

Medicine

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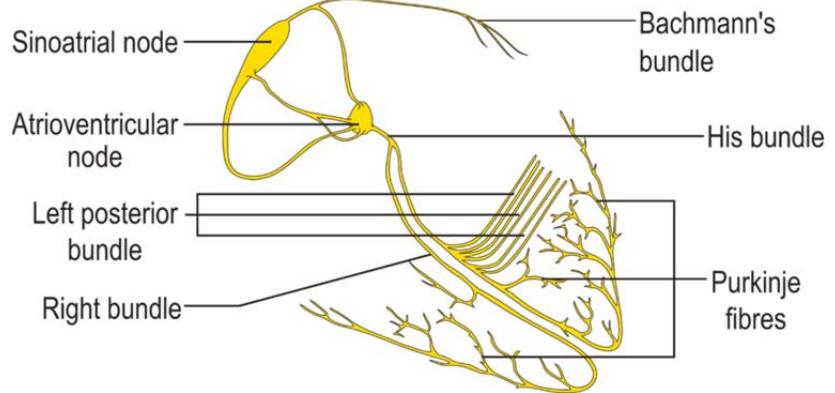
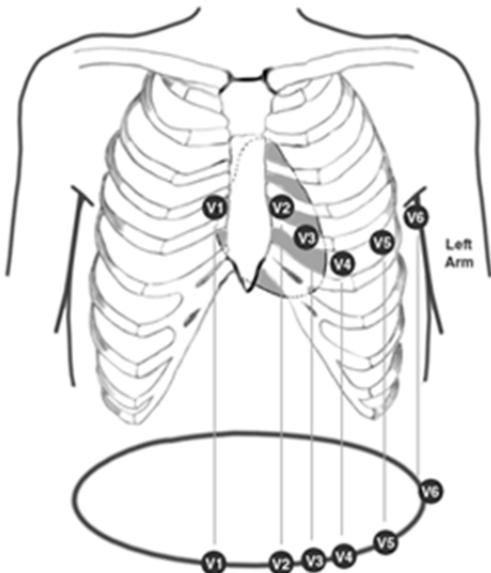
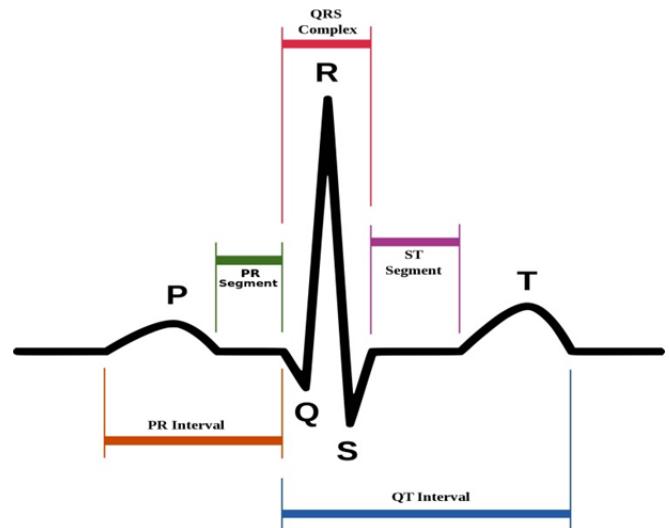
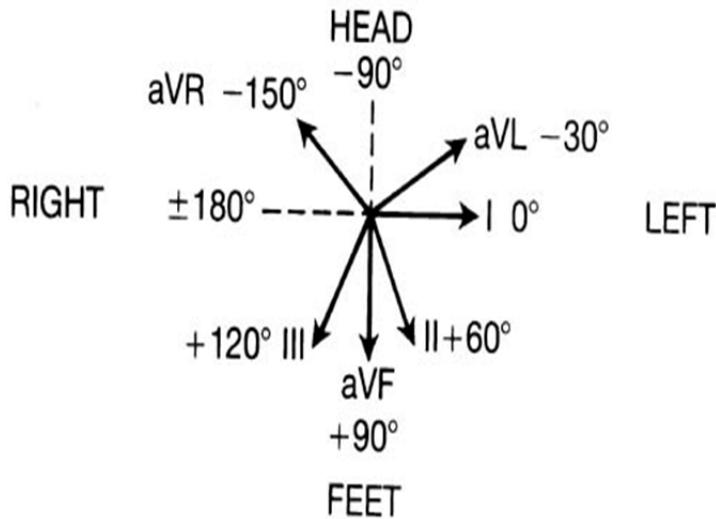
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Cardiology

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Cardiac Electrophysiology



View	Leads	Vessel
Inferior	II, III, aVF	RCA
Anterolateral	I, aVL, V5 + V6	L circumflex
Anteroseptal	V2-V4	LAD
Anterior	V2-V6	Left main stem
Posterior	V1, V2, V3 (recip)	RCA

ECG Analysis

1. Rate

- 300 / no. of large squares
- 6 = 50
- 5 = 60
- 4 = 75
- 3 = 100
- 2 = 150
- 1 = 300

2. Rhythm

- Look for P waves followed by QRS complexes
- **AF**
 - No discernable P waves
 - Irregularly irregular QRS
- **Atrial flutter:** saw-toothed baseline
- **Nodal rhythm:** regular QRS but no P waves

3. Axis

- I and II +ve = normal axis (-30 – +90)
- I +ve and II -ve (leaving) = LAD (-30 – -90)
- I -ve and II +ve (reaching) = RAD (+90 – +180)

RAD (> +90)	LAD (<-30)
Anterolateral MI	Inferior MI
RVH, PE	LVH
L post. hemiblock	L ant. Hemiblock
WPW	WPW
ASD secundum	ASD primum

4. P Waves

- **Absent:** AF, SAN block, nodal rhythm
- **Dissociated:** complete heart block
- **P mitrale:** bifid P waves = LA hypertrophy
 - HTN, AS, MR, MS
- **P pulmonale:** peaked P waves= RA hypertrophy
 - pulmonary HTN, COPD

5. QRS

- Wide QRS (>120ms)
 - Ventricular initiation
 - Conduction defect
 - WPW
- Pathological Q wave
 - >1mm wide and > 2mm deep
 - Full Thickness MI
- **RVH:** Dominant R wave in V1 + deep S wave in V6
- **LVH**
 - R wave in V6 >25mm
 - R wave in V5/V6 + S wave in V1 > 35mm

6. PR interval (120-200ms)

- Start of P wave to start of QRS
- **Long:** heart block
- **Short**
 - Accessory conduction: e.g. WPW
 - Nodal rhythm
 - HOCM
- **Depressed:** pericarditis

7. QTc (380-420ms)

- Start of QRS to end of T wave
- **Bazett's formula:** QTc = actual QT/ $\sqrt{R-R}$
- **Long (>420ms): TIMME**
 - Toxins
 - Macrolides
 - Anti-arrhythmics (Ia/III): quinidine, amiod
 - TCAs
 - Histamine antagonists
 - Inherited: e.g. Romano-Ward, Jervell (\bar{C} SNHL)
 - Ischaemia
 - Myocarditis
 - Mitral valve prolapse
 - Electrolytes: \downarrow Mg, \downarrow K, \downarrow Ca, \downarrow temp
- **Short (<380ms)**
 - Digoxin
 - β -B
 - Phenytoin

8. ST Segments

- **Elevated** (limbs: >1mm, chest: >2mm)
 - Acute MI
 - Prinzmetal's angina
 - Pericarditis: saddle-shaped
 - Aneurysm: ventricular
- **Depressed (>0.5mm)**
 - Ischaemia: flat
 - Digoxin: down-sloping

9. T-waves

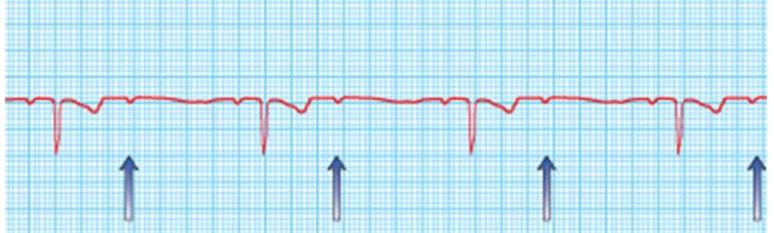
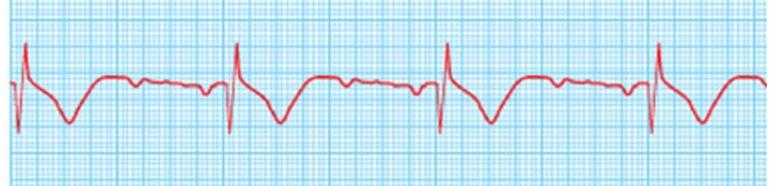
- Normally inverted in aVR and V1
 - + V2-V3 in blacks
- Abnormal if inverted in: I, II and V4-6
 - Strain
 - Ischaemia
 - Ventricular hypertrophy
 - BBB
 - Digoxin
- Peaked in $\uparrow K^+$
- Flattened in $\downarrow K^+$

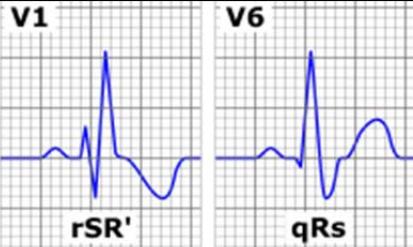
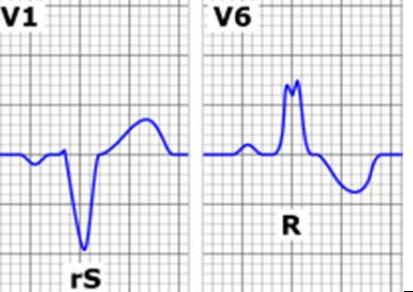
10. Extras

- **U waves**
 - Occur after T waves
 - Seen in $\downarrow K$
- **J waves / Osborne wave**
 - Occur between QRS and ST segment
 - Causes
 - hypothermia $< 32^\circ C$
 - SAH
 - Hypercalcaemia

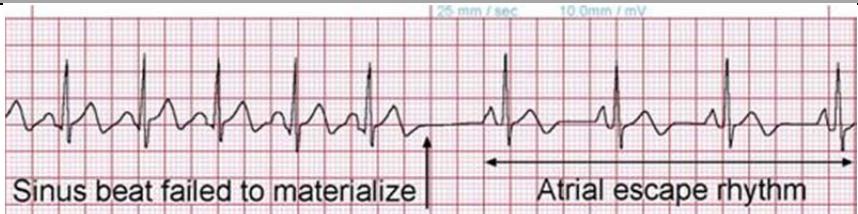
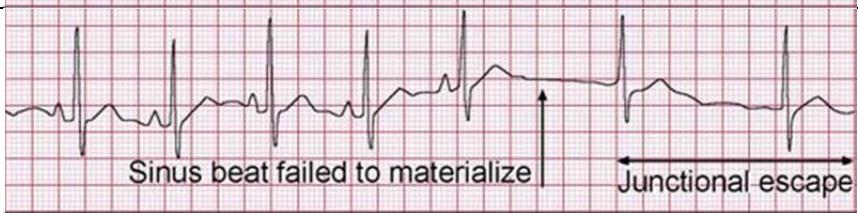
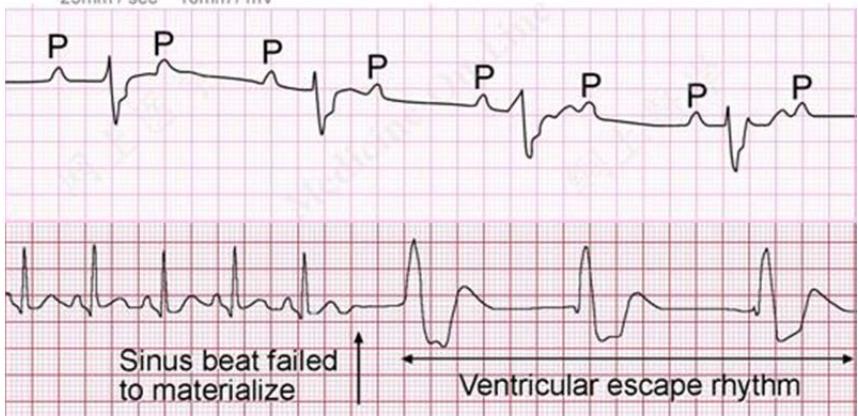
ECG Abnormalities

Conduction Defects

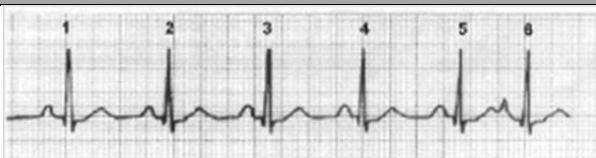
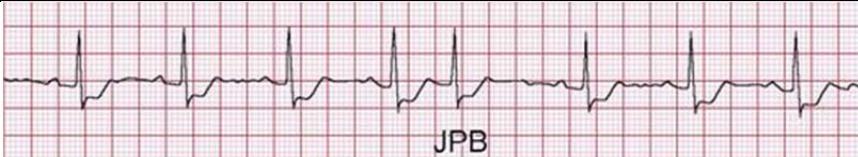
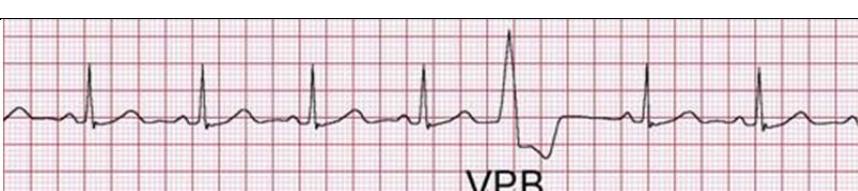
Abnormality	Features	ECG
1 st Degree Heart Block	PR > 200ms	
2 nd Degree Heart Block - Wenckebach / Mobitz I	Progressive lengthening of PR interval One non-conducted P wave Next conducted beat has shorter PR interval	
2 nd Degree Heart Block - Mobitz II	Constant PR Occasional non-conducted P waves Often wide QRS - block is usually in bundle branches of Purkinje fibres	
2 nd Degree Heart Block - 2:1 Block	Two P waves per QRS Normal consistent PR intervals	
3 rd Degree Heart Block	P waves and QRS @ different rates - dissociation Abnormally shaped QRS - ventricular origin (40bpm)	

Abnormality	Features	ECG	Aetiology
Right BBB	MaRRoW Wide QRS RSR pattern in V1		Infarct – Inferior MI Normal variant Congenital – ASD, VSD, Fallot's Hypertrophy – RVH (PE, Cor Pulmonale)
Left BBB	WiLLiaM Wide QRS – notched top T wave inversion in lat leads		Fibrosis LVH – AS, HTN Infarct – Inf. MI Coronary HD
Bifascicular Block	RBBB + LAD		RBBB + Left ant. hemiblock
Trifascicular Block	RBBB + LAFB + 1 st degree AV block		

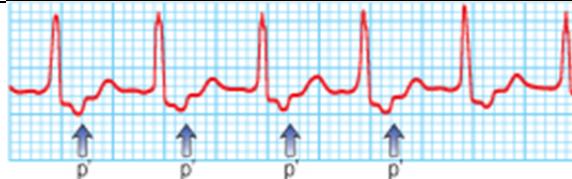
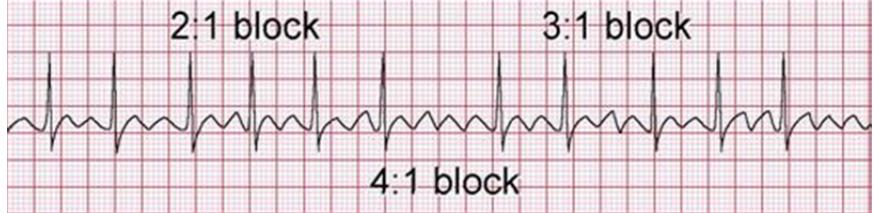
Escape Rhythms: appear late (after anticipated beat)

Abnormality	Features	ECG
Atrial Escape	SAN fails to depolarise Abnormal P wave Normal QRS 60-80bpm	
Junctional Escape	Usually no P waves (occasionally after QRS) Normal QRS 40-60bpm	
Ventricular Escape	Usually result of complete AV block ∴ regular P waves seen (top). May be SAN failure → no P waves (below). Wide QRS, 20bpm	

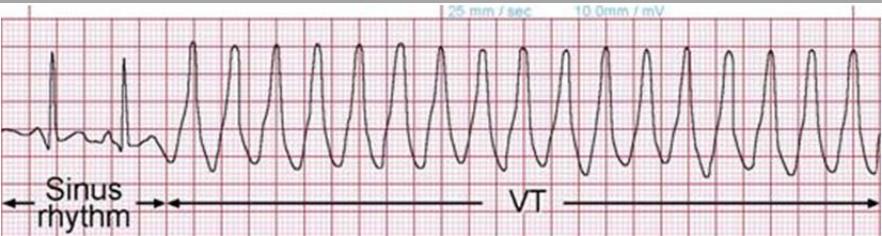
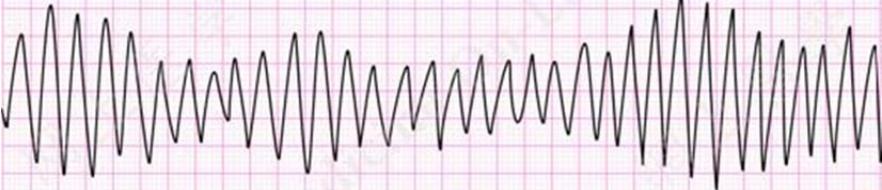
Extrasystoles: appear early (before anticipated beat)

Abnormality	Features	ECG
Atrial Extrasystole	Abnormal P wave Normal QRS	
Nodal Extrasystole	P wave buried in QRS or sometimes immediately before/after QRS. - may be negative Normal QRS	
Ventricular Extrasystole	No P wave. Wide QRS and abnormal T wave.	

Narrow Complex Tachycardias

Abnormality	Features	ECG
AV Nodal Re-entrant Tachycardia	P wave absent or immediately before/after QRS Normal QRS	
AVRT	P waves usually visible between QRS complexes QRS may be narrow or wide Accessory conduction bundle	
Atrial Tachycardia	Abnormally shaped P waves Normal QRS complexes. Rate > 150bpm May be assoc. w/ AV block.	
Atrial Flutter	“Saw-toothed” baseline as atria contract @ 300bpm. AVN can’t conduct > 200bpm ∴ AV block occurs. - 2:1(150), 3:1(100), 4:1(75) Normal QRS	
Atrial Fibrillation	No P waves – irregular line Irregularly irregular QRS	

Broad Complex Tachycardias

Abnormality	Features	ECG
VT	No P waves Regular, wide QRS No T waves	
Torsades		
VF	Shapeless, rapid oscillations and no organised complexes.	

Ventricular tachycardia vs. SVT with bundle branch block

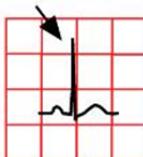
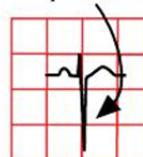
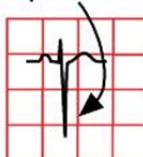
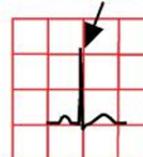
VT more likely if:

- **Hx:** recent infarction
- Atrioventricular dissociation
- Broad QRS complexes (>140ms)
- Concordant QRS direction in V1-V6
- Fusion and capture beats

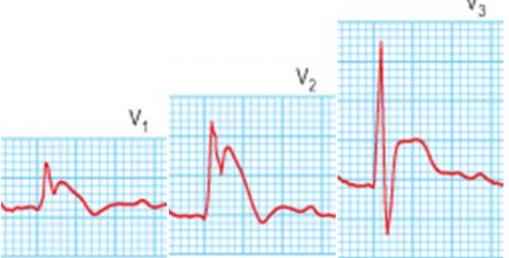
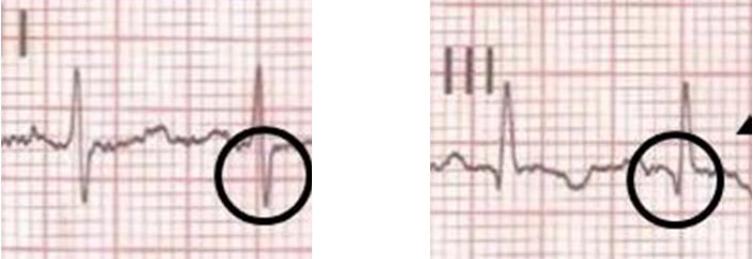
P Wave Abnormalities

Abnormality	Features	ECG	Aetiology
P pulmonale	Peaked P wave		RAH - pulmonary HTN - tricuspid stenosis
P mitrale	Broad, bifid P wave		LAH - mitral stenosis

QRS Abnormalities

Abnormality	Features	ECG	Aetiology
RVH	Tall R wave in V1 Deep S wave in V6 RAD Normal QRS width May be T wave inversion in V1-V3	<p>tall R-wave in V1</p>  <p>deep S-wave in V6</p> 	Cor pulmonale
LVH	S in V1 + R in V6 >35mm and/or R wave in V6 >25mm May be LAD May be T wave inversion in II, aVL, V5, V6	<p>deep S-wave in V1</p>  <p>tall R-wave in V6</p> 	HTN AS COA H(O)CM

Miscellaneous

Abnormality	Features	ECG
WPW	Accessory conducting bundle. Short PR interval Slurred upstroke of QRS called a delta wave (V3/4). Can establish re-entrant circuit → SVT (antidromic AVRT) AF + WPW → irregularly irregular broad QRS complexes (below).	
Brugada Syndrome	RBBB Coved ST elevation in V1-V3	
Digoxin	Reverse tick - Down-sloping ST depression - T wave inversion	
PE	SI QIII TIII (rare) - deep S wave in I (RAD) - pathological Q in III - T inversion in III Right vent strain - RAD (S wave in I) - Dominant R wave and T wave inversion in V1-V3	
↑ K ⁺	Tall tented T waves Widened QRS Absent P waves Sine wave appearance Fig shows serial ↓ in K ⁺	
↓ K ⁺	Small T waves ST depression Prolonged QT interval Prominent U waves	

Bradycardias (<60bpm)

Causes: DIVISIONS

Drugs

- Antiarrhythmics (type 1a, amiodarone)
- β -blockers
- Ca^{2+} -channel blockers (verapamil)
- Digoxin

Ischaemia / Infarction

- Inferior MI

Vagal hypertonia

- Athletes
- Vasovagal syncope
- Carotid sinus syndrome

Infection

- Viral myocarditis
- Rheumatic fever
- Infective endocarditis

Sick sinus syndrome

- Structural damage or fibrosis of SAN, AVN or conducting tissue
- **PC**
 - SVT alternating w/ either sinus bradycardia ± arrest or SA/AV block
- **Rx**
 - Bradyarrhythmias: pace
 - Tachyarrhythmias: amiodarone

Infiltration: restrictive / dilated cardiomyopathy

- Autoimmune
- Sarcoid
- Haemochromatosis
- Amyloid
- Muscular dystrophy

O

- hypothyroidism
- hypokalaemia (or ↑)
- hypothermia

Neuro: ↑ ICP

Septal defect: primum ASD

Surgery or catheterisation

Classification

- Sinus bradycardia
- First degree heart block: PR > 200ms
- Second degree heart block
 - Wenkebach / Mobitz I
 - Mobitz II
- Complete heart block
 - Junctional: narrow QRS @ ~50bpm
 - Ventricular: broad QRS @ ~40bpm

Rx

- If asymptomatic and rate >40: no Rx needed

Urgent / rate <40bpm

1. **Rx underlying cause:** e.g. drugs, MI
2. **Medical**
 - Atropine 0.6–1.2g (max 3g) IV
 - Isoprenaline IVI
3. **Pacing:** External

Elective

1. **Permanent pacing**
 - Mobitz II
 - Complete AV block
 - Sick sinus
 - AF
 - Drug-resistant tachyarrhythmias

Narrow Complex Tachycardias = SVT

Definition: Rate >100bpm, QRS width < 120ms

Differential

1. Sinus tachycardia

2. Atrial

- AF
- Atrial flutter
- Atrial tachycardia

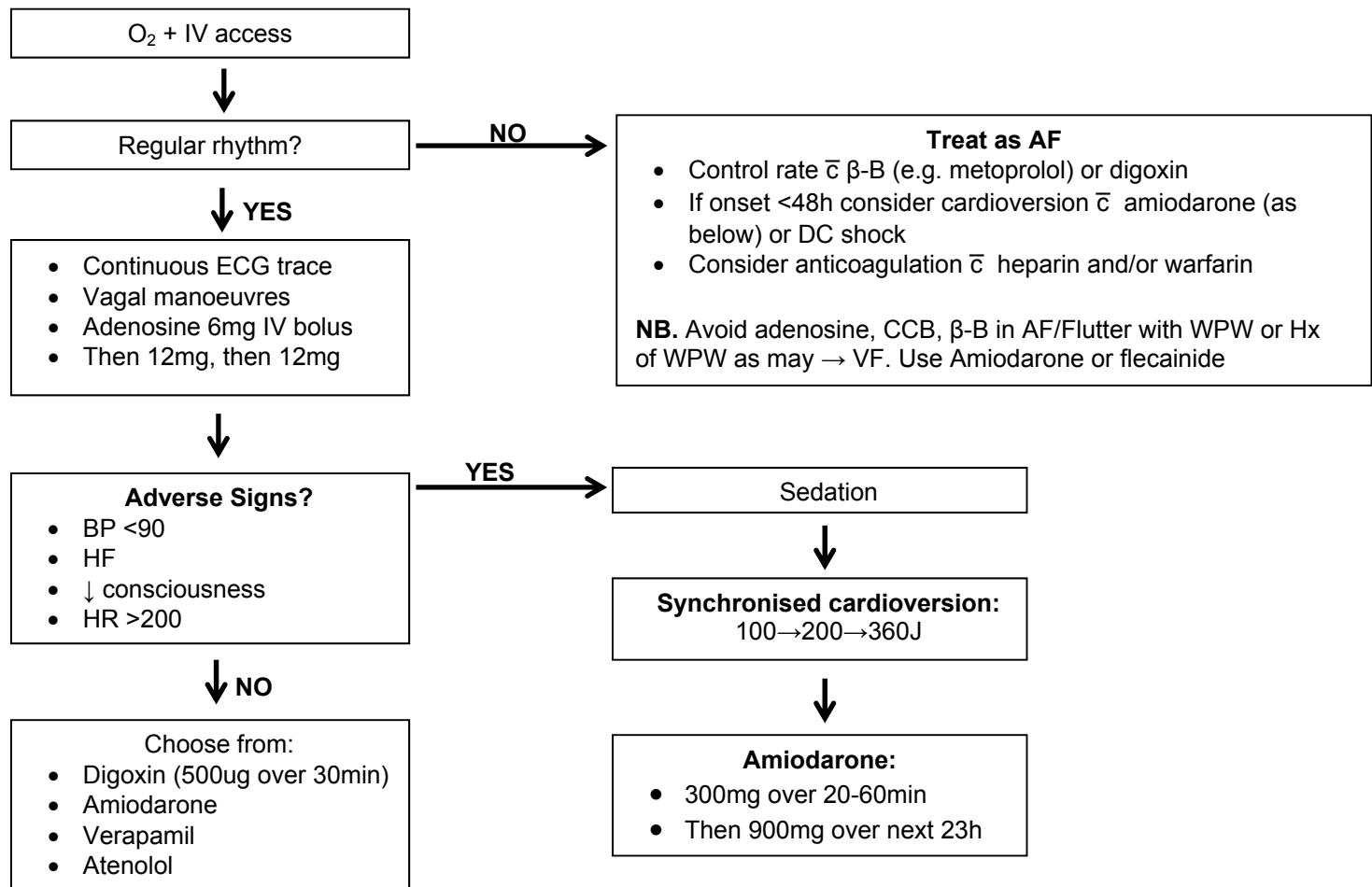
3. AV nodal re-entry tachycardia

4. AV re-entry tachycardia

Principles of Mx

- If pt. compromised → sedate + DC cardioversion
- Otherwise ID rhythm and Rx accordingly
 - Key to ID irregular rhythm = AF = different Rx
- Vagal manoeuvres (carotid sinus massage, valsalva) transiently ↑ AV block and may unmask underlying atrial rhythm.
- If manoeuvres unsuccessful, give adenosine while recording rhythm strip
 - → transient AV block, unmasking atrial rhythm
 - → cardioverts AVNRT/AVRT to sinus rhythm
- If adenosine fails, choose from:
 - Digoxin
 - Atenolol
 - Verapamil (not if on β-blocker)
 - Amiodarone
- If unsuccessful → DC cardioversion

Mx



Adenosine

- MOA: temporary AVN block
- SEs: Transient chest tightness, dyspnoea, flushing, headache
- Relative CIs: asthma, 2nd/3rd degree block
- Interactions
 - fx ↑d by dipyridimole
 - fx ↓d by theophylline

Prophylaxis

- β -B
- AVRT: flecainide
- AVNRT: verapamil

Broad Complex Tachycardias

Definition: Rate >100bpm, QRS width > 120ms

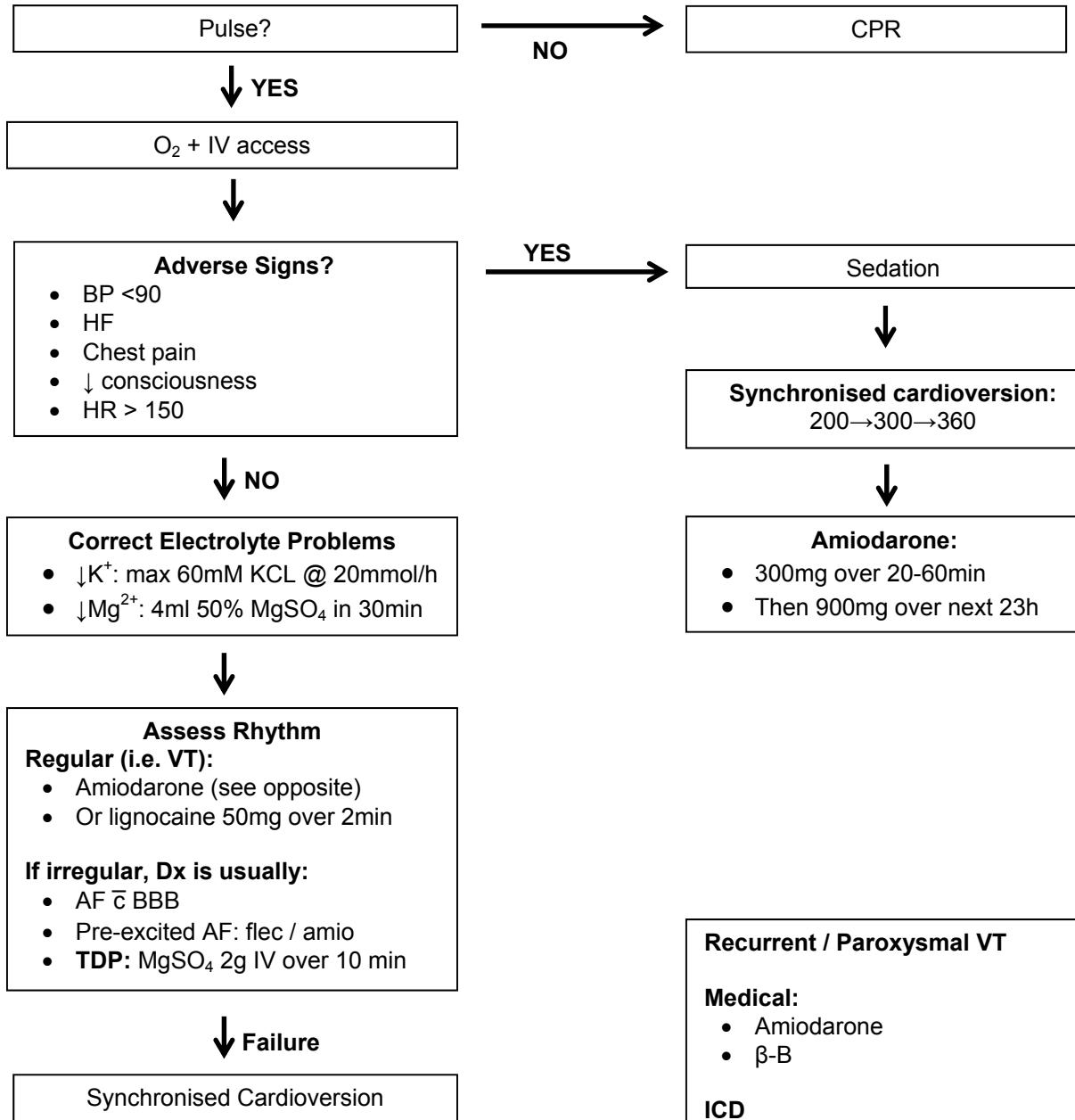
Differential

1. VT
2. Torsades de points
3. SVT \neq BBB

VT Causes: I'M QVICK

- Infarction (esp. \rightarrow ventricular aneurysm)
- Myocarditis
- QT interval↑
- Valve abnormality: mitral prolapse, AS
- Iatrogenic: digoxin, antiarrhythmics, catheter
- Cardiomyopathy (esp. dilated)
- $K\downarrow, Mg\downarrow, O_2\downarrow$, acidosis

Mx



Atrial Fibrillation

Pathology

- LA loses refractoriness before the end of atrial systole.
- recurrent, uncoordinated contraction @ 300-600bpm
- Atrial contraction responsible for ~25% of CO
 - ∴ often triggers heart failure

Causes

Common

- IHD
- Rheumatic heart disease
- Thyrotoxicosis
- Hypertension

Other

- Alcohol
- Pneumonia
- PE
- Post-op
- Hypokalaemia
- RA

Symptoms

- Asympto
- Chest pain
- Palpitations
- Dyspnoea
- Faintness

Signs

- Irregularly irregular pulse
- Pulse deficit: difference between pulse and HS
 - Fast AF → loss of diastolic filling → no palpable pulse
- Signs of LVF

Ix

- ECG
- FBC, U+E, TFTs, Trop
- Consider TTE: structural abnormalities

Acute AF ($\leq 48\text{h}$)

- Haemo unstable → emergency cardioversion
 - (IV amiodarone 2nd line)

Control ventricular rate

- 1st line: diltiazem or verapamil or metoprolol
- 2nd line: digoxin or amiodarone

Start LMWH

Cardioversion: only if acute AF $<48\text{hrs}$

- Electrical cardioversion or pharmacological
 - 1st: Flecainide (if no structural heart disease)
 - 2nd: Amiodarone
- Long-term anticoagulation not needed if sinus restored no RFs (0 CHADSVAS) + low recurrence risk.

Paroxysmal AF

- Self-limiting, $<7\text{d}$, recurs
- Anticoagulate: use CHADSVAS
- Rx “pill-in-pocket”: flecainide, propafenone
- Prevention: β -B, sotalol or amiodarone

Persistent AF

- $>7\text{d}$, may recur even after cardioversion

Try rhythm control first-line if:

- Symptomatic or CCF
- Younger (<65)
- Presenting first time & lone AF
- Secondary to treated precipitant

Rhythm Control

- TTE first: structural abnormalities
- Anticoagulate & warfarin for $\geq 3\text{wks}$
 - or use TOE to exclude intracardiac thrombus.
- Pre-Rx $\geq 4\text{wks}$ & sotalol or amiodarone if \uparrow risk of failure
- Electrical or pharmacological cardioversion
- ≥ 4 wks anticoagulation afterwards (target INR 2.5)

Maintenance antiarrhythmic

- Not needed if successfully treated precipitant
- 1st: β -B (e.g. bisoprolol, metoprolol).
- 2nd: amiodarone

Other options

- Radiofrequency ablation of AV node
- Maze procedure
- Pacing

Rate control (target $<90\text{bpm}$ at rest):

- 1st line: β -B or rate-limiting CCB (NOT both!)
- 2nd line: add digoxin (don't use as monotherapy)
- 3rd line: consider amiodarone

Mx of Permanent AF

- Failed cardioversion / unlikely to succeed
 - AF $>1\text{yr}$, valve disease, poor LV function
- Pt. doesn't want cardioversion
- Rate control

Mx of Atrial Flutter

- Manage as for AF
- Anti-AF drugs may not work, but try
 - Amiodarone to restore sinus
 - Amiodarone or sotalol to maintain it
- Cavotricuspid isthmus ablation (RA) is Rx of choice.

CHA₂-DS₂-VAS Score

- Determines necessity of anticoagulation in AF
- Warfarin CI in AF
 - Bleeding diathesis, ↓plts, BP $> 160/90$, poor compliance
- Dabigatran may be cost-effective alternative.

CHA₂-DS₂

- CCF
- HTN
- Age ≥ 75 (2 points)
- DM
- Stroke or TIA (2 points)

VAS

- Vascular disease
- Age: 65-74yrs
- Sex: female

Score

- 0: aspirin 300mg
- ≥ 1 : Warfarin

Acute Coronary Syndromes

Definition

- ACS = unstable angina + evolving MI
- Divided into:
 - ST elevation or new onset LBBB
 - NSTEMI

Epidemiology

- Incidence 5/1000 for STEMI

Pathophysiology

- Plaque rupture, thrombosis and inflammation.
- Rarely due to coronary spasm

Risk Factors

Modifiable Non-modifiable

- | | |
|---|---|
| <ul style="list-style-type: none">• HTN• DM• Smoking• ↑cholesterol• Obesity | <ul style="list-style-type: none">• Age• Male• FH (MI < 55yrs) |
|---|---|

Symptoms

- Acute central/left chest pain >20min
- Radiates to left jaw or arm
- Nausea
- Sweating
- Dyspnoea
- Palpitations

May get silent MIs in elderly/diabetics

- Syncope
- Delirium
- Post-op oliguria / hypotension

Signs

- Anxiety
- Pallor Sweating
- Pulse ↑/↓
- BP ↑/↓
- 4th heart sound
- Signs of LVF (basal creps, ↑ JVP, 3rd HS)
- PSM: papillary muscle dysfunction / rupture

Differential

- Angina
- Peri / endo / myocarditis
- Dissection
- PE, pneumothorax, pneumonia
- Costochondritis
- GI: e.g. GORD, spasm
- Anxiety

Investigations

ECG

- **STEMI Sequence**
 - Normal
 - ST elevation + hyperacute (tall) T waves
 - Q waves: full-thickness infarct
 - Normalisation of ST segments
 - T wave inversion
 - (New onset LBBB also = STEMI)
- **NSTEMI**
 - ST depression
 - T wave inversion
- No Q waves = subendocardial infarct

View	Leads	Vessel	Complication
Inferior	II, III, aVF	RCA	Bradyarrhythmias
Anterolateral	I, aVL, V4-V6	LCx	
Anteroseptal	V2-V4	LAD	
Anterior	V2-V6	LMS	LVF
Posterior	V1, V2, V3 (recip)	RCA	

Bloods

- Troponin T/I
 - Myofibrillar proteins linking actin and myosin
 - Elevated from 3-12h
 - ∴ need 12h trop to exclude MI
 - Peak 24h
 - Baseline from 5-14d
- FBC, U+E, glucose, lipids, clotting

CXR

- Cardiomegaly
- Pulmonary oedema
- Widened mediastinum: aortic rupture

Diagnosis

- **STEMI / LBBB:** Typical symptoms + ST elevation (/LBBB)
- **NSTEMI:** Typical symptoms + no ST elevation + +ve trop
- **UA:** Typical symptoms + no ST elevation + -ve trop

Treatment

- **STEMI:** PCI or thrombolysis
- **NSTEMI / UA:** medical + elective angio ± PCI/CABG

Prognosis

- Varies by pt. factors
- **STEMI:** 30 day mortality ~15%
- **NSTEMI:** overall mortality 1-2%

MI Complications

Death Passing PRAED st.

Death: VF, LVF, CVA

Pump Failure

Pericarditis

Presentation

- Occurs early
- Mild fever
- Central chest pain / change in pain
- Relieved by sitting forward
- Pericardial friction rub

ECG

- Saddle-shaped ST elevation
- \pm PR depression

Rx

- NSAIDs: ibuprofen
- Echo to exclude effusion

Rupture: myomalacia cordis

- **Cardiac tamponade:** Left ventricular free wall rupture
 - Beck's triad (\downarrow BP, \uparrow JVP, muffled heart sounds)
 - Pulsus paradoxus
- **Papillary muscle / chordae \rightarrow MR**
 - PSM
 - Pulmonary oedema.
- **Septum**
 - PSM
 - \uparrow JVP
 - Heart failure

Arrhythmias

Tachycardias

- **SVT**
 - Sinus tachycardia – give O₂ + analgesia
 - AF or flutter
 - Compromised \rightarrow DC cardioversion
 - Otherwise \rightarrow rate control: digoxin \pm β -B
- **Ventricular**
 - Frequent PVC common after acute MI: no Rx
 - Sustained VT
 - Compromised \rightarrow DC cardioversion
 - Else \rightarrow amiodarone or lignocaine
 - May need pacing
 - VF
 - Early (<48hrs): reperfusion (good prog)
 - Late (>48hrs): extensive heart damage
 - Rx: DC shock

Bradycardias

- **Sinus bradycardia**
 - esp. in inferior MI.
 - Rx: atropine 0.6 – 1.2mg
- **AV block**
 - Pace Mobitz II
- **Ventricular bradycardia**
 - Suggests SA and AV node damage

Aneurysm: ventricular

Presentation

- 4-6wk
- LVF
- Angina
- Recurrent VT
- Systemic emboli.

ECG: persistent ST elevation.

Rx

- Anticoagulate
- Consider Excision

Embolism

- Arise from LV mural thrombus
- Consider warfarin for 3mo after large anterior MI

Dressler's Syndrome: pleuro-pericarditis

- Due to auto-antibodies vs. myocyte sarcolemma.

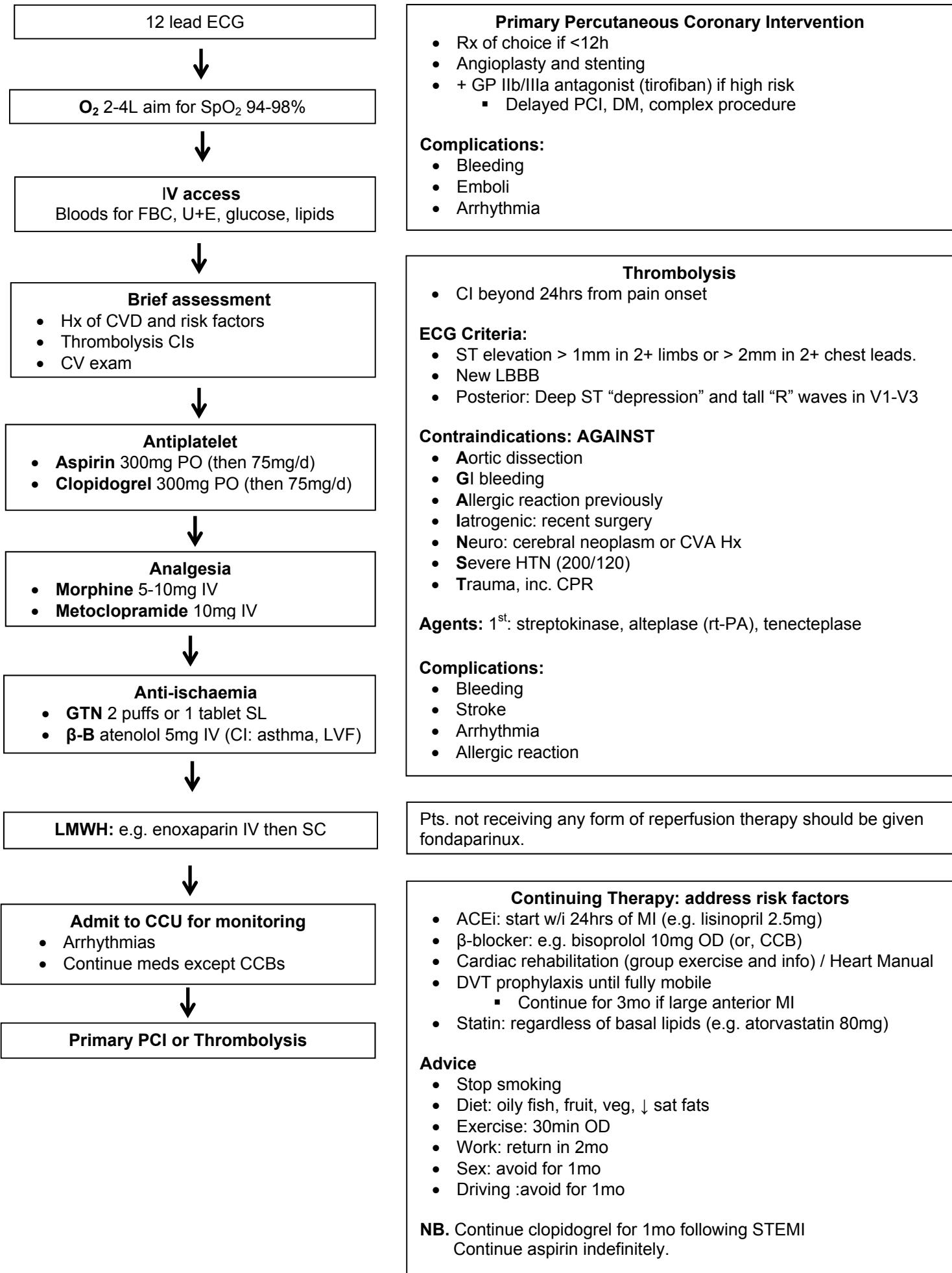
Presentation

- 2-6wks
- Recurrent pericarditis
- Pleural effusions
- Fever
- Anaemia
- \uparrow ESR

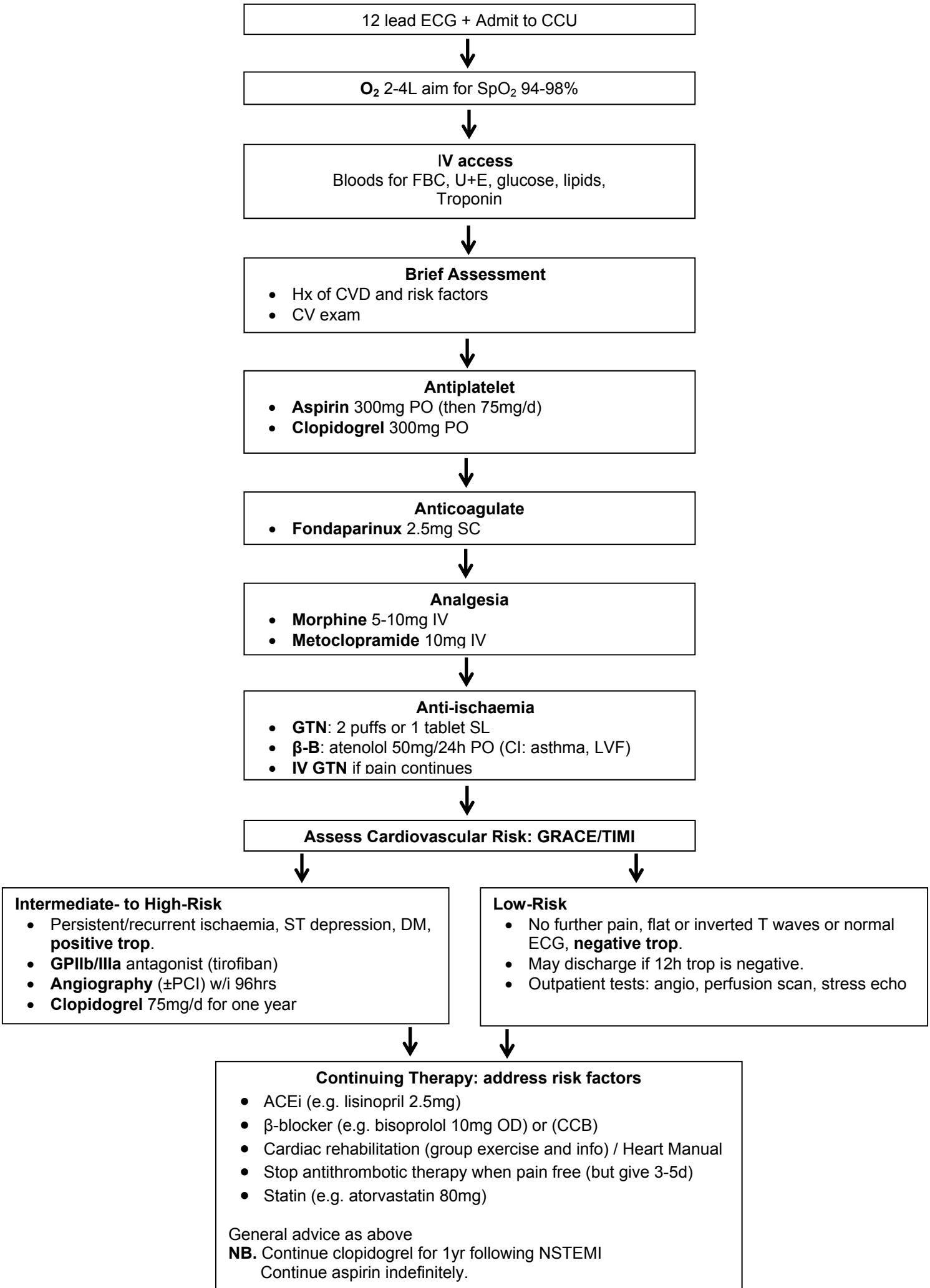
Rx

- NSAIDs
- Steroids if severe

STEMI Management



NSTEMI and UA Management



Angina Pectoris

Pathophysiology

- Atherosclerosis → myocardial ischaemia

Aetiology

- Mostly atheroma.
- Anaemia
- AS
- Tachyarrhythmias
- Arteritis

Risk Factors

Modifiable:

- HTN
- DM
- Smoking
- ↑cholesterol
- Obesity

Non-modifiable:

- Age
- Male
- FH (MI < 55yrs)
- Genetic: e.g. hyperlipidaemia

Symptoms

- Central chest tightness or heaviness
- Brought on by exertion, relieved by rest
- May radiate to one/both arms, neck, jaw or teeth
- Other pts: emotion, cold weather, heavy meals

Classification

- **Stable:** induced by effort
- **Unstable:** occurs at rest / minimal exertion
- **Decubitus:** induced by lying down
- **Prinzmetal's / variant:** occurs during rest
 - Due to coronary spasm
 - ST elevation during attack: resolves as pain subsides.
 - Rx: CCB + long-acting nitrate
- **Syndrome X:** angina pain + ST elevation on exercise test but no evidence of coronary atherosclerosis.
 - Probably represents small vessel disease

Differential

- AS
- Aortic aneurysm
- GI: GORD, spasm
- Musculoskeletal

Ix

- **Bloods:** FBC, U+E, lipids, glucose, ESR, TFTs
- **ECG:** usually normal
 - May show ST ↓, flat/inverted T waves, past MI
 - Consider exercise ECG
- Stress echo
- Perfusion scan
- CT coronary Ca²⁺ score
- Angiography (gold standard)

Mx

Lifestyle

- Stop smoking
- Wt. loss and ↑ exercise
- Healthy diet: oily fish, fruit, veg, ↓ sat fats

Medical

- **2^o Prevention:** prevent cardiovascular events
 - Aspirin 75mg OD
 - ACEi (esp. if angina + DM)
 - Statins: simvastatin 40mg
 - Antihypertensives
- **Anti-anginals:** prevents angina episodes
 1. **GTN** (spray or SL) + either
 - 1st: **β-B** (e.g. Atenolol 50-100mg OD)
 - 2nd: **CCB** (e.g. Verapamil 80mg TDS)
 2. If either β-B or CCB doesn't control symptoms, try the other option.
 3. Can try β-B + dihydropyridine CCB
 - e.g. amlodipine MR 10mg/24h
 4. If symptoms still not controlled
 - ISMN 20-40mg BD (8h washout @ PM) or slow-release nitrate (Imdur 60mg OD)
 - Ivabradine (esp. if can't take β-B)
 - Nicorandil 10-30mg BD
 - Ranolazine

Interventional: PCI

- **Indications**
 - Poor response to medical Rx
 - Refractory angina but not suitable for CABG
- **Complications**
 - Re-stenosis (20-30% @ 6mo)
 - Emergency CABG (<2%)
 - MI (<2%)
 - Death (<0.5%)
- **Clopidogrel ↓s risk of re-stenosis**
 - Bare metal stent: 1mo
 - Drug-eluting (e.g. sirolimus) stent: 1yr

Surgical: CAGB

- **Indications**
 - L main stem disease
 - Triple vessel disease
 - Refractory angina
 - Unsuccessful angioplasty
- **Complications**
 - MI
 - Stroke
 - Pericardial tamponade or haemothorax
 - Postperfusion syn.
 - Post-op AF
 - Nonunion of sternum
 - Graft stenosis

Heart Failure: Concepts and Causes

Definition: CO is inadequate for the body's requirements despite adequate filling pressures.

Epidemiology

- Prev: 2% @ 50yrs → 10% @ 80yrs

Pathophysiology

Reduced CO initially → compensation

- Starling effect dilates heart to enhance contractility
- Remodelling → hypertrophy
- RAS and ANP/BNP release
- Sympathetic activation

Progressive ↓ in CO → decompensation

- Progressive dilatation → impaired contractility + functional valve regurgitation
- Hypertrophy → relative myocardial ischaemia
- RAS activation → Na^+ and fluid retention → ↑ venous pressure → oedema
- Sympathetic excess → ↑ afterload → ↓ CO

Low Output: CO ↓ and fails to ↑ \bar{c} exertion

1. Pump failure

- **Systolic failure** → impaired contraction
 - Ischaemia/MI (commonest cause)
 - Dilated cardiomyopathy
 - Hypertension
 - Myocarditis
- **Diastolic failure** → impaired filling
 - Pericardial effusion / tamponade / constriction
 - Cardiomyopathy: restrictive, hypertrophic
- **Arrhythmias**
 - Bradycardia, heart block
 - Tachycardias
 - Anti-arrhythmics (e.g. beta-blocker, verapamil)

2. Excessive pre-load

- AR, MR
- Fluid overload

3. Excessive afterload

- AS
- HTN
- HOCM

High Output: ↑ needs → RVF initially, then LVF

- Anaemia, AVM
- Thyrotoxicosis, Thiamine deficiency (beri beri)
- Pregnancy, Paget's

RVF

Causes

- LVF
- Cor pulmonale
- Tricuspid and pulmonary valve disease

Symptoms

- Anorexia and nausea

Signs

- ↑JVP + jugular venous distension
- Tender smooth hepatomegaly (may be pulsatile)
- Pitting oedema
- Ascites

LVF

Causes

- 1st: IHD
- 2nd: idiopathic dilated cardiomyopathy
- 3rd: Systemic HTN
- 4th: Mitral and aortic valve disease
- Specific cardiomyopathies

Symptoms

- Fatigue
- Exertional dyspnoea
- Orthopnoea + PND
- Nocturnal cough (\pm pink, frothy sputum)
- Wt. loss and muscle wasting

Signs

- Cold peripheries \pm cyanosis
- Often in AF
- Cardiomegaly \bar{c} displaced apex
- S3 + tachycardia = gallop rhythm
- Wheeze (cardiac asthma)
- Bibasal creps

Acute vs. Chronic

- **Acute**
 - New onset or decompensation of chronic
 - Peripheral / pulmonary oedema
 - \pm evidence of peripheral hypoperfusion
- **Chronic**
 - Develops / progresses slowly
 - Venous congestion common
 - Arterial pressure maintained until v. late

Chronic Heart Failure

Dx of CCF: Framingham Criteria

- 2 major criteria or 1 major + 2 minor

Major

- PND
- +ve abdominojugular reflux
- Neck vein distension
- S3
- Basal creps
- Cardiomegaly
- Acute pulmonary oedema
- ↑ CVP ($>16\text{cmH}_2\text{O}$)
- Wt. loss $>4.5\text{kg}$ in 5d 2^o to Rx

Minor

- Bilat ankle oedema
- SOBOE
- ↑HR >120
- Nocturnal cough
- Hepatomegaly
- Pleural effusion
- 30% ↓ vital capacity

Ix

- **Bloods:** FBC, U+E, BNP, TFTs, glucose, lipids
- **CXR:** ABCDE
 - Alveolar shadowing
 - Kerley B lines
 - Cardiomegaly (cardiothoracic ratio $>50\%$)
 - Upper lobe Diversion
 - Effusions
 - Fluid in the fissures
- **ECG**
 - Ischaemia
 - Hypertrophy
 - AF
- **Echo:** the key investigation
 - Global systolic and diastolic function
 - Ejection fraction normally $\sim 60\%$
 - Focal / global hypokinesia
 - Hypertrophy
 - Valve lesions
 - Intracardiac shunts

B-type Natriuretic Peptide: BNP or NTproBNP

- Secreted from ventricles in response to
 - ↑ pressure → stretch
 - Tachycardia
 - Glucocorticoids
 - Thyroid hormones
- Actions
 - ↑ GFR and ↓ renal Na reabsorption
 - ↓ preload by relaxing smooth muscle
- BNP is a biomarker of heart failure
 - ↑ BNP (>100) better than any other variable and clinical judgement in diagnosing heart failure
 - BNP correlates w/ LV dysfunction
 - i.e. ↑ most in decompensated heart failure
 - ↑ BNP = ↑ mortality
 - BNP <100 excludes heart failure (96% NPV)
 - BNP also ↑ in RHF: cor pulmonale, PE

New York Heart Association Classification

1. No limitation of activity
2. Comfortable @ rest, dyspnoea on ordinary activity
3. Marked limitation of ordinary activity
4. Dyspnoea @ rest, all activity → discomfort

General Mx

1^o/2^o Cardiovascular Risk

- Stop smoking
- ↓ salt intake
- Optimise wt.: ↑ or ↓ - dietitian
- Supervised group exercise based rehab programme
- Aspirin
- Statins

Rx Precipitants / Causes

- Underlying cause
 - Valve disease
 - Arrhythmias
 - Ischaemia
- Exacerbating factors
 - Anaemia
 - Infection
 - ↑BP

Specific Mx

- ACEi, β-B and spiro → ↓ mortality

1st line: ACEi/ARB + β-B + loop diuretic

- **ACEi/ARB:** e.g. lisinopril or candesartan
 - Hydralazine + ISDN if not tolerated
- **β-B:** e.g. carvedilol or bisoprolol (licensed)
 - Start low, go slow
 - E.g. carvedilol 3.125mg/12h → 25-50mg/24h
 - Wait ≥ 2 wks between increments
 - Switch stable pts taking a β-B for a comorbidity to a β-B licensed for heart failure
 - β-B therapy may be particularly good in COPD
- **Loop diuretic:** frusemide or bumetanide

2nd line: get specialist advice

- **Spironolactone / eplerenone**
 - Watch K carefully (on ACEi too...)
- **ACEi + ARB**
- **Vasodilators:** hydralazine + ISDN
 - Additional Rx in Blacks

3rd line

- Digoxin
- Cardiac resynchronisation therapy ± ICD

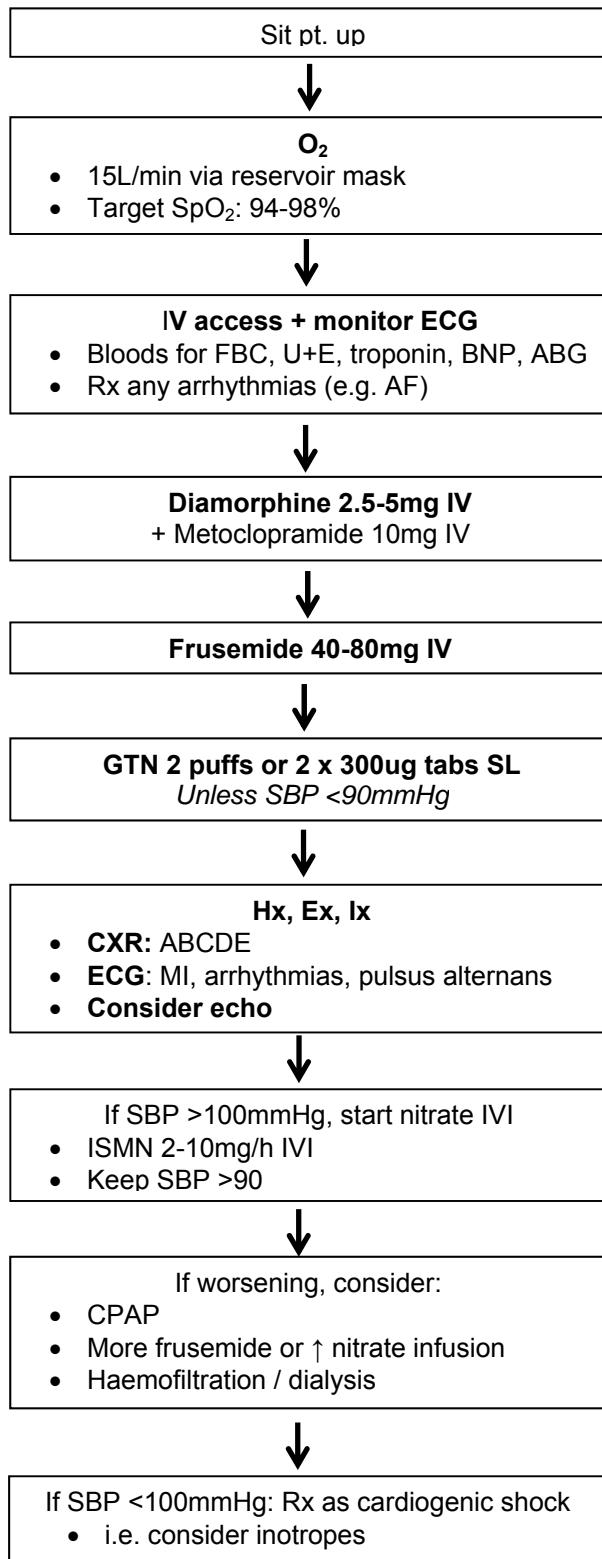
Other Considerations

- **Monitoring**
 - BP: may be v. low
 - Renal function
 - Plasma K
 - Daily wt.
- Use amlodipine for comorbid HTN or angina
- Avoid verapamil, diltiazem and nifedipine (short-acting)

Invasive Therapies

- Cardiac resynchronisation ± ICD
- Intra-aortic balloon counterpulsation
- LVAD
- Heart transplant (70% 5ys)

Severe Pulmonary Oedema



Causes

Cardiogenic

- MI
- Arrhythmia
- Fluid overload: renal, iatrogenic

Non-cardiogenic

- ARDS: sepsis, post-op, trauma
- Upper airway obstruction
- Neurogenic: head injury

Symptoms

- Dyspnoea
- Orthopnoea
- Pink frothy sputum

Signs

- Distressed, sweaty, cyanosed
- ↑HR, ↑RR
- ↑JVP
- S3 / gallop rhythm
- Bibasal creps
- Pleural effusions
- Wheeze (cardiac asthma)

Differential

- Asthma/COPD
- Pneumonia
- PE

Monitoring Progress

- BP
- HR and RR
- JVP
- Urine Output
- ABG

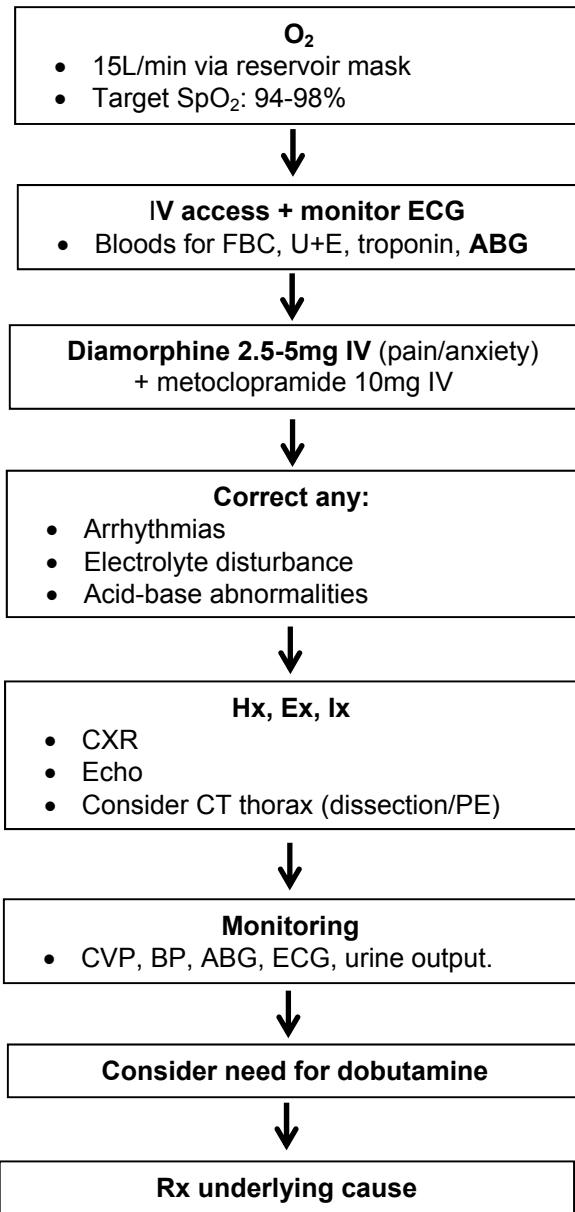
Continuing Therapy

- Daily weights
- DVT prophylaxis
- Repeat CXR
- Change to oral frusemide or bumetanide
- ACEi + β-B if heart failure
- Consider spironolactone
- Consider digoxin ± warfarin (esp. if in AF)

Morphine in Pulmonary Oedema

- Make pt. more comfortable
- Pulm venodilators → ↓ pre-load → optimise position on Starling Curve

Cardiogenic Shock



Definition

- Inadequate tissue perfusion primarily due to cardiac dysfunction.

Causes: MI HEART

- MI
- Hyperkalaemia (inc. electrolytes)
- Endocarditis (valve destruction)
- Aortic Dissection
- Rhythm disturbance
- Tamponade

Obstructive

- Tension pneumo
- Massive PE

Presentation

- Unwell: pale, sweaty, cyanosed, distressed
- Cold clammy peripheries
- ↑RR ± ↑HR
- Pulmonary oedema

Tamponade

Causes:

- Trauma
- Lung/breast Ca
- Pericarditis
- MI
- Bacteria (e.g. TB)

Mx:

- ABCs
- Pericardiocentesis (preferably under echo guidance)

Signs:

- Beck's triad:** ↓BP, ↑JVP, muffled heart sounds
- Kussmaul's sign:** ↑JVP on inspiration
- Pulsus paradoxus** (pulse fades on inspiration)

Ix:

- Echo:** diagnostic
- CXR:** globular heart

Hypertension

Definitions

- **Stage 1:** Clinic BP > 140/90
- **Stage 2:** Clinic BP > 160/100
- **Severe:** Clinic BP > 180/110
- **Malignant:** BP > 180/110 + papilloedema and/or retinal haemorrhage
- **Isolated SHT:** SBP ≥140, DBP <90

Aetiology: PREDICTION

- **Primary:** 95%
- **Renal:** RAS, GN, APKD, PAN
- **Endo:** ↑T4, Cushing's, phaeo, acromegaly, Conn's
- **Drugs:** cocaine, NSAIDs, OCP
- **ICP ↑**
- **CoA**
- **Toxaemia of Pregnancy (PET)**
- **Increased viscosity**
- **Overload with fluid**
- **Neurogenic:** diffuse axonal injury, spinal section

Aetiological clues

- ↑HR: Thyrotoxicosis
- RF-delay: CoA
- Renal bruits: RAS
- Palpable kidneys: APKD
- Paroxysmal headache, tachycardia, sweating, palpitations, labile or postural hypotension: phaeo

End-organ damage: CANER

Cardiac

- IHD
- LVH → CCF
- AR, MR

Aortic

- Aneurysm
- Dissection

Neuro

- CVA: ischaemic, haemorrhagic
- Encephalopathy (malignant HTN)

Eyes: hypertensive retinopathy

- Keith-Wagener Classification:
 1. Tortuosity and silver wiring
 2. AV nipping
 3. Flame haemorrhages and cotton wool spots
 4. Papilloedema
- Grades 3 and 4 = malignant hypertension

Renal

- Proteinuria
- CRF

Ix

- **24h ABPM**
- **Urine:** haematuria, Alb:Cr ratio
- **Bloods:** FBC, U+Es, eGFR, glucose, fasting lipids
- **12 lead ECG:** LVH, old infarct
- **Calculate 10yr CV risk**

Management

- Do ABPM to confirm Dx before Rx (unless severe HTN)

Lifestyle interventions

- ↑ exercise
- ↓ smoking, ↓ EtOH, ↓ salt, ↓ caffeine

Indications for Pharmacological Rx

- <80yrs, stage 1 HTN (>140/90) and one of:
 - Target organ damage (e.g. LVH, retinopathy)
 - 10yr CV risk ≥20%
 - Established CVD
 - DM
 - Renal disease
- Anyone with stage 2 HTN (>160/100)
- Severe / malignant HTN (specialist referral)
- Consider specialist opinion if <40yrs with stage 1 HTN and no end organ damage.

BP Targets

- Under 80yrs: <140/90 (<130/80 in DM)
- Over 80yrs: <150/90

CV Risk Mx

- Statins indicated for 1^o prevention if 10yr CVD risk ≥20%
- Aspirin may be indicated: evaluate risk of bleeding

Antihypertensive Rx

	< 55	> 55 / Black
1:	A	C (or D)
2:		A + C (/D)
3:		A + C + D
4:	Resistant HTN <ul style="list-style-type: none">• A+C+D+ consider further diuretic (e.g. spiro) or α-blocker or β-B.• Seek expert opinion	
A: ACEi or ARB <ul style="list-style-type: none">• e.g. lisinopril 10mg OD (↑ to 30-40mg)• e.g. candesartan 8mg OD (max 32mg OD)		C: CCB: e.g. nifedipine MR30-60mg OD
D: Thiazide-like diuretic: e.g. chlortalidone 25-50mg OD		
In step 2, use ARB over ACEi in blacks. Avoid thiazides + β-B if possible (↑ risk of DM). Only consider β-B if young and ACEi/ARB not tolerated.		

Malignant HTN

- Controlled ↓ in BP over days to avoid stroke
- Atenolol or long-acting CCB PO
- Encephalopathy/CCF: fruse + **nitroprusside** / labetalol IV
 - Aim to ↓ BP to 110 diastolic over ~4h
 - Nitroprusside requires intra-arterial BP monitoring

Aortic Stenosis

Causes

- **Senile calcification (60yrs +)**: commonest
- **Congenital**: Bicuspid valve (40-60yrs), William's syn.
- **Rheumatic fever**

Symptoms

- **Triad**: angina, dyspnoea, syncope (esp. \bar{c} exercise)
- **LVF**: PND, orthopnoea, frothy sputum
- Arrhythmias
- Systemic emboli if endocarditis
- Sudden death

Signs

- Slow rising pulse \bar{c} narrow PP
- Aortic thrill
- **Apex**: Forceful, non-displaced (pressure overload)
- **Heart Sounds**
 - Quiet A2
 - Early syst. ejection click if pliable (young) valve
 - S4 (forceful A contraction vs. hypertrophied V)
- **Murmur**
 - ESM
 - Right 2nd ICS
 - Sitting forward in end-expiration
 - Radiates to carotids

Clinical Indicators of Severe AS

- Quiet / absent A2
- S4
- Narrow pulse pressure
- Decompensation: LVF

Differential

- Coronary artery disease
- MR
- Aortic sclerosis
 - Valve thickening: no pressure gradient
 - Turbulence \rightarrow murmur
 - ESM \bar{c} no radiation and normal pulse
- HOCM
 - ESM murmur which \uparrow in intensity \bar{c} valsalva (AS \downarrow)

Aortic Stenosis	Aortic Sclerosis
Valve narrowing due to fusion of the commissures	Valve thickening
Narrow PP, slow rising pulse	
Forceful apex	
ESM radiating \rightarrow carotids	ESM \bar{c} no radiation
ECG: LVF	

Ix

Bloods: FBC, U+E, lipids, glucose

ECG

- LVH
- LV strain: tall R, ST depression, T inversion in V4-V6
- LBBB or complete AV block (septal calcification)
 - **May need pacing**

CXR

- Calcified AV (esp. on lateral films)
- LVH
- Evidence of failure
- Post-stenotic aortic dilatation

Echo + Doppler: diagnostic

- Thickened, calcified, immobile valve cusps
- Severe AS (AHA / ACC 2006 guidelines):
 - Pressure gradient $>40\text{mmHg}$
 - Jet velocity $>4\text{m/s}$ (or \uparrow by 0.3m/s in a yr)
 - Valve area $<1\text{cm}^2$

Cardiac Catheterisation + Angiography

- Can assess valve gradient and LV function
- Assess coronaries in all pts. planned for surgery

Exercise Stress Test

- Contraindicated if symptomatic AS
- May be useful to assess ex capacity in asympto pts.

Mx

Medical

- **Optimise RFs**: statins, anti-hypertensives, DM
- **Monitor**: regular f/up \bar{c} echo
- **Angina**: β -B
- **Heart failure**: ACEi and diuretics
- Avoid nitrates

Surgical

- Poor prog. if symptomatic
 - Angina/syncope: 2-3yrs
 - LVF: 1-2yrs
- Indications for valve replacement
 - Severe symptomatic AS
 - Severe asymptomatic AS $\bar{c} \downarrow$ EF ($<50\%$)
 - Severe AS undergoing CABG or other valve op
- Valve types
 - Mechanical valves last longer but need anticoagulation: young pts.
 - Bioprosthetic don't require anticoagulation but fail sooner (10-15yrs)

Options for unfit patients

- **Balloon Valvuloplasty**
 - Limited use in adults as complication rate is high ($>10\%$) and restenosis occurs in 6-12mo
- **Transcatheter Aortic Valve Implantation (TAVI)**
 - Folded valve deployed in aortic root.
 - \uparrow perioperative stroke risk cf. replacement
 - \downarrow major bleeding
 - Similar survival @ 1yr
 - Little Long-term data

Aortic Regurgitation

Causes

Acute

- Infective endocarditis
- Type A aortic dissection

Chronic

- Congenital: bicuspid aortic valve
- Rheumatic heart disease
- Connective tissue: Marfan's, Ehler's Danlos
- Autoimmune: Ankylosing spondylitis, RA

Symptoms

- **LVF:** Exertional dyspnoea, PND, orthopnoea
- Arrhythmias (esp. AF) → palpitations
 - Forceful heart beats
- Angina

Signs

- Collapsing pulse (Corrigan's pulse)
- Wide PP
- **Apex:** displaced (volume overload)
- **Heart Sounds**
 - Soft / absent S2
 - ± S3
- **Murmur**
 - EDM
 - URSE + 3rd left IC parasternal
 - Sitting forward in end-expiration
 - ± ejection systolic flow murmur
 - ± Austin-Flint murmur
- **Underlying cause**
 - High-arched palate
 - Spondyloarthropathy
 - Embolic phenomena

Eponyms

- **Corrigan's sign:** carotid pulsation
- **De Musset's:** head nodding
- **Quincke's:** capillary pulsation in nail beds
- **Traube's:** pistol-shot sound over femorals
- **Austin-Flint murmur**
 - Rumbling MDM @ apex due to regurgitant jet fluttering the ant. mitral valve cusp.
 - = severe AR
- **Duroziez's**
 - Systolic murmur over the femoral artery \bar{c} proximal compression.
 - Diastolic murmur \bar{c} distal compression

Clinical Indicators of Severe AR

- Wide PP and collapsing pulse
- S3
- Long murmur
- Austin Flint murmur
- Decompensation: LVF

Ix

Bloods: FBC, U+E, lipids, glucose

ECG: LVH ($R_6+S_1 > 35\text{mm}$)

CXR

- Cardiomegaly
- Dilated ascending aorta
- Pulmonary oedema

Echo

- Aortic valve structure and morphology (e.g. bicuspid)
- Evidence of infective endocarditis (e.g. vegetations)
- Severity
 - Jet width ($>65\%$ of outflow tract = severe)
 - Regurgitant jet volume
 - Premature closing of the mitral valve
- LV function: ejection fraction, end-systolic dimension

Cardiac Catheterisation

- Coronary artery disease
- Assess severity, LV function, root size

Mx

Medical

- **Optimise RFs:** statins, anti-hypertensives, DM
- **Monitor:** regular f/up \bar{c} echo
- \downarrow **systolic hypertension:** ACEi, CCB
 - \downarrow afterload $\rightarrow \downarrow$ regurgitation

Surgery: aortic valve replacement

- Definitive therapy
- Indicated in severe AR if:
 - Symptoms of heart failure
 - Asymptomatic LV dysfunction: \downarrow EF/ \uparrow ES dimension

Mitral Stenosis

Causes

- Rheumatic fever
- Prosthetic valve
- Congenital (rare)

Pathophysiology

- Valve narrowing → ↑ left atrial pressure → loud S1 and atrial hypertrophy → AF
- → pulmonary oedema and PHT → loud P2, PR
- → RVH → left parasternal heave
- → TR → large v waves
- → RHF → ↑JVP, oedema, ascites

Symptoms

- Dyspnoea
- Fatigue
- Chest pain
- **AF** → palpitations + emboli
- Haemoptysis: rupture of bronchial veins

Signs

- Symptoms manifest when orifice <2cm² (norm 4-6)
- **AF**, low volume pulse
- **Malar flush** (↓CO → backpressure + vasoconstriction)
- JVP may be raised late on
 - Prominent a waves: PTH
 - Large v waves: TR
 - Absent a waves: AF
- Left parasternal heave (RVH 2^o to PHT)
- **Apex**: Tapping (palpable S1), non-displaced
- **Heart sounds**
 - Loud S1
 - Loud P2 (if PHT)
 - Early diastolic opening snap
- **Murmur**
 - Rumbling MDM
 - Apex
 - Left lateral position in end expiration
 - Radiates to the axilla
 - ± Graham Steell murmur (EDM 2^o to PR)

Clinical Indicators of Severe MS

- Mitral facies
- Longer murmur
- Opening snap closer to 2nd heart sound
 - High LA pressure forcing valve open early
- Decompensation: RVF

Complications

- Pulmonary HTN
- Emboli: TIA, CVA, PVD, ischaemic colitis
- Hoarseness: rec laryngeal N. palsy = Ortner's Syn
- Dysphagia (oesophageal compression)
- Bronchial obstruction

Ix

Bloods: FBC, U+E, LFTs, glucose, lipids

ECG

- AF
- P mitrale (if in sinus)
- RVH c strain: ST depression and T wave inversion in V1-V2

CXR

- LA enlargement
- Pulmonary oedema: ABCDE
- Mitral valve calcification

Echo + Doppler

- Severe MS (AHA 2006 Criteria)
 - Valve orifice <1cm²
 - Pressure gradient >10mmHg
 - Pulmonary artery systolic pressure >50mmHg
- Use TOE to look for left atrial thrombus if intervention considered.

Cardiac Catheterisation

- Assess coronary arteries

Mx

Medical

- **Optimise RFs:** statins, anti-hypertensives, DM
- **Monitor:** regular f/up c echo
- Consider prophylaxis vs. rheumatic fever: e.g. Pen V
- **AF:** rate control and anticoagulate
- Diuretics provide symptom relief

Surgical

- Indicated in mod-severe MS (asympto and symptomatic)
- Percutaneous balloon valvuloplasty
 - Rx of choice
 - Suitability depends on valve characteristics
 - Pliable, minimally calcified
 - CI if left atrial mural thrombus
- Surgical valvotomy / commissurotomy: valve repair
- Valve replacement if repair not possible

Mitral Regurgitation

Causes

- Mitral valve prolapse
- LV dilatation: AR, AS, HTN
- Annular calcification → contraction (elderly)
- Post-MI: papillary muscle dysfunction/rupture
- Rheumatic fever
- Connective tissue: Marfan's, Ehlers-Danlos

Symptoms

- Dyspnoea, fatigue
- AF → palpitations + emboli
- Pulmonary congestion → HTN + oedema

Signs

- AF
- Left parasternal heave (RVH)
- **Apex:** displaced
 - Volume overload as ventricle has to pump forward SV and regurgitant volume
 - → eccentric hypertrophy
- **Heart Sounds**
 - Soft S1
 - S2 not heard separately from murmur
 - Loud P2 (if PTH)
- **Murmur**
 - Blowing PSM
 - Apex
 - Left lateral position in end expiration
 - Radiates to the axilla

Clinical Indicators of Severe MR

- Larger LV
- Decompensation: LVF
- AF

Differential

- AS
- TR
- VSD

Ix

Bloods: FBC, U+E, glucose, lipids

ECG

- AF
- P mitrale (unless in AF)
- LVH

CXR

- LA and LV hypertrophy
- Mitral valve calcification
- Pulmonary oedema

Echo

- Doppler echo to assess MR severity: multiple criteria
 - Jet width (vena contracta) >0.6cm
 - Systolic pulmonary flow reversal
 - Regurgitant volume >60ml
- TOE to assess severity and suitability of repair cf. replacement.

Cardiac Catheterisation

- Confirm Dx
- Assess CAD

Mx

Medical

- **Optimise RFs:** statins, anti-hypertensives, DM
- **Monitor:** regular f/up c echo
- **AF:** rate control and anticoagulate
 - Also anticoagulate if: Hx of embolism, prosthetic valve, additional MS
- Drugs to ↓ afterload can help ↓ symptoms
 - ACEi or β-B (esp. carvedilol)
 - Diuretics

Surgical

- Valve replacement or repair
- Indications
 - Severe symptomatic MR
 - Severe asymptomatic MR c diastolic dysfunction: ↓EF

Mitral Valve Prolapse (Barlow Syndrome)

- Commonest valve prob. (~5%)

Causes

- Primary: myxomatous degeneration
 - Often young women
- MI
- Marfan's, ED
- Turner's

Symptoms

- Usually asymptomatic
- Autonomic dysfunction: Atypical chest pain, palpitations, anxiety, panic attack
- MR: SOB, fatigue

Signs

- Mid-systolic click ± late-systolic murmur

Complications

- MR
- Cerebral emboli
- Arrhythmias → sudden death

Mx

- β-B may relieve palpitations and chest pain
- Surgery if severe (commonest reason for MV surgery)

Right Heart Valve Disease

Tricuspid Regurgitation

Causes

- Functional: RV dilatation
- Rheumatic fever
- Infective endocarditis
- Carcinoid syndrome

Symptoms

- Fatigue
- Hepatic pain on exertion
- Ascites, oedema

Signs

- ↑JVP $\ddot{\text{C}}$ giant V waves
- RV heave
- **Murmur:**
 - PSM
 - LLSE in inspiration (Carvallo's sign)
- Pulsatile hepatomegaly
- Jaundice

Ix

- LFTs
- Echo

Mx

- **Rx cause**
- **Medical:** diuretics, ACEi, digoxin
- **Surgical:** valve replacement

Tricuspid Stenosis

Causes

- Rheumatic fever (with MV and AV disease)

Symptoms

- Fatigue
- Ascites
- Oedema

Signs

- Large A waves
- Opening snap
- **Murmur:**
 - EDM
 - LLSE in inspiration

Mx

- **Medical:** diuretics
- **Surgical:** repair, replacement

Pulmonary Regurgitation

Causes

- Any cause of pulmonary HTN
- PR 2° to MS = Graham-Steell murmur

Signs

- **Murmur:** Decrescendo EDM @ ULSE

Pulmonary Stenosis

Causes

- Usually congenital: e.g. Turner's, Fallot's
- Rheumatic fever
- Carcinoid syndrome

Symptoms

- Dyspnoea, fatigue
- Ascites
- Oedema

Signs

- Dysmorphia
- Large A wave
- RV heave
- Ejection click, soft P2
- **Murmur**
 - ESM
 - ULSE \rightarrow L shoulder

Ix

- **ECG**
 - P pulmonale
 - RAD
 - RBBB
- **CXR:**
 - Prominent pulmonary arteries: post-stenotic dilatation
- **Catheterisation:** diagnostic
- **Mx:** valvuloplasty or valvotomy

Infective Endocarditis

Definition

- Cardiac valves develop vegetations composed of bacteria and platelet-fibrin thrombus.

Risk Factors

Cardiac disease → Subacute Normal valves → Acute

- | | |
|-----------------------|--------------------------|
| • Prosthetic valves | • Dental caries |
| • Degen. valvulopathy | • Post-op wounds |
| • VSD, PDA, CoA | • IVDU (tricuspid valve) |
| • Rheumatic fever | • Immunocomp. (inc. DM) |

Aetiology

Culture +ve

- S. viridans (>35%)
- S. bovis
- S. aureus
- S. epidermidis
- Enterococci
- Pseudomonas

Culture -ve

- Haemophilus
- Actinobacillus
- Cardiobacterium
- Eikenella
- Kingella
- Coxiella
- Chlamydia

Non-infective

- SLE
- Marantic

Clinical Features

Sepsis

- Fever, rigors
- Night sweats
- Wt. loss
- Anaemia
- Splenomegaly
- Clubbing

Cardiac

- New/changing murmur (MR: 85%, AR: 55%)
- AV block
- LVF

Embolic phenomena

- Abscesses in brain, heart, kidney, spleen, gut and lung (if right-sided)
- Janeway lesions

Immune complex deposition

- Micro haematuria due to GN
- Vasculitis
- Roth spots
- Splinter haemorrhages
- Osler's nodes

Roth spots: boat-shaped retinal haemorrhages ⚡ pale centre

Janeway lesions: painless palmar macules

Osler's nodes: painful, purple papules on finger pulps

Dx: Duke Criteria

Major

1. +ve blood culture

- Typical organism in 2 separate cultures, or
- Persistently +ve cultures, e.g. 3, >12h apart

2. Endocardium involved

- +ve echo (vegetation, abscess, valve dehiscence) or
- New valvular regurgitation

Minor

- Predisposition:** cardiac lesion, IVDU
- Fever >38**
- Emboli:** septic infarcts, splinters, Janeway lesions
- Immune phenomenon:** GN, Osler nodes, Roth spots, RF
- +ve blood culture not meeting major criteria

Dx if:

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

Ix

Bloods

- N.chromic, N.cytic anaemia
- ↑ESR, ↑CRP
- +ve IgG RF (immune phenomenon)
- Cultures x 3, >12h apart
- Serology for unusual organisms

Urine: Micro haematuria

ECG: AV block

Echo

- TTE detects vegetations > 2mm
- TOE is more sensitive (90-100% vs. 50-60%)

Rx

- Empiric**
 - Acute severe:** Fuclox + gent IV
 - Subacute:** Benpen + gent IV

- Streps:** benpen + gent IV
- Enterococci:** amoxicillin + gent IV
- Staphs:** flucloxacillin ± rifampicin IV
- Fungi:** flucytosine IV + fluconazole PO.
 - Amphotericin if flucytosine resistance or *Aspergillus*.

Consider surgery if

- Heart failure
- Embolii
- Valve obstruction
- Prosthetic valve

Prophylaxis

- Abx prophylaxis solely to prevent IE not recommended

Mortality

- 30% ⚡ staphs
- 14% ⚡ bowel flora
- 6% ⚡ sensitive streps

Rheumatic Fever

Aetiology

- Group A β-haemolytic strep. (pyogenes)

Epidemiology

- 5-15yrs
- Rare in West. Common in developing world.
- Only 2% of population susceptible

Pathophysiology

- Ab cross-reactivity following *S. pyogenes* infection → T2 hypersensitivity reaction (molecular mimicry).
- Abs. vs. M protein in cell wall.
- Cross react \bar{C} myosin, muscle glycogen and SM cells.
- **Path:** Aschoff bodies and Anitschkow myocytes.

Dx: revised Jones Criteria

- Evidence of GAS infection plus:
 - 2 major criteria, or
 - 1 major + 2 minor

Evidence of GAS infection

- +ve throat culture
- Rapid strep Ag test
- ↑ ASOT or DNase B titre
- Recent scarlet fever

Major Criteria

- Pancarditis
- Arthritis
- Subcutaneous nodules
- Erythema marginatum
- Sydenham's chorea

Minor criteria

- Fever
- ↑ESR or ↑CRP
- Arthralgia (not if arthritis is major)
- Prolonged PR interval (not if carditis is a major)
- Prev rheumatic fever

Symptomatology

Pancarditis (60%)

- **Pericarditis:** chest pain, friction rub
- **Myocarditis:** sinus tachy, AV block, HF, ↑CK, T inversion
- **Endocarditis:** murmurs
 - MR, AR, Carey Coombs' (MDM)

Arthritis (75%)

- Migratory polyarthritis of large joints (esp. knees)

Subcutaneous nodules (2-20%)

- Small mobile, painless nodules on extensor surfaces (esp. elbows)

Erythema marginatum (2-10%)

- Red, raised edges \bar{C} central clearing.
- Trunk, thighs and arms.

Sydenham's Chorea (10%)

- Occurs late
- Grimacing, clumsy, hypotonia (stops in sleep)

Ix

Bloods

- Strep Ag test or ASOT
- FBC, ESR/CRP

ECG

Echo

Rx

- Bed rest until CRP normal for 2wks
- **Benpen** 0.6-1.2mg IM for 10 days
- **Analgesia** for carditis/arthritis: aspirin / NSAIDs
- Add oral **pred** if: CCF, cardiomegaly, 3rd degree block
- Chorea: **Haldol** or diazepam

Prognosis

- Attacks last ~ 3mo.
- 60% \bar{C} carditis develop chronic rheumatic heart disease.
- Recurrence ppter by
 - Further strep infection
 - Pregnancy
 - OCP
- Valve disease: regurgitation → stenosis
 - Mitral (70%)
 - Aortic (40%)
 - Tricuspid (10%)
 - Pulmonary (2%)

Secondary Prophylaxis

- Prevent recurrence
- Pen V 250mg/12h PO
 - Carditis + valve disease: until 40yrs old
 - Carditis w/o valve disease: 10yrs
 - No carditis: 5yrs

Pericardial Disease

Acute Pericarditis

Causes

- **Viral:** coxsackie, flu, EBV, HIV
- **Bacterial:** pneumonia, rheumatic fever, TB, staphs
- **Fungi**
- **MI, Dressler's**
- **Drugs:** penicillin, isoniazid, procainamide, hydralazine
- **Other:** uraemia, RA, SLE, sarcoid, radiotherapy

Clinical Features

- Central / retrosternal chest pain
 - Sharp
 - Pleuritic
 - Worse lying down
 - Relieved by sitting forward
 - Radiates to left shoulder
- Pericardial friction rub.
- Fever
- Signs of effusion / tamponade

Ix

- **ECG:** saddle-shaped ST-elevation ± PR depression
- **Bloods:** FBC, ESR, trop (may be ↑), cultures, virology

Mx

- **Analgesia:** ibuprofen 400mg/8h PO
- Rx cause
- Consider steroids / immunosuppression

Constrictive Pericarditis

- Heart encased in a rigid pericardium.

Causes

- Often unknown
- May occur after any pericarditis

Clinical features

- RHF \bar{C} ↑JVP (prominent x and y descents)
- **Kussmaul's sign:** ↑JVP \bar{C} inspiration
- Quiet heart sounds
- S3
- Hepatosplenomegaly
- Ascites, oedema

Ix

- **CXR:** small heart + pericardial calcification
- **Echo**
- **Cardiac Catheterisation**

Mx

- Surgical excision

Pericardial Effusion

Causes

- Any cause of pericarditis

Clinical Features

- Dyspnoea
- ↑JVP (prominent x descent)
- Bronchial breathing @ left base
 - Ewart's sign: large effusion compressing left lower lobe
- Signs of cardiac tamponade may be present.

Ix

- **CXR:** enlarged, globular heart
- **ECG**
 - Low-voltage QRS complexes
 - Alternating QRS amplitude (electrical alternans)
- **Echo:** echo-free zone around heart

Mx

- Treat cause
- Pericardiocentesis may be diagnostic or therapeutic
 - Culture, ZN stain, cytology

Tamponade

- Accumulation of pericardial fluid → ↑ intra-pericardial pressure → poor ventricular filling → ↓ CO

Causes

- Any cause of pericarditis
- Aortic dissection
- Warfarin
- Trauma

Signs

- **Beck's Triad:** ↓ BP, ↑ JVP, quiet heart sounds
- **Pulsus paradoxus:** pulse fades on inspiration
- **Kussmaul's sign**

Ix

- **ECG:** low-voltage QRS ± electrical alternans
- **CXR:** large, globular heart
- **Echo:** diagnostic, echo-free zone around heart

Mx

- Urgent pericardiocentesis
 - 20ml syringe + long 18G cannula
 - 45°, just left of xiphisternum, aiming for tip of left scapula.
 - Aspirate continuously and watch ECG.
- Treat cause
- Send fluid for cytology, ZN stain and culture

Myocardial Disease

Acute Myocarditis

Causes

- Idiopathic (~50%)
- **Viral:** coxsackie B, flu, HIV
- **Bacterial:** S. aureus, syphilis
- **Drugs:** cyclophosphamide, Herceptin, CBZ, phenytoin
- **Autoimmune:** Giant cell myocarditis assoc. w/ SLE

Symptoms

- **Flu-like prodrome:** fever, sore throat, myalgia
- Dyspnoea, fatigue
- Chest pain (may coexist w/ Bornholm disease)
- Arrhythmia → palpitations

Signs

- Soft S1
- S4 gallop

Ix

- **ECG**
 - ST-elevation or depression
 - T wave inversion
 - Transient AV block
- **Bloods:** +ve troponin, ↑CK

Mx

- Supportive
- Rx cause

Hypertrophic Obstructive Cardiomyopathy

- LVOT obstruction from asymmetric septal hypertrophy
- AD inheritance (but 50% sporadic)
- β-myosin heavy chain mutation commonest
- Ask re family Hx of sudden death

Symptoms

- Angina
- Dyspnoea
- Palpitations: AF, WPW, VT
- Exertional syncope or sudden death

Signs

- Jerky pulse
- Double apex beat
- Harsh ESM @ LLSE w/ systolic thrill
- S4

Ix

- **ECG**
 - LHV/LAD/L strain,
 - Ventricular ectopics, VT, VF
- **Echo:** ASH
- Exercise test ± holter monitor to quantify risk

Mx

- **Medical**
 - -ve inotropes: 1st – β-B, 2nd – verapamil
 - **Amiodarone:** arrhythmias
 - **Anticoagulate** if AF or emboli
- **Non-medical**
 - Septal myomectomy (surgical or chemical) if severe symptoms
- Consider ICD

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Cardiac Myxoma

- Rare, benign cardiac tumour
- F>M=2:1
- May be familial: e.g. Carney Complex
 - Cardiac and cutaneous myxoma, skin pigmentation, endocrinopathy (e.g. Cushing's)
- 90% in left atrium (fossa ovalis)
- **Features:**
 - Clubbing, fever, ↓wt., ↑ESR
 - Signs similar to MS (MDM, systemic emboli, AF) but vary w/ posture.
- **Dx:** Echo
- **Rx:** Excision

Restrictive Cardiomyopathy

Causes: miSSHAPEN

- Sarcoid
- Systemic sclerosis
- Haemochromatosis
- Amyloidosis
- Primary: endomyocardial fibrosis
- Eosinophilia (Loffler's eosinophilic endocarditis)
- Neoplasia: carcinoid (→ TR and PS)

Clinical Features: as constrictive pericarditis

Dx: Catheterisation

Rx: Rx cause

Dilated Cardiomyopathy

Causes: DILATE

- Dystrophy: muscular, myotonic, glycogen storage disease
- Infection: complication of myocarditis
- Late pregnancy: peri-, post-partum
- Autoimmune: SLE
- Toxins: EtOH, doxorubicin, cyclophosphamide, DXT
- Endocrine: thyrotoxicosis

Presentation

- LVF and RVF
- Arrhythmias

Signs

- JVP ↑↑
- Displaced apex
- S3 gallop
- ↓BP
- MR/TR

Ix

- **CXR:** cardiomegaly, pulmonary oedema
- **ECG:** T inversion, poor progression
- **Echo:** globally dilated, hypokinetic heart + ↓EF
- **Catheter + biopsy:** myocardial fibre disarray

Mx

- Bed rest
- **Medical:** diuretics, ACEi, digoxin, anticoagulation
- **Non-medical:** biventricular pacing, ICD
- **Surgical:** heart Tx

Congenital Heart Disease

Bicuspid Aortic Valve

- No problems @ birth
- Most eventually develop stenosis ± regurgitation
 - Pre-disposes to IE/SBE

Atrial Septal Defect

- Hole connects the atria
- Secundum defects high in the septum are commonest
- Often asymptomatic until adulthood
 - LV compliance ↓ → ↑ L→R shunt

Symptoms

- Dyspnoea
- Pulmonary HTN
- Arrhythmia
- Chest pain

Signs

- AF
- ↑ JVP
- Pulmonary ESM
- PHT → TR or PR

Complications

- Paradoxical emboli
- Eisenmenger's syndrome
 - ↑ RA pressure: R→L shunt → cyanosis

Ix

- ECG:
 - Secundum: RAD
- CXR: pulmonary plethora
- Echo: diagnostic

Rx

- Transcatheter closure
- Recommended in adults if high pulmonary to systemic blood flow ratio ($\geq 1.5:1$)

Coarctation of the Aorta

- Congenital narrowing of the aorta
- Usually occurs just distal to origin of left subclavian
- M>F

Associations

- Bicuspid aortic valve
- Turner's syndrome

Signs

- Radio-femoral delay + weak femoral pulse
- Hypertension
- Systolic murmur / bruit heard best over left scapula

Complications

- Heart failure
- IE

Ix

- CXR: rib notching
- ECG: LV strain
- CT angiogram

Rx: balloon dilatation + stenting

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Ventricular Septal Defect

- Hole connects ventricles

Causes

- Congenital
- Acquired: post-MI

Presentation

- Severe HF in infancy or incidental discovery in later life

Signs

- Small holes which are haemodynamically less significant
 - louder murmurs
 - Harsh, pansystolic murmur @ left sternal edge
 - Systolic thrill
 - Left parasternal heave
- Larger holes → PHT

Complications

- Infective endocarditis
- PHT
- Eisenmenger's

ECG

- Small: normal
- Large: LVH + RVH

CXR

- Small: mild pulmonary plethora
- Large: cardiomegaly + marked pulmonary plethora

Rx

- Surgical closure indicated if symptomatic VSD & large shunt.

Fallot's Tetralogy

- Commonest congenital cyanotic heart defect
- Abnormal separation of truncus arteriosus into aorta and pulmonary arteries.

Pathology

1. VSD
2. Pulmonary stenosis
3. RVH
4. Overriding aorta

Associations

- Di George: CATCH-22

Presentation

- Infants: hypercyanotic episodes, squatting, clubbing
- Adult
 - Often asymptomatic
 - Unoperated: cyanosis, ESM of PS
 - Repaired: dyspnoea, palpitations, RVF

ECG: RVH + RBBB

CXR: Coeur en sabot

Echo: anatomy + degree of stenosis

Rx: Surgical (usually before 1yr)

- Closure of VSD
- Correction of the pulmonary stenosis

Inherited Connective Tissue Disorders

Marfan's Syndrome

Epidemiology

- Autosomal dominant
- Spontaneous mutation in 25%
- M=F
- Prevalence = 1/5000

Pathophysiology

- Mutation in FBN1 gene on Chr 5
 - Encodes fibrillin-1 glycoprotein
- Fibrillin-1 is an essential component of elastin
- Histology: "cystic medial necrosis"

Presentation

- **Cardiac**
 - Aortic aneurysm and dissection
 - Aortic root dilatation → regurgitation
 - MV prolapse ± regurgitation
- **Ocular**
 - Lens dislocation: superotemporal
- **MSK**
 - High-arched palate
 - Arachnodactyly
 - Arm-span > height
 - Pectus excavatum
 - Scoliosis
 - Pes planus
 - Joint hypermobility

Complications

- Ruptured aortic aneurysm
- Spontaneous pneumothorax
- Diaphragmatic hernia
- Hernias

Dx

- Two 2/3 organ systems must be involved

Differential Diagnosis

- MEN-2b
- Homocystinuria
- Ehlers-Danlos

Ix

- **Slit-lamp examination:** ectopia lentis
- **CXR**
 - Widened mediastinum
 - Scoliosis
 - Pneumothorax
- **ECG**
 - Arrhythmias: premature atrial and ventricular ectopics
- **Echo**
 - Aortic root dilatation → AR
 - MVP and MR
- **MRI:** dural ectasia (dilation of neural canal)
- **Genetic testing:** FBN-1 mutation

Mx

- Refer to ortho, cardio and ophtho
- Life-style alteration: ↓ cardiotensive sports
- Beta-blockers slow dilatation of the aortic root
- Regular cardiac echo
 - Surgery when aortic root ≥5cm wide

Ehlers-Danlos Syndrome

Pathogenesis

- Rare heterogeneous group of collagen disorders.
- 6 subtypes varying severity
- Commonest types (1 and 2) are autosomal dominant

Presentation

- Hyperelastic skin
- Hypermobile joints
- Cardiac: MVP, AR, MR and aneurysms
- Fragile blood vessels → easy bruising, GI bleeds
- Poor healing

Differential Diagnosis

- Cutis Laxa: loose skin + hypermobile joints
- Pseudoxanthoma elasticum: skin laxity
- Marfan's

Pulmonology

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Clubbing

Features and Stages

1. Bogginess / ↑ fluctuance of nail bed
2. Loss of concave nail fold angle
3. ↑ longitudinal and transverse curvature
4. Soft tissue expansion at distal phalanx (drumstick)

Causes

Respiratory

- **Carcinoma**
 - Bronchial
 - Mesothelioma
- **Chronic lung suppuration**
 - Empyema, abscess
 - Bronchiectasis, CF
- **Fibrosis**
 - Idiopathic pulmonary fibrosis / CFA
 - TB

Cardiac

- Infective Endocarditis
- Congenital cyanotic heart disease
- Atrial myxoma

GIT

- Cirrhosis
- Crohn's, uC
- Coeliac
- Cancer: GI lymphoma

Other

- Familial
- Thyroid Acropachy
- Upper limb AVMs or aneurysms
 - Unilateral clubbing

Cyanosis

Definition

- Blue discolouration of mucosal membranes or skin
- Deoxygenated Hb >5g/dl

Classification

- **Peripheral:** cold, blue nails
- **Central:** blue tongue, lips

Causes

- Think of O₂ cascade

Respiratory

- **Hypoventilation:** COPD, MSK
- ↓ **diffusion:** pulm oedema, fibrosing alveolitis
- **V/Q mismatch:** PE, AVM (e.g. HHT)

Cardiac

- **Congenital:** Fallot's, TGA
- ↓ **CO:** MS, systolic LVF
- **Vascular:** Raynaud's, DVT

RBCs

- Low affinity Hb, may be hereditary or acquired

Pneumonia

Epidemiology

- Incidence: 1/100
- Mortality: 10% in hospital, 30% in ITU

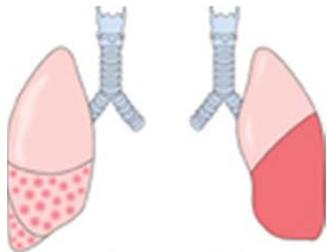
Anatomic Classification

Bronchopneumonia

- Patchy consolidation of different lobes

Lobar Pneumonia

- Fibrosuppurative consolidation of a single lobe
- Congestion → red → grey → resolution



Aetiological Classification

Community Acquired Pneumonia

- Pneumococcus, mycoplasma, haemophilus
- S. aureus, Moraxella, Chlamydia, Legionella
- Viruses: 15%

Hospital Acquired Pneumonia

- >48hrs after hospital admission
- Gm-ve enterobacteria, S. aureus

Aspiration

- ↑ Risk: stroke, bulbar palsy, ↓GCS, GORD, achalasia
- Anaerobes

Immunocompromised

- The usual suspects, plus
- PCP, TB, fungi, CMV/HSV

Symptoms

- Fever, rigors
- Malaise, anorexia
- Dyspnoea
- Cough, purulent sputum, haemoptysis
- Pleuritic pain

Signs

- ↑RR, ↑HR
- Cyanosis
- Confusion
- **Consolidation**
 - ↓ expansion
 - Dull percussion
 - Bronchial breathing
 - ↓ air entry
 - Crackles
 - Pleural rub
 - ↑VR

Ix

- **Bloods:** FBC, U+E, LFT, CRP, culture, ABG (if ↓SpO₂)
- **Urine:** Ag tests (Pneumococcal, Legionella)
- **Sputum:** MC&S
- **Imaging:** CXR
 - infiltrates, cavities, effusion
- **Special**
 - Paired sera Abs for atypicals
 - Mycoplasma, Chlamydia, Legionella
 - Immunofluorescence (PCP)
 - BAL
 - Pleural tap

Severity: CURB-65 (only if x-ray changes)

	Score
• Confusion (AMT ≤ 8)	• 0-1 → home Rx
• Urea >7mM	• 2 → hospital Rx
• Resp. rate >30/min	• ≥3 → consider ITU
• BP <90/60	
• ≥65	

Mx

- Abx
- O₂: PaO₂≥8, SpO₂ 94-98%
- Fluids
- Analgesia
- Chest physio
- Consider ITU if shock, hypercapnoea, hypoxia
- F/up @ 6wks \bar{C} CXR
 - Check for underlying Ca

Empirical Abx

CAP

Mild	amoxicillin 500mg TDS PO for 5d or clarithro 500mg BD PO for 7d
Mod	amoxicillin 500mg TDS and clarithro 500mg BD PO/IV (clarithro alone if pen allergy) for 7d
Sev	Co-amoxiclav 1.2g TDS IV / cefuroxime 1.5g TDS IV and clarithro 500mg BD IV for 7-10d Add flucloxx if staph suspected.
Atyp	Chlamydia: tetracycline PCP: Co-trimoxazole Legionella: Clarithro + rifampicin

HAP

- **Mild / <5d:** Co-amoxiclav 625mg PO TDS for 7d
- **Severe / >5d:** Tazocin ± vanc ± gent for 7d

Aspiration

- Co-amoxiclav 625mg PO TDS for 7d

Pneumovax (23 valent)

- ≥65yrs
- Chronic HLKP failure or conditions
- DM
- Immunosuppression: hyposplenism, chemo, HIV
- **CI:** P, B, fever

NB. revaccinate every 6yrs

Complications of Pneumonia

Respiratory failure

- Type 1: $\text{PaO}_2 < 8 \text{kPa}$ + $\text{PaCO}_2 < 6 \text{kPa}$
- Type 2: $\text{PaO}_2 < 8 \text{kPa}$ + $\text{PaCO}_2 > 6 \text{kPa}$
- Mx: O_2 therapy, ventilation

Hypotension

- Cause: dehydration + septic vasodilatation
- Mx
 - If SBP < 90 → 250ml fluid challenge over 15min
 - If no improvement: central line + IV fluids
 - If refractory: ITU for inotropes

AF

- Usually resolves \bar{c} Rx
- Mx: Digoxin or β -B for rate control

Pleural effusion

- Exudate
- Mx: tap and send for MC+S, cytology and chemistry

Empyema

- Pus in the pleural cavity
- Anaerobes, Staph, Gm-ve
- Assoc. \bar{c} recurrent aspiration
- Pt. \bar{c} resolving pneumonia develops recurrent fever
- Tap: turbid, pH < 7.2, ↓ glucose, ↑ LDH
- Mx: US guided chest drain + Abx

Lung Abscess

Causes

- Aspiration
- Bronchial obstruction: tumour, foreign body
- Septic emboli: sepsis, IVDU, RH endocarditis
- Pulmonary infarction
- Subphrenic / hepatic abscess

Features

- Swinging fever
- Cough, foul purulent sputum, haemoptysis
- Malaise, wt. loss
- Pleuritic pain
- Clubbing
- Empyema

Tests

- Blood: FBC, ESR, CRP, cultures
- Sputum: micro, culture, cytology
- CXR: cavity \bar{c} fluid level
- Consider CT and bronchoscopy

Mx

- Abx according to sensitivities
- Aspiration
- Surgical excision

Other Complications

- Sepsis
- Pericarditis / myocarditis
- Jaundice
 - Usually cholestatic
 - Causes: sepsis, drugs (flucloxa, Augmentin), Mycoplasma, Legionella

Systemic Inflammatory Response Syndrome

Inflammatory response to a variety of insults manifest by ≥ 2 of:

- Temperature: $> 38^\circ\text{C}$ or $< 36^\circ\text{C}$
- Heart rate: > 90
- Respiratory rate: > 20 or $\text{PaCO}_2 < 4.6 \text{ kPa}$
- WCC: $> 12 \times 10^9/\text{L}$ or $< 4 \times 10^9/\text{L}$ or $> 10\%$ bands

Sepsis

- SIRS caused by infection

Severe Sepsis

- Sepsis \bar{c} at least 1 organ dysfunction or hypoperfusion

Septic Shock

- Severe sepsis with refractory hypotension

MODS

- Impairment of ≥ 2 organ systems
- Homeostasis cannot be maintained without therapeutic intervention.

Specific Pneumonias

Organism	Risk Factors	Pulmonary Features	Extrapulmonary	Mx
Pneumococcus	Elderly EtOH Immunosuppressed CHF Pulmonary disease	Lobar consolidation	Herpes labialis	Amoxicillin Benpen Cephalosporins
S. aureus	Influenza infection IVDU Co-morbidities	Bilateral cavitating bronchopneumonia		Fluclox Vanc
Klebsiella	Rare Elderly EtOH DM	Cavitating pneumonia Esp. upper lobes		Cefotaxime
Pseudomonas	Bronchiectasis CF			Taz
Mycoplasma	Epidemics	Dry cough Reticulo-nodular shadowing or patchy consolidation	Flu-like prodrome - headache - myalgia/arthralgia Cold agglutinins → AIHA Cryoglobulin Erythema multiforme SJS GBS Hepatitis	Dx: serology Clarithro Cipro
Legionella	Travel Air conditioning	Dry cough Dyspnoea Bi-basal consolidation	Flu-like prodrome Anorexia D&V Hepatitis Renal Failure Confusion SIADH → ↓Na	Lymphopenia ↓Na ⁺ Deranged LFTs Dx: Urinary Ag or serology Clarithro ± rifa
Chlam. pneumoniae		Pharyngitis, otitis → pneumonia	Sinus pain	Dx: serology Clarithro
Chlam. psittaci	Parrots	Dry cough Patchy consolidation	Horder's spots ~ rose spots Splenomegaly Epistaxis Hepatitis, nephritis Meningo-encephalitis	Dx: serology Clarithro
PCP	Immunocompromised	Dry cough Exertional dyspnoea Bilateral creps CXR: normal or bilateral perihilar interstitial shadowing		Dx: visualisation from BAL, sputum, biopsy High dose co-trimoxazole or pentamidine Prophylaxis if CD4<200 or after 1 st attack

Bronchiectasis

Pathophysiology

- Chronic infection of bronchi/bronchioles → permanent dilatation.
- Retained inflammatory secretions and microbes → airway damage and recurrent infection
- Organisms:
 - H. influenza
 - Pneumococcus
 - S. aureus
 - Pseudomonas

Causes

- Idiopathic in 50%

Congenital

- CF (mainly upper lobe infiltration)
- Kartagener's / PCD
- Young's syn. (azoospermia + bronchiectasis)

Post-infectious

- Measles
- Pertussis
- Pneumonia
- TB
- Bronchiolitis

Immunodeficiency

- Hypogammaglobulinaemia
 - X-linked agammaglobulinaemia: Bruton's
 - CVID
 - IgG subclass deficiency
 - IgA deficiency

Other

- Bronchial obstruction: LNs, tumour, foreign body
- ABPA
- RA
- UC
- Yellow nail syndrome
 - Yellow nail discoloration and dystrophy
 - Lymphoedema
 - Pleural effusions
 - Bronchiectasis

Symptoms

- Persistent cough → purulent sputum
- Haemoptysis (may be massive)
- Fever, wt. loss

Signs

- Clubbing
- Coarse inspiratory creps
- Wheeze
- Purulent sputum
- Cause**
 - Situs inversus (+ PCD = Kartagener's syn.)
 - Splenomegaly: immune deficiency

Complications

- Pneumonia
- Pleural effusion
- Pneumothorax
- Pulmonary HTN
- Massive haemoptysis
- Cerebral abscess
- Amyloidosis

Ix

- Sputum MCS
- Blood:** Se Ig, Aspergillus precipitins, RF, α1-AT level
 - Test Ig response to pneumococcal vaccine
- CXR:** thickened bronchial walls (**tramlines and rings**)
- Spirometry:** obstructive pattern
- HRCT chest**
 - Dilated and thickened airways
 - Saccular dilatations in clusters → pools of mucus
- Bronchoscopy + mucosal biopsy
 - Focal obstruction
 - PCD
- CF sweat test (pilocarpine iontophoresis)

Rx

- Chest physio:** expectoration, drainage, pulm. rehab
- Abx for exacerbations:** e.g. cipro for 7-10d
- Bronchodilators:** nebulised β agonists
- Treat underlying cause**
 - CF:** DNAase
 - ABPA:** Steroids
 - Immune deficiency:** IVIg
- Surgery may be indicated in severe localised disease

Cystic Fibrosis

Pathogenesis

- Auto recessive, 1:2000 live Caucasian births
- Mutation in CFTR gene on Chr 7 (commonly $\Delta F508$)
- $\rightarrow \downarrow$ luminal Cl⁻ secretion and \uparrow Na reabsorption \rightarrow viscous secretions.
- In sweat glands, \downarrow Cl⁻ and Na reabsorption \rightarrow salty sweat

Clinical Features

Neonate

- FTT
- Meconium ileus
- Rectal prolapse

Children / Young Adults

- **Nose:** nasal polyps, sinusitis
- **Resp:** cough, wheeze, infections, bronchiectasis, haemoptysis, pneumothorax, cor pulmonale
- **GI:**
 - Pancreatic insufficiency: DM, steatorrhoea
 - Distal Intestinal Obstruction Syndrome
 - Gallstones
 - Cirrhosis (2^o biliary)
- **Other:** male infertility, osteoporosis, vasculitis

Signs

- Clubbing \pm HPOA
- Cyanosis
- Bilateral coarse creps

Common Respiratory Organisms

- **Early**
 - S. aureus
 - H. influenza
- **Late**
 - P. aeruginosa: 85%
 - B. cepacia: 4%

Dx

- Sweat test: Na and Cl⁻ $> 60\text{mM}$
- Genetic screening for common mutations
- Faecal elastase (tests pancreatic exocrine function)
- Immunoreactive trypsinogen (neonatal screening)

Ix

- **Bloods:** FBC, LFTs, clotting, ADEK levels, glucose TT
- **Sputum MCS**
- **CXR:** bronchiectasis
- **Abdo US:** fatty liver, cirrhosis, pancreatitis
- **Spirometry:** obstructive defect
- Aspergillus serology / skin test (20% develop ABPA)

Mx

General

- **MDT:** physician, GP, physio, dietitian, specialist nurse

Chest

- **Physio:** postural drainage, forced expiratory techniques
- **Abx:** acute infections and prophylaxis
- **Mucolytics:** DNase
- Bronchodilators
- Vaccinate

GI

- Pancreatic enzyme replacement: pancreatin (Creon)
- ADEK supplements
- Insulin
- Ursodeoxycholic acid for impaired hepatic function
 - Stimulates bile secretion

Advanced Lung Disease

- O₂
- Diuretics (Cor pulmonale)
- NIV
- Heart/lung transplantation

Other

- Rx of complications: e.g. DM
- Fertility and genetic counselling
- DEXA osteoporosis screen

Pulmonary Aspergillus Infections

Diseases

- 1. Asthma: T1HS reaction to spores
- 2. ABPA
- 3. Aspergilloma (mycetoma)
- 4. Invasive aspergillosis
- 5. Extrinsic allergic alveolitis

Allergic Bronchopulmonary Aspergillosis

- T1 and T3 HS reaction to Aspergillus fumigatus
- Bronchoconstriction → bronchiectasis

Symptoms

- Wheeze
- Productive cough
- Dyspnoea

Ix

- **CXR:** bronchiectasis
- Aspergillus in sputum (black on silver stain)
- Aspergillus skin test or IgE RAST
- +ve se precipitins
- ↑ IgE and ↑ eosinophils

Rx

- Pred 40mg/d + itraconazole for acute attacks
- Pred maintenance 5-10mg/d
- Bronchodilators for asthma

Aspergilloma (mycetoma)

- Fungus ball within a pre-existing cavity
 - e.g. TB or sarcoid

Features

- Usually asymptomatic
- Can → haemoptysis (may be severe)
- Lethargy, ↓ wt.

Ix

- **CXR:** round opacity w/i a cavity, usually apical
- Sputum culture
- +ve se precipitins
- Aspergillus skin test / RAST

Rx

- Consider excision for solitary lesions / severe haemoptysis

Invasive Aspergillosis

- Aflatoxins → liver cirrhosis and HCC (especially A. flavus)

Risk factors

- Immunocompromise: HIV, leukaemia, Wegener's
- Post-broad spectrum Abx

Ix

- **CXR:** consolidation, abscess
- Sputum MCS
- BAL
- +ve se precipitins
- Serial galactomannan

Rx

- Voriconazole (better cf amphotericin)

Prog

- 30% mortality

Extrinsic Allergic Alveolitis

- Sensitivity to Aspergillus clavatus → Malt worker's lung

Lung Cancer: Presentation

Classification

- Clinically, the most important distinction is between small-cell and non-small-cell (SCC, adeno and large-cell)

Type	Epidemiology	Pathology	Behaviour
SCC	35% M>F Smoking Radon gas	Centrally located Histo: Evidence of squamous differentiation - Keratinisation	Locally invasive Metastasise late (via LN) PTHRP → ↑ Ca ²⁺
Adeno	25% Females, Non-smokers Far East	Peripherally located Histo: Glandular differentiation - Gland formation - Mucin production	Extrathoracic mets common and early. - 80% present with mets
Large-cell	10%	Peripheral or central Histo: Large, poorly differentiated cells	Poor prognosis
Small-cell	20% Smoking	Central location, near bronchi Histo: Small, poorly differentiated cells	80% present at advanced disease V. chemosensitive but v. poor prog Ectopic hormone secretion

Other Lung Tumours: all rare

- Adenoma: 90% are carcinoid tumours
- Hamartoma
- Mesothelioma

Epidemiology

- 19% of all cancers
- 27% of cancer deaths (commonest)

Symptoms

- Cough and haemoptysis
- Dyspnoea
- Chest pain
- Recurrent or slow resolving pneumonia
- Anorexia and ↓wt.
- Hoarseness

Signs

Chest

- Consolidation
- Collapse
- Pleural effusion

General

- Cachexia
- Anaemia
- Clubbing and HPOA (painful wrist swelling)
- Supraclavicular and/or axillary LNs

Metastasis

- Bone tenderness
- Hepatomegaly
- Confusion, fits, focal neuro
- Addison's

Complications

Local

- Recurrent laryngeal N. palsy
- Phrenic N. palsy
- SVC obstruction
- Horner's (Pancoast's) tumour
- AF

Paraneoplastic

- Endo**
 - ADH → SIADH (euvolaemic ↓Na⁺)
 - ACTH → Cushing's syndrome
 - Serotonin → carcinoid (flushing, diarrhoea)
 - PTHRP → 1⁰ HPT (↑Ca²⁺, bone pain) – SCC
- Rheum**
 - Dermatomyositis / polymyositis
- Neuro**
 - Purkinje Cells (CDR2) → cerebellar degeneration
 - Peripheral neuropathy
- Derm**
 - Acanthosis nigricans (hyperpigmented body folds)
 - Trousseau syndrome: thrombophlebitis migrans

Metastatic

- Pathological #
- Hepatic failure
- Confusion, fits, focal neuro
- Addison's

Lung Cancer: Investigation and Management

ix

Bloods: FBC, U+E, Ca²⁺, LFTs

Cytology: sputum, pleural fluid

Imaging

- **CXR**

- Coin lesion
- Hilar enlargement
- Consolidation, collapse
- Effusion
- Bony secondaries

- **Contrast-enhanced Volumetric CT**

- Staging: lower neck, chest, upper abdomen
- Consider CT brain

- **PET-CT:** exclude distant mets

- **Radionucleotide bone scan**

Biopsy

- **Percutaneous FNA:** peripheral lesions and LNs
- **Bronchoscopy:** biopsy and assess operability
- **Endoscopic bronchial US biopsy:** mediastinal LNS
- **Mediastinoscopy**

Lung Function Tests

- Assess treatment fitness

CXR Coin Lesion Differential

- Foreign body
- Abscess: Staph, TB, Klebsiella, Mycetoma
- Neoplasia (1^o or 2^o)
- Granuloma: RA, Wegener's, TB, Sarcoid
- Structural: AVM

TNM Staging for NSCLC

Tx Malignant cells in bronchial secretions

Tis CIS

T0 None evident

T1 ≤3cm, in lobar or more distal airway

T2 >3cm and >2cm from carina or pleural involvement

T3 <2cm from carina or involves chest wall, diaphragm

T4 Involves mediastinum or malignant effusion is present

N0 None involved

N1 Peribronchial or ipsilateral hilum

N2 Ipsilateral mediastinum

N3 Contralateral hilum or mediastinum or supraclavicular

Mx

- **MDT:** pulmonologist, oncologist, radiologist, histopathologist, cardiothoracic surgeon, specialist nurses, palliative care, GP
- Assess risk of operative mortality: e.g. Thoracoscore
 - Cardiorespiratory function
 - Co-morbidities
- Advise smoking cessation

NSCLC

- **Surgical Resection**

- Rx of choice for peripheral lesions \bar{c} no metastatic spread = stage I/II (~25%)
- Need good cardiorespiratory function
- Wedge resection, lobectomy or pneumonectomy
- \pm adjuvant chemo

- **Curative radiotherapy**

- If cardiorespiratory reserve is poor

- **Chemo \pm radio for more advanced disease**

- Platinum-based regimens
- MAbs targeting EGFR (e.g. cetuximab) or TKI (e.g. erlotinib)

SCLC

- Typically disseminated @ presentation
- May respond to chemo but invariably relapse

Palliation

- **Radio:** bronchial obstruction, haemoptysis, bone or CNS mets
- **SVC obstruction:** stenting + radio + dexamethasone
- **Endobronchial therapy:** stenting, brachytherapy
- **Pleural drainage / pleurodesis**
- **Analgesia**

Prognosis

- **NSCLC:** 50% 5ys w/o spread; 10% \bar{c} spread
- **SCLC:** 1-1.5yrs median survival treated; 3mo untreated

ARDS

Pathogenesis

- May result from direct pulmonary insult or be 2^o to severe systemic illness.
- Inflamm mediators → ↑ capillary permeability and non-cardiogenic pulmonary oedema.

Clinical Features

- Tachypnoea
- Cyanosis
- Bilateral fine creps
- SIRS

Ix

- **Bloods:** FBC, U+E, LFTs, clotting, amylase, CRP, cultures, ABG.
- **CXR:** bilateral perihilar infiltrates

Dx

- Acute onset
- CXR shows bilateral infiltrates
- No evidence of congestive cardiac failure
- $\text{PaO}_2:\text{FiO}_2 < 200$

Mx

- Admit to ITU for organ support and Rx underlying cause

Ventilation

- **Indications**
 - $\text{PaO}_2 < 8 \text{ kPa}$ despite 60% FiO_2
 - $\text{PaCO}_2 > 6 \text{ kPa}$
- **Method**
 - 6ml/kg + PEEP (e.g. 10cm H₂O)
- **SEs**
 - VILI
 - VAP
 - Weaning difficulty

Circulation

- Invasive BP monitoring
- Maintain CO and DO₂ & inotropes
 - E.g. norad or dobutamine
- RF may require haemofiltration

Sepsis

- Abx

Other

- Nutritional support: enteral (best), TPN

Prognosis

- 50-75% mortality

Causes

Pulmonary

- Pneumonia
- Aspiration
- Inhalation injury
- Contusion

Systemic

- Shock
- Sepsis
- Trauma
- Haemorrhage and multiple transfusions
- Pancreatitis
- Acute liver failure
- DIC
- Obs: eclampsia, amniotic embolism
- Drugs: aspirin, heroin

Differential Dx of Pulmonary Oedema

Transudates

- ↑ capillary hydrostatic pressure
 - CCF
 - Iatrogenic fluid overload
 - Renal failure
 - Relative ↑ in negative pressure pulmonary oedema
- ↓ capillary oncotic pressure
 - Liver failure
 - Nephrotic syndrome
 - Malnutrition, malabsorption, protein-losing enteropathy
- ↑ interstitial pressure
 - ↓ lymphatic drainage: e.g. Ca

Exudates

- ARDS

Respiratory Failure

Type 1

- $\text{PaO}_2 < 8 \text{ kPa}$ and $\text{PaCO}_2 < 6 \text{ kPa}$
- V/Q mismatch and diffusion failure

Type 2

- $\text{PaO}_2 < 8 \text{ kPa}$ and $\text{PaCO}_2 > 6 \text{ kPa}$
- Alveolar hypoventilation \pm V/Q mismatch

Causes

V/Q Mismatch ($\uparrow A-a$ gradient)

- Vascular
 - PE
 - PHT
 - Pulmonary Shunt ($R \rightarrow L$)
- Asthma (early)
- Pneumothorax
- Atelectasis

Alveolar Hypoventilation

- **Obstructive**
 - COPD
 - Asthma
 - Bronchiectasis
 - Bronchiolitis
 - Intra- and Extra-thoracic (Ca, LN, epiglottitis...)
- **Restrictive**
 - \downarrow drive: CNS sedation, trauma, tumour
 - **NM disease:** cervical cord lesion, polio, GBS, MG
 - **Chest:** flail, kyphoscoliosis, obesity
 - **Fluid and fibrosis**

Diffusion Failure ($\uparrow A-a$ gradient)

- **Fluid**
 - Pulmonary oedema
 - Pneumonia
 - Infarction
 - Blood
- **Fibrosis**

NB. Both fluid and fibrosis also \rightarrow V/Q mismatch and alveolar hypoventilation due to \downarrow compliance

A-a Gradient

- $\text{PAO}_2 = (95 \times \text{FiO}_2) - (\text{PaCO}_2 / 0.8)$
- $\uparrow (\text{PAO}_2 - \text{PaO}_2)$ suggests lung pathology

Clinical Features

Hypoxia

- **Acute**
 - Dyspnoea
 - Agitation
 - Confusion
 - Cyanosis
- **Chronic**
 - Polycythaemia
 - PHT
 - cor pulmonale

Hypercapnoea

- Headache
- Flushing and peripheral vasodilatation
- Bounding pulse
- Flap
- Confusion \rightarrow coma

Mx: Rx underlying cause

Type 1

- Give O_2 to maintain SpO_2 94-98%
- Assisted ventilation if $\text{PaO}_2 < 8 \text{ kPa}$ despite 60% O_2

Type 2

- Controlled O_2 therapy @ 24% O_2 aiming for SpO_2 88-92% and a $\text{PaO}_2 > 8 \text{ kPa}$
- Check ABG after 20min
 - If PaCO_2 steady or lower can $\uparrow \text{FiO}_2$ if necessary
 - If $\text{PaCO}_2 \uparrow > 1.5 \text{ kPa}$ and pt. still hypoxic, consider NIV or respiratory stimulant (e.g. doxapram)

Oxygen Therapy

Principles

- Critically ill pts. should receive high conc O_2 immediately.
- O_2 should be prescribed to achieve target SpO_2
 - 94-98% for most patients
 - 88-92% for those at risk or hypercapnic resp failure
- In pts. at risk of hypercapnic resp failure:
 - Start O_2 therapy at 24% and do an ABG
 - Blue Venturi @ 2-4L/min
 - Clinically: \downarrow RR $\bar{c} \text{O}_2$ may be useful sign
 - If $\text{PCO}_2 \leq 6 \text{ kPa}$: \uparrow target SpO_2 to 94-98%
 - If $\text{PCO}_2 > 6 \text{ kPa}$: maintain target SpO_2

Mechanisms

Nasal Prongs: 1-4L/min = 24-40% O_2

Simple Face Mask

Non-rebreathing Mask

- Reservoir bag allows delivery of high concentrations of O_2 .
- 60-90% at 10-15L

Venturi Mask

- Provide precise O_2 concentration at high flow rates
 - Yellow: 5%
 - White: 8%
 - Blue: 24%
 - Red: 40%
 - Green: 60%

Chronic Asthma

Definition

- Episodic, reversible airway obstruction due to bronchial hyper-reactivity to a variety of stimuli.

Epidemiology

- Incidence 5-8% (\uparrow in children vs. adults)
- Peaks at 5yrs, most outgrow by adolescence

Pathophysiology

Acute (30min)

- Mast cell-Ag interaction \rightarrow histamine release
- Bronchoconstriction, mucus plugs, mucosal swelling

Chronic (12h)

- T_H2 cells release IL-3,4,5 \rightarrow mast cell, eosinophil and B cell recruitment
- Airway remodelling

Causes

Atopy

- T1 hypersensitivity to variety of antigens
- Dust mites, pollen, food, animals, fungus

Stress

- Cold air
- Viral URTI
- Exercise
- Emotion

Toxins

- Smoking, pollution, factory
- Drugs: NSAIDS, β -B

Symptoms

- Cough \pm sputum (often at night)
- Wheeze
- Dyspnoea
- Diurnal variation \bar{c} morning dipping

Hx

- Precipitants
- Diurnal variation
- Exercise tolerance
- Life effects: sleep, work
- Other atopy: hay fever, eczema
- Home and job environment

Signs

- Tachypnoea, tachycardia
- Widespread polyphonic wheeze
- Hyperinflated chest
- \downarrow air entry
- Signs of steroid use

Associated Disease

- GORD
- Churg-Strauss
- ABPA

Differential

- Pulmonary oedema (cardiac asthma)
- COPD

Ix

Bloods

- FBC (eosinophilia)
- \uparrow IgE
- Aspergillus serology

CXR: hyperinflation

Spirometry

- Obstructive pattern \bar{c} FEV1:FVC < 0.75
- $\geq 15\%$ improvement in FEV1 \bar{c} β -agonist

PEFR monitoring / diary

- Diurnal variation >20%
- Morning dipping

Atopy: skin-prick, RAST

Mx

General Measures: TAME

- Technique for inhaler use
- Avoidance: allergens, smoke (ing), dust
- Monitor: Peak flow diary (2-4x/d)
- Educate
 - Liaise \bar{c} specialist nurse
 - Need for Rx compliance
 - Emergency action plan

Drug Ladder

1 SABA PRN

- If use >1/d or nocte symptoms \rightarrow step 2

2 Low-dose inhaled steroid: beclometasone 100-400ug bd

3 LABA: salmeterol 50ug bd

- Good response: continue
- Benefit but control still poor: \uparrow steroid to 400ug bd
- No benefit: discontinue + \uparrow steroid to 400ug bd

If control is still poor consider trial of:

- Leukotriene receptor antagonist (e.g. montelukast)
 - Esp. if exercise- / NSAID-induced asthma
- SR Theophylline

4 Trials of

- \uparrow inhaled steroid to up to 1000ug bd
- Leukotriene receptor antagonist
- SR Theophylline
- MR β agonist PO

5 Oral steroids: e.g. prednisolone 5-10mg od

- Use lowest dose necessary for symptom control
- Maintain high-dose inhaled steroid
- Refer to asthma clinic

Acute Severe Asthma

Presentation

- Acute breathlessness and wheeze

Hx

- Precipitant: infection, travel, exercise?
- Usual and recent Rx?
- Previous attacks and severity: ICU?
- Best PEFR?

Ix

- PEFR
- ABG
 - PaO_2 usually normal or slightly ↓
 - PaCO_2 ↓
 - If PaCO_2 ↑: send to ITU for ventilation
- FBC, U+E, CRP, blood cultures

Assessment

Severe: any one of

- PEFR <50%
- RR >25
- HR >110
- Can't complete sentence in one breath

Life Threatening: any one of

- PEFR <33%
- SpO_2 <92%, PCO_2 >4.6kPa, PaO_2 <8kPa
- Cyanosis
- Hypotension
- Exhaustion, confusion
- Silent chest, poor respiratory effort
- Tachy-/brady-/arrhythmias

Differential

- Pneumothorax
- Acute exacerbation of COPD
- Pulmonary oedema

Admission Criteria

- Life-threatening attack
- Feature of severe attack persisting despite initial Rx
- May discharge if PEFR > 75% 1h after initial Rx

Discharge When

- Been stable on discharge meds for 24h
- PEFR > 75% & diurnal variability < 20%

Discharge Plan

- TAME pt.
- PO steroids for 5d
- GP appointment w/i 1 wk.
- Resp clinic appointment w/i 1mo

Mx

O_2 , Nebs and Steroids

1. Sit-up
2. 100% O_2 via non-rebreathe mask (aim for 94-98%)
3. Nebulised salbutamol (5mg) and ipratropium (0.5mg)
4. Hydrocortisone 100mg IV or pred 50mg PO (or both)
5. Write "no sedation" on drug chart

If Life Threatening

- Inform ITU
- MgSO_4 2g IVI over 20min
- Nebulised salbutamol every 15min (monitor ECG)

If Improving

- Monitor: SpO_2 @ 92-94%, PEFR
- Continue pred 50mg OD for 5 days
- Nebulised salbutamol every 4hrs

IV Rx if No Improvement in 15-30min:

- Nebulised salbutamol every 15min (monitor ECG)
- Continue ipratropium 0.5mg 4-6hrly
- MgSO_4 2g IVI over 20min
- Salbutamol IVI 3-20ug/min
- Consider aminophylline
 - Load: 5mg/kg IVI over 20min
 - Unless already on theophylline
 - Continue: 0.5mg/kg/hr
 - Monitor levels
- ITU transfer for invasive ventilation

Monitoring

- PEFR every 15-30min
 - Pre- and post-β agonist
- SpO_2 : keep >92%
- ABG if initial PaCO_2 normal or ↑

COPD

Definition

- Airway obstruction: FEV1 <80%, FEV1:FVC <0.70
- Chronic bronchitis: cough and sputum production on most days for 3mo of 2 successive years.
- Emphysema: histological diagnosis of enlarged air spaces distal to terminal bronchioles \bar{c} destruction of alveolar walls.

Epidemiology

- Prevalence: 10-20% of >40s

Causes

- Smoking
- Pollution
- α 1ATD

Symptoms

- Cough + sputum
- Dyspnoea
- Wheeze
- Wt. loss

Signs

- Tachypnoea
- Prolonged expiratory phase
- Hyperinflation
 - ↓ Cricosternal distance (normal = 3 fingers)
 - Loss of cardiac dullness
 - Displaced liver edge
- Wheeze
- May have early-inspiratory crackles
- Cyanosis
- Cor pulmonale: ↑JVP, oedema, loud P2
- Signs of steroid use

Pink Puffers in emphysema

- ↑ alveolar ventilation \rightarrow breathless but not cyanosed
- Normal or near normal PaO₂
- Normal or low PaCO₂
- Progress \rightarrow T1 respiratory failure

Blue Bloaters in chronic Bronchitis

- ↓ alveolar ventilation \rightarrow cyanosed but not breathless
- ↓PaO₂ and ↑ PaCO₂: rely on hypoxic drive
- Progress \rightarrow T2 respiratory failure and cor pulmonale

mMRC Dyspnoea Score

1. Dyspnoea only on vigorous exertion
2. SOB on hurrying or walking up stairs
3. Walks slowly or has to stop for breath
4. Stops for breath after <100m / few min
5. Too breathless to leave house or SOB on dressing

Complications

- Acute exacerbations \pm infection
- Polycythaemia
- Pneumothorax (ruptured bullae)
- Cor Pulmonale
- Lung carcinoma

Ix

- **BMI**
- **Bloods:** FBC (polycythaemia), α 1-AT level, ABG
- **CXR**
 - Hyperinflation (> 6 ribs anteriorly)
 - Prominent pulmonary arteries
 - Peripheral oligaemia
 - Bullae
- **ECG:**
 - R atrial hypertrophy: P pulmonale
 - RVH, RAD
- **Spirometry:** FEV1 <80%, FEV1:FVC <0.70, ↑TLC, ↑RV
- **Echo:** PHT

Chronic Rx

Assess Severity

- **Mild:** FEV1 >80% (but FEV/FVC <0.7 and symptomatic)
- **Mod:** FEV1 50-79%
- **Severe:** FEV1 30-49%
- **Very Severe:** FEV1 < 30%

General Measures

- **Stop smoking**
 - Specialist nurse
 - Nicotine replacement therapy
 - Bupropion, varenicline (partial nicotinic agonist)
 - Support programme
- Pulmonary rehabilitation / exercise
- Rx poor nutrition and obesity
- Screen and Mx comorbidities
 - e.g. cardiovasc, lung Ca, osteoporosis
- Influenza and pneumococcal vaccine
- Review 1-2x/yr
- Air travel risky if FEV1<50%

Mucolytics

- Consider if chronic productive cough
- E.g. Carbocisteine (Cl in PUD)

Breathlessness and/or exercise limitation

- SABA and/or SAMA (ipratropium) PRN
- SABA PRN may continue at all stages

Exacerbations or persistent breathlessness

- **FEV1 \geq 50%:** LABA or LAMA (tiotropium) (stop SAMA)
- **FEV1 <50%:** LABA+ICS combo or LAMA

Persistent exacerbations or breathlessness

- LABA+LAMA+ICS
- Roflumilast / theophylline (PDIs) may be considered
- Consider home nebs

LTOT

- **Aim:** PaO₂ \geq 8 for \geq 15h / day (\uparrow survival by 50%)
- Clinically stable non-smokers \bar{c} PaO₂ <7.3 (stable on two occasions >3 wks apart)
- PaO₂ 7.3 – 8 + PHT / cor pulmonale / polycythaemia / nocturnal hypoxaemia
- Terminally ill pts.

Surgery

- Recurrent pneumothoraces
- Isolated bullous disease
- Lung volume reduction

Acute Exacerbation of COPD

Causes

- Viral URTI (30%)
- Also bacterial infections

Presentation

- Cough + sputum
- Breathlessness
- Wheeze

Hx

- Smoking status
- Exercise capacity
- Current treatment
- Previous exacerbations

Ix

- PEFR
- Bloods: FBC, U+E, ABG, CRP, cultures
- Sputum culture
- CXR: infection, pneumothorax
- ECG

Differential

- Pneumothorax
- Pulmonary oedema
- PE
- Asthma

Discharge

- Spirometry
- Establish optimal maintenance therapy
- GP and specialist f/up
- Prevention using home oral steroids and Abx
- Pneumococcal and Flu vaccine
- Home assessment

Management

Controlled O₂ Therapy

- Sit-up
- 24% O₂ via Venturi mask: SpO₂ 88-92%,
- Vary FiO₂ and SpO₂ target according to ABG
- Aim for PaO₂ >8 and ↑ in PCO₂ of <1.5kPa



Nebulised Bronchodilators

- Air driven → nasal specs
- Salbutamol 5mg/4h
- Ipratropium 0.5mg/6h



Steroids (IV and PO)

- Hydrocortisone 200mg IV
- Prednisolone 40mg PO for 7-14d



Abx

- If evidence of infection
- Doxy 200mg PO STAT then 100mg OD PO for 5d

NIV if no response:

- Repeat nebs and consider aminophylline IV
- Consider NIV (BiPAP) if pH<7.35 and/or RR >30
- Consider invasive ventilation if pH<7.26
 - Depends on pre-morbid state: exercise capacity, home O₂, comorbidity

Pulmonary Embolism

Causes

- Usually arise from DVTs in proximal leg or iliac veins
- Rarely:
 - Right ventricle post MI
 - Septic emboli in right sided endocarditis

Risk Factors: SPASMODICAL

- Sex: F
- Pregnancy
- Age: ↑
- Surgery (classically 10d post-op straining at stool)
- Malignancy
- Oestrogen: OCP/HRT
- DVT/PE previous Hx
- Immobility
- Colossal size
- Antiphospholipid Abs
- Lupus Anti-coagulant

Presentation

- Symptoms and signs depend on size, number and distribution of emboli

Symptoms

- Dyspnoea
- Pleuritic pain
- Haemoptysis
- Syncope

Signs

- Fever
- Cyanosis
- Tachycardia, tachypnoea
- RHF: hypotension, ↑JVP, loud P₂
- Evidence of cause: DVT

Ix

- Bloods:** FBC, U+E, clotting, D-dimers
- ABG:** normal or ↓PaO₂ and ↓PaCO₂, ↑pH
- CXR:** normal or oligaemia, linearatectasis
- ECG:** sinus tachycardia, RBBB, right ventricular strain (inverted T in V1-V4)
 - S1, Q3, T3 is rare
- Doppler US:** thigh and pelvis (+ve in 60%)
- CTPA** + venous phase of legs and pelvis
 - 85-95% sensitivity
- V/Q scan no longer used

Dx

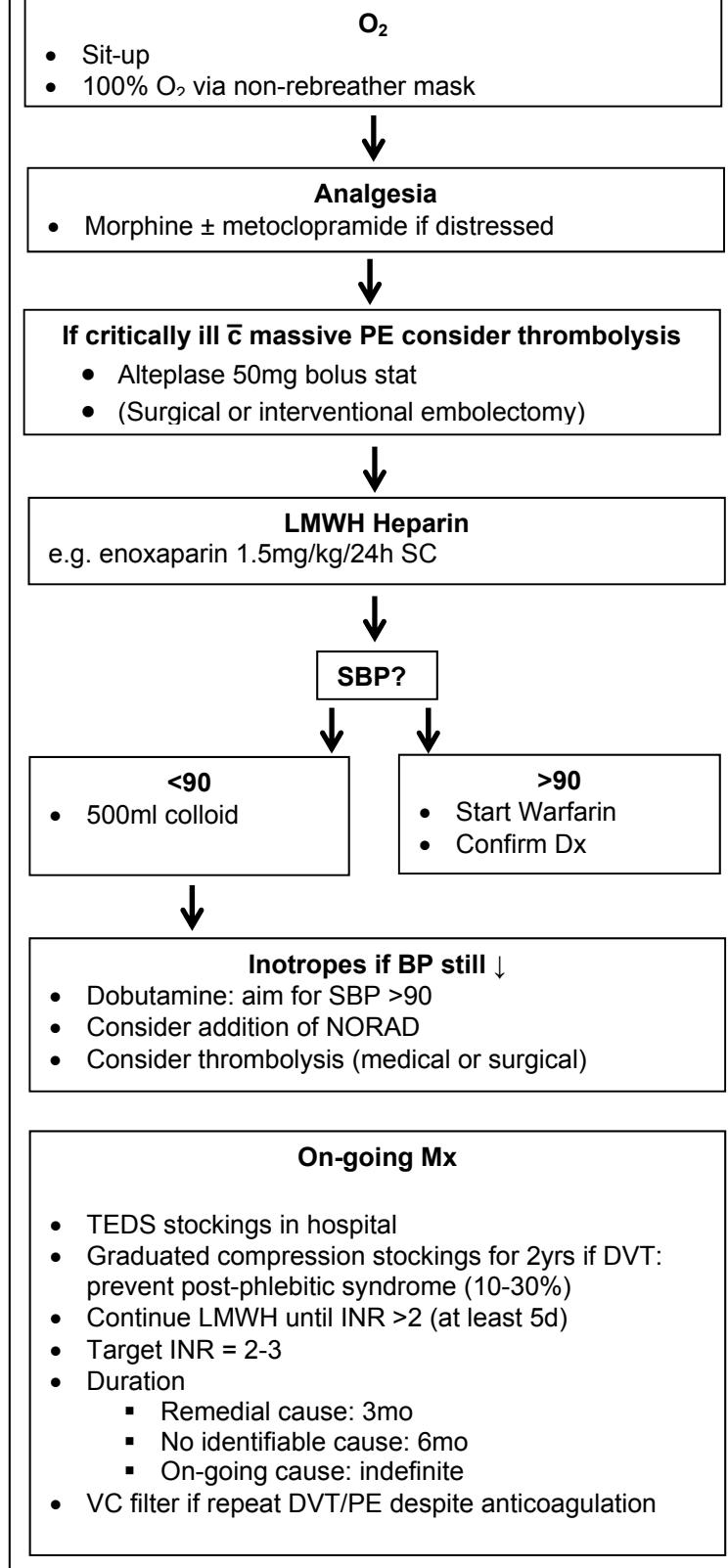
- Assess probability using Wells' Score
- Low-probability → perform D-dimers
 - Negative → excludes PE
 - Positive → CTPA
- High probability → CTPA

NB. -ve D-dimer has 95% NPV for PE

Prevention

- Risk assessment for all pts
- TEDS
- Prophylactic LMWH
- Avoid OCP/HRT if @ risk

Management



Pneumothorax

Definition

- Accumulation of air in the pleural space → 2^o lung collapse.

Classification

- **Closed:** intact chest wall and air leaks from lung into pleural cavity.
- **Open:** defect in the chest wall allows communication between PTX and exterior: may be sucking.
- **Tension:** air enters pleural cavity through one-way valve and cannot escape → mediastinal compression.

Causes

Spontaneous

- 1^o: no underlying lung disease
 - Young, thin men (ruptured subpleural bulla)
 - Smokers
- 2^o: underlying lung disease
 - COPD
 - Marfan's, Ehler's Danlos
 - Pulmonary fibrosis, sarcoidosis

Trauma

- Penetrating
- Blunt ± rib #s

Iatrogenic

- Subclavian CVP line insertion
- Positive pressure ventilation
- Transbronchial biopsy
- Liver biopsy

Presentation

Symptoms

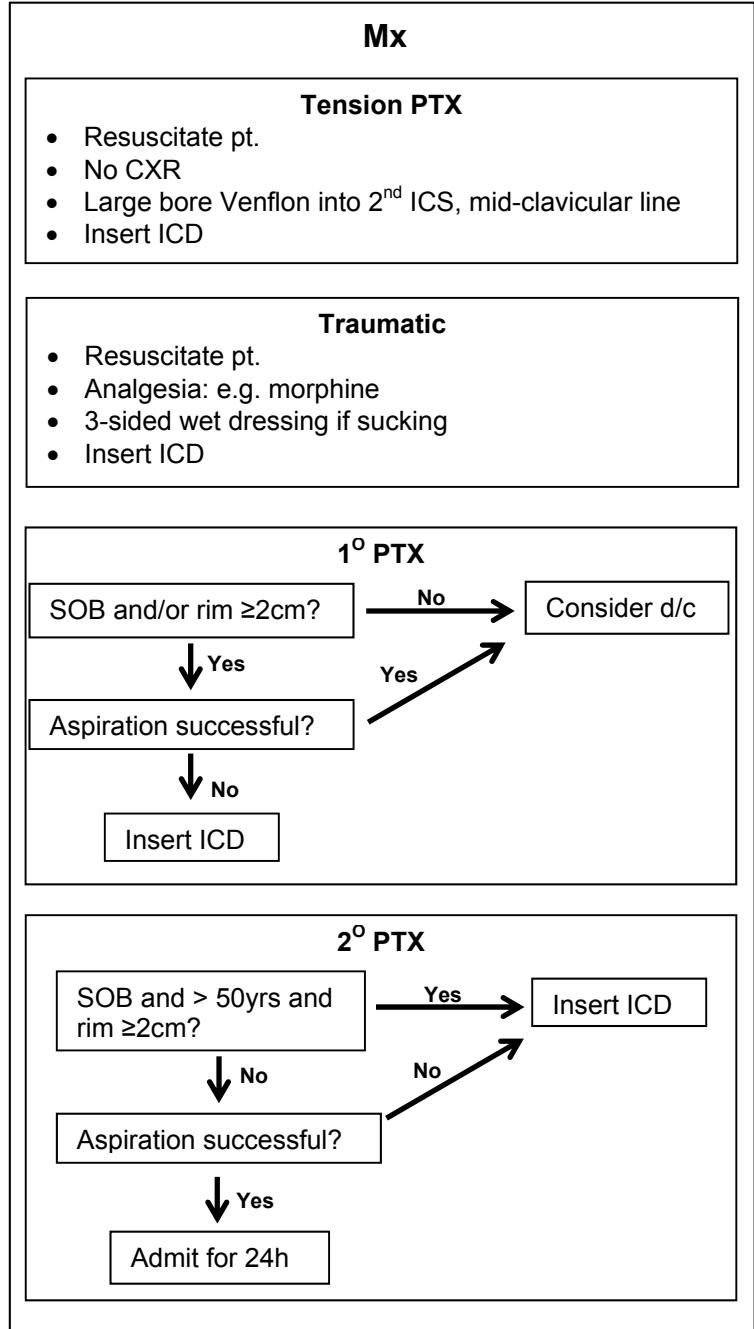
- Sudden onset
- Dyspnoea
- Pleuritic chest pain
- **Tension:** respiratory distress, cardiac arrest

Signs

- **Chest**
 - ↓ expansion
 - Resonant percussion
 - ↓ breath sounds
 - ↓VR
- **Tension:** ↑JVP, mediastinal shift, ↑HR, ↓BP
- **Crepitus:** surgical emphysema

Ix

- ABG
- US
- CXR (expiratory film may be helpful)
 - Translucency + collapse (2cm rim = 50% vol loss)
 - Mediastinal shift (away from PTX)
 - Surgical emphysema
 - **Cause:** rib #s, pulmonary disease (e.g. bullae)



Pleural Effusion

Classification

- Effusion protein < 25g/L = transudate
- Effusion protein >35g/L = exudate
- Between 25-35g/L: apply Light's Criteria

Light's Criteria

- An exudate has one of:
 - Effusion : serum protein ratio >0.5
 - Effusion : serum LDH ratio >0.6
 - Effusion LDH is 0.6 x ULN

Causes

Exudates: ↑ capillary permeability

- **Infection:** pneumonia, TB
- **Neoplasm:** bronchial, lymphoma, mesothelioma
- **Inflammation:** RA, SLE
- **Infarction**

Transudates: ↑ capillary hydrostatic or ↓ oncotic pressure

- CCF
- Renal failure
- ↓ albumin: nephrosis, liver failure, enteropathy
- Hypothyroidism
- Meig's Syndrome
 - Right pleural effusion
 - Ascites
 - Ovarian fibroma

Presentation

Symptoms

- Asymptomatic
- Dyspnoea
- Pleuritic chest pain

Signs

- **Chest**
 - Tracheal deviation away from effusion
 - ↓ expansion
 - Stony dull percussion
 - ↓ air entry
 - Bronchial breathing just above effusion
 - ↓VR
- **Associated disease**
 - **Ca:** cachexia, clubbing, HPOA, LNs, radiation burn, radiation tattoo
 - Chronic liver disease
 - Cardiac failure
 - RA, SLE
 - Hypothyroidism

Ix

- **Blood:** FBC, U+E, LFT, TFT, Ca, ESR
- **CXR**
 - Blunt costophrenic angles
 - Dense shadow ⊖ meniscus
 - Mediastinal shift away
 - Cause: coin lesion, cardiomegaly
- **US:** facilitates tapping
- **Volumetric CT**

Diagnostic Tap

- Percuss upper boarder and go 1-2 spaces below
- Infiltrate down to pleura ⊖ lignocaine.
- Aspirate ⊖ 21G needle
- Send for
 - **Chemistry:** protein, LDH, pH, glucose, amylase
 - **Bacteriology:** MCS, auramine stain, TB culture
 - **Cytology**
 - **Immunology:** SF, ANA, complement

Empyema, Ca, TB, RA and SLE

- ↑ protein
- ↓ glucose <3.3mM
- ↓ pH <7.2
- ↑ LDH > 0.6 x serum / ULN

Oesophageal Rupture

- ↓ pH <7.2
- ↑ amylase (also ↑ in pancreatitis)

Pleural Biopsy

- If pleural fluid is inconclusive
- CT-guided ⊖ Abrams needle

Mx

- Rx underlying cause
- May use drainage if symptomatic ($\leq 2L/24h$)
 - Repeated aspiration or ICD
- Chemical pleurodesis if recurrent malignant effusion
- Persistent effusions may require surgery

Sarcoidosis

Definition

- Multisystem granulomatous disorder of unknown cause

Epidemiology

- Age:** 20-40yrs
- Sex:** F>M
- Geo:** Afro Caribbean
- HLA-DRB1 and DQB1 alleles

Clinical Features: GRAULOMAS

- In 20-40% the disease presents incidentally on CXR
- Acute sarcoidosis:** EN, fever, polyarthralgia, BHL

General

- Fever
- Anorexia and ↓ wt.
- Fatigue
- Lymphadenopathy and HSM

Respiratory

- Upper:** otitis, sinusitis
- Lower (seen in 90%)**
 - Dry cough, SOB, chest pain, ↓ lung function
 - Stage 1:** BHL
 - Stage 2:** BHL + peripheral infiltrates
 - Stage 3:** Peripheral infiltrates alone
 - Stage 4:** Progressive mid-zone fibrosis → bullae

Arthralgia

- Polyarthralgia
- Dactylitis

Neurological

- Peripheral and cranial polyneuropathy (esp. Bell's palsy)
- Meningitis, transverse myelitis, SOL

Urine

- ↑Ca → Renal stones, nephrocalcinosis, DI

Low Hormones

- Pituitary dysfunction: e.g. amenorrhoea

Ophthalmological

- Uveitis
- Keratoconjunctivitis
- Sicca / Mikulicz / Sjogrens syndrome

Myocardial

- Restrictive cardiomyopathy 2^o to granulomas + fibrosis
- Pericardial effusion

Abdominal

- Hepatomegaly + cholestatic LFTs
- Splenomegaly

Skin

- EN:** painful erythematous nodules on shins (paniculitis)
- Lupus pernio:** raised, dusky purple plaque on nose, cheek, fingers

Ix

Bloods

- ↑ESR
- ↑Ca
- Lymphopenia
- ↑ se ACE
- ↑ Ig
- ↑LFTs

CXR, CT, MRI

Tuberculin skin test

- Negative in 2/3

Lung function tests

- Restrictive pattern → ↓FVC
- ↓ transfer factor

Tissue Biopsy

- Lung, LNs, skin nodules, liver
- Diagnostic: non-caseating granulomas

Ophthalmology assessment

Rx

- Pts. → asymptomatic BHL do not require Rx.
- Acute sarcoidosis**
 - Usually resolves spontaneously
 - Bed rest and NSAIDs
- Chronic sarcoidosis**
 - Steroids:** pred 40mg/d for 4-6wks
 - Additional immunosuppression: methotrexate, cyclosporin, cyclophosphamide

Prognosis

- 60% → thoracic sarcoidosis resolve over 2yrs
- 20% respond to steroids
- 20% no improvement despite Rx

BHL Differential

- Sarcoidosis
- Infection: TB, mycoplasma
- Malignancy: lymphoma, carcinoma
- Interstitial disease: EAA, silicosis

Granulomatous Disease Differential

- Infections: TB, leprosy, syphilis, crypto, schisto
- AI: PBC
- Vasculitis: GCA, PAN, Wegener's, Takayasu's
- Idiopathic: Crohns, Sarcoid
- Interstitial lung: EAA, silicosis

Interstitial Lung Disease

Principal Features

- Dyspnoea
- Dry cough
- Abnormal CXR / CT
- Restrictive Spirometry

Causes

Known Cause

- **Environmental:** asbestosis, silicosis
- **Drugs: BANS ME**
 - Bleomycin, Busulfan
 - Amiodarone
 - Nitrofurantoin
 - Sulfasalazine
 - MEthotrexate, MEthysergide
- **Hypersensitivity:** EAA
- **Infection:** TB, viral, fungi

Assoc. c systemic disease

- Sarcoidosis
- RA
- SLE, systemic sclerosis, Sjogren's, MCTD
- UC, ankylosing spondylitis

Idiopathic

- Idiopathic pulmonary fibrosis (CFA)

Cause by Location

Upper Zone: A PENT

- Aspergillosis : ABPA
- Pneumoconiosis: Coal, Silica
- Extrinsic allergic alveolitis
- Negative, sero-arthropathy
- TB

Lower Zone: STAIR

- Sarcoidosis (mid zone)
- Toxins: **BANS ME**
- Asbestosis
- Idiopathic pulmonary fibrosis
- Rheum: RA, SLE, Scleroderma, Sjogren's, PM/DM

Extrinsic Allergic Alveolitis

- Acute allergen exposure in sensitised pts. → T3HS
- Chronic exposure → granuloma formation and obliterative bronchiolitis (T4HS)

Causes

- Bird fancier's lung: proteins in bird droppings
- Farmer's / mushroom worker's
- Malt worker's lung: Aspergillus clavatus

Clinical Features

4-6h post-exposure

- Fever, rigors, malaise
- Dry cough, dyspnoea
- Crackles (no wheeze)

Chronic

- Increasing dyspnoea
- Wt. loss
- T1 respiratory failure
- Cor pulmonale

Ix

- **Bloods**
 - Acute: neutrophilia, ↑ESR
 - +ve se precipitins
- **CXR**
 - Upper zone reticulonodular opacification or fibrosis → honeycomb lung
 - BHL (rare)
- **Spirometry**
 - Restrictive defect
 - ↓ transfer factor during acute attacks
- **BAL**
 - ↑ lymphocytes and mast cells

Mx

- Avoid exposure
- **Steroids:** acute / long-term
- Compensation may be payable

Industrial Lung Disease

Coal-workers Pneumoconiosis

- CWP → Progressive Massive Fibrosis
- Presents as progressive dyspnoea and chronic bronchitis
- **CXR:** upper zone fibrotic masses

Silicosis

- Quarrying, sand-blasting
- Upper zone reticular shadowing and egg shell calcification of hilar nodes → PMF

Asbestosis

- Demolition and ship building
- Basal fibrosis, pleural plaques
- ↑ risk of mesothelioma
 - Chest pain, wt. loss, clubbing, recurrent effusions, dyspnoea.
 - **CXR:** pleural effusions, thickening
 - Dx by histology of pleural biopsy
 - <2yr survival

Idiopathic Pulmonary Fibrosis (CFA)

Epidemiology

- Commonest cause of interstitial lung disease
- Middle age
- M>F = 2:1
- Assoc. w/ other AI disease in 30%

Presentation

Symptoms

- Dry cough
- Dyspnoea
- Malaise, wt. loss
- Arthralgia
- OSA

Signs

- Cyanosis
- Clubbing
- Crackles: fine, end-inspiratory

Complications

- ↑ risk Ca lung
- Type 2 respiratory failure and cor pulmonale

Ix

Bloods

- ↑CRP
- ↑Ig
- ANA+ (30%)
- RF+ (10%)
- **ABG:** ↓PaO₂, ↑PaCO₂

CXR

- ↓ lung volume
- Bilat lower zone retic-nod shadowing
- Honeycomb lung

HRCT

- Shows similar changes to CXR
- More sensitive

Spiro

- Restrictive defect
- ↓ transfer factor

Other

- **Lung biopsy:** Usual interstitial pneumonia
- **BAL:** may indicate disease activity
 - ↑ lymphocytes: good prognosis
 - ↑ PMN or eosinophils: bad prognosis
- DTPA scan: may reflect disease activity

Mx

- Supportive care
 - Stop smoking
 - Pulmonary rehabilitation
 - O₂ therapy
 - Palliation
 - Rx symptoms of heart failure
- Lung Tx offers only cure

Prognosis

- 50% 5yr survival

Pulmonary Hypertension

Definition

- PA pressure >25mmHg

Causes

Left Heart Disease

- Mitral stenosis
- Mitral regurgitation
- Left ventricular failure
- L → R shunt

Lung Parenchymal Disease

- Mechanism
 - Chronic hypoxia → hypoxic vasoconstriction
 - Perivascular parenchymal changes
- COPD
- Asthma: severe, chronic
- Interstitial lung disease
- CF, bronchiectasis

Pulmonary Vascular Disease

- Idiopathic pulmonary hypertension
- Pulmonary vasculitis: scleroderma, SLE, Wegener's
- Sickle cell
- Pulmonary embolism: acute or chronic
- Portal HTN: portopulmonary HTN

Hypoventilation

- OSA
- Morbid obesity (Pickwickian syn.)
- Thoracic cage abnormality: kyphosis, scoliosis
- Neuromuscular: MND, MG, polio

Ix

- ECG
 - P pulmonale
 - RVH
 - RAD
- Echo
 - Velocity of tricuspid regurgitation jet
 - Right atrial or ventricular enlargement
 - Ventricular dysfunction
 - Valve disease
- Right heart catheterisation: gold standard
 - Mean pulmonary artery pressure
 - Pulmonary vascular resistance
 - CO
 - Vasoreactivity testing to guide Rx

Cor Pulmonale

Definition

- RHF due to chronic PHT

Symptoms

- Dyspnoea
- Fatigue
- Syncope

Signs

1. ↑ JVP c prominent a wave
2. Left parasternal heave
3. Loud P2 ± S3
4. Murmurs
 - PR: Graham Steell EDM
 - TR: PSM
5. Pulsatile hepatomegaly
6. Fluid: Ascites + Peripheral oedema

Ix

- **Bloods:** FBC, U+E, LFTs, ESR, ANA, RF
- **ABG:** hypoxia ± hypercapnoea
- **CXR**
 - Enlarged R atrium and ventricle
 - Prominent pulmonary arteries
 - Peripheral oligaemia
- **ECG:** P pulmonale + RVH
- **Echo:** RVH, TR, ↑ PA pressure
- **Spirometry**
- **Right heart catheterisation**

Mx

- Rx underlying condition
- ↓ pulmonary vascular resistance
 - LTOT
 - CCB: e.g. nifedipine
 - Sildenafil (PDE-5 inhibitor)
 - Prostacycline analogues
 - Bosentan (endothelin receptor antagonist)
- Cardiac failure
 - ACEi + β-B (caution if asthma)
 - Diuretics
- Heart-Lung Tx

Prognosis

- 50% 5ys

Obstructive Sleep Apnoea

Definition

- Intermittent closure/collapse of pharyngeal airway → apnoeic episodes during sleep.

Risk Factors

- Obesity
- Male
- Smoker
- EtOH
- Idiopathic pulmonary fibrosis
- Structural airway pathology: e.g. micrognathia
- NM disease: e.g. MND

Ix

- SpO₂
- Polysomnography is diagnostic

Rx

- Wt. loss
- Avoid smoking and EtOH
- CPAP during sleep

Clinical Features

Nocturnal

- Snoring
- Choking, gasping, apnoeic episodes

Daytime

- Morning headache
- Somnolence
- ↓ memory and attention
- Irritability, depression

Complications

- Pulmonary hypertension
- Type 2 respiratory failure
- Cor pulmonale

Mx

- ↓ wt.
- Stop smoking
- CPAP @ night via a nasal mask
- Surgery to relieve pharyngeal obstruction
 - Tonsillectomy
 - Uvulopalatopharyngoplasty

Smoking Cessation

Very Brief Advice

- **Ask:** enquire as to smoking status
- **Advise:** best way to stop is with support and medication
- **Act:** provide details of where to get help
 - E.g. NHS stop smoking helpline

Facilitating Quitting

- Refer to specialist stop smoking service
- Nicotine replacement
 - Gum
 - Patches
- **Varenicline:** selective partial nicotine receptor agonist
 - Recommended by NICE
 - 23% abstinence @ 1yr vs. 10% for placebo
 - Start while still smoking
- Bupropion: also an option

Endocrinology

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DM: Classification, Dx and Causes

Definition

- Multisystem disorder due to an absolute or relative lack of endogenous insulin → metabolic and vascular complications.

Classification

T1DM

- Path:** autoimmune destruction of β -cells → absolute insulin deficiency.
- Age:** usually starts before puberty
- Presentation:** polyuria, polydipsia, ↓wt., DKA
- Genetics:** concordance only 30% in MZs
- Assoc.:** HLA-D3 and -D4, other AI disease
- Abs:** anti-islet, anti-GAD

T2DM

- Path:** insulin resistance and β -cell dysfunction → relative insulin deficiency
- Age:** usually older patients
- Presentation:** polyuria, polydipsia, complications
- Genetics:** concordance 80% in MZs
- Assoc.:** obesity, ↓exercise, calorie and EtOH excess

Dx

- Symptomatic:** Polyuria, polydipsia, ↓wt., lethargy
 - ↑ plasma venous glucose detected once
 - Fasting ≥7mM
 - Random ≥11.1mM
- Asymptomatic:**
 - ↑ venous glucose on 2 separate occasions
 - Or, 2h OGTT ≥ 11.1mM

Glucose Testing

- OGTT only needed if borderline fasting or random glucose measurements.

	Normal	IFG	IGT	Diabetes
Fasting	<6.1	6.1 – 6.9		≥7.0
75g OGTT	<7.8		7.8 – 11	≥11.1

Secondary Causes of DM

- Drugs:** steroids, anti-HIV, atypical neuroleptics, thiazides
- Pancreatic:** CF, chronic pancreatitis, HH, pancreatic Ca
- Endo:** Phaeo, Cushings, Acromegaly, T4
- Other:** glycogen storage diseases

Metabolic Syndrome

- Central obesity (↑ waist circumference) and two of:
 - ↑ Triglycerides
 - ↓ HDL
 - HTN
 - Hyperglycaemia: DM, IGT, IFG

DM: Conservative Mx

MDT

- GP, endocrinologist, surgeons, specialist nurses, dieticians, chiropodists, fellow patients (education groups).

Monitoring: 4Cs

Control, glycaemic

- Record of complications: DKA, HONK, hypos
- Capillary blood glucose
 - Fasting: 4.5-6.5mM
 - 2h post-prandial: 4.5-9mM
- HbA1c
 - Reflects exposure over last 6-8wks
 - Aim <45 - 50mM (7.5 - 8%)
- BP, lipids

Complications

- Macro**
 - Pulses
 - BP
 - Cardiac auscultation
- Micro**
 - Fundoscopy
 - ACR + U+Es
 - Sensory testing plus foot inspection

Competency

- With insulin injections
- Checking injection sites
- BM monitoring

Coping

- Psychosocial: e.g. ED, depression
- Occupation
- Domestic

Lifestyle Modification: DELAYS

Diet

- Same as that considered healthy for everyone
- ↓ total calorie intake
- ↓ refined CHO, ↑ complex CHO
- ↑ soluble fibre
- ↓ fat (especially saturated)
- ↓ Na
- Avoid binge drinking

Exercise

Lipids

- Rx of hyperlipidaemia
- 1^o prevention c statins if >40yrs (regardless of lipids)

ABP

- ↓ Na intake and EtOH
- Keep BP <130/80
- ACEIs best (β -B: mask hypos, thiazides: ↑ glucose)

Aspirin

- 1^o prevention if >50yrs or <50 c other CVD RFs

Yearly / 6 monthly check-up: 4Cs

Smoking cessation

DM: Oral Hypoglycaemics

1. Lifestyle Modification: DELAYS

2. Start Metformin

(if HbA1c >target after lifestyle changes)

- **SE:** nausea, diarrhoea, abdo pain, lactic acidosis
- **CI:** GFR<30, tissue hypoxia (sepsis, MI), morning before GA and iodinated contrast media
- 500mg after evening meal, ↑ing to 2g max.

3. Metformin + Sulfonylurea

(if HbA1c >target)

- E.g. gliclazide MR 30mg c breakfast
- **SE:** hypoglycaemia, wt. gain
- **CI:** omit on morning of surgery

Other Options

- Consider adding a rapid-acting insulin secretagogue (e.g. nateglinide) to metformin instead of a sulfonylurea.
 - May be preferable if erratic lifestyle.
- Consider adding pioglitazone to metformin instead of a sulfonylurea

4. Additional Therapy

1st line

- Add insulin → **insulin + metformin + sulfonylurea**

2nd line

- Add **sitagliptin** or **pioglitazone** if insulin unacceptable
 - Employment, social or recreational issues
 - Obesity
- **metformin + sulfonylurea + sitagliptin / pio**

3rd line

- Add **exenatide** (SC) if insulin unacceptable or BMI>35
- **metformin + sulfonylurea + exenatide**

4th line

- Consider **acarbose** if unable to use other glucose-lowering drugs

Insulin

Principles

- Ensure pt. education about
 - Self-adjustment c exercise and calories
 - Titrate dose
 - Family member can abort hypo c sugary drinks or GlucoGel
- Pre-prandial BM don't tell you how much glucose is needed
- Fasting BM before meal informs re long-acting insulin dose.
- Finger-prick BM after meal informs re short-acting insulin dose (for that last meal)

Common Regimes

BD Biphasic Regime

- BD insulin mixture 30min before breakfast and dinner
 - Rapid-acting: e.g. actrapid
 - Intermediate- / long-acting: e.g. insulatard
- T2 or T1 DM c regular lifestyle: children, older pts.
- Assoc, c fasting hyperglycaemia

Basal-Bolus Regime

- Bedtime long-acting (e.g. glargine) + short acting before each meal (e.g. lispro)
 - Adjust dose according to meal size
 - ~50% of insulin given as long-acting
- T1DM allowing flexible lifestyle
- Best outcome

OD Long-Acting Before Bed

- Initial regime when switching from tablets in T2DM

Illness

- Insulin requirements usually ↑ (even if food intake ↓)
- Maintain calories (e.g. milk)
- Check BMs ≥4hrly and test for ketonuria
- ↑ insulin dose if glucose rising

Side-Effects

- **Hypoglycaemia**
 - At risk: EtOH binge, β-B (mask symptoms), elderly
 - Need to admit sulfonylurea-induced hypo
- **Lipohypertrophy**
 - Rotate injection site: abdomen, thighs
- **Wt. gain in T2DM**
 - ↓ wt. gain if insulin given c metformin

Diabetic Complications

Summary

- Hyperglycaemia: DKA, HONK
- Hypoglycaemia
- Infection
- Macrovascular: MI, CVA
- Microvascular

Macrovascular

- **MI:** May be “silent” due to autonomic neuropathy
- **PVD:** claudication, foot ulcers
- **CVA**

Rx: Manage CV risk factors

- BP (aim <130/80)
- Smoking
- Lipids
- HbA1c

Prevention

- Good glycaemic control (e.g. HbA1c <6%) prevents both macro- and micro-vascular complications.
- Proved by DCCT, EDIC and UKPDS trials
- Regular screening: fundoscopy, ACR, foot check

Diabetic Feet

Ischaemia

- Critical toes
- Absent pulses (do ABPI)
- **Ulcers:** painful, punched-out, foot margins, pressure points

Neuropathy

- **Loss of protective sensation**
- Deformity: Charcot’s joints, pes cavus, claw toes
- Injury or infection over pressure points
- **Ulcers:** painless, punched-out, metatarsal heads, calcaneum

Mx

- **Conservative**
 - Daily foot inspection (e.g. \bar{c} mirror)
 - Comfortable / therapeutic shoes
 - Regular chiropody (remove callus)
- **Medical**
 - Rx infection: benpen + fluclo \pm metronidazole
- **Surgical**
 - Abscess or deep infection
 - Spreading cellulitis
 - Gangrene
 - Suppurative arthritis

Nephropathy

Pathophysiology

- Hyperglycaemia \rightarrow nephron loss and glomerulosclerosis

Features

- Microalbuminuria: urine albumin:Cr (ACR) $\geq 30 \text{ mg/mM}$
- If present \rightarrow ACEi / ARA
- Refer if UCR > 70

Retinopathy, Maculopathy and Cataracts

Pathogenesis

- Microvascular disease \rightarrow retinal ischaemia \rightarrow ↑VEGF
- ↑ VEGF \rightarrow new vessel formation

Presentation

- Retinopathy and maculopathy
- Cataracts
- Rubeosis iris: new vessels on iris \rightarrow glaucoma
- CN palsies

Diabetic Retinopathy and Maculopathy

- Commonest cause of blindness up to 60yrs
- Refer if pre-proliferative retinopathy / maculopathy
- **Ix:** fluorescein angiography
- **Rx:** laser photocoagulation

Background Retinopathy

- Dots: microaneurysms
- Blot haemorrhages
- Hard exudates: yellow lipid patches

Pre-proliferative Retinopathy

- Cotton-wool spots (retinal infarcts)
- Venous beading
- Haemorrhages

Proliferative Retinopathy

- New vessels
- Pre-retinal or vitreous haemorrhage

Maculopathy

- ↓ acuity may be only sign
- Hard exudates w/i one disc width of macula

Neuropathy

Pathophysiology

- **Metabolic:** glycosylation, ROS, sorbitol accumulation
- **Ischaemia:** loss of vasa nervorum

Symmetric sensory polyneuropathy

- **Glove and stocking:** length-dependent (\therefore feet 1st)
 - Loss of all modalities
- **Absent ankle jerks**
- Numbness, tingling, **pain** (worse @ night)
- **Rx**
 - Paracetamol
 - Amitriptyline, Gabapentin, SSRI
 - Capsaicin cream
 - Baclofen

Mononeuropathy / Mononeuritis Multiplex

- E.g. CN3/6 palsies

Femoral Neuropathy / Amyotrophy

- Painful asymmetric weakness and wasting of quads \bar{c} loss of knee jerks
- **Dx:** nerve conduction and electromyography

Autonomic Neuropathy

- Postural hypotension – Rx: fludrocortisone
- Gastroparesis \rightarrow early satiety, GORD, bloating
- Diarrhoea: Rx \bar{c} codeine phosphate
- Urinary retention
- ED

Diabetic Ketoacidosis

Pathogenesis

Ketogenesis

- ↓ insulin → ↑ stress hormones and ↑ glucagon
- → ↓ glucose utilisation + ↑ fat β-oxidation
- ↑ fatty acids → ↑ ATP + generation of ketone bodies.

Dehydration

- ↓ insulin → ↓ glucose utilisation + ↑ gluconeogenesis → severe hyperglycaemia
- → osmotic diuresis → dehydration
- Also, ↑ ketones → vomiting

Acidosis

- Dehydration → renal perfusion
- Hyperkalaemia

Precipitants

- Infection / stress ± stopping insulin
- New T1DM

Presentation

- Abdo pain + vomiting
- Gradual drowsiness
- Sighing "Kussmaul" hyperventilation
- Dehydration
- Ketotic breath

Dx

- Acidosis ($\uparrow AG$): pH <7.3 ($\pm HCO_3 <15mM$)
- Hyperglycaemia: $\geq 11.1mM$ (or known DM)
- Ketonaemia: $\geq 3mM$ ($\geq 2+$ on dipstick)

Ix

- Urine: ketones and glucose, MCS
- Cap glucose and ketones
- VBG: acidosis + $\uparrow K$
- Bloods: U+E, FBC, glucose, cultures
- CXR: evidence of infection

Subtleties

- Hyponatraemia is the norm
 - Osmolar compensation for hyperglycaemia
 - $\uparrow/\downarrow Na$ indicates severe dehydration
- Avoid rapid ↓ in insulin once glucose normalised
 - Glucose decreases faster than ketones and insulin is necessary to get rid of them.
- Amylase is often ↑ (up to 10x)
- Excretion of ketones → loss of potential bicarbonate → hyperchloraemic metabolic acidosis after Rx

Complications

- Cerebral oedema: excess fluid administration
 - Commonest cause of mortality
- Aspiration pneumonia
- Hypokalaemia
- Hypophosphataemia → resp and skeletal muscle weakness
- Thromboembolism

Mx: in HDU

- Gastric aspiration
- Rehydrate
- Insulin infusion
- Potassium replacement

Management

Fluids

- 0.9% NS infusion via large bore cannula
 - SBP<90 → 1L stat + more until SBP >90
 - SBP>90 → 1L over 1h
- Then: 1L over next 2h, 1L/2h, 1L/4h, 1L/4h, 1L/6h
- Switch to 10% dex 1L/8h when glucose <14mM

Start Potassium Replacement in 2nd Bag of Fluids

- $>5.5mM$ → Nil
- 3.5-5.5mM → 40mmol/L
- $<3.5mM$ → consult senior for review



Insulin Infusion

- Actrapid 0.1u/kg/h IVI (6u if no wt., max 15u)



Assessment

- Hx + full examination
- Investigations: capillary, urine, blood, imaging



Additional Measures

- Urinary catheter (aim: 0.5ml/kg/hr)
- NGT if vomiting or $\downarrow GCS$
- Thromboprophylaxis \bar{C} LMWH
- Refer to Specialist Diabetes Team
- Find and treat precipitating factors



Monitoring

- Hrly capillary glucose and ketones
- VBG @ 60min, 2h and then 2hrly
- Plasma electrolytes 4hrly

Aims

- \downarrow ketones by $\geq 0.5mM/h$ or $\uparrow HCO_3$ by $\geq 3mM/h$
- \downarrow plasma glucose by $\geq 3mM/h$
- Maintain K in normal range
- Avoid hypoglycaemia



Resolution

- Ketones $<0.3mM$ + venous pH >7.3 ($HCO_3 >18mM$)
- Transfer to sliding scale if not eating
- Transfer to SC insulin when eating and drinking



Transfer to SC Insulin

- When biochemically resolved and eating
- Start long-acting insulin the night before
- Give short-acting insulin before breakfast
- Stop IVI 30min after short acting



Pt. Education

- ID precipitating factors and provide action plan
- Provision of ketone meter \bar{C} education on use.

Hyperosmolar Non-Ketotic Coma

The Patient

- Usually T2DM, often new presentation
- Usually older
- Long hx (e.g. 1wk)

Metabolic Derangement

- Marked dehydration and glucose >35mM
- No acidosis (no ketogenesis)
- Osmolality >340mosmol/kg

Complications

- Occlusive events are common: DVT, stroke
 - Give LMWH

Mx

- Rehydrate \bar{c} 0.9% NS over 48h
 - May need ~9L
- Wait 1h before starting insulin
 - It may not be needed
 - Start low to avoid rapid changes in osmolality
 - E.g. 1-3u/hr
- Look for precipitant
 - MI
 - Infection
 - Bowel infarct

Hypoglycaemia

Hypoglycaemia: Whipple's Triad

- Low plasma glucose $\leq 3\text{mM}$
- Symptoms consistent w/ hypoglycaemia
- Relief of symptoms by glucose administration

Symptoms

Autonomic: 2.5-3 Neuroglycopenic: <2.5

- | | |
|---|--|
| <ul style="list-style-type: none">• Sweating• Anxiety• Hunger• Tremor• Palpitations | <ul style="list-style-type: none">• Confusion• Drowsiness• Seizures• Personality change• Focal neurology (e.g. CN3)• Coma (<2.2) |
|---|--|

Fasting Hypoglycaemia

Causes: EXPLAIN

- Usually insulin or sulfonylurea Rx in a known diabetic
 - Exercise, missed meal, OD
- Exogenous drugs
- Pituitary insufficiency
- Liver failure
- Addison's
- Islet cell tumours (insulinomas)
- Immune (insulin receptor Abs: Hodgkin's)
- Non-pancreatic neoplasms: e.g. fibrosarcomas

Ix

- 72h fast w/ monitoring
- Sympto: Glucose, insulin, C-peptide, ketones

Dx

- Hyperinsulinaemic hypoglycaemia
 - Drugs
 - ↑ C-pep: sulfonylurea
 - Normal C-pep: insulin
 - Insulinoma
- ↓ insulin, no ketones
 - Non-pancreatic neoplasms
 - Insulin receptor Abs
- ↓ insulin, ↑ ketones
 - Alcohol binge w/ no food
 - Pituitary insufficiency
 - Addison's

Insulinoma

- Path: 95% benign β-cell tumour usually seen w/ MEN1
- Pres: fasting- / exercise-induced hypoglycaemia
- Ix:
 - Hypoglycaemia + ↑ insulin
 - Exogenous insulin doesn't suppress C-pep
 - MRI, EUS pancreas
- Rx: excision

Post-Prandial Hypoglycaemia

- Dumping post-gastric bypass

Mx

Alert and Orientated: Oral Carb

- Rapid acting: lucozade
- Long acting: toast, sandwich

Drowsy / confused but swallow intact: Buccal Carb

- Hypostop / Glucogel
- Consider IV access

Unconscious or Concerned re Swallow: IV dextrose

- 100ml 20% glucose (50ml 50% dextrose: not used)

Deteriorating / refractory / insulin-induced / no access

- 1mg glucagon IM/SC
- Won't work in drunks + short duration of effect (20min)
- Insulin release may → rebound hypoglycaemia

Thyrotoxicosis

Definition

- The clinical effect of ↑T4, usually from gland hyperfunction.

Symptoms

- Diarrhoea
- ↑ appetite but ↓ wt.
- Sweats, heat intolerance
- Palpitations
- Tremor
- Irritability
- Oligomenorrhoea ± infertility

Signs

Hands

- Fast / irregular pulse
- Warm, moist skin
- Fine tremor
- Palmer erythema

Face

- Thin hair
- Lid lag
- Lid retraction

Neck

- Goitre or nodules

Graves' Specific

- Ophthalmopathy**
 - Exophthalmos
 - Ophthalmoplegia: esp. up-gaze palsy
 - Eye discomfort and grittiness
 - Photophobia and ↓ acuity
 - Chemosis
- Dermopathy:** pre-tibial myxoedema
- Thyroid acropachy**

Ix

- ↓TSH, ↑T4/↑T3
- Abs: TSH receptor, TPO
- ↑Ca, ↑LFTs
- Isotope scan
 - ↑ in Graves'
 - ↓ in thyroiditis
- Ophthalmopathy: acuity, fields, movements

Graves' Disease

Epidemiology

- 60% of cases of thyrotoxicosis
- Prev:** 0.5%
- Sex:** F>>M=9:1
- Age:** 40-60yrs

Features

- Diffuse goitre & ↑iodine uptake
- Ophthalmopathy and dermopathy**
- Triggers: stress, infection, child-birth

Associations

- T1DM
- Vitiligo
- Addison's

Other Causes

Toxic Multinodular Goitre = Plummer's Disease

- Autonomous nodule develops on background multinodular goitre.
- Elderly and iodine-deficient areas
- Iodine scan shows hot nodules

Toxic Adenoma

- Solitary hot nodule ± producing T3/T4
- Most nodules are non-functional

Thyrotoxic Phase of Thyroiditis

- Hashimoto's
- de Quervain's
- Subacute lymphocytic

Drugs

- Thyroxine
- Amiodarone

Rx

Medical

- Symptomatic: β-B (e.g. propranolol 40mg/6h)
- Anti-thyroid: carbimazole (inhibits TPO)
 - Titrate according to TFTs or block and replace
 - In Graves' Rx for 12-18mo then withdraw
 - ~50% relapse → surgery or radioiodine
 - SE: agranulocytosis

Radiological: Radio-iodine

- Most become hypothyroid
- Cl: pregnancy, lactation

Surgical: Thyroidectomy

- Recurrent laryngeal N. damage → hoarseness
- Hypoparathyroidism
- Hypothyroidism

Thyroid Storm

Features

- ↑ temp
- Agitation, confusion, coma
- Tachycardia, AF
- Acute abdomen
- Heart failure

Precipitants

- Recent thyroid surgery or radio-iodine
- Infection
- MI
- Trauma

Rx

- Fluid resuscitation + NGT
- Bloods: TFTs + cultures if infection suspected
- Propranolol PO/IV**
- Digoxin may be needed
- Carbimazole then Lugol's Iodine** 4h later to inhibit thyroid
- Hydrocortisone
- Rx cause

Hypothyroidism

Epidemiology

- Incidence: 4/1000/yr
- Sex: F>>M=6:1
- Age: >40yrs

Symptoms

- Lethargy
- Cold intolerance
- ↓ appetite but ↑wt.
- Constipation
- Menorrhagia
- ↓ mood

Signs

- Cold hands
- Bradycardic
- Slow-relaxing reflexes
- Dry hair and skin
- Puffy face
- Goitre
- Myopathy, neuropathy
- Ascites
- Myxoedema
 - SC tissue swelling in severe hypothyroidism
 - Typically around eyes and dorsum of hand

Causes

Primary

- Atrophic thyroiditis (commonest UK)
- Hashimoto's thyroiditis
- Subacute thyroiditis (e.g. post-partum)
- Post De Quervain's thyroiditis
- Iodine deficiency (commonest worldwide)
- Drugs: carbimazole, amiodarone, lithium
- Congenital: thyroid agenesis

Post-surgical

- Thyroidectomy
- Radioiodine

Secondary

- Hypopituitarism (v. rare cause)

Atrophic Thyroiditis

- Thyroid antibodies +ve: anti-TPO, anti-TSH
- Lymphocytic infiltrate → atrophy (no goitre)
- Associations
 - Pernicious anaemia
 - Vitiligo
 - Endocrinopathies

Hashimoto's Thyroiditis

- TPO +ve
- Atrophy + regeneration → goitre
- May go through initial thyrotoxicosis phase
- May be euthyroid or hypothyroid

Ix

- ↑TSH, ↓T3/T4
- ↑MCV ± normochromic anaemia
- ↑ triglyceride + ↑ cholesterol
- Hyponatraemia (SIADH)
- ↑ CK if assoc. myopathy
- Abs: TPO, TSH

Rx

- Levothyroxine
 - Titrate to normalise TSH
 - Enzyme inducers ↑ thyroxine metabolism
 - Clinical improvement takes ~2wks
- Check for other AI disease: e.g. Addison's, PA

Myxoedema Coma

Features

- Looks hypothyroid
- Hypothermia
- Hypoglycaemia
- Heart failure: bradycardia and ↓BP
- Coma and seizures

Precipitants

- Radioiodine
- Thyroidectomy
- Pituitary surgery
- Infection, trauma, MI, stroke

Mx

- Bloods: TFTs, FBC, U+E, glucose, cortisol
- Correct any hypoglycaemia
- T3/T4 IV slowly (may ppt. myocardial ischaemia)
- Hydrocortisone 100mg IV
- Rx hypothermia and heart failure

Benign Thyroid Disease

Disease	Clinical Features	Cause	Management
Simple goitre	Diffuse painless goitre Mass effects: - dysphagia - stridor - SVC obstruction Usually euthyroid, may → hypothyroid	Endemic - iodine deficiency Sporadic - autoimmune - goitrogens (e.g. sulphonylureas) - hereditary (dyshormogenic)	Thyroxine Total or subtotal thyroidectomy if pressure symptoms.
Multinodular goitre	Evolves from long-standing simple goitre. Mass effects. Euthyroid (or subclinical hyperthyroid)	As for simple goitre	Thyroxine Total or subtotal thyroidectomy if pressure symptoms.
Plummer's Toxic multinodular goitre	Multinodular goitre Thyrotoxicosis Uneven iodine uptake with hot nodule	Autonomous nodule develops on background multinodular goitre	Anti-thyroid drugs Total or subtotal thyroidectomy.
Graves'	Diffuse goitre \pm bruit Ophthalmopathy Dermopathy Thyrotoxicosis Assoc. \pm other AI disease (T1DM, PA) \uparrow uptake on radionucleotide scan	Autoimmune (T2 hypersensitivity) - anti-TSH	Propranolol Carbimazole Radioiodine Thyroidectomy
Hashimoto's thyroiditis	Diffuse painless goitre May have transient thyrotoxicosis, then hypothyroidism Assoc. \pm other AI disease (T1DM, PA)	Autoimmune (T2 and T4) - anti-TPO, -Tg	Levothyroxine
de Quervain's	Diffuse painful goitre Preceding viral URTI common Thyrotoxicosis → hypo→eu \downarrow iodine uptake	Viral: Coxsackie common Autoimmune	Self-limiting
Subacute lymphocytic	Diffuse painless goitre May occur post-partum Thyrotoxicosis → hypo→eu	Autoimmune	Self-limiting
Riedel's thyroiditis	Hard fixed thyroid mass Mass effects Assoc. \pm retroperitoneal fibrosis	Autoimmune fibrosis	Conservative
Follicular adenoma	Single thyroid nodule \pm thyrotoxicosis (majority are cold) May get pressure symptoms		Hemithyroidectomy
Thyroid cysts	Solitary thyroid nodule Asymptomatic or pressure symptoms Can → localised pain due to cyst bleed		Aspiration or excision

Malignant Thyroid Disease

Disease	Frequency	Age	Cell Origin	Spread	Mx
Papillary	80% Assoc. C irradiation	20-40	Follicular cells Tg tumour marker	Nodes and lung - JDG node = lateral aberrant thyroid	Total thyroidectomy ± node excision ± radioiodine T4 to suppress TSH >95% 10ys
Follicular	10% F>M = 3:1	40-60	Follicular cells Tg tumour marker	Blood → bone and lungs	Total thyroidectomy + T4 suppression + Radioiodine >95% 10ys
Medullary	5% 30% are familial - e.g. MEN2	Men: young Sporadic: 40-50	Parafollicular C-cells CEA and calcitonin markers		Do phaeo screen pre-op Thyroidectomy + Node clearance Consider radiotherapy
Anaplastic	Rare F>M = 3:1	>60	Undifferentiated follicular cells	Rapid growth Aggressive: local, LN and blood.	Usually palliative May try thyroidectomy + radiotherapy <1% 10ys
Lymphoma	5%		Lymphocytes - MALToma in Hashi's		Chemo-radiotherapy

Presentation:

- Non-functional (cold)
- Painless neck mass
- Cervical mets
- Compression symptoms
 - Dysphagia
 - Stridor
 - SVC obstruction

Risk factors for malignancy in thyroid nodules

- Solitary
- Solid
- Younger
- Male
- Cold
- Risk factor: e.g. radiation exposure

Thyroid Surgery

Indications

- Pressure symptoms
- Relapse hyperthyroidism (>1 failed drug Rx)
- Cosmesis
- Carcinoma

Practicalities

- Render euthyroid pre-op C antithyroid drugs
 - Stop 10 days prior to surgery (they ↑ vascularity)
 - Alternatively just give propranolol
- Check for phaeo pre-op in medullary carcinoma
- Laryngoscopy: check vocal cords pre- and post-op

Procedure

- Collar incision

Complications of Thyroid Surgery

Early

- Reactionary haemorrhage → haematoma (<1%)**
 - Can → airway obstruction.
 - Call anaesthetist and remove wound clips
 - Evacuate haematoma and re-explore wound
- Laryngeal oedema**
 - Damage during intubation or surgical manipulation
 - Can → airway obstruction
- Recurrent laryngeal nerve palsy (0.5%)**
 - Right RLN more common (oblique ascent)
 - Damage to one → hoarse voice
 - Damage to both → obstruction needing trachyostomy
- Hypoparathyroidism (2.5%)**
 - ↓ Ca²⁺ → Chvostek's and Troussseau's
- Thyroid storm**
 - Severe hyperthyroidism
 - Rx: propranolol, antithyroid drugs, Lugol's iodine and hydrocortisone sodium succinate

Late

- Hypothyroidism
- Recurrent hyperthyroidism
- Keloid scar

Hyperparathyroidism

Physiology

- PTH secreted in response to $\downarrow \text{Ca}^{2+}$
 - \uparrow osteoclast activity
 - $\uparrow \text{Ca}^{2+}$ and $\downarrow \text{PO}_4$ reabsorption in kidney
 - \uparrow 1 α -hydroxylation of 25OH-Vit D₃

Presentation: $\uparrow \text{Ca}^{2+}$

- **Stones**
 - Renal stones
 - Polyuria and polydipsia (nephrogenic DI)
 - Nephrocalcinosis
- **Bones**
 - Bone pain
 - Pathological #s
- **Moans:** depression
- **Groans**
 - Abdo pain
 - n/v and constipation
 - Pancreatitis
 - PUD (\uparrow gastrin secretion)
- **Other:**
 - \uparrow BP (check Ca^{2+} in all with HTN)

Primary Hyperparathyroidism

Causes

- **Solitary adenoma:** 80%
- Hyperplasia: 20%
- Pathyroid Ca: <0.5%

Ix

- $\uparrow \text{Ca}^{2+}$ + \uparrow or inappropriately normal PTH, $\uparrow \text{ALP}$, $\downarrow \text{PO}_4$
- **ECG:** $\downarrow \text{QTc} \rightarrow$ bradycardia \rightarrow 1st degree block
- **X-ray:** osteitis fibrosa cystica \rightarrow phalangeal erosions
- **DEXA:** osteoporosis

Rx

- **General**
 - \uparrow fluid intake
 - Avoid dietary Ca^{2+} and thiazides (\uparrow serum Ca)
- **Surgical: excision of adenoma**
 - Hypoparathyroidism
 - Recurrent laryngeal N. palsy

Secondary Hyperparathyroidism

Causes

- Vitamin D deficiency
- Chronic renal failure

Ix

- $\uparrow \text{PTH}$, $\downarrow \text{Ca}$, $\uparrow \text{PO}_4$, $\uparrow \text{ALP}$, $\downarrow \text{vit D}$

Rx

- Correct causes
- Phosphate binders
 - With Ca: calcichew
 - W/o Ca: sevelamer, lanthanum
- Vit D: calcitriol (active), cholecalciferol (inactive)
- Cinacalcet: \uparrow parathyroid Ca-sensitivity

Tertiary Hyperparathyroidism

- Prolonged 2^o HPT \rightarrow autonomous PTH secretion
- $\uparrow \text{Ca}^{2+}$, $\uparrow \text{PTH}$, $\downarrow \text{PO}_4$, $\uparrow \text{ALP}$

Hypoparathyroidism

- \downarrow PTH due to gland failure

Presentation: $\downarrow \text{Ca} \rightarrow \text{SPASMODIC}$

- Spasms (carpopedal = Trousseau's sign)
- Perioral paraesthesia
- Anxious, irritable
- Seizures
- Muscle tone $\uparrow \rightarrow$ colic, wheeze, dysphagia
- Orientation impaired (confusion)
- Dermatitis
- Impetigo herpetiformis ($\downarrow \text{Ca}$ + pustules in pregnancy)
- Chovsteeks, cardiomyopathy ($\uparrow \text{QTc} \rightarrow \text{TdP}$)

Causes

- Autoimmune
- Congenital: DiGeorge
 - Cardiac abnormality: Fallot's
 - Abnormal facies
 - Thymic aplasia
 - Cleft palate
 - Hypocalcaemia
 - Chr 22
- Iatrogenic
 - Surgery
 - Radiation

Ix

- $\downarrow \text{Ca}$, $\uparrow \text{PO}_4$, $\downarrow \text{PTH}$, normal ALP

Rx

- Ca supplements
- Calcitriol

Pseudohypoparathyroidism

- Failure of target organ response to PTH
- Symptoms of hypocalcaemia
- Short 4th and 5th metacarpals, short stature
- **Ix:** $\downarrow \text{Ca}$, $\uparrow \text{PTH}$
- **Rx:** Ca + calcitriol

Pseudopseudohypoparathyroidism

- Normal (maternal) receptor in kidney \rightarrow normal biochem
- Abnormal (paternal) receptors in body \rightarrow pseudohypoparathyroidsm phenotype

Cushing's Syndrome

Definition

- Clinical state produced by chronic glucocorticoid excess

Features

Catabolic Effects

- Proximal myopathy
- Striae
- Bruising
- Osteoporosis

Glucocorticoid Effects

- DM
- Obesity

Mineralocorticoid Effects

- HTN
- Hypokalaemia

Appearance

- Moon face
- Acne and hirsutism
- Interscapular and supraclavicular fat pads
- Centripetal obesity
- Striae
- Thin limbs
- Bruising
- Thin skin

ACTH-Independent

- ↓ACTH due to -ve FB
- No suppression \bar{c} any dose of dex

Causes

- Iatrogenic steroids: commonest cause
- Adrenal adenoma / Ca: carcinoma often \rightarrow virilisation
- Adrenal nodular hyperplasia
- Carney complex: LAME Syndrome
- McCune-Albright

ACTH-Dependent

- ↑ ACTH

Causes

- Cushing's disease
 - Bilat adrenal hyperplasia from ACTH-secreting pituitary tumour (basophilic microadenoma)
 - Cortisol suppression \bar{c} high-dose dex
- Ectopic ACTH
 - SCLC
 - Carcinoid tumour
 - Skin pigmentation, metabolic alkalosis, wt. loss, hyperglycaemia
 - No suppression \bar{c} any dose of dex

Ix

- 1st: 24h urinary free cortisol
- Late night serum or salivary cortisol
 - Highest @ AM, lowest @ midnight
- Dexamethasone suppression tests
- ACTH (but ACTH degrades v. quick after venepuncture)
- Localisation: CT, MRI
- DEXA scan

Rx: Treat Causes

- Cushing's disease: trans-sphenoidal excision
- Adrenal adenoma / Ca: adrenalectomy
- Ectopic ACTH: tumour excision, metyrapone (inhibits cortisol synthesis)

Nelson's Syndrome

- Rapid enlargement of a pituitary adenoma following bilateral adrenalectomy for Cushing's syndrome
 - Not typically performed nowadays
- Presentation
 - Mass effects: bitemporal hemianopia
 - Hyperpigmentation

Hyperaldosteronism

Primary Hyperaldosteronism

- Excess aldosterone, independent of RAS

Features

- Hypokalaemia: weakness, hypotonia, hyporeflexia, cramps
- Paraesthesia
- ↑BP

Causes

- Bilateral adrenal hyperplasia (70%)
- Adrenocortical adenoma (30%): Conn's syndrome

Ix

- U+E: ↑/↔ Na, ↓K, alkalosis
 - Care for diuretics, hypotensives, laxatives, steroids
- Aldosterone:renin ratio: ↑ primary
- ECG: flat / inverted T waves, U waves, depressed ST segments, prolonged PR and QT intervals
- Adrenal CT/MRI

Rx

- Conn's: laparoscopic adrenalectomy
- Hyperplasia: **spironolactone**, eplerenone or amiloride

Secondary Hyperaldosteronism

- Due to ↑ renin from ↓ renal perfusion

Causes

- RAS
- Diuretics
- CCF
- Hepatic failure
- Nephrotic syndrome

Ix

- Aldosterone:renin ratio: normal

Bartter's Syndrome

- Autosomal recessive
- Blockage of NaCl reabsorption in loop of Henle (as if taking furosemide)
- Congenital salt wasting → RAS activation → hypokalaemia and metabolic alkalosis
- Normal BP

Adrenal Insufficiency

Primary Adrenal Insufficiency: Addison's

- Destruction of adrenal cortex → glucocorticoid and mineralocorticoid deficiency

Causes

- Autoimmune destruction: 80% in the UK
- TB: commonest worldwide
- Metastasis: lung, breast, kidneys
- Haemorrhage: Waterhouse-Friedrichson
- Congenital: CAH

Symptoms

- Wt. loss + anorexia
- n/v, abdo pain, diarrhoea/constipation
- Lethargy, depression
- **Hyperpigmentation:** buccal mucosa, palmer creases
- Postural hypotension → dizziness, faints
- Hypoglycaemia
- Vitiligo
- Addisonian crisis

Ix

- **Bloods**
 - ↓Na/↑K
 - ↓glucose
 - ↓Ca
 - Anaemia
- **Differential**
 - Short synACTH test
 - Cortisol before and after tetracosactide
 - Exclude Addison's if ↑ cortisol
 - ↑ 9am ACTH (usually low)
- **Other**
 - 21-hydroxylase Abs: +ve in 80% of AI disease
 - Plasma renin and aldosterone
 - CXR: evidence of TB
 - AXR: adrenal calcification

Rx

- **Replace**
 - Hydrocortisone
 - Fludrocortisone
- **Advice**
 - Don't stop steroids suddenly
 - ↑ steroids during intercurrent illness, injury
 - Wear a medic-alert bracelet
- **F/up**
 - Watch for autoimmune disease

Secondary Adrenal Insufficiency

- i.e. hypothalamo or pituitary failure

Causes

- Chronic steroid use → suppression of HPA axis
- Pituitary apoplexy / Sheehan's
- Pituitary microadenoma

Features

- Normal mineralocorticoid production
- No pigmentation (ACTH ↓)

Addisonian Crisis

Presentation

- Shocked: ↑HR, postural drop, oliguria, confused
- Hypoglycaemia
- Usually known Addisonian or chronic steroid user

Precipitants

- Infection
- Trauma
- Surgery
- Stopping long-term steroids

Mx

- **Bloods:** cortisol, ACTH, U+E, cultures
- Check CBG: glucose may be needed
- Hydrocortisone 100mg IV 6hrly
- IV crystalloid
- Septic screen
- Treat underlying cause

Phaeochromocytoma

Pathology

- Catecholamine-producing tumours arising from sympathetic paraganglia
- Usually found in adrenal medulla
- Extra-adrenal phaeo's found by aortic bifurcation

Rule of 10s

- 10% malignant
- 10% extra-adrenal
- 10% bilateral
- 10% part of hereditary syndromes

Associations

- 10% part of hereditary syndromes
 - MEN2a and 2b
 - Neurofibromatosis
 - Von Hippel-Lindau: RCC + cerebellar signs

Presentation

- Triad: episodic headache, sweating and tachycardia
- Other adrenergic features
 - ↑BP, palpitations
 - Headache, tremor, dizziness
 - Anxiety
 - d/v, abdo pain
 - Heat intolerance, flushes
- May have precipitant
 - Straining, abdo palpation
 - Exercise, stress
 - β-B, IV contrast, TCAs, GA

Ix

- Plasma + urine metadrenalin
 - Also vanillylmandelic acid
- Abdo CT/MRI
- MIBG (meta-iodobenzylguanidine) scan

Rx

Medical

- If malignant
- Chemo or radiolabelled MIBG

Surgery: adrenalectomy

- α-blocker first, then β-blockade pre-op
 - Avoids unopposed α-adrenergic stimulation
 - Phenoxybenzamine = α-blocker
- Monitor BP post-op for ↓BP

Hypertensive Crisis

Features

- Pallor
- Pulsating headache
- Feeling of impending doom
- ↑BP
- ↑ ST and cardiogenic shock

Rx

- Phentolamine 2-5mg IV (α-blocker) or labetalol 50mg IV
 - Repeat to safe BP (e.g. 110 diastolic)
- Phenoxybenzamine 10mg/d PO when BP controlled
- Elective surgery after 4-6wks to allow full α-blockade and volume expansion

Multiple Endocrine Neoplasia

Definition

- Functioning hormone tumours in multiple organs
- All autosomal dominant

MEN1

- Pituitary adenoma: prolactin or GH
- Parathyroid adenoma / hyperplasia
- Pancreatic tumours: gastrinoma or insulinoma

MEN2

- Thyroid medullary carcinoma
- Adrenal phaeochromocytoma
 - A) Hyperthyroidism
 - B) Marfanoid habitus

Carney Complex / LAME Syndrome

- Lentigenes: spotty skin pigmentation
 - Differential: Peutz-Jehgers
- Atrial Myxoma
- Endocrine tumours: pituitary, adrenal hyperplasia
- Schwannomas

Peutz-Jeghers

- Mucocutaneous freckles on lips, oral mucosa and palms / soles
- GI hamartomas: obstruction, bleeds
- Pancreatic endocrine tumours
- ↑ risk of cancer: CRC, pancreas, liver, lungs, breast

Von Hippel-Lindau

- Renal cysts
- Bilateral renal cell carcinoma
- Haemangioblastomas
 - Often in cerebellum → cerebellar signs
- Phaeochromocytoma
- Pancreatic endocrine tumours

Neurofibromatosis

- Dermal neurofibromas
- Café-au-lait spots
- Lisch nodules
- Axillary freckling
- Phaeochromocytoma

Autoimmune Polyendocrine Syndromes

Type 1

- Autosomal recessive
- Addison's
- Candidiasis
- Hypoparathyroidism

Type 2: Schmidt's Syndrome

- Polygenic
- Addison's
- Thyroid disease: hypothyroidism or Graves'
- T1DM

Hypopituitarism

Causes

- **Hypothalamic**
 - Kallmann's (anosmia + GnRH deficiency)
 - Tumour
 - Inflam, infection, ischaemia
- **Pituitary Stalk**
 - Trauma
 - Surgery
 - Tumour (e.g. craniopharyngioma)
- **Pituitary**
 - Irradiation
 - Tumour
 - Ischaemia: apoplexy, Sheehan's
 - Infiltration: HH, amyloid

Commonest causes of panhypopituitarism

- Surgery
- Tumour
- Irradiation

Features

Hormone Deficiency

- **GH:** central obesity, atherosclerosis, ↓CO, ↓strength
- **LH/FSH**
 - M: ↓libido, ED, ↓hair
 - F: ↓libido, amenorrhoea, breast atrophy
- **TSH:** hypothyroidism
- **ACTH:** 2^o adrenal failure

Cause

- Mass effects
- Other hormones: e.g. prolactin excess

Ix

- Basal hormone tests
- Dynamic pituitary function test
 - Insulin → ↑ cortisol + ↑ GH
 - GnRH → ↑ LH/FSH
 - TRH → ↑T4 + ↑ PRL
- MRI brain

Rx

- Hormone replacement
- Treat underlying cause

Pituitary Tumours

- 10% of intracranial tumours

Classification

Size

- Microadenoma: <1cm
- Macroadenoma: >1cm

Pathology

- Many are non-secretory
- ~50% produce PRL
- Others produce GH or ACTH

Features

Mass Effects

- Headache
- Visual field defect: bitemporal hemianopia
- CN palsies: 3, 4, 5, 6 (pressure on cavernous sinus)
- Diabetes insipidus
- CSF rhinorrhoea

Hormone Effects

- **PRL** → galactorrhoea, ↓libido, amenorrhoea, ED
 - ↑PRL → ↓GnRH → ↓LH/FSH
- **GH** → acromegaly
- **ACTH** → Cushing's Disease

Ix

- MRI
- Visual field tests
- Hormones: PRL, IGF, ACTH, cortisol, TFTs, LF/FSH
- Suppression tests

Rx

Medical

- Replace hormones
- Treat hormone excess

Surgical: Trans-sphenoidal excision

- Pre-op hydrocortisone
- Post-op dynamic pituitary tests

Radiotherapy: stereotactic

Pituitary Apoplexy

- Rapid pituitary enlargement due to bleed into a tumour
- Mass effects
 - Headache, meningism, ↓GCS
 - Bitemporal hemianopia
- Cardiovascular collapse due to acute hypopituitarism
- **Rx:** urgent hydrocortisone 100mg IV

Craniopharyngioma

- Originates from Rathke's pouch
- Commonest childhood intracranial tumour
 - → growth failure
- Calcification seen on CT/MRI

Hyperprolactinaemia

Causes

- Excess pituitary production
 - Pregnancy, breastfeeding
 - Prolactinoma (PRL >5000)
 - Hypothyroidism (\uparrow TRH)
- Disinhibition by compression of pituitary stalk
 - Pituitary adenoma
 - Craniopharyngioma
- Dopamine antagonists (commonest cause)
 - Antiemetics: metoclopramide
 - Antipsychotics: risperidone, haldol

Symptoms

- Amenorrhoea
- Infertility
- Galactorrhoea
- \downarrow libido
- ED
- Mass effects from prolactinoma

Ix

- Basal PRL: >5000 = prolactinoma
- Pregnancy test, TFTs
- MRI

Rx

- 1st line:** Cabergoline or bromocriptine
 - DA agonist
 - \downarrow PRL secretion and \downarrow tumour size
 - SE:** nausea, postural hypotension, fibrosis (lung and heart)
- 2nd line:** Trans-sphenoidal excision
 - If visual or pressure symptoms don't respond to medical Rx

Acromegaly

Causes

- Pituitary acidophil adenoma in 99%**
- Hyperplasia from GHRH secreting carcinoid tumour
- GH stimulates bone and soft tissue growth through \uparrow IGF1

Symptoms

- Acroparaesthesia
- Amenorrhoea, \downarrow libido
- Headache
- Snoring
- Sweating
- Arthralgia, back ache
- Carpal tunnel (50%)

Signs

Hands

- Spade-like
- Thenar wasting
- Boggy sweaty palms (if active)
- \uparrow skin fold thickness
- Carpal tunnel: \downarrow sensation + thenar wasting

Face

- Prominent supraorbital ridges
- Scalp folds: *cutis verticis gyrata*
- Coarse face, wide nose and big ears
- Prognathism: look from side
- Macroglossia
- Widely-spaced teeth
- Goitre

Other

- Puffy, oily, darkened skin
- Proximal weakness + arthropathy
- Pituitary mass effects: bitemporal hemianopia

Complications

- Endocrine**
 - Impaired glucose tolerance (40%)
 - DM (15%)
- Cardiovascular**
 - \uparrow BP
 - LVH
 - Cardiomyopathy
 - \uparrow IHD and \uparrow stroke
- Neoplasia**
 - \uparrow risk of CRC

Ix

- \uparrow IGF1
- \uparrow glucose, \uparrow Ca, \uparrow PO₄
- Glucose tolerance test
 - GH fails to suppress \bar{c} glucose in acromegaly
- Visual fields and acuity
- MRI brain

Rx

- 1st line:** trans-sphenoidal excision
- 2nd line:** somatostatin analogues – octreotide
- 3rd line:** GH antagonist – pegvisomant
- 4th line:** radiotherapy

Diabetes Insipidus

Symptoms

- Polyuria
- Polydipsia
- Dehydration
- Hypernatraemia: lethargy, thirst, confusion, coma

Causes

Cranial

- Idiopathic: 50%
- Congenital: DIDMOAD / Wolfram Syndrome
- Tumours
- Trauma
- Vascular: haemorrhage (Sheehan's syn.)
- Infection: meningoencephalitis
- Infiltration: sarcoidosis

Nephrogenic

- Congenital
- Metabolic: ↓K, ↑Ca
- Drugs: Li, demeclocycline, vaptans
- Post-obstructive uropathy

Ix

- Bloods: U+E, Ca, glucose
- Urine and plasma osmolality
 - Exclude DI if U:P osmolality >2

Dx

- Water deprivation test → desmopressin trial

Differential

- DM
- Diuretics or Lithium
- Primary polydipsia

Rx

Cranial

- Find cause: MRI brain
- Desmopressin PO

Nephrogenic

- Treat cause

Sexual Characteristics

Hirsutism

Causes

- Familial
- Idiopathic
- ↑ androgens:
 - Ovary: PCOS
 - Adrenals: Cushing's, adrenal Ca
 - Drugs: steroids

PCOS

- **Features**
 - 2° oligo-/amenorrhoea → infertility
 - Obesity
 - Acne, hirsutism
- **US:** bilateral polycystic ovaries
- **Hormones:** ↑ testosterone, ↓ SHBG, ↑LH:FSH ratio
- **Mx**
 - Metformin
 - COCP
 - Clomifene for infertility

Gynaecomastia

- Abnormal amount of breast tissue in men
- May occur in normal puberty

Causes

- Cirrhosis
- Hypogonadism
- Hyperthyroidism
- Oestrogen- or HCG-producing tumours: e.g. testicular
- Drugs: spiro, digoxin, oestrogen

ED

Organic Causes

- Smoking
- EtOH
- DM
- Endo: hypogonadism, hyperthyroidism, ↑Prl
- Neuro: MS, autonomic neuropathy, cord lesion
- Pelvic surgery: bladder, prostate
- Penile abnormalities: Peyronie's disease

Gastroenterology

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Diarrhoea

Definitions

- Diarrhoea = ↑ stool water → ↑ stool frequency
- Steatorrhoea = ↑ stool fat → pale, float, smelly
- Faecal urgency = suggests rectal pathology

Clinical Features and Causes

Acute

- Suspect gastroenteritis
- Travel, diet, contacts?

Chronic

- Diarrhoea alternating w/ constipation: IBS
- Anorexia, ↓wt., nocturnal diarrhoea: organic cause

Bloody

- **Vascular:** ischaemic colitis
- **Infective:** campylobacter, shigella, salmonella, E. coli, amoeba, pseudomembranous colitis
- **Inflammatory:** UC, Crohn's
- **Neoplastic:** CRC, polyps

Mucus

- IBS, CRC, polyps

Pus

- IBD, diverticulitis, abscess

Assoc. C. diff medical disease

- ↑ T4
- Autonomic neuropathy (e.g. DM)
- Carcinoid

Assoc. C. diff drugs

- Abx
- PPI, cimetidine
- NSAIDs
- Digoxin

Ix

Bloods

- **FBC:** ↑ WCC, anaemia
- **U+E:** ↓K⁺, dehydration
- **↑ESR:** IBD, Ca
- **↑CRP:** IBD, infection
- **Coeliac serology:** anti-TTG or anti-endomysial Abs

Stool

- MCS and C. diff toxin

Rx

- Treat cause
- Oral or IV rehydration
- Codeine phosphate or loperamide after each loose stool
- Anti-emetic if assoc. C. diff n/v: e.g. prochlorperazine
- Abx (e.g. cipro) in infective diarrhoea → systemic illness

C. diff Diarrhoea

Pathogen

- Gm+ve spore-forming anaerobe
- Release enterotoxins A and B
- Spores are v. robust and can survive for >40d

Epidemiology

- Commonest cause (25%) of Abx assoc. diarrhoea
 - 100% of Abx assoc. pseudomembranous colitis
- Stool carriage in 3% of healthy adults and 15-30% of hospital pts.

Risk Factors

- Abx: e.g. clindamycin, cefs, augmentin, quinolones
- ↑ age
- In hospital: ↑ C. diff length of stay, ↑ C. diff +ve contact
- PPIs

Clinical Presentations

- Asymptomatic
- Mild diarrhoea
- Colitis w/o pseudomembranes
- Pseudomembranous colitis
- Fulminant colitis
- May occur up to 2mo after discontinuation of Abx

Pseudomembranous Colitis

- Severe systemic symptoms: fever, dehydration
- Abdominal pain, bloody diarrhoea, mucus PR
- Pseudomembranes (yellow plaques) on flexi sig
- Complications
 - Paralytic ileus
 - Toxic dilatation → perforation
 - Multi-organ failure

Ix

- Bloods: ↑CRP, ↑WCC, ↓albumin, dehydration
- CDT ELISA
- Stool culture

Severe Disease: ≥1 of

- WCC >15
- Cr >50% above baseline
- Temp >38.5
- Clinical / radiological evidence of severe colitis

Rx

General

- Stop causative Abx
- Avoid antidiarrhoeals and opiates
- Enteric precautions

Specific

- **1st line:** Metronidazole 400mg TDS PO x 10-14d
- **2nd line:** Vanc 125mg QDS PO x 10-14d
 - Failed metro
- **Severe:** Vanc 1st (may add metro IV)
 - ↑ to 250mg QDS if no response (max 500mg)
 - Urgent colectomy may be needed if
 - Toxic megacolon
 - ↑ LDH
 - Deteriorating condition
- **Recurrence** (15-30%)
 - Reinfection or residual spores
 - Repeat course of metro x 10-14d
 - Vanc if further relapse (25%)

Constipation

Definition

- Infrequent BMs ($\leq 3/\text{wk}$) or passing BMs less often than normal or \bar{c} difficulty, straining or pain.

Causes: OPENED IT

Obstruction

- **Mechanical:** adhesions, hernia, Ca, inflammatory strictures, pelvic mass
- **Pseudo-obstruction:** post-op ileus

Pain

- Anal fissure
- Proctalgia fugax

Endocrine / Electrolytes

- **Endo:** $\downarrow T4$
- **Electrolytes:** $\downarrow \text{Ca}$, $\downarrow \text{K}$, uraemia

Neuro

- MS
- Myelopathy
- Cauda equina syndrome

Elderly

Diet / Dehydration

IBS

Toxins

- Opioids
- Anti-mACh

Mx

General

- Drink more
- \uparrow dietary fibre

Bulking:

- \uparrow faecal mass \rightarrow \uparrow peristalsis
- **CI:** obstruction and faecal impaction
 - Bran
 - Ispaghula husk (Fybogel)
 - Methylcellulose

Osmotic:

- retain fluid in the bowel
- Lactulose
 - MgSO_4 (rapid)

Stimulant:

- \uparrow intestinal motility and secretion
- **CI:** obstruction, acute colitis
 - **SE:** abdo cramps
 - Bisacodyl PO or PR
 - Senna
 - Docusate sodium
 - Sodium picosulphate (rapid)

Softeners

- Useful when managing painful anal conditions
- Liquid paraffin

Enemas

- Phosphate enema (osmotic)

Suppositories

- Glycerol (stimulant)

IBS

Definition

- Disorders of enhanced visceral perception \rightarrow bowel symptoms for which no organic cause can be found.

Dx: ROME Criteria

- Abdo discomfort / pain for $\geq 12\text{wks}$ which has 2 of:
 - Relieved by defecation
 - Change in stool frequency (D or C)
 - Change in stool form: pellets, mucus
- + 2 of:
 - Urgency
 - Incomplete evacuation
 - Abdo bloating / distension
 - Mucous PR
 - Worsening symptoms after food
- **Exclusion criteria**
 - $>40\text{yrs}$
 - Bloody stool
 - Anorexia
 - Wt. loss
 - Diarrhoea at night

Ix

- **Bloods:** FBC, ESR, LFT, coeliac serology, TSH
- **Colonoscopy:** if $>60\text{yrs}$ or any features of organic disease

Rx

- Exclusion diets can be tried
- Bulking agents for constipation and diarrhoea (e.g. fybogel).
- Antispasmodics for colic/bloating (e.g. mebeverine)
- Amitriptyline may be helpful
- CBT

Dysphagia

Definition

- Difficulty swallowing

Causes

Inflammatory

- Tonsillitis, pharyngitis
- Oesophagitis: GORD, candida
- Oral candidiasis
- Aphthous ulcers

Mechanical Block

- **Luminal**
 - FB
 - Large food bolus
- **Mural**
 - **Benign stricture**
 - Web (e.g. Plummer-Vinson)
 - Oesophagitis
 - Trauma (e.g. OGD)
 - **Malignant stricture**
 - Pharynx, oesophagus, gastric
 - Pharyngeal pouch
- **Extra-mural**
 - Lung Ca
 - Rolling hiatus hernia
 - Mediastinal LNs (e.g. lymphoma)
 - Retrosternal goitre
 - Thoracic aortic aneurysm

Motility Disorders

- **Local**
 - Achalasia
 - Diffuse oesophageal spasm
 - Nutcracker oesophagus
 - Bulbar / pseudobulbar palsy (CVA, MND)
- **Systemic**
 - Systemic sclerosis / CREST
 - MG

Presentation

- Dysphagia for liquids and solids at *start*
 - Yes: motility disorder
 - No, solids > liquids: stricture
- Difficulty making swallowing movement: bulbar palsy
- Odonophagia: Ca, oesophageal ulcer, spasm
- Intermittent: oesophageal spasm
- Constant and worsening: malignant stricture
- Neck bulges or gurgles on drinking: pharyngeal pouch

Signs

- Cachexia
- Anaemia
- Virchow's node (+ve = Troisier's sign)
- Neurology
- Signs of systemic disease (e.g. scleroderma)

Ix

- Bloods: FBC, U+E
- CXR
- OGD
- Barium swallow ± video fluoroscopy
- Oesophageal manometry

Achalasia

- **Pathophysiology**
 - Degeneration of myenteric plexus (Auerbach's)
 - ↓ peristalsis
 - LOS fails to relax
- **Cause**
 - **1^o / idiopathic:** commonest
 - **2^o:** oesophageal Ca, Chagas' disease (*T. cruzi*)
- **Presentation**
 - Dysphagia: liquids and solids at same time
 - Regurgitation
 - Substernal cramps
 - Wt. loss
- **Comps:** Chronic achalasia → oesophageal SCC
- **Ix**
 - **Ba swallow:** dilated tapering oesophagus (Bird's beak)
 - **Manometry:** failure of relaxation + ↓ peristalsis
 - **CXR:** may show widened mediastinum
 - **OGD:** exclude malignancy
- **Rx:**
 - **Med:** CCBs, nitrates
 - **Int:** endoscopic balloon dilatation, botulinum toxin injection
 - **Surg:** Heller's cardiomyotomy (open or endo)

Pharyngeal Pouch: Zenker's Diverticulum

- Outpouching of oesophagus between upper border of cricopharyngeus muscle and lower border of inferior constrictor of pharynx
 - Weak area called **Killian's dehiscence**.
- Defect usually occurs posteriorly but swelling usually bulges to left side of neck.
- Food debris → pouch expansion → oesophageal compression → dysphagia.
- **Pres:** regurgitation, halitosis, gurgling sounds
- **Rx:** excision, endoscopic stapling

Diffuse Oesophageal Spasm

- Intermittent dysphagia ± chest pain
- Ba swallow shows corkscrew oesophagus

Nutcracker Oesophagus

- ↑ contraction pressure \overline{c} normal peristalsis

Dyspepsia

Definition

- Non-specific group of symptoms
- Epigastric pain
- Bloating
- Heartburn

ALARM Symptoms

- Anaemia
- Loss of wt.
- Anorexia
- Recent onset progressive symptoms
- Melaena or haematemesis
- Swallowing difficulty

Causes

- **Inflammation:** GORD, gastritis, PUD
- **Ca:** oesophageal, gastric
- **Functional:** non-ulcer dyspepsia

Mx of New Onset Dyspepsia

- OGD if >55 or ALARMS
- Try conservative measures for 4 wks
 - Stop drugs: NSAIDs, CCBs (relax LOS)
 - Lose wt., stop smoking, ↓ EtOH
 - Avoid hot drinks and spicy food
 - OTC
 - Antacids: magnesium trisilicate
 - Alginate: gaviscon advance
- Test for H. pylori if no improvement: breath or serology
 - +ve → eradication therapy
 - Consider OGD if no improvement
 - -ve → PPI trial for 4wks
 - Consider OGD if no improvement
 - PPIs can be used intermittently to control symptoms.
- **Proven GORD**
 - Full dose PPI for 1-2mo
 - Then, low-dose PPI PRN
- **Proven PUD**
 - Full dose PPI for 1-2mo
 - H. pylori eradication if positive
 - Endoscopy to check for resolution if GU
 - Then, low-dose PPI PRN

Eradication Therapy

- 7 days Rx
- NB. PPIs and cimetidine → false -ve C¹³ breath tests and antigen tests ∴ stop >2wks before.

PAC 500

- PPI: Lansoprazole 30mg BD
- Amoxicillin 1g BD
- Clarithromycin 500mg BD

PMC 250

- PPI: Lansoprazole 30mg BD
- Metronidazole 400mg BD
- Clarithromycin 250mg BD

Failure

- 95% success
- Mostly due to poor compliance
- Add bismuth
 - Stools become tarry black

Peptic Ulcer Disease

Classification

- **Acute:** usually due to drugs (NSAIDs, steroids) or “stress”
- **Chronic:** drugs, H. pylori, ↑Ca, Zollinger-Ellison

Features

	Duodenal Ulcers	Gastric Ulcers
Pathology	<ul style="list-style-type: none"> • 4x commoner cf. GU • 1st part of duodenum (cap) • M>F 	<ul style="list-style-type: none"> • Lesser curve of gastric antrum • Beware ulcers elsewhere (often malignant)
Risk Factors	<ul style="list-style-type: none"> • H. pylori (90%) • Drugs: NSAIDs, steroids • Smoking • EtOH • ↑ gastric emptying • Blood group O 	<ul style="list-style-type: none"> • H. pylori (80%) • Smoking • Drugs • Delayed gastric emptying • Stress <ul style="list-style-type: none"> ▪ Cushing's: intracranial disease ▪ Curling's: burns, sepsis, trauma
Presentation	<ul style="list-style-type: none"> • Epigastric pain: <ul style="list-style-type: none"> ▪ Before meals and at night ▪ Relieved by eating or milk 	<ul style="list-style-type: none"> • Epigastric pain: <ul style="list-style-type: none"> ▪ Worse on eating ▪ Relieved by antacids • Wt. loss

Complications

Haemorrhage

- Haematemesis or melaena
- Fe deficiency anaemia

Perforation

- Peritonitis

Gastric Outflow Obstruction

- Vomiting, colic, distension

Malignancy

- ↑ risk cf. H. pylori

Ix

- **Bloods:** FBC, urea (↑ in haemorrhage)
- C¹³ breath test
- OGD (stop PPIs >2wks before)
 - CLO / urease test for H. pylori
 - Always take biopsies of ulcers to check for Ca
- Gastrin levels if Zollinger-Ellison suspected

Mx

Conservative

- Lose wt.
- Stop smoking and ↓ EtOH
- Avoid hot drinks and spicy food
- Stop drugs: NSAIDs, steroids
- OTC antacids

Medical

- OTC antacids: Gaviscon, Mg trisilicate
- H. pylori eradication: PAC500 or PMC250
- Full-dose acid suppression for 1-2mo
 - PPIs: lansoprazole 30mg OD
 - H2RAs: ranitidine 300mg nocte
- Low-dose acid suppression PRN

Surgery for PUD

Concepts

- No acid → no ulcer
- Secretion stimulated by gastrin and vagus N.

Vagotomy

- **Truncal:** ↓ acid secretion but prevents pyloric sphincter relaxation ∴ must be combined w/ pyloroplasty or gastroenterostomy.
- **Selective:** vagus nerve only denervated where it supplies lower oesophagus and stomach
 - Nerves of Laterjet (supply pylorus) left intact

Antrectomy cf. vagotomy

- Distal half of stomach removed + anastomosis:
 - Directly to duodenum: Billroth 1
 - To small bowel loop cf. duodenal stump oversewn: Billroth 2 or Polya

Subtotal gastrectomy cf. Roux-en-Y

- Occasionally performed for Zollinger-Ellison

Complications

Physical

- Stump leakage
- Abdominal fullness
- Reflux or bilious vomiting (improves cf. time)
- Stricture

Metabolic

- Dumping syndrome
 - Abdo distension, flushing, n/v
 - Early: osmotic hypovolaemia
 - Late: reactive hypoglycaemia
- Blind loop syndrome → malabsorption, diarrhoea
 - Overgrowth of bacteria in duodenal stump
 - Anaemia: Fe + B12
 - Osteoporosis
- Wt. loss: malabsorption of ↓ calories intake

GORD

Pathophysiology

- LOS dysfunction → reflux of gastric contents → oesophagitis.

Risk Factors

- Hiatus hernia
- Smoking
- EtOH
- Obesity
- Pregnancy
- Drugs: anti-AChM, nitrates, CCB, TCAs
- Iatrogenic: Heller's myotomy

Symptoms

Oesophageal

- Heartburn
 - Related to meals
 - Worse lying down / stooping
 - Relieved by antacids
- Belching
- Acid brash, water brash
- Odonophagia

Extra-oesophageal

- Nocturnal asthma
- Chronic cough
- Laryngitis, sinusitis

Complications

- Oesophagitis: heartburn
- Ulceration: rarely → haematemesis, melaena, ↓Fe
- Benign stricture: dysphagia
- Barrett's oesophagus
 - Intestinal metaplasia of squamous epithelium
 - Metaplasia → dysplasia → adenocarcinoma
- Oesophageal adenocarcinoma

Differential Dx

- Oesophagitis
 - Infection: CMV, candida
 - IBD
 - Caustic substances / burns
- PUD
- Oesophageal Ca

Ix

- Isolated symptoms don't need Ix
- **Bloods:** FBC
- **CXR:** hiatus hernia may be seen
- **OGD if:**
 - >55yrs
 - Symptoms >4wks
 - Dysphagia
 - Persistent symptoms despite Rx
 - Wt. loss
 - OGD allows grading by **Los Angeles Classification**
- **Ba swallow:** hiatus hernia, dysmotility
- 24h pH testing ± manometry
 - pH <4 for >4hrs

Rx

Conservative

- Lose wt.
- Raise head of bed
- Small regular meals ≥ 3h before bed
- Stop smoking and ↓ EtOH
- Avoid hot drinks and spicy food
- Stop drugs: NSAIDs, steroids, CCBs, nitrates

Medical

- OTC antacids: Gaviscon, Mg trisilicate
- **1:** Full-dose PPI for 1-2mo
 - Lansoprazole 30mg OD
- **2:** No response → double dose PPI BD
- **3:** No response: add an H2RA
 - Ranitidine 300mg nocte
- Control: low-dose acid suppression PRN

Surgical: Nissen Fundoplication

- Indications: all 3 of:
 - Severe symptoms
 - Refractory to medical therapy
 - Confirmed reflux (pH monitoring)

Nissen Fundoplication

- **Aim:** prevent reflux, repair diaphragm
- Usually laparoscopic approach
- Mobilise gastric fundus and wrap around lower oesophagus
- Close any diaphragmatic hiatus
- **Complications:**
 - Gas-bloat syn.: inability to belch / vomit
 - Dysphagia if wrap too tight

Hiatus Hernia

Classification

Sliding (80%)

- Gastro-oesophageal junction slides up into chest
- Often assoc. w/ GORD

Rolling (15%)

- Gastro-oesophageal junction remains in abdomen but a bulge of stomach rolls into chest alongside the oesophagus
- LOS remains intact so GORD uncommon
- Can → strangulation

Mixed (5%)

Ix

- **CXR:** gas bubble and fluid level in chest
- **Ba swallow:** diagnostic
- **OGD:** visualises the mucosa but can't exclude hernia
- **24h pH + manometry:** exclude dysmotility or achalasia

Rx

- Lose wt.
- Rx reflux
- Surgery if intractable symptoms despite medical Rx.
 - Should **repair rolling hernia** (even if asymptomatic) as it may strangulate.

Haematemesis Differential

VINTAGE

Varices

Inflammation

- Oesophago-gastro-duodenitis
- PUD: DU is commonest cause

Neoplasia

- Oesophageal or gastric Ca

Trauma

- Mallory-Weiss Tear
 - Mucosal tear due to vomiting
- Boerhaave's Syndrome
 - Full-thickness tear
 - 2cm proximal to LOS

Angiodysplasia + other vascular anomalies

- Angiodysplasia
- HHT
- Dieulafoy lesion: rupture of large arteriole in stomach or other bowel

Generalised bleeding diathesis

- Warfarin, thrombolytics
- CRF

Epistaxis

Rectal Bleeding Differential

DRIPPING Arse

Diverticulae

Rectal

- Haemorrhoids

Infection

- Campylobacter, shigella, E. coli, C. diff, amoebic dysentery

Polyps

Inflammation

- UC, Crohn's

Neoplasia

Gastric-upper bowel bleeding

Angio

- Ischaemic colitis
- HHT
- Angiodysplasia

Upper GI Bleeding

Hx

- Previous bleeds
- Dyspepsia, known ulcers
- Liver disease or oesophageal varices
- Dysphagia, wt. loss
- Drugs and EtOH
- Co-morbidities

o/e

- Signs of CLD
- PR:melaena
- Shock?
 - Cool, clammy, CRT>2s
 - ↓BP (<100) or postural hypotension (>20 drop)
 - ↓ urine output (<30ml/h)
 - Tachycardia
 - ↓GCS

Common Causes

- PUD: 40% (DU commonly)
- Acute erosions / gastritis:20%
- Mallory-Weiss tear: 10%
- Varices: 5%
- Oesophagitis: 5%
- Ca Stomach / oesophagus:<3%

Rockall Score: (Prof T Rockall, St. Mary's)

- Prediction of re-bleeding and mortality
- 40% of re-bleeders die
- Initial score pre-endoscopy
 - Age
 - Shock: BP, pulse
 - Comorbidities
- Final score post-endoscopy
 - Final Dx + evidence of recent haemorrhage
 - Active bleeding
 - Visible vessel
 - Adherent clot
- Initial score ≥3 or final >6 are indications for surgery

Oesophageal Varices

- Portal HTN → dilated veins @ sites of porto-systemic anastomosis: L. gastric and inferior oesophageal veins
- 30-50% of portal HTN will bleed from varices
- Overall mortality 25%: ↑ severity of liver disease.

Causes of portal HTN

- Pre-hepatic: portal vein thrombosis
- Hepatic: cirrhosis (80% in UK), schisto (commonest worldwide), sarcoidosis.
- Post-hepatic: Budd-Chiari, RHF, constrict pericarditis

Bleed Prevention

- 1^o: β-B, repeat endoscopic banding
- 2^o: β-B, repeat banding, TIPSS

Transjugular Intrahepatic Porto-Systemic Shunt (TIPSS)

- IR creates artificial channel between hepatic vein and portal vein → ↓ portal pressure.
- Colapinto needle creates tract through liver parenchyma which is expand using a balloon and maintained by placement of a stent.
- Used prophylactically or acutely if endoscopic therapy fails to control variceal bleeding.

Management

Resuscitate

- Head-down.
- 100% O₂, protect airway
- 2 x 14G cannulae + IV crystalloid infusion up to 1L.
- **Bloods:** FBC, U+E (↑ urea), LFTs, clotting, x-match 6u, ABG, glucose



Blood if remains shocked

- Group specific or O- until X-matched



Variceal Bleed

- Terlipressin IV (splanchnic vasopressor)
- Prophylactic Abx: e.g. ciprofloxacin 1g/24h



Maintenance

- Crystalloid IVI, transfuse if necessary (keep Hb≥10)
- Catheter + consider CVP (aim for >5cm H₂O)
- Correct coagulopathy: vit K, FFP, platelets
- Thiamine if EtOH
- Notify surgeons of severe bleeds



Urgent Endoscopy

Haemostasis of vessel or ulcer:

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

Variceal bleeding:

- 2 of: banding, sclerotherapy, adrenaline, coagulation
- Balloon tamponade → Sengstaken-Blakemore tube
 - Only used if exsanguinating haemorrhage or failure of endoscopic therapy
- TIPSS if bleeding can't be stopped endoscopically



After endoscopy

- Omeprazole IV + continuation PO (↓s re-bleeding)
- Keep NBM for 24h → clear fluids → light diet @ 48h
- Daily bloods: FBC, U+E, LFT, clotting
- H. pylori testing and eradication
- Stop NSAIDs, steroids et.c.

Indications for Surgery

- Re-bleeding
 - Bleeding despite transfusing 6u
 - Uncontrollable bleeding at endoscopy
 - Initial Rockall score ≥3, or final >6.
- Open stomach, find bleeder and underrun vessel.

NB. Avoid 0.9% NS in uncompensated liver disease (worsens ascites). Use blood or albumin for resus and 5% dex for maintenance.

Jaundice

Physiology

- Normal BR = 3-17uM
- Jaundice visible @ 50uM (3 x ULN)
- Hb → unconjugated to BR by splenic macrophages
- uBR → cBR by BR-UDP-glucuronyl transferase in liver
- Secreted in bile then cBR → urobilinogen (colourless)
 - Some urobilinogen is reabsorbed, returned to liver and re-excreted into bile.
 - Some reabsorbed urobilinogen is excreted into the urine
 - The urobilinogen that remains in the GIT is converted to stercobilin (brown) and excreted.

Causes

Pre-Hepatic	Hepatic		Post-Hepatic
	Unconjugated	Conjugated	
Excess BR production <ul style="list-style-type: none"> Haemolytic anaemia Ineffective erythropoiesis <ul style="list-style-type: none"> e.g. thalassaemia 	<p>↓ BR Uptake</p> <ul style="list-style-type: none"> Drugs: contrast, RMP CCF <p>↓ BR Conjugation</p> <ul style="list-style-type: none"> Hypothyroidism Gilbert's (AD) Crigler-Najjar (AR) <p>Neonatal jaundice is both ↑ production + ↓ conjug.</p>	<p>Hepatocellular Dysfunction</p> <ul style="list-style-type: none"> Congen: HH, Wilson's, α1ATD Infection: Hep A/B/C, CMV, EBV Toxin: EtOH, drugs AI: AIH Neoplasia: HCC, mets Vasc: Budd-Chiari <p>↓ Hepatic BR Excretion</p> <ul style="list-style-type: none"> Dubin-Johnson Rotor's 	<p>Obstruction</p> <ul style="list-style-type: none"> Stones Ca pancreas Drugs PBC PSC Biliary atresia Choledochal cyst Cholangio Ca

Drug-induced Jaundice

Mechanism	Drug
Haemolysis	<ul style="list-style-type: none"> Antimalarials (e.g. dapsone)
Hepatitis	<ul style="list-style-type: none"> Paracetamol OD RMP, INH, PZA Valproate Statins Halothane MOAIs
Cholestasis	<ul style="list-style-type: none"> Flucloxa (may be wks after Rx) Co-amoxiclav OCP Sulfonylureas Chlorpromazine, prochlorperazine

Gilbert's

- Auto dom partial UDP-GT deficiency
- 2% of the population
- Jaundice occurs during intercurrent illness
- Dx:** ↑ uBR on fasting, normal LFTs

Crigler-Najjar

- Rare auto rec total UDP-GT deficiency
- Severe neonatal jaundice and kernicterus
- Rx:** liver Tx

Ix

	Pre-Hepatic	Hepatic	Post-Hepatic
Urine	<ul style="list-style-type: none"> No BR (acholuric) ↑ urobilinogen ↑Hb if intravascular haemolysis 	<ul style="list-style-type: none"> ↑BR ↑ urobilinogen 	<ul style="list-style-type: none"> ↑↑ BR No urobilinogen
LFTs	<ul style="list-style-type: none"> ↑ uBR ↑ AST ↑ LDH 	<ul style="list-style-type: none"> ↑ cBR (usually) ↑AST:↑ALT <ul style="list-style-type: none"> > 2 = EtOH < 1 = Viral ↑ GGT (EtOH, obstruction) ↑ ALP Function: ↓ albumin, ↑ PT 	<ul style="list-style-type: none"> ↑↑ cBR ↑ AST, ↑ ALT ↑↑ ALP ↑ GGT
Other	<ul style="list-style-type: none"> FBC and film Coombs Test Hb electrophoresis 	<ul style="list-style-type: none"> FBC: anaemia Anti-SMA, LKM, SLA, ANA α1AT, ferritin, caeruloplasmin Liver biopsy 	<ul style="list-style-type: none"> Abdo US: ducts >6mm ERCP, MRCP Anti-AMA, ANCA, ANA

Liver Failure

Causes

- Cirrhosis (see below)
- **Acute**
 - **Infection:** Hep A/B, CMV, EBV, leptospirosis
 - **Toxin:** EtOH, paracetamol, isoniazid, halothane
 - **Vasc:** Budd-Chiari
 - **Other:** Wilson's, AIH
 - **Obs:** eclampsia, acute fatty liver of pregnancy

Signs

- Jaundice
- Oedema + ascites
- Bruising
- Encephalopathy
 - Aterixis
 - Constructional apraxia (5-pointed star)
- Fetur hepaticus
- Signs of cirrhosis / chronic liver disease

Ix

Blood

- **FBC:** infection, GI bleed, ↓ MCV (EtOH)
- **U+E**
 - ↓U, ↑Cr: hepatorenal syndrome
 - Urea synth in liver ∵ poor test of renal function
- **LFT**
 - AST:ALT > 2 = EtOH
 - AST:ALT < 1 = Viral
 - Albumin: ↓ in chronic liver failure
 - PT: ↑ in acute liver failure
- **Clotting:** ↑INR
- **Glucose**
- **ABG:** metabolic acidosis
- **Cause:** Ferritin, α1AT, caeruloplasmin, Abs, paracetamol levels

Microbiology

- Hep, CMV, EBV serology
- Blood and urine culture
- Ascites MCS + SAAG

Radiology

- CXR
- Abdo US + portal vein duplex

Hepatorenal Syndrome

- Renal failure in pts. ∵ advanced CLF
- Dx of exclusion

Pathophysiology: "Underfill theory"

- Cirrhosis → splanchnic arterial vasodilatation → effective circulatory volume → RAS activation → renal arterial vasoconstriction.
- Persistent underfilling of renal circulation → failure

Classification

- **Type 1:** rapidly progressive deterioration (survival <2wks)
- **Type 2:** steady deterioration (survival ~6mo)

Rx

- IV albumin + splanchnic vasoconstrictors (terlipressin)
- Haemodialysis as supportive Rx
- Liver Tx is Rx of choice

Mx

- Manage in ITU
- Rx underlying cause: e.g. NAC in paracetamol OD
- Good nutrition: e.g. via NGT ∵ high carbs
- Thiamine supplements
- Prophylactic PPIs vs. stress ulcers

Monitoring

- **Fluids:** urinary and central venous catheters
- **Bloods:** daily FBC, U+E, LFT, INR
- **Glucose:** 1-4hrly + 10% dextrose IV 1L/12h

Complications

- **Bleeding:** Vit K, platelets, FFP, blood
- **Sepsis:** tazocin (avoid gent: nephrotoxicity)
- **Ascites:** fluid and salt restrict, spiro, fruse, tap, daily wt
- **Hypoglycaemia:** regular BMs, IV glucose if <2mM
- **Encephalopathy:** avoid sedatives, lactulose ± enemas, rifaximin
- **Seizures:** lorazepam
- **Cerebral oedema:** mannitol

Prescribing in Liver Failure

- **Avoid:** opiates, oral hypoglycaemics, Na-containing IVI
- Warfarin effects ↑
- **Hepatotoxic drugs:** paracetamol, methotrexate, isoniazid, salicylates, tetracycline

Poor Prognostic Factors

- Grade 3/4 hepatic encephalopathy
- Age >40yrs
- Albumin <30g/L
- ↑INR
- Drug-induced liver failure

Liver Transplant

Types

- **Cadaveric:** heart-beating or non-heart beating
- **Live:** right lobe

Kings College Hospital Criteria in Acute Failure

Paracetamol-induced	Non-paracetamol
pH < 7.3 24h after ingestion	PT > 100s
Or all of: PT > 100s Cr > 300uM Grade 3/4 encephalopathy	Or 3 out of 5 of: Drug-induced Age <10 or >40 >1wk from jaundice to encephalopathy PT > 50s BR ≥ 300uM

Cirrhosis

Causes

- Common
 - Chronic EtOH
 - Chronic HCV (and HBV)
 - NAFLD / NASH
- Other
 - **Genetic:** Wilson's, α1ATD, HH, CF
 - **AI:** AH, PBC, PSC
 - **Drugs:** Methotrexate, amiodarone, methyldopa, INH
 - **Neoplasm:** HCC, mets
 - **Vasc:** Budd-Chiari, RHF, constrict. pericarditis

Signs

Hands

- Clubbing (\pm periostitis)
- Leuconychia (\downarrow albumin)
- Terry's nails (white proximally, red distally)
- Palmer erythema
- Dupuytren's contracture

Face

- Pallor: ACD
- Xanthelasma: PBC
- Parotid enlargement (esp. \bar{c} EtOH)

Trunk

- Spider naevi (>5, fill from centre)
- Gynaecomastia
- Loss of 2^o sexual hair

Abdo

- Striae
- Hepatomegaly (may be small in late disease)
- Splenomegaly
- Dilated superficial veins (Caput medusa)
- Testicular atrophy

Complications

1. Decompensation → Hepatic Failure

- Jaundice (conjugated)
- Encephalopathy
- Hypoalbuminaemia → oedema + ascites
- Coagulopathy → bruising
- Hypoglycaemia

2. SBP

3. Portal Hypertension: SAVE

- Splenomegaly
- Ascites
- Varices
 - Oesophageal varices (90% of cirrhotics)
 - Caput medusa
 - Worsens existing piles
- Encephalopathy

4. ↑ risk of HCC

Ix

Bloods

- FBC: \downarrow WCC and \downarrow platelets indicate hypersplenism
- \uparrow LFTs
- \uparrow INR
- \downarrow Albumin

Find Cause

- **EtOH:** \uparrow MCV, \uparrow GGT
- **NASH:** hyperlipidaemia, \uparrow glucose
- **Infection:** Hep, CMV, EBV serology
- **Genetic:** Ferritin, α1AT, caeruloplasmin (\downarrow in Wilson's)
- **Autoimmune:** Abs (there is lots of cross-over)
 - **AIH:** SMA, SLA, LKM, ANA
 - **PBC:** AMA
 - **PSC:** ANCA, ANA
 - **Ig:** \uparrow IgG – AIH, \uparrow IgM – PBC
- **Ca:** α-fetoprotein

Abdo US + PV Duplex

- Small / large liver
- Focal lesions
- Reversed portal vein flow
- Ascites

Ascitic Tap + MCS

- PMN >250mm³ indicates SBP

Liver biopsy

Mx

General

- Good nutrition
- EtOH abstinence: baclofen helps \downarrow cravings
- Colestyramine for pruritus
- Screening
 - **HCC:** US and AFP
 - Oesophageal varices: endoscopy

Specific

- **HCV:** Interferon-α
- **PBC:** Ursodeoxycholic acid
- **Wilson's:** Penicillamine

Complications

- **Varices:** OGD screening + banding
- **HCC:** US + AFP every 3-6mo

Decompensation

- **Ascites:** fluid and salt restrict, spiro, fruse, tap, daily wt
- **Coagulopathy:** Vit K, platelets, FFP, blood
- **Encephalopathy:** avoid sedatives, lactulose \pm enemas, rifaximin
- **Sepsis / SBP:** tazocin (avoid gent: nephrotoxicity)
- **Hepatorenal syndrome:** IV albumin + terlipressin

Child-Pugh Grading of Cirrhosis

- Predicts risk of bleeding, mortality and need for Tx
- Graded A-C using severity of 5 factors
 - Albumin
 - Bilirubin
 - Clotting
 - Distension: Ascites
 - Encephalopathy
- Score >8 = significant risk of variceal bleeding

Portal Hypertension

Causes

- Pre-hepatic:** portal vein thrombosis (e.g. pancreatitis)
- Hepatic:** cirrhosis (80% in UK), schisto (commonest worldwide), sarcoidosis.
- Post-hepatic:** Budd-Chiari, RHF, constrictive pericarditis, TR

Portosystemic Anastomoses

Effect	Portal	Systemic
Oesophageal varices	Left and short gastric veins	Inf. oesophageal veins
Caput medusae	Peri-umbilical veins	Superficial abdo wall veins
Haemorrhoids (worsened)	Sup. rectal veins	Inf. and mid. Rectal veins

Prominent Abdominal Veins

- A lot more common than caput medusa
- Blood flow down *below the umbilicus*: portal HTN
- Blood flow up *below the umbilicus*: IVC obstruction

Encephalopathy

Pathophysiology

- ↓ hepatic metabolic function
- Diversion of toxins from liver directly into systemic system.
- Ammonia accumulates and pass to brain where astrocytes clear it causing glutamate → glutamine
- ↑ glutamine → osmotic imbalance → cerebral oedema.

Classification

- 1: Confused** – irritable, mild confusion, sleep inversion
- 2: Drowsy** – ↑ disorientated, slurred speech, asterixis
- 3: Stupor** – rousable, incoherence
- 4: Coma** – unrousable, ± extensor plantars

Presentation

- Asterixis, ataxia
- Confusion
- Dysarthria
- Constructional apraxia
- Seizures

Precipitants → HEPATICS

- Haemorrhage: e.g. varices
- Electrolytes: ↓K, ↓Na
- Toxins: diuretics, sedatives, anaesthetics
- Alcohol
- Tumour: HCC
- Infection: SBP, pneumonia, UTI, HDV
- Constipation (commonest cause)
- Sugar (glucose) ↓: e.g. low calorie diet

Ix

- ↑ plasma NH₄

Rx

- Nurse 20° head up
- Correct any precipitants
- Avoid sedatives
- Lactulose** ± PO₄ enemas to ↓ nitrogen-forming bowel bacteria → 2-4 soft stools/d
- Consider rifaximin PO to kill intestinal microflora

Sequelae: SAVE

- Splenomegaly
- Ascites
- Varices
- Encephalopathy

Ascites

Pathophysiology

- Back-pressure → fluid exudation
- ↓ effective circulating volume → RAS activation
- (In cirrhosis: ↓ albumin → ↓ plasma oncotic pressure and aldosterone metabolism impaired)

Symptoms

- Distension → abdominal discomfort and anorexia
- Dyspnoea
- ↓ venous return

Differential: Serum Ascites Albumin Gradient (SAGG)

- SAAG ≥1.1g/dL = Portal HTN** (97% accuracy)
 - Pre-, hepatic and post
 - Cirrhosis in 80%
- SAAG <1.1g/dL = Other Causes**
 - Neoplasia: peritoneal or visceral (e.g. ovarian)
 - Inflammation: e.g. pancreatitis
 - Nephrotic Syndrome
 - Infection: TB peritonitis

Ix

- Bloods:** FBC, U+E, LFTs, INR, chronic hepatitis screen
- US:** confirm ascites, liver echogenicity, PV duplex
- Ascitic tap**
 - MCS and AFB
 - Cytology
 - Chemistry: albumin, LDH, glucose, protein
 - SAAG = serum albumin – ascites albumin
- Liver biopsy**

Rx

- Daily wt. aiming for ≤0.5kg/d reduction
- Fluid restrict <1.5L/d and low Na diet
- Spironolactone + furosemide (if response poor)
- Therapeutic paracentesis & albumin infusion (100ml 20% albumin /L drained)
 - Respiratory compromise
 - Pain / discomfort
 - Renal impairment
- Refractory: TIPSS

SBP

- Pt. & ascites and peritonitis abdomen
- E. coli, Klebsiella, Streps
- Complicated by hepatorenal syn. in 30%
- Ix:** ascitic PMN > 250mm³ + MC+S
- Rx:** Tazocin or cefotaxime until sensitivities known
- Prophylaxis:** high recurrence ∴ cipro long-term

Splenomegaly

- Splenic congestion
- Hypersplenism: ↓ WCC, ↓ plts

Alcoholism

Effects

Hepatic

- Fatty liver → hepatitis → cirrhosis
- AST:ALT >2, ↑ GGT

GIT

- Gastritis, erosions
- PUD
- Varices
- Pancreatitis
- Carcinoma

CNS

- Poor memory / cognition
- Peripheral polyneuropathy (mainly sensory)
- **Wernicke's encephalopathy**
 - Confusion
 - Ophthalmoplegia (nystagmus, LR palsy)
 - Ataxia
- Korsakoff's: amnesia → confabulation
- Fits, falls

Heart

- Arrhythmias: e.g. AF
- Dilated cardiomyopathy
- ↑BP

Blood

- ↑ MCV
- Folate deficiency → anaemia

Dx: CAGE

- Cut down?
- Annoyed by people's criticisms
- Guilty about drinking
- Eye opener?

Withdrawal

- 10-72h after last drink
- Consider in new ward pt ($\leq 3d$) \bar{c} acute confusion
- **Signs**
 - ↑HR, ↓BP, tremor
 - Confusion, fits, hallucinations: esp formication (DTs)
- **Rx**
 - Tapering regimen of chlordiazepoxide PO / lorazepam IM
 - Thiamine

Mx

- Group therapy or self-help (e.g. AA)
- Baclofen: ↓ cravings
- Acamprosate: ↓ cravings
- Disulfiram: aversion therapy

Alcoholic Hepatitis

Presentation

- Anorexia
- D/V
- Tender hepatomegaly
- Ascites
- Severe: Jaundice, bleeding, encephalopathy

Ix

- **Bloods:** ↑MCV, ↑GGT, AST:ALT>2
- Ascitic tap
- Abdo US + PV duplex

Rx

- Stop EtOH
- Rx withdrawal
- High dose B vitamins: Pabrinex
- Optimise nutrition
- Daily wt., LFT, U+E, INR
- Mx complications of failure

Prognosis

- Maddrey score predicts mortality
 - Mild: 0-5% 30d mortality
 - Severe: 50% 30d mortality
 - 1yr after admission: 40% mortality

Viral Hepatitis

Types

Type	Spread	Cause
A	FO	Seafood, especially abroad
B	IV	Blood, body fluids, babies (vertical)
C	IV	Mainly blood. Less vertical cf. HCV
D	IV	Dependent on prior HBV infection
E	FO	Developing world

Presentation

Prodromal Phase

- Seen particularly in HAV and BV
- Flu-like, malaise, arthralgia, nausea
- Distaste for cigarettes in Hep A

Icteric Phase

- Acute jaundice in A>B>C (99, 75 and 25%)
- Hepatitis
 - Abdo pain
 - Hepatomegaly
 - Cholestasis: dark urine, pale stools
- Extrahepatic features due to complexes (esp. Hep B)
 - Urticaria or vasculitic rash
 - Cryoglobulinaemia
 - PAN
 - GN
 - Arthritis

Chronic Phase

- Mainly HCV and childhood HBV
- Cirrhosis → ↑ risk of HCC

Hep B

- Carrier:** 10%
 - HBsAg +ve > 6mo
- Chronic hepatitis:** 10%
- Cirrhosis:** 5%

Hep C

- Carrier:** 80%
 - HCV RNA+ve >6mo
- Chronic hepatitis:** 80%
- Cirrhosis:** 20%

Ix

- FBC, LFTs, clotting
- Hep A/B/C serology

Rx

- Supportive**
 - No EtOH
 - Avoid hepatotoxic drugs (e.g. aspirin)
- Anti-viral**
 - Indicated in chronic disease
 - HBV:** PEGinterferon
 - HCV:** PEGinterferon + ribavarin
 - Seroconversion: HBV – 40%, HCV – 10%

Non-alcoholic Fatty Liver Disease (NAFLD)

- Cryptogenic cause of hepatitis and cirrhosis assoc. Č insulin resistance and the metabolic syndrome.
- Non-alcoholic steatohepatitis (NASH) is most extreme form and → cirrhosis in 10%

Risk Factors

- Obesity
- HTN
- T2DM
- Hyperlipidaemia

Presentation

- Mostly asymptomatic
- Hepatomegaly and RUQ discomfort may be present.

Metabolic Syndrome

- Central obesity (\uparrow waist circumference) and two of:
 - ↑ Triglycerides
 - ↓ HDL
 - HTN
 - Hyperglycaemia: DM, IGT, IFG

Ix

- BMI
- Glucose, fasting lipids
- \uparrow transaminases: AST:ALT <1
- Liver biopsy

Mx

- Lose wt.
- Control HTN, DM and lipids

Budd-Chiari Syndrome

- Hepatic vein obstruction → ischaemia and hepatocyte damage → liver failure or insidious cirrhosis.

Causes

- Hypercoagulable states:** myeloproliferative disorders (PV = commonest cause), PNH, anti-phospholipid, OCP
- Local Tumour:** HCC
- Congenital:** membranous obstruction of IVC

Presentation

- RUQ pain:** stretching of Glisson's capsule
- Hepatomegaly**
- Ascites:** SAAG ≥ 1.1 g/dL
- Jaundice (and other features of liver failure)

Ix

- Bloods:** FBC, clotting, LFTs
- US** + hepatic vein Doppler
- Ascitic tap:** $\uparrow\uparrow$ protein (>2.5 g/dL) Č \uparrow SAAG (≥ 1.1 g/dL)
- Other:** JAK2 mutation analysis, RBC CD55 and CD59

Rx

- Anticoagulate** unless there are varices
- Ascites:** fluid and salt restrict, spiro, fruse, tap, daily wt
- Other options:** thrombolysis, angioplasty, TIPSS
- Transplant if fulminant hepatic failure or cirrhosis
- Rx underlying cause

Hereditary Haemochromatosis

Epidemiology

- Prevalence: 1/3000, 10% are carriers.
- Age of onset: 40-60yrs (women later due to menses)
- Genetics: AR, HFE gene (High FE) on Chr6 (C282Y)

Pathophysiology

- Inherited, multisystem disorder resulting from abnormal iron metabolism.
- ↑ intestinal Fe absorption (↑ enterocyte DMT + ↓ hepatocyte hepcidin) → deposition in multiple organs.

Clinical Features: iron MEALS

Myocardial

- Dilated cardiomyopathy
- Arrhythmias

Endocrine

- Pancreas: DM
- Pituitary: hypogonadism → amenorrhoea, infertility
- Parathyroid: hypocalcaemia, osteoporosis

Arthritis

- 2nd and 3rd MCP joints, knees and shoulders

Liver

- Chronic liver disease → cirrhosis → HCC
- Hepatomegaly

Skin

- Slate grey discolouration

Ix

- **Bloods:** ↑LFT, ↑ferritin, ↑Fe, ↓TIBC, glucose, genotype
- **X-ray:** chondrocalcinosis
- **ECG, ECHO**
- **Liver biopsy:** Pearl's stain to quantify Fe and severity
- **MRI:** can estimate iron loading

Rx

- **Iron removal**
 - Venesection: aim for Hct <0.5
 - Desferrioxamine is 2nd line
- **General**
 - Monitor DM
 - Low Fe diet
- **Screening**
 - Se ferritin and genotype
 - Screen 1st degree relatives
- Transplant in cirrhosis

Prognosis

- Venesection returns life expectancy to normal if non-cirrhotic and non-diabetic.
- Cirrhotic patients have >10% chance of HCC

α1-Antitrypsin Deficiency

Epidemiology

- Prevalence: 1/4000, 10% are carriers
- Genetics: AR, Chr 14
 - Homozygotes have PiZZ phenotype

Pathophysiology

- α1AT is a serpin involved in control of the inflammatory cascade by inhibiting neutrophil elastase.
- α1AT is synthesised in the liver and comprises 90% se α1-globulin on electrophoresis.

Presentation

- Variable presentation
 - Neonatal and childhood hepatitis
 - 15% of adults develop cirrhosis by 50yrs
 - 75% of adults have emphysema (esp. smokers)

Ix

- **Blood:** ↓ se α1AT levels
- **Liver biopsy:** PAS+ve, diastase-resistant globules
- **CXR:** emphysematous changes
- **Spirometry:** obstructive defect
- **Prenatal Dx:** possible by CVS

Mx

- Mostly supportive for pulmonary and hepatic complications.
- Quit smoking
- Can consider α1AT therapy from pooled donors.

Wilson's Disease

Epidemiology

- **Prevalence:** 3/100,000
- **Age:** presents between childhood and 30 (never >56)
- **Genetics:** AR, ATP7B gene on Chr 13

Pathophysiology

- Mutation of Cu transporting ATPase
- Impaired hepatocyte incorporation of Cu into caeruloplasmin and excretion into bile.
- Cu accumulation in liver and, later, other organs

Clinical Features: CLANKAH

Cornea

- Kayser-Fleischer rings (70%, may need slit-lamp)

Liver Disease

- Children usually present w/ acute hepatitis.
- Fulminant necrosis may occur
- → cirrhosis

Arthritis

- Chondrocalcinosis
- Osteoporosis

Neurology

- **Parkinsonism:** bradykinesia, tremor, chorea, tics
- Spasticity, dysarthria, dysphagia
- Ataxia
- Depression, dementia, psychosis

Kidney

- Fanconi's syn. (T2 RTA) → osteomalacia

Abortions

Haemolytic anaemia

- Coombs' negative

Ix

- **Bloods:** ↓Cu, ↓caeruloplasmin

NB. Caeruloplasmin is an acute-phase protein and may be high during infection. It may also be low protein-deficient states: nephrotic syndrome, malabsorption

- ↑ 24h urinary Cu
- **Liver biopsy:** ↑ hepatic Cu
- **MRI:** basal-ganglia degeneration

Rx

- **Diet:** avoid high Cu foods: liver, chocolate, nuts
- **Penicillamine lifelong** (Cu chelator)
 - SE: nausea, rash, ↓WCC, ↓Hb, ↓plts, lupus, haematuria
 - Monitor FBC and urinary Cu excretion
- Liver Tx if severe liver disease
- Screen siblings

Autoimmune Hepatitis

Pathophysiology

- Inflammatory disease of unknown cause characterised by Abs directed vs. hepatocyte surface antigens
- Predominantly young and middle-aged women
- Classified according to Abs
 - **T1:** Adult, SMA+ (80%), ANA+ (10%), ↑IgG
 - **T2:** Young, LKM+
 - **T3:** Adult, SLA+

Presentation

- **Teens and early 20s (25%)**
 - **Constitutional:** fatigue, fever, malaise
 - **Cushingoid:** hirsute, acne, striae
 - **Hepatitis**
 - HSM
 - Fever
 - Amenorrhoea
 - Polyarthritis
 - Pulmonary infiltration
 - Pleurisy
- **Post-/peri-menopausal**
 - Present insidiously w/ chronic liver disease

Associated Diseases

- Autoimmune thyroiditis
- DM
- Pernicious anaemia
- PSC
- UC
- GN
- AIHA (Coombs +ve)

Ix

- ↑LFTs
- ↑IgG
- Auto Abs: SMA, LKM, SLA, ANA
- ↓WCC and ↓plts = hypersplenism
- Liver biopsy

Mx

- **Immunosuppression**
 - **Prednisolone**
 - Azathioprine as steroid-sparer
- Liver transplant (disease may recur)

Prognosis

- Remission in 80% of patients
- 10yr survival 80%

Primary Biliary Cirrhosis

Epidemiology

- Prev: ≤4/100,000
- Sex: F>>M = 9:1
- Age: 50s

Pathology

- **Intrahepatic** bile duct destruction by chronic granulomatous inflammation → cirrhosis

Presentation: PPBCCS

- Often asymptomatic and Dx incidentally (↑ALP)
- Jaundice occurs late
- Pruritus and fatigue
- Pigmentation of face
- Bones: osteoporosis, osteomalacia (↓ vit D)
- Big organs: HSM
- Cirrhosis and coagulopathy (↓ vit K)
- Cholesterol ↑: xanthelasma, xanthomata
- Steatorrhoea

Associated Diseases

- Thyroid disease
- RA, Sjogrens, scleroderma
- Coeliac disease
- RTA
- Membranous GN

Ix

- **LFTs:** ↑↑ALP, ↑↑GGT, ↑AST/ALT
 - Late: ↑BR, ↑PT, ↓albumin
- **Abs:** AMA+ (98%)
- ↑IgM
- ↑ cholesterol
- ± ↑ TSH
- US to exclude extra-hepatic cholestasis
- **Liver biopsy:** non-caseating granulomatous inflam

Rx

- **Symptomatic**
 - **Pruritus:** colestyramine, naltrexone
 - **Diarrhoea:** codeine phosphate
 - **Osteoporosis:** bisphosphonates
- **Specific**
 - **ADEK vitamins**
 - **Ursodeoxycholic acid:** ↓LFTs but no effect on mortality or need for transplant
- **Liver transplant**
 - End-stage disease or intractable pruritus
 - Recurrence occurs in ~20% but doesn't usually → graft failure.

Prognosis

- Once jaundice develops survival is <2yrs

Primary Sclerosing Cholangitis

Pathophysiology

- Inflammation, fibrosis and strictures and **intra- and extra-hepatic** ducts.
- Chronic biliary obstruction → 2^o biliary cirrhosis → liver failure

Epidemiology

- Age: 30-50yrs
- Sex: M>F = 2:1

Presentation

- May be asymptomatic and Dx incidentally (↑ALP)

Symptoms

- Jaundice
- Pruritus and fatigue
- Abdo pain

Signs

- Jaundice: dark urine, pale stools
- HSM

Complications

- Bacterial cholangitis
- ↑ Cholangiocarcinoma
- ↑ CRC

Associated Diseases

- **UC**
 - 3% of those w/ UC have PSC
 - 80-100% of those w/ PSC have UC/Crohn's
- Crohn's (much rarer)
- AIH
- HIV

Ix

- **LFTs:** ↑ALP initially, then ↑BR
- **Abs:** pANCA (80%), ANA and SMA may be +ve
- **ERCP/MRCP:** "beaded" appearance of ducts
- **Biopsy:** fibrous, obliterative cholangitis

Rx

- No curative medical therapy: transplant needed
- **Symptomatic**
 - **Pruritus:** colestyramine, naltrexone
 - **Diarrhoea:** codeine phosphate
- **Specific**
 - **ADEK vitamins**
 - Ursodeoxycholic acid improves cholestasis only
 - Abx for cholangitis
 - Endoscopic stenting for dominant strictures
- **Screening**
 - **Cholangiocarcinoma:** US + Ca19-9
 - **CRC:** colonoscopy
- **Transplant**
 - Recurrence occurs in 30%

Liver Tumours

Pathology

- 90% of liver tumours are 2° metastases
 - 1° in men: stomach, lung, colon
 - 1° in women: breast, colon, stomach, uterus
 - Less common: pancreas, leukaemia, lymphoma
- 90% of primary tumours are HCC.
- Benign tumours: haemangiomas, adenomas, cysts

Symptoms

- Benign tumours are usually asymptomatic
- Systemic: fever, malaise, wt. loss, anorexia
- RUQ pain: stretching of Glisson's capsule
- Jaundice is often late, except in cholangiocarcinoma
- May rupture → intraperitoneal haemorrhage

Signs

- Hepatomegaly: smooth or hard and irregular
- Signs of chronic liver disease
- Abdominal mass
- Hepatic bruit (HCC)

Ix

- Bloods: LFTs, hepatitis serology, AFP
- Imaging:
 - US or CT / MRI ± guided diagnostic biopsy
 - ERCP + biopsy in suspected cholangiocarcinoma
- Biopsy (seeding may occur along tract)
- Find primary: e.g. colonoscopy, mammography

Liver Mets

- Rx and prognosis vary by type and extent of 1°
- Small, solitary CRC mets may be resectable
- Advanced disease ∴ prognosis: < 6mo

HCC

- Rare in West, common in China and sub-Saharan Africa

Causes

- Viral hepatitis
- Cirrhosis: EtOH, HH, PBC
- Aflatoxins (produced by Aspergillus)

Mx

- Resection of solitary tumours improves prognosis (13 → 59%), but 50% have recurrence.
- Also: chemo, percutaneous ablation and embolization

Cholangiocarcinoma

- Biliary tree malignancy (10% of liver 1° tumours)

Causes

- Flukes (Clonorchis)
- PSC
- Congenital biliary cysts
- UC

Presentation

- Fever, malaise
- Abdominal pain, ascites, jaundice
- ↑BR, ↑ALP

Mx

- 30% resectable
- Palliative stenting: percutaneous or ERCP

Liver Transplant in CLD

Types

- Cadaveric: heart-beating or non-heart beating
- Live: right lobe

Indications

- Advanced cirrhosis
- HCC

Contraindications

- Extra-hepatic malignancy
- Severe cardiorespiratory disease
- Systemic sepsis
- HIV infection
- Non-compliance to drug therapy

Post-op

- 12-24h on ITU
- Immunosuppression
 - Ciclosporin / Tacrolimus +
 - Azathioprine / Mycophenolate Mofetil +
 - Prednisolone

Complications

- Acute rejection (T-cell mediated)
 - 50% @ 5-10 days
 - Pyrexia, tender hepatomegaly
 - ↑ or change immunosuppressants
- Sepsis
- Hepatic artery thrombosis
- CMV infection
- Chronic rejection (6-9mo): shrinking bile ducts
- Disease recurrence (e.g. HBV)

Prognosis

- Depends on disease aetiology
- 60-90% 5ys

Inflammatory Bowel Disease: Pathology and Presentation

Epidemiology

	UC	Crohn's
Prev	100-200 /100,000	50-100 /100,000
Age	30s	20s
Sex		F>M (just)
Aet	Concordance = 10% Smoking protective TH2-mediated	Concordance = 70% Smoking ↑ risk TH1/TH17-mediated

Pathology

	UC	Crohn's
Macroscopic		
Location	Rectum + colon ± backwash ileitis	Mouth to anus esp. terminal ileum
Distribution	Contiguous	Skip lesions
Strictures	No	Yes
Microscopic		
Inflammation	Mucosal Crypt Abscesses	Transmural
Ulceration	Shallow, broad	Deep, thin, serpiginous → cobblestone mucosa
Fibrosis	None	Marked
Granulomas	None	Present
Pseudopolyps	Marked	Minimal
Fistulae	No	Yes

Presentation

	UC	Crohn's
Symptoms		
Systemic		
Abdominal	<ul style="list-style-type: none"> Diarrhoea Blood ± mucus PR Abdominal discomfort Tenesmus, faecal urgency 	<ul style="list-style-type: none"> Diarrhoea (not usually bloody) Abdominal pain Wt. loss
Signs		
Abdominal	<ul style="list-style-type: none"> Fever Tender, distended abdomen 	<ul style="list-style-type: none"> Aphthous ulcers, glossitis Abdominal tenderness RIF mass Perianal abscesses, fistulae, tags Anal / rectal strictures
Extra-abdominal	<p>Skin</p> <ul style="list-style-type: none"> Clubbing Erythema nodosum Pyoderma gang (esp. UC) <p>Eyes</p> <ul style="list-style-type: none"> Iritis Episcleritis Conjunctivitis 	<p>Joints</p> <ul style="list-style-type: none"> Arthritis (non-deforming, asymm) Sacroiliitis Ank spond <p>HPB</p> <ul style="list-style-type: none"> PSC + cholangiocarcinoma (esp. UC) Gallstones (esp. Crohn's) Fatty liver <p>Other</p> <ul style="list-style-type: none"> Amyloidosis Oxalate renal stones (esp. Crohns)
Complications	<ul style="list-style-type: none"> Toxic megacolon <ul style="list-style-type: none"> Diameter >6cm Risk of perforation Bleeding Malignancy <ul style="list-style-type: none"> CRC in 15% c pancolitis for 20yrs Cholangiocarcinoma Strictures → obstruction Venous thrombosis 	<ul style="list-style-type: none"> Fistulae <ul style="list-style-type: none"> Enter-enteric/colonic → diarrhoea Enterovesical → frequency, UTI Enterovaginal Perianal → “pepperpot” anus Strictures → obstruction Abscesses <ul style="list-style-type: none"> Abdominal Anorectal Malabsorption <ul style="list-style-type: none"> Fat → Steatorrhoea, gallstones B12 → megaloblastic anaemia Vit D → osteomalacia Protein → oedema Toxic megacolon and Ca may occur (< cf. UC)

Ulcerative Colitis: Management

Ix

- Bloods:**
 - FBC: ↓Hb, ↑WCC
 - LFT: ↓albumin
 - ↑CRP/ESR
 - Blood cultures
- Stool**
 - MCS: exclude Campy, Shigella, Salmonella...
 - CDT: C. diff may complicate or mimic
- Imaging**
 - AXR: megacolon (>6cm), wall thickening
 - CXR: perforation
 - CT
 - Ba / gastrograffin enema
 - Lead-pipe: no haustra
 - Thumbprinting: mucosal thickening
 - Pseudopolyps: regenerating mucosal island
- Ileocolonoscopy + regional biopsy:** Baron Score

Severity

Truelove and Witts Criteria

	Mild	Moderate	Severe
Motions	<4	4-6	>6
PR bleed	small	moderate	large
Temp	Apyrexic	37.1-37.8	>37.8
HR	<70	70-90	>90
Hb	>11	10.5-11	<10.5
ESR	<30		>30

Acute Severe UC

- Resus:** Admit, IV hydration, NBM
- Hydrocortisone:** IV 100mg QDS + PR
- Transfuse if required
- Thromboprophylaxis:** LMWH
- Monitoring**
 - Bloods: FBC, ESR, CRP, U+E
 - Vitals + stool chart
 - Twice daily examination
 - ± AXR

NB. RCTs show no benefit of Abx: not routinely recommended

- May use: megacolon, perforation, uncertain Dx

Acute Complications

- Perforation
- Bleeding
- Toxic megacolon (>6cm)
- VTE

Improvement → oral therapy

- Switch to oral pred + a 5-ASA
- Taper pred after full remission

No Improvement → rescue therapy

- On day 3: stool freq >8 or CRP >45
 - Predicts 85% chance of needing a colectomy during the admission
- Discussion between pt, physician and surgeon
- Medical:** ciclosporin, infliximab or vedolizumab (anti-T cell)
- Surgical**

Inducing Remission in Mild / Mod Disease

- OPD-based

Oral Therapy

- 1st line: 5-ASAs
- 2nd line: prednisolone

Topical Therapy:

 mainly left-sided disease

- Proctitis:** suppositories
- More proximal disease:** enemas or foams
- 5-ASAs ± steroids (prednisolone or budesonide)

Additional Therapy:

 steroid sparing

- Azathioprine or mercaptopurine
- Infliximab: steroid-dependent pts

Maintaining Remission

- 1st line: 5-ASAs PO – sulfasalazine or mesalazine
 - Topical Rx may be used in proctitis
- 2nd line: Azathioprine or 6-mercaptopurine
 - Relapsed on ASA or are steroid-dependent
 - Use 6-mercaptopurine if azathioprine intolerant
- 3rd line: Infliximab / adalimumab

Emergency Surgery

- 20% require surgery at some stage
- 30% UC colitis require surgery w/i 5yrs

Indications

- Toxic megacolon
- Perforation
- Massive haemorrhage
- Failure to respond to medical Rx

Procedures

- Total / subtotal colectomy + end ileostomy ± mucus fistula
- Followed after ~3mo by either
 - Completion proctectomy + ileal-pouch anal anastomosis (IPAA) or end ileostomy
 - Ileorectal anastomosis (IRA)
- Panproctocolectomy + permanent end ileostomy
- Acute colitis op mortality: 7% (30% if perforated)

Elective Surgery

Indications

- Chronic symptoms despite medical therapy
- Carcinoma or high-grade dysplasia

Procedures

- Panproctocolectomy + end ileostomy or IPAA
- Total colectomy + IRA

Surgical Complications

- Abdominal**
 - SBO
 - Anastomotic stricture
 - Pelvic abscess
- Stoma:** retraction, stenosis, prolapse, dermatitis
- Pouch**
 - Pouchitis (50%):** metronidazole + cipro
 - ↓ female fertility
 - Faecal leakage

Crohn's Disease: Management

Ix

- **Bloods:** (top 3 are severity markers)
 - **FBC:** ↓Hb, ↑WCC
 - **LFT:** ↓albumin
 - **↑CRP/ESR**
 - **Haematinics:** Fe, B12, Folate
 - **Blood cultures**
- **Stool**
 - **MCS:** exclude Campy, Shigella, Salmonella...
 - **CDT:** C. diff may complicate or mimic
- **Imaging**
 - **AXR:** obstruction, sacroileitis
 - **CXR:** perforation
 - **MRI**
 - Assess pelvic disease and fistula
 - Assess disease severity
 - **Small bowel follow-through or enteroclysis**
 - **Skip lesions**
 - **Rose-thorn ulcers**
 - **Cobblestoning:** ulceration + mural oedema
 - **String sign of Kantor:** narrow terminal ileum
- **Endoscopy**
 - **Ileocolonoscopy + regional biopsy:** Ix of choice
 - Wireless capsule endoscopy
 - Small bowel enteroscopy

Severe Attack

Assessment

- ↑temp, ↑HR, ↑ESR, ↑CRP, ↑WCC, ↓albumin

Management

- **Resus:** Admit, NBM, IV hydration
- **Hydrocortisone:** IV + PR if rectal disease
- **Abx:** metronidazole PO or IV
- **Thromboprophylaxis:** LMWH
- **Dietician Review**
 - Elemental diet
 - Liquid prep of amino acids, glucose and fatty acids
 - Consider parenteral nutrition
- **Monitoring**
 - Vitals + stool chart
 - Daily examination

Improvement → oral therapy

- Switch to oral pred (40mg/d)

No Improvement → rescue therapy

- Discussion between pt, physician and surgeon
- **Medical:** methotrexate ± infliximab
- **Surgical**

Inducing Remission in Mild / Mod Disease

- OPD treatment
- **Supportive**
 - High fibre diet
 - Vitamin supplements

Oral Therapy

- **1st line**
 - **Ileocaecal:** budesonide
 - **Colitis:** sulfasalazine
- **2nd line:** prednisolone (tapering)
- **3rd line:** methotrexate
- **4th line:** infliximab or adalimumab

Perianal Disease

- Occurs in ~50%
- **Ix:** MRI + EUA
- **Rx**
 - Oral Abx: metronidazole
 - Immunosuppression ± infliximab
 - Local surgery ± seton insertion

Maintaining Remission

- **1st line:** azathioprine or mercaptopurine
- **2nd line:** methotrexate
- **3rd line:** Infliximab / adalimumab

Surgery

- 50-80% need ≥1 operation in their life
- Never curative
- Should be as conservative as possible

Indications

- **Emergency**
 - Failure to respond to medical Rx
 - Intestinal obstruction or perforation
 - Massive haemorrhage
- **Elective**
 - Abscess or fistula
 - Perianal disease
 - Chronic ill health
 - Carcinoma

Procedures

- Limited resection: e.g. ileocaecal
- Strictureplasty
- Defunction distal disease → temporary loop ileostomy

Complications

- Stoma complications
- Enterocutaneous fistulae
- Anastomotic leak or stricture

Short gut

- <1-2m small bowel
- **Features**
 - Steatorrhoea
 - ADEK and B12 malabsorption
 - Bile acid depletion → gallstones
 - Hyperoxaluria → renal stones
- **Rx**
 - Dietician
 - Supplements or TPN
 - Loperamide

Coeliac Disease

Epidemiology

- **Prev:** 0.5 – 1%
- **Age:** Any, bimodal: infancy and 50-60yrs
- **Sex:** F>M
- **Geo:** ↑ in Ireland and N. Africa

Pathophysiology

- HLA-DQ2 (95%) and DQ8
- CD8+ mediated response to gliadin in gluten

Presentation: GLIAD

GI Malabsorption: fatigue, weakness

- Carb
 - N/V/D
 - Abdo distension + colic
 - Flatus
 - Wt. ↓
- Fat
 - Steatorrhoea
 - Hyperoxaluria → renal stones
- Protein
 - Protein-losing enteropathy if severe
- Haematinics
 - ↓ Folate and Fe → anaemia
- Vitamins
 - Vit D and Ca → bone pain, osteoporosis
 - Vit K → petechiae and ↑INR
 - B2 (riboflavin) → angular stomatitis
 - B1 and B6 → polyneuropathy

Lymphoma and Carcinoma

- Enteropathy-associated T-cell lymphoma
- Adenocarcinoma of small bowel
- Other Ca: breast, bladder, breast

Immune Associations

- IgA deficiency
- T1DM
- PBC

Anaemia

- ↑ or ↓ MCV
- Hyposplenism: Howell-Jolly bodies, target cells

Dermatological

- Dermatitis herpetiformis: 15-20%
 - Symmetrical vesicles, extensor surfaces
 - Esp. elbows
 - Very itchy
 - Responds to gluten-free diet or dapsone
 - Biopsy: granular deposition of IgA
- Aphthous ulcers

Ix

- **Bloods:** FBC, LFTs (↓alb), INR, Vit D and bone, red cell folate, serum B12
- **Abs**
 - Anti-endomysial IgA (95% specificity)
 - Anti-TTG IgA
 - Both above ↓ c exclusion diet
 - Anti-gliadin IgG persist c exclusion diet
 - IgA ↑ in most but may have IgA deficiency
- **Stools**
 - Stool cysts and antibody: exclude Giardia
- **OGD and duodenal biopsy**
 - Subtotal villous atrophy
 - Crypt hyperplasia
 - Intra-epithelial lymphocytes

Rx

- Lifelong gluten-free diet
 - **Avoid:** barley, rye, oats, wheat
 - **OK:** Maize, soya, rice
 - Verify diet by endomysial Ab tests
- Pneumovax as hyposplenic
- Dermatitis herpetiformis: dapsone

Malabsorption

Presentation

- Diarrhoea / Steatorrhoea
- Wt. loss
- Lethargy

Causes

- **Common in UK:** Coeliac, Chronic pancreatitis, Crohn's
- **Rarer**
 - ↓Bile: PBC, ileal resection, colestyramine
 - **Pancreatic insufficiency:** Ca, CF, chronic panc
 - **Small bowel:** resection, tropical sprue, metformin
 - **Bacterial overgrowth:** spontaneous, post-op blind loops, DM, PPIs
 - **Infection:** Giardia, Strongyloides, Crypto parvum
 - **Hurry:** post-gastrectomy dumping

Ix

- Coeliac tests
- Stool microscopy
- Faecal elastase
- Hydrogen breath test
- MRI / CT
- ERCP (chronic pancreatitis)
- Small bowel endoscopy

Pancreatic Cancer

Risk Factors: SINED

- Smoking
- Inflammation: chronic pancreatitis
- Nutrition: ↑fat diet
- EtOH
- DM

Pathology

- Mostly ductal adenocarcinoma
- Metastasis early, present late
- 60% head
- 25% body
- 15% tail
- Endocrine tumours are rare

Presentation

- Typically male >60yrs
- **Head:** painless obstructive jaundice
 - C dark urine + pale stools
- **Body / Tail:** epigastric pain
 - Radiates to back, relieved sitting forward
- Anorexia and wt. loss
- Acute pancreatitis
- Sudden onset DM in the elderly

Signs

- Epigastric mass
- Jaundice
- Palpable gallbladder
- Thrombophlebitis migrans (Trousseau Sign)
- Splenomegaly: PV thrombosis → portal HTN
- Ascites

Ix

- **Bloods:** cholestatic LFTs, ↑Ca19-9, ↑Ca
- **Imaging**
 - US: pancreatic mass, dilated ducts, hepatic mets, allows biopsy
 - EUS: better than CT/MRI for staging
- **ERCP**
 - Shows anatomy
 - Allows stenting

Rx

- **Surgery**
 - Fit, no mets, tumour ≤3cm (≤10% of pts)
 - Whipple's pancreateoduodenectomy
 - Post-op chemo delays progression
 - 5ys = 5-14%
- **Palliation**
 - Endoscopic / percutaneous stenting of CBD
 - Palliative bypass surgery
 - Pain relief: may need coeliac plexus block

Prognosis

- Mean survival <6mo
- 5ys = <2%

Chronic Pancreatitis

Causes: AGITS

- Alcohol
- Genetic
 - CF
 - HH
 - Hereditary pancreatitis
- Immune
 - Lymphoplasmacytic sclerosing pancreatitis (↑IgG4)
- Triglycerides ↑
- Structural
 - Obstruction by tumour
 - Pancreas divisum

Presentation

- **Epigastric pain**
 - Bores through to back
 - Relieved by sitting back or hot water bottle → erythema ab igne
 - Exacerbated by fatty food or EtOH
- Steatorrhoea
- Wt. loss
- DM
- Epigastric mass: pseudocyst

Ix

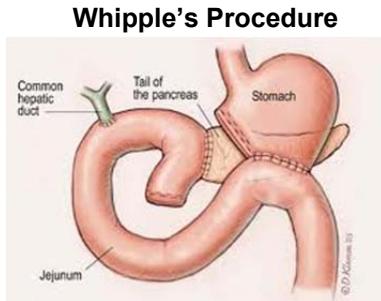
- ↑ glucose
- ↓ faecal elastase
- US: pseudocyst
- AXR: speckled pancreatic calcifications
- CT: pancreatic calcifications

Rx

- **Drugs**
 - Analgesia: may need coeliac plexus block
 - Creon
 - ADEK vitamins
 - DM Rx
- **Diet**
 - No EtOH
 - ↓ fat, ↑ carb
- **Surgery**
 - Ind: unremitting pain, wt. loss
 - Pancreatectomy

Complications

- Pseudocyst
- DM
- Pancreatic Ca
- Biliary obstruction
- Splenic vein thrombosis → splenomegaly



Carcinoid Tumours

Pathology

- Diverse group of neuroendocrine tumours of enterochromaffin cell origin capable of producing 5HT
- May secrete: 5-HT, VIP, gastrin, glucagon, insulin, ACTH
- Carcinoid syndrome suggest bypass of first-pass metabolism and is strongly assoc. w/ metastatic disease.
- 10% part of MEN1
- Sites
 - Appendix: 45%
 - Ileum: 30%
 - Colorectum: 20%
 - Stomach: 10%
 - Elsewhere in GIT and bronchus
- Consider all as malignant

Presentation

Local

- Appendicitis
- Intussusception or obstruction
- Abdominal pain

Carcinoid Syndrome: FIVE HT

- **Flushing:** paroxysmal, upper body ± wheals
- **Intestinal:** diarrhoea
- **Valve fibrosis:** tricuspid regurg and pulmonary stenosis
- **whEEze:** bronchoconstriction
- **Hepatic involvement:** bypassed 1st pass metabolism
- **Tryptophan deficiency** → pellagra (3Ds)

Ix

- ↑ urine 5-hydroxyindoleacetic acid
- ↑ plasma chromogranin A
- CT/MRI: find primary

Rx

- **Symptoms:** octreotide or loperamide
- **Curative**
 - Resection: tumours are v. yellow
 - Give octreotide to avoid carcinoid crisis

Carcinoid Crisis

- Tumour outgrows blood supply or is handled too much → massive mediator release
- Vasodilatation, hypotension, bronchoconstriction, hyperglycaemia
- **Rx:** high-dose octreotide

Prognosis

- Median survival is 5-8yrs (~3yrs if mets present)

Nutritional Deficiencies

Vitamin A → Xerophthalmia

- Dry conjunctivae, develop spots (Bitots spots)
- Corneas become cloudy then ulcerate
- Night blindness → total blindness

Thiamine (B1) → Beri Beri

- **Wet:** heart failure + oedema
- **Dry:** polyneuropathy
- **Wernicke's:** ophthalmoplegia, ataxia, confusion

Niacin / Nicotinic acid (B3) → Pellagra

- Diarrhoea, Dermatitis, Dementia
- Also: neuropathy, depression, ataxia
- **Causes:** dietary, isoniazid, carcinoid syndrome

Pyridoxine (B6)

- Peripheral sensory neuropathy
- **Cause:** PZA

Cyanocobalamin (B12)

- Glossitis → sore tongue
- **Peripheral neuropathy**
 - Paraesthesia
 - Early loss of vibration and proprioception
 - → ataxia
- **SCDC**
 - Dorsal and corticospinal tracts
 - Sensory loss and UMN weakness
- Overall mixed UMN and LMN signs w/ sensory disturbance
 - Extensor plantars + absent knee and ankle jerks

Vitamin C → Scurvy

- Gingivitis
- Bleeding: gums, nose, hair follicles (petechial)
- Muscle pain / weakness
- Oedema
- Corkscrew hairs

Vitamin D → Osteomalacia

- Bone pain
- #s

Vitamin K

- ↓ factors: 2, 7, 9, 10, C and S
- Bruising, petechiae
- Bleeding: e.g. epistaxis, menorrhagia

Nephrology

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Renal Physiology

The Glomerulus

- Epithelial pouch invaginated by capillary tuft
- Semi-permeable filter
 - Endothelium
 - Basement membrane
 - Epithelium
- Mesangial cells are specialised smooth muscle cells that support the glomerulus and regulate blood flow and GFR

Filtration

- Receive 25% of CO (1200ml/min)
- 20% of blood volume is filtered (~250ml/min)
- GBM is -vely charged → retention of anionic proteins such as albumin which are small enough to pass.
- Filtration is key to excretion of waste and remains constant over a range of pressures (80-200mmHg).
- Flow will depend on Na and water reabsorption.

Na Reabsorption

- Main factor determining extracellular volume
- ↓BP and ↓NaCl @ macula densa (DCT) → renin release → aldosterone release → more Na/K pumps.

Water Reabsorption

- Determines ECF osmolality
- ↑osmolality or ↓BP → ADH release

The Nephron

PCT: Reabsorption of filtrate

- 70% of total Na^+ reabsorption
- Reabsorption of amino acids, glucose, cations
- Bicarbonate reabsorbed using carbonic anhydrase

Thick Ascending Limb: Creation of osmolality gradient

- 20% of Na reabsorption
- Na/K/2Cl triple symporter

DCT: pH and Ca reabsorption

- 5% of Na reabsorption
- Apical NaCl co-transporter
- Ca^{2+} reabsorption under control of PTH

Medullary CD: pH and K regulation

- Na reabsorption coupled to K or H excretion
- Basolateral aldosterone-sensitive Na/K pump

Cortical CD: Regulation of water reabsorption

- Water reabsorption controlled by aquaporin-2 channels

Endocrine Function

- Secretion of renin by juxtaglomerular apparatus
- EPO synthesis
- 1 α -hydroxylation of vitamin D (controlled by PTH)

Diuretics

Carbonic Anhydrase Inhibitors (acetazolamide)

- **MOA:** inhibit carbonic anhydrase in PCT
- **Effect:** ↓ HCO_3^- reabsorption → small ↑ Na loss
- **Use:** glaucoma
- **SE:** drowsiness, renal stones, metabolic acidosis

Loop Diuretics (furosemide, bumetanide)

- **MOA:** inhibit Na/K/2Cl symporter in thick ascending limb
- **Effect:** massive NaCl excretion, Ca and K excretion
- **Use:** Rx of oedema – CCF, nephrotic syndrome, hypercalcaemia
- **SE:** hypokalaemic met alkalosis, ototoxic, Hypovolaemia

Thiazide Diuretics (bendroflumethiazide)

- **MOA:** inhibit NaCl co-transporter in DCT
- **Effect:** moderate NaCl excretion, ↑ Ca reabsorption
- **Use:** HTN, ↓ renal stones, mild oedema
- **SE:** ↓K, hyperglycaemia, ↑ urate (Cl in gout)

K-Sparing Diuretics (spironolactone, amiloride)

- **MOA**
 - **Spiro:** aldosterone antagonist
 - **Amiloride:** blocks DCT/CD luminal Na channel
- **Effect:** ↑ Na excretion, ↓K and H excretion
- **Use:** used w/ loop or thiazide diuretics to control K loss, spiro has long-term benefits in aldosteronism (LF, HF)
- **SE:** ↑K, anti-androgenic (e.g. gynaecomastia)

Osmotic Diuretics (mannitol)

- **MOA:** freely filtered and poorly reabsorbed
- **Effect:** ↓ brain volume and ↓ ICP
- **Use:** glaucoma, ↑ICP, rhabdomyolysis
- **SE:** ↓Na, pulmonary oedema, n/v

Urine

Haematuria

Renal

- Congenital: PCK
- Trauma
- Infection: pyelonephritis
- Neoplasm
- Immune: GN, TIN

Extra-renal

- Trauma: stones, catheter
- Infection: cystitis, prostatitis, urethritis
- Neoplasm: bladder, prostate
- Bleeding diathesis
- Drugs: NSAIDs, frusemide, cipro, cephalosporins

NB. False +ve: myoglobin, porphyria

Proteinuria

- 30mg/dL = 1+
- 300mg/dL = 3+
- PCR < 20mg/mM is normal, >300 = nephrotic

Causes

- **Commonest**
 - DM
 - Minimal change
 - Membranous
 - Amyloidosis
 - SLE
- **Other**
 - HTN (inc. PET)
 - ATN
 - TIN
 - UTI
 - Fever, orthostatic

NB. False -ve: Bence-Jones protein

Microalbuminuria

- Albumin 30-300mg/24h
- **Causes:** DM, ↑BP, minimal change GN

Casts

- RBC: glomerular haematuria
- WBC: interstitial nephritis or pyelonephritis
- Tubular: ATN

Differential

Pathology	Urine
Glomerular	Haematuria, proteinuria, red cells / casts
Tubular	White cell casts, small protein, leukocyturia
Pre-renal	Nothing
CRF	Depends on cause

Urea and Creatinine

Creatinine

- Creatinine is synthesised during muscle turnover.
- Freely filtered and small proportion secreted by PCT
- ↑ muscle → ↑ creatinine: age, sex, race
- Plasma Cr doesn't ↑ above normal until 50% ↓ in GFR

Urea

- Produced from ammonia by liver in ornithine cycle
- ↑ C protein meal (e.g. upper GI bleed, supplements)
- ↓ C hepatic impairment
- 10-70% is reabsorbed: depends on urine flow.
- ↓ flow → ↑ urea reabsorption (e.g. in dehydration)

Interpretation

- Isolated ↑ urea = ↓ flow (i.e. hypoperfusion / dehydration)
- ↑ U and ↑ Cr = ↓ filtration (i.e. renal failure)

Creatinine Clearance

- Vol of blood that can be cleared of a substance in 1min
- CrC roughly approximates GFR as it is freely filtered and only a small proportion secreted (~10%)
 - Slightly overestimates GFR
- Requires urine concentration from 24h collection
- Can use radiolabelled EDTA: very rarely done

eGFR

- Modification of Diet in Renal Disease (MDRD) equation
- Serum Cr, sex, age, race
- Obviates need for urine collection

Problems

- Validated for patients C established renal failure:
?applicable to general population.
- Most elderly people are in ≥ stage 3 CRF by eGFR:
may not progress or impinge on their health.
- eGFR is too pessimistic in mild renal impairment

Causes of Renal Disease

Pre-renal

- Shock
- Renal Vascular
 - RAS
 - Toxins: NSAIDs, ACEI
 - Thrombosis
 - Hepatorenal syn.

Renal

- Glomerulonephritis
- Acute Tubular Necrosis
- Interstitial disease

Post-renal

- Diseases of renal papillae, pelvis, ureters, bladder or urethra.
- **SNIPPIN**
 - Stone
 - Neoplasm
 - Inflammation: stricture
 - Prostatic hypertrophy
 - Posterior urethral valves
 - Infection: TB, schisto
 - Neuro: post-op, neuropathy

Presentation of Renal Failure

Uraemia (need GFR <15ml/min)

Symptoms	Signs
Pruritus	Pale, sallow skin
n/v, anorexia, wt. loss	Striae
Lethargy	Pericardial or pleural rub
Confusion	Fits
Restless legs	Coma
Metallic taste	
Paraesthesia: neuropathy	
Bleeding	
Chest pain: serositis	
Hiccoughs	

Protein loss and Na⁺ retention

Symptoms	Signs
Polyuria, polydipsia	Oedema
Oliguria, anuria	↑ JVP
Breathlessness	HTN (or ↓BP)

Acidosis

Symptoms	Signs
Breathlessness	Kussmaul respiration
Confusion	

Hyperkalaemia

Symptoms	Signs
Palpitations	Peaked T waves
Chest pain	Flattened P waves
Weakness	↑ PR interval
	Widened QRS
	Sine-wave pattern → VF

Anaemia

Symptoms	Signs
Breathlessness	Pallor
Lethargy	Tachycardia
Faintness	Flow murmur (ESM @ apex)
Tinnitus	

Vitamin D Deficiency

Symptoms	Signs
Bone pain #s	Osteomalacia - Looser's zones (pseudo#s) - Cupped metaphyses

Urinary Tract Infection

Definitions

- **Bacteriuria:** bacteria in urine, symptomatic or asymptomatic
- **UTI:** symptomatic \bar{c} +ve culture or dipstick
- **Urethral Syndrome:** symptomatic but no bacteriuria

Classification

- **Uncomplicated:** normal GU tract and function
- **Complicated:** abnormal GU tract, outflow obstruction, \downarrow renal function, impaired host defence, virulent organism
- **Recurrent:** further infection \bar{c} new organism
- **Relapse:** further infection \bar{c} same organism

Presentation

Pyelonephritis

- Fever, rigors
- Loin pain and tenderness
- Vomiting
- Oliguria if ARF

Cystitis

- Frequency and urgency
- Polyuria
- Haematuria
- Dysuria
- Suprapubic tenderness
- Foul smelling urine

Prostatitis

- Flu-like symptoms
- Low backache
- Dysuria
- Tender swollen prostate on PR

Sterile Pyuria

- TB
- Treated UTI
- Appendicitis
- Calculi
- TIN
- Papillary necrosis
- Polycystic Kidney
- Chemical cystitis (e.g. cyclophosphamide)

Risk Factors

- Female
- Sex
- Pregnancy
- Menopause
- DM
- Abnormal tract: stone, obstruction, catheter, malformation

Organisms

- **E. coli**
- **Staphylococcus saprophyticus**
- **Proteus** (alkaline urine \rightarrow struvite renal stones)
- **Klebsiella**

Ix

- Dipstick
- MSU for MCS
- **Bloods:** FBC, U+E, blood cultures (if systemic signs)
- **US:** children, men, recurrence, pyelonephritis

Positive Culture

- $>10^4$ CFU/ml pure growth
- $>10^3$ CFU/ml pure growth of E. coli or S. saprophyticus
- $>10^5$ CFU/ml mixed growth \bar{c} one predominant organism

Rx

General

- Drink plenty, urinate often

Cystitis

- Rx for 3-6d
- Trimethoprim 200mg BD
- Nitrofurantoin 50mg QDS (not in RF)
- Cefalexin 500mg BD (good in RF)
- Co-amoxiclav 625mg TDS

Pyelonephritis

- Cefotaxime 1g IV BD for 10d
- No response: Augmentin 1.2g IV TDS + gentamicin

Prevention

- Drink more
- Abx prophylaxis
- ? cranberry juice

Glomerulonephritis

Features

- Group of disorders resulting from glomerular damage
- Can → proteinuria ± haematuria
- Can → AKI or ESRF

Presentations

- Asymptomatic haematuria
- Nephrotic syndrome
- Nephritic syndrome

Causes

- Idiopathic
- Immune: SLE, Goodpastures, vasculitis
- Infection: HBV, HCV, Strep, HIV
- Drugs: penicillamine, gold
- Amyloid

Ix

Blood

- **Basic:** FBC, U+E, ESR
- Complement (C3 and C4)
- **Abs:** ANA, dsDNA, ANCA, GBM
- Serum protein electrophoresis and Ig
- **Infection:** ASOT, HBC and HCV serology

Urine

- Dipstick: proteinuria ± haematuria
- Spot PCR
- MCS
- Bence-Jones protein

Imaging

- CXR: infiltrates (Goodpasture's, Wegener's)
- Renal US ± biopsy

General Mx

- Refer to nephrologist
- Rx HTN aggressively ($\leq 130/80$)
- Include and ACEi / ARA

Asymptomatic Haematuria

Causes

1. IgA Nephropathy
2. Thin BM
3. Alport's

1. IgA Nephropathy / Berger's Disease

- Commonest GN in developed world

Features

- Young male → episodic macroscopic haematuria occurring a few days after URTI.
- Rapid recovery between attacks
- ↑IgA
- Can occasionally → nephritic syndrome

Biopsy: IgA deposition in mesangium

Rx: Steroids or cyclophosphamide if ↓renal function

Prognosis: 20% ESRF after 20yrs

2. Thin BM Disease

- Autosomal dominant
- Commonest cause of asymptomatic haematuria

Features

- Persistent, asymptomatic microscopic haematuria
- V. small risk of ESRF

3. Alport's Syndrome

- 85% X-linked inheritance

Features

- **Haematuria, proteinuria → progressive renal failure**
- Sensorineural deafness
- Lens dislocation and cataracts
- Retinal "flecks"
- Females: haematuria only

Nephritic Syndrome / Acute GN

- Haematuria (macro / micro) + red cell casts
- Proteinuria → oedema (esp. periorbital)
- Hypertension
- Oliguria and progressive renal impairment

Causes

1. Proliferative / post-streptococcal
2. Crescentic / RPGN

1. Proliferative / Post-streptococcal

Features

- Young child develops malaise and nephritic syndrome \bar{C} smoky urine 1-2wks after sore throat or skin infection.
- \uparrow ASOT
- \downarrow C3

Biopsy: IgG and C3 deposition

Rx: Supportive

Prognosis

- 95% of children recover fully
- Minority develop RPGN

2. Crescentic / RPGN

- Most aggressive GN which can → ESRF in days

Type 1: Anti-GBM (Goodpasture's) – 5%

- Ab to NC domain of collagen 4
- Haematuria and haemoptysis
- CXR shows infiltrates
- **Rx:** Plasmapheresis and immunosuppression

Type 2: Immune Complex Deposition – 45%

- Complication of any immune complex deposition
 - Berger's, post-strep, endocarditis, SLE

Type 3: Pauci Immune – 50%

- cANCA: Wegener's
- pANCA: microscopic polyangiitis, Churg-Strauss
- Even if ANCA+ve, may still be idiopathic
 - i.e. no features of systemic vasculitis

Nephrotic Syndrome

- **Proteinuria:** PCR >300mg/mM or >3g/24h
- **Hypoalbuminaemia:** <35g/L
- **Oedema:** periorbital, genital, ascites, peripheral
 - Often intravascularly depleted \bar{C} ↓ JVP (cf. CCF)

Complications

- **Infection:** \downarrow Ig, \downarrow complement activity
- **VTE:** up to 40%
- **Hyperlipidaemia:** \uparrow cholesterol and triglycerides

Ix

- As for GN, check lipids
- **Biopsy**
 - All adults
 - Steroids 1st \bar{C} children: mostly minimal change

Secondary to Systemic Disease

- **DM:** glomerulosclerosis
- **SLE:** membranous
- Amyloidosis

1. Minimal Change Glomerulonephritis

- Commonest cause of nephrotic syndrome in children
- **Assoc.:** URTI
- **Biopsy:** normal light micro, fusion of podocytes on EM
- **Rx:** steroids
- **Prog:** 1% → ESRF

2. Membranous Nephropathy

- 20-30% of adult nephrotic syndrome
- **Associations**
 - **Ca:** lung, colon, breast
 - **AI:** SLE, thyroid disease
 - **Infections:** HBV
 - **Drugs:** Penicillamine, gold
- **Biopsy:** subepithelial immune complex deposits
- **Rx:** immunosuppression if renal function declines
- **Prog:** 40% spontaneous remission

3. FSGS

- Commoner in Afro-Caribs
- Idiopathic or Secondary: VUR, Berger's, SCD, HIV
- **Biopsy:** focal scarring, IgM deposition
- **Rx:** steroids or cyclophosphamide/ciclosporin
- **Prog:** 30-50% → ESRF (may recur in transplants)

5. Membranoproliferative / Mesangiocapillary GN

- Rare
- May → nephrotic (60%) or nephritic (30%) syndrome
- Asooc. \bar{C} HBV, HCV, endocarditis
- **Prog:** 50% → ESRF

Mx

- Monitor U+E, BP, fluid balance, wt.
- Treat underlying cause
- **Symptomatic / Complication Rx:**
 - **Oedema:** salt and fluid restrict + frusemide
 - **Proteinuria:** ACEi / ARA \downarrow proteinuria
 - **Lipids:** Statin
 - **VTE:** Tinzaparin
 - Rx HTN

Acute Kidney Injury

Definition

- Significant decline in renal function over hrs or days manifesting as an abrupt and sustained ↑ in Se U and Cr

Causes (Pre-renal and ATN account for ~80%)

Pre-renal: commonest cause

- Shock or renovascular compromise (e.g. NSAIDs, ACEi)

Renal

- ATN:**
 - Ischaemia: shock, HTN, HUS, TTP
 - Direct nephrotoxins: drugs, contrast, Hb
- Acute TIN:** drug hypersensitivity
- Nephritic syndrome

Post-renal: SNIPPIN

Presentation

- Uraemia / Azotaemia
- Acidosis
- Hyperkalaemia
- Fluid overload
 - Oedema, inc. pulmonary
 - ↑ BP (or ↓)
 - S3 gallop
 - ↑ JVP

Clinical Assessment

1. Acute or chronic?

- Can't tell for sure: Rx as acute
- Chronic features**
 - Hx of comorbidity: DM, HTN
 - Long duration of symptoms
 - Previously abnormal bloods (GP records)

2. Volume depleted?

- Postural hypotension
- ↓ JVP
- ↑ pulse
- Poor skin turgor, dry mucus membranes

3. GU tract obstruction?

- Suprapubic discomfort
- Palpable bladder
- Enlarged prostate
- Catheter
- Complete anuria (rare in ARF)

4. Rare cause?

- Assoc. c proteinuria ± haematuria
- Vasculitis: rash, arthralgia, nosebleed

Ix

- Bloods:** FBC, U+E, LFT, glucose, clotting, Ca, ESR
- ABG:** hypoxia (oedema), acidosis, ↑K⁺
- GN screen:** if cause unclear
- Urine:** dip, MCS, chemistry (U+E, PCR, osmolality, BJP)
- ECG:** hyperkalaemia
- CXR:** pulmonary oedema
- Renal US:** Renal size, hydronephrosis

NB. in pre-renal failure, urine is concentrated and Na is reabsorbed → ↑osmolality, Na <20mM

RIFLE Classification

- 3 grades of AKI and 2 outcomes
- Classification determined by worst criteria

Classification	GFR	UO
Risk	↑Cr x 1.5 ↓GFR >25%	<0.5ml/kg/h x 6h
Injury	↑Cr x 2 ↓GFR >50%	<0.5ml/kg/h x 12h
Failure	↑Cr x 3 ↓GFR >75%	<0.3ml/kg/h x 24h, or anuria x12h
Loss	Persistent ARF = complete LOF >1mo	
ESKD	complete LOF >3mo	

Rx

General

- Identify and Rx pre-renal or post-renal causes
- Urgent US
- Rx exacerbating factors: e.g. sepsis
- Give PPIs
- Stop nephrotoxins: NSAIDs, ACEi, gent, vanc
- Stop metformin if Cr > 150mM

Monitor

- Catheterise and monitor UO
- Consider CVP
- Fluid balance
- Wt.

Hyperkalaemia

- ECG Features (in order)**
 - Peaked T waves
 - Flattened P waves
 - ↑ PR interval
 - Widened QRS
 - Sine-wave pattern → VF
- Mx**
 - 10ml 10% calcium gluconate
 - 100ml 20% glucose + 10u insulin (Actrapid)
 - Salbutamol 5mg nebulizer
 - Calcium resonium 15g PO or 30g PR
 - Haemofiltration (usually needed if anuric)

Pulmonary Oedema

- Sit up and give high-flow O₂
- Morphine 2.5mg IV (± metoclopramide 10mg IV)
- Furosemide 120-250mg IV over 1h
- GTN spray ± ISMN IVI (unless SBP <100)
- If no response consider:
 - CPAP
 - Haemofiltration / haemodialysis ± venesection

Bleeding

- ↑ urea impairs haemostasis
- FFP + plats as needed
- Transfuse to maintain Hb >10

Indications for Acute Dialysis (AEIOU)

- Persistent hyperkalaemia (>7mM)
- Refractory pulmonary oedema
- Symptomatic uraemia: encephalopathy, pericarditis
- Severe metabolic acidosis (pH <7.2)
- Poisoning (e.g. aspirin)

Management of Acute Renal Failure

Common Causes

- Pre-renal: shock (e.g. sepsis, hypovolaemia), HRS
- Renal: ATN, TIN, GN
- Post-renal: Stone, neoplasm, catheter

Presentation

- Usually presents in the context of critical illness
- Uraemia
- Hyperkalaemia
- Acidosis
- Oedema and ↑BP

Ix

- **Bloods:** FBC, U+E, LFT, glucose, clotting, Ca, ESR
- **ABG:** hypoxia (oedema), acidosis, ↑K⁺
- **GN screen:** if cause unclear
- **Urine:** dip, MCS, chemistry (U+E, CRP, osmolality, BJP)
- **ECG:** hyperkalaemia
- **CXR:** pulmonary oedema
- **Renal US:** Renal size, hydronephrosis

Hyperkalaemia

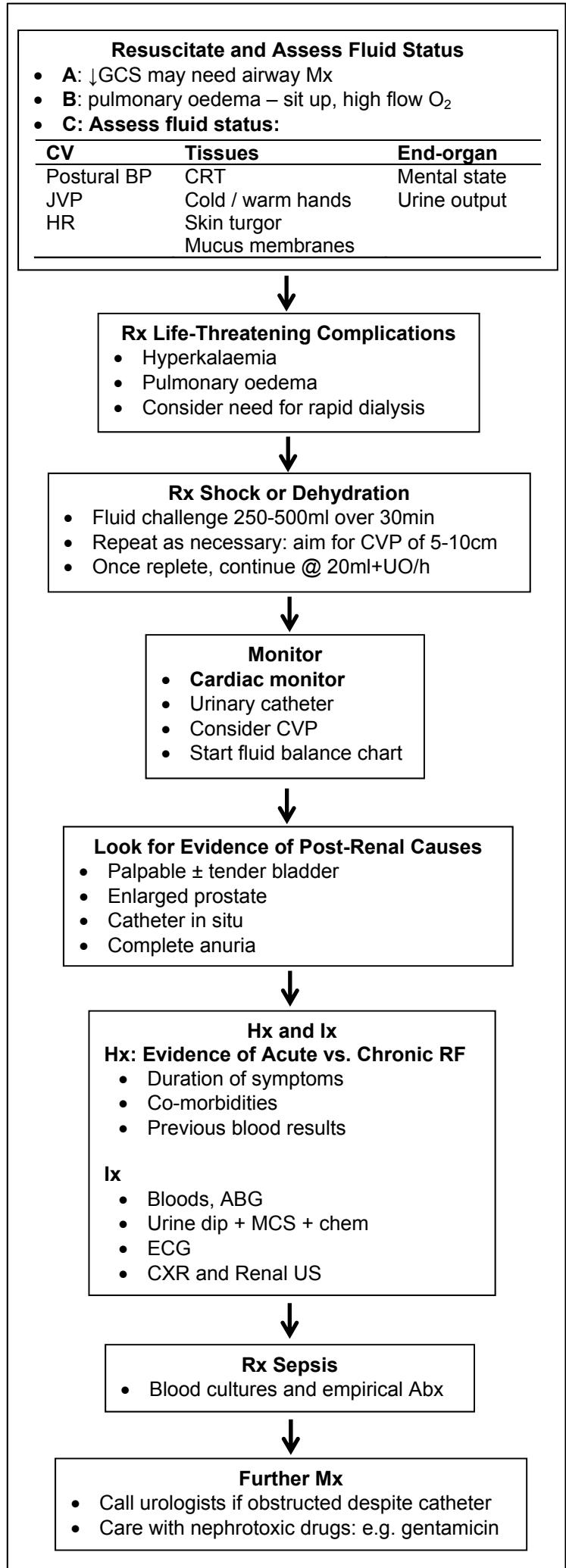
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Indications for Acute Dialysis (AEIOU)

1. Persistent hyperkalaemia (>7mM)
2. Refractory pulmonary oedema
3. Symptomatic uraemia: encephalopathy, pericarditis
4. Severe metabolic acidosis (pH <7.2)
5. Poisoning (e.g. aspirin)



Interstitial Nephritides

Acute Interstitial / Tubulointerstitial Nephritis

- Immune-mediated hypersensitivity → either drugs or other Ag acting as haptans

Causes

- **Drug hypersensitivity in 70%**
 - NSAIDs
 - Abx: Cephs, penicillins, rifampicin, sulphonamide
 - Diuretics: frusemide, thiazides
 - Allopurinol
 - Cimetidine
- **Infections in 15%**
 - Staphs, streps
- **Immune disorders**
 - SLE, Sjogren's

Presentation

- Fever, arthralgia, rashes
- AKI → olig/anuria
- Uveitis

Ix

- ↑IgE, eosinophilia
- Dip: haematuria, proteinuria, sterile pyuria

Rx

- Stop offending drug
- Prednisolone

Prognosis: Most recover renal function

Chronic TIN

- Fibrosis and tubular loss
- Commonly caused by:
 - Reflux and chronic pyelonephritis
 - DM
 - SCD or trait

Analgesic Nephropathy

- Prolonged heavy ingestion of compound analgesics
- Often a Hx of chronic pain: headaches, muscle pain

Features

- Sterile pyuria ± mild proteinuria
- Slowly progressive CRF
- Sloughed papilla can → obstruction and renal colic

Ix: CT w/o contrast (papillary calcifications)

Rx: stop analgesics

Acute Urate Crystal Nephropathy

- AKI due to urate precipitation
- Usually after chemo-induced cell lysis
- **Rx:** hydration, urinary alkalinisation

Nephrocalcinosis

- Diffuse renal parenchymal calcification
- Progressive renal impairment

Causes

- Malignancy
- ↑PTH
- Myeloma
- Sarcoidosis
- Vit D intoxicification
- RTA

Nephrotoxins

- Either directly toxic → ATN
- Or cause hypersensitivity → TIN

Exogenous

- NSAIDs
- Antimicrobials: AVASTA
 - Aminoglycosides
 - Vancomycin
 - Aciclovir
 - Sulphonamides
 - Tetracycline
 - Amphotericin
- ACEi
- Immunosuppressants
 - Ciclosporin
 - Tacrolimus
- Contrast media
- Anaesthetics: enflurane

Endogenous

- Haemoglobin, myoglobin
- Urate
- Ig: e.g. light chains in myeloma

Rhabdomyolysis

Pathogenesis

- Skeletal muscle breakdown → release of:
 - K⁺, PO₄, urate
 - Myoglobin, CK
- ↑K and AKI

Causes

- **Ischaemia:** embolism, surgery
- **Trauma:** immobilisation, crush, burns, seizures, compartment syndrome
- **Toxins:** statins, fibrates, ecstasy, neuroleptics

Clinical

- Muscle pain, swelling
- Red/brown urine
- AKI occurs 10-12h later

Ix

- Dipstick: +ve Hb, -ve RBCs
- Blood: ↑CK, ↑K, ↑PO₄, ↑urate

Rx

- Rx hyperkalaemia
- IV rehydration: 300ml/h
- CVP monitoring if oliguric
- IV NaHCO₃ may be used to alkalinize urine and stabilise a less toxic form of myoglobin.

Chronic Renal Failure

Features

- Kidney damage ≥3mo indicated by ↓ function
- Symptoms usually only occur by stage 4 (GFR<30)
- ESRF is stage 5 or need for RRT

Classification

Stage	GFR
1	>90
2	60-89
3a	45-59
3b	30-44
4	16-29
5	<15

Causes

- Common
 - DM
 - HTN
- Other
 - RAS
 - GN
 - Polycystic disease
 - Drugs: e.g. analgesic nephropathy
 - Pyelonephritis: usually 2° to VUR
 - SLE
 - Myeloma and amyloidosis

Hx

- Past UTI
- HTN, DM
- FH
- DH
- Symptoms

Ix

Blood

- ↓Hb, U+E, ESR, glucose, ↓Ca/↑PO₄, ↑ALP, ↑PTH
- Immune: ANA, dsDNA, ANCA, GBM, C3, C4, Ig, Hep
- Film: burr cells

Urine: dip, MCS, PCR, BJP

Imaging

- CXR: cardiomegaly, pleural/pericardial effusion, oedema
- AXR: calcification from stones
- Renal US
 - Usually small (<9cm)
 - May be large: polycystic, amyloid
- Bone X-rays: renal osteodystrophy (pseudofractures)
- CT KUB: e.g. cortical scarring from pyelonephritis

Renal biopsy: if cause unclear and size normal

Complications: CRF HEALS

- Cardiovascular disease
- Renal osteodystrophy
- Fluid (oedema)
- HTN
- Electrolyte disturbances: K, H
- Anaemia
- Leg restlessness
- Sensory neuropathy

Renal Osteodystrophy

Features

- **Osteoporosis:** ↓ bone density
- **Osteomalacia:** ↓ mineralisation of osteoid (matrix)
- **2°/3° HPT** → osteitis fibrosa cystica
 - Subperiosteal bone resorption
 - Acral osteolysis: short stubby fingers
 - Pepperpot skull
- May get spinal **osteosclerosis** → Rugger Jersey spine
 - Sclerotic vertebral end-plate ☐ lucent centre

Mechanism

- ↓ 1α-hydroxylase → ↓ vit D activation → ↓ Ca → ↑ PTH
- **Phosphate retention** → ↓ Ca and ↑ PTH (directly)
- ↑ PTH → activation of osteoclasts ± osteoblasts
- Also **acidosis** → bone resorption

Mx

General

- Rx reversible causes
- Stop nephrotoxic drugs

Lifestyle

- Exercise
- Healthy wt.
- Stop smoking
- Na, fluid and PO₄ restriction

CV Risk

- Statins (irrespective of lipids)
- Low-dose aspirin
- Rx DM

Hypertension

- Target <140/90 (<130/80 if DM)
- In DM kidney disease give ACEi/ARB (inc. if normal BP)

Oedema

- Frusemide

Bone Disease

- **Phosphate binders:** sevelamer, calcichew
- Vit D analogues: alfacalcidol (1 OH-Vit D₃)
- Ca supplements
- Cinacalcet: Ca mimetic

Anaemia

- Exclude IDA and ACD
- EPO to raise Hb to 11g/dL (higher = thrombosis risk)

Restless Legs

- Clonazepam

Renal Transplant

Treatment of choice for ESRF

Assessment

- Virology status: CMV, HCV, HBV, HIV, VZV, EBV
- CVD
- TB
- ABO and HLA haplotype

Contraindications

- Active infection
- Cancer
- Severe HD or other co-morbidity

Types of Graft

- Cadaveric: brainstem death \bar{c} CV support
- Non-heart beating donor: no active circulation
- Live-related
 - Optimal surgical timing
 - HLA-matched
 - Improved graft survival
- Live unrelated

Immunosuppression

- Pre-op: campath / alemtuzumab (anti-CD52)
- Post-op: prednisolone short-term and tacro/ciclo long-term

Prognosis

- $t_{1/2}$ for cadaveric grafts: 15yrs

Complications

Post-op

- Bleeding
- Graft thrombosis
- Infection
- Urinary leaks

Hyperacute rejection (minutes)

- ABO incompatibility
- Thrombosis and SIRS

Acute Rejection (<6mo)

- \uparrow ing Cr (\pm fever and graft pain)
- Cell-mediated response
- Responsive to immunosuppression

Chronic Rejection (>6mo)

- Interstitial fibrosis + tubular atrophy
- Gradual \uparrow in Cr and proteinuria
- Not responsive to immunosuppression

Ciclosporin / tacrolimus nephrotoxicity

- Acute: reversible afferent arteriole constriction $\rightarrow \downarrow$ GFR
- Chronic: tubular atrophy and fibrosis

\downarrow Immune Function

- \uparrow risk of infection: opportunists, fungi, warts
- \uparrow risk of malignancy: BCC, SCC, lymphoma (EBV)

Cardiovascular Disease

- Hypertension and atherosclerosis

Differential of Rising Cr in Tx pt.

- Rejection
- Obstruction
- ATN
- Drug toxicity

Renal Complications of Systemic Disease

Diabetic Nephropathy

- Causes ~20% of ESRF
- Advanced / ESRF occurs in 40% of T1 and T2 DM

Pathology

- Diabetic nephropathy describes conglomerate of lesions occurring concurrently.
- Hyperglycaemia → renal hyperperfusion → hypertrophy and ↑ renal size
- Hypertrophy and metabolic defects inc. ROS production → **glomerulosclerosis** and **nephron loss**
- **Nephron loss** → RAS activation → **HTN**

Clinically

- Microalbuminuria (30-300mg/d or albumin:creatinine >3)
 - Strong independent RF for CV disease
- Progresses to proteinuria (albuminuria >300mg/d)
- Diabetic retinopathy usually co-exists and HTN is common

Screening

- T2DMs should be screened for microalbuminuria 6moly

Rx

- Good glycaemic control delays onset and progression
- BP target 130/80
- Start ACEi/ARB even if normotensive
- Stop smoking
- Combined kidney pancreas Tx possible in selected pts

Amyloidosis

- Renal involvement usually caused by AL/AA amyloid
- **Features:**
 - Proteinuria
 - Nephrotic syndrome
 - Progressive renal failure
- **Dx**
 - Large kidneys on US
 - Biopsy

Infection

- **GN:** post-strep, HCV, HBV, HIV, SBE/IE, visceral abscess
- **Vasculitis:** HBV, HCV, post-strep
- **TIN:** bacterial pyelonephritis, CMV, HBV, toxo

Malignancy

- **Direct**
 - Renal infiltration: leukaemia, lymphoma
 - Obstruction: pelvic tumour
 - Mets
- **Nephrotoxicity**
 - Toxic chemo
 - Analgesics
 - Tumour lysis syndrome

Hyperparathyroidism

- → hypercalcaemia

Sarcoidosis

- ↑ Ca and TIN

Myeloma

Pathology

- Excess production of monoclonal Ab ± light chains (excreted and detected in 60% as urinary BJP).
- Light chains block tubules and have direct toxic effects → ATN.
- Myeloma also assoc. $\bar{c} \uparrow \uparrow \text{Ca}^{2+}$

Presentation

- ARF / CRF
- Amyloidosis

Rx

- Ensure fluid intake of 3L/d to prevent further impairment
- Dialysis may be required in ARF

Rheumatological Disease

RA

- NSAIDs → ATN
- Penicillamine and gold → membranous GN
- AA amyloidosis occurs in 15%

SLE

- Involves glomerulus in 40-60% → ARF/CRF
- Proteinuria and ↑BP common
- **Rx**
 - Proteinuria: ACEi
 - Aggressive GN: immunosuppression

Diffuse Systemic Sclerosis

- Renal crisis: malignant HTN + ARF
 - Commonest cause of death
- **Rx:** ACEi if ↑BP or renal crisis

Renal Vascular Disease

Hypertension

- HTN can be both the cause and effect of renal damage.
- Renal diseases are commonest causes of 2^o HTN
 - Activation of RAS
 - Retention of Na and water due to ↓ excretion

Renovascular Disease: RAS

Cause

- Atherosclerosis in 80%
- Fibromuscular dysplasia
- Thromboembolism
- External mass compression

Features

- Refractory hypertension
- Worsening renal function after ACEi/ARB
- Flash pulmonary oedema (no LV impairment on echo)

Ix

- US + doppler: small kidney + ↓ flow
- CT/MR angio
- **Renal angiography: gold standard**

Rx

- Rx medical CV risk factors
- Angioplasty and stenting

Haemolytic Uraemic Syndrome (HUS)

- E. coli O157:H7: verotoxin → endothelial dysfunction

Features

- Young children eating undercooked meat (burgers)
- Bloody diarrhoea and abdominal pain precedes:
 - MAHA
 - Thrombocytopenia
 - Renal failure

Ix

- Schistocytes, ↓ plts
- ↓Hb
- Normal clotting

Rx

- Usually resolves spontaneously
- Dialysis or plasma exchange may be needed

Thrombotic Thrombocytopenia Purpura (TTP)

- Genetic or acquired deficiency of ADAMTS13 → giant vWF multimers

Features

- Adult females
- Pentad
 - Fever
 - CNS signs: confusion, seizures
 - MAHA
 - Thrombocytopenia
 - Renal failure

Ix: As HUS

Rx: Plasmapheresis, immunosuppression, splenectomy

Renal Tubular Disease

Renal Tubular Acidosis

- Impaired acid excretion → hyperchloraemic met acidosis
- Both → RAS activation → K⁺ wasting and hypokalaemia

Type 1 (Distal)

- Inability to excrete H⁺, even when acidotic
- May complicate other renal disorders
- **Causes**
 - **Hereditary:** Marfan's, Ehler's Danlos
 - **AI:** Sjogren's, SLE, thyroiditis
 - Drugs
- **Features**
 - Rickets / osteomalacia (bone buffering)
 - Renal stones and UTIs
 - Nephrocalcinosis → ESRF
- **Dx**
 - Failure to acidify urine (pH >5.5) despite acid load

Type 2 (Proximal)

- Defect in HCO₃ reabsorption in PCT
- Tubules can reabsorb some HCO₃ so can acidify urine in systemic acidosis when HCO₃ ↓
- Usually assoc. w/ Fanconi syndrome
- **Dx**
 - Urine will acidify w/ acid load (pH <5.5)

Fanconi Syndrome

- Disturbance of PCT function → generalised impaired reabsorption
 - amino acids, K⁺, HCO₃, phosphate, glucose
- **Causes**
 - Idiopathic
 - **Inherited:** inborn errors, Wilson's
 - **Acquired:** tubule damage (drugs, myeloma...)
- **Features**
 - Polyuria (osmotic diuresis)
 - Hypophosphataemic rickets (Vit D resistant)
 - Acidosis, ↓K

Hereditary Hypokalaemic Tubulopathies

- **Bartter's Syndrome**
 - Blockage of NaCl reabsorption in loop of Henle (as if taking furosemide)
 - Congenital salt wasting → RAS activation → hypokalaemia and metabolic alkalosis
 - Normal BP
- **Gitelman Syndrome**
 - Blockage of NaCl reabsorption in DCT (as if taking thiazides)
 - Congenital salt wasting → RAS activation → hypokalaemia and metabolic alkalosis + hypocalciuria
 - Normal BP

Renal Cystic Diseases

Auto Dom Polycystic Kidney Disease

- Prev: 1:1000
- Age: Adults 40-60yrs
- Genetics
 - PKD1 on Chr16, polycystin 1 (80%): cell-cell and cell-matrix membrane receptor
 - PKD2 on Chr4, polycystin 2: Ca^{2+} channel that interacts with polycystin 1
- Path
 - Large cysts arising from all parts of nephron
 - Progressive decline in renal function
 - 70% ESRF by 70yrs

Presentation: MISSHAPES

- Mass: abdo mass and flank pain
- Infected cyst
- Stones
- SBP ↑
- Haematuria or haemorrhage into cyst
- Aneurysms: berry → SAH
- Polyuria + nocturia
- Extra-renal cysts: liver
- Systolic murmur: mitral valve prolapse

Rx

- General
 - ↑ water intake, ↓ Na, ↓ caffeine (may ↓ cyst formation)
 - Monitor U+E and BP
 - Genetic counselling
 - MRA screen for Berry aneurysms
- Medical
 - Rx HTN aggressively: <130/80 (ACEi best)
 - Rx infections
- Surgical
 - Pain may be helped by laparoscopic cyst removal or nephrectomy.
- ESRF in 70% by 70yrs
 - Dialysis or transplant

Auto Rec Polycystic Kidney Disease

- Prev: 1:40,000
- Infancy
- Renal cysts and congenital hepatic fibrosis

Medullary Sponge Kidney

- Multiple cystic dilatations of the CDs in the medulla
- Typically presents in 20-30s
- Commoner in females
- Often asymptomatic, but predisposes to
 - Hypercalciuria and nephrolithiasis
 - Recurrent UTIs and pyelonephritis
 - Haematuria
- Renal function is usually normal

Tuberous Sclerosis (Bourneville's Disease)

- AD condition → hamartomas in skin, brain, eye, kidney
- Skin: nasolabial adenoma sebaceum, ash-leaf macules, peri-ungual fibromas
- Neuro: ↓IQ, epilepsy
- Renal: cysts, angiomyolipomas

Renal Enlargement Differential: PHONOS

- Polycystic kidneys: ADPKD, ARPKD, TS
- Hypertrophy 2^O to contralateral renal agenesis
- Obstruction (hydronephrosis)
- Neoplasia: RCC, myeloma, amyloidosis
- Occlusion (renal vein thrombosis)
- Systemic: early DM, amyloid

Haematology

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Anaemia Classification and Causes

Low Hb

- Men: <13.5g/dl
- Women: <11.5g/dl

Symptoms

- Fatigue
- Dyspnoea
- Faintness
- Palpitations
- Headache
- Tinnitus

Signs

- Pallor
- Hyperdynamic circulation
 - Tachycardia
 - Flow murmur: apical ESM
 - Cardiac enlargement
- Ankle swelling $\ddot{\text{c}}$ heart failure

Microcytic

- **Haem Defect**
 - IDA
 - ACD
 - Sideroblastic / lead poisoning
- **Globin Defect**
 - Thalassaemia

Normocytic

- Recent blood loss
- Bone marrow failure
- Renal failure
- Early ACD
- Pregnancy (\uparrow plasma volume)

Macrocytic

- **Megaloblastic**
 - Vit B12 or folate deficiency
 - Anti-folate drugs: phenytoin, methotrexate
 - Cytotoxics: hydroxycarbamide
- **Non-megaloblastic**
 - Reticulocytosis
 - Alcohol or liver disease
 - Hypothyroidism
 - Myelodysplasia

Haemolytic Anaemia

\uparrow red cell breakdown

1. Anaemia $\ddot{\text{c}}$ \uparrow MCV + polychromasia = reticulocytosis
2. \uparrow unconjugated bilirubin
3. \uparrow urinary urobilinogen
4. \uparrow se LDH
5. Bile pigment stones

Intravascular

1. Haemoglobinaemia
2. Haemoglobinuria
3. \downarrow se haptoglobins
4. \uparrow urine haemosiderin
5. Methaemalbuminaemia

Extravascular

1. Splenomegaly

Acquired

- **Immune-mediated DAT+ve**
 - AIHA: warm, cold, PCH
 - Drugs: penicillin, quinine, methyldopa
 - Allo-immune: acute transfusion reaction, HDFN
- **PNH**
- **Mechanical:**
 - MAHA: DIC, HUS, TTP
 - Heart valve
- **Infection:** malaria
- **Burns**

Hereditary

- **Enzyme:** G6PD and pyruvate kinase deficiency
- **Membrane:** HS, HE
- **Haemoglobinopathy:** SCD, thalassaemia

Microcytic Anaemia

IDA

Signs

- Koilonychia
- Angular stomatitis / cheilosis
- Post-cricoid Web: Plummer-Vinson

Causes

Mechanism	Examples
↑ Loss	Menorrhagia GI bleeding Hookworms
↓ Intake	Poor diet
Malabsorption	Coeliac Crohn's

Ix

- **Haematinics:** ↓ ferritin, ↑TIBC, ↓ transferrin saturation
- **Film:** Anisocytosis, poikilocytosis, pencil cells
- Upper and lower GI endoscopy

Rx

- Ferrous sulphate 200mg PO TDS
 - SE: GI upset

Sideroblastic Anaemia

- Ineffective erythropoiesis
 - ↑ iron absorption
 - Iron loading in BM → ringed sideroblasts
 - Haemosiderosis: endo, liver and cardiac damage

Causes

- Congenital
- Acquired
 - Myelodysplastic / myeloproliferative disease
 - Drugs: chemo, anti-TB, lead

Ix

- Microcytic anaemia not responsive to oral iron
- ↑ Ferritin, ↑ se Fe, ↔ TIBC

Rx

- Remove cause
- Pyridoxine may help

Thalassaemia

Pathophysiology

- Point mutations (β) / deletions (α) → unbalanced production of globin chains
- → precipitation of unmatched globin
- → membrane damage → haemolysis while still in BM and removal by the spleen

Epidemiology

- Common in Mediterranean and Far East

β Thalassaemia Trait / Heterozygosity

- β / β^+ (↓ production) or β / β^0 (no production)
- Mild anaemia which is usually harmless
- ↓ MCV ("too low for the anaemia"): e.g. <75
- ↑ HbA_2 ($\alpha_2\delta_2$) and ↑HbF ($\alpha_2\gamma_2$)

β Thalassaemia Major

- β^0 / β^0 or β^0 / β^+ or β^+ / β^+
- **Features develop from 3-6mo**
 - Severe anaemia
 - Jaundice
 - FTT
 - Extramedullary erythropoiesis
 - Frontal bossing
 - Maxillary overgrowth
 - HSM
 - Haemochromatosis after 10yrs (transfusions)
- **Ix**
 - ↓Hb, ↓MCV, ↑↑HbF, ↑HbA₂ variable
 - **Film:** Target cells and nucleated RBCs
- **Rx**
 - Life-long transfusions
 - SC desferrioxamine Fe chelation
 - BM transplant may be curative

α Thalassaemia

- **Trait**
 - --/aa or α -/ α -
 - Asymptomatic
 - Hypochromic microcytes
- **HbH Disease**
 - --/- α
 - Moderate anaemia: may need transfusions
 - Haemolysis: HSM, jaundice
- **Hb Barts**
 - --/--
 - Hydrops fetalis → death in utero

Macrocytic Anaemia

Ix

Film

- **B12/Folate**
 - Hypersegmented PMN
 - Oval macrocytes
- **EtOH/Liver**
 - Target cells

Blood

- LFT: mild ↑ bilirubin in B12/folate deficiency
- TFT
- Se B12
- Red cell folate: reflects body stores over 2-3mo

BM biopsy: if cause not revealed by above tests

- Megaloblastic erythropoiesis
- Giant metamyelocytes

Folate Deficiency

Folate

- **Source:** Green veg, nuts, liver
- **Stores:** 4mo
- **Absorption:** proximal jejunum

Causes

Mechanism	Examples
↓ Intake	Poor diet
↑ Demand	Pregnancy Haemolysis Malignancy
Malabsorption	Coeliac Crohn's
Drugs	EtOH Phenytoin Methotrexate

Rx

- Assess for underlying cause
- Give B12 first unless B12 level known to be normal
 - May precipitate or worsen SACD
- Folate 5mg/d PO

B12 Deficiency

Vit B12

- **Source:** meat, fish and dairy (vegans get deficient)
- **Stores:** 4yrs
- **Absorption:** terminal ileum bound to intrinsic factor (released from gastric parietal cells)
- **Role:** DNA and myelin synthesis

Causes

Mechanism	Examples
↓ Intake	Vegan
↓ intrinsic factor	Pernicious anaemia Post-gastrectomy
Terminal ileum	Crohn's Ileal resection Bacterial overgrowth

Features

- **General**
 - Symptoms of anaemia
 - Lemon tinge: pallor + mild jaundice
 - Glossitis (beefy, red tongue)
- **Neuro**
 - Paraesthesia
 - Peripheral neuropathy
 - Optic atrophy
 - SACD

Subacute Combined Degeneration of the Cord

- Usually only caused by pernicious anaemia
- Combined symmetrical dorsal column loss and corticospinal tract loss.
- → distal sensory loss: esp. joint position and vibration
 - → ataxia → wide-gait and +ve Romberg's test
- **Mixed UMN and LMN signs**
 - Spastic paraparesis
 - Brisk knee jerks
 - Absent ankle jerks
 - Upgoing plantars
- Pain and temperature remain intact

Ix

- ↓ WCC and platelets if severe
- Intrinsic factor Abs: specific but lower sensitivity
- Parietal cell Abs: 90% +ve in PA but ↓ specificity

Rx

- Malabsorption → parenteral B12 (hydroxocobalamin)
 - Replenish: 1mg/48h IM
 - Maintain: 1mg IM every 3mo
- Dietary → oral B12 (cyanocobalamin)
- Parenteral B12 reverses neuropathy but not SACD

Pernicious Anaemia

- Autoimmune atrophic gastritis caused by autoAbs vs. parietal cells or IF → achlorhydria and ↓ IF.
- Usually >40yrs, ↑ incidence → blood group A
- Associations:
 - AI: thyroid disease, Vitiligo, Addison's, ↓HPT
 - Ca: 3x risk of gastric adenocarcinoma

Haemolytic Anaemias

AIHA

Warm

- IgG-mediated, bind @ 37°C
- Extravascular haemolysis and spherocytes
- **Ix:** DAT+ve
- **Causes:** idiopathic, SLE, RA, Evan's
- **Rx:** immunosuppression, splenectomy

Cold

- IgM-mediated, bind @ <4°C
- Often fix complement → intravascular haemolysis
- May cause agglutination → acrocyanosis or Raynaud's
- **Ix:** DAT+ve for complement alone
- **Causes:** idiopathic, mycoplasma
- **Rx:** avoid cold, rituximab

Paroxysmal Cold Haemoglobinuria

- Rare: assoc. w/ measles, mumps, chickenpox
- IgG "Donath-Landsteiner" Abs bind RBCs in the cold and → complement-mediated lysis on rewarming

PNH

- Absence of RBC anchor molecule (GPI) → ↓ cell-surface complement degradation proteins → IV lysis
- Affects stem cells and ∴ may also → ↓ plts + ↓ PMN

Features

- Visceral venous thrombosis (hepatic, mesenteric, CNS)
- IV haemolysis and haemoglobinuria

Ix

- Anaemia ± thrombocytopenia ± neutropenia
- FACS: ↓ CD55 and ↓ CD59

Rx

- Chronic disorder ∴ long-term anticoagulation
- Eculizumab (prevents complement MAC formation)

Haemolytic Uraemic Syndrome (HUS)

Features

- E. coli O157:H7 from undercooked meat
- Bloody diarrhoea and abdominal pain precedes:
 - MAHA
 - Thrombocytopenia
 - Renal failure

Ix: schistocytes, ↓ plts, normal clotting

Rx

- Usually resolves spontaneously
- Exchange transfusion or dialysis may be needed

Thrombotic Thrombocytopenia Purpura (TTP)

- Genetic or acquired deficiency of ADAMTS13

Features

- Adult females
- Pentad
 - Fever
 - CNS signs: confusion, seizures
 - MAHA
 - Thrombocytopenia
 - Renal failure

Ix: schistocytes, ↓ plts, normal clotting

Rx: Plasmapheresis, immunosuppression, splenectomy

Hereditary Spherocytosis

- Commonest inherited haemolytic anaemia in N. Europe

Pathophysiology

- Autosomal dominant defect in RBC membrane
- Spherocytes get trapped in spleen → extravascular haemolysis

Features

- Splenomegaly
- Pigment gallstones
- Jaundice

Complications

- Aplastic crisis
- Megaloblastic crisis

Ix

- ↑ osmotic fragility
- Spherocytes
- **DAT-ve**

Rx

- Folate and splenectomy (after childhood)

Hereditary Elliptocytosis

- Autosomal dominant defect → elliptical RBCs
- Most pts. are asymptomatic
- **Rx:** folate, rarely splenectomy

G6PD deficiency

Pathophysiology

- X-linked disorder of pentose phosphate shunt
- ↓ NADPH production → RBC oxidative damage
- Affects mainly Mediterranean and Mid / Far East

Haemolysis Triggers

- Broad (Fava) beans
- Mothballs (naphthalene)
- Infection
- **Drugs:** antimalarials, henna, dapsone, sulphonamides

Ix

- **Film**
 - Irregularly contracted cells
 - Bite cells, ghost cells and blister cells
 - Heinz bodies
- G6PD assay after 8wks (reticulocytes have high G6PD)

Rx

- Treat underlying infection
- Stop and avoid precipitants
- Transfusion may be needed

Pyruvate Kinase Deficiency

- Autosomal recessive defect in ATP synthesis
- → rigid red cells phagocytosed in the spleen
- **Features:** splenomegaly, anaemia ± jaundice
- **Ix:** PK enzyme assay
- **Rx:** often not needed or transfusion ± splenectomy

Sickle Cell Disease

Epidemiology

- Africa, Caribbean's, Middle-East
- UK prevalence = 1/2000

Pathogenesis

- Point mutation in β globin gene: glu \rightarrow val
 - SCA: HbSS
 - Trait: HbAS
- HbS insoluble when deoxygenated \rightarrow sickling
- Sickle cells have \downarrow life-span \rightarrow haemolysis
- Sickle cells get trapped in microvasc \rightarrow thrombosis

Ix

- Hb 6-9, \uparrow retics, \uparrow bilirubin
- Film: sickle cells and target cells
- Hb electrophoresis
 - Dx at birth \bar{c} neonatal screening

Presentation

- Clinical features manifest from 3-6mo due to \downarrow HbF
- Triggers
 - Infection
 - Cold
 - Hypoxia
 - Dehydration
- Splenomegaly: may \rightarrow sequestration crisis
- Infarction: stroke, spleen, AVN, leg ulcers, BM
- Crises: pulmonary, mesenteric, pain
- Kidney disease
- Liver, Lung disease
- Erection
- Dactylitis

Complications

- Sequestration crisis
 - Splenic pooling \rightarrow shock + severe anaemia
- Splenic infarction: atrophy and hyposplenism
- \uparrow infection: osteomyelitis
- Aplastic crisis: parvovirus B19 infection
- Gallstones

Mx Chronic Disease

- Pen V BD + immunisations
- Folate
- Hydroxycarbamide if frequent crises

Mx Acute Crises

General

- Analgesia: opioids IV
- Good hydration
- O₂
- Keep warm

Ix

- FBC, U+E, reticulocytes, cultures
- Urine dip
- CXR

Rx

- Blind Abx: e.g. ceftriaxone
- Transfusion: exchange if severe

Bleeding Diatheses

Coagulation Tests

APTT

- Intrinsic: 12, 11, 9, 8
- Common: 10, 5, 2, 1
- **Increased**
 - Lupus anti-coagulant
 - Haemophilia A or B
 - vWD (carries factor 8)
 - Unfractionated heparin
 - DIC
 - Hepatic failure

PT

- Extrinsic: 7
- Common: 10, 5, 2, 1
- **Increased**
 - Warfarin / Vit K deficiency
 - Hepatic failure
 - DIC

Bleeding Time / PFA-100

- Platelet function
- **Increased**
 - ↓ platelet number or function
 - vWD
 - Aspirin
 - DIC

Thrombin Time

- Fibrinogen function
- **Increased**
 - Quantitative/ qualitative fibrinogen defect
 - DIC, dysfibrinogenaemia
 - Heparin

Clinical Features

Vascular or Platelet Disorder

- Bleeding into skin: petechiae, purpura, ecchymoses
- Bleeding mucus membranes: epistaxis, menorrhagia, gums
- Immediate, prolonged bleeding from cuts

Coagulation Disorder

- Deep bleeding: muscles, joints, tissues
- Delayed but severe bleeding after injury

Vascular Disorders

Congenital

- HHT
- Ehler's Danlos (easy bruising)
- Pseudoxanthoma elasticum

Acquired

- Senile purpura
- Vitamin C deficiency
- Infection: e.g. meningococcus
- Steroids
- Vasculitis: e.g. HSP

Platelet Disorders

Thrombocytopenia

- ↓ production
 - BM failure: aplastic, infiltration, drugs (EtOH, cyto)
 - Megaloblastic anaemia
- ↑ destruction
 - Immune: ITP, SLE, CLL, heparin, viruses
 - Non-immune: DIC, TTP, HUS, PNH, anti-phospholipid
- **Splenic pooling**
 - Portal hypertension
 - SCD

ITP

- Children: commonly post-URTI, self-limiting
- Adults: F>M, long-term
- **Ix:** Anti-platelet Abs present
- **Rx:** conservative, steroids, IVIg, splenectomy

Functional Defects

- **Drugs:** aspirin, clopidogrel
- **2^o:** paraproteinaemias, uraemia
- **Hereditary**
 - Bernard-Soulier: Gplb deficiency
 - Glanzmann's: Gpllb/Illa deficiency

Coagulation Disorders

Acquired

- Severe liver disease
- Anticoagulants
- Vitamin K deficiency

Haemophilia A: F8 Deficiency

- X-linked, affects 1/5000 males
- **Pres:** haemoarthroses, bleeding after surgery/extraction
- **Ix:** ↑APTT, normal PT, ↓F8 assay
- **Mx**
 - Avoid NSAIDs and IM injections
 - Minor bleeds: desmopressin + tranexamic acid
 - Major bleeds: rhF8

Haemophilia B: F9 deficiency

- X-linked, 1/20,000 males

VWD

- Commonest inherited clotting disorder (mostly AD)
- **vWF**
 - Stabilises F8
 - Binds plats via Gplb to damaged endothelium
- **Ix**
 - If mild, APTT and bleeding time may be normal
 - ↑ APTT, ↑ bleeding time, normal plat, ↓ vWF AG
- **Rx:** desmopressin + tranexamic acid

DIC

- ↑PT, ↑APTT, ↑TT, ↓plats, ↓fibrinogen, ↑FDPs
- Schistocytes
- Thrombosis and bleeding
- **Causes:** sepsis, malignancy (esp. APML), trauma, obs
- **Rx:** FFP, plats, heparin

Thrombophilia

Definition

- Coagulopathy predisposing to thrombosis, usually venous.

Inherited

Factor V Leiden / APC resistance

- Protein C deactivates F5 and F8
 - C protein S and thrombomodulin cofactors
- Degradation resistance present in 5% of population
 - Most don't develop thrombosis
- Heterozygotes: 5x \uparrow VTE
- Homozygotes: 50x \uparrow VTE

Prothrombin Gene Mutation

- \uparrow prothrombin levels
- \uparrow thrombosis due to \downarrow fibrinolysis by thrombin-activated fibrinolysis inhibitor

Protein C and S Deficiency

- Heterozygotes for either have \uparrow risk of thrombosis.
 - Skin necrosis occurs – esp. C warfarin
- Heterozygotes \rightarrow neonatal purpura fulminans

Antithrombin III Deficiency

- AT is heparin co-factor \rightarrow thrombin inhibition
- Deficiency affects 1/500
- Heterozygotes have $\uparrow\uparrow$ thrombosis risk
- Homozygosity is incompatible C life

Acquired

- Progesterones in OCPs
- **Anti-phospholipid syndrome**
 - **CLOTs:** venous and arterial
 - Coagulation defect: \uparrow APTT
 - Livedo reticularis
 - Obstetric complications: recurrent 1st trimester abortion
 - Thrombocytopenia

Thrombophilia Screen

Indications

- Arterial thrombosis <50 yrs (?APL)
- Venous thrombosis <40 yrs \bar{C} no RFs
- Familial VTE
- Unexplained recurrent VTE
- Unusual site: portal, mesenteric
- Recurrent foetal loss
- Neonatal

Investigations

- FBC, clotting, fibrinogen concentration
- Factor V Leiden / APC resistance
- Lupus anticoagulant and anti-cardiolipin Abs
- Assays for AT, protein C and S deficiencies
- PCR for prothrombin gene mutation

Rx

- Rx acute thrombosis as per normal
- Anticoagulate to INR 2-3
- Consider lifelong warfarin
- If recurrence occurs on warfarin \uparrow INR to 3-4

Prevention

- Lifelong anticoagulation not needed if asymptomatic
- \uparrow VTE risk \bar{C} OCP or HRT
- Prophylaxis in high risk situations
 - Surgery
 - Pregnancy

Blood Transfusion

Products

Packed red cells

- Stored @ 4°C in SAGM
- Hct ~70%
- Use to correct anaemia or blood loss
- 1u → ↑Hb by 1-1.5g/dL

Platelets

- Stored @ RT under agitation
- Not needed if count >20 or not actively bleeding
- Should be x-matched

FFP

- Stored @ -18°C
- Should be X-matched
- Uses: DIC, liver disease, TTP, massive haemorrhage

Human Albumin Solution

- Protein replacement
 - After abdominal paracentesis
 - Liver failure, nephrotic syndrome

Immediate Transfusion Reactions

Reaction	Time	Clinical Features	Mechanism	Rx
Haemolytic	Minutes	Agitation Fever Abdo/chest pain ↓ BP → shock DIC → haemorrhage Renal failure	ABO incompatibility → IV haemolysis	Stop transfusion Tell lab Keep IV line open → NS Treat DIC
Bacterial Contamination	<24h	↑ temp + rigors ↓ BP → Shock	Bacterial proliferation Esp. plats (Transfuse blood w/i 5h)	Stop transfusion Send unit to lab Abx: Taz+gent
Febrile non-Haemolytic	<24h	Fever, rigors, chills	Recipient anti-HLA Abs	Slow transfusion Paracetamol 1g
Allergic	Immediate	Urticaria, itch Angioedema Anaphylaxis	Recipient IgA deficiency Anti-IgA IgE	Slow Chlorphenamine 10mg IV/IM
TRALI	<6h	ARDS: SOB, cough Bilat infiltrates on CXR	Anti-WBC Abs in donor plasma	Stop transfusion Rx ARDS
Fluid Overload	<6h	CCF		Slow transfusion O₂ + frusemide 40mg IV
Massive Transfusion	24h	↑K ↓ Ca (citrate chelation) ↓ F5 and F8 ↓ plats Hypothermia	Whole blood vol in 24h (5L = 10units)	Massive Transfusion Protocol - 1:1:1 ratio of PRBC:FFP:PLT - → ↑ survival Warm the blood

Delayed Transfusion Reactions

Reaction	Time	Clinical Features	Mechanism	Rx
Delayed Haemolytic	1-7d	Jaundice Anaemia / ↓ing Hb Fever ± Haemoglobinuria	Recipient anti-Rh Abs Extravasc haemolysis	
Fe Overload	Chronic	SCA or Thal Major Haemochromatosis	Chronic transfusions	Desferrioxamine SC
Post-transfusion Purpura	7-10d	Thrombocytopenia Purpura	AlloAbs attack recipient + donor plats	Ivlg Plat transfusions
GvHD	4-30d	Diarrhoea Skin rash Liver Failure → ↑ LFTs Pancytopenia	Viable lymphocytes transfused into immunocompromised host Irradiate blood for vulnerable hosts	

Bone Marrow Failure

Pancytopenia

Congenital

- Fanconi's anaemia: aplastic anaemia

Acquired

- Idiopathic aplastic anaemia
- BM infiltration
- Haematological
 - Leukaemia
 - Lymphoma
 - Myelofibrosis
 - Myelodysplasia
 - Megaloblastic anaemia
- Infection: HIV
- Radiation
- Drugs
 - **Cytotoxic:** cyclophosphamide, azathioprine, methotrexate
 - **Abx:** chloramphenicol, sulphonamides
 - **Diuretic:** thiazides
 - **Anti-thyroid:** carbimazole
 - **Anti-psychotic:** clozapine
 - **Anti-epileptic:** phenytoin

Aplastic Anaemia

- Rare stem cell disorder

Key Features

- Pancytopenia
- Hypocellular marrow

Presentation: Pancytopenia

- **Age:** 15-24 yrs and >60 yrs
- Anaemia
- Infections
- Bleeding

Causes

- **Inherited**
 - **Fanconi's anaemia:** Ashkenazi, short, pigmented
 - **Dyskeratosis congenita:** premature ageing
 - **Swachman-Diamond syn.:** pancreatic exocrine dysfunction
- **Acquired**
 - Drugs
 - Viruses: parvovirus, hepatitis
 - Autoimmune: SLE

Ix

- **BM:** Hypocellular marrow

Mx

- **Supportive:** transfusion
- **Immunosuppression:** anti-thymocyte globulin
- **Allogeneic BMT:** may be curative

Myelodysplastic Syndromes

Pathophysiology

- Heterogeneous group of disorders → BM failure
- Clone of stem cells → abnormal development
 - → functional defects
 - → quantitative defects
- May be primary or secondary
 - Chemo or radiotherapy

Characteristics

- Cytopenias
- Hypercellular BM
- Defective cells: e.g. ringed sideroblasts
- 30% → AML

Clinical Features

- Elderly
- BM failure: anaemia, infection, bleeding, bruising
- Splenomegaly

Ix

- **Film:** blasts, Pelger-Huet anomaly, dimorphic
- **BM:** Hypercellular, blasts, ringed sideroblasts

Mx

- **Supportive:** transfusions, EPO, G-CSF
- **Immunosuppression**
- **Allogeneic BMT:** may be curative

Chronic Myeloproliferative Disorders

Classification

- RBC → Polycythaemia Vera
- WBC → CML
- Platelets → Essential thrombocythaemia
- Megakaryocytes → Myelofibrosis

Polycythaemia Vera

Features

- **Hyperviscosity**
 - Headaches
 - Visual disturbances
 - Tinnitus
 - Thrombosis
 - Arterial: strokes, TIA, peripheral emboli
 - Venous: DVT, PE, Budd-Chiari
- **Histamine Release**
 - Aquagenic pruritus
- **Erythromelalgia**
 - Sudden, severe burning in hands and feet \bar{c} redness of the skin
- **Splenomegaly:** 75%
- **Hepatomegaly:** 30%
- **Gout**

Ix

- 99% JAK2+ve
- \uparrow RBC, Hb and Hct
- \uparrow WCC and \uparrow plts
- BM: hypercellular \bar{c} erythroid marrow
- \downarrow EPO
- \uparrow red cell mass \bar{c} isotope studies

Rx

- Aim to keep Hct <0.45 to \downarrow thrombosis
 - Aspirin 75mg OD
 - Venesection if young
 - Hydroxycarbamide if older / higher risk

Prognosis

- Thrombosis and haemorrhage are main complications
- 30% \rightarrow MF
- 5% \rightarrow AML

Polycythaemia Differential

True Polycythaemia: \uparrow total volume of red cells

- **Primary:** PV
- **Secondary**
 - Hypoxia: altitude, COPD, smoking
 - EPO: renal cysts/tumours

Pseudopolycythaemia: \downarrow plasma volume

- **Acute**
 - Dehydration
 - Shock
 - Burns
- **Chronic**
 - Diuretics
 - Smoking

Essential Thrombocythaemia

Features

- **Thrombosis**
 - Arterial: strokes, TIA, peripheral emboli
 - Venous: DVT, PE, Budd-Chiari
- **Bleeding** (abnormal platelet function)
 - E.g. mucus membranes
- **Erythromelalgia**

Ix

- Plts >600 (often >1000)
- BM: \uparrow megakaryocytes
- 50% JAK2+ve

Rx

- Plts 400-1000: aspirin alone
- Thrombosis or plts >1000: hydroxycarbamide
- Anagrelide may be used
 - Inhibits platelet maturation
 - \downarrow platelet count and function

Prognosis

- 5% \rightarrow AML/MF over 10yrs

Thrombocythaemia Differential

- **Primary:** ET
- **Secondary:**
 - Bleeding
 - Infection
 - Chronic inflammation: RA, IBD
 - Trauma / surgery
 - Hyposplenism / splenectomy

Primary Myelofibrosis

- Clonal proliferation of megakaryocytes \rightarrow \uparrow PDGF \rightarrow Myelofibrosis
- Extramedullary haematopoiesis: liver and spleen

Features

- Elderly
- **Massive HSM**
- **Hypermetabolism:** wt. loss, fever, night sweats
- **BM failure:** anaemia, infections, bleeding

Ix

- **Film:** leukoerythroblastic \bar{c} teardrop poikilocytes
- Cytopenias
- **BM:** dry tap (need trephine biopsy)
- 50% JAK2+ve

Rx

- **Supportive:** blood products
- Splenectomy
- Allogeneic BMT may be curative in younger pts.

Prognosis

- 5yr median survival

Acute Lymphoblastic Leukaemia

Epidemiology

- Children 2-5yrs (commonest childhood Ca)
- Rare in adults

Aetiology

- Arrest of maturation and proliferation of lymphoblasts
- 80% B lineage, 20% T lineage

Risk Factors

- Genetic susceptibility (often Chr translocations)
- Environmental trigger
 - Radiation (e.g. during pregnancy)
 - Down's

Features

BM Failure

- Anaemia
- Thrombocytopenia → bleeding
- Leukopenia → infection

Infiltration

- Lymphadenopathy
- Orchidomegaly
- Thymic enlargement
- HSM
- CNS: CN palsies, meningism
- Bone pain

Ix

- ↑WCC: lymphoblasts
- ↓RBC, ↓PMN, ↓plts
- BM aspirate
 - ≥20% blasts
 - Cytogenetic and molecular analysis
- CXR+CT: mediastinal + abdominal LNs
- LP: CNS involvement

Mx

Supportive

- Blood products
- Allopurinol
- Hickman line or Portacath

Infections

- Gentamicin + tazocin
- Prophylaxis: e.g. co-timoxazole, ciprofloxacin

Chemotherapy (recruited into national trials)

1. Remission induction
2. Consolidation + CNS Rx
3. Maintenance for 2-3yrs

BMT

- Best option for younger adults

Prognosis

- 85% survival in children
- Worse in adults

Acute Myeloid Leukaemia

Epidemiology

- ↑ risk c age: mean 65-70
- Commonest acute leukaemia of adults

Aetiology

- Neoplastic proliferation of myeloblasts

Risk Factors

- Chromosomal abnormalities
- Radiation
- Down's
- Chemotherapy: e.g. for lymphoma
- Myelodysplastic and myeloproliferative syndromes

FAB Classification (based on cell type)

- M2: granulocyte maturation
- M3: acute promyelocytic leukaemia – t(15;17)
- M4: acute myelomonocytic leukaemia
- M7: megakaryoblastic leukaemia – trisomy 21

Features

BM Failure

- Cytopenias

Infiltration

- Gum infiltration → hypertrophy and bleeding (M4)
- HSM
- Skin involvement
- Bone pain

Blood

- DIC: APML (M3)
- Hyperviscosity: ↑WCC may → thrombi

Ix

- ↑ WCC blasts (occasionally normal)
- Anaemia and ↓ plts
- BM aspirate
 - ≥20% blasts
 - Auer rods are diagnostic

Dx

- Made by immunological and molecular phenotyping
 - Flow cytometry
- Cytogenetic analysis affects Rx and guides prognosis

Mx

Supportive: as for ALL

Infections: as for ALL

Chemotherapy

- V. intensive → long periods of neutropenia and ↓ plts
- ATRA for APML

BMT

- Allogeneic if poor prognosis
 - Destroy BM and leukemic cells c chemotherapy and total body irradiation.
 - Repopulate marrow c HLA-matched donor HSCs
- Autologous if intermediate prognosis
 - HSCs taken from pt.

Chronic Lymphocytic Leukaemia

Epidemiology

- Commonest leukaemia in Western World
- M>F=2:1
- Elderly: 70s

Aetiology

- Clone of mature B cells (memory cells)

Features

- Often asymptomatic incidental finding
- Symmetrical painless lymphadenopathy
- HSM
- Anaemia
- **B symptoms:** wt. loss, fever, night sweats

Complications

- Autoimmune haemolysis
 - Evan's = AIHA and ITP
- Infection (↓ Ig): bacterial, zoster
- Marrow failure / infiltration

Ix

- ↑ WCC, lymphocytosis
- Smear cells
- ↓ se Ig
- +ve DAT
- Rai or Binet staging

Dx

- Immunophenotyping to distinguish from NHL

Natural Hx

- Some remain stable for years
- Nodes usually enlarge slowly (± lymphatic obstruction)
- Death often due to infection: e.g. encapsulates, fungi
- **Richter Transformation:** CLL → large B cell lymphoma

Rx

- **Indications**
 - Symptomatic
 - Ig genes un-mutated (bad prognostic indicator)
 - 17p deletions (bad prognostic indicator)
- **Supportive care**
- **Chemotherapy**
 - Cylophosphamide
 - Fludarabine
 - Rituximab
- **Radiotherapy**
 - Relieve LN or splenomegaly

Prognosis

- 1/3 never progress
- 1/3 progress \bar{c} time
- 1/3 are actively progressing

Chronic Myeloid Leukaemia

Epidemiology

- 15% of leukaemia
- Middle-aged: 60-60yrs

Aetiology

- Myeloproliferative disorder: clonal proliferation of myeloid cells.

Features

- Systemic: wt. loss, fever, night sweats, lethargy
- Massive HSM → abdo discomfort
- Bruising / bleeding (platelet dysfunction)
- Gout
- Hyperviscosity

Philadelphia Chromosome

- Reciprocal translocation: t(9;22)
- Formation of BCR-ABL fusion gene
 - Constitutive tyrosine kinase activity
- Present in >80% of CML
- Discovered by Nowell and Hungerford in 1960

Ix

- ↑↑WBC
 - PMN and basophils
 - Myelocytes
- ± ↓Hb and ↓plat (accelerated or blast phase)
- ↑urate
- BM cytogenetic analysis: Ph+ve

Natural Hx

- **Chronic phase:** <5% blasts in blood or DM
- **Accelerated phase:** 10-19% blasts
- **Blast crisis:** usually AML, ≥20% blasts

Rx

- **Imatinib:** tyrosine kinase inhibitor
 - → >90% haematological response
 - 80% 5ys
- Allogeneic SCT
 - Indicated if blast crisis or TK-refractory

Non-Hodgkin's Lymphoma (80%)

Features

Lymphadenopathy: 75% @ presentation

- Painless
- Symmetric
- Multiple sites
- Spreads discontinuously

Extranodal

- Skin: esp. T cell lymphomas
- CNS
- Oropharynx and GIT
- Splenomegaly

B Symptoms

- Fever
- Night sweats
- Wt. loss (>10% over 6mo)

Blood

- Pancytopenia
- Hyperviscosity

Ix

- FBC, U+E, LFT, LDH
 - ↑ LDH = worse prognosis
- Film
 - Normal or circulating lymphoma cells
 - ± pancytopenias
- Classification: LN and BM biopsy
- Staging: CT/MRI chest, abdomen, pelvis
 - Stage \bar{C} Ann Arbor System

Classification

B Cell (commonest)

- **Low Grade:** usually indolent but often incurable
 - Follicular
 - Small cell lymphocytic (=CLL)
 - Marginal Zone (inc. MALTomas)
 - Lymphoplasmacytoid (e.g. Waldenstrom's)
- **High Grade:** aggressive but may be curable
 - Diffuse large B cell (commonest NHL)
 - Burkitt's

T Cell

- Adult T cell lymphoma: Caribs and Japs – HTLV-1
- Enteropathy-assoc. T cell lymphoma: chronic coeliac
- Cutaneous T cell lymphoma: e.g. Sezary syn.
- Anaplastic large cell

Mx

- Diagnosis and management in an MDT

High Grade (e.g. DLBCL)

- **R-CHOP regimen**
- BMT for relapse
- ~30% 5ys

Low Grade (e.g. follicular)

- Rx when clinically indicated (e.g. chlambucil)
- >50% 5ys

Hodgkin's Lymphoma (20%)

Epidemiology

- M>F=2:1 (esp. in paeds)
- Bimodal age incidence: 20-29yrs and >60yrs
- May be assoc. \bar{C} EBV

Features

Lymphadenopathy

- Painless
- Asymmetric
- Spreads contiguously to adjacent LNs
- Cervical nodes in 70% (also axillary and inguinal)
- May be alcohol-induced LN pain
- Mediastinal LN may → mass effects
 - SVC obstruction
 - Bronchial obstruction

B Symptoms

- Fever
- Night sweats
- Wt. loss (>10% over 6mo)

Other

- Itch
- Pel Ebstein Fever: cyclical fever
- Hepato- and/or spleno-megaly

Ix

- FBC, film, ESR, LFT, LDH, Ca
 - ↑ESR or ↓Hb = worse prognosis
- LN excision biopsy or FNA
 - Reed-Sternberg Cells (owl's eye nucleus)
- Staging: CT/MRI chest, abdomen, pelvis
- BM biopsy if B symptoms or Stage 3/4 disease

Staging: Ann Arbor System

1. Single LN region
 2. ≥2 nodal area on same side of diaphragm
 3. Nodes on both sides of diaphragm
 4. Spread beyond nodes: e.g. liver, BM
- + B if constitutional symptoms

Mx

- Chemo, radio or both
- **ABVD regimen**
- BMT for relapse

Prognosis

- Depends on stage and grade
 - 1A: >95% 5ys
 - 4B: <40% 5ys

Multiple Myeloma

Epidemiology

- M=F
- Blacks>White=2:1
- ~70yrs

Pathogenesis

- Clonal proliferation of plasma cells → monoclonal ↑Ig
 - Usually IgG or IgA
- Clones may also produce free light chain (λ or κ): ~2/3
 - Excreted by kidney → urinary BJP
 - Light chains only seen in plasma in renal failure
- Clones produce IL-6 which inhibits osteoblasts (\leftrightarrow ALP) and activates osteoclasts.

Symptoms

Osteolytic Bone Lesions

- Backache and bone pain
- Pathological #s
- Vertebral collapse

BM Infiltration

- Anaemia, neutropenia or thrombocytopenia

Recurrent Bacterial Infections

- Neutropenia
- Immunoparesis (= ↓Ig)
- Chemotherapy

Renal Impairment

- Light chains
- ↑Ca
- AL-amyloid

Complications

- Hypercalcaemia
- Neurological: ↑Ca, compression, amyloid
- AKI
- Hyperviscosity
- AL-amyloid (15%)

Ix

NB. Do ESR and Se electrophoresis if >50% back pain

Bloods

- FBC: normocytic normochromic anaemia
- Film: rouleaux ± plasma cells ± cytopenias
- ↑↑ESR/PV, ↑U+Cr, ↑Ca, **normal ALP**
- Se electrophoresis and β2-microglobulin

Urine

- Stix: ↑ specific gravity (BJP doesn't show)
- Electrophoresis: BJP

BM trephine biopsy

X-ray: Skeletal Survey

- Punched-out lytic lesions
- Pepper-pot skull
- Vertebral collapse
- Fractures

Dx

- Clonal BM plasma cells ≥10%
- Presence of se and/or urinary monoclonal protein
- End-organ Damage: **CRAB** (1 or more)
 - Ca ↑ (>2.6mM)
 - Renal insufficiency
 - Anaemia (<10g/dL)
 - Bone lesions

Mx

Supportive

- Bone pain: Analgesia (avoid NSAIDs) + bisphosphonates
- Anaemia: Transfusions and EPO
- Renal impairment: ensure good hydration ± dialysis
- Infections: broad spectrum Abx ± IVIg if recurrent

Complications

- ↑Ca: aggressive hydration, frusemide, bisphosphonates
- **Cord compression:** MRI, dexamethasone + local radio
- **Hyperviscosity:** Plasmapheresis (remove light chains)
- **AKI:** rehydration ± dialysis

Specific

- **Fit pts.**
 - Induction chemo: lenalidomide + low-dose dex
 - Then allogeneic BMT
- **Unfit pts.**
 - Chemo only: melphalan + pred + lenalidomide
 - Bortezomib for relapse

Prognosis

- Mean survival: 3-5yrs
- Poor prognostic indicators
 - ↑β2-microglobulin
 - ↓albumin

Other Paraproteinaemias

Smouldering / Asymptomatic Myeloma

- Se monoclonal protein and/or BM plasma cells $\geq 10\%$
- No CRAB

MGUS

- Se monoclonal protein $<30\text{g/L}$
- Clonal BM plasma cells $<10\%$
- No CRAB

Solitary Plasmacytoma

- Solitary bone/soft tissue plasma cell lesion
- Se or urinary monoclonal protein
- Normal BM and normal skeletal survey (except lesion)
- No CRAB

Waldenstrom's Macroglobulinaemia

- Lymphoplasmacytoid lymphoma → monoclonal IgM band
- **Features:**
 - Hyperviscosity: CNS and ocular symptoms
 - Lymphadenopathy + splenomegaly
- **Ix:** ↑ESR, IgM paraprotein

Primary AL Amyloid

- Occult proliferation of plasma cells → production of amyloidogenic monoclonal protein.
- Se or urinary light chains

Paraproteinaemia in lymphoma or leukaemia

- E.g. seen in 5% of CLL

Amyloidosis

Definition

- Group of disorders characterised by extracellular deposits of a protein in an abnormal fibrillar form that is resistant to degradation.

AL Amyloidosis

- Clonal proliferation of plasma cells → production of amyloidogenic light chains.
- 1° : occult plasma cell proliferation
- 2° : myeloma, Waldenstrom's, MGUS, lymphoma

Features

- **Renal:** proteinuria and nephrotic syndrome
- **Heart:** restrictive cardiomyopathy, arrhythmias, echo
 - "Sparkling" appearance on echo
- **Nerves:** peripheral and autonomic neuropathy, carpal tunnel.
- **GIT:** macroglossia, malabsorption, perforation, haemorrhage, hepatomegaly, obstruction.
- **Vascular:** periorbital purpura (characteristic)

AA Amyloidosis

- Amyloid derived from serum amyloid A
 - SAA is an acute phase protein
- Chronic inflammation
 - RA
 - IBD
 - Chronic infection: TB, bronchiectasis

Features

- **Renal:** proteinuria and nephrotic syndrome
- Hepatosplenomegaly

Familial Amyloidosis

- Group of AD disorders caused by mutations in transthyretin (produced by liver)
- **Features:** sensory or autonomic neuropathy

Others: non-Systemic Amyloidosis

- β -amyloid: Alzheimer's
- β_2 microglobulin: chronic dialysis
- Amylin: T2DM

Dx

- Biopsy of affected tissue
 - Rectum or subcut fat is relatively non-invasive
- Apple-green birefringence → Congo Red stain under polarized light.

Rx

- AA amyloid may improve → underlying condition
- AL amyloid may respond to therapy for myeloma
- Liver Tx may be curative for familial amyloidosis

Prognosis

- Median survival: 1-2yrs

Complications of Haematological Malignancies

Neutropenic Sepsis

General Precautions

- Barrier nursing in a side room
- Avoid IM injections (may → infected haematoma)
- Swabs + septic screen
- TPR 4hrly

Antimicrobials

- Start broad spectrum Abx: check local guidelines
- Consider G-CSF

Hyperviscosity Syndrome

Causes

- ↑↑RBC / Hct >0.5: e.g. PV
- ↑↑WCC > 100: e.g. leukaemia
- ↑↑ plasma proteins: Myeloma, Waldenstrom's

Features

- **CNS:** headache, confusion, seizures, faints
- **Visual:** retinopathy → visual disturbance
- **Bleeding:** mucus membranes, GI, GU
- **Thrombosis**

Ix

- ↑ plasma viscosity (PV)
- FBC, film, clotting
- Se + urinary protein electrophoresis

Rx

- Polycythaemia: venesection
- Leukopheresis: leukaemia
 - Avoid transfusing before lowering WCC
- Plasmapheresis: myeloma and Waldenstrom's

DIC

- Widespread activation of coagulation from release of pro-coagulants into the circulation.
- Clotting factors and plats are consumed → bleeding
- Fibrin strands → haemolysis

Causes

- Malignancy: e.g. APML
- Sepsis
- Trauma
- Obstetric events: e.g. PET

Signs

- Bruising
- Bleeding
- Renal failure

Ix

- ↓plats, ↓Hb, ↑APTT, ↑PT, ↑FDPs, ↓fibrinogen (∴↑TT)

Rx

- Rx cause
- Replace: cryoprecipitate, FFP
- Consider heparin and APC

Tumour Lysis Syndrome

- Massive cell destruction
 - High count leukaemia or bulky lymphoma
- ↑K, ↑urate → renal failure
- Prevention: ↑ fluid intake + allopurinol

Spleen and Splenectomy

Anatomy

- Intraperitoneal structure lying in the LUQ
- Measures 1x3x5 inches
- Weighs ~7oz
- Lies anterior to ribs 9-11

Features

1. Dull to percussion
2. Enlarges to RIF
3. Moves inferiorly on respiration
4. Can't get above it
5. Medial notch

Function:

part of the mononuclear phagocytic system

- Phagocytosis of old RBCs, WBCs and opsonised bugs
- Antibody production
- Haematopoiesis
- Sequestration of formed blood elements

Causes of Massive Splenomegaly: >20cm

- CML
- Myelofibrosis
- Malaria
- Leishmaniasis
- Gaucher's (AR, glucocerebrosidase deficiency)

All Causes of Splenomegaly

- **Haematological**
 - Haemolysis: HS
 - Myeloproliferative disease: CML, MF, PV
 - Leukaemia, lymphoma
- **Infective**
 - EBV, CMV, hepatitis, HIV,
 - TB, infective endocarditis
 - Malaria, leishmaniasis, hydatid disease
- **Portal HTN:** cirrhosis, Budd-Chiari
- **Connective tissue:** RA, SLE, Sjogrens
- **Other**
 - Sarcoid
 - Amyloidosis
 - Gaucher's
 - 1^o Ab deficiency (e.g. CVID)

Splenomegaly may → Hypersplenism

- Pancytopenia as cells are sequestered

Splenectomy → Hyposplenism

Indications

- Trauma
- Rupture (e.g. EBV infection)
- AIHA
- ITP
- HS
- Hypersplenism

Complications

- Redistributive thrombocytosis → early VTE
- Gastric dilatation (ileus)
- Left lower lobe atelectasis: v. common
- ↑ susceptibility to infections
 - Encapsulates: haemophilus, pneumo, meningo

Film

- Howell-Jolly bodies
- Pappenheimer bodies
- Target cells

Mx

- **Immunisation:** pneumovax, HiB, Men C, yrly flu
- **Daily Abx:** Pen V or erythromycin
- **Warning:** Alert Card and/or Bracelet

Other Causes of Hyposplenism

- SCD
- Coeliac disease
- IBD

The Lab

ESR

- How far RBCs fall through anti-coagulated blood in 1h
- Normal: ~20mm/h (M: age/2, F: (age+10)/2)
- ↑ se proteins cover RBCs → clumping → rouleaux → faster settling → ↑ESR.

↑ ESR

- Plasma factors
 - ↑ fibrinogen: inflammation
 - ↑ globulins: e.g. myeloma
- Red cell factors
 - Anaemia → ↑ESR

ΔΔ of ESR >100

- Myeloma
- SLE
- GCA
- AAA
- Ca prostate

Differential White Count

Neutrophilia

- Bacterial infection
 - Left shift
 - Toxic granulation
 - Vacuolation
- Stress: trauma, surgery, burns, haemorrhage
- Steroids
- Inflammation: MI, PAN
- Myeloproliferative disorders: e.g. CML

Neutropenia

- Viral infection
- Drugs: chemo, cytotoxics, carbimazole, sulphonamides
- Severe sepsis
- Hypersplenism: e.g. Felty's

Lymphocytosis

- Viral infections: EBV, CMV
- Chronic infections: TB, Brucella, Hepatitis, Toxo
- Leukaemia, lymphoma: esp. CLL

Lymphopenia

- Drugs: steroids, chemo
- HIV

Monocytosis

- Chronic infection: TB, Brucella, Typhoid
- AML

Eosinophilia

- Parasitic infection
- Drug reactions: e.g. c-EM
- Allergies: asthma, atopy, Churg-Strauss
- Skin disease: eczema, psoriasis, pemphigus

Basophilia

- Parasitic infection
- IgE-mediated hypersensitivity: urticarial, asthma
- CML

The Peripheral Film

Feature	Causes
Acanthocytes	Abetalipoproteinaemia Alcoholic liver disease
Basophilic stippling	Lead poisoning Thalassaemia
Blasts	Leukaemia
Burr cels	Uraemia
Dimorphic picture	Myelodysplasia
Howell-Jolly bodies	Hyposplenism
Heinz bodies	G6PD deficiency
Irregularly contracted cells	G6PD deficiency
Leukoerythroblastic film	BM infiltration
Pappenheimer bodies	Hyposplenism
Pencil cells	IDA
Reticulocytes	Haemolysis Haemorrhage
Spherocytes	AIHA Hereditary spherocytosis
Schistocytes	MAHA Prosthetic valve
Target cells	Hyposplenism Thalassaemia Liver disease
Tear-drop cells / Dacrococytes	BM infiltration

Cytochemistry

- Myeloblasts
 - Sudan black B
 - MPO
- Hairy cell leukaemia: tartrate resistant acid phosphatase
- Leukocyte alkaline phosphatase
 - ↑: PV, ET, MF
 - ↓: CML, PNH

Infectious Disease

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Tuberculosis

Pathophysiology

Primary TB

- Childhood or naïve TB infection
- Organism multiplies @ pleural surface → Ghon Focus
- Macros take TB to LNs
 - Nodes + lung lesion = Ghon complex
- **Mostly asymptomatic:** may → fever and effusion
- Cell mediated immunity / DTH controls infection in 95%
 - Fibrosis of Ghon complex → calcified nodule (Ranke complex)
- Rarely may → 1^o progressive TB (immunocompetent)

Primary Progressive TB

- Resembles acute bacterial pneumonia
- Mid and lower zone consolidation, effusions, hilar LNs
- Lymphohaematogenous spread → extra-pulmonary and milliary TB

Latent TB

- Infected but no clinical or x-ray signs of active TB
- Non-infectious
- May persist for years
- Weakened host resistance → reactivation

Secondary TB

- Usually reactivation of latent TB due to ↓ host immunity
- May be due to reinfection
- Typically develops in the upper lobes
- Hypersensitivity → tissue destruction → cavitation and formation of caseating granulomas.

Clinical Features

Pulmonary

- Cough, sputum
- Malaise
- Fever, night sweats, wt. loss
- Haemoptysis
- Pleurisy
- Pleural effusion
- Aspergilloma / mycetoma may form in TB cavities

Meningitis

- Headache, drowsiness
- Fever
- Vomiting
- Meningism
- Worsening over 1-3wks
- **CNS signs**
 - Papilloedema
 - CN palsies

Lymph Nodes

- Cervical lymphadenitis: scrofula
- Painless neck mass: no signs of infection (cold)

GU TB

- Frequency, dysuria, loin/back pain, haematuria
- Sterile pyuria

Bone TB: vertebral collapse and Pott's vertebra

Skin: Lupus vulgaris (jelly-like nodules)

Peritoneal TB: abdominal pain, GI upset, ascites

Adrenal: Addison's disease

Dx

Latent TB

- **Tuberculin Skin Test**
- If +ve → IGRA

Active TB

- **CXR**
 - Mainly upper lobes.
 - Consolidation, cavitation, fibrosis, calcification
- If suggestive CXR take ≥3 sputum samples (one AM)
 - May use BAL if can't induce sputum
 - Microscopy for AFB: Ziehl-Neelsen stain
 - **Culture:** Lowenstein-Jensen media (Gold standard)

PCR

- Can Dx rifampicin resistance
- May be used for sterile specimens

Tuberculin Skin Test

- Intradermal injection of purified protein derivative
- Induration measured @ 48-72h
 - Had BCG: +ve = ≥15mm
 - No BCG: +ve = ≥6mm
- False +ve: BCG, other mycobacteria, prev exposure
- False -ve: HIV, sarcoid, lymphoma

Interferon Gamma Release Assays (IGRAs)

- Pt. lymphocytes incubated w/ M. tb specific antigens → IFN-γ production if previous exposure.
- Will not be positive if just BCG (uses M. bovis)
- E.g. Quantiferon Gold and T-spot-TB

Mx

- Rx w/o culture if clinical picture is consistent w/ TB
 - Continue even if culture results are negative
- Stress importance of compliance
- Check FBC, liver and renal function
 - CrCl 10-50ml/min → ↓ R dose by 50%, avoid E
- Test visual acuity and colour vision
- Give pyridoxine throughout Rx

Initial Phase (RHZE): 2mos

- **RMP:** hepatitis, orange urine, enzyme induction
- **INH:** hepatitis, peripheral sensory neuropathy, ↓PMN
- **PZA:** hepatitis, arthralgia (Cl: gout, porphyria)
- **EMB:** optic neuritis

Continuation Phase (RH): 4mos

- RMP
- INH

TB Meningitis

- RHZE: 2mos
- RH: 10mos
- ± dexamethasone

Chemoprophylaxis in latent TB

- RH for 3mo or H alone for 6mo

Other Mycobacterial Disease

Leprosy / Hansen's Disease

Pathogenesis

- Transmitted via nasal secretions
 - Not very infectious
- M. leprae

Classification

- **Tuberculoid**
 - Less severe
 - T_H1-mediated control of bacteria → paucibacillary
 - Anaesthetic hypopigmented macules
- **Lepromatous**
 - Weak T_H1/2 → multibacillary
 - Skin nodules
 - Nerve damage (esp. ulnar and peroneal)

Clinical Features

- Hypopigmented, insensate plaques
- Trophic ulcers
- Thickened nerves
- Keratitis

Rx

- Tuberculoid: 6mo Rx
 - Rifampicin monthly
 - Clofazamine daily
- Lepromatous: 2yrs
 - Rifampicin monthly
 - Clofazamine + dapsone daily

MAI

- Complicates HIV infection
- Widely disseminated: **lungs** / GIT
- Fever, night sweats, wt. loss
- Diarrhoea
- Hepatomegaly

Buruli Ulcer

- M. ulcerans
- Australia and the Tropics
- Transmitted by insects
- Nodule → ulcer

Fish Tank Granuloma

- M. marinum
- Skin lesion appearing ~3wks after exposure

Influenza

Pathophysiology

- **Spread:** droplet
- **Incubation:** 1-4d
- **Infectivity:** 1d before symptoms start to 7d after
- **Immunity:** only strains which have already attacked pt

Presentation

- Fever
- Headache
- Malaise
- Myalgia
- n/v
- Conjunctivitis

Complications

- Bronchitis
- Pneumonia: esp. Staph
- Sinusitis
- Encephalitis
- Pericarditis
- Reyes: rash, vomiting, ↑LFTs in children give aspirin

Ix

- **Bloods:** paired sera (takes 14d), lymphopenia, thrombocytopenia
- **Culture:** 1wk from nasal swabs
- **PCR:** takes 36h, 94% sensitivity, 100% specificity

Rx

- Bed rest + paracetamol
- **If severe**
 - Mx in ITU
 - Cipro and co-amoxiclav: prevent Staph and Strep
- **Oseltamivir**
 - Neuraminidase inhibitor active vs. flu A and B
 - May be indicated if >1yr **symptoms of <48hr**
- **Zanamivir**
 - Inhaled NA inhibitor active vs. influenza A and B
 - >5yrs **symptoms <48h**

Prevention

- Good hygiene
- Trivalent Vaccine
 - >65yrs
 - DM, COPD, heart, renal, liver failure
 - Immunosuppression: splenectomy, steroids
 - Medical staff
- Oseltamivir
 - Prophylactic use if influenza A/B is circulating and >1yr old and <48hr since exposure.

HIV

Immunology

- HIV binds via gp120 to CD4
 - T_H cells, monocytes, macrophages, neural cells
- CD4+ cells migrate to lymphoid tissue where virus replicates → infection of new CD4+ cells
- Depletion and impaired function of CD4+ cells → immune dysfunction.

Virology

- RNA retrovirus
- After entry, viral **reverse transcriptase** makes DNA copy of viral RNA genome.
- Viral **integrase** enzyme integrates this into host DNA
- Core viral proteins synthesised by host and then cleaved by viral **protease** into mature subunits.
- Completed virions released by budding

Natural Hx

Acute Infection: usually asymptomatic

Seroconversion

- Transient illness 2-6wks after exposure
- Fever, malaise, myalgia, pharyngitis, maculopapular rash
- Rarely meningoencephalitis

Asymptomatic Infection

- But 30% will have PGL
 - Nodes >1cm in diameter
 - ≥2 extra-inguinal sites
 - ≥3mo

AIDS-related Complex (ARC)

- AIDS prodrome
- Constitutional symptoms: fever, night sweats, wt. loss
- Minor opportunistic infections
 - Oral candida
 - Oral hairy leukoplakia (EBV)
 - Recurrent HSV
 - Seborrhoeic dermatitis

AIDS

- Defining illness
- CD4 usually <200

Other Effects of HIV

- Osteoporosis
- Dementia
- Neuropathy
- Nephropathy

Dx

- **ELISA:** detect serum (or salivary) anti-HIV Abs
- **Western Blot:** for confirmation
- If recent exposure, may be window period
 - Usually 1-3wks
 - Can be 3-6mo
- **PCR:** can detect HIV virions in the window period
- **Rapid Antibody Tests:** false positives are a problem and results should be confirmed by Western Blot

Ix

- HIV diagnostic tests
- Drug resistance studies
 - e.g. genotyping for reverse transcriptase or protease mutations
- Mantoux test
- Serology: toxo, CMV, HBV, HCV, syphilis

Monitoring

- CD4 count
- Viral load (HIV RNA)
- FBC, U+E, LFTs, lipids, glucose

HAART

Indications

- CD4 ≤350
- AIDS-defining illness
- Pregnancy
- HIVAN
- Co-infected with HBV when Rx is indicated for HBV

Regimens

- **1 NNRTI + 2 NRTIs**
 - NNRTI = Efavirenz
 - NRTI = emtricitabine + tenofovir (Truvada)
 - Atripla = efavirenz + emtricitabine + tenofovir
- **PI + 2 NRTIs**
 - PI = lopinavir (+ low dose ritonavir = Kaletra)

Aim

- Undetectable VL after 4mo
- If VL remains high despite good compliance
 - Change to a new drug combination
 - Request resistance studies

Prophylaxis

- CD4 <200: PCP – co-trimoxazole
- CD4 <100: Toxo – co-trimoxazole
- CD4 <50: MAC – azithromycin

HIV Exposure

- Seroconversion post-needle-stick = ~0.3% (1/300)
- Report to occupational health
- Immunise against hep B (active + passive)
- Test blood from both parties: HIV, HBC, HCV
- Repeat recipient testing @ 3 and 6mo

PEP

- Start PEP in high-risk exposure from HIV+ or unknown source.
- Start ASAP as possible.
- Continue for at least 28d
- E.g. Truvada + Kaletra

Complications of HIV Infection

Major AIDS-Defining Illnesses

- Candidiasis: oesophageal or pulmonary
- Cryptococcal meningitis
- Cryptosporidiosis
- CMV retinitis
- Kaposi's sarcoma
- Lymphoma: Burkitt's, 1^o brain
- MAC
- PCP
- PML
- Toxo
- TB

TB and HIV

- ↑ reactivation of latent TB
- ↑ risk of disseminated TB
- Higher bacterial loads but ↑ false -ve smears
 - Fewer bacteria in sputum
- False -ve skin tests (T cell anergy)
- Absence of characteristic granulomas
- ↑ toxicity combining anti-TB and anti-HIV drugs
- IRIS: HAART → ↑ CD4 → paradoxical worsening of TB symptoms

PCP

- *P. jiroveci*: fungus
- **Presentation**
 - Dry cough
 - Exertional dyspnoea
 - Fever
- **CXR**: bilateral perihilar interstitial shadowing
- **Dx**: visualisation from sputum, BAL or lung biopsy
- **Rx**
 - High-dose co-trimoxazole IV
 - Or, pentamidine IVI
 - Prednisolone if severe hypoxaemia
- **Prophylaxis**
 - Co-trimoxazole if CD4 <200 or after 1st attack

CMV

- Mainly → **retinitis**
 - ↓ acuity
 - Eye pain, photophobia
 - "Pizza" sign on Fundoscopy
 - **Rx**: ganciclovir eye implant
- Also: pneumonitis, colitis, hepatitis

Toxoplasmosis

- **Presentation**
 - Posterior uveitis
 - Encephalitis
 - Focal neurology
- **Dx**
 - Toxoplasma serology
 - Toxo isolation from LN or CNS biopsy
 - CT/MRI: ring-shaped contrast enhancing lesions
- **Rx**: pyrimethamine + sulfadiazine + folate
- **Prophylaxis**
 - Co-trimoxazole if CD4 <100
 - Lifelong 2^o prophylaxis

Candidiasis

- **Oral**: nystatin suspension
- **Oesophageal**
 - Dysphagia
 - Retrosternal pain
 - **Rx**: itraconazole PO

Cryptococcal Meningitis

- **Presentation**
 - Chronic Hx
 - Headache
 - Confusion
 - Papilloedema
 - CN lesions
- **Ix**
 - India ink CSF stain
 - ↑ CSF pressure
 - CrAg in blood and CSF
- **Rx**
 - Amphotericin B + flucytosine for 2wks then fluconazole for 6mo / until CD4 >200

PML

- Progressive multifocal leukoencephalopathy
- Demyelinating inflammation of brain white matter caused by JC virus.
- **Presentation**
 - Weakness
 - Paralysis
 - Visual loss
 - Cognitive decline
- **Ix**: JC viral PCR
- **Rx**: HAART, mefloquine may halt progression

Kaposi's Sarcoma

- Neoplasm derived from capillary endothelial cells or fibrous tissue.
- Caused by HHV8 infection
- **Presentation**
 - Purple papules
 - May have visceral involvement
- **Rx**
 - HAART
 - Radiotherapy or chemotherapy

Other Presentations

- **Pulmonary**
 - MAI
 - Fungi: aspergillus, crypto, histoplasma
 - CMV
- **↑ LFT and Hepatomegaly**
 - Drugs
 - Viral hepatitis
 - AIDS sclerosing cholangitis
 - MAI
- **Chronic Diarrhoea**
 - Bacteria: Salmonella, shigella, campylobacter
 - Protozoa: cryptosporidium, microsporidium
 - Virus: CMV
- **Neuro**
 - CMV encephalitis
 - Lymphoma

Herpes Infections

Herpes Simplex

Virology	Disease	Features	Diagnosis	Treatment
α-neurotrophic Persists in DRG Mucocutaneous spread	Oropharyngeal / primary stomatitis	HSV-1 Severe painful ulceration Fever + Submandibular lymphadenopathy		Topical Aciclovir
	Encephalitis	90% HSV-1, 10% HSV-2 Flu-like prodrome Headache, focal neuro, fits, odd behaviour, ↓GCS Haemorrhagic necrosis of temporal lobes	CSF: ↑lympho, normal gluc CSF PCR MRI	Aciclovir IV
	Mollaret's Meningitis	HSV-2 mostly Benign recurrent aseptic meningitis		Aciclovir IV
	Herpes Gladiatorum	Rugby players, wrestlers Painful vesicular rash, lymphadenopathy, fever		Aciclovir PO
	Herpetic Whitlow	Healthcare workers, children Painful red finger		Topical Aciclovir
	Eczema Herpeticum	Herpes infection at the site of skin damage		Aciclovir
	Genital Herpes	HSV-2 Flu-like prodrome Dysuria, inguinal LNs, painful ulcers Sacral radiculomyelitis → urinary retention + sacral sensory loss (Elsberg syndrome) Herpes meningitis in 4-8% primary genital herpes	Urinary PCR	Aciclovir PO
	Herpetic Keratitis	Unilat/bilat conjunctivitis + pre-auricular LNs May cause a corneal ulcer = dendritic ulcer		

Varicella Zoster

Virology	Disease	Features	Diagnosis	Treatment
α-neurotrophic Droplet or contact spread Replication in LN, then liver and spleen	Chickenpox = varicella zoster	Flu-like prodrome followed by vesicular rash that crops Not contagious after lesions scab Droplet spread Complications: pneumonitis, haemorrhage, encephalitis - ↑ risk in immunocompromised and adults	DIF of scrapings Tzanck cells	Calamine lotion Aciclovir - adults - immunocomp - pregnant VZIg if contact
	Shingles = herpes zoster	Zoster reactivation due to ↓ immunity/stress Lifetime prevalence = 20% Painful vesicular rash in dermatomal distribution - Thoracic and ophthalmic most commonly - Multidermatomal / disseminated in immunocomp Rx may ↓ progression to post-herpetic neuralgia Post-Herpetic neuralgia = severe dermatomal pain Ramsay Hunt = ear zoster, facial palsy, ↓ taste, ↓ hearing		Aciclovir PO/IV Famciclovir Valaciclovir

EBV

Virology	Disease	Features	Diagnosis	Treatment
<p>γ-lymphotrophic Infects B-cells</p>	Glandular fever Infectious mononucleosis	<p>Saliva or droplet spread Fever, malaise, sore throat, cervical LNs +++ Splenomegaly, hepatitis (→ hepatomegaly and jaundice)</p> <p>Complications: splenic rupture, CN lesion (e.g. 7), ataxia GBS, pancytopenia with megaloblastic marrow, meningoencephalitis, chronic fatigue</p>	<p>Lymphocytosis Atypical Lymphocytes</p> <p>+ve Heterophile Abs - Monospot - Paul Bunnell</p> <p>↑LFTs Blood: serology, PCR</p>	
	Burkitt's lymphoma	Jaw or abdo mass Endemic: Africa, malaria Sporadic: non-African, impaired immunity Immunodeficiency: HIV or post-Tx	Starry-sky appearance CD10, BCL6 t(8;14)	
	PTLD	Lymphoma following solid organ TX	Viral load > 10 ⁵ c/ml	Rituximab
	Oral hairy leukoplakia	HIV+ Painless shaggy white plaque along lateral tongue border		Aciclovir
	Primary brain lymphoma	HIV+ Mass effects + systemic symptoms	CT/MRI: Ring-enhancing lesion	
	Nasopharyngeal Ca	Especially in Asia		

False +ve Heterophile Abs: hepatitis, parvovirus, leukaemia, lymphoma, SLE, pancreatic Ca

CMV

Virology	Disease	Features	Diagnosis	Treatment
<p>β-epitheliotropic Mucocutaneous spread Infected cells become swollen</p>	Primary Infection	80% asymptomatic Flu-like illness can occur (±hepatitis)		
	Reactivation	Immunocompromise HIV: retinitis > colitis > CNS disease Transplant: pneumonitis > colitis > hepatitis > retinitis	Blood: PCR, serology Owl's Eye intranuclear inclusions Atypical Lymphocytes	1 = Ganciclovir 2 = Foscarnet 3 = Cidofovir
	Congenital	Petechiae at birth + hepatosplenomegaly		

BMT Prevention

- Do weekly PCR for first 100d
- If viraemia +ve → ganciclovir IV
- Use CMV-ve irradiated blood products

Solid Organ Transplant Prevention

- Greatest risk = seroneg recipient and seropos donor
- Renal Tx prophylaxis = valganciclovir

Viral Hepatitis

Types

Type	Spread	Cause
A	FO	Seafood, especially abroad
B	IV	Blood, body fluids, babies (vertical)
C	IV	Mainly blood. Less vertical cf. HCV
D	IV	Dependent on prior HBV infection
E	FO	Developing world

Hepatitis A

Presentation

- **Prodromal Phase**
 - Fever, malaise, arthralgia, nausea, anorexia
 - Distaste for cigarettes
- **Icteric Phase**
 - Jaundice, HSM, lymphadenopathy, cholestasis

Ix

- ↑↑ALT, ↑AST (AST:ALT <2)
- IgM+ ~25d after exposure
 - = recent infection
- IgG+ for life

Rx

- Supportive
- Avoid alcohol
- IFN-α for fulminant hepatitis (rare)

Prevention

- Passive Ig → <3mo protection (e.g. travellers)
- Can give active vaccine

Hep B

Incubation: 1-6mo

Presentation

- Prodromal phase and icteric phase as for Hep A
- Extra-hepatic features due to immune complexes
 - Urticaria or vasculitic rash
 - Cryoglobulinaemia
 - PAN
 - GN
 - Arthritis

Ix

- **HBsAg +ve** = current infection
 - +ve >6mo = chronic disease
- **HBeAg +ve** = high infectivity
- **Anti-HBc IgM** = recent infection
- **Anti-HBc IgG** = past infection
- **Anti-HBs** = cleared infection or vaccinated
- **HBV PCR**: monitoring response to Rx

Rx

- Supportive
- Avoid EtOH
- Chronic disease: PEGinterferon α2b

Complications

- Fulminant hepatic failure (rare)
- Chronic hepatitis (5-10%) → cirrhosis in 5%
- HCC

Hep C

- Mainly spread by blood.
- Thousands of UK cases due to transfusion (eligible for compensation from Skipton fund)

Presentation

- Initial infection is usually asymptomatic
- 25% have acute icteric phase
- 85% → chronic infection
- 20-30% → cirrhosis w/i 20yrs
- ↑ risk of HCC

Ix

- Anti-HCV Abs
- HCV-PCR
- Liver biopsy if PCR+ve to assess liver damage and need for Rx
- HCV genotype

Rx

- Indications
 - Chronic hepatitis
 - ↑ ALT
 - Fibrosis
- PEGinterferon α2b + ribavirin
- ↓ efficacy if
 - Genotype 1, 4, 5 or 6
 - ↑ VL
 - Older
 - Black
 - Male

Hep D

- Incomplete RNA virus that can only exist c HBV
- ↑ risk of acute hepatic failure and cirrhosis
- Ix: anti-HDV Ab

Hep E

- Similar to HAV
- Common in Indochina

Differential

Acute

- **Infection:** CMV, EBV, leptospirosis
- **Toxin:** EtOH, paracetamol, isoniazid, halothane
- **Vasc:** Budd-Chiari
- **Obs:** eclampsia, acute fatty liver of pregnancy
- **Other:** Wilson's, AIH

Cirrhosis

- **Common:**
 - Chronic EtOH
 - NAFLD / NASH
- **Other:**
 - **Genetic:** Wilson's, α1ATD, HH, CF
 - **AI:** AH, PBC, PSC
 - **Drugs:** Methotrexate, amiodarone, isoniazid
 - **Neoplasm:** HCC, mets
 - **Vasc:** Budd-Chiari, RHF, constrict. pericarditis

Gastrointestinal Infections 1

Organism	Aetiology	Inc	Clinical Features	Dx	Mx
Staph aureus	Meat	1-6h	Diarrhoea, vomiting, abdo pain, ↓BP Rapid resolution		
Bacillus cereus	Reheated rice	1-6h	Watery diarrhoea and vomiting		
E. coli ETEC	Travelling		Watery diarrhoea		Cipro
E. coli EHEC (O157:H7)	Undercooked minced beef - e.g. burgers	12-72h	Dysentery HUS	Stool MC+S	Dialysis if necessary
Campylobacter jejuni	Unpasteurised milk Animal faeces (cats, dogs)	2-5d	Commonest bacterial diarrhoea Bloody diarrhoea, fever Guillain-Barre Reactive arthritis	Stool MC+S	Cipro - 250-750mg BD PO - 200-400mg BD IVI over 30min – 1h
Shigella		1-7d	Bloody diarrhoea, abdo pain, fever Reactive arthritis	Stool MC+S	Cipro
Salmonella enteritidis	Poultry, eggs, meat	12-48h	Diarrhoea, vomiting, fever, abdo pain		Cipro or ceftriaxone
Listeria monocytogenes	Refrigerated food - cold enhancement Pates, soft cheeses		Watery diarrhoea, cramps, flu-like Pneumonia Meningoencephalitis Miscarriage	Blood culture	Ampicillin
Clostridium difficile	Antibiotic use - ceph, cipro, clinda FO spread Environment: spores	1-7d	Bloody diarrhoea, abdo pain, fever - foul smelling Pseudomembranous colitis Toxic megacolon GI perforation	Stool MC+S CDT ELISA	Stop causative Abx 1st: Metronidazole 400mg TDS PO for 10d 2nd: Vanc 125mg QDS PO Colectomy may be needed
Clostridium botulinum	Canned / vac-packed food Kids=honey Students=beans	12-36h	Afebrile Descending symmetric flaccid paralysis No sensory signs Autonomic: dry mouth, fixed dilated pupils	Toxin in blood samples	Antitoxin Benpen + metro
Clostridium perfringens	Reheated meat	8-24h	Watery diarrhoea + cramps	Stool MC+S	Benpen + metro
Vibrio cholera	FO spread Dirty water	Hrs-5d	Rice-water stools Shock, acidosis, renal failure	Stool MC+S	Rehydrate - Cooked rice powder solution - Hartmann's + K ⁺ supplements Cipro Zn supplement
Vibrio parahaemolyticus	Raw/undercooked seafood - Japan		Profuse diarrhoea, abdo pain, vomiting		Doxy 100-200mg/d PO
Norovirus		12-48h	Commonest cause in adults 50% of all gastroenteritis worldwide Fever, diarrhoea, projectile vomiting		
Rotavirus		1-7d	Commonest cause in children Secretory diarrhoea and vomiting		

Gastrointestinal Infections 2

Organism	Aetiology	Inc	Features	Dx	Mx
Salmonella typhi/paratyphi	FO spread Tropics	3-21d	Malaise, headache, cough, constipation High fever \bar{c} relative bradycardia Rose spots: patchy red macules Epistaxis, splenomegaly Diarrhoea after 1 st wk	Leukopenia Blood culture Urine or stool culture	Cefotaxime or cipro
Yersinia enterocolitica	Food contaminated by domestic animal faeces	24-36h	Abdo pain, fever, diarrhoea Mesenteric adenitis Reactive arthritis, pharyngitis, pericarditis Erythema Nodosum	Serology	Cipro
Entameoba histolytica	MSM Travelling	1-4wk	Dysentery, wind, tenesmus Wt. loss if chronic Liver abscess - RUQ pain, swinging fever, sweats - Mass in R lobe Flask-shaped ulcer on histo	Stool micro - Motile trophozoite \bar{c} 4 nuclei Stool Ag	Metro Tinidazole if severe or abscess
Giardia lamblia	MSM Hikers Travellers	1-4wk	Bloating, explosive diarrhoea, offensive gas Malabsorption → steatorrhoea and wt. loss	Direct fluorescent Ab assay Stool micro - Pear-shaped trophozoites \bar{c} 2 nuclei Duodenal fluid analysis on swallowed string	Tinidazole
Cryptosporidium parvum	Waterborne	4-12d	Severe acute watery diarrhoea in HIV	Stool micro - protozoan	Paromomycin
Strongyloides stercoralis	Endemic in sub-tropics Hyperinfestation in AIDS		Migrating urticarial rash on trunk and legs Pneumonitis, enteritis Malabsorption → chronic diarrhoea	Stool MC+S Serology	Ivermectin

Secretory Diarrhoea

- Bacteria only found in lumen: don't activate innate immunity
- No / low fever
- No faecal leukocytes
- Caused by bacterial toxins: Cholera, E. coli (except EIEC), S. aureus
- Toxin \rightarrow \uparrow cAMP \rightarrow open CFTR channel \rightarrow Cl loss followed by HCO₃, Na and H₂O loss \rightarrow secretory diarrhoea

Inflammatory Diarrhoea

- Bacteria invade lamina propria: activate innate immunity
- Fever
- PMN in stool
- Campylobacter, shigella, non-typhoidal salmonella, EIEC

Enteric Fever

- Abdo pain, fever, mononuclear cells in stool
- Typhoidal salmonella, Yersinia enterocolitica, Brucella

Sexually Transmitted Infections

Disease	Risk Factors	Clinical Features	Diagnosis	Management	Complications
Gonorrhoea	Young, Black M	Men: - Purulent urethral d/c, dysuria, prostatitis Women: - Usually asymptomatic, dysuria, d/c	Urine NAATs Culture is gold standard - Intracellular Gm- diplococci - Transport in Stuart's Medium	Cefixime PO Ceftriaxone IM + Azithro for C	Prostatitis Epididymitis Salpingitis / PID Reactive Arthritis Ophthalmia neonatorum
Chlamydia - D-K	10% <25	Asymptomatic in 50% men and 80% women Men: - Urethritis Women: - Cervicitis, urethritis, salpingitis	NAATs - Urine Culture - Endocervical swab - Discharge	Azithromycin / doxycycline	Prostatitis Epididymitis Salpingitis / PID Reactive Arthritis Ophthalmia neonatorum
LGV	Tropical STI Outbreak in MSM	Primary Stage: - painless genital ulcer, heals fast - balanitis, proctitis, cervicitis Inguinal Syndrome: - Painful inguinal buboes - Fever, malaise → genital elephantiasis Anogenitorectal syndrome: - Proctocolitis → Rectal strictures → Abscesses and fistulae	Chlamydia serovars L1, L2, L3 NAATs	Azithromycin / doxycycline	Genital elephantiasis Rectal strictures
HPV 6, 11		Often asymptomatic Cauliflower warts		Podophyllotoxin Cryotherapy	
HSV 2 (/1)		Flu-like prodrome Inguinal LNs Painful grouped vesicles → ulcers Dysuria	PCR Serology	Analgesia Aciclovir	Meningitis Elsberg Syndrome - sacral radiculomyelitis → retention + saddle paraesthesia
Syphilis	MSM	Painless, indurated ulcer Mac pap rash: soles, palms Aortic aneurysms Tabes dorsalis	Dark ground microscopy RPR/VDRL: cardiolipin Abs - not treponeme specific - indicate active disease TPHA/FTA - treponeme-specific	Benzathine Pen	Jarisch-Herxheimer Reaction - Hrs after 1 st Pen dose - Fever, ↑HR, vasodilation
Chancroid H. ducreyi	Mainly Africa	Papule → Painful soft genital ulcer - base covered in yellow/grey Progressing to inguinal bubo es	Culture PCR	Azithromycin	
Granuloma inguinale (Donovanosis) Klebsiella granulomatis	Africa India	Painless, beefy-red ulcer Subcutaneous inguinal granulomas - Pseudobubo	Donovan bodies - Giemsa stain	Erythromycin	

Syphilis

Stages

Stage	Features: due to endarteritis obliterans
Primary	<ul style="list-style-type: none"> Mac→pap→indurated, painless ulcer = Chancre Regional LNs Heals in 1-3wks
Secondary	<ul style="list-style-type: none"> 6wks -6mo wks after chancre Systemic bacteraemia → fever, malaise Skin rash: <ul style="list-style-type: none"> Symmetrical, non-itchy, mac pap / pustular Palms, soles, face, trunk Buccal snail-track ulcers Warty lesions: condylomata lata
Tertiary	<ul style="list-style-type: none"> 2-20yrs latency Gummas <ul style="list-style-type: none"> Granulomas in skin, mucosa, bones, joints
Quaternary	<ul style="list-style-type: none"> Syphilitic aortitis <ul style="list-style-type: none"> Aortic aneurysm Aortic regurg Neurosyphilis <ul style="list-style-type: none"> Paralytic dementia Meningovascular: CN palsies, stroke Tabes dorsalis <ul style="list-style-type: none"> Degeneration of sensory neurones, esp. legs Ataxia and +ve Romberg's Areflexia Plantars ↑↑ Charcot's joints Argyll-Robertson pupil <ul style="list-style-type: none"> accommodates, doesn't react

Dx

Cardiolipin antibody

- E.g. VDRL, RPR
- Not treponeme specific
 - False +ve: pregnancy, pneumonia, SLE, malaria, TB
- +ve in 1^o and 2^o syphilis (wanes in late disease)
- Reflects disease activity: -ve after Rx

Treponeme-specific Ab

- +ve in 1^o and 2^o syphilis
- Remains +ve despite Rx
- TPHA and FTA

Treponemes

- Seen by dark ground microscopy of chancre fluid
- Seen in lesions of 2^o syphilis
- May not be seen in late syphilis

Rx

- 2-3 doses (1wk apart of benzathine penicillin)
- Or, doxycycline for 28d

Jarisch-Herxheimer Reaction

- Fever, ↑HR, vasodilatation hrs after first Rx
- ? sudden release of endotoxin
- Rx: steroids

Zoonoses

Disease	Risk Factors	Presentation	Diagnosis	Management
Leptospirosis Weil's Disease	Infected rat urine - swimming - canoeing	High fever, headache, myalgia / myositis Cough, chest pain ± haemoptysis ± hepatitis & jaundice ± meningitis	Blood culture Serology	Doxycycline
Brucellosis Melitensis - goats, commonest Abortus: cattle Suis: pigs	Middle and Far East, Malta Unpasteurised milk / cheeses - esp. goat Vets, farmers, abattoir workers	Undulant fever (PUO): peak PM, normal AM Sweats, malaise, anorexia Arthritis, spinal tenderness LN, HSM Rash, jaundice	Pancytopenia Positive Rose Bengal Test Anti-O-polysaccharide Ag	Doxy + RMP + gent
Lyme disease Borrelia burgdorferi	Ixodes tick bite Walkers, hikers	Early localised: - Erythema migrans (target lesions) Early disseminated: - Malaise, LN, migratory arthritis , hepatitis Late persistent : - Arthritis, focal neuro (Bell's palsy), heart block, myocarditis - Lymphocytoma: blue/red ear lobe	Biopsy ECM edge + Ab ELISA	Rash: Doxy Complications: IV benpen
Cat-Scratch Disease <i>Bartonella henselae</i>	Hx of cat scratch	Tender regional LNs	+ve cat scratch skin Ag test	Azithro
Toxoplasmosis	Cats are definitive hosts Sheep / pig intermediate hosts	Mostly asympto Reactivated in immunodeficiency - Encephalitis: confusion, seizures, focal - SOL/↑ICP - Posterior uveitis	CT/MRI: ring-shaped contrast enhancing CNS lesions Serology	Pyrimethamine + sulfadiazine Septrin prophylaxis in HIV
Rabies	Animal bites - Bats, dogs, foxes	Prodrome - Headache, malaise, bite itch, odd behaviour Furious Rabies - Hydrophobia - Muscle spasms Dumb Rabies - flaccid limb paralysis	"Bullet-shaped" RNA virus Negri bodies	Immunised - diploid vaccine Unimmunised - vaccine + rabies Ig
Anthrax	Spread by infected carcasses or hides - abattoir workers, farmers	Cutaneous - ulcer with BLACK centre - rim of oedema Inhalational - massive lymphadenopathy - mediastinal haemorrhage - resp failure GI - severe bloody diarrhoea	Microscopy - Gm+ spore forming rod	Cipro + clindamycin

Malaria

Species

Species	Inc	Liver stage?	Rhythm	Rx
Falciparum	7-10d	No	Tertian: 48h	Artemether-lumefantrine (Riamet) (Quinine + Doxy)
Vivax	10-17d	Chronic liver stage	Tertian: 48h	Chloroquine then primaquine
Ovale	10-17d	Chronic liver stage	Tertian: 48h	Chloroquine then primaquine
Malariae	18-40d	No	Quartan: 72h	Chloroquine then primaquine

Biology

- Plasmodium sporozoites injected by females Anopheles mosquito.
- Sporozoites migrate to liver, infect hepatocytes and multiply asymptotically (incubation period) → merozoites
- Merozoites released from liver and infect RBCs
- Multiply in RBCs
 - Haemolysis
 - RBC sequestration → splenomegaly
 - Cytokine release

Falciparum Malaria

- 90% present w/i 1mo

Flu-like Prodrome

- Headache, malaise, myalgia, anorexia

Fever Paroxysms

- Shivering ≤1h
- Hot stage for 2-6h: ~41°C
 - Flushed, dry skin, headache, n/v
- Sweating for 2-4h as temp falls

Signs

- Anaemia
- Jaundice
- HSM
- No rash, no LNs

Complications

- Cerebral malaria: confusion, coma, fits
- Lactic acidosis → Kussmaul respiration
- Hypoglycaemia
- Acute renal failure: 2° to ATN
- ARDS

Dx

- Serial thick and thin blood films
- Parasitaemia level
- FBC: anaemia, thrombocytopenia
- Clotting: DIC
- Glucose
- ABG: lactic acidosis
- U+E: renal failure
- Urinalysis: haemoglobinuria

Mx

Uncomplicated Ovale, Vivax, Malariae

- Chloroquine base
- Then primaquine

Uncomplicated Falciparum

- Artemether-lumefantrine

Severe Falciparum Malaria

- Need ITU Mx
- IV antimalarials

Prophylaxis

- No resistance:** proguanil + chloroquine
- Resistance:** mefloquine or malarone
 - Malarone:** atovaquone + proguanil

Antimalarial SEs

- Chloroquine:** retinopathy
- Fansidar:** SJS, ↑LFTs, blood dyscrasias
- Primaquine:** haemolysis if G6PD deficient
- Malarone:** abdo pain, nausea, headache
- Mefloquine:** dysphoria, neuropsychiatric signs

Other Tropical Diseases

Disease	Aetiology	Presentation	Diagnosis
African Trypanosomiasis "Sleeping sickness"	Tsetse fly	<p>Tender subcut nodule @ site of infection</p> <p>Haemolymphatic Stage</p> <ul style="list-style-type: none"> - rash, fever, rigors, headaches - LNs and HSM - Posterior cervical nodes (Winterbottom's sign) <p>Meningoencephalitic Stage</p> <ul style="list-style-type: none"> - Wks – Mos after original infection - Convulsions, agitation confusion - Apathy, depression, hypersomnolence, coma <p>T. gambiense: West Africa T. rhodesiense: East Africa - More severe than gambiense</p>	Thick and thin films - flagellated protozoa Serology
American Trypanosomiasis "Chagas Disease"	Reduviids	<p>T. cruzi</p> <ul style="list-style-type: none"> - Latin America - Erythematous nodule, fever, LN, HSM Swelling of eyelid (Romana's Sign) - Cardiac disease 	
Leishmaniasis	<p>Sandflies</p> <p>South + Central Am Asia Africa</p>	<p>Cutaneous (L. major, L. tropica)</p> <ul style="list-style-type: none"> - Skin ulcer @ bite → depigmented scar <p>Diffuse cutaneous</p> <ul style="list-style-type: none"> - Widespread nodules (fail to ulcerate) <p>Mucocutaneous (L. brasiliensis)</p> <ul style="list-style-type: none"> - South America - Ulcer in mucous mems of mouth and nose <p>Visceral = Kala Azar (L. donovani)</p> <ul style="list-style-type: none"> - Dry, warty hyperpigmented skin lesions (dark face and hands) - Prolonged fever - Massive splenomegaly, LNs, abdo pain 	<p>Visceral:</p> <ul style="list-style-type: none"> - Leucopaenia - ↑Ig - Pancytopaenia - Serology <p>Visualisation of Leishman-Donovan bodies</p>
Filariasis	Asia Africa South America	<p>Lymphatic Filariasis</p> <ul style="list-style-type: none"> - Wuchereria bancrofti - elephantiasis 	Nemotodes Microfilariae in the blood Eosinophilia
Dengue Fever RNA virus	<p>Aedes mosquito</p> <p>South + Central Am Asia Africa</p>	Flushes: facem neck, chest Central macpap rash Headache, arthralgia HSM Jaundice Haemorrhage: petechial, GI, gums or nose, GU NB. can exclude if fever starts >2wks after leaving endemic area.	Serology Tourniquet test
Schistosomiasis	Tremotode (Fluke) Snail vector	<p>Itchy papular rash at site of penetration</p> <ul style="list-style-type: none"> - Swimmer's Itch <p>Mansoni</p> <ul style="list-style-type: none"> - abdo pain D&V - later hepatic fibrosis and portal HTN - HSM <p>Haematobium</p> <ul style="list-style-type: none"> - frequency, dysuria, haematuria - may → hydronephrosis and renal failure - ↑ risk of bladder SCC 	

Miscellaneous Infections

Tetanus

Pathophysiology

- Clostridium tetani spores live in faeces, dust, soil and medical instruments.
 - Mucosal breach admits spores
 - Spores germinate and produce exotoxin
- Exotoxin prevents the release of inhibitory transmitters
 - GABA and glycine
- → generalised muscle over-activity

Presentation

- Prodrome: fever, malaise, headache
- Trismus
- Risus sardonicus
- Opisthotonus
- Spasms: may → respiratory arrest
- Autonomic dysfunction: arrhythmias, fluctuating BP

Rx

- Mx on ITU: may need intubation
- Human tetanus Ig
- Metronidazole, benzpen

Prevention

- Active immunisation w/ tetanus toxoid
- **Clean minor wounds**
 - Uncertain Hx / <3 doses: give vaccine
 - ≥3 doses: only vaccinate if >10yrs since last dose
- **Heavily contaminated wounds**
 - Uncertain Hx / <3 doses: vaccine + TIG
 - ≥3 doses: vaccinate if ≥5yrs since last dose

Actinomycosis

- Actinomyces israelii
- Subcut infections: esp. on jaw
- Forms sinuses which discharge pus containing sulphur granules.
- **Rx:** ampicillin for 30d, then pen V for 100d

Approach to Nosocomial Fever

Epidemiology

- 2-30% of hospital inpatients
- Mostly due to bacterial infection

Definition

- Oral temp ≥38 that occurs ≥48hrs after admission and is recorded on at least two separate occasions over 48h

Causes

- Infection (commonest cause)
- Inflammation
- Ischaemia
- Malignancy
- Drug-induced

Mx

- Careful Hx and examination
- Study drug list
- Basic Ix
 - Urinalysis
 - FBC, LFT, ESR, cultures
 - Swabs
 - CXR

Neurology

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Basic Neuroscience

The Spinal Cord

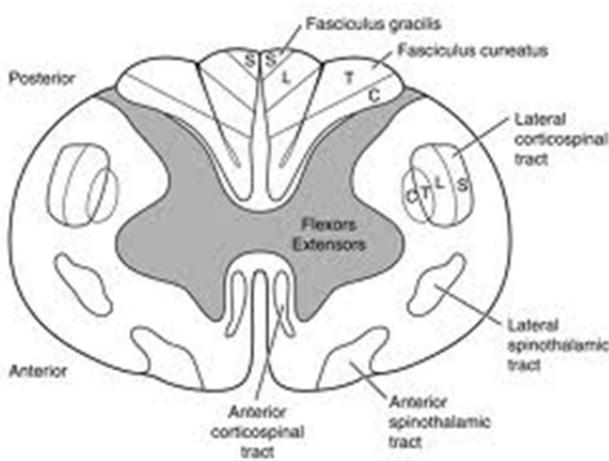
Gross Anatomy

- Foramen magnum to L1
- Terminates as conus medullaris
- Spinal nerves continue inferiorly as corda equina
- Denticulate ligament and filum terminale are pial extensions that suspend cord in subarachnoid space.

Blood Supply

- 3 longitudinal vessels
 - 2 posterior spinal arteries: dorsal 1/3
 - 1 anterior spinal artery: ventral 2/3
- Reinforced by segmental feeder arteries
 - E.g. artery of Adamkiewicz
- Longitudinal veins drain into extradural vertebral plexus

Organisation



Dorsal Columns (FG + FC)

- **Mode:** fine touch, vibration and proprioception
- **Cell body:** DRG
- **Decussation:** in medulla forming medial lemniscus

Lateral Spinothalamic Tract

- **Mode:** pain and temperature
- **Cell body:** DRG
- **Decussation:** in cord, at entry level

Lateral Corticospinal Tract

- **Mode:** motor (body)
- **Cell body:** 1° motor cortex
- **Decussation:** pyramidal decussation in ventral medulla

Thalamic Nuclei

- **VPL:** somatosensory body
- **VPM:** somatosensory head
- **LGN:** visual
- **MGN:** auditory

Cerebellum and Basal Ganglia

- Output to cortex via thalamus
- Regulation of posture, locomotion, coordination and movement.

Internal Capsule

- White matter carrying axonal fibres from motor cortex to pyramids of medulla.
- Infarction → contralateral hemiparesis

Brain Lobar Function

Frontal

- Cognition and memory
- Executive function
- Motor cortex
- Dominant hemisphere: motor speech (Broca's area)

Parietal

- Sensory cortex
- Body orientation

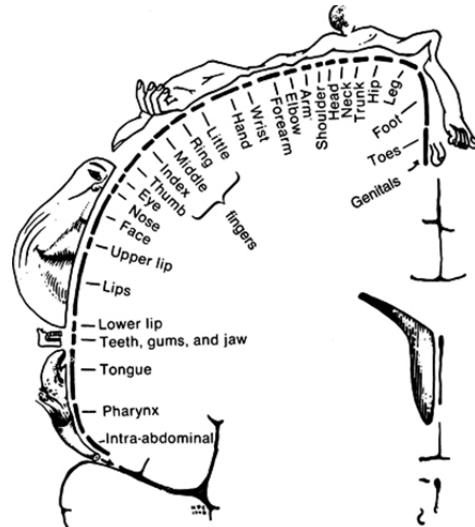
Temporal

- Memory
- Dom hemisphere: receptive language (Wernicke's)

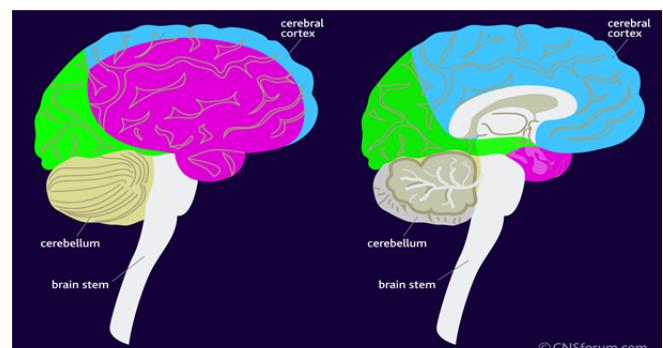
Occipital

- Visual cortex

Homunculus

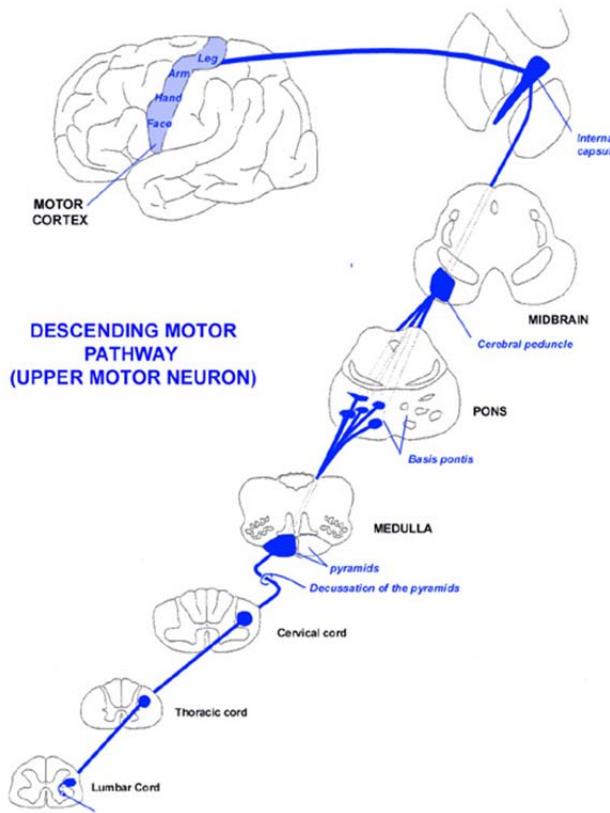


Brain Blood Supply

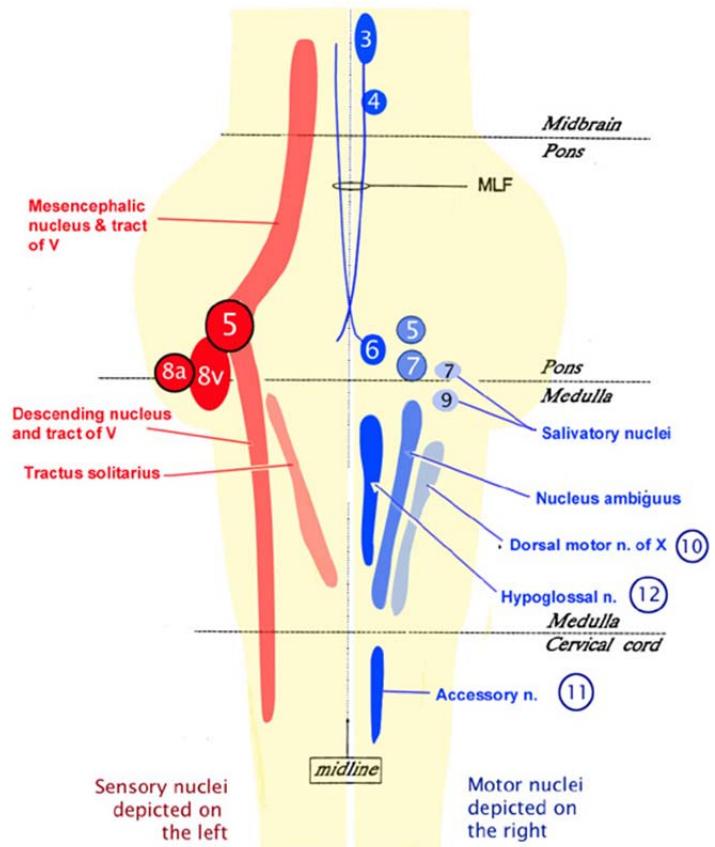


Long Tracts

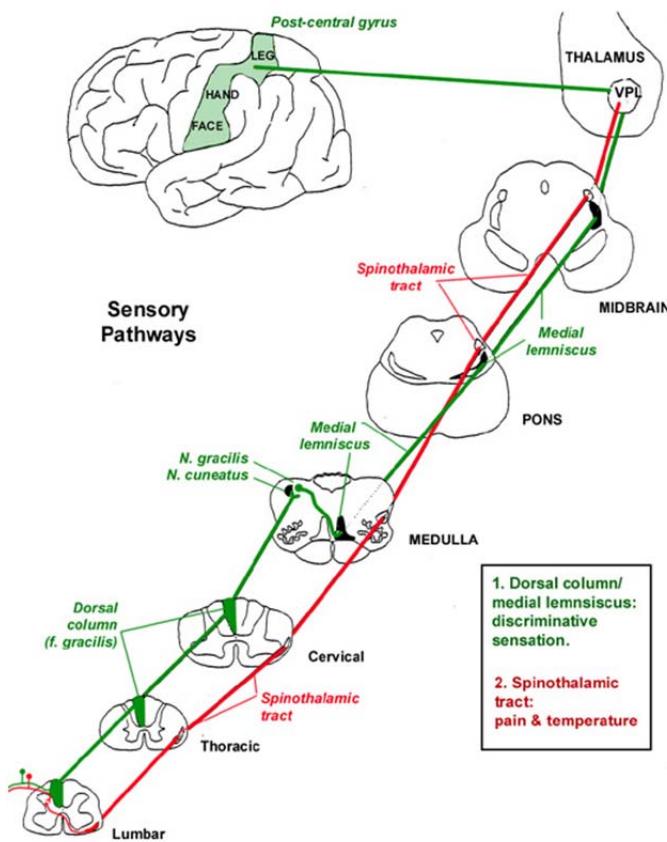
Motor Pathway



Cranial Nerve Nuclei



Sensory Pathway



NMJ

Transmission

1. Presynaptic voltage-gated Ca^{2+} channels open $\rightarrow \text{Ca}^{2+}$ influx
2. ACh vesicles released from presynaptic terminal
3. ACh diffuses across cleft
4. ACh binds to **nicotinic** receptors on post-synaptic terminal
5. $\rightarrow \text{Na}^+$ influx \rightarrow depolarisation $\rightarrow \text{Ca}^{2+}$ release from SR \rightarrow muscle contraction
6. ACh is degraded by acetylcholinesterase and choline is taken up into presynaptic terminal.

Blockade

1. Block presynaptic choline uptake: hemicholinium
2. Block ACh vesicle fusion: botulinum, LEMS
3. Block nicotinic ACh receptors
 - Non-depolarising: atracurium, vecuronium
 - Depolarising: suxamethonium

Dopamine Pathways

- **Mesocorticolimbic:** SCZ
- **Nigrostriatal:** Parkinsonism
- **Tuberoinfundibular:** Hyperprolactinaemia

Sympathetic NS

- Cell bodies from T1-L2
- GVE preganglionic fibres synapse @ either:
 - Paravertebral ganglia
 - Prevertebral ganglia
 - Chromaffin cells of adrenal medulla
- Preganglionic fibres are myelinated and release ACh @ nicotinic receptors
- Postganglionic fibres are unmyelinated and release NA @ adrenergic receptors
 - Except @ sweat glands where they release ACh for muscarinic receptors.

Parasympathetic NS

- **Cranial:** CN 3, 7, 9, 10
 - **Ciliary:** ciliary muscle and sphincter pupillae
 - **Pterygopalatine:** mucus mems of nose and palate, lacrimal gland
 - **Submandibular:** submandibular and sublingual glands
 - **Otic:** parotid gland
 - Vagus supplies thoracic and abdo viscera
- **Sacral:** pelvic splanchnic nerves (S2-4) innervate pelvic viscera
- Preganglionic fibres release ACh @ nicotinic receptors
- Postganglionic fibres release ACh @ muscarinic receptors

CN Nuclei

- Midbrain: 3, 4, (5)
- Pons: 5, 6, 7, 8
- Medulla: (5), 9, 10, 11, 12

NB. All nuclei except 4, innervate ipsilateral side. Fibres from trochlear nucleus decussate in medulla and supply contralateral SOB muscle.

Vestibulo-ocular Pathways

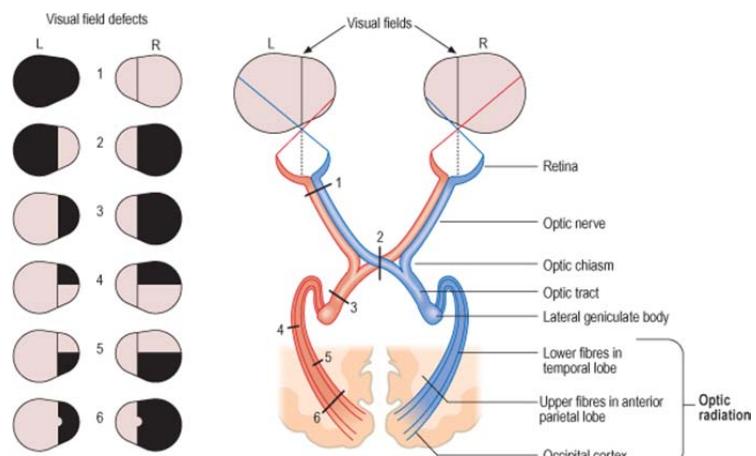
Vestibulo-ocular reflex (VOR)

- Axons from vestibular neurones project via MLF to abducens and oculomotor nuclei
- Head turns L \rightarrow eyes turn R
- Absent Doll's Eye sign = brainstem death

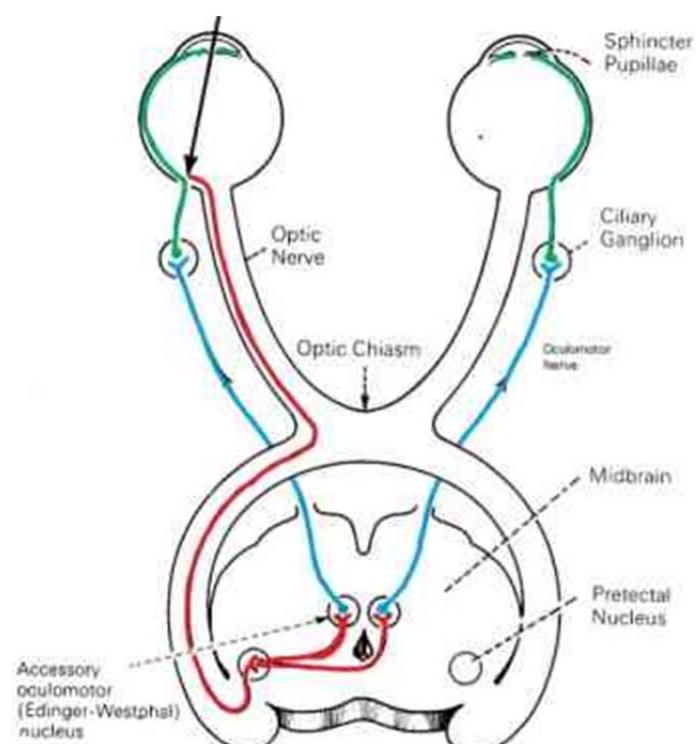
Caloric Tests

- Warm \rightarrow \uparrow firing of vestibular N. \rightarrow eyes turn to contralateral side \therefore nystagmus to ipsilateral side
- Remember fast direction of nystagmus – COWS
 - Cold: Opposite
 - Warm: Same
- Absence of eye movements = brainstem damage on side being tested.

Visual Field Defects



Pupillary Light Reflex



Motor and Sensory Patterns

Patterns of Motor Deficits

Cortical Lesions

- Hyperreflexia proximally in arm or leg
- Unexpected patterns: e.g. all movements in hand/foot

Internal Capsule and Corticospinal Lesions

- Contralateral hemiparesis \bar{c} pyramidal distribution.
- Lesion \bar{c} epilepsy, \downarrow cognition or homonymous hemianopia = in a cerebral hemisphere
- Lesion \bar{c} contralateral CN palsy = brainstem lesion on the side of the palsy (E.g. Millard-Gubler syn.)

Cord Lesions

- Quadripareisis / paraparesis
- Motor and reflex level: LMN signs at level of lesion and UMN signs below

Peripheral Neuropathies

- Usually distal weakness
- In GBS weakness is proximal (root involvement)
- Single nerve = mononeuropathy: trauma or entrapment
- Several nerves = mononeuritis multiplex: vasculitis or DM

UMN Lesions

- Motor cells in pre-central gyrus to anterior horn cells in the cord
- Pyramidal weakness: extensors in UL, flexors in LL
- No wasting
- Spasticity: \uparrow tone \pm clonus
- Hyperreflexia
- Up-going plantars

LMN Lesions

- Anterior horn cells to peripheral nerves
- Wasting
- Fasciculation
- Flaccidity: \downarrow tone
- Hyporeflexia
- Down-going plantars

Primary Muscle Lesions

- Symmetrical loss
- Reflexes lost later vs. neuropathies
- No sensory loss
- Fatigability in myasthenia

Patterns of Sensory Deficits

- Pain and temp travel in small fibres in peripheral nerves and in anterolateral spinothalamic tracts
- Touch, joint position and vibrations travel in large fibres peripherally and in dorsal columns centrally

Distal Sensory Loss

- Suggests a neuropathy

Sensory Level

- Hallmark of cord lesion
- Hemi-cord lesion \rightarrow Brown-Séquard syndrome
 - Ipsilateral loss of proprioception / vibration and UMN weakness with contralateral loss of pain

Dissociated Sensory Loss

- Selective loss of pain and temp \bar{c} conservation of proprioception and vibration
- Occurs in cervical cord lesions: e.g. syringomyelia

Specific Neurological Patterns and Causes

Cerebellar Syndrome

Effects: DANISH

- Dysdiadochokinesia
- Dysmetria: past-pointing
- Ataxia: limb / trunkal
- Nystagmus: horizontal = ipsilateral hemisphere
- Intention tremor
- Speech: slurred, staccato, scanning dysarthria
- Hypotonia

Common Causes: PASTRIES

- Paraneoplastic: e.g. from bronchial Ca
- Alcohol: thiamine and B12 deficiency
- Sclerosis
- Tumor: e.g. CPA lesion
- Rare: MSA, Friedrich's, Ataxia Telangiectasia
- Iatrogenic: phenytoin
- Endo: hypothyroidism
- Stroke: vertebrobasilar

Anterior Cerebral Artery

- Supplies frontal and medial part of cerebrum
- Contralateral motor / sensory loss in the legs > arms
- Face is spared
- Abulia (pathological laziness)

Middle Cerebral Artery

- Supplies lateral / external part of hemisphere
- Contralateral motor / sensory loss in face and arms > legs.
- Contralateral homonymous hemianopia due to involvement of optic radiation
- Cognitive changes
 - Dominant (L): aphasia
 - Non-dominant (R): neglect, apraxia

Posterior Cerebral Artery

- Supplies occipital lobe
- Contralateral homonymous hemianopia \bar{c} macula sparing.

Vertebrobasilar Circulation

- Supplies cerebellum, brainstem and occipital lobes
- Combination of symptoms
 - Visual: hemianopia, cortical blindness
 - Cerebellar: DANISH
 - CN lesions
 - Hemi- / quadriplegia
 - Uni- / bi-lateral sensory symptoms

Lateral Medullary Syn. / Wallenberg's Syn.

- Occlusion of one vertebral A. or PICA
- Features: DANVAH
 - Dysphagia
 - Ataxia (ipsilateral)
 - Nystagmus (ipsilateral)
 - Vertigo
 - Anaesthesia
 - Ipsilateral facial numbness + absent corneal reflex
 - Contralateral pain loss
 - Horner's syndrome (ipsilateral)

Millard-Gubler Syndrome: crossed hemiplegia

- Pontine lesions (e.g. infarct)
- Effects: 6th and 7th CN palsy + contralateral hemiplegia

Locked-in Syndrome

- Pt. is aware and cognitively intact but completely paralysed except for the eye muscles.
- Causes
 - Ventral pons infarction: basilar artery
 - Central pontine myelinolysis: rapid correction of hyponatraemia

Cerebellopontine Angle Syndrome

- Causes: acoustic neuroma, meningioma, cerebellar astrocytoma, metastasis (e.g. breast)
- Effects: ipsilateral CN 5, 6, 7, 8 palsies + cerebellar signs
 - Absent corneal reflex
 - LMN facial palsy
 - LR palsy
 - Sensorineural deafness, vertigo, tinnitus
 - DANISH

Subclavian Steal Syndrome

- Subclavian A. stenosis proximal to origin of vertebral A. may → blood being stolen from this vertebral artery by retrograde flow.
- Syncope / presyncope or focal neurology on using the arm.
- BP difference of >20mmHg between arms

Anterior Spinal Artery / Beck's Syndrome

- Infarction of spinal cord in distribution of anterior spinal artery: ventral 2/3 or cord.
- Causes: Aortic aneurysm dissection or repair
- Effects
 - Para- / quadri-paresis
 - Impaired pain and temperature sensation
 - Preserved touch and proprioception

Muscle Weakness Differential

1. Cerebrum / Brainstem

- Vascular: infarct, haemorrhage
- Inflammation: MS
- SOL
- Infection: encephalitis, abscess

2. Cord

- Vascular: anterior spinal artery infarction
- Inflammation: MS
- Injury

3. Anterior Horn

- MND, polio

4. Roots / Plexus

- Spondylosis
- Cauda equina syndrome
- Carcinoma

5. Motor Nerves

- Mononeuropathy: e.g. compression
- Polyneuropathy: e.g. GBS, CMT

6. NMJ

- GB, LEMS, botulism

7. Muscle

- Toxins: steroids
- Poly- / Dermato-myositis
- Inherited: DMD, BMD, FSH

Hand Wasting Differential

1. Cord

- Anterior Horn: MND, polio
- Syringomyelia

2. Roots (C8 T1)

- Compression: spondylosis, neurofibroma

3. Brachial Plexus

- Compression
 - Cervical rib
 - Tumour: Pancoast's, breast
- Avulsion: Klumpke's palsy

4. Neuropathy

- Generalised: CMT
- Mononeuritis multiplex: DM
- Compressive mononeuropathy
 - Median: thenar wasting
 - Ulnar: hypothenar and interossei wasting

5. Muscle

- Disuse: RA
- Compartment syndrome: Volkman's ischaemic contracture
- Distal myopathy: myotonic dystrophy
- Cachexia

Gait Disturbance Differential

Motor

Basal Ganglia: festinating / shuffling

- PD
- Parkinsonism: MSA, PSP, Lewy body dementia, CBD

UMN Bilateral: spastic, scissoring

- **Cord:** compression, trauma, hereditary spastic paraparesis, syringomyelia, transverse myelitis
- **Bihemispheric:** CP, MS

UMN Unilateral: spastic circumducting

- **Hemisphere lesion:** CVS, MS, SOL
- **Hemicord:** MS, tumour

LMN Bilateral: bilat foot drop

- **Polyneuropathy:** CMT, GBS
- Cauda equina

LMN Unilateral: foot drop → high stepping gait

- **Ant horn:** polio
- **Radicular:** L5 root lesion
- **Sciatic / common peroneal nerve:** trauma, DM

Mixed UMN and LMN: MAST

- MND
- Ataxia: Friedrich's
- SACD
- Taboparesis

Sensory

Vestibular (Romberg's +ve)

- Meniere's
- Viral labyrinthitis
- Brainstem lesion

Cerebellar: ataxic

- EtOH
- Infarct

Proprioceptive Loss (Romberg's +ve)

- Dorsal columns: B12 deficiency
- Peripheral neuropathy: DM, EtOH, uraemia

Visual Loss

Other

- Myopathy, MG/LEMS
- Medical: postural hypotension, Stokes-Adams, arthritis

Blackouts

Causes: CRASH

Cardiac: Stokes-Adams Attacks

- **Brady:** heart block, sick sinus, long-QT
- **Tachy:** SVT, VT
- **Structural**
 - Weak heart: LVF, tamponade
 - Block: AS, HOCM, PE

Reflexes

1. Vagal overactivity
 - Vasovagal syncope
 - Situational: cough, effort, micturition
 - Carotid sinus syncope
2. Sympathetic underactivity = Post. Hypotension
 - Salt deficiency: hypovolaemia, Addison's
 - Toxins
 - Cardiac: ACEi, diuretics, nitrates, α-B
 - Neuro: TCAs, benzos, antipsychotics, L-DOPA
 - Autonomic Neuropathy: DM, Parkinson's, GBS
 - Dialysis
 - Unwell: chronic bed-rest
 - Pooling, venous: varicose veins, prolonged standing

Arterial

- Vertebrobasilar insufficiency: migraine, TIA, CVA, subclavian steal
- Shock
- Hypertension: phaeochromocytoma

Systemic

- Metabolic: ↓glucose
- Resp: hypoxia, hypercapnoea (e.g. anxiety)
- Blood: anaemia, hyperviscosity

Head

- Epilepsy
- Drop attacks

Examination

- Postural hypotension: difference of >20/10 after standing for 3min vs. lying down
- Cardiovascular
- Neurological

Ix

- ECG ± 24hr ECG
- U+E, FBC, Glucose
- Tilt table
- EEG, sleep EEG
- Echo, CT, MRI brain

Presentation and Investigation

Cardiogenic Syncope

- **Trigger:** exertion, drug, unknown
- **Before:** palpitations, chest pain, dyspnoea
- **During:** pale, slow/absent pulse, clonic jerks may occur
- **After:** rapid recovery
- **Ix:** ECG, 24hr ECG, Echo

Reflex: Vasovagal

- **Trigger:** prolonged standing, heat, fatigue, stress
- **Before**
 - Gradual onset: secs→mins
 - Nausea, pallor, sweating, tunnel vision, tinnitus
 - Cannot occur lying down
- **During**
 - Pale, grey, clammy, brady
 - Clonic jerks and incontinence can occur, but no tongue biting
- **After:** rapid recovery
- **Ix:** Tilt-table testing

Reflex: Postural Hypotension

- **Trigger:** Standing up
- Before, During and After as for vagal above
- **Ix:** Tilt-table testing

Arterial

- **Trigger:** Arm elevation (subclavian steal), migraine
- Before, During and After as for vasovagal ± brainstem Sx (diplopia, nausea, dysarthria)
- **Ix:** MRA, duplex vertebrobasilar circulation

Systemic

- **Hypoglycaemia:** tremor, hunger, sweating, light-headedness → LOC

Head: Epileptic

- **Trigger:** flashing lights, fatigue, fasting
- **Before:** e.g. aura in complex partial seizures – feeling strange, epigastric rising, déjà/jamais vu, smells, lights, automatisms
- **During:** Tongue biting, incontinence, stiffness→jerking, eyes open, cyanosis, ↓SpO₂
- **After:** headache, confusion, sleeps, Todd's palsy
- **Ix:** EEG, ↑ se prolactin at 10-20min

Head: Drop Attacks

- **Trigger:** nil
- **Before:** no warning
- **During:** sudden weakness of legs causes older woman to fall to the ground.
- **After:** no post-ictal phase

Vertigo and Dizziness

Vertigo

- The illusion of movement: usually rotatory
- Of patient or surroundings
- Worse on movement

Not Vertigo

- Faintness
- Light-headedness
- Lost awareness

Dizziness

- \bar{c} Impaired consciousness = blackout
- w/o impaired consciousness
 - Vertigo: vestibular
 - Imbalance: vestibular, cerebellar, extrapyramidal

Causes of Vertigo: IMBALANCE

- Infection / Injury
 - Labyrinthitis: post-viral severe vertigo, n/v
 - Ramsay Hunt
 - Trauma: to petrous temporal bone
- Meniere's
 - Recurrent vertigo (~20min) \pm n/v
 - Fluctuating SNHL
 - Tinnitus
 - Aural fullness
- Benign Positional Vertigo
 - Sudden vertigo provoked by head rotation
- Aminoglycosides / frusemide
- Lymph, Peri-, fistula
 - Path: Connection between inner and middle ears
 - Causes: Congenital, trauma
 - PC: vertigo, SNHL
 - o/e: Tullio's phen – nystagmus evoked by loud sound
- Arterial
 - Migraine
 - TIA / stroke
- Nerve
 - Acoustic neuroma / vestibular schwannoma
- Central lesions
 - Demyelination, tumour, infarct (e.g. LMS)
- Epilepsy
 - Complex partial

Causes of Hearing Loss

Conductive: WIDENING

- Wax or foreign body
- Infection: otitis media, OME
- Drum perforation
- Extra: ossicle discontinuity – otosclerosis, trauma
- Neoplasia: carcinoma
- INjury: e.g. barotrauma
- Granulomatous: Wegener's, Sarcoid

Sensorineural: DIVINITY

Developmental

- Genetic: Alport's, Waardenburgs
- Congenital: TORCH
- Perinatal: anoxia

Degenerative

- Presbyacusis

Infection

- VZV, measles, mumps, influenza
- Meningitis

Vascular

- Ischaemia: Internal Auditory Artery (AICA) → sudden hearing loss and vertigo
- Stroke

Inflammation

- Vasculitis
- Sarcoidosis

Neoplasia

- CPA tumours: acoustic neuroma (commonest cause of unilateral SNHL)

Injury

- Noise
- Head trauma

Toxins

- Gentamicin
- Frusemide
- Aspirin

Lymph

- Endolymphatic Hydrops = Meniere's
- Perilymphatic fistula: ruptured round window

Abnormal Involuntary Movements – Dyskinesias

Tremor

- Regular, rhythmic oscillation
- NB. Asterixis = rhythmic myoclonus

Types and Causes: RAPID

Resting

- **Features**
 - 4-6Hz, pill-rolling
 - Abolished on voluntary movement
 - ↑ \bar{C} distraction (e.g. counting backwards)
- **Causes:** Parkinsonism
- **Rx:** Da agonists, antimuscarinic (e.g. procyclidine)

Action / Postural

- **Features**
 - 6-12Hz
 - Absent at rest
 - Worse \bar{C} outstretched hands or movement
 - Equally bad at all stages of movement
- **Causes:** BEATS
 - Benign essential tremor
 - Endocrine: thyrotoxicosis, ↓ glucose, phaeo
 - Alcohol withdrawal (or caffeine, opioids...)
 - Toxins: β -agonists, theophylline, valproate, PHE
 - Sympathetic: physiological tremor may be enhanced: e.g. in anxiety

Intention

- **Features**
 - >6Hz, irregular, large amplitude
 - Worse at end of movement
 - E.g. past-pointing
- **Causes:** cerebellar damage

Dystonic

- **Features:** variable
- **Causes:** mostly idiopathic, as for dystonia

Benign Essential Tremor

- Autosomal dominant
- Occur \bar{C} action and worse \bar{C} anxiety, emotion, caffeine
- Arms, neck, voice
- Doesn't occur during sleep
- Better \bar{C} EtOH

Myoclonus

- Sudden, involuntary jerks

Causes

- Metabolic = Asterixis (L, R, ↑CO₂)
- Neurodegenerative diseases (LSDs)
- CJD
- Myoclonic epilepsies (e.g. infantile spasms)

Benign Essential Myoclonus

- Auto dom
- Childhood onset frequent generalised myoclonus w/o progression.
- May respond to valproate

Dystonia

- Prolonged muscle contracture → unusual joint posture or repetitive movements

Idiopathic generalised dystonia

- Often autosomal dominant
- Childhood onset: starts in one leg and spreads on that side of the body over 5-10yrs

Idiopathic focal dystonia

- Commonest form of dystonia
- Confined to one part of the body
- Worsened by stress
- Types:
 - Spasmodic torticollis
 - Blepharospasm
 - Oromandibular
 - Writer's / Musician's cramp

Acute Dystonia

- Torticollis, trismus and/or oculogyric crisis
- Typically a drug reaction:
 - Neuroleptics
 - Metoclopramide
 - L-DOPA
- **Rx:** procyclidine (antimuscarinic)

Chorea

- Non-rhythmic, purposeless, jerky, flitting movements
- E.g. facial grimacing, flexing / extending the fingers
- **Causes**
 - Huntington's
 - Sydenham's
 - Wilson's
 - L-DOPA

Athetosis

- Slow, sinuous, writhing movements
- **Causes**
 - Cerebral palsy
 - Kernicterus

Hemiballismus

- Large amplitude, flinging hemichorea
- Contralateral to a vascular lesion in the subthalamic nucleus: often elderly diabetics
- Recovers spontaneously over months

Tardive Syndromes

- Delayed onset following chronic exposure to Da agonists (e.g. antipsychotics, antiemetics, L-DOPA)

Classification

- Dyskinesia: orobuccolingual, truncal or choreiform movements
- Dystonia: sustained, stereotyped muscle spasms of twitching or turning
- Akathisia: unpleasant sense of inner restlessness ± repetitive movements (e.g. pacing)

Rx

- Change (e.g. to atypical) or slowly withdraw drug
- Dyskinesia: Da antagonist (tetrabenazine)
- Akathisia: β -B

Dementia

Definition

- Chronically impaired cognition that affects multiple domains: memory, attention, language
- No impairment of consciousness
- Acquired and progressive (cf. LD)

Alzheimer's Disease

- **Epi:** 50%
- **Path:** neurofibrillary tangles and β amyloid plaques
- **PC:** progressive, global cognitive decline
- **RFs:** ApoE4 allele, presenilin 1/2 mutations, Down's
- **Ix:** MRI – medial temporal lobe atrophy
- **Rx:** cholinesterase inhibitors (donepezil, rivastigmine) if MMSE is 10-20

Vascular Dementia

- **Epi:** 20%
- **Path:** multiple infarcts
- **PC:** sudden onset, stepwise deterioration, patchy deficits, vascular RFs
- **Ix:** MRI – extensive infarcts or small vessel disease
- **Rx:** manage predisposing factors

Lewy Body Dementia

- **Epi:** 20%
- **Path:** Lewy Bodies in occipito-parital cortex
- **PC:** Fluctuating cognitive dysfunction, visual hallucinations, parkinsonism
- **Rx:** cholinesterase inhibitors

Frontotemporal Dementia (Pick's)

- **Epi:** <5%
- **Path:** Pick Bodies
- **PC:** disinhibition, personality change, early memory preservation, progressive aphasia
- **Ix:** MRI – frontal or temporal atrophy

Ameliorable Causes

Infection

- Viral: HIV, HSV, PML
- Helminth: cysticercosis, toxo

Vascular

- Chronic subdural haematoma

Inflammation

- SLE
- Sarcoid

Neoplasia

Nutritional

- Thiamine deficiency
- B12 and folate deficiency
- Pellagra (B3 / niacin deficiency)

Hypothyroid

Hypoadrenalinism

Hypercalcaemia

Hydrocephalus (normal pressure)

Delirium / ACS

Definition

- Globally impaired cognition and impaired consciousness

Features

- Disorientation to person, time and place
- Reversal of sleep-wake cycle (hyperactive at night)
- Labile mood
- Illusions, delusions and hallucinations
- Cognitive impairment: mem, language, concentration...

Causes: DELIRIUMS

- **Drugs:** opioids, sedatives, L-DOPA
- **Eyes, ears and other sensory deficits**
- **Low O₂ states:** MI, stroke, PE
- **Infection**
- **Retention:** stool or urine
- **Ictal**
- **Under- hydration / -nutrition**
- **Metabolic:** DM, post-op, sodium, uraemia
- **Subdural haemorrhage** or other intracranial pathology

Ix

- **Bloods:** FBC, U+E, LFTs, glucose, ABG
- Urine dip
- Septic screen
- ECG, LP

Mx

- ID and Rx underlying cause
- Surround \bar{c} familiar people
- Nurse in moderately lit, quiet room
- Find glasses, hearing aids...
- Avoid sedatives if possible, but if disruptive:
 - Haldol 0.5-2mg PO/IM
 - Chlorpromazine 50-100mg PO/IM (avoid in elderly)

Headache: Differential and Investigation

Acute: VICIOUS

Vascular

- Haemorrhage: SAH, intracranial, intracerebral
- Infarction: esp. posterior circulation
- Venous: Sinus / cortical thrombosis

Infection/Inflammation

- Meningitis
- Encephalitis
- Abscess

Compression

- Obstructive hydrocephalus: tumour
- Pituitary enlargement: apoplexy

ICP

- Spontaneous intracranial hypotension
 - Acute dural CSF leak
 - Worse on standing initially.

Ophthalmic

- Acute glaucoma

Unknown

- Situational: cough, exertion, coitus

Systemic

- HTN: Phaeo, PET
- Infection: sinusitis, tonsillitis, atypical pneumonia
- Toxins: CO

Investigations:

Bloods

Urine

Micro

- Blood cultures
- Serology: enterovirus (common cause of viral meningitis), HSV, HIV, syphilis, crypto
- CSF

Radiology

- Non-contrast CT
 - SAH: blood in sulci, cisterns (white). 90% sensitivity in first 24h
- MRI
 - MRA: aneurysm
 - MRV: sinus thrombosis

Special: CSF

- Opening pressure (norm = 5-20cm H₂O):
 - ↑: SAH, meningitis
 - ↓: spontaneous intracranial hypotension
- Xanthochromia: yellow appearance of CSF due to bilirubin. Detect by spectrophotometry.

Chronic: MCD TINGS

Migraine

Cluster headaches

Drugs

- Analgesics
- Caffeine
- Vasodilators: Ca²⁺ antagonists, nitrates

Tension headaches

ICP ↑/↓

- ↑: tumour, aneurysm, AVM, benign intracranial HTN
- ↓: spontaneous intracranial hypotension

Neuralgia (trigeminal)

Giant cell arteritis

Systemic

- HTN
- Organ failure: e.g. uraemia

Findings	Bacterial	TB	Viral
Appearance	Turbid	Fibrin web	Clear
Cells	PMN	Lympho / mononuc	Lympho / mononuc
Count	100-1000	10-1000	50-1000
Glucose	↓ (< ½ plasma)	↓ (< ½ plasma)	> ½ plasma
Protein (g/L)	↑↑ (>1.5)	↑↑↑ (1-5)	mild ↑ (<1)

Headaches: Key Features

SAH

- Sudden onset, worst ever, occipital headache.
- Meningism, focal signs, ↓consciousness

Venous Sinus Thrombosis

- **Sagittal:** headache, vomiting, seizures, ↓vision, papilloedema
- **Transverse:** headache ± mastoid pain, focal CNS signs, seizures, papilloedema

Cortical Vein Thrombosis

- Thunderclap headache
- Stroke-like focal symptoms over days
- Focal seizures are common

Meningitis

- Fever, photophobia, neck stiffness, kernig's +ve
- Purpuric rash
- ↓consciousness

Encephalitis

- Fever, odd behaviour, fits, focal neuro, ↓consciousness

Acute Glaucoma

- Constant unilat eye pain, radiating to forehead
- ↓ acuity, haloes, n/v
- Red eye, cloudy cornea.
- Dilated, non-responsive pupil

Tension Headache

- Bilateral / vertex-bitemporal, non-pulsatile, band-like

Migraine

- Prodrome → aura → headache
- Unilat, throbbing
- n/v, phono/photophobia

Cluster

- Rapid onset very severe pain around/behind one eye.
- Red, watery eye, nasal congestion
- Miosis, ptosis
- Attacks last 15min–3hrs, 1-2x/day, mostly nocturnal
- Clusters last 4-12wks, remission lasts 3mo-3yrs. Can be chronic vs. episodic.
- **Rx:** 100% O₂ via non-rebreath mask, Sumitriptan
- **Prevention:** verapamil, topiramate, Li

Hemicrania

- Paroxysmal hemicranias: cluster-like headache lasting 5-45min, 5-30x/day
- SUNCT: short-lasting unilateral neuralgia with conjunctival injection and tearing, attacks last 15-60s, recur 5-30x/hr
- Hemicrania continua: continuous cluster-like headache
- **Rx:** all respond well to indomethacin

Trigeminal neuralgia

- Paroxysms of unilateral intense stabbing pain in trigeminal distribution (usually V2/3)
- **Triggers:** washing area, shaving, eating, talking
- Male > 50yrs
- 2^o in 14%: compression of CNV, MS, Zoster, Chiari malformation
- **Ix:** exclude 2^o cause by MRI.
- **Rx Med:** CBZ, lamotrigine, gabapentin
- **Rx Surg:** microvascular decompression

Analgesia Overuse

- Episodic headache becomes daily chronic headache
- Use OTC analgesia on 6 days/month max

ICP

- ↑: worse in AM, stooping, visual probs (papilloedema), obese women
- ↓: worse sitting or standing

TMJ Dysfunction

- Preauricular pain on chewing
- Assoc. Č crepitus
- Earache, headache

Giant Cell Arteritis (>60yrs, ESR>60, pred 60mg)

- Unilateral temple/scalp pain and tenderness.
- Thickened, pulseless temporal artery
- Jaw claudication, amaurosis fugax, sudden blindness
- Assoc. Č PMR in 50%
- **Ix:** ESR↑↑, plats↑, ALP↑, Hb↓, temporal artery biopsy
- **Rx**
 - High dose pred (60mg/d PO) for 5-7d
 - Guided by symptoms and ESR.
 - Give PPI+bisphosphonate.
- **Prog:** 2yr course then complete remission

Migraine

Epidemiology

- 8% prev
- F:M = 2:1

Risk Factors

- Obesity
- PFO

Pathophysiology

- Vascular: cerebrovascular constriction → aura, dilatation → headache.
- Brain: spreading cortical depression
- Inflammation: activation of CN V nerve terminals in meninges and cerebral vessels.

Triggers

- CHOCOLATE
- CHeese
- OCP
- Caffeine
- alcohOL
- Anxiety
- Travel
- Exercise

Symptoms

Headache

- Aura lasting 15-30min then unilat, throbbing headache
- Phono/photophobia
- n/v
- Allodynia
- Often premenstrual

Prodrome (50%): precede migraine by hrs - days

- Yawning
- Food cravings
- Changes in sleep, appetite or mood

Aura (20%): precedes migraine by mins and may persist

- **Visual:** distortion, lines, dots, zig-zags, scotoma, hemianopia
- **Sensory:** paraesthesia (fingers → face)
- **Motor:** dysarthria, ataxia, ophthalmoplegia, hemiparesis (hemiplegic migraine)
- **Speech:** dysphasia, paraphasia

Classification

- Migraine w/o aura (common migraine)
- Migraine w/ aura (classical migraine)

Diagnostic Criteria

- Typical aura + headache, or
- ≥ 5 headaches lasting 4-72h with either n/v or photo/phonophobia + ≥2 of:
 - Unilat
 - Pulsating
 - Interferes with normal life
 - Worsened by routine activity

Differential

- Cluster / tension headache
- Cervical spondylosis
- HTN
- Intracranial pathology
- Epilepsy

Treatment

Acute episode

- 1st: Paracetamol + metoclopramide / domperidone
- 2nd: NSAID (e.g. ketoprofen) + M/D
- 3rd: Rizatriptan
 - CI: IHD, uncontrolled HTN, SSRIs
- 4th: ergotamine

Prophylaxis

- Avoid triggers
- 1st: Propanolol, topiramate
- 2nd: Valproate, pizotifen (↑ wt.), gabapentin

Subarachnoid Haemorrhage

Epidemiology

- 9/100,000
- 35-65yrs

Causes

- Rupture of saccular aneurysms (80%)
- AVMs (15%)

Risk Factors

- Smoking
- HTN
- EtOH
- Bleeding diathesis
- Mycotic aneurysms (SBE)
- FH (close relatives have 3-5x risk)

Berry Aneurysms

Sites

- Junction of post. communicating $\overline{\text{C}}$ IC
- Junction of ant. communicating $\overline{\text{C}}$ ACA
- Bifurcation of MCA

Associations

- Adult polycystic kidneys
- CoA
- Ehlers Danlos

Symptoms

- Sudden, severe occipital headache
- Collapse
- Meningism: neck stiffness, n/v, photophobia
- Seizures
- Drowsiness \rightarrow coma

Signs

- Kernig's
- Retinal or subhyaloid haemorrhage
- Focal neuro
 - @ presentation suggests aneurysm location
 - Later deficits suggests complications

Sentinel Headache

- ~6% of pts. experience sentinel headache from small warning bleed.

Differential

- In 1^o care, 25% of those $\overline{\text{C}}$ thunderclap headache have SAH
- 50-60% no cause found
- Rest: meningitis, intracerebral bleeds, cortical vein thrombosis

Investigations

CT

- Detects >90% of SAH w/i first 48hrs

LP

- If CT-ve and no CIs >12h after start of headache
- Xanthochromia due to breakdown of bilirubin

Mx

- Frequent neuro obs: pupils, GCS, BP
- Maintain CPP: keep SBP >160
- Nimodipine for 3wks \rightarrow ↓ cerebral vasospasm
- Endovascular coiling (preferable to surgical clipping)

Complications

Rebleeding: 20%

- Commonest cause of mortality

Cerebral Ischaemia

- Due to vasospasm
- Commonest cause of morbidity

Hydrocephalus

- Due to blockage of arachnoid granulations
- May require ventricular or lumbar drain

Hyponatraemia

- Common
- Don't Mx $\overline{\text{C}}$ fluid restriction

Mx of Unruptured Aneurysms

- Young pts. $\overline{\text{C}}$ aneurysms >7mm in diameter may benefit from surgery.

Stroke: Causes and Investigation

Definition

- Rapid onset, focal neurological deficit due to a vascular lesion lasting >24h

Pathogenesis

- Infarction due ischaemia (80%) or intracerebral haemorrhage (20%).

Ischaemia (80%)

- Atheroma
 - Large (e.g. MCA)
 - Small vessel perforators (lacunar)
- Embolism
 - Cardiac (30% of strokes): AF, endocarditis, MI
 - Atherothromboembolism: e.g. from carotids

Haemorrhage (20%)

- ↑BP
- Trauma
- Aneurysm rupture
- Anticoagulation
- Thrombolysis

Rarer Causes

- Watershed stroke: sudden ↓ in BP (e.g. in sepsis)
- Carotid artery dissection
- Vasculitis: PAN, HIV
- Cerebral vasospasm 2^o to SAH
- Venous sinus thrombosis
- Anti-phospholipid syndrome, thrombophilia

Risk Factors

- **HYPERTENSION**
- Smoking, DM, ↑ lipids, FH
- Cardiac: **AF**, valve disease
- Peripheral vascular disease
- Previous history
- Ethnicity: ↑ in Blacks and Asians
- ↑ PCV/Hct
- OCP

Cardiac Causes of Stroke

- AF: 4.5% /yr
- External cardioversion: 1-3%
- Prosthetic valves
- Acute MI: esp. large anterior
- Paradoxical systemic emboli
- Cardiac surgery
- Valve vegetations

Ix

- ID risk factors for further strokes

HTN

- Retinopathy
- Nephropathy
- Big heart on CXR
- (Don't treat acutely)

Cardiac emboli

- ECG ± 24hr tape: AF
- Echo: mural thrombus, hypokinesis, valve lesions, ASD, VSD (paradoxical emboli)

Carotid artery stenosis

- Doppler US ± angio
- Endarterectomy beneficial if ≥ 70% symptomatic stenosis

Bleeding / thrombotic tendency

- Thrombophilia screen
- Thrombocytopenia

Hyperviscosity

- Polycythaemia
- SCD
- Myeloma

Metabolic

- ↑↓ glucose
- ↑ lipids
- Hyperhomocystinaemia

Vasculitis

- ↑ESR
- ANA

Stroke: Presentation

Oxford / Bamford Classification

- Based on clinical localisation of infarct
- S=syndrome: prior to imaging
- I=infarct: after imaging when atheroembolic infarct confirmed

Total Anterior Circulation Stroke (TACS)

- Highest mortality (60% @ 1yr) + poor independence
- Large infarct in carotid / MCA, ACA territory
- All 3 of:
 1. Hemiparesis (contralateral) and/or sensory deficit (≥ 2 of face, arm and leg)
 2. Homonymous hemianopia (contralateral)
 3. Higher cortical dysfunction
 - Dominant (L usually): dysphasia
 - Non-dominant: hemispatial neglect

Partial Anterior Circulation Stroke (PACS)

- Carotid / MCA and ACA territory
- 2/3 of TACS criteria, usually:
 1. Hemiparesis (contralateral) and/or sensory deficit (≥ 2 of face, arm and leg)
 2. Higher cortical dysfunction
 - Dominant: dysphasia
 - Non-dom: neglect, constructional apraxia
- Deficit is less dense and/or incomplete

Posterior Circulation Stroke (POCS)

- Infarct in vertebrobasilar territory
- Any of
 1. Cerebellar syndrome
 2. Brainstem syndrome
 3. Contralateral homonymous hemianopia

Lacunar Stroke (LACS)

- Small infarcts around basal ganglia, internal capsule, thalamus and pons.
- Absence of
 - Higher cortical dysfunction
 - Homonymous hemianopia
 - Drowsiness
 - Brainstem signs
- 5 syndromes
 - Pure motor: post. limb of internal capsule
 - Commonest
 - Pure sensory: post. thalamus (VPL)
 - Mixed sensorimotor: internal capsule
 - Dysarthria / clumsy hand
 - Atactic hemiparesis: ant. limb of internal capsule
 - Weakness + dysmetria

Other Signs

- Ischaemic pointers
 - Carotid bruit
 - AF
 - Past TIA
 - IHD
- Haemorrhagic pointers
 - Meningism
 - Severe headache
 - Coma

Brainstem Infarcts

- Complex signs depending on relationship of infarct to CN nuclei, long tracts and brainstem connections

Features

Feature	Structure
Hemi- / quadr-paresis	Corticospinal tracts
Conjugate gaze palsy	Oculomotor system
Horner's syndrome	Sympathetic fibres
Facial weakness (LMN)	CN7 nucleus
Nystagmus, vertigo	CN8 nucleus
Dysphagia, dysarthria	CN9 and CN10 nuclei
Dysarthria, ataxia	Cerebellar connections
↓ GCS	Reticular activating syndrome

Lateral Medullary Syndrome / Wallenberg's Syndrome

- PICA or vertebral artery
- Features: DANVAH
 - Dysphagia
 - Ataxia (ipsilateral)
 - Nystagmus (ipsilateral)
 - Vertigo
 - Anaesthesia
 - Ipsilateral facial numbness + absent corneal reflex
 - Contralateral pain loss
 - Horner's syndrome (ipsilateral)

Millard-Gubler Syndrome

- Pontine infarct
- 6th and 7th CN nuclei + corticospinal tracts
 - Diplopia
 - LMN facial palsy + loss of corneal reflex
 - Contralateral hemiplegia

Locked-in Syndrome

- Pt. is aware and cognitively intact but completely paralysed except for the eye muscles.
- Causes
 - Ventral pons infarction: basilar artery
 - Central pontine myelinolysis: rapid correction of hyponatraemia

Stroke Differential

- Head injury ± haemorrhage
- ↑ glucose
- SOL
- Hemiplegic migraine
- Todd's palsy
- Infections: encephalitis, abscesses, Toxo, HIV, HTLV
- Drugs: e.g. opiate overdose

Stroke: Management

Acute Management

Resuscitate

- Ensure patent airway: consider NGT
- NBM until swallowing assessed by SALT
- Don't overhydrate: risk of cerebral oedema

Monitor

- Glucose: 4-11mM: sliding scale if DM
- BP: <185/110 (for thrombolysis)
 - Rx of HTN can → ↓ cerebral perfusion
- Neuro obs

Imaging

- Urgent CT/MRI
- Diffusion-weighted MRI is most sensitive for acute infarct
- CT will exclude primary haemorrhage

Medical

- Consider thrombolysis if 18-80yrs and <4.5hrs since onset of symptoms
 - Alteplase (rh-tPA)
 - → ↓ death and dependency (OR 0.64)
 - CT 24h post-thrombolysis to look for haemorrhage
- **Aspirin 300mg** PO/PR once haemorrhagic stroke excluded ± PPI
 - Clopidogrel if aspirin sensitive

Surgery

- Neurosurgical opinion if intracranial haemorrhage
- May coil bleeding aneurysms
- Decompressive hemicraniectomy for some forms of MCA infarction.

Stroke Unit

- Specialist nursing and physio
- Early mobilisation
- DVT prophylaxis

Secondary Prevention

Rehabilitation

Primary Prevention

- Control RFs: HTN, ↑ lipids, DM, smoking, cardiac disease
- Consider life-long anticoagulation in AF (use CHADS2)
- Carotid endarterectomy if symptomatic 70% stenosis
- Exercise

Secondary Prevention

- Risk factor control as above
 - Start a statin after 48h
- Aspirin / clopi 300mg for 2wks after stroke then either
 - Clopidogrel 75mg OD (preferred option)
 - Aspirin 75mg OD + dipyridamole MR 200mg BD
- Warfarin instead of aspirin/clopidogrel if
 - Cardioembolic stroke or chronic AF
 - Start from 2wks post-stroke (INR 2-3)
 - Don't use aspirin and warfarin together.
- Carotid endarterectomy if good recovery + ipsilateral stenosis ≥70%

Rehabilitation: MENDS

- **MDT:** physio, SALT, dietitian, OT, specialist nurses, neurologist, family
- **Eating**
 - Screen swallowing: refer to specialist
 - NG/PEG if unable to take oral nutrition
 - Screen for malnutrition (MUST tool)
 - Supplements if necessary
- **Neurorehab:** physio and speech therapy
 - Botulinum can help spasticity
- **DVT Prophylaxis**
- **Sores:** must be avoided @ all costs

Occupational Therapy

- **Impairment:** e.g. paralysed arm
- **Disability:** e.g. inability to write
- **Handicap:** e.g. can't work as accountant
- OT aims to minimise disability and abolish handicap

Prognosis @ 1yr

- 10% recurrence
- **PACS**
 - 20% mortality
 - 1/3 of survivors independent
 - 2/3 of survivors dependent
- **TACS** is much worse
 - 60% mortality
 - 5% independence

Transient Ischaemic Attack

Definition

- Sudden onset focal neurology lasting <24h due to temporary occlusion of part of the cerebral circulation.
- ~15% of 1st strokes are preceded by TIAs.

Signs

- Symptoms usually brief
- Global events (e.g. syncope, dizziness) are not typical
- Signs mimic those of CVA in the same arterial territory

Signs of Causes

- Carotid bruits
- ↑BP
- Heart murmur
- AF

Causes

- Atherothromboembolism from carotids is main cause
- Cardioembolism: post-MI, AF, valve disease
- Hyperviscosity: polycythaemia, SCD, myeloma

Differential

- Vascular: CVA, migraine, GCA
- Epilepsy
- Hyperventilation
- Hypoglycaemia

Ix

- Aim to find cause and define vascular risk
- **Bloods:** FBC, U&E, ESR glucose, lipids
- CXR
- ECG
- Echo
- Carotid doppler ± angiography
- Consider brain imaging
 - Diffusion weighted MRI is best

Mx: ACAS

- Time to intervention is crucial.
 - Intervention w/i 72hrs → 2% strokes @ 90d
 - Intervention w/i 3wks → 10% strokes @ 90d
- Avoid driving for 1mo

1. Antiplatelet Therapy / Anticoagulate

- Aspirin/clopi 300mg/d for 2wks then 75mg/d
 - Add dipyridamole MR to aspirin
- Warfarin if cardiac emboli: AF, MI, MS
 - After 2wks

2. Cardiac Risk Factor Control

- BP, lipids, DM, smoking
- Exercise
- Diet: ↓ salt

3. Assess risk of subsequent stroke

- ABCD2 score

4. Specialist referral to TIA clinic

- ABCD2 ≥4: w/i 24hrs
- ABCD2 <4: w/i 1wk

Carotid Endarterectomy

- Beneficial if ≥70% symptomatic stenosis
- 50-70% stenosis may benefit if operative risk is <3%
- Surgery should be performed w/i 2wks.
- Endovascular stenting is an alternative, but safety and long-term benefits (in-stent restenosis is common) are still under Ix.
- Major complications are stroke and death.

Prognosis

- Combined risk of stroke and MI is ~9%/yr
- 3x ↑ in mortality cf TIA-free populations

ABCD2 Score

- Predicts stroke risk following TIA
- Score ≥6 = 8% risk w/i 2d, 35% risk w/i 1wk
- Score ≥4 = pt. assessment by specialist w/i 24hrs
- All pts with suspected TIA should be seen by specialist w/i 7d.

1. Age ≥ 60

2. BP ≥ 140/90

3. Clinical features

- a. Unilateral weakness (2 points)
- b. Speech disturbance w/o weakness

4. Duration

- a. ≥ 1h (2 points)
- b. 10-59min

5. DM

NB. 7 points max.

Subdural Haemorrhage

- Bleeding from bridging veins between cortex and sinuses
- Haematoma between dura and arachnoid
- Often due to minor trauma that occurred a long time previously – especially deceleration injuries

Risk Factors

- Elderly: brain atrophy
- Falls: epileptics, alcoholics
- Anticoagulation

Symptoms

- Headache
- Fluctuating GCS, sleepiness
- Gradual physical or mental slowing
- Unsteadiness

Signs

- ↑ ICP (can → tentorial herniation)
- Localising signs occur late

Imaging: CT / MRI

- Crescentic haematoma over one hemisphere
- Clot goes from white → grey → time
- Mid-line shift

Mx

- 1st line: irrigation/evacuation via burr-hole craniostomy
- 2nd line: craniotomy
- Address causes of trauma

Differential

- Stroke
- Dementia
- SOL

Extradural Haemorrhage

- Often due to # temporal or parietal bone → laceration of middle meningeal artery and vein.
- Blood between bone and dura
- Suspect if after head injury GCS falls, is slow to improve or there is a lucid interval.

Presentation

Lucid Interval

- Deterioration of GCS after head injury that caused no LOC, or following initial improvement in GCS.
- Lucid interval may be hrs or days

↑ ICP

- Headache
- Vomiting
- Confusion → coma
- Fits
- Ipsilateral blown pupil (3rd nerve palsy)
- ± hemiparesis → upgoing plantars and ↑ reflexes

Brainstem Compression

- Deep irregular breathing (brainstem compression)
- Cushing response (↑BP, ↓HR) is late
- Death by cardiorespiratory arrest

Imaging: CT

- Lens-shaped haematoma
- Skull # (↑↑ risk of extradural haemorrhage)

Mx

- Neuroprotective ventilation ($O_2 > 100$, CO_2 35-40)
- Consider mannitol (1g/kg IV via central line)
- Craniectomy for clot evacuation and vessel ligation

Intracranial Venous Thrombosis

Dural Venous sinus Thrombosis

- Symptoms come one gradually over days-wks
- Sinus thrombosis may extend to cortical veins

Sagittal Sinus

- 45% of IVT
- Often co-exists if other sinuses are thrombosed
- Headache, vomiting, seizures, ↓ vision, papilloedema

Transverse Sinus

- 35% of IVT
- Headache ± mastoid pain, focal neuro, seizures, papilloedema

Sigmoid Sinus

- Cerebellar signs, lower CN palsies

Inferior Petrosal Sinus

- 5th and 6th CN palsies (Gradenigo's syn.)

Cavernous sinus

- Spread from facial pustules or folliculitis
- Headache, chemosis, eyelid oedema, proptosis, painful ophthalmoplegia, fever

Cortical Vein Thrombosis

- Often → venous infarcts & stroke-like focal symptoms that evolve over days
- Thunderclap headache
- Focal-seizures

Differential

- SAH
- Meningitis
- Encephalitis
- Intracranial abscess
- Arterial stroke

Common Causes

- Pregnancy / puerperium
- OCP
- Head injury
- Dehydration
- Intracranial / extracranial malignancy
- Thrombophilia

Ix

- Exclude SAH and meningitis
- CT/MRI venography: absence of a sinus
- LP: ↑ pressure, may show RBCs and xanthochromia

Mx

- LMWH → warfarin (INR 2-3)
- Fibrinolytics (e.g. streptokinase) can be used via selective catheterisation.
- Thrombophilia screen

Meningitis

Features

Meningitic

- Headache
- Neck stiffness
 - Kernig's: Straightening leg $\overline{\text{C}}$ hip @ 90°
 - Brudzinski's: lifting head → lifting of legs
- Photophobia
- n/v

Neurological

- \downarrow GCS → coma
- Seizures (20%)
- Focal neuro (20%): e.g. CN palsies

Septic

- Fever
- \downarrow BP, \uparrow HR
- \uparrow CRT
- Purpuric rash
- DIC

Abx Therapy

- Community: benpen 1.2g IV/IM
- <50: ceftriaxone 2g IVI/IM BD
- >50: ceftriaxone + ampicillin 2g IVI /4h
- If viral suspected: aciclovir

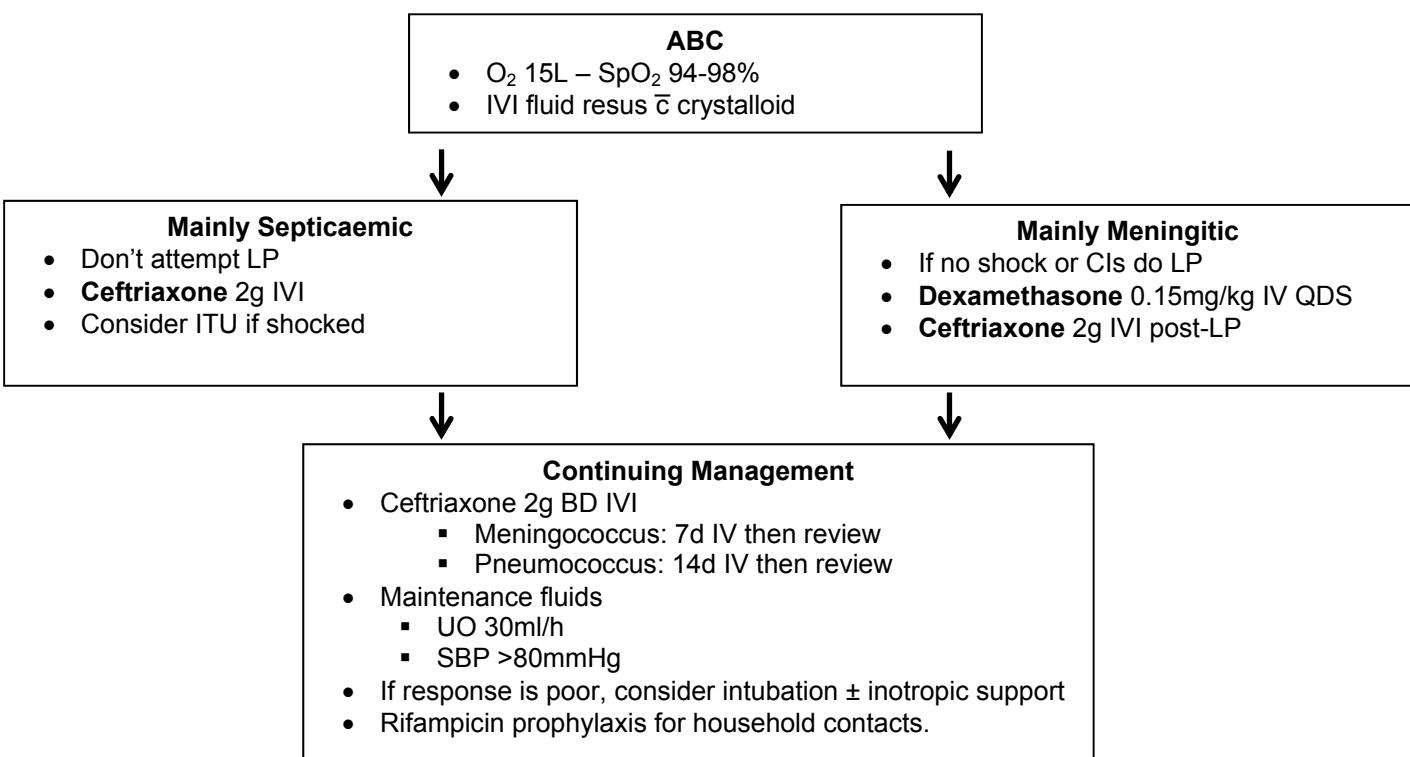
Organisms

- Viruses: enteroviruses (Coxsackie, echovirus), HSV2
- Meningococcus
- Pneumococcus
- Listeria
- Haemophilus
- TB
- Cryptococcus

Ix

- Bloods: FBC, U+Es, clotting, glucose, ABG
- Blood cultures
- LP: MCS, glucose, virology/PCR, lactate

Acute Management



Cl's to LP: Try LP Unless Contraindicated

- Thrombocytopenia
- Lateness (delay in antibiotic admin)
- Pressure (signs of raised ICP)
- Unstable (Cardio + resp systems)
- Coagulation disorder
- Infection at LP site
- Neurology (focal neurological signs)

CSF Findings

Findings	Bacterial	TB	Viral
Appearance	Turbid	Fibrin web	Clear
Cells	PMN	Lympho / mononuc	Lympho / mononuc
Count	100-1000	10-1000	50-1000
Glucose	\downarrow ($< \frac{1}{2}$ plasma)	\downarrow ($< \frac{1}{2}$ plasma)	$> \frac{1}{2}$ plasma
Protein (g/L)	$\uparrow\uparrow$ (>1.5)	$\uparrow\uparrow$ (1-5)	mild \uparrow (<1)

Encephalitis

Presentation

- Infectious prodrome: fever, rash, LNs, cold sores, conjunctivitis, meningeal signs.
- Bizarre behaviour or personality change
- Confusion
- ↓ GCS → coma
- Fever
- Headache
- Focal neuro
- Seizures
- Hx of travel or animal bite

Causes

Usually viral

- HSV1/2
- CMV, EBV, VZV
- Arboviruses
- HIV

Non-viral

- Any bacterial meningitis
- TB
- Malaria
- Lyme disease

Ix

- **Bloods:** cultures, viral PCR, malaria film
- **Contrast CT:** focal bilat temporal involvement suggests HSV
- **LP:** ↑ CSF protein, lymphocytes, PCR
- **EEG:** shows diffuse abnormalities, may confirm Dx

Mx

- Aciclovir STAT: 10mg/kg/8h IVI over 1h for 14/7
- Supportive measures in HDU/ITU
- Phenytoin for seizures

Prognosis

- 70% mortality if untreated

w/o fever, consider encephalopathy

- ↓ glucose
- Hepatic
- DKA
- Drugs
- SLE
- Uraemia
- Hypoxic brain injury
- Beri-Beri

Cerebral Abscess

Pre-disposing Factors

- Infection: ear, sinus, dental or periodontal
- Skull #
- Congenital heart disease
- Endocarditis
- Bronchiectasis
- Immunosuppression

Organisms

- Frontal sinus/teeth: strep. Milleri, oropharyngeal anaerobes
- Ear: Bacteroides, other anaerobes

Signs

- Seizures
- Fever
- Localizing signs
- Signs of ↑ ICP
- Signs of infection elsewhere

Ix

- CT/MRI: ring-enhancing lesion
- ↑WCC, ↑ESR

Rx

- Neurosurgical referral
- Abx: e.g. ceftriaxone
- Treat ↑ ICP

Epilepsy: Features

Definition

- Recurrent tendency to spontaneous, intermittent, abnormal electrical activity in part of the brain, manifest as seizures.

Causes

- 2/3 are idiopathic (often familial)
- **Congenital**
 - NF
 - Tuberous Sclerosis
 - TORCH
 - Perinatal anoxia
- **Acquired**
 - Vascular: CVA
 - Cortical scarring: trauma, infection
 - SOL
 - Other: SLE, PAN, MS, sarcoidosis
- **Non-epileptic / provoked seizures**
 - **Withdrawal:** EtOH, opiates, benzos
 - **Metabolic:** glucose, Na, Ca, urea, NH₃
 - ↑ICP: trauma, haemorrhage, cortical venous thrombosis
 - **Infection:** meningitis, encephalitis, cysticercosis, HIV
 - Eclampsia
 - Pseudoseizures

NB. 3-10% of provoked seizures tend to recur, cf 30-50% of unprovoked seizures

Seizure Terms

- **Prodrome**
 - pt. or others may notice change in mood or behaviour lasting hrs – days.
 - Not part of seizure.
- **Aura**
 - A simple partial seizure (usually temporal) which may precede other manifestations.
 - Experienced as a strange feeling:
 - Epigastric rising
 - Deja/jamias vu,
 - Automatisms,
 - Smells, lights, sounds
- **Partial (focal)**
 - Features referable to part of one hemisphere
- **Primary Generalised**
 - No warning / aura
 - Discharge throughout cortex w/o localising features
- **Simple:** awareness unimpaired
- **Complex:** awareness impaired
- **Secondary Generalised**
 - Focal seizure → generalised
 - E.g. aura → tonic-clonic

Diagnostic Pointers

- Aura
- Specific trigger: e.g. flashing lights
- Lateral tongue biting (> incontinence)
- Typical movements: e.g. tonic-clonic
- Cyanosis
- Post-ictal phase

Presenting Features

Simple Partial

- Focal motor, sensory, autonomic or psychic symptoms

Complex Partial: 5As

- **Aura**
- **Autonomic:** change in skin colour, temperature, palps
- **Awareness lost:** motor arrest, motionless stare
- **Automatisms:** lip-smacking, fumbling, chewing, swallowing
- **Amnesia**

NB. Usually arise from temporal lobe

Absences (Petit mal)

- **ABrupt onset and offset**
- **Short:** <10s
- **Eyes:** glazed, blank-stare
- **Normal:** intelligence, examination, brain-scan
- **Clonus** or automatisms may occur
- **EEG:** 3Hz spike and wave
- **Stimulated by hyperventilation and photics**

Tonic-Clonic (Grand mal)

- LOC
- Tonic: limbs stiffen
- Clonic: rhythmic jerking of limbs
- ± cyanosis, incontinence, tongue biting (lateral)
- Post-ictal confusion and drowsiness

Myoclonic Seizure

- Sudden jerk of limb, face or trunk.

Atonic (akinetic seizures)

- Sudden loss of muscle tone → fall
- No LOC

West Syndrome / Infantile Spasms

- Clusters of head nodding and arm jerks
- EEG shows hypsarrhythmia

Localising Features

Temporal

- Automatisms: lip smacking, chewing, fumbling
- Deja/jamias vu
- Delusional behaviour
- Abdominal: rising, n/v
- Emotional disturbance: terror, panic, anger, elation
- Tastes, smells

Frontal

- Motor features: arrest, Jacksonian march, Todd's palsy

Parietal

- Sensory disturbance: tingling, numbness

Occipital

- Visual phenomena: spots, lines, flashes

Epilepsy: Investigation and Management

General Principles

- After any seizure advise against driving, swimming, etc. until a Dx is established
- Don't diagnose epilepsy from a single seizure
- Diagnosis should be made by a specialist
- After Dx, cannot drive until seizure-free for >1yr
 - 10yrs for HGV (no meds)

Investigations

- Basic bloods: FBC, U+Es, glucose
- Se ↑ Prl 10min after fit (relative to baseline)
- Se AED levels
- Urine toxicology
- ECG

EEG

- Use to support Dx (cannot exclude or prove)
- Helps classification and prognosis
- Use \bar{C} hyperventilation and photic stimulation

Neuroimaging: typically MRI

- Not routine for idiopathic generalised epilepsy
- **Indications**
 - Developed epilepsy as an adult
 - Any evidence of focal onset
 - Seizures continue despite 1st-line Rx

Drug Therapy

Seizure Type	1 st line	2 nd line
Tonic-Clonic	Valproate	Lamotrigine
Absences	Valproate Ethosuximide	Lamotrigine
Tonic, atonic or myoclonic	Valproate	Levetiracetam
Focal ± 2 ^o gen	Lamotrigine	CBZ

In Women / Pregnancy

- Avoid valproate: take lamotrigine (or CBZ)
- 5mg folic acid daily if child-bearing age
- CBZ and PHE are enzyme inducers and ↓ the effectiveness of the OCP

Other Options

- Neurosurgical resection can be an option if a single epileptogenic focus is identified
- Vagal nerve stimulation can ↓ seizure frequency and severity in ~33%

Side Effects of Common AEDs

Enzyme Effects

- Inducers: CBZ, PHE and barbiturates
- Inhibitors: Valproate

Lamotrigine

- Skin rash → SJS: occurs w/i 1st 8wks
- Rash may be assoc. \bar{C} hypersensitivity → fever, ↑LFTs, DIC.
- Diplopia, blurred vision
- Levels affected by enzyme inhibitors/inducers

Valproate

- Appetite ↑ → ↑wt.
- Liver failure: monitor LFTs over 1st 6mo
- Pancreatitis
- Reversible hair loss
- Oedema
- Ataxia
- Teratogenicity, Tremor, Thrombocytopaenia
- Encephalopathy: due to ↑ ammonia

Carbamazepine

- Leukopenia
- Skin reactions
- Diplopia, blurred vision
- SIADH → hyponatraemia

Phenytoin

- Gingival hypertrophy
- Hirsutism
- Cerebellar syn.
 - Ataxia
 - Nystagmus
 - Dysarthria
- Peripheral sensory neuropathy
- Diplopia
- Tremor

Status Epilepticus

Definition

- Seizure lasting >30min, or
- Repeated seizures w/o intervening consciousness

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- BM
- **Bloods:** glucose, ABG, U+E, FBC, Ca²⁺
- ECG, EEG
- **Consider:** AED levels, tox screen, LP, βhCG, CT

Drugs

Lorazepam

- 2-4mg IV bolus over 30s
- 2nd dose if no response w/i 2min
- Alternatives:
 - Diazepam 10mg IV/PR (20mg max)
 - Midazolam 10mg buccal

Phenytoin

- 18mg/kg IVI @ 50mg/min
- 100mg/6-8h maintenance
- Monitor ECG and BP
- CI: bradycardia or heart block

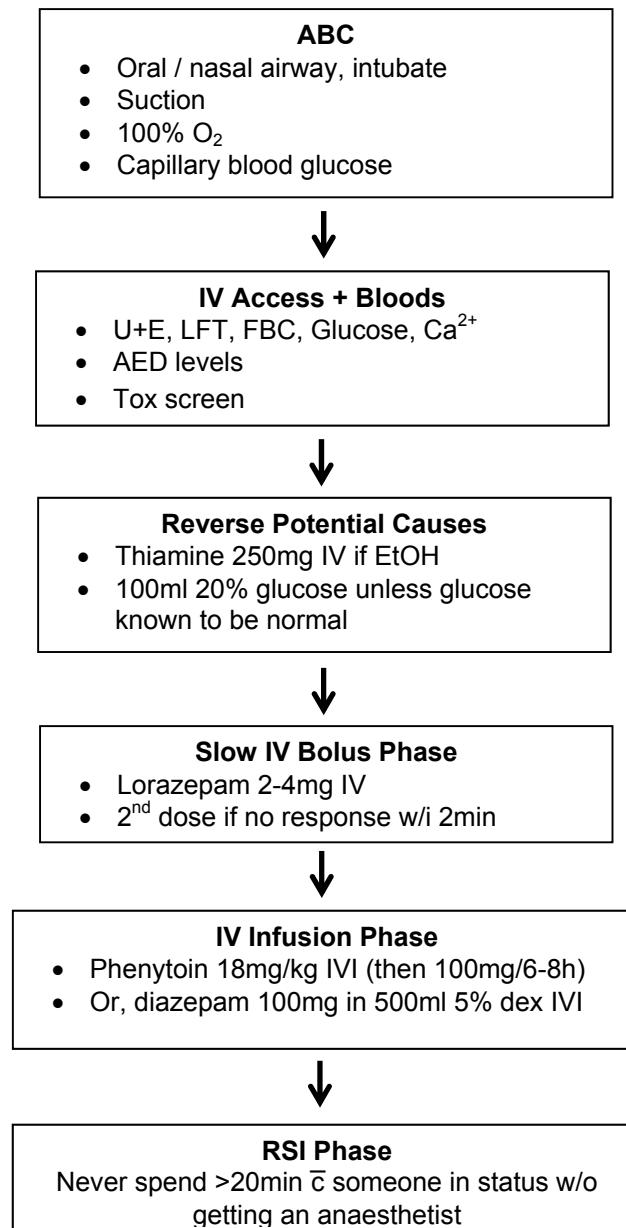
Diazepam Infusion

- 100mg in 500ml 5% dex @ 40ml/hr (3mg/kg/24h)

Dexamethasone

- 10mg IV if vasculitis / cerebral oedema (tumour) possible

Acute Management



Head Injury

Initial Mx

1^o Survey

- **A:** ? intubation, immobilise C-spine
- **B:** 100% O₂, RR
- **C:** IV access, BP, HR
- **D:** GCS, pupils
- Treat seizures
 - Lorazepam 2-4mg IV
 - Phenytoin 18mg/kg IVI then 100mg/6-8h
- **E:** expose pt. and look for other obvious injuries

2^o Survey

- Look for:
 - Lacerations
 - Obvious facial/skull deformity
 - CSF leak from nose or ears
 - Battle's sign, Raccoon eyes
 - Blood behind TM
 - C-spine tenderness ± deformity
- Head-to-toe examination for other injuries
- Log role

Hx if possible

- How and when?
- GCS and other vitals immediately after injury
- Headache, fits, vomiting, amnesia, EtOH

Ix

- **Bloods:** FBC, U+E, glucose, clotting, EtOH level, ABG
- ? CT head + c-spine

Rx

- Neurosurgical opinion if signs of ↑ICP, CT evidence of intracranial bleed significant skull #
- Admit if:
 - Abnormalities on imaging
 - Difficult to assess: EtOH, post-ictal
 - Not returned to GCS 15 after imaging
 - CNS signs: vomiting, severe headache
- Neuro-obs half-hrly until GCS 15
 - GCS
 - Pupils
 - HR, BP
 - RR, SpO₂
 - Temperature

Discharge Advice

- Stay with someone for first 48hrs
- Give advice card advising return on:
 - Confusion, drowsiness, unconsciousness
 - Visual problems
 - Weakness
 - Deafness
 - V. painful headache that won't go away
 - Vomiting
 - Fits

Intubate

- GCS ≤ 8
- PaO₂ <9KPa on air / <13KPa on O₂ or PCO₂ >6KPa
- Spontaneous hyperventilation: PCO₂ <4KPa
- Respiratory irregularity

CT head guidelines: BANGS LOC

- **Break:** open, depressed or base of skull
- **Amnesia** >30min retrograde
- **Neuro deficit** or seizure
- **GCS:** <13 @ any time or <15 2h after injury
- **Sickness:** vomited > once
- **LOC** or any amnesia and any of:
 - Dangerous mechanism: RTA, great height
 - Age ≥ 65
 - Coagulopathy (inc. warfarin)

Risk of Intracranial Haematoma in Adults:

- Fully conscious, no skull # = <1:1000
- Confused, no skull # = 1:100
- Fully conscious, skull # = 1:30
- Confused, skull # = 1:4

GCS

Eyes: 4

- 4 – Spontaneous eye opening
- 3 – Open to voice
- 2 – Open to pain
- 1 – No opening

Verbal: 5

- 5 – Orientated conversation
- 4 – Confused conversation
- 3 – Inappropriate speech
- 2 – Incomprehensible sounds
- 1 – No speech

Motor: 6

- 6 – Obeys commands
- 5 – Localises pain
- 4 – Withdraws to pain
- 3 – Decorticate posturing to pain (flexor)
- 2 – Decerebrate posturing to pain (extensor)
- 1 – No movement

Space Occupying Lesions

Presentation

↑ ICP

- Headache: worse on waking, lying down, bending forward, coughing, straining.
- Vomiting
- Papilloedema
- ↓GCS

Seizures

- Exclude SOL in adult-onset seizures, especially \neg localising aura or post-ictal weakness (Todd's)

Evolving Focal Neurology

- May be false-localising (esp. CN6 palsy)

Subtle Personality Change

Causes

- **Vascular:** chronic subdural haematoma, AVM, aneurysm
- **Infection:** abscess, cyst (cysticercosis)
- **Neoplasm:** primary or secondary
- **Granuloma:** TB, sarcoid

Tumours

- 30% metastatic: breast, lung, melanoma
- Astrocytoma
- Glioblastoma multiforme
- Ependyoma
- Meningiomas
- Cerebellar haemangioblastoma
- CNS lymphoma

Differential

- Vasc: stroke, venous sinus thrombosis
- Traumatic head injury
- Infection: encephalitis
- Inflam: vasculitis, MS
- Metabolic disturbance
- Idiopathic intracranial hypertension

Ix

- CT or MRI (better for post. cranial fossa)
- Consider biopsy

Idiopathic Intracranial Hypertension

Presentation

- Typically obese females
- **As if SOL**
 - ↑ ICP
 - Headache
 - Papilloedema
- **Visual**
 - Blurred vision
 - 6th CN palsy
 - Enlarged blind spot

Cause

- Usually idiopathic
- May be 2^o to venous sinus thrombosis or drugs

Mx

- Wt. loss
- Acetazolamide
- Loop diuretics
- Prednisolone
- Lumbar-peritoneal shunt may be necessary if drugs fail and visual loss deteriorates.

Prognosis

- Usually self-limiting
- Permanent visual loss in 10%.

Raised ICP

Types of Cerebral Oedema

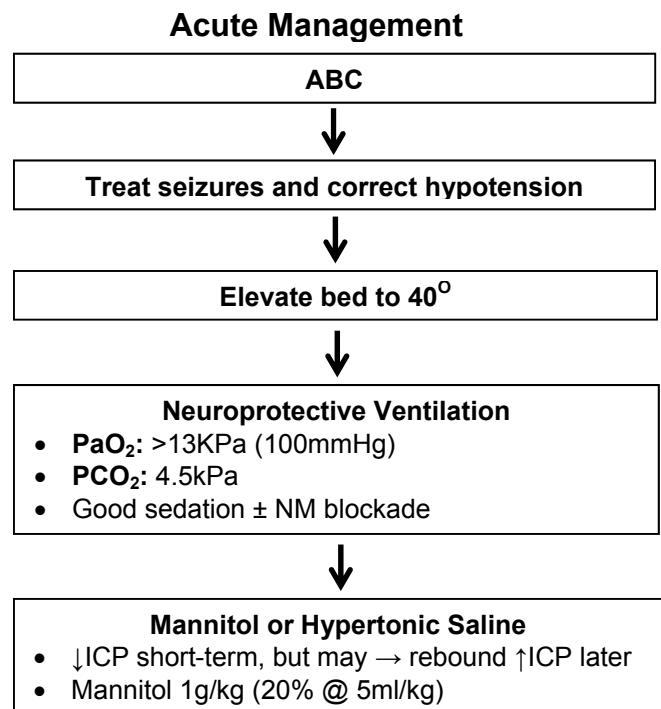
1. Vasogenic (\uparrow cap permeability): trauma, tumour, ischaemia, infection
2. Cytotoxic: e.g. from hypoxia
3. Interstitial: e.g. obstructive hydrocephalus, $\downarrow \text{Na}^+$

Causes

- Haemorrhage
- Tumours
- Infection: meningitis, encephalitis, abscess
- Hydrocephalus
- Status
- Cerebral oedema

Signs and Symptoms

- Headache
- n/v
- Seizures
- Drowsiness \rightarrow coma
- Cushing's reflex: $\uparrow \text{BP}$, $\downarrow \text{HR}$, irregular breathing
- 6th CN palsy (may be false localising)
- Cheyne-Stokes respiration
- Pupils: constriction \rightarrow dilatation
- Papilloedema, loss of venous pulsation @ disc



Herniation Syndromes

Tonsillar (Coning)

- \uparrow pressure in posterior fossa \rightarrow displacement of cerebellar tonsils through foramen magnum
- \rightarrow compression of brainstem and cardioresp centres in medulla
- CN6 palsy, upgoing plantars \rightarrow irregular breathing \rightarrow apnoea

Transtentorial / Uncal

- Lateral supratentorial mass \rightarrow compression of ipsilateral inferomedial temporal lobe (uncus) against free margin of tentorium cerebelli.
- Ipsilateral CN3 palsy: mydriasis (dilation) then down-and-out
- Ipsilateral corticospinal tract: contralateral hemiparesis
- May \rightarrow compression of contralateral corticospinal tracts \rightarrow ipsilateral hemiparesis (Kernohan's Notch: False Localising)

Subfalcine

- Frontal mass
- Displacement of cingulate gyrus (medial frontal lobe) under falx cerebri
- Compression of ACA \rightarrow stroke
 - Contralateral motor/sensory loss in legs>arms
 - Abulia (pathological laziness)

Parkinsonism

Causes

Degenerative

1. Parkinson's disease
2. Parkinson's-plus syndromes (basal ganglia degeneration + other system)
 - a. **Multiple Systems Atrophy / Shy-Drager**
 - Autonomic dysfunction: post hypotension, bladder dysfunction
 - Cerebellar + pyramidal signs
 - Rigidity > Tremor
 - b. **Progressive Supranuclear Palsy**
 - Postural instability → falls
 - Speech disturbance (+ dementia)
 - Palsy: vertical gaze
 - c. **Corticobasilar Degeneration:**
 - Aphasia, dysarthria, apraxia
 - Akinetic rigidity in one limb
 - Astereognosis (cortical sensory loss)
 - Alien limb phenomenon
 - d. **Lewy Body Dementia:**
 - Fluctuating cognition
 - Visual hallucinations

Infection

- Syphilis
- HIV
- CJD

Vascular: Multiple infarcts in SN

Drugs: Antipsychotics, metoclopramide

Trauma: dementia pugilistica

Genetic: Wilson's disease

Symptoms

Tremor

- Worse at rest
- Exacerbated by distraction
- 4-6hz, pill-rolling

Rigidity

- ↑ tone in all muscle groups: lead-pipe rigidity
- Rigidity + tremor → cog-wheel rigidity

Bradykinesia

- Slow initiation of movement → reduction of amplitude on repetition
- Expressionless face
- Monotonous voice
- Micrographia

Gait

- ↓ arm swing
- Festinane
- Freezing (esp. in doorways)

Parkinson's Disease

Epidemiology

- Mean onset 65yrs
- 2% prevalence

Pathophysiology

- Destruction of dopaminergic neurones in **pars compacta** of **substantia nigra**.
- β -amyloid plaques
- Neurofibrillary tangles: hyperphosphorlated tau

Features: TRAPPS PD

- Asymmetric onset: side of onset remains worst
- Tremor: ↑ by stress, ↓ by sleep
- Rigidity: lead-pipe, cog-wheel
- Akinesia: slow initiation, difficulty → repetitive movement, micrographia, monotonous voice, mask-like face
- Postural instability: stooped gait → festination
- Postural hypotension: + other autonomic dysfunction
- Sleep disorders: insomnia, EDS, OSA, RBD
- Psychosis: esp. visual hallucinations
- Depression / Dementia / Drug SEs

Sleep Disorder

- Affects ~90% of PD pts.
- Insomnia + frequent waking → EDS
 - Inability to turn
 - Restless legs
 - Early morning dystonia (drugs wearing off)
 - Nocturia
 - OSA
- REM Behavioural sleep Disorder
 - Loss of muscle atonia during REM sleep
 - Violent enactment of dreams
- Da SEs: insomnia, drowsiness, EDS

Autonomic Dysfunction

- Combined effects of drugs and neurodegeneration
- Postural hypotension
- Constipation
- Hypersalivation → dribbling (↓ ability to swallow saliva)
- Urgency, frequency, Nocturia
- ED
- Hyperhidrosis

L-DOPA SEs: DOPAMINE

- Dyskinesia
- On-Off phenomena = Motor fluctuations
- Psychosis
- ABP↓
- Mouth dryness
- Insomnia
- N/V
- EDS (excessive daytime sleepiness)

Motor Fluctuations

- **End-of-dose:** deterioration as dose wears off → progressively shorter benefit.
- **On-Off effect:** unpredictable fluctuations in motor performance unrelated to timing of dose.

Ix

- DaTSCAN

Mx

- MDT: neurologist, PD nurse, physio, OT, social worker, GP and carers
- Assess disability
 - e.g. UPDRS: Unified Parkinson's Disease Rating Scale
- Physiotherapy: postural exercises
- Depression screening

Medical

- **Young onset ± biologically fit**
 1. **Da agonists:** ropinirole, pramipexole
 2. **MOA-B inhibitors:** rasagiline, selegiline
 3. **L-DOPA:** co-careldopa or co-beneldopa
- **Biologically frail ± comorbidities**
 1. **L-DOPA**
 2. **MOA-B inhibitors**
- **Other therapies**
 - **COMT inhibitor:** tolcapone, entacapone
 - Lessen end-of-dose effect
 - **Apomorphine:** potent Da agonist
 - SC rescue pen for sudden "off" freezing
 - **Amantidine:** weak Da agonist
 - Rx of drug-induced dyskinésias
 - **Atypical antipsychotics:** e.g. quetiapine
 - Disease-induced psychosis
 - **SSRIs:** citalopram, sertraline
 - Depression

Surgical

- Interrupt basal ganglia
- Deep brain stimulation

Prognosis

- ↑ mortality
- Loss of response to L-DOPA w/i 2-5yrs

Differential

- Parkinson plus syndromes
- Multiple infarcts
- Drugs: neuroleptics
- Inherited: Wilson's
- Infection: HIV, syphilis, CJD
- Dementia pugilistica

Multiple Sclerosis

Definition

- A chronic inflammatory condition of the CNS characterised by multiple plaques of demyelination disseminated in time and space.

Epidemiology

- **Lifetime risk:** 1/1000
- **Age:** mean @ onset = 30yrs
- **Sex:** F>M = 3:1
- **Race:** rarer in blacks

Aetiology

- Genetic (HLA-DRB1), environmental, viral

Pathophysiology

- CD4 cell-mediated destruction of oligodendrocytes → demyelination and eventual neuronal death.
- Initial viral inflam primes humoral Ab responses vs. MBP
- Plaques of demyelination are hallmark

Classification:

- Relapsing-remitting: 80%
- Secondary progressive
- Primary progressive: 10%
- Progressive relapsing

Presentation: TEAM

- Tingling
- Eye: optic neuritis (\downarrow central vision + eye move pain)
- Ataxia + other cerebellar signs
- Motor: usually spastic paraparesis

Clinical features

Sensory:

- Dysparaesthesia
- \downarrow vibration sense
- Trigeminal neuralgia

Motor

- Spastic weakness
- Transverse myelitis

Eye:

- Diplopia
- Visual phenomena
- Bilateral INO
- Optic neuritis → atrophy

Cerebellum:

- Trunk and limb ataxia
- Scanning dysarthria
- Falls

GI:

- Swallowing disorders
- Constipation

Sexual/GU:

- ED + anorgasmia
- Retention
- Incontinence

Lhermitte's Sign

- Neck flexion → electric shocks in trunk/limbs

Optic Neuritis

- **PC:** pain on eye movement, rapid \downarrow central vision
- **Uhthoff's:** vision \downarrow \bar{c} heat: hot bath, hot meal, exercise
- **o/e:** \downarrow acuity, \downarrow colour vision, white disc, central scotoma, RAPD

INO / ataxic nystagmus / conjugate gaze palsy

- Disruption of MLF connecting CN6 to CN3
- Weak adduction of ipsilateral eye
- Nystagmus of contralateral eye
- Convergence preserved

Ix

- **MRI:** Gd-enhancing or T2 hyper-intense plaques
 - Gd-enhancing = active inflammation
 - Typically located in periventricular white matter
- **LP:** IgG oligoclonal bands (not present in serum)
- **Abs**
 - **Anti-MBP**
 - **NMO-IgG:** highly specific for Devic's syn.
- **Evoked potentials:** delayed auditory, visual and sensory

Diagnosis: clinical

- Demonstration of lesions disseminated in time and space
- May use **McDonald Criteria**

Differential

Inflammatory conditions may mimic MS plaques:

- CNS sarcoidosis
- SLE
- Devic's: Neuromyelitis optica (NMO)
 - MS variant \bar{c} transverse myelitis and optic atrophy
 - Distinguished by presence of NMO-IgG Abs

Mx

- **MDT:** neurologist, radiologist, physio, OT, specialist nurses, GP, family

Acute Attack

- **Methylpred** 1g IV/PO /24h for 3d
 - Doesn't influence long-term outcome
 - \downarrow duration and severity of attacks

Preventing Relapse: DMARDs

- **IFN- β :** \downarrow relapses by 30% in relapsing remitting MS
- **Glatiramer:** similar efficacy to IFN- β

Preventing Relapse: Biologicals

- **Natalizumab:** anti-VLA-4 Ab
 - \downarrow Relapses by 2/3 in RRMS
- **Alemtuzumab (Campath):** anti-CD52
 - 2nd line in RRMS

Symptomatic

- **Fatigue:** modafinil
- **Depression:** SSRI (citalopram)
- **Pain:** amitriptyline, gabapentin
- **Spasticity:** physio, baclofen, dantrolene, botulinum
- **Urgency / frequency:** oxybutynin, tolterodine
- **ED:** sildenafil
- **Tremor:** clonazepam

Prognosis

Poor Prognostic Signs

- Older
- Male
- Motor signs @ onset
- Many relapses early on
- Many MRI lesions
- Axonal loss

Better Prognostic Signs

- Female
- <25
- Sensory signs @ onset
- Long interval between relapses
- Few MRI lesions

Cord Compression

Symptoms

- Deep, local spinal pain
- Stabbing, radicular pain in a dermatomal distribution and LMN weakness @ lesion level
- Progressive UMN weakness and sensory loss below lesion
- Bladder hesitancy, frequency → painless retention
- Faecal incontinence or constipation

Signs

- Look for motor, reflex and sensory level
- Shooting, radicular pain @ level, anaesthesia below
- LMN signs @ level, UMN signs below level
- Tone and reflexes are usually reduced in acute cord compression

Causes

- Trauma
- Infection: epidural abscess, TB
- 2^{o} to malignancy: breast, thyroid, bronchus, kidney, prostate
- Disc prolapse
- Haematoma: warfarin
- Intrinsic cord tumour
- Myeloma

Ix

- MRI is definitive modality
- CXR for primaries

Rx

- This is a neurosurgical emergency
- Malignancy
 - Dexamethasone IV
 - Consider chemo, radio and decompressive laminectomy
- Abscess: abx and surgical decompression

Differential

- Transverse myelitis
- MS
- Cord vasculitis
- Spinal artery thrombosis
- Aortic dissection

Cauda Equina and Conus Medullaris Lesions

- Spinal cord tapers to its end at L1
- Compared to lesions higher up the cord, these lesions are flaccid and areflexic (cf, spastic and hyperreflexic)

Conus Medullaris Lesions

- Mixed UMN/LMN weakness
- **Early constipation and retention**
- Back pain
- Sacral sensory disturbance
- ED

Cauda Equina Lesions

- Saddle anaesthesia
- Back pain
- Radicular pain down legs
- Bilateral flaccid, areflexic lower limb weakness
- Incontinence / retention of faeces / urine
- **Poor anal tone**

Mx

- As for cord compression
- These are neurosurgical emergencies and require urgent imaging and surgical decompression

Cervical and Lumbar Degeneration

Spondylosis

- Degeneration due to trauma or ageing
- IV disc / vertebral collapse
- Osteophytes
- May → central (myelopathy) and/or lateral (radiculopathy) pathology

Cervical Spondylosis

- 90% of men > 60 and women > 50

Presentation

- Usually asymptomatic
- Neck stiffness ± crepitus
- Stabbing / dull arm pain (brachialgia)
- Upper limb motor and sensory disturbances according to compression level (often C7)
- Can → myelopathy → quadraparesis and sphincter dysfunction

Specific Signs

- Lhermitte's sign: neck flexion → tingling down spine
- Hoffman reflex: flick to middle finger pulp → brief pincer flexion of thumb and index finger

Typical Deficits

Root	Disc	Motor Weakness	Sensory
C5	C4/5	Deltoid Supraspinatus ↓ supinator jerk	Numb elbow
C6	C5/6	Biceps Brachioradialis ↓ biceps jerk	Numb thumb and index finger
C7	C6/7	Triceps Finger extension ↓ triceps jerk	Numb middle finger
C8	C7/T1	Finger flexors Intrinsic hand	Numb ring and little fingers

Ix

- MRI

Rx

- **Conservative:** stiff collar, analgesia
- **Medical:** transforaminal steroid injection
- **Surgical:** decompression: laminectomy or laminoplasty

Differential

- MS
- Nerve root neurofibroma
- SACD

Lumbosacral Spondylosis

Presentation

- L5 and S1 roots most commonly compressed by prolapse of L4/5, L5/S1 discs.
- May present as severe pain on sneezing/coughing, a few days after low back strain
- Lumbago – low back pain
- Sciatica – shooting radicular pain down buttock and thigh

Signs

- Limited spinal flexion
- Pain on straight-leg raise

L4/5 → L5 Root Compression

- Weak hallux extension ± foot drop
 - In foot drop due to L5 radiculopathy, weak inversion (tib. post.) helps distinguish from peroneal N. palsy.
- ↓ sensation on inner dorsum of foot

L5/S1 → S1 Root Compression

- Weak foot plantarflexion and eversion
- Loss of ankle-jerk
- Calf pain
- ↓ sensation over sole of foot and back of calf

Central Compression

- Cauda equina syndrome

Ix

- MRI is definitive (emergency if cauda-equina syndrome)

Rx

- **Conservative:** rest, analgesia, mobilisation/physio
- **Medical:** transforaminal steroid injection
- **Surgical:** discectomy or laminectomy may be considered in cauda-equina syndrome, continuing pain or muscle weakness.

Spinal Stenosis

- Developmental predisposition ± facet joint osteoarthritis → generalized narrowing of lumbar spinal canal.

Presentation

- **Spinal claudication**
 - Aching or heavy buttock and lower limb pain on walking
 - Rapid onset
 - May c/o paraesthesiae/numbness
 - Pain eased by leaning forward (e.g. on bike)
- Pain on spine extension
- Negative straight leg raise

Ix

- MRI

Rx

- Corsets
- NSAIDs
- Epidural steroid injection
- Canal decompression surgery

Facial Nerve Palsy

Bell's Palsy

- Inflammatory oedema from entrapment of CNVII in narrow facial canal
- Probably of viral origin (HSV1)
- 75% of facial palsy

Features

- Sudden onset: e.g. overnight
- Complete, unilateral facial weakness in 24-72h
 - Failure of eye closure → dryness
 - Bell's sign: eyeball rolls up on attempted closure
 - Drooling, speech difficulty
- Numbness or pain around ear
- ↓ taste (ageusia)
- Hyperacusis: stapedius palsy

Ix

- Serology: Borrelia or VZV Abs
- MRI: SOL, stroke, MS
- LP

Mx

- Give **prednisolone** w/i 72hrs
 - 60mg/d PO for 5/7 followed by tapering
- **Valaciclovir** if zoster suspected
 - Otherwise antivirals don't help
- **Protect eye**
 - Dark glasses
 - Artificial tears
 - Tape closed @ night
- Plastic surgery may help if no recovery

Prognosis

- **Incomplete paralysis:** recovers completely w/i wks
- **Complete:** 80% get full recovery
 - Remainder have delayed recovery or permanent neurological / cosmetic abnormalities.

Complications: Aberrant Neural Connections

- **Synkinesis:** e.g. blinking causes up-turning of mouth
- **Crocodile tears:** eating stimulates unilateral lacrimation, not salivation

Ramsay Hunt Syndrome

- American neurologist James Ramsay Hunt in 1907
- Reactivation of VZV in geniculate ganglion of CNVII

Features

- Preceding ear pain or stiff neck
- Vesicular rash in auditory canal ± TM, pinna, tongue, hard palate (no rash = *zoster sine herpete*)
- Ipsilateral facial weakness, ageusia, hyperacusis,
- May affect CN8 → vertigo, tinnitus, deafness

Mx

- If Dx suspected give valaciclovir and prednisolone w/i first 72h

Prognosis

- Rxed w/i 72h: 75% recovery
- Otherwise: 1/3 full recovery, 1/3 partial, 1/3 poor

Other Causes of Facial Palsy

May be suggested by

- Bilat symptoms: Lyme, GBS, leukaemia, sarcoid, MG
- UMN signs: sparing of frontalis and orbicularis oculi
 - Due to bilateral cortical representation
- Other CN palsies (but seen in 8% of Bell's)
- Limb weakness
- Rashes

Intracranial

- Vascular, MS, SOL
 - Motor cortex → UMN
 - Assoc. \bar{C} ipsilateral hemiplegia
 - Brainstem nuclei → LMN
 - Usually assoc. \bar{C} CN6 palsy + contralateral hemiplegia
- Cerebello-pontine angle: acoustic neuroma, meningioma
 - Both may be accompanied by 5th, 6th and 8th CN palsies and cerebellar signs
 - Loss of corneal reflex
 - Sensorineural deafness, tinnitus, vertigo
 - DANISH

Intra-temporal

- Cholesteatoma
- Ramsay Hunt
- Otitis media
- Trauma

Infra-temporal

- Parotid tumours
- Trauma

Systemic

- Peripheral neuropathy
 - Demyelinating: GBS
 - Axonal: DM, Lyme, HIV, Sarcoid
- Pseudopalsy: MG, botulism

Mononeuropathies

- Lesions of individual peripheral or cranial nerves
 - Usually local cause: trauma, entrapment
- Mononeuritis multiplex: 2 or more peripheral nerves affected
 - Usually systemic cause: DM most commonly
 - **WAARDS PLC:** Wegener's, AIDS, Amyloid, RA, DM, Sarcoidosis, PAN, Leprosy, Carcinomatosis
- Electromyography (EMG) helps define site of lesion

Nerve	Location / Cause	Motor Features	Sensory Loss/ Features
Median: C6-T1	Wrist: carpal tunnel, trauma	LLOAF muscles Thenar wasting	Radial 3½ fingers and palm Aching pain in hand ↓ 2-point discrimination Tinel's and Phalen's +ve
Ulnar: C7-T1	Elbow trauma - e.g. supracondylar #	Partial claw hand Hypothenar wasting Can't do good luck sign Weakness and wasting of 1 st dorsal interosseous Froment's +ve	Ulnar 1½ fingers
Radial: C5-T1	Low: wrist High: humerus V. high: Axilla	Low: finger drop High: wrist drop V. high: triceps paralysis, wrist drop	Dorsal thumb root (snuff box)
Brachial plexus	Trauma Radiotherapy (e.g. breast)	High (C5-6): Erb's palsy → waiter's tip Low (C8-T1): Klumpke's → claw hand	High: C5-6 dermatome Low: C8-T1 dermatome
Phrenic: C3-5	Neoplastic: Lung Ca Myeloma Thymoma Mechanical: Cervical spondylosis Big left atrium Infective: C3-5 zoster HIV Lyme TB	Orthopnoea + raised hemidiaphragm	
Lat. cut. N. thigh: L2-3	Entrapment under inguinal ligament		Meralgia paraesthesia – anterolat. burning thigh pain
Sciatic: L4-S3	Pelvic tumours Pelvic or femur #s	Hamstrings All muscles below knee	Below knee laterally and foot
Common peroneal: L4-S1	Fibular head: trauma, sitting cross legged	Foot drop: can't walk on heals Weak ankle dorsiflexion, eversion NB. inversion intact!	Below knee laterally
Tibial: L4-S3		Can't plantar flex → can't stand on tiptoe Foot inversion Toe flexion	Sole of foot

Polyneuropathies

Features

- Generalised disorders of peripheral or cranial nerves
- Distribution is symmetrical and widespread
- Distal weakness and sensory loss (glove + stocking)
- Classification
 - Time-course:** acute, chronic
 - Function:** motor, sensory, autonomic, mixed
 - Path:** demyelination, axonal degeneration, both

Causes

Metabolic (mostly axonal)

- DM
- Renal failure / uraemia
- Hypothyroid
- \downarrow B1 or \downarrow B12 (EtOH)

Inflammatory

- GBS
- Sarcoidosis

Inherited

- CMT
- Refsum's syndrome

Drugs

- Isoniazid
- EtOH
- Phenytoin
- Vincristine

History

- Time-course
- Precise symptoms
- Assoc. events
 - D&V: GBS
 - \downarrow wt: Ca
 - Arthralgia: connective tissue
- Travel, EtOH, drugs

Ix

- LFTs, U+E, glucose, ESR, B12
- TFTs B1, ANA, ANCA
- Genetic tests: e.g. PMP22 in CMT
- Nerve conduction studies
- EMG

Sensory Neuropathy

Main Causes

- Alcohol
- B12
- CRF and Ca (paraneoplastic)
- DM
- Every vasculitis

General Features

- Glove and stocking distribution: length dependent
- Deep tendon reflexes may be \downarrow or absent
 - E.g. loss of ankle jerks in diabetic neuropathy
- Signs of trauma or joint deformity (Charcot's joints)
- Diabetic and alcoholic neuropathies are painful
- Some aetiologies favour loss of particular fibres

Large Myelinated Fibres (A α): e.g. B12

- Loss of proprioception \rightarrow ataxia
- Pins and needles

Small Unmyelinated Fibres (C): e.g. EtOH

- Loss of pain and temperature sensation
- Painful dysesthesia: e.g. burning, hyperalgesia

Motor Neuropathy

Main Causes

- GBS (+ botulism)
- HMSN / CMT
- Paraneoplastic
- Lead poisoning

Features

- Weakness/clumsiness of hands, difficulty walking
- LMN signs
- CN: diplopia, dysarthria, dysphagia
- Involvement of respiratory muscles \rightarrow \downarrow FVC

Autonomic Neuropathy

Causes

- DM
- HIV
- SLE
- GBS, LEMS

Features

- Postural hypotension
- ED, ejaculatory failure
- \downarrow sweating
- Constipation / Nocturnal diarrhoea
- Urinary retention
- Horner's

Autonomic Function Tests

- BP:** Postural drop $>$ 20/10mmHg
- ECG:** variation $>$ 10bpm \bar{c} respiration

Primary Autonomic Failure

- Idiopathic or part of MSA or PD

Guillain-Barré Syndrome

Classification

- **AIDP:** Acute autoimmune demyelinating polyneuropathy
- **AMAN:** Acute motor (\pm sensory) axonal neuropathy
- **Miller-Fisher:** Ophthalmoplegia + ataxia + areflexia

Causes

- Abs cross-react to gangliosides
- No precipitant identified in 40%
- **Bacteria:** C. jejuni, mycoplasma
- **Viruses:** CMV, EBV, HSV, HIV, flu
- **Vaccines:** esp. rabies

Features and Ix: GBS=AIDP

Growing Weakness

- Symmetrical, ascending flaccid weakness / paralysis
- LMN signs: areflexia, fasciculations may occur
- Proximal > distal (trunk, respiratory, CNs [esp. 7])
- Progressive phase lasts \leq 4wks

Breathing and Bulbar Problems

Back Pain

- Back / limb pain is common

Sensory disturbance

- Paraesthesia in extremities
- Sensory ataxia in Miller-Fisher

Autonomic Neuropathy

- Arrhythmias, \uparrow HR
- Labile BP
- Sweating
- Urinary retention

Immune

- Serology for anti-ganglioside Abs
- Evidence of infection: e.g. stool sample

Demyelinating Nerve Conduction Studies

- Slow conduction velocities

Protein in CSF

- Protein often $>$ 5.5g/L
- Normal white cell count

Mx

Supportive

- Airway / ventilation: ITU if FVC $<$ 1.5L
- Analgesia: NSAIDs, gabapentin
- Autonomic: may need inotropes, catheter
- Antithrombotic: TEDS, LMWH

Immunosuppression

- IVIg
- Plasma exchange

Physiotherapy

- Prevent flexion contractures

Prognosis

- 85% complete recovery
- 10% unable to walk alone at 1yr
- 5% mortality

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Charcot-Marie-Tooth Syndrome

= Peroneal Muscular Atrophy

= Hereditary Motor and Sensory Neuropathy

Pathophysiology

- Group of inherited motor and sensory neuropathies

HMSN1

- Commonest form
- Demyelinating
- AD mutation in the peripheral myelin protein 22 gene

HMSN2

- Second commonest form
- Axonal degeneration (\therefore near normal conduction velocity)

Clinical Features

- Onset at puberty

Nerves

- Thickened, enlarged nerves: esp. common peroneal

Motor

- Foot drop \rightarrow high stepping gait
- Weak ankle dorsiflexion and toe extension
- Absent ankle jerks
- Symmetrical muscle atrophy: mainly distal
 - Peroneal muscles \rightarrow "Champagne Bottle"
 - Hand and arm muscles \rightarrow "Claw Hand"
- Pes cavus (high-arched feet)

Sensory

- Variable loss of sensation in a stocking distribution
- Neuropathic pain in some

Ix

- Genetic tests: PMP22 gene mutation
- Nerve conduction studies: \downarrow conduction speed in CMT1

Mx

- Supportive
 - Physio
 - Podiatry
 - Orthoses: e.g. ankle braces

Motor Neurone Disease

Characteristics

- Cluster of degenerative disease characterised by axonal degeneration of neurones in the motor cortex, CN nuclei and anterior horn cells.
- UM and LM neurones affected (cf. polyneuropathy)
- **No sensory loss or sphincter disturbance** (cf. MS)
- **Never affects eye movements** (cf. MG)

Epidemiology

- **Prevalence:** 6/100,000
- **Sex:** M>F=3:2
- **Median age @ onset** = 60yrs
- Often fatal in 2-4yrs

Causes

- Unknown
- ~10% familial: SOD1 mutation in 20% of those

Ix

- **Brain/cord MRI:** exclude structural cause
 - Cervical cord compression → myelopathy
 - Brainstem lesions
- **LP:** exclude inflammatory cause
- **EMG:** shows denervation

Features

- **UMN:** spasticity, ↑ reflexes, ↑ plantars
- **LMN:** wasting, fasciculation of tongue / abdo / thigh
- Speech or swallowing impairment
- Fronto-temporal dementia

Diagnosis

- MRI to exclude structural lesions
- LP to exclude inflammation
- EMG shows acute denervation
- Use **Revised El Escorial Diagnostic Criteria**

Mx

- **MDT:** neurologist, physio, OT, dietitian, specialist nurse, GP, family
- Discussion of end-of-life decisions
 - E.g. Advanced directive
 - DNAR

Specific

- **Riluzole:** antiglutamatergic that prolongs life by ~3mo

Supportive

- **Drooling:** propantheline or amitriptyline
- **Dysphagia:** NG or PEG feeding
- **Respiratory failure:** NIV
- **Pain:** analgesic ladder
- **Spasticity:** baclofen, botulinum

Prognosis

- Most die w/i 3yrs
 - Bronchopneumonia and respiratory failure
- Worse prog: elderly, female, bulbar involvement

Classification

Amyotrophic Lateral Sclerosis: 50%

- Loss of motor neurones in cortex and anterior horn → UMN signs and LMN wasting + fasciculation

Progressive Bulbar Palsy: 10%

- Only affects CN 9-12 → bulbar palsy

Progressive Muscular Atrophy: 10%

- Anterior horn cell lesion → **LMN signs only**
- Distal to proximal
- Better prognosis cf. ALS

Primary Lateral Sclerosis

- Loss of Betz cells in motor cortex → mainly UMN signs
- Marked spastic leg weakness and pseudobulbar palsy
- No cognitive decline

Bulbar Palsy

- Diseases of nuclei of CN 9-12 in the medulla
- LMN lesions of tongue, talking and swallowing
- **Signs**
 - Flaccid, fasciculating tongue
 - Speech: quiet or **nasal** ("Donald Duck" speech)
 - Normal / absent jaw jerk
 - Loss of gag reflex
- **Causes**
 - MND
 - GBS
 - MG
 - Central pontine myelinolysis (CPM)

Pseudobulbar / Corticobulbar Palsy

- Commoner than bulbar palsy
- Bilateral lesions above mid-pons (e.g. corticobulbar tracts) → UMN lesions of swallowing and talking
 - CN motor nuclei have bilateral cortical representation except lower half of CN7
- **Signs**
 - Spastic tongue
 - Slow tongue movements & slow deliberate speech: "hot-potato" speech
 - Brisk jaw jerk
 - Emotional incontinence
- **Causes**
 - MS
 - MND
 - Stroke
 - CPM

Polio

- RNA virus
- Affects anterior horn cells
- Fever, sore throat, myalgia
- 0.1% develop paralytic polio
 - **Asymmetric LMN paralysis**
 - **No sensory involvement**
 - May be confined to upper or lower limbs or both
 - Respiratory muscle paralysis can → death

Myopathies

Myopathy vs. Neuropathy

Myopathy

- Gradual onset
- Symmetrical, *proximal* weakness: difficulty combing hair, climbing stairs, getting up from chairs
- Dystrophies usually affect specific muscle groups
- Preserved tendon reflexes

Neuropathy

- Paraesthesia, bladder problems
- Distal weakness

Other Pointers

- Rapid onset: neuropathy, or drug, toxic or metabolic myopathy
- Fatigability: MG, LEMS
- Spontaneous pain and tenderness @ rest: inflam myopathy
- Pain on exercise: ischaemia or metabolic myopathy
- Oddly firm muscles: pseudohypertrophy in muscular dystrophies
- Fasciculation: anterior horn cell or root disease

Ix

- ESR, CK, AST, LDH
- EMG

Muscular Dystrophies

- Group of genetic disease \bar{c} progressive degeneration and weakness of specific muscle groups.

DMD

- Commonest: 3/1000 male births
- X-linked recessive, 30% spontaneous \rightarrow non-functional dystrophin
- **Presentation**
 - ~4yrs old
 - Difficulty standing
 - Calf pseudohypertrophy
 - Respiratory failure
- **Ix:** \uparrow CK
- **Prog:** some survive > 20yrs

BMD

- 0.3/1000 male births
- X-linked recessive
- Partially functioning dystrophin
- Presents later, is less severe and has better prognosis

Facioscapulohumeral MD (Landouzy-Dejerine)

- Almost as common as DMD
- AD inheritance
- **Presentation**
 - Onset @ 12-14yrs
 - Difficulty puffing cheeks and raising arms above head
- **Signs**
 - Weakness of face, shoulders and upper arms (often asymmetric \bar{c} deltoids spared)
 - Winging of scapula
 - Foot drop.
- **Prog:** <20% need wheelchair by 20yrs

Myotonic Dystrophy

- AD Cl^- channelopathy
- Onset in 20s
- Tonic muscle spasm (myotonia)

Presentation

- **Face**
 - Myopathic facies: long, thin, expressionless
 - Wasting of facial muscles and SCM
 - Bilateral ptosis
 - Dysarthria: myotonia of tongue and pharynx
- **Hands**
 - Myotonia: slow relaxation
 - E.g. inability to release hand after shake
 - Wasting and weakness of distal muscles + areflexia \rightarrow wrist drop
 - Percussion myotonia: percuss thenar eminence \rightarrow involuntary thumb flexion
- **Other**
 - Frontal balding
 - Cataracts
 - DM
 - Cardiomyopathy, tachy- / brad-arrhythmias
 - Dysphagia
 - Testicular atrophy

Rx

- No Rx for weakness
- Phenytoin may improve myotonia
- Caution \bar{c} GA: high risk of anaesthetic complications

Prognosis

- Most die in middle-age of intercurrent illness

Acquired myopathies of late onset

- Usually part of systemic disease
- Hyperthyroidism, Cushing's, $\uparrow/\downarrow \text{Ca}^{2+}$
- Drugs: steroids, statins, EtOH

Inflammatory Myopathies

- Inclusion body myositis
- Polymyositis
- Dermatomyositis

Inclusion Body Myositis

- Asymmetric weakness affecting distal and prox muscles
 - Early involvement of quads, ankle dorsiflexors and wrist/finger flexors
 - \rightarrow loss of grip strength and \downarrow dexterity
- Dysphagia is very common
- Myalgia is relatively uncommon

Myasthenia Gravis

Pathophysiology

- Autoimmune disease mediated by Abs vs. nicotinic Ach receptors.
- Interferes w/ NM transmission via depletion of working post-synaptic receptor sites

Presentation

- ↑ing muscular fatigue
 - Extra-ocular:** bilateral ptosis, diplopia
 - Bulbar:** voice deteriorates on counting to 50
 - Face:** myasthenic snarl on attempting to smile
 - Neck:** head droop
 - Limb:** asymmetric, prox. weakness
- Normal tendon reflexes
- Weakness worsened by pregnancy, infection, emotion, drugs (β -B, gent, opiates, tetracyclines)

Investigations

- Tensilon Test**
 - Give edrophonium IV
 - +ve if power improves w/i 1min
- Anti-AChR Abs:** ↑ in 90%, MuSK Abs
- EMG:** ↓ response to a train of impulses
- Respiratory function: ↓FVC
- Thymus CT
- TFTs

Differential of Muscle Fatigability

- Polymyositis
- SLE
- Botulism

Associations

- <50yrs MG is commoner in women and assoc. w/ other AI disease (DM, RA, Graves) and thymic hyperplasia.
- >50yrs MG is commoner in men and assoc. w/ thymic atrophy or thymic tumour.

Treatment

Symptom Control

- Anticholinesterase: e.g. pyridostigmine.
- Cholinergic SEs = SLUDGEM

Immunosuppression

- Rx relapses w/ pred
- Steroids may be combined w/ azathioprine or methotrexate

Thymectomy

- Consider if young onset and disease not controlled by anticholinesterases
- Remission in 25%, benefit in further 50%.

Complications

Myasthenic Crisis

- Weakness of respiratory muscles during relapse may be lethal.
- Monitor FVC: vent support if <20ml/kg
- Plasmapheresis or IVIg
- Rx trigger for relapse (drugs, infection...)

Prognosis

- Relapsing or slow progression

Lambert-Eaton Myasthenic Syndrome (LEMS)

Pathophysiology

- Abs to VGCC ↓ influx of Ca^{2+} during presynaptic excitation → ↓ presynaptic ACh-vesicle fusion.

Causes

- Paraneoplastic: e.g SCLC
- Autoimmune

Presentation

- As for MG except: **LEMS**
 - Leg weakness early (before eyes)
 - Extra: Autonomic and areflexia
 - Movement improves symptoms
 - Small response to edrophonium
- Anti-VGCC Abs

Mx

- 3,4-diaminopyridine or IVIg
- Do regular CXRs / HRCTs as symptoms may precede Ca by 4yrs

Botulism

- Botulinum toxin prevents ACh vesicle release
- Descending flaccid paralysis w/ no sensory signs
- Anti-cholinergic effects: mydriasis, cycloplegia, n/v, dry mouth, constipation
- Rx:** benzen + antiserum

Neurofibromatosis 1 – von Recklinghausen's

Epidemiology

- AD Chr 17
- Variable expression
- Prev: 1/2500

Features: CAFÉ NOIR

Café-au-lait spots

- 1st yr of life
- ↑ in size and no. \propto age
- Adults: >6, >15mm across

Axillary Freckling

- in skin folds

Fibromas, neuro-:

- **Subcutaneous**
 - Small, gelatinous, violaceous nodules
 - Appear @ puberty
 - May itch
 - Nos. $\uparrow \propto$ age
- **Plexiform**
 - Overgrowth of nerve trunk and overlying tissue
 - Large cutaneous mass
- **Complications**
 - Sarcomatous change
 - Compression:
 - Nerve roots: weakness, pain, paraesthesia
 - GI: bleeds and obstruction

Eye

- Lisch nodules
 - Brown/translucent iris hamartomas
 - Use a slit lamp
- Optic N. glioma

Neoplasia

- CNS: meningioma, ependymoma, astrocytoma
- Phaeochromocytoma
- Chronic or acute myeloid leukaemia

Orthopaedic

- Kyphoscoliosis
- Sphenoid dysplasia

IQ↓ and Epilepsy

Renal

- RAS \rightarrow ↑ BP

Mx

- MDT orchestrated by GP
- Yearly BP and cutaneous review
- Excise some neurofibromas
- Genetic counselling

Café-au-Lait Spots Differential

- NF
- McCune-Albright
- Multiple Lentigenes
- Urticaria Pigmentosa

Neurofibromatosis 2

Epidemiology

- AD inheritance (Chr 22), but 50% are *de novo*
- Prev: 1/35,000

Signs

Café-au-lait spots

- Rare
- Fewer cf. NF1

Bilateral Vestibular Schwannomas

- Characteristic
- Symptomatic by 20yrs
- SNHL is first sign, then tinnitus, vertigo

Juvenile Posterior Subcapsular Lenticular Opacity

- Form of cataract
- Bilateral
- Occur before other manifestations and may be useful for screening those @ risk

Complications

- Tender schwannomas of cranial and peripheral nerves and spinal nerve roots.
- Meningiomas: often multiple
- Gliomas

Mx

- Hearing tests from puberty in affected families
- MRI brain if abnormality detected

Prognosis

- Mean survival from Dx is 15yrs

Intrinsic Cord Disease

Presentation

- Painless
- Early sphincter / erectile dysfunction
- Bilateral motor and sensory disturbance below lesion

Causes: DIVINITY

Degenerative

- MND

Developmental

- Friedrich's Ataxia
- Hereditary spastic paraparesis

Infection

- Viral: HIV, HTLV-1
- Syphilis: Tabes Dorsalis

Vascular Infarction

- Aortic dissection/aneurysm
- Thromboembolism
- Atheroma
- Vasculitis: esp. PAN

NB. ant. spinal A. infarction → spinothalamic and corticospinal tract loss → bilat loss of pain/temp and spastic paresis
▪ = Beck's Syndrome

Inflammation

- Demyelination: MS
- Transverse myelitis

Neoplasia

- Glioma
- Ependymoma

Injury

Toxin / Nutrition

- B12 deficiency

sYringomyelia

Syringomyelia

Characteristics

- Syrinx: tubular cavity in central canal of the cervical cord.
- Onset @ 30yrs
- Symptoms may be static for yrs but then worsen fast
 - e.g. on coughing, sneezing as ↑ pressure → extension
- Commonly located in cervical cord
- Syrinx expands ventrally affecting:
 - Decussating spinothalamic neurones
 - Anterior horn cells
 - Corticospinal tracts

Causes

- Blocked CSF circulation → ↓ flow from posterior fossa
 - Arnold-Chiari malformation (cerebellum herniates through foramen magnum)
 - Masses
- Spina bifida
- 2^o to cord trauma, myelitis, cord tumours and AVMs

Cardinal Signs

1. **Dissociated Sensory Loss**
 - Absent pain and temperature → scars from burns
 - Preserved touch, proprioception and vibration.
 - Root distribution reflects syrinx location
 - Usually upper limbs and chest: "cape"
2. **Wasting/weakness of hands ± Claw hand**
3. **Loss of reflexes in upper limb**
4. **Charcot Joints:** shoulder and elbow

Other Signs

- UMN weakness in lower limbs → upgoing plantars
- Horner's syndrome
- Syringobulbia: cerebellar and lower CN signs
- Kyphoscoliosis

Ix

- MRI spine

Surgery

- Decompression at the foramen magnum for Chiari mal

Brown-Sequard Syndrome

- Hemi-cord lesion
- Ipsilateral loss of proprioception and vibration sense
- Ipsilateral UMN weakness
- Contralateral loss of pain sensation

Miscellaneous Conditions

Friedreich's Ataxia

- Auto recessive progressive degeneration of DRGs, spinocerebellar and corticospinal tracts and cerebellar cells
- Mitochondrial disorder
- Onset in teenage years
- Assoc. c HOCM and mild dementia

Presentation

- Pes cavus and scoliosis
- Bilateral cerebellar signs
 - Ataxia
 - Dysarthria
 - Nystagmus
- Leg wasting + areflexia but extensor plantars
- Loss of lower limb proprioception and vibration sense
- Optic atrophy
- Cardiac: HOCM → ESM + 4th heart sound
- DM → hyperglycaemia

Hereditary Spastic Paraparesis

- Lower limb spasticity
- Ataxia
- Extrapyramidal signs

Human T-lymphotropic Virus-1

- Retrovirus
- ↑ prevalence in Japan and Caribbean

Features

- Adult T cell leukaemia / lymphoma
- Tropical spastic paraparesia / HTLV myelopathy
 - Slowly progressing spastic paraparesia
 - Sensory loss and paraesthesia
 - Bladder dysfunction

Rheumatology

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Patterns of Presentation

Monoarthritis

- Septic arthritis
- Crystal arthritis: gout, CPPD
- Osteoarthritis
- Trauma: haemarthrosis

Oligoarthritis (≤ 5 joints)

- Crystal arthritis
- Psoriatic arthritis
- Reactive arthritis
- Ankylosing spondylitis
- Osteoarthritis

Polyarthritis (>5 joints)

Symmetrical

- RA
- Osteoarthritis
- Viruses: Hep A,B,C, mumps

Asymmetrical

- Reactive arthritis
- Psoriatic arthritis

Either

- Systemic disease: SLE, sarcoid, endocarditis

Rheumatological Investigations

Joint Aspiration

- The key investigation in a monoarthritis
- Appearance
- Send for
 - WCC
 - Gram stain and culture
 - Polarized light microscopy

Bloods

- Basic: FBC, U+E, ESR, CRP, urate
- Culture: septic arthritis
- Abs: RF, ANA, others
- HLA-B27
- Viral serology, urine chlamydia PCR: reactive arthritis

Radiology

- CXR: RA, SLE, Vasculitis, TB, Sarcoid
- US/MRI: more sensitive for synovitis, enthesitis, infection

Osteoarthritis

- Loss of joint space
- Osteophytes
- Subchondral cysts
- Subchondral sclerosis

Rheumatoid Arthritis

- Loss of joint space
- Soft tissue swelling
- Peri-articular osteopenia
- Deformity
- Subluxation

Gout

- Normal joint space
- Soft tissue swelling
- Periarticular erosions

Back Pain

Red Flags

- Age <20 or >55yrs
- Neurological disturbance (inc. sciatica)
- Sphincter disturbance
- Bilateral or alternating leg pain
- Current or recent infection
- Fever, wt. loss, night sweats
- History of malignancy
- Thoracic back pain
- Morning stiffness
- Acute onset in elderly people
- Constant or progressive pain
- Nocturnal pain

Causes

- **Mechanical**
 - Strain/idiopathic
 - Trauma
 - Pregnancy
 - Disc prolapse
 - Spondylolisthesis (forward shift of one vertebra)
- **Degenerative:** spondylosis, vertebral collapse, stenosis
- **Inflammatory:** Ank spond, Paget's
- **Neoplasm:** Mets, myeloma
- **Infection:** TB, abscess

Nerve Root Lesions

Root	Weakness	Reflex
L2	Hip flexion + adduction	
L3	Knee extension Hip adduction	Knee Jerk
L4	Foot inversion + dorsiflexion Knee extension	Knee Jerk
L5	Great toe dorsiflexion Foot inversion + dorsiflexion Knee Flexion Hip extension + abduction	
S1	Foot eversion Foot and toe plantarflexion Knee flexion	Ankle Jerk

Rx

- Usually only necessary if red flags present
- FBC, ESR, CRP, ALP, se electrophoresis, PSA
- MRI

Mx

- Neurosurgical referral if neurology
- **Conservative**
 - Max 2d bed rest
 - Education: keep active, how to lift / stoop
 - Physiotherapy
 - Psychosocial issues re. chronic pain and disability
 - Warmth
- **Medical**
 - Analgesia: paracetamol ± NSAIDs ± codeine
 - Muscle relaxant: low-dose diazepam (short-term)
 - Facet joint injections
- **Surgical**
 - Decompression
 - Prolapse surgery: e.g. microdiscectomy

Neurosurgical Emergencies

Acute Cord Compression

- Bilateral pain: back and radicular
- LMN signs at compression level
- UMN signs and sensory level below compression
- Sphincter disturbance

Acute Cauda Equina Compression

- Alternating or bilateral radicular pain in the legs
- Saddle anaesthesia
- Loss of anal tone
- Bladder ± bowel incontinence

Rx

- **Large prolapse:** laminectomy / discectomy
- **Tumours:** radiotherapy and steroids
- **Abscesses:** decompression

Osteoarthritis

Definition

- Degenerative joint disorder in which there is progressive loss of hyaline cartilage.

Aetiology / Risk Factors

- Age (80% > 75yrs)
- Obesity
- Joint abnormality

Classification

- Primary:** no underlying cause
- Secondary:** obesity, joint abnormality

Symptoms

- Affects: knees, hips, DIPs, PIPs, thumb CMC
- Pain:** worse \ominus movement, background rest/night pain, worse @ end of day.
- Stiffness:** especially after rest, lasts ~30min (e.g. AM)
- Deformity**
- \downarrow ROM

Signs

- Bouchard's (prox), Heberden's (dist.) nodes
- Thumb CMC squaring
- Fixed flexion deformity

Hx and Ix

- Focus on ADLs and social circumstances
- X-ray

Differential

- Septic
- Crystal
- Trauma

Mx

Conservative

- \downarrow wt.
- Alter activities: \uparrow rest, \downarrow sport
- Physio: muscle strengthening
- Walking aids, supportive footwear, home mods

Medical

- Analgesia**
 - Paracetamol
 - NSAIDs: e.g. arthrotec (diclofenac + misoprostol)
 - But misoprostol \rightarrow diarrhoea
 - Tramol
- Joint injection:** local anaesthetic and steroids

Surgical

- Arthroscopic washout:** esp. knee.
 - Trim cartilage, remove foreign bodies.
- Arthroplasty:** replacement (or excision)
- Osteotomy:** small area of bone cut out.
- Arthrodesis:** last resort for pain management
- Novel Techniques**
 - Microfracture: stem cell release \rightarrow fibro-cartilage formation
 - Autologous chondrocyte implantation

Septic Arthritis

Pathophysiology

- Source:** local or haematogenous.
- Organisms**
 - Staph:** commonest overall (60%)
 - Gonococcus:** commonest in young sexually active
 - Streps
 - Gm-ve bacilli
- RFs**
 - Joint disease (e.g. RA)
 - CRF
 - Immunosuppression (e.g. DM)
 - Prosthetic joints

Symptoms

- Acutely inflamed tender, swollen joint
- \downarrow ROM
- Systemically unwell

Investigations

- Joint aspiration for MCS
 - $\uparrow\uparrow$ WCC (e.g. $>50,000/\text{mm}^3$): mostly PMN
- \uparrow ESR/CRP, \uparrow WCC, Blood cultures
- X-ray

Management

- IV Abx: vanc + cefotaxime
- Consider joint washout under GA
- Splint joint
- Physiotherapy after infection resolved

Complications

- Osteomyelitis
- Arthritis
- Ankylosis: fusion

Differential

- Crystal arthropathy
- Reactive arthritis

Rheumatoid Arthritis

Definition

- Chronic systemic inflammatory disease characterised by a symmetrical, deforming, peripheral polyarthritis.

Epidemiology

- Prev:** 1% (\uparrow in smokers)
- Sex:** F>M=2:1
- Age:** 5th-6th decade
- Genetics:** HLA-DR4/DR1 linked

Features: ANTI CCP Or RF

Arthritis

- Symmetrical, polyarthritis of MCPs, PIPs of hands and feet \rightarrow pain, swelling, deformity
 1. Swan neck
 2. Boutonniere
 3. Z-thumb
 4. Ulnar deviation of the fingers
 5. Dorsal subluxation of ulnar styloid
- Morning stiffness >1 h
- Improves \bar{c} exercise
- Larger joints may become involved

Nodules

- Commonly elbows also fingers, feet, heel
 - Firm, non-tender, mobile or fixed
- Lungs

Tenosynovitis

- De Quervain's
- Atlanto-axial subluxation

Immune

- AIHA
- Vasculitis
- Amyloid
- Lymphadenopathy

Cardiac: pericarditis + pericardial effusion

Carpal Tunnel Syndrome

Pulmonary

- Fibrosing alveolitis (lower zones)
- Pleural effusions (exudates)

Ophthalmic

- Epi-/scleritis
- 2^o Sjogren's Syndrome

Raynaud's

Felty's Syndrome

- RA + splenomegaly + neutropenia
- Splenomegaly alone in 5%, Felty's in 1%

Dx – 4/7 of:

- Morning stiffness >1 h (lasting >6 wks)
- Arthritis ≥ 3 joints
- Arthritis of hand joints
- Symmetrical
- Rheumatoid nodules
- +ve RF
- Radiographic changes

Ix

- Bloods:** FBC (anaemia, \downarrow PMN, \uparrow plat), \uparrow ESR, \uparrow CRP
- RF +ve in 70%
 - High titre assoc. \bar{c} severe disease, erosions and extra-articular disease
 - ve = "seronegative rheumatoid"
- Anti-CCP: 98% specific (Ag derived from collagen)
- ANA: +ve in 30%
- Radiography, US, MRI

Mx

Conservative

- Refer to rheumatologist
- Regular exercise
- PT
- OT: aids, splints

Medical

- DAS28:** Monitor disease activity
- DMARDs and biologicals:** use early
- Steroids:** IM, PO or intra-articular for exacerbations
 - Avoid giving until seen by rheumatologist
- NSAIDs:** good for symptom relief
- Mx CV risk:** RA accelerates atherosclerosis
- Prevent osteoporosis and gastric ulcers

Surgical

- Ulna stylectomy
- Joint prosthesis

DMARDs

- 1st line for treating RA
- Early DMARD use assoc. \bar{c} better long-term outcome
- All DMARDs can \rightarrow myelosuppression \rightarrow pancytopenia

Main agents

- Methotrexate:** hepatotoxic, pulmonary fibrosis
- Sulfasalazine:** hepatotoxic, SJS, \downarrow sperm count
- Hydroxychloroquine:** retinopathy, seizures

Other Agents

- Leflunomide:** \uparrow risk of infection and malignancy
- Gold:** nephrotic syndrome
- Penicillamine:** drug-induced lupus, taste change

Biologicals

Anti-TNF

- Severe RA not responding to DMARDs
- Screen and Rx TB first
- Infliximab:** chimeric anti-TNF Ab
- Etanercept:** TNF-receptor
- Adalimumab:** human anti-TNF Ab
- SEs:** \uparrow infection (sepsis, TB), \uparrow AI disease, \uparrow Ca

Rituximab (anti-CD20 mAb)

- severe RA not responding to anti-TNF therapy

Anatomy of Rheumatoid Hands

- Boutonniere's:** rupture of central slip of extensor expansion \rightarrow PIPJ prolapse through "button-hole" created by the two lateral slips.
- Swan:** rupture of lateral slips \rightarrow PIPJ hyper-extension

Differential of Rheumatoid Hands

- Psoriatic arthritis:** nail changes and plaques
- Jaccoud's arthropathy:** reducible in extension
- Chronic crystal arthritis**

Gout

Pathophysiology

- Deposition of monosodium urate crystals in and around joints → erosive arthritis
- May be ppter by surgery, infection, fasting or diuretics

Presentation

- M>F=5:1
- Acute monoarthritis → severe joint inflammation
 - ~60% occur @ great toe MTP = **Podagra**
 - Also: ankle, foot, hand joints, wrist, elbow, knee
- Also: asymmetric oligoarthritis
- Urate deposits in pinna and tendons = **Tophi**
- Renal disease: radiolucent stones and interstitial nephritis

Differential

- Septic arthritis
- Pseudogout
- Haemarthrosis

Causes

- Hereditary
- Drugs:** diuretics, NSAIDs, cytotoxics, pyrazinamide
- ↓ excretion: ↑ gout, renal impairment
- ↑ cell turnover: lymphoma, leukaemia, psoriasis, haemolysis, tumour lysis syndrome
- EtOH excess**
- Purine rich foods:** beef, pork, lamb, seafood

Associations

- Check for:
 - HTN
 - IHD
 - Metabolic syndrome

Ix

- Polarised light microscopy
 - Negatively birefringent needle-shaped crystals
- ↑ serum urate (may be normal)
- X-ray changes occur late**
 - Punched-out erosions in juxta-articular bone
 - ↓ joint space

Acute Rx

- NSAID:** diclofenac or indomethacin
- Colchicine**
 - NSAIDs CI: warfarin, PUD, HF, CRF
 - SE: diarrhoea
- In renal impairment:** NSAIDs and colchicine are CI
 - Use steroids

Prevention

- Conservative**
 - Lose wt.
 - Avoid prolonged fasts and EtOH excess
- Xanthine Oxidase Inhibitors:** Allopurinol
 - Use if recurrent attacks, tophi or renal stones
 - Introduce → NSAID or colchicine cover for 3/12
 - SE: rash, fever, ↓WCC (→ azathioprine)
 - Use febuxostat (XO inhibitor) if hypersensitivity
- Uricosuric drugs:** e.g. probenecid, losartan
 - Rarely used
- Recombinant urate oxidase:** rasburicase
 - May be used pre-cytotoxic therapy

Ca Pyrophosphate Dehydrate Arthropathy

- Pseudogout / Chondrocalcinosis

Acute CPPD

- Presents as acute monoarthropathy
 - Usually knee, wrist or hip
- Usually spontaneous and self-limiting

Chronic CPPD

- Destructive changes like OA
- Can present as poly-arthritis (pseudo-rheumatoid)

Risk Factors

- ↑ age
- OA
- DM
- Hypothyroidism
- Hyperparathyroidism
- Hereditary haemochromatosis
- Wilson's disease

Ix

- Polarized light microscopy
 - Positively birefringent rhomboid-shaped crystals
- X-ray may show chondrocalcinosis
 - Soft-tissue Ca deposition (e.g. knee cartilage)

Rx

- Analgesia
- NSAIDs
- May try steroids: PO, IM or intra-articular

Seronegative Spondyloarthropathies

Definition

- Group of inflammatory arthritides affecting the spine and peripheral joints w/o production of RFs and associated c HLA-B27 allele.

Common Features

- Axial arthritis and sacroiliitis
- Asymmetrical large-joint oligoarthritis or monoarthritis
- Enthesitis
- Dactylitis
- Extra-articular: iritis, psoriaform rashes, oral ulcers, aortic regurg, IBD

Ankylosing Spondylitis

- Chronic disease of unknown aetiology characterised by stiffening and inflammation of the spine and sacroiliac joints.

Epidemiology

- **Sex:** M>F=6:1
- **Age:** men present earlier – late teens, early 20s
- **Genetics:** 95% are HLA-B27+ve

Presentation

- **Gradual onset back pain**
 - Radiates from SI joints to hips and buttocks
 - Worse @ night c morning stiffness
 - Relieved by exercise.
- **Progressive loss of all spinal movements**
 - Schober's test <5cm
- Some develop thoracic kyphosis and neck hyperextension = question mark posture
- **Enthesitis:** Achilles tendonitis, plantar fasciitis
- **Costochondritis**

Extra-articular manifestations

- Osteoporosis: 60%
- Acute iritis / anterior uveitis: 30%
- Aortic valve incompetence: <3%
- Apical pulmonary fibrosis

Ix

- Clinical Dx as radiological changes appear late
 - Sacroiliitis: irregularities, sclerosis, erosions
 - Vertebra: corner erosions, squaring syndesmophytes (bony proliferations)
 - Bamboo spine: calcification of ligaments, periosteal bone formation
- FBC (anaemia), ↑ESR, ↑CRP, HLA-B27
- DEXA scan and CXR

Mx

- **Conservative**
 - Exercise
 - Physio
- **Medical**
 - **NSAIDs:** e.g. indomethacin
 - Anti-TNF: if severe
 - Local steroid injections
 - Bisphosphonates
- **Surgical**
 - Hip replacement to ↓ pain and ↑ mobility

Psoriatic Arthritis

- Develops in 10-40% and may predate skin disease

Patterns of joint involvement

- Asymmetrical oligoarthritis: 60% (commonest)
- Distal arthritis of the DIP joints: 15% (classical)
- Symmetrical polyarthritis: 15% (like RA but c DIPJs)
- Arthritis mutilans (rare, ~3%)
- Spinal (like AS)

Other Features

- Psoriatic plaques
- Nail changes
 - Pitting
 - Subungual hyperkeratosis
 - Onycholysis
- Enthesitis: Achilles tendonitis, plantar fasciitis
- Dactylitis

X-Ray

- Erosion → “pencil-in-cup” deformity

Rx

- NSAIDs
- Sulfasalazine, methotrexate, ciclosporin
- Anti-TNF

Reactive Arthritis

- Sterile arthritis 1-4wks after urethritis or dysentery
 - Urethritis: chlamydia, ureaplasma
 - Dysentery: campy, salmonella, shigella, yersinia

Presentation

- Asymmetrical lower limb oligoarthritis: esp. knee
- **Iritis, conjunctivitis**
- Keratoderma blenorrhagica: plaques on soles/palms
- Circinate balanitis: painless serpiginous penile ulceration
- Enthesitis
- Mouth ulcers

Ix

- ↑ESR, ↑CRP
- Stool culture if diarrhoea
- Urine chlamydia PCR

Mx

- NSAIDs and local steroids
- Relapse may need sulfasalazine or methotrexate

Enteropathic Arthritis

- Occurs in 15% of pts. c UC or Crohn's

Presentation

- Asymmetrical large joint oligoarthritis mainly affecting the lower limbs.
- Sacroiliitis may occur

Rx

- Treat the IBD
- NSAIDs or articular steroids for arthritis
- Colectomy → remission in UC

Autoimmune Connective Tissue Disease

Types

- SLE
- Systemic Sclerosis
- 1^o Sjogren's
- Myositis
- Mixed Connective Tissue Disease
- Relapsing Polychondritis
- Behcet's Disease

Autoantibodies

RF

- Sjogren's 100%
- Felty's 100%
- RA 70%

ANA

- SLE >95%
- AIH 75%
- Sjogren's 70%

dsDNA

Histone Drug-induced lupus

Centromere CREST Syndrome

ENAs

- Ro	SLE, Sjogren's, heart block
- La	SLE, Sjogren's
- Sm	SLE
- RNP	SLE, MCTD
- Jo-1	Polymyositis, Dermatomyositis
- Scl70	Diffuse Systemic Sclerosis
- RNA pol 1/2/3	Diffuse Systemic Sclerosis

Relapsing Polychondritis

- Rare inflammatory disease of cartilage

Presentation

- Tenderness, inflammation and destruction of cartilage
- Ear → floppy ears
- Nose → saddle-nose deformity
- Larynx → stridor

Associations

- Aortic valve disease
- Polyarthritis
- Vasculitis

Rx

- Immunosuppression

Behcet's Disease

- Systemic vasculitis of unknown cause

Presentation

- Turks, Mediterraneans and Japanese
- **Recurrent oral and genital ulceration**
- **Eyes:** ant/post uveitis
- **Skin lesions:** EN
- Vasculitis
- Joints: non-erosive large joint oligoarthropathy
- Neuro: CN palsies
- GI: diarrhoea, colitis

Ix: skin pathergy test (needle prick → papule formation)

Rx: immunosuppression

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Sjogren's Syndrome (= Keratoconjunctivitis Sicca)

Classification

- **Primary**
 - F>>M=9:1
 - Onset 4th-5th decade
- **Secondary**
 - RA
 - SLE
 - Systemic Sclerosis

Features

- ↓ tear production → dry eyes
- ↓ salivation → xerostomia
- Bilateral parotid swelling
- Vaginal dryness → dyspareunia
- Systemic
 - Polyarthritis
 - Raynaud's
 - Bibasal pulmonary fibrosis
 - Vasculitis
 - Myositis

Associations

- **AI:** thyroid disease, AIH, PBC
- Marginal zone MALT lymphoma

Ix

- Schirmer tear test
- Abs: ANA – Ro and La, RF
- Hypergammaglobulinaemia
- Parotid biopsy

Rx

- Artificial tears
- Saliva replacement solutions
- NSAIDs and hydroxychloroquine for arthralgia
- Immunosuppression for severe systemic disease

Raynaud's Phenomenon

- Peripheral digital ischaemia precipitated by cold or emotion.

Classification

- **Idiopathic / 1^o:** Raynaud's Disease
- **Secondary:** Raynaud's Syndrome
 - Systemic sclerosis, SLE, RA, Sjogren's
 - Thrombocytosis, PV
 - β-blockers

Presentation

- Digit pain + triphasic colour change: **WBC**
 - White, Blue, Crimson
- Digital ulceration and gangrene

Rx

- Wear gloves
- CCBs: nifedipine
- ACEi
- IV prostacyclin

MCTD / UCTD

- Combined features of SLE, PM, RA, SS
- Ab: RNP

Systemic Sclerosis

Epidemiology

- F>M=3:1
- 30-50yrs

Limited Systemic Sclerosis: 70%

(includes CREST syndrome)

- **Calcinosis**
- **Raynaud's**
- **Esophageal and gut dysmotility → GOR**
- **Sclerodactyly**
- **Telangiectasia**
- **Skin involvement limited to face, hands and feet**
 - Beak nose
 - Microstomia
- Pulmonary HTN in 15%

Diffuse Systemic Sclerosis: 30%

- Diffuse skin involvement
- Organ fibrosis
 - **GI:** GOR, aspiration, dysphagia, anal incontinence
 - **Lung:** fibrosis and PHT
 - **Cardiac:** arrhythmias and conduction defects
 - **Renal:** acute hypertensive crisis (commonest cause of death)

Ix

- **Bloods:** FBC (anaemia), U+E (renal impairment)
- **Abs**
 - Centromere: limited
 - Scl70 / topoisomerase: diffuse
 - RNA pol 1,2,3: diffuse
- **Urine:** stix, PCR
- **Imaging**
 - CXR: cardiomegaly, bibasal fibrosis
 - Hands: calcinosis
 - Ba swallow: impaired oesophageal motility
 - HiRes CT
 - Echo
- **ECG + Echo:** evidence of pulmonary HTN

Mx

- **Conservative**
 - Exercise and skin lubricants: ↓ contractures
 - Hand warmers: Raynaud's
- **Medical**
 - Immunosuppression
 - Raynaud's: CCBs, ACEi, IV prostacyclin
 - Renal: intensive BP control – ACEi 1st line
 - Oesophageal: PPIs, prokinetics (metoclopramide)
 - PHT: sildenafil, bosentan

Polymyositis and Dermatomyositis

- Striated muscle inflammation

Principal Features

- Progressive **symmetrical proximal** muscle **weakness**.
 - Wasting of shoulder and pelvic girdle
 - **Dysphagia**, dysphonia, respiratory weakness
- Assoc. myalgia and arthralgia
- Commoner in females
- Often a paraneoplastic phenomenon
 - Lung, pancreas, ovarian, bowel

Dermatomyositis = myositis + skin signs

- **Heliotrope rash** on eyelids ± oedema
- **Macular rash** (shawl sign +ve: over back and shoulders)
- **Nailfold erythema**
- **Gottron's papules:** knuckles, elbows, knees
- **Mechanics hands:** painful, rough skin cracking of finger tips
- Retinopathy: haemorrhages and cotton wool spots
- Subcutaneous calcifications

Extra-Muscular Features

- Fever
- Arthritis
- Bibasal pulmonary fibrosis
- Raynaud's phenomenon
- Myocardial involvement: myocarditis, arrhythmias

Ix

- **Muscle enzymes:** ↑CK, ↑AST, ↑ALT, ↑LDH
- **Abs:** Anti-Jo1 (assoc. w extra-muscular features)
- **EMG**
- Muscle biopsy
- Screen for malignancy
 - Tumour markers
 - CXR
 - Mammogram
 - Pelvic/abdo US
 - CT

Differential

- Inclusion body myositis
- Muscular dystrophy
- Polymyalgia rheumatica
- Endocrine / metabolic myopathy
- Drugs: steroids, statins, colchicine, fibrates

Mx

- Screen for malignancy
- Immunosuppression
 - Steroids
 - Cytotoxics: azathioprine, methotrexate

Systemic Lupus Erythematosus

Definition

- Multisystemic autoimmune inflammatory disease in which autoAbs to a variety of autoantigens result in the formation and deposition of immune complexes.

Epidemiology

- **Prev:** 0.2%
- **Sex:** F>>M=9:1
- **Age:** child-bearing age
- **Genetic:** ↑ in Afro-Caribs and Asians

Features

- Relapsing, remitting history
- Constitutional symptoms: fatigue, wt. loss, fever, myalgia

A RASH POINts an MD

- **Arthritis**
 - Non-erosive, involving peripheral joints
 - Jaccoud's: reducible deforming arthropathy
- **Renal**
 - proteinuria and ↑BP
- **ANA** (+ve in 95%)
- **Serositis**
 - Pleuritis: pleuritic pain, dyspnoea, effusion
 - Pericarditis: chest pain relieved by sitting forwards
- **Haematological**
 - AIHA
 - ↓WCC
 - ↓Plts
- **Photosensitivity**
- **Oral ulcers**
- **Immune phenomenon**
 - Anti-dsDNA
 - Anti-Sm
 - Anti-phospholipid
- **Neurological**
 - Seizures, psychosis
- **Malar Rash**
 - Facial erythema sparing the nasolabial folds
- **Discoid Rash**
 - Erythema → pigmented hyperkeratotic papules → atrophic depressed lesions
 - Mainly affects face and chest

Immunology

- 95% ANA+ve
- **dsDNA is very specific** (sensitivity 60%)
- 30% ENA+ve: Ro, La, Sm, RNP
- Anticardiolipin Abs → false +ve syphilis serology

Monitoring Disease Activity

- Anti-dsDNA titres
- Complement: ↓C3, ↓C4
- ↑ESR

Other Ix

- **Bloods:** FBC, U+E, CRP, clotting (usually normal)
- **Urine:** stix, PCR

Drug-Induced Lupus

- Causes: procainamide, phenytoin, hydralazine, isoniazid
- Anti-histone Abs in 100%
- Mostly skin and lung signs
- Disease remits if drug stopped

Anti-Phospholipid Syndrome

Classification

- Primary: 70%
- Secondary to SLE: 30%

Pathology

- Anti-phospholipid Abs: anti-cardiolipin and lupus anticoagulant

Features

- **CLOTs:** venous (e.g. DVT) and arterial (e.g. stroke)
- Coagulation defect: ↑APTT
- Livedo reticularis
- Obstetric complications: recurrent 1st trimester abortion
- Thrombocytopenia

Rx

- Low-dose aspirin
- Warfarin if recurrent thromboses: INR 3.5

Mx

- In specialist SLE and lupus nephritis clinics

Severe Flares: Acute SLE

- AIHA, nephritis, pericarditis or CNS disease
- High-dose prednisolone + IV cyclophosphamide

Cutaneous Symptoms

- Treat w/ topical steroids and prevent sun cream

Maintenance

- For joint and skin symptoms
- NSAIDs and hydroxychloroquine ± low-dose steroids

Lupus Nephritis

- Proteinuria: ACEi
- Aggressive GN: immunosuppression

Rx Complications

- ↑ risk of osteoporosis and CV disease

Prognosis

- 80% survival @ 15yrs

Vasculitis

Classification

Large Vessel

- Giant Cell Arteritis
- Takayasu's Arteritis

Medium Vessel

- Polyarteritis Nodosa
- Kawasaki Disease

Small Vessel

- pANCA
 - Churg-Straus
 - Microscopic Polyangiitis
- cANCA: Wegener's Granulomatosis
- ANCA -ve
 - Henoch-Schonlein Purpura
 - Goodpasture's Disease
 - Cryoglobulinaemia
 - Cutaneous Leukocytoclastic Vasculitis

Giant Cell Arteritis / Temporal Arteritis

- Common in elderly (rare <55)
- Assoc. c PMR in 50%

Features

- Systemic signs: fever, malaise, fatigue
- Headache
- Temporal artery and scalp tenderness
- Jaw claudication
- Amaurosis fugax
- Prominent temporal arteries ± pulsation

Mx and Rx

- If suspect GCA: Do ESR and start **pred 40-60mg/d PO**
- ↑ESR and CRP
- ↑ALP
- ↓Hb (normo normo), ↑Plts
- Temporal artery biopsy w/i 3d: but skip lesion occur

Continuing Rx

- Taper steroids gradually, guided by symptoms and ESR
- PPI and alendronate cover (~2yr course usually)

PMR

Presentation

- >50yrs old
- Severe **pain** and **stiffness** in shoulders, neck and hips
 - Sudden / subacute onset
 - Symmetrical
 - **Worse in the morning:** stops pt. getting out of bed
 - **No weakness** (cf. myopathy or myositis)
- ± mild polyarthritis, tenosynovitis and **carpal tunnel syn.**
- Systemic signs: fatigue, fever, wt. loss
- 15% develop GCA

Rx

- ↑ESR and CRP (+ ↑plasma viscosity)
- ↑ALP
- **Normal CK**

Rx

- Pred 15mg/d PO: taper according to symptoms and ESR
- PPI and alendronate cover (~2yr course usually)

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Takayasu's Arteritis = Pulseless Disease

Epidemiology

- **Geo:** Rare outside Japan
- **Sex:** F>M
- **Age:** 20-40yrs

Features

- Constitutional symptoms: fever, fatigue, wt. loss
- Weak pulses in upper extremities
- Visual disturbance
- HTN

Polyarteritis Nodosa

Epidemiology

- **Prev:** rare in UK
- **Sex:** M>F=2:1
- **Age:** young adults

Features

- Assoc. c Hep B
- Constitutional symptoms
- Rash
- Renal → HTN
- GIT → melaena and abdo pain

Rx

- Pred + cyclophosphamide

Kawasaki's Disease

- Childhood PAN variant

Features

- 5-day fever
- Bilat non-purulent conjunctivitis
- Oral mucositis
- Cervical lymphadenopathy
- Polymorphic rash (esp. trunk)
- Extremity changes (erythema + desquamation)
- Coronary artery aneurysms

Rx

- IVIg + aspirin

ANCA Positive Vasculitides

Wegener's Granulomatosis

- Necrotizing granulomatous inflammation and small vessel vasculitis → a predilection for URT, LRT and Kidneys

Features

URT

- Chronic sinusitis
- Epistaxis
- Saddle-nose deformity

LRT

- Cough
- Haemoptysis
- Pleuritis

Renal

- RPGN
- Haematuria and proteinuria

Other

- Palpable purpura
- Ocular: conjunctivitis, keratitis, uveitis

Ix

- cANCA
- Dipstick: haematuria and proteinuria
- CXR: bilat nodular and cavity infiltrates

Churg-Strauss

- Late-onset asthma
- Eosinophilia
- Granulomatous small-vessel vasculitis
 - RPGN
 - Palpable purpura
 - GIT bleeding
- pANCA
- May be ssoc. → montelukast

Microscopic Polyangiitis

- RPGN
- Haemoptysis
- Palpable purpura
- pANCA

ANCA Negative Vasculitides

HSP (Childhood IgA nephropathy variant)

- Children 3-8yrs
- Post-URTI
- Palpable purpura on buttocks
- Colicky abdo pain
- Arthralgia
- Haematuria

Goodpastures

- Anti-GBM Abs
- RPGN
- Haemoptysis
- CXR: Bilat lower zone infiltrates (haemorrhage)

Rx

- Immunosupresion + plasmapheresis

Cryoglobulinaemia

Simple

- Monoclonal IgM
- 2^o to myeloma / CLL / Waldenstroms
- Hyperviscosity
 - Visual disturbance
 - Bleeding from mucus mems
 - Thrombosis
 - Headache, seizures

Mixed (80%)

- Polyclonal IgM
- 2^o to SLE, Sjog, HCV, Mycoplasma
- Immune complex disease
 - GN
 - Palpable purpura
 - Arthralgia
 - Peripheral neuropathy

Cutaneous Leukocytoclastic Vasculitis

- Palpable purpuric rash
- ± arthralgia ± GN
- Causes
 - HCV
 - Drugs: sulphonamides, penicillin

Fibromyalgia

Epidemiology

- 10% of new rheum referrals
- **Prev:** 0.5-4%
- **Sex:** F>>M=10:1

Risk Factors

- Neurosis: depression, anxiety, stress
- Dissatisfaction at work
- Overprotective family or lack of support
- Middle age
- Low income
- Divorced
- Low educational status

Associations

- Chronic fatigue syndrome
- Irritable bowel syndrome
- Chronic headache syndromes

Features

- Chronic, widespread musculoskeletal pain and tenderness
- Morning stiffness
- Fatigue
- Poor concentration
- Sleep disturbance
- Low mood

Ix

- All normal
- Rule out organic cause: FBC, ESR, CRP, CK, TFTs, Ca

Mx

- Educate pt.
- CBT
- Graded exercise programs
- Amitriptyline or pregabalin
- Venlafaxine

Clinical Chemistry

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Major Disease Patterns

Disease	Biochemistry
Dehydration	↑↑ U, ↑Cr ↑albumin ↑HCT
Low GFR	↑U, ↑Cr, ↑H, ↑K, ↑urate ↑PO ₄ , ↓Ca
Tubular Dysfunction	Normal U and Cr ↓K, ↓urate, ↓PO ₄ , ↓HCO ₃
Thiazide and Loop Diuretics	↓Na, ↓K, ↑HCO ₃ , ↑U
Hepatocellular Disease	EtOH: AST:ALT>2, ↑GGT Viral: AST:ALT<2 ↑bilirubin, ↑ALP, ↓albumin, ↑PT (↑APTT if end-stage)
Cholestasis	↑↑ALP, ↑↑GGT, ↑Bilirubin, ↑AST
Excess EtOH intake	↑GGT, ↑MCV, evidence of hepatocellular disease
Addison's	↑K, ↓Na
Cushing's	May show: ↓K, ↑Na, ↑HCO ₃
Conn's	↓K, ↑Na, ↑HCO ₃
DM	↑glucose
DI	↑Na, ↑ serum osmolality, ↓ urine osmolality
SIADH	↓Na, ↓ serum osmolality, ↑ urine osmolality (>500), ↑ urine Na

Hyponatraemia

Presentation

- <135: n/v, anorexia, malaise
- <130: headache, confusion, irritability
- <125: **seizures**, non-cardiogenic pulmonary oedema
- <115: coma and death

Causes

Hypovolaemic

- **U Na >20mM** (= renal loss)
 - Diuretics
 - Addison's
 - Osmolar diuresis (e.g. glucose)
 - Renal failure (diuretic phase)
- **U Na >20mM** (= extra-renal loss)
 - Diarrhoea
 - Vomiting
 - Fistula
 - SBO
 - Burns

Hypervolaemic

- Cadiac failure
- Nephrotic syndrome
- Cirrhosis
- Renal failure

Euvolaemic

- **U osmolality >500**
 - SIADH
- **U osmolality <500**
 - Water overload
 - Severe hypothyroidism
 - Glucocorticoid insufficiency

Mx

- Correct the underlying cause
- Replace Na and water at the same rate they were lost
 - Too fast → central pontine myelinolysis
 - Chronic: 10mM/d
 - Acute: 1mM/hr
- Asymptomatic chronic hyponatraemia
 - Fluid restrict
- Symptomatic / acute hyponatraemia / dehydrated
 - Cautious rehydration with 0.9% NS
- If hypervolaemic consider frusemide
- Emergency: seizures, coma
 - Consider hypertonic saline (e.g. 1.8%)

SIADH

- Concentrated urine: Na >20mM, osmolality >500
- Hyponatraemia or plasma osmolality <275
- Absence of hypovolaemia, oedema or diuretics

Causes

- **Resp:** SCLC, pneumonia, TB
- **CNS:** meningoencephalitis, head injury, SAH
- **Endo:** hypothyroidism
- **Drugs:** cyclophosphamide, SSRIs, CBZ

Rx

- Rx cause and fluid restrict
- Vasopressin receptor antagonists
 - Demeclocycline
 - Vaptans

Hypernatraemia

Presentation

- Thirst
- Lethargy
- Weakness
- Irritability
- Confusion, fits, coma
- Signs of dehydration

Causes

- Usually caused by dehydration (\downarrow intake or \uparrow loss)

Hypovolaemic

- **GI loss:** diarrhoea, vomiting
- **Renal loss:** diuretics, osmotic diuresis (e.g. DM)
- **Skin:** sweating, burns

Euvolaemic

- \downarrow fluid intake
- DI
- Fever

Hypervolaemic

- Hyperaldosteronism (\uparrow BP, \downarrow K, alkalosis)
- Hypertonic saline

Mx

- Give water PO if possible
- Otherwise, 5% dextrose IV slowly
- Use 0.9% NS if hypovolaemic or Na >170mM
 - Causes less marked fluid shifts
- Aim for Na $\downarrow \leq 12\text{mM/d}$
 - Too fast → cerebral oedema

Free Water Deficit

- $\text{TBW (L)} = \text{coeff} \times \text{wt.}$
 - Coeff = men:0.6, women:0.5
- $\text{Def (L)} = \text{TBW} \times (1 - [140/\text{Na}])$

Diabetes Insipidus

- Polyuria
- Polydipsia
- Dehydration

Causes

- **Nephrogenic**
 - Inherited
 - \uparrow Ca
 - Drugs: Li, demeclocycline
 - Post-obstructive uropathy
- **Cranial**
 - Idiopathic
 - Congenital: DIDMOAD
 - Tumor
 - Trauma
 - Vascular: haemorrhage
 - Infection: meningoencephalitis

Ix

- \uparrow Na
- Dilute urine
- Dx: Water deprivation test

Rx

- Treat cause
- Desmopressin if cranial

Hypokalaemia

Symptoms

- Muscle weakness
- Hypotonia
- Hyporeflexia
- Cramps
- Tetany
- Palpitations
- Arrhythmias

NB. ↓K exacerbates digoxin toxicity

ECG

- Result from delayed ventricular repolarisation
- Flattened / inverted T waves
- Prominent U waves (after T waves)
- ST depression
- Long PR interval
- Long QT interval

Causes

Internal Distribution

- Alkalosis
- ↑ insulin
- β-agonists

↑ Excretion

- GI: vomiting, diarrhoea, rectal villous adenoma
- Renal: RTA (esp. type 2), Bartter syn.
- Drugs: diuretics, steroids
- Endo: Conn's syn., Cushing's syn.

↓ Input

- Inappropriate IV fluid management

Mx

- 1mM K ↓ = ~200-300mmol total deficit
- Don't give K if oliguric
- Never give STAT fast bolus

Mild: K >2.5

- Oral K supplements
- ≥80mmol/d

Severe: K <2.5 and/or dangerous symptoms

- IV KCl cautiously
- 10mmol/h (20mmol/h max)
- Best to give centrally (burning sensation peripherally)
 - Max central conc: 60mM
 - Max peripheral conc: 40mM

Mg Replacement

- Pts. are often Mg deplete too
- Until Mg is replaced the K will not return to normal levels despite K replacement
- Give empiric Mg replacement

Hyperkalaemia

Symptoms

- Fast, irregular pulse
- Palpitations
- Chest pain
- Weakness

ECG

- Tall tented T waves
- Flattened P waves
- ↑ PR interval
- Widened QRS
- Sine-wave pattern → VF

Causes

Artefact

- Haemolysis
- K₂EDTA contamination from FBC bottle
- Leucocytosis, thrombocytosis
- Drip arm

Internal Distribution

- Acidosis
- ↓ insulin
- Cell death / tissue trauma / burns
- Digoxin poisoning
- Suxamethonium

↓ Excretion

- Oliguric renal failure
- Addison's
- Drugs: ACEi, NSAIDs, K⁺-sparing diuretics

↑ Input

- Excessive K therapy
- Massive transfusion

Mx

Non-urgent

- Treat cause: review meds
- Polystyrene sulphonate resin (Calcium Resonium)
 - Binds K in the GIT and ↓K over days

Emergency: evidence of myocardial instability or K >6.5

- 10ml 10% calcium gluconate
- 100ml 20% glucose + 10u insulin (Actrapid)
- Salbutamol 5mg nebulizer
- Haemofiltration (usually needed if anuric)
- Calcium resonium 15g PO or 30g PR

Ca and PO₄ Physiology

PTH

- Overall: ↑Ca and ↓PO₄
- ↓ ionised Ca → PTH release

Renal

- ↑ Ca reabsorption
- ↓ PO₄ reabsorption
- ↑ 1α-hydroxylation of 25-OH-Vit D3 in kidney
- ↑ HCO₃ excretion (may → mild met acidosis)

Bone

- ↑ osteoclast activity → ↑Ca, ↑PO₄

Vitamin D and Calcitriol

- Hepatic 25 hydroxylation → 25-OH-Vit D3 (Calcidiol)
- Renal 1α-hydroxylation in kidney → 1,25(OH)₂ Vit D3 (Calcitriol)
 - ↑ by ↑PTH, ↓Ca or ↓PO₄

GIT

- ↑Ca and ↑PO₄ absorption
- Inhibition of PTH release

Renal

- ↑Ca and ↑PO₄ reabsorption

Magnesium

- ↓Mg prevents PTH release
 - May → ↓Ca

Plasma Binding

- 2.2-2.6mM
- 50% albumin bound (∴ ↓Alb → ↓Ca)
 - Labs measure total Ca
 - cCa: ↑ Ca by 0.1mM for every 4g/L albumin ↓ below 40g/L
- Alkalosis → ↓albumin protonation → ↑Ca binding → ↓[Ca]

NB. Prolonged tourniquet application → ↑ albumin → ↑ Ca
▪ Take uncuffed specimen if concerned

Hypocalcaemia

Presentation: SPASMODIC

- Spasms (carpopedal = Trousseau's sign)
- Perioral paraesthesia
- Anxious, irritable
- Seizures
- Muscle tone ↑: colic, wheeze, dysphagia
- Orientation impaired (confusion)
- Dermatitis: atopic, exfoliative
- Impetigo herpetiformis (↓Ca + pustules in cyesis)
- Chovsteeks, Cardiomyopathy (↑ QTc → TdP)
 - ↑ Ca → ↑threshold for action potential

Causes

- Commonest cause is CRF

With ↑ PO₄

- CKD
- Hypoparathyroidism / pseudohypoparathyroidism
- ↓ Mg
- Acute rhabdomyolysis (muscle Ca deposition)

With normal or ↓ PO₄

- Osteomalacia
- Active pancreatitis
- Respiratory alkalosis

Rx

Mild

- Ca 5mmol QDS PO
- Daily Ca levels

CKD

- Alfacalcidol (1-OH-Vit D₃)

Severe

- 10ml 10% Ca gluconate IV (2.25mmol) over 30min
- Repeat as necessary

Hypercalcaemia

Presentation

- **Stones**
 - Renal stones
 - Polyuria and polydipsia (nephrogenic DI)
 - Nephrocalcinosis
- **Bones**
 - Bone pain
 - Pathological #s
- **Moans:** depression, confusion
- **Groans**
 - Abdo pain
 - n/v and constipation
 - Pancreatitis
 - PUD (\uparrow gastrin secretion)
- **Other:**
 - \uparrow BP (check Ca^{2+} in all with HTN)
 - \downarrow QT interval

Causes

- **Most commonly malignancy or 1^o HPT**

With $\uparrow \text{PO}_4$

- \uparrow ALP (e.g. \uparrow bone turnover)
 - Bone mets
 - thyroid, breast, lung, kidney, prostate, colon
 - Sarcoidosis
 - Thyrotoxicosis
 - Lithium
- **Normal ALP**
 - Myeloma
 - Hypervitaminosis D
 - Sarcoidosis
 - Milk alkali syn.

With normal or $\downarrow \text{PO}_4$

- 1^o or 3^o HPT
- Familial benign hypercalciuria
 - AD
 - \uparrow Ca-sensing receptor set-point
- Paraneoplastic: PTHrP (but \downarrow PTH)

Ix

- \uparrow PTH = 1^o or 3^o HPT
- \downarrow PTH: most likely Ca
- FBC, protein electrophoresis, CXR, bone scan

Mx

- Dx and Rx underlying cause

Rehydrate

- 1L 0.9% NS / 4h
- Monitor pts. hydration state

Frusemide

- Only start once pt. is volume replete
- Calciuric + makes room for more fluids

Bisphosphonates

- Ca bisphosphonate can't be resorbed by osteoclasts
- Only used in hypercalcaemia of malignancy
 - Can obscure Dx as $\rightarrow \downarrow \text{Ca}, \downarrow \text{PO}_4$ and $\uparrow \text{PTH}$
- E.g. Pamidronate, Zoledronate (IV)

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Osteoporosis

Definition

- \downarrow bone mass
- 1^o: age-related
- 2^o: drugs or other condition

Risk Factors: SHATTERED

- Steroids
- Hyperthyroidism, HPT, HIV
- Alcohol and Cigarettes
- Thin (BMI <22)
- Testosterone Low
- Early Menopause
- Renal / liver failure
- Erosive / inflam bone disease (e.g. RA, myeloma)
- Dietary Ca low / malabsorption

Presentation

- Vertebral crush #s
- # NOF and other long bone #s

Ix: Bone profile, FBC, U+E

DEXA Scan

- **Indications**
 - Low-trauma #
 - Women ≥ 65 yrs \bar{c} one or more risk factors
 - Before giving long-term steroids (>3mo)
 - Parathyroid disorders, myeloma, HIV
- **Interpretation**
 - T: no. of SDs away from youthful average
 - Z: no. of SDs away from matched average
 - T > -1 = normal
 - T $-1 - -2.5$ = osteopenia
 - T < -2.5 = osteoporosis

Rx

- Decision to instigate pharmacological Rx is based upon age, RFs, and BMD.
 - FRAX can estimate 10yr # risk

Conservative

- Stop smoking, \downarrow EtOH
- Wt. bearing or balancing exercise (e.g. Tai Chi)
- Ca and vit-D rich diet
- Home-based fall-prevention program \bar{c} visual assessment.

Primary and secondary prevention of #s

- **Bisphosphonates:** alendronate is 1st line
- Ca and Vit D supplement's: e.g Calcium D₃ Forte
- Strontium ranelate: bisphosphonate alternative

Alternative for 2^o prevention of osteoporotic #s

- Raloxifene: SERM, \downarrow breast Ca risk cf. HRT
- Teriparatide: PTH analogue \rightarrow new bone formation
- Denosumab: anti-RANKL \rightarrow \downarrow osteoclast activation

Bisphosphonate SEs

- GI upset
- Oesophageal ulceration / erosion
 - Take \bar{c} plenty of water on an empty stomach and refrain from lying and don't eat for 30min.
- Diffuse musculoskeletal pain
- Osteonecrosis of the jaw

Osteomalacia

Definition

- ↓ bone mineral content
 - Excess uncalcified osteoid and cartilage

Presentation

Rickets: children

- Knock-kneed / bow-legged
- Bone pain
- Craniotabes
- Osteochondral swelling: rachitic rosary
- Harrison's sulcus

Osteomalacia: adults (after epiphyseal fusion)

- Bone pain and tenderness
- #s: esp. NOF
- Proximal myopathy due to ↓PO₄

Causes

- **Vitamin D deficiency:** malabsorption, poor diet, ↓sunlight
- **Renal osteodystrophy:** ↓ 1α hydroxylation
- **Drugs:** AEDs →↑ hepatic vit D metabolism
- **Vit D resistance:** inherited conditions
 - Type 1: ↓ renal hydroxylation
 - Type 2: end-organ resistance
- **Hepatic disease:** malabsorption and ↓ 25 hydroxylation
- **Malignancy:** oncogenic hypophosphataemia
 - ↑ fibroblast growth factor-23 → hyperphosphaturia

Ix

- ↓Ca, ↓PO₄, ↑ALP, ↑PTH, ↓25-OH Vit D₃ (unless resistance)
- **X-ray**
 - Loss of cortical bone
 - **Looser's zones: pseudofractures**
 - Cupped metaphyses in Rickets

Rx

- Dietary: Calcium D₃ Forte
- Malabsorption or hepatic disease
 - Vit D₂ (ergocalciferol) PO
 - Parenteral calcitriol
- Renal disease or vit D resistance
 - 1α-OH-Vit D₃ (alfacalcidol)
 - ↓1,25-(OH)₂ Vit D₃ (calcitriol)
- Monitor plasma Ca

Paget's Disease / Osteitis Deformans

Pathophysiology

- Affects 3% over 55yrs
- ↑ bone turnover → bone remodelling, enlargement, weakness and deformity.
 - ↑ bone mass but disordered and weak
- Commoner in temperate climes and Anglo-Saxons

3 Phases

- Osteolytic
- Mixed Osteolytic-osteoblastic
- Quiescent osteosclerotic stage

Presentation

- Asymptomatic in 70%
- Predominantly affects the axial skeleton
 - Pelvis, lumbar spine, skull, femur and tibia
 - Polyostotic in 85%
- Bone pain
- Pathological #
- Deformity
 - Sabre tibia
 - Head enlargement

Complications

- Nerve compression: **deafness**, radiculopathy
- High output CCF
- Osteosarcoma (<1% after 10yrs)
 - Sudden onset or worsening of bone pain

Ix

- ↑↑ALP, (Ca and PO₄ normal)
- Bone scan: hot spots
- **X-ray**
 - Bone enlargement
 - Sclerosis
 - Patchy cortical thickening
 - Deformity
 - Wedge-shaped lytic lesions
 - Osteoporosis circumscripta
 - Well-defined lytic skull lesions

Mx

- Analgesia
- Alendronate: ↓ pain and/or deformity

Metabolic Bone Disease Summary

Disease	Aetiology	Characteristics	Symptoms	Risk Factors	Biochemistry			
					Ca	PO ₄	ALP	PTH
Osteoporosis	1 ^o : age, post-menopausal 2 ^o : drugs, systemic disease	Normal bone quality, ↓ bone density: T -1 - -2.5 = osteopenia T <-2.5 = osteoporosis	Back pain Fractures	SHATTERED	N	N	N	N
Osteomalacia	Vit D or PO ₄ deficiency	Defective bone mineralisation - ↑ osteoid - widened osteoid seams	Bone pain #s Proximal weakness Bone deformity ↓ Ca → SPASMODIC	Vegan Breast milk Malabsorption ↓ sun CLD CRD	↓	↓	↑	↑
Rickets		Looser's zones on X-ray - pseudofractures	Craniotabes Frontal bossing Rachitic rosary Bowed legs Cupped metaphysis @ wrist		↓/N	↓	↑	↑
1 ^o HPT	80% parathyroid adenomas 20% gland hyperplasia <0.5% parathyroid Ca	Osteitis fibrosa cystica - Subperiosteal erosions - Acral osteolysis - Cysts - Brown tumours (fibrous, vascular) - Pepperpot skull	Stones, bones, moans, groans		↑	↓	↑	↑ /N
2 ^o HPT	Chronic renal failure Vit D deficiency Malabsorption				↓	↑	↑	↑
3 ^o HPT	Parathyroid hyperplasia due to prolonged 2 ^o HPT		Stones, bones, moans, groans	Post-renal Tx	↑	↑/N	↑	↑
Hypo-PTH	Surgical Autoimmune Congen – Di George		Spasmodic		↓	↑	N	↓/N
Paget's	Unknown	Disorder of bone turnover → ↑ bone mass but bone is disordered + weak - disorganised mosaic pattern of lamellar bone - sclerosis + cortical thickening Axial skeleton, esp. skull, pelvis ↑ risk of osteosarcoma Wedge-shaped lytic lesions Osteoporosis circumscripta	Bone pain Sabre tibia Chalkstick # Nerve compression - deafness Heart failure		N	N	↑↑↑	N
Renal osteodystrophy	PO ₄ retention + ↓vit D →↓Ca →↑PTH Met acidosis of RF → release of hydroxyapatite	↑ bone resorption → osteitis fibrosa Osteomalacia Osteosclerosis: rugger jersey spine Osteoporosis	Bone pain #s Uraemia		↓	↑	↑ /N	↑

Hyperlipidaemia

Biology

- **Chylomicrons**
 - Mainly TG
 - Carry dietary TG tissues
- **VLDL**
 - Mainly TG
 - Take endogenous TG from liver → tissue
- **LDL**
 - Mainly cholesterol
 - Carry cholesterol from liver to tissues
- **HDL**
 - Mainly phospholipid
 - Take cholesterol from tissues → liver for excretion
- **Apolipoproteins**
 - Contained in lipoproteins and control transport and uptake.
 - ApoB contained in LDL and binds to cell receptors → uptake

Classification

- **Common 1^o hyperlipidaemia**
 - 70%
 - Dietary and genetic factors
 - ↑ LDL only
- **Familial primary hyperlipidaemia**
 - Multiple phenotypes
 - ↑ risk of CVD
- **2^o hyperlipidaemia**
 - ↑ LDL
 - Nephrotic syn.
 - Cholestasis: lipoprotein x
 - Hypothyroidism
 - Cushing's
 - Drugs: thiazides, steroids
 - **Mixed:** ↑LDL and ↑TG
 - T2DM
 - EtOH
 - CRF

Familial Primary Hyperlipidaemias

1^o Hypercholesterolaemia

- Commonest
- ApoB (LDL receptor) defect → ↑↑ LDL-C

Combined Hyperlipidaemia

- 2nd commonest
- ↑LDL-C + ↑TG

Lipoprotein Lipase Deficiency

- ↑↑ chylomicrons

Hypertriglyceridaemia

Remnant Particle Disease

Presentation

- CVD
- Xanthomata
 - Eruptive: itchy nodules in crops (\uparrow TG)
 - Tuberous: plaques on elbows, knees
 - Planar: orange streaks in palmar creases
 - Remnant hyperlipidaemia
- Xanthelasma: eyelids
- Arcus: cornea
- Pancreatitis (\uparrow TG)

Ix

- Plasma cholesterol
- Plasma HDL
- Fasting TGs
- TC:HDL ratio is best predictor of CV risk

Mx

Aims

- TC <4
- TC:HDL ratio <4.5

Lifestyle

- Lose wt.
- ↓ saturated fat, ↑ fibre, ↑ fruit and veg
- ↑ exercise

Treatment Priorities

- Known CVD
- Those \bar{c} DM
- Those \bar{c} 10yr CVD risk >20%
 - Irrespective of baseline lipids

1st-line: Statins

- E.g. simvastatin 40mg PO nocte
- HMG-CoA reductase inhibitors → ↓ cholesterol synth.

2nd-line:

- **Fibrates:** PPAR α antagonists, ↓ TGs
- **Ezetimibe:** inhibits cholesterol absorption
- **Niacin / nicotinic acid:** ↑HDL, ↓LDL

Porphyrias

Pathogenesis

- Deficiencies of enzymes in haem biosynthesis
- → overproduction of toxic haem precursors
 - Porphyrins: induce photosensitivity
 - Porphyrin precursors: neurotoxic
- Genetic or acquired
 - EtOH, lead and Fe → abnormal porphyrin metabolism

Acute Intermittent Porphyria

- The Madness of King George
- 2nd commonest porphyria

Pathophysiology

- AD ♂ partial penetrance
- Porphyrobilinogen deaminase deficiency
- F>M = 2:1
- Presents @ 20-40yrs

Presentation

- **GI:** Abdo pain, n/v, constipation
- **CV:** ↑HR, ↑BP (sympathetic overactivity)
- **Neuropsych:** peripheral motor neuropathy, seizures, psychosis
- **Other:** Red urine, fever, ↑WCC

NB. Can mimic surgical abdomen (anaesthesia = disaster)

Precipitants

- P450 inducers: AEDs, EtOH, OCP/HRT
- Infection / stress
- Fasting
- Pre-menstrual

Ix

- ↑ urine PBG and ALA

Rx

- **Supportive**
 - Analgesia: opiate (avoid oxycodone)
 - IV fluids
 - Carbohydrate
 - Rx ↑HR and ↑BP ♂ β-B
- **Specific**
 - IV haematin

Porphyria Cutanea Tarda

- Commonest porphyria
- Cutaneous manifestations only
- Uroporphyrinogen decarboxylase deficiency

Presentation

- Photosensitivity: blistering skin lesions
- Facial hyperpigmentation and hypertrichosis

Precipitants

- Sunlight
- EtOH

Ix

- ↑ urine and se porphyrins
- ↑ se ferritin

Rx

- Avoid sun
- Phlebotomy / iron chelators
- Chloroquine

Rare Inherited Metabolic Disorders

Homocystinuria

- Auto recessive
- Cystathione β -synthetase deficiency
- Accumulation of homocystine

Presentation

- Marfanoid habitus
- Downward lens dislocation
- Mental retardation
- Heart rarely affected
- Recurrent thrombosis

Rx

- Some response to high-dose pyridoxine

Gaucher's Disease

- Commonest lysosomal storage disease
- Autosomal recessive glucocerebrosidase deficiency
 - → accumulation of glucosylceramide in the lysosomes of the reticuloendothelial system.
 - Liver
 - BM
 - Spleen
- High incidence in Ashkenazi Jews (1/450)

Presentation

- 3 clinical types: type 1 is commonest
 - Presents in adulthood
 - Gross HSM
 - Brown skin pigmentation: forehead, hands
 - Pancytopenia
 - Pathological fractures

Mx

- Most have normal life expectancy in type 1
- Can give recombinant enzyme replacement

Oncology

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Genetic Oncology

Familial Breast and Ovarian Ca

- ~10% of breast Ca is familial
- ~5% is caused by BRCA1 or BRCA2 mutations
 - Both TSGs
 - **BRCA1:** Breast Ca – 80%, Ovarian Ca – 40%
 - **BRCA2:** Breast Ca – 80%, male breast Ca
- May opt for prophylactic mastectomy and oophorectomy.

Familial Prostate Ca

- ~5% of those w/ prostate Ca have +ve fam Hx
- Multifactorial inheritance
- BRCA1/2 → moderately ↑ risk

Familial CRC

- ~20% of those w/ CRC have +ve fam Hx
- Relative risk of CRC for individual w/ FH related to
 - Closeness of relative
 - Age of relative when Dx.

Familial Adenomatous Polyposis

- Mutation in **APC** gene on **Chr 5**
 - TSG
 - Promotes β-catenin degradation
 - β-catenin is an oncogene which → cell proliferation
- Cells then acquire another mutation to become Ca
 - p53
 - kRAS
- AD transmission
- ~100% risk of CRC by 50yrs

HNPPCC

- Familial clustering of cancers
 - **Lynch 1:** CRC
 - **Lynch 2:** CRC + other Ca
 - Ovarian
 - Endometrial
 - Pancreas
 - Small Bowel
 - Renal pelvis
- Mutations in DNA mismatch repair genes
- AD transmission (variable penetrance)
- Often Right-sided CRC
- Present @ young age: <50yrs

Peutz-Jehgers

- AD transmission
- Multiple GI hamartomatous polyps
- Mucocutaneous hyperpigmentation
 - Lips
 - Palms
- 10-20% lifetime risk of CRC
- Also ↑ risk of other Ca
 - Pancreas
 - Lung
 - Breast
 - Ovaries and uterus
 - Testes

Epidemiology

- Cancer affects 30% of the population
- 20% of people die from cancer

Commonest Incidence

1. Skin cancers
2. Breast / Prostate
3. Lung
4. CRC

Commonest Mortality

- Lung
- Breast / Prostate
- CRC

Oncological Emergencies

Febrile Neutropenia

- PMN $<1 \times 10^9/L$
- Isolation + barrier nursing
- Meticulous antisepsis
- Broad-spectrum Abx, anti-fungals, anti-virals
- Prophylaxis: co-trimoxazole

Spinal Cord Compression

Presentation

- Back pain, radicular pain
- Motor, reflex and sensory level
- Bladder and bowel dysfunction

Causes

- Usually extradural metastasis
- Crush fracture

Ix

- Urgent MRI spine

Mx

- Dexamethasone
- Discuss with neurosurgeon and oncologist
- Consider radiotherapy or surgery

SVC Obstruction Airway Compromise

- SVC not an emergency unless there's tracheal compression or airway compromise.

Causes

- Usually lung Ca
- Thymus malignancy
- LNs
- SVC thrombosis: central lines, nephrotic syndrome
- Fibrotic bands: lung fibrosis after chemo

Presentation

- Headache
- Dyspnoea and orthopnoea
- Plethora + thread veins in SVC distribution
- Swollen face and arms
- Engorged neck veins

Pemberton's Sign

- Lifting arms above head for >1min → facial plethora, ↑JVP and inspiratory stridor
- Due to narrowing of the thoracic inlet

Ix

- Sputum cytology
- CXR
- CT
- Venography

Mx

- Dexamethasone
- Consider balloon venoplasty + SVC stenting
- Radical or palliative chemo / radio

Hypercalcaemia

- Affects 10-20% of those with Ca
- Affects 40% of those with myeloma

Causes

- Lytic bone metastases
- Production of PTHrP

Symptoms

- Confusion
- Renal stones
- Polyuria and polydipsia → dehydration
- Abdominal pain, constipation
- Depression
- Lethargy
- Anorexia

Ix

- ↑ Ca (often >3mM)
- ↓ PTH (key to exclude 1^o HPT)
- CXR
- Isotope bone scan

Rx

- Aggressive hydration
 - 0.9% NS (e.g. 1L/4h)
 - Monitor volume status
 - Frusemide when full to make room for more fluid
- If 1^o HPT excluded, give maintenance therapy with bisphosphonate: zoledronate is good

Raised ICP

Presentation

- Headache: worse AM and bending over
- n/v
- Focal neuro and fits
- Papilloedema

Ix

- CT/MRI

Rx

- Dexamethasone
- Radio- / chemo-therapy

Tumour Lysis Syndrome

- Massive cell destruction
 - High count leukaemia or bulky lymphoma
- ↑K, ↑urate, ↑PO₄, ↓Ca
- → renal failure
- Prevention
 - ↑ fluid intake + allopurinol 24h before chemo
 - Rasburicase is an option

Cancer Therapy

Cancer must be managed in an MDT

Chemotherapy

- **Neoadjuvant**
 - Shrink tumour to ↓ need for major surgery
 - Control early micrometastases
- **Primary Therapy**
 - E.g. sole Rx in haematological Ca
- **Adjuvant**
 - ↓ chance of relapse: e.g. breast and GI Ca
- **Palliative**
 - Provide relief from symptoms
 - Prolong survival

Important Cytotoxic Classes

Alkylating agents

- Cyclophosphamide, chlorambucil, busulfan

Antimetabolites: methotrexate, 5-FU

Vinca alkaloids: vincristine, vinblastine

Cytotoxic Abx: doxorubicin, bleomycin, actinomycin D

Taxanes: paclitaxel

Immune Modulators: thalidomide, lenalidomide

MAbs

- Trastuzumab (anti-Her2): breast Ca
- Bevacizumab (anti-VEGF): RCC, CRC, lung
- Cetuximab (anti-EGFR): CRC
- Rituximab (anti-CD20): NHL

Tyrosine Kinase Inhibitors

- Erlotinib: lung Ca
- Imatinib: CML

Endocrine Modulators: tamoxifen, anastrazole

Common Side Effects

- **n/v:** prophylactic granisetron + dexamethasone
- **Alopecia**
- **Neutropenia:** 10-14d after chemo
- **Extravasation of chemo agent**
 - Pain, burning, bruising @ infusion site
 - Stop infusion, give steroids, apply cold pack
 - Liaise early w/ plastics

Specific Problems

Drug	Problems
Cyclophosphamide	Haemorrhagic cystitis: give mesna Hair loss BM suppression
Doxorubicin	Cardiomyopathy
Bleomycin	Pulmonary fibrosis
Vincristine	Peripheral neuropathy (don't give IT)
Carboplatin	Peripheral neuropathy n/v Nephrotoxic
Paclitaxel	Hypersensitivity
5-FU	Mucositis

Radiotherapy

Mechanism

- Ionising radiation → free radicals which damage DNA
- Normal cells better at repairing damage cf. Ca cells.
- Radiation dose: gray (Gy)
- Given in daily fractions
- India ink tattoo for reproducible targeting

Radical Rx

- Curative intent
- 40-70Gy
- 15-30 daily fractions

Palliation

- Symptom relief
 - Bone pain, haemoptysis, cough, dyspnoea, bleeding.
- 8-30Gy
- 1-10 fractions

Early Reactions

- **Tiredness**
- **Skin reactions:** erythema → ulceration
- **Mucositis**
- **n/v:** occur w/ stomach, liver or brain Rx
- **Diarrhoea:** pelvic or abdo Rx
- **Cystitis**
- **BM suppression**

Late Reactions (months or yrs)

- **Brachial plexopathy**
 - Follows axillary radiotherapy
 - Numb, weak, painful arm
- **Lymphoedema**
- **Pneumonitis**
 - Dry cough ± dyspnoea
 - Rx: prednisolone
- **Xerostomia**
- **Benign strictures**
- **Fistulae**
- **↓ fertility**
- **Panhypopituitarism**

Surgery

- **Diagnostics:** tissue biopsy or complete removal
- **Excision:** GI, soft-tissue sarcomas, gynae
 - Often w/ neo-/adjunctive chemo or radiotherapy
- **Palliation:** e.g. bypass procedures, stenting

Analgesia

- Oral where possible
- Fixed interval to give continuous relief
- Stepwise approach

Tumour Markers

Marker	Malignant	Non-malignant
AFP	HCC Teratoma	Hepatitis Cirrhosis Pregnancy
CA 125	Ovary Uterus Breast	Cirrhosis Pregnancy
CA 15-3	Breast	Benign breast disease
CA 19-9	Pancreas Cholangiocarcinoma CRC	Cholestasis Pancreatitis
CA 27-29	Breast	
Neuron-specific enolase	SCLC	
CEA	CRC	Pancreatitis Cirrhosis
β HCG	Germ cell tumour	Pregnancy
PSA	Prostate	BPH
Mono Ig	Multiple myeloma	
S-100	Melanoma	Sarcoma
PLAP	Seminoma	
Acid phosphatases	Prostate Ca	
Thyroglobulin	Thyroid Ca	

Immunology

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Phagocyte Deficiencies

Condition	Mechanisms	Presentation	PMN	Adhesion Mol	NBT/DHR	Pus
Reticular dysgenesis	HSC defect Deficiency of PMN, lymphos, monos Type of SCID					
Kostmann's Syndrome	Congenital neutropenia Auto Recessive	Rx: G-CSF or BMT	Absent	Normal	Absent	No
Cyclic neutropenia	Episodic neutropenia every 4-6 wks Auto Dominant Mutation in ELA2 gene	Rx: G-CSF				
LAD	CD18 ($\beta 2$ -integrin) deficiency	Delayed umbilical cord separation Neonatal bacterial infections	↑↑	Absent	Normal	No
CGD	NADPH oxidase deficiency X-linked recessive Can resist catalase negative bacteria	Recurrent pneumonias and abscesses Granulomas Lymphadenopathy HSM Rx: gamma-IFN therapy	Normal	Normal	Abnormal	Yes
Cytokine Failure	gIFN / gIFN-R and IL-12 / IL-12-R deficiency	Susceptible to mycobacteria and salmonella BCG infection after vaccination No granulomas				

T Cell Deficiencies

Condition	Mechanisms	Presentation	CD4	CD8	B Cell	IgM	IgG	IgA
Reticular dysgenesis	HSC defect Deficiency of PMN, lymphos, monos Type of SCID		↓	↓	↓			
SCID	X-linked: (common) IL2R gamma chain mutation - T-/B+ ADA deficiency: auto recessive - T-/B-	Unwell by 3mo Infections FTT Persistent diarrhoea Unusual skin disease FH of early infant death	↓	↓	N/↓	N/↓	↓	↓
Di George	Defect of 3 rd /4 th pharyngeal arches Thymic aplasia CATCH-22	Immune function improves with age. Rx: Thymus transplant	↓	↓	N	N	↓	↓
BLS-II	Absent MHC-II	Unwell by 3mo FTT Assoc. with sclerosing cholangitis FH of early infant death	↓	N	N	N	↓	↓
Cytokine Failure	gIFN / gIFN-R and IL-12 / IL-12-R deficiency	Susceptible to mycobacteria and salmonella BCG infection after vaccination No granulomas						

B Cell Deficiencies

Condition	Mechanisms	Clinical	CD4	CD8	B Cell	IgM	IgG	IgA
SCID	X-linked: (common) IL2R gamma chain mutation - T-/B+ ADA deficiency: auto recessive - T-/B-	Unwell by 3mo Infections FTT Persistent diarrhoea Unusual skin disease FH of early infant death	↓	↓	N/↓	N/↓	↓	↓
Bruton's	X-linked B-cell tyrosine kinase deficiency Pre-B cells cannot mature	No Ig after ~3mo Recurrent childhood infections - bacterial - enterovirus	N	N	↓	↓	↓	↓
Hyper IgM	X-linked CD40L (CD154) mutation (T cells) No germinal centre development in LN/spleen Failure of isotype switching	Boys present in first few yrs Recurrent bacterial infections FTT PCP, autoimmune disease, Ca	N	N	N	↑↑	↓	↓
IgA deficiency		Assoc. with coeliac disease Recurrent GIT and RT infections Not severe	N	N	N	N	N	↓
Common variable ID		Recurrent bacterial infections - bronchiectasis - sinusitis Autoimmune disease Granulomatous disease	N	N	N	N	↓	↓
Wiskott-Aldrich	WASP gene mutation X-linked	Immunodeficiency Thrombocytopenia Eczema Malignant Lymphoma ↑ IgE				↓	↑	↑

Complement Dysfunction

Pathway	Deficiency	Outcome
Classical	C1, C2, C4 C2 deficiency = commonest	SLE
MBL	MBL deficiency	↑ infection in patient's with other cause of immune impairment - prems, chemo, HIV, Ab deficiency
Alternative	B, I, P deficiency	Infection (esp. with encapsulates) - Meningococcus - Pneumococcus - H. influenzae - Hib FH of infection
Terminal pathway	C5-9 deficiency Inability to make MAC	Infection (esp. with encapsulates) - Meningococcus - Pneumococcus - H. influenzae - Hib FH of infection
C3 deficiency	C3 deficiency Acquired C3 deficiency due to C3 nephritic factor – assoc. with membranoproliferative (mesangiocapillary) GN	Infections as above + SLE

ix

- C3, C4 level
- **CH50:** classical pathway
- **AP50:** alternative pathway
- If CH50 and AP50 both abnormal with normal C3, C4 = final common pathway deficiency (C5-9)

Hereditary Angioedema / C1 Esterase Deficiency

- Auto dominant: commoner than complement deficiencies
- Acquired form may be caused by splenic marginal zone lymphoma

Pathophysiology

- Serpin that inhibits
 - C1
 - F12 of coag cascade
 - Kallikrein (Cleaves HMWK → Bradykinin)
- Deficiency → ↑ bradykinin → symptoms

Presentation

- Attacks may be ppterred by EtOH, emotional stress, exercise.
- **Angioedema but NO rash and NOT itchy**
 - Skin
 - Oropharynx – asphyxia
 - GIT – nausea, vomiting diarrhoea
- ↓ C2 and ↓C4 (normal C1 and C3)

Infections Associated With Immune Deficiencies

	Antibody Deficiency B cell	Cellular Deficiency T cell	Combined Deficiency B+T cell	Phagocyte (PMN) Deficiency	Complement Deficiency
Viruses	Enterovirus	CMV, VAZ, HSV, EBV, measles, resp viruses	All		
Bacteria	Encapsulates: Pneumococcus Meningococcus Haemophilus	Mycobacteria Salmonella Listeria	As for Ab deficiency S. typhi Listeria Enterics	S. aureus Other Gm+ and Gm- Mycobacteria	Encapsulates Esp. Meningococcus
	Staph. aureus Pseudomonas				
Fungi		Candida Aspergillus Histoplasma Crypto PCP	Candida Aspergillus Histoplasma Crypto PCP	Candida Aspergillus	Candida
Protozoa	Giardia lamblia	Toxoplasma	Toxoplasma		
Clinical	Respiratory and GI sepsis	Systemic viral / fungal infections Early malignancy	Systemic viral/fungal infections and gastroenteritis	Lymphadenitis, skin/mouth infections, liver and lung abscesses, granulomas	Systemic bacterial infections Autoimmune disease

Dx of Immune Deficiency

Infections

- 2 major or 1 major + recurrent minor infections in 1 year
- Unusual organisms
- Unusual sites
- Unresponsive to oral Abx
- Chronic infections
- Early structural damage

Other

- FTT
- Skin disease
- Chronic diarrhoea
- Mouth ulceration
- Family Hx

Dermatology

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Malignant and Pre-malignant Skin Lesions

Malignant Melanoma

Epidemiology

- F>M = 1.5:1
- UK incidence = 10 000/yr and 2000 deaths/yr
 - ↑80% in 20yrs

Features

- Asymmetry
- Boarder: irregular
- Colour: non-uniform
- Diameter > 6mm
- Evolving / Elevation

Risk Factors

- Sunlight: esp. intense exposure in early years.
- Fair skinned (Low Fitzpatrick Skin Type)
- ↑ no. of common moles
- +ve FH
- ↑ age
- Immunosuppression

Classification

- **Superficial Spreading:** 80%
 - Irregular boarders, colour variation
 - Commonest in Caucasians
 - Grow slowly, metastasise late = better prognosis
- **Lentigo Maligna Melanoma**
 - Often elderly pts.
 - Face or scalp
- **Acral Lentiginous**
 - Asians/blacks
 - Palms, soles, subungual (C Hutchinson's sign)
- **Nodular Melanoma**
 - All sites
 - Younger age, new lesion
 - Invade deeply and metastasis early = poor prog
- **Amelanotic**
 - Atypical appearance → delayed Dx

Staging and Prognosis

- **Breslow Depth**
 - Thickness of tumour to deepest point of dermal invasion
 - <1mm = 95-100% 5ys
 - >4mm = 50% 5ys
- **Clark's Staging**
 - Stratifies depth by 5 anatomical levels
 - Stage 1: Epidermis
 - Stage 5: sc fat

Metastasis

- Liver
- Eye

Mx

- Excision + 2° margin excision depending on Bres depth
- ± lymphadenectomy
- ± adjuvant chemo (may use isolated limb perfusion)

Poor prognostic indicators

- Male sex (more tumours on trunk cf females)
- ↑ mitoses
- Satellite lesions (lymphatic spread)
- Ulceration

Squamous Cell Carcinoma

- Ulcerated lesion C hard, raised **everted** edges
- Sun exposed areas

Causes

- Sun exposure: scalp, face, ears, lower leg
- May arise in chronic ulcers: Marjolin's Ulcer
- Xeroderma pigmentosa

Evolution

- Solar/actinic keratosis → Bowen's → SCC
- Lymph node spread is rare

Rx

- Excision + radiotherapy to affected nodes

Actinic Keratoses

- Irregular, crusty warty lesions.
- Pre-malignant (~1%/yr)

Rx

- Cautery
- Cryo
- 5-FU
- Imiquimod
- Photodynamic phototherapy

Bowen's Disease

- Red/brown scaly plaques
- SCC *in situ*

Rx

- As for AKs

Keratoacanthoma

- A well differentiated SCC that arises in a hair follicle.
- Fast-growing, dome-shaped C a keratin plug.
- Usually regress but may be excised

Basal Cell Carcinoma

- Commonest cancer
- Pearly nodule C **rolled telangiectatic** edge
- May ulcerate
- Typically on face in sun-exposed area
 - Above line from tragus → angle of mouth

Behaviour

- Low-grade malignancy → very rarely metastasise
- Locally invasive

Rx

- Excision
 - **Mohs:** complete circumferential margin assessment using frozen section histology
- Cryo/radio may be used.

Psoriasis

Epidemiology

- **Prevalence:** 2% of Caucasians
- **Age:** peaks in 20s and 50s
- **Sex:** F=M
- **Genetics:** 30% have FH
 - Genetic predisposition

Pathology

- TIV hypersensitivity reaction
- Epidermal proliferation
- T-cell driven inflammatory infiltration
- **Histo**
 - Acanthosis: thickening of the epidermis
 - Parakeratosis: nuclei in stratum corneum
 - Munro's microabscesses: neutrophils

Triggers

- Stress
- Infections: esp. streps
- Skin trauma: Körner phenomenon
- Drugs: β-B, Li, anti-malarials, EtOH
- Smoking

Signs

Plaques

- Symmetrical well-defined red plaques \overline{c} silvery scale
- Extensors: elbows, knees
- Flexures (no scales): axillae, groins, submammary
- Scalp, behind ears, navel, sacrum

Nail Changes (in 50%)

- Pitting
- Onycholysis
- Subungual hyperkeratosis

10-40% Develop Seronegative Arthritis

- Mono-/oligo-arthritis: DIPs commonly involved
- Rheumatoid-like
- Asymmetrical polyarthritis
- Psoriatic spondylitis
- Arthritis mutilans
- May \rightarrow dactylitis

Variants

Guttate

- Drop-like salmon-pink papules \overline{c} fine scale
- Mainly on trunk
- Occurs in children assoc. \overline{c} strep infection

Pustular

- Sterile pustules
- May be localised to palms and soles

Erythroderma and Generalised Pustular

- Generalised exfoliative dermatitis
- Severe systemic upset: fever, \uparrow WCC, dehydration
- May be triggered by rapid steroid withdrawal

Differential

- Eczema
- Tinea: asymmetrical
- Seborrhoeic dermatitis

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Mx

Education

- Avoid triggers

Soap Substitute

- Aqueous cream
- Dermol cream
- Epaderm ointment

Emollients

- Epaderm
- Dermol
- Diprobase

Topical Therapy

- Vit D₃ analogue: e.g. calcipotriol
- Steroids: e.g. betamethasone
 - Dovobet = Calcipotriol + betamethasone
- Tar: mainly reserved for in-patient use
- Dithranol
- Retinoids: e.g. tazarotene

UV Phototherapy

- Causes local immunosuppression
- Narrow band UVB
- Psoralen + UVA: PUVA
 - Psoralen is a photosensitising agent and can be topical or oral
- PUVA is more effective but \uparrow skin Ca risk

Non-Biologicals

- Methotrexate
- Ciclosporin
- Acetretin (oral retinoid / vit A analogue)
 - SE: \uparrow lipids, \uparrow glucose

Biologicals

- Infliximab
- Etanercept
- Adalimumab

Eczema

Presentation

- Extremely itchy
- Poorly demarcated rash
 - Acute: oozing papules and vesicles
 - Subacute: red and scaly
- Chronic eczema → lichenification
 - Skin thickening & exaggeration of skin markings

Pathology

- Epidermal spongiosis

Atopic Eczema

- TH2 driven inflammation & ↑ IgE production
- Affects 2% of infants
- Most children grow-out of it by 13yrs

Cause

- FH of atopy common
- Specific allergens
 - House dust mite
 - Animal dander
- Diet: e.g. dairy products

Presentation

- Face: esp. around eyes, cheeks
- Flexures: knees, elbows
- May become 2^o infected
 - Staph → flucloxacillin
 - HSV → aciclovir

Associations

- Asthma
- Hay fever

Ix

- ↑ IgE
- RAST testing: identify specific Ag

Irritant Contact Dermatitis

- Everyone is susceptible to irritants
- Causes: detergents, soaps, oils, solvents, venous stasis

Allergic Contact Dermatitis

- Type IV hypersensitivity reaction
- Common allergens
 - Nickel: jewellery, watches, coins
 - Chromates: leather
 - Lanolin: creams, cosmetics
- Location: correlates sharply with allergen exposure
- Ix: Patch testing

Adult Seborrhoeic Dermatitis

- Red, scaly, rash
- Cause: overgrowth of skin yeasts (e.g. malassezia)
- Location: scalp (dandruff), eyebrows, cheeks, nasolabial folds
- Rx: mild topical steroids / antifungal
 - Daktacort: miconazole + hydrocortisone

Mx of Atopic Eczema

Education

- Avoid triggers: e.g. soap

Soap Substitute

- Aqueous cream
- Dermol cream
- Epaderm ointment

Emollients

- Epaderm
- Dermol
- Diprobase
- Oilatum (bath oil)

Topical Therapy

Steroids

- 1% Hydrocortisone: face, groins
- Eumovate: can use briefly (<1wk) on face
- Betnovate
- Dermovate: very strong, brief use on thick skin
 - Palms, soles

2nd line Therapies

- Topical tacrolimus
- Phototherapy
- Ciclosporin or azathioprine

Pruritus

Generalised

- CRF
- Cholestasis
- Haematological
 - Polycythaemia
 - Hodgkin's
 - Leukaemia
 - Iron deficiency
- Endocrine
 - DM
 - Hyper- / hypo-thyroidism
 - Pregnancy

Very Itchy Dermatological Diseases

- Eczema
- Urticaria
- Scabies
- Dermatitis herpetiformis

Skin Infections

Tinea

- A superficial mycosis caused by dermatophytes
 - Microsporum
 - Epidermophyton
 - Trichophyton

Presentation

- Round scaly lesion
- Itchy
- Central clearing
- Scalp, body, foot, groin, nails

Rx

- **Skin:** terbinafine or topical ketoconazole / miconazole
- **Scalp:** griseofulvin or terbinafine
- **Nails:** terbinafine

Candida

- Common
- RFs: immunosuppression, Abx, steroid inhalers

Presentation

- Pink + white patches
- Moist
- Satellite lesions
- Mouth, vagina, skin folds, toe web

Rx

- **Mouth:** nystatin
- **Vagina:** clotrimazole cream and pessary

Pityriasis versicolor

- Caused by Malassezia furfur

Presentation

- Common in hot and humid environments
- Circular hypo-/hyper-pigmented patches
- Fine white scale
- Itchy
- Back of neck and trunk

Ix

- “Spaghetti and meatballs” appearance \bar{c} KOH stain

Rx

- Selenium sulphate or ketoconazole shampoos

Impetigo

- Contagious superficial skin rash caused by S. aureus

Presentation

- Age: peak @ 2-5yrs
- Honey-coloured crusts on erythematous base
- Common on face

Rx

- **Mild:** topical Abx (fusidic acid, mupirocin)
- **More severe:** flucloxo PO

Erysipelas

- Sharply defined superficial infection by S. pyogenes
- Often affects the face
- High fever + \uparrow WCC
- **Rx**
 - Benpen IV
 - Pen V and flucloxo PO

Cellulitis

- Acute infection of skin and soft tissues

Cause: β -haemolytic Strep + staph. aureus

Presentation

- Deeper and less well defined than erysipelas
- Pain, swelling, erythema and warmth
- Systemic upset
- \pm lymphadenopathy

Rx

- Empiric: flucloxo IV
- Confirmed Strep: Benpen or Pen V
- Pen allergic: clindamycin

Warts

- Caused by HPV infection

Rx

- Expectant
- Destructive
 - Topical salicylic acid
 - Cryotherapy
 - Podophyllin
 - Imiquimod

Molluscum

- Pox virus
- Pink papules \bar{c} umbilicated central punctum
- Resolve spontaneously

Herpes Zoster / Shingles

- Recurrent VZV infection
- Dermatomal distribution of cropping vesicles and crust
 - Thoracic: 50%
 - Ophthalmic: 20%
 - Cornea affected in 50% \rightarrow keratitis, iritis
- May \rightarrow post-herpetic neuralgia
- **Rx:** aciclovir or famciclovir PO if severe

Herpes Simplex

- Gingivostomatitis or recurrent genital or oral infections
- Triggered by infection (e.g. CAP), sunlight and immunosuppression
- May complicate eczema: eczema herpeticum
- Grouped painful vesicles on an erythematous base
- **Rx:** acyclovir or famciclovir indicated if immunosuppressed or recurrent genital herpes.

Pityriasis Rosea

- HHV-6/-7
- Herald patch precedes rash, mainly on the trunk

Miscellaneous Skin Disorders

Lichen Planus

Skin Presentation

- Flexors: wrists, forearms, ankles, legs
- Display Kobner phenomenon
- Purple
- Pruritic
- Polygonal
- Planar
- Papules
- Lacy white marks: Wickham's Striae

Lesions Elsewhere

- Scalp: scarring alopecia
- Nails: longitudinal ridges
- Mouth: lacy white plaques on inner cheeks
- Genitals

Rx

- Mild:** topical steroids
- Severe:** systemic steroids

Bullous Pemphigoid

- Autoimmune blistering disease due to auto-abs against hemidesmosomes

Presentation

- Mainly affects the elderly
- Tense bullae on erythematous base
- Can be itchy

Ix

- Biopsy shows linear IgG along the BM and subepidermal bullae

Rx

- Clobetasol (Dermavate)

Pemphigus Vulgaris

- Autoimmune blistering disease due to auto-abs against desmosomes.
- May be ppted by drugs
 - NSAIDs
 - ACEi
 - L-dopa

Presentation

- Younger pts.
- Large flaccid bullae which rupture easily
- Nikolsky's sign +ve
- Mucosa is often affected**

Ix

- Intraepidermal bullae

Rx

- Prednisolone
- Rituximab
- IVIg

Acne Vulgaris

Pathophysiology

- ↑ sebum production: androgens and CRH
- P. acnes is a skin commensal that flourishes in the anaerobic environment of the blocked follicle
 - inflammation

Presentation

- Inflammation of pilosebaceous follicles
- Comedones (white- or black-heads), papules, pustules nodules, cysts
- Face, neck, upper chest and back

Mx

- Pt. education
- Remember that topical therapy is difficult to apply to the back.

Mild: topical therapy

- Benzoyl peroxide
- Erythromycin, Clindamycin
- Tretinoin / Isotretinoin

Moderate

- Topical benzoyl peroxide + oral Abx (doxy or erythro)

Severe

- Isotretinoin (vitamin A analogue)
 - 60-70% have no further recurrence
 - SE: teratogenic, hepatitis, ↑lipids, depression, dry skin, myalgia
 - Monitor: LFTs, lipids, FBC
- May try Dianette in women

Acne Rosacea

- Chronic relapsing remitting disorder affecting the face

Presentation

- Chronic flushing ppted. by alcohol or spicy foods.
- Fixed erythema: chin, nose, cheeks, forehead
- Telangiectasia, papules, pustules (no comedones)

Associations

- Rhinophyma:** swelling and soft tissue overgrowth of the nose in males
- Blepharitis:** scaling and irritation at the eyelashes

Rx

- Avoid sun exposure
- Topical azelaic acid
- Oral doxycycline or azithromycin

Drug Eruptions

Maculopapular

- Commonest type
- Generalized erythematous macules and papules
- ± fever and ↑ eosinophils
- Develops w/i two weeks of onset of drug
- Penicillins, cephalosporins, AEDs

Urticaria

- Wheals ± angioedema and anaphylaxis
- Rapid onset after taking drug
- Immune (IgE)
 - Penicillins
 - Cephalosporins
- Non-immune (direct mast cell degranulation)
 - Morphine
 - Codeine
 - NSAIDs
 - Contrast

Erythema Multiforme

- Symmetrical target lesions on palms, soles and limbs
- Occurs 1-2wks after insult
- Infections are commoner cause of EM

Causes

- Idiopathic
- **Infections:** HSV, mycoplasma
- **Drugs**
 - Sulphonamides, NSAIDs, allopurinol, penicillin phenytoin

Stevens-Johnson Syndrome

- More severe variant of EM,
- Blistering mucosa: conjunctiva, oral, genital

Toxic Epidermal Necrolysis

- Extreme form of SJS
- Nearly always a drug reaction
- **Features**
 - Severe mucosal ulceration
 - Widespread erythema followed by epidermal necrosis
 ↳ loss of large sheets of epidermis
 - → dehydration
- ↑↑ risk in HIV+
- **Rx:** dexamethasone, IVIg
- **Mortality:** 30%

Infestations

Scabies

- Sarcoptes scabiei
- Highly contagious: spread by direct contact
- Female mite digs burrows and lays eggs

Presentation

- Burrows: short, serpiginous grey line, block dot
- Hypersensitivity rash: eczematous, vesicles
- Extremely itchy → escoriaction
- Particularly affects the finger web spaces (esp. 1st)
- Also: axillae, groin, umbilicus

Mx

- Permethrin cream: applied from neck down for 24hrs
- 2nd line: Malathion
- 3rd line: oral ivermectin
- Treat all members of the household

Headlice

- Pediculus humanus capitis
- Spread by head to head contact
- Nits = empty eggs

Presentation

- Itch
- Papular rash @ the nape of the neck

Rx

- Malathion
- Combing

Skin Manifestations of Systemic Disease

Skin Conditions

Erythema Nodosum

- Painful blue-red lesions on anterior shins
- 3 S's:** sarcoid, strep infections and sulfonamides
- Also:** OCP, IBD and TB, Behcet's

Erythema Multiforme

- Symmetrical target lesions on palms, soles and limbs
- Possibly mediated by IgM deposition
- Usually 2^o to infection
- Infections:** HSV (70%), mycoplasma
- Drugs:** SNAPP

Stevens-Johnson Syndrome and TEN

- Severe variants of EM
- Nearly always drug-induced
- Fever, mucosal and skin ulceration and necrosis

Pyoderma Gangrenosum

- Wide (10cm), deep ulceration \bar{c} violaceous border
- Purulent surface
- Undermined edge
- Commonly occurs on legs
- Heal \bar{c} cribriform (pitted) scars
- Assocs.:** IBD, AIH, Wegener's, RA, leukaemia
- Rx:** High-dose systemic steroids

Vitiligo

- Chalky white patches \bar{c} hyperpigmented borders
- Itch in sunlight
- Assocs.:** autoimmune disorders

Livedo Reticularis

- Persistent mottled red/blue lesions that don't blanch
- Commonly found on the legs
- Triggered by cold
- Causes**
 - Idiopathic
 - Vasculitis: RA, SLE, PAN
 - Obstruction: anti-phos, cryoglobulinaemia
 - Sneddon's syn.: LR + CVAs

Diseases

Disease	Skin Manifestation
Rheumatic fever	Erythema marginatum
Lyme (<i>Borrelia burgdorferi</i>)	Erythema chronicum migrans
Crohn's	Perianal ulcers and fistulae EN Pyoderma gangrenosum
Dermatomyositis	Heliotrope rash on eyelids Shawl sign (macular rash) Gottron's Papules Mechanic's hands Nailfold erythema, telangiectasia
DM	Ulcers Candida Kyrle disease Acanthosis nigricans Necrobiosis lipoidica (shins) Granuloma annulare (hands, feet)
Sarcoidosis	Erythema nodosum Erythema multiforme Lupus pernio Hypopigmented areas Red/violet plaques
Coeliac	Dermatitis herpetiformis (elbows)
Graves'	Pre-tibial myxoedema (lat mal)
RA	Rheumatoid nodules Vasculitis (palpable purpura)
SLE	Facial butterfly rash
Systemic sclerosis	Calcinosis Raynaud's Sclerodactyly Telangiectasia Generalised skin thickening
Liver disease	Palmar erythema Spider naevi Gynaecomastia \downarrow 2 ^o sexual hair Jaundice Bruising Excoriations
ESRD	Assoc. c Cause - DM, vasculitis, sclero, RA, SLE Assoc. c ESRD - Pruritus, xerosis, pigment change Bullous disease Assoc. c Transplant - Cushingoid, gingival hyperplasia, Infections, BCC, SCC, melanoma Kaposi's
Neoplasia	Acanthosis nigricans Dermatomyositis Thrombophlebitis migrans Acquired ichthyosis

Epidemiology

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Health Information

Routine Data

- Data that are routinely collected and recorded in an ongoing systematic way, often for administrative purposes.

Advantages

- Relatively cheap
- Already collected and available
- Standardised collection procedures

Disadvantages

- May not answer the question
- Variable quality
- Not every case captured

Sources

- **Demographics:** census
- **Health:** births, deaths, admissions, prescriptions, hospital episode statistics, cancer
- **Exposures:** smoking, air pollution, crime
- **Disease prevention:** screening, immunisation uptake

Hospital Episode Statistics

- Electronic record of every inpatient or day-case episode of patient care in every NHS hospital.
- 300 fields of information, including:
 - Pt demographics
 - Diagnosis using ICD-10
 - Procedures using OPCS4

Advantages

- Comprehensive
- Unbiased
- Based on case notes

Disadvantages

- Data may not be complete
- In-hospital death only

Mortality

UK

1. **Heart and Circulatory disorders:** 33%
 - a. IHD (23%)
 - b. Stroke (10%)
2. **Cancer:** 30%
 - a. Trachea, bronchus, lung
 - b. Breast, prostate
 - c. Colorectum
3. **Respiratory disorders:** 13%
 - a. Pneumonia
 - b. COPD

Worldwide

1. IHD
2. Stroke and other cerebrovascular disease
3. LRTI
4. COPD
5. Diarrhoeal diseases

Clinical Governance

Definition

- A transparent system for the continual maintenance and improvement of healthcare standards both on an individual and organisational level within the NHS.

Elements

- Education and Training
- Clinical audit
- Clinical effectiveness
- Research and Development
- Openness
- Risk Management

Agencies

- The Care Quality Commission
 - Independently inspect healthcare services against standards set by the Department of Health.
 - Investigate serious failures in healthcare services.
 - Publish regular ratings of NHS trusts.

Clinical Audit

- Are pts. given the best care?

Definition

- A quality improvement process that seeks to improve pt. care and outcomes through the systematic review of care against explicit criteria and the implementation of change.

Outcome Measures

- Are pts. better and do they feel better?

Patient Reported Outcomes (PROMs)

- Calculate the health gain from the pts. perspective after surgical Rx using pre- and post-operative surveys.
 - Arthroplasty, hernia repairs, varicose veins
 - Hip replacement gives largest improvement in specific condition and general health.

Quality and Outcomes Framework (QOF)

- Voluntary annual reward and incentive programme for all GP surgeries in England, detailing practice achievement results.

Public Health Issues

Major Contributions to Health

- Drugs and medical intervention
- Obstetric and perinatal care
- Immunisation
- Screening
- Chronic disease Mx

Major Mortality Risk Factors

- Heart and Circulatory Disorders
 - Smoking
 - ↓ exercise
 - Diet: ↑fat, ↑calorie, ↑salt, EtOH
 - ?Stress
- Neoplasms
 - Smoking
 - ↓ exercise
 - Diet: ↓fruit and veg, ↓fibre, ↑fat
- Pulmonary Disease
 - Smoking
 - ↓ exercise
 - Occupation: asbestos, dust exposure

Major Public Health Issues

- Smoking
- Obesity / unhealthy diet
- ↓ Exercise
- EtOH abuse
- Sexual health
- Mental health

Obesity

- 20% obese
- 50% of females overweight or obese

Nurses' Health Study

- Overwt. → ↓3yrs of life
- Obese → ↓7yrs of life
- Active lifestyle (30min walk/d) prevents 30% of obesity and 45% of new DM.

Evidence for Changing Nutrition

- Mediterranean diet can ↓ cardiac death post-MI
- Low Na diet → ↓ BP

Sexual Health

- 10% of 16-24yr olds have ≥1 STI
- ↑ in urban areas and amongst Blacks and Minorities
- → infertility, ectopics, Cervical Ca, HIV

Some Strategies

- Improving access to sexual health services
- Chlamydia screening

Smoking

- Commonest cause of preventable death in the UK
- 2nd hand smoking
 - Respiratory infections
 - Asthma
 - SIDS
 - ↑ lung Ca and CHD risk
- Social gradient in mortality is partially explained by social gradient in smoking.

Some Strategies

- Health education
- Restrict advertising
- Remove from display in shops
- ↑ price
- Smoking ban in public places
- Very brief advice

Alcohol

- 5% of men and 2% of women report problems
- Recommended
 - Men: 21u/wk or 3-4u/d
 - Women: 14u/wk or 2-3u/d
 - NB. 1u = 10ml EtOH

Some Strategies

- National Alcohol Harm Reduction Strategy
- ↑ minimum price / unit

Mental Health

- Common: ~15% lifetime risk
- Depression and anxiety disorders most commonly

Some Strategies

- GPs get rewarded for depression screening
- Expansion of psychological therapies (e.g. CBT)

Clinical Evidence

Hierarchy of Evidence

- 1. Systematic reviews and meta-analyses
- 2. RCTs
- 3. Cohort or case-control studies
- 4. Descriptive studies
- 5. Case reports

Study Types

Observational

- Analytical / Aetiological
 - Studies determinants of disease by judging whether exposure causes or prevents disease
- Descriptive
 - Studies distribution of disease
 - Person, place and time

Experimental

- RCTs

Descriptive Studies

- Can be used to generate hypotheses
- Provide frequency data
 - Incidence
 - Point prevalence
- Can't determine causation

Examples

- **Cross-sectional Surveys**
 - Household interview surveys asking questions regarding illness, social circumstances and demographics.
- **Cross-sectional Census**
- **Ecological studies**
 - Use populations rather than individual as unit of observation.
 - Subject to significant confounding: age, sex, SES
- **Other routine data**

Case-Control Studies

- Retrospective study of exposure in a case grp & the disease and a control grp w/o the disease.
- Proportion of exposed in each group → odds ratio

Advantages

- Quick and cheap
- Well-suited for diseases & long latent periods
- Good for evaluation of rare diseases
- Can examine multiple aetiological factors for a single disease.

Disadvantages

- Inefficient for evaluating rare exposures
- Cannot calculate incidence rates
- Temporal relationship between exposure and disease can be difficult to establish
- Recall bias
 - E.g. testicular cancer sufferers more likely to report preceding trauma
- Selection bias
 - E.g. non-random selection of study grp.

Cohort Study

- Prospective study comparing development of disease in exposed and non-exposed grp.
- Incidence of disease in each grp → relative risk

Examples

- Million Women study
- Framingham Heart Study
- Nurses' Health Study

Advantages

- Good for evaluation of rare exposures
- Can examine multiple effects of a single exposure
- Can elucidate temporal relationship
- Direct incidence calculation

Disadvantages

- Inefficient for evaluation of rare diseases
- Expensive and time-consuming
- Loss to f/up affects results

RCTs

- Planned experiment designed to assess the efficacy of an intervention.
- Randomisation: ↓ selection bias.
- Blinding: ↓ measurement bias

Advantages

- Most reliable demonstration of causality

Disadvantages

- Non-compliance
- Loss to f/up
- Validity depends on quality of study
- Ethical issues
- Selection criteria may limit generalisability

Meta-Analyses

- Observational study of evidence
- Systematic identification of relevant trials and assessment of their quality
- Allow accurate interpretation of multiple RCTs

Forest plots

- Square = OR
 - Size = size of study
- Line = 95% CI of OR
- Diamond = combined odds ratio
 - Width = 95% CI

Epidemiological Concepts

5 Steps of EBM

- 1. Question
- 2. Search
- 3. Appraise
- 4. Apply
- 5. Evaluate

Association and Causation

- **Association:** a relationship between two factors
- **Causation:** $X \rightarrow Y$

Bradford Hill Causation Criteria

- Strong association: i.e. ↑ RR or OR
- Consistency with other investigations
- Specificity
- Temporal relationship
- Dose response relationship
- Plausibility
- Coherence
- Experimental evidence
- Analogy

Chance

- Studies are based on estimates from samples and are therefore subject to random variation.
- Random variation can be minimised by ↑ sample size.
- The role of chance is assessed by statistical significance tests and by calculating confidence intervals.

Bias

- Inaccurate data due to systematic error in selection, measurement or analysis.

Selection Bias

- Systematic difference between the characteristics of those selected for a study and those who were not or differences between study groups.
- E.g. self-selection, healthy worker effect

Measurement Bias

- Occurs when measurements or classifications of disease or exposure are inaccurate.
- E.g. inaccuracies of the instruments, expectations of observers or participants.

Analysis Bias

- Error caused by participants being lost to f/u or switching treatment groups.
- Take into account using an intention to treat analysis.

Confounding

- Error in the interpretation of an accurate measurement.
- Any factor which is prognostically linked to the outcome and is unevenly distributed between study groups.
- Not a confounder if it lies on the causal pathway between the variables of interest.
- Common confounders: age, sex, SES

Reducing Confounding

- Randomisation
- Stratification: e.g. stratify by age
- Standardisation: e.g. SMR
 - Ratio of observed:expected deaths
 - Expected deaths derived from larger population
- Regression

Odds Ratio

$OR = \text{odds of exposure in cases} / \text{odds of exposure in controls}$
 $= (A/C) / (B/D) = AD/BC$

	Case	Control
Exposed	A	B
Not Exposed	C	D

$OR = \sim RR$ if disease is rare (<10%)

Relative Risk

- ↑/↓ in probability of disease given a particular RF

$RR = \text{incidence in exposed} / \text{incidence in unexposed}$
 $= (A/A+B) / (C/C+D)$

Risk Estimates

- **Absolute risk:** probability of disease occurrence
- **Relative risk:** ↑/↓ in probability of disease given a RF
- **Attributable risk:** measure of excess risk due to a factor

Number Needed To Treat

- $NNT = (1 / \text{Absolute risk reduction}) \times 100$
- Absolute risk reduction = 1 - hazard ratio

Screening

Modified Wilson Criteria

- **Disease**
 - Important health problem
 - Well recognised pre-clinical stage
 - Natural Hx well understood
- **Test**
 - Valid and reliable
 - Simple and cheap
 - Safe and acceptable
- **Dx and Rx**
 - Adequate facilities
 - Acceptable Rx
 - Early intervention is of more benefit than later Rx
- **Cost effective**

Validity

- **Sensitivity:** detect true positives
- **Specificity:** exclude true negatives
- **PPV:** how likely to have disease if positive
- **NPV:** how likely not to have disease if negative
 - PPV and NPV depend on disease frequency

	Disease	No Disease	
Positive	A	B	PPV $A/(A+B)$
Negative	C	D	NPV $C/(C+D)$
	Sensitivity $A/(A+C)$	Specificity $B/(B+D)$	

Effectiveness

- **Selection bias:** healthiest come for screening
- **Lead-time bias:** disease Dx earlier → ↑ survival time
- **Length-time bias:** outcome appears better because more disease → good outcome detected.

Disease Prevention

Primordial Prevention

- Prevention of factors promoting the emergence of risk factors: lifestyle, behaviours, exposure patterns

Examples

- Healthy eating programmes in schools
- Social policies to ↓ poverty and inequality
- Programmes that promote walking, cycling and public transport.
- Encouragement of positive health behaviour.

Primary Prevention

- Prevention of disease onset

Examples

- Vaccination
- Smoking cessation
- Healthy diet
- Condom use
- Detection and Rx of hyperlipidaemia

Secondary Prevention

- Halting progression of established disease
- Early detection followed by prompt, effective Rx

Examples

- Screening for Ca
- Smoking cessation after MI

Tertiary Prevention

- Rehabilitation of people w/ established disease to minimise residual disability and complications.

Examples

- Rapid Rx of MI or stroke to ↓ disability
- HAART

Disease Prevention in General Practice

- General advice for a healthy lifestyle
- Identifying and facilitating reduction of risk factors
- Ensuring availability of preventative interventions
- Identifying early disease and offering treatment

Prevention Paradox

- Many people exposed to a small risk may generate more disease than a few exposed to a large risk.
- ∴ when many people receive a small benefit the total benefit may be large.
- However, individual inconvenience may be high to the many while benefit may only be to a few.

Health Promotion

- Process of enabling people to increase control over, and to improve, their health.
 - Public policy, supportive environments...
- Health promotion is specific requirement of the GMC Good Medical Practice guidelines.

Likelihood Ratios

Pre- and Post-test Probability

- Pre-:** estimate of probability that pt. has a certain disease based on presentation or epidemiology.
- Test:** diagnostic test or sign or symptom that you elicit
- Post-:** new probability taking into account the "test" result
- Likelihood ratio: measure of how much the test alters your probability of the disease.

Calculation

$$\text{Odds} = \text{probability} / (1 - \text{probability})$$

- i.e. the ratio of the probability something will happen to the probability that it won't.

$$\text{Probability} = \text{odds} / (\text{odds} + 1)$$

$$\text{LR} = p[\text{test result if disease present}] / p[\text{test result if disease absent}]$$

$$\text{LR for positive test result} = \text{sensitivity} / (1 - \text{specificity})$$

$$\text{LR for negative test result} = (1 - \text{sensitivity}) / \text{specificity}$$

$$\text{Post-test odds} = \text{pre-test odds} \times \text{likelihood ratio}$$

Example

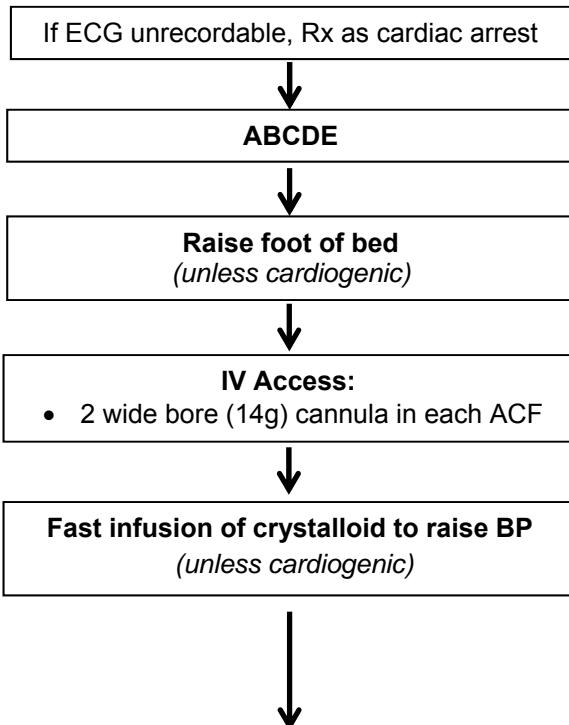
- Pre-test probability could be disease incidence in that population.
- Convert pre-test probability to odds.
- Calculate likelihood ratio based on the result of your test.
- Apply likelihood ratio to get post-test odds.
- Convert post-test odds to post-test probability

Emergencies

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Shock



Causes : CHOD

Cardiogenic

- MI
- Arrhythmia

Hypovolaemic

- Haemorrhage: internal and external
- Endocrine: Addisonian crisis, DKA
- Excess loss: burns, diarrhoea
- Third-spacing: pancreatitis

Obstructive

- PE
- Tension pneumothorax

Distributive

- Sepsis
- Anaphylaxis
- Neurogenic

Assessment

History

- Chest pain: MI, PE, dissection, anaphylaxis
- Abdo pain: AAA, DKA, peritonitis, ruptured ectopic
- Back pain: AAA

Hands

- ↑CRT: hypovolaemia, cardiogenic

Pulse

- Tachy (unless β-B or bradyarrhythmia)
- Small, thread: hypovolaemia
- Bounding: sepsis

ABP

- ↓PP: hypovolaemia
- R-L differential > 20mmHg: dissection

Appearance

- Cold, clammy: cardiogenic or hypovolaemic
- Warm, well perfused: septic
- Urticaria, angioedema, wheeze: anaphylaxis

JVP

- ↑: cardiogenic
- ↓: hypovolaemic, distributive

Abdomen

- Tender, guarding: trauma, aneurysm, peritonitis.
- Melaena: GI bleed

Ix

- FBC, U+E, glucose, ABG, CRP, trop
- X-match, clotting
- Blood cultures, urine MCS
- ECG, CXR, USS, Echo, CT

Monitoring

- Catheter (>30ml/hr)
- Art line
- CVP line

Specific Measures

Anaphylaxis:

- Adrenaline (0.5mg), hydrocortisone (200mg), chlorphenamine (10mg), salbutamol

Cardiogenic:

- Rx arrhythmias/MI. Consider dobutamine.

Septic shock:

- IV Abx (e.g. meropenem 1g/8h IV + tazocin 4.5g/8h IV)
- Fluids, vasopressors (e.g. norad)

Hypovolaemic

- Fluid replacement: crystalloid, colloid, blood (grp specific/O neg)
- Titrate to: urine output, CVP, BP
- Haemodialysis if ATN

Anaphylactic Shock

Pathogenesis

- Type 1 IgE mediated hypersensitivity reaction
- T_H2 driven IgE production following 1^o allergen exposure
- Re-exposure → biphasic inflammatory response

Early phase: w/i minutes

- IgE cross-linking → mast cell degranulation
- Vasoactive mediator release
 - Histamine
 - Tryptase
- Lipid mediator synthesis
 - Leukotrienes: ↑ vasc perm + → bronchial constriction
 - Prostacyclin
- Chemokines: e.g. eotaxin
 - Promote leukocyte recruitment (esp. eosinophils)

Late Phase: 2-24hrs

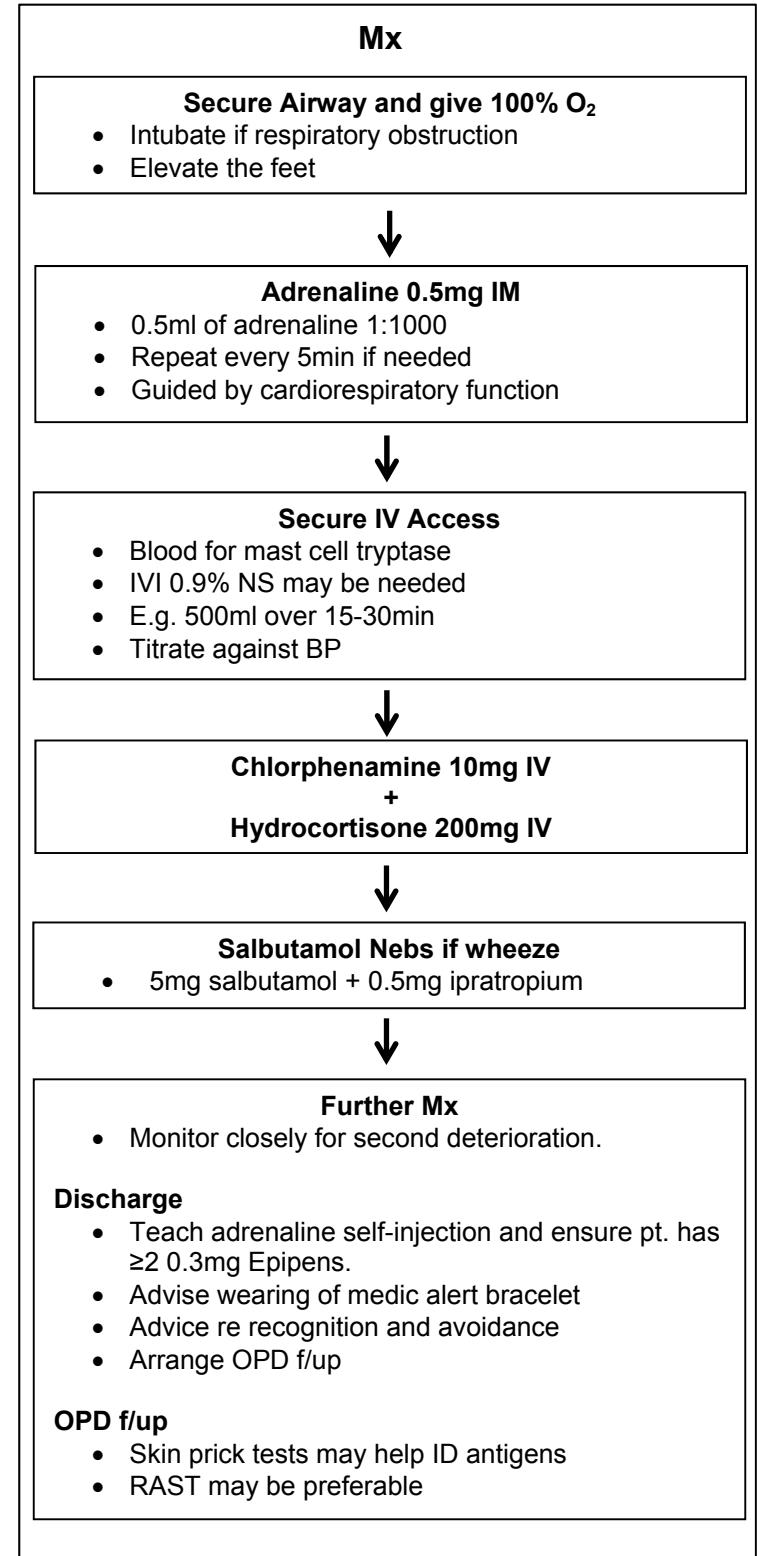
- Eosinophils recruited in early phase.
- Release enzymes and stimulate mast cells.
- Amplify and sustain the initial response

Common Precipitants

- Drugs: penicillin, contrast media
- Food: peanuts, eggs, fish, semen
- Latex
- Stings

Presentation

- Sweating, d/v
- Urticaria, itching, oedema
- Wheeze, laryngeal obstruction, cyanosis
- Tachycardia, hypotension
- Possible improvement and then deterioration as late phase initiates.



Narrow Complex Tachycardias = SVT

Definition: Rate >100bpm, QRS width < 120ms

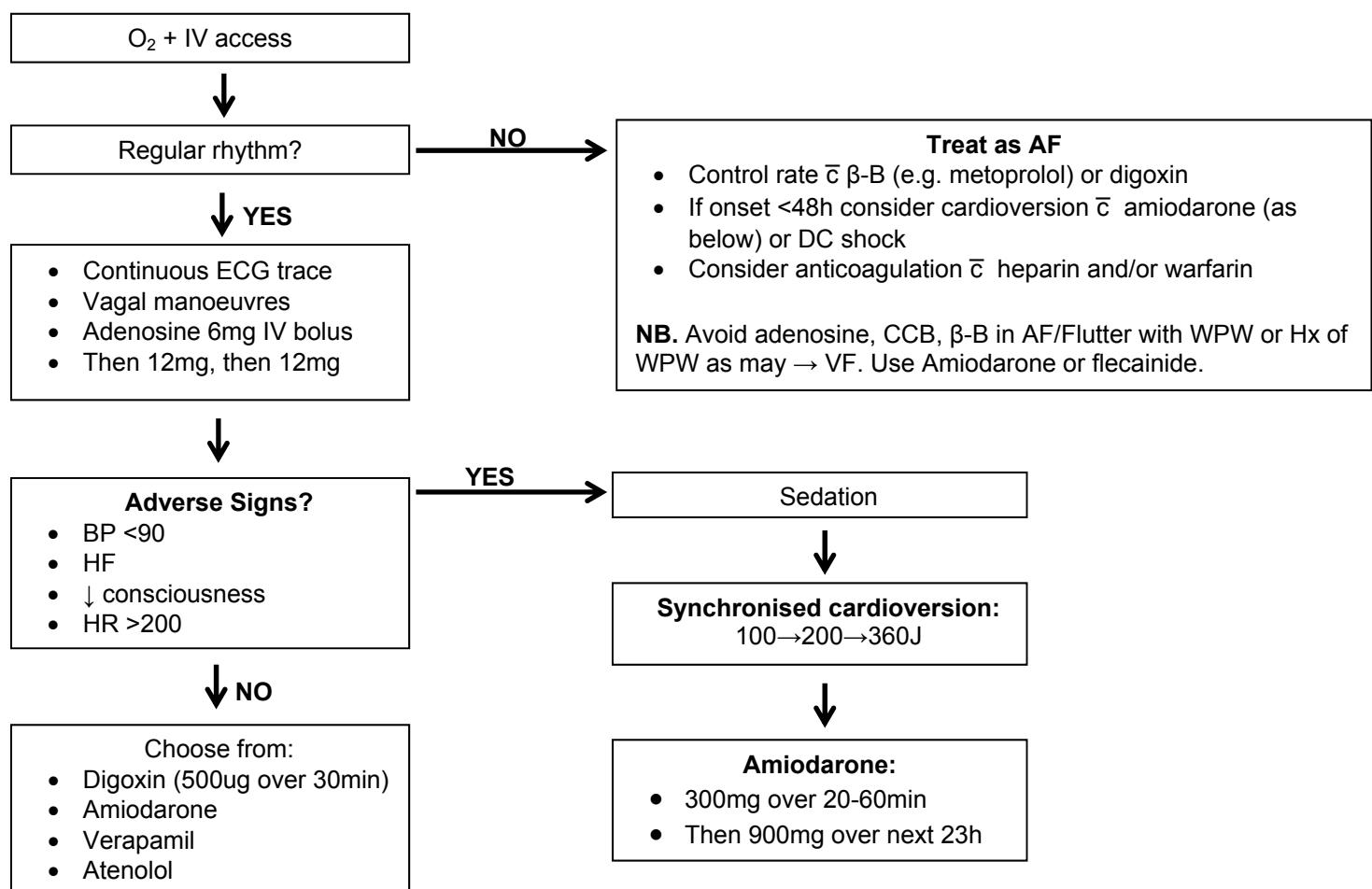
Differential

1. Sinus tachycardia
2. Atrial
 - AF
 - Atrial flutter
 - Atrial tachycardia
3. AV nodal re-entry tachycardia
4. AV re-entry tachycardia

Principles of Mx

- If pt. compromised → sedate + DC cardioversion
- Otherwise ID rhythm and Rx accordingly
 - Key to ID irregular rhythm = AF = different Rx
- Vagal manoeuvres (carotid sinus massage, valsalva) transiently ↑ AV block and may unmask underlying atrial rhythm.
- If manoeuvres unsuccessful, give adenosine while recording rhythm strip
 - → transient AV block, unmasking atrial rhythm
 - → cardioverts AVNRT/AVRT to sinus rhythm
- If adenosine fails, choose from:
 - Digoxin
 - Atenolol
 - Verapamil (not if on β-blocker)
 - Amiodarone
- If unsuccessful → DC cardioversion

Mx Flowchart



Adenosine

- MOA: temporary AVN block
- SEs: Transient chest tightness, dyspnoea, flushing, headache
- Relative CIs: asthma, 2nd/3rd degree block
- Interactions
 - fx ↑d by dipyridimole
 - fx ↓d by theophylline

Prophylaxis

- β -B
- AVRT: flecainide
- AVNRT: verapamil

Broad Complex Tachycardias

Definition: Rate >100bpm, QRS width > 120ms

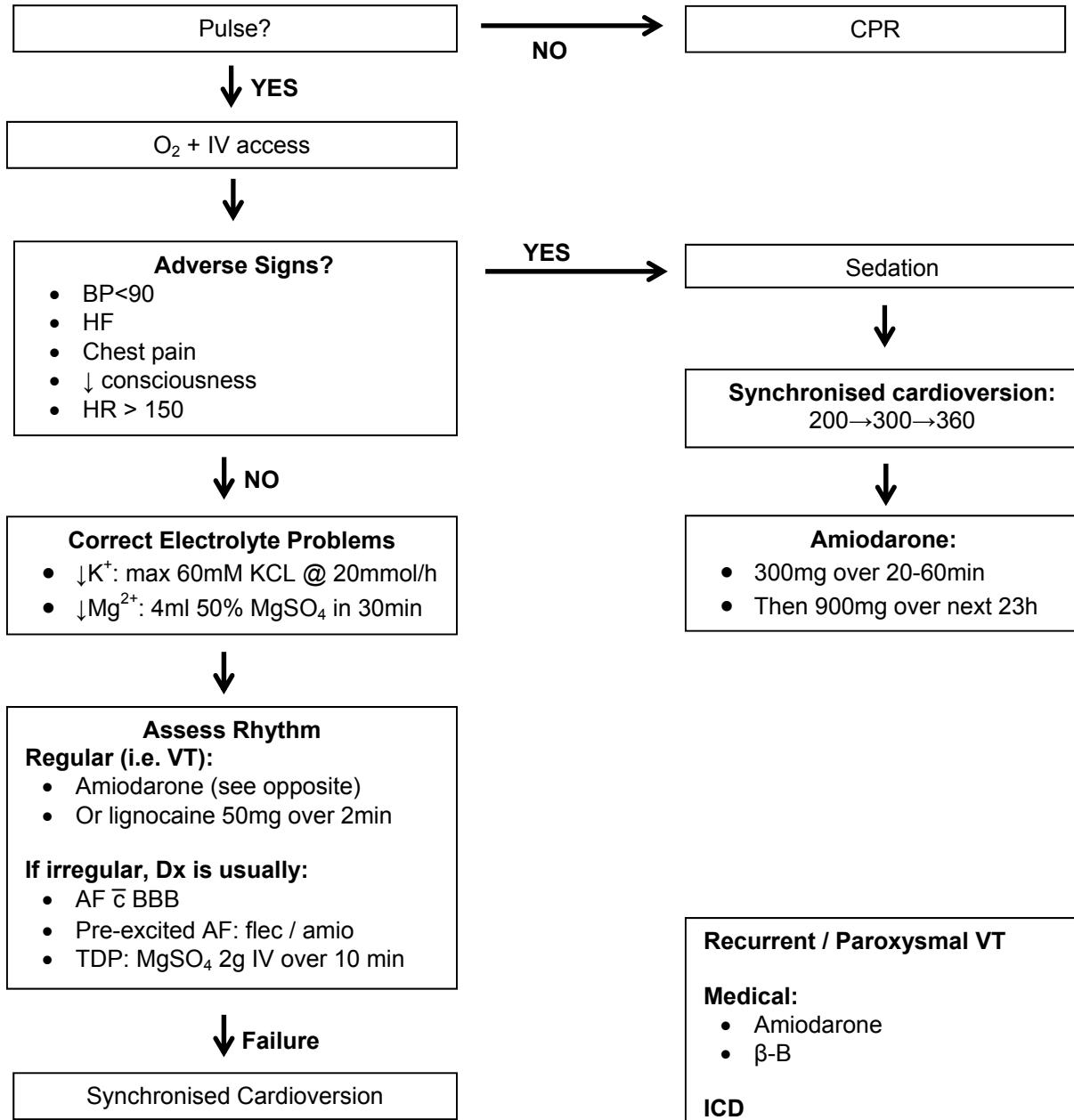
Differential

1. VT
2. Torsades de points
3. SVT $\overline{\text{C}}$ BBB

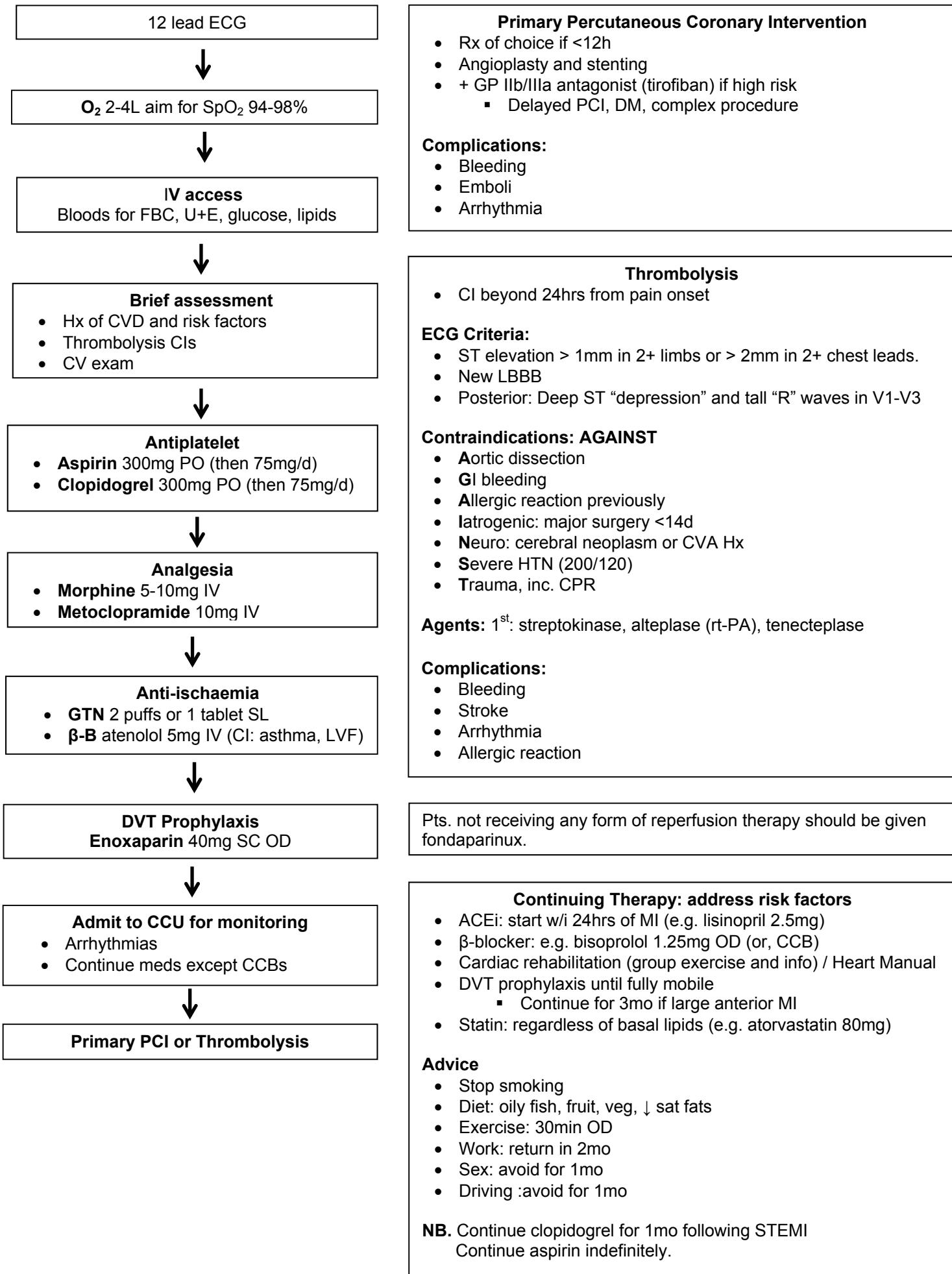
VT Causes: I'M QVICK

- Infarction (esp. $\overline{\text{C}}$ ventricular aneurysm)
- Myocarditis
- QT interval \uparrow
- Valve abnormality: mitral prolapse, AS
- Iatrogenic: digoxin, antiarrhythmics, catheter
- Cardiomyopathy (esp. dilated)
- $K\downarrow, Mg\downarrow, O_2\downarrow$, acidosis

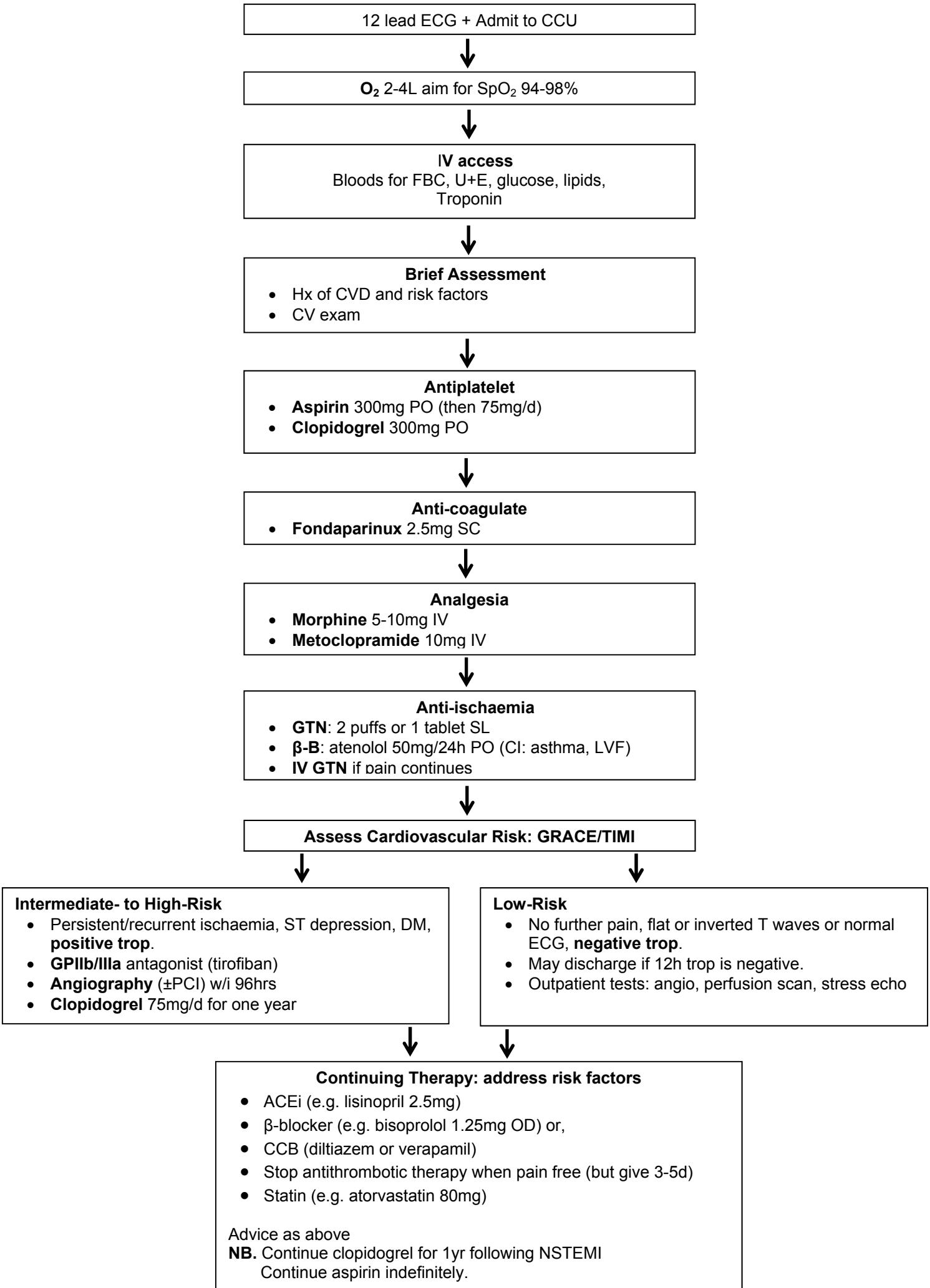
Mx Flowchart



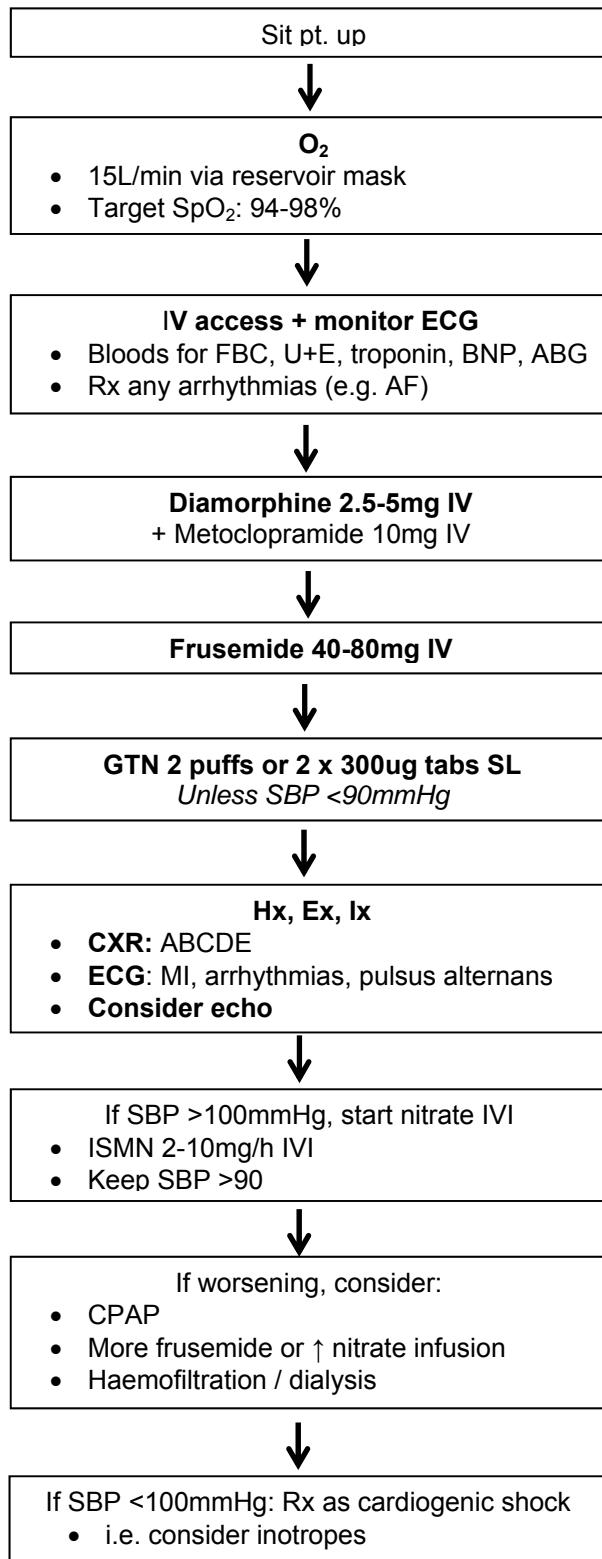
STEMI



NSTEMI + UA



Severe Pulmonary Oedema



Causes

Cardiogenic

- MI
- Arrhythmia
- Fluid overload: renal, iatrogenic

Non-cardiogenic

- ARDS: sepsis, post-op, trauma
- Upper airway obstruction
- Neurogenic: head injury

Symptoms

- Dyspnoea
- Orthopnea
- Pink frothy sputum

Signs

- Distressed, pale, sweaty, cyanosed
- ↑HR, ↑RR
- ↑JVP
- S3 / gallop rhythm
- Bibasal creps
- Pleural effusions
- Wheeze (cardiac asthma)

Differential

- Asthma/COPD
- Pneumonia
- PE

Monitoring Progress

- BP
- HR and RR
- JVP
- Urine Output
- ABG

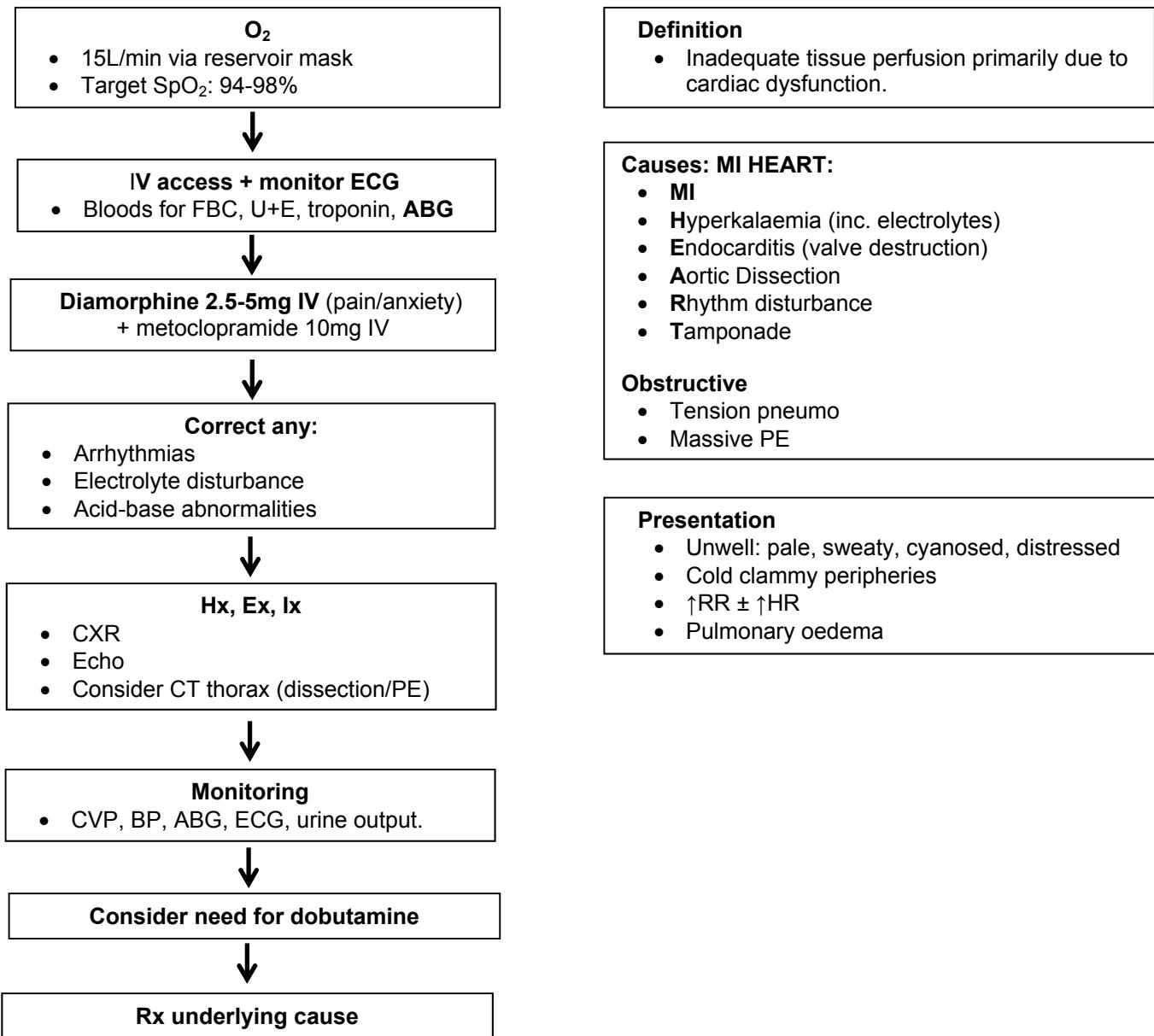
Continuing Therapy

- Daily weights
- DVT prophylaxis
- Repeat CXR
- Change to oral frusemide or bumetanide
- ACEi + β-B if heart failure
- Consider spironolactone
- Consider digoxin ± warfarin (esp. if in AF)

Morphine in Pulmonary Oedema

- Make pt. more comfortable
- Pulm venodilators → ↓ pre-load → optimise position on Starling Curve

Cardiogenic Shock



Tamponade

Causes:

- Trauma
- Lung/breast Ca
- Pericarditis
- MI
- Bacteria (e.g. TB)

Mx:

- ABCs
- Pericardiocentesis (preferably under echo guidance)

Signs:

- **Beck's triad:** ↓BP, ↑JVP, muffled heart sounds
- **Kussmaul's sign:** ↑JVP on inspiration
- **Pulsus paradoxus** (pulse fades on inspiration)

Ix:

- **Echo:** diagnostic
- **CXR:** globular heart

Meningitis

Features

Meningitic

- Headache
- Neck stiffness
 - Kernig's: Straightening leg → hip @ 90°
 - Brudzinski's: lifting head → lifting of legs
- Photophobia
- n/v

Neurological

- ↓ GCS → coma
- Seizures (20%)
- Focal neuro (20%): e.g. CN palsies

Septic

- Fever
- ↓BP, ↑HR
- ↑CRT
- Purpuric rash
- DIC

Abx Therapy

- Community: benpen 1.2g IV/IM
- <50: ceftriaxone 2g IVI/IM BD
- >50: ceftriaxone + ampicillin 2g IVI /4h
- If viral suspected: aciclovir

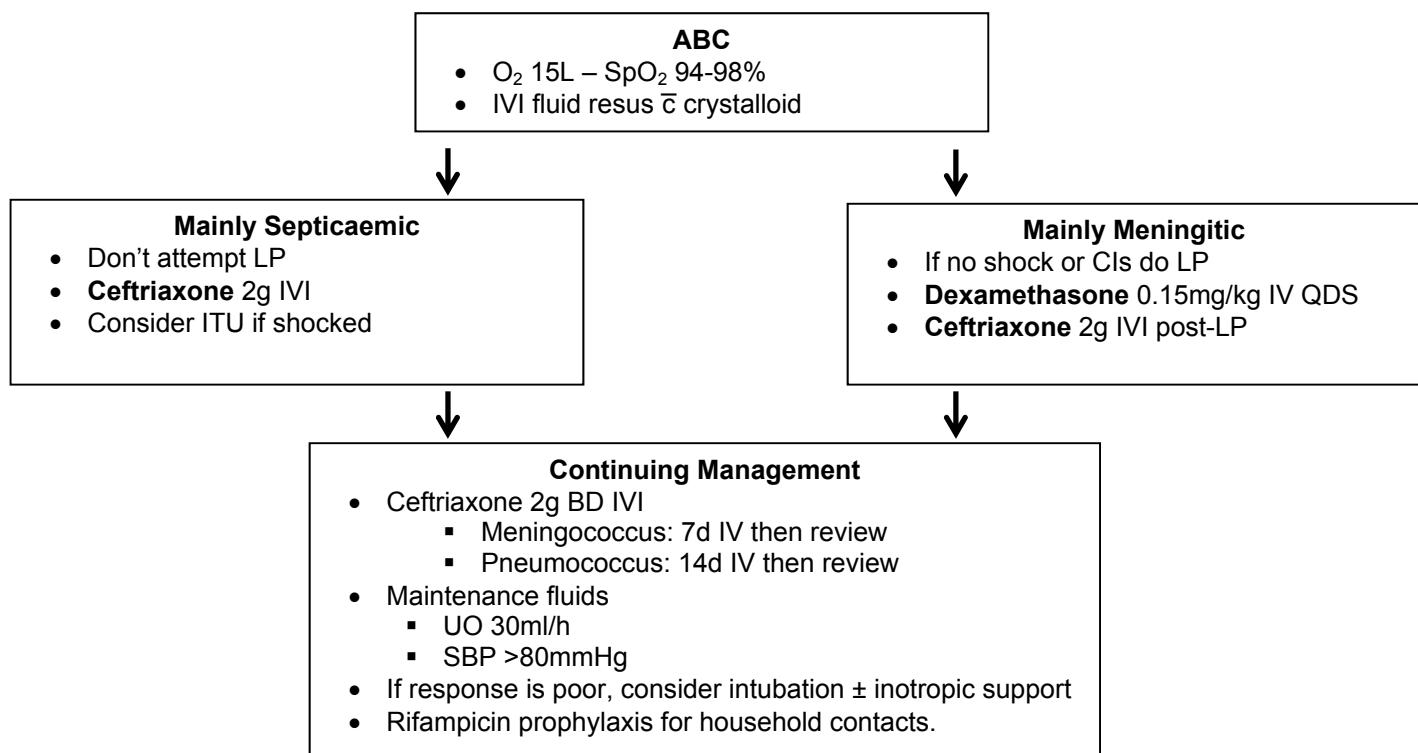
Organisms

- Viruses: enteroviruses (Coxsackie, echovirus), HSV2
- Meningococcus
- Pneumococcus
- Listeria
- Haemophilus
- TB
- Cryptococcus

Ix

- Bloods: FBC, U+Es, clotting, glucose, ABG
- Blood cultures
- LP: MCS, glucose, virology/PCR, lactate

Acute Management



ClIs to LP: Try LP Unless ContraINDicated

- Thrombocytopenia
- Lateness (delay in antibiotic admin)
- Pressure (signs of raised ICP)
- Unstable (Cardio + resp systems)
- Coagulation disorder
- Infection at LP site
- Neurology (focal neurological signs)

CSF Findings

Findings	Bacterial	TB	Viral
Appearance	Turbid	Fibrin web	Clear
Cells	PMN	Lympho / mononuc	Lympho / mononuc
Count	100-1000	10-1000	50-1000
Glucose	↓ (< ½ plasma)	↓ (< ½ plasma)	> ½ plasma
Protein (g/L)	↑↑ (>1.5)	↑↑↑ (1-5)	mild ↑ (<1)

Encephalitis

Presentation

- Infectious prodrome: fever, rash, LNs, cold sores, conjunctivitis, meningeal signs.
- Bizarre behaviour or personality change
- Confusion
- ↓ GCS → coma
- Fever
- Headache
- Focal neuro
- Seizures
- Hx of travel or animal bite

Causes

Usually viral

- HSV1/2
- CMV, EBV, VZV
- Arboviruses
- HIV

Non-viral

- Any bacterial meningitis
- TB
- Malaria
- Lyme disease

Ix

- **Bloods:** cultures, viral PCR, malaria film
- **Contrast CT:** focal bilat temporal involvement suggests HSV
- **LP:** ↑ CSF protein, lymphocytes, PCR
- **EEG:** shows diffuse abnormalities, may confirm Dx

Mx

- Aciclovir STAT: 10mg/kg/8h IVI over 1h for 14/7
- Supportive measures in HDU/ITU
- Phenytoin for seizures

Prognosis

- 70% mortality if untreated

w/o fever, consider encephalopathy

- ↓ glucose
- Hepatic
- DKA
- Drugs
- SLE
- Uraemia
- Hypoxic brain injury
- Beri-Beri

Cerebral Abscess

Pre-disposing Factors

- Infection: ear, sinus, dental or periodontal
- Skull #
- Congenital heart disease
- Endocarditis
- Bronchiectasis
- Immunosuppression

Organisms

- Frontal sinus/teeth – strep. Milleri, oropharyngeal anaerobes
- Ear – Bacteroides, other anaerobes

Signs

- Seizures
- Fever
- Localizing signs
- Signs of ↑ ICP
- Signs of infection elsewhere

Ix

- CT/MRI – ring-enhancing lesion
- ↑WCC, ↑ESR

Rx

- Neurosurgical referral
- Abx – e.g. ceftriaxone
- Treat ↑ ICP

Status Epilepticus

Definition

- Seizure lasting >30min, or
- Repeated seizures w/o intervening consciousness

Ix

- BM
- **Bloods:** glucose, ABG, U+E, FBC, Ca²⁺
- ECG, EEG
- **Consider:** AED levels, tox screen, LP, βhCG, CT

Drugs

Lorazepam

- 2-4mg IV bolus over 30s
- 2nd dose if no response w/i 2min
- Alternatives:
 - Diazepam 10mg IV/PR (20mg max)
 - Midazolam 10mg buccal

Phenytoin

- 18mg/kg IVI @ 50mg/min
- 100mg/6-8h maintenance
- Monitor ECG and BP
- CI: bradycardia or heart block

Diazepam Infusion

- 100mg in 500ml 5% dex @ 40ml/hr (3mg/kg/24h)

Dexamethasone

- 10mg IV if vasculitis / cerebral oedema (tumour) possible

Acute Management



ABC

- Oral / nasal airway, intubate
- Suction
- 100% O₂
- Capillary blood glucose



IV Access + Bloods

- U+E, LFT, FBC, Glucose, Ca²⁺
- AED levels
- Tox screen



Reverse Potential Causes

- Thiamine 250mg IV if EtOH
- 100ml 20% glucose unless glucose known to be normal



Slow IV Bolus Phase

- Lorazepam 2-4mg IV
- 2nd dose if no response w/i 2min



IV Infusion Phase

- Phenytoin 18mg/kg IVI (then 100mg/6-8h)
- Or, diazepam 100mg in 500ml 5% dex IVI

RSI Phase

Never spend >20min c someone in status w/o getting an anaesthetist

Head Injury

Initial Mx

1^o Survey

- **A:** ? intubation, immobilise C-spine
- **B:** 100% O₂, RR
- **C:** IV access, BP, HR
- **D:** GCS, pupils
- Treat seizures
 - Lorazepam 2-4mg IV
 - Phenytoin 18mg/kg IVI then 100mg/6-8h
- **E:** expose pt. and look for other obvious injuries

2^o Survey

- Look for:
 - Lacerations
 - Obvious facial/skull deformity
 - CSF leak from nose or ears
 - Battle's sign, Raccoon eyes
 - Blood behind TM
 - C-spine tenderness ± deformity
- Head-to-toe examination for other injuries
- Log role

Hx if possible

- How and when?
- GCS and other vitals immediately after injury
- Headache, fits, vomiting, amnesia, EtOH

Ix

- **Bloods:** FBC, U+E, glucose, clotting, EtOH level, ABG
- ? CT head + c-spine

Rx

- Neurosurgical opinion if signs of ↑ICP, CT evidence of intracranial bleed significant skull #
- Admit if:
 - Abnormalities on imaging
 - Difficult to assess: EtOH, post-ictal
 - Not returned to GCS 15 after imaging
 - CNS signs: vomiting, severe headache
- Neuro-obs half-hrly until GCS 15
 - GCS
 - Pupils
 - HR, BP
 - RR, SpO₂
 - Temperature

Discharge Advice

- Stay with someone for first 48hrs
- Give advice card advising return on:
 - Confusion, drowsiness, unconsciousness
 - Visual problems
 - Weakness
 - Deafness
 - V. painful headache that won't go away
 - Vomiting
 - Fits

Intubate

- GCS ≤ 8
- PaO₂ <9KPa on air / <13KPa on O₂ or PCO₂ >6KPa
- Spontaneous hyperventilation: PCO₂ <4KPa
- Respiratory irregularity

CT head guidelines: BANGS LOC

- **Break:** open, depressed or base of skull
- **Amnesia** > 30min retrograde
- **Neuro deficit** or seizure
- **GCS:** <13 @ any time or <15 2h after injury
- **Sickness:** vomited > once
- **LOC** or any amnesia and any of:
 - Dangerous mechanism: RTA, great height
 - Age ≥ 65
 - Coagulopathy (inc. warfarin)

Risk of Intracranial Haematoma in Adults:

- Fully conscious, no skull # = <1:1000
- Confused, no skull # = 1:100
- Fully conscious, skull # = 1:30
- Confused, skull # = 1:4

GCS

Eyes: 4

- 4 – Spontaneous eye opening
- 3 – Open to voice
- 2 – Open to pain
- 1 – No opening

Verbal: 5

- 5 – Orientated conversation
- 4 – Confused conversation
- 3 – Inappropriate speech
- 2 – Incomprehensible sounds
- 1 – No speech

Motor: 6

- 6 – Obeys commands
- 5 – Localises pain
- 4 – Withdraws to pain
- 3 – Decorticate posturing to pain (flexor)
- 2 – Decerebrate posturing to pain (extensor)
- 1 – No movement

Raised ICP

Types of Cerebral Oedema

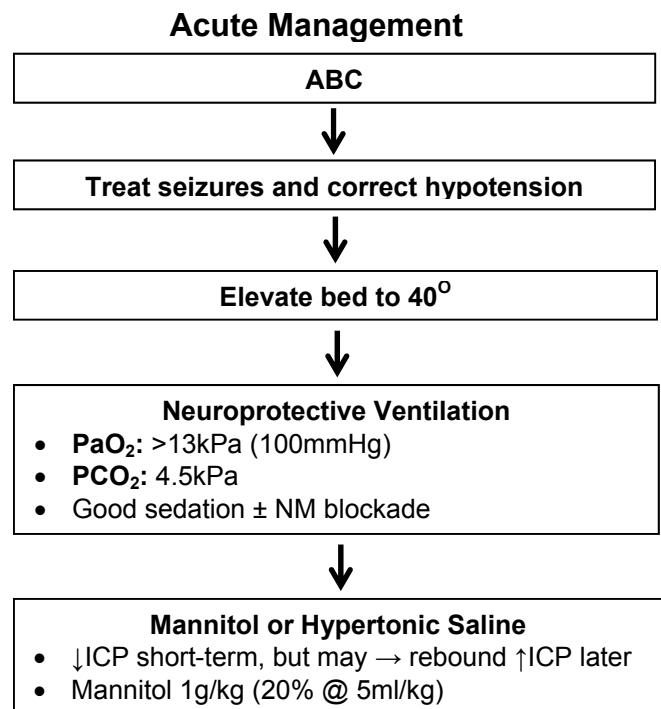
1. Vasogenic (\uparrow cap permeability): trauma, tumour, ischaemia, infection
2. Cytotoxic: e.g. from hypoxia
3. Interstitial: e.g. obstructive hydrocephalus, $\downarrow \text{Na}^+$

Causes

- Haemorrhage
- Tumours
- Infection: meningitis, encephalitis, abscess
- Hydrocephalus
- Status
- Cerebral oedema

Signs and Symptoms

- Headache
- n/v
- Seizures
- Drowsiness \rightarrow coma
- Cushing's reflex: $\uparrow \text{BP}$, $\downarrow \text{HR}$, irregular breathing
- 6th CN palsy (may be false localising)
- Cheyne-Stokes respiration
- Pupils – constriction \rightarrow dilatation
- Papilloedema, loss of venous pulsation @ disc



Herniation Syndromes

Tonsillar (Coning)

- \uparrow pressure in posterior fossa \rightarrow displacement of cerebellar tonsils through foramen magnum
- \rightarrow compression of brainstem and cardioresp centres in medulla
- CN6 palsy, upgoing plantars \rightarrow irregular breathing \rightarrow apnoea

Transtentorial / uncal

- Lateral supratentorial mass \rightarrow compression of ipsilateral inferomedial temporal lobe (uncus) against free margin of tentorium cerebelli.
- Ipsilateral CN3 palsy: mydriasis (dilation) then down-and-out
- Contralateral hemiparesis
- Compression of contralateral corticospinal tracts \rightarrow ipsilateral hemiparesis (Kernohan's Notch)

Subfalcine

- Frontal mass
- Displacement of cingulate gyrus (medial frontal lobe) under falx cerebri
- Compression of ACA \rightarrow stroke
 - Contralateral motor/sensory loss in legs>arms
 - Abulia (pathological laziness)

Acute Severe Asthma

Presentation

- Acute breathlessness and wheeze

Hx

- Precipitant: infection, travel, exercise?
- Usual and recent Rx?
- Previous attacks and severity: ICU?
- Best PEFR?

Ix

- PEFR
- ABG
 - PaO_2 usually normal or slightly ↓
 - PaCO_2 ↓
 - If PaCO_2 ↑: send to ITU for ventilation
- FBC, U+E, CRP, blood cultures

Assessment

Severe

- PEFR <50%
- RR >25
- HR >110
- Can't complete sentence in one breath

Life Threatening

- PEFR <33%
- SpO_2 <92%, PCO_2 >4.6kPa, PaO_2 <8kPa
- Cyanosis
- Hypotension
- Exhaustion, confusion
- Silent chest, poor respiratory effort
- Tachy-/brady-/arrhythmias

Differential

- Acute exacerbation of COPD
- Pneumothorax
- Pulmonary oedema

Admission Criteria

- Life-threatening attack
- Feature of severe attack persisting despite initial Rx
- May discharge if PEFR > 75% 1h after initial Rx

Discharge When

- Been stable on discharge meds for 24h
- PEFR > 75% & diurnal variability < 25%

Discharge Plan

- TAME pt.
- PO steroids for 5d
- GP appointment w/i 1 wk.
- Resp clinic appointment w/i 1mo

Mx

O_2 , Nebs and Steroids

1. Sit-up
2. 100% O_2 via non-rebreathe mask (aim for 94-98%)
3. Nebulised salbutamol (5mg) and ipratropium (0.5mg)
4. Hydrocortisone 100mg IV or pred 50mg PO (or both)
5. Write "no sedation" on drug chart

If Life Threatening

- Inform ITU
- MgSO_4 2g IVI over 20min
- Nebulised salbutamol every 15min (monitor ECG)

If Improving

- Monitor: SpO_2 @ 92-94%, PEFR
- Continue pred 50mg OD for 5 days
- Nebulised salbutamol every 4hrs

IV Rx if No Improvement in 15-30min:

- Nebulised salbutamol every 15min (monitor ECG)
- Continue ipratropium 0.5mg 4-6hrly
- MgSO_4 2g IVI over 20min
- Salbutamol IVI 3-20ug/min
- Consider Aminophylline
 - Load: 5mg/kg IVI over 20min
 - Unless already on theophylline
 - Continue: 0.5mg/kg/hr
 - Monitor levels
- ITU transfer for invasive ventilation

Monitoring

- PEFR every 15-30min
 - Pre- and post-β agonist
- SpO_2 : keep >92%
- ABG if initial PaCO_2 normal or ↑

Acute Exacerbation of COPD

Causes

- Viral URTI (30%)
- Also bacterial infections

Presentation

- Cough + sputum
- Breathlessness
- Wheeze

Hx

- Smoking status
- Exercise capacity
- Current treatment
- Previous exacerbations

Ix

- PEFR
- **Bloods:** FBC, U+E, ABG, CRP, cultures
- Sputum culture
- CXR: infection, pneumothorax
- ECG

Differential

- Pneumothorax
- Pulmonary oedema
- PE
- Asthma

Discharge

- Spirometry
- Establish optimal maintenance therapy
- GP and specialist f/up
- Prevention using home oral steroids and Abx
- Pneumococcal and Flu vaccine
- Home assessment

Management

Controlled O₂ Therapy

- Sit-up
- 24% O₂ via Venturi mask: Target SpO₂ 88-92%
- Vary FiO₂ and SpO₂ target according to ABG
- Aim for PaO₂ >8 and ↑ in PCO₂ of <1.5kPa



Nebulised Bronchodilators

- Air driven → nasal specs
- Salbutamol 5mg/4h
- Ipratropium 0.5mg/6h



Steroids (IV and PO)

- Hydrocortisone 200mg IV
- Prednisolone 40mg PO for 7-14d



Abx

- If evidence of infection
- Doxy 200mg PO STAT then 100mg OD PO for 5d

NIV if no response:

- Repeat nebs and consider aminophylline IV
- Consider NIV (BiPAP) if pH<7.35 and/or RR >30
- Consider invasive ventilation if pH<7.26
 - Depends on pre-morbid state: exercise capacity, home O₂, comorbidity

Pulmonary Embolism

Causes

- Usually arise from DVTs in proximal leg or iliac veins
- Rarely:
 - Right ventricle post MI
 - Septic emboli in right sided endocarditis

Risk Factors: SPASMODICAL

- Sex: F
- Pregnancy
- Age: ↑
- Surgery (classically 10d post-op straining at stool)
- Malignancy
- Oestrogen: OCP/HRT
- DVT/PE previous Hx
- Immobility
- Colossal size
- Antiphospholipid Abs
- Lupus Anti-coagulant

Presentation

- Symptoms and signs depend on size, number and distribution of emboli

Symptoms

- Dyspnoea
- Pleuritic pain
- Haemoptysis
- Syncope

Signs

- Fever
- Cyanosis
- Tachycardia, tachypnoea
- RHF: hypotension, ↑JVP, loud P₂
- Evidence of cause: DVT

Ix

- Bloods:** FBC, U+E, clotting, D-dimers
- ABG:** normal or ↓PaO₂ and ↓PaCO₂, ↑pH
- CXR:** normal or oligaemia, linearatectasis
- ECG:** sinus tachycardia, RBBB, right ventricular strain (inverted T in V1-V4)
 - S1, Q3, T3 is rare
- Doppler US:** thigh and pelvis (+ve in 60%)
- CTPA** + venous phase of legs and pelvis
 - 85-95% sensitivity
- V/Q scan no longer used

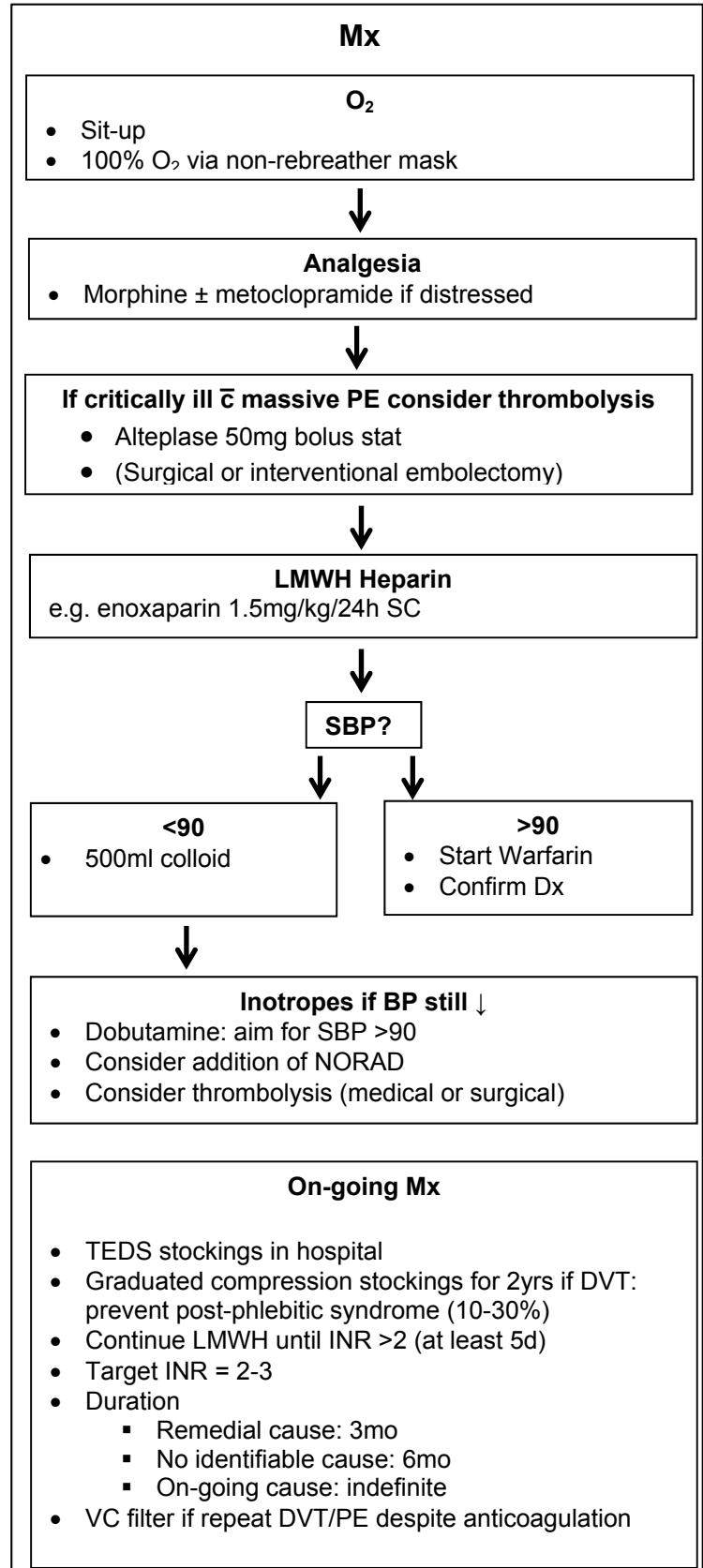
Dx

- Assess probability using Wells' Score
- Low-probability → perform D-dimers
 - Negative → excludes PE
 - Positive → CTPA
- High probability → CTPA

NB. -ve D-dimer has 95% NPV for PE

Prevention

- Risk assessment for all pts
- TEDS
- Prophylactic LMWH
- Avoid OCP/HRT if @ risk



Pneumothorax

Definition

- Accumulation of air in the pleural space → 2^o lung collapse.

Classification

- **Closed:** intact chest wall and air leaks from lung into pleural cavity.
- **Open:** defect in the chest wall allows communication between PTX and exterior: may be sucking.
- **Tension:** air enters pleural cavity through one-way valve and cannot escape → mediastinal compression.

Causes

Spontaneous

- 1^o: no underlying lung disease
 - Young, thin men (ruptured subpleural bulla)
 - Smokers
- 2^o: underlying lung disease
 - COPD
 - Marfan's, Ehler's Danlos
 - Pulmonary fibrosis, sarcoidosis

Trauma

- Penetrating
- Blunt ± rib #s

Iatrogenic

- Subclavian CVP line insertion
- Positive pressure ventilation
- Transbronchial biopsy
- Liver biopsy

Presentation

Symptoms

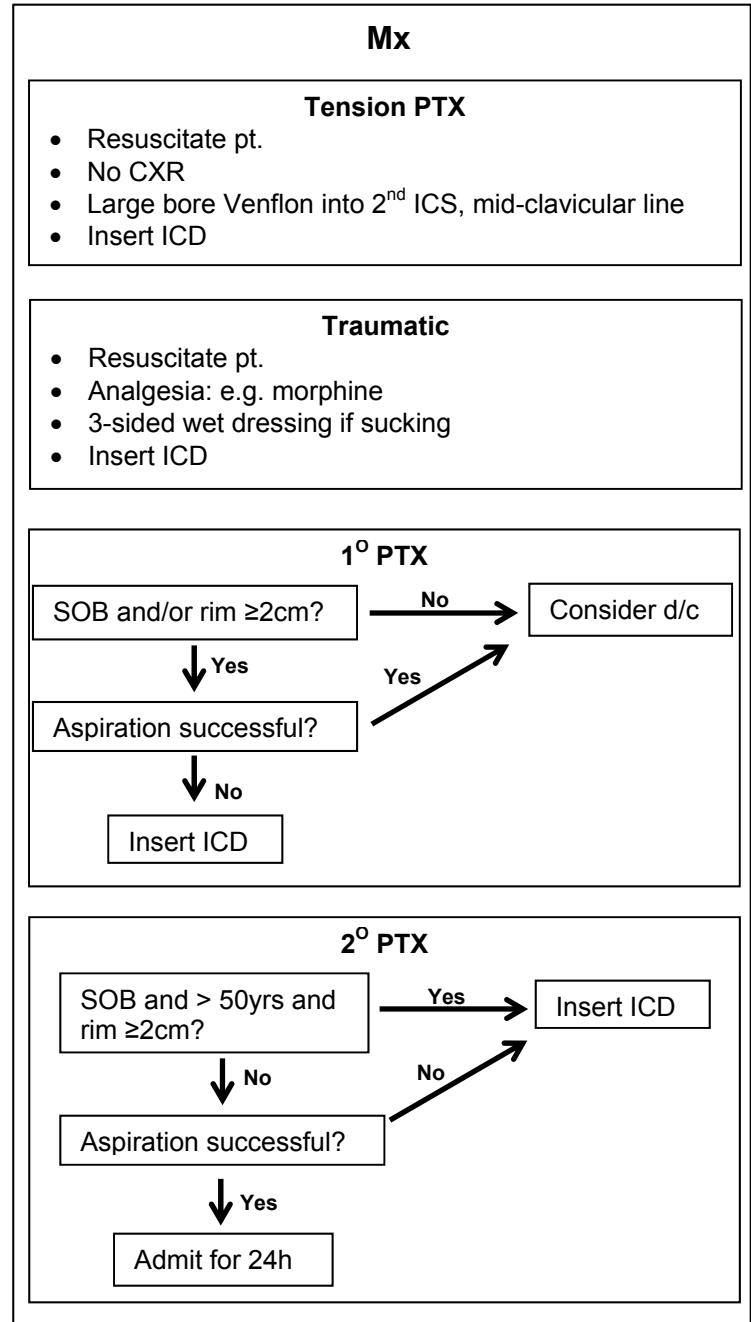
- Sudden onset
- Dyspnoea
- Pleuritic chest pain
- **Tension:** respiratory distress, cardiac arrest

Signs

- **Chest**
 - ↓ expansion
 - Resonant percussion
 - ↓ breath sounds
 - ↓VR
- **Tension:** ↑JVP, mediastinal shift, ↑HR, ↓BP
- **Crepitus:** surgical emphysema

Ix

- ABG
- US
- CXR (expiratory film may be helpful)
 - Translucency + collapse (2cm rim = 50% vol loss)
 - Mediastinal shift (away from PTX)
 - Surgical emphysema
 - **Cause:** rib #s, pulmonary disease (e.g. bullae)



Upper GI Bleeding

Hx

- Previous bleeds
- Dyspepsia, known ulcers
- Liver disease or oesophageal varices
- Dysphagia, wt. loss
- Drugs and EtOH
- Co-morbidities

o/e

- Signs of CLD
- PR:melaena
- Shock?
 - Cool, clammy, CRT>2s
 - ↓BP (<100) or postural hypotension (>20 drop)
 - ↓ urine output (<30ml/h)
 - Tachycardia
 - ↓GCS

Common Causes

- PUD: 40% (DU commonly)
- Acute erosions / gastritis:20%
- Mallory-Weiss tear: 10%
- Varices: 5%
- Oesophagitis: 5%
- Ca Stomach / oesophagus:<3%

Rockall Score: (Prof T Rockall, St. Mary's)

- Prediction of re-bleeding and mortality
- 40% of re-bleeders die
- Initial score pre-endoscopy
 - Age
 - Shock: BP, pulse
 - Comorbidities
- Final score post-endoscopy
 - Final Dx + evidence of recent haemorrhage
 - Active bleeding
 - Visible vessel
 - Adherent clot
- Initial score ≥3 or final >6 are indications for surgery

Oesophageal Varices

- Portal HTN → dilated veins @ sites of porto-systemic anastomosis: L. gastric and inferior oesophageal veins
- 30-50% of portal HTN will bleed from varices
- Overall mortality 25%: ↑ severity of liver disease.

Causes of portal HTN

- Pre-hepatic: portal vein thrombosis
- Hepatic: cirrhosis (80% in UK), schisto (commonest worldwide), sarcoidosis.
- Post-hepatic: Budd-Chiari, RHF, constrict pericarditis

Bleed Prevention

- 1^o: β-B, repeat endoscopic banding
- 2^o: β-B, repeat banding, TIPSS

Transjugular Intrahepatic Porto-Systemic Shunt (TIPSS)

- IR creates artificial channel between hepatic vein and portal vein → ↓ portal pressure.
- Colapinto needle creates tract through liver parenchyma which is expand using a balloon and maintained by placement of a stent.
- Used prophylactically or acutely if endoscopic therapy fails to control variceal bleeding.

Management

Resuscitate

- Head-down.
- 100% O₂, protect airway
- 2 x 14G cannulae + IV crystalloid infusion up to 1L.
- **Bloods:** FBC, U+E (↑ urea), LFTs, clotting, x-match 6u, ABG, glucose



Blood if remains shocked

- Group specific or O- until X-matched



Variceal Bleed

- Terlipressin IV (splanchnic vasopressor)
- Prophylactic Abx: e.g. ciprofloxacin 1g/24h



Maintenance

- Crystalloid IVI, transfuse if necessary (keep Hb≥10)
- Catheter + consider CVP (aim for >5cm H₂O)
- Correct coagulopathy: vit K, FFP, platelets
- Thiamine if EtOH
- Notify surgeons of severe bleeds



Urgent Endoscopy

Haemostasis of vessel or ulcer:

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

Variceal bleeding:

- 2 of: banding, sclerotherapy, adrenaline, coagulation
- Balloon tamponade → Sengstaken-Blakemore tube
 - Only used if exsanguinating haemorrhage or failure of endoscopic therapy
- TIPSS if bleeding can't be stopped endoscopically



After endoscopy

- Omeprazole IV + continuation PO (↓s re-bleeding)
- Keep NBM for 24h → clear fluids → light diet @ 48h
- Daily bloods: FBC, U+E, LFT, clotting
- H. pylori testing and eradication
- Stop NSAIDs, steroids et.c.

Indications for Surgery

- Re-bleeding
 - Bleeding despite transfusing 6u
 - Uncontrollable bleeding at endoscopy
 - Initial Rockall score ≥3, or final >6.
- Open stomach, find bleeder and underrun vessel.

NB. Avoid 0.9% NS in uncompensated liver disease (worsens ascites). Use blood or albumin for resus and 5% dex for maintenance.

Acute Renal Failure

Common Causes

- Pre-renal: shock (e.g. sepsis, hypovolaemia), HRS
- Renal: ATN, TIN, GN
- Post-renal: Stone, neoplasm, catheter

Presentation

- Usually presents in the context of critical illness
- Uraemia
- Hyperkalaemia
- Acidosis
- Oedema and ↑BP

Ix

- **Bloods:** FBC, U+E, LFT, glucose, clotting, Ca, ESR
- **ABG:** hypoxia (oedema), acidosis, ↑K⁺
- **GN screen:** if cause unclear
- **Urine:** dip, MCS, chemistry (U+E, CRP, osmolality, BJP)
- **ECG:** hyperkalaemia
- **CXR:** pulmonary oedema
- **Renal US:** Renal size, hydronephrosis

Hyperkalaemia

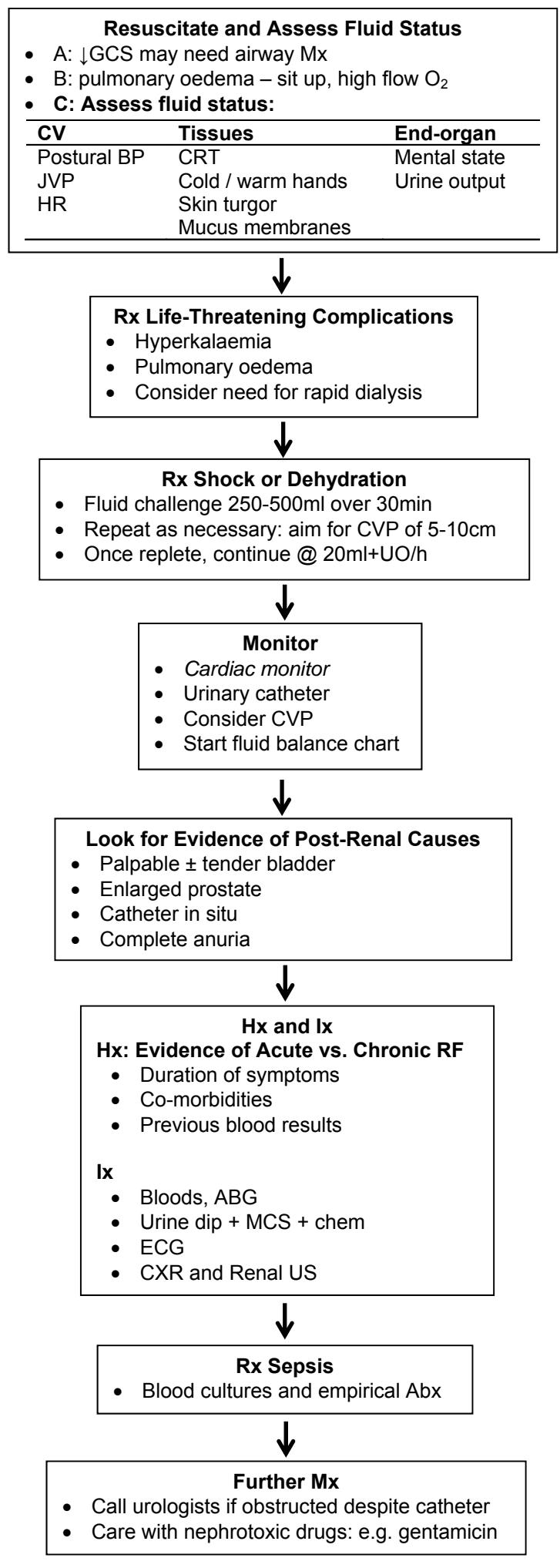
- **ECG Features (in order)**
 - Peaked T waves
 - Flattened P waves
 - ↑ PR interval
 - Widened QRS
 - Sine-wave pattern → VF
- **Mx**
 - 10ml 10% calcium gluconate
 - 50ml 50% glucose + 10u insulin (Actrapid)
 - Salbutamol 5mg nebulizer
 - Calcium resonium 15g PO or 30g PR
 - Haemofiltration (usually needed if anuric)

Pulmonary Oedema

- Sit up and give high-flow O₂
- Morphine 2.5mg IV (± metoclopramide 10mg IV)
- Frusemide 120-250mg IV over 1h
- GTN spray ± ISMN IVI (unless SBP <90)
- If no response consider:
 - CPAP
 - Haemofiltration / haemodialysis ± venesection

Indications for Acute Dialysis (AEIOU)

1. Persistent hyperkalaemia (>7mM)
2. Refractory pulmonary oedema
3. Symptomatic uraemia: encephalopathy, pericarditis
4. Severe metabolic acidosis (pH <7.2)
5. Poisoning (e.g. aspirin)



Poisoning: Recognition and Management

Drug	Features	Mx
Benzodiazepines	↓ GCS Respiratory depression	Flumazenil
β-Blockers	Severe bradycardia or hypotension	Atropine
Cyanide	Inhibits the cytochrome system Almond smell Phase 1: Anxiety ± confusion Phase 2: ↓/↑ pulse Phase 3: Fits, coma	Dicobalt edentate
Carbon monoxide	Headache, dizziness, nausea Hypoxaemia (SpO_2 may be normal) Metabolic acidosis	Hyperbaric O_2
Digoxin	↓ GCS Yellow-green visual halos Arrhythmias	Anti-digoxin antibodies
Ethanol	↓ GCS Respiratory depression	
Ethylene glycol	↑ AG metabolic acidosis with ↑ OG Intoxication with no visual disturbance Found in antifreeze	Ethanol Haemodialysis
Heparin	Bleeding	Protamine
Iron	Nausea, vomiting, abdo pain	Desferrioxamine
Lithium	n/v Ataxia, coarse tremor Confusion Polyuria and renal failure	Saline
Methanol	↑ AG metabolic acidosis with ↑ OG Intoxication with visual disturbance	Ethanol Haemodialysis
Opiates	Respiratory depression ↓GCS Pin-point pupils	Naloxone
Organophosphates e.g. malathion	SLUDGEM	Atropine + Pralidoxime
Tricyclics	↑ QTc → Torsade de pointes Metabolic acidosis Anticholinergic effects	Activated charcoal NaHCO_3 IV
Warfarin	Major bleed	Vit K IV Prothrombin complex or (FFP)

Aspirin

Effects

- Respiratory stimulant → respiratory alkalosis
- Uncouples oxidative phosphorylation → met acidosis

Presentation

- Vomiting and dehydration
- Hyperventilation
- Tinnitus, vertigo
- Hyper- or hypo-glycaemia
- Respiratory alkalosis initially then lactic acidosis
 - Mixed picture usually

Mx

- Activated charcoal if <1h since ingestion
- **Bloods**
 - Paracetamol and salicylate levels
 - Glucose, U+E, LFTs, INR, ABG
- **Alkalise urine:** $\text{NaHCO}_3 \pm \text{KCl}$
- **Haemodialysis** may be needed

Paracetamol

Effects

- Normal metabolism overloaded and paracetamol converted to highly toxic NAPQI by CyP450.
- NAPQI can be detoxified by glutathione conjugation
 - Overwhelmed in OD

Presentation

- Vomiting, RUQ pain
- Jaundice and encephalopathy ± liver failure
- Cerebral oedema → ↑ ICP
 - ↓HR, decerebrate posture, poor pupil responses

Mx

- Activated charcoal if <1h since ingestion
- **Bloods**
 - Paracetamol level 4h post ingestion
 - Glucose, U+E, LFTs, INR, ABG
- **NAC:** if levels above treatment line on graph

Diabetic Ketoacidosis

Pathogenesis

Ketogenesis

- ↓ insulin → ↑ stress hormones and ↑ glucagon
- → ↓ glucose utilisation + ↑ fat β-oxidation
- ↑ fatty acids → ↑ ATP + generation of ketone bodies.

Dehydration

- ↓ insulin → ↓ glucose utilisation + ↑ gluconeogenesis → severe hyperglycaemia
- → osmotic diuresis → dehydration
- Also, ↑ ketones → vomiting

Acidosis

- Dehydration → renal perfusion
- Hyperkalaemia

Precipitants

- Infection / stress ± stopping insulin
- New T1DM

Presentation

- Abdo pain + vomiting
- Gradual drowsiness
- Sighing "Kussmaul" hyperventilation
- Dehydration
- Ketotic breath

Dx

- Acidosis ($\uparrow AG$): pH <7.3 ($\pm HCO_3 <15mM$)
- Hyperglycaemia: $\geq 11.1mM$ (or known DM)
- Ketonaemia: $\geq 3mM$ ($\geq 2+$ on dipstick)

Ix

- Urine: ketones and glucose, MCS
- Cap glucose and ketones
- VBG: acidosis + $\uparrow K$
- Bloods: U+E, FBC, glucose, cultures
- CXR: evidence of infection

Subtleties

- Hyponatraemia is the norm
 - Osmolar compensation for hyperglycaemia
 - $\uparrow/\downarrow Na$ indicates severe dehydration
- Avoid rapid ↓ in insulin once glucose normalised
 - Glucose decreases faster than ketones and insulin is necessary to get rid of them.
- Amylase is often ↑ (up to 10x)
- Excretion of ketones → loss of potential bicarbonate → hyperchloraemic metabolic acidosis after Rx

Complications

- Cerebral oedema: excess fluid administration
 - Commonest cause of mortality
- Aspiration pneumonia
- Hypokalaemia
- Hypophosphataemia → resp and skeletal muscle weakness
- Thromboembolism

Mx: in HDU

- Gastric aspiration
- Rehydrate
- Insulin infusion
- Potassium replacement

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Management

Fluids

- 0.9% NS infusion via large bore cannula
 - SBP<90 → 1L stat + more until SBP >90
 - SBP>90 → 1L over 1h
- Then: 1L over next 2h, 1L/2h, 1L/4h, 1L/4h, 1L/6h
- Add 10% dextrose 1L/8h when glucose <14mM

Start Potassium Replacement in 2nd Bag of Fluids

- $>5.5mM$ → Nil
- 3.5-5.5mM → 40mM/L
- $<3.5mM$ → consult senior for review



Insulin Infusion

- 0.1u/kg/h Actrapid (6u if no wt., max 15u)



Assessment

- Hx + full examination
- Investigations: capillary, urine, blood, imaging



Additional Measures

- Urinary catheter (aim: 0.5ml/kg/hr)
- NGT if vomiting or $\downarrow GCS$
- Thromboprophylaxis \bar{C} LMWH
- Refer to Specialist Diabetes Team
- Find and treat precipitating factors



Monitoring

- Hrly capillary glucose and ketones
- VBG @ 60min, 2h and then 2hrly
- Plasma electrolytes 4hrly

Aims

- ↓ ketones by $\geq 0.5mM/h$ or $\uparrow HCO_3$ by $\geq 3mM/h$
- ↓ plasma glucose by $\geq 3mM/h$
- Maintain K in normal range
- Avoid hypoglycaemia



Resolution

- Ketones $<0.3mM$ + venous pH >7.3 ($HCO_3 >18mM$)
- Transfer to sliding scale if not eating
- Transfer to SC insulin when eating and drinking



Transfer to SC Insulin

- When biochemically resolved and eating
- Start long-acting insulin the night before
- Give short-acting insulin before breakfast
- Stop IVI 30min after short acting



Pt. Education

- ID precipitating factors and provide action plan
- Provision of ketone meter \bar{C} education on use.

Hyperosmolar Non-Ketotic Coma

The Patient

- Usually T2DM, often new presentation
- Usually older
- Long hx (e.g. 1wk)

Metabolic Derangement

- Marked dehydration and glucose >35mM
- No acidosis (no ketogenesis)
- Osmolality >340mosmol/kg

Complications

- Occlusive events are common: DVT, stroke
 - Give LMWH

Mx

- Rehydrate \bar{c} 0.9% NS over 48h
 - May need ~9L
- Wait 1h before starting insulin
 - It may not be needed
 - Start low to avoid rapid changes in osmolality
 - E.g. 1-3u/hr
- Look for precipitant
 - MI
 - Infection
 - Bowel infarct
- LMWH

Hypoglycaemia

Symptoms

- | | |
|---|---|
| Autonomic | Neuroglycopenic |
| <ul style="list-style-type: none">• Sweating• Anxiety• Hunger• Tremor• Palpitations | <ul style="list-style-type: none">• Confusion• Drowsiness• Seizures• Coma• Personality change |

Cause

- Usually Exogenous: insulin, gliclazide
- Pituitary insufficiency
- Liver failure
- Addison's
- Insulinomas

Mx

Alert and Orientated: Oral Carb

- **Rapid acting:** lucozade
- **Long acting:** toast, sandwich

Drowsy / confused but swallow intact: Buccal Carb

- Hypostop / Glucogel
- Consider IV access

Unconscious or Concerned re Swallow: IV dextrose

- 50ml 50% or 100ml 20% glucose

Deteriorating / refractory / insulin-induced / no access

- 1mg glucagon IM/SC
- Won't work in drunks + short duration of effect (20min)
- Insulin release may → rebound hypoglycaemia

Thyroid Storm

Presentation

- ↑ temp
- Agitation, confusion, coma
- Tachycardia, AF
- Acute abdomen
- Heart failure

Precipitants

- Recent thyroid surgery or radio-iodine
- Infection
- MI
- Trauma

Mx

1. Fluid resuscitation + NGT
2. Bloods: TFTs + cultures if infection suspected
3. **Propranolol** PO/IV
4. Digoxin may be needed
5. **Carbimazole** then **Lugol's Iodine** 4h later to inhibit thyroid
6. Hydrocortisone
7. Rx cause

Myxoedema Coma

Presentation

- Looks hypothyroid
- Hypothermia
- Hypoglycaemia
- Heart failure: bradycardia and ↓BP
- Coma and seizures

Precipitants

- Radioiodine
- Thyroidectomy
- Pituitary surgery
- Infection, trauma, MI, stroke

Mx

- Bloods: TFTs, FBC, U+E, glucose, cortisol
- Correct any hypoglycaemia
- T3/T4 IV slowly (may ppt. myocardial ischaemia)
- Hydrocortisone 100mg IV
- Rx hypothermia and heart failure

Addisonian Crisis

Presentation

- Shocked: ↑HR, postural drop, oliguria, confused
- Hypoglycaemia
- Usually known Addisonian or chronic steroid user

Precipitants

- Infection
- Trauma
- Surgery
- Stopping long-term steroids

Mx

- **Bloods:** cortisol, ACTH, U+E
- Check CBG: glucose may be needed
- Hydrocortisone 100mg IV 6hrly
- IV crystalloid
- Septic screen
- Treat underlying cause

Hypertensive Crisis

Cause

- Phaeochromocytoma

Presentation

- Pallor
- Pulsating headache
- Feeling of impending doom
- ↑↑BP
- ↑ ST and cardiogenic shock

Precipitants

- Stress
- Abdominal palpation
- General anaesthetic
- Parturition
- Contrast media

Rx

- Phentolamine 2-5mg IV (α -blocker) or labetalol 50mg IV
 - Repeat to safe BP (e.g. 110 diastolic)
- Phenoxybenzamine 10mg/d PO when BP controlled
- May now give β -B to control tachycardia / arrhythmias
- Elective surgery after 4-6wks to allow full α -blockade and volume expansion

NB. Never give β -B alone first

Burns

Risk Factors

- Age: children and elderly
- Co-morbidities: epilepsy, CVA, dementia, mental illness
- Occupation

Classification

Superficial

- Erythema
- Painful
- E.g. sunburn

Partial Thickness

- Heal w/i 2-3wks if not complicated
- **Superficial**
 - No loss of dermis
 - Painful
 - Blisters
- **Deep**
 - Loss of dermis but adnexae remain
 - Healing from adnexae: e.g. follicles
 - V. painful

Full Thickness

- Complete loss of dermis
- Charred, waxy, white, skin
- Anaesthetic
- Heal from the edges → scar

Complications

Early

- **Infection:** loss of barrier function, necrotic tissue, SIRS, hospital
- **Hypovolaemia:** loss of fluid in skin + ↑ cap permeability
- **Metabolic disturbance:** ↑↑K, ↑↑myoglobin, ↑Hb → AKI
- **Compartment syndrome:** circumferential burns
- **Peptic ulcers:** Curling's ulcers
- **Pulmonary:** CO poisoning, ARDS

Intermediate

- VTE
- Pressure sores

Late

- Scarring
- Contractures
- Psychological problems

Assessment

Wallace rule of 9s: % BSA burnt

- Head and neck: 9%
- Arms: 9% each
- Torso: 18% front and back
- Legs: 18% each
- Perineum: 1%
- (Palm: 1%)

NB. may also use Lund and Browder charts

Mx

- Based on ATLS principals
- Specific concerns ē burns
 - Secure airway
 - Manage fluid loss
 - Prevent infection

Airway

- Examine for respiratory burns
 - Soot in oral or nasal cavity
 - Burnt nasal hairs
 - Hoarse voice, stridor
- Flexible laryngoscopy can be helpful
- Consider early intubation + dexamethasone (↓ inflam)

Breathing

- 100% O₂
- Exclude constricting burns
- Signs of CO poisoning
 - Headache
 - n/v
 - Confusion
 - Cherry red appearance
- ABG
 - COHb level
 - SpO₂ unreliable if CO poisoning

Circulation

- Fluid losses may be huge
- 2x large-bore cannulae in each ACF
- Bloods: FBC, U+E, G+S/XM
- Start 2L warmed Hartmann's immediately

Parkland Formula to guide replacement in 1st 24hrs

- 4 x wt. (kg) x % burn = mL of Hartmann's in 24h
- Replace fluid from *time of burn*
- Give half in 1st 8h
- Best guide is UO: 30-50mL/h

Muir and Barclay Formula to guide fluid replacement

- (wt. x % burn)/2 = mL of Colloid per unit time
- Time units: 4, 4, 4, 6, 6, 12 = 36hrs total
- May need to use blood

Burn Treatments

- **Analgesia:** morphine
- **Dress partial thickness burns**
 - Biological: e.g. cadaveric skin
 - Synthetic
 - Cream: e.g. Flamazine (silver sulfadiazine) + sterile film.
- **Full thickness burns**
 - Tangential excision debridement
 - Split-thickness skin grafts
- Circumferential burns may require escharotomy to prevent compartment syndrome.
- Anti-tetanus toxoid (0.5ml ATT)
- Consider prophylactic Abx: esp. anti-pseudomonal

Hypothermia

Definition

- Core (rectal) temperature $<35^{\circ}\text{C}$

Pathophysiology

- Body heat is lost via 4 mechanisms

1. Radiation: 60%

- Infra-red emissions

2. Conduction: 15%

- Direct contact
- 1° means in cold water immersion

3. Convection: 15%

- Removes warmed air from around the body
- \uparrow d in windy environments

4. Evaporation: 10%

- Removal of warmed water
- \uparrow in dry, windy environments

Aetiological Classification

- Primary:** environmental exposure
- Secondary:** change in temperature set-point
 - E.g.: age-related, hypothyroidism, autonomic neuropathy

Presentation

Mild: $32.2 - 35^{\circ}\text{C}$

- Shivering
- Tachycardia
- Vasoconstriction
- Apathy

Moderate: $28 - 32.2^{\circ}\text{C}$

- Dysrhythmia, bradycardia, hypotension
- J waves
- \downarrow reflexes, dilated pupils, \downarrow GCS

Severe: $<28^{\circ}\text{C}$

- VT → VF → Cardiogenic shock**
- Apnoea
- Non-reactive pupils
- Coagulopathy
- Oliguria
- Pulmonary oedema

Ix

- Rectal / ear temperature
- FBC, U+E, **glucose**
- TFTs, blood gas
- ECG**
 - J waves:** between QRS and T wave
 - Arrhythmias

Mx

- Cardiac monitor
- Warm IVI 0.9% NS
- Urinary catheter
- Consider Abx for prevention of pneumonia
 - Routine if temp <32 and >65 yrs

Slowly Rewarm

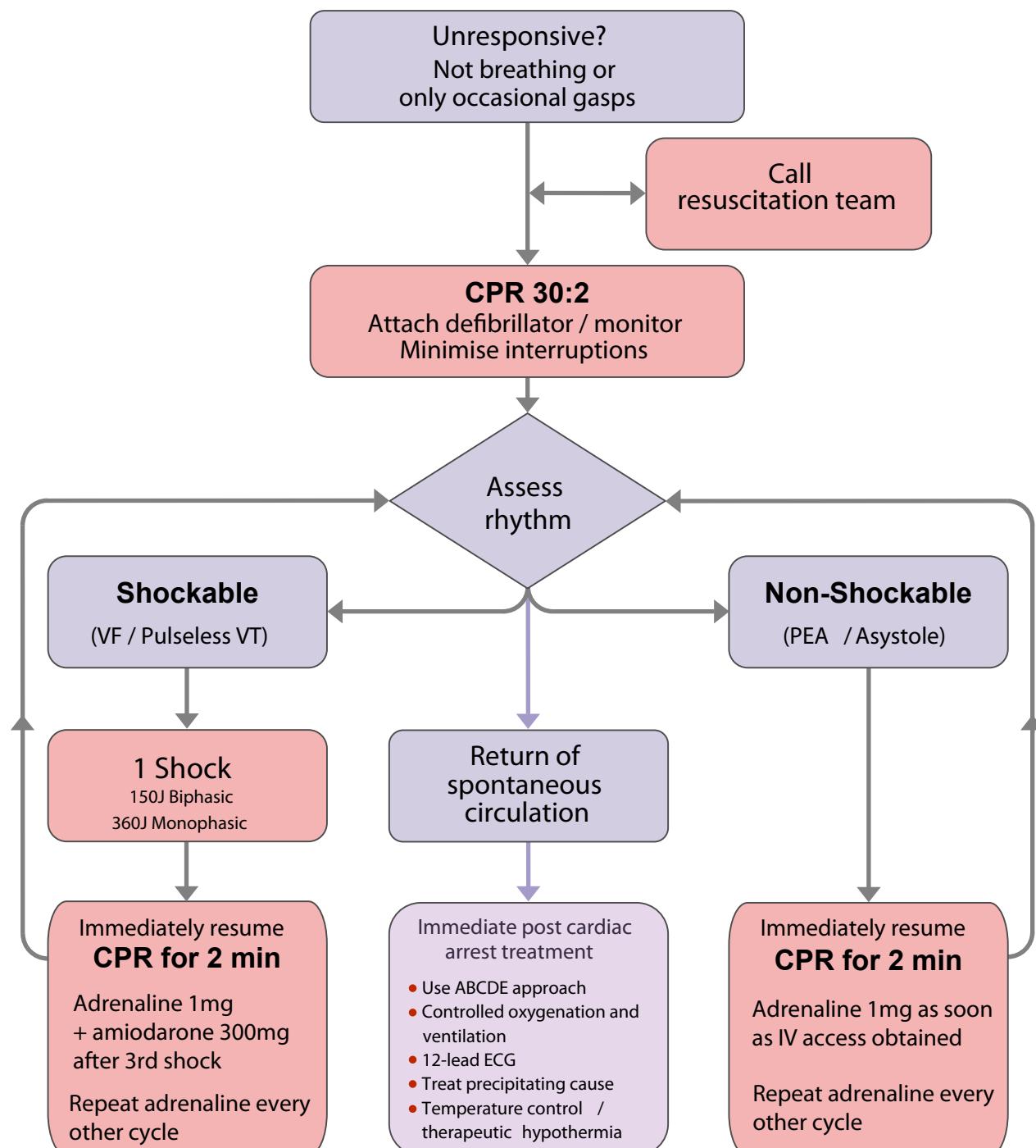
- Reheating too quickly \rightarrow peripheral vasodilatation and shock.
- Aim for $0.5^{\circ}\text{C} / \text{hr}$
- Passive external:** blankets, warm drinks
- Active external:** warm water or warmed air
- Active internal:** mediastinal lavage and CPB
 - Severe hypothermia only

Complications

- Arrhythmias**
- Pneumonia
- Coagulopathy
- Acute renal failure



Adult Advanced Life Support



During CPR

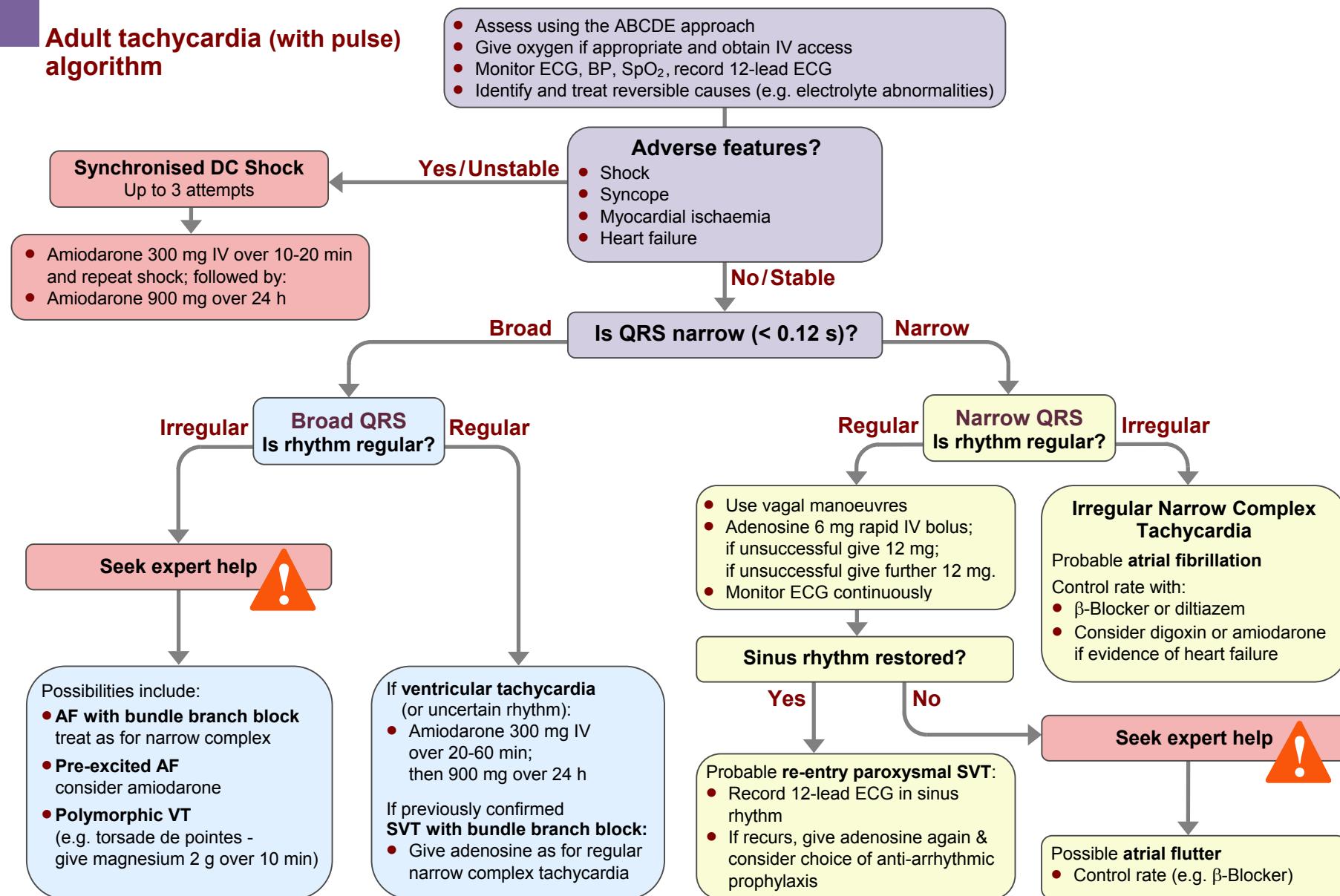
- Ensure high-quality CPR: 100/min, 4cm deep
- Plan actions before interrupting CPR
- Give oxygen
- Consider advanced airway and capnography
- Continuous chest compressions when advanced airway in place
- Vascular access (intravenous, intraosseous)
- Give adrenaline every 3-5 min
- Correct reversible causes

Reversible Causes

- Hypoxia
- Hypovolaemia
- Hypo- / hyperkalaemia / metabolic
- Hypothermia
- Thrombosis - coronary or pulmonary
- Tamponade - cardiac
- Toxins
- Tension pneumothorax



Adult tachycardia (with pulse) algorithm





Adult bradycardia algorithm

