochromocytoma, hyperthyroidism
- Congenital
  - Glycogen storage diseases

Diagnosis of DM

- Fasting blood glucose > 7mmol/L or 2 hour post prandial (OGTT)/random blood glucose> 11.1mmol/L once in the presence of symptoms of hyperglycaemia
  - Polyuria
  - Polydipsia
  - Weight loss
  - Blurred vision
  - Diabetic ketoacidosis
- Fasting blood glucose > 7mmol/L or 2 hour post prandial (OGTT)/random blood glucose > 11.1mmol/L on two separate occasions in the absence of symptoms of hyperglycaemia
- HbA1c > 48mmol/L
  - Less sensitive in situations of increased red cell turnover

Differentiating Type 1 & 2 Diabetes

	Type 1	Type 2
Epidemiology	Typically children/young adults	Typically older (> 40) More common in males, obese patients
Genetics	90% HLA-DR3/4 Associated with other AI disease 30% identical twin concordance	80% identical twin concordance
Presentation	Subacute (over weeks) weight loss, polyuria & polydipsia	Asymptomatic/long standing polyuria/polydipsia Presence of complications
Specific Tests	Low C-peptide levels Ketones in urine Diabetes specific autoantibodies: – Anti-Glutamic acid decarboxylase (GAD) 80% – Islet cell (ICA) 70-80% – Insulin autoantibodies (IAA) Presence decreases with age – Insulinoma-associated-2-antibodies (IA-2A)	HbA1c more useful

Complications of Diabetes Mellitus

Macrovascular Complications

- Vascular disease (cardiovascular, peripheral vascular, cerebrovascular) is the chief cause of death in diabetes
- Caused by increased oxidative stress and endothelial damage
- MI is 4 times more common, stroke is twice as common
- Primary prevention dose of a statin can be used even if cholesterol levels are normal

Microvascular Complications

- Nephropathy
- Retinopathy
- Neuropathy

Diabetic Nephropathy

- Hyperglycaemia leads to glomerulosclerosis, albuminuria and chronic kidney disease

Microalbuminuria

- Defined as a negative dipstick for protein but a urinary albumin:creatinine ratio (ACR) of > 2.5

Screening

- Annual ACR

Management

- Dietary protein restriction
- ACE-i or ARB is protective by blocking the renin-angiotensin system
- Spironolactone may also help
- Tight glycaemic control
- Blood pressure control < 130/80

Diabetic Neuropathy

Peripheral Neuropathy

- Sensory loss/pain in a “glove and stocking” distribution
- Contributes to diabetic foot disease

Gastrointestinal Autonomic Neuropathy

- Gastroparesis: erratic glucose control, bloating, vomiting
- Chronic diarrhoea, often occurring at night
- GORD due to decreased lower oesophageal sphincter tone

Diabetic Foot Disease

- Combined results of vascular disease & neuropathy
- Presents as neuropathy/ischaemia/complications
  - Ulcers, Charcot foot, cellulitis, osteomyelitis, gangrene
- Long term consequence is ulceration

Screening

- Done annually
- Palpation of pedal pulses
- Monofilament sensation testing

Diabetic Retinopathy

- Leading cause of blindness <60 years
- Hyperglycaemia leads to increased retinal blood flow and endothelial dysfunction, eventually causing exudates, ischaemia, & neovascularisation

Classification

- **Mild NPDR**
  - 1+ microaneurysm
- **Moderate NPDR**
  - Microaneurysms
  - Blot haemorrhages
  - Hard exudates
  - Cotton wool spots
  - Mild IRMA/venous beading/looping
- **Severe NPDR**
  - Blot haemorrhages & microaneurysms
  - Venous beading
  - IRMA
- **Proliferative Diabetic Retinopathy**
  - Retinal neovascularisation
  - More common in T1, 50% blind in 5 years
- **Diabetic Maculopathy**
  - Based on location rather than severity
  - Hard exudates/other background changes on macula/within 1 disc width of macula
  - More common in T2

Investigations

- Annual screening with fundal photography
- Fluorescein angiography for detected NPDR/PDR/maculopathy

Management

- Prevention with blood pressure and glycaemic control
- Laser photocoagulation of proliferative retinopathy or maculopathy

Other Eye Involvement in DM

- Increased risk of cataract formation due to conversion of glucose to sorbitol by aldose reductase in lens
- Cranial nerve palsies

Management of Type 1 Diabetes

Lifestyle

Exercise

- Increases sensitivity to insulin

Diet

- Less saturated fats
- Less simple/processed sugars
- More complex/unprocessed carbohydrates

Risks/Comorbidities

- Aggressive treatment of hyperlipidaemia
- BP control < 130/85
- Foot care

Monitoring

HbA1c

- Checked every 3-6 months
- General target is < 48mmol/L
  - Account for factors such as frequency of hypoglycaemic episodes, daily activities, comorbidities, likelihood of complications

Glucose Self-Monitoring

- Capillary glucose should be self-checked with a glucometer at least 4 times a day (before each meal & before bed)
- Targets are 5-7mmolL on waking and 4-7mmol/L before meals/other times

Screening for Complications

- ACR, fundal photography & foot check at least annually

Insulin

Patient Education

- Vital to educate about recognising & managing hypoglycaemia (patient & family/partner)
- Knowledge about adjusting for pre-meal blood glucose and carbohydrate intake
  - Patient needs to know their own carbohydrate:insulin unit ratio
- Need to rotate sites to prevent lipohypertrophies which can cause unpredictable insulin absorption
- **Sick day rules**
  - Don't decrease insulin intake, requirement often increased during illness
  - Try to maintain caloric intake (eg with milk)
  - Admit if vomiting/dehydrated/ketotic

Regimes

- Basal long acting insulin
  - Insulin glargine (Lantus) once daily before bed
  - Insulin detemir (Levemir) twice daily
- Rapid acting pre-meal insulin analogues
  - Insulin lispro (Humalog)
  - Insulin aspart (NovoRapid)
  - Need to be titrated to planned caloric intake

Insulin Pumps

- Considered when attempts to meet HbA1c targets are unsuccessful or result in profound hypoglycaemias

Others

- NICE recommend considering adding metformin if BMI is > 25

Management of Type 2 Diabetes

Lifestyle

Diet

- Low glycaemic, high fibre diet
- Oily fish, vegetables, etc
- Diet & exercise alone can cure T2DM

Exercise

- Exercise and weight loss optimise HbA1c targets and can cure T2DM with dietary changes

Others

- Quit smoking

Risks/Comorbidities

- Aggressive treatment of hyperlipidaemia
- BP control < 130/85
- Foot care

Monitoring

HbA1c

- Should be checked every 3-6 months until stable, then monthly

HbA1c Targets (mmol/L)	
Lifestyle	48
Lifestyle + metformin	48
HbA1c > 58mmol/L while on at least 1 drug	53
Regime with any drug that can cause hypoglycaemia	53

Drug Treatment

- Start with diet & exercise if HbA1c is not dramatically elevated
- Step up as follows if HbA1c rises to/remains above 58 mmol/L:

1. Metformin
   - Titrated up from initial dose of 500mg OD to a maximum of 2g daily to achieve targets
2. Metformin plus 1 of:
   - DPP-4 inhibitor
   - Sulphonylurea
   - Pioglitazone
   - SGLT-2 inhibitor
3. Metformin plus:
   - DPP-4 inhibitor + sulphonylurea
   - Pioglitazone + sulphonylurea
   - Sulphonylurea/pioglitazone + SGLT-2 inhibitor
4. Insulin
   - OR metformin + sulphonylurea + GLP-1 mimetic
   - If insulin not suitable or BMI > 35

- If metformin is not tolerated, the same ladder applies excluding metformin & SGLT-2 inhibitors

Screening for Complications

- ACR, fundal photography & foot check at least annually

Drugs For Type 2 Diabetes

Class	Examples	Mechanism	Weight Effect	Hypoglycaemia	Other Side Effects
Biguanides	Metformin	Increases insulin sensitivity Decreases hepatic glucose production	Neutral	No	Lactic acidosis
Thiazolidinediones	Pioglitazone	Increases insulin sensitivity Decreases hepatic glucose production	Gain	No	Fluid retention Heart failure Anaemia
Sulphonylureas	Gliclazide	Stimulate insulin secretion	Gain	Yes	Risk of IHD as monotherapy
DPP-4 inhibitors	Sitagliptin Linagliptin	Inhibits DPP-4 which increases GLP-1 activity & the incretin effect	Neutral	No	Pancreatitis
GLP-1 mimetics (SC)	Exanatide Liraglutide Semaglutide	Mimics GLP-1 conveying the incretin effect	Loss	Low risk	GI upset Dizziness
SGLT-2 inhibitors	Dapagliflozin Empagliflozin	Prevents glucose reabsorption in proximal tubules	Loss	Yes	Glucosuria UTIs DKA with normal glucose levels

Diabetic Ketoacidosis

- Complication or first presentation (6%) of T1DM, rarely complicates T2DM in situations of extreme stress
- Mortality < 1%

Pathophysiology

- Inadequate/absent insulin prevents glucose from being taken up by cells
- Cells resort to proteolysis for metabolism generating acidic ketone bodies which cause a raised anion gap metabolic acidosis
  - Beta-hydroxybutyric acid
  - Acetoacetate
  - Acetone
- Elevated blood glucose causes osmotic diuresis & dehydration
- Lack of insulin causes potassium derangement
  - Typically raised serum potassium but low total body potassium

Common Precipitants

- New onset T1DM
- Missed insulin dose
- Acute illness (infection)
- Myocardial infarction

Features

- Polyuria & polydipsia
- Dehydration, hypotension, weight loss
- Confusion/coma
- Abdominal pain, nausea & vomiting
- Fruity (acetone) smelling breath
- Kussmaul respiration
- Symptoms of trigger (eg sepsis, MI)

Diagnostic Criteria

- Blood glucose > 11mmol/L or known diabetes
- Blood pH < 7.3
- Ketones > 3mmol/L or ++ ketones on dipstick
- Bicarb < 15mmol/L

Investigations

Bloods

- VBG
  - ABG if reduced GCS/hypoxia
- Capillary & lab glucose
- Ketones
- Bicarb
- U+E
- FBC & CRP
- Cultures

Urine

- Ketones
- MSU

Other

- ECG (hyperkalaemia)
- CXR (infection)

Management

1. Fluids

- Patients are up to ~100ml/kg fluid depleted
- Normal saline is preferred
- Gradual rehydration to avoid cerebral oedema
  - Slower infusions in patients < 25
- Intense fluid monitoring with catheterisation may be required
- Typical regimen:
  - 1 litre in the first hour
  - 1 litre in the next 2 hours
  - 1 litre in the next 2 hours
  - 1 litre In the next 4 hours
  - 1 litre in the next 4 hours
  - 1 litre in the next 6 hours

2. Insulin

- Human soluble insulin started after the first hour at a rate of 0.1 units/kg/hour
- If patient has a long acting insulin it should be taken as normal

3. Glucose

- Once glucose reaches < 15mmol/L, 5% dextrose infusion should be started

4. Potassium

- Serum potassium may initially be high but total body potassium is depleted and levels will drop once insulin takes effect
- Potassium may be added to saline from the second litre onwards as per blood levels:
  - > 5.5mmol/L: None
  - 3.5-5.5mmol/L: 40mmol/L
  - < 3.5mmol/L: Senior review

5. Cause

- Treat any precipitating event (infection)

6. Resolution

- Defined as:
  - pH > 7.3
  - Ketones < 0.6mmol/L
  - Bicarbonate > 15mmol/L
- Insulin and glucose must be continued until these results are met
- Subcutaneous insulin regime should be started

Complications

- Gastric stasis
- Thromboembolism
- Arrhythmias
- ARDS
- AKI
- Cerebral oedema
- Hypokalaemia/hypoglycaemia

Hyperglycaemic Hyperosmolar State

- Complication typically of unwell T2DM patients where hyperglycaemia leads to osmotic diuresis, dehydration and electrolyte disturbances
- Hyperviscosity of blood (typically > 320mosmol/kg) can lead to thrombotic events

Features

- Subacute (days - a week)

General

- Lethargy
- Nausea & vomiting

Dehydration

- Hypotension & tachycardia

Neurological

- Altered consciousness
- Headaches, papilloedema
- Weakness

Hyperviscosity

- Stroke, MI, acute limb ischaemia

Diagnosis

1. Hypovolaemia
2. Hypoglycaemia (> 30mmol/L) without ketoacidosis
   - Ketones < 3mmol/L
   - pH > 7.3
3. Raised serum osmolarity (> 320mosmol/kg)

Management

1. Fluids

- Patients can be 100-220ml/kg deplete
- Aim to replace over 24-48 hours
  - Slowed by heart failure, CKD
- Normal saline should be effective as it is relatively hypotonic to the hyperosmolar serum
  - Half normal saline can be used if serum osmolarity does not fall

2. Monitoring Osmolarity

- Osmolarity, sodium and glucose should be plotted hourly
- Rapid changes can cause cardiovascular collapse or central pontine myelinolysis
- Aim for:
  - Glucose reduction of 4-6mmol/L/hour
  - Sodium reduction < 10mmol/L/day

3. Insulin

- Should not be used unless there is insufficient fall in glucose or if there is ketonaemia
- Start at 0.05units/kg/hour

4. Potassium

- Replace depending on need as per DKA

5. Cause

- Treat any precipitating event – MI, bowel infarct, sepsis, etc

Hypoglycaemia

- Loosely defined as plasma glucose < 3mmol/L but threshold for symptoms varies between individuals

Causes

- **Ex**ogenous
  - Insulin
  - Oral hypoglycaemics (SU & SGLT-2)
  - Alcohol
  - ACE inhibitors
  - Beta blockers
- **P**ituitary insufficiency
- **L**iver failure/inherited enzyme defects
- **A**drenal failure
- **I**nsulinoma/immune hypoglycaemia (insulin receptor antibodies in Hodgkin's lymphoma)
- **N**on-pancreatic neoplasms
  - Fibrosarcomas
  - Haemoangiopericytomas

Features

Autonomic Symptoms < 3.3mmol/L	Neuroglycopenic Symptoms < 2.8mmol/L
Sweating	Weakness
Shaking	Vision changes
Hunger	Confusion
Anxiety	Dizziness
Nausea	Convulsions
	Coma

Investigations

- Investigate if cause unknown & Whipple's triad:
  - Signs & symptoms of hypoglycaemia
  - Low blood glucose
  - Resolution of symptoms on glucose correction

High Insulin

- Insulin overdose (No detectable C peptide)
- Insulinoma
- Oral hypoglycaemics

Low Insulin & Low Ketones

- Non-pancreatic neoplasm
- Immune hypoglycaemia

Low Insulin & Raised Ketones

- Alcohol
- Pituitary insufficiency
- Adrenal failure

Acute Management

Conscious

- Fast acting carbohydrate drink (juice) if able to drink
- Squirt drink between gums and teeth if unable to drink

Unconscious

- 10% dextrose infusion or glucagon 1mg IV/IM

Insulinoma

- Neuroendocrine tumour of pancreatic islet beta cells
- 10% malignant
- 10% multiple
  - 50% of these are associated with MEN-1

Features

- Whipple's triad (hypoglycaemia)
  - Typically early morning or before meal
- Rapid weight gain

Investigations

- Supervised 72 hour fast
  - Hypoglycaemia & hyperinsulinaemia
- Suppression test
  - High C-peptide following IV insulin
- Imaging
  - CT pancreas

Management

- Surgical excision
- Diazoxide/somatostatin if surgery unsuitable/fails

Nesidioblastosis

- Diffuse beta cell hyperplasia
- Presents the same as insulinoma but cannot be excised surgically
- Treat with diazoxide/somatostatin

Hyperthyroidism/Thyrotoxicosis

- Symptomatic increased free T4 typically from gland hyperfunction

Causes

Grave's Disease

- 60% of cases, F>M 9:1
- Diffuse goitre
- Caused by TSH receptor/TPO antibodies, associated with other AI disease

Toxic Multinodular Goitre (Plummer's Disease)

- Autonomous nodule developing on nodular thyroids

Toxic Adenoma

- Solitary functioning nodule

Acute Phase of Thyroiditis

- De Quervian's
- Hashimoto's
- Post-partum

Drugs

- Thyroxine
- Amiodarone

Features

Symptoms

- Diarrhoea
- Weight loss with increased appetite
- Sweats
- Palpitations
  - High output cardiac failure in elderly patients
- Heat intolerance
- Tremor
- Agitation/anxiety
- Oligo/amenorrhoea

Signs

- Tachycardia/irregular pulse
- Warm, moist skin
- Fine tremor
- Palmar erythema
- Lid lag/lid retraction
- Thin hair
- Goitre/nodular thyroid

Grave's Disease Specific

- Ophthalmopathy
  - Exophthalmos
  - Ophthalmoplegia
  - Discomfort/grittiness
  - Photophobia & reduced acuity
  - Chemosis
- Pre-tibial myxoedema
- Thyroid acropachy
  - Clubbing
  - Soft tissue swelling in hands & feet
  - Periosteal new bone formation

Investigations

TFTs

- Raised T3/T4
- Low TSH

Thyroid Autoantibodies

- Anti-TSH receptor in 90% of Grave's
- Anti-TPO in 75% of Grave's

Management

Medical

- Rapid symptomatic treatment with beta-blockers
- Anti-thyroid (carbimazole)
  - Titrate to TFTs or block & replace with levothyroxine
  - In Grave's withdraw treatment after 12-18 months
    - 50% relapse
  - Risk of agranulocytosis

Radioiodine

- Most will become hypothyroid
- No evidence for increased cancer/infertility/birth defects
- Contraindicated in pregnancy/breastfeeding

Surgery (Total Thyroidectomy)

- Hypothyroidism is inevitable
- Hypoparathyroidism & recurrent laryngeal nerve palsy are potential complications

Subclinical Hyperthyroidism

- Normal T3 & T4 with low TSH
- Caused by multinodular goitre or exogenous thyroxine
- Risk of AF, osteoporosis, & dementia

Management

- Only if persistent low TSH
- 6 month trial of anti-thyroid medication

Hypothyroidism/Myxoedema

- Symptomatic reduced free T4
- 5-10 times more common in women, very common in women > 40

Causes

Primary

- Hashimoto's thyroiditis
  - Most common in the developed world
  - Firm non-tender goitre
  - Anti-TPO & anti-Tg antibodies
  - Associated with other autoimmune disease & development of MALT lymphoma
  - May be hyperthyroid in acute phase
- Iodine deficiency
  - Most common in developing world
- Subacute (De Quervian's) thyroiditis
- Riedel's thyroiditis
- Postpartum thyroiditis

Iatrogenic

- Treatment of hyperthyroidism
  - Carbimazole
  - Radioiodine
  - Thyroidectomy
- Amiodarone
- Lithium

Secondary/Central (Rare)

- Pituitary failure
- Down's syndrome
- Turner's syndrome
- Coeliac disease

Features

Symptoms

- Weight gain
- Cold intolerance
- Lethargy
- Hair loss
- Constipation
- Menorrhagia
- Hoarse voice

Signs

- Goitre
- Decreased deep tendon reflexes with slow relaxation
- Cold dry skin
- Non-pitting oedema of hands, eyes, feet
- Ascites
- Heart failure

Investigations

TFTs

- Raised TSH & low T4 in primary causes
- Low TSH & low T4 in central causes

Other Bloods

- Macrocytosis
- Hypercholesterolaemia

Management – Levothyroxine

Dosing

- 50-100mcg OD starting dose for healthy young patients
- 25mcg OD starting dose for patients > 50, patients with cardiac disease, or patients with severe hypothyroidism
  - Dose increased by 25mcg every ~4 weeks according to TSH

Monitoring

- Priority is normalisation of TSH (0.5-2.5mU/L)
- TSH checked 8-12 weeks after any dose change

Side Effects

- Hyperthyroidism from over-treatment
- Reduced mineral bone density
- Worsening of angina
- Atrial fibrillation

Interactions

- Enzyme inducers increase metabolism of levothyroxine
- Iron & calcium carbonate decrease absorption and should be given > 4 hours apart

Subclinical Hypothyroidism

- Normal T3 & T4 with raised TSH
- Risk of progression to hypothyroidism

Management

- TSH 4-10 mU/L
  - Observe and repeat TFTs in 6 months
- TSH > 10mU/L
  - Treat with levothyroxine
- Don't treat elderly (> 80) patients unless they become symptomatic

Thyroid Storm

- Rare crisis of hyperthyroidism – almost never the first presentation

Precipitants

- Thyroid or non-thyroid surgery
- Radioiodine
- Infection
- Trauma
- Iodine loading (eg contrast)

Features

- Fever > 38.5
- Confusion & agitation
- Nausea & vomiting
- Tachycardia
- Hypertension
- Heart failure
- Abnormal LFTs ± jaundice
- Goitre with thyroid bruit
- Acute abdomen – rule out surgical cause

Investigations

- TFTs – don't wait for results if urgent
- Cultures if indicated

Management

1. IV access, fluids if necessary, TFTs
2. Beta-blockers
   - Propranolol IV 60mg/4-6hrs
   - Diltiazem if beta-blockers contraindicated
3. Antithyroid drugs
   - Carbimazole 15-25mg q6 hours PO
   - Lugol's iodine solution PO after 4 hours
4. Dexamethasone
   - 2mg/6hrs
5. Treat precipitant (infection)
6. Continuing treatment
   - Reduce carbimazole to 15mg/8hrs after 5 days
   - Stop propranolol & iodine after 10 days

Myxoedema Coma

- Severe hypothyroidism presentation leading to death in untreated

Precipitants

- Infection
- MI
- Stroke
- Trauma

Features

- Hypothermia
- Cyanosis
- Confusion
- Coma
- Hypoglycaemia
- Hyporeflexia
- Bradycardia
- Hypotension
- Seizures
- Evidence of thyroid/pituitary surgery
- Goitre

Management

1. Oxygen if cyanosed
2. IV access & bloods
   - TFTs
   - Glucose
   - Cortisol
   - FBC + CRP + cultures
   - U+Es
3. Fluid resuscitation if necessary
4. Correct hypoglycaemia
5. IV thyroid replacement
   - Levothyroxine/liothyronine
6. IV hydrocortisone until pituitary/adrenal failure excluded
7. Treatment of infection if present
8. Active warming

Primary Hyperparathyroidism

Causes

- Solitary adenoma 80%
- Hyperplasia 15%
- Multiple adenomas 4%
- Carcinoma 1%

Features

- Relate to hypercalcaemia & bone resorption
- Polyuria & polydipsia
- Peptic ulceration
- Constipation
- Pancreatitis
- Bone pain/pathological fracture
- Renal stones
- Depression
- Hypertension
- Associated with MEN-I & II

Investigations

Bloods

- Hypercalcaemia & hypophosphataemia
- PTH raised or inappropriately normal
- ALP raised

Imaging

- Osteitis fibrosa cystica
  - Subperiosteal erosions/cysts
  - Brown tumours of phalanges
  - Acro-osteolytis
  - Pepper-pot skull
- DEXA shows osteoporosis

Others

- Raised 24 hour urinary calcium

Management

Surgery

- Removal of adenoma/all 4 parathyroid glands is the definitive treatment
- Indicated if < 50 years old with symptoms of hypercalcaemia/bone resorption
- Intraoperative PTH sampling can confirm removal
- **Complications**
  - Hypoparathyroidism
  - Recurrent laryngeal nerve damage

Conservative

- Offered if unsuitable for surgery or > 50 years old with calcium < 0.25mmol/L above ULN with no end-organ damage
- **Cinacalcet** increases parathyroid sensitivity to calcium to reduce PTH secretion

Secondary Hyperparathyroidism

- Raised PTH & gland hyperplasia due to decreased calcium, almost always due to CKD (also dietary vitamin D deficiency)

Features

- Often asymptomatic
- Development of bone disease
  - Osteoporosis
  - Osteitis fibrosa cystica
  - Soft tissue calcification

Investigations

- Hypocalcaemia
- Appropriately raised PTH
- Low vitamin D

Management

- Treat cause if possible (eg renal transplant)
- Vitamin D supplementation
- Phosphate binder
- Cinacalcet if PTH > 85pmol/L
- Surgery if bone pain/soft tissue calcifications

Tertiary Hyperparathyroidism

- Caused by gland hyperplasia as a result of 2° hyperparathyroidism and autonomous function following correction of cause

Features

- Bone pain/fracture
- Nephrolithiasis
- Metastatic calcification
- Pancreatitis

Investigations

- Raised calcium
- Raised PTH
- Raised ALP
- Normal/decreased vitamin D & phosphate

Management

- Allow 12 months to resolve following renal transplant
- Surgery (autonomous gland or total parathyroidectomy) if non-resolving

Hypoparathyroidism

Causes

Primary

- Autoimmune (associated with other AI conditions)
- Congenital (Di George syndrome)

Secondary

- Radiation
- Surgery
- Hypomagnesaemia

Features

- Features of hypocalcaemia
- Features of other AI diseases

Investigations

- Low PTH
- Low calcium
- High phosphate

Management

- Calcium supplements + vitamin D (alfacalcidol)
- Subcutaneous PTH avoids hypercalciuria

Pseudohypoparathyroidism

- Congenital insensitivity of target cells to PTH

Features

- Hypocalcaemia
- Low IQ
- Short stature
- Short 4^{th} & 5^{th} metacarpals
- Round face

Investigations

- High PTH
- Low calcium
- Calcified basal ganglia seen on CT

PTH Infusion

	HypoPTH	PseudohypoPTH Type I	PseudohypoPTH Type 2
Urinary cAMP	↑	↔	↑
Urinary Phosphate	↑	↔	↔

Management

- Calcium supplements + vitamin D (alfacalcidol)

Pseudopseudohypoparathyroidism

- Morphological phenotype of pseudohypoparathyroidism with normal biochemistry

Cushing's Syndrome

- Clinical syndrome caused by excess levels of corticosteroids

Causes

ACTH Dependent

- Cushing's disease
  - 80% of endogenous cases
  - Functioning pituitary adenoma secreting ACTH causing bilateral adrenal hyperplasia
- Ectopic ACTH
  - 5-10% of endogenous cases
  - Particularly small cell lung cancer and carcinoid tumours
  - Hyperpigmentation common, other Cushing's phenotypes uncommon
  - Mineralocorticoid effects (hypokalaemic metabolic acidosis)

ACTH Independent

- Exogenous steroids (most common cause)
- Adrenal adenoma
  - 5-10% of endogenous cases
- Adrenal carcinoma (rare)
- Micronodular adrenal dysplasia (very rare)
- Carney complex
  - Cushing's + cardiac myxomas
- McCune-Albright syndrome

Pseudo-Cushing's

- Mimics Cushing's syndrome & causes false positive DST & 24 hour urinary free cortisol
- Caused by alcohol excess/severe depression
- Insulin stress test differentiates

Features

Phenotype

- Central obesity
- Round "moon" face
- Upper back fat pad (buffalo hump)
- Proximal muscle wasting (thin limbs)
- Abdominal striae
- Thin skin
- Hyperpigmentation in ACTH dependant causes

Stress Hormone Effects

- Hypertension & cardiac hypertrophy
- Hyperglycaemia
- Depression
- Insomnia
- Immunosuppression

Others

- Osteoporosis
- Easy bruising & poor healing
- Gonadal dysfunction
  - Irregular periods
  - Erectile dysfunction
  - Hirsutism

Diagnosis

Overnight Dexamethasone Suppression Test

- 1st line to diagnose Cushing's syndrome
- 1mg dexamethasone PO given at midnight
- 8am serum cortisol – positive result is > 50nmol/L

24 Hour Urinary Free Cortisol

- Alternative to overnight DST
- Should be < 280nmol/24 hours

Localisation Tests

9am & Midnight Plasma ACTH Levels

- Differentiates ACTH-dependant and non-dependant causes
- If ACTH is undetectable, ACTH-independent cause is likely
- If ACTH is detected, do high dose DST

48 Hour High Dose Dexamethasone Suppression Test

Cause	Cortisol	ACTH
Cushing's Disease	Suppressed	Suppressed
Ectopic ACTH	Not suppressed	Not suppressed
ACTH Independent	Not suppressed	Suppressed

ACTH Independent Cause Likely

- CT/MRI of adrenal glands
- Adrenal venous sampling if no mass visible

Cushing's Disease Likely

- MRI of pituitary
- Inferior petrosal sinus blood sampling

Ectopic ACTH Likely

- Contrast CT thorax, abdomen, pelvis ± MRI of neck, thorax & abdomen (for small carcinoid tumours)

Management

Iatrogenic

- Stop/reduce steroids if possible

Cushing's Disease

- Trans-sphenoidal removal of pituitary adenoma
- Bilateral adrenalectomy if source unlocatable or recurrence post-op
  - **Nelson's syndrome** may occur, hyperpigmentation from increased ACTH following removal of adrenals – responds to pituitary radiation
  - Requires replacement steroids for life

Adrenal Adenoma/Carcinoma

- Adrenalectomy cures adenomas, carcinomas require follow-up radiotherapy & adrenolytics (mitotane)

Ectopic ACTH

- Surgical removal of secreting tumour + oncological follow-up

Adrenal Insufficiency

- Reduced/absent production of glucocorticoids & mineralocorticoids by the adrenal cortices

Causes

Primary

- Autoimmune destruction
  - AKA Addison's disease, 80% of primary cases
- Tuberculosis
- Metastases (eg lung ca)
- Waterhouse-Friderichsen syndrome (meningococcal sepsis)
- HIV
- Antiphospholipid syndrome

Secondary

- HPA axis depression from exogenous steroid use
  - Only apparent on withdrawal of steroids
- Pituitary failure (surgery, trauma, radiation, infiltration)

Features

- Lethargy & weakness
- Anorexia & weight loss
- Nausea & vomiting
- Salt craving
- Hypotension
- Hypoglycaemia, hyponatraemia, hyperkalaemia
- Non-anion gap metabolic acidosis
- Hyperpigmentation **in primary** adrenal failure
  - ACTH stimulation of melanocytes
  - Most apparent in palmar creases

Crisis

- Shock, collapse, pyrexia

Investigations

Short Synacthen (ACTH) Test

- Serum cortisol measured before & 30 minutes after Synacthen 250ug IM
- Negative if 30 minute cortisol is >550nmol/L
- Positive if fails to rise to double of baseline

9am Cortisol

- If short Synacthen unavailable
- > 500nmol/L – adrenal failure unlikely
- 100-500nmol/L – equivocal
- <100nmol/L – adrenal failure likely

9am ACTH

- High (> 300ng/L) in primary failure
- Low in secondary failure

21 Hydroxylase Adrenal Antibodies

- Positive in 80% of Addison's disease

Aldosterone/Renin Ratio

- Assess mineralocorticoid status

Imaging

- CT/MRI adrenals if structural cause suspected
- MRI pituitary if pituitary cause suspected
- CXR for TB

Management

Exogenous Steroids

- Hydrocortisone 15-25mg/day
  - Given in 2-3 doses
  - Avoid evening doses as they may cause insomnia
  - Titrate clinically
- Fludrocortisone 50-100mcg/day
  - If postural hypotension/hyperkalaemia /hyponatraemia

Steroid Safety

- Add 5-10mg before strenuous exercise
- Double dose while sick
- Give prefilled IM syringes in case of vomiting preventing oral intake
- Advise bracelet indicating steroid use

Monitoring

- Yearly BP
- Screening for other autoimmune disease (eg pernicious anaemia)

Adrenal/Addisonian Crisis

- Life-threatening absence of steroids

Precipitants

- Infection
- Trauma
- Surgery
- Missed dose
- New onset (eg meningococcal sepsis)

Features

- Reduced consciousness
- Hypotension
- Hypoglycaemia, hyponatraemia, hyperkalaemia
- Non-anion gap metabolic acidosis
- Pyrexia

Investigations

- Don't delay treatment
- Urgent bloods – cortisol & ACTH, U+E, glucose, cultures
- ECG if hyperkalaemia - calcium gluconate if needed

Management

- Hydrocortisone 100mg IM/IV
- 1L NS over 30-60 minutes
  - With dextrose if hypoglycaemic
- Repeat hydrocortisone 6 hourly until stable
  - Fludrocortisone not always needed due to mineralocorticoid effect of high dose glucocorticoid – get senior advice
- Change to oral steroids after 72hours if stable
- Search for & treat precipitant

Primary Hyperaldosteronism

- Excess production of aldosterone independent of the RAAS, causing sodium & water retention and loss of potassium

Causes

- Bilateral idiopathic adrenal hyperplasia
  - Most common (~70%) per recent studies
- Solitary aldosterone secreting adrenal adenoma (Conn's syndrome)
- Rare adrenal carcinomas
- Glucocorticoid-remediable aldosteronism
  - Rare genetic defect linking ACTH to aldosterone synthesis

Features

- May be asymptomatic
- Hypokalaemia (muscle weakness, cramps, parasthesiae)
- Hypertension
- Alkalosis

Investigations

Aldosterone/renin ratio (1st line)

- High aldosterone with low renin

High resolution CT adrenals

- Adenoma/carcinoma

Bilateral adrenal vein sampling

- Distinguish between bilateral hyperplasia and adenoma if CT is negative

Others

- Genetic testing for GRA if there is a family history of early hypertension

Management

Bilateral Hyperplasia

- Aldosterone receptor antagonists
  - Spironolactone
  - Eplerenone

Adenoma/Carcinoma

- Laparoscopic adrenalectomy
- Post-operative adrenolytics (mitotane) if carcinoma, poor prognosis

Glucocorticoid-Remediable Aldosterone

- Dexamethasone 1mg/day PO for 4 weeks

Secondary Hyperaldosteronism

- Caused by heart failure, renal artery stenosis/obstruction, liver failure
- High aldosterone & high renin
- Managed with treatment of cause (eg renal artery angioplasty)

Phaeochromocytoma

- Rare catecholamine producing tumours of sympathetic paraganglionic cells
- Most commonly of the adrenal medulla

10% Rule

- 10% familial
  - MEN II
  - Neurofibromatosis
  - Von Hippel-Lindau
- 10% bilateral
- 10% malignant
- 10% extra-adrenal
  - Most common site is the organ of Zuckerkandl adjacent to aortic bifurcation

Features

- Typically episodic/paroxysmal

Cardiac

- **Tachycardia & palpitations**
- Arrhythmias, syncope, angina

CNS

- **Headache**
- Dizziness, tremor, visual disturbance
- Horner's syndrome in paraganglioma

GIT

- Nausea, vomiting, diarrhoea
- Pain over tumour site

Other

- Sweating, flushing

Investigations

Diagnosis

- 24 hour urinary metanephrines
  - More sensitive than adrenaline/VMA

Localisation

- Abdominal CT/MRI
- Meta-iodobenzylguanidine (MIBG) scan
  - Chromaffin seeking isotope
  - Can locate extra-adrenal tumours

Management

- Stabilisation with α-blockers (phenoxybenzamine) **before** β-blockers (propranolol)
  - Prevents crisis from unopposed α stimulation
- Surgical removal

Monitoring

- Monitor for hypotension post-op
- 24 hour urinary metanephrines 2 weeks post op
- Lifelong follow-up for recurrence (can occur late)

Pituitary Adenomas

- 10% of all brain tumours
- Present in 10% of people but most are asymptomatic and never found

Classification

Size

- < 1cm: microadenoma
- > 1cm: macroadenoma

Hormonal Status

1. Prolactinoma
2. Non-secreting
3. GH secreting
4. ACTH secreting

Histological

- **Chromophobe (70%):** Prolactin or non-secreting. Pressure effect in 30%
- **Acidophil (15%):** Prolactin or GH. Pressure effect in 10%
- **Basophil (15%):** ACTH. Pressure effect rare

Features

Hormonal Effects

- Cushing's disease/ acromegaly/hyperprolactinaemia
- Hypopituitarism (non-secreting tumour compressing glang)

Pressure Effects

- Headaches
- Bitemporal hemianopia
- CN III/IV/VI palsies (pressure/invasion of cavernous sinus)
- Hypothalamic pressure (DI, fever)
- Sella floor erosion & CSF rhinorrhoea

Investigations

- Pituitary blood profile (GH, prolactin, ACTH, FH, LSH, TFTs)
- Pituitary MRI
- Formal visual field testing

Differential

- Pituitary hyperplasia
- Craniopharyngioma
- Meningioma/lymphoma/brain metastases
- Hypophysitis
- Vascular malformation

Management

- Hormone therapy as needed
- Surgical (transsphenoidal removal)
  - Assess pituitary function & need for replacement post-op
- Radiation for residual/recurrent adenomas

Craniopharyngioma

- Tumour originating from Rathke's pouch between pituitary and 3rd ventricle floor
- Rare in adults, most common intracranial tumour in children

Features

Children (50%)

- Faltering growth

Adults (50%)

- Amenorrhoea
- Decreased libido
- Hypothalamic effects
- Pressure effects

Investigations

- CT/MRI
- Calcification is present in 50% and may be seen on skull x-ray

Management

- Surgery ± post-op radiation
  - Assess pituitary function & need for replacement post-op

Pituitary Apoplexy

- Sudden enlargement of pituitary tumour – usually a non-functioning microadenoma – secondary to haemorrhage or infarction

Precipitants

- Hypertension
- Pregnancy
- Trauma
- Anticoagulation

Features

- Acute onset of headache similar to SAH +
- Meningism
- Reduced consciousness
- Visual field defect/CN palsies
- Cardiovascular collapse from hypopituitarism

Investigation

- MRI is diagnostic

Management

- Urgent steroid replacement (hydrocortisone 100mg)
- Careful fluid balance
- Surgery
- Find & treat cause

Acromegaly

- Clinical manifestation of excess growth hormone in adults

Causes

- Pituitary adenoma (>95%)
- Ectopic GHRH/GH from tumours (eg carcinoid, pancreatic)
- 5% associated with MEN I

Features

Symptoms

- Old rings/shoes etc not fitting
- Acroparaesthesia (acro = extremities)
- Headache
- Arthralgia & backache
- Snoring
- Bitemporal hemianopia may occur

Signs

- Growth of hands, jaw, & feet
- Coarse facial features with wide nose
- Large supraorbital ridges
- Macroglossia
- Scalp skin folds (cutis verticis gyrata)
- Acanthosis nigricans

Complications

- Diabetes mellitus (10%)
- Capral tunnel syndrome (50%)
- Hypertension
- Cardiomyopathy
- Colorectal cancer

Investigations

Serum IGF-1

- 1st line & used to monitor disease
- If raised/equivocal, do an OGTT

OGTT

- Oral glucose load followed by serial GH measurement at 0, 30, 60, 90, 120 & 150 minutes
- Positive if lowest GH measurement is > 1ug/L

Imaging

- Pituitary MRI for presence of tumour

Management

Surgical

- 1st line – transsphenoidal resection of pituitary tumour/resection of tumour secreting ectopic hormone

Medical (Surgical failed/unsuitable)

- Somatostatin analogues (octreotide) effective in 50-70%
- Pegvisomant (GH receptor antagonist) given SC – effective in 90%, no effect on tumour size
- Dopamine agonists (bromocriptine) – largely superseded

Hyperprolactinaemia

- Most common pituitary hormone disturbance

Causes

- Prolactin producing pituitary adenoma (prolactinoma)
- Disinhibition by compression of pituitary stalk (decreased dopamine reaching pituitary)
- Dopamine antagonists (antipsychotics, anti-emetics)
- Pregnancy
- Acromegaly
- Primary hypothyroidism
- Stress/exercise

Features

Females

- Oligo/amenorrhoea
- Infertility
- Weight gain
- Vaginal dryness

Males

- Erectile dysfunction
- Facial hair loss

Both

- Gynaecomastia
- Osteoporosis
- Tumour pressure effects

Investigations

- Basal prolactin – non traumatic venepuncture
- TFT, U+E, βhCG
- MRI if other causes ruled out

Management

- Specialist referral

Medical

- Dopamine agonists (eg bromocriptine/carbogoline) 1st line
- SEs: nausea, depression, postural hypotension

Surgical

- If unsuitable for or not responding to surgery

Hypopituitarism

- Inadequate production of one or more pituitary hormones
- **Panhypopituitarism** is inadequate production of all anterior pituitary hormones, usually caused by surgery/trauma/radiation

Causes

- Compression of gland by non-secretory macroadenoma
- Apoplexy
- Sheehan's syndrome
- Compression by craniopharyngioma, meningioma, lymphoma, etc
- Trauma
- Radiation
- Surgery
- Infiltration (hemochromatosis, sarcoidosis)

Features

ACTH

- Lethargy
- Postural hypotension
- Adrenal crisis

GH

- Central obesity
- Atherosclerosis
- Depression
- Hypoglycaemia
- Decreased strength, balance, exercise tolerance
- Short stature if occurring in childhood

FSH/LH

- **Female**
  - Amenorrhoea
  - Infertility
  - Osteoporosis
  - Breast atrophy
- **Male**
  - Loss of libido
  - Loss of hair
  - Testicular shrinking
  - Loss of muscle mass
- **Both**
  - Loss of libido

PRL

- Absent lactation

TSH

- Hypothyroidism

Investigations

- Pituitary blood profile (GH, prolactin, ACTH, FH, LSH, TFTs)
- Pituitary MRI

Insulin Stress Test

- Insulin given in controlled circumstances to induce hypoglycaemia of < 2.2mmol/L
- GH and cortisol will not rise in hypopituitarism

Management

- Surgical removal of tumour/treatment of underlying cause
- Hormone replacement as required
  - Hydrocortisone must be given before others

Diabetes Insipidus

- Polyuria & polydipsia due to decreased secretion of ADH from the posterior pituitary (cranial) or decreased sensitivity to ADH in the nephron (nephrogenic)

Causes

Cranial

- Idiopathic
- Post head injury/surgery
- Tumour (pituitary/craniopharyngioma)
- Autoimmune hypophysitis
- Meningitis
- Infiltration (histiocytosis, sarcoidosis, haemochromatosis)
- Wolfram's syndrome/DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, deafness)

Nephrogenic

- Inherited
  - ADH receptor gene (common)
  - AQP2 gene (rare)
- Hypercalcaemia, hypokalaemia
- Tubulointerstitial disease: obstruction, sickle cell disease, pyelonephritis
- Drugs: lithium, demeclocycline

Investigation

Urine & Plasma Osmolality

- DI ruled out by:
  - Urine:plasma osmolality ratio of > 2 with plasma osmolality > 295mOsmol/L
  - Urine osmolality > 700mOsmol/L

Water Deprivation Test

- Patient empties bladder and drinks no water for 8 hours
- Urine sample every 2 hours & venous sample every 4 hours for osmolality
- Give desmopressin (stage 2) if plasma osmolality rises above 300 or if urine osmolality is < 600 after 8 hours

	8 hour urine osm	Post desmopressin urine osm
Normal	> 600	> 600
Psychogenic polydipsia	> 400	> 400
Cranial DI	< 300	> 600
Nephrogenic DI	< 300	< 300

Management

Cranial

- Desmopressin

Nephrogenic

- Thiazides
- Low salt/protein diet

SIADH

- Hyponatraemia due to excessive water retention due to ADH secretion

Causes

Malignancy

- **SCLC**
- Pancreatic
- Prostate

Neurological

- Stroke
- SAH
- Subdural haemorrhage
- Meningitis/encephalitis/abscess

Infections

- Tuberculosis
- Pneumonia

Drugs

- Sulfonylureas
- SSRIs & tricyclics
- Carbamazepine
- Vincristine
- Cyclophosphamide

Other

- PEEP
- Porphyrias

Investigations/Diagnosis

- Urinary sodium > 20mmol/L & osmolality > 100mOsmol/kg with plasma sodium < 125mmol/L & osmolality 260mOsmol/kg
- Absence of hypovolaemia/oedema/diuretics

Management

- Treat cause if possible
- Fluid restriction
- Vasopressin receptor antagonists – tolvaptan

Multiple Endocrine Neoplasia

- Autosomal dominant disorders predisposing to endocrine/neuroendocrine tumours

Type	MEN 1	MEN 2a	MEN 2b
Genetics	• Parathyroid adenoma/hyperplasia → hyperparathyroidism (95%) • Pituitary tumours (75%) – Prolactinoma – GH tumours → acromegaly • Pancreatic tumours (50%) – Insulinoma – Gastrinoma (causing Zollinger-Ellison)	• Medullary thyroid cancer (70-100%) • Parathyroid hyperplasia (80%, but < 20% have hypercalcaemia) • Pheochromocytoma (50%) – Usually benign & bilateral	• Medullary thyroid cancer • Phaeochromocytoma • Marfanoid habitus • Neuromas
Features	MEN1 gene Many sporadic, present in 3rd – 5th decades	RET proto-oncogene	RET proto-oncogene

Gastroenterology

Acute Upper GI Bleed

Causes

Oesophageal

- Oesophagitis (rarely major)
- Oesophageal cancer (rarely major unless preterminal vessel erosion)
- Mallory-Weiss tears
- Varices

Gastric

- Gastric ulcer (small bleeds more common unless vessel erosion)
- Gastric cancer
- Diffuse erosive gastritis
- Dieulafoy Lesion
- GAVE syndrome

Duodenal

- Duodenal ulcer (posteriorly sited duodenal ulcer is the most common cause of major haemorrhage)

Glasgow-Blatchford Score (1st Asessment)

- Stratifies risk of upper GI bleed

Urea	6.5 - 8		2
	8 - 10		3
	10 - 25		4
	25		6
Haemoglobin	**Men**	**Women**	
	12 - 13	10-12	1
	10 - 12		3
	< 10	< 10	6
Systolic BP	100 - 109		1
	90 - 99		2
	< 90		3
Pulse	> 100		1
Melaena			1
Syncope			2
Hepatic failure			2
Cardiac failure			2

- Discharge for patients with a score of 0

Rockall Score (After Endoscopy)

- Calculates risk of re-bleeding after endoscopy
- Take into account:
  - Age
  - Features of shock
  - Co-morbidities
  - Cause of bleeding
  - Endoscopic stigmata of recent haemorrhage

Initial Management

Resuscitation

- Protect airway
- 2x large bore IV cannulae
- Bloods
  - Hb & platelets
  - Urea
  - Coagulation
  - LFTs
  - Crossmatch 6 units
- Rapid fluids up to 1L
  - Crystalloids
  - Avoid normal saline in cirrhotics/varcies

Transfusions

- Blood (O -ve if crossmatched not ready) if still shocked after 1L of fluids/Hb < 10g/dL
- Platelets in active bleeding/platelets < 50
- Prothrombin complex concentrate if taking warfarin
- Fresh frozen plasma if INR/APPT > 1.5x ULN

Varices Suspected

- IV terlipressin & antibiotics
- Urgent endoscopy
- Sangstaken-Blakemore tube if rapidly exsanguinating/failure of endoscopy

Endoscopy

- ASAP if severe bleed
- Within 24 hours for all patients

Vessel/Ulcer

- Adrenaline injection
- Thermal/laser coagulation
- Fibrin glue
- Clips

Variceal Bleeding

- Banding + sclerotherapy/adrenaline/coagulation
- TIPSS if bleeding cannot be stopped endoscopically

Surgery Indications

- Re-bleeding
- Uncontrollable bleeding
- Initial Rockall score > 3 or final > 6

Dysphagia

- Difficulty swallowing, requires urgent investigation to exclude malignancy (unless acute & associated with pharyngitis)

Causes

Extrinsic

- Mediastinal masses
- Cervical spondylosis

Oesophageal Wall

- Achalasia
- Diffuse oesophageal spasm
- Hypertensive lower oesophageal sphincter
- Systemic sclerosis

Intrinsic

- Malignant stricture
  - Pharyngeal, oesophageal, or gastric cancer
- Benign stricture
  - Oesophageal web/ring
  - Peptic stricture

Neurological

- CVA
- Parkinson's disease
- Multiple sclerosis
- Myasthenia gravis
- Bulbar palsies

Specific Features

Malignancy

- Recent weight loss, anorexia
- Virchow's node
- History of GORD, Barrett's oesophagus, alcohol, smoking

Oesophagitis

- History of heartburn
- Odynophagia without weight loss

Candidiasis

- History of HIV/other immunosuppression/steroid inhaler use

Achalasia

- Both solids & liquids from the onset
- Regurgitation ± aspiration

Pharyngeal Pouch

- Neck gurgle/bulging on swallow

Systemic Sclerosis

- Other features of CREST syndrome

Myasthenia Gravis

- Extraocular muscle weakness/ptosis
- Liquids and solids

Globus Hystericus

- History of anxiety
- Painless
- Intermittent symptoms relieved by swallowing

Investigations

- FBC
- Upper GI endoscopy unless clear & compelling benign diagnosis
- Manometry for achalasia
- Fluoroscopic swallow studies for dysmotility

Achalasia

- Degenerative loss of ganglia from Auerbach's plexus leading to LOS contraction and oesophageal dilatation above

Features

- Dysphagia of solids & liquids
- Variation of severity
- Heartburn
- Food regurgitation
- Aspiration
- Malignant change in minority of patients

Investigations

Manometry

- Excessive LOS tone which doesn't relax on swallowing

Barium Swallow

- Grossly distended oesophagus with fluid level
- Beak appearance

CXR

- Wide mediastinum
- Fluid level

Management

Balloon Dilatation

- Increasingly preferred over surgery
- Patients should be fit for surgery in case of complications

Surgery

- Heller cardiomyotomy for recurrent/persistent symptoms

Botox

- Intra-sphincteric injections for those at high surgical risk

GORD

- Stomach acid refluxes through lower oesophageal sphincter causing irritation & damage to oesophageal mucosa

Complications

- Oesophagitis
- Benign stricture
- Barrett's oesophagus
- Malignancy
- Ulceration
- Iron deficiency

Causes/Risk Factors

- LOS hypotension
- Hiatus hernia
- Oesophageal dysmotility
- Obesity
- Pregnancy

Presentation

- Heartburn
- Acid regurgitation
- Retrosternal/epigastric pain
- Bloating
- Nocturnal cough
- Hoarse voice

Investigation

Criteria for urgent endoscopy referral

- **Dysphagia**
- Age over 55 with:
  - Weight loss
  - Upper abdominal pain
  - Treatment resistant dyspepsia/lasting > 4 weeks
  - Nausea/vomiting
  - Anaemia
  - Raised platelets

24hr oesophageal pH monitoring

- Gold standard for diagnosis
- Performed if endoscopy is negative with persistent symptoms

Management

- Test & treat H. pylori

Lifestyle

- Reduce tea/coffee/alcohol
- Weight loss
- Avoid smoking
- Smaller/lighter meals
- Avoid heavy meals before bed
- Stay upright after meals

PRN Acid Neutralisers

- Rennie/Gaviscon

PPIs

- Omeprazole/lansoprazole
  - 1-2 months followed by PRN low-dose prescription if responsive

H2RAs

- Alternative to PPIs

Surgery

- Laparoscopic fundoplication
- Newer options focusing on increasing LOS resting tone:
  - Radiofrequency induced hypertrophy
  - Magnetic bead band insertion

Barrett's Oesophagus

- Columnar metaplasia of lower oesophageal mucosa
- Short (< 3cm) or long (> 3cm)
- 50 - 100x (3-5% lifetime risk) risk of oesophageal adenocarcinoma
- Typically diagnosed on endoscopy for dyspepsia

Risk Factors

- **GORD**
- Male sex (7:1)
- Smoking
- Obesity

Management

- High-dose PPI (evidence not too great)
- Evidence for aspirin but not in the guidelines yet

Endoscopic Surveillance + Biopsies

- Every 3-5 years if metaplasia, but not dysplasia, is present

Endoscopic Intervention

- Offered if any grade of dysplasia is present
- Endoscopic mucosal resection/radiofrequency ablation

H. pylori

- Gram negative aerobic bacteria which lives in & damages gastric mucosa

Associations

- PUD (95% of duodenal ulcers, 75% of gastric ulcers)
- Gastric cancer
- B cell MALT lymphoma (H. pylori eradication causes regression in 80%)
- Atrophic gastritis

Testing

- Tested for in dyspepsia – Patient must not take PPI for 2 weeks before test/antibiotic for 4 weeks before test

Urea Breath Test

- Initial test & test of eradication

Stool Antigen Test

- Initial test only

Rapid Urease/CLO Test

- Performed on endoscopic biopsy

Eradication

- 2 antibiotics + PPI for 7 days
  - Amoxicillin + clarithromycin/metronidazole
  - Clarithromycin + metronidazole in penicillin allergy
- Bismuth/tetracycline/levofloxacin can be added in failed eradication

Peptic Ulcer Disease

- Ulceration of duodenal (more common) or gastric mucosa

Risk Factors

Loss of protective layer

- H. pylori (95% of duodenal ulcers, 75% of gastric ulcers)
- Steroids, NSAIDs, SSRIs, bisphosphonates

Increased acid

- Stress
- Alcohol
- Caffeine
- Smoking
- Spicy foods
- Zollinger-Ellison syndrome (gastrin-secreting tumour)

Presentation

- Epigastric discomfort/pain
  - Gastric ulcer pain **worsened** by eating
  - Duodenal ulcer pain **relieved** by eating
- Nausea & vomiting
- Iron deficiency anaemia
- Haematemesis/"coffee-ground" vomiting/melaena

Investigations

- Diagnosed on endoscopy
- Biopsy should be taken for CLO test & to differentiate from cancers which can appear similar

Management

H. pylori positive

- Eradication therapy

H. pylori negative

- PPI until ulcer is healed

Perforation

- Features of peritonitis
- Possible syncope

Investigation

- Erect CXR: air under diaphragm in 75%

Acute Bleeding

- Most common cause of upper GI bleed
- Can be life-threatening
  - Involvement of gastroduodenal artery
- Presents with haematemesis ± haemodynamic compromise

Management

- ABC as per any upper GI bleed
- IV PPI
- Endoscopic intervention 1st line
  - Fails in 10%, requires embolization or surgery

Oesophageal Cancer

Classification

	Adenocarcinoma	Squamous Cell
Epidemiology	Most common in developed world	Most common in developing world
Location	Lower third	Upper two thirds
Risk Factors	GORD Barrett's oesoph. Smoking Achalasia Obesity	Smoking Alcohol Achalasia Plummer-Vinson syndrome Nitrosamine rich diet

Features

- Dysphagia (most common presenting complaint)
  - Progressive
- Anorexia & weight loss
- Vomiting
- Odynophagia
- Hoarseness
- Melaena
- Cough

Investigations

Diagnosis

- Upper GI endoscopy is first line

Staging

- CT-TAP
- PET-CT if CT-TAP positive for overt metastatic disease
- Endoscopic ultrasound for localised disease if PET-CT is negative
- Staging laparotomy for peritoneal disease

Management

- Surgery (if operable) plus adjuvant chemotherapy
- Ivor-Lewis type oesophagectomy
  - Risk of anastomotic leak & mediastinitis

Gastric Cancer

- M:F 2:1, 50% > 75 years
- Increasing incidence of adenocarcinoma at the gastro-oesophageal junction in western world

Risk Factors

- H. pylori
- Pernicious anaemia
- Atrophic gastritis
- Smoking
- Blood group A
- Diet
  - Salt
  - Nitrosamines

Features

- Notoriously vague

Symptoms

- Abdominal pain
  - Non-specific
  - Epigastric
  - May present as dyspepsia
- Weight loss & anorexia
- Nausea & vomiting
- Dysphagia, particularly if in proximal stomach
- Melaena
- Overt upper GI bleeding in minority of patients

Signs

- Epigastric mass
- Hepatomegaly, jaundice, ascites
- Virchow's node
- Sister Mary Joseph node (periumbilical)

Investigations

Diagnosis

- Upper GI endoscopy with biopsy
  - Signet ring cells – higher count relates to worse prognosis

Staging

- CT-TAP for advanced disease
- Endoscopic ultrasound for local invasion
- Staging laparotomy/peritoneal washings for peritoneal disease

Management

- Surgery + adjuvant chemotherapy
  - Endoscopic mucosal resection
  - Partial gastrectomy
  - Total gastrectomy

Malabsorption

- Failure of the intestine to absorb adequate nutrients despite no deficiency in intake

Causes

Decreased Bile

- PBC
- Ileal resection
- Bile obstruction
- Cholestyramine

Pancreatic Insufficiency

- **Chronic pancreatitis**
- Pancreatic cancer
- Cystic fibrosis

Small Intestine Mucosa

- **Coeliac Disease**
- **Crohn's Disease**
- Whipple's Disease
- Radiation enteritis
- Tropical sprue
- Resection
- Brush border enzyme deficiencies (eg lactase)
- Drugs – metformin, neomycin, alcohol

Bacterial Overgrowth

- Spontaneous, common in elderly
- Jejunal diverticula, post-op blind loops

Infection

- Giardia
- Cryptosporidium
- Strongloides

Intestinal Hurrying

- Post-gastrectomy
- Post-vagotomy
- Gastrojejunostomy

Features

Symptoms

- Weight loss
- Fatigue
- Bloating & abdominal pain
- Diarrhoea
- Steatorrhoea

Signs

- Signs of anaemia (Fe, folate, B12)
- Bleeding (vit K)
- Oedema (protein)
- Metabolic bone disease (vit D)
- Neuropathy

Investigations

Bloods

- FBC, Ca, Fe, B12 & folate, INR, lipid profile, coeliac antibodies

Stool

- Sudan stain for fat globules
- Microscopy for infestation
- Elastase pancreatic insufficiency

Others

- Breath hydrogen analysis for overgrowth
- Endoscopy & small bowel biopsy

Coeliac Disease

- Autoimmune damage to small intestine mucosa leading to villous atrophy & malabsorption in response to gluten intake
- 95% HLA-DQ2 & 80% HLA-DQ8

Features

- Malabsorption
- Aphthous ulcers
- Angular stomatitis

Associated Conditions:

- Dermatitis herpetiformis
- Autoimmune thyroid disease
- T1DM
- Addison's disease
- IBS

Complications

- Anaemia
- Hyposplenism
- Osteoporosis
- Lactose intolerance
- Enteropathy-associated T cell lymphoma
- Subfertility

Investigations

- Screening for anyone with symptoms of malabsorption, associated disease, or first degree relative with coeliac disease
- Patients already on a gluten-free diet should reintroduce gluten for 6 weeks prior to testing

Antibodies

- Anti-TTG & anti-EMA
  - IgA antibodies so total IgA levels must be measured to avoid false negative in selective IgA deficiency

Endoscopy & Biospy

- Duodenal > jejunal biopsy
- Shows villous atrophy, crypt hyperplasia, intraepithelial & lamina propria lymphocytes

Management

- Gluten free diet is curative
- Relapse will occur if gluten is reintroduced

Nutritional Deficiencies

Nutrient	Function	Absorption Site	Deficiency Cause	Deficiency Syndrome
Vitamin A (Retinol)	Visual pigment Epithelial cell differentiation Anti-oxidant	Small intestine	Malnutrition	Night blindness **Xerophthalmia** • Common cause of blindness in tropics • Dry conjunctivae with oval/triangular Bitot's spots • Cloudy soft cornea
Vitamin B1 (Thiamine)	(As thiamine pyrophosphate) Co-factor in sugar & amino acid catabolism	Small intestine	Malnutrition Alcoholism	**Wernicke's Encephalopathy** • Ataxia, nystagmus, ophthalmoplegia **Korsakoff syndrome** • Amnesia & confabulation **Wet beriberi** • Dilated cardiomyopathy **Dry beriberi** • Peripheral neuropathy
Vitamin B2 (Riboflavin)	Precursor of cofactors for metabolism (including of other B vitamins)	Proximal small intestine	Malnutrition	Stomatitis, angular cheilitis
Vitamin B3 (Niacin)	Formation of NAD & NADP	Derived from tryptophan	Malnutrition Isoniazid **Hartnup's Disease** • Hereditary reduced tryptophan absorption **Carcinoid syndrome** • Increased tryptophan metabolism to serotonin	**Pellagra** • Diarrhoea • Dementia • Dermatitis • ± neuropathy, depression, insomnia, tremor, rigidity, ataxia, seizures
Vitamin B6 (Pyridoxine)	Formation of pyridoxal phosphate	Small intestine	Malnutrition Isoniazid	Polyneuropathy Sideroblastic anaemia
Vitamin B12 (Cobalamin)	Red cell development & nervous system maintenance	Terminal ileum bound to intrinsic factor secreted by gastric parietal cells	Pernicious anaemia Gastrectomy Vegan diet Malnutrition Metformin Terminal ileum disease (Crohn's disease, resection)	Megaloblastic anaemia Glossitis Neurological symptoms (dorsal column affected first) Neuropsychiatric symptoms (eg depression)
Folic Acid	(As THF) DNA & RNA synthesis	Jejunum	Phenytoic Methotrexate Pregnancy Alcohol excess	Megaloblastic anaemia Neural tube defects in pregnancy

Jaundice

- Yellowing of sclerae, skin & mucosa from bilirubin deposition, usually occurs around 60umol/L

History

- Alcohol use
- Blood transfusions, IV drug use, piercings & tattoos
- Sexual activity
- Travel, jaundiced contacts
- Family history, complete drug history
- Pale urine in **unconjugated** hyperbilirubinaemia as it is water insoluble and does not enter urine
- Dark urine & pale stools in **conjugated** hyperbilirubinaemia as it is water soluble and enters urine
- Intractable pruritis in severe **conjugated** hyperbilirubinaemia

Examination

- Stigmata of liver disease
- Hepatic encephalopathy
- Lymphadenopathy, HSM, gall bladder, ascites

Investigations

Urine

- Bilirubin absent in pre-hepatic, urobilinogen absent in post-hepatic

Bloods

- FBC, film, reticulocyte count, DCT
- U+E, LFTs, total protein, albumin
- Paracetamol levels
- Cultures, hepatitis serology, Paul-Bunnell

Imaging

- Liver & bile ducts ultrasound
- ERCP/MRCP if bile ducts dilated
- CT/MRI if abdominal malignancy suspected

Biopsy

- If other investigations normal

Classification

By Site

- Pre-hepatic
- Hepatocellular
- Post-hepatic

By Bilirubin Type

- Unconjugated or unconjugated hyperbilirubinaemia

Causes

- Bold are common causes in a previously stable cirrhotic patient

<table>
<tr><th></th><th>Unconjugated</th><th colspan="3">Conjugated</th></tr>
<tr><td>Pre-hepatic</td><td>Overproduction
• Haemolytic anaemia
• Ineffective erythropoiesis
• Upper GI bleed
Impaired Conjugation
• Gilbert Syndrome
• Crigler-Najjar Syndrome</td><td colspan="3"></td></tr>
<tr><td>Hepatocellular</td><td>Impaired Hepatic Uptake
• Drugs:
– Paracetamol
– Rifampicin
• Ischaemic hepatitis</td><td colspan="2">Hepatocellular Damage
• Viruses
– Hepatitis, CMV, EBV
• Drugs
• Cirrhosis
• Liver Ca/metastases/ abscess
• Sepsis
• Autoimmune hepatitis
• A1AT deficiency
• Wilson’s disease
• Budd-Chiari syndrome
• Leptospirosis
• Syphilis</td><td>Failure to Excrete Bilirubin
• Dubin-Johnson Syndrome
• Rotor Syndrome</td></tr>
<tr><td>Post-hepatic (Cholestasis)</td><td></td><td colspan="2">PBC
PSC
Drugs
Common bile duct stones
Pancreatic cancer</td><td>CBD compression (porta hepatitis lymph nodes)
Cholangiocarcinoma
Choledochal cysts</td></tr>
</table>

Drug-Induced Jaundice

Haemolysis	Antimalarials		
Hepatitis	Paracetamol overdose Valproate	Halothane MAOIs	Statins Isoniazid, rifampicin, pyrazinamide
Cholestasis	Flucloxacillin (up to weeks after use) Co-amoxiclav Fusidic acid	Nitrofurantoin Steroids (anabolic, COCP) Prochlorperazine	Chlorpromazine Sulfonylureas

Ascites

- Abnormal accumulation of fluid in the peritoneal cavity
- Classified according to the serum ascitic albumin gradient (SAAG)

Causes

SAAG < 1.1	SAAG > 1.1 (Portal Hypertension)
Hypoalbuminaemia • Nephrotic syndrome • Severe malnutrition (Kwashiorkor) **Malignancy** • Peritoneal carcinomatosis **Infection** • Tuberculous peritonitis **Others** • Pancreatitis • Bowel obstruction • Biliary ascites • Postoperative lymphatic leak • Serositis in connective tissue disease	**Hepatic** • Cirrhosis • Acute liver failure • Liver metastases **Cardiac** • Right heart failure • Constrictive pericarditis **Others** • Budd-Chiari syndrome • Portal vein thrombosis • Veno-occlusive disease • Myxoedema

Management

General

- Reduce dietary sodium
- Fluid restrict if sodium is < 125mmol/L

Medical

- Aldosterone antagonist (spironolactone)
  - Loop diuretic may also be added
- Prophylactic antibiotics to prevent SBP

Interventional

- Drainage (therapeutic abdominal paracentesis)
  - If tense ascites
  - Requires albumin cover
  - Risk of paracentesis induced circulatory dysfunction in large drainage
    - Ascites recurrence
    - Hepatorenal syndrome
    - Dilutional hyponatraemia
    - High mortality
- TIPS

Spontaneous Bacterial Peritonitis

- Typically seen in ascites secondary to liver cirrhosis

Features

- Ascites
- Abdominal pain
- Fever

Microbiology

- Most commonly E. coli

Diagnosis

- Ascitic tap neutrophil count > 250/uL

Management

- IV antibiotics (ceftriaxone)

Prophylaxis

- Oral ciprofloxacin
- Indications:
  - Previous episode of SBP
  - Ascitic fluid protein < 15g/L + hepatorenal syndrome/Child-Pugh score of 9

Liver Failure

- Occurs most often on a background of cirrhosis
- Can occur acutely:
  - Hyperacute: < 7 days
  - Acute: 8-21 days
  - Subacute: 4-26 weeks

Causes

Infectious

- **Viral hepatitis (particularly B, C, & CMV)**
- Yellow fever
- Leptospirosis

Drugs

- **Paracetamol overdose**
- Halothane/isoniazid/methotrexate/salicylates

Vascular

- Budd-Chiari syndrome
- Right ventricular failure

Autoimmune/Inflammatory

- Autoimmune hepatitis/PBC/PSC

Neoplastic

- Hepatocellular/metastatic

Genetic

- A1AT/Wilson's/hemochromatosis

Others

- Alcohol
- NAFLD/Acute fatty liver of pregnancy

Presentation

- Jaundice
- Oedema & ascites
- Bruising & coagulopathy
- Encephalopathy
- Renal failure (hepatorenal syndrome)
- Fetor hepaticus (pear drops)
- Signs of chronic disease

Diagnosis

- Elevated transaminases
- Encephalopathy
- INR > 1.5

Investigations

Bloods

- FBC, U+E, LFTs, clotting, glucose
- Cause: paracetamol levels, α1AT, caeruloplasmin, antibodies
- ABG

Micro

- Viral antibodies (hep, CMV, EBV)
- HIV
- Blood & urine culture

Imaging

- US & doppler
- CT/MRI if malignancy suspected

Management

- Supportive care in ICU
- Nutrition & thiamine supplements
- Treat underlying cause

Complications

- **Bleeding:** vitamin K, platelets, FFP, blood
- **Hypoglycaemia:** regular BGs & IV glucose if < 2mM
- **Cerebral oedema:** mannitol
- **Encephalopathy:** correct electrolytes, lactulose, rifamixin
- **Seizures:** lorazepam
- **Renal failure:** haemodialysis/haemofiltration

Poor Prognostic Factors

- Grade III/IV encephalopathy
- Age > 40
- Albumin < 30
- Raised INR
- Drug-induced

Transplant

King College Hospital criteria in acute liver failure

Paracetamol	Non-paracetamol
pH < 7.3 24h post-ingestion	PT > 100s
OR all of: • PT > 100s • Cr > 300 • Grade III/IV encephalopathy	Or 3/5 of: • Drug induced • Age < 10/> 40 • > 1wk from jaundice to encephalopathy • PT > 50s • Bilirubin > 300

Hepatic Encephalopathy

Grade

I: Irritability
II: Confusion, inappropriate behaviour, slurred speech
III: Incoherent, restless, hepatic flap
IV: Coma

Management

- Correct electrolytes
- Be wary of raised ICP
- Lactulose
- Rifaximin

Hepatorenal Syndrome

- Renal failure resulting from severe hepatic failure
- Diagnosis of exclusion

Classification

- **Type 1:** Rapidly progressive, survival < 2 weeks
- **Type 2:** Steady deterioration, survival ~ 6 months

Management

- Transplant is definitive treatment
- Dialysis, IV albumin, terlipressin can help

Liver Cirrhosis

Causes

Common

- Alcoholic liver disease
- Non-alcoholic fatty liver disease
- Hepatitis B/C

Rarer

- **Drugs**
  - Halothane/isoniazid/methotrexate/salicylates
- **Vascular**
  - Budd-Chiari syndrome
  - Right ventricular failure
- **Autoimmune/Inflammatory**
  - Autoimmune hepatitis/PBC/PSC
- **Neoplastic**
  - Hepatocellular/metastatic
- **Genetic**
  - A1AT/Wilson's/hemochromatosis

Presentation

Hands

- Clubbing
- Leuconychia
- Terry's nails
- Palmar erythema
- Dupuytren's

Face

- Pallor – anaemia of chronic disease
- Parotid enlargement in alcoholism

Trunk

- Spider naevi (> 5)
- Gynaecomastia

Abdomen

- Ascites
- Hepatosplenomegaly
  - Liver may be small in late disease
- Caput medusae

Complications

- Decompensation – liver failure
- Spontaneous bacterial peritonitis
- Portal hypertension
  - Splenomegaly
  - Ascites
  - Varices
  - Encephalopathy
- Hepatocellular carcinoma

Child-Pugh Grading

- Predicts risk of bleeding, mortality & need for transplant
- Score > 8: significant variceal bleeding risk

	1	2	3
Albumin	> 35	28-35	< 28
Bilirubin	< 34	34-50	> 50
INR	< 1.7	1.7-2.3	> 2.3
Ascites	None	Mild	Moderate-severe
Encephalopathy	None	Mild	Moderate-severe

Investigations

Bloods

- LFTs may be normal!
- Raised INR, reduced albumin (decreased synthetic function)
- Hyponatraemia due to fluid retention in severe disease
- U+Es raised in hepatorenal syndrome
- Tests to find cause

Cause (Non-Invasive Liver Screen)

- **Alcohol:** ↑MCV, ↑GGT
- **NASH:** hyperlipidaemia, ↑ glucose
- **Infection:** Hep, CMV, EBV serology
- **Genetic:** Ferritin, α1AT, caeruloplasmin (↓ in Wilson's)
- **Autoimmune:** Abs (there is lots of cross-over)
  - **AIH:** SMA, SLA, LKM, ANA
  - **PBC:** AMA
  - **PSC:** ANCA, ANA
  - **Ig:** ↑IgG – AIH, ↑IgM – PBC
- **Cancer:** α-fetoprotein

Transient Elastography (FibroScan)

- Largely replaced liver biopsy for diagnosis
- Retesting every 2 years for those at risk:
  - Hepatitis C
  - Heavy alcohol drinkers (men drinking > 50 units or women drinking > 35 units per week)
  - Diagnosed alcoholic liver disease
  - Non-alcoholic fatty liver disease and evidence of fibrosis on the ELF blood test
  - Chronic hepatitis B (**yearly**)

Liver Biopsy

- Definitive diagnosis

Monitoring

Ultrasound

- Features in cirrhosis:
  - Nodular liver surface
  - Corkscrew arteries
  - Large portal vein with reduced flow
  - Ascites
  - Splenomegaly
- Screening for HCC (every 6 months) with αFP

Endoscopy

- Check for varices in new diagnoses of cirrhosis & every 3 years

MELD Score

- Completed every 6 months
- Gives percentage estimated 3 month mortality based on bilirubin, creatinine INR, sodium & dialysis
- Guides transplant decision

General Management

- High protein, low sodium diet
- Ethanol abstinence
- Cholestyramine for pruritis
- Consideration of a liver transplant
- Managing complications

Managing Complications of Cirrhosis

Ascites

- Low sodium diet
- Anti-aldosterone diuretics (spironolactone)
- Paracentesis (ascitic tap or ascitic drain)
- Prophylactic antibiotics against spontaneous bacterial peritonitis (ciprofloxacin or norfloxacin) in patients with less than 15g/litre of protein in the ascitic fluid
- Consider TIPSS procedure in refractory ascites
- Consider transplantation in refractory ascites

Spontaneous Bacterial Peritonitis

- 10% of patients with ascites secondary to cirrhosis
- 10-20% mortality

Features

- May be asymptomatic
- Fever
- Abdominal pain
- Hypotension
- Ileus

Management

- IV ceftriaxone

Stable Varices

- Propranolol reduces portal hypertension by acting as a non-selective beta blocker
- Elastic band ligation of varices
- Injection of sclerosant (less effective than band ligation)
- TIPSS if all else fails

Hepatic Encephalopathy

Grade

I: Irritability
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Management

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Management

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Non-Alcoholic Fatty Liver Disease

- Most common cause of cirrhosis in the developed world
- Affects 3-4% of population
- Spectrum of disease:
  1. Steatosis: fat in the liver
  2. Steatohepatitis: fat & inflammation in the liver
  3. Fibrosis
  4. Cirrhosis

Causes/Associated Factors

- Metabolic syndrome
  - Obesity
  - T2DM
  - Hyperlipidaemia
  - Hypertension
- Jejunoileal bypass
- Sudden weight loss/starvation
- Smoking

Features

- Usually asymptomatic
- Hepatomegaly

Investigations

- ALT > AST

Ultrasound

- Typically diagnosed incidentally on ultrasound – no role for screening
- No indication of severity

ELF Test

- 1st line to assess severity
- Algorithm based on measurement of:
  - Hyaluronic acid
  - Procollagen III
  - Tissue inhibitor of metalloproteinase I

< 7.7	None-mild
7.7 – 9.8	Moderate
> 9.8	Severe

NAFLD Fibrosis Score

- If ELF test is unavailable
- Algorithm of age, BMI, liver enzymes, platelets, albumin, diabetes
- No indication of severity

Transient Elastography (Fibroscan)

- Ultrasound assessment of fibrosis

Management

- Lifestyle changes – weight loss, exercise, stopping smoking, control of diabetes, blood pressure & cholesterol
- Role of vitamin E & pioglitazone in specialist centres

Alcohol & Alcohol Dependence

Alcohol Complications

- Alcoholic liver disease, cirrhosis, HCC
- Other cancers – oesophageal, oral, breast
- Dependence & withdrawal
- Wernicke – Korsakoff syndrome
- Pancreatitis
- Alcoholic cardiomyopathy
- Alcoholic ketoacidosis

Recommended Consumption

- No more than 14 units/week for men & women, spread evenly over 3+ days
- Any level is associated with increased risk of cancer of breast, mouth and throat

Screening

CAGE Questionnaire

- **C**ut down?
  - Ever thought you should cut down?
- **A**nnoyed?
  - Do you get annoyed by people commenting on your drinking?
- **G**uilty?
  - Do you ever feel guilty about drinking?
- **E**ye opener?
  - Do you ever drink in the morning to help hangover/nerves?

Alcohol Use Disorders Identification Test (AUDIT)

- 10 multiple choice questions
- Score of 8+ indicates harmful use

Alcoholic Liver Disease

Stages

1. Alcoholic fatty liver
   - Reverses within 2 weeks with no drinking
2. Alcoholic hepatitis
   - Develops over longer period ± binge drinking
   - Can be reversible with permanent abstinence
3. Cirrhosis
   - Irreversible
   - Abstinence can prevent progression
   - Continued drinking has very poor prognosis

Specific Investigation Results

- Gamma-GT characteristically elevated
- AST:ALT normally > 2
  - > 3 suggestive of acute alcoholic hepatitis

Management (General)

- Stop drinking alcohol permanently (consider detox regime)
- Nutrition support with vitamins (particular thiamine) & a high protein diet
- Treat complications of cirrhosis
- Referral for transplant in severe disease – requires 3 months abstinence before referral

Management (Acute Alcoholic Hepatitis)

- Thiamine
- Glucocorticoids improve short term outcomes
  - Determined with Maddrey's discriminatory function (DF) using PT & bilirubin

Wernicke – Korsakoff Syndrome

- Wernicke's encephalopathy untreated can lead to Korsakoff's syndrome

Wernicke's Encephalopathy

- Petechial haemorrhages in variety of brain structures including mamillary bodies & ventricle walls due to thiamine deficiency
- **Features**
  - Nystagmus
  - Ophthalmoplegia
  - Ataxia
  - Confusion & altered GCS
  - Peripheral sensory neuropathy
- **Investigations**
  - Decreased red cell transketolase
  - MRI
- **Management**
  - Urgent thiamine replacement (IV Pabrinex followed by oral thiamine)

Korsakoff Syndrome

- Retro- & anterograde amnesia
- Confabulation
- Often occurs as a later addition to Wernicke's encephalopathy
- Often untreatable & irreversible

Alcoholic Ketoacidosis

- Long term malnourishment plus and alcohol binge leads to ketone metabolism

Features

- Anion gap metabolic acidosis
- Ketonaemia
- Normal or low glucose

Management

- IV fluids & thiamine

Alcohol Withdrawal

- Caused by imbalance of NMDA > GABA neurotransmission

Features

- 6-12 hours: Tremor, sweating, tachycardia, anxiety
- 36 hours: peak incidence of seizures

Delirium Tremens

- Peak incidence 48-72 hours
- Coarse tremor, confusion, delusions, auditory & visual hallucinations, fever, tachycardia

Management

- Long acting BZD: chlordiazepoxide/diazepam
- Lorazepam may be preferred in hepatic failure
- Continued for 5-7 days
- IV Pabrinex followed by oral thiamine

Detox Drugs

Disulfiram

- Inhibition of acetaldehyde causes severe hangover – like reaction to any ingested ethanol
- Contraindicated in IHD/psychosis

Acamprosate

- Reduces craving by weak NMDA antagonism

Viral Hepatitis

Type	Virology	Spread	Incubation	Chronic	Features		Complications	Investigations	Management
A	RNA picovirus	• Faecal – oral: seafood, endemic in Africa & South America • Vaccine available	2-4wks	No	**Prodromal Phase** • Especially A & B • Flu-like symptoms, malaise, arthralgia, nausea **Icteric Phase** • Acute jaundice (A > B > C)	• Prodromal phase • Icteric phase – jaundice in 99% • No progression to chronic phase	• Fulminant hepatitis *rarely*	• AST & ALT rise 22-40d after infection & normalise after 5-20wks • IgM from day 25, indicates recent infection • IgG detectable for life	• Supportive • Interferon alpha for fulminant hepatitis
B	DNA virus (hepadnavirus)	• Blood & bodily fluids, vertical • Endemic in Asia, Africa, Mediterranean • IV drug users, haemophiliacs, MSM, children of mothers with HBV are at risk • Vaccine available	6-20wks	Yes, 5-10%	• Hepatitis – Abdo pain – Hepatomegaly – Cholestasis **Chronic Phase** • B & C • Progression to cirrhosis & risk of HCC	• Prodromal phase • Icteric phase – jaundice in 75% • 5-10% progression to chronic phase, 5% develop cirrhosis	• Fulminant liver failure in 1% • HCC **Extrahepatic:** • Glomerulonephritis • Polyarteritis nodosa • Cryoglobinaemia	**HBsAg** • Acute disease if present for 1-6 months • Chronic disease if present for > 6 months **Anti-HBs** • Immunity (vaccine or past infection), negative in chronic disease **Anti-HBc** • Past (IgG) or current (IgM) infection **HBeAg** • Marker of viral replication & infectivity	• Avoid alcohol, immunise sexual contacts, notify public health **Chronic:** • Pegylated interferon-α • Antivirals – Tenofovir – Entecavir – Telbivudine
C	RNA flavivirus	• Blood & bodily fluids, vertical • IV drug users & haemophiliacs at risk • Higher risk of vertical transmission with coexistent HIV • No vaccine available	6-9wks	Yes, 80%		• Prodromal/icteric phase in only 30%, silent infection in 70%	• 55-85% develop chronic infection **Chronic Infection** • Cirrhosis in 5-20% • HCC • Cryoglobinaemia • Glomerulonephritis • Porphyria cutanea tarda • Arthralgia, arthritis, Sjogren's	• Raised LFTs • Anti-HCV antibodies confirm infection or past exposure • HCV PVR confirms ongoing infection • Test for viral genotype (1-6)	• Avoid alcohol **Chronic:** • Antivirals depending on genotype – Daclatasvir – Sofosbivir – Simeprivir – Ribavarin • 95% cure rate
D	Incomplete RNA virus	• Blood & bodily fluids • Requires HBV					• Increased risk of fulminant hepatitis/cirrhosis	• HDV PCR, only if HBsAg+	• Interferon-α (limited evidence) • Transplant
E	RNA hepevirus	• Faecal-oral	3-8wks	No		• As HAV	• 20% mortality in pregnancy	• Serology	• No specific Rx

Primary Biliary Cholangitis	Primary Sclerosing Cholangitis
Epidemiology	
• 90-95% females, most commonly 30-65	• M > F 2:1, 30-50 years
Pathophysiology	
• T-cell mediated destruction of intralobular (intrahepatic) bile ducts resulting in cholestasis, cirrhosis & liver failure	• Inflammation, fibrosis & stricturing of large intra & extrahepatic bile ducts
Presentation	
• 50-60% asymptomatic & diagnosed incidentally **Symptoms** • Fatigue • Pruritis • RUQ discomfort • Memory/concentration impairment • Malabsorption/steatorrhoea **Signs** • Jaundice • Hyperpigmentation (melanin, cause unknown) • Xanthoma/xanthelasma • Hepatosplenomegaly • Late signs of cirrhosis	• 50-60% asymptomatic & diagnosed incidentally **Symptoms** • Severe pruritis • Fevers & chills • Night sweats • RUQ discomfort **Signs** • Jaundice • Hepatosplenomegaly • Excoriations
Associations	
• Sjogren's syndrome in 40-65% – Usually precedes symptoms of PBC • Thyroid disease in 10-15% – Most commonly Hashimoto's • Inflammatory arthritis – Classic RA in 5-10% – Arthritis of PBC (non-deforming seronegative arthritis of 1 or more peripheral joints) in 10% • Systemic sclerosis	• **Ulcerative Colitis** – 90% of patients with PSC have UC – < 5% of patients with UC have PSC • Crohn's (much rarer) • AIH • HIV
Investigations	
• **LFTs:** Cholestatic picture • **Antibodies:** AMA positive in 98%, sp100, gp120 • Raised IgM • Raised cholesterol • Potentially raised TSH • **US:** no extrahepatic bile duct pathology • **Liver Biopsy:** nonsuppurative destructive cholangitis & destruction of interlobular bile ducts + granulomas **Diagnostic Criteria** • No extrahepatic biliary obstruction + no liver comorbidity + 2 of: – ALP 1.5x ULN – AMA or other Ab +ve – Histologic evidence of PBC	• **LFTs:** cholestatic picture, transaminases usually < 300 • **Antibodies:** pANCA (30-80%), antinuclear, anti-smooth muscle • Raised IgM • May have raised IgG4 – **IgG4-associated cholangitis may be a distinct disease** • **US:** extrahepatic bile duct pathology may or may not be visible • **MRCP/ERCP:** alternating strictures & dilatations giving a beaded appearance (**diagnostic**)
Management	
• 1st line: ursedeoxycholic acid – Improves symptoms & progression – Obeticholic acid if inadequate response – LFT monitoring every 3-6 months • Cholestyramine for pruritis • Fat-soluble vitamin supplementation (ADEK) • **Transplantation** based on MELD score	• Symptomatic treatment (ursedeoxycholic acid, cholestyramine (pruritis), codeine (diarrhoea) • Fat-soluble vitamin supplementation (ADEK) • **Endoscopic** dilatation of dominant strictures • **Transplantation** indicated if MELD score > 15 • **Screening** for cholangiocarcinoma (US + Ca19-9) and CRC (colonoscopy)
Complications	
• Cirrhosis • Hepatocellular carcinoma • Osteomalacia & osteoporosis	• Cholangiocarcinoma • Colorectal cancer

Autoimmune Hepatitis

- Inflammatory hepatitis with unknown cause
- Predominantly affects young & middle aged women

Associations

- Autoimmune disorders
- Hypergammaglobinaemia
- HLA-B8 & DR3

Classification

Type I (80%)

- ANA (80%) or SMA (10%) antibodies
- Affects adults & children
- 25% have cirrhosis at presentation

Type II

- LKM1 antibodies
- Affects children only

Type III

- Soluble liver-kidney antigen
- Affects adults in middle-age

Features

- Acute hepatitis in 40%
  - Fever
  - Jaundice
- Other autoimmune disease
- Amenorrhoea
- Signs of chronic liver disease

Investigations

- Raised LFTs, IgG
- Anaemia, leukocytopenia, thrombocytopenia (hypersplenism)
- Autoantibodies as above
- Liver biopsy:
  - Mononuclear infiltration of portal & periportal areas
  - Piecemeal necrosis
  - Fibrosis
- MRCP to rule out PSC

Diagnosis

- Hypergammaglobinaemia, autoantibodies & histology in the absence of other diagnosis (ie virology negative)

Management

Steroids

- Prednisolone 30mg/day reducing by 5mg each month to 5-10mg maintenance dose
- Sometimes stopped after 2 years, relapse in 50-85%

Azathioprine

- Steroid sparing option

Transplant

- Decompensated cirrhosis or disease refractory to medical treatment
- Recurrence my occur

Prognosis

- Remission achievable in 80% within 3 years
- Steroid side effects have significant impact
- 10YSR reduced (94% to 62%) by presence of cirrhosis at presentation

Wilson's Disease

- Inherited disorder of copper excretion leading to deposition in liver & CNS (basal ganglia)

Genetics

- AR defect in ATP7B copper binding protein gene on chromosome 13
- Impaired copper incorporation into caeruloplasmin in liver & excretion in bile
- 3/100,000

Features

Hepatic

- Seen in children
- Jaundice, hepatitis, cirrhosis

CNS

- Basal ganglia degeneration
- Speech, behavioural & psychiatric problems often seen first
- Asterixis
- Chorea
- Parkinsonism
- Dementia

Others

- Kayser-Fleischer rings
  - Green/brown rings on iris periphery
  - Caused by copper accumulation in Descemet membrane
  - 50% of patients with isolated liver disease & 90% of patients with CNS involvement
- Renal tubular acidosis & Fanconi syndrome
- Haemolysis
- Blue nails

Investigations

Bloods

- Reduced serum caeruloplasmin
- Reduced serum total copper
- Increased serum free copper
- Raised LFTs
- Molecular genetic testing to confirm diagnosis

Urine

- Increased 24 hour copper excretion

Slit-lamp exam

- For Kayser-Fleischer rings

Liver Biopsy

- Increased hepatic copper, hepatitis, cirrhosis

MRI

- Degeneration: basal ganglia, fronto-temporal, cerebellar, brainstem

Management

- Avoid high copper foods (liver, chocolate, nuts)
- Check water sources
- Lifelong penicillamine (copper chelator)
  - Monitor FBC & urinary copper & protein
  - Alternative: trientene hydrochloride
- Liver transplant if indicated
- Screen siblings

Hereditary Haemochromatosis

- Inherited disorder of iron absorption & metabolism leading to accumulation

Genetics

- AR disorder of HFE gene on chromosome 6
  - 60-90% C282Y
  - 1-3% H63D
- Common in Celtic ethnicity (1/10 carriers, 1/200 affected)

Features

Early Symptoms

- Fatigue
- Erectile dysfunction
- Arthralgia

Skin

- Bronze pigmentation (reversible)

Hepatic

- Stigmata of chronic liver disease
- Hepatomegaly
- Cirrhosis

Cardiac

- Dilated cardiomyopathy (reversible)

Endocrine

- Diabetes mellitus
- Hypogonadotropic hypogonadism

MSK

- Arthritis (especially of hands, stressed joints before rested joints)

Investigations

- Iron study profile 1st line in general population, genetic testing 1st line in relatives of affected patients

Iron Study Profile

- Transferrin saturation > 55% (men)/50% (women)
- Raised ferritin & iron
- Low TIBC

Imaging

- Chondrocalcinosis
- Liver & cardiac MRI shows iron loading

Diagnostic Tests

- Genetic screening for C282Y & H63D
- Liver biopsy: Pearl's stain quantifies iron loading & shows disease severity

Management

Venesection

- 0.5-2 units/1-2wks until ferritin is < 50mcg/L
- 1 unit/2-3 months maintenance
- Monitoring goals
  - Haematocrit < 50%
  - Ferritin < 100mcg/L
  - Transferrin saturation < 40%

Desferrioxamine

- Used if venesection is not meeting targets

Prognosis

- Venesection returns life expectancy to normal if not diabetic/cirrhotic

α1-Antitrypsin Deficiency

- Inherited lack of α1-antitrypsin, a serine protease inhibitor (serinopathy) which inhibits the action of elastase

Pathophysiology

- AR/co-dominant inheritance, gene located on chromosome 14
- Excess elastase activity in the lung leads to emphysema & bronchiectasis
- Defective protein build up in the liver causes hepatitis & cirrhosis
- Alleles classified by electrophoretic ability
  - M: normal
  - S: slow
  - Z: slow
- PiMM: normal
- PiMZ: heterozygous
  - Carrier
  - Potential increased risk of emphysema in smokers
- PiSS: 50% normal levels
- PiZZ: 10% normal levels
  - Most with symptoms are PiZZ

Features

Liver

- Cholestasis in children
- Cirrhosis & HCC in adults (> 50)

Lungs

- Panacinar emphysema most notable in lower lobes
- Occurs ~ 30 years

Investigations

α1-AT Levels

- Usually < 75% of LLN/< 11umol/L
- Acute phase reactant, so may be normal in inflammation
  - Causes some cases to be labelled as cryptogenic cirrhosis

Spirometry

- Obstructive pattern

Liver Biopsy

- PAS positive

Genotyping

- Definitive diagnosis

Management

- Smoking cessation
- Symptomatic management

α1-AT

- IV & inhaled replacement have mixed evidence

Transplantation

- For end-stage lung or liver disease

Monitoring

- For cirrhosis/HCC

Liver Tumours

- 90% are metastases (most commonly from breast, lung, GI tract)

Primary Liver Malignancies

- **Hepatocellular Carcinoma (75%)**
- **Cholangiocarcinoma**
- Hepatoblastoma
- Sarcoma
- Lymphoma
- Carcinoid (more commonly secondary)

Benign Tumours

- Haemangioma
  - Seen incidentally, need no treatment
  - Avoid biopsy (bleeding)
- Adenoma
  - Caused by anabolic steroids, COCP, pregnancy
  - Treat if symptomatic or > 5cm

General Features

Symptoms

- Benign tumours typically asymptomatic
- Fever
- Malaise
- Weight loss
- RUQ pain
- Jaundice is late (except with cholangiocarcinoma)
- Peritonitis with tumour rupture

Signs

- Hepatomegaly
  - Smooth or hard & irregular due to cirrhosis
- Signs of liver decompensation
- Liver bruit

Investigations

- Deranged LFTs & clotting

Type	Causes	Specific Features	Diagnosis	Management	Prognosis
Hepatocellular Carcinoma	HBV (most common worldwide) Other causes of cirrhosis • HCV • Alcohol • AIH • NAFLD Aflatoxins Chlonorchis sinensis Anabolic steroids	Fatigue Anorexia Weight loss RUQ pain Jaunduce Ascites Haemobilia Pre-existing cirrhosis in 80%	CT/MRI/both α-fetoprotein elevated (used as a marker for treatment) Biospy should be avoided to prevent tumour seeding Testes should be examined in males (raised aFP)	Tumour resection Liver transplant Percutaneous ablation Embolisation Palliative chemoradiotherapy (not very sensitive)	Overall 5YSR 15%
Cholangiocarcinoma	Primary sclerosing cholangitis Chlonorchis Biliary cysts HBV HCV Diabetes mellitus N-nitroso toxins	80% arise from extrahepatic bile ducts Fever Abdominal pain Ascites Malaise	Cholestatic LFTs (bilirubin, ALP) CA19-9, CEA, CA-125 Imaging: CT/MRI & MRCP	Surgical resection offers best chance of cure but is contraindicated in 70% • 76% recur Stenting of obstructed biliary tree improves QOL Liver transplant rarely possible	Overall 5YSR 5-10% Median survival ~5 months

Chronic Pancreatitis

- Chronic inflammatory condition affecting both endocrine & exocrine functions of the pancreas

Causes

- Alcohol excess (80%)
- Smoking
- Autoimmune
- Genetic
  - Cystic fibrisis
  - Haemochromatosis
- Ductal obstruction
  - Tumours
  - Stones
  - Pancreas divisum
  - Annular pancreas

Features

Pain

- Epigastric pain radiating to back
- Typically worse 15-30 minutes after meals
- Relieved by sitting forward, hot water bottles to epigastrium/back

Exocrine

- Steatorrhoea, bloating & weight loss secondary to pancreatic insufficiency developing 5-25 years after onset of pain

Endocrine

- Diabetes mellitus in most patients ~20 years after onset of pain

Investigations

Imaging

- CT most sensitive (80%) & specific (85%) for pancreatic calcifications

Functional

- Faecal elastase

Management

Diet

- No alcohol
- Low fat diet
- Fat soluble vitamin supplements

Medical

- Analgesia
- Pancreatic enzyme supplements if exocrine function impaired
- Insulin if endocrine function impaired

Pancreatic Cancer

Pathology

Type

- 80% ductal adenocarcinoma

Site

- 60% head of pancreas
- 25% body
- 15% tail

Mutations

- KRAS (95%)
- BRCA2

Risk Factors

- Increasing age > 70
- Smoking
- Diabetes
- Chronic pancreatitis
  - Alcohol not an independent risk factor
- HNPCC
- Multiple endocrine neoplasis

Features

- Painless progressive jaundice is classic of carcinoma of pancreatic head
  - Pale stools, dark urine
  - Cholestatic LFTs
- Non-specific epigastric pain radiating to back in carcinoma of pancreatic body/tail
- Anorexia
- Weight loss
- Loss of endocrine/exocrine function
- Thrombophlebitis migrans (Trousseau's sign)
- Ascites/epigastric mass/hepatosplenomegaly/ lymphadenopathy

Investigations

Bloods

- Cholestatic jaundice
- CA19-9 (non-specific)

Imaging

- Ultrasound/CT (high resolution CT is best) shows pancreatic mass, duct dilatation ("double duct sign"), hepatic metastases

Management

- < 20% suitable for surgery at time of diagnosis
  - Whipple's pancreaticoduodenectomy
    - Side effects: dumping syndrome, PUD
  - Laparoscopic excision for tail lesions
- Adjuvant chemotherapy
- ERCP with biliary stenting as part of palliation

Irritable Bowel Syndrome

- Functional bowel disorder affecting 20% of adults
- More commonly women & young adults

Features

- Diarrhoea
- Constipation
- Fluctuating bowel habit
- Abdominal pain
- Bloating
- Worsened by eating
- Improved by opening bowels

Diagnosis

- Requires:

Typical Features

- Abdominal pain/discomfort lasting at least 6 months which is either:
  - Relieved by opening bowels
  - Associated with changed bowel habit
- Plus at least 2 of:
  - Abnormal passage (straining/urgency/incomplete evacuation)
  - Bloating
  - Symptoms worsened by eating
  - Passage of mucous

Exclusion of Other Pathology

- FBC, CRP, ESR normal
- Faecal calprotectin negative
- Anti-TTG antibodies negative
- Cancer not suspected

Management

Lifestyle & General

- Regular meals that aren't rushed
- Adequate fluid intake
- Limit processed foods, caffeine, alcohol, & fibre intake
- Oats & linseeds for wind & bloating
- Low FODMAP diet with dietician input
- Probiotic supplements

1st Line Medical

- Loperamide for diarrhoea
- Laxatives (avoiding lactulose) for constipation
- Anti-spasmodics (hyoscine) for pain

2nd Line

- Low dose TCA (amitriptyline 5-10mg nocte)

3rd Line

- SSRIs

Inflammatory Bowel Disease

Crohn's Disease	Ulcerative Colitis
Associations	
• 3-4x more common in smokers	• 3-4x more common in non-smokers • 5% have PSC • Ankylosing spondylitis/sacroileitis
Intestinal Features	
• Diarrhoea – typically non-bloody • Abdominal pain • Perianal disease – skin tags/ulcers • Abdominal mass (typically in RIF)	• Diarrhoea – typically bloody, frequency relates to severity • Abdominal pain commonly in LLQ • Tenesmus
Extra-intestinal Features	
• Episcleritis • Weight loss • Arthritis – Polyarticular symmetric – Pauciarticular asymmetric • Aphthous ulcers • Erythema nodosum • Pyoderma gangrenosum • Clubbing • Osteoporosis • Uveitis	
Complications	
• Abscess formation, fistulae, small bowel obstruction • Toxic megacolon	• Toxic megacolon • Colorectal cancer
Location	
• Anywhere from mouth to anus • Most common site is terminal ileum	• Continuous inflammation from rectum proximally – maximum extension is to ileocaecal junction
Diagnosis	
• Faecal calprotectin is a very sensitive marker • CRP & ESR correlate with disease activity • Anaemia common • Endoscopy + biopsy is gold standard • Rule out infective cause (stool culture + C. diff toxin assay	
• B12 deficiency common **Endoscopy (ileocolonoscopy/capsule endoscopy)** • Skip lesions • Deep ulceration	**Endoscopy (sigmoidoscopy -> ileocolonoscopy)** • Red mucosa which bleeds easily • Pseudopolyps • Loss of haustrations
Histology	
• Inflammation in full thickness of mucosa • Goblet cells • Granulomas	• Inflammation doesn't extend beyond submucosa • Crypt abscesses • Depletion of goblet cells
Radiology	
Small Bowel Enema • Strictures – Kantor's string sign • Rose thorn ulcers • Fistulae **MRI** • Assessment of pelvic disease, stricutres, fistulas, etc	**Barium Enema** • Loss of haustrations • Superficial ulceration & pseudopolyps • Lead pipe colon in long standing disease
Assessment of Severity	
Mild-Moderate • Systemically well **Severe** • Haemodynamic compromise/systemically unwell	**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

Management of IBD

Crohn's Disease

Inducing Remission

Mild-Moderate Disease

- Oral/IV/topical steroids first line
- Budesonide ileal release may be used in mild-moderate disease/if steroids are contraindicated
- Aminosalicylates not recommended
- Budesonide not suitable for severe flares

Moderate-Severe Disease

- Systemic corticosteroids first line
- Early use of biologics considered in severe disease or high risk features:
  - Stricturing/penetrating disease
  - Perianal disease
  - Proximal jejunal/extensive small bowel disease
  - Age < 40
  - Need for steroids to control index flare
- Biologics:
  - Anti-TNF (infliximab, adalimumab)
  - Vedolizumab
  - Ustekinumab

Maintaining Remission

Immunomodulation

- Azathioprine/mercaptopurine 1st line
- Methotrexate second line
- Do not use steroids/budesonide

Biologic Therapy

- If not responding to optimum immunomodulation
- Infliximab + thiopurine combination therapy is more effective

After surgery

- Azathioprine with up to 3 months protective metronidazole
- Do not start biologics but biologics already in use can be continued

Surgery

- Required in 50-80%

Disease limited to distal ileum

- Surgery may be considered early as an alternative to medical treatment (ileocecal resection)
- Surgery not advised in colonic disease due to high recurrence

Fistulae

- Requires control of sepsis and nutrition as well as definitive surgical management

Strictures

- Consider balloon dilatation of strictures that are short, straight and accessible by colonoscopy

Ulcerative Colitis

Inducing Remission

Proctitis

- Rectal mesasalazine
- If no remission in 4wks, add oral aminosalicylate
- If no remission still, topical/oral steroid

Proctosigmoiditis/left-sided UC

- Rectal aminosalicylate
- If no remission in 4wks, add high-dose oral aminosalicylate ± switch rectal treatment to steroid
- If no remission still, stop topicals and give oral steroids and high-dose oral aminosalicylates

Extensive disease

- Rectal aminosalicylate and high-dose oral aminosalicylate
- If no remission in 4wks, stop topicals and give oral steroids and high-dose oral aminosalicylates

Acute Severe Disease

- Hospital admission
- Urgent FBC, CRP, U+E, LFT, stool culture, C. diff toxin assay, flexible sigmoidoscopy (less risk of perforation)

Steroids

- High dose corticosteroids first line
- 60mg methylpred/day or hydrocortisone 100mg/6hrs

Rescue Therapy

- If inadequate response after 3 days
- IV infliximab/ciclosporin

Maintaining Remission

Following mild-moderate flare

- Proctitis/proctosigmoiditis
  - Rectal aminosalicylate alone
  - An oral aminosalicylate plus a rectal aminosalicylate
  - An oral aminosalicylate by itself: this may not be as effective as the other two options
- Left-sided and extensive ulcerative colitis
  - Low maintenance dose of an oral aminosalicylate

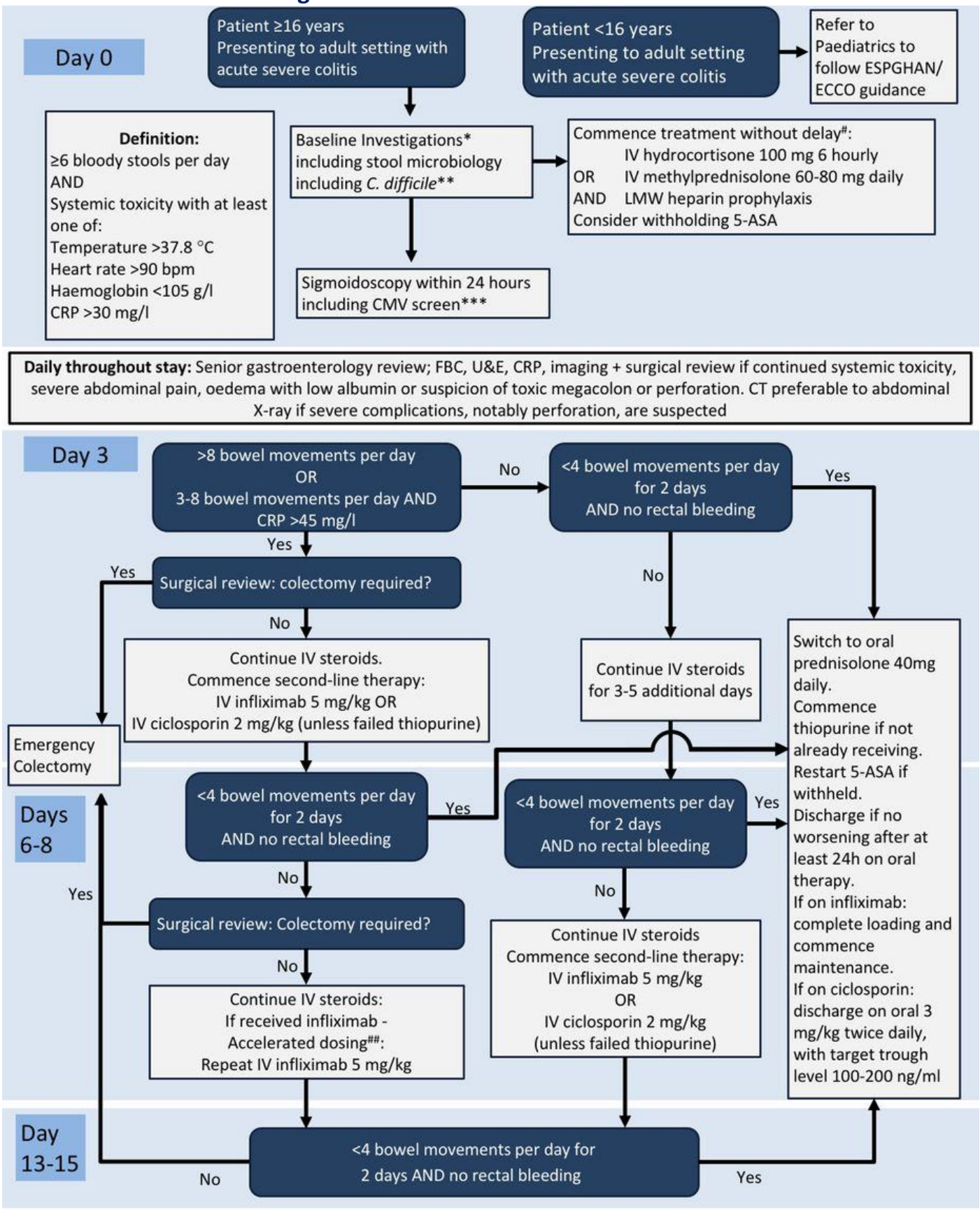
Severe flare or ≥ 2 exacerbations/year

- Oral azathioprine/mercaptopurine/biologic

Surgery

- Required in ~20%
- Subtotal colectomy + end ileostomy in:
  - Failed medical management or fulminant colitis with toxic dilatation
  - Chronic disease not responding to optimum medical management
- Can be a permanent stoma or later formation of a J pouch
  - Pouchitis may occur, increased risk if coexistent PSC

Management of Acute Severe Ulcerative Colitis



Additional Notes

* Baseline investigations: full blood count, CRP, urea & electrolytes, liver function tests, magnesium; stool infection screen & *Clostridium difficile*; radiology (abdominal X-ray or CT); screening tests for second-line therapy including hepatitis B and C virus, HIV, and VZV (if no history of chicken pox, shingles or varicella vaccination), Screening for tuberculosis with clinical risk stratification stratification, chest X-ray and interferon-gamma release assay

** If *C. difficile* diagnosed, treat with oral vancomycin 500 mg 6 hourly for 10 days and continue steroids

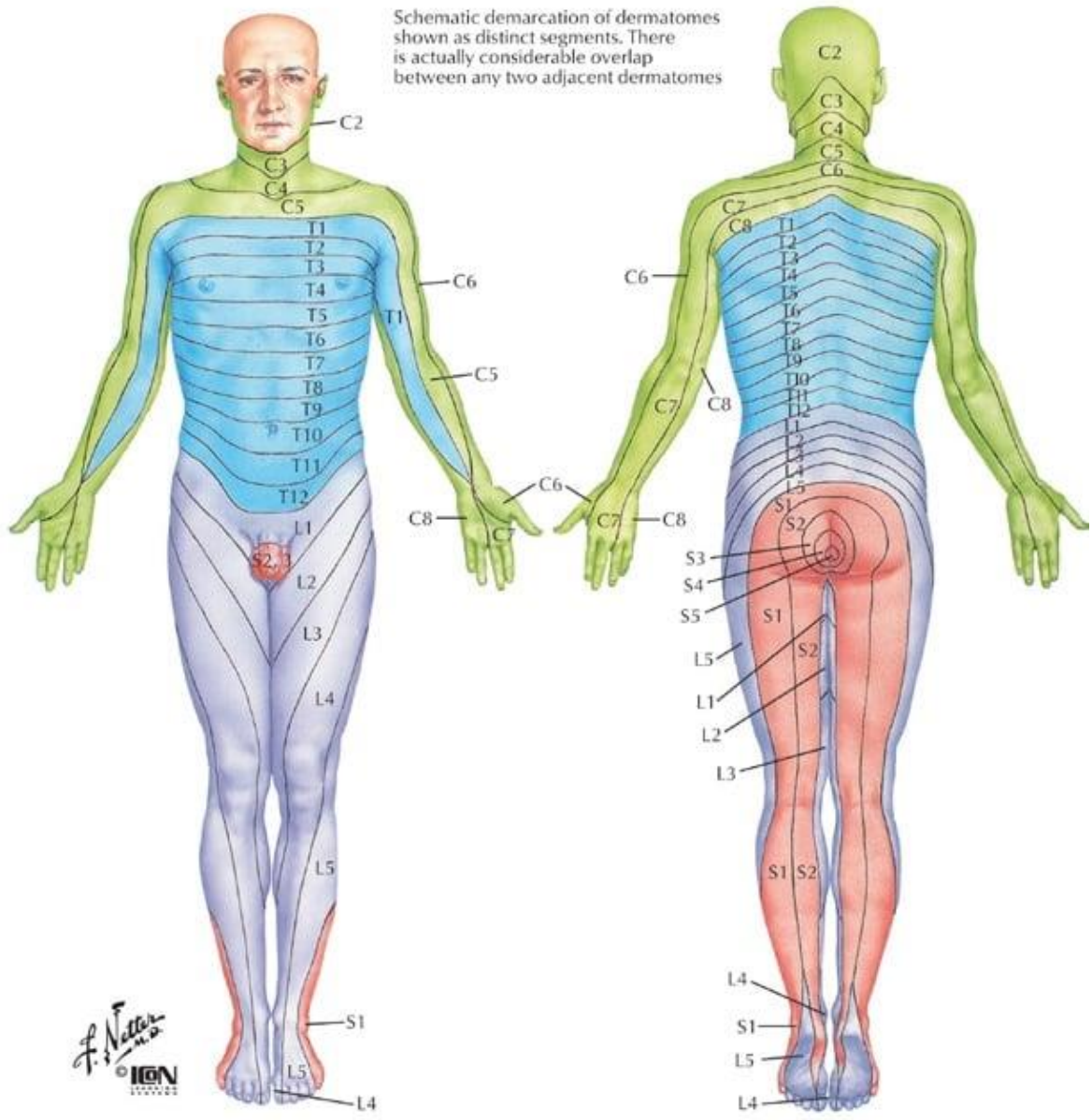
*** Flexible sigmoidoscopy with biopsies for urgent histology including specific assessment for CMV. Deep ulceration is associated with poor outcome. If CMV colitis diagnosed, treat with IV ganciclovir 5 mg/kg 12-hourly for 3-5 days then oral valganciclovir 900 mg 12-hourly for 2-3 weeks. Take advice from virology regarding immunosuppressive therapies

Do not delay steroids while awaiting stool culture results

Accelerated dosing is beneficial, but the optimal dosing regimen is unclear

Neurology

Dermatomes



Landmarks

C2	Cap of skull	**T10**	Umbilicus
C3-4	Clavicles	**L1**	Inguinal ligament
C5	Ventral axial line of arm	**L2-3**	Anterior & inner thigh
C6	Thumb	**L4**	Knee caps
C7	Middle finger	**L5**	Big toe & dorsum of foot
C8	Little finger	**S1**	Lateral foot & small toe
T1	Medial arm	**S2-3**	Perineum
T4	Nipples		

Myotomes

Upper Limb			**Lower Limb**		
Shoulder	Abduction	C5	**Hip**	Flexion	L1-2
	Adduction	C5-7		Adduction	L2-3
Elbow	Flexion	C5-6		Extension	L5-S1
	Extension	C7	**Knee**	Flexion	L5-S1
Wrist	Flexion	C7-8		Extension	L3-L4
	Extension	C7	**Ankle**	Dorsiflexion	L4
Fingers	Flexion	C8		Eversion	L5-S1
	Extension	C7		Plantarflexion	S1-S2
	Abduction	T1	**Toe**	Extension	L5

Neurological Lesion Patterns

UMN Lesions	LMN Lesions
• From motor cortex to anterior horn cells • Pyramidal weakness – Extensor weakness in upper limb, flexor weakness in lower limb • No wasting • Spasticity (tone & clonus) in opposite direction to pyramidal weakness • Hyperreflexia • Up-going plantars	• From anterior horn cells to peripheral nerves • Wasting • Fasciculation • Flaccidity • Hyporeflexia • Down-going planters

Cortical Lesions

- Localised problem (such as all movements in hand/foot)
- UMN signs in arm/leg
- Potential sensory loss isolated to one modality
  - E.g. two-point discrimination or proprioception

Internal Capsule/Corticospinal Lesions

- Contralateral hemiparesis with pyramidal distribution
- With contralateral CN palsy: brainstem lesion on side of palsy

Cord Lesions

- Quadriparesis/paraparesis
- LMN signs at level of lesion & UMN signs below lesion
- Loss of sensation below level – hallmark of spinal lesions

Peripheral Neuropathies

- Mostly distal weakness & sensory loss
- Single nerve: mononeuropathy
- Multiple nerves: mononeuritis multiplex

Muscular Lesions

- Symmetrical loss
- Reflexes lost later
- No sensory loss
- Fatiguability

Specific Neurological Patterns

Cerebellar Syndrome

Features

- Dysdiadokinesis
- Dysmetria (past-pointing)
- Ataxia
- Nystagmus (direction of damaged hemisphere)
- Intention tremor
- Slurred/staccato speech
- Hypotonia

Causes

- Paraneoplastic (lung Ca)
- Alcohol
- Stroke
- MS
- Neoplastic (cerebellar haemangioma)
- Hypothyroidism
- Friedrich's ataxia/ataxic telangiectasia
- Drugs: phenytoin, led poisoning

Arteries

Anterior Cerebral Artery

- Contralateral motor & sensory loss in legs > arms
- Face spared
- Abulia (pathological laziness)

Middle Cerebral Artery

- Contralateral motor & sensory loss in arms > legs
- Contralateral homonymous hemianopia
- Aphasia (dominant) or neglect/apraxia (non-dominant)

Posterior Cerebral Artery

- Contralateral homonymous hemianopia with macular sparing
- Visual agnosia

Weber's Syndrome

- Branches of posterior cerebral artery to midbrain
- Ipsilateral CNIII palsy
- Contralateral weakness of upper & lower limbs

Lateral Pontine Syndrome

- Anterior inferior cerebellar artery
- Ipsilateral facial paralysis & deafness
- Contralateral pain & temperature loss
- Ataxia & nystagmus

Lateral Medullary/Wallenberg's Syndrome

- Anterior inferior cerebellar artery or one vertebral artery
- Dysphagia
- Ataxia
- Nystagmus
- Vertigo
- Ipsilateral facial numbness & corneal reflex loss
- Contralateral pain loss
- Horner's syndrome

Locked-in Syndrome

- Basilar artery/central pontine myelinolysis
- Complete paralysis except for extra-ocular muscles

Beck's Syndrome

- Anterior spinal artery
- Bilateral spinal paresis
- Bilateral pain & temperature loss

Headache

History

Timing/onset	Acute Onset	• Subarachnoid haemorrhage • Meningitis • Encephalitis • Post-coital headache
	Subacute onset	• Venous sinus thrombosis • Sinusitis • Intracranial hypotension • Temporal arteritis
	Recurrent	• Tension type headache • Cluster headache • Migraine • Trigeminal neuralgia • Mollaret's recurrent meningitis • Medication overuse headache
	Chronic	• Idiopathic intracranial hypertension • Paget's disease • Psychological
Character	Tight	• Tension type headache
	Throbbing/ pulsatile	• Migraine
Associated Features	Fever/ Meningism	• Meningitis • Encephalitis
	Aura	• Migraine
	Vomiting	• Raised ICP
	Jaw Claudication	• Temporal arteritis
	Eye injection/ lacrimation	• Cluster headache
	Eye pain/ blurred vision	• Acute closed angle glaucoma
Other	Travel	• Tropical illness eg Malaria
	Chronic analgesic use	• Medication overuse headache
	Head trauma	• Traumatic headache • Subdural/extradural haemorrhage

Red Flags

- Immunocompromise
- Age > 20
- History of malignancy
- Vomiting with no obvious cause
- Worsening headache with fever
- Hyperacute onset – "thunderclap"
- New onset neurological/cognitive deficit
- Personality changes
- Reduces GCS
- Recent head trauma
- Triggered by Valsalva/cough/sneeze etc
- Orthostatic headache
- Substantial change in characteristics of headache
- Symptoms suggestive of temporal arteritis/acute closed angle glaucoma
- Pregnancy

Primary Headache Disorders

Tension Headache

- Episodic primary headache
- Most common cause of headache

Features

- Bilateral "tight band" or pressure sensation
- Not associated with nausea/vomiting
- Not aggravated by exercise/physical activity
- May be related to stress & may co-exist with migraine

Chronic Tension-Type Headache

- Tension headache occurring on 15 or more days/month

Management

- Aspirin/paracetamol/NSAIDs

Prophylaxis

- Acupuncture
- Amitriptyline widely used but not recommended

Cluster Headache

- More common in men & smokers, may be exacerbated by alcohol

Features

- Typically occurs 1-2 times per day lasting 15mins-2hrs
- Clusters last 4-12 weeks
- Extreme sharp, stabbing pain around one eye (almost always the same side)
- Accompanied by scleral injection, lacrimation, lid swelling, nasal stuffiness & sometimes miosis/proptosis

Management

- 100% oxygen via NRB
- Subcutaneous triptan

Prophylaxis

- Verapamil
- Tapering dose of prednisolone

Trigeminal Autonomic Cephalgia

- Encompasses cluster headache, paroxysmal hemicrania and short lived unilateral neuralgiform headache with conjunctival injection & tearing (SUNCT)

Trigeminal Neuralgia

- Paroxysms of severe, sharp pain typically affecting unilateral mandibular/maxillary branches of trigeminal nerve distribution
- Lasts seconds at a time & usually remits for variable periods

Triggers

- Shaving
- Washing/touching face
- Brushing teeth
- Talking
- Smoking

Investigations

- MRI for possible secondary causes (compression, MS, herpes zoster, chronic meningeal inflammation)

Management

- Carbamazepine 1st line
- Surgery/radiation may be necessary (to peripheral nerve, trigeminal ganglion, or nerve root)

Migraine

- Affects 15%, females:males 3:1

Types

- Migraine with aura
- Migraine without aura
- Silent migraine (aura with no pain)
- Hemiplegic migraine

Stages

1. Prodromal phase
   - 2-3 days before migraine
   - Yawning/fatigue/mood changes
2. Aura
3. Headache
4. Resolution
5. Postdromal/recovery

Aura

- Occurs in 1/3 of patients with migraine

Visual

- Most common, progressive visual disturbance lasting 5-60 minutes:
  - Transient hemianopic disturbance
  - Spreading scintillating scotoma

Somatosensory

- Parasthesiae spreading from fingers to face

Motor

- Dysarthria & ataxia (basilar migraine)
- Ophthalmoplegia

Speech

- Dysphasia
- Paraphasia

Headache

- Severe, unilateral, throbbing headache
- Associated with nausea, photophobia, & phonophobia
- Can last up to 72 hours
- May be relieved by vomiting/sleeping

Triggers

- Chocolate
- Cheese
- Red wine
- Citrus
- Tiredness/stress
- Alcohol (& hangovers)
- COCP
- Hunger/dehydration
- Sex
- Menstruation
- Bright lights

Diagnosis

- Clinical, International Headache Society diagnostic criteria

A	At least 5 attacks fulfilling B-E
B	Headache lasts 4-72 hours untreated or successfully treated
C	Headache has at least 2 of the following features: **1.** Unilateral location **2.** Pulsating quality **3.** Moderate – severe intensity **4.** Aggravated by/causing avoidance of physical activity
D	Headache is accompanied by at least 1 of the following: **1.** Nausea/vomiting **2.** Photophobia & phonophobia
E	No other disorder is indicated clinically/any other potential causes are ruled out

Management

Acute

- Oral triptan + NSAID/paracetamol
- Nasal triptan preferred in children aged 12-17
- Non-oral metoclopramide or prochlorperazine can be used if the above fails/is not tolerated

Prophylaxis

- Offered if patients are experiencing 2 or more attacks per month
- Effective in 60%
- Propranolol or topiramate first line
  - Propranolol preferred in women of reproductive age
- Acupuncture (up to 10 sessions over 5-8 weeks)
- Riboflavin
- Frovatriptan/zolmitriptan as “mini-prophylaxis” in predictable menstrual migraine

Blackouts

Causes

Reflex Syncope (most common)

- Vasovagal
- Situational
- Carotid sinus reflex syncope

Orthostatic Syncope

- Primary autonomic failure (Parkinson's, Lewy body dementia)
- Secondary autonomic failure (diabetic neuropathy, amyloidosis, uraemia)
- Drug induced (diuretics, vasodilators, alcohol)
- Volume depletion (haemorrhage, diarrhoea)

Cardiac Syncope

- Arrhythmias (Stokes-Adams attacks)
- Structural (valvular, MI, HOCM)
- PE

CNS

- Epilepsy
- Drop attacks
- Arterial
  - Vertebrobasilar insufficiency (migraine, TIA, CVA, subclavian steal)

Others

- Hypoglycaemia
- Anxiety (hyperventilation)
- Factitious

Assessment

History

- Before, during, after
- Onset & general course
- Family history

Exam

- Cardiovascular with lying & standing blood pressure
- Neurological

Investigations

- ECG (± 24hrs)
- FBC, U+E, glucose
- Tilt table test
- EEG

	Trigger	Before	During	After	Investigations
Vasovagal/ situational	Standing/heat/fatigue/ stress/specific phobias	Nausea, pallor, sweating, tunnel vision, tinnitus	Pale, grey, clammy Clonic jerks/ incontinence can occur No tongue biting	Rapid recovery, no post-ictal phase	Tilt table testing
Carotid Sinus	Head turning, shaving				Carotid sinus massage
Orthostatic	Standing up from sitting or prolonged standing				
Cardiac	Exertion, drugs, none	Palpitations, chest pain, dyspnoea	Pallor, slow/ absent pulse, clonic jerks can occur		24 hours ECG
Arterial	Arm elevation, migraine	As for vagal ± brainstem symptoms			MRA, duplex of vertebrobasilar circulation
Epilepsy	As per epilepsy page	Aura	Tongue biting, incontinence, stiffness & jerking, open eyes, cyanosis	Headache, confusion, sleep, Todd's paresis	EEG
Drop Attacks	No trigger	No warning	Sudden weakness of the legs results in fall Common in elderly women	Rapid recovery, no post-ictal phase	

Stroke Introduction

- Rapid onset focal neurological deficit due to vascular lesion which lasts for more than 24 hours or leads to death

Pathogenesis

- Ischaemic in 85%
- Haemorrhagic in 15%

Risk Factors/Causes

Haemorrhagic

- Hypertension
- Aneurysms
- AVMs
- Anticoagulation
- Trauma

Atheromatous

- Hypertension
- Smoking
- Diabetes
- Hyperlipidaemia
- Family history
- PVD/IHD
- Previous history
- Polycythaemia
- COCP
- Black/Asian ethnicity

Cardiac Causes (30%)

- Atrial fibrillation
- Cardioversion
- Prosthetic valves
- Acute MI
- Paradoxical systemic emboli
- Cardiac surgery
- Infective endocarditis (vegetations)

Rare Causes/Causes In Young Patients

Vascular

- Vasculitis
- Venous sinus thrombosis
- Carotid/vertebral artery dissection
- Migraine induced stroke

Haematological

- Genetic/acquired hypercoagulable states, antiphospholipid syndrome, sickle cell disease, myeloproliferative disorders

Genetic

- Marfan's syndrome, neurofibromatosis

Infectious

- HIV, neurosyphilis, TB, neurocystercosis

Other

- Watershed stroke in hypotension

Differentials

- Head injury
- Hypoglycaemia
- Intracranial haemorrhage/tumours/abscess
- Hemiplegic migraine
- Todd's paresis
- Drug overdose
- Wernicke's/hepatic encephalopathy
- Encephalitis

Transient Ischaemic Attack

- Transient (lasting < 24 hours) focal neurological deficit caused by ischaemia without infarction
- Often precede full strokes – crescendo TIAs refer 2 or more within a week and are highly indicative of an imminent stroke

Causes

- As for atheromatous/cardiac stroke
- Carotid atherothromboembolism is the most common cause

Features

- Acute focal neurology
  - Weakness
  - Sensory loss
  - Aphasia
  - Brainstem signs
  - Amaurosis fugax
- Signs of cause
  - Carotid bruit
  - Valvular murmurs

Investigations

- FBC, U+E, ESR, glucose, lipids
- ECG & echo
- CXR
- Carotid dopplers ± angiography

Management

- Aspirin 300mg unless already on antiplatelet dose of aspirin or has coagulopathy/is on an anticoagulant
- Urgent imaging if patient has coagulopathy/is on an anticoagulant
- Stroke secondary prevention
- Anticoagulation if there is a cardiac source for emboli
- Carotid endarterectomy if there is > 70% stenosis

Stroke Presentation & Acute Management

Bamford Classification

- Clinical classification of stroke based on assessment of the following features:

1. Unilateral hemiparesis and/or hemisensory loss of face, arm, & leg
2. Homonymous hemianopia
3. High function loss (such as aphasia)

Total Anterior Circulation Infarct (15%)

- Middle & anterior cerebral arteries
- 3 of the above features

Partial Anterior Circulation Infarct (25%)

- Smaller branches of anterior circulation
- 2 of the above features

Lacunar Infarct (25%)

- Perforating arteries of basal ganglia, internal capsule, thalamus & pons
- Lack of higher cortical dysfunction, homonymous hemianopia, drowsiness, or brainstem signs
- **Pure motor:** Unilateral weakness of face/arm/leg/all 3
- **Pure sensory:** Unilateral numbness of face/arm/leg/all 3
- **Sensorimotor:** Both of the above
- **Ataxic Hemiparesis**

Posterior Circulation Infarct (25%)

- Vertebrobasilar arteries
- Any of:
  - Cerebellar/brainstem syndromes
  - Loss of consciousness
  - Isolated homonymous hemianopia

Other/Brainstem Syndromes

Corticospinal tracts	Hemi/quadriparesis
Oculomotor system	Conjugate gaze palsy
Sympathetic fibres	Horner's syndrome
CN7 nucleus	Facial weakness
CN8 nucleus	Nystagmus & vertigo
CN9&10 nucleus	Dysphagia & dysarthria
Reticular activating system	Reduced consciousness

Weber's Syndrome

- Branches of posterior cerebral artery to midbrain
- Ipsilateral CNIII palsy
- Contralateral weakness of upper & lower limbs

Lateral Pontine Syndrome

- Anterior inferior cerebellar artery
- Ipsilateral facial paralysis & deafness
- Contralateral pain & temperature loss
- Ataxia & nystagmus

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- Anterior inferior cerebellar artery or one vertebral artery
- Dysphagia
- Ataxia
- Nystagmus
- Vertigo
- Ipsilateral facial numbness & corneal reflex loss
- Contralateral pain loss
- Horner's syndrome

Locked-in Syndrome

- Basilar artery stroke/central pontine myelinolysis
- Complete paralysis except for extra-ocular muscles

Resus

- Assess & protect airway
- Maintain homeostasis: glucose, hydration, oxygen saturation & temperature within normal limits
- Avoid lowering blood pressure acutely unless there is hypertensive encephalopathy
- NBM until swallow screen is performed

Assessment

- Time of onset/time patient was last seen healthy is vital for deciding treatment

Rosier Score

- Score of > 0 indicates stroke is likely

LOC/syncope	-1
Seizure activity	-1
Asymmetric facial weakness	+1
Asymmetric arm weakness	+1
Asymmetric leg weakness	+1
Speech disturbance	+1
Visual field disturbance	+1

NIHSS

- Focused neuro exam proforma giving score of 0-30 assessing likelihood & severity of stroke

Imaging

- CT brain (stroke code) ASAP within 1 hour

Thrombolysis (Alteplase)

- Ischaemic stroke < 4.5 hours duration, NIHSS ≥ 3
- Repeat CT in 24 hours (5% risk of haemorrhagic transformation) & start aspirin if clear

Contraindications

Absolute	Relative
Active bleeding	Concurrent anticoagulation (INR > 1.7)
Previous ICH	Coagulopathy
Seizure at stroke onset	Active haemorrhagic diabetic retinopathy
Intracranial neoplasm	Suspected intracardiac thrombosis
Suspected SAH	Major surgery/trauma in previous 2 weeks
Recent stroke/brain injury/GI bleed/LP	
Oesophageal varices	
Pregnancy	
Uncontrolled HTN > 185/110	

Thrombectomy

- Significant stroke (NIHSS ≥ 6)
- Within 6 hours if:
  - Occlusion of proximal anterior circulation on CTA/MRA
- Within 24 hours if:
  - Occlusion of proximal anterior OR posterior circulation on CTA/MRA with potentially salvageable brain tissue as per imaging
- Concurrent thrombolysis if indicated

Other

- Aspirin 300mg if NIHSS < 3/other options unsuitable
- Permissive hypotension (<160), coagulopathy correction & neurosurgery input if haemorrhagic stroke

Stroke Ongoing Management & Prevention

Inpatient Management

- Admission to dedicated stroke unit

Hydration & Blood Pressure Management

- Oral hydration preferred if swallow is safe
- Anti-hypertensives should only be used following ischaemic stroke if there is one of:
  - Hypertensive encephalopathy
  - Hypertensive nephropathy
  - Hypertensive cardiac failure/myocardial infarction
  - Aortic dissection
  - Pre-eclampsia/eclampsia

Glycaemic Control

- Required especially in diabetic or NBM patients
- 4-11mmol/L recommended

Feeding

- Swallow assessment within 24 hours if possible, NBM until deemed safe
- Nasogastric tube if swallow is unsafe/PEG tube if nasogastric tube is not tolerated

Disability & Rehab

- Assessment of function with Barthel index
- Rehab in specialist centre if there are disabilities

Investigating Cause

Hypertension

- Look for nephropathy/retinopathy/cardiomegaly

Cardiac Emboli

- 24 hour ECG
- Echo (transoesophageal preferable over transthoracic

Carotid Stenosis

- Doppler ± CT/MR angiogram
- Carotid endarterectomy offered to those with > 70% stenosis & not significantly disabled

Metabolic

- Glucose & lipids

Vasculitis

- ESR & ANCA

Prothrombotic State

- Thrombophilia screen
- FBC

Primary Prevention

- Manage hypertension, hyperlipidaemia, diabetes, smoking, etc
- Anticoagulation in atrial fibrillation
- Carotid endarterectomy if stenosis > 70%

Secondary Prevention

- Statin started after 48 hours
- Clopidogrel (or aspirin) + MR dipyridamole
- Carotid endarterectomy if stenosis > 70% & patient is not severely disabled

Subarachnoid Haemorrhage

- Bleeding into the subarachnoid space
- Traumatic is more common than spontaneous

Spontaneous Causes

- Berry aneurysms (85%)
  - Associated with adult polycystic kidney disease, Ehler's Danlos syndrome & aortic coarctation
- AV malformation
- Pituitary apoplexy
- Arterial dissection
- Mycotic aneurysms
- Perimesencaphalic (idiopathic venous bleed)

Features

- Headache
  - Hyperacute onset & severe (thunderclap)
  - Typically occipital
  - May occur during strenuous activity
- Sentinel headache
  - Minor preceding headache due to leaking aneurysm
  - Occurs in 6%
- Nausea & vomiting
- Meningism
- Seizures
- Coma
- ECG changes

Diagnosis

Urgent CT Brain

- Acute (< 24hrs) bleeding hyperdense on CT
- Seen in basal cisterns, sulci, & ventricles in severe bleeds
- Negative in 7% of cases

Lumbar Puncture

- Confirms diagnosis if CT is negative & LP is not contraindicated
- Must be 12 hours after onset to allow breakdown of RBCs
- Xanthochromia distinguishes from traumatic tap

Management

- Urgent referral to neurosurgery
- Monitor pupils, BP, & CNS, repeat CT if deteriorating

Maintain Perfusion

- Hypervolaemia, but SBP < 160
- Bed rest
- Nimodipine for 21 days to prevent vasospasm

Treat Cause

- Aneurysms treated with endovascular coiling or open clipping

Complications

- Death
- Rebleed (10%, most common in first 24 hours, 70% mortality)
- Vasospasm (delayed ischaemia, 7-14 days)
- Hydrocephalus (treated with external or VP shunt)
- Hyponatraemia (SIADH)
- Seizures

Subdural Haematoma

- Rupture of bridging veins from brain to venous sinuses leading to blood accumulation & mass effect
- Mostly due to trauma and may present acutely or chronically (up to 9 months later)

Risk Factors

- Elderly patients
  - Fragile bridging veins
- Falls
  - Epilepsy
  - Alcoholics
  - Elderly
- Anticoagulation

Features

- Fluctuating/decreasing level of consciousness
- Insidious neurological deficits
  - Intellectual/physical slowing
  - Sleepiness
  - Headache
  - Personality change
  - Unsteadiness
- Signs of raised ICP
- Seizures

Differentials

- Stroke
- Dementia
- CNS mass

Diagnosis

CT Brain

- Blood appears hyperdense (acute) or hypodense (chronic) to brain tissue
- Crescentic haematoma overlying hemisphere, not limited by suture lines
- Midline shift may be present

Management

- Urgent reversal of anticoagulation/coagulopathy

Surgery

- Indicated if haematoma is > 10mm or there is a midline shift > 5mm, or if clinical picture is severe
- Craniotomy/burr hole with clot evacuation

Extradural Haematoma

- Collection of blood between dura and skull typically due to rupture of middle meningeal artery in temporal artery where it cross the thin bone of the pterion
- Almost always causes by trauma, typically low impact
- Suspect in any skull fracture/patient with lucid interval

Presentation

- Lucid interval
  - Patient loses/has reduced consciousness, regains it, and loses it again
  - May last hours to days
- Increasingly severe headache
- Vomiting
- Confusion
- Seizures
- Hemiparesis with UMN signs
- Ipsilateral fixed pupil dilatation
  - Late sign caused by herniation of temporal lobe uncus which compresses CNIII
- Brainstem compression
  - Irregular (Cheyne-Stokes) breathing
  - Bradycardia & hypertension (Cushing's reflex)
  - Bilateral limb weakness
  - Coma
  - Respiratory arrest & death

Differentials

- Epilepsy
- Carotid artery dissection
- Carbon monoxide poisoning

Diagnosis

CT Brain

- Biconvex (lentiform) collection limited by suture lines

Management

- Urgent reversal of anticoagulation/coagulopathy
- Stabilisation, intubation if necessary
- Reduction of ICP (eg IV mannitol)

Surgery

- Urgent clot evacuation & ligation of bleeding vessel

Head Trauma

- Early neurosurgical involvement

Resus

ABC

- Protect airway & immobilise cervical spine if potentially injured
- High flow 100% oxygen if SpO2 < 92% (anaesthetic intubation if necessary)
- Stop blood loss, support circulation

Disability

- Treat seizures as per status epilepticus
- Assess GCS, ICU care & intubation if ≤ 8
- Assess for anterograde/retrograde amnesia (correlated to injury severity)

Exposure/Examination

- Rapid survey for injuries & neurological examination
- **Pupils:**

Size	Light Reaction	Interpretation
Unilaterally dilated	Sluggish or fixed	3rd nerve compression secondary to tentorial herniation
Bilaterally dilated	Sluggish or fixed	Poor CNS perfusion Bilateral 3rd nerve palsy
Unilaterally dilated or equal	Cross reactive (Marcus - Gunn)	Optic nerve injury
Bilaterally constricted	May be difficult to assess	Opiates Pontine lesions Metabolic encephalopathy
Unilaterally constricted	Preserved	Sympathetic pathway disruption

Initial Investigations

- U+Es, glucose, FBC, blood alcohol, toxicology screen, clotting
- ABG

Further Assessment

- Brief history of trauma, lucid interval, alcohol
- Evaluate cuts to face/scalp for step deformity/obvious skull fractures
- Check for CSF leak/blood in middle ear
- Palpate neck posteriorly for tenderness/deformity

Radiology

CT Head < 1 Hour:

- GCS < 13 initially/< 15 at 2 hours
- Suspected skull fracture
- Post-trauma seizure
- Focal neurological deficit
- > 1 episode of vomiting

CT Head < 8 Hours:

- Any LOC/amnesia + one of:
  - Age > 65
  - Bleeding/clotting disorders
  - High velocity injury
  - Retrograde amnesia > 30 minutes

Coma

- Unrousable unconsciousness

Causes

Metabolic	Neurological
• Drugs/poisoning • Hypoglycaemia/DKA/ HONK • Hypoxia/CO2 narcosis • Sepsis • Hypothermia • Myxoedema, Addisonian crisis • Hepatic/uraemic encephalopathy • Wernicke's encephalopathy	• Trauma • Infection • Tumour (1° or 2°) • Vascular (stroke, intracranial haemorrhage, hypertensive encephalopathy) • Epilepsy (non-convulsive status/post-ictal)

Resus

ABC

- Protect airway & immobilise cervical spine if potentially injured
- High flow 100% oxygen if SpO2 < 92% (anaesthetic intubation if necessary)
- Vital signs
- Support circulation

Disability

- Blood glucose
- Treat seizures as per status epilepticus
- Assess GCS, ICU care & intubation if ≤ 8
- Assess pupils
- Rapid collateral history & exam

Treat Potential Causes

- Glucose for hypoglycaemia
- Thiamine for Wernicke's encephalopathy
- Naloxone for opiate toxicity
- Other antidotes

Examination

- Signs of trauma
- Stigmata of underlying illness
- Skin for needle marks, cyanosis, rash, poor turgor
- Smell breath (alcohol, hepatic fetor, ketosis, uraemia)
- Opisthotonus (tetanus/meningism) & meningism
- Pupils
- Heart/lung/abdominal/rectal exam

Investigations

- FBC, U+E, LFT, CRP, ethanol, toxicology screen, drug levels
- Blood/urine cultures, consider malaria
- CXR/CT head
- LP if not contraindicated after CT

Intracranial Venous Thrombosis

- Cause of cerebral infarction, much less common than arterial causes
- Death is rare & typically due to herniation from mass effect/oedema

Features

All

- Gradual onset over days - weeks
- Headache
- Nausea & vomiting
- Late features due to raised ICP & herniation

Sagittal Sinus (47% & often coexisting)

- Seizures
- Hemiplegia
- Decreased vision

Transverse Sinus (35%)

- Headache with mastoid pain
- Focal neurology
- Seizures

Sigmoid Sinus

- Cerebellar signs
- Lower cranial nerve palsies

Inferior Petrosal Sinus

- 5^{th} & 6^{th} nerve palsies
- Temporal & retroorbital pain
- May develop from otitis media

Cavernous Sinus

- Chemosis
- Proptosis
- Painful ophthalmoplegia
- Fever
- May develop from facial pustules/folliculitis

Cortical Vein Thrombosis

- Stroke-like features developing over days
- Seizures
- Thunderclap headache

Causes/Risk Factors

Common

- Pregnancy/COCP use
- Dehydration
- Malignancy (extracranial – hypercoagulability)
- Local mass affect/trauma
- LP

Rare

- Infection
- SLE/vasculitis
- IBD

Investigations

- Rule out SAH if there is thunderclap headache
- Thrombophilia screen
- MR/CT venogram

Management

- Treat raised ICP if necessary
- Expert advice & anticoagulation

Acute Raised ICP

- Normal ICP is 7-15mmHg
- Raised ICP causes decreased cerebral perfusion pressure (MAP - ICP) and later herniation

Causes

- Primary/metastatic tumours
- Traumatic injury
- Haemorrhage
  - Intracerebral, intraventricular, subarachnoid, subdural, extradural
- Infection
  - Meningitis
  - Encephalitis
  - Abscess
- Hydrocephalus
- Cerebral oedema
- Status epilepticus

Features

- Headache
  - Worse in morning, on coughing, leaning over, lying down
- Vomiting
- Reduced GCS
- Papilloedema
- Pupillary changes
  - Constriction followed by dilatation
- Visual field changes
  - Reduced acuity
  - Enlarged blind spot
  - Narrowed field of view
- Cushing's triad
  - Widening pulse pressure
  - Bradycardia
  - Irregular breathing

Investigations

- CT/MRI brain to assess midline shift/herniation/cause
- U+E, FBC, LFT, glucose, serum osmolality, clotting
- LP if safe (measure opening pressure)

Acute Management

- Investigate & treat underlying cause
- Maintain MAP > 90mmHg & treat seizures
- Head angle of 30-40°
- If intubated hyperventilate to 3.5-4kPa PaCO2

Mannitol 20%

- 0.25-5g/kg over 10-20 minutes
- Monitor serum osmolality, don't exceed 310

Dexamethasone

- ONLY if pressure is caused by oedema surrounding tumour

CSF Removal

- Insertion of & drainage via intraventricular monitor
- Repeated LP
- Ventriculoperitoneal shunt

Brain Herniation

- Forceful displacement of brain structures due to raised pressure which causes compression of other structures
- Ominous sign & indicates urgent management of raised ICP

Uncal/Transtentorial Herniation

- Supratentorial mass displaces ipsilateral uncus of temporal lobe underneath tentorium cerebelli causing:

1. Ipsilateral Pupil Dilatation & Ophthalmoplegia
   - Due to CNIII compression
2. Contralateral Hemiparesis
   - Due to cerebral peduncle compression
3. Coma
   - Due to RAS compression

Tonsillar Herniation (Coning)

- Increased posterior fossa pressure forces cerebellar tonsils through foramen magnum causing brainstem compression and:

1. Ataxia, 6th nerve palsy, & upgoing plantars
2. Irregular breathing & coma

Subfalcine/Cingulate Herniation

- Frontal mass forces cingulate gyrus (medial frontal lobe) under falx cerebri
- May be silent unless compression of anterior cerebral artery occurs & causes stroke

Transcalvarial Herniation

- Brain is displaced through skull defect
  - Fracture
  - Craniotomy site

Idiopathic Intracranial Hypertension

Risk Factors

- **Obesity**
- **Female sex**
- Pregnancy
- Endocrine abnormalities
  - Cushing's syndrome
  - Hypoparathyroidism
  - Hyper/hypothyroidism
- Drugs
  - COCP
  - Tetracyclines
  - Steroids
  - Vitamin A
  - Lithium

Features

- Headache
- Papilloedema
- Visual
  - Blurred vision
  - Enlarge blind spot
  - Narrowed peripheral vision
- 6th nerve palsy

Investigation

- Neuroimaging negative for any structural pathology

Management

- Weight loss

Medical

- Acetazolamide
- Topiramate (also induces weight loss)
- Repeated LP

Surgical

- Optic nerve sheath decompression/fenestration if damage to optic nerve is occurring
- Lumboperitoneal/ventriculoperitoneal shunt

Space-Occupying Lesions

Features

Raised ICP

- Headache worse in morning, on coughing, leaning forward

Seizures

- Seen in ~50%
- SOL must be ruled out in all adult-onset seizures, especially those with focal neurology/aura/Todd's paresis

Evolving Focal Neurology

Temporal	Dysphasia Contralateral homonymous hemianopia Amnesia Varied strange phenomena
Frontal	Hemiparesis Personality change Broca's dysphagia Unilateral anosmia Executive dysfunction
Parietal	Hemisensory loss Decreased 2 point touch discrimination Astereognosis Sensory inattention Dysphasia
Occipital	Contralateral visual field defects Palinopsia Polyopia
Cerebellum	DANISH
Cerebello-pontine angle	Ipsilateral deafness Nystagmus Reduced corneal reflex Facial weakness Cerebellar signs
Midbrain	Failure of up/down gaze Nystagmus on convergent gaze

Causes

- Tumours
- Aneurysm
- Abscess
- Chronic subdural haematoma
- Granuloma (including tuberculoma)
- Cyst (including third ventricle colloid cysts)

Differentials

- Stroke
- Head injury
- Venous thrombosis
- Vasculitis
- MS
- Encephalitis
- IIH

Diagnosis

- CT/MRI brain
- Consider biopsy
- Avoid LP before imaging

Brain Tumours

Types

Metastases (30%)

- Most common
- Commonly spread from:
  - Lung
  - Breast
  - Bowel
  - Skin (melanoma)
  - Kidney

Glioblastoma Multiforme

- Most common adult primary tumour
- Poor prognosis - ~1 year
- Solid tumours with central necrosis & ring enhancement on imaging
- Cause vasogenic cerebral oedema due to disruption of blood-brain barrier

Meningioma

- 2nd most common adult primary tumour
- Typically benign arising from arachnoid cap cells of meninges & located next to dura
- Imaging shows well circumscribed ring enhancing tumour attached to dura
  - Dural tails seen in 65%

Ependymoma

- Commonly seen in 4th ventricle & may cause hydrocephalus

Oligodendroma

- Benign & slow growing, typically seen in frontal lobes

Astrocytoma

- Commonly seen in children

Haemangioblastoma

- Vascular tumour of cerebellum
- Associated with VHL syndrome

Medulloblastoma

- Aggressive tumour seen in children

Pituitary Adenoma

- Functioning/non-functioning

Craniopharyngioma

- Most common paediatric supratentorial tumour

Vestibular Schwannoma

- 5% of intracranial tumours & 90% of cerebellopontine angle tuomurs
- Vertigo, hearing loss, unilateral tinnitus, absent corneal reflex, facial palsy
- Seen bilaterally in NF2

Management

Benign

- Surgical excision if possible

Malignant

- Surgical excision of glioblastoma difficult as margins are rarely tumour free
- Debulking before radiotherapy/local chemotherapy
- Chemoradiotherapy as sole management if surgery is not possible

Cerebral Oedema

- Dexamethasone
- Mannitol if ICP is acutely raised

Meningitis

- Inflammation of the meninges typically due to bacterial/viral infection

Microbiology

Bacterial	Viral
Streptococcus pneumoniae Neisseria meningitidis (most severe presentations) Haemophilus influenzas Listeria monocytogenes (especially in elderly/immunocompromised) TB (immunocompromise)	More common and less severe HSV VZV Enteroviruses CMV HIV

Features

Early

- Headache
- Fever
- Leg pains
- Cold peripheries
- Pale skin

Later

- Meningism
  - Neck stiffness
  - Photophobia
  - **Kernig's sign:** passive extension of a flexed knee with hip flexed at 90° causes spinal pain/resistance to movement
  - **Brudzinski's sign:** passive neck flexion causes involuntary knee/hip flexion in a supine patient
  - Opsithotonus
- Decreased GCS/coma
- Petechial non-blanching rash (meningococcus)
- Seizures (~20%), focal CNS signs
- Shock & DIC

Signs of Underlying Disease

- Zoster
- Cold sore/genital vesicles (HSV)
- Lymphadenopathy/dermatitis/candidiasis/uveitis (HIV)
- Parotid swelling (mumps)

Complications

- Sensorineural hearing loss
- Seizures
- Focal neurological deficit
- Sepsis
- Brain abscess
- Hydrocephalus
- Brain herniation
- Waterhouse-Friderichsen syndrome (meningococcal sepsis)

Investigations

- Don't delay management if diagnosis is clear
- FBC, CRP, U+E, LFT, coagulation, glucose
- ABG
- Cultures, viral serology, meningococcal PCR
- Lumbar puncture unless contraindicated

Lumbar Puncture

Contraindications

- Raised intracranial pressure
  - Focal neurology
  - Papilloedema
  - Herniation
  - Reduced consciousness
- Cardiovascular/haemodynamic compromise
- DIC/thrombocytopenia/coagulopathy
- Respiratory compromise
- Infection over puncture site

Results

	Bacterial	Viral	TB
Appearance	Cloudy	Clear/cloudy	Cloudy, fibrin web
Glucose	< ½ plasma	> ½ plasma	< ½ plasma
Protein	High (> 1.5g/L)	Low/normal (< 1g/L)	High (1-5 g/L)
White Cells	10-5,000/ml Polymorphs	15-1,000/ml Lymphocytes	30-300/ml Lymphocytes

Management

- ABCD assessment with airway support & fluid resuscitation
- Blood cultures ASAP (before antibiotics)

Mainly Meningitic	Mainly Septicaemic
LP < 1 hour (unless C/Id) IV antibiotics (LP first unless LP delayed > 1 hour) IV dexamethasone 10mg	IV antibiotics Delay LP until stable

Antibiotics

- Benzylpenicillin 1.2g IM in the community
- Ceftriaxone 2g BD standard empirical
- Add vancomycin 500mg 6-hrly if:
  - LP delayed
  - Patient from area where penicillin resistant pneumococci are common
- Add IV amoxicillin + gentamycin in patients > 50 (listeria)
- Chloramphenicol + vancomycin ± co-trimoxazole in clear beta lactam allergy
- Consult microbiology & adjust as per cultures

Contact Prophylaxis

Eligibility

- Family/household contacts
- Kissing contacts
- Children under 5 who were at a party with/in creche class with a child incubating infection (within 7 days of onset)
- Healthcare workers exposed to respiratory secretion with no mask

Antibiotics

- Rifampicin or ciprofloxacin

Encephalitis

Causes

Viral

- **HSV1 (95% of cases)** & HSV2
- CMV, EBV, VZV, HIV (seroconversion), measles, mumps, etc

Non-Viral

- Any bacterial cause of meningitis
- TB
- Malaria
- Lyme disease
- Toxoplasmosis

Features

- Infectious prodrome
  - Fever, rash, meningism, lymphadenopathy
- Focal features
  - Eg aphasia
- Raised ICP
  - Headache, vomiting, reduced consciousness, seizures
- Personality change/odd behaviour

Investigations

Bloods

- Cultures
- Viral PCR
- Malaria

CT/MRI

- Medial temporal & inferior frontal lobe changes
- Meningeal enhancement in meningoencephalitis

LP

- Viral PCR
- Lymphocytosis, ↑ protein, ↓ glucose

EEG

- Diffuse abnormalities, lateralised periodic discharges at 2Hz

Management

- Urgent empirical intravenous acyclovir
  - 14 days (21 if immunosuppressed)
- Supportive & symptomatic treatment (eg ventilatory support, management of seizures)
- 70% mortality if untreated

Brain Abscess

Causes

- Extension from middle ear/sinuses/oral cavity etc
- Trauma/surgery to scalp
- Penetrating head injuries
- Septic emboli

Features

- Headache
- Fever
  - May be absent, typically not swinging fever of other abscesses
- Focal neurology depending on site
  - Critical areas such as the motor cortex will present earlier
- Raised ICP
  - Headache, vomiting, reduced consciousness, seizures

Investigations

Bloods

- Raised WCC, CRP, ESR

Imaging

- Ring enhancing mass on CT/MRI

Management

- Surgery: craniotomy & abscess cavity debridement
  - May recur as head is closed following drainage
- IV antibiotics
  - Eg ceftriaxone + metronidazole
- ICP management (mannitol, dexamethasone)

Delirium/Acute Confusional State

- Affects up to 30% of elderly patients admitted to hospital

Risk Factors

- Age > 65
- Background cognitive impairment
- Acute illness/pain
- Hip fracture
- Polypharmacy

Causes

- Infection
  - UTI
  - Pneumonia
  - Intracranial infection
  - Wounds
  - Lines
  - Sepsis
- Pain
- Constipation
- Urinary retention/catheter in situ
- Metabolic
  - Hypercalcaemia
  - Hyper/hypoglycaemia
  - Hyper/hyponatraemia
  - Dehydration
  - Uraemia
  - Liver failure
- Drugs/drug withdrawals
  - Opiates
  - Sedatives
  - Alcohol
  - Recreational
- Stroke
- Hypoxia
- Change of environment

Features

- Global reduction in cognition, perception, & consciousness over hours to days
- Impaired memory
- Disordered thinking/speech
- Tactile/visual hallucination
- Sundowning
  - Symptoms get worse as day gets dark

Hyperactive

- Restlessness & agitation
- Aggression

Hypoactive

- Patient slow & withdrawn

Mixed

- Difficult to recognise, must compare with baseline

Differentials

- Dementia
- Anxiety
- Atypical (non-convulsive) epilepsy (up to 6%)

Investigation/Assessment

- FBC, U+E, LFT, glucose
- ABG
- Septic screen
- Consider EEG
- Examine drug Kardex – any new/stopped prescriptions of relevance
- PR exam

Management

- Identify & treat underlying cause
- Reorientate patient
  - Explain & remind who you are & where patient is
  - Find glasses/hearing aids
  - Clocks/calendars if possible
- Encourage visits from friends/family
- Monitor fluid balance & encourage oral intake
- Practice sleep hygiene
- Remove urinary catheter if not needed
- Adjust unnecessary medication

Sedation

- Avoid if possible
- Haloperidol/olanzapine 1st line
- Quetiapine/clozapine preferred in Parkinson's disease
- Benzodiazepines nocté may be used

Dementia

- Neurodegenerative syndrome with progressive decline in several cognitive domains
- Massive burden on elderly patients, their families & carers, & the health system
- Increases with age, 20% over 80 are affected (at least, half of cases are likely undiagnosed)
- Cognitive assessments (eg MMSE) are useful in diagnosis
  - MMSE score < 24/30 may indicate dementia

Subtypes

- Alzheimer's disease is the leading cause

Common Non-Alzheimer's Dementias

	%	Pathology	Features	Investigations/ Diagnosis	Management
Vascular Dementia	25%	Stroke related: multiple infarcts Subcortical: small vessel disease Rarely inherited (CADASIL)	Cognitive decline occurs in step-wise fashion Features of arteriopathy	MRI shows extensive infarcts & white matter changes	No pharmacological management
Lewy Body Dementia	20%	Alpha synuclein cytoplasmic inclusions (Lewy bodies) in substantia nigra, paralimbic & neocortical areas Association with Parkinson's disease but distinct from Parkinson's dementia	Deterioration in executive function & attention before memory Fluctuating cognition Parkinsonism Hallucinations/delusions	SPECT (single photon emission computed tomography) 90% sensitive & 100% specific	AChE inhibitors & memantine as per AD Avoid neuroleptics
Frontotemporal Lobar Degeneration		Gyral atrophy with loss of > 70% of spindle neurons Includes frontotemporal dementia (Pick's disease), Chronic Progressive Aphasia (CPA), & semantic dementia	Insidious onset before 65yrs Memory & visuospatial skills preserved until late **FTD** Executive impairment Behaviour/personality change Hyperorality Disinhibition **CPA** Non fluent speech, short agrammatic sentences **Semantic Dementia** Fluent speech containing little meaning Recent > remote memory	MRI shows focal gyral atrophy with knife-blade appearance	AChE inhibitors & memantine not recommended
Others					
Alcohol(Korsakoff's)/drug abuse Repeated head trauma		Pellagra Parkinson's disease		Huntington's disease Creutzfeldt-Jakob disease	

Investigations

Bloods

- Rule out reversible causes
- FBC, U+E, LFT, TFT, B12, folate, calcium, glucose

Neuroimaging

- Rule out reversible causes
  - Normal pressure hydrocephalus
  - Subdural haematoma
- Aid diagnosis & management

Non-Pharmacological Management

- Tailored to individual
- Cognitive stimulation programmes, art/music therapy, multisensory stimulation
- Manage challenging behaviours (address pain, avoid overcrowding, clear communication)

Alzheimer's Disease

- Progressive neurodegenerative disease, most common form of dementia

Risk Factors

- Increasing age
- Family history
- Apoprotein E allele E4
- Presenilin/amyloid precursor protein mutations
- Caucasian ethnicity
- Down's syndrome
- Depression
- Smoking

Early Onset Alzheimer's

- Familial form accounting for ~5% of cases
- Mutations in amyloid precursor protein (chr 21), presenilin 1 (chr 14), & presenilin 2 (chr 1)

Pathology

Macroscopic

- Widespread cerebral atrophy
- Cortex & hippocampus particularly affected
- Hydrocephalus ex vacuo
- 95% have concurrent vascular dementia

Microscopic

- Cortical plaques of deposited type A β-amyloid protein
- Neurofibrillary tangles
- Hyperphosphorylation of tau protein

Biochemical

- Acetylcholine deficit

Features

- Persistent, progressive, global cognitive impairment
  - Visuo-spatial
  - Memory
  - Speech
  - Executive function
- Lack of insight into disease
  - Leads to missed appointments, mishandling of money, etc

Late Symptoms

- Irritability
- Mood disturbance
- Behavioural changes
  - Disinhibition
  - Wandering
  - Aggression
- Psychosis
- Agnosia
- Sedentary state

Prognosis

- 7 year mean survival from unequivocal symptom onset (USy)

Pharmacological Management

- Primarily aimed at delaying progression, cognitive recovery is not usually seen

	Mechanism	Indications	Administration	Side Effects/ Contraindications
Donepezil	Acetylcholinesterase inhibitors	First line treatment of AD, Lewy Body dementia & Parkinson's dementia	5mg PO, doubled after a month	Cause or worsen bradycardia/ conduction block (especially donepezil) Exacerbation of peptic ulcer disease Donepezil can cause insomnia
Rivastigmine			1.5mg/12hrs titrated up to 3-6mg/12hrs	
Galantamine			4mg/12hrs titrated up to 8-12mg/12hrs	
Memantine	NMDA antagonist	Moderate AD where AChE inhibitors are not tolerated/contraindicated Add-on to AChE inhibitors in moderate-severe AD Monotherapy in severe AD	5mg/24hrs titrated up to 10mg/12hrs	Hallucinations Confusion Hypertonia Hypersexuality

Others

- Antipsychotics
  - Severe AD with aggression/psychosis
  - Avoid in Lewy Body dementia (especially first generation agents)
- Vitamin supplementation
  - Vitamin E may slow functional progression

Epilepsy

- Condition characterised by recurrent seizures (episodes of abnormal electrical activity in the brain)

Causes/Associations

- 2/3 are idiopathic
- Cerebral palsy
- Tuberous sclerosis
- Mitochondrial disease
- Cortical scarring
- SOL
- Stroke
- Vascular malformations

Non-Epileptic Seizure Causes

Febrile Convulsions

- Occur in children from 6 months to 5 years
- Typically occur in association with viral infection

Alcohol Withdrawal Seizures

- History of alcohol excess & sudden stop
- Peak incidence at 36 hours following withdrawal

Psychogenic Non-Epileptic Seizures

- Epileptic-like seizures without epileptiform electrical activity
- May have history of mental health issues/personality disorders

Features

Prodrome

- Change in mood/behaviours for hours/days before seizure

Aura

- Focal symptoms pre-seizure, typically associated with focal seizures
- Temporal lobe often involved
- Déjà vu/flashing lights/strange smells/"gut" feelings

Post-Ictal

- Lethargy, headache, confusion, myalgia
- Lasts 10-15 minutes following a seizure
- Muscle weakness following motor cortex focal seizures (**Todd's paresis**)
- Aphasia following temporal lobe focal seizures

Localising Focal Seizures

Temporal Lobe

- Hallucinations
  - Auditory/gustatory/olfactory
- Epigastric rising
- Emotional changes
- Automatisms
  - Lip smacking/grabbing/plucking
- Déjà vu
- Post-ictal dysphasia

Frontal Lobe

- Head/leg movements/posturing
- Jacksonian march
- Todd's paresis

Parietal Lobe

- Paraesthesia/anaesthesia/pain

Occipital Lobe

- Visual floaters/flashes etc

Seizure Classifications

- Determined by origin of seizure, level of consciousness, & other seizure features

Focal Seizures

- Originating in one hemisphere
- **Focal Aware**
- **Focal Impaired Awareness**
- **Focal to Bilateral**
  - Typically tonic-clonic
- Further classified by localising features

Generalised Seizures

- Involving networks in both sides of brain from outset
- Consciousness always lost
- **Tonic-Clonic**
  - Limbs stiffen (tonic) then jerk (clonic)
- **Tonic**
- **Clonic**
- **Myoclonic**
  - Sudden jerk of limb/arm/face
- **Absence**
  - Non-motor
  - Pauses (eg in talking) lasting < 10 seconds
- **Atonic**
  - Non-motor
  - Sudden loss of tone causing fall

Diagnosis

History

- Typical features (incontinence, tongue-biting, post-ictal phase)
- Past funny turns/strange behaviour including déjà vu, episodic feelings of fear
- Triggers

Rule Out Provoking Causes

- Trauma
- Stroke
- Haemorrhage
- Raised ICP
- Alcohol/BZD withdrawal
- Metabolic disturbance
- Infection/fever
- Drugs
  - Tricyclics, cocaine

Investigations

Provoking Causes

- Routine bloods
- Drug levels
- Drug screen
- Brain MRI

EEG

- Cannot exclude epilepsy & false positives are common

Epilepsy Management

	Mechanism	Indications	Side Effects	Contraindications/ Interactions
Carbamazepine (Tegretol)	Inhibition of neuronal sodium channels	**1.** Seizure prophylaxis in focal (1st line) or GTC (2nd line) seizures **2.** Trigeminal neuralgia	• Hypersensitivity (10%) (maculopapular rash) • AHS • Dizziness & ataxia • Leucopenia • SIADH • **CYP Induction**	• Myoclonic seizures • Absence seizures • Prior AHS
Sodium Valproate (Epilim)	Weak inhibition of neuronal sodium channels Increase in GABA levels	**1.** Seizure prophylaxis in all seizure types **2.** Status epilepticus not responding to benzodiazepines **3.** Acute treatment & prophylaxis of manic episodes in BPAD	• Teratogenicity • AHS • Hair loss • Tremor & ataxia • Behavioural disturbances • Thrombocytopenia • Idiosyncratic liver failure/pancreatitis (rare) • **CYP Inhibition**	• Prior AHS • Women of childbearing age, particularly around conception & 1st trimester of pregnancy • Hepatic/renal impairment
Lamotrigine	Inhibition of neuronal sodium channels Inhibition of AMPA glutamate receptor	**1.** Seizure prophylaxis in focal, GTC, or absence seizures **2.** Bipolar depression	• Headache • Drowsiness, dizziness, irritability • Mild skin rash • AHS	• Metabolised by glucuronidation (inhibited by valproate, induced by CBZ, PHT, oestrogens)
Levetiracetam (Keppra)	Inhibition of synaptic vesicle protein 2A (SV2A) reducing neurotransmitter release	**1.** 2nd line seizure prophylaxis in focal, GTC, or myoclonic seizures 2. Status epilepticus not responding to benzodiazepines	• Drowsiness, weakness, dizziness • Mood/psychiatric disturbance (rare)	• Few interactions, safe for use with other AEDs, hormonal contraceptives, & warfarin

Drugs By Seizure Type

Seizure Type	1st line	2nd line
Focal	Carbamazepine Lamotrigine	Levetiracetam Oxcarbazepine Topiramate
Generalised Tonic-Clonic	Sodium valproate	Lamotrigine Carbamazepine Levetiracetam
Myoclonic	Sodium valproate	Levetiracetam Lamotrigine Topiramate
Atonic	Sodium valproate	Lamotrigine
Absence	Sodium valproate Ethosuximide	Lamotrigine

AEDs & Liver Enzymes

Induction	Inhibition
Carbamazepine Phenytoin Barbiturates	Valproate

AEDs & Pregnancy

- **Sodium Valproate is contraindicated in pregnancy/women of childbearing age unless absolutely necessary**
- Lamotrigine & levetiracetam are safe in pregnancy
- All except barbiturates are safe in breastfeeding

Starting AEDs

- Specialist prescription
- Started after 2 seizures OR 1 seizure where the patient has any of the following:
  - Neurological deficit
  - Structural abnormality on brain imaging
  - Unequivocal epileptic activity on EEG
  - Patient/family/carers consider risk of further seizure unacceptable
- Single agent only unless all suitable monotherapy options have failed
- Brand name prescribing preferred

Changing AEDs

- New drug should be introduced slowly
- Withdraw 1st drug when established on 2nd

Stopping AEDs

- Specialist supervision
- Considered if patient is seizure free for 2 years

Status Epilepticus

- Continuous or intermittent seizure activity lasting > 5 minutes without neurological recovery

Investigations

- Capillary glucose ASAP, others can wait until management is underway
- Pulse oximetry & cardiac monitor
- Lab glucose, FBC, U+E, Ca2+, ABG, ECG
- Consider AED levels, cultures, toxicology screen

Management

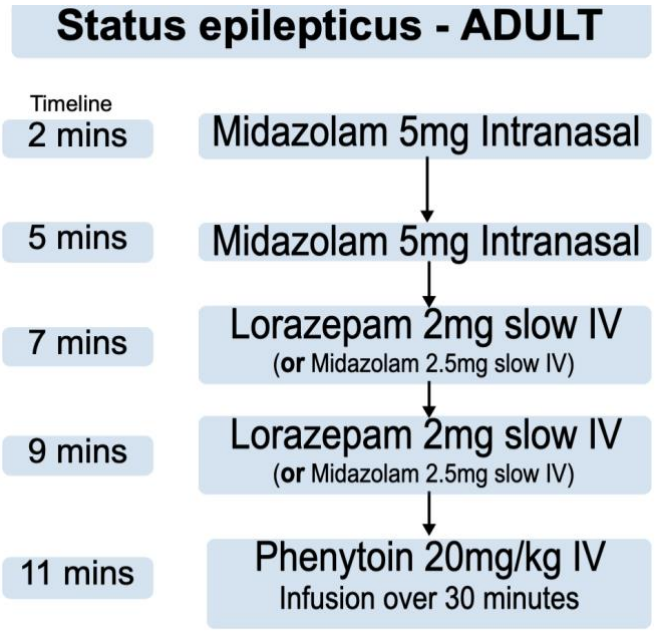
Community

- Buccal midazolam 10mg
- Repeat after 10-20 minutes

Hospital

A	Airway protection (adjunct) Suction as required
B	High flow 100% O2
C	IV access & send blood
D	**1. Lorazepam** • 4mg slow bolus IV • Can be repeated once after 10-20 minutes • Not if community benzodiazepines were given **2. Phenytoin** • If continuing after 2 benzodiazepine doses • 20mg/kg infusion over 30 minutes **3. Anaesthetics** • Anaesthetics should be involved in any status ongoing > 20 minutes • Intubation & ventilation in ICU under anaesthetic (eg propofol) with continuous EEG monitoring is indicated if above measures fail

CUH Guidelines:



Dyskinesia

- Overall term for abnormal involuntary movements

Tremor

Resting Tremor

- Abolished on voluntary movement
- **Cause:** Parkinsonism

Intention Tremor

- Irregular, large amplitude, worse at end of purposeful act such as finger pointing
- **Cause:** Cerebellar damage (MS, stroke)

Postural Tremor

- Present on maintained posture such as arms outstretched
- **Causes:** Benign essential tremor, thyrotoxicosis, anxiety, β-agonists

Re-emergent Tremor

- Postural tremor developing after a delay of ~10 seconds
- **Cause:** Parkinsonism

Chorea

- Non-rhythmic, jerky, purposeless movements going from one place to another

Causes

- Huntington's disease
- Sydenham chorea
- Worsened by levodopa

Hemiballismus

- Large amplitude flinging movements on proximal muscles on one side

Cause

- Vascular damage to contralateral subthalamic nucleus, recovers over ~ months

Athetosis

- Slow, sinuous, confluent movements
- Affect digits, face, hands, tongue
- Difficult to distinguish from chorea

Cause

- Cerebral palsy
- Pseudoathetosis: caused by proprioceptive loss

Myoclonus

- Sudden involuntary focal/generalised jerks arising from cord/brainstem/cortex

Causes

- Neurodegenerative disease (eg lysosomal storage diseases)
- CJD
- Myoclonic epilepsy
- Asterixis (liver/kidney failure, CO2 retention, gabapentin, thalamic stroke, hyponatraemia

Dystonia

- Describes prolonged muscle contractions causing abnormal posture/repetitive movements

Idiopathic Generalised Dystonia

- Childhood onset
- Starts in 1 leg with ipsilateral progression over 5-10 years

Focal Dystonias

- Confined to one part of the body
- Typically idiopathic & benign
- Worsened by stress
- **Spasmodic torticollis:** Head pulled to one side
- **Blepharospasm:** Orbicularis oculi muscle
- **Writer's cramp:** Hand muscles

Management

- Geste antagoniste: patient developed movement/action to counter dystonia, such as touching the side of the jaw in spasmodic torticollis
- Botox injection in overactive muscles

Acute Dystonia

- Typically occurs after starting neuroleptics/anti-emetics
- Torticullis, trismus, oculogyric crisis

Management

- Procyclidine

Parkinsonism

Features

- Extrapyramidal triad of:

Tremor

- "Pill-rolling
- 3-5Hz
- Improves with voluntary movement

Bradykinesia

- Difficulty initiating movement
- Actions decrease in amplitude with repetition
- Shuffling gait with reduced arm swing
- Micrographia, microphonia, expressionless face

Hypertonia

- Rigidity + tremor gives cogwheel rigidity

Causes

- Parkinson's Disease
- Drug induced
  - Antipsychotics (1^{st} > 2^{nd} generation)
  - Metoclopramide
  - Prochlorperazine
- Progressive supranuclear palsy
- Multiple system atrophy
- Wilson's disease
- Post-encephalitis
- Dementia pugilistica
- Toxins
  - Carbon monoxide
  - MPTP

Parkinson's Disease

Pathology
- Loss of dopaminergic neurons in substantia nigra, associated with Lewy bodies in basal ganglia, brainstem, & cortex
- Majority of cases are sporadic but there may be familial cases

Epidemiology
- Mean age of onset 60yrs
- M:F 2:1

Features
- Typically asymmetrical

Tremor
- "Pill-rolling"
- 3-5Hz
- Improves with voluntary movement

Bradykinesia
- Difficulty initiating movement
- Actions decrease in amplitude with repetition
- Shuffling gait with reduced arm swing
- Micrographia, microphonia, expressionless face

Hypertonia
- Rigidity + tremor gives cogwheel rigidity

Others
- Flexed posture
- Drooling
- Depression, dementia, psychosis, sleep disturbance
- Impaired olfaction
- Fatigue
- Autonomic dysfunction causing postural hypotension

Diagnosis
- Typically clinical based on above features
  - Improvement with dopaminergic therapy is supportive
- SPECT may be used if there is difficulty differentiating from essential tremor
- MRI may be used if other causes for features are suspected (eg symmetrical features)

Parkinson's-Plus Syndromes

Multiple Systems Atrophy (Shy-Drager)
- Parkinsonian presentation (rigidity > tremor)
- Autonomic dysfunction
  - Postural hypotension, impotence, incontinence, abnormal sweating
- Cerebellar dysfunction
  - Ataxia
- "Hot cross bun" sign on axial MRI of pons

Progressive Supranuclear Palsy
- Early postural instability & vertical gaze palsy (falls)
- Symmetric onset
- Speech & swallowing problems
- "Hummingbird" sign on sagittal MRI of midbrain

Cortico-Basal Degeneration
- Akinetic rigidity of 1 limb
- Cortical sensory loss (stereognosis)
- Apraxia

Lewy Body Dementia

Management
- Regular assessment of disability, cognitive impairment, and affect
- Levodopa first line if motor symptoms are affecting QOL
- DA/MAO-Bi/COMTi adjunctive if levodopa is insufficiently effective

Levodopa
- Dopamine precursor, given with dopa-decarboxylase inhibitors:
  - Carbidopa (co-careldopa)
  - Benserazide (co-benyldopa)
- Greatest effect on motor symptoms & QOL, but most motor side effects
- Effectiveness reduces with time (~50% response at 6 years), so starting should be delayed if possible (eg until >70 or disease significantly interfering with life)
- Significant "on-off" effect, where parkinsonism is pronounced at the end of a dose effect period
- **Side Effects:**
  - Dyskinesia (chorea, athetosis, dystonia) when dose is too high
  - Psychosis & visual hallucination
  - Nausea & vomiting

Dopamine Agonists
- Bromocriptine, ropinirole, cabergoline, pramipexole
- Allow delayed starting of levodopa/reduced levodopa doses
- **Side Effects:**
  - Bromocriptine & cabergoline (ergot-derived) cause pulmonary fibrosis & are not preferred
  - Drowsiness
  - Nausea
  - Hallucinations
  - Compulsive behaviour

Apomorphine
- Dopamine agonist used to even end of dose effects or as rescue pen for sudden "off" freezing

MAO-B Inhibitors
- Rasagiline, selegiline
- Alternatives to dopamine agonists in early PD
- **Side effects:**
  - Postural hypotension
  - Atrial fibrillation

COMT Inhibitors
- Entacapone, tolcapone
- May help motor complications/lessen "off" period combined with levodopa
- **Side Effects:**
  - Tolcapone has severe hepatic complications and requires LFT monitoring

Antimuscarinics
- Procyclidine, benzotropine, trihexyphenydil
- Used to treat drug-induced parkinsonism

Cerebellar Diseases

Cerebellar Syndrome

- Dysdiadokinesis
- Dysmetria (past-pointing)
- Ataxia
- Nystagmus (direction of damaged hemisphere)
- Intention tremor
- Slurred/staccato speech
- Hypotonia

Causes

- Paraneoplastic (lung Ca)
- Alcohol
- Stroke
- MS
- Neoplastic (cerebellar haemangioma)
- Hypothyroidism
- Friedrich's ataxia/ataxia telangiectasia
- Drugs: phenytoin, lead poisoning

Friedrich's Ataxia

- Most common hereditary ataxia, typical onset 10-15 years

Pathology

- AR trinucleotide expansion (GAA) of X25 gene on Chr 9
- Degeneration of spinocerebellar, corticospinal tracts, dorsal columns, & other nerve pathways
- Does not demonstrate anticipation

Features

- Spinocerebellar: DANISH
- Corticospinal: weakness & up-going plantars
  - Paradoxical hyporeflexia due to peripheral nerve damage
- Dorsal columns: Loss of positional & vibration sense
- Other:
  - Optic atrophy
  - Kyphoscoliosis
  - HOCM (90%)
  - Diabetes mellitus
  - High arched palate

Management

- No cure, mean LE 50 years
- Treat CCF, arrhythmias, DM

Ataxia Telangiectasia

- Onset 1-5 years

Pathology

- AR defect of ATM gene (code DNA repair enzymes)

Features

- Ataxia
- Telangiectasia
- IgA deficiency – recurrent chest infections
- 10% risk of malignancy (esp lymphoma/leukaemia)

Huntington's Disease

- Inherited progressive incurable neurodegenerative disease

Pathology

- AD trinucleotide repeat (CAG) in Huntingtin (HTT) gene on Chr 4
- Degeneration of cholinergic & GABAergic neurons in striatum of basal ganglia

Anticipation

- Feature of trinucleotide repeat disorders where symptoms become more severe and onset becomes earlier in progressive degenerations

Features

- Typically develop after 35 years
- Early personality changes (irritability, apathy, depression) & intellectual impairment
- Chorea & dystonia
- Dysarthria & dysphagia
- Saccadic eye movements
- Fits
- Death within 15-20 years of onset
  - Eg due to RTI
  - Suicide more common than in general population

Management

- Incurable
- Genetic & family counselling
- Speech & language therapy
- Advanced care directive & palliative care

Symptomatic Management

- Motor symptoms:
  - Benzodiazepines
  - Antipsychotics
  - Dopamine-depleting agents (eg tertrabenzine)
- Antidepressants

Multiple Sclerosis

- Chronic immune cell mediated disorder featuring plaques of demyelination disseminated in space & time

Epidemiology

- F:M 3:1
- Peak diagnosis 20-40
- More common at higher geographical latitudes
- 30% monozygotic twin concordance

Subtypes

Relapsing-Remitting

- 85% of patients
- Acute attacks lasting 1-2 months are followed by periods of remission before further attacks

Secondary Progressive

- Relapsing-remitting patients who no longer fully recover after attacks & suffer lasting neurological signs & symptoms
- Occurs in 65% with relapsing-remitting disease within 15 years of diagnosis

Primary Progressive

- 10% of patients
- No remission, progressive deterioration from the onset

Features

- Attacks are typically neurologically monosymptomatic
- Accompanied by non-specific symptoms (fatigue in 75%)

Visual

- Optic neuritis (presenting feature in 20%)
  - Pain on eye movement
  - Reduced central vison
- Optic atrophy
- Uhthoff's phenomenon: symptoms worsen with rising body temperature (bath, exercise)
- Internuclear ophthalmoplegia

Sensory

- Paraesthesia
- Numbness
- Reduced vibration sense
- Trigeminal neuralgia
- Lhermitte's syndrome: paraesthesia in limbs on neck flexion

Motor

- Spastic weakness
- Myelitis

GU

- Erectile dysfunction
- Urinary retention/incontinence

GI

- Swallowing difficulties
- Constipation

Cerebellar

- DANISH

Cognitive/Visuospatial

- Amnesia
- Decreased mood & executive function

Investigations

- Not always needed if clinical diagnosis is clear

MRI

- Periventricular white matter plaques
  - High signal in T2 MRI
- Dawson fingers: Lesions perpendicular to corpus callosum on sagittal imaging

CSF

- IgG oligoclonal bands that are not present in serum

Visual Evoked Potential

- Delayed waveform

Diagnosis

McDonald Criteria

- Attacks must be > 1 hour with > 30 days between

Attacks	Clinical Lesions	Extra Evidence Needed
2	2	None
2	1	Spatially disseminated MRI lesions
1	2	MRI lesions disseminated in time (3 month repeat MRI) OR Positive CSF
1	1	DIS by another clinical attack/MRI OR DIT by another clinical attack/MRI OR Positive CSF
Insidious onset (1° progressive)		Positive CSF & DIS on MRI/continued progression > 1 year

Management

Acute Relapses

- Methylprednisolone 500mg-1g PO/IV for 3-5 days
- Shortens relapse but does not alter prognosis

Disease Modifying Treatment

- Dimethyl fumarate
- Beta-interferon
- Alemtuzumab (anti T cell monoclonal antibody)
- Natalizumab (acts against alpha-4-beta-1 integrin which allows leucocytes to cross BBB)
- Fingolimod (sphingosine-1-phosphate receptor modulator, prevents lymphocytes from leaving lymph nodes)
- Glatiramer acetate (immune decoy)

Symptomatic Treatment

- Spasticity: baclofen/gabapentin
- Fatigue: amantadine
- Bladder dysfunction: anticholinergics/intermittent self-catheterisation
- Oscillopsia: gabapentin

Neuromyelitis Optica

- AKA Devic's syndrome
- MS variant with transverse myelitis (motor, sensory & autonomic loss below lesion) & optic atrophy
- Anti-AQP4 antibodies

Paraneoplastic & Autoimmune Encephalitis

- Inflammatory conditions of the brain with various aetiologies
- Overlap between conditions, defined by autoantibody targets

Paraneoplastic Encephalitis

- Antibodies against intracellular neuronal (onconeuronal) proteins
  - Hu, Ma2, CRMP5
- Often manifests before cancer is diagnosed

Autoimmune Encephalitis

- Antibodies against neuronal cell surface/synaptic proteins
  - NMDA, AMPA, GABA-A, GABA-B, LGI1, Caspr2
- May occur as a paraneoplastic syndrome

Features

Limbic Encephalitis

- Mood & behavioural changes
- Short term memory impairment
- Focal seizures with impaired awareness
- Cognitive dysfunction

Brainstem Encephalitis

- Extraocular movement defects
- Opsoclonus
- Nystagmus
- Dysphagia
- Dysarthria
- Vertigo/SNHL

Myelitis

- Sensory neuropathy
- Limb ataxia
- Motor neuron syndrome

Encephalomyelitis

- All of the above

Investigations

- MRI
- EEG to exclude nonconvulsive seizures
- CSF
  - Inflammatory markers (IgG index & oligoclonal bands)
  - Viral PCR
  - Antibody testing (& in serum)

Management

Immunotherapy

- Glucocorticoids
- IVIg
- Plasma exchange
- Cyclophosphamide
- Rituximab

Prognosis

- Paraneoplastic encephalitis is typically rapid & irreversible
- Autoimmune encephalitis has a varied prognosis
- Delayed diagnosis is associated with worse prognosis

Motor Neuron Disease

- Neurodegenerative condition of unknown aetiology characterised by selective loss of neurons in the motor cortex, cranial nerve nuclei, & anterior horn cells

Epidemiology

- 6/100,000
- M:F 3:2
- Typically affects patients > 40 years old

Types

Amyotrophic Lateral Sclerosis (50%)

- Loss of both motor cortex & anterior horn cells
- Typically LMN signs in arms & UMN signs in legs
- Familial cases linked to superoxide dismutase gene on Chr 21

Progressive Bulbar Palsy (10-20%)

- Affects cranial nerves IX-XII

Progressive Muscular Atrophy (10%)

- Anterior horn cells (and so LMN signs) only
- Affects distal muscle before proximal
- Best prognosis

Primary Lateral Sclerosis (Rare)

- Loss of Betz cells in motor cortex leads to UMN signs only
- Spastic leg weakness & pseudobulbar palsy

Bulbar Palsies

Bulbar Palsy	Pseudobulbar Palsy
• Disease of cranial nerve nuclei IX-XII in medulla • Flaccid fasciculating tongue • Jaw jerk normal/absent • Quiet/hoarse/nasal speech • **Causes:** – MND – GBS – Polio – Myasthenia gravis – Syringobulbia – Brainstem tumours – Central pontine myelinolysis	• UMN lesions of muscle of swallowing & talking due to bilateral lesions above mid-pons – MND – MS – Stroke – Central pontine myelinolysis • More common • Slow tongue movements & slow deliberate speech • Increased jaw jerk, pharyngeal & palateal reflexes • Emotional incongruence

Features

- Mixed UMN & LMN signs
- Fasciculations
- Absence of sensory symptoms
- Wasting of small muscles of hand/tibialis anterior
- Extraocular movements not affected
- Cerebellum not affected
- Abdominal reflexes typically preserved

Investigations

- No specific diagnostic test
- MRI rules out cord compression/myelopathy
- Nerve conduction studies show normal motor conduction
- EMG shows reduced number of action potentials with increased amplitude

Diagnosis

Revised El Escorial Criteria

Definite	LMN + UMN signs in 3 regions
Probable	LMN + UMN signs in 2 regions
Probable with lab support	LMN + UMN signs in 1 region OR UMN signs in 1+ region with +ve EMG in 2+ limbs
Possible	LMN + UMN signs in 1 region
Suspected	LMN or UMN signs only in 1 region

Management

- MDT input with neurologist, palliative care, physio, OT, speech therapy, etc

Riluzole

- Inhibitor of glutamate release & NMDA antagonist
- Mainly used in ALS
- Prolongs life by an average of 3 months

Respiratory Support

- BIPAP used at night
- Prolongs life by 7 months

Excess Saliva

- Advise on positioning, oral care, suctioning
- Antimuscarinic/glycopyrronium bromide/botox

Dysphagia

- Blended food
- Option of gastrostomy

Spasticity

- Exercise & orthotics
- Baclofen/gabapentin

Prognosis

- 50% mortality in 3 years

Mononeuropathies

- Lesions of individual peripheral or cranial nerves, typically with a local cause

	Spinal levels	Location/Path	Lesion Cause	Motor function & loss/features	Sensory function & loss/features
Median	C6-T1	Descends lateral to brachial artery & crosses anteriorly to medial side Passes deep to bicipital aponeurosis & median cubital vein Runs deep to EDS muscle & passes through carpal tunnel	Trauma Carpal tunnel syndrome (wrist)	**Wrist (carpal tunnel):** Thenar paralysis & wasting **Elbow:** Above plus inability to pronate, weakness of flexion, & ulnar deviation of hand **Anterior Interosseous Nerve:** Inability to pronate & weakness of long flexors of thumb & index finger	Palmar aspect of lateral/radial 2½ fingers
Ulnar	C7-T1	Travels through posteromedial aspect of upper arm to flexor compartment of the forearm Enters palm via Guyon's canal (superficial to flexor retinaculum & lateral to pisiform)	Trauma (particularly vulnerable to damage at elbow)	**Wrist:** "Claw hand" – hyperextension of MCP & flexion of PIP & DIP joints of 4th & 5th digits Wasting & paralysis of intrinsic hand muscles & hypothenar muscles **Elbow:** Claw hand (ulnar paradox: claw hand worse in distal lesions) Radial deviation of wrist	Ulnar 1½ fingers
Radial	C5-T1	Spirals around posterior face of humerus to descend in front of lateral epicondyle	Trauma Compression against humerus/in axila	**Wrist:** Finger drop **Elbow:** Wrist drop **Axilla/upper arm:** Triceps paralysis	Dorsal thumb root (anatomical snuff box)
Brachial Plexus		Axilla	Trauma Radiotherapy (eg to breast)	**High (C5-6):** Erb's palsy (waiter's tip) **Low (C8-T1):** Klumpke's palsy (claw hand)	**High:** C5-6 dermatome **Low:** C8-T1 dermatome
Phrenic	C3-5	Descends in mediastinum	Lung Ca, TB, paraneoplastic, myeloma, thymoma, thoracic surgery, infections, etc	Orthopnoea & raised hemidiaphragm	
Lat. Cut. Of thigh	L2-3		Entrapment under inguinal ligament		**Meralgia paraesthetica** Anterolateral burning thigh pain
Sciatic	L4-S3		Pelvic tumours Pelvic/femur fractures	Hamstrings & all muscles below knee	Below knee laterally & foot
Common Peroneal	L4-S1	Originates from sciatic just above knee & winds around fibular head	Trauma to fibular head Sitting cross legged	Foot drop: can't walk on heels Weak ankle dorsiflexion & eversion (NOT inversion)	
Tibial	L4-S3	Originated from sciatic just above knee		Can't plantar flex (walk on toes), invert foot, or flex toes	Sole of foot

Mononeuritis Multiplex

- 2 or more peripheral mononeuropathies

Causes (Systemic)

- DM
- Connective tissue disease (RA, SLE)
- Vasculitis (Wegener's, PAN)
- Sarcoid, amyloid, leprosy, HIV

Cranial Nerve Palsies

3rd – Oculomotor

Features

- Eye deviated down & out
- Ptosis
- Dilated pupil – "surgical third"

Causes

- Microvascular disease (most common)
  - Diabetes
  - Hypertension
- Compression
  - Posterior communicating artery aneurysm
  - Tentorial herniation
  - Pituitary tumours
  - Cavernous sinus thrombosis
- Midbrain stroke (Weber's syndrome)
- Demyelination
  - MS
- Trauma
- Post-neurosurgery
- Vasculitis
  - SLE
  - Temporal arteritis
- Amyloidosis

4th – Trochlear

Features

- Vertical diplopia
  - Reading book, going down stairs
- Torsional diplopia
  - Perceived tilting of objects
- Eye deviated up & out
- Head tilt away from affected side
  - Diplopia worsened when head is tilted towards affected side – Bielchowski phenomenon

Causes

- Idiopathic/congenital (most common)
- Trauma
- Microvascular disease
  - Hypertension
  - Diabetes
- Neoplasms
- Cavernous sinus thrombosis

6th – Abducens

Features

- Eye deviated medially
- Diplopia worsened on looking to the affected side

Causes

- Microvascular disease
  - Hypertension
  - Diabetes
- Idiopathic
- Trauma
- Cavernous sinus thrombosis
- Tumours
- Vasculitis
  - SLE
  - Temporal arteritis

8th – Vestibulocochlear

Features

- Tinnitus
- Sensorineural hearing loss
- Vertigo
- Nystagmus

Causes

- Posterior circulation stroke
- Vestibular neuronitis
- Acoustic neuromas
  - Bilateral in NF2
- Multiple sclerosis
- Congenital deafness

9th – Glossopharyngeal

Features

- Loss of sensation & taste over posterior 1/3 of tongue, palate, pharynx
- Throat/ear pain
- Dysphagia
- Loss of carotid sinus reflex
- Loss of gag reflex

Causes

- Microvascular disease
  - Hypertension
  - Diabetes
- Idiopathic
- Compression
  - Aneurysm
  - Tumour
  - Retropharyngeal abscess
- Trauma – skull base fractures

10th – Vagus

Features

- Flaccid paralysis, ipsilateral soft palate lowering, deviation of uvula away from affected side
- Nasal speech
- Dysphagia & aspiration
- Vocal cord paralysis
  - Dysphonia if unilateral
  - Acute airway obstruction if bilateral
- Gastroparesis

Causes

- Microvascular disease
  - Hypertension
  - Diabetes
- Trauma – skull base fractures
- Compression
  - Tumours
  - Aortic aneurysm
- Iatrogenic
  - Carotid endarterectomy/thyroidectomy

Facial Nerve

Facial Nerve Path

- Lateral brainstem between pons and medulla
- Exits cranial cavity through internal acoustic meatus
- Travels in facial canal of petrous temporal bone
- Widens into geniculate ganglion and gives off greater petrosal nerve
- Gives off nerve to stapedius and chorda tympani
- Exits skull through stylomastoid foramen
- Divides within parotid gland:
  - Temporal
  - Zygomatic
  - Buccal
  - Marginal mandibular
  - Cervical

Facial Nerve Functions

- Motor – Muscles of facial expression
- Sensory – External ear
- Secretomotor – submandibular & lacrimal
- Special sensory – Taste via chorda tympani

Facial Nerve Palsies

Idiopathic

- Bell's palsy

Infective/imflammatory

- CSOM
- Sarcoidosis – Heerfordt's syndrome
- Lyme disease
- Ramsay Hunt Syndrome

Trauma

- Temporal bone fracture
- Surgery
- Forceps delivery

Tumour

- Acoustic neuroma
- Parotid

Metabolic

- DM

Other

- Pregnancy
- Congenital
- Moebius syndrome

House-Brackmann grading of VII palsy

I: Normal movement
II: Slight asymmetry
III: Weak at rest, eye closure, synkinesis
IV: Incomplete eye closure, synkinesis
V: Flicker of movement
VI: No movement

Bell's Palsy

- Diagnosis of exclusion
- Peak incidence 20-40 years, more common in pregnancy

Presentation

- Prodrome in 60%
  - Viral symptoms
  - Post-auricular pain
- Rapid onset LMN weakness (forehead affected)
- Altered taste, dry eyes, hyperacusis

Management

- Steroids (oral pred)
- Eye protection

Prognosis

- Most make full recovery in 3-4 months
- 5-10% have residual weakness, 10% recur

Ramsay Hunt Syndrome

- Herpes Zoster Oticus – reactivation of varicella in geniculate ganglion of CNVII

Features

- Auricular pain often first feature
- Facial paralysis ± polyneuropathy
- Painful vesicular rash around ear/face/intra-orally/on TM
- Vertigo, tinnitus

Complications

- SNHL
- Vertigo
- Encephalitis
- Post-herpetic neuralgia

Management

- Acyclovir
- Analgesia
- Corticosteroids

Trauma

- Facial Trauma
- Direct trauma to branch of CNVII
- Temporal bone fracture
- Transverse or longitudinal
- Diagnosed on CT
- Battle's sign – postauricular bruising

Parotid Tumours

- Usually malignant if involving CNVII
- Facial skin malignancy can metastasise to intraparotid LNs
- Parotidectomy can cause CNVII palsy

MRI in CNVII Palsy

- Low threshold if recurrent or failure to resolve

Polyneuropathies

- Motor/sensory/autonomic disorders of multiple peripheral/cranial nerves

Features

- Typically symmetrical, widespread, & worse distally (glove & stocking distribution)
- Described according to chronicity, function (motor vs sensory) & pathology (demyelination, axonal degeneration)

Common Causes

A. Alcohol
B. B12 deficiency
C. Cancer & CKD
D. Diabetes & drugs (Cisplatin, isoniazid, amiodarone)
E. Every vasculitis

Causes By Pathology

Metabolic

- DM
- Hypothyroidism
- Hypoglycaemia
- Mitochondrial disorders
- Renal failure

Vasculitis

- PAN
- RA

Malignancy

- Paraneoplastic syndromes
- Polycythaemia rubra vera

Inflammatory

- GBS
- Sarcoidosis

Infectious

- Leprosy
- HIV
- Syphilis
- Lyme disease

Nutritional

- Thiamine/pyridoxine/B12/folate deficiency

Inherited

- Charcot-Marie-Tooth
- Refsum's syndrome
- Porphyria
- Leucodystrophy

Drugs

- Cisplatin
- Isoniazid
- Vincristine
- Amiodarone
- Nitrofurantoin
- Phenytoin
- Metronidazole

Others

- Paraproteinaemias
- Amyloidosis
- Lead, arsenic

Investigations

Bloods

- FBC, ESR, glucose, U+E, LFT, TSH, B12
- Electrophoresis, ANA, ANCA, anti-ganglioside ABs
- Specific genetic tests for inherited causes
- Lead, arsenic

Others

- LP
- CXR
- Nerve conduction studies

Management

- Treat cause
- Physio & OT
  - Shoe choice & foot care
- Treat neuropathic pain

Autonomic Neuropathy

- May be isolated or associate with sensorimotor neuropathy

Causes

- DM, GBS, Sjogren's, amyloidosis, HIV, leprosy, SLE, toxins, paraneoplastic
- Primary: MSA/PD

Features

- Sympathetic
  - Postural hypotension
  - Anhidrosis
  - Ejaculatory failure
  - Horner's syndrome
- Parasympathetic
  - Constipation
  - Nocturnal diarrhoea
  - Urinary retention
  - Erectile dysfunction
  - Homes-Aldie pupil

Investigations

- Lying & standing BP
- ECG (variation with respiration)
- Cystometry
- Paraneoplastic antibodies

Alcoholic Neuropathy

- Secondary to both toxic alcohol effects & malabsorption of B vitamins
- Typically sensory before motor

Guillain-Barré Syndrome

- Acute paralytic inflammatory demyelinating polyneuropathy

Pathology

- Cross reaction of antibodies with gangliosides in the peripheral nervous system typically following infection (~4 weeks)

Triggers

- Campylobacter jejuni
- EBV, zoster
- Vaccination
- None found (40%)

Features

- Recent history of gastroenteritis
- Back/leg pain in early stages (65%)
- Symptoms peak 2-4 weeks from onset
- Progressive, symmetrical weakness of limbs
  - Classically ascending
  - Reflexes reduced/absent
  - Sensory symptoms mild (eg distal paraesthesia) with no sensory signs
- Respiratory muscle weakness (may require ICU care)
- Cranial nerve involvement
  - Diplopia
  - Bilateral facial nerve palsy
  - Oropharyngeal weakness
- Autonomic involvement
  - Urinary retention
  - Diarrhoea

Investigations

Nerve Conduction Studies

- Decreased motor conduction velocity

CSF

- Rise in protein with normal white cell count (65%) (albuminocytologic dissociation)

Forced Vital Capacity

- Performed regularly (eg 4hrly) if there is respiratory muscle weakness
- Low threshold for ventilation

Management

- IVIg or plasma exchange
- Thromboprophylaxis
- Respiratory support if needed

Prognosis

- 80% fully recover
  - May take weeks-months
- 15% are left with permanent neurological deficit
- 5% mortality

Variants

Chronic Inflammatory Demyelinating Polyradiculopathy

- Slower onset & recovery

Miller Fisher Syndrome

- Ophthalmoplegia, ataxia, areflexia
- Associated with anti-GQ1b antibodies

Charcot-Marie-Tooth Syndrome

- Hereditary peripheral, predominantly motor, neuropathy

Pathology

- Multiple forms, most common is CMT1A on Chr 17 (AD)
- Typical onset of symptoms is before 10 but may be delayed until after 40

Features

- Weakness in lower legs (particularly dorsiflexion – foot drop)
- Distal peroneal muscle wasting leads to inverted champagne bottle appearance
- Reduced reflexes & muscle tone
- High foot arches
- Atrophy of upper limb muscles also occurs
- Variable degree of peripheral sensory loss

Management

- No cure

MDT Approach:

- Neurologist & geneticist to diagnose
- Physio to maintain strength & range of motion
- Occupational therapy to assist with ADLs

Prognosis

- Total disability rare, overall quality of life preserved

Neuropathic Pain

- Abnormal functioning of sensory nerves causing pain (in the absence of painful stimulus)

Causes

- Postherpetic neuralgia
- Iatrogenic/traumatic nerve damage
- Multiple sclerosis
- Diabetic neuralgia (typically affects feet)
- Trigeminal neuralgia
- Compression
  - Radiculopathy from prolapsed intervertebral disc
- Complex regional pain syndrome

Features

- Dermatomal/anatomic nerve distribution
- Burning, tingling, pins & needles, electric shocks
- Loss of sensation to affected area
- May be corresponding motor symptoms (eg compression)

Management

1st Line

- Amitriptyline
- Pregabalin
- Gabapentin
- Duloxetine
- Use 1 at a time – if unsuccessful, use another until all 4 fail

Others

- Tramadol as a rescue therapy
- Capsaicin cream
- Carbamazepine for trigeminal neuralgia

Complex Regional Pain Syndrome

- Number of conditions with areas of neuropathic pain, causalgia, and reflex sympathetic dystrophy (lasting pain following an injury, worse than the injury itself)

Types

I: Most common, no demonstrable nerve lesion
II: Demonstrable nerve lesion

Features

- Progressive symptoms disproportionate to original injury/surgery
- Allodynia
- Skin temperature & colour changes
- Oedema & sweating
- Abnormal hair growth
- Motor dysfunction

Management

- As per neuropathic pain
- Specialist input

Myelopathies

Tracts Affected	Clinical
Brown-Sequard Syndrome	
1. Lateral corticospinal **2.** Dorsal columns **3.** Lateral spinothalamic	**1.** Ipsilateral spastic paresis **2.** Ipsilateral proprioception & vibration loss **3.** Contralateral pain & temperature loss
SACD	
1. Lateral corticospinal **2.** Dorsal columns **3.** Spinocerebellar	**1.** Bilateral spastic paresis **2.** Bilateral proprioception & vibration loss **3.** Bilateral limb ataxia
Anterior Spinal Artery Occlusion	
1. Lateral corticospinal **2.** Lateral spinothalamic	**1.** Bilateral spastic paresis **2.** Bilateral pain & temperature loss
Syringomyelia	
1. Ventral horns **2.** Lateral spinothalamic	**1.** Flaccid paralysis (typically of intrinsic hand muscles) **2.** Bilateral pain & temperature loss
Cord Compression	
• Depends on extent & locations of compression	• UMN signs

Cauda Equina Syndrome

- Serious condition where lumbosacral nerve roots below the spinal cord are compressed in the spinal cavity

Causes

- Central disc prolapse (L4/L5 or L5/S1)
- Tumours (primary or metastatic)
- Infection (abscess or discitis)
- Trauma
- Haematoma

Features

- Low back pain
- Bilateral sciatica
- Perianal paraesthesia/numbness
- Decreased anal sphincter tone
- Urinary dysfunction

Investigation

- Urgent MRI

Management

- Surgical decompression

Cervical Spondylosis

- Degeneration of the cervical spine leading to a wide clinical spectrum of cervical spinal cord compression

Pathogenesis

- Degeneration of annulus fibrosus & adjacent vertebral osteopohyte formation anteriorly + ligamentum flavum thickening posteriorly cause compression of cervical cord & nerve roots
- When neck is flexed the cord is dragged over these protrusions

Features

Symptoms

- Neck stiffness
- Crepitus on moving neck
- Stabbing/dull arm pain
- Forearm/wrist pain

Signs

- Limited painful neck movements & crepitus
- Lhermitte's sign: neck flexion produces tingling down spine
- **Root compression**
  - Pain/shock sensations in arms at level of root compression
  - Numbess, dull reflexes, LMN signs
  - Muscle wasting
- **Cord compression**
  - Progressive signs (weakness, clumsy hands, gait disturbance)
  - UMN leg signs
  - LMN arm signs
  - Incontinence & urinary symptoms are late features

Differential

- MS
- Nerve root neurofibroma
- SACD
- Compression by bone/cord tumours

Investigations

- MRI cervical spine

Management

- Analgaesia
- Encourage gentle activity

Surgery

- Referral if no improvement in 4-6 weeks
- Interlaminar cervical epidural injections
- Transforaminal injections
- Surgical decompression
  - Anterior approach (discectomy)
  - Posterior approach (laminectomy)

Syringomyelia/Syrinx

- Collection of CSF within or near the central canal of the spinal cord
- Symptoms may be static for years and suddenly worsen
  - Eg on coughing as raised ICP causes sudden extension

Causes

- Blocked CSF flow from basal posterior fossa to caudal space
  - Chiari malformation
  - Trauma
  - Basal arachnoiditis (post infection/radiation/SAH)
  - Basilar invagination (upward displacement of odontoid process)
  - Tumours
  - Idiopathic

Features

Sensory

- Loss of pain & temperature sensation due to crossing of spinothalamic tracts in anterior commissure being first affected
- Root distribution reflecting location
  - Typically back, shoulders, & arms (cape distribution)
- Neuropathic pain

Motor

- Flaccid paralysis (LMN) of upper limbs (intrinsic hand muscles)
- Spastic paralysis (UMN) of lower limbs

Autonomic

- Horner's syndrome
  - Can be bilateral
- Bowel & bladder dysfunction

Others

- Scoliosis if left untreated

Syringobulbia

- Brainstem involvement

Features

- Nystagmus
- Tongue atrophy
- Dysphagia
- Pharyngeal/palateal weakness
- Trigeminal sensory loss

Investigations

- Full spine MRI to exclude tumour/tethered cord
- Brain MRI to exclude Chiari malformation

Management

- Surgical decompression my improve symptoms & reduce progression
- A shunt may be insert for persistent/recurrent syrinx

Myasthenia Gravis

- Autoimmune disease mediated by antibodies to nicotinic ACh receptors in the neuromuscular junction

Epidemiology

- F:M 2:1
- **< 50 Years:** More common in women & associated with thymic hyperplasia
- **> 50 Years:** More common in men & associated with thymic atrophy/tumour

Pathophysiology

- AChR antibodies in 85%
- LDL receptor-related protein 4 (LRP4) or muscle specific kinase (MuSK) antibodies in 15%

Associations

- Thymomas in 15%, thymic hyperplasia in 50-75%
- Autoimmune disorders: pernicious anaemia, thyroid disease, RA, SLE

Features

- Slowly increasing/relapsing muscular fatigue
- Exertion **increases** fatiguability
- Muscle groups affected by frequency:
  - Extraocular
  - Bulbar
  - Face
  - Neck
  - Limb girdle
  - Trunk

Signs

- Ptosis
- Diplopia
- Myasthenic snarl on smiling

Exacerbating Factors

- Exertion
- Pregnancy
- Hypokalaemia
- Over treatment
- Drugs: gentamycin, opiates, tetracycline, quinine, beta-blockers

Investigations

Antibodies

- Look for anti-AChR antibodies
- Look for anti-MuSK if not present

Imaging

- CT thorax to rule out thymoma

EMG

- Single fibre EMG 92-100% sensitive
- Decremental response to repeated stimulation

Tensilon Test

- IV edrophonium reduces weakness temporarily but is not used anymore due to cardiac side effects

Management

Acetylcholinesterase Inhibitors

- Pyridostigmine first line

Immunosuppression

- Treat relapses with prednisolone
- Rituximab/azathioprine/ciclosporin/mycophenylate may be used

Thymectomy

- Proven beneficial even in those without thymomas

Myasthenic Crisis

- Ventilatory support
- Plasmaphoresis/IVIg

Lambert-Eaton Myasthenic Syndrome

- Autoimmune disease mediated by antibodies to presynaptic voltage-gated calcium channels

Causes

- Paraneoplastic (50%)
  - **Small cell lung cancer**
  - Breast cancer
  - Ovarian cancer
- Primary autoimmune

Features

- Muscle weakness & fatiguability
  - Repeated contractions **reduce** fatiguability
- Limb girdle weakness first
  - Lower limbs, gait problems
- Hyporeflexia
- Autonomic symptoms
  - Dry mouth
  - Impotence
  - Urinary hesitance
- Diplopia & respiratory muscle weakness are rare

Investigations

EMG

- Incremental response to repetitive stimulation

Imaging

- Regular CXR/CT
- Symptoms may precede cancer by 4 years

Management

- Treatment of underlying cancer
- 3,4-diaminopyridine
  - Blocks potassium efflux in nerve terminal to prolong action potential
  - AKA amifampridine
- Pyridostigmine
- Immunosuppression (steroids, azathioprine)
- IVIg

Myopathies

- Primary disorder of muscle weakness, may be confused with neuropathy

Myopathy	Neuropathy
Gradual onset Symmetrical proximal weakness (combing hair, climbing stairs, etc) Specific muscle groups may be affected Tendon reflexes preseved	Sensory symptoms (paraesthesia/anaesthesia) Urinary problems Fasciculations

Specific Features

Rapid Onset

- Toxic/drug induced/metabolic myopathy
- (Or neuropathy)

Fatiguability

- MG/LEMS

Pain/Tenderness At Rest

- Inflammatory myopathy

Pain On Exercise

- Ischaemia
- Metabolic myopathy (eg McArdle's disease)

Disproportionately Firm Muscles

- Pseudohypertrophy (eg Duchenne's)

Investigations

- ESR, CK, AST, & LDH may be raised
- EMG
- Tests for systemic disease (eg TFTs)
- Muscle biopsy/genetic testing (eg for Duchenne's)

Muscular Dystrophies

- Genetic diseases characterised by progressive weakness & deterioration of specific muscle groups

Duchenne Muscular Dystrophy

- XLR defects in dystrophin gene (responsible for connecting muscle cell membrane with actin cytoskeleton)
  - Frameshift mutations
- 3/1000 live male births
- **Features:**
  - Progressive proximal muscle weakness from 4/5 years old
  - Calf pseudohypertrophy
  - Gower's sign
  - Intellectual impairment in 30%
- **Management**
  - No cure – MDT approach, genetic counselling, home ventilation, etc
  - Death usually in 20s/teens

Becker's Muscular Dystrophy

- Milder form of DMD
- Typically presents in teens, better prognosis

Fascioscapulohumeral Muscular Dystrophy

- Multiple possible genetic defects, all AD
- Presents in teens with weakness of face, shoulders, & upper arms, scapular winging, foot drop, scoliosis
- ~40% require wheelchair by 40 years old

Myotonic Dystrophy

- Most common myotonic disorder, which are characterised by tonic muscle spasm clinically and long chains of central nuclei within muscle fibres on histology
- Autosomal dominant trinucleotide repeat disorder

Types

DM1	DM2
DMPK gene on Chr 19 Distal weakness more prominent More common, more severe Typically presents aged 20-40	ZNF9 gene on Chr 3 Proximal weakness more prominent

Features

- Myotonia
- Muscle weakness
  - Distal (foot drop)
  - Sternocleidomastoids
  - Facial muscles – long, haggard appearance
  - Bilateral ptosis
  - Dysarthria
  - Dysphagia
- Cardiac involvement
  - Heart block
  - Cardiomyopathy
- Mild mental impairment
- Cataracts
- Male frontal baldness
- Testicular atrophy
- Diabetes mellitus

Prognosis

- Most DM1 patients die in late middle age of respiratory complications
- Genetic counselling important

Inflammatory Myopathies

- Feature spontaneous pain at rest & local tenderness

Inclusion Body Myositis

- > 50 years
- Quadriceps, finger flexors, pharyngeal muscles (ventral muscles more affected)
- Most patients need assistance with ADLs within a decade

Rheumatological

- Polymyositis & dermatomyositis

Others

Metabolic

- McArdle's disease (glycogen storage disease)

Acquired Myopathies of Late Onset

- Hyperthyroidism, malignancy, Cushing's, hypo/hypercalcaemia

Drugs

- Alcohol, statins, steroids, chloroquine, zidovudine, vincristine, cocaine

Neurofibromatosis Type 1

- AKA von Recklinghausen's syndrome
- Autosomal dominant (but variably expressed) defect in neurofibromin gene on Chr 17
- 1/2,500 affected

Features

Café-au-lait Spots

- Flat coffee coloured patches of skin seen in 1st year of life
- More visible under UV light
- Increase in size & number with age
- Clinically relevant if > 6 & >15mm in size
- No increases skin cancer risk

Freckling

- In skin folds
- Present by age 10

Dermal Neurofibromas

- Small violaceous nodules
- Appear at puberty & numbers increase with age
- May become papillomatous
- Non-painful but may be itchy

Nodular Neurofibromas

- Arise from nerve trunks
- Firm & clearly demarcated
- Cause paraesthesia when pressed

Lisch Nodules

- Brown/translucent hamartomas in iris seen with slit lamp
- < 2mm diameter
- Present by 6 years old in 90%

Complications

- Local effects (eg nerve root compression)
- Renal artery stenosis
- GI stroma tumour
- Malignant nerve sheath tumours (eg optic glioma)
- Bony dysplasia (eg scoliosis)
- Epilepsy
- Migraine
- Learning disability

Diagnosis

- Clinical, based on presence of 2 or more of:
  - Café-au-lait spots (> 6, > 15mm)
  - Relative (1st degree) with NF1
  - Axillary/inguinal freckles
  - Bony dysplasia
  - Iris hamartomas (Lisch nodules)
  - Neurofibromas (2+ or 1 plexiform)
  - Glioma (optic nerve)
- Genetic testing if in doubt
- Imaging to investigate complications

Management

- MDT approach
- Annual cutaneous survey & measurement of BP
- Excision of troublesome neurofibromas

Neurofibromatosis Type 2

- Autosomal dominant, but 50% of cases are de novo
- 1/35,000-100,000 affected

Features

Café-au-lait Spots

- Fewer than in NF1

Bilateral Vestibular Schwannomas

- Symptomatic by ~20 years
- Growth rate unpredictable
- SNHL, tinnitus, vertigo
- Mass effect

Juvenile Posterior Subcapsular Lenticular Opacity

- Form of cataract
- Occurs before other manifestations

Complications

- Schwannomas of cranial & spinal nerves
- Meningiomas
- Gliomas

Diagnosis

Either Of:

1. Bilateral vestibular Schwannomas
2. 1st degree relative with NF2 & either:
   - Unilateral vestibular Schwannoma
   - One of:
     - Neurofibroma
     - Meningioma
     - Glioma
     - Schwannoma
     - Juvenile cataract

Management

- Formal hearing assessment yearly from puberty in affected families
- MRI brain if any abnormality detected

Optic Neuropathy

- Any damage to the optic nerve
- **Optic Neuritis:** Refers to demyelination (eg MS)
- **Optic Atrophy:** Refers to pale optic disc on fundoscopy

Causes

Demyelination

- MS
- Neuromyelitis optica
- PML

Compression

- Pituitary tumour
- Meningioma

Ischaemia

- DM
- Giant cell arteritis

Toxic

- Methanol
- Ethambutol

Infective

- HIV (PML)
- Syphilis

Others

- Trauma
- Secondary to papilloedema/raised ICP

Features

- Reduced visual acuity
- Red colour desaturation/red dyschromatopsia
- Central scotoma
- RAPD
- Pale optic disc

Optic Neuritis

- 20% bulbar neuritis (optic disc appears pale as plaque is anterior)
- 80% retrobulbar neuritis (optic disc appears normal)
- Optic atrophy after 6 weeks

Management

- High dose steroids

Visual Field Defects

Tunnel Vision (Concentric Diminution)

- Glaucoma
- Papilloedema
- Syphilis

Enlarged Blind Spot

- Optic disc enlargement (Eg papilloedema)

Central Scotoma

- Optic neuropathy

Unilateral Loss of Vision

- Complete optic nerve lesion

Bitemporal Hemianopia

- Optic chiasm lesion (pituitary tumour, sella meningioma)

Homonymous Hemianopia

- Optic tract to occipital cortex
- Occipital stroke causes macular sparing

Homonymous Quadrantopias

- Superior: Lesion of inferior optic radiations in temporal lobe (Meyer's loop)
- Inferior: Lesion of superior optic radiations in parietal lobe

Horner's Syndrome

- Damage to sympathetic nervous system supply to the face leading to unilateral:
  1. Miosis
  2. Ptosis
  3. Enophthalmos
  4. Anhidrosis

Causes

Congenital

- Associated heterochromia

Central (Anhidrosis of Face, Arms, Trunk)

- Stroke
- Multiple sclerosis
- Syringomyelia
- Tumours
- Encephalitis

Pre-Ganglionic (Anhidrosis of Face)

- Tumour (Pancoast's)
- Thyroidectomy
- Trauma
- Cervical rib

Post-Ganglionic (No Anhidrosis)

- Carotid artery dissection
- Carotid aneurysm
- Cavernous sinus thrombosis
- Cluster headache

Sensorineural Hearing Loss

Causes

Bilateral

- Presbycusis
- Inflammatory
- Noise-induced
- Drug-induced
  - Aminoglycosides
  - Cisplatin

Unilateral

- Idiopathic
- Acoustic neuroma
- Meniere's disease
- Cochlear otosclerosis

Sudden (Idiopathic) SNHL

Potential Causes

- Viral
- Autoimmune
- Ischaemic

History

- Recent infection
- Cardiovascular history
- Autoimmune history

Investigations

- MRI to rule out acoustic neuroma
- ECG
- Blood tests
  - FBC, ESR, glucose
  - ACE, ANCA, auto-antibodies, syphilis serology

Management

- High-dose oral steroids
- Antivirals

Prognosis

- 60% have spontaneous recovery
- Recovery less likely if:
  - Elderly
  - Dizzy
  - Long Hx
  - High ESR

Vertigo

- False sensation that the body/environment is moving

Causes

Viral Labyrinthitis

- Recent viral infection
- Sudden onset vertigo with nausea & vomiting
- Hearing may be affected

Vestibular Neuronitis

- Sudden onset of severe vertigo with nausea & vomiting
- Hearing not affected
- Causes by recent viral infection/vascular lesion
- Attack lasts hours-days

Benign Paroxysmal Positional Vertigo

- Triggered by change in position & lasts 10-20 seconds
- Caused by movement of debris in semicircular canals (canalolithiasis)
- Positive Dixie-Hallpike manoeuvre

Meniere's Disease

- Increased endolymphatic pressure
- Occurs in one or both ears
- Vertigo attacks lasting > 20 mins with:
  - Hearing loss/tinnitus
  - Sense of aural fullness
- Severe symptoms may be helped by cinnarizine/prochlorperazine

Ototoxicity

- Aminoglycosides
- Cisplatin
- Loop diuretics

Vestibular Schwannoma

- Vertigo, hearing loss, unilateral tinnitus, absent corneal reflex, facial palsy

Others

- Posterior circulation stroke
- Trauma
- MS
- Ramsay Hunt syndrome
- Alcohol intoxication

Renal Medicine

Urinary Tract Infection

Definitions

- **Bacteriuria**
- Bacteria present in urine, may or may not be symptomatic

UTI

- Diagnosis based on symptoms & signs – no gold standard bacterial count

Lower UTI

- Bladder infection (cystitis)/prostate infection (prostatitis)

Upper UTI

- AKA pyelonephritis – infection of kidney & renal pelvis

Abacterial Cystitis/Urethral Syndrome

- Dysuria & frequency with no demonstrable infection

Classification

Uncomplicated

- Normal renal tract structure & function

Complicated

- Structural/functional abnormality of GU tract
  - Obstruction, catheter, stones, neurogenic bladder, renal transplant

Risk Factors

Increased Bacterial Inoculation

- Female gender
- Sexual activity
- Urinary/faecal incontinence
- Constipation

Increased Binding of Uropathogenic Bacteria

- Spermicide use
- Menopause

Decreased Urine Flow

- Dehydration
- Obstructed urinary tract

Increased Bacterial Growth

- Diabetes mellitus
- Immunosuppression
- Catheter in situ
- Pregnancy

Causes

- E. coli: 75-95% in community, less in hospital
- Staphylococcus saprophyticus: 5-10%
- Klebsiella pneumoniae
- Pseudomonas aeruginosa
- Proteus mirabilis (associated with stones)
- Enterococcus
- Candida albicans

Sterile Pyuria

- WBCs on dipstick with negative culture

Infective	Non-infective	
TB Recent/ inadequately treated UTI Appendicitis Prostatitis Chlamydia	Calculi Renal tract tumour Papillary necrosis TIN	Polycystic kidney Recent catheter Pregnancy SLE

Features

Cystitis

- Frequency
- Urgency
- "Burning" dysuria
- Suprapubic pain & tenderness
- Cloudy/offensive smelling urine
- Low grade fever
- Confusion (may be only symptom in older patients)

Prostatitis

- Perineal/scrotal/penile/lower back/bladder pain
- Fever, malaise, nausea
- Swollen, boggy, tender prostate

Pyelonephritis

- Fever & rigors
- Sepsis
- Loin/back/costovertebral pain & tenderness

Investigations

- Treat empirically in non-pregnant women with 3 or more symptoms & no vaginal discharge

Dipstick

- Nitrates & white cells
- Negative dipstick reduces chances of UTI to < 20%

MSU Culture

- If dipstick is positive
- Standard cut-off is > 10^5 colony-forming units
- Catheterised sample if septic

Bloods

- If systemically unwell
- FBC, U+E, CRP
- Culture – positive in ~25% of pyelonephritis cases

Imaging

- Consider USS & urology referral for: men with upper UTI/recurrent UTI/UTI failing to respond to treatment/pyelonephritis

Management of Lower UTIs

Non-Pregnant Women

- Empiric treatment with nitrofurantoin/trimethoprim/cefalexin for 3 days
- Cultures if > 65 years or haematuria

Men

- Empiric treatment with nitrofurantoin/trimethoprim/cefalexin for 7 days

Catheterised Patients

- Treat only if symptomatic
- Empiric treatment with nitrofurantoin/trimethoprim/cefalexin for 7 days

Prostatitis

- Ciprofloxacin or co-trimoxazole

Management of Pyelonephritis/Complicated UTI

- Hospital admission
- Tazocin (ciprofloxacin in penicillin allergy) ± gentamycin
- Meropenem if documented history of ESBL

Acute Kidney Injury

- Reduction in renal function over hours-days occurring as a result of insult to the kidneys
- Occurs to 15-18% of inpatients and has a mortality of up to 25/30%

Definition Criteria

- Rise in creatinine of ≥ 25umol/L in 48hrs
- Rise in creatinine of ≥ 50% in 7 days
- Urine output of < 0.5ml/kg/hr for > 6 hours

Risk Factors

- Chronic kidney disease
- Heart failure
- Diabetes
- Liver disease
- History of AKI
- Use of nephrotoxic drugs/iodinated contrast in last week
- Age > 65
- Cognitive impairment/physical disability that prevents patient from drinking fluids

Causes

Pre-Renal (80%)	↓ Vascular volume	Haemorrhage, D&V, burns, pancreatitis, surgery
	↓ Cardiac output	Cardiogenic shock, MI
	Systemic vasodilation	Sepsis, drugs, anaphylaxis
	Renal vasoconstriction	NSAIDs, ACE-i/ARBs, hepatorenal syndrome, RAS
Renal (10%)	Glomerular	Glomerulonephritis, ATN due to prolonged hypoperfusion or toxins
	Interstitial	Drug reaction, infection, infiltration (eg sarcoid)
	Vessels	Vasculitis, HUS, TTP, DIC
Post-Renal (10%)	Within renal tract	Stone, urothelial malignancy, stricture, clot
	External compression	Pelvic/abdominal malignancy, prostatic hypertrophy, retroperitoneal fibrosis

By Frequency

1. Sepsis
2. Major surgery
3. Cardiogenic shock
4. Other hypovolaemia
5. Drugs
6. Hepatorenal syndrome
7. Obstruction

Nephrotoxic Drugs

- NSAIDs (excluding aspirin 75mg)
- Aminoglycosides
- ACE inhibitors/ARBs
- Diuretics
- Metformin, lithium & digoxin are not technically toxic themselves & may potentially be continued but risk of toxicity is increased
- Gentamycin, NSAIDs, & contrast die cause ATN directly

Features/Complications

Hyperkalaemia

- Chest pain, palpitations, light-headedness
- ECG: tall tented T waves → prolonged PR interval → small P waves → widened QRS complexes → sinusoidal rhythm → asystole

Metabolic Acidosis

- **Mild:** pH 7.3-7.35
- **Moderate:** pH 7.2-7.3
- **Severe:** pH < 7.2
- Breathlessness, confusion, Kussmaul respiration

Fluid Overload

- Heart failure & pulmonary oedema

Uraemia

- Pruritis
- Anorexia
- Bleeding
- Encephalopathy
  - Lethargy, confusion, fits, coma
  - Restless legs
- Neuropathy (paraesthesia)
- Serositis
  - Chest pain
  - Pleural/pericardial rub

Investigations

Urine

- Dipstick pre-catheter
  - Haematuria/proteinuria indicate intrinsic renal disease
- ACR to quantify proteinuria
- Microscopy – muddy-brown casts in ATN

Bloods

- Urgent blood gas potassium
- U+Es, FBC (platelets – if low, blood film), LFTs (hepatorenal)
- Ix for intrinsic disease if indicated

Imaging

- USS renal tract if cause unknown & not improving

Staging (KDIGO)

1	As per definition criteria
2	Rise in creatinine to 2x baseline or Urine output of < 0.5ml/kg/hr for > 12 hours
3	Rise in creatinine to 3x baseline or Rise in creatinine to 353.6umol/L or Urine output < 0.3ml/kg/hr for > 24 hours or Initiation of renal replacement therapy

Referral Criteria (ICU/Renal)

- AKI not responding
- AKI with complications
- Stage 3 AKI
- AKI with difficult fluid balance (hypoalbuminaemia, HF, pregnancy)
- AKI with possible intrinsic disease
- AKI with hypertension

Management of AKI

- Diagnosis and treatment of underlying cause
  - Correct volume depletion/renal pefusion in pre-renal AKI
  - Refer for specialist treatment in intrinsic renal disease
  - Remove obstruction in post-renal AKI
- In the meantime, removal of nephrotoxic drugs & supportive management of complications

Fluid Balance

Hypovolaemia

- Hypovolaemic renal failure will improve with volume replacement
- Care in cardiogenic shock/third space losses
- Dynamic assessment before & after administration to avoid overload

1. 500ml over 15 minutes
2. Reassess fluid state
3. Further boluses of 250-500ml with assessment
4. Stop when euvolaemic or after giving 2L (requires expert input)

Hypervolaemia

- Oxygen supplementation as required & fluid restriction
- Loop diuretics ONLY in symptomatic fluid overload
- Referral for RRT if AKI with fluid overload & oliguria

Acidosis

- Treatment of underlying cause stops acidosis
- Severe acidosis (pH < 7.2) warrants referral to renal/ICU

Hyperkalaemia

- Treat potassium > 6.5mmol/L or if there are any ECG features of hyperkalaemia

1. Myocardial Stabilisation

- 10ml calcium chloride/30ml calcium gluconate IV over 5-10 minutes
- ECG should improve in ~3 minutes
- Lasts 30-60 minutes

2. Temporary Intracellular Potassium Shift

- IV soluble insulin (10u) in 25g glucose (50ml 50% or 125ml 20%)
- Monitor hourly for hypoglycaemia
- Nebulised salbutamol 10-20mg is an alternative but limited by IHD (10mg) and tachyarrhythmias (contraindicated)

3. Definitive Potassium Removal

- Calcium resonium
- Loop diuretics
- Renal replacement therapy

Renal Replacement Therapy in AKI

Types

- Haemodialysis
- Haemofiltration
- Peritoneal dialysis is rarely used in AKI

Indications

- Fluid overload unresponsive to medical treatment
- Severe/prolonged acidosis
- Recurrent/persistent hyperkalaemia
- Symptomatic uraemia
- Poisoning (eg salicylates)

Chronic Kidney Disease

- Abnormal kidney structure or function which is present for longer than 3 months and has an impact on health
- Typically permanent and progressive once eGFR is < 50, prognosis worse with concurrent proteinuria

Risk Factors

- Increasing age
- Hypertension
- Diabetes
- Smoking
- Nephrotoxic medications

Causes

- Frequently presents with no known cause

	Renal	Systemic
Glomerular	Minimal change **Glomerulonephritis**	**Diabetic nephropathy** Amyloid
Tubulo-interstitial	**Pyelonephritis** Stones	Drugs/toxins Sarcoid Myeloma
Blood flow/ vessels	Renal limited vasculitis	Heart failure **HTN nephropathy** TTP
Congenital	**PCKD**	Alport/Fabry
Transplant	Recurrence of renal disease	Rejection Calcineurin toxicity

Features

- Symptoms typically only occur at stage G4 or A3

Symptoms	Signs
Protein Loss & Sodium Retention	
Polyuria & polydipsia Oliguria/anuria Dyspnoea	Peripheral/pulmonary oedema Raised JVP Hypertension Frothy urine
Anaemia	
Dyspnoea Lethargy Faintness Tinnitus	Pallor Tachycardia Flow murmurs
Vitamin D Deficiency	
Bone pain Fractures	Looser's zones Cupped metaphyses
Uraemia (If GFR < 15)	
Pruritis Anorexia & weight loss Encephalopathy: – Lethargy – Confusion – Fits – Restless legs Paraesthesia (neuropathy) Serositis (chest pain)	Pale yellow tinged skin Pericardial/pleural rub Coma

Complications

- Anaemia
- Renal bone disease
- Cardiovascular disease
- Peripheral neuropathy
- Dialysis complications

Investigations

Urine

- Dipstick for proteinuria
- Albumin:Creatinine ratio (ACR)
  - < 3mg/mmol: normal-mild proteinuria
  - 3-30mg/mmol: moderate proteinuria
  - >30mg/mmol: severe proteinuria

Bloods

- U+E, FBC, glucose, HbA1c
- Calculate eGFR
- Investigation for intrinsic renal disease if indicated

Imaging

- In CKD kidneys are bilaterally small on USS (< 9cm)
- Exceptions:
  - Infiltrative (amyloidosis, myeloma)
  - Adult polycystic kidney disease
  - Diabetes

Grading

eGFR

- If eGFR is > 60ml/min with no signs of CKD (normal U+Es, no proteinuria), there is no CKD

G1	> 90ml/min with other evidence of CKD
G2	60-89ml/min with other evidence of CKD
G3a	45-59ml/min
G3b	30-44ml/min
G4	15-29ml/min
G5	< 15ml/min – established kidney failure

Proteinuria

A1	< 3 mg/mmol
A2	3-30mg/mmol
A3	> 30mg/mmol

Referral to Renal

- Stage G4 & G5
- ACR > 70mg/mmol not caused by diabetes
- ACR > 30mg/mmol with haematuria
- Declining eGFR
  - Reduction > 25% & crossing eGFR CKD grades
  - Sustained reduction >15% within 12 months
- Hypertension poorly controlled despite 4 agents
- Known/suspected rare/genetic cause of CKD

Monitoring

- eGFR & albuminuria at least annually
- Increase frequency depending on risk as per G & A grading

Prognosis

- Reduced GFR & proteinuria are independently associated with:
  - All-cause mortality
  - CV mortality
  - Progressive kidney disease & kidney failure
  - AKI

Management of CKD

Principles

- Slowing progression of renal disease
- Treatment of renal complications
- Treatment of extra-renal complications
- Preparation for renal replacement therapy

Slowing Progression of Renal Disease

- Treat glomerulonephritis if present

Lifestyle

- Advise about exercise, healthy weight & smoking cessation
- Reduce salt intake to < 2g sodium/5g sodium chloride per day

Blood Pressure

- Target < 140/90 or < 130/80 in diabetes or ACR > 70mg/mmol

Renin Angiotensin System

- Treat the following with RAS antagonist (ACEi/ARB)
  - Diabetes with ACR > 3mg/mmol
  - Hypertension with ACR > 30mg/mmol
  - Any CKD with ACR > 70mg/mmol
- Check renal function & potassium before starting & 1-2 weeks after
- Stop if potassium rises above 6mmol/L or eGFR reduces by 25%

Glycaemic Control

- Target HbA1c to < 53mmol/mol unless risk of hypoglycaemia or limited life expectancy

Treatment of Renal Complications

Anaemia

- Exclude other causes of anaemia including blood loss
- Target Hb of 10-12g/dL
- IV iron infusions may be necessary in patients on haemodialysis
- ESAs such as erythropoietin/darbapoietin

Acidosis

- Consider sodium bicarbonate supplements in patients with eGFR < 30 & serum bicarbonate < 20mmol/L

Oedema

- Fluid & sodium restriction
- Diuretic treatment under specialist supervision
  - Loop & thiazides in combination – prevent distal tubule sodium reabsorption

Bone Mineral Disease

- Dietary phosphate restriction with phosphate binders if phosphate is > 1.5mmol/L
- Vitamin D supplements if deficient
- Paricalcitol (PTH suppressor) has fewer side effects

Restless Legs/Cramps

- Treatment of severe cases with gabapentin/pregabalin/ dopamine agonists is off-label

Treatment of Extra-Renal Complications

Cardiovascular Disease

- Increased risk via hypertension, vascular stiffening, inflammation, oxidative stress & abnormal endothelial function
- Aspirin 75mg & atorvastatin 20mg

Renal Replacement Therapy

Indications

Acute

- Fluid overload unresponsive to medical treatment
- Severe/prolonged acidosis
- Recurrent/persistent hyperkalaemia
- Symptomatic uraemia
- Poisoning (eg salicylates)

Chronic

- End stage renal failure (CKD stage G5)
- Any acute indications continuing in the long term

Methods

- Haemodialysis
- Peritoneal dialysis
- Haemofiltration
- Renal transplant

Haemodialysis

- Blood filtered by passing over semi-permeable membrane against dialysis fluid flowing in opposite direction
- Solutes diffuse across concentration gradient
- Hydrostatic gradients are used to clear excess water (ultrafiltration)
- Requires venous access with tunnelled cuffed catheter or AV fistula (preferred)
- Given at least 3-4 times/week, daily dialysis & home dialysis are possible

Advantages

- Less infection risk than peritoneal dialysis
- Daily haemodialysis improves outcomes

Complications/Problems

- Tunnelled venous line infection/site infection/endocarditis
- AV fistula complications
- Dialysis disequilibrium leading to cerebral oedema
- Haemodynamic instability/hypotension/arrhythmias
- Anaphylaxis to sterilising agents
- Time consuming
- Psychosocial issues

AV Fistula

- Created by surgically joining an artery & vein causing vein to dilate with high pressure & flow arterial blood
- Radio-cephalic, brachio-cephalic, or brachio-basilic (rare)
- Takes 4 weeks – 4 months to be functional
- A fistula vein should never be used for routine IV access

Examination

- Skin integrity
- Aneurysms
- Continuous thrill & machinery murmur

Complications

- Aneurysm
- Infection
- Thrombosis
- Stenosis
- Steal syndrome
- High-output cardiac failure

Peritoneal Dialysis

- Utilises peritoneum as semi-permeable membrane
- Peritoneal cavity is filled with fluid via indwelling Tenckhoff catheter & solutes diffuse slowly across
- Osmotic agents such as glucose & glucose polymers are added for ultrafiltration

Continuous Ambulatory Peritoneal Dialysis

- Dialysis solution is in the peritoneum at all times
- Fluid is exchanged regularly (eg 2 litres 4 times/day)

Automated Peritoneal Dialysis

- Occurs overnight while a machine continuously replaces fluid in the abdomen
- Takes 8-10 hours

Advantages

- Does not require regular hospital visits

Complications/Problems

- Bacterial peritonitis
- Peritoneal sclerosis
  - This reduces the efficacy of peritoneal dialysis over time
- Ultrafiltration failure
  - Due to loss of membrane integrity & absorption of dextrose
- Weight gain
  - Due to absorption of dextrose
- Psychosocial effects

Haemofiltration

- Blood filtered by positive pressure across semipermeable membrane
- Ultrafiltrate is replaced by fluid either pre or post filtration

Advantages

- Used in the intensive care setting as it is more haemodynamically stable than haemodialysis
- Better removal of large molecules

General Complications of RRT

Cardiovascular

- Increased CV disease risk (hypertension, endothelial dysfunction, oxidative stress)

Nutrition

- Protein-calorie malnutrition

Amyloid

- B2-microglobulin accumulates in long term dialysis causing:
  - Carpal tunnel syndrome
  - Arthralgia
  - Visceral effects

Renal Transplantation

- Treatment of choice for ESRF as long as risks do not outweigh benefits, many patients unsuitable due to comorbidities/frailty

Contraindications

Absolute

- Metastatic cancer

Temporary

- Active infection
- HIV with active viral replication
- Unstable cardiovascular disease

Relative

- Cardiovascular disease/heart failure

Graft Types

Living Donor

- Best graft function & survival if HLA type is matched

Deceased Donor

- Donor after brain death (DBD/heart beating donor)
- Expanded criteria donor (ECD)
  - Older kidney or kidney from a patient with history of hypertension/CKD
  - Worse outcomes than other grafts, better outcomes than dialysis
- Donor after cardiac death (DCD/non heart beating donor)
  - Increased risk of delayed graft function

Procedure

- Donor kidney is anastomosed to pelvic (usually external iliac) blood vessels without removal of the recipient's own kidneys
- Donor kidney ureter is anastomosed directly to recipient's bladder
- Transplanted kidney is typically palpable in the iliac fossa & a "hockey stick" scar is typical

Matching

- Based on HLA antigens (Chr 6)
- Does not have to be a perfect match, but "closeness" of match is proportional to prognosis & graft survival
- Class 1 (A, B, C) & class 2 (DP, DQ, DR)
- Order of importance of matching is:
  - DR > B > A

Graft Rejection

Hyperacute Rejection (Minutes-Hours)

- Widespread thrombosis in the graft due to pre-existing ABO/HLA antibodies
- Type II hypersensitivity
- No treatment, graft must be removed

Acute Rejection (< 6 Months)

- Cell-mediated rejection due to HLA mismatch
- Usually asymptomatic, diagnosed by rising creatinine, pyuria or proteinuria
- May be reversible with immunosuppressants & steroids

Chronic Failure (> 6 Months)

- Fibrosis of kidney by cell & antibody mediated rejection
- Recurrence of original intrinsic renal disease

Immunosuppression

Regimes

- Induction: Calcineurin inhibitor + monoclonal antibody
- Maintenance: Calcineurin inhibitor + mycophenolate/ sirolimus

Calcineurin Inhibitors

- Cyclosporin, tacrolimus
- Inhibit T cell activation & proliferation
- Drug level monitoring required due to narrow therapeutic index & variation between patients
- Clearance is CYP450 dependent
- Side effects:
  - Nephrotoxicity in graft
  - CV risk (hypertension, hyperlipidaemia, new-onset diabetes after transplantation (NODAT))
- Tacrolimus has lower incidence of acute rejection, hypertension, & hyperlipidaemia but higher incidence of diabetes

Monoclonal Antibodies

- Daclizumab & basilximab block activated T cells via CD25 (IL-2 receptor)
- Alemtuzumab causes B & T cell depletion

Mycophenolate Mofetil

- Blocks purine synthesis and so prevents proliferation of lymphocytes
- GI side effects & bone marrow suppression

Sirolimus

- Blocks T cell activation via CD25 (IL-2 receptor)
- Can cause hyperlipidaemia

Steroids

- First line treatment of acute rejection
- Only added to maintenance immunosuppression if there has been multiple steroid-sensitive acute rejection episodes

Non-Rejection Complications

Surgical

- Bleed, VTE, infection, urinary leaks, lymphocele, hernia

Delayed Graft Function

- Affects up to 40%, more common with DCD

Infection

- All infections more common with immunosuppression
- Hospital/donor acquired infections in month 1
- Opportunistic (PCP, CMV, etc) in months 1-6
  - Prophylaxis
- Usual community acquired infections after 6 months

Malignancy

- 25x malignancy risk with immunosuppression, especially:
  - Skin SCC
  - Post-transplant lymphoproliferative disorder
  - Gynaecological

Cardiovascular Disease

- 3-5x risk compared to general complication but 80% less than dialysis

Glomerulonephritis

- Encompasses conditions which are caused by glomerular pathology, present with haematuria/proteinuria/both, are diagnosed on renal biopsy, and can cause AKI/CKD/ESRF

Presentations

- Asymptomatic haematuria
- Nephritic syndrome/acute nephritis
- Nephrotic syndrome

Causes

- Intrinsic renal disease
- Idiopathic
- Immune (SLE, Anti-GBM, vasculitis)
- Infection (HBV, HCV, HIV, strep)
- Drugs (penicillamine, gold)
- Amyloidosis

General Investigations

Bloods

- FBC, U+E, ESR
- C3 & C4
- Antibodies (ANA, ANCA, anti-GBM, dsDNA)
- Ig & serum protein electrophoresis
- ASOT, hepatitis serology

Urine

- Dipstick for haematuria & proteinuria
- Spot ACR
- MCS
- Bence-Jones protein

Imaging

- Renal ultrasound (+ biopsy)
- CXR: infiltrates in anti-GBM/Wegener's

Renal Biopsy

Complications

- Back/loin pain
- Haematuria
- Bleeding
- Angiographic intervention

Results

- Proportion of glomeruli involved (focal vs diffuse)
- Amount of each glomerulus involved (segmental vs global)
- Hypercellularity, sclerosis, presence of crescents
- Immunohistology for deposits
- Electron microscopy for superstructure

General Management

- Nephrology referral
- Management as per CKD
- Treat hypertension aggressively with RAS inhibition
- Specific treatment depending on underlying diagnosis, severity, & comorbidities

Nephritic Syndrome

Features

- Haematuria with red cell casts
- Proteinuria & oedema (especially periorbital)
- Hypertension
- Oliguria & renal impairment

Causes

- IgA nephropathy
- Post-streptococcal glomerulonephritis
- Anti-GBM disease
- Immune complex deposition (SLE, endocarditis)
- Vasculitis

Rapidly Progressive/Crescentic Glomerulonephritis

- Most aggressive form which can lead to ESRF in days

Causes

1. Anti-GBM disease (5%)
2. Immune complex deposition (SLE, post-strep, IgA) (45%)
3. Pauci-immune (vasculitis) (50%)

Management

- Specific treatments as per cause

Nephrotic Syndrome

1. Proteinuria > 3g/24hrs or PCR > 300mg/mmol or ACR > 250mg/mmol
2. Hypoalbuminaemia < 30g/L
3. Oedema

Causes

Primary Renal Disease

- Minimal change disease
- Membranous nephropathy
- Focal segmental glomerulosclerosis
- Membranoploriferative/mesangiocapillary GN

Secondary to Systemic Disease

- DM, SLE, amyloid, pre-eclampsia

Complications

Thromboembolism risk

- Loss of ATIII in urine
- Includes renal vein thrombosis causing sharp drop in renal function

Infection risk

- Loss of immunoglobulins & other mediators in urine

Hyperlipidaemia

- Increased hepatic synthesis due to ↓ oncotic pressure

Others

- Hypocalcaemia
- CKD

Management

1. Reduce oedema (fluid & salt restriction & loop diuresis)
2. Treat underlying cause
3. Reduce proteinuria with ACEi/ARB
4. Treat complications (thromboprophylaxis, immunisations, statins)

Causes of Nephritic Syndrome

	Epidemiology	Associations	Pathophysiology	Specific Features	Diagnosis	Management	Prognosis
IgA Nephropathy	Young males	Henoch-Scheinlen purpura Alcoholic cirrhosis Coeliac disease	IgA deposition in mesangium	May follow URTI by 1-3 days Typically causes intermittent macroscopic haematuria without nephritic syndrome	IgA deposition in mesangium	ACEi/ARBs if there is proteinuria > 1g Steroids if there is a falling eGFR or failure to respond to ACEi/ARBs	25% develop ESRF in 30 years **Good markers**: frank haematuria **Poor markers**: male, proteinuria > 2g/day, hypertension, smoking, hyperlipidaemia
Post-Streptococcal GN	Young children		Immune complex deposition	Follows group A strep infection by 1-2 weeks Varies from isolated haematuria to acute nephritis	Evidence of group A strep infection (↑ASOT, ↑anti-DNAse B) Low C3 Renal biopsy: endothelial proliferation, immune complex deposits	Supportive Antibiotics	Good prognosis
Anti-GBM Disease	M:F 2:1 Bimodal peaks: 20-30 & 60-70	HLA-DR2	Antibodies to type IV collagen	Pulmonary haemorrhage Rapidly progressive glomerulonephritis – haematuria, oliguria, AKI, renal failure	Renal biopsy: linear IgG depositis along mesangium Anti-GBM antibodies Raised transfer factor due to pulmonary haemorrhages	Plasmapheresis Steroids Cyclophosphamide	
RPGN			Any cause of GN leading to renal failure over days/weeks Type 1: Anti-GBM Type 2: immune complex deposition Type 3: ANCA vasculitis	Haemoptysis with anti-GBM, vasculitis rash/sinusitis with Wegener's	Crescents seen on biopsy due to break in GBM & influx of inflammatory cells	Corticosteroids & cyclophosphamide Specifics depending on cause: plasma exchange for anti-GBM/ANCA vasculitis, monoclonal antibodies for lupus nephritis	

Causes of Nephrotic Syndrome

	Epidemiology	Associations	Pathophysiology	Specific Features	Diagnosis	Management	Prognosis
Minimal Change Disease	75% of cases in children, 25% in adults	10-20% secondary to: Drugs: NSAIDs, rifampicin Paraneoplastic: Hodgkin's lymphoma, thymoma Infectious mononucleosis	T-cell & cytokine mediated damage resulting in polyanion loss & reduction in electrostatic charge of GBM	Normotension Highly selective proteinuria – intermediate size proteins: albumin, transferrin	Renal biopsy: normal light microscopy, foot process effacement on electron microscopy	Steroids 1st line, 80% respond Cyclophosphamide 2nd line	1/3 have single episode 1/3 have infrequent relapses 1/3 have frequent relapses which stop before adulthood
FSGS	Young adults Commonest GN seen on biopsy	Idiopathic/secondary to: HIV, heroin, lithium, lymphoma, SCD, Alport syndrome, other renal pathology		30-50% recurrence in renal transplants	Focal & segmental sclerosis & hyalinosis in light microscopy, effacement of foot processes on light microscopy	RAS inhibition & BP control for all Steroids for idiopathic cases Calcineurin inhibitors 2nd line Plasma exchange/rituximab for recurrence in transplants	Risk of progression to renal failure increases with proteinuria < 10% spontaneous remission, 25-50% with treatment
Membranous Nephropathy	Most common GN in adults	Idiopathic/secondary to: Malignancy: lung, breast, GI, prostate Infection: Hep B/C, strep, malaria, schistosomiasis Immune: SLE, RA, sarcoid, sjogrens Drugs: gold, penicillamine	Idiopathic disease caused by anti-phospholipase A2 antibodies		Anti-phospholipase A2 antibodies Diffusely thickened GBM IgG4 in idiopathic disease, other IgGs in secondary disease Spikes on silver stain	RAS inhibition & BP control for all Immunosuppression (steroids + cyclophosphamide/chlorambucil) for those at high risk of progression: proteinuria > 4g despite ACEi/ARB for 6 months	1/3 have spontaneous remission 1/3 remain proteinuric 1/3 develop ESRF
Membranoproliferative GN	10% of adult nephrotic syndrome	**Immune complex associated:** infection, cryoglobinaemia, monoclonal gammopathy, autoimmunity **C3 glomerulopathy:** partial lipodystrophy, factor H deficiency	**Immune complex associated (90%):** Immune complex deposition & complement activation **C3 glomerulopathy:** Defect in alternative complement pathway (C3 nephritic factor)	May cause nephrotic (60%) or nephritic (30%) syndrome	Renal biopsy: proliferative glomerulonephritis with electron dense deposits Immune deposits in immune complex associated disease	RAS inhibition & BP control for all Mx of underlying cause in immune complex disease Steroids	

Renal Manifestations of Systemic Disease

Diabetic Nephropathy

- Most common cause of ESRF with ~40% of patients requiring renal replacement

Pathophysiology

- Hyperglycaemia causes increased growth factors, RAS activation, & oxidative stress leading to increased glomerular capillary pressure
- Podocyte damage & endothelial dysfunction occurs first
- Later scarring (glomerulosclerosis), formation of Kimmelstiel-Wilson nodules, & fibrosis with progressive loss of renal function

Diagnosis

- Microalbuminuria screened for annually
  - ACR 3-30mg/mmol
  - Not detected on dipstick
  - Damage reversible at this level

Management

- Tight glycaemic control aiming for HbA1c of 53mmol/mol
- Blood pressure control aiming for < 130/80
  - ACEi/ARBs beneficial for renal protection even if normotensive
- Sodium restriction to < 2g/day
- Statins to reduce CV risk

Lupus Nephritis

- Nephropathy occurs in 50% of cases of SLE in the first year, 75% overall
- Can be nephritic or nephrotic

Diagnosis

- Clinical
- Antibodies
  - ANA sensitive, not specific
  - Anti-dsDNA 75-100% specific & correlates to disease activity
- Biopsy

Histological Subtypes

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 is the most common & severe

Management

- Treat hypertension
- Steroids + mycophenolate/cyclophosphamide for class III/IV/V

Small Vessel Vasculitis

- ANCA-associated vasculitides cause RPGN without immune deposits (pauci-immune)

Diagnosis

- Clinical (other features) + ANCA + biopsy

Management

- Steroids + cyclophosphamide/rituximab
- Plasma exchange if renal failure/pulmonary haemorrhage

Myeloma

- Associated renal disease in 40%

Pathophysiology

- Tubular obstruction due to light chain casts (Bence-Jones protein)
- Deposition of IgG/light chains in glomerulus causing proteinuria
- Renal tract infection due to immunoparesis

Management

- Adequate hydration
- Bisphosphonates for hypercalcaemia
- Anti-myeloma treatment (including glucocorticoids)

Amyloidosis

- AL or AA amyloids can accumulate in kidneys/glomeruli causing renal impairment

Diagnosis

- Congo red stain on biopsy

Management

- Treat underlying condition

Scleroderma Renal Crisis

- ~5% of cases of systemic sclerosis
- Risk increases with: diffuse disease, anti-RNA pol II antibodies, < 2 years since diagnosis

Features

- Accelerated hypertension & AKI

Diagnosis

- Collapsed glomeruli & onion-skin thickening of arterioles on biopsy

Management

- ACEi/ARBs
- IV vasodilators

Sickle Cell Nephropathy

- Associated with hyperfiltration (creatinine lower than expected) & albuminuria
- 75% of young patients have CKD
- Progression to renal failure associated with other triggers (infection, papillary necrosis)

Diagnosis

- Clinical

Management

- ACEi/ARBs

Renal Tubular Disorders

Renal Tubular Acidosis

- All associated with hyperchloraemic/normal anion gap metabolic acidosis

Type 1 (Distal)

- Inability to secrete hydrogen ions into distal tubule
- **Causes**
  - Genetic
  - Idiopathic
  - Autoimmune (Sjogren's, SLE, RA)
  - Toxins (lithium, amphotericin B, analgaesics)
- **Complications**
  - Hypokalaemia
  - Nephrocalcinosis
  - Renal stones
- **Diagnosis**
  - Urine pH > 5.3 despite metabolic acidosis
- **Management**
  - Bicarbonate replacement & treatment of underlying cause

Type 2 (Proximal)

- Failure of bicarbonate reabsorption in proximal tubule
- Distal reabsorption intact so serum bicarbonate is usually normal
- **Causes**
  - Fanconi syndrome
  - Wilson's disease
  - Cystinosis
  - Carbonic anhydrase inhibitors
- **Complications**
  - Hypokalaemia
  - Osteomalacia
- **Diagnosis**
  - IV bicarbonate causes increased urine bicarbonate & pH (~7.5)
- **Management**
  - Bicarbonate & potassium replacement

Type 3 (Mixed)

- Extremely rare
- Deficiency of carbonic anhydrase II
- Results in hypokalaemia

Type 4 (Hyperkalaemic)

- Reduced aldosterone leads to reduced proximal tubular ammonium secretion
- Results in hyperkalaemia
- **Causes**
  - Hypoaldosteronism
  - Diabetes

Fanconi Syndrome

- Generalised resorptive disorder of proximal tubule

Features

- Type 2 RTA
- Polyuria
- Phosphaturia, glycosuria, aminoaciduria
- Osteomalacia

Causes

- Cystinosis
- Sjogren's
- Multiple myeloma
- Wilson's disease
- Nephrotic syndrome

Management

- Phosphate replacement

Bartter's Syndrome

- Inherited (usually AR) disorders of defective salt reabsorption in the thick ascending loop
- Type 1 most common, involves NKCC2 transporter (like taking excessive loop diuretic)

Features

- Failure to thrive in childhood
- Polyuria & polydipsia
- Hypokalaemic, hypochloraemic metabolic acidosis
- Normotension
- Weakness

Management

- Salt replacement
- NSAIDs

Gitelman Syndrome

- Loss of function of NaCl cotransporter in distal tubule mimicking thiazide diuretic use

Features

- Incidental finding of electrolyte abnormalities in adolescence/adulthood

Management

- Salt replacement

Acute Tubulointerstitial Nephritis

- Presents with AKI & should be considered in all cases of AKI where there is no obvious pre- or post-renal cause

Causes

Drugs

- Penicillin, rifampicin
- NSAIDs
- Allopurinol
- Furosemide
- PPIs
- Anticonvulsants
- Warfarin

Systemic Disease

- SLE
- Sjogren's
- Sarcoid
- ANCA vasculitis

Infection

- Streptococci, Staphylococci, E. coli, Mycoplasma, Campylobacter
- CMV, EBV, HSV, hepatitis A-C

Features

- AKI
- Fever + rash + arthralgia in 10%
- Hypertension

Tubulointerstitial Nephritis with Uveitis

- Occurs in young females
- Fever, weight loss, painful red eyes
- Leucocytes & protein on urinalysis

Investigations

- Sterile pyuria
- White cell casts
- Eosinophilia in 30%

Biopsy

- Oedema & infiltration of interstitium ± tubule

Management

- Stop/treat underlying cause
- Steroids often used despite poor evidence

Chronic Tubulointerstitial Nephritis

- Insidious onset & slowly progressive renal impairment

Causes

- As above
- Pyelonephritis
- Lead, calcium, mercury, aristolochic acid
- Genetic interstitial disease

Biopsy

- Interstitial fibrosis & tubular atrophy

Management

- Stop/treat underlying cause
- Manage CKD
- Steroids under specialist supervision

Acute Tubular Necrosis

- Most common cause of AKI
- Necrosis & detachment of tubular epithelial cells which obstruct the tubule lumen
- Reversible, recovery takes 7-21 days

Causes

Ischaemia

- Shock
- Sepsis
- Dehydration
- Haemorrhage

Toxins

- Aminoglycosides
- Myoglobin
- Radiocontrast agents
- Lead
- NSAIDs

Features/Investigations

- AKI
- Muddy brown casts on urinalysis

Phases

1. Oliguric
2. Polyuric
3. Recovery

Management

- As per AKI
  - Fluids
  - Stop nephrotoxins
  - Treat complications

Renal Papillary Necrosis

- Coagulative necrosis of renal papillae

Causes

- Severe acute pyelonephritis
- Diabetic nephropathy
- Obstructive nephropathy
- Analgesic nephropathy
- Sickle cell disease

Features

- Visible haematuria
- Loin pain
- Proteinuria

Nephrotoxins

Analgesic Nephropathy

- Occurs in long term analgesic use – history of chronic pain
- Prevalence reduced since withdrawal of phenacetin

Causes

- NSAIDs
- Aspirin
- Paracetamol

Features

- Often silent until advanced CKD
- Sudden flank pain: obstruction due to sloughed papilla

Investigations

- Sterile pyuria/mild proteinuria/normal urinalysis
- Small & irregular kidneys on USS
- Cup & spill appearance of IVU
- CTIN secondary to papillary necrosis on biopsy

Management

- Discontinue analgesia
- Manage CKD

Aminoglycoside Nephropathy

- Most prominently gentamycin
- Cause AKI due to ATN

Risk Factors

- Increased dose
- Prolonged use
- Existing CKD
- Volume depletion
- Other nephrotoxins

Presentation

- Mild AKI after 1-2 weeks of treatment

Management

- Discontinue & treat AKI

Prevention

- Single daily dose reduces risk

Radiocontrast Nephropathy

- AKI 48-72 hours after contrast administration

Risk Factors

- Existing CKD
- Diabetes
- Increased contrast dose
- Volume depletion
- Other nephrotoxins

Management

- None specific

Prevention

- Pre-hydrate with IV crystalloid
- Stop other nephrotoxins 24hrs before until 24hrs after contrast

Radiation Nephritis

- Presents 6 months-years after total body radiation/local field radiotherapy/targeted radionucleotide therapy

Features

- Hypertension, protein/haematuria, renal failure

Management

- As per CKD

Rhabdomyolysis

- Muscle breakdown with release of intracellular contents
- Increased cytokines & reduced NO cause renal vasoconstriction
- Myoglobin is filtered & causes obstruction & inflammation

Causes

- Seizure
- Collapse/coma/fall with long lie
- Crush injury
- McArdle's syndrome
- Drugs
  - Statins (especially if co-prescribed with clarithromycin)
  - Fibrates
  - Ecstasy

Features

- Muscle pain, swelling, tenderness
- Red/brown urine
- AKI

Investigations

- Disproportionately raised creatinine
- Elevated CK
- Hypocalcaemia
- Hyperphosphataemia
- Hyperkalaemia
- Metabolic acidosis

Management

- IV fluids to maintain urine output
- Treat hyperkalaemia if necessary
- Renal replacement may be needed
- Urinary alkalinisation may be used but has poor evidence

Urate Nephropathy

- Precipitation of uric acid crystals in tubulointerstitium causing renal impairment & inflammation
- Seen in tumour lysis syndrome
- Increased serum uric acid is also an independent risk factor for CKD

Management

- Tumour lysis: aggressive hydration & allopurinol/rasburicase

Inherited Kidney Disease

Autosomal Dominant Polycystic Kidney Disease

- Most common inherited kidney disease, 1/1,000 caucasians
- De novo mutation in 10%
- 2/3 will require renal replacement

Types

ADPKD Type 1	ADPKD Type 2
85%	15%
PKD1 on chromosome 16	PKD2 on chromosome 4
ESRF by 50s	ESRF by 70s

Features

- May be asymptomatic
- Hypertension
- Recurrent UTIs
- Abdominal/flank pain
- Renal stones
- Haematuria
- CKD
- Palpable enlarged kidneys

Extra-Renal Manifestations

- Liver cysts (70%) & hepatomegaly
- Berry aneurysms (8%) & SAH
- Cardiovascular
  - Mitral prolapse
  - Mitral/tricuspid regurgitation
  - Aortic root dilatation
  - Aortic dissection
- Cysts in:
  - Pancreas
  - Spleen
  - Oesophagus
  - Ovary
  - Thyroid

Diagnosis (Ultrasound)

- < 30: 2 cysts, unilateral or bilateral
- 30-59: 2 cysts in each kidney
- >60: 4 cysts in each kidney

Screening

- Ultrasound if family history
- MRI for intracranial aneurysms if < 65 with personal/family history of aneurysms

Management

- 3-4L of water intake daily
- Treat BP aiming for < 130/80
  - Avoid CCBs
- Antibiotics ± drainage for infected cysts
- Cyst decompression for persistent/severe pain
- Tolvaptan slows cyst progression in select patients

Autosomal Recessive Polycystic Kidney Disease

- 1/20,000, mutation on chromosome 6
- Presents ante/perinatally
- No specific management

Features

- Salt & pepper appearance on USS
- Congenital hepatic fibrosis & portal hypertension
- Oligohydramnios
- Respiratory distress (poor prognosis)
- ESRF in childhood

Von Hippel-Lindau Syndrome

- AD mutation in VHL gene (chr 3) predisposing to neoplasia

Features

- Pre-malignant renal cysts
- Clear cell renal carcinoma
- Phaeochromocytoma
- Cerebellar haemangiomas
- Retinal haemangiomas
- Endolymphatic sac tumours

Management

- Regular screening for tumours

Alport Syndrome

- XD (85%) defect in gene for type IV collagen resulting in abnormal GBM
- More severe in males
- Usually presents in childhood

Features

- Microscopic haematuria
- Progressive renal failure
- Bilateral high-tone sensorineural deafness
- Anterior lenticonus
- Retinitis pigmentosa
- Failing renal transplant
  - Due to presence of anti-GBM antibodies

Diagnosis

- Renal biopsy
  - Splitting of lamina densa with basket-weave appearance
- Molecular genetic testing

Prognosis

- Mean age of ESRF in men: 30-40 years
- 30% ESRF in women by 60 years

Fabry Disease

- X-linked lysosomal storage disorder due to deficiency of α-galactosidase-A
- Proteinuria & progressive renal failure in men & some female carriers
- Treated with enzyme replacement

Cystinuria

- AR defect of absorption of cystine & dibasic amino acids in proximal tubule
- Cystinuria & cystine stone formation
- Managed with diet, increased fluid intake, & urinary alkalinisation

Cystinosis

- AR lysosomal storage disorder with accumulation of cystine
- Fanconi syndrome & progressive renal impairment
- Visual impairment, myopathy, hypothyroidism

Rheumatology

Osteoarthritis

- Most common joint condition, affects > 10% of adults > 60
- Multifactorial (overuse, genetics, injury)
- "Wear and repair", not primary inflammation

Risk Factors

- Increasing age
- Obesity
- Occupation
- Trauma
- Female gender
- Family history

Affected Joints

- Hips
- Knees
- Sacroiliac joints
- PIPs & DIPs
- CMC joint (base of thumb)
- Wrist
- Cervical spine

Presentation

- Joint pain & stiffness
- Worsened by activity with background ache
- Leads to deformity, instability, & reduced function

Localised Disease

- Typically knee/hip
- Pain & crepitus on movement
- "Gelling" - ~15 minutes of increased stiffness after rest
- Unstable sensation
- Perceived lack of power due to pain

Generalised Disease ("Nodal OA")

- Typically affecting hands & knees
- Joint tenderness & swelling
- Weak grip
- Reduced range of motion
- **Heberden's Nodes:** DIP joints
- **Bouchard's Nodes:** PIP joints
- Squaring at base of thumb

X-Ray Features

- Loss of joint space
- Osteophytes
- Subchondral cysts
- Subchondral sclerosis

Diagnosis

- Can be made clinically if > 45 with typical features of pain on use and no morning stiffness/stiffness lasting < 30 minutes

Management

Conservative

- Education, weight loss, physio & OT
- Heat/cold packs

Analgesia

- Paracetamol + topical NSAID ± topical capsaicin
- Short term/intermittent oral NSAIDs if needed
- Codeine/other opiates if severe
- Intra-articular steroid injections for short-term relief from severe symptoms

Surgery

- Joint replacement (hips/knees) is the most effective management of severe OA with substantial impact on quality of life

Septic Arthritis

- To be considered in any acutely inflamed joint as can destroy joint in < 24hrs and has mortality of up to 11%

Pathophysiology

Micro

- Staph aureus most common overall
- Neisseria gonorrhoeae most common in young sexually active adults

Spread

- Most commonly haematogenous from distant infection

Location

- Most commonly knee joint (> 50%)

Risk Factors

- Pre-existing joint disease, DM, immunosuppression, CKD, recent joint surgery, prosthetic joints, IV drug use, age > 80

Features

- Acute swollen joint, warm to touch & fluctuant
- Reduced range of movement in 80%
- Fever present in majority

Investigations

- Blood cultures & joint aspiration for microscopy & culture BEFORE antibiotics

Management

- Empirical IV abx (flucloxacillin or clindamycin) later narrowed to cultures, for 2 weeks, then oral for up to 12
- Needle aspiration for decompression
- Orthopaedic review for washout/debridement

Rheumatoid Arthritis

- Chronic systemic inflammatory disease characterised by a symmetrical, deforming, peripheral polyarthritis

Epidemiology

- ~1% prevalence, increased in smokers
- F:M 2:1
- Peak onset in 40s & 50s
- Associated with HLA DR4/DR1

Features

Typical Presentation

- Insidious presentation over months
- Symmetrical swelling, pain, & stiffness of small joints of hands & feet
- Worse in mornings
- Gradual progression & involvement of large joints

Others

- Sudden onset widespread arthritis with systemic disturbance
- Relapsing/remitting monoarthritis of large joints (palindromic RA)
- Systemic illness with extra-articular symptoms

Signs

- Early (inflammation without damage)
  - Swollen MCP, PIP, wrist or MTP joints
  - Positive squeeze test
  - Tenosynovitis/bursitis
- Late (joint damage & deformity)
  - Ulnar deviation & volar subluxation of wrist & MCP
  - Boutonnière & swan-neck deformities of fingers
  - Z-deformity of thumbs

Extra-Articular Features (40% of patients)

Systemic

- Fatigue
- Weight loss
- Muscle aches & weakness

Nodules

- Elbow
- Lungs
- Heart
- CNS
- Lymph nodes

Pulmonary

- Exudative pleural effusion with low glucose
- Interstitial lung disease
- Bronchiolitis obliterans

Cardiac

- IHD
- Pericarditis/pericardial effusion

Neuro

- Peripheral neuropathy
- Carpal tunnel syndrome
- Atlantoaxial instability -> cervical myelopathy

Ocular

- Episcleritis/scleritis
- Keratoconjuncivitis sicca

Others

- Splenomegaly (5%, 1% have Felty's syndrome)

Antibodies

Rheumatoid Factor

- IgM targeting the Fc portion of the IgG molecule
- Present in 70-80% & titre levels are proportional to disease severity & progression (NOT disease activity)
- Also positive in:
  - **Felty's syndrome** (100%)
    - RA + splenomegaly + neutropenia
  - Sjogren's syndrome (~50%)
  - Infective endocarditis (~50%)
  - SLE (20-30%)
  - Systemic sclerosis (30%)
  - General population (5%)

Anti-Cyclic Citrullinated Peptide

- 98% specific & 70-80% sensitive
- Detectable up to 10 years before onset of RA

Investigations

Bloods

- Anaemia of chronic disease
- Thrombocytosis
- Raised ESR & CRP
- RF & Anti-CCP (if RF is negative)

Imaging

- X-rays of affected joints
  - Soft tissue swelling
  - Juxta-articular osteopenia
  - Decreased joint space
  - Erosions & subluxation later

Diagnosis (2010 American College of Rheumatology)

- Patients who have at least 1 joint with tenosynovitis not better explained by another cause
- Score of 6/10 is diagnostic

Joint involvement	1 large	0
	2-10 large	1
	1-3 small	2
	4-10 small	3
	10, at least 1 small	5
Serology	Negative RF & Anti-CCP	0
	Low positive RF/Anti-CCP	2
	High positive RF/Anti-CCP	3
Reactants	Normal CRP & ESR	0
	Raised CRP/ESR	1
Duration	< 6 weeks	0
	> 6 weeks	1

Prognosis

Poor Prognostic Features:

- RF/Anti-CCP positive
- Poor functional status at presentation
- Erosions on XR after < 2 years
- HLA-DR4
- Insidious onset

Management of Rheumatoid Arthritis

Conservative Measures

- MDT approach with specialist physiotherapy & occupational therapy input
- Manage risk factors for IHD/CVD as RA accelerates atherosclerosis
- Monitor DAS28 & CRP score for disease activity & response to treatment

Medical

- NICE guidelines recommend DMARD monotherapy ± bridging prednisolone 1st line

Steroids

- Effective in acute exacerbations
  - E.g. methylpred 100mg IM
- Oral steroids (e.g. prednisolone 7.5mg/day) effective in controlling symptoms but side effects preclude long term use
- Prednisolone used as bridging therapy when starting a DMARD

NSAIDs

- Help with symptoms but have no effect on disease process

DMARDs

- Early use improves outcomes
- Monitoring for side effects essential:
- **Methotrexate**
  - Myelosuppression (monitor FBC)
  - Cirrhosis (monitor LFTs)
  - Interstitial lung disease (pre-treatment CXR)
- **Sulfasalazine**
  - Rash
  - Low sperm count
  - GI upset
- **Hydroxychloroquine**
  - Retinopathy (pre-treatment & annual eye screen)
- **Leflunomide**
  - Teratogenicity
  - Hepatotoxicity

Biologics

- Specialist prescription where there has been an inadequate response to 2 DMARDs
- Pre-treatment screening for TB, HIV, Hep B&C essential

Anti-TNF

- Etanercept
- Infliximab
- Adalimumab

B-Cell Depletion

- Rituxumab
- Where 2 DMARDs & an anti-TNF have failed

T-Cell Co-stimulation Inhibition

- Abatacept

IL-6 Inhibition

- Tocilizumab

Surgical

- Orthopaedic management of joint deformities
- Less common due to DMARDs & biologics

Anaesthetics/Procedure Considerations

- Risk of atlanto-axial subluxation
  - Arrange lateral spine radiograph in gentle flexion

Seronegative Spondyloarthropathies

Common Features

- Associated with HLA-B27
- Rheumatoid factor negative
- Axial arthritis or
- Asymmetrical large joint oligo/monoarthritis
- Enthesitis (Achilles tendonitis, plantar fasciitis)
- Dactylitis
- Extra-articular manifestations: anterior uveitis, upper zone pulmonary fibrosis, amyloidosis, aortic regurgitation

Ankylosing Spondylitis

- 20-30 years, M:F 3:1
- 85-95% HLA-B27 positive

Features

- Insidious onset of low back pain & stiffness
- Worse in morning & improves with use
- Reduced lateral & forward flexion (Schober's test < 5cm) & chest expansion

Extraarticular Manifestations

- Apical lung fibrosis
- Anterior uveitis
- Aortic regurgitation
- Achilles tendonitis
- AV block
- Cauda equina syndrome

Investigations

- Typically raised CRP & ESR
- **X-Ray**
  - Sacroiliitis: joint narrowing, subchondral erosions, sclerosis
  - Squaring of lumbar vertebrae
  - Syndesmophytes
  - "Bamboo spine" (late)
- **MRI**
  - Active inflammation (bone marrow oedema)

Management

- Exercise regimes with physio guidance for back mobility
- NSAIDs 1st line medical treatment
- DMARDs only if peripheral joint involvement
- Anti-TNF therapy for severe disease not responding

Poor Prognostic Markers

- ESR > 30
- Onset < 16 years
- Early hip involvement
- Poor response to NSAIDs

Enteric Arthropathy

- Associated with IBD, GI bypass, coeliac disease, & Whipple's disease
- Arthropathy usually improves with treatment of GI condition
- Avoid NSAIDs
- DMARDs for resistant cases

Psoriatic Arthritis

- Occurs in 10-20% with psoriasis
- Often precedes skin lesions

Patterns

- **Symmetrical Polyarthritis – Rheumatoid Pattern**
  - Most common (30-40%)
  - Hands, wrists, ankles
- **Asymmetrical Oligoarthritis**
  - 20-30%, previously thought to be most common
  - Typically affects hands & feet
- **Spondylitic Pattern**
  - More common in men
  - Back stiffness
  - Sacroiliitis
  - Antlanto-axial involvement
- **Distal/DIP disease**
  - 10%
- **Arthritis Mutilans**
  - Most severe form
  - Osteolysis around IP joints leading to shortening & telescoping of fingers

Other Signs

- Psoriatic skin lesions
- Periarticular disease
  - Enthesitis
  - Tenosynovitis
  - Dactylitis
- Nail changes
  - Pitting
  - Onycholysis

Investigations

- Psoriasis Epidemiological Screening Tool (PEST)
- X-ray features:
  - Periosteitis, ankylosis, osteolysis, dactylitis
  - Pencil-in-cup appearance

Management

- NSAIDs (potentially alone for mild disease)
- DMARDs
- Anti-TNF
- Ustekinumab (last line)

Reactive Arthritis

- Triad of arthritis, conjunctivitis & urethritis following dysenteric illness or sexually transmitted infection

Features

- 4 weeks after infection, lasts 4-6 months
- Asymmetric oligoarthritis of LL
  - Typically hot, red, swollen knee with negative aspiration cultures
- Urethritis/circinate balanitis
- Conjunctivitis/anterior uveitis
- Keratoderma blenorrhagica

Causes

- Post-STI (Chalmydia) (M:F 10:1)
- Post-dysentery (Shigella, Salmonella, Campylobacter)

Management

- Symptomatic: analgesia, NSAIDs, intra-articular steroids
- Sulfasalazine/methotrexate if persistent
- Symptoms rarely last > 12 months

Gout

- Inflammatory crystal arthropathy caused by deposition of monosodium urate monohydrate in synovium

Predisposing Factors

- Chronic hyperuricaemia (> 0.45mmol/L)

Decreased Urate Excretion

- Diuretics
- CKD
- Lead toxicity

Increased Urate Production

- Myeloproliferative/lymphoproliferative disorder
- Cytotoxic drugs
- Severe psoriasis

Lesch-Nyhan Syndrome

- XR hypoxanthine-guanine phosphoribosyl transferase (HGPRTase) deficiency

Features

- Recurrent acute monoarthritis lasting days, peaking after 12 hours
  - Pain, swelling, erythema
- 70% of first episodes involve 1st MTP joint (podagra)
- Also: ankle, wrist, knee

Chronic

- Gouty tophi in pinna, tendons, joints
- Urate renal stones

Investigations

Joint aspiration

- No bacterial growth (exclude septic arthritis)
- Needle shaped urate crystals
- Negatively birefringent in polarised light

Joint X-Ray

- Joint effusion
- Juxta-articular punched out erosions with sclerotic margins (overhanging edges)
- Late loss of joint space

Acute Management

- NSAIDs (+ PPI)/colchicine 1st line
- Steroids 2nd line
- Continue allopurinol if already taking, don't start in acute setting

Prophylaxis

Lifestyle

- Reduce alcohol & avoid in acute attack
- Lose weight of obese/overweight
- Avoid foods high in purines (liver, seafood, kidney)
- Increased Vitamin C uptake

Medical

- Allopurinol 1st line
  - Recommended after 1st attack (~2 weeks later)
  - Colchicine/NSAID cover (up to 6 months)
- Febuxostat 2nd line
- Refractory option: pegloticase infusions
- Consider stopping/changing diuretics

CPPD

- Acute calcium pyrophosphate dihydrate crystal arthritis, AKA pseudogout

Predisposing Factors

- Age > 60. Others most likely have one of:
- Haemochromatosis
- Hyperparathyroidism
- Hypomagnesaemia/hypophosphataemia
- Acromegaly
- Wilson's disease

Features

Acute

- Acute monoarthropathy of large joints (knee, wrist, shoulders)
- Spontaneous or provoked by illness/surgery/trauma

Chronic

- Rheumatoid-like polyarthritis & synovitis
- Osteoarthritis with superimposed acute attacks

Investigations

Joint Aspiration

- No bacterial growth (exclude septic arthritis)
- Rhomboid shaped CPPD crystals
- Positively birefringent in polarised light

Joint X-Ray

- Chondrocalcinosis

Management

- Rest, cool packs
- NSAIDs (+PPI) ± colchicine
- Joint aspiration
- Intra-articular/oral steroids

Systemic Lupus Erythematosus

- Multisystem autoimmune disease caused by type 3 hypersensitivity to a variety of autoantigens

Epidemiology

- F:M 9:1
- Onset typically 20-40
- More common in Asians & Black Americans
- Rising incidence in the last 50 years
- 10% with SLE have 1st or 2nd degree relative with SLE
- Associated with HLA-B8, DR2 & DR3

Pathophysiology

- Type 3 hypersensitivity (immune complex deposition) affecting any organ

Autoantibodies

- Anti-nuclear antibodies (ANA) +ve in > 99%
  - Low specificity
- Anti-dsDNA +ve in 70%
  - 99% specific
- Anti-Smith +ve in 30%
  - 99% specific
- Anti-Ro, anti-La, anti-RNP (ENA) in 20-40%
- Antiphospholipid antibodies

Associations

- Sjogren's 15-20%
- AI thyroid disease 5-10%

Features

General

- Fatigue
- Fever
- Lymphadenopathy
- Mouth ulcers

Skin

- Malar (butterfly) rash
  - Photosensitive rash on face sparing nasolabial folds
- Discoid rash
  - Scaly erythematous well-demarcated rash in sun exposed areas → hyperpigmented & keratotic → atrophic
- Other photosensitivity
- TEN
- Livedo reticularis
- Reynaud's

MSK

- Arthralgia & myalgia
- Non-erosive arthritis

Cardiovascular

- Pericarditis (most common cardiac)/myocarditis

Respiratory

- Pleurisy
- Fibrosing alveolitis

Renal

- Proteinuria
- Glomerulonephritis

Neuropsychiatric

- Anxiety/depression
- Psychosis
- Seizures
- Mononeuritis multiplex

Investigations

- Autoantibodies
- C3 & C4 (low in active disease)
- ESR (useful for monitoring)
- BP, urine dip, urine microscopy
- Skin/renal biopsies

Diagnosis (SLICC Criteria)

- 4 or more criteria (at least 1 clinical & 1 laboratory)

Clinical

1. Acute cutaneous lupus
2. Chronic cutaneous lupus
3. Non-scarring alopecia
4. Oral/nasal ulcers
5. Synovitis
6. Serositis
7. Urinalysis (proteinuria/red cell casts)
8. Neurological features
9. Haemolytic anaemia
10. Leucopenia
11. Thrombocytopenia

Laboratory

1. ANA
2. Anti-dsDNA
3. Anti-Smith
4. Antiphospholipid Abs
5. Low complement
6. Positive direct coombs test

Management

General

- High factor sunblock
- Screen for drug causes
- Topical steroids for skin disease

Maintenance

- Hydroxychloroquine
  - Reduces disease activity & improves survival
- NSAIDs if no renal disease
- **Resistant Disease**
  - Methotrexate
  - Azathioprine
  - Mycophenylate
  - Tacrolimus
  - Ciclosporin
  - Biologics (rituximab, belimumab)

Acute Flares

- Hydroxychloroquine & steroids
- DMARDs/mycophenylate/biologics in severe flares with organ involvement

Prognosis

- 80% 15 year survival
- Increased long term risk of CVD & osteoporosis

Lupus Nephritis

- Nephropathy occurs in 50% of cases of SLE in the first year, 75% overall
- Can be nephritic or nephrotic

Diagnosis

- Clinical
- Antibodies
  - ANA sensitive, not specific
  - Anti-dsDNA 75-100% specific & correlates to disease activity
- Biopsy

Histological Subtypes

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 is the most common & severe

Management

- Treat hypertension
- Steroids + mycophenolate/cyclophosphamide for class III/IV/V

Drug-Induced Lupus

- Occurs with over 80 known drugs
- Typically skin, lung & musculoskeletal involvement, renal & neurological involvement is unusual
- Remits when offending drug is stopped

Common Causes

- Procainamide
- Hydralazine
- Isoniazid
- Chlorpromazine
- Phenytoin
- Minocycline

Antibodies

- ANA +ve
- dsDNA -ve
- Anti-histone in 90%

Antiphospholipid Syndrome

- Acquired disorder of predisposition to both arterial & venous thromboses, obstetric complications & thrombocytopenia
- Primary or secondary (typically to SLE)

Antiphospholipid Antibodies

- Lupus anticoagulant
- Anti-cardiolipin
- Anti-beta-2 glycoprotein I

Features

Venous Thrombosis

- DVT
- PE

Arterial Thrombosis

- Stroke
- MI
- Renal artery thrombosis

Obstetric Complications

- Recurrent pregnancy loss
- Pre-eclampsia

Others

- Livedo reticularis
- Pulmonary hypertension

Investigations

- Thrombocytopenia
- Prolonged APTT
  - Ex-vivo reaction of lupus anticoagulant & phospholipids involved in coagulation cascade

Diagnosis

- History of thrombosis/pregnancy loss + persistent positive antibodies

Management

- Jointly between rheumatology, haematology & obstetrics if pregnant/attempting pregnancy

Primary Thromboprophylaxis

- Low-dose aspirin

Secondary Thromboprophylaxis

- Lifelong warfarin
- Target INR:
  - VTE: 2-3
  - VTE while on warfarin: 3-4
  - Arterial thrombosis: 2-3

Pregnancy

- Aspirin + LMWH

Systemic Sclerosis

- Condition of unknown aetiology characterised by sclerotic hardening of skin & other connective tissue
- ANA, anti-centromere & anti-Scl70

Epidemiology

- F:M 4:1
- Associated with other CT diseases (SLE, Sjogren's, MCTD)

Types

Limited Cutaneous Systemic Sclerosis

- Scleroderma affecting face & distal limbs predominantly
- Associated with anti-centromere antibodies
- Pulmonary hypertension may occur & should be actively looked for
- **CREST Syndrome**
  - Subtype/former name
  - Calcinosis, Reynaud's phenomenon, oEsophageal dysmotility, Sclerodactyly, Telangiectasia

Diffuse Cutaneous Systemic Sclerosis

- Whole body & organ involvement
  - Skin of trunks & proximal limbs predominantly
- Associated with anti-Scl70 antibodies
- Poor prognosis
- Respiratory involvement (80%) most common cause of death
  - Interstitial lung disease
  - Pulmonary artery hypertension
- Renal disease
- Hypertension

Scleroderma Without Organ Involvement

- Tightening/fibrosis of skin
  - Plaques (morphea)
  - Linear

Specific Signs

- Sclerodactyly
  - Reduced range of movement
  - Ulceration
- Microstomia
- Telangiectasia common on face
- Calcinosis common on fingertips

Investigations/Diagnosis

- Nailfold capillaroscopy showing abnormal capillaries, micro-haemorrhages & avascular areas supportive of diagnosis & useful in ruling out systemic sclerosis in patients with Reynaud's
- ACR/EULAR diagnostic criteria use clinical features, autoantibodies & nailfold capillaroscopy

Management

General

- Avoid smoking & Reynaud's triggers
- Physio & OT

Medical

- Steroids & immunosuppression for end-organ involvement & progressive skin disease
- Treat BP (ACEi)

Sjogren's Syndrome

- Autoimmune disorder affecting exocrine glands resulting in dry mucosal surfaces
- F:M 9:1
- 40-60x risk of lymphoid malignancy

Causes

Primary (PSS)

- Anti-Ro positive in 70%
- Anti-La positive in 30%

Secondary

- May occur up to 10 years after onset of initial disease
- Rheumatoid arthritis
- SLE

Features

- Dry eyes (keratoconjunctivitis sicca)
- Dry mouth
- Vaginal dryness
- Arthralgia
- Sensory polyneuropathy
- Recurrent parotiditis
- Subclinical RTA

Investigations

Antibodies

- RF positive in 50%
- ANA positive in 70%
- ENAs
  - Anti-Ro positive in 70% with PSS
  - Anti-La positive in 30% with PSS

Schirmer's Test

- Folded strip of filter paper placed under lower eyelid and left hanging out
- Length of tear soakage measured after 5 minutes
- >15mm normal, <10mm significant

Others

- Hypergammaglobinaemia
- Low C4

Management

- Artificial saliva/tears
- Vaginal lubrication
- Pilocarpine may stimulate tear production
- Hydroxychloroquine may slow disease progression

Complications

- Conjunctivitis, corneal ulcers
- Dental cavities, candida infections
- Vaginal candidiasis, sexual dysfunction
- Pneumonia, bronchiectasis
- Peripheral neuropathy
- Vasculitis
- Renal impairment

Polymyositis & Dermatomyositis

- Inflammatory disorder causing symmetrical proximal muscle weakness (polymyositis) ± skin lesion (dermatomyositis)
- Typically middle age, female:male 3:1

Pathophysiology

- T-cell mediated cytotoxic process against muscle fibres
- Idiopathic or associated with other connective tissue disorders
- **May be a paraneoplastic syndrome of underlying malignancy**
  - Lung
  - Breast
  - Ovarian
  - Gastric

Features

Both

- Progressive symmetrical proximal muscle weakness
- Myalgia & arthralgia
- Develops over weeks
- Dysphagia, dysphonia, respiratory weakness

Dermatomyositis

- Gottron lesions (scaly erythematous patches) on knuckles, elbows & knees
- Photosensitive erythematous rash on back, shoulders & neck
- Periorobital heliotrope rash
- "Mechanic's hands" – dry & scaly hands with cracks on palmar & lateral aspects
- Nail fold capillary dilatation

Extra-Muscular Features

- Fever
- Reynaud's
- Interstitial lung disease

Investigations/Diagnosis

- Elevated CK, LDH, AST, ALT
- EMG
- Muscle biopsy
- 80% ANA positive
- Anti-synthetase antibodies:
  - Anti-Jo-1 (polymyositis > dermatomyositis)
  - Anti-Mi-2 (dermatomyositis)

Management

General

- Physio & OT
- Assess new cases for underlying cancer

Medical

- Corticosteroids 1st line
- Immunosuppressants/IVIg/biologics for resistant cases
- Hydroxychloroquine/topical tacrolimus for skin disease

Polymyalgia Rheumatica

- Inflammatory condition of pain & stiffness of pelvic & shoulder girdles with strong association with temporal arteritis

Epidemiology

- Typically > 50
- F>M
- More common in white patients

Features

- Bilateral shoulder pain which may radiate to elbow
- Bilateral pelvic girdle pain
- Worse with movement & in morning
  - Stiffness for at least 45 minutes in morning
- Upper arm/shoulders/back tenderness
- Disturbs sleep
- Systemic
  - Weight loss
  - Fever
  - Malaise
  - Anorexia
  - Low mood
- Carpal tunnel syndrome

Differentials

- Osteoarthritis/RA/seronegative arthropathy
- SLE
- Myosotis
- Cervical spondylosis
- Osteoporosis

Investigations

- Raised ESR
- CK & EMG normal

Rule Out Other Causes

- FBC, U+Es, LFTs, TFT
- RF, anti-CCP, ANA
- Urinary Bence Jones protein
- CXR

Management

- Prednisolone 15mg daily
  - Assess response after 1 week, poor response indicates alternative diagnosis
- Reducing regimen
  - 15mg for 3-4wks
  - 12.5mg for 3-4wks
  - 10mg for 3-4wks
  - Reduce by 1mg every 4-8 weeks

Vasculitides

- Inflammatory disorders of blood vessels classified by modified Chapel Hill Criteria
- Can affect any organ
- Primary or secondary to systemic disease (RA, SLE, viral hepatitis)
- General features include purpura, polyarthralgia, iritis/scleritis, peripheral neuropathy, GI disturbance, renal impairment & systemic features

Large Vessel	Medium Vessel	Small Vessel	Variable Vessel
• Temporal/Giant Cell arteritis • Takayasu's arteritis	• Polyarteritis nodosa • Kawasaki disease	**ANCA Associated** • Microscopic polyangiitis • Granulomatosis with polyangiitis • Eosinophilic granulomatosis with polyangiitis **Immune Complex Vasculitis** • Goodpasture's disease • HSP • Cryoglobulinaemic vasculitis	• Behcet's disease • Cogan's syndrome

Temporal/Giant Cell Arteritis

- Large vessel vasculitis with strong association with polymyalgia rheumatica

Features

- Subacute (< 1 month) onset
- Features of PMR in 50%
- Headache in 85%
  - Severe & unilateral
  - Temporal/frontal region
- Jaw claudication in 65%
- Scalp tenderness
- Tender palpable temporal artery

Visual (AION)

- Amaurosis fugax
- Blurring
- Double vision
- Sudden & permanent blindness

Systemic

- Lethargy
- Depression
- Low-grade fever
- Anorexia
- Night sweats

Investigations

- Raised ESR > 50mm/hr
- Raised CRP
- Temporal artery biopsy shows multinucleated giant cells
  - Skip lesions present so biopsy may be ne negative

Management

Steroids

- High dose steroids as soon as diagnosis is suspected
- Prednisolone (with IV methylpred if there is visual loss)
- 60mg/day

Others

- Aspirin
- PPI gastroprotection
- Bisphosphonate bone protection
- Urgent ophthalmology review

Takayasu's Arteritis

- Large vessel vasculitis typically affecting aortic arch
- More common in females & Asian people

Features

- Absent limb pulse
- Unequal BP in upper limbs
- Intermittent claudication
- Dizziness
- Visual changes
- Aortic regurgitation in 20%
- Hypertension (renal artery stenosis)

Systemic

- Fever
- Fatigue
- Weight loss
- Malaise

Complications

- Stroke
- Ischaemic heart disease

Investigations

- Raised ESR & CRP
- Angiography/PET-CT/MRI

Management

- Steroids
- Methotrexate/cyclophosphamide for resistant cases
- Angioplasty/stenting/bypass for critical stenoses

Polyarteritis Nodosa

- Medium vessel necrotising vasculitis causing aneurysms & thrombosis which can occur in isolation or association with hepatitis B, C, or HIV
- More common in middle aged men

Features

- Fever, weight loss, malaise
- Livedo reticularis
- Renal involvement (main cause of death)
  - Renal artery stenosis
  - Glomerular ischaemia
  - Haematuria & renal failure
- Peripheral neuropathy/mononeuritis multiplex
- Arthralgia

Investigations

- Raised ESR & CRP
- Renal/mesenteric angiography/renal biopsy diagnostic

Management

- Steroids/immunosuppression
- Control BP

Microscopic Polyangiitis

- Small vessel ANCA vasculitis

Features

- RPGN
- Cough, dyspnoea, haemoptysis
- Palpable purpura
- Mononeuritis multiplex
- Fever & systemic features

Investigations

- pANCA (MPO) +ve in 75%
- cANCA (PR3) +ve in 40%

Management

- Steroids/immunosuppression

Granulomatosis with Polyangiitis

- AKA Wegener's granulomatosis
- Autoimmune necrotising granulomatous vasculitis affecting upper & lower respiratory tract & kidneys

Features

URT

- Epistaxis
- Chronic sinusitis
- Saddle-nose deformity
- Nasal crusting

LRT

- Cough
- Dyspnoea
- Haemoptysis
- Pleurisy

Renal

- Pauci-immune RPGN in 80% of patients
  - Haematuria & proteinuria

Others

- Skin lesions: palpable purpura
- Ocular lesions: conjunctivitis, keratitis, uveitis
- Cranial nerve lesions

Investigations

- cANCA (PR3) positive in 90%, pANCA (MPO) positive in 25%
- CXR can show a wide variety of lesions
  - Bilateral nodular lesions
  - Cavitation
- Renal biopsy showing epithelial crescents

Management

- Steroids
- Cyclophosphamide
- Plasma exchange
- Median survival 8-9 years

Eosinophilic Granulomatosis with Polyangiitis

- AKA Churg-Strauss syndrome
- Small-medium vessel vasculitis
- May be precipitated by montelukast

Features

- Late onset asthma
- Paranasal sinusitis
- Mononeuritis multiplex
- RPGN
- Palpable skin purpura
- GIT bleeding

Investigations

- Eosinophilia
- pANCA (MPO) positive in 60%

Behcet's Syndrome

- Multisystem inflammatory disorder of unknown aetiology affecting arteries & veins

Epidemiology

- More common in Eastern Mediterranean to Asia, men, & those aged 20-40
- 30% have positive family history
- Associated with HLA-B51

Features

- Classic triad of oral ulcers, genital ulcers, & anterior uveitis

Oral Ulcers

- 3+ episodes per year
- Painful
- Sharply circumscribed with red halo
- Heal over 2-4 weaks

Genital Ulcers

- "Kissing ulcers": on 2 opposing surfaces

Eyes

- Anterior uveitis
- Retinal vasculitis
- Retinal haemorrhage

Skin

- Erythema nodosum
- Vasculitis type rashes
- Papulopustular lesions

Musculoskeletal

- Morning stiffness & arthralgia
- Oligoarthritis of knee/ankle

GI

- Colitis

CNS

- Pyramidal signs
- Headache

Vascular

- DVT/Thrombophlebitis
- Budd-Chiari syndrome
- Intracranial venous thrombosis

Investigations

- Diagnosis mainly clinical

Pathergy Test

- Sterile needle prick leads to papule formation within 48 hours
- Tests for non-specific skin hypersensitivity

Management

- Topical steroids for ulcers
- Colchicine for ulcers
- Steroids/immunosuppressants/biologics for systemic disease

Back Pain

- Very common & usually mechanical/musculoskeletal & self limiting

Red Flag Causes & Features

- Age < 20 or > 55
- Neurological disturbance (including sciatica)

Spinal Fracture

- Acute onset in the elderly
- Thoracic back pain

Spinal Malignancy

- Constant/progressive pain
- Fever/night sweats/weight loss
- History of malignancy
- Abdominal mass

Ankylosing Spondylosis

- Age < 40
- Nocturnal pain
- Pain worse while supine
- Morning stiffness

Spinal Infection

- Current/recent infection
- Immunosuppression
- Fever/night sweats/weight loss

Cauda Equina

- Sphincter disturbance
- Saddle anaesthesia
- Urinary retention
- Bilateral/alternating leg pain

Spinal Stenosis

- Leg claudication/exercise related leg weakness/numbness (spinal stenosis)

Common Causes By Age

15-30 Years

- Prolapsed disc
- Trauma/fractures
- AS
- Spondylolisthesis
- Pregnancy

30-50 Years

- Degenerative spinal disease
- Prolapsed disc
- Malignancy

> 50 Years

- Degenerative spinal disease
- Osteoporotic vertebral collapse
- Paget's
- Malignancy
- Myeloma
- Spinal stenosis

Mechanical Causes

- Muscle/ligament sprain
- Facet joint dysfunction
- Sacroiliac joint dysfunction
- Herniated disc
- Spondylolisthesis
- Scoliosis
- Degenerative disease of discs/facet joints

Investigation

Imaging

- Lumbar X-rays should not be offered
- Spinal MRI should be offered only if it is expected to change the management of the patient and if any of the following are suspected:
  - Malignancy
  - Infection
  - Fracture
  - Cauda Equina
  - Ankylosing spondylitis
- If any features of cauda equina syndrome are present and emergency MRI should be arranged (within hours)

Bloods

- Only to test for clinical suspicions
- FBC, ESR, CRP, U&E
  - Myeloma
  - Infection
  - Malignancy
  - AS
- ALP
  - Paget's
- Serum/urine electrophoresis
  - Myeloma
- PSA
  - Prostate Ca

Management

General

- Educate
- Encourage exercise & self-management
- Physiotherapy, acupuncture, exercise programme
- Address psychosocial issues which may predispose to chronic pain & disability

Analgesia

- NSAIDs + PPI cover first line
  - Evidence shows paracetamol alone is ineffective
- Neuropathic pain management
  - Amitriptyline

Referral

- Urgent neurosurgical referral for features of cauda equina syndrome
- Referral to chronic pain specialists/surgeons for intractable symptoms

Osteoporosis

- Disorder characterised by loss of bone mass, defined as bone mineral density less than 2.5 standard deviations below the mean young adult mineral density
- Associated with significant risk of fragility fractures which carry significant morbidity and mortality

Risk Factors

- Increasing age
- Female gender
- Steroid use/Cushing's syndrome
- Smoking
- Alcohol
- Low BMI
- Family history
- Caucasian/Asian ethnicity
- CKD
- Sedentary lifestyle

Risk Assessment (FRAX)

- Estimates 10 year risk of fragility fracture, valid from 40-90
- Uses: Age, sex, weight, height, previous fragility fracture, parental fragility fracture, current smoking, glucocorticoids, RA, secondary osteoporosis, alcohol intake, BMD (if available)

Interpretation

- **Low risk:** Reassure & give lifestyle advice
- **Intermediate risk:** Offer DEXA
- **High risk:** Offer bone protection treatment

Indications

- Women aged > 65
- Men aged > 75
- Younger patients with above risk factors

DEXA Scan

- Direct assessment of bone mineral density
- T score: standard deviations below average for young healthy adult
- Z score: standard deviations below average for patients own risk factors

T Score Interpretation

- **> -1.0:** Normal
- **-1.0 - -2.5:** Osteopenia
- **< -2.5:** Osteoporosis (severe osteoporosis if fragility fracture)

Management

- Alendronate is 1st line for confirmed osteoporosis
- Further bisphosphonates have lower T-score eligilibilty criteria, and further agents have lower cut-offs again

General/Lifestyle/Prevention

- Activity & weight bearing exercise
- Maintain healthy weight
- Adequate calcium & vitamin D
- Avoid falls
- Stop smoking
- Reduce alcohol consumption

Calcium & Vitamin D

- Calcichew D3: 1000mg Ca + 800U vitamin D
- Recommended for all with risk factors
- No strong evidence in general population, may reduce fracture rates in frail housebound patients

Bisphosphonates

- 1st line treatment for osteoporosis
- **Examples:**
  - Alendronate 70mg weekly PO (1st line)
  - Risedronate 35mg weekly PO
  - Zoledronic acid 5mg yearly IV
- **Side Effects:**
  - Reflux & oesophageal erosions
    - Oral bisphosphonates should be taken on an empty stomach followed by 30 minutes sitting upright without moving or eating
  - Atypical femoral fractures
  - Osteonecrosis of the jaw
  - Osteonecrosis of the external auditory canal

Denosumab

- Monoclonal antibody inhibiting RANK ligand and therefore maturation of osteoclasts
- Subcutaneous injection every 3 months

Strontium Ranelate

- Increases osteoblast & decreases osteoclast activity
- Risk of cardiovascular events, thromboembolic events, & Stevens-Johnson syndrome
  - Specialist last line prescription only

Raloxifene

- SERM
- Proven to decrease risk of vertebral fractures only
- May decrease risk of breast cancer
- Increased risk of thromboembolic events & worsened menopause symptoms

Hormone Replacement Therapy

- For women who have gone through early menopause

Osteomalacia

- Softening of bones secondary to insufficient vitamin D, resulting in reduced mineral bone content
- Referred to as rickets in children

Causes

- Vitamin D deficiency
  - Malabsorption
  - Lack of sunlight
  - Dietary
- Chronic kidney disease
- Drug induced (eg anticonvulsants)
- Inherited (eg hypophosphataemic rickets)
- Liver disease/cirrhosis

Features

- Bone pain
- Bone/muscle tenderness
- Fractures, especially of femoral neck
- Proximal myopathy, may lead to waddling gait

Investigation

Bloods

- Low vitamin D
- Low calcium & phosphate in 30%
- Raised ALP in 95-100%

X-ray

- Looser's zones/pseudofractures (translucent bands)

Management

- Vitamin D supplementation with initial loading dose
- Calcium supplementation if dietary intake is inadequate

Paget's Disease of Bone

- Disease of excessive & disordered bone turnover, lead primarily by excessive osteoclastic activity & secondary osteoblastic activity
- Skull, spine, pelvis, & long bones of lower limbs most affected
- Present in up to 5% of adults but only 5% of patients are symptomatic

Risk Factors

- Increasing age
- Male sex
- Northern latitude
- Family history

Features

- Bone pain
- Bony deformities
  - Bowing of tibia
  - Bossing of skull
- Fractures
- Hearing loss (involvement of ossicles)

Investigations

Bloods

- Isolated raised ALP
- Other markers of bone turnover
  - Procollagen type I N-terminal propeptide (PINP)
  - Serum C-telopeptide (CTx)
  - Urinary N-telopeptide (NTx)
  - Urinary hydroxyproline

Imaging (XR)

- Osteolysis later developing to mixed osteolysis/osteosclerosis
- Bone enlargement and deformity
- Osteoporosis circumscripta: well defined osteolytic lesions
- Cotton wool appearance of skull
- V-shaped osteolytic lesions of long bones

Bone Scintigraphy

- Increased uptake at site of active lesions

Management

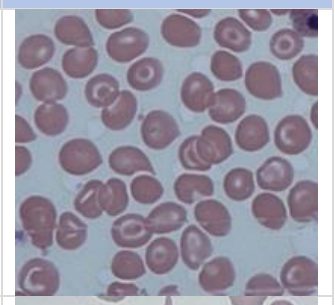
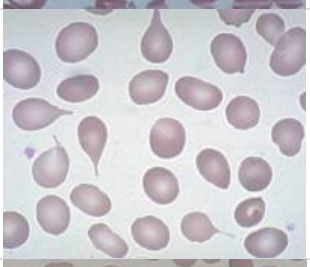
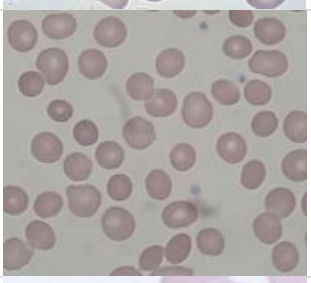
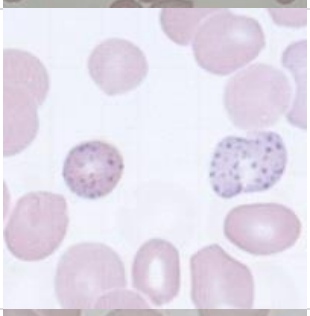
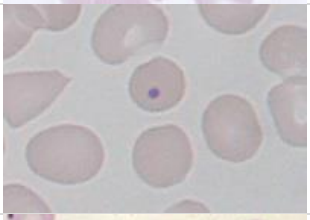
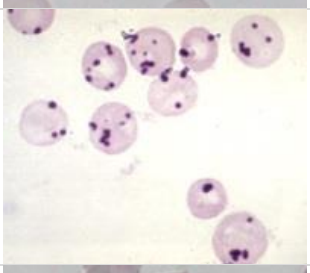
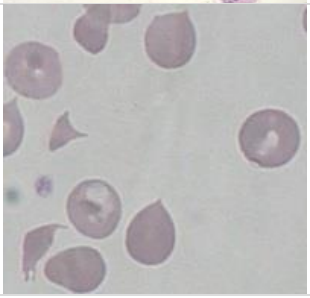
- Bisphosphonates
- Indications:
  - Bone pain
  - Skull/long bone deformity
  - Fracture
  - Periarticular disease

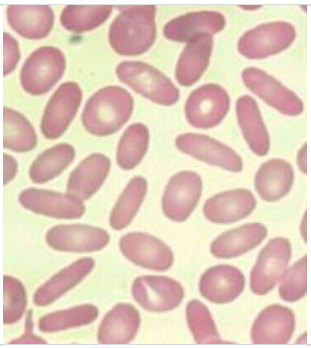
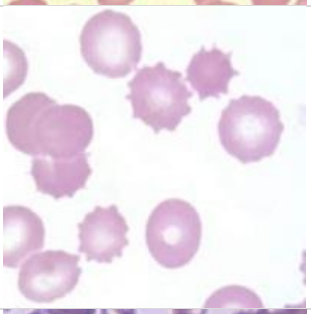
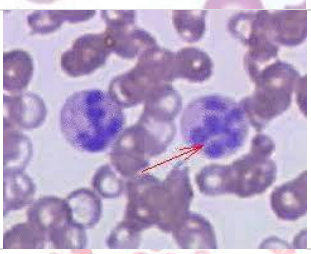
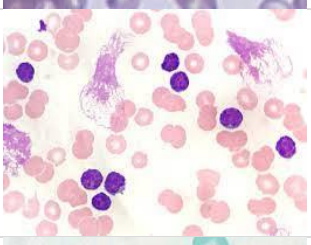
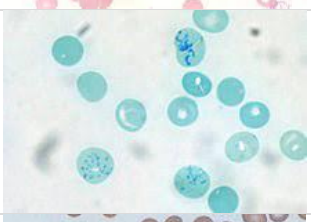
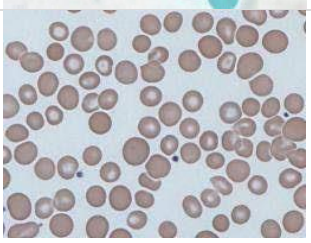
Complications

- Osteosarcoma (< 1% in 10 years)
- Deafness (cranial nerve entrapment/involvement of ossicles)
- Skull thickening
- Spinal stenosis
- High-output cardiac failure

Haematology

Peripheral Blood Film Results

Abnormality	Association	Appearance
Target Cells	Sickle-cell/thalassaemia Iron-deficiency anaemia Hyposplenism Liver disease	
"Tear-Drop" Poikilocytes	Myelofibrosis	
Spherocytes	Hereditary spherocytosis Autoimmune haemolytic anaemia	
Basophilic Stippling	Lead poisoning Thalassaemia Sideroblastic anaemia Myelodysplasia	
Howell-Jolly Bodies	Hyposplenism	
Heinz Bodies	G6PD deficiency Alpha-thalassaemia	
Schistocytes ("Helmet Cells")	Intravascular haemolysis Mechanical heart valve Disseminated intravascular coagulation	

"Pencil" Poikilocytes	Iron Deficiency anaemia	
Burr Cells/Echinocytes	Uraemia Pyruvate kinase deficiency	
Hypersegmented Neutrophils	Megaloblastic anaemia	
Smudge Cells	Chronic lymphocytic leukaemia	
Reticulocytes	Haemolytic anaemia	
Anisocytosis (unequal cell sizes)	Myelodysplastic syndromes	

Anaemia

- Reduced haemoglobin concentration - < 13.5g/dL for men, < 11.5g/dL for women

Causes

- Grouped according to Mean Cell Volume (MCV)
- Normal is 76-96 femtolitres

Microcytic

- Thalassaemia
- Anaemia of chronic disease
- Iron deficiency anaemia
- Lead poisoning
- Sideroblastic anaemia

Normocytic

- Acute blood loss
- Anaemia of chronic disease
- Aplastic anaemia
- Haemolytic anaemia
- Hypothyroidism
- CKD

Macrocytic

- **Megaloblastic**
  - Vitamin B12 deficiency
  - Folate deficiency
- **Normoblastic Macrocytic**
  - Reticulocytosis (from haemolysis/blood loss)
  - Alcohol excess/liver disease
  - Hypothyroidism
  - Myelodysplastic syndromes
  - Marrow infiltration
  - Drugs (cytotoxics, azathioprine, antifolates)

Features

Symptoms

- Fatigue
- Dyspnoea
- Faintness
- Headaches
- Tinnitus
- Anorexia
- Angina if preexisting IHD

Signs

- Pallor (conjunctivae, palmar creases)
- Hyperdynamic circulation
  - Tachycardia
  - Flow murmur (systolic heard over apex)
  - Cardiac enlargement
  - Heart failure

Underlying Causes

- Iron deficiency (koilonychia, angular cheilitis, atrophic glossitis, brittle hair & nails)
- Jaundice due to haemolytic anaemia
- Oedema, hypertension, excoriations in CKD
- Bone deformities in thalassaemia

Initial Investigations

- Hb & MCV
- B12 & folate
- Ferritin
- Blood film

Iron Deficiency Anaemia

Causes

Inadequate Dietary Intake

- Vegans/vegetarians may be more at risk
- Red meat & dark leafy vegetable are good sources

Blood Loss

- Menorrhagia
- Any cause of GI bleeding
  - Important to rule out malignancy

Poor Absorption

- E.g. Coeliac disease, hookworm
- Causes refractory IDA

Increased Iron Requirements

- Childhood/adolescence
- Pregnancy

Features

- Fatigue, SOBOE, palpitations
- Pallor
- Angular stomatitis
- Atrophic glossitis
- Hair loss
- Koilonychia

Investigations

FBC

- Hypochromic microcytic anaemia

Iron Studies

- Reduced ferritin (correlates with iron stores)
  - Acute phase reactant so unreliable in inflammatory conditions
- TIBC high
- Transferrin saturation low

Blood Film

- Anisopoikilocytosis
  - RBCs of different sizes & shapes
- Target cells
- Pencil poikilocytes

Endoscopy

- To rule out malignancy
- Post-menopausal women with Hb < 10 & men with Hb < 11 should be referred to gastroenterology within 2 weeks

Management

- Treat cause
- Iron rich foods
- Oral ferrous sulphate 200mg/8hrs
  - Should increase Hb by .1g/dL per week
  - Continue for 3 months after normalising
  - Side effects: abdominal discomfort, diarrhoea/constipation, black stools
- IV iron if oral route is impossible/ineffective

Anaemia of Chronic Disease

- Most common anaemia in inpatients & 2nd most common worldwide
- Mechanisms involve polypeptide hepcidin

Mechanisms

- Poor use of iron in erythropoiesis
- Cytokine induced shortening of RBC survival
- Decreased production of & response to erythropoietin

Causes

- Chronic infection
- Vasculitis
- Rheumatoid
- Malignancy
- Renal failure

Investigations

FBC

- Microcytic anaemia

Iron Studies

- Normal or high ferritin
- Low transferrin saturation & TIBC

Management

- Treatment of underlying cause if possible
- Erythropoietin
- IV iron

Sideroblastic Anaemia

- Defective haem production resulting in deposits of iron in the mitochondria which forms a ring around nucleus (ring sideroblast)

Causes

Congenital

- Delta-aminolevulinate synthetase-2 deficiency

Acquired

- Myelodysplasia
- Alcohol
- Lead
- Anti-TB medications
- Vitamin B6 (pyridoxine) deficiency

Investigations

FBC

- Microcytic anaemia

Iron Studies

- High ferritin, iron, & transferrin saturation

Blood Film

- Basophilic stippling of RBCs

Bone Marrow

- Prussian blue stain stows ring sideroblasts

Management

- Supportive
- Treatment of any underlying cause
- Pyridoxine may help

B12 Deficiency

- Vitamin B12 is actively absorbed in the terminal ileum, bound to intrinsic factor secreted by gastric parietal cells
- Important for red blood cell development & maintenance of the nervous system

Causes

- Pernicious anaemia (most common)
- Post gastrectomy
- Vegan/poor diet
- Disorders/surgery to the terminal ileum
  - Crohn's disease
- Metformin (rare)

Pernicious Anaemia

- Antibodies to intrinsic factor/gastric parietal cells result in B12 deficiency

Risk Factors/Associations

- More common in females (1.6:1)
- Other autoimmune disease
- Blood group A

Specific Tests

- Intrinsic factor antibodies
  - High specificity, low sensitivity
- Parietal cell antibodies
  - High sensitivity, low specificity

Complications

- Increased risk of gastric cancer

Features

General

- Macrocytic anaemia
- Glossitis & angular cheilitis
- Lemon tinge to skin

Neurological

- Dorsal column disease: loss of fine touch/vibration/proprioception
- Paraesthesia
- SACD

Neuropyschiatric

- Mood disturbance

Subacute Combined Degeneration of the Cord

- Combined peripheral neuropathy and both upper and lower motor neuron signs due to B12 deficiency
- Dorsal columns & lateral corticospinal tracts affected

Features

- Joint position & vibration sense loss followed by distal parasthesia & ataxia
- Mixed motor neuron signs in the legs, classically extensor plantars, absent ankle jerks, absent/brisk knee jerks
- Stiffness & weakness persist if untreated

Management

- IM hydroxycobalamin: 3x/week for 2 weeks (or until resolution of neuro symptoms), then once every 2 months
- Must be normalised before folate to avoid SACD

Causes of Haemolytic Anaemia

- Haemolysis is the premature breakdown of RBCs
- Haemolytic anaemia occurs when RBC production cannot match RBC breakdown

General Features/Investigations

- FBC, MCV, LDH, haptoglobin, urinary urobilinogen, thick & thin screens, blood film, direct antigen/Coombs test

Increased RBC Breakdown

- Anaemia with normal/raised MCV
- Raised unconjugated bilirubin & urinary urobilinogen
- Raised LDH

Increased RBC Production

- Reticulocytosis, raised MCV, polychromasia

Intravascular vs Extravascular

- **Intravascular**
  - Raised free plasma haemoglobin
  - Methaemoglobinaemia
  - Decreased plasma haptoglobin
  - Haemoglobinuria & haemosiderinuria
- **Extravascular**
  - Splenomegaly

Hereditary Causes

Membrane

- Hereditary spherocytosis
- Hereditary elliptocytosis

Metabolism

- G6PD deficiency

Haemoglobin

- Thalassaemia
- Sickle cell disease

Immune Causes (DAT +ve)

Autoimmune

- Warm/cold AIHA

Alloimmune

- Transfusion reactions
- Haemolytic disease of the newborn

Drugs

- Methyldopa
- Penicillin

Non-Immune Acquired Causes (DAT -ve)

Microangiopathic Haemolytic Anaemia

- TTP/HUS
- DIC
- Malignancy
- Pre-eclampsia

Infections

- Malaria

Drugs

- Dapsone

Others

- Paroxysmal nocturnal haemoglobinuria
- Prosthetic heart valves
- DAT -ve AIHA
  - 2% of AIHA
  - Associated with viral hepatitis, autoimmune hepatitis, post flu/vaccinations

Autoimmune Haemolytic Anaemia

- Most commonly idiopathic
- May be secondary to lymphoproliferative disorders/drugs
- Direct antigen/Coombs test (DAT) positive

Warm AIHA

- Antibodies (typically IgG) bind best at body temperature & cause extravascular haemolysis

Causes

- Idiopathic
- AI disease (SLE)
- Neoplasia
  - Lymphoma
  - CLL
- Drugs
  - Methyldopa

Management

- Treatment of underlying disorder if possible
- Steroids ± rituximab 1st line
- Splenectomy

Cold AIHA

- Antibodies (typically IgM) bind best at 4°C causing complement mediated intravascular haemolysis
- Features include chronic anaemia made worse by cold, & Raynaud's phenomenon/acrocyanosis
- Poor response to steroids

Causes

- Neoplasia
  - Lymphoma
- Post-infection
  - Mycoplasma
  - EBV

Management

- Keep warm
- Chlorambucil may help

Paroxysmal Cold Haemoglobinuria

- Seen with viruses/syphilis
- Donath-Landsteiner antibodies stick to RBCs in cold & cause self-limiting haemolysis on rewarming

Paroxysmal Nocturnal Haemoglobinuria

- Rare acquired stem cell disorder leading to:
  - Intravascular haemolysis, typically at night
  - Venous thrombosis

Pathophysiology

- Lack of glycoprotein glycosyl-phosphatidylinositol (GPI) which acts as an anchor to attach surface proteins to cell membrane
- Complement-regulating surface proteins, such as delay-activating factor (DAF), are not properly bound
  - Increased sensitivity to complement causing haemolysis
- CD59 is not properly bound to platelet membranes
  - Platelet aggregation & thrombosis

Features

- Haemolytic anaemia
- Pancytopenia may be present
- Haemoglobinuria
  - Red-brown urine
  - Typically in morning but can occur throughout day
- Thrombosis
  - E.g. Budd-Chiari syndrome

Investigations

- Raised urinary haemosiderin
- Flow cytometry positive for low levels of CD59 & CD55
  - Gold standard
- Ham's test: acid-induced haemolysis
  - Previous gold standard

Management

- Blood product replacement
- Anticoagulation
- Eculizumab
  - MAb to terminal protein C5
- Stem cell transplantation

Haemolytic Uraemic Syndrome

- Common in younger children, presents in adults also

Causes

Typical/Secondary

- Following infection
  - E. coli O157:H7 (Shiga toxin/STEC/ verotoxigenic/enterohaemorrhagic)
    - Most common, especially in children (> 90%)
  - Pneumococcal infection
  - HIV
- Rare causes
  - SLE
  - Malignancy
  - Drugs

Atypical/Primary

- Complement dysregulation
- ~5% of cases
- Cam be triggered by pregnancy

Features (Triad)

- Acute kidney injury
- Microangiopathic haemolytic anaemia
- Thrombocytopenia

Investigations

- FBC, U+E, film
- Stool culture & PCR for Shiga toxin
- Complement levels

Management

Typical

- Supportive
  - Fluids, transfusion, dialysis if required
- No role for antibiotics

Atypical

- Plasma exchange/eculizimab

Thrombotic Thrombocytopenic Purpura

- Deficiency of ADAMTS13, a metalloproteinases which cleaves large multimers of vWF
- vWF multimers lead to platelet aggregation

Causes

- Post-infection
- Pregnancy
- Malignancy
- SLE
- HIV
- Drugs: ciclosporin, OCP, penicillin, clopidogrel, acyclovir

Features (Pentad)

- Features of HUS
- Fever
- Fluctuating neurological signs (headache, palsies, seizure, confusion, coma)

Management

- Urgent plasma exchange ± steroids ± rituximab

Thalassaemia

- Autosomal recessive defects in alpha or beta globin chains
- Unmatched globin chains precipitate and lead to haemolysis while still in marrow
- Cause a microcytic anaemia & are specifically diagnosed with haemoglobin electrophoresis ± genetic testing
- Features of anaemia +
  - Splenomegaly
  - Poor growth/development in children
  - Pronounced forehead & malar eminences

Beta Thalassaemia

- Point mutations in beta-globin gene on chromosome 11 leading to:
  - Decreased production (β^+)
  - Absence (β^o)

Beta Thalassaemia Minor/Trait

- β/β^+ heterozygous state
- Typically asymptomatic carrier state with Hb >90
  - Drops in pregnancy
  - Microcytosis disproportionate to anaemia
- HbA_2 > 3.5%, slight increase in HbF

Beta Thalassaemia Intermedia

- Intermediate state with multiple causes
  - β^+/β^+
  - Beta thalassaemia trait with another haemoglobinopathy
- Moderate anaemia not typically requiring transfusions
- Splenomegaly

Beta Thalassaemia Major

- Significant abnormalities in both beta-globin genes
- Significant anaemia & failure to thrive in 1st year of life
- Extramedullary haematopoiesis results in:
  - Skull bossing
  - Hepatosplenomegaly
- Lifelong blood transfusions which result in iron overload and endocrine failure, liver disease & cardiac toxicity after ~10 years

Investigations

- FBC (microcytic anaemia), HbA_2 (↑), HbF (↑), HbA (↓/absent)
- Haemoglobin electrophoresis
- Blood film: target cells, basophilic stippling

Management

- Repeated (~2-4 weekly) transfusions with iron chelation therapy (desferrioxamine)
- Splenectomy if hypersplenism persists requiring more frequent transfusions
- Hormonal replacement for endocrine complications
- Bone marrow transplant may offer cure

Alpha Thalassaemia

- Defects in some/all of the two alpha-globin genes on each chromosome 16 (αα/αα)
- (--/--): Death in utero (Bart's Hydrops)
- (--/-α) HbH disease
  - Moderate anaemia & features of haemolysis, β_4 tetramers on blood film
- (--/αα)/(-α/-α): asymptomatic carrier state

Hereditary Spherocytosis

- Most common hereditary haemolytic disorder of north-eastern European populations

Pathophysiology

- AD defect of RBC cytoskeleton resulting in fragile spherical RBCs which are destroyed in the spleen

Features

- Neonatal jaundice, failure to thrive
- Jaundice
- Gallstones
- Splenomegaly
- Aplastic crises precipitated by parvovirus infection

Investigations

- Raised MCHC
- Blood film: reticulocytosis & spherocytosis
- Clinical features + above lab tests + family history is diagnostic
- Osmotic fragility test no longer considered reliable

Equivocal Cases

- EMA binding test & cryohaemolysis test

Management

Long Term

- Folate replacement
- Splenectomy

Acute Crises

- Supportive treatment with transfusion if necessary

Hereditary Elliptocytosis

- Milder AD condition with elliptical red blood cells
- Presentation & management are the same

G6PD Deficiency

- X-linked recessive condition, most common RBC enzyme defect, particularly in Mediterranean & Africa

Pathophysiology

- G6PD started the pathway of NADPH generation which is required to (chemically) reduce oxidised glutathione
- Reduced (in amount) glutathione leaves the RBC susceptible to oxidative stress resulting in intravascular haemolysis

Features

- Neonatal jaundice
- Gallstones
- Splenomegaly
- Haemolytic crises triggered by Fava beans, antimalarials, ciprofloxacin, sulpha drugs, infection

Investigations

- G6PD assay (at least 3 months after crisis) is diagnostic
- Blood film: Heinz bodies, bite cells, blister cells

Management

- Avoid precipitants, transfuse if severe

Sickle Cell Disease

Pathophysiology

- Autosomal recessive condition of beta-globin gene on chromosome 11 resulting in formation of abnormal haemoglobin chain (HbS)
  - One copy (HbAS): sickle cell trait
  - Two copies (HbSS): sickle cell disease
- HbS is insoluble and crystalises (causing the cell to "sickle") when deoxygenated
  - HbAS sickles at pO2 2.5-4kPa
  - HbSS sickles at pO2 5-6kPa
- Does not present until ~ 6 months when adult haemoglobin replaces fetal haemoglobin
- Common in patients of African/Indian/Middle-Eastern/Caribbean descent as the trait is protective against malaria

Presentation/Complications

- Anaemia
- Increased infection risk
- Avascular necrosis of large joints
- Stroke
- Pulmonary hypertension
- Priapism
- Chronic kidney disease
- Crises

Diagnosis

- Haemoglobin electrophoresis
- Pregnant women at risk of being carriers are offered testing during pregnancy

General Management

- Avoid dehydration/other crisis triggers
- Up to date vaccines
  - NICE recommend polysaccharide pneumococcal vaccine every 5 years
- Antibiotic prophylaxis
  - Usually penicillin V
- Hydroxycarbamide (AKA hydroxyurea)
  - Stimulates production of HbF instead of HbS
- Transfusion for severe anaemia
- Bone marrow transplant can be curative

General Management of Crises

- Analgesia
- Hydration
- Oxygen
- Keep warm
- Antibiotics if evidence of infection
- Blood transfusion if severe
- Exchange transfusion if very severe (eg neurological complications)

Thrombotic/Vaso-Occlusive/"Painful" Crises

- Precipitated by infection/dehydration/ deoxygenation
- Sickled cells block capillaries and cause distal ischaemia/micro-infarcts

Features

- Pain
- Fever
- Features of infarcts
  - Brain
  - Lung
  - Hip (avascular necrosis)
  - Bones of hands/feet
- Priapism

Diagnosis

- Clinical

Management

- Supportive
- Aspiration of priapism

Sequestration Crises

- Sickled cells block flow and cause pooling in spleen (or lungs)

Features

- Severe anaemia
- Hypovolaemic shock
- Splenic infarction & later hyposplenism

Management

- Fluid resuscitation & blood transfusion
- Splenectomy in recurrent cases

Acute Chest Syndrome

- Triggered by infection (pneumonia/bronchiolitis) or other cause (pulmonary thrombotic crisis, embolus)
- Most common cause of death in SCD after childhood

Features/Diagnosis

- Fever/respiratory symptoms AND
- New pulmonary infiltrates on CXR

Management

- Antibiotics/antivirals for infections
- Blood transfusion
- Incentive spirometry
- Invasive ventilation may be necessary

Aplastic Crises

- Triggered by Parvovirus B19

Features

- Sudden severe anaemia
- Resolves within 1 week

Management

- Supportive with transfusions if necessary

Coagulation Disorders

Causes

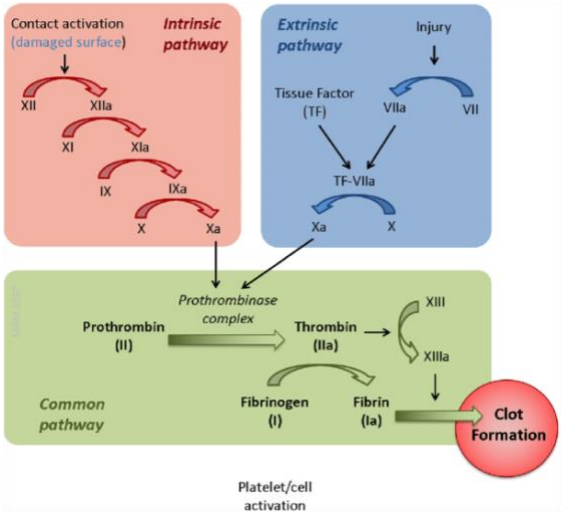
Congenital

- Von Willebrand's Disease
- Haemophilia

Acquired

- Acquired haemophilia
- Liver disease
- Vitamin K deficiency
- DIC
- Anticoagulants

Coagulation Cascade



Coagulation Screen

Test	Factors	Prolonged/Raised
PT (INR)	I, II, V, VII, X	Warfarin Vit K deficiency Liver disease DIC
APTT	I, II, V, VIII, IX, X, XI, XII	Heparin Haemophilia Vit K deficiency Liver disease DIC vWD
Thrombin time	Fibrinogen	Heparin DIC Dysfibrinogenaemia

Von Willebrand's Disease

- Most common inherited bleeding disorder
- Behaves like platelet disorder (epistaxis, menorrhagia)

Von Willebrand Factor

- Forms large multimers which promote platelet aggregation & act as a carrier molecule for Factor VIII

Types

1. Partial reduction in vWF (80%) (AD)
2. Abnormal forms of vWF
3. Complete absence of vWF (AR)

Investigations

- Prolonged bleeding time & APTT
- Potentially reduced Factor VIII levels

Management

- Tranexamic acid, desmopressin, factor VIII concentrate

Haemophilia A

- X-linked recessive defect of Factor VIII
- Up to 30% have no family history
- 1:10,000 male births
- Antibodies to recombinant Factor VIII develop in up to 15%

Features

- Haemarthroses
  - Can be destructive to joints
- Haematomas
  - Can occur in muscles causing nerve palsies/compartment syndrome
- Prolonged bleeding after surgery/trauma
- Other abnormal bleeding:
  - Haematuria
  - GI bleeding
  - Retroperitoneal bleeding
  - Intracranial bleeding

Investigations

- Prolonged APTT
- Normal bleeding time, thrombin time, prothrombin time
- Reduced Factor VIII assay

Management

- Lifestyle advice re avoiding trauma
- Avoid NSAIDs & IM injections
- **Minor bleeding**
  - Pressure & elevation
  - Desmopressin (stimulates release of vWF)
  - Tranexamic acid
- **Major bleeding**
  - Recombinant factor VIII to raise levels to 50% normal
- **Life threatening bleeding**
  - Recombinant factor VIII to raise levels to 100% normal

Haemophilia B

- AKA Christmas disease
- X-linked recessive defect of Factor IX
- Up to 30% have no family history
- Clinically similar to haemophilia A

Management

- Tranexamic acid
- Desmopressin
- Recombinant factor IX

Acquired Coagulation Disorders

Acquired Haemophilia

- Development of antibodies interfering with factor VIII

Features

- Large mucosal bleeds in both males and females

Investigations

- Prolonged APTT
- Positive factor VIII autoantibody
- Factor VIII activity < 50%

Management

- Steroids

Liver Disease

- Complicated bleeding disorder due to decreased clotting factor synthesis, decreased vitamin K absorption, & platelet dysfunction

Investigations

- Prolonged PT/INR & APTT
- Other features of liver disease

Management

- No routine bleeding prophylaxis in asymptomatic coagulation defects
- Vitamin K if deficiency suspected (poor diet, cholestatic disease, diarrhoea)
  - 10mg IVI or 10mg PO x3/7
- Cryoprecipitate may be used in active/uncontrolled bleeding

Vitamin K Deficiency

- Vitamin K required for synthesis of factors II, VII, IX & X

Causes

- Malabsorption
- Poor diet
- Liver disease/cholestasis
- Diarrhoea

Management

- Vitamin K replacement
  - 10mg IVI
- FFP or human prothrombin complex in acute bleeding

Disseminated Intravascular Coagulation

- Dysregulation of coagulation & fibrinolysis, resulting in widespread clotting & bleeding

Causes

- Sepsis (particularly meningococcal)
- Trauma
- Obstetric complications
  - Amniotic fluid embolism
  - HELLP syndrome
- Malignancy

Investigations

- Prolonged PT, APTT, & bleeding time
- Raised D-dimers
- Low platelets

Management

- Treatment of underlying cause
- Treatment of bleeding with FFP/cryoprecipitate

Thrombophilias

- Conditions which predispose to thrombosis, particularly DVT & PE

Inherited Causes

Gain of Function Polymorphisms

- Factor V Leiden (activated Protein C resistance)
  - Most common inherited thrombophilia
- Prothrombin gene mutation
  - Second most common inherited thrombophilia

Natural Anticoagulant Deficiencies

- Antithrombin III deficiency
- Protein C deficiency
- Protein S deficiency

Acquired Causes

- Antiphospholipid syndrome
- Drugs (COCP)

Prevalence & VTE Risk

Condition	Prevalence	Relative VTE risk
Factor V Leiden (heterozygous)	5%	4
Factor V Leiden (homozygous)	0.05%	10
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

Screening

- Not routinely recommended post DVT/PE, as a previous DVT/PE itself is a risk factor which will guide ongoing management

Heparin

Indications

1. Primary prevention of VTE in hospital inpatients (usually LMWH)
2. Treatment of VTE until oral anticoagulation is established/if oral anticoagulation is not suitable (eg pregnancy)
3. Acute coronary syndrome, in combination with antiplatelet agents

Mechanism

- Enhance the anticoagulant effects of Antithrombin (AT)
- UFH promotes inactivation of factors Xa, IIa, IXa, XIa, XIIa
- LMWH & fondaparinux are more specific for factor Xa

Adverse Effects

- Haemorrhage
- Bruising at injection sites
- Heparin-induced thrombocytopenia
  - Immune reaction characterised by low platelet count & thrombosis
  - More common with UFH than LMWH, does not occur with fondaparinux
- Hyperkalaemia (inhibition of renal aldosterone secretion)
- Osteoporosis

Contraindications

Relative

- Clotting disorders
- Uncontrolled hypertension
- Recent surgery/trauma
- Invasive procedures
  - Eg lumbar puncture
  - Should be withheld immediately before & after
- Renal impairment
  - UFH may be used

Interactions

- Additive effects with other anticoagulants/antiplatelets
  - May be desirable (eg ACS) but increases bleeding risk

Prescription

Dosing

- Tinzaparin (innohep) dose depends on indication
  - 3500 units SC OD thrombophylaxis in general surgery patients
  - 175 units/kg SC OD for treatment of VTE
  - 175 units/kg SC OD for thromboprophylaxis in active cancer
- Unfractionated heparin dose depends on indication
  - 5000 units SC q8-12hrs for inpatient thromboprophylaxis
  - Loading dose of 5,000/10,000 units + 18 unit/kg/hr IV infusion in treatment of VTE
    - Daily lab monitoring essential

Administration

- SC injections should be given in the abdominal wall
- For surgical patients, dose is to be given 2hrs before surgery

Communication

- Avoid activities that increase risk of bruising/bleeding
- Patient/carer will need training in giving SC injections if taking long-term

Monitoring

Efficacy

- LMWH & fondaparinux are predictable & only need monitoring (antifactor Xa activity) in special circumstances
  - Renal impairment
  - Pregnancy
- UFH needs monitoring by APTT (target 1.5-2.5)

Safety

- As above
- Baseline FBC, U+E, & clotting profile
- Platelet count & serum potassium need monitoring in treatment > 4 days

Reversal

- UFH can be reversed with protamine sulphate
- LMWH/fondaparinux can be reversed with andexanet alfa

Warfarin

Indications

1. Treatment & secondary prevention of VTE
   - Treatment required bridging with heparin
   - DOACs are a (generally preferred) alternative
2. Prevention of arterial thromboembolism in atrial fibrillation/prosthetic heart valves
   - DOACs are a (generally preferred) alternative in non-valvular AF
   - Short term after tissue valve replacement, lifelong after mechanical valve replacement

Mechanism

- Inhibition of vitamin K epoxide reductase
  - Reduced synthesis of vitamin K dependant clotting factors (II, VII, IX, X)

Adverse Effects

- Haemorrhage
- Teratogenic, but safe in breastfeeding
- Skin necrosis
  - Due to superficial venule occlusion in initial pro-thrombotic state
  - Usually prevented by LMWH bridging
- Purple toes

Contraindications

Absolute

- Bleeding/immediate risk of haemorrhage (trauma/surgery)
- Pregnancy
  - Teratogenic in 1st trimester
  - Risk of ante/intra/postpartum haemorrhage later in pregnancy

Relative

- Hepatic impairment (dose reduction)

Interactions

Potentiation of Warfarin Effect

- CYP inhibitors
  - Fluconazole
  - Macrolides
  - Amiodarone
  - Ciprofloxacin
  - Cranberry/grapefruit juice
- Displacement of warfarin from plasma proteins
  - NSAIDs
- Synergistic effect
  - NSAIDs, antiplatelets

Reduction of Warfarin Effect

- CYP inducers
  - Phenytoin
  - Carbamazepine
  - Rifampicin
  - St John's Wort

Prescription

Dosing

- Typical starting dose 5-10mg OD
  - Titrated based on INR

Administration

- Typically taken at ~ 18:00 for accurate INR testing the following morning
- LMWH bridging if immediate anticoagulation is needed
- Duration depends on indication
  - 3 months for provoked VTE
  - 6 months for unprovoked VTE
  - Lifelong for recurrent VTE/mechanical valve replacement/AF

Communication

- Patients must understand balance between clot risk & bleeding risk
- Patients must understand effects of drug & food interactions
- Patients must understand importance of INR monitoring
- Patients for lifelong treatment should be involved in the decision between warfarin & a DOAC
  - Warfarin is cheaper, more established, but has more drug & food interactions & requires monitoring
  - DOACs are more expensive, newer, need less monitoring & have fewer drug & no food interactions

Monitoring

Efficacy & Safety: INR

- Measured daily in hospital inpatients, every few days in outpatients newly starting warfarin, & less frequently in those established on warfarin
- Target ranges vary by indication:
  - 2.5 in VTE
  - 3.5 in recurrent VTE
  - 2.5 in AF
  - Typically higher in mechanical valves

Reversal

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 1-5mg 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

Direct Oral Anticoagulants (DOACs)

Indications

1. Treatment & secondary prevention of VTE
2. Primary prevention of VTE in patients undergoing elective hip/knee replacement surgery
3. Prevention of artierial thromboembolism in non-valvular AF with at least 1 risk factor
   - Previous stroke
   - Symptomatic heart failure
   - DM
   - Hypertension

Mechanism

- Apixaban/edoxaban/rivaroxaban directly inhibit factor Xa, preventing conversion of prothrombin to thrombin
- Dabigatran directly inhibits thrombin

Adverse Effects

- Bleeding
  - Epistaxis
  - GI/GU haemorrhage
  - Less risk of ICH/major bleeding than with warfarin
- Anaemia
- Elevated LFTs
- GI disturbance
- Dizziness

Contraindications

Absolute

- Active bleeding
- Risk factors for major bleeding
  - Peptic ulceration
  - Cancer
  - Trauma
  - Surgery
- Pregnancy/breastfeeding (effects unknown)

Relative

- Hepatic impairment
- Renal impairment

Interactions

- Synergistic effects
  - Antiplatelets
  - Aspirin
- Anticoagulant effects increased by CYP inhibitors
  - Macrolides
  - Protease inhibitors
  - Fluconazole
- Anticoagulant effects decreased by CYP inducers
  - Phenytoin
  - Carbamazepine
  - Rifampicin

Prescription

Dosing

- Varies with indication & agent
- Rivaroxaban:
  - 15mg 12-hrly for VTE treatment
  - 10mg OD for VTE prevention after hip/knee replacement
  - 20mg OD in AF
- Apixaban:
  - 10mg BD (for 7 days then 5mg BD) for VTE treatment
  - 2.5mg BD for VTE prophylaxis after hip/knee surgery/recurrent VTE
  - 5mg BD in AF

Administration

- Rivaroxaban must be taken with food

Communication

- Advise about bleeding risk and need to be seen if they develop prolonged bleeding or symptoms of anaemia
- Importance of not missing a dose & taking at regular times

Monitoring

- Not routinely needed
- Factor Xa assay can be performed in certain situations (overdose, emergency surgery)

Reversal

- Factor Xa inhibitors can be reversed with andexanet alfa
- Dabigatran can be reversed with idarucizumab

Blood Products

Blood Product	Content	Indications	Expected Increase
Red Cells	RBCs packed to HCT of 70%	Hb less than: • 7g/dL • 8g/dL in ACS	1-1.5 g/dL per unit
Platelets	Platelets concentrated by low (platelet rich plasma) or high (platelet concentrate) speed centrifugation	Platelet count < 20 x 10^9/L or clinical bleeding with any thrombocytopenia	20 x 10^9/L per unit
Fresh Frozen Plasma	Clotting factors Albumin Immunoglobulin	DIC Warfarin overdose where vitamin K would be too slow Liver disease with acute bleeding TTP	
Cryoprecipitate	Supernatant of FFP, rich in Factor VIII & fibrinogen	Haemophilia A/acquired factor VIII deficiency vWD	
Human Albumin Solution	4.5% or 20% protein content	Liver failure Nephrotic syndrome Abdominal paracentesis	
Prothrombin Complex Concentrate (Octaplex)	Factors II, VII, IX, X	Reversal of warfarin in massive bleeding Trauma with massive transfusion	

Acute Transfusion Reactions

Reaction	Timing	Mechanism	Features	Management
Acute Haemolytic Reaction	Minutes	ABO incompatible blood products	Agitation, fever, flushing, abdo/chest pain, hypotension & shock, DIC, haemorrhage, oozing venepuncture sites, renal failure	STOP transfusion Check ID & inform lab Keep line open with NS Manage DIC
Transfusion Associated Circulatory Overload (TACO)	Within 6 hours	Excess transfusion rate/pre-existing heart failure	Dyspnoea, hypoxia, tachyardia, raised JVP, basal crackles	Slow transfusion Oxygen & furosemide 40mg IV
Transfusion Related Acute Lung Injury (TRALI)	Within 6 hours	Antileucocyte antibodies in donor plasma resulting in ARDS	Dyspnoea, cough, bilateral infiltrates/"white-out" on CXR	STOP transfusion 100% O2 & treat ARDS Remove donor from donor list
Anaphylaxis	Immediate	Patients with IgA deficiency & anti-IgA antibodies	Bronchospasm, cyanosis, urticaria & soft tissue swelling, hypotension	STOP transfusion IM adrenaline Oxygen & airway support Contact anaesthetics
Minor Allergic Reactions	Immediate	Foreign plasma proteins	Urticaria, itch	Slow transfusion IV chlorphenamine 10mg Monitor closely
Febrile Non-Haemolytic	30-60 minutes	Antibodies reacting to white cell fragments in blood products Cytokines released from cells during storage	Fever & chills More common in platelet transfusions	Slow/stop transfusions Paracetamol 1g Monitor
Bacterial Contamination	30-60 minutes	Bacterial proliferation	Fever, hypotension, rigors	STOP transfusion Send unit to lab Broad spectrum antibiotics

Delayed Transfusion Reactions

Reaction	Timing	Mechanism	Features	Management
Delayed Haemolytic	1-7d	Recipient anti-Rh	Jaundice, anaemia, fever, haemoglobinuria	
Iron Overload	Chronic	Chronic transfusions	Haemochromatosis	Desferrioxamine
Graft Vs Host Disease	4-30d	Lymphocytes transfused to immunocompromised host	Diarrhoea, rash, liver failure, pancytopenia	Irradiate blood for vulnerable recipients

Bone Marrow Failure

Pancytopenia

- Reduction in all cell lines

Causes

- **Decreased Marrow Production**
  - Aplastic anaemia
  - Infiltration (acute leukaemia, myeloma, lymphoma, myelodysplasia, solid tumours, TB)
  - Myelofibrosis
  - Megaloblastic anaemia
  - Radiation
  - Drugs
    - **Cytotoxic:** cyclophosphamide, azathioprine, methotrexate
    - **Abx:** Chloramphenicol, sulphonamide
    - Thiazide diuretics
    - Carbimazole
    - Clozapine
    - Phenytoin
- **Increased Peripheral Destruction**
  - Hypersplenism

Aplastic Anaemia

- Rare stem cell disorder with complete cessation of cell production by bone marrow

Causes

- Congenital
  - Fanconi's anaemia
  - Dyskeratosis congenita
  - Swachman-Diamond syndrome
- Autoimmune
- Drugs
- Viruses
- Radiation

Investigations

- Hypocellular bone marrow on biopsy

Management

- Transfusions as needed
- Immunosuppression
  - Ciclosporin
  - Anti-thymocyte globulin
- Allogenic bone marrow transplant may be curative

Agranulocytosis

- Lack of granulocytes (neutrophils, basophils & eosinophils)
- Typically caused by drugs, patients should be warned to report any fever/sore throat etc

Causes

- Carbimazole
- Procainamide
- Sulphonamides
- Dapsone
- Clozapine
- Gold

Thrombocytopenia

- < 150 x 10^9/L

Causes of Severe Thrombocytopenia

- ITP
- DIC
- TTP
- Haematological malignancy

Causes of Moderate Thrombocytopenia

- HIT
- Drug-induced (quinine, diuretics, sulphonamides, aspirin, thiazides)
- Alcohol
- Liver disease
- Hypersplenism
- Viral infection (EBV, HIV, hepatitis)
- Pregnancy
- SLE/APS
- Vitamin B12 deficiency

Myelodysplastic Syndromes

- Heterogenous group of disorders manifesting as marrow failure
- **30% transform to acute myeloid leukaemia**

Pathophysiology

- Clonal proliferation of abnormal myeloid stem cells
  - Functional & quantitative defects of myeloid cells
- Mostly primary
  - More common over 60
- Some secondary
  - Chemo/radiotherapy

Features

- Elderly patients
- Cytopenias (anaemia, infection, bleeding & bruising)
- Splenomegaly

Investigations

- Pancytopenia with reduced reticulocyte count
- BM biopsy: hypercellularity, blasts, ring sideroblasts

Management

- Depends on symptoms, risk of progression, frailty & comorbidities
- Blood product transfusions
  - Erythropoietin ± G-CSF may reduce need
- Allogenic stem cell transplant is curative but often not suitable
- Chemotherapy

Myeloproliferative Disorders

- Clonal proliferation of one type of haematopoietic myeloid stem cell in the bone marrow
- Overlap with & include chronic myeloid leukaemia

Polycythaemia Vera

- Malignant proliferation of pluripotent stem cell leading to increased red cell volume ± increased neutrophils/platelets
- More common over 60 years
- 95% associated with JAK2 mutation

Features

- Hyperviscosity
  - Headache
  - Dizziness
  - Tinnitus
  - Visual disturbance
  - Arterial/venous thrombosis
- Aquagenic pruritis
- Erythromelalgia
  - Paroxysmal burning in hands & feet with redness of skin
- Facial plethora
- Splenomegaly (60%)
- Hepatomegaly (30%)
- Gout
- Haemorrhage
  - Abnormal platelet function

Investigations

- Raised RBC, Hb, HCT, WCC, platelets, B12
- Decreased EPO & ESR
- JAK2 mutation
- Hypercellular erythroid bone marrow
- Raised red cell mass on ^{51}Cr with a normal PaO_2

Management

- Aspirin to reduce thrombotic events
- Venesection
  - 1st line to keep HCT < 0.45
  - Young/low risk patients
- Chemotherapy
  - Higher risk patients
  - Hydroxycarbamide
  - Phosphorous-32

Prognosis

- Thrombotic events major cause of morbidity & mortality
- 30% progress to myelofibrosis
- 5-15% progress to acute leukaemia
  - Risk increased with chemotherapy

Causes of Polycythaemia

True Polycythaemia (↑ RBC mass as per ^{51}Cr)

- Primary
  - Polycythaemia vera
- Secondary
  - Hypoxia (high altitude, cyanotic heart disease, COPD, heavy smoking)
  - ↑ EPO (RCC, HCC)

Relative Polycythaemia (↑ HCT due to ↓ plasma volume)

- Acute
  - Dehydration
- Chronic
  - Obesity, HTN, alcohol, smoking

Essential Thrombocythaemia

- Clonal proliferation of megakaryocytes leading to raised platelets

Features

- Venous & arterial thrombosis
- Haemorrhage
- Microvascular occlusion
  - Headache
  - Atypical chest pain
  - Erythromelalgia
  - Light-headedness

Investigations

- Platelet count > 600 x 10^9/L
- JAK2 mutation in 50%
- Increased megakaryocytes on BM biopsy

Management

- Aspirin to reduce thrombotic events
- Hydroxyurea
- Interferon-α
- Anagralide

Causes of Thrombocytosis

Primary

- Essential thrombocytosis

Secondary

- Bleeding
- Infection
- Malignancy
- Trauma
- Post-surgery
- Iron deficiency

Myelofibrosis

- Clonal proliferation of abnormal megakaryocytes with PDGF release leading to dramatic marrow fibrosis
- Extramedullary erythropoiesis in liver & spleen

Features

- Night sweats
- Fever
- Weight loss
- Abdominal discomfort (splenomegaly)
- Cytopenias

Investigations

- Anaemia
- High WBC & platelets early
- High urate & LDH
- Tear-drop poikilocytes in blood film
- Dry bone marrow tap – needs trephine biopsy

Management

- Blood product transfusions as needed
- Allogenic BM transplant may be curative in younger patients
- Splenectomy

Prognosis

- 5 year median survival

Acute Myeloid Leukaemia

- Malignant proliferation of myeloid blast cells

Epidemiology

- Most common acute leukaemia of adults (1/10,000 per year), more common over 75 years

Risk Factors/Aetiology

- Myelodysplastic syndrome (30% progress)
- Myeloproliferative disorders
- Chemotherapy (eg lymphoma)/radiation
- Down's syndrome

FAB Classification

- M0 (undifferentiated) – M7 based on differentiation
- **M3 (Acute Promyelocytic)**
  - Associated with t(15;17)
  - Presents younger than other types (average = 25)
  - DIC or thrombocytopenia often at presentation
  - Good prognosis

Features

Bone Marrow Failure

- Anaemia
- Bleeding/petechiae/purpura
- Infection

Infiltration

- HSM
- Bone pain
- Gum hypertrophy

Systemic

- Fever
- Weight loss

Investigations

Bloods

- Typically raised WBC, may be low or normal
- Raised LDH
- Blood film may show blasts with Auer rods

Bone Marrow Biopsy

- Blasts with Auer rods

Immunophenotyping/Cytogenetic Analysis

- Guides management & prognosis

Management

Supportive

- Blood products, fluids, allopurinol
- Hickmann line/subcutaneous port system

Chemotherapy

- Intensive, typically include daunorubicin & cytarabine

Bone Marrow Transplant

- Refractory/relapsing disease
- 10% mortality

Complications

- Opportunistic infection
- Tumour lysis syndrome
- Hyperviscosity/leucostasis

Prognosis

- Death in ~ 2 months untreated, 20% 3YSR treated

Poor Prognostic Factors

- > 60 years
- > 20% blasts after first course of chemotherapy
- Deletions of chromosomes 5 or 7

Acute Lymphoblastic Leukaemia

- Malignant proliferation of lymphoid blast cells

Epidemiology

- Most common (80%) childhood malignancy, rare in adulthood
- Peaks at ages 2-5 & > 45

Risk Factors/Aetiology

- Radiation exposure (eg x-ray during pregnancy)
- Down's/Klinefelter/Noonan Syndrome

Types

- Common ALL (75%): Pre-B phenotype (CD10 present)
- T-cell ALL (20%)
- B-cell ALL (5%)

Features

Bone Marrow Failure

- Anaemia
- Bleeding
- Petechiae
- Purpura
- Infection

Infiltration

- HSM
- Bone pain
- Testicular swelling

Systemic

- Fever
- Weight loss
- Night sweats
- Lymphadenopathy

Investigations

Establishing Diagnosis

- FBC & blood film
  - Abnormal white cells/blast cells
- Bone marrow/lymph node biopsies

Staging

- CXR
- CT
- Lumbar puncture for CNS involvement
- Genetic analysis & immunophenotyping abnormal cells

Management

Supportive

- Blood products, fluids, allopurinol
- Hickmann line/subcutaneous port system

Chemotherapy

- Complex multi drug & phase regimens
- Personalised treatment with cytotoxics, monoclonal antibodies, steroids, T-cell infusions

Bone Marrow Transplant

- In 1st remission

Haematological Remission

- No peripheral blasts, normal/recovering FBC, < 5% blasts in marrow

Prognosis

- 85% survival in children
- 40% in adults, better when rituximab/imatinib are used

Poor Prognostic Factors

- Male
- Philadelphia chromosome
- B-cell ALL
- WBC > 100 x 10^9/L

Chronic Myeloid Leukaemia

- Myeloproliferative disorder – uncontrolled proliferation of myeloid cells

Epidemiology

- 60-70 years
- Slight male predominance

Risk Factors/Aetiology

Philadelphia Chromosome

- t(9;22) translocation
- Fusion of ABL proto-oncogene (chr 9) with BCR gene (chr 22)
  - BCR-ABL fusion oncogene with tyrosine kinase activity
- Present in > 95% with CML
- Detected by cytogenetics/molecular techniques in a masked translocation

Features

- Chronic & insidious:
  - Weight loss
  - Fatigue
  - Fever
  - Sweats
- Gout
- Bleeding/brusiing
- Abdominal discomfort
- Massive hepatosplenomegaly
- 30% diagnosed incidentally

Phases

Chronic

- ~5 years with mild or no symptoms

Accelerated

- Increasing symptoms, spleen size, & WBC count

Blast Transformation

- Transformation to acute leukaemia (AML 80%, ALL 20%)
- Increased blast cell count (> 30%)

Investigations

- Raised WBC (often > 100 x 10^9/L)
- Raised urate & LDH
- Hypercellular bone marrow
- Cytogenetic analysis of blood/BM for Philadelphia chromosome

Management

- BCR-ABL tyrosine kinase inhibitors
  - Imatinib, dasatinib, nilotinib
- Hydroxycarbamide
- Interferon-alpha
- Allogenic bone marrow transplant
- Treatment of acute leukaemia if transformed

Chronic Lymphocytic Leukaemia

- Malignant proliferation of well-differentiated lymphocytes (99% B-cells)

Epidemiology

- Most common adult leukaemia
- F:M 2:1

Features

- Often asymptomatic
- Infections, anaemia, bruising/bleeding
- Fever, weight loss, sweats
- Marked lymphadenopathy
  - Rubbery, non-tender

Complications

Richter's Transformation

- Transformation to high-grade non-Hodgkin's lymphoma
- Patients become suddenly unwell with:
  - Lymph node swelling
  - Fever without infection
  - Weight loss
  - Night sweats
  - Nausea
  - Abdominal pain

Hypogammaglobinaemia

- Reduced IgG
- Opportunistic infections

Warm AIHA

- 10-15% of patients

Investigations

- FBC
  - Early lymphocytosis
  - Later marrow infiltration with anaemia, thrombocytopenia, neutropenia
- Blood Film
  - Smudge cells
- Immunophenotyping

Management

Supportive

- Transfusions
- IVIg for recurrent infections

Drugs/Chemotherapy

- If symptomatic
- Fludarabine + rituximab + cyclophosphamide
- Steroids for AIHA

Radiotherapy

- Helps splenomegaly/lymphadenopathy

Stem Cell Transplant

- Select patients

Prognosis

- 1/3 never progress & may regress
- 1/3 progress slowly
- 1/3 progress actively

Hodgkin's Lymphoma

- Malignant proliferation of lymphocytes characteries by the Reed-Sternberg cell
  - Abnormally large lymphocytes with multiple nuclei & nucleoli, owl face appearance

Epidemiology

- Bimodal age distribution, 20s & 60s
- 1/5 of all lymphomas

Risk Factors

- HIV/EBV
- Autoimmune conditions (RA, sarcoid)
- Family history

Histological Classification

Type	Frequency	Prognosis	Notes
Nodular Sclerosing	70%	Good	↑ in women Lacunar cells
Mixed Cellularity	20%	Good	↑↑ RS cells
Lymphocyte Predominant	5%	Best	
Lymphocyte Depleted	Rare	Worst	

Features

Lymphadenopathy

- Rubbery & non-tender
- Pain with alcohol consumption in some patients

B Symptoms

- Weight loss > 10% in 6 months
- Fever 38°C
- Night sweats

Others

- Fatigue
- Itching
- Abdominal pain
- Recurrent infections
- Mediastinal lymphadenopathy (cough, SOB, SVC obstruction)

Investigations

- Raised LDH
- Lymph node biopsy with RS cells diagnostic
- PET-CT/MRI for staging

Ann Arbor Staging

1. 1 lymph node region
2. Multiple LN regions on same side of diaphragm
3. Multiple LN regions on both sides of diaphragm
4. Involvement of non-lymphatic organs

- **A** with no B symptoms, **B** with B symptoms

Management

- Chemoradiotherapy usually curative, risk of relapse/other haematological malignancies
  - ABVD (**A**driamycin (doxorubicin), **B**leomycin, **V**inblastine, **D**acarbazine)

Prognosis

- 5YSR > 95% for LP IA, < 40% for LD IVB

Non-Hodgkin's Lymphoma

- Every other type of lymphoma excluding Hodgkin's

Epidemiology

- 4/5 of all lymphomas
- Different subtypes affect different ages, risk generally increases with age

Risk Factors

- Caucasian ethnicity
- Viral infection (esp EBV)
- Family history
- Chemotherapy/radiotherapy
- Immunodeficiency
- Autoimmune diseases

Subtypes

- Very long list, notable examples:

	Low-Grade	High-Grade
B-Cell	Follicular lymphoma MALT lymphoma	Diffuse large B cell lymphoma (most common)
T-Cell (Rare)	Mycosis fungoides/Sezary syndrome Anaplastic large cell lymphoma Extranodal NK/T-cell lymphoma	

Features

Nodal (75% at presentation)

- Superficial lymphadenopathy

Extranodal (50% at presentation)

- GIT involvement
  - Gastric MALT lymphoma responds to eradication of H. pylori, other GIT lymphomas do not
- Skin involvement (common in T cell lymphomas)
- Oropharyngeal (Waldeyer's ring) (breathing difficulty)
- Bone/CNS/lung involvement

B Symptoms

- Less common & later than HL

Investigations

Diagnosis

- Excisional lymph node biopsy

Staging

- PET-CT/MRI
- Ann Arbor system

Prognostic Indicators

- ESR & LDH

Management

- Chemoradiotherapy depending on subtype

Complications

- Cytopenias
- SVC syndrome/spinal cord compression

Prognosis

- **Low-Grade**: Better prognosis
- **High-Grade:** Worse prognosis, higher cure rate

Multiple Myeloma

- Chronic (deemed incurable) malignancy of plasma cells leading to immunoglobulin (paraprotein/monoclonal band) secretion (plasma cell dyscrasia)

Epidemiology

- Peak age 70 years
- Twice as common in patients of African-Caribbean descent
- 2nd most common haematological malignancy

Pathophysiology

- Occurs due to genetic mutations occurring while B lymphocytes mature into plasma cells
- Secreted immunoglobulins cause end organ damage & immunoparesis
  - IgG in 2/3, IgA in 1/3, IgM/IgD rare

Risk Factors

- Older age
- Male gender
- Black African ethnicity
- Family history
- Obesity

Features (CRABBI)

Calcium

- Increased osteoclastic activity
- Constipation, anorexia, confusion, abdominal pain

Renal

- Light chain deposition in renal tubules causes renal damage
- Dehydration & increasing thirst
- Other renal involvement: amyloidosis, nephrocalcinosis, nephrolithiasis

Anaemia

- Due to bone marrow crowding

Bleeding

- Thrombocytopenia due to bone marrow crowding

Bone

- Bone marrow infiltration by plasma cells and cytokine-mediated osteoclast overactivity creates lytic bone lesions
- Bone pain (especially back)
- Fragility fractures

Infection

- Recurrent bacterial infections due to:
  - Immunoparesis
  - Neutropenia from disease & chemotherapy

Investigations

Bloods

- Anaemia, thrombocytopenia
- Raised U+Es & calcium

Serum/Urine Protein Electrophoresis

- Monoclonal IgG/IgA bands
- Urinary Bence-Jones protein in 2/3
  - Ig free light chains of kappa or lambda subtype

Bone Marrow Biopsy

- Raised plasma cells

Imaging

- Whole body MRI/CT/skeletal survey for lytic lesions
  - Rain-drop skull on x-ray

Diagnostic Criteria

1. Monoclonal band on serum/urine electrophoresis
2. > 10% monoclonal plasma cells on BM biopsy
3. End-organ dysfunction (anaemia, renal impairment, hypercalcaemia
4. Bone lesions

Management

Complications

- **Hypercalcaemia:** Rehydration & bisphosphonates
- **Bone Pain:** Analgesia (not NSAIDs)
- **Fracture Risk:** Bisphosphonates
- **Anaemia/Thrombocytopenia:** Transfusions ± EPO
- **Renal Failure:** Hydrate, aim for 3L/day
- **Infections:** Rapid broad spectrum abx if febrile
- **Spinal Cord Compression:** Urgent MRI, dexamethasone & local radiotherapy
- **Hyperviscosity:** Plasmaphoresis to remove light chains
- VTE prophylaxis

Chemotherapy & Stem Cell Transplantation

- Induction with Bortezonib & dexamethasone if suitable for autologous stem cell transplant
- Induction with thalidomide + an alkylating agent + dexamethasone if not suitable for autologous stem cell transplant
  - For 12-18 months/until paraprotein levels plateau
- Monitoring every 3 months
- Treatment held until paraprotein levels rise again

Prognosis

- Incurable, death typically due to renal failure/infection
- 50% 5YSR

Poor Prognostic Factors

- > 2 osteolytic lesions
- β^2-microglobulin > 5.5mg/L
- Hb < 11g/dL
- Albumin < 30g/L

Paraproteinaemia

- Presence of immunoglobulins secreted by single clone of plasma cells recognised as a monoclonal band on serum electrophoresis

Causes

1. Multiple myeloma
2. Waldenström's macroblobinaemia
3. Primary amyloidosis
4. Monoclonal gammopathy of uncertain significance (MGUS)
5. Paraproteinaemia in leukaemia/lymphoma
6. Heavy chain disease (neoplastic cells produce free Ig heavy chains)

Waldenström's Macroglobinaemia

- Lymphoplasmacytoid malignancy characterised by secretion of IgM paraprotein
- Uncommon, seen in older men

Features

- Systemic upset: weight loss, lethargy
- Lymphadenopathy
- Hepatosplenomegaly
- Hyperviscosity (pronounced due to pentameric IgM)
  - CNS/ocular symptoms
- Cryoglobulinaemia
  - Reynaud's

Management

- None if asymptomatic
- Chemotherapy
- Plasmapheresis for hyperviscosity

MGUS

- Benign paraproteinaemia/monoclonal gammopathy
- 3% > 70 years

Features

- Typically asymptomatic
- 10-30% have demyelinating neuropathy
- No BJP
- Normal immune function
- No bone symptoms/lesions
- No renal impairment
- Bone marrow plasma cells < 10%

Progression

- 10% develop myeloma at 10 years, 50% at 15
- Risk of lymphoma

Management

- Monitoring by haematologist

Amyloidosis

- Group of disorders caused by extracellular deposition of abnormal proteins in fibrillar forms resistant to degradation
- Local amyloid deposition occurs in Alzheimer's disease, type 2 DM, haemodialysis related amyloidsis

Diagnosis

Affected Tissue Biopsy

- Skin/rectal mucosa/abdominal adipose tissue
- Positive Congo Red stain with apple-green birefringence under polarised light microscopy

AL (Primary) Amyloidosis

- Plasma cell clone producing amyloidogenic monoclonal immunoglobulins
- Light chains form amyloids

Causes

- Multiple myeloma
- Waldenström's macroglobinaemia
- Lymphoma

Systems & Features

- **Renal:** Proteinuria & nephrotic syndrome
- **Cardiac:** Restrictive cardiomyopathy/arrhythmias
- **Neuro:** Peripheral & autonomic neuropathy, carpal tunnel syndrome
- **GIT:** Macroglossia, malabsorption, perforation, haemorrhage, obstruction, hepatosplenomegaly
- **Vascular:** Purpura, especially periorbital

Management

- Optimise nutrition
- Melphalan & prednisolone prolong survival

AA (Secondary) Amyloidosis

- Amyloid derived from serum amyloid A (an acute phase reactant) in chronic inflammation

Causes

- Inflammatory bowel disease
- Rheumatoid arthritis
- Familial Mediterranean fever
- Chronic infections

Features

- Affects kidney, liver, & spleen
  - Proteinuria, nephrotic syndrome, hepatosplenomegaly
- Cardiac involvement rare
- Macroglossia not seen

Management

- Treat underlying condition

Familial Amyloidosis

- AD mutations in transthyretin (liver protein)
- Neuro ± renal ± cardiac involvement
- Liver transplant may be curative

Prognosis

- 1-2 year median survival

Neutropenic Sepsis

- Common consequence of chemotherapy, typically occurring after 7-14 days

Definition

- Neutrophil count < $.5x10^9$ or < $1x10^9$ & falling +
- Fever > 38 for more than 1 hour OR
- Fever > 38.3 on one occasion OR
- Other signs/symptoms of sepsis

Prophylaxis

- Flouroquinolone if neutrophil count is expected to be < $0.5x10^9$ due to treatment

Examination

- Vitals
- Mouth
- Chest
- Line sites
- Skin & perineum
- Fundi

Investigations

- FBC & CRP, U+E, LFT
- Blood culture & peripheral & lines
- Swab from inflamed sites/MSU if indicated
- Aspergillus precipitins & PCR
- Stool culture & C. diff toxin if diarrhoea
- CXR

Management

- Immediate IV antibiotics
  - Tazocin + gentamycin
  - Add vancomycin if skin/soft tissue/line infection/septic shock
  - Replace gentamycin with ciprofloxacin if multiple myeloma/renal impairment
- Treat for 7-14 days
- Consider treatment for fungal infections if not improving after 4-7 days
- Manage in isolation room with barrier precautions and ideally HEPA air filters
- G-CSF for select patients

Tumour Lysis Syndrome

- Consequence of haematological cancers, which may occur spontaneously or be triggered by the introduction of chemotherapy

Pathophysiology

- Cell breakdown & release of contents causes hyperkalaemia & hyperphosphataemia in the setting of a low calcium
- Uric acid release causes AKI

Diagnosis

Laboratory TLS

- 2+ of the following occurring within 3 days before & 7 days after chemotherapy
  - Uric acid > 475umol or 25% increase
  - Potassium > 6mmol or 25% increase
  - Phosphate >1.125mmol or 25% increase
  - Calcium < 1.75mmol or 25% decrease

Clinical TLS

- Laboratory TLS + one of:
  - Serum creatinine 1.5 x ULN
  - Cardiac arrhythmia/sudden death
  - Seizure

Prophylaxis

- IV rasburicase + IV allopurinol + aggressive IV hydration immediately before & during initial days of chemotherapy cycles for those at high risk
  - High grade lymphomas & leukaemias

Management

- Supportive management of AKI & electrolyte abnormalities
  - Particularly hyperkalaemia
  - Dialysis if indicated