
FRACP Study Notes

Compiled by David Tripp

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I am indebted to many people and sources, including but not limited to my study group (thanks Ben, Chris and Michelle) and the notes of a former group (thanks Matt, Travis and Phil), Harrison's 17th Edition, physicians teaching the Wellington exam preparation programme, the DeltaMed Exam Preparation course, CMTD 2008, the BNF and a zillion journal articles.

And special thanks to Helen, Laura and Esther, my lovely and long suffering wife and daughters.

All profits from these notes are going to World Vision – including helping build a maternity clinic in Rwanda currently 3 hours from any other health facility. The exam is hard, but others have an even rougher deal!

Finding your way around: Page cross-references link to the page containing the heading of the section in which the cross referenced material occurs – so if it's a long section the actual material may be over the page

***Disclaimer:** This document was an attempt to organise two metres of paper into a form I had some hope of studying from for the FRACP exam. It is shared with the hope that it will help you too. However, I accept no responsibility for mistakes – it is your challenge to find them! This is also not intended as a guide to clinical practice – your patients deserve something authoritative.*

God bless (He designed it – so might also be a useful reference point!)

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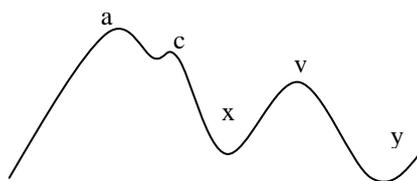
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Physiology

- Cardiac myocytes have a long action potential of muscle cells (200 – 400 ms of 1 – 5 ms)
- Most ion channels are voltage gated
- Na (initially) & Ca (after Na) are the primary depolarising channels, K repolarisation hyperpolarises the heart back to negative resting membrane potential
- Automaticity is usually caused by spontaneous phase 4 diastolic depolarisation – autonomic tone important in modulating phase 4. \uparrow extracellular K \rightarrow more positive diastolic potential \rightarrow increased rate of pacemaker cells
- Haemodynamic assessment:
 - Cardiac output:
 - Thermodilution: use Swann-Granz catheter with side hole in RA for injecting cooled 5% dextrose and thermistor distally – calculations allow assessment of CO if no shunt
 - Fick principle if shunts: Measure expired O₂, O₂ in aorta, (mixed venous O₂), calculating the systemic A-V O₂ difference....
 - Shunts: degree of shunt estimated by pulmonary:systemic flow ratio (Q_p:Q_s)
 - Pulmonary Vascular Resistance: Pressure drop across pulmonary circulation, normal < 4 Woods Units
 - VO₂ Max: the maximum capacity of the CVS to deliver O₂ to the exercising muscles. Is limited by maximum cardiac output during exercise. Maximal HR decreases as a function of age
- Antiarrhythmic drugs:
 - Relegated to an ancillary role due to complexity and adverse effects
 - Vaughan Williams classification: remember – “Some Block K Channels”
 - Class I: local anaesthetic effect due to blockade of Na⁺ current
 - Class II: interfere with β -adrenergic receptor
 - Class III: delay repolarisation due to inhibition of K⁺ current
 - Class IV: interfere with Ca conduction
 - Most drugs have actions across several classes
- Radiofrequency energy is used for catheter ablation

Examination

- Pressure waves in atria:



- a wave: atrial contraction at end of diastole \rightarrow \uparrow atrial pressure. Coincides with first heart sound and precedes carotid pulse. Closely followed by ...
- c point: bulging of AV valves into atria during systole \rightarrow \uparrow atrial pressure. Not usually visible
- x descent: atrial relaxation between S1 and S2
- v wave: End of atrial filling during systole – venous inflow into atria with AV valve closed \rightarrow \uparrow atrial pressure
- y descent: rapid ventricular filling following opening of the AV valve
- Differential:
 - Causes of \uparrow height: Right ventricular failure, tricuspid stenosis or regurgitation, pericardial effusion or constrictive pericarditis, SVC obstruction (no waves), fluid overload, hyperdynamic circulation
 - Should normally fall on inspiration. If it rises then ?constrictive pericarditis
 - Dominant a wave: tricuspid stenosis (also causes a slow descent), pulmonary stenosis, pulmonary hypertension
 - Cannon a waves ($\uparrow\uparrow$ wave – right atrium contracts against closed tricuspid valve): intermittently in complete heart block (two chambers beating independently), retrograde conduction
 - Dominant v wave: tricuspid regurgitation (should never miss this, watch for movement of ear lobe)
 - x descent: absent in AF, exaggerated in cardiac tamponade, constrictive pericarditis

- y descent: Sharp: severe tricuspid regurgitation, constrictive pericarditis, slow in tricuspid stenosis, right atrial myxoma

ECG Interpretation

P Wave

- RA enlargement: normal duration, ↑amplitude inferiorly (II, III, aVL), +ive in V1
- LA enlargement: ↑duration, ↑amplitude inferiorly, -ive in V1

LV Hypertrophy

- S in V1 + R in V5 or V6 > 35 mm: Sokolow-Lyan Criteria (32% sensitive, 95% specific – the other 5% are tall and thin)
- Other more sensitive criteria include: ↑ limb lead voltages, LA enlargement, LAD
- With ST change in lateral leads (I, aVL, V5, V6) = strain pattern

RV Hypertrophy

- Prominent R in V1 (R > S with R > 5mm) – but also happens in RBBB, Posterior MI, pre-excitation
- Deep S wave in V6
- RAD
- RA enlargement
- With ST change in anterior leads (V1 – V3) = RV strain

Ventricular Depolarisation

- See diagnosis of STEMI, page 27
- Septum depolarises L → R. Initial upwards deflection in V1
- BBB requires wide complexes (> 0.12 secs) and atrial pacing:
 - RBBB: RSR' in V1 (the R' is the late depolarisation of the RV towards V1)
 - LBBB: septum depolarises R → L at the same time as RV depolarises, LV is bigger so still a +ive deflection in V1, followed by a late, slow depolarisation of the LV away from V1
 - So, to differentiate LBBB from RBBB look at the 2nd half of QRS in V1 – if +ive then RBBB, if negative then LBBB
 - Hemiblocks: if LBBB look at the electrical axis:
 - If I is +ive and II is -ive (LAD) then L anterior hemiblock
 - If I is -ive and II is +ive (RAD) then L posterior hemiblock
 - Bifascicular block: RBBB + hemiblock
- Downward sloping ST segments – consider digoxin toxicity (ask about appetite)
- U wave: hypokalaemia (also potentiates digoxin)
- If TWI in chest leads and no clinical suspicion of MI then think cardiomyopathy

Arrhythmias

- See PMJ, 2006:82

Atrial Fibrillation

- >5% over 70
- May be triggered by other supraventricular tachycardias
- →loss of atrial appendage contractility and emptying leading to risk of clot formation
- 3rd degree block + AF → regular rhythm
- Causes:
 - LA enlargement: can be 2nd to AF, LVF, HTN, valvular heart disease
 - Surgery: CAGB: 30 – 60% (80% revert spontaneously within 24 hours), non-cardiac surgery 4 – 12%
- Acute Treatment:
 - Rate control with beta-blockers or Ca-channel blockers. Digoxin rarely used as stand alone in acute setting
 - Anticoagulate: Heparin till INR 1.8, then warfarin for 1 month
 - Cardioversion: 200J biphasic shock → conversion in 90%

- Thromboembolic risk of acute reversion: No difference in TE risk with cardioversion vs drugs vs spontaneous has been demonstrated – but lack of trial data. ACUTE study (JACC 2003) – no difference in TE risk between 4 weeks of anticoagulation vs immediate TEE guided DCR
- Rhythm control:
 - Amiodarone:
 - Reasonable revering agent, best maintenance agent, no myocardial depression. Can be used in CHF (little negative inotropic effect), minimal effect on BP
 - SE:
 - Sun sensitivity
 - Ocular toxicity: photosensitivity (50%), corneal deposits (90%), optic neuritis (1%)
 - pulmonary fibrosis (1 – 17%): usually reversible with steroids and/or withdrawal
 - Dose dependent abnormal LFTs in 25%, cirrhosis < 2%
 - Thyroid toxicity: see page 82
 - Peripheral neuropathy on long term high doses
 - Inhibits and is a substrate of 3A4. Doubles digoxin concentration (a p-glycoprotein effect, not CYP450)
 - Prolongs Qt
 - Disadvantages: long half life – may take weeks or months to reach steady state. Very poor dose-response relationship between individuals ⇒ drug monitoring not useful
 - Sotalol:
 - Primarily class III action + β -blockade. Weak efficacy in reverting AF. Less effective than amiodarone at maintenance of AF
 - Cessation in 15% due to fatigue, dyspnoea or bradycardia. Proarrhythmia: 2.5% Torsades at 6 months, QT prolongation
 - Flecainide:
 - 150 mg IV successful in 55 – 60% (better than sotalol and amiodarone)
 - “Pill in the pocket” with 200 – 300 mg flecainide significantly reduced ED attendances (5 vs 46 per month) in 210 patients. 9% reversion at average 2 hours. (NEJM 2004;351:2384)
 - Reasonable choice in an athlete – although still going to ↓ peak pump function
 - Increased mortality with LVF (CAST Trial) – only use if no structural heart disease
 - SE: dizziness, visual disturbance
- AFFIRM and RACE trials: survival and embolic risk not different between rate and rhythm control:
 - AFFIRM: Inclusion: Age > 65, another risk factor for stroke or death. 4060 patients, follow up 3.5 years, CHF in 23%, rhythm control group more expensive, low but material risk of Torsades in rhythm control group, ↑ strokes in rhythm control due to inefficiency of drug therapy in maintaining rhythm and frequent silent AF but anticoagulation removed
 - RACE study: Recurrent AF after cardioversion, 522 patients, 2.3 year follow-up, half with symptomatic CHF. No difference. 39% of rhythm control group in SR vs 10% of rate control group
 - PIAF: Diltiazem for rate vs Amiodarone for rhythm, 252 patients with AF > 7 days. Amiodarone maintained sinus in 56% vs 10%. No difference in symptomatic endpoints. Rhythm control had slightly better exercise tolerance
 - STAF: 200 patients, rate vs rhythm, 3 year follow-up. No difference in major endpoints
 - AF-CHF: rate vs rhythm control in 1376 patients with EF < 35%. No difference in any endpoint (NEJM 19 June 2008)
 - Conclusions:
 - Reduction in adverse events from the rhythm control groups, but no change in primary end points
 - Survival advantage of SR negated by survival disadvantage of anti-arrhythmic therapy. AF is bad. Trying to get rid of AF is just as bad!
 - Current advice: if AF well tolerated, rate control reasonable. If symptomatic, should try to convert to sinus
 - Bottom line: AF is associated with increased risk of death. But fixing it doesn't seem to change this. Is AF just a marker of poor prognosis (ie is the main problem poor LV function, neurohormonal or inflammation). Next step is to test non-drug rhythm control (ie ablation) against rate control – thus eliminating any toxicity of antiarrhythmic drugs from the equation
 - Pulse > 80 at rest or > 100 with modest exercise → insufficient control
- Anticoagulation for stroke risk 2nd to AF:
 - < 60 with no risk factors annual risk is 0.5%, with all risk factors risk is ~15%

- Stroke risk greatest in the first year
- CHADS Score

CHADS 2 Score	
CHF	1
Prior History of HTN	1
Age \geq 75	1
Diabetes	1
Ischaemic stroke, TIA	2

CHADS2 Score	NNT with Warfarin to prevent one stroke per year
0	417
1	125
2	81
3	33
4	27
5 or 6	44

- 0 points – don't anticoagulate. 1 – 2 points – consider anticoagulation and weigh up risk benefits, \geq 3 points – anticoagulate
- Revised CHADS score has scores from 1 to 6 for age bands from 40 – 64 to 85 – 115, and adds up to 14. More reliable prediction. History of stroke/TIA still the most significant factor
- Other risk factors for stroke:
 - Mitral stenosis
 - LV dysfunction
 - Marked left atrial enlargement ($>$ 5 cm)
 - Thyrotoxicosis
- Options:
 - Warfarin:
 - Optimal range 2 – 2.9 – minimum of ischaemic and haemorrhagic events, 3 – 3.9 fairly close behind (European Atrial Fibrillation Trial Study Group, NEJM 1995; 333:5)
 - Risk of major bleed on Warfarin: $>$ 80 years is 13.7 per 100 patient years, vs 4.7 if $<$ 80
 - Even CHADS2 score of 1 is able to derive small benefit from warfarin, and bleeding risk only 1.3% per year
 - Aspirin roughly halves the all comers risk (ie 5 – 7% per annum to \sim 3% per annum). Warfarin reduces risk to $<$ 1 %
 - Aspirin + Warfarin: Modest \uparrow in bleeding – CHAMP 0.72 vs 1.28%, WARIS II 0.17 vs 0.62 (ie 2 – 3 times the risk)
 - Aspirin + Clopidogrel (ACTIVE W trial): stopped after 1.3 years due to an excess in both ischaemic and major events (Lancet 2006 10;367:1903)
 - Subcut idraparinix 2.5 mg weekly has same efficacy but more bleeding than Warfarin (Lancet 2008: 371)
 - Lower blood pressure results in lower stroke
- Ablation for AF:
 - Old school – Maze procedure – open surgery
 - Now catheter ablation: pulmonary vein isolation or left atrial circumferential ablation (PV isolation superior in PABA-CHF Trial, NEJM 23 Oct 2008)
 - Cure rates of 90% for PAF and slight less for persistent, low adverse effects in pioneering centres, less elsewhere
 - Improvements in LV fn, heart failure symptoms, all cause mortality, stroke
 - Risks: permanent pacing 2nd to AV damage, cardiac tamponade and pulmonary vein stenosis, rarely atrio-oesophageal fistula

Atrial Flutter

- = Macro-reentrant atrial tachycardia
- Counter-clockwise right atrial AFL represents 80% of all AFL \rightarrow saw tooth pattern inferiorly and F wave (atrial wave) in V1
- Usually 2:1 block with an atrial rate of \sim 300, but if atrial conduction disease or rate slowing drugs, the atrial rate can drop to $<$ 200 leading to 1:1 conduction

- Treat:
 - DC cardioversion, biphasic shock 50 – 100 J
 - Anticoagulate: probably same risks as AF
 - CHF 2nd to tachycardia induced severe LV dysfunction
 - Amiodarone may cardiovert, or assist electrical cardioversion
 - Recurrent: catheter ablation therapy successful in > 90%. RCT shows ablation has better outcomes than medical management
 - If also AF will need continued rhythm control

Bradycardias

- SA and AV node disease the most common cause

SA node disease

- Causes:
 - Extrinsic (often reversible):
 - Autonomic: carotid sinus hypersensitivity, vasovagal (cardioinhibitory) stimulation
 - Drugs: β -blockers, Ca blockers, digoxin, class I & III anti-arrhythmics, adenosine, clonidine, lithium, cimetidine, amitriptyline, methadone
 - Hypothyroidism, OSA, hypoxia, ET suctioning (vagal stimulation), hypothermia, \uparrow intra-cranial pressure
 - Atrial depolarisation may vary with respiration (varying vagal discharges), especially in the young – normal
 - Intrinsic (usually not reversible):
 - Sick Sinus Syndrome
 - Coronary artery disease
 - Inflammatory: pericarditis, myocarditis, rheumatic heart disease, collagen vascular disease, Lyme disease
 - Senile amyloidosis
 - Congenital heart disease: TGA and Fontan repairs
 - Radiation therapy & post surgical
 - Familial genetic disorders, myotonic dystrophy and Friedreich's ataxia
- 1/3 to 1/2 patients with SA node dysfunction will develop AF or AFL
- 1/4 will have AV node disease
- Sinus rate < 40 when awake and not super fit is abnormal
- Sinus pauses > 3 secs common in an awake athletic, should prompt monitoring in the elderly
- Types:
 - 2nd degree SA exit block:
 - Type 1: progressive lengthening of SA node conduction \rightarrow progressive lengthening of P-R interval then a pause
 - Type 2: no change in the P-R interval before a pause
 - 3rd degree exit block: no p waves
 - Chronotropic incompetence: failure to increase the heart rate with exercise
 - Atrial bigeminy: premature atrial P after every P
- Treatment:
 - Not associated with increased mortality – aim is alleviation of symptoms. So PPM only if symptomatic
 - Digoxin may help (reduce SNRT). Theophylline has too many complications
 - Only one trial: dual chamber pacing has significantly better symptoms than theophylline or not treatment
 - Tachy-brady variant at similar risk to AF patients of thromboembolism: especially if > 65, history of CVA, valvular heart disease, LV dysfunction, atrial enlargement

AV Conduction Disease

- Causes:
 - Autonomic: carotid sinus hypersensitivity, vasovagal
 - Metabolic/endocrine: \uparrow K, \uparrow Mg, \downarrow Thyroid, adrenal insufficiency
 - Drugs: Betablockers, Ca blockers, digoxin, adenosine, antiarrhythmics, lithium
 - Infections: endocarditis, Lyme disease, syphilis, TB, diphtheria, toxoplasmosis
 - Congenital and genetic disorders

- Inflammatory: SLE, RA, scleroderma
- Infiltrative: amyloidosis, sarcoidosis, haemochromatosis
- Neoplastic/traumatic: lymphoma, mesothelioma, melanoma, radiation, ablation
- Acute MI
- Degenerative: idiopathic progressive fibrosis
- Blocks:
 - 1st degree: intranodal. Often associated with drugs
 - 2nd degree:
 - Mobitz type 1/Wenckebach: intranodal, progressively lengthening type PR interval then a pause. Relatively safe
 - Mobitz Type 2: intermittent failure of conduction, no change in PR or RR interval. Occurs in HIS conduction system (ie infranodal), associated with intraventricular conduction delays (BBB), more likely to proceed to type III block. Indication for permanent pacing (esp if symptomatic or very bradycardia and asymptomatic)
 - 3rd degree: AV dissociation – the lower down the conduction tree the slower the rhythm, the less reliable the escape rhythm and the wider the QRS complex. PPM unless asymptomatic. Rate > 40 may elect to observe
- Treatment:
 - Acutely atropine. Pacing
 - In acute MI (esp inferior): usually transient. Pace if 2nd or 3rd degree block and symptomatic

Pacemakers

- Nomenclature:
 - XXXXX
 - First letter: chambers that are paced: O none, A atrium, V ventricle, D dual, S single
 - Second letter: chambers that are sensed: O none, A atrium, V ventricle, D dual, S single
 - Third: response to a sensed event: none, I inhibition, T Triggered, D inhibition + triggered
 - Programmability or rate response: R rate responsive
 - Antitachycardia functions if present: O non, P Antitachycardia pacing, S shock, D pace + shock
- Studies have failed to demonstrate difference in mortality in elderly with AV block treated with single (VVI) compared to dual (DDD) chamber pacing (DAVID trial). ?Chronic AF and stroke decreased with physiologic pacing – modest ↑ risk of dual chamber insertion probably worth it
- Pacemaker induced ventricular dyssynchrony:
 - RV pacing → LBBB pattern → dyssynchrony
 - RVOT septum pacing gaining attention – more physiological, less remodelling
- Pacemaker syndrome: low cardiac output due to single pacing of the ventricle, independent of the atrial kick. Either set the pacemaker to tolerate a slower native rhythm (Hysteresis), or insert an DD pacemaker
- Safety: stay away from heavy electrical motors and arch welders. Don't put a mobile in a pocket over the pacemaker.

Tachyarrhythmias

- Exclude non-cardiac causes of high output: pregnancy, thyrotoxicosis, anaemia, volume loss, CO2 retention, beriberi, Paget's disease
- 24 hr Holter monitor only for those with daily symptoms
- Most not associated with structural heart disease. However, if atrial tachycardia, AF or AFL should echo for chamber size and valve function
- VT with decreased LV function → ?IHD
- Polymorphic VT in the absence of QT prolongation → ?unstable IHD
- Mechanisms:
 - Abnormal automaticity – increased slope of phase 4 or decrease in threshold for phase 0
 - Early or late after-depolarisations due to alteration of plateau currents or ↑intracellular Ca
 - Re-entry: requires 2 pathways with different conduction speeds
- Carotid Sinus Massage:
 - 5 secs, with 30 secs pause between sides
 - Longitudinal, 2 FB below angle of jaw
 - Upright if no supine result
 - Beat to beat monitoring
- Contraindications:

- Carotid bruit (until Doppler Study)
- MI or stroke within 3 months
- History of VT
- Complications (mainly TIA): 0.1%

Premature complexes

- Atrial: Typically asymptomatic, uncommonly require intervention. May be compensatory pause afterwards – or if the His system is still partially refractory may conduct with a BBB pattern. Premature P may hide in the previous T
- Ventricular:
 - Premature wide QRS – one focus can produce different morphology – not necessarily multifocal
 - Compensatory pause due to refractory AV node
 - Ventricular bigeminy: one premature beat after every normal QRS
 - Treat for symptomatic relief. If very frequent can → reversible cardiomyopathy
 - In structural heart disease, frequent PVCs and non-sustained VT → increased risk of SCD. But no study has shown eliminating PVCs alters prognosis

Inappropriate Sinus Tachycardia

- Heart rate increases too much
- Often after a viral illness – settles over 3 – 12 months. Titrate beta-blockers

Multifocal Atrial Tachycardia

- 60% occurs with significant pulmonary disease
- At least 3 distinct P wave morphologies, different P-R intervals, atrial and ventricular rates of 100 – 150 bpm
- Treatment: Verapamil, β blockers or maybe flecainide. ??Ablation of AV node
- Exclude digoxin toxicity

AV Nodal Re-entrant Tachycardia

- Re-entry: excitable gap exists when tachycardia circuit is longer than the tachycardia wavelength
- Most common paroxysmal SVT, F > M in 2 – 4th decade
- 2 distinct pathways through the AV node – fast and slow pathways → reentrant circuit
- Narrow QRS rate 120 – 250. *Retrograde P* – may be buried (look in V1)
- Treatment:
 - Carotid massage, vagal stimulation
 - Adenosine. Note: can be given with a beta-blocker (unlike verapamil). Half life prolonged in those taking dipyridamole
 - Then beta-blockers or Ca channel blockers (not verapamil if WPW)
 - If unstable, R wave synchronous DC cardioversion
- Prevention:
 - Drug that slows conduction in the slow pathway: digoxin, beta blockers, ca blockers
 - Catheter ablation of the slow pathway successful in >95%, with 1% risk of needing a permanent pacemaker

Tachycardias associated with Accessory Pathways (APs)

- Short or long PR interval 2nd to a large macro-reentrant circuit including the ventricles
- If concurrent AF or AFL then there is no hold-up if antero-grade conduction → very fast ventricular rate which can be life threatening
- Direction of conduction:
 - APs usually conduct rapidly in both antegrade and retrograde direction. Impulse bypasses the AV node → ventricular pre-excitation (ie short PR interval and delta wave)
 - If retrograde conduction only then narrow complex SVT – Orthodromic SVT (Antidromic AVRT has QRS widening)
- **Wolfe Parkinson White:**
 - Usually retrograde conduction over the AP
 - Localising the pathway:
 - Type A (commonest): left sided accessory pathway – V1 – V3 +ive with right axis (resembles RV hypertrophy)
 - Type B: right sided pathway – resembles LV hypertrophy

- Treatment:
 - Carotid massage/vagal manoeuvre may slow AV conduction sufficiently to terminate it
 - Adenosine (caution in AF with accessory pathway – conduction down the accessory pathway may increase)
 - Beta blockers, Ca channel blockers – **not digoxin** (contraindicated) or verapamil (may actually ↑ AV conduction and predispose to VF)
 - If unstable with AF then DC cardioversion
- Prevention:
 - Catheter ablation effective in > 95%
 - If asymptomatic finding, many never has a tachy episode. Watch and wait (controversy about athletes, pilots, etc)
- Idiopathic ventricular fibrillation does seem to be associated with early repolarisation (NEJM 11 May 2008)

Ventricular Tachycardia/Fibrillation

- Tachycardia: Rate >100, usually > 120. Non-sustained if < 30 secs
- Causes:
 - Ischaemia: Post AMI β-blockers reduce VT and SCD
 - Cardiomyopathy
 - Arrhythmogenic RV dysplasia (ARVD)
 - HOCM
- Arise from:
 - Abnormal ventricular pacemaker: usually in acute MI or electrolyte disturbances
 - Re-entrant VT: circuits forming around areas of scarring
- Need to distinguish VT from SVT with aberrant conduction: Don't give adenosine or verapamil to VT – can lead to collapse. Often AV dissociation → cannon waves and fusion beats (Ps buried in QRS). If in doubt assume VT. Characteristics of VT:
 - QRS > 140 ms
 - Bizarre QRS complex, concordance of QRS complex in all precordial leads
 - Slurring of the initial portion of the QRS
 - Large S wave in V6
- Fibrillation: disorganised, multiple re-entry circuits
- Treatment:
 - If monomorphic VT then R wave synchronous shock. Drugs successful in < 30%
 - If polymorphic VT or VF asynchronous defibrillation +/- IV lignocaine or amiodarone
- Prevention:
 - ICD + sotalol (also decreases energy needed to terminate VF) or amiodarone (may be better tolerated if marginal usual haemodynamic status, often the drug of choice as other drugs pro-arrhythmic). MADIT-I, MADIT-II, SCD-HeFT, MUSTT trials. Instead of dying of sudden death, they are now in severe HF
 - If no structural heart disease then catheter ablation successful in > 90%
- VT Storm (greater than 2 episodes in 24 hours – usually lost more):
 - In absence of long QT, then active ischaemia or fulminant myocarditis. IV lignocaine or amiodarone (although these can worsen VT)+ PCI
 - If long QT, remove offending drugs, raise K and Mg, emergency pacing to prevent pause dependent VT
- Torsade De Points: occurs when QT is prolonged, eg in
 - Drugs prolonging repolarisation eg sotalol, amiodarone
 - Electrolyte disturbances
 - Bradycardia
 - Congenital long QT
 - Other drugs, eg TCAs, erythromycin, etc

Unique VT Syndromes

- Idioventricular Rhythm
- Idiopathic Outflow Tract VT:
 - 80% from RV, 20% from LV
 - Usually well tolerated and non-sustained
 - Typically large R waves in inferior leads

- Not associated with SCD. Palpitations with exercise, stress, caffeine, hormone triggers
- If very frequent may → VT induced cardiomyopathy
- Vagal manoeuvres, adenosine and beta blockers (esp sotalol) tend to terminate the VTs
- Catheter ablation successful in > 90%
- Betablockers prevent attacks
- In some, somatic mutation of inhibitory G protein, others unknown
- Arrhythmogenic Right Ventricular Dysplasia: co-existing cardiomyopathy is present – fibro-fatty infiltration of the RV (MRI useful)
- Non-ischaemic dilated cardiomyopathy

Genetic Abnormalities Predisposing to Polymorphic Ventricular Arrhythmias

- Ion channel defect → impaired ventricular repolarisation due to intracellular surplus of positive charge → late inflow of Ca → early after-depolarisations (seen on ECG as pathological U wave). If these reach a threshold → ventricular arrhythmias
- Most arrhythmias are preceded by a pause. Torsade is not usually sustained – can wait for sedation. Shock if it degenerates to VT or if patient loses consciousness. If recurrent, treatment includes acceleration of heart rate (faster pacing → shorter QT, and don't beta-block), magnesium (20 ml of 10% over 2 mins), K supplements to increase serum K to 4.5
- **Long QT Syndrome:**
 - See Lancet 6 Nov 1999
 - 8 known genetic defects, Autosomal dominant → abnormal repolarisation (most K channelopathies)
 - Men QTc > 460 ms, women > 480 ms (Harrison's – different to Card Soc of Aus and NZ guidelines), > 500 ms → ↑risk
 - QT may be normal, but fail to shorten with exercise. QTc is not a reliable predictor of risk
 - Presentation: syncope or sudden death following exercise. Can be misdiagnosed as epilepsy. Detailed family history essential
 - Prognosis depends on which genetic variant – identifying it helps management:
 - LQT1: most common, QT prolongs with exercise, broad T. VT with exercise (especially swimming) or stress. First attack before 20. Respond to beta-blockers
 - LQT2: Notched/bifid T wave. Triggered by stress, sleep or auditory stimulation. Responds to beta-blockers, K supplements. Don't have alarm clock or phone by the bed
 - LQT3: poor prognosis, occurs in sleep, beta-blockers not recommended (slow heart further during sleep → ↑risk)
 - Management:
 - ICD if:
 - Prior arrest
 - Persistent syncope on beta-blockers or beta-blockers contraindicated
 - Very long QT (>550) without symptoms – esp LQT3 males
 - Treat with Betablockers (ie metoprolol, not sotalol – lengthens QT). Significant reduction in events (depending on genotype). 80% of LQT1 dead in 15 years, reduces to < 5% on treatment – greatest benefit in LQT1. Increased risk on withdrawal of beta-blockers. Use with ICD to ↓inappropriate discharges
 - Avoid QT prolonging drugs (includes amiodarone)
 - Avoid extremes of exercise (esp LQT1 – no swimming/diving – either exercise or shock of cold water on the face)
 - Only cardiac condition where genetic testing is currently recommended for risk stratification
 - ECGs on all first-degree relatives
 - Acquired Long QT:
 - Causes: Metabolite abnormalities (low K and Mg). Many drugs: Class I and III (sotalol, amiodarone) antiarrhythmics, macrolides, cotrimoxazole, fluoxetine, TCAs, carbamazepine, mefloquine, methadone... see www.qtdrugs.org
 - Risk factors: female, recent heart rate slowing, low K
- **Brugada Syndrome:**
 - Autosomal dominant mutation of SCN5A gene with variable expression → shortening of RV outflow tract repolarisation → ST elevation in V1 – V3
 - Predisposes to re-entry, life-threatening arrhythmias, peak in 4th decade
 - Most common in young Asian males
 - No benefit from beta-blockers, amiodarone and sotalol

- Na channel blockers (eg procainamide and flecainide) can exacerbate symptoms (used in provocative testing if limited expression in family members)
- Consider ICD (debate about asymptomatic people...)

Valvular Heart Disease

- Mortality Rates for surgery:
 - AVR isolated 2.8%
 - MVR isolated 5.3%
 - AVR + CABG 5.2%
 - MVR + CABG 10.3%
 - AVR + MVR 8.8%
- Pregnancy: See page 461
- Who needs an echo:
 - Symptoms: SOB, chest pain, VTE, syncope, endocarditis
 - Abnormal ECG or CXR
 - Murmurs: diastolic, continuous or murmur > grade 3
- Bio-Prosthetic (ie not metal) valves:
 - No thromboembolic complications after 3 months
 - Need replacement in up to 30% of patients by 10 years, and 50% by 15 years (rates higher for mitral than aortic valves)
 - Increasing trend to using prosthetic valves under 65 years (the old cut-off) due to better implants, ↓risk of re-operation, and patient preference to avoid anticoagulation

Mitral Stenosis

- See also Circulation 2005:112
- Causes:
 - *Rheumatic Fever* – leaflets diffusely thickened by fibrous tissue and calcium deposits → “fish-mouth” valve
 - Congenital
 - Severe mitral annular calcification
 - SLE, RA
- Pathology: commissural fusion, thickening of leaflets and shortening and fusion of chordae
- Physiology:
 - Normal area of mitral valve orifice is 4 – 6 cm²
 - If < 2 cm², blood flows into LV only if propelled by ↑pressure gradient
 - < 1cm² is “severe”, requires LA pressure of 25 mmHg to maintain CO
 - It is primarily the RV that generates force necessary to drive blood across the stenotic MV so MS → RV pressure overload
 - LV diastolic pressure and EF are normal in isolated MS, elevated LA and PA wedge pressures
 - Up to moderate MS, CO is normal at rest, subnormal rise with exertion
 - ↑HR → ↓time in diastole and ↓time for flow through mitral valve → ↑problems
 - Pulmonary vascular bed: fibrous thickening of alveoli walls and the pulmonary capillaries → ↓vital capacity, TLC, O₂ uptake
 - Risk of thrombi in enlarged atrial appendages
 - MS often accompanied by AR → blunts presentation of AR
- Symptoms:
 - Asymptomatic → SOB + orthopnea + PND. May be haemoptysis
 - New onset AF – poorly tolerated – treat aggressively
 - Enlarged LA can cause hoarseness 2nd to left recurrent laryngeal nerve impingement (Ortner Syndrome)
 - Mitral facies: plethoric cheeks with bluish patches. Probably 2nd to ↓CO
 - Pulmonary HTN and RHF
- ECG: P waves shows LA enlargement, RAD and RVH if 2ndary pulmonary HTN
- Severity:

	MVA (cm ²)	Gradient	PCWP	CO	CO
Mild	> 1.8	2-4	<12	↔	Nil
Moderate	1.2 – 1.6	4-9		↔	
Mod-Severe	1.0 – 1.2	10-15		↔	SOB

- | | | | | | |
|--------|------|-----|-----|---|-------------|
| Severe | <1.0 | >15 | >18 | ↓ | SOB at rest |
|--------|------|-----|-----|---|-------------|
- ↑Pulmonary vascular resistance worse than ↑pulmonary hypertension – sign of critical stenosis
 - Imaging:
 - Increasing use of CMR
 - Males over 45 and females over 55 need angiography prior to surgery to exclude need for concurrent CABG. CT angiography increasingly used as a rule-out test for concurrent coronary artery disease
 - Treatment:
 - Medical Therapy: Beta-blockers, Ca blockers, diuretics for HF +/- digoxin for AF
 - Warfarin if in SR with LA enlargement > 5.5 cm is controversial. Certainly if in AF
 - Prophylaxis for rheumatic fever
 - Balloon mitral valvotomy (not if significant MR):
 - If favourable valve morphology, class II-IV symptoms and valve area (effective orifice) < 1.5 cm² – long terms results similar to replacement but ↓complications
 - Also consider if PASP > 60 mmHg (ie severe pulmonary HTN), PAWP > 25 mmHg or MVG > 15 mmHg
 - No evidence of benefit if slight or no functional impairment
 - Most require re-operation in ~ 10 years
 - Surgical risk increases with increasing pulmonary hypertension
 - Open commissurotomy – place in treatment unknown
 - MV replacement if MS and MR or calcified valve

Mitral Regurgitation

- Causes:
 - Anything affecting leaflets, annulus, chordae tendineae, papillary muscles and adjacent myocardium
 - MR begets MR: it's progressive – LA enlargement pulls posterior leaflet away from the orifice. LV dilatation increases regurgitation, etc
 - Acute: Endocarditis, papillary muscle rupture (post MI), trauma, chordal rupture/leaflet flail (MVP)
 - Chronic:
 - MVP prolapse. Myxomatous thickening of leaflets. Good prognosis unless mod/severe MR or reduced LV function
 - Rheumatic Fever
 - Old Endocarditis
 - Mitral annular calcification
 - Congenital: cleft on the anterior valve leaflet, AV canal
 - HOCM
 - Ischaemic remodelling
 - Dilated cardiomyopathy
- Pathophysiology:
 - LV decompressed into the LA during ejection. Compensates with ↑ LV volume over time → ↓forward CO
 - ↑EF in presence of normal LV function *so any drop in EF (60%) reflects significant dysfunction*
 - In chronic mild-moderate MR, LV volume overload is well tolerated
- Assessment: area of Doppler jet more important than length, so measured in terms of jet relative to atrial size (> 40% is severe) – but is problematic with eccentric jets. Assessments of regurgitant volume help (> 60 cc severe). Also regurgitant fraction > 55% is severe
- Treatment:
 - Medical Therapy: diuretics for HF, vasodilators for acute MR
 - Warfarin when AF
 - No prospective trails to validate vasodilators in the absence of systemic hypertension
 - If severe, avoid isometric forms of exercise (→ ↑ LV volume)
 - Surgery: Don't let the LV function deteriorate
 - Risks significantly lower for valve repair than replacement (ie do it before it gets too bad)
 - Operate if:
 - Pulmonary HTN (PA pressure > 50 mmHg at rest or > 60 with exercise)
 - LVEF declining below 60% and/or LVESD > 40 mm (fairly aggressive recommendations, based on perioperative mortality risk < 1%)

- Recent onset AF (not an absolute indication)
- If EF < 30%, LV recovery incomplete

Mitral Valve Prolapse

- =Systolic Click Murmur
- Common, highly variable, diverse mechanisms
- In some caused by a collagen disorder. Frequent finding in Marfan's and osteogenesis imperfecta
- Mitral valve annulus often dilated + elongated chordae tendineae
- Usually benign, in females 15 – 30 years
- In US, most common cause of severe MR requiring surgery
- Can → AF and VT
- Valsalva → ↓venous return 2nd to ↑intrathoracic pressure: accentuates HOCM and mitral valve prolapse murmurs only

Aortic Stenosis

- See NEJM 25 Sept 2008
- Causes:
 - Congenital (bicuspid – can be autosomally inherited via NOTCH1 gene, unicuspid)
 - Degenerative Calcific. Rare < 70 years, the most common > 70 years. Aortic sclerosis correlates with atherosclerosis. Linkage studies suggesting polymorphisms in the vitamin D receptor, and other genes
 - Rheumatic Fever – produces commissural fusion – MV always involved
 - Others: SLE
 - Rather than just being bad luck, is starting to be viewed as an active disease process, with:
 - Risk factors: Age, male sex, high LDL and lipoprotein (a), smoking, HTN, diabetes
 - Initiating features (eg mechanical stress)
 - Molecular and cellular pathways that mediate progression: local protein production (eg osteopontin, osteocalcin) which mediates calcification, activation of inflammatory signalling pathways, changes in tissue matrixes
 - This raises the possibility of targeted therapy to slow progression (there is no such treatment proven at present)
- Presence of only mild valve changes is associated with 50% increase in risk of MI or cardiovascular death within 5 years
- Symptoms:
 - Dyspnoea: diastolic dysfunction, ↑ pressure transmitted back to pulmonary circulation
 - Dizziness/syncope: usually exertional. ?peripheral vasodilation with exercise but fixed output
 - Angina: myocardial mass and O2 demand exceed perfusion, ↑ diastolic filling pressures → ↓perfusion. Concurrent IHD
 - Other associations: angiodysplasia, acquired von Willebrand's, conduction disturbances
 - Asymptomatic AS has same mortality as general population – but need to watch for deterioration. 50% develop symptoms in 5 years. Recommend annual echo
 - Natural history: 80% who died of AS had symptoms < 4 years
- Pathophysiology:
 - LV output maintained by concentric LV hypertrophy. As this becomes maladaptive, LV declines
 - LVH elevates myocardial O2 requirements, and may reduce coronary artery blood flow due to compression of coronary arteries (CAD also often present)
 - CO at rest may be within normal limits but fails to rise normally in exercise
 - Aneurysmal enlargement of the root or ascending aorta (> 4.5 cm) occurs in ~ 20% of bicuspid valves. Severe AS may → post-stenotic dilatation (seen on CXR)
 - Risk of arrhythmias: AF, VT, bradyarrhythmias due to annular calcification
- Assessment:
 - ECG: LV hypertrophy and LV strain (ST depression and T wave inversion in I, aVL and left chest leads)
 - Echo:
 - Gradients:
 - Measured using modified Bernoulli equation $\Delta P = 4V^2$
 - Peak-to-peak: Peak LV and aortic pressures
 - Mean gradient: Average aortic-ventricle pressure during ejection (ie the area between the two curves)

- Jet velocity > 4 m/s is severe
- AS will be underestimated when LV function is impaired. Important to know as the LVF may improve dramatically with surgery, but the surgical risks are greater. Dobutamine stress echo: AS will → ↑gradient (ie LV function can increase if pushed). Cardiomyopathy will show no change in gradient
- Catheterisation to check valve if:
 - They have multi-valve disease and the impact of each valve needs to be known to plan surgery
 - Young, asymptomatic people without calcified valve
 - If unsure if it's the valve or an outflow tract problem
- Grading:
 - Severe = mean systolic pressure gradient > 40 mmHg (given a normal CO) and effective aortic orifice area < ~1.0 cm² (about 1/3rd normal). [Note: Dynamic Severity Index (DSI) is a ratio that compensates for LV function and is therefore a better basis for surgery. Use Dynamic Performance Index (DPI) for artificial valve] If symptomatic and severe, 50% 1 year survival – but don't do so well after surgery – the damage is done.
 - Moderate: valve area 1.0 – 1.5 cm²
 - Mild: valve area 1.5 – 2.0 cm²
- Management:
 - Avoid strenuous exercise and dehydration
 - Medical Therapy: diuretics for HF. No proven therapy to alter natural history
 - Variable evidence that statins slow progression of valve damage. SEAS Trial (Simvastatin and Ezetimibe in Aortic Stenosis), NEJM 2 Sept 2008: Ezetimibe + Simvastatin vs placebo doesn't affect progression nor the number of ischaemic events in mild-moderate stenosis, but does lead to less CABGs at the time of AVR
 - Surgery if severe AS and symptomatic, if LV function < 50%, or if aneurysmal or expanding aortic root (> 4.5 cm or increasing in size > 0.5 cm/year) even if asymptomatic (want to operate before ↓LV function). Operative risk 3% (> than risk of sudden death)
 - If asymptomatic and normal LVEF, may do well for years so watch and wait. ETT may assist assessment of symptoms
 - If moderate AS, and having CABG, then concurrent AVR
 - If poor LV Fn then perioperative risk of 15 – 20%
 - Percutaneous balloon aortic valvuloplasty used in young people with congenital valves, not in old calcified valves due to high re-stenosis rate

Aortic Regurgitation

- Causes:
 - Valvular:
 - Rheumatic Fever (2/3rds of cases, but much less common if no MR)
 - Congenital: bicuspid
 - Endocarditis
 - Myxomatous (prolapse)
 - Traumatic
 - Syphilis (can also affect valve 2nd to aortic disease)
 - Ank Spond (can also affect valve 2nd to aortic disease)
 - Root disease:
 - Aortic dissection
 - Cystic medial degeneration: Marfan's, Bicuspid aortic valve
 - Aortitis
 - HTN
- Natural history:
 - Asymptomatic for many years
 - Once symptoms, mortality > 10% per year
 - Dyspnoea → orthopnoea, PND and diaphoresis. Angina unusual
- Pathophysiology:
 - ↑Total stroke volume (=forward + regurgitant volume)
 - LV dilation to accommodate volume load. ↑End diastolic volume compensates. Eventually ↑preload and ↑afterload → ↑↑ EDV, ↓forward stroke volume and ↓EF
 - Can have severe AR with normal LV EF and forward volume
 - CO fails to rise normally with exercise

- Findings: water hammer pulse and displaced, heaving LV
- ECG: LV hypertrophy and LV strain
- Echo findings in severe: central jet exceeds > 65% outflow track, regurgitant volume > 60 ml/beat, regurgitant fraction > 50%, diastolic flow reversal in the proximal descending aorta
- Grading:
 - Class 1: EF < 50%
 - Class IIa: Normal EF, SD > 55 mm, DD > 75 mm
 - Class IIb: Normal EF, SD 50 – 55mm, DD 70 – 75 mm, and abnormal response to exercise
 - LV dysfunction is worse than it appears: eg LVEF 45% may be LVEF 20% post surgery
- Management:
 - Acute: diuretics and vasodilators. Intraaortic balloon pump contraindicated
 - Chronic: Aim for BP < 140, vasodilators first choice
 - Timing of surgery: Usually not symptomatic until LV fails, and if surgery delayed > 1 year from the onset of symptoms, treatment does not restore LV function
 - Operate if: symptomatic, severe, significant aortic dilatation, LVEF < 50%, ESD > 55 mm, ESV > 55 mL/m², or LVDD > 75 mm

Tricuspid Valve

- Tricuspid Stenosis:
 - Causes: *Rheumatic*, congenital
 - Pressure gradient of 4 mmHg between RA and RV → systemic congestion. Corresponds to tricuspid orifice < 1.5 – 2.0 cm
 - Findings: “the tricuspid valve may occasionally be heard approximately 0.06 seconds after pulmonic valve closure”! (Harrison’s page 1478)
 - Dry out before surgery → improved liver function → ↓ complications (especially bleeding)
 - Tricuspid valves more prone than any other to thromboembolic complications
- Tricuspid Regurgitation:
 - Causes:
 - Primary: Rheumatic, endocarditis, myxomatous (TVP), carcinoid, congenital, trauma, papillary muscle injury (post MI)
 - Secondary: RV and tricuspid annular dilatation (most common cause, eg inferior infarct, pulmonary HTN from any cause), chronic RV apical pacing
 - If isolated TR (eg endocarditis) without pulmonary HTN, well tolerated and doesn’t need surgery
 - If TR second to MR, TR usually spontaneously improves if MR fixed – although may improve faster with tricuspid annuloplasty, tricuspid repair or, rarely, TVR
- Treatment: tricuspid valve replacement complicated by high rate of valve thrombosis

Pulmonary Valve

- Causes of Stenosis: Congenital (eg Tetralogy), carcinoid. Treatment: balloon valvuloplasty
- Causes of regurgitation:
 - Valve disease: congenital, postvalvotomy, endocarditis (rarely affected, also rarely affected by RF)
 - Annular enlargement: Pulmonary HTN (most common), Marfan’s, idiopathic

Congenital Heart Disease

Atrial Septal Defect/ASD

- Asymptomatic. Heart failure/arrhythmias (due to ↑RA) don’t occur until well into 3rd – 4th decade
- Findings: RV+, pulmonary systolic flow murmur, fixed splitting of S2
- Generally doesn’t cause cyanosis
- Bigger PA and cardiac enlargement on CXR
- **Ostium Secundum** (most common, in the region of the fossa ovalis):
 - Fossa ovalis
 - Findings:
 - Range in size. Large lesion doesn’t cause a murmur – large hole and low pressure gradient → low flow. Murmur in pulmonary area 2nd to volume load
 - Fixed splitting – delayed pulmonary S2
 - RV heave given volume loading
 - Mid-diastolic murmur (pulmonary regurgitation)

- ECG: RVH with RAD
- NOT a thrill – requires high velocity jet
- Not an endocarditis risk
- **Ostium Primum:**
 - In the lower part of the atrial septum. AVSD – associated with mitral valve abnormalities and Trisomy 21
 - ECG: LAD
- Device closure with aspirin only for 6 months following generally advised:
 - Decreases morbidity, and if < 25 then decreases mortality
 - Contraindicated in fixed pulmonary hypertension
- **Patent Foramen Ovale (PFO):**
 - Failure of the foramen to close after delivery
 - Approx incidence in autopsy studies 20%
 - Cryptogenic stroke < 55 yrs: 40% incidence of PFO. Closure may prevent recurrent CVA – no trial evidence but becoming standard practice. Little evidence of benefit of warfarin over aspirin (PICCS trial). If had stroke should be on life long warfarin
 - Migraines: Incidence of PFO in 45% of migraine and aura. Postulated vaso-active substances bypass the lungs. MIST trial: Migraines modest improvement (not cessation) with closure. See page 146
 - Associated with decompression sickness ⇒ don't dive
 - Atrial septal aneurysm then stroke risk

Ventricular Septal Defects

- 20% of cardiac anomalies
- Types: perimembranous (commonest), muscular (more likely to close spontaneously), outlet (may affect aortic valve)
- Variety of presentations: asymptomatic, Eisenmenger's complex, early fulminant heart failure
- Close surgically if symptoms of CHF, or a large lesion and pulmonary hypertension developing
- Small risk of endocarditis 2nd to turbulence (jet damages endothelium on opposite wall...)

Tetralogy of Fallot

- Commonest form of cyanotic congenital heart disease – 10% of cardiac malformations
- Features: VSD, over-riding aorta, RVOT narrowing (subvalvular or valvular level – eg pulmonary stenosis or atresia), RVH
- Requires patent ductus for survival
- Operated on in childhood with shunts or formal repair

Transposition of the Great Arteries

- 5 – 7% of cardiac anomalies
- Treat with arterial switch procedure (→RBBB, RVH and RAD)

Patent Ductus Arteriosus

- 5 – 10 % of cardiac defects – higher in preterm infants, unusual to present in adulthood
- Present with CHF due to LV volume load, machinery murmur upper L sternal border, maybe signs of pulmonary HT, maybe clubbing of toes not fingers
- Closure with surgery or device
- Significant risk of endocarditis → ?closure of silent duct

Eisenmenger's Syndrome

- Due to VSD, PDA, ASD
- Severe pulmonary HTN → shunt reversal
- Features: clubbed, cyanosed, little or no systolic murmur (much reduced pressure differential between RV and LV), features of pulmonary HTN (loud P2, decrescendo diastolic murmur)
- Pulmonary HTN very poorly tolerated during pregnancy (50% mortality)
- Key prognostic measure of PAH is *pulmonary vascular resistance* – higher is a worse prognosis
- Pulmonary arterial hypertension drugs typically don't help
- Complications:
 - ↑risk of arrhythmias and SCD
 - Embolic events more likely

- Bleeding (due to ↓ platelet function) and clotting problems (2nd to polycythaemia)
- Significant risk of haemoptysis: pulmonary infarct or pulmonary haemorrhage
- Inoperable. ?heart lung transplant

Aortic Coarctation

- 6 – 8% of cardiac anomalies, M > F
- Most commonly a discrete stenosis opposite the insertion of the ligamentum arteriosum
- Associated with bicuspid aortic valve, mitral valve disease, aneurysm of circle of Willis (hypertensive complication), VSD
- Features: CHF in infancy, upper limb HTN as child/young adult, murmur (may be continuous if severe), radio-femoral delay, rib notching on xray
- Treatment: surgery, role of balloon dilatation controversial
- Reduced lifespan even if repaired, ↑risk of dissection

Hypertension

- See Lancet 2006: 367 and Lancet 2003:361
- See also Hypertension in Geriatric Medicine, page 473
- > 25 % of population
- Definition:

	Systolic	Diastolic
Normal (previously “optimal”)	<120	and <80
Prehypertension	120 – 139	Or 80 – 90
Stage 1 hypertension	140 – 159	Or 90 – 99
Stage 2 hypertension	≥160	Or ≥100
Isolated systolic Hypertension	≥140	And <90

- Essential Hypertension: primary or secondary inability of the kidney to excrete sodium at a normal blood pressure. CNS, endocrine factors, large arteries and microcirculation all involved
- Genetically complex on environmental background
- Measurement:
 - Seated and rested for 5 minutes
 - Arm at heart level
 - If cuff is too short or too narrow it will over-read by 5 – 15 mmHg
 - Smoking in the last 15 – 30 minutes → ↑BP of 5 – 20 mmHg
 - Can be falsely elevated in severely sclerotic arteries in the elderly (ie pseudohypertension) – suggested if radial pulse is still palpable when the brachial artery is occluded by the cuff (Osler manoeuvre)
- History:
 - Diet
 - Risk factors: weight change, dyslipidaemia, smoking, DM, inactivity
 - Evidence of 2ndary HTN: renal disease, change in appearance, muscle weakness, spells of sweating, palpitations, tremour, erratic sleep, snoring, daytime somnolence, symptoms of hypo or hyper thyroidism
 - Target organ damage: TIA, stroke, transient blindness, angina, MI, CHF, sexual dysfunction
 - Drug history
 - Family history of HTN and CVD
 - Duration
 - Previous treatment
- On exam, listen for renal bruit, fundi, LV hypertrophy
- Basic investigations:
 - Renal: urinalysis, albumin excretion, serum BUN or Cr
 - Endocrine: Na, K, Ca, ?TSH
 - Metabolic: Fasting glucose, lipids
 - Other: haematocrit, ECG
- Hypertensive Retinopathy:
 - Grade 1: tortuous retinal arteries, silver wiring
 - Grade 2: AV nipping
 - Grade 3: flame-shaped haemorrhages and cotton wool spots
 - Grade 4: papilloedema

- The older you are the more important is systolic over diastolic HTN
- Resulting pathology:
 - Most important cause of:
 - Stroke/ICH – treatment can ↓ by 35 – 40%
 - Premature cardiovascular disease
 - A major cause of:
 - Renal failure
 - Heart failure – treatment can ↓ by 50%
 - LVH
- Causes of secondary hypertension:
 - Common:
 - Renal:
 - Parenchymal disease: usually diabetic nephropathy or hypertensive nephrosclerosis
 - Renovascular: arteriosclerotic (renal artery stenosis)
 - Hyperaldosteronism (Conn's) – main presentation is HTN and normal K. See page 73
 - OSA
 - Uncommon:
 - Renal:
 - Renal cysts (including polycystic disease)
 - Renal tumours
 - Obstructive uropathy
 - Adrenal: Cushing's Disease, 17a, 11b hydroxylase deficiencies, pheochromocytoma
 - Endocrine: *both* hypothyroidism *and* hyperthyroidism, hypercalcaemia, acromegaly
 - Aortic coarctation
 - Pre-eclampsia/eclampsia
 - Neurogenic: psychogenic, dysautonomia, acute porphyria, acute ↑ICP, acute spinal chord section
 - Mendelian forms: many
 - Medications: high dose estrogens (eg *OCP*), adrenal steroids, decongestants, appetite suppressors, cyclosporin, TCAs, MOAIs, erythropoietin, NSAIDs, cocaine

Resistant Hypertension

- See NEJM 27 July 2006 – good article
- Definition: BP of at least:
 - 140/90, or
 - 130/80 in patients with diabetes or renal disease (Cr > 133 or 24 urinary protein > 300 mg)
 - Despite “good” therapy (ie triple therapy, including a diuretic)
- → more target-organ damage and ↑ CV risk
- Differential:
 - Exclude:
 - Most common cause: suboptimal medical therapy
 - *White Coat HTN* (?up to a third of “resistant patients”): *No evidence of end organ damage.* Check with home or 24 hour BP measurement
 - Poor compliance: check cost, side-effects, understanding of effects
 - Drugs: sympathomimetic drugs (phenylephrine, cocaine, amphetamines), herbal supplements (eg ginseng), anabolic steroids, appetite suppressants, EPO, NSAIDS (cause volume retention, and ACEI and loop diuretics are dependent on the availability of PGs)
 - Lifestyle: alcohol, salt, obesity (common in resistant HTN, and may require higher doses of anti-HTN meds)
 - Volume expansion (eg overloaded)
 - Underlying secondary causes: see Hypertension, page 17
- Treatment:
 - ↓alcohol, salt, weight and ↑exercise – see Treatment of Primary HTN, page 19, for benefits
 - Combination pills may improve adherence
 - Involvement of nurse specialists has been shown to improve BP control
 - Choose right diuretic:
 - Cr < 130 then thiazide
 - Cr > 130 then loop diuretic

- Short acting loop diuretics (eg frusemide) given once daily may → ↑renin – so give TDS
- Getting better mileage out of antihypertensives:
 - Cover all bases:
 - ↓volume load with diuretics/aldosterone antagonists
 - ↓sympathetic over-activity (β-blockers)
 - ↓vascular resistance: ACEI and ARBs
 - Smooth muscle relaxation: dihydropyridine CCBs and α-blockers
 - Direct vasodilation: hydralazine (although less well tolerated) – but will need β-blockers to counter reflex tachycardia
 - Balance them well – eg have an ACEI to cover the ↑renin from diuretics
 - Combined α and β blockers (eg labetalol and carvedilol) may get extra traction
 - Double up on classes, eg:
 - Combination diuretics: thiazide and spironolactone, potentially reduction up to 20 mmHg
 - Combination CCBs: dihydropyridine, eg amlodipine (incremental reduction ~ 6 mmHg)
 - ACEI + ARB (incremental reduction of 5 – 6 mmHg)
 - Centrally acting agents: Clonidine, α2-blockers

Treatment

Lifestyle changes

- Recommendation for pre-hypertension (120 – 139): Good evidence for weight reduction, Na restriction, aerobic physical activity and moderate alcohol consumption to reduce BP
- Weight loss:
 - Trials show *sustained* weight loss → ↓BP of 3 – 6/2 – 5. Popular diets don't work
 - Greater drops with gastric bypass
 - Slightly greater drop with weight-reducing drugs
- Exercise: regular aerobic exercise → ↓of 4.9/3.9
- Sodium restriction: reduction from 150 to 80 mmol/day caused 5/3 mmHg reduction
- Bottom line – small but clinically important differences from each of these

Drugs in General

- Joint Nation Committee (JNC 7) recommendations (Ann Int Med 2005;142: 433)
 - Stage 1 HTN and no other complications → diuretic as first choice
 - Stage 2 HTN: initial treatment with a diuretic and another class
 - Individualised treatment in diabetes, kidney disease, stroke: include ACEI
 - History of CVD: include B-blocker
 - Most patients will require 2 drugs – but 65% of doctors try to control with just one
- Key points:
 - ALLHAT (Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack): all classes of drugs reduced total and CV mortality equally – no benefit of ACEI over diuretics as first line treatment. α-blockers less effective than diuretics in prevent heart failure
 - Heart failure: ACE-I and diuretic/β-blocker based regimes more effective than CCB
 - Stroke prevention: CCB best
 - More intensive BP lowering → larger reduction in stroke and total cardiovascular events
 - Size of the reduction seems to be an important determinant of outcome
- Hyperuricaemia:
 - Diuretics ↑uric acid levels
 - ↑ uric acid → ↑ blood pressure and predicts target organ damage
 - But uric acid is an anti-oxidant and hence free-radical scavenger – balances out....?
- The future: Lancet 2008:371 reported a phase II trial of immunisation against angiotensin II that showed reduced BP at 14 weeks (gets around problems with compliance...)

Thiazides

- Moderately potent diuretics
- Inhibit sodium reabsorption at the beginning of the distal convoluted tubule
- Bendroflumazide (aka bendroflumethazide) 2.5 mg produces near maximal blood pressure lowering effect – higher doses cause ↓K, ↑Ca, ↑uric acid, ↑glucose and ↑lipids without any extra blood pressure effect
- Generally ineffective at GRF < 30 – need a loop

- Metolazone effective in combination with a loop diuretic in resistant oedema – but needs careful monitoring of electrolytes.

β-blockers

- See page 75 for α and β receptor function
- Classifications:
 - Water soluble:
 - Atenolol, celiprolol, nadolol, sotalol
 - Less likely to enter the brain → less likely to cause sleep disturbance and nightmares
 - Excreted by the kidney → accumulate in renal failure
 - Longer acting (ie once daily may be enough): atenolol, bisoprolol, carvedilol, celiprolol, nadolol
 - Cardioselective: β_1 selective (not specific): atenolol, bisoprolol, metoprolol (not sotalol – it has additional class III action). Better in asthma
 - Non-selective β -blockers (β_1 and β_2): propranolol
 - Additional arteriolar vasodilating action (ie β_1 , β_2 and α_1 which lowers peripheral resistance): Labetalol, celiprolol, carvedilol
- Use in hypertension:
 - Effect on blood pressure: not well understood, a combination of: ↓cardiac output (→ ↓cardiac work), alter baroreceptor reflex sensitivity, block peripheral adrenoceptors, some depress renin secretion, some ?central effect
 - Atenolol:
 - Provided no cardio-protection (?absence of 24 hour protection)
 - ASCOT: only slight reduction in stroke cf placebo
 - Meta-analysis showed B-blockers as a group showed the risk of stroke was 16% higher than other therapies, and in comparison with placebo ↓ stroke by only half of what was previously predicted
 - Cochrane Review 2007: Evidence does not support β -blockers (atenolol most common in trials) as first line treatment of hypertension – weak effect to reduce stroke and no effect on CVD vs placebo. Worse outcomes than CCD, ACEI and thiazides
- Other Uses:
 - Antiarrhythmic effect mainly by attenuating the effects of the sympathetic system on automaticity and conductivity
 - Heart Failure: bisoprolol and metoprolol reduced mortality in any grade of heart failure
 - Thyrotoxicosis: propranolol reverses clinical symptoms within ~ 4 days
 - Migraine prophylaxis (also TCAs and valproate have efficacy): propranolol, metoprolol, nadolol, timolol
 - Reduce the tendency for diuretics to cause hypokalaemia
 - Used for glaucoma, eg timolol
- Complications and SE:
 - Contraindicated in 2nd and 3rd degree heart block
 - Sexual dysfunction, adverse blood-lipid changes, *small but significant weight gain*
 - In diabetes can lead to a small deterioration in glucose tolerance and interfere with metabolic and autonomic response to hypoglycaemia. Associated with ↑*insulin resistance* (?part of the reason why they don't work so well for CVD compared to other agents) – carvedilol (non-selective) doesn't affect insulin resistance
 - Care with β -blockers and verapamil together, and never iv verapamil when on oral β -blockers due to risk of asystole
 - Cessation → ↑arterial hypertension and 4 fold risk of a CV event in the following months
- Multiple polymorphisms identified in the β_2 receptor appear linked to specific phenotypes in asthma and CHF, and are related to responses to β_2 receptor agonists in asthma

Renin-angiotensin-aldosterone system

- See page 73 for pathophysiology
- ACEIs and ARBs:
 - ACEIs block ACE: so angiotensin II type 1 and 2 receptors not stimulated
 - Angiotensin-receptor blockers block angiotensin II type 1 receptor and stimulate type 2 receptor
 - Both ACEI and ARBs demonstrated in heart failure, data for equivalence of ARBs in other settings less robust:
 - TRANSCEND trial: No dramatic difference between Telmisartan and placebo in high risk patients intolerant to an ACEI (already variously treated with statins, β -blockers, aspirin). No

reduction in incidence of diabetes or admissions for CHF (other ARBs has shown this in post-hoc analysis). Powered to find too high a risk reduction? Safe of ACEIs (all were intolerant)

- HOPE (Heart Outcomes Prevention Evaluation): Ramipril reduced primary endpoint by 22%, but less use of statins, β -blockers and aspirin (? \rightarrow \uparrow impact from additional therapies)
- ONTARGET: telmisartan non-inferior to ramipril – but combination had more adverse events
- Spironolactone and Eplerenone are an aldosterone-receptor blockers
- Aliskiren:
 - Renin increases whenever ACEI or ARBs are used long term
 - Renin exerts actions through a renin receptor independent of production of angiotensin
 - Aliskiren is an oral renin inhibitor
 - Measured renin may increase as most assays also measure pro-renin which is inactive
 - Doesn't decrease BP in normotensive patients but lowers elevated blood pressure
 - Role versus ACEI and ARBs as yet unclear
 - AVOID Trial (NEJM 5 June 2008) 599 patients with Aliskiren + losartan vs placebo + losartan reduced urinary albumin-to-creatinine ratio by 20% in patients with HTN and T2DM with neuropathy. Those with high potassium or GRF $<$ 30 excluded (potentially at risk from renin blockade)

Calcium Channel Blockers

- Block inward movement of Ca through slow ion channels \rightarrow effect on myocytes, conduction systems and vascular smooth muscle
- Dihydropyridine CCBs:
 - Amlodipine, felodipine, nifedipine
 - For angina (including with coronary vasospasm) and HTN. Do not reduce cardiac contractility
 - SE: vasodilation (\rightarrow flushing and headaches) and ankle swelling (which may be resistant to diuretics)
- Non-dihydropyridines:
 - Avoid in heart failure \rightarrow further depress function
 - Verapamil: treatment of angina, HTN and arrhythmias, highly negative inotrope, contra-indicated with β -blockers, SE constipation
 - Diltiazem: effective for angina, long acting forms for HTN, less negatively inotropic than verapamil. Can still cause bradycardia with β -blockers

Therapy for specific complications

- CHD:
 - Comparable degree of protection from therapy based on diuretics +/- beta-blocker, ACE-I and CCB
 - More trials on ARBs required (did not reduce MI as much as placebo, beta blockers, CCBs or ACEI). ONTARGET Trial (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial, NEJM 2008:358). Head to head trial (ie non-inferiority) of ACEI and ARB in high risk patients – similar reduction in BP (a little more with combination). Equivalent outcome in both arms, with more side-effects and no treatment benefit from combination
- Stroke: Dihydropyridine CCBs (eg amlodipine, felodipine, nifedipine) significantly reduce stroke by 10% compared to other therapies
- Renal Disease: By strict evidence ACEI should be used in T1DM and ARB in T2DM – no different in renal outcomes between the two but only ACEIs were shown to prevent death

Renal Vascular Disease

Renal Artery Stenosis

- Only 2 – 3 % of the hypertensive population
- Suspect if:
 - Young, or old and new HTN (old people don't suddenly develop HTN)
 - Severe or refractory HTN: BP recently harder to control or $>$ 3 drugs required
 - History of other vascular disease
 - Renal function deteriorates with ACEI or ARB. Kidney is hypo-perfused due to stenosis in afferent blood flow, GFR is dependent on Angiotensin II vasoconstriction of the efferent arteriole. An ACEI will vasodilate the efferent arteriole \rightarrow \downarrow GFR
 - Abdo bruit
 - "Flash" pulmonary oedema

- Unilateral small kidney (most kidney diseases are bilateral, if just one think ?vascular)
- Screening not particularly useful unless something will be done about it
- Diagnosis:
 - Angiography the gold standard
 - CT (beware contrast load if ↓GFR) > MRI (beware gadolinium if GFR < 30 → nephrogenic systemic fibrosis) > US (harder with ↑BMI) > Captopril renogram (nuclear medicine scan)
- Treatment:
 - Little evidence in either unilateral or bilateral that angioplasty, stenting or surgery is any better than medical management [eg even cautious use of ACEI] in most cases (unless onset of HTN at < 30 years, severe HTN > 55 years, or resistant or malignant HTN)
 - Angioplasty of little value alone, trials underway for stenting (CORAL). Complications include cholesterol emboli
 - Repair does reduce the incidence of renal artery thrombosis (but that may even be a good thing if you knock off that kidney → ↓renin and the other kidney's OK), but BP may still remain high after repair

Fibromuscular Dysplasia

- See NEJM 29 April 2004
- Unknown cause
- More common in young females 20 – 40
- Affects renal and carotid arteries mainly
- Usually middle or distal portions of the artery in a young person without CVS risk factors, compared with atherosclerosis occurring in the original or proximal portion of an artery in an old person with risk factors
- Types:
 - Medial hyperplasia the most common subtype → tortuous “beaded” lumen on angiography
 - Intimal fibroplasia: long, smooth, concentric stenosis
 - Adventitial hyperplasia – rare
- Treatment very successful with PTA +/- stent

Malignant Hypertension

- Hypertensive emergency: A high BP (SBP > 200, DBP > 120) which is complicated by acute target organ dysfunction (brain, heart, kidney)
- Presentation:
 - Retinopathy (retinal haemorrhages, exudates and papilloedema): aka accelerated HTN
 - Hypertensive encephalopathy (headache, nausea, vomiting → restlessness, ↓LOC, seizures. Principally due to oedema): T2 MRI may show white matter oedema. BP doesn't need to be very high – but urgent treatment required. Eg occurs in dialysis patients with a bit of overload and have forgotten their pills for a few days, and present with headache, visual loss, and confusion. May have odd seizures (eg focal with retained consciousness)
 - Malignant nephrosclerosis
- Pathophysiology: if severe, necrotising vasculitis of arterioles, renal failure, heart failure, microangiopathic haemolytic anaemia and DIC
- Causes: in addition to the general HTN differential, consider:
 - Renal: Acute renal occlusion, acute GN, vasculitis, scleroderma
 - Endocrine disorders
 - Eclampsia
 - Vasculitis
 - Drugs: cocaine, amphetamines, cyclosporine, β-blocker and Clonidine withdrawal
 - Spinal chord injury → autonomic hyperactivity
- Treatment:
 - Often MRI to exclude stroke or haemorrhage (although these occur with more sudden onset), as these aren't treated with such aggressive BP lowering
 - Early features: β-blocker, CCB
 - Late features:
 - In no LVF then labetalol infusion
 - If LVF then nitroprusside: arteriolar and venous dilator, short half life so good control (drug of choice if LVF or encephalopathy, but only for 48 hours otherwise SE from a cyanide metabolite) or hydralazine (may provoke angina)

- Pulmonary oedema: frusemide
- Cautious start of ACEI (given likely very high levels of renin) – first dose can cause hypotension
- Aim to lower DBP to 100, or by 15 – 20, over the first 24 hours (1 – 2 hours if encephalopathy)

Ischaemic Heart Disease

- For Lipid disorders, see page 61
- Vast number of variable quality trials
- Risk Stratification:
 - Framingham Risk Score: underestimates long term risk amongst younger people
 - INTERHEART Study (Lancet 2004:364): Population attributable risk of first MI due to:
 - Dyslipidaemia 49%
 - Hypertension 18%. Cumulative history more important than recent. Pulse pressure (large artery compliance) also predictive
 - Diabetes 10%. Copenhagen Heart Study showed 2 -3 times ↑risk of IHC. Treat all diabetes as for secondary prevention (except new evidence that aspirin adds no benefit if no history of IHD)
 - Smoking 36% (more predictive in men than women)
 - Family history: 20% of attributable risk. Males only if < 60 and first degree. Females < 80 and first degree
 - Lack of exercise 12% of attributable risk. Peak exercise capacity a stronger predictor of mortality than any other risk factor – each extra MET achieved was 12% protective (Myers, NEJM 2002)
 - Lipids: Debate about how to measure lipids: *LDL (most important)*, and HDL cholesterol, or, for example, Apolipoprotein B/A1 – better for risk prediction in some large studies (eg AMORIS prospective study of 175 000 individuals in Sweden, INTERHEART case-control study of 9000 patients – Lancet 19 July 2008)
- Other markers of risk:
 - Bio-markers:
 - Additional risk capture by any one biomarker is modest → attempts to meaningfully combine multiple biomarkers
 - hs-CRP: highest quartile 2 – 3 times the risk of the lowest quartile
 - Troponin I, NT pro-BNP, cystatin C and CRP improve risk stratification (NEJM 15 May 2008, sample was a relatively healthy group of 71 year old men). Cystatin C more accurately reflects glomerular filtration than Cr
 - Carotid Intima Media thickness: every 0.2 mm in IMT increases risk by 20%. ?just a marker for HTN and ↑lipids
 - Carotid bruit are associated with increased risk of MI and CVD death (Meta-analysis Lancet 10 May 2008)
 - Coronary Calcium Score (assessed by CT) is an independent risk factor over and above standard Framingham assessment – but unclear if this changes anything in terms of management. Is it just assessing atheroma? Just treat clinically
 - Hyperuricaemia and homocysteine are risk factors for CVD (no trial shows benefit of folate)
- COX-2s:
 - Selective COX2 inhibition → ↓prostacyclin but does not affect thromboxane A2 (theoretical double whammy)
 - Can also → ↑ BP
 - Rofecoxib: NNH was 139 for excess cardiac events (APPROVe trial)
 - Celecoxib: RR 3.5 with 400 mg bd, 2.5 with 200 bd (fairly high doses)
- Socio-economic inequalities in coronary disease could be largely eliminated by best-practice interventions on four classic risk factors: smoking, cholesterol, blood pressure, and diabetes (Lancet 8 Nov 2008). These risk factors cause 80% of coronary disease

Angina/Chest Pain

- Diagnostic strategy with chest pain:
 - Intermediate risk: further diagnosis to shift to high or low risk (eg ETT)
 - Low risk: optimise medical therapy and discharge for follow up
- TIMI Risk score: which factors predict adverse outcome, prospectively validated:
 - Age > 65
 - ≥ 3 CAD risk factors

- Prior stenosis > 50%
- ST deviation
- ≥ 2 anginal events ≤ 24 hours
- Aspirin in the last 7 days (ie had an event while on aspirin)
- Elevated cardiac markers (principally Trop)
- Assessment of Chest Pain:

	Sensitivity	Specificity
ETT	68%	70%
Nuclear Imaging	87 – 92%	80 – 85%
Stress Echo	80 – 85%	88 – 95%

- Exercise Treadmill Test:
 - Not suitable for WPW, > 1 mm depression at rest, taking digoxin, or with hypertrophy on ECG, as these interfere with interpretation
 - Is better at picking up 3 vessel disease, worse at single vessel
 - 1 MET = 3.5 ml O₂/kg/min (equivalent to O₂ requirement seated at rest). On Bruce Protocol (there are others) Stage 2 = 7 METS, Stage 3 = 10 METS
 - Adverse predictors:
 - Low workload (< 5 METS) predicts worse survival in both normal and IHD. In the elderly is probably the most significant indicator
 - Systolic pressure should \uparrow and diastolic pressure should \downarrow with exercise. Fall in BP with exercise suggests LMS disease. Slow fall in BP during recovery also bad
 - > 1 mm flat or down-sloping ST depression during exercise or recovery (sensitivity 60%, specificity 90%). If occurring in Stage 1 or 2 then 85% 1 year survival
 - Exercise limiting angina, or occurring at low workload
 - Chronotropic incompetence: failure to achieve 85% of age adjusted heart rate
 - Interpretation:
 - ECG sensitivity and specificity as low as 60 – 70% (\Rightarrow test accuracy as low as 50% – may as well toss a coin for a middle aged woman with atypical pain)
 - The lower the risk of a person having an ETT, the worse the positive predictive value, so treadmilling a low risk person may not help with diagnostic certainty. So use for assessment of stable angina or a suspicious story, not for assessment of atypical chest pain
 - Determinant of positivity is ECG change not chest pain
 - False positive rate higher in a low risk group, higher in women
 - False negatives in diabetics, men with multiple risk factors, previous CABG/stents and poor exercise tolerance
 - Duke Treadmill score is a validated formula using exercise, size of ST depression and presence of angina to risk stratify patients
 - Normal treadmill \Rightarrow medical therapy = surgical therapy (ie CABG). Abnormal treadmill \Rightarrow surgery > medical (consistent finding in 4 studies)
 - Nuclear imaging (Thallium/Mibi) looks for abnormal perfusion that normalises with rest (recovery pictures done 3 – 4 hours later). Has less inter-observer variability but comes with radiation
 - Stress echo looks at wall motion at rest then at \uparrow rate, relies on good image quality but gives EF estimate and valve assessment
 - CT angiography: Diagnostic not therapeutic. Requires slow heart rate (60 – 70 bpm), images acquired in diastole so AF and VEs a problem. Can look for non-cardiac diagnosis for chest pain. High radiation dose but coming down, requires contrast... Artefact from Ca and stents. Need to hold breath for 15 – 20 seconds. Negative predictive value of 98 – 99%. Sensitivity (cf angiography) of ~ 85 – 95%. Excellent for CABG grafts (usually large vessels)
 - MRI: very good at looking at structure, not at vessels
- Medical vs PCI management: COURAGE Trial (14 August 2008) of optimal medical therapy (21% had PCI within 3 months) vs initial PCI in patients with stable angina with 4.6 years follow up – similar rates of death and MI, both groups showed substantial improvements in health status. Initial small quality of life benefit for PCI lost by 24 months. NNT for 1 patient to show benefit in angina frequency or quality of life was 17 PCIs. High crossover from medical to PCI arm
- A German trial (Circulation, 2004;109:1371-8) did an RCT of PCI with stenting vs 12 months exercise (20 minutes a day on an exercycle) in patients with stable single vessel disease. The exercise group did better with fewer symptoms, fewer hospitalisations and less disease progression
- Top shelf treatments:
 - Nicorandil (K channel activator): reduced death/MI in study of 5216 patients with stable angina

- Perhexiline: Inhibits fatty acid metabolism → shift to glucose oxidation which is more metabolically efficient. Older drug. Narrow TI. Needs monitoring to prevent hepatotoxicity and peripheral neuropathy
- Ranolazine (Lancet 11 October 2008): New antianginal. Mechanism unknown, ?selective inhibitor of late sodium influx → attenuates the abnormalities of ventricular repolarisation and contractility associated with ischaemia. Increases exercise tolerance. SE dizziness, constipation, nausea, and QT prolongation. CYP3A substrate. Drug interactions with digoxin, simvastatin and verapamil. NNT of 60 (21.8 vs 23.5%) for composite of cardiovascular death, MI or recurrent ischaemia. No head to head or combination trials with Duride, Nicorandil, etc
- Ivabradine: specific inhibitor of the If channel (I for inward, f for funny current!) in the SA node, which slows heart rate. Is antianginal, also thought (not proven) to reduce plaque load. In those with IHD, systolic dysfunction and on a beta-blocker with HR > 60, it reduces MI, angina and revascularisation, but not mortality, only in those with a heart rate > 70 (no change if heart rate was < 70). The study also noted HR > 70 is a risk factor for worse outcomes. Lancet 6 Sept 2008

Myocardial Infarction

- See Lancet 16 August 2008 (good review)
- Prevalence and mortality are both falling
- Risk stratification:
 - Guides treatment:
 - Low risk, hard to make better
 - High risk, more bang for your treatment dollar
 - Poor prognostic factors: age > 75, rest pain lasting > 20 mins, haemodynamic instability, pulmonary congestion, new or worsening MR murmur, presence of a third heart sound
 - ECG findings (more sensitive during pain):
 - ST depression is predictive of three vessel disease or LMS coronary disease – bad. Worse than ST elevation. > 2mm depression → trop rise
 - There is a relationship between size of ST elevation and risk
 - T wave inversion without ST shift → intermediate risk
 - Q wave was supposed to correlate with full thickness (and therefore an occluded artery) but angiography has shown it's use to be unhelpful
- Lesions:
 - Most lesions causing stable angina are > 70% luminal diameter and rarely cause infarction
 - Most lesions causing MI are only 20 – 30% of luminal diameter (prior to becoming unstable). The plaque is more lipid with more macrophages

NSTEMACS

- ECG change is a stronger predictor of 30 day mortality than ↑ Trop
- Serum markers:
 - Troponin T or I are markers of choice:
 - Significance of minimal rises unknown – can't see it on an echo
 - Sensitivity and specificity 80 – 90% for MI
 - Lots of things cause an ↑:
 - Cardiac: CHF (~ 30% of stable CHF), tachyarrhythmias, DC cardioversion
 - Non-cardiac: renal failure, PE, acute exacerbation COPD, sepsis, SAH, stroke, chemotherapy (ie anything that makes you really sick)
 - Level of risk proportional to Trop rise → helps risk stratification
 - < 0.4 1% 42 day mortality
 - > 9.0 7% 42 day mortality
 - Maximum sensitivity is around 12 hours, 9 hours pretty good. Myoglobin is 60% sensitive at 3 hours
 - BNP adds further prognostic value
 - Myoglobin, heart fatty acid binding protein and CKMB are earlier markers (may be helpful in LBBB ?new) – but don't add further prognostic info to ↑Trop
 - CKMB to diagnose reinfarction within 14 days. Rises within 2 – 8 hours, falls in 1 – 3 days
 - High sensitivity CRP, interleukin-6 and CD-40 ligand have independent prognostic information – but measurement not recommended
 - LDH overtaken by other tests. Non-specific. Rises later (24- 48 hours) and ↑ for 7 – 14 days
- Aspirin:

- Inhibits platelet cyclooxygenase (COX-1), blocking Arachidonic Acid → Thromboxane A2
- Unless contraindicated: relative risk reduction of 25% regardless of indication
- In STEMI is equivalent to streptokinase alone (added benefit from both) – Lancet 1998
- Absolute risk reduction of ~5% across a number of trials in unstable angina
- Clopidogrel:
 - Irreversibly blocks ADP (P2Y₁₂) receptor on platelets
 - Takes 5 – 7 days to reach maximum effect if no loading
 - 600 mg loading dose inhibits platelet function faster than 300 mg. About 3 hours to onset. Being trialled in MI
 - Caution with renal and liver impairment, CI in breastfeeding, SE dyspepsia, abdo pain, diarrhoea, bleeding, less commonly leucopenia, ↓platelets, eosinophilia, rash, pancreatitis, hepatitis
 - Is metabolised to the active metabolite by 2C9 and 3A5. Two loss of function alleles of 2C9 (and therefore ↓activation) is associated with worse outcomes, especially following PCI (event rates of 21.5% vs 13.3%) NEJM 22 Jan 2009. Coadministration with omeprazole also ↓ effect (competes for 2C9 elimination)
 - CURE trial: 12,562 patients (77% managed conservatively), clopidogrel in combination with aspirin for up to 12 months. Death, non-fatal MI and stroke reduced from 11.5% to 9.3% (P<0.001). 20% reduction in relative risk, NNT 50. ↑major bleeding (3.7 vs 2.7%), so the main value is in high risk groups where benefit outweighs risk. Most of the risk reduction is early on (so Pharmac only approved it for 3 months). In PCI-CURE (post stenting) 1 year composite endpoint of 12.6 vs 8.8 for aspirin alone
 - Excess of major bleeding, but life threatening bleeding not increased
 - If CABG within 5 days then increase in major bleeding from 6.3 to 9.6% (P = 0.05) – compared with 7 major events per 1000 prevented within the first 24 hours with clopidogrel – but this was ↑ test tube drainage, actually trend to ↑survival with clopidogrel. Withhold for 5 days before CABG
 - PRI-CURE trial: pre-treatment with clopidogrel for 10 days prior to PCI → ↓30 days composite or death, non-fatal MI or urgent revascularisation (4.6% vs 6.4%, p = 0.03)
 - CAPRIE trial: patients with previous MI, stroke, PVD. Clopidogrel vs aspirin was better at reducing vascular death, MI and ischaemic stroke
 - CHARISMA trial: High risk but stable CVS patients: aspirin vs aspirin + clopidogrel in 15,000. No difference in death, MI or stroke
 - Prasugrel is a more potent platelet P2Y₁₂ receptor antagonist than clopidogrel, can be given iv and has a short half life. May be greater benefit in stented patients than clopidogrel (excess bleeding reported in other uses). Lancet 19 April 2008
- High risk patients: aspirin, clopidogrel, heparin or LMW heparin, beta-blocker, +/- tirofiban or eptifibatide
- Antithrombin:
 - Meta-analysis of enoxaparin trials shows a 9% reduction in death and MI at 30 days compared to therapy with UFH (data was never that robust for UFH...)
 - Pentasaccharides: the “active” part of heparin, current trials suggest ‘not-inferior’ to LMWH
- Beta-blockers:
 - No strong evidence base in NSTEMI – but may reduce progression. Evidence of benefit in unstable angina (less progression but no difference in mortality). If beta-blockers are contraindicated, diltiazem should be given (evidence of relief of symptoms, maybe a protective effect. Nifedipine – a dihydropyridine – increases mortality)
 - COMMIT trial: Clopidogrel and Metoprolol in MI trial – all previous evidence of β-blocker use was pre-thrombolysis. This trial evaluated in the current treatment context. Early β-blockers → ↓arrhythmic death, ↑heart failure death ⇒ use unless if CHF or shock
- IIb/IIIa antagonists:
 - 4 different agents with different pharmacology in different risk groups
 - Types:
 - Abciximab (Reopro) – irreversible. Prevents binding of fibrinogen and vWF to GP IIa/IIIb receptors. GUSTO V Trial. Small risk of severe thrombocytopenia
 - Tirofiban – reversible (in about 6 hours). Prism Plus Trial in Unstable angina – benefit only with heparin (alone was worse).
 - Not useful with thrombolysis – just high risk PCI (EPISTENT Trial):
 - Abciximab superior to Tirofiban in PCI (ie use post-angio if clot seen on angio)
 - Tirofiban superior in trop +ive ACS (ie as a bridge to angio)

- ST depression > 0.5 mm, elevated troponins and/or diabetes: better outcomes with IIb/IIIa antagonists
- NO benefit if troponin negative or low risk, or if not going to revascularise
- No oral agents – all showed ↑ mortality in PCI and ACS
- PCI:
 - An early invasive strategy together with intensive antithrombotic therapy is recommended for patients with ↑Troponin (level 1++A), diabetes, continuing ischaemic symptoms at rest or mild exertion despite medical therapy, and patients with interstitial or pulmonary oedema
 - Benefit in ↑Trop (stops representation, ↓mortality), minimal if Trop –ive
 - Elderly at highest risk
- Nitroglycerine: vasodilate that works mainly by ↓preload
- NSAIDs are bad

STEMI

- See Cardiac Society of Australia and New Zealand Guidelines 2006
- Greatest gains in terms of lives saved will come from increasing the number of patients treated with reperfusion, and on time, compared with novel therapies. Eg increasing the number reperfused would save 270 lives per 10,000 STEMI patients. A novel therapy reducing mortality by 20% to patients receiving optimal PCI (PCI less than 2 hours) would save 1 life per 10,000 STEMI (Lancet 16 August 2008)
- Diagnosis:
 - STEMI: ST elevation at the J point of ≥ 2 mm in chest leads V1-3 *or* > 1 mm in 2 contiguous leads *or* presumed new LBBB.
 - Inferior infarctions: do V3R and V4R to detect right ventricular infarction
 - Posterior recordings V7-9 if a posterior MI (circumflex) is suspected – normal ECG may show ST depression in V1 – 4 and tall R waves and upright T waves in V1-3
 - Anterior wall: V2 – V4
 - Anteroseptal wall: V1 – V3
- Should have aspirin and clopidogrel (<75 years load with 300 mg, if > 75 then no loading) unless contraindicated
- Percutaneous Intervention (PCI):
 - In the absence of persistent ST-segment elevation acute reperfusion confers no benefits and may even be harmful
 - PCI only extends life in STEMIs and recurrent pain (ie those most likely to die)
 - If present within 12 hours of onset of ischaemic symptoms should have a reperfusion strategy implemented. Within 3 hours of onset, considerable myocardial salvage
 - Aim is prompt reperfusion:
 - Only 20% benefit from thrombolysis from 4 – 6 hours
 - GUSTO-1:
 - < 2 hrs to reperfusion had 30 day mortality of 6%
 - > 2 hrs to reperfusion had 30 day mortality of 10%
 - Lots of focus on early triage and pre-hospital fibrinolysis or direct to cath lab
 - PCI is the treatment of choice. Maximum acceptable delay from presentation to balloon time if presenting after 1 hour of symptoms is 60 minutes, or 90 minutes if presenting later. Otherwise consider fibrinolysis
 - PCI generally superior (↓mortality, ↓recurrent MI, big ↓ in recurrent ischaemia), but early presentation fibrinolysis may be better (PRAQUE, GUSTO-1 and CAPTIM studies – ?clot susceptible to thrombolysis early on)
 - If transfer can be achieved within 3 hours, transfer for primary PCI is superior to lysis (DANAMI-2 trial in Denmark) – mainly driven by reinfarction rates
 - Facilitated PCI (ie giving thrombolysis and/or IIb/IIIa inhibitors immediately before doing PCI) is worse than PCI alone
 - Rescue PCI:
 - Failed to re-perfuse after thrombolysis. Lack of ST resolution by 30% of baseline indicative of failed reperfusion → consider rescue
 - No ideal criteria for “failure” – usually failure for ST segments to drop by > 50% over 90 minutes, or ongoing arrhythmia, or shock. Better indicator than pain
 - REACT trial: rescue better than no treatment or re-thrombolysis (but the bigger the infarct, the more there is to gain – saving every bit of myocardium counts)

- Late Presentation: Occluded Artery Trial: no benefit from opening an occluded artery in all comers – but only if there is on going ischaemia (eg on stress echo) ⇒ needs careful selection
- For Left Main Stem disease, debate continues over whether PCI or CABG is superior. MAIN-COMPARE study, NEJM 24 April 2008, showed equivalent endpoints but ↑ need for revascularisation in PCI group. Head to head RCT needed
- Bivalirudin (a direct thrombin inhibitor) better than heparin + Iib/IIIa inhibitor in Primary PCI, is equal in outcomes, but fewer side effects (major bleeds) and mortality (NEJM 22 May 2008, 14 August 2008)
- Initial trial evidence shows that cyclosporine at the time of PCI limits infarct size by reducing reperfusion injury (NEJM 31 July 2008), mechanism involves mitochondrial inhibition
- Fibrinolysis:
 - Fibrinolysis: 2nd generation bolus agents are the treatment of choice
 - Door to balloon time of 90 minutes roughly equivalent to door to needle time of 30 minutes (thrombolysis takes time to work)
 - Risk of bleeding: 1% intracranial, 2% other life-threatening
 - 5 week absolute benefit is 3% for lysis within 5 – 6 hours
 - No benefit in cardiogenic shock
 - Streptokinase is inappropriate if previous exposure to the drug or in Aboriginal/Torres Strait Islanders. If using and hypotension – 250 ml bolus normal saline * 2 – 3. If allergy or fever, hydrocortisone +/- promethazine
- Nitrates: two large randomised controlled trials showed no significant benefit from nitrate therapy in persistent STEMI
- Antithrombin therapy (eg heparin) should be given in combination with PCI or fibrinolytic therapy but is optional in conjunction with streptokinase
- Glycoprotein IIb/IIIa inhibitors:
 - Data suggests more platelet inhibition (over aspirin/clopidogrel) is beneficial
 - Blocks fibrinogen receptor on platelets
 - eg abciximab – RrePro (~\$2,000 per patient), tirofiban – Aggrastat – shorter half life than abciximab
 - In conjunction with PCI, but generally avoid or give a ↓dose with fibrinolytics
 - PURSUIT trial: Aspirin + Heparin + Iib/IIIa of benefit (Clopidogrel not around then)
 - CAPTURE trial: Abciximab of benefit given close to PCI
 - If Trop +ive (ie high risk) and:
 - No PCI then small benefit
 - PCI then treat prior to PCI: ↓reinfarction while waiting and ↓ peri-procedural MI
 - But if clopidogrel used, do you still need Iia/IIIb – answer seems to be yes, if high risk
 - Key issue is getting it on board quickly enough – On-TIME 2 trial (Lancet 16 August) showed benefit from pre-hospital administration
- Adjunctive therapies:
 - O₂ to keep sats at 96% – higher concentrations ↑arterial vasoconstriction and ↑afterload
 - Beta-blockers: 5 mg iv every 2 minutes up to 15 mg then 50 mg at 15 min (unless asthma, SBP < 110, HR < 50, 2nd degree type 2, 3rd degree HB). If heart failure, start after 24 – 48 hours
 - ACEI: if CHF, anterior infarction or previous MI, ACE at 2 hours if BP > 100 mg. Start low. Start in all others on day 1. If low BP then ACEI preferred over beta-blocker
 - RV infarction: at least 2 litres fluids in first 24 hours
- Angiography: two approaches:
 - Initial invasive (routine angiography) vs initial conservative strategy (ie selective angiography) – a lot of evidence is from the US where conservative treatment is usually aggressive so “do nothing” trials are hard to recruit to – lots of selection bias as no-one will enter a high risk person
 - Do it if ischaemia symptoms or ECG changes despite medical therapy, or ischaemic changes from stress test
 - All patients who would be candidates for CABG. GRACIA 1 showed lower incidence of combined rate of death, reinfarction and revascularisation at 1 year
 - All patients should have echo and undergo some form of stress testing (day 5) if they have not had angiography

Secondary Prevention

- Before discharge initiate antiplatelet, β-blocker, ACEI (esp DM, CHF, EF < 40%, HTN), statin
- Aim for BP 135/85, incremental benefit down to 115

- No driving for 2 weeks
- Consider ICDs in patients who, despite medical therapy, have persistently depressed LVEF more than 6 weeks after STEMI
- If LV thrombus then warfarin for 3 – 6 months and repeat echo. If low EF and no thrombus, treatment controversial
- Education
- Cardiac rehabilitation services
- Assess for depression and level of social support
- Dipyridamole does not confer any additional reduction in coronary events when added to aspirin
- Succinobucol (antioxidant) given after ACS has no effect on composite endpoint, but a variety of beneficial and harmful other clinical outcomes (fewer MIs, strokes, worse lipids and BP) (Lancet 24 May 2008)

Stents

- Balloon angioplasty (from 1980): 40 – 50% of target vessels “bounced back” within 12 months
- Bare-metal stents (1990’s, \$600 – 1000) reduced the rate of revascularisation to ~10%. But → endothelial proliferation → *restenosis*. Risk highest in diabetics and small calibre vessels. Presents with angina, not infarction (ie annoying but not fatal)
- Drug eluting stents (\$2,500 – 5,000):
 - Local immunosuppression stops re-stenosis, but may affect the vessel wall
 - Are not FDA approved for primary angioplasty
 - Sirolimus:
 - Produced by *Streptomyces hygroscopicus*
 - Binds to FK506 binding protein inhibiting a kinase → ↓IL-2 and IL-4 cell driven proliferation and an inhibition of smooth muscle cell migration
 - No action of calcineurin (cf Tacrolimus)
 - Sirolimus coated stents → ↓re-stenosis
- Small studies and retrospective studies (but not large RCTs) shows drug-eluting stents are better than bare metal for revascularisation and possibly mortality (NEJM 25 Sept 2008). Lots of revascularisation was driven by mandated repeat angiograms, not by clinical symptoms
- In-stent *thrombosis*:
 - Thrombosis in a stent before it has endothelialised (4 – 6 weeks with BMS)
 - Presents with STEMI and mortality of 45 – 60%
 - Clopidogrel reduces this
 - Late stent thrombosis in BMS (beyond 6 months) is incredibly uncommon – so aspirin alone is safe
 - Drug eluting stents don’t endothelialise well, so greater risk of in-stent thrombosis ⇒ need clopidogrel for longer
- ⇒ a relatively safe problem (restenosis) has been replaced by a less common but devastating problem (in-stent thrombosis)
- Surgery vs Stenting:
 - For patients with multi-vessel disease, CABG is associated with lower rates of death, MI or repeat vascularisation than drug-eluting stents (NEJM 2008:358-4) [SYNTAX Trial]
 - Otherwise surgery and stenting probably equivalent in terms of survival, but much higher risk of revascularisation if stented
 - In stable patients there may be no benefit to multi-vessel PCI over plain medical management
- Trials are underway of biodegradable drug-eluting stents with a view to reduce late stent restenosis. A bare metal stent is coated with a biodegradable polymer (as opposed to a non-biodegradable polymer) which releases the sirolimus (or equivalent). Over time the drug and polymer dissolve, leaving a bare metal stent (by about 9 months)

Cardiomyopathy

- Types:
 - Dilated (D): RV and/or LV enlargement, impaired systolic function, CHF, arrhythmias. 1/5 to 1/3 have a family history usually with autosomal dominant transmission
 - Restrictive (R): Endomyocardial scarring or myocardial infiltration resulting in restriction of filling
 - Hypertrophic (H): disproportionate LV hypertrophy, typically involving septum > free wall
- Characteristics findings of each on CXR, ECG, echo, radionuclide studies and catheterisation
- Causes:

- Primary myocardial involvement:
 - Idiopathic (D, R, H)
 - Familial (D, R, H)
 - Eosinophilic Endomyocardial disease (R)
 - Endomyocardial fibrosis (R)
- Secondary:
 - Chronic uncontrolled tachycardia
 - Infective (D): viral, bacterial, fungal, protozoal myocarditis (Chagas disease, caused by *Trypanosoma cruzi*, insect transmission in Central/South America, ~18 million affected), spirochetal (ie Lyme disease), rickettsial
 - Metabolic (D): Hypothyroid
 - Familial Storage Disease (D,R): glycogen storage disease, mucopolysaccharidoses, haemochromatosis
 - Deficiency (D): electrolytes, nutritional
 - Connective Tissue Disorders (D): SLE, polyarteritis nodosa, RA, progressive systemic sclerosis, dermatomyositis, Duchenne's
 - Infiltrations and granulomas (R,D): amyloidosis, sarcoidosis, malignancy, carcinoid
 - Neuromuscular (D): muscular dystrophy, myotonic dystrophy, Friedreich's ataxia (H,D)
 - Sensitivity and toxic reactions: alcohol (increased risk with a polymorphism of alcohol dehydrogenase and DD form for ACE gene), radiation, drugs (cocaine!), chemo (anthracyclines such as Adriamycin/doxorubicin – dose dependent myocyte damage. May recover some function with aggressive ACEI use. Also trastuzumab/Herceptin and cyclophosphamide)
 - Peripartum heart disease (D): last trimester through to 6 months post partum. Cause unknown. More common > 30, African, multiparous. May remit. 10% mortality
 - Tak-Tsubo (Stress) cardiomyopathy: Apical ballooning syndrome. Abrupt onset of severe chest discomfort following stress. Women > 50. ST elevation in chest leads
- General Management: Dilated: usually die within 4 years of symptoms. Avoid alcohol, CCB and NSAIDs. Consider ICD or CRT. Consider anticoagulation

Restrictive Cardiomyopathy

- Suspect where:
 - Predominant RH failure
 - LV systolic function relatively preserved
 - Diastolic dysfunction
 - Atria dilated (→ AF)
 - AV regurgitation is severe
- Differential:
 - HTN, HOCM
 - Infiltrative disease: amyloid, glycogen storage disease, haemochromatosis, sarcoidosis
 - Interstitial disease: idiopathic, familial, radiation, chronic allograft rejection
 - Pericardial disease, especially constrictive. Clinically differentiating constrictive pericarditis from cardiac tamponade:
 - Y descent (rapid ventricular filling following the opening of the tricuspid valve) is sharp in constrictive but absent in tamponade
 - Kussmaul's sign is present in both: more marked ↑ in JVP on inspiration (→ ↑ venous return), due to limited ventricular filling – present in any condition in which right ventricular filling is limited (constrictive pericarditis, cardiac tamponade, RV MI)
 - Primary pulmonary hypertension
- Treatment: poor response

Myocarditis

- Causes:
 - Usually infectious (esp Coxsackievirus B, adenovirus, Hep C and 10% of HIV, ¼ of patients with diphtheria), may be complicated by autoimmunity
 - Drug sensitivity: TCAs, ABs, Antipsychotics
- Features (usually younger age than would expect for IHD):
 - Preceding febrile illness
 - ECG: ST abnormalities, arrhythmias
 - Trop T

- Management generally supportive. Avoid exercise

Hypertrophic Cardiomyopathy

- = Primary cardiac hypertrophy (usually of the LV) in the absence of other loading conditions (eg AS, HTN or thyroid disease)
- Autosomal dominant with variable penetrance, about 1 in 500. Sporadic disease uncommon
- Genetically heterogeneous. Screening for the 8 most common HCM-causing genes has a pickup of 50 – 60%
- Variable course from asymptomatic to heart failure
- Most common cause of SCD under age 35
- Signs and Symptoms: “jerky” rapidly rising pulse, LV impulse, apical systolic murmur ↑ with valsalva (→ ↑preload: ↑intrathoracic pressure → narrowing of outflow track and therefore greater turbulence). Squatting → ↓preload and may reduce murmur. Angina 2nd to small vessel disease and hypertrophy
- Echo:
 - LV hypertrophy = LV wall thickness > 13 mm in an adult
 - Various patterns: asymmetric septal, mid-ventricular, apical (giant negative T waves), LV obstruction
 - Outflow tract obstruction in ~ 25% (→LVOT gradient on echo) and MR
 - Always diastolic dysfunction
- ECG: Higher sensitivity than echo in detecting affected individuals in family studies, but low specificity in screening. Can mimic any ECG
- Histology: gross disorganisation of muscle bundles and intracellular architecture
- Major risks for SCD (any one qualifies for an ICD):
 - LV wall thickness > 30 mm
 - FHx of sudden death < 35
 - Previous cardiac arrest/ventricular tachycardia
- Prognosis: marked variability
 - Annual mortality rate 1 – 3%. SCD occurs most commonly during or after exercise
 - Risks factors (if > 2 of them then consider ICD): HTN, haemodialysis, elite athletes, aortic stenosis, cardiac amyloidosis, cardiac thrombus
- Management:
 - Avoid competitive sports
 - Symptom management (controversial): Ca blockers, beta-blockers (improve diastolic filling, reduce contractility → ↓outflow obstruction), diuretics (no impact survival)
 - Positive inotropic agents increase outflow obstruction – avoid digoxin
 - ?Endocarditis prophylaxis
 - Surgery:
 - Septal myotomy if resting outflow gradient > 50 mmHg – will reduce it to < 10 mmHg in 90%. Mortality 3%
 - Alcohol septal ablation (ie cause an MI in the septum)
 - VT associated with Hypertrophic Cardiomyopathy: If hypertrophic cardiomyopathy, history of sustained VT/VF, unexplained syncope, family history of SCD, or LV septal thickness > 30 mm then risk of SCD is high → ICD. *ICD easily surpasses other preventative strategies* (amiodarone, sotalol) for avoiding SCD
 - Limited experience with ablative therapy
 - Screen first degree relatives (ECG, echo) every 2 – 5 years (maybe annually as a teenager – usually develops following growth spurt). No established role for genetic testing (yet) – although cause found in 50 – 60%
 - Genetic counselling

Heart Failure

- See Lancet 2005:365
- See Biomarkers in Heart Failure, NEJM 15 May 2008
- Survival prediction for 1, 2 and 5 years (validated on retrospective data): <http://depts.washington.edu/shfm> (doesn't take into account other comorbidities)
- Only heart disease increasing in prevalence
- Prognosis of heart failure bad – 30 – 40% 1 year mortality, correlates fairly well with functional status
- Causes:

- Depressed EF (systolic failure, about half are asymptomatic, * = can also cause diastolic failure):
 - Coronary artery disease*
 - Chronic pressure overload: hypertension* & obstructive valvular disease*
 - Chronic volume overload: Regurgitant valvular disease, L-R shunting
 - Non-ischaemic dilated cardiomyopathy:
 - Familial/genetic disorders (often affecting the cytoskeleton)
 - Infiltrative disorders*
 - Toxic/drug induced
 - Metabolic*
 - Viral
 - Disorders of rate and rhythm
 - 20 – 30 % cases cause unknown. Referred to as non-ischaemic, dilated or idiopathic cardiomyopathy
 - Impact of DM unclear
- Preserved EF (diastolic failure EF > 40 – 50%) – < 30% of patients, but common with systolic failure:
 - “Stiffening” of the ventricle → ↑ pressures to fill it
 - Pathological hypertrophy:
 - Primary/Hypertrophic cardiomyopathies
 - Secondary (HTN)
 - Aging
 - Restrictive cardiomyopathy:
 - Infiltrative disorders (amyloid, sarcoidosis)
 - Storage disease (haemochromatosis)
 - Fibrosis
 - Pulmonary Heart Disease: Cor pulmonale and Pulmonary vascular disorders
 - High-output states:
 - Metabolic disorders: Thyrotoxicosis, nutritional disorders (beriberi – Thiamine deficiency)
 - Excessive blood-flow requirements: systemic AV shunting, chronic anaemia, Paget’s
- Symptoms and signs:
 - Fatigue and breathlessness
 - Orthopnea: redistribution of fluid from splanchnic circulation and lower extremities when recumbent → ↑ pulmonary capillary pressure
 - Liver may be pulsatile if tricuspid regurgitation present
 - Orthopnea in the last week is a reliable symptom (84% in moderate and 100% in severe), creps in < 25% and ↑ JVP in < 60% of people even with severe failure (PCWP > 35) JAMA 1989;261:884
- Assessment:
 - EF is altered by afterload and preload. Eg ↑ EF in mitral regurgitation due to the ejection blood of blood into LA
 - Biomarkers:
 - Many potential bio-markers (including CRP but lacks specificity, big endothelial 1)
 - B-type natriuretic peptide (BNP) and N-terminal (or NT) pro-BNP:
 - Increase with age, renal impairment, F>M, and RHF. Low in obesity
 - Released when ventricles are dilated, hypertrophic or subject to increased wall tension
 - Prohormone BNP is cleaved into inactive NT-pro-BNP and active BNP (which causes arterial vasodilation, diuresis, and natriuresis, and dampens R-A-A system (ie opposes physiological abnormalities of heart failure))
 - Decreased renal clearance in renal failure (esp NT-pro-BNP)
 - BNP measurement increases the accuracy of heart failure treatment in patients presenting to ED with dyspnoea (< 100 pg/ml ⇒ HF unlikely, > 400 makes diagnosis likely). Correlates with in hospital mortality. Very good negative predictive test
 - BNP may normalise in chronic heart failure
 - Can normalise with treatment – some evidence of value as a guide for therapy
 - NT-pro-BNP vs BNP: NT-pro-BNP slightly better at predicting in hospital mortality. Has longer half life so perhaps a more accurate index of ventricular stress
 - Other investigations:
 - Echo: Normal EDD is 5.5 cm
 - Cardiac catheter if inducible ischaemia

- Myocardial biopsy ?amyloid – but low yield
- Hyponatraemia is a poor predictor, as is MVO₂ < 10 – 12 ml/kg (effectively measures exercise capacity). Cut off for transplantation is < 14 – below that transplant mortality < CHF mortality
- New York Heart Classification (very subjective but has stuck):
 - I: no symptoms with ordinary physical activity
 - II: Slight limitation of physical activity
 - III: Marked limitation of physical activity
 - IV: Discomfort with any physical activity, symptoms at rest

Pathogenesis

- Not just pump failure....
- Complex interplay between genetic, neurohormonal, inflammatory and biochemical changes acting on myocytes, cardiac interstitium or both
- Process:
 - Index event (may be on going) damages myocardium
 - Pressure load: aortic stenosis, HTN
 - Volume load: MR, AR
 - Myocardial failure: MI (75%), dilated cardiomyopathy
 - Impaired filling: restrictive cardiomyopathy, pericardial disease, obstruction to flow
 - Neurohormonal imbalance results to try and restore function:
 - Beneficial: ANP (↑atrial distension), BNP (ventricular overload), CNP (endothelial stress), bradykinin and NO
 - Harmful: adrenergic, endothelin, renin-angiotensin-aldosterone (→ ↑Na, ↑LV mass, ↑fibrosis, ↓K and Mg so arrhythmias...)
 - Sustained activation of these mechanisms leads to end-organ damage in the ventricle, worsening remodelling and subsequent decompensation
- Remodelling includes:
 - Myocyte hypertrophy
 - Changes in contractile properties – transcriptional changes in genes and proteins regulating coupling
 - Loss of myocytes – necrosis and apoptosis
 - β-adrenergic desensitization
 - Reorganisation of the extracellular matrix with dissolution of structural collagen
 - All leads to changes in LV mass, volume, shape (from elliptical → spherical, which is less efficient) and composition
- End result is progressive decline in BP perceived as ↓circulating volume + abnormal reflex control → peripheral vasoconstriction, Na + H₂O retention, ↓organ blood flow
- Diastolic dysfunction: Slowed myocardial relaxation → ↑pulmonary capillary pressures – can be 2ndary to:
 - Ischaemia induced reductions in ATP (necessary for relaxation)
 - If LV filling is delayed because of ↓LV compliance (eg hypertrophy or fibrosis) then → ↑End diastolic filling pressure
 - Disputed area

Management of Depressed Ejection Fraction

- General: Do the simple things well
 - Treat comorbidities:
 - HTN, CAD, DM, **OSA**
 - Anaemia: usually chronic disease, ↑with CHF severity, also malnutrition and dilutional – small trial evidence of benefit from EPO
 - Sleep Apnoea: 30% have obstructive, 35 – 40% have central (ask “do you snore”, “do you wake refreshed”). Arousals at night compound neurohormonal problem. See page 218
 - Depression (rates of 14 – 36%)
 - Immunized for influenza and pneumococcal
 - Stop smoking
 - Avoid precipitants – eg NSAIDs – relative contraindication due to risk of renal failure given ACE inhibitor on background of already poor renal function
 - Educate: diet and compliance. No evidence of benefit from intentional weight loss
 - Record weight daily

- Serial measurement of BNP to guide therapy is not well established
- Activity: Routine modest exercise of benefit for class I – III – improves well being, unclear effect on prognosis. Not swimming – standing neck deep in water → ↑ venous return by up to 700 ml
- Diet:
 - Na restriction to 2 – 3 gm daily (in systolic and diastolic) – no evidence it's beneficial
 - Fluid restriction if difficult to control oedema – no evidence it's beneficial
 - Caloric supplements if unintentional weight loss
 - Limit alcohol: no evidence alcohol in moderation is harmful, unless alcoholic cardiomyopathy in which case stop
- Management Programmes:
 - Trials from the mid 90s suggested that multidisciplinary programmes led by a nurse specialist reduced mortality from all causes, and admission to hospital from CHF, by 13 – 30%, with flexible diuretic dosing and improved compliance
 - Recent trials (eg COACH study) shows no difference from normal follow up (Lancet 6 Sept 2008)
 - Problem with meta-analysis is that all programmes are not equally effective
 - Need trials picking into what works for whom and when and why with longer follow up, in populations more representative of clinical populations
- Thiamine: Small trial evidence that frusemide (especially doses > 80 mg/day for > 3 months) → thiamine deficiency (“Wet Beriberi”) due to increased loss of water soluble vitamins (none other known to be affected). Also that correcting this can improve EF%

Medication and Devices for Depressed Ejection Fraction

- Summary (Lancet, 4 Oct 2008):

	Relative risk reduction in <i>all cause mortality</i>
β blockers	34 – 35%
ACEI or ARBs	17 – 25%
Aldosterone antagonists*	15 – 30%
Hydralazine-isosorbide dinitrate*	43%
Implantable defibrillator*	23%
Cardiac resynchronisation*	36%
n-3 polyunsaturated fatty acid supplementation	9%

* = for patients with specific indications

- Improvement in *symptoms* (not mortality): diuretics, digoxin
- **Diuretics** (all have risk of azotemia – ↑urea): use flexibly and minimum dose to achieve dry weight
 - Symptomatic benefit only, no change in mortality (other than spironolactone)
 - Monitor K and ?Cr weekly during titration, then 3 monthly
 - If mild: Thiazide (↓K, increase fractional Na excretion by 5 – 10 % and less effective in renal insufficiency) and metolazone (longer acting and more potent, but more electrolyte abnormalities)
 - If moderate-severe: Loop (↓K): Frusemide, torsemide, bumetanide – increase fractional excretion of Na by 20 – 25%
- **β-blockers:**
 - *Proven in all cause class II – IV CHF, and in post infarct class I only*
 - Bisoprolol, carvedilol and Metoprolol CR have been shown to reduce mortality (nb not atenolol)
 - RRR up to 35% (better than ACEI), and also ↓SCD (cf no change in ACEI)
 - NNT for 1 year mortality range from 14 in severe HF (COPERNICUS trial with carvedilol) to 26 in moderate HF (metoprolol in MERIT-HF)
 - Most valuable effects through β1 blockade
 - Reverse remodelling
 - Studies titrated up metoprolol CR 200 mg. Mortality decreases with ↑dose (shown with carvedilol) – *titrate slowly – may acutely worsen oedema due to withdrawal of adrenergic support.* Don't start when acutely unwell – diurese first
 - Tolerated by > 85% including patients with diabetes, COPD and PVD. COPERNICUS trail of Carvedilol showed increased withdrawal from the placebo arm. Only 50% of asthmatics tolerate β-blocker (and remains a contraindication)
 - Consider once stabilised (eg one month) on adequate doses of ACEI and diuretics
 - Decrease if HR < 50 or 2nd or third degree heart block develops. Not if bronchospasm or SBP < 80
- **ACEI:**

- Overwhelming evidence of benefit in EF < 40% – initiate as soon as there is structural heart disease:
 - Indicated in all grades of heart failure: 16% overall reduction in mortality (Class I – IV, Consensus trial 50% in Class IV), but no reduction in SCD
 - SOLVD trial in Mild HF with Enalapril, NNT for 1 year mortality 59
 - HOPE trial: large RCT in people with normal EF, ramipril vs placebo. Development of HF over 5 years in high risk groups reduced from 11.5 to 9.0%. NNT for 1 year mortality > 1000! Similar results in PROGRESS trial
 - Stabilise remodelling, improve symptoms, reduce hospitalisation, prolong life in both ischaemic and other CHF
 - In addition to R-A-A effect, also inhibit kininase II (causes cough) → ↑bradykinin → further benefit
 - Fluid overload can reduce effect → optimise diuretics first
 - Titrate over 2-3 weeks to doses used in trials: Enalapril 10 mg bd, captopril 50 mg tds
 - Monitor K⁺/Cr/BP weekly while titrating
 - SE:
 - ↑K, ↑Cr, angioedema in 1%. Stop if K⁺ > 5.5, Cr > 250, SBP < 80
 - Renal problems will also occur with ARBs – consider hydralazine
 - First dose hypotension if SBP < 90 or over-diuresis
- **ARBs:** Use if ACEI intolerant (other than ↑K or renal impairment). ELITE II, ValHef and CHARM trials. Some trials have demonstrated benefit in addition to ACEI in HF, others no difference to placebo. CHARM trial showed trend to improved mortality and significant CV mortality benefit in people intolerant to and ACEI and in addition to an ACEI. Trials titrate to 32 mg/d Candesartan or 50 mg/d Losartan. Candesartan and valsartan are approved for the treatment of HF
- **Aldosterone Agonists** (spironolactone and eplerenone):
 - ACEI initially blocks aldosterone but it rapidly returns to pre-treatment levels, so added benefit from spironolactone
 - Use if EF < 35% and class III or IV
 - Not if CrCl < 30 mL/min. Monitor K⁺/Cr 3-4 days after starting. *Stop if K > 5.0*. Don't do triple therapy with ACEI and ARB due to risk of ↑K
 - RALES Trial (NEJM 2003;348:1309):
 - Class II/IV heart failure (not tested in milder CHF) – spironolactone → 30% ↓all cause mortality in 3 years
 - Trial doses titrated to 25 – 50 mg/d
 - Tested only on inpatients with severe HF, most were receiving an ACEI, *few on a beta-blocker*
 - Significant increase in the number of hyperkalaemia-related hospital admissions and deaths – take care!
 - Painful gynaecomastia in men in 10 – 15%
 - EPHEsus trial 2003: in patients post MI with EF < 40%, 87% on ACEI, 75% on β-blocker (ie better than RALES). Eplerenone reduced 16 month cardiac mortality from 14 to 12%. No androgen side effects
- CCB: Amlodipine – use in CHF if needed as an anti-HTN over and above ACEI and β-blockers (PRAISE Trial) as non-dihydropyridines ↑ mortality
- **Digoxin:**
 - If AF and rate not well controlled by β-blocker
 - Consider if in SR and still symptoms of HF on maximal standard therapy
 - RCT of 6,800 patients with digoxin in class II or III CHF, all in SR, showed no change in mortality but reduced hospitalisation
 - Generally 0.125 mg/d – higher doses less beneficial. Check level in 2 -3 weeks. No indication for loading doses
 - Toxicity: confusion, anorexia, nausea, visual disturbance, arrhythmias
 - Levels increased with: antibiotics, amiodarone, diltiazem, verapamil, quinidine
- **Hydralazine/isosorbide dinitrate** standard therapy if African-American with Class II – IV HF – exact mechanism unclear
- Anticoagulation:
 - In HF trials, stroke rate from 1.3 to 2.4% per year
 - Treat ischemic cardiomyopathy + recent large anterior MI for 3 months
 - In the absence of AF or previous VTE the value of anticoagulation is not well established (Uptodate summary of AHA guidelines)

- AF often occurs with HF: Can cause cardiac decompensation. Only amiodarone (note → ↑digoxin and ↑INR) and dofetilide don't cause negative inotropic effects
- **Statins:** *doesn't make any difference in chronic heart failure.* Clinical benefit is reduction in acute coronary events. Once heart failure is established, statins may not help patients escape the mortality associated with the underlying heart-failure disease process:
 - CORONA Trial (Controlled Rosuvastatin Multinational Trial in Heart Failure, 2007): 5011 patients, history of ischaemia, EF < 40%. No difference in primary endpoints, modest reductions in hospital admissions for cardiovascular events
 - GISSI-HF Trial: 4573 patients with HYMA class II – IV irrespective of cause of HF. Rosuvastatin 10 mg daily did not affect outcomes
- **N-3 polyunsaturated fatty acids** (Lancet 4 Oct 2008):
 - In CHD result in 10 – 20% ↓ in fatal and non-fatal cardiac events
 - GISSI-HF Trial: 6975 patients with class II – IV CHF to 1 gm daily of n-3 PFA vs placebo. Death from any cause ↓ from 29% to 27%. Modest but incremental benefit to all other existing therapies – lots of questions about formulation, optimal dosing and action – but it joins a short list of things demonstrated to work
- **Device therapy:**
 - Resynchronisation:
 - About 30% have widened QRS, this is associated with ↑mortality
 - If QRS > 120 -150 ms (the wider the greater the benefit), EF < 35 %, SR and class III or ambulatory class IV then there'll be ventricular dyssynchrony → suboptimal filling, prolonged duration of mitral regurgitation
 - Measured on echo with SPWMD (Septal to Posterior Wall Motion Delay)
 - Biventricular pacing (or LV wall only via coronary sinus) = cardiac resynchronisation therapy (CRT) → ↓mortality and hospitalisation (COMPANION Trial of 1634 patients, but included defibrillation which we know works), reversal of remodelling, ↑exercise tolerance (CARE-HF study, without defibrillation – still substantial benefit). Also ↓AHI in OSA. Neurohormonal benefit
 - Benefits not established in AF
 - 25-30% non-response rate. Less benefit in ischaemic cardiomyopathy than other causes
 - ICDs:
 - Primary prevention: shown to ↓SCD by 23 % in Class II – III HF with systolic dysfunction (EF < 30%), and a reasonable expectation of > 1 year survival (SCD-HeFT trial, EF < 30%, head-to-head with amiodarone showed benefit, mortality 28.9 vs 34% at 5 years). MADIT II trial (Most placebo patients on amiodarone). Early post infarct insertion patients do worse – wait 40 days
 - Secondary prevention: recommended (AHA) for history of arrest, VF or destabilising VT
 - For 100 patients over 5 years expect: 8 to be saved by the device, 30 to die anyway, 10 – 20 to get a shock they don't need, 5 – 15 to have other complications (infection, lead fracture...)
 - Discuss inactivation if patient becomes end-stage. Don't insert in class IV – they're going to die soon of pump failure anyway. Reassess if they improve
- Cardiac transplantation:
 - Indications:
 - VO2 max < 10 ml/kg/min + anaerobic metabolism
 - Severe ischaemia not amenable to intervention
 - Recurrent refractory ventricular arrhythmias
 - Not sufficient: EF < 20%
 - Survival: 80% at 1 year, then die at 4% per year. Half life 9.1 years
- Avoid:
 - Anti-inflammatories: Steroids (Na and fluid retention), NSAIDs (Na and fluid retention, blunted response to diuretics)
 - Cardiac drugs: Class I antiarrhythmics (negative inotropy, proarrhythmic), Sotalol (proarrhythmic), Ca blockers (negative inotropy, neurohumoral activation). No evidence/agreement that class I or III antiarrhythmic drugs should be used to prevent ventricular arrhythmias
 - Psych meds: Carbamazepine, Clozapine, ergot alkaloids, TCAs (negative inotrope, proarrhythmia)
 - Metformin (lactic acidosis) and glitazones (fluid retention) with care
 - Partial left ventriculectomy in non-ischaemic cardiomyopathy is not supported
- Comparison of trials to the real world (Journal of Cardiac Failure, 2000;6:272):

	Clinical Trials	Community
Age	63	77

% Women	21	50 – 60
Cause	CAD	HTN
Normal LVEF (%)	0	50
Compliance	Optimal	Poor
Comorbidity	Limited	Common

- ESCAPE Trial (2004): “If you had 24 months to live in your current state of health, how many months would you trade to feel better” – average answer 9 months. We are aiming for survival, but patients want quality of life even at the expense of survival

Management in Preserved Ejection Fraction

- No proven drugs or devices for HF and a preserved EF (ie diastolic failure)
- CHARM trial of Candesartan in EF > 45% – showed no significant reduction in composite death but a trend to ↓ admission
- I-PRESERVE Trial (Irbesartan in Heart Failure with Preserved Ejection Fraction Study): No impact from Irbesartan in EF > 45%
- Beta-blockers increase relaxation and should increase diastolic filling, as should CCB
- Good rate control of AF – they need the atrial kick to help LV filling
- Take care with fluids – fine line between orthostatic hypotension and overload
- Focus on the underlying processes – HTN, IHD etc

Acute HF

- Identify precipitants
- Positive troponin associated with lower systolic BP, lower EF, and higher in hospital mortality in acute presentations of HF (8.0 vs 2.6%, all had Cr < 177, NEJM 15 May 2008)
- Usually O₂, iv morphine, diuretic and nitrate is sufficient. CPAP may be helpful
- Two determinants occur separately or together:
 - Elevated LV filling pressures (→ “wet”): creps, oedema, ↑JVP
 - Depressed cardiac output and 2ndary increased systemic vascular resistance (→ “cold” extremities)
 - → combinations of wet and warm, wet and cold, dry and cold. Treat each component
 - Cold and dry: ?occult elevation of LV filling pressures. If PCWP < 12 trial of fluid repletion
- Scenarios (Critical Care Med 2008):

	Characteristics	Treatment
CS1	SBP > 140, abrupt onset Pulmonary oedema (a problem of fluid redistribution not overload) Minimal systemic oedema (may be hypovolaemic)	NIV and nitrates. Rarely diuretics
CS2	SBP 100 – 140, gradual onset, systemic > pulmonary oedema. May have renal impairment. Metabolic acidosis	NIV and nitrates. Diuretics if systemic fluid retention
CS3	SBP < 100, hypoperfused, minimal oedema +/- cardiogenic shock (cold, clammy). May have end stage HF. Metabolic acidosis	Fluid challenge if no overt fluid retention. Inotrope. Not vasodilators. If not improvement consider vasoconstrictors
CS4	Acute Heart Failure in the context of ACS	NIV, and treat as for ACS
CS5	Right Ventricular Dysfunction	Diuretics if > 90 and fluid overload. Inotropes if < 90

- Treatment objectives: ↓dyspnoea, ↑well being, ↓HR, Urine output > 0.5 ml/kg/min, maintain/improve SBP, restore perfusion
- Specific practice points:
 - Initiate treatment in ED (mean time to therapy 1 – 2 hrs) cf ward (mean time to therapy 20 – 22 hours)
 - Measure urine output, but no catheter needed
- Ultrafiltration: Removal of excess volume mechanically – evaluated in observational studies, further trials underway (including in Perth) – rapid and safe removal of isotonic Na/H₂O (up to 5 litres a day without electrolyte imbalance), with benefit sustained to 90 days. EUPHORIA, RAPID-CHF and UNLOAD trials

Treatment Options for Acute CHF

- NIV:
 - CPAP at 5 – 7.5 cm H₂O

- Inexpensive, minimal adverse effects, effective
- Augments CO, ↓ LV afterload, ↑ functional residual capacity, ↓ work of breathing
- Meta-analyses show CPAP → ↓ mortality in acute cardiogenic pulmonary oedema (ARR of 13%) and ↓ need for ventilation (and better than BIPAP → ↓ ventilation with CPAP but non-significant ↓ in mortality with BIPAP over standard treatment [a later study shows BIPAP is better than standard], and weak evidence of ↑ MI with BIPAP over CPAP). (Lancet 8 April 2006, NEJM 10 July 2008)
- One large trial: NIV (CPAP or BiPAP) had no effect on 7 or 30 day mortality compared with O₂ (NEJM 2008;359:142-151). CPAP should only be used to relieve symptoms and correct metabolic disturbances (ie ↑ CO₂)
- Generous use of morphine may assist patient tolerance
- Diuretics:
 - Aggressive monotherapy not necessary in the majority of patients
 - Only if evidence of systemic volume overload
- Vasodilators:
 - Nitroglycerine infusion – ↓ arterial resistance and ↑ venous capacitance → ↓ LV filling pressure, ↓ mitral regurgitation, ↑ cardiac function. Can cause hypotension. 10 – 20 mcg/min, ↑ 5 – 10 mcg/min every 3 – 5 mins as needed. Frequent BP measurement
 - Nitroprusside but side effects from cyanide which accumulates if hepatic impairment. Associated with ↑ mortality in AMI
 - Nesiritide – a recombinant BNP – more effective at lowering pulmonary pressures. Needs further evidence – ?Initial promise not lived up to
- Inotropic agents:
 - Mainly for CS3 – low CO, low SBP (< SBP 85 – 90), high filling pressures, not responding to other therapy
 - Stimulate cardiac contractility as well as peripheral vasodilation
 - Dobutamine stimulates β₁ and β₂ but not α₁
 - Milrinone : a phosphodiesterase inhibitor. ↑ in CO and relaxes smooth muscle. More likely to cause tachyarrhythmias and ischaemic events than vasodilators. OPTIME-CHF trial of 0.5 mcg/kg/min for 48 hours (mean EF 23%) showed ↑ AF and ↓ BP, no statistical change in mortality
 - Levosimendan: Trop C Ca sensitiser that improves cardiac contractility via ↑ sarcoplasmic reticulum release and reuptake of Ca. ATP mediated arterial and venous dilation. Safe in ACS. No arrhythmogenicity. RUSSLAN trial: ↓ mortality and readmissions cf placebo. REVIVE trial: benefit in AHF. SURVIVE trial: better than dobutamine for early but not 180 day mortality. Not recommended if SBP < 85. Long T_{1/2} (13 days) so don't use in a setting where they may become hypotensive (eg ICU). First 6 hours is what confers the benefit
- Vasoconstrictors: support systemic blood pressure and inotropy through β₁ and α₁ receptors. Noradrenaline recommended, 0.2 – 1.0 mcg/kg/min
- Devices:
 - Intubate if SBP < 80 despite therapy
 - Intraaortic balloon pump if potential for myocardial recovery
 - Ultrafiltration if not responding to diuretic therapy

Cor Pulmonale

- Dilation/hypertrophy of RV in response to pulmonary disease (and technically not due to LH problems)
- Diagnosis clinically or via lab tests insensitive. Echo and BNP better
- Causes:
 - Hypoxic vasoconstriction: Chronic bronchitis, COPD, CF, chronic hypoventilation (obesity, neuromuscular disease), high altitudes
 - Occlusion of pulmonary vascular bed: PE, primary hypertension, collagen vascular disease, drug induced lung disease
 - Parenchymal disease: Chronic bronchitis, COPD, bronchiectasis, CF, pneumoconiosis, sarcoid, IPF
- 50% due to COPD, but pulmonary artery pressures higher in interstitial lung disease. Not caused by OSA unless also COPD and daytime hypoxemia
- RV thin walled and better at handling volume than pressure loads
- Symptoms and signs: dyspnoea, not orthopnea or PND. Prominent V waves if tricuspid regurgitation. RV heave at LSE. ECG shows P pulmonale, RAD, RV hypertrophy
- Pulmonary hypertension of any cause → loud P₂, decrescendo diastolic murmur of pulmonary regurgitation

- Treatment: reduce work of breathing with NIV, bronchodilation, adequate oxygenation, etc

Aortic Disease

- With age: ↑aortic diameter, ↓aortic distensibility, ↑velocity of conduction of pulse wave

Aortitis

- Vasculitis: Takayasu's arteritis (see page 272), giant cell arteritis
- Rheumatic: HLA-B27 associated spondyloarthropathies, Behcet's syndrome, Cogan's syndrome
- Infective: Syphilis, TB
- Mycotic: salmonella, staph, strep, fungal

Aortic Aneurysm

- > 50% diameter of the aorta involving all 3 layers of the wall
- If not involving all 3 layers: false or pseudoaneurysm
- Fusiform or saccular (localised to one side)
- Underlying mechanism is breakdown of extracellular matrix and elastin
- Causes:
 - Degenerative/Atherosclerosis: aging, cigarette smoking, male gender, family history
 - Cystic Medial Necrosis (common endpoint in many diseases – a histology diagnosis):
 - Marfan syndrome (see page 275)
 - Ehlers-Danlos Syndrome type IV (see page 275)
 - Familial etiology
 - Bicuspid Aortic Valve
 - Volume or pressure load: AR, HTN, post stenotic dilation 2nd to AS
 - Infective: syphilis, TB
 - Hypertension
 - Trauma
- Presentation:
 - Usually incidental finding
 - Don't screen unless family/genetic history
 - Physical exam sensitive for abdominal aneurysm > 5 cm
- Thoracic aneurysm:
 - Symptoms due to compression: hoarseness (nerve compression), dysphagia, pneumonia, SVCS
 - Aortic regurgitation due to valve root distortion
 - Distal embolisation
 - Risk of rupture: > 6 cm ~12%, > 7 cm ~25 % per year
 - Mortality in rupture ~ 80%
 - Medical treatment: β-blockers. If not meeting the following thresholds for surgery annual US as effective as repair
 - Prophylactic surgery if expanding > 0.5 – 1 cm per year (usual rate 0.1 – 0.2) *or* absolute diameter of:
 - AAA: males > 55 mm, females > 45 mm
 - Ascending thoracic aorta: 50 – 60 mm
 - Descending thoracic aorta 60 – 70 mm
 - Options: endovascular vs open repair

Aortic Dissection

- See Lancet 5 July 2008
- Tear in aortic intima or haemorrhage within media with propagation proximally or distally. Can lead to acute AR (involving aortic root), tamponade, or inferior MI (as usually dissects RCA)
- Classification:
 - Stanford A: if it involves any part of the ascending aorta regardless of where the tear is – twice as common, 30% involving aortic arch
 - Stanford B: all other dissections
- Risks:
 - Age > 70: HTN, diabetes, existing aneurysm, inflammatory vasculitis
 - Age < 70: Marfan's, cocaine

- Age < 40: collagen disorder (Marfan's/Ehler's Danlos), bicuspid aortic valve 2nd to congenital defect in aortic wall, coarctation, Turner's
- Presentation: diagnosis often delayed due to failure to include it as a differential. Ascending → anterior chest pain, descending → posterior chest pain. Ischaemia in affected aortic branches
- Imaging:
 - CT good acutely
 - TOE helpful as can assess AVR and LV fn
 - MRI helpful for monitoring, not acutely
- Management:
 - No randomised trials
 - Aggressive BP lowering to SBP 100 – 120 with β-blockers (propranolol, labetalol [an α and β blocker], metoprolol) and/or vasodilators
 - Stanford A: mortality 1 – 2 % per hour. Operative mortality 10 – 30%. Medical mortality 10 – 30%
 - Stanford B: surgical intervention reserved for occlusion of a major aortic branch, expansion or extending dissection

Coarctation of the Aorta

- Associations:
 - Turner's Syndrome
 - Bicuspid aortic valve
 - Berry Aneurysm
- Complications: cardiomegaly, aortic valve disease, CHF
- Classic sign: rib notching on CXR
- Complications of surgery: spinal cord injury, early post op HTN, re-coarctation, aneurysm, endocarditis on bicuspid valve

Pericardial Disease

Pericarditis

- Inflammation of the pericardium
- Features: chest pain (sharp, worse in recumbent position), friction rub (LSE on full expiration), ECG (diffuse concave ST elevation, PR segment depression). Maybe fever (eg if viral)
- CXR: may have enlarged silhouette (suggestive of pleural effusion)
- Echo: 60% have an effusion
- Causes:
 - Idiopathic
 - Infectious: Viral, bacterial, TB
 - Uremia
 - Acute MI
 - Post MI (Dressler's Syndrome)
 - Neoplasm
 - Medications: hydralazine, procainamide, warfarin, heparin
 - Radiation
- Outpatient management OK as long as:
 - Not a MI/Dissection/PE
 - Typical presentation
 - Exclusion of a large effusion
- Treatment:
 - ABs and drainage if bacterial
 - NSAIDS for 7 days
 - If severe pain continues consider prednisone
 - Avoid anticoagulants (risk of haemopericardium)
 - Colchicine

Pericardial Effusion

- Normal pericardial fluid is ~50 ml
- ↑ in pericarditis (all above causes) and hypothyroidism

- If large, then muffled HS and percussible dullness
- Diagnosis:
 - Echo: confirms effusion and checks cardiac function
 - Not noticeable on CXR until ~250 ml
 - CT/MRI can differentiate from epicardial fat
 - ECG: pulsus alternans (swinging heart)
- Management:
 - Pericardiocentesis if ?bacterial, TB or systemic inflammation
 - Pericardial biopsy if ?malignant
 - If stable, drainage has a low diagnostic yield, maybe drain if it persists > 3 months
 - Avoid anticoagulants

Pericardial Tamponade

- Haemodynamic instability: dyspnoea, pulsus paradoxus (failure of SBP to ↑ by 10 mmHg on inspiration, also occurs in asthma), tachy/bradycardia, JVP distension, hypotension
- May look like an MI or PE
- Effusion can be circumferential or loculated
- Effect is due to rapidness of accumulation rather than the size
- Echo: invagination of ventricular/atrial free wall with diastolic collapse, IVC dilation
- Treatment: saline/vasopressors to manage hypotension, drainage/surgery (if dissection, drainage makes it worse)

Constrictive Pericarditis

- Thickened, fibrotic and adherent pericardium. Typically visceral and parietal pericardium is fused
- Calcification in chronic phase → stiffening
- Impaired diastolic filling 2nd to restrained ventricular diastolic expansion
- Presents with: dyspnoea, fatigue, JVP distension, oedema, etc. Usually no pulmonary oedema
- Auscultation: pericardial knock
- Causes:
 - Post pericarditis
 - Post cardiac surgery
 - Viral infection/TB
 - Rarely radiation or RA
- Differential: restrictive cardiomyopathy – in which case ECG may show BBB or hypertrophy. MRI/CT can show pericardial thickness, and catheterisation may show elevated and equalised L and V ventricular diastolic pressures in constrictive pericarditis
- Echo:
 - Shifting ventricular septum to and fro – ventricles compete with each other during diastolic filling
 - Absence of change with respiration
- Treatment: depends on high preload to maintain stroke volume:
 - Be cautious of diuretics
 - Control AF but avoid bradycardia
 - Can be transient
 - Pericardectomy is treatment of choice but may → ↓EF and high mortality (6 – 19%)

Endocarditis

- Predisposing factors for native valve endocarditis (more common than prosthetic valve – lower relative risk but higher absolute numbers):
 - Abnormal valves: mitral valve prolapse, rheumatic heart disease, congenital heart disease. Regurgitant valves greater risk than stenotic
 - Bacterial virulence
 - Vulnerable host: underlying conditions, medical interventions (eg IV lines)
- Identical risk to general population:
 - Isolated secundum atrial septal defect
 - Surgical repair of septal defect (atrial or ventricular)
 - Previous CABG
 - Mitral valve prolapse without valve regurgitation
 - Functional heart murmur

- Previous rheumatic fever without valve dysfunction
- Cardiac pacemaker
- Diagnosis:
 - Bloods:
 - Anaemia, inflammatory markers
 - Culture (take 3 sets at least one hour apart, culture positive in about 95%, enterococci disproportionate in culture-negative)
 - Serology if rare cause suspected: Coxiella, Brucella, chlamydia, legionella, bartonella
 - ECG: new conduction delays \Rightarrow ?abscess formation
 - Echo: transthoracic 55 – 65% sensitivity, TOE 90% sensitive (useful for detecting valve ring abscesses)
 - *Modified Duke Criteria* proposed for diagnosis – major criteria: 2 positive blood cultures, evidence on echo, new regurgitant murmur... Divides into definite and probable
 - Rheumatoid factor can be positive
- Clinical signs:
 - Janeway lesions (eg palms or soles of feet): non-tender, red, haemorrhagic or pustular
 - Splinter haemorrhages
 - Conjunctival petechiae
 - Osler's nodes: tender, raised subcutaneous nodules on fingers, toes or feet
 - Roth spots: exudative lesions in the retina
- Surgical indications:
 - Absolute: severe regurgitation or cardiac failure
 - Relative: peri-valvular extension with conduction defects or abscess, multiple or severe embolism, uncontrolled infection (ie virulent organism), prosthetic valve, etc
- Complications:
 - Neurologic complications: in 25% within a week of commencing therapy. Embolic (vegetation fragments), arteritis? (multiple infarcts on MRI), mycotic aneurysm \rightarrow haemorrhagic stroke
 - Embolisation: infarctions in brain and heart
 - Septic emboli – eg spleen and kidney
- Pathogens:
 - Used to be subacute – general shift to S Aureus (ie acute)
 - Staph most common: aureus and coagulase negative
 - Strep viridans
 - Other strep
 - Enterococci, eg faecalis – more resistant to ABs (including cephalosporins)
 - HACEK: group of oral aerobic G –ive bacilli causing infective endocarditis, may be β -lactamase producing:
 - Haemophilus (several subtypes), Actinobacillus actinomycetocometans, Cardiobacterium hominus, Eikenella corrodens, Kingella kingae
 - Can be hard to culture – a cause of culture negative endocarditis
 - Culture negative results may be due to:
 - Fungus
 - Bacteria requiring special growth media: Legionella, Bartonella, Abiotrophia
 - Bacteria that don't grow on artificial media: Tropheryma whippelii
 - Slow growing needing prolonged incubation: Brucella, anaerobes, HACEK
- Treatment:
 - β -lactams: key issue in antibiotic effectiveness is time above MIC, given time for penetration into vegetations and short half life of penicillins frequent doses given (cf area under the curve \rightarrow peak dose more important)
 - Aminoglycosides: synergy (always with β -lactams even if penicillin sensitive) \rightarrow shorter duration of bacteraemia with staph, shorter treatment with streps, better outcome in enterococci, dosing (eg od or tds) unknown, usually multiple risks for nephrotoxicity. Needed for enterococci
 - Staph:
 - Native valve: just flucloxacillin
 - Prosthetic valve: add gentamicin (\rightarrow shorter bacteraemia) or rifampicin (good penetration into the protein biofilm which forms on prosthetic material. Rapid resistance if sole therapy. Usually need to double the dose of warfarin given interaction)
 - Issues in long term therapy:

- ~20% penicillin resistant strains
- Penicillin G: stable for 12 hours ⇒ bd infusion possible
- Amoxicillin: unstable at room temperature ⇒ TDS dosing
- Vancomycin: BD infusion, weekly monitoring

Prophylaxis

- AHA guidelines (2007) for endocarditis prophylaxis:
 - Recommended for:
 - Prosthetic cardiac valve
 - Previous infective endocarditis
 - Congenital Heart Disease: unrepaired cyanotic CHD, repaired with prosthetic material (but only needed for 6 months), repaired with residual defects
 - Recommended when:
 - Dental procedures involving manipulation of gingival tissues or perforation of the oral mucosa
 - Procedures on the respiratory tracts or infected skin, skin structures or musculoskeletal tissues
 - Not now for genito-urinary or GI tract procedures (except oesophageal dilation)
 - Give: IV or oral amoxicillin 2g, alternative Cefaclor 2 g or clindamycin 600 mg
- Prophylaxis for dental treatment (Lancet, 19 April 2008):
 - Few cases are due to oral streptococci (⇒ ?benefit of dental prophylaxis – cumulative exposure to bacteraemia from teeth brushing much greater...)
 - Most common pathogen is Staph aureus (often 2nd to nosocomial infection of IVDU)
 - No randomised trial evidence, but animal models show antibiotics before bacterial challenge (as results from a bacteraemia 2nd to an invasive procedure) reduces risk
 - Risk from a dental procedure without antibiotic prophylaxis is ~ 1 in 46,000, falling to one in 150,000 with prior antibiotic treatment
 - NICE guidelines 2007 (controversial): no pre-dental prophylaxis at all – meticulous dental and skin hygiene more important. . Infective endocarditis is much more likely to result from frequent exposure to random bacteraemia than from dental procedures. Prophylaxis prevents an extremely small number of cases of IE (if any). Optimal oral hygiene is more important as it may reduce random bacteraemias

Syncope

- Causes:
 - Reflex mediated:
 - Vasovagal: neurocardiogenic (30-40%):
 - Cause unknown
 - Bimodal peak in teenagers and 70s
 - Classically precipitated by emotional trigger with pre-syncopal symptoms
 - 3 main types: Cardio-inhibitory (↓heart rate – bradycardia/asystole can be very profound but always resolves), vasodilatory (BP drops), or both
 - Investigations: Holter has poor yield. Head Up Tilt Test (HUTT) gold standard – specific but not sensitive
 - Treatment: behavioural modification +/- PPM for cardio-inhibitory type
 - Carotid sinus hypersensitivity: “drop attacks”, quick recovery, always over 50, atherosclerosis, dementia is common, injuries are common. Either cardioinhibitory (→ bradycardia) or vasopressor
 - Orthostatic hypotension (5 – 10%): autonomic failure, drugs & alcohol, volume depletion. Advice, bed-tilt, ?stockings
 - Situational (cough, swallow, micturition)
 - Cardiac: More likely if exercise or supine related, associated palpitations, structural or IHD, abnormal ECG, age > 65 years, drugs associated with Torsade VT
 - Arrhythmias (20 – 30%)
 - Conduction issues
 - Mechanical: AS, HOCM, Myxoma, Pulmonary HT
 - Neurological:
 - Epilepsy (fit vs faint) 5%
 - Narcolepsy
 - Subclavian Steal

- Vertebrobasilar migraine
- Others:
 - Psychiatric (Hyperventilation)
 - Endocrine (Hypoglycaemia)
 - Hypoxia
 - Drugs and alcohol (5%)
- Recurs in 30 – 40% of first eventers
- Admit only if a likely cardiac cause or “frail” elderly

Other

- Intermittent Claudication: Naftidrofuryl (a peripheral vasodilator) → 37% more pain-free walking (Cochrane Review 2008). Should also give aspirin and statin. May also help Raynaud’s

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Diabetes Mellitus

Types

- Type 1
- Type 2: ranges from insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance
- **Latent Autoimmune Diabetes of the Adult** – (LADA) aka Autoimmune Diabetes not Requiring Insulin at Diagnosis:
 - 5 – 10 % with phenotypic T2 don't have absolute insulin deficiency but have GAD antibodies suggestive of type 1 (not usually IA2)
 - Require insulin much sooner than if normal T2
 - Presentation often hyperglycaemia not ketosis
 - Distinguishing features from type 2: age < 50, acute symptoms, BMI < 25, personal history of autoimmunity, family history of autoimmunity
 - Why care?: theoretical risk of DKA, plan for more rapid escalation of treatment, screen for associated autoimmune conditions
- Gestational Diabetes: see page 462
- **Maturity Onset Diabetes of the Young (MODY)**
 - Heterogeneous group of *autosomal dominantly* inherited, young onset *disorders of β -cell function*
 - At least 2 generations are affected with a family member diagnosed before age 25 → differential in diabetes presenting from 1st to 3rd decade (but still less common than idiopathic type 2 diabetes at this age)
 - Mutations affecting:
 - Glucokinase gene (MODY2)
 - 15% of MODY
 - Mild, non-progressive hyperglycaemia caused by a resetting of the pancreatic glucose sensor
 - Treated with diet, complications rare. Don't respond to sulphonylureas
 - Attention needed in pregnancy
 - Transcription factor (MODY1, 3, 4, 5):
 - Progressive defect with increasing treatment requirements and diabetic complications
 - Mutations in the hepatocyte nuclear factor gene and insulin promoter factor gene
 - MODY1: 5%, HNF-4 α gene
 - MODY3: 65%, HNF-1 α gene, sensitive to sulphonylureas
 - MODY4: <1%, IPF-1 gene (Insulin Promoter Factor)
 - MODY5: 1%, HNF-1A, renal cysts and renal failure
 - MODY X – more to be characterised
- Others:
 - Genetic defects in insulin action: Type A insulin resistance, lipodystrophy syndromes, others
 - Diseases of exocrine pancreas: pancreatitis, neoplasia, CF, haemochromatosis, stones, etc
 - Endocrinopathies: acromegaly, Cushing's Syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma
 - Drug induced: glucocorticoids, thyroxine, β -agonists, thiazides, phenytoin, α -interferon, clozapine, β -blockers
 - Genetic syndromes associated with diabetes: Down's, Klinefelter's, Turner's, Friedreich's ataxia, Huntington's, porphyria, Prader-Willi....

Insulin production and metabolism

- Insulin production: preproinsulin → proinsulin (similar to insulin like growth factors 1 and 2) → insulin (linked A & B peptides) + C-peptide
- 50% insulin degraded by 1st pass metabolism. C-peptide less susceptible to hepatic degradation → useful marker
- Intracellular signalling from insulin and IGF receptors is horrendously complex. Bottom line is:
 - GLUT-4 glucose transporter is shifted to cell membrane → ↑cell uptake of glucose
 - ↑Protein metabolism (ie insulin is a growth factor)
 - ↑Lipid synthesis via aPKC
 - ↑Cell growth and differentiation (via MAP kinase)

- There is a link with inflammatory pathways (ie ↓inflammation via blocking of JNK and IKK signalling cascade → ↓insulin resistance)
- Low insulin →
 - ↑ Counter-regulatory hormones, first is glucagon
 - ↑ hepatic gluconeogenesis, glycogenolysis, ↓glycogen synthesis, ↓glucose uptake

Type 1 Diabetes Mellitus

- Types:
 - Immune Mediated: T-cell mediated autoimmune attack on beta cells. Huge geographical variation – Finland = 100 * China
 - Idiopathic: no immunologic markers of autoimmune destruction – much less common, more common in African/Asians
- Genetic Risks:
 - Lifetime risk of T1DM if proband developed T1DM < 25 years:
 - Identical twins: ~ 50%
 - First degree relatives have 10 times risk but absolute level low. 3% risk if mother has it, 6% risk if father has it
 - Sibling: HLA identical 16%, HLA non-identical 1%
 - HLA MHC class II genes account for 50% of the genetic susceptibility. At least 10 further loci contribute
 - HLA-associated disease DR-DQ8 or DR3-DQ2:
 - Autoimmune thyroiditis: 1 in 15
 - Coeliac disease: 1 in 12
 - There are protective as well as susceptibility genes
- Can develop at any age (5 – 10% after age 30)
- Features evident once ~80 – 90% cells destroyed → “honeymoon phase” with only modest doses of insulin required
- Pathophysiology:
 - Proposed triggers/environmental risk modifiers: viruses (enteroviruses, coxsackie, rubella), toxins (nitrosamines), ??some foods (early cow’s milk, gluten...), vitamin D deficiency
 - Mechanism of β cell destruction unclear – related cells have the same targets but survive....
 - Not just a trigger acting on a genetically susceptible target – but fluctuating immune dysregulation in the context of variable or continuous triggers...
 - ?Due to defects in the capacity of educator immune cells (eg dendritic cells and macrophages at lymphatic sites) to present the full range of self-peptides to newly forming T cells → release of auto-reactive T cells. Normal education destroys autoreactive T cells
 - After about 7 years also start to lose glucagon cells – so ↑risk of hypoglycaemia
 - Hypoglycaemic unawareness:
 - Sympathoadrenal response when glucose < 3.5 – but this affect is blunted with repeat hypos
 - Neuroglycopenic response (eg confusion) with < 2.5
- Mechanism of ↑ cardiovascular risk (Lancet 24 May 2008):
 - Type 1 diabetes ↑risk of CVD by 10 times relative to general population
 - Endothelial cells at particular risk of intracellular hypoglycaemia as they can’t down regulate glucose uptake → accelerated atherosclerosis
 - Coronary vessels: endothelial dysfunction, ↑artery stiffness, coronary artery calcification, accelerate atherosclerosis
 - Cardiac muscle: Diastolic dysfunction (impaired relaxation, ↑ventricular stiffness), systolic dysfunction
 - Neuropathy: ↓heart rate variability, ↑resting heart rate, ↓coronary vasomotor capacity, arrhythmia
- Antibodies:
 - Immune response is driven by reactivity to not just one, but many, self antigens
 - ICA (Islet cell antibodies – poor assay) overtaken by:
 - GAD (Glutamic acid decarboxylase). Interesting aside: GAD protein is also present in the brain, is also an autoantigen in Stiff Person Syndrome – a disabling neurological condition
 - Tyrosine phosphatase IA2 (insulinoma-associated-2) antibodies
 - Insulin autoantibody (IAA)
 - Islet-specific glucose-6-phosphatase-related protein (IGRP)
 - All have modest sensitivity, much better specificity (ie don’t say whether you’ll get it, but tell you what you’ll get)

- One or other present in > 75% of newly diagnosed 1A, 5 – 10% of type 2 and < 5% GDM
- Measurement in a non-diabetic is a research tool only. Presence can precede overt disease by many years
- Serum insulin or C-peptide measurements do not always distinguish T1 from T2 (new onset T1 still have some C-peptide) but a low C-peptide confirms a patient's need for insulin
- Prevention:
 - Nothing found to reverse progression
 - Insulin in antibody positive pre-diagnosis individuals not effective – tested in Diabetes Prevention Trial
 - Nicotinamide not effective
 - Cyclosporine worse than placebo for new onset T1DM – reduced insulin requirement but nephrotoxicity
 - Anti-CD3 antibodies reduced insulin requirements, but adverse events (fewer than cyclosporine)
 - Immunotherapy: immunisation with GAD (glutamic acid decarboxylase) in children 10 – 18 with new onset. Trend towards benefit if < 6 months since diagnosis (NEJM 8 Oct 2008)

Treatment

- Insulin dosing (see page 52 for types of insulin):
 - Require 0.5 – 1.0 units/kg each day, initially 40 – 50% insulin as basal
 - Twice daily regime: 2/3rds in morning, 1/3 at night, each dose 2/3rds intermediate acting (isophane = protaphane or Humulin N), 1/3rd short acting – convenient but not physiological profile
- Usual target HbA1C 7% – ↑↑ hypos below this – will vary for every person
- Exercise – prone to hypo or hyper – depends on pre-exercise glucose, circulating insulin, exercise induced catecholamines. Don't exercise if < 5.5 or > 14, or if ketones. Decrease insulin before exercise, inject into non-exercising area
- Diabetes Control and Complications Trial (DCCT):
 - Reduction in chronic hyperglycaemia in T1 (intensive over conventional treatment HbA1c of ~ 9% vs 7%) over 10 years → ↓ complications – retinopathy (↓RR 50%), microalbuminuria (↓RR39%), nephropathy and neuropathy, and non-significant ↓ macrovascular events
 - Intensive therapy has longer term protective benefits than conventional therapy but 2.5 – 3 * risk of hypos
 - Data doesn't support intensive treatment in patients with macrovascular complications or children < 13
- Epidemiology of Diabetes Intervention and Complications (EDIC) Trial – followed both arms of DCCT – intensive group slipped in control without the intensive follow-up, but benefits of earlier tighter control persisted ('legacy effect')
- Continuous glucose monitoring: lowers HbA1C in > 25, but not younger. No difference in hypos (NEJM 2 Oct 2008)
- Continuous Subcutaneous Insulin Infusion Pumps (CSII):
 - Modest decreases in HbA1c, hypos, insulin dose, weight gain
 - Uses rapid acting analogues with more predictable absorption
 - Programmable delivery – simulates normal pancreatic function
 - Drawbacks: cost (pump \$5,000, consumables \$200 per month), site infection, dislodgement → DKA
- Islet cell transplantation hasn't worked yet
- Pancreas + renal transplants – 50% 5 yr pancreas survival (helpful to do the two together as kidneys can be biopsied for rejection, pancreas' can't)
- Stem cells the hoped for magic bullet for type 1

Diabetic Ketoacidosis

- Can (rarely) occur in patients without T1A and who are subsequently treated with oral agents (usually Hispanic or African-American descent)
- Presentation: Short course, nausea, vomiting, severe abdo pain, Kussmaul respirations, cerebral oedema (mainly kids, as a complication of over-rapid rehydration with free water)
- Pathophysiology:
 - Absolute insulin deficiency and counter-regulatory hormone excess (glucagon, catecholamines, cortisol and GH) → gluconeogenesis, glycogenolysis and ketone body formation. Hepatic handling of pyruvate shifts from glycolysis to glucose synthesis

- Ketosis: $\uparrow\uparrow$ free fatty acids from adipocytes \rightarrow \uparrow ketone body synthesis in liver (would normally be converted to TGs or VLDL). Ketone bodies usually exist as ketoacids, balanced by HCO_3^- . pH drops as HCO_3^- depleted
- Labs:
 - Anion gap raised ($\text{Na} - [\text{Cl} + \text{HCO}_3^-]$)
 - Acetoacetate may falsely \uparrow reported Cr
 - \downarrow Measured Na 2^{nd} to \uparrow glucose (add 1.6 meq to measured sodium for each 5.6 mmol/L rise in serum glucose)
 - The ketone body β -hydroxybutyrate is produced at a threefold rate to acetoacetate – but the latter is detected by a commonly used ketosis detection reagent (nitroprusside – also detects acetone – used in dip sticks – captopril or penicillamine may cause false-positive reactions). Serum β -hydroxybutyrate more accurately reflects true ketone level. As ketosis improves, β -hydroxybutyrate is converted to acetoacetate
- Treatment:
 - Will be K deplete – although initially measured high due to acidosis. K replacement once into normal range
 - Trials do not support the routine use of HCO_3^- – although recommended by ADA if $\text{pH} < 7.0$

Type 2 Diabetes Mellitus

Background

- See Lancet 28 June 2008 for a good update
- Risk factors: family history, obesity, inactivity, ethnicity (eg Pacific Islander), previous IFG, history of GDM, HTN, HDL < 0.9 , TG > 2.8 , PCOS, history of vascular disease
- Concordance in identical twins 70 – 90%. 40% risk if both parents type 2
- Genetic factors increasingly elucidated: polymorphisms in PPAR, KCNJ11 and many others
- Usual presentation: > 30 , 80% are obese (elderly may be lean), may not require insulin initially, no associated autoimmune problems, cardiovascular risk factors
- Cardiovascular mortality is 2 – 3 times higher in men with diabetes, and 3 – 5 times higher in women with diabetes than in people without diabetes

Epidemiology

- Rates are increasing dramatically
- Prevalence is $\sim 7\%$, 50% of those with diabetes are undiagnosed. Prevalence of impaired glucose levels (IGT, IFG and T2DM) in Australian/NZ adults is 25%
- Australian data:
 - For every person with diabetes, there are 2 with IGT or IFG. Only half of those with diabetes are diagnosed (AusDiab study)
 - 23% of over 75s have diabetes (compared with 15% in 1981)

Pathophysiology

- Three abnormalities:
 - Peripheral insulin resistance:
 - Aging, genes and obesity contribute
 - Visceral fat: \uparrow lipolysis in visceral fat and \downarrow clearance of TG \rightarrow \uparrow FFA + \downarrow glucose uptake
 - Muscle: \downarrow clearance of TG, \downarrow glucose uptake, \downarrow glucose utilisation
 - Metabolic syndrome, insulin resistance syndrome, and syndrome X describe a constellation of metabolic derangements (see Metabolic Syndrome, page 57)
 - Also includes rare forms of resistance in which Acanthosis Nigricans (brown-black skin papillomas – usually axilla) and hyperandrogenism (hirsutism, acne, oligomenorrhoea) are common. Type A have a defect in insulin signalling, Type B have insulin receptor autoantibodies
 - Seen in a significant subset of women with PCOS \rightarrow \uparrow risk of type 2 independent of obesity
 - Excessive hepatic production of glucose: *hepatic insulin resistance the driving force of hyperglycaemia* 2^{nd} to \uparrow gluconeogenesis and \downarrow glucose uptake
 - Impaired insulin secretion (ie β cell decompensation, cause unclear). Onset of frank diabetes when insulin secretion falls away, and can no longer continue to increase with increasing insulin resistance. 50% reduction in β -cell function at diagnosis (\Rightarrow benefit of pre-diagnostic intervention)

Diagnosis

- Classification (American Diabetes Association)

	Fasting (no calories for 8 hours)		2 hour post 75 gm glucose load
Diabetes	≥ 7.0	or	≥ 11.1
IGT	< 7.0	and	7.8 – 11.0
IFG	5.6 – 6.9	and	< 7.8 (some say 7.0)
Normal	< 5.6	and	< 7.8 (some say 7.0)

- Impaired Fasting Glucose:
 - Must be repeated if abnormal for diagnosis
 - vaguely ~ Impaired glucose tolerance: 7.8 – 11.0 two hours post challenge
 - 40% risk of DM over the next 2 years
- Impaired glucose tolerance not recommended as part of routine care
- Fasting glucose is valid as a screening tool as there are many asymptomatic people, and treatment will help
- Screening should be offered to people with (Med J Aust. 6 Oct 2003):
 - One of:
 - Age > 55 years (or > 35 years if Aboriginal, Pacific Islander, Indian, Chinese)
 - Known IGT or IFG
 - Ischaemic cardiovascular disease
 - Prior gestational diabetes
 - PCOS + obesity (should have OGTT not IFG)
 - Two of:
 - Age 45 – 55 years
 - BMI > 30
 - First degree relative with T2DM
 - HTN
- No glycaemic threshold predicts retinopathy. FPG of > 7.0 has sensitivity $< 40\%$ for detecting retinopathy (Lancet 2008:371)
- HbA1C:
 - HbA1C is not currently recommended for the diagnosis of diabetes. It is however correlated with cardiovascular mortality, even in the normal range (BMJ 2001;3221:15)
 - Depending on assay, anaemias and uremia may interfere with result

HbA1C (%)	Mean plasma glucose (mmol/L)
6	7.5
7	9.5
8	11.5
9	13.5
- ADA recommends measuring twice per year, ideal is ≤ 6.0
- Target is a factor of age, ability to understand, complications, ability to recognise hypoglycaemic symptoms, lifestyles, support, etc

Prevention

- Diabetes Prevention Programme: Mean age 52 years, mean BMI 33 (ie obese \Rightarrow high risk population). Demonstrated that intensive diet + exercise (30 min 5 days per week, weight loss 7 kg over 3 years) prevented or delayed T2 by 58% compared to placebo. Metformin prevented or delayed by 31% cf placebo.
- Exercise combined with 7% weight loss reduced new onset diabetes: 6.9 people exercising for 3 years prevented 1 new case
- 6 years of diet and exercise intervention in people with impaired glucose tolerance lead to delays in diabetes diagnosed over the following 14 years (cumulative diagnosis of 80 vs 93%) but no difference in CVD mortality or all cause mortality (China Da Qing Diabetes Prevention Study, Lancet 24 May 2008)
- Ramipril + pravastatin reduced new cases of T2 in cardiovascular trials (not primary end point)
- Thiazolidinediones have been shown to reduce risk of progression. DREAM Trial (Diabetes Reduction Approaches using Ramipril and Rosiglitazone Medication). High doses Ramipril (15 mg/d) + rosiglitazone (8 mg/d) in 2 by 2 trial in 5269 patients with IGT or IFG, follow up 3 years, with diabetes or death as outcome. Ramipril: no significant \downarrow in progression to DM or death, but \uparrow

likelihood of regression to normoglycaemia. Rosiglitazone reduced new DM by 60% and regression to normoglycaemia, 3% ↑ in weight but shift from visceral to subcutaneous, ↑CHF. For every 1,000 treated for ~ 3 years, 144 cases of DM are prevented with excess of 4 cases of CHF

Treatment Overview

- Has 3 strands:
 - Glycaemic control: diet/lifestyle, exercise, medication
 - Treat associated conditions: lipids, HTN, obesity, IHD
 - Screen/manage complications: retinopathy, CVD, nephropathy, neuropathy, feet
- Non-pharmacological treatment:
 - Multidisciplinary team: including diabetes educator, nutritionist, podiatrist
 - Nutrition: Low glycaemic index diets can significantly improve control in less than optimally controlled diabetes with HbA1C reductions of ~0.5% (Cochrane 2009)
 - BSL log book
 - Vaccination for pneumococcal and influenza
 - Depression and eating disorders more frequent
 - Pregnancy: high glucose is teratogenic – most important time for control is early. Pregnancy → ↑insulin resistance (insulin doesn't cross the placenta)
- Any improvement in glycaemic control → ↓glucose toxicity to islet cells → ↑insulin secretion
- ADA Clinical practice guidelines 2007 [with percentage of patients that reach the target in brackets]:
 - Glycaemia:
 - HbA1c < 7.0% [43%]
 - Pre-prandial glucose 5.0 – 7.0
 - Peak post prandial glucose < 10
 - BP: < 130/80 (<120/75 in patients with retinopathy) [66% < 140/90]
 - Cholesterol:
 - LDL < 2.6 (no CVD) or < 1.0 (with CVD) or 30% reduction in LDL with a statin if over age 40 and total cholesterol > 3.5 [11% < 2.6]
 - TG < 1.7
 - HDL > 1.0 (men), 1.3 (women)

Important trials in Type 2 Diabetes

- United Kingdom Prospective Diabetes Study (UKPDS- BMJ 2000, 321:400):
 - Followed > 5000 newly diagnosed T2DM patients for > 10 years. Diet control or intensive therapy (sulfonylurea or insulin or if overweight then metformin). 1148 with HTN were randomised to tight or less tight regimes for BP
 - “Intensive” is somewhat misleading – corresponds to usual management in many centres
 - Each 1% drop in HbA1C → ↓35% in microvascular complications (mainly retinal photocoagulation), ↓21% in diabetes related deaths, ↓14% in MI (p = 0.052)
 - Did not conclusively reduce cardiovascular complications (but was associated with improved lipoprotein profiles) and no change in all-cause death or diabetes related death
 - Strict blood pressure control even more effective than glycaemic control
 - More weight gain in intensive group (~ 5 kg vs ~ 2.5kg)
 - Glycaemic control worsened over time in each treatment group
 - Demonstrated **Legacy Effect** (NEJM 9 Oct 2008) after a median of 9 years post trial follow up:
 - Long after trial finished, and intensive glucose control arm had returned to “normal” HbA1C, benefits persisted (parallels findings of DCCT/EDIC in Type 1) for microvascular complications, *and* differences emerged in diabetes related death (RR 17%), MI (RR 15%) and death from any cause (RR 13%, p =0.007) up to 5 years only – previously no difference in macrovascular complications has been observed during trials
 - Interesting aside – the metformin vs dietary control in overweight group (only trial of it's kind) reduced macrovascular but not microvascular complications, and Cr was 15% higher in the metformin group
 - No legacy effect with the intensive BP control arm of UKPDS – ie once BP returned to “normal” (ie less well controlled), trial benefits were lost
 - Postulated that the legacy effect is due to ↓burden of advanced glycation end products, or slowed progression of kidney disease which mediates other risks
- ACCORD and ADVANCE [Action Diamicon Modified Release Controlled Evaluation] trials (both ~10,000 patients, RCT):

- Tried to see if tighter control lead to reduced macrovascular complications in people at high risk (value for microvascular complications established in UKPDS)
- Found little correlation – ie diabetes is a risk for MI, but tighter control doesn't necessarily reduce MI
- ADVANCE showed ↓ mortality, ACCORD showed ↑ mortality
- Lots of complicated arguments about the differences. ADVANCE trial had more metformin/Gliclazide therapy, ACCORD trial had much more rosiglitazone (<20% in ADVANCE, > 90% in treatment arm of ACCORD) + insulin in it's treatment arm, tighter target, greater weight gain, and had a net all cause mortality increase (although no difference in cardiovascular death, and decreased non-fatal MI. ?death due to undetected hypoglycaemia). NEJM 12 June 2008
- ADOPT Trial (A Diabetes Outcome Progression Trial):
 - Head to head trial. Approx 4,500 people randomised to rosiglitazone, metformin or glibenclamide for 4 – 6 years – a race to failure of monotherapy (FPG > 10)
 - Glibenclamide worse than metformin which was just worse than rosiglitazone for failure of monotherapy
 - Weight: rosiglitazone continued weight gain over 5 years, glibenclamide gained a bit then plateaued, metformin lost
 - CVD of any sort: Glibenclamide better than metformin and rosiglitazone
 - Fractures in women (men equal): 9.3% with rosiglitazone, 5.1% on metformin, 3.5% on glibenclamide – mainly upper limb and lower limb (including small bones of the feet), no difference in spine or hip between rosiglitazone and metformin
- Steno-2 Study: Multifactorial Intervention in T2DM with intensive targets across lifestyle modifications, BP, HbA1c, Cholesterol, Microalbuminuria, Aspirin: ARR 20%, NNT 4 for 7.8 years for cardiovascular death or diabetic complications

Hyperglycemic Hyperosmolar State (HONK)

- Presentation: elderly with several week history of weight loss and polyuria leading to confusion. Little or no nausea/vomiting
- Exam: profoundly dehydrated, hypotensive and tachycardic. Screen for precipitating infections
- Reason for absence of ketosis is not well understood, presumed to be because of relative not absolute insulin deficiency
- Labs: High glucose and osmolarity. Ketonuria (if present) due to starvation
- Higher mortality than DKA
- Once haemodynamically stable, reverse free water deficit over 1 – 2 days. Usually needs insulin

Diabetes Medication

- Impact of therapies on HbA1c reduction (NEJM Oct 2002, 347:17, JAMA July 2007, 298:2):

	% HbA1c Reduction	12 mth kg weight change
Diet and exercise	0.5 – 2.0	
Sulphonylureas	1.0 – 2.0	+2
Metformin	1.0 – 2.0	-2
α-glycosidase inhibitors	0.5 – 1.0	
Thiazolidinedione	0.5 – 1.0	+5
Incretin mimetics/enhancers	0.5 – 1.0	
Insulin	> 5.0 (??)	+3.5
Laposcopic banding	1.5	-23

Insulins

- Injected insulin by passes liver – so liver gets subphysiologic insulin levels
- Types of insulins:
 - Short acting have less tendency towards subcutaneous aggregation (normal insulins form hexamers) → absorbed quicker. Use for post prandial replacement and pumps
 - Rapid acting insulins: aspart (novorapid), lispro (humalog)
 - Insulin glargine (Lantus):
 - Long acting – lower incidence of hypos – especially at night – but little difference in glycaemic control (non inferior to tds prandial rapid acting for T2DM, HBA1C reduction of ~1.7%). Both have weight gain. NEJM 29 March 2008
 - Requires 20% dose reduction when converting from normal insulins

- Not stable at room temperature. Can mix other insulins for injection – but don't store mixed
- Inhaled insulin coming – slightly less efficacious than sc, preferred by patients, questions about pulmonary toxicity not answered yet
- Augmenting oral medication in T2:
 - Adding a basal insulin more effective than biphasic or meal time insulin (Treating to Target in Type 2 Diabetes – the 4-T trial)
 - Initial treatment with insulin rather than oral hypoglycaemics, with cessation after 2 weeks normoglycaemia, followed by diet and exercise alone, lead to higher remission rates at 1 year (Chinese study reported in Lancet, 24 May 2008)

Insulin Secretagogues (mainly Sulphonylurea)

- Anticipated 1 – 2 % reduction in HbA1C
- Stimulate insulin secretion by interacting with the ATP-sensitive K channel on β -cells – most effective in recently diagnosed, obese, and residual insulin production
- Decrease both fasting and post-prandial glucose
- Initiate at low dose and increase at 1 – 2 weekly intervals
- SEs:
 - Hypos generally related to delayed meals, \uparrow physical activity, alcohol, renal insufficiency
 - Metabolised in liver, secreted by kidneys – avoid in renal and hepatic insufficiency
 - Weight gain results from improved glycaemic control
 - First generation sulphonylureas (eg Tolbutamide, none available in NZ) have shorter half life, more hypos and more interactions than 2nd generation
- Contraindicated in some blood disorders and SIADH
- Interactions with alcohol, warfarin, aspirin, fluconazole
- Available in NZ:
 - Glibenclamide – max 20 mg daily – longer acting \rightarrow \uparrow risk of hypo
 - Gliclazide – max 320 mg daily – metabolised in liver – best in renal impairment
 - Glipizide – max 20 mg daily

Biguanides (eg Metformin)

- Anticipated 1 – 2 % reduction in HbA1C
- Effects:
 - Reduces hepatic glucose production from lactate, pyruvate, glycerol and amino acids (mechanism uncertain, ?primary site is mitochondria)
 - Increased peripheral insulin sensitivity in skeletal muscle and fat (increases tyrosine kinase activity in insulin receptors and enhances glucose transporter (GLUT) trafficking), improves lipid profile (inhibits FFA production and oxidation)
 - \rightarrow modest weight loss
 - No hypoglycaemia (some case reports....)
- Initially 500 mg od or bd
- Rapidly excreted unchanged by the kidney. Impaired kidney function \rightarrow accumulation
- SE:
 - Nausea, diarrhoea reduced with gradual dose escalation
 - Can cause lactic acidosis: avoid if renal insufficiency (Cr > 133 in men, > 124 in women), any form of acidosis, CHF, liver disease or severe hypoxia. Withhold if seriously ill, nothing orally, or getting contrast
- Used in pregnancy: see page 462
- PCOS \rightarrow dramatic decline of early miscarriage rate outweighs any concerns about teratogenicity

Thiazolidinediones

- Action:
 - Insulin sensitiser \rightarrow reduce insulin resistance
 - Peroxisome proliferator-activated receptor γ (PPAR γ) agonists (as opposed to fibrates which act on PPAR α) – a nuclear receptor in adipocytes. Ameliorate insulin resistance, especially in the liver (\rightarrow reduced liver fat). Action modifies expression of hundreds of genes – results from one drug may not be generalisable across the class. In adipose tissue \rightarrow \uparrow fat storage, \downarrow lipolysis, \uparrow adiponectin
 - Equipotent in terms of \downarrow HbA1C with metformin and sulphonylureas
 - CRP reduction found in rosiglitazone trials

- Indications:
 - Can be used in patients with reduced renal function and have fewer GI side-effects than metformin
 - Use if they don't tolerate metformin and want an insulin sensitiser
 - ↑Benefit even with sulphonylureas
 - Induce ovulation in PCOS
- Pioglitazone available in NZ – dose 15 – 45 mg od. Special Authority due to cost
- SE:
 - Don't cause hypos
 - *Small weight gain* – but subcutaneous rather than visceral
 - ↑LDL, ↑HDL, ↓TGs – ? significance
 - Rosiglitazone found in pooled data to ↑humeral fractures in women only
 - The prototype (troglitazone) was withdrawn due to hepatic failure. Now routine to test LFTs with others
 - ↑peripheral oedema
 - ↑↑Weight gain in combination with insulin, and increased risk of oedema and CHF – combination not allowed in most European countries
- Contraindicated: *liver disease or CHF* (class III or IV). Not triple therapy with metformin and sulphonylureas. Better with metformin than sulphonylureas
- PROACTIVE trial (Lancet 2005), average follow-up 3 years: Pioglitazone reduced all cause mortality (ARR 2.2%), non-fatal MI and stroke in high risk T2DM (ie macro-vascular complications). Increased admissions, but not mortality, from CHF. Average weight gain of 4 kg cf placebo
- Cardiovascular events: Pooled data (eg NEJM 2007;356:2457) from small (generally safety) studies of short duration not designed to assess cardiovascular outcomes suggests ↑cardiovascular risk. Another meta-analysis (JAMA 2007;298:1189) suggests ↑MI risk with rosiglitazone, ↓MI risk with Pioglitazone but ↑CHF
- Cochrane Review 2007 of Rosiglitazone: no benefit in HbA1C compared to other oral agents, no benefit in terms of clinical outcomes. More oedema. ↑Fracture rates in women
- American Diabetes Association issued new guidelines (Lancet 1 Nov 2008) advising against the use of Rosiglitazone, due to ↑MI and cardiovascular mortality. Based on ACCORD trial results

α-Glucosidase Inhibitors

- Acarbose (= Glucobay available in NZ) and miglitol
- Decrease glucose absorption by inhibiting the enzyme that cleaves oligosaccharides into simple sugars in the intestinal lumen (→ ↓postprandial hyperglycaemia). Anticipated ↓ in HbA1C of 0.5 – 1.0%
- No risk of hypos. *No significant effect on weight* (although potentially diarrhoea associated weight loss). GI flatulence and diarrhoea (risk reduced by slow titration), ↑LFTs, contraindicated in renal/liver disease and inflammatory bowel disease

Other treatments

- Amylin agonist: see Gut and Adipocyte Peptides, page 57
- Incretins: see Gut and Adipocyte Peptides, page 57

Complications of DM

- Mechanisms:
 - Non-enzymatic glycosylation of intra and extracellular proteins → advanced glycosylation end products (AGEs)
 - Conversion of glucose to sorbitol via aldose reductase (but aldose reductase inhibitors have not proved beneficial)
 - ↑Growth factors 2nd to ↑glucose:
 - ↑Vascular endothelial growth factor (VEGF) → proliferative retinopathy
 - ↑TGF-β → basement membrane production of collagen and fibrinogen
 - ↑susceptibility to intracellular oxidative stress and impaired cell signalling
- **Eyes:**
 - Leading cause of blindness in adults
 - 1/3 of patients with T2DM have diabetic retinopathy at diagnosis
 - Non-proliferative retinopathy: after 5 – 10 years – retinal vascular microaneurysms, blot haemorrhages, cotton wool spots
 - Proliferative retinopathy later 2nd to hypoxia 2nd to non-proliferative complications. No benefit shown from aspirin

- Photocoagulation has a proven role in proliferative retinopathy
 - Protein Kinase C inhibitors (Roboxisturin) → ↓risk of visual loss but did not prevent DR progression
 - **Kidneys:**
 - Diabetic nephropathy accounts for 40% of ESRF (Aussi data). 20 – 30% of T2DM have overt nephropathy (proteinuria, HT, ↓GFR)
 - Progression:
 - Initially: glomerular hyper-perfusion and renal hypertrophy → ↑GFR
 - Then: thickening of GBM and mesangial volume expansion → GRF normalises
 - After 5 – 10 years: microalbuminuria. Can be reversed with tight glycaemic control. Progression to overt nephropathy better predicted by microalbuminuria in T1 than in T2
 - Then overt proteinuria (usually irreversible at this point) – 50% of these individuals reach ESRD in 7 – 10 years
 - Type IV renal tubular acidosis (↓renin, ↓aldosterone) occurs in T1 and T2. Risk of hyperkalaemia (care with drugs – including ACEI and ARBs)
 - Albuminuria is a better predictor of death than of renal progression
 - Annual screening recommendations:
 - Albumin excretion rate in timed overnight or 24 hour urine sample, or
 - Spot albumin:creatinine ratio (if positive should repeat)
- | | Albuminuria | ACR |
|------------------|-------------|--------------------|
| Normal | < 30 | < 2.5 (m), 3.5 (f) |
| Microalbuminuria | 30 – 300 | |
| Macroalbuminuria | >300 | |
- Treatment:
 - Trials with clinical endpoints in later stage disease: IDNT (Irbesartan), RENAAL (Losarten)
 - Once overt proteinuria, BP control more important than glycaemic control
 - ACEI has effect over and above BP control – mechanisms likely to include ↓trophic effect of angiotensin on mesangium (effect reduced in smokers). Also have anti-inflammatory, anti-proliferative and oxidative stress lowering properties. Renal protective effect greater when GRF < 60 ml/min (most studies showing reno-protective effect done in this group of high risk patients). Less evidence of delayed progression prior to the onset of ↓GFR or proteinuria (Lancet 16 August 2008)
 - Prevention with glucose control (shown to delay onset of proteinuria), strict BP control, ACEI or ARBs, treatment of lipids
 - Insulin requirements may fall as kidneys fail – one site of degradation
 - BP target: < 130/80 without proteinuria, < 125/75 if proteinuria
 - Treat with ACEI/ARBs until microalbuminuria resolves or maximum dose achieved. Drug specific benefit independent of BP shown with ACEI in type 1 and ARBs in type 2
 - Small RCT trial evidence that ARBs in addition to ACEI reduce proteinuria further (Ann Int Med 15 March 2005)
 - ADA recommends modest protein restriction with microalbuminuria – conclusive proof lacking
 - See Aliskiren (renin inhibitor) in Hypertension, page 20
 - **Neuropathy:**
 - Most common presentation is distal sensory loss
 - 10 g monofilament assesses protective sensation. 128Hz tuning fork more sensitive for early polyneuropathy, less predictive of ulceration
 - Mononeuropathy: less common – pain and motor weakness due to a single nerve (??vascular etiology). 3rd nerve common → diplopia
 - Autonomic: including gastroparesis (treatment – try cisapride), bladder emptying abnormalities, hyperhidrosis...
 - Diabetic amyotrophy (femoral neuropathy, proximal diabetic neuropathy) – in T2DM, abrupt onset of severe pain affecting the anterior thigh worse at night, with weakness/wasting. Stabilises then improves
 - Treatment of neuropathic pain: amitriptyline → anticonvulsants → gabapentin
 - Meta-analysis of alpha lipoic acid (thioctic acid, an antioxidant) 600 mg iv/day for 3 weeks is safe and improves symptoms of neuropathy
 - **Cardiovascular disease:**

- Bottom line: hyperglycaemia associated with increased cardiovascular risk, but it has been difficult to prove that reducing glycaemia by any drug has a direct cardiovascular benefit (NEJM 11 Sept 2008)
- Framingham Heart Study [Framingham is in Massachusetts]: marked increase in peripheral arterial disease, CHF, coronary artery disease, MI and sudden death in T2DM
- T2 DM confers the same risk for MI as a previous MI
- Coronary artery disease is more likely to involve multiple vessels in DM
- No proof that improved glycaemic control reduces macrovascular complications (in DCCT number of events in both arms low)
- CAGB and PCI less efficacious in diabetic patients (higher re-stenosis rates, lower survival)
- Clear benefit from beta-blockers
- No specific evidence of aspirin in primary prevention in T2DM – just follow general trials
- **Lipids** (see also Lipid Disorders, page 61):
 - Target values in T2 DM without cardiovascular disease (ADA and AHA): LDL < 2.6 mmol (some recommend < 1.8 if very high risk ie T2DM and CVD), HDL > 1.1 mmol (men) 1.38 mmol (women), TGs < 1.7 [attack them in that order]
 - Trials only in T2 (not T1) and have used statins only:
 - Heart Protection Study: simvastatin 40 mg in “high risk” patients. Subgroup analysis showed benefits of intensive statin therapy on CVD extend to patients with T2DM irrespective of baseline lipid levels. ↓risk of MI, CVA and revascularisation by about 1/3rd
 - Collaborative Atorvastatin Diabetes Study (CARDS): Atorvastatin 10mg. Solely focused on T2DM. Stopped early due to overwhelming evidence of benefit on a population that wouldn't previously have been considered dyslipidaemic (mean baseline LDL 3.0). NNT 27 to prevent one event over 4 years
 - Treating to New Targets (TNT) Diabetes sub-study: Atorvastatin 80 mg vs 10 mg: Post hoc analysis of diabetics: LDL 2.0 (80mg) vs 2.5 (10 mg) → ↓25% cardiovascular events (similar to main study endpoint). No significant ↓ in mortality (
 - Treatment:
 - Dietary and lifestyle modifications (usually modest response)
 - Improving glycaemic control will ↓ TGs and ↑ HDL
 - Statins agents of choice
 - Consider fibrates if HDL low
 - Don't use bile acid-binding resins if high TGs
- **Hypertension:**
 - ACEI → modest ↓LDL slightly, ↓insulin resistance, ↑HDL
 - α-Adrenergic blockers slightly improve insulin resistance but may worsen orthostatic hypotension if autonomic neuropathy
 - β-blockers and thiazides can increase insulin resistance, and worsen lipids
 - Ca blockers, central adrenergic antagonists and vasodilators are lipid and glucose neutral – but impact on cardiovascular endpoints independent of BP lowering is controversial/unknown. Verapamil and diltiazem [non-dihydropyridine ca blockers preferred over dihydropyridine (amlodipine and nifedipine) in diabetics]
- **Feet:**
 - Disordered proprioception → abnormal weight bearing
 - Motor and sensory neuropathy → abnormal foot mechanics → hammer toes, prominent metatarsal heads, Charcot joint
 - Subcutaneous infection can be difficult to distinguish from osteomyelitis (bone scan may help, Indium labelled white cell studies good but technically difficult). MRI specific but may confuse osteomyelitis from eg Charcot joint
 - Osteomyelitis: Abs, ?debridement, ?vascular insufficiency repair
 - Ulcer management: off-loading (no weight bearing), debridement, wound dressings, ABs (if no response in 48 hours broaden cover to include MRSA and Pseudomonas cover), revascularization, limited amputation. No place for antiseptic agents and topical ABs. No evidence for hyperbaric O2. Emerging evidence of growth factors (eg basic fibroblast growth factor) and platelet-derived growth factor
- Immune: ↓phagocytosis, ↓granulocyte adherence
- Inflammation: ↑CRP, Il-6, Il-18, TNFα
- Thrombosis: ↑PAI-1, ↓fibrinolysis, ↑fibrinogen

- Endothelial dysfunction: ↓vasodilation

Obesity

- Daily caloric use:
 - Basal metabolic rate: 60 – 80%
 - Energy expended during physical exercise (including fidgeting): 20 – 30%
 - Metabolism of food: 10%
- Visceral adipose tissue is an “adipo-endocrine” organ, secreting:
 - Hormones: ↑visfatin, ↑resistin, ↑leptin, ↓adiponectin → ↑insulin resistance → ↑circulating FFA (as ↑insulin → ↑inhibition of lipolysis in adipose tissue – very sensitive insulin pathway)
 - FFA → ↑FFA to liver → ↑ApoB containing triglyceride rich VLDL
 - Cytokines: TNF α , IL-6, PAI-1, MCP-1, hsCRP
 - ↑TG → ↓cholesterol content of HDL
 - Patients of normal weight can also be insulin resistant
 - Hepatic production of CRP increased and adiponectin decreased with increasing obesity
- Relationship with HTN:
 - Insulin is a vasodilator with secondary effects on Na resorption
 - In insulin resistance, vasodilatory effect lost, Na resorption unchanged → modest impact on HTN

Epidemiology of Obesity

- Approx 20% ↑ in calorie intake in the US over the last 30 years corresponding to a 20% ↑ in average weight – the biggest contributor to obesity
- The difference in average daily energy expenditure between 100 years ago and today is equivalent to a daily 15 km walk
- Of all sedentary behaviours, TV watching time correlates strongest with obesity
- Up to 70% of variation in weight is genetic

Gut and Adipocyte Hormones

- Adipose tissue acts as an endocrine gland. Secretes:
 - Estrogen
 - Adipsin: complement related protein that is suppressed in obesity
 - Cytokines: including TNF- α & CRP. Postulated that T2DM is partly an inflammatory syndrome. Macrophages infiltrates adipose, release inflammatory cytokines which → disordered lipid metabolism. Macrophage number ↑ with increasing adipocyte size
 - Angiotensinogen
 - Adipokines:
 - **Adiponectin:**
 - Produced by adipocytes
 - ↓ in obesity. Also low in inflammation and atherosclerosis
 - ↓ in diabetes compared with weight matched controls
 - ↑ with exercise, calorie-restricted diets, *thiazolidinediones* (cf metformin)
 - Increases hepatocyte sensitivity to insulin → an endogenous insulin sensitiser
 - *Correlates better with insulin resistance than BMI*
 - One of the modulators is PPAR γ
 - A number of polymorphisms are associated with diabetes
 - Evidence in mouse models that it plays a protective role in atherosclerosis
 - Restin
 - **Leptin:**
 - Rises with ↑adipocyte mass, signals brain to decrease food intake. Most obese people resistant to its central actions (leptin resistance) and have ↑ levels of leptin
 - Low levels with starvation → suppression of energy expenditure, changes in thyroid and reproductive hormones. Falls dramatically with weight loss (compared to the reduction in BMI) → potent hunger stimulator
 - Ob/Ob knock out mice (ie recessive inheritance) are leptin deficient, ObR mutation is defective leptin signalling (less severe obesity)
 - Gut and pancreatic hormones:
 - **Amylin:**
 - Amino acid co-secreted with insulin from β -cell. Mechanism uncertain

- One of its actions is to ↓gastric emptying
- Used in type 1 and 2 DM. Injected. Modest reduction in HbA1C – reduces post prandial highs and slows gastric emptying
- **“Incretins”**:
 - Glucagon-Like Peptide 1 (**GLP-1**):
 - Endogenous GLP-1 is secreted by L cells of the small intestine and:
 - Stimulates β-cells (amplifies insulin secretion) – accounts for the ↑insulin release seen from an equivalent oral glucose load over iv administration
 - MAY stimulate β-cell replication and maturation
 - slows gastric emptying
 - ↓glucagon secretion and ↓ appetite
 - is quickly broken down by DPP-4, so only therapeutically effective as an infusion
 - ↓ in T2DM → ↑post-prandial hyperglycaemia
 - Incretins are agents which act as GLP-1 agonists or enhance endogenous GLP-1
 - Not with insulin. Modest AIC reduction. No trials yet showing effect on diabetes complications
 - Advocated as an alternative to starting insulin – which is often delayed due to fears about hypos and weight gain
 - **Exenatide** (Byetta):
 - Recombinant GLP-1 receptor agonist not deactivated by DPP-4 – sc bd. 3 RCTs showing similar reductions in HbA1C as glargine OD or insulin 30/70 bd with less hypos and weight gain (HbA1C reduction of 1 – 1.5%)
 - ↓weight
 - Not hypoglycaemic – as it’s glucose dependent. It won’t increase insulin without ↑glucose
 - SE: nausea, vomiting, rare acute pancreatitis
 - DURATION-1 Trial (Lancet 4 Oct 2008) showed once weekly long-acting Exenatide vs bd Exenatide → lower HbA1C (77 vs 61% reached < 7%), same number of hypos, less nausea
 - Vildagliptin (Galvus), Sitagliptin (Januvia):
 - Oral medication inhibiting DPP-4 enzyme → prolonged action of GLP-1
 - Lower HbA1c by ~1.0%, weight neutral (ie not same degree of weight loss)
 - Effective add-on – for dual therapy with metformin or sulphonylureas
 - GIP (Gastric Inhibitory Polypeptide): another incretin, not so important
- **Ghrelin**:
 - Released from the stomach pre-prandially
 - The hormone of hunger. Higher levels in leaner people
 - ↑ following gastric banding, ↓following gastric bypass
- Appetite signalling:
 - A complex mix of gut hormones, hypothalamus peptides and adiposity signals. There are more inhibitory signals (eg PYY, PP, CCK, GLP-1, insulin, leptin) than stimulating signals (eg Ghrelin). We are wired to eat unless told not to
 - Weight is homeostatically regulated – whatever weight we’re at we defend

Metabolic Syndrome

- Several definitions in use – bottom line is obesity related risk is a continuum. WHO definition is “glucocentric”, NCEP ATP III definition is “lipocentric”
- Most common definition (International Diabetes Federation): Central obesity (waist circumference ≥ 94 cm for European men, ≥ 80 cm for European women – other values for Asian and Japanese – note measures subcutaneous and visceral fat), plus any two of the following (or treatment for the following):
 - Raised TG level: ≥ 150 mg/dl, 1.7 mmol/L
 - Reduced HDL: < 1.03 mmol/L in males and 1.29 in females
 - Raised blood pressure: systolic ≥ 130, diastolic ≥ 85
 - Raised FPG > 5.6 mmol/L
- Prevalence is highly age dependent
- Waist circumference (rather than waist to hip ratio) is best correlated with visceral adipose tissue
- Risk assessment:
 - Framingham Heart Study – adding abdominal obesity, TGs and fasting glucose yields little increase in predictive power
 - Elevated CRP seems to carry increased risk for CAD

- Metabolic syndrome and its components are associated with T2DM, but only a weak association with vascular risk in the elderly (Lancet, 7 June 2008)
- Risks of Metabolic Syndrome:
 - 1.5 – 3 times risk of CVD in the absence of T2DM
 - 3 – 5 times risk of T2DM
 - Non-alcoholic Fatty Liver Disease
 - Hyperuricemia: reflects defects in insulin action on renal tubular resorption of uric acid
 - Women with PCOS are 2 – 4 times more likely to have metabolic syndrome than women without PCOS
 - Obstructive Sleep Apnoea – obvious relationship to obesity, but insulin resistance more severe in patients with OSA than weight matched controls

Management of Obesity

Assessment

- See NEJM 1 May 2008
- History:
 - Weight gain
 - Maximum body weight
 - Medications contributing to weight (steroids, thiazolidinediones, antipsychotics)
 - Previous approaches to weight gain
 - Patterns of food intake
 - Readiness for weight reduction (may be important in predicting success)
- Risks:
 - BMI > 30 associated with ↑ risk of death from all causes and from CVD
 - BMI > 40 has a RR for cancer of 1.5 males, 1.6 females. Estimated that 30 – 40% of cancers are avoidable through diet, nutrition and physical activity
 - Waist circumference is an independent predictor of risk. >102 cm male, > 88 cm female
- Predictors of maintenance of weight loss:
 - Low-fat diet
 - Frequent self-monitoring
 - High levels of physical activity
 - Long term patient-provider contact
- Bottom line: caloric restriction key to short-term weight loss and maintenance depends on ↑ physical activity. Key uncertainties are around how to facilitate adherence
- Metabolically healthy but obese individuals (see Lancet 11 Oct 2008):
 - A subset of individuals (up to 30%) seem to be protected from the metabolic complications of obesity
 - Have high insulin sensitivity, no HTN, normal lipids, inflammation and hormone profiles (ie low TG and CRP, high HDL and adiponectin). Have lower visceral, liver and muscle fat content
 - We don't know why – ?better ability of adipose tissue to trap fat
 - Not spared non-metabolic complications – OA, OSA, etc

Diets

- Weight loss (caloric restriction) and exercise (more important for maintenance of weight loss than weight loss initially). Adherence to diet is more important than the diet chosen
- ↓500 k-calories → ↓0.45 kg per week
- Meal replacements have RCT evidence, eating breakfast and adding fibre also recommended
- Dietary composition:
 - Low fat diets, eg restricting fat to < 30% caloric intake: controversial. Lifestyle Heart Trial results in weight loss and ↓CV risk at 5 years on fat content < 7%. Low fat diets difficult to maintain
 - Low Carbohydrate Diets (eg Atkins): RCTs show ↑loss at 6 months compared with low fat diets, but little difference at 12 months. Low Carbohydrate diets also → ↓glucose, ↓TGs, ↑HDL, and maybe ↑LDL
 - Low GI index diets: no ↑ weight loss beyond caloric restriction (but ↓insulin levels – clinical significance unknown)
 - High Protein Diets: (usually also high in fat). Substitution of protein for CHO in calorie-restricted diets → ↑ weight loss
- Head to head trials of specific commercial diets show little significant difference

- Weight loss in RCTs → ↓BP, ↓total:HDL cholesterol, ↓CRP, ↓glucose

Physical Activity

- ↑Physical activity without ↓caloric intake → only modest weight reduction but ↓abdominal (visceral adipose tissue) and improved insulin resistance
- Diet + exercise better than either alone
- Resistance training may be particularly beneficial in modifying body composition

Behavioural modification

- Goal setting, self-monitoring, stimulus control, cognitive restructuring (↑awareness of perceptions of oneself and one's weight), relapse prevention
- Reported to result in losses of 8 – 10% of body weight at 6 months
- Most studies in academic settings – the success in other treatment settings less clear

Bariatric Surgery

- Surgery if BMI > 40, or >35 with obesity related complications
- Weight loss from combinations of diet, exercise and behavioural therapy are modest (1 – 4 kg lost at > 2 years). Average loss from surgery > 30 kg sustained > 2 years. Is dramatically more effective. Weight loss sustained for > 10 years in long term follow up
- Options:
 - Gastric stapling
 - Laparoscopic adjustable gastric banding (LAGB): most common in Australia. Perioperative mortality in experienced centres = 1 in 2000
 - Jejunum-ileal bypass (Roux-en-Y)
 - Liposuction (no metabolic effect)
- Swedish Obesity Study (SOS): Follow up 15 years, 30% reduction in mortality (including perioperative complications), mortality 129/2037 vs 101/2010 (matched controls) – 6.3 vs 5.0%
- Although costly, surgery may be cost effective in morbidly obese patients after just 2 years

Anti-obesity Drugs

- If BMI > 30
- Orlistat (Xenical):
 - 120 mg/meal
 - Triacylglycerol lipase inhibitor → ↓absorption of dietary fat by about 30%
 - Some effect from ↓fat intake to avoid side-effects (eg steatorrhoea, flatus – but usually short lived)
 - ↓body weight by ~ 3% more than life style alone (10.2% reduction vs 6.1 % placebo at 1 year)
 - May → ↓absorption of fat soluble vitamins (esp D)
 - No experience for durations > 2 yrs – so don't use long term
- Sibutramine (Reductil):
 - Centrally acting appetite suppressant – an SNRI inhibiting reuptake of noradrenaline and serotonin
 - Weight loss ~ 5% greater than placebo. Reduction greater than with Sibutramine or caloric restriction alone
 - Not licensed for use > 1 year
 - Contraindications: history of depression, IHD, etc, etc. SE: HTN and tachycardia. Need to monitor BP closely
 - In trials, the weight lost has crept back on again afterwards (STORM trial, Lancet 2000;356:2219)
- No added benefit to Sibutramine and Orlistat in combination
- Tesofensine: Phase II RCT of Tesofensine vs placebo while on an energy restricted diet showed weight loss over 6 months of 12kg vs 2 kg with a low drop out rate (21%), ↓HbA1C and ↑adiponectin (Lancet 29 Nov 2008) – about double the losses with any other drug
- Also:
 - Phentermin (Duromine) and diethylpropion – adrenergic stimulants. Efficacy and safety data limited. SE HTN, dependency
 - Cannabinoid system blockers. CB1 receptors play a key role in energy balance. Endocannabinoid system stimulated by food deprivation and high fat diets. Rimonabant approved in Europe but not by FDA, effect via central and peripheral blockade of CB1 → improved metabolic parameters over and above that explained by weight loss
- Fluoxetine for concurrent depression enhances weight loss

Lipid Disorders

- Atherogenic dyslipidaemia = raised TGs + low HDL-c + elevated apolipoprotein B (ApoB) + small dense LDL particles + small HDL particles. Low HDL-c and high TG correlated with insulin resistance with or without T2DM, and both independent risk factors for CAD
- Measurement:
 - LDL is calculated using $LDL-C = \text{total cholesterol} - TGs/5 - HDL-C$. Doesn't work if $TG > 4.5$
 - VLDL = $TGs/5$ (reflects the ratio of cholesterol to TGs in VLDL particles)
 - Screening tests if high lipids: fasting glucose if $\uparrow TG$, urine protein and serum Cr (for nephrotic syndrome and renal impairment), LFTs (for hepatitis and cholestasis), TFTs for hypothyroidism
- A variety of genetic disorders – most common are (ie take family history):
 - Familial combined hyperlipidaemia: $\uparrow VLDL$ ($\rightarrow \uparrow TG$), $\uparrow LDL$, $\downarrow HDL$. 1 in 200 and 20% of patients with CHD under age 60
 - Familial hypercholesterolemia: genetic defect of the LDL receptor, 1 in 500. Tendon xanthomas are most suggestive of autosomal dominant familial hypercholesterolemia compared to other causes of hypercholesterolaemia
 - Familial hypertriglyceridemia, 1 in 500, autosomal dominant, cause unknown
- Causes of secondary hyperlipidaemia:
 - Nephrotic syndrome causes a predominant LDL increase, DM, obesity, alcohol and hypothyroidism tend to cause TG predominant lipid disorders
 - LDL increased: hypothyroidism, nephrotic syndrome, cholestasis, acute intermittent porphyria, anorexia nervosa, drugs: thiazides, cyclosporin, tegretol
 - LDL reduced: severe liver disease, malabsorption, malnutrition, chronic infectious disease, hyperthyroidism, Drugs: niacin
 - HDL elevated: alcohol, exercise, oestrogen
 - HDL Reduced: smoking, T2DM, obesity, malnutrition, drugs: anabolic steroids, beta blockers, If stubbornly low (< 20 mg/dl) consider genetic disorder
 - VLDL elevated: obesity, T2DM, glycogen storage disease, hepatitis, alcohol, renal failure, sepsis, Cushing's Syndrome, pregnancy, acromegaly, Drugs: oestrogen, beta-blockers, glucocorticoids, bile acid binding resins, retinoic acid
- Triglycerides:
 - Independent risk fact for CAD
 - If very high (> 5.7) then \uparrow risk pancreatitis
 - If very high, treat TG before LDL

Targets

- Cardiac Society of Australia and New Zealand (2005):
 - All CVD: statin. Also consider fibrate if $\uparrow TG$, $\downarrow HDL$, overweight
 - DM (after lifestyle and sugars stabilised of course!): statin for $LDL-C > 2.5$ mmol/L. Fibrate for $TG > 2.0$ mmol/L
 - Kidney disease: trials awaited. Start a statin on an individualised basis
 - Also consider if:
 - Absolute risk of CVD event in 5 years is $> 15\%$
 - Absolute risk of CVD event in 5 years is 10 – 15% and first degree relative developed CHD before age 60, or patient has metabolic syndrome
 - Targets:
 - $LDL < 2.0$ (< 1.6 after MI)
 - $HDL-C > 1.0$ mmol/l
 - $TGs < 1.5$ mmol/L
 - Only a minority of patients achieve targets for modifiable risk factors. Gap between evidence and practice greater for disadvantaged communities
 - Monitor 6 – 12 monthly
- Framingham (1991) equation not reliable for people over 70 – but they are at higher risk
- 1 mmol/L lower total cholesterol is associated with half lower IHD mortality in 40 – 49, a third lower IHD mortality in 50 – 69 and sixth lower IHD mortality in 70 – 89 years. Absolute effects of cholesterol and blood pressure were approximately equal. The total/HDL cholesterol ratio was the strongest predictor of IHD mortality. Lancet Meta-analysis of 900,000 patients, 1 Dec 2007
- Monitoring: there is considerable short term variation in cholesterol levels. There is debate that we might be monitoring too often (Lancet 16 August 2008)

Diet and Lifestyle

- Diet:
 - Decrease saturated fat, cholesterol and calories
 - Decreases of < 10% LDL on the Step-1 Diet (AHA)
 - Most have ↓HDL with a reduction in total fat intake
 - If ↑TG, reduction in simple carbohydrates. If very high TG restriction of total fat is critical
- Plant sterol and sterol esters ↓cholesterol absorption and ↓ LDL by ~10% when taken tds (psyllium, soy protein)
- Weight loss → ↓TG and ↑HDL
- HDL (NEJM 2005:353):
 - Exercise increases HDL by 3 – 9% – little evidence of effect from walking
 - Smoking cessation → ↑HDL by 0.1 mmol/L
 - Weight loss → ↑by 0.009 mmol/L per Kg lost
 - Alcohol intake 1 – 3 drinks per day → ↑0.1 mmol/L
 - Low fat diet reduces LDL and HDL
 - High GI foods → ↓HDL
 - N-3polyunsaturated fats (olives, fish, nuts) → ↑HDL

Lipid Lowering Medications

Summary

	LDL	TGs	HDL	Action	SE
Niacin	↓↓	↓↓↓	↑20 – 30 %	↓VLDL synthesis. Inhibits hepatic uptake of apolipoprotein A-I on HDL	Flushing, GI upset, ↑glucose and uric acid
Fibrates	↓	↓↓↓	↑10 – 20%	Activate PPAR α . ↑lipoprotein lipase activity. ↓VLDL synthesis	GI upset, myalgia, gallstones, ↑LFTs
Statins	↓↓↓	↓	↑2-15%	↓hepatic cholesterol synthesis ↑hepatic LDL receptors	Myalgia, arthralgia, dyspepsia, ↑LFTs
Cholestyramine	↓↓	↑ or →	Minimal effect	Inhibits bile acid reabsorption and ↑LDL receptors	Bloating, constipation
Ezetimibe	↓↓	↓↓	↑	Inhibits absorption of cholesterol in small intestine	Myalgia, ↑ LFTs
Glitazones	Rosiglitazone ↑ Pioglitazone ↓ or →	↓↓	↑	Activate PPAR γ	Weight gain, fluid retention
Fish oil		↓↓ 25%	↑	Reduces chylomicron and VLDL production	Dyspepsia, diarrhoea, fish breath

Trials

- LDL-c Reduction:
 - Scandinavian Simvastatin Survival Study: Men with CHD and high cholesterol – ↓ major coronary events by 44% and total mortality by 30%
 - Cholesterol and Recurrent Events (CARE) study and Long-Term Intervention with Pravastatin in Ischemic Heart Disease (LIPID): in women and men with established CHD and normal to only mildly elevated LDL: reduced cardiac events and cardiovascular deaths
 - Heart Protection Study (HPS): 20,536 men and women, age 40 – 80, established CVD or DM: 24% reduction in major coronary events and 13% reduction in all cause mortality. Benefit even for the subgroup with initial low LDL
 - Treat to New Targets (TNT) Trial: 10,000 patients with CHD and LDL-C < 130 mg/d, randomised to 80mg vs 10 mg atorvastatin. LDL 1.8 (80 mg) vs 2.6 (10 mg). 80mg associated with 22% reduction in major cardiovascular events, but 25% ↑ in non-cardiac deaths (lots of causes, some haemorrhagic strokes). Overall no mortality benefit

- Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT – TIMI22, NEJM 2004, 350:15) – 26.3% vs 22.4% (NNT 26) of primary endpoint at 2 years following Atorvastatin 80mg (intensive treatment) vs Pravastatin (standard treatment) following ACS
- PROSPER Trial (Pravastatin in elderly individuals at risk of vascular disease, Lancet 2000:360): UK trial of 5804 people aged 70 – 82, follow up 3.2 years, 40 mg Pravastatin, risk of primary endpoint (fatal or non-fatal MI or stroke) was 16.2% vs 14.1%, NNT 50, no difference in stroke (postulated this effect takes longer than 3 years). No difference in smokers
- Most major statin trials have excluded people with TG > 3.5-4.5, so little data on effectiveness of statins in reducing CV risk with high TGs
- JUPITER Trial: RCT in 18,000 with LDL < 3.4 and hsCRP > 2.0 mg/L, with Rosuvastatin vs placebo. Stopped after 1.9 years. Cardiac events 1.8% vs 0.9%. 120 treated for 1.9 years to prevent one event. Higher HbA1c in the treatment arm (3.0% vs 2.4%). Long term safety of very low cholesterol (1.4 mmol/L) unknown. Treatment according to hsCRP has not been demonstrated to have clinical benefit in RCT. NB statins lower hsCRP as well as LDL
- TG-HDL axis:
 - Abnormalities more common, but less evidence
 - Helsinki Heart Study (HHS): gemfibrozil vs placebo in ↑cholesterol but no CHD → 36% reduction in coronary events
 - FIELD Study Lancet 2005: Fenofibrate Intervention and Event Lowering in Diabetes Study:
 - 9795 participants aged 50 – 72 with T2DM not taking a statin at entry, 5 year duration
 - More in the placebo arm commenced statins (17% vs 8%). May have masked a larger treatment benefit
 - Reduction in non-fatal MI, no difference in cardiac deaths. No overall difference in mortality. Slight increase in pancreatitis and PE
 - No fibrate trial has been performed specifically in subjects with high TG
- Bottom line:
 - No evidence for trying to raise an isolated ↓HDL
 - Statins: ↓LDL
 - Stable patients. Mortality benefit. Minimal survival benefit for higher over lower dose, but reduction in nonfatal events and revascularisation
 - Unstable/high risk: aggressive lipid lowering as survival benefit
 - Fibrates – no survival benefit proven. Use as additional therapy to statins or if high TG
 - Ezetimibe: no endpoint data for survival. Minimal drop in LDL as sole drug, useful in combination for further ↓LDL or if statin intolerant
 - Combination of fibrate and a statin has never been tested against either a statin or fibrate alone in reducing cardiovascular events
 - Resins: further ↓LDL or if statin intolerant, pregnant/breastfeeding, but not if ↑TG
 - Niacin: most effective drug for ↑HDL, also ↓TG, but watch side-effects. Use in combination with statin if ↑LDL and ↓HDL is primary abnormality
 - Fish oils if high TG, often in combination with fibrates
 - For severe, refractory (usually genetic) ↑LDL can get LDL apheresis (a haemo-dialysis sort of treatment)

Statins

- HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitors – the rate limiting step in cholesterol synthesis – about 30 steps from acetyl-coenzyme A to cholesterol. Inhibits incorporation of acetate into cholesterol
- Discovered by Akira Endo (Japan) in 1976 who isolated it from a broth of the fungus penicillium citrinum (the 6,000th one he'd tried!)
- ↓Cholesterol synthesis → ↑hepatic LDL receptor expression on hepatocytes → ↑clearance of circulating LDL. Steady state cholesterol concentration is restored in hepatocytes but at the expense of a lower plasma concentration
- Doubling dose → further 6% reduction in LDL-C
- ↓LDL 18 – 55%, small dose dependent ↓TG
- Small (~5 – 10%) ↑HDL – not dose dependent
- Other effects:
 - Decreased inflammation (↓CRP)
 - Improved endothelial function
 - ↓thrombotic state

- Plaque stabilisation
- Metabolised via P450 (except pravastatin ⇒ useful in HIV treatment where there's lots of CYP interactions)
- SE:
 - Safe: Meta-analyses of large trials show no significant ↑ in non-cardiac disease, no evidence of change in neuropsychological function
 - Myalgia: CK < 10 * normal. 1- 5%
 - Myopathy:
 - Muscle pain or weakness with blood CK levels more than 10 * normal. 0.1 – 0.5% with monotherapy, 0.5 – 2.5% with combination therapy
 - ↑risk of myopathy if old, frail, *renal impairment*, drugs: erythromycin (suspend treatment), antifungals, immunosuppressives, fibrates (especially gemfibrozil). Check CK if muscle symptoms. Routine measurement not recommended
 - Spectrum: hyper CK → myalgia → necrotising myopathy → acute rhabdomyopathy
 - Mechanism: affects cholesterol in muscle cell membrane with a variety of downstream effects
 - Rhabdomyolysis (myoglobin release and risk of renal failure) risk is ~ 1 in 20,000
 - Mild ↑in AST and ALT (in ~1%). Check at baseline, 3 months then annually. Elevation of > 3 times abnormal, less than this does not mandate discontinuing – try dose reduction

Selective Cholesterol Absorption Inhibitors

- Cholesterol in the intestinal lumen is 1/3rd diet, 2/3rd from bile
- Actively absorbed through a process involving protein NPC1L1. Bound and inhibited by Ezetimibe → 10 mg ↓absorption by 60%
- → ↓hepatic cholesterol → ↑ hepatic LDL receptors → ↓plasma levels (*mean reduction 18% – additive effect with statins* but monitor transaminases)
- Negligible effect on TG and HDL
- **Ezetimibe** (Ezetrol): funded if resistant/intolerant or statins, and high risk. Rarer SE: myopathy, rhabdomyolysis, hepatitis, pancreatitis, thrombocytopenia
- No cardiovascular outcome data reported. Long term safety data awaited
- ENHANCE Trial (Ezetimibe and Simvastatin in Hypercholesterolaemia Enhances Atherosclerosis Regression, NEJM 2008:358) – Trial of Simvastatin 80 mg +/- Ezetimibe in 720 patients with familial hypercholesterolaemia. Despite lowering LDL (4.98 vs 3.65 mmol/L) the intima-media thickness (surrogate endpoint for vascular disease) was not significantly different. ?an effect of previous statin treatment depleting intimal lipid deposits....? Lots of questions raised
- No credible evidence of increased cancer risk with ezetimibe (had been suggestions of this in the SEAS trial for the effectiveness of cholesterol lowering on aortic stenosis) NEJM 25 September 2008

Fibrates

- Agonists of PPARα nuclear receptor (as opposed to thiazolidinediones which act on PPARγ). Enhance TG hydrolysis, ↓apoC-III syntheses (enhancing lipoprotein remnant clearance) and may ↓VLDL production
- ↓TG, may ↑HDL (~ 5 – 15%), variable effects on LDL (may ↑)
- Treatment of choice with TG > 500 mg/dl. Also in combination with statins for mixed dyslipidaemia but 2.5% chance of myopathy (risk greater for gemfibrozil than fenofibrate)
- SE:
 - Dyspepsia
 - Promote cholesterol secretion into bile → ↑gallstones
 - Potentiate effect of warfarin and oral hypoglycaemic agents
 - Rarely myopathy and hepatitis
 - Excess of incident cancers in RCTs, ?due to chance... need more trials (NEJM 2 Sept 2008)
- Bezafibrate funded in NZ

Bile Acid Sequestrants/Resins

- Anion exchange resins: bind bile acids in the intestine → liver diverts cholesterol to bile synthesis → ↑LDL receptors → ↑LDL clearance
- Cholestyramine: Colestipol, coleserelam
- ↓HDL, ↑TG
- Efficacy demonstrated in the Coronary Primary Prevention Trial – 7 year trial in 3800 men, 20% in fatal and non fatal MI

- Poorer compliance
- SE: bloating, constipation, ↓drug absorption but the resin is not absorbed so safe – good for pregnant, breastfeeding

Fish and Flax Oil

- N-3 polyunsaturated fatty acids
- ↓TG in doses of 3 – 4 gm/d – ↓liver production
- Can ↑LDL
- Lower dose (1 g/d) has been associated with ↓ in CV events

Nicotinic Acid/Niacin

- B-complex vitamin, has been used for decades
- Suppresses release of NEFA by adipocytes → ↓TG, ↓VLDL, ↑HDL (by up to 30%, although some non-responders)
- No evidence that ↑HDL decreases CV events
- Effective in combination with statins
- Very cheap and safe long term
- SE:
 - Cutaneous flushing – reduced with slower release formulations
 - Mild ↑ in transaminases in ~ 15%
 - Not in PUD – can exacerbate reflux
 - Can ↑uric acid → gout
 - ?slight ↑fasting glucose
 - Infrequent: Acanthosis nigricans and maculopathy

Other

- Torcetrapib, a cholesteryl ester transfer protein (CETP) inhibitor, trialled in ILLUMINATE trail, showed ↑mortality despite ↓LDL and ↑HDL in conjunction with atorvastatin, also ↑BP. Was this an off-target effect? Initially found as some Japanese people have a genetic defect of CETP discovered after their cause of high HDL was investigated

Pituitary Gland

- Anterior pituitary releases: ACTH (adrenocorticotropic hormone), GH, FSH, LH, TSH, PRL
- Posterior pituitary releases: ADH, oxytocin (critical for breastfeeding, can labour without it)
- Under dominant tonic control (stalk failure → hormone failure): LH, FSH, GH, TSH, ACTH
- Under dominant inhibitory control (stalk failure → ↑): PRL
- Vasopressin (ADH): produced in hypothalamus, released in pituitary. Stalk failure → polyuria for a few weeks until ↑release in median eminence

Imaging the Pituitary

- Incidentalomas found on up to 10% of MRIs
- Pituitary fossa is in the superior sphenoid bone, covered superiorly by the diaphragm sellae, with a central aperture for the infundibulum. The suprasellar cistern includes the infundibulum and the optic chiasm
- Pituitary is usually 6 mm in kids, 8 mm in men and postmenopausal women, 10 mm in women of child bearing age, 12 mm in pregnancy and postpartum. Gradual involution beyond 50 years old
- ‘Pituitary bright spot’: posterior pituitary is normally hyperdense. Lost in diabetes insipidus
- Normal pituitary fossa has a flat top, or concave (dips down)
- Microadenomas: < 10 mm, don’t normally take up contrast. Are usually hormone secreting (that’s why they’re found)
- Macroadenomas: > 10 mm, most are not hormone secreting, found because of space occupying effect
- Sellae and suprasellar lesions:
 - An empty sellae is due to herniation of the suprasellar cistern in to the sellae → flattening of gland (with or without disturbance). Also secondary to hypophysectomy, post-radiation or infarction
 - Craniopharyngiomas: suprasellar tumours that may extend into the sellae. Kids and young adults. Cause pituitary insufficiency, visual impairment, hydrocephalus, hypothalamic disturbance. Treatment difficult – often unresectable
 - Meningiomas: MRI shows close meningeal attachment and enhancement post-contrast
 - Optic nerve gliomas: in kids. Extend along optic nerve

- Parasellar inflammatory conditions: neurosarcoid, langerhans cell histiocytosis

Assessment of Pituitary Function

- Menstrual history: if normal then pituitary likely normal
- Screening panel:
 - Basal PRL: a very high PRL indicates a prolactinoma, which can cause pan-hypopituitarism
 - TFT for TSH
 - IGF-1 for GH
 - ACTH:
 - Cortisol too variable to be a useful check of pituitary. But if 9 am cortisol is normal, pituitary insufficiency unlikely
 - For overactivity then 24 hour urinary cortisol and/or overnight 1 mg dexamethasone suppression test
 - For insufficiency then short Synacthen test
 - α subunit of HCG, FSH, LH and testosterone. LH and FSH insufficient on their own, without checking testosterone as well (may be \downarrow due to \uparrow testosterone). Also LH & FSH tests are not sensitive enough to distinguish low from low-normal
 - Also U&E (hyponatraemia), FBC (normochromic normocytic anaemia)
- Tests of Pituitary Sufficiency:
 - Triple stimulation test (unless heart disease or epilepsy – use glucagon instead): As inpatient with iv access, inject *insulin* (aim for glucose < 2.2), TRH and GnRH. Look for \uparrow GH, \uparrow Cortisol (due to \uparrow ACTH), \uparrow TSH, \uparrow PRL (due to \uparrow TRH). Pretty unpleasant test
 - An overnight Metyrapone test – give Metyrapone orally at midnight and measure plasma cortisol and its biosynthetic precursor at 8.30am. Metyrapone blocks the synthesis of cortisol leading to a build-up of 11-deoxycortisol and reduced negative cortisol feedback \rightarrow a raised ACTH. Cortisol, ACTH and 11-deoxycortisol all remain low in hypopituitarism or long-standing suppression of the HP adrenal axis by drugs
- Assessing severity:
 - Gonadal: Males – testosterone, LH and FSH. Females: menstrual history, LH and FSH
 - Thyroid: fT4 and TSH
 - Adrenal: Short Synacthen test (false negatives possible) or urine free cortisol (not sensitive)
 - Growth Hormone: simple sample (after 10 am) or IGF1
 - Vasopressin: overnight urine concentration (osmolality)
- T1 weighted MRI with gadolinium only if hormonal abnormality

Hypopituitarism

- Causes: hypophysectomy, pituitary irradiation, adenoma (either functional or non-functional – usually monoclonal), other intracranial tumours (incl lymphoma and leukaemia), Sheehan's Syndrome (pituitary necrosis after post-partum haemorrhage), TB, pneumocystis carinii, infiltrative (eg Sarcoidosis), vascular (eg pituitary apoplexy), pituitary metastases (~3 % cancer patients), increasing evidence that trauma is more significant than previously thought
- Differentials: depression, dementia, subdural bleed (although more acute), slowly progressive tumour
- Check symptoms of:
 - Gonadal and GH (\rightarrow bone strength): early to fail
 - Thyroid: intermediate to fail
 - Adrenal: last to go.
 - Also look for PRL (need a little for LH peak to happen), vasopressin, space occupying lesions (test visual fields and for oculomotor palsy)
 - ADH/Oxytocin only fail completely if hypothalamic tumour or major suprasellar extension
- Symptoms:
 - Hormone effects: insidious onset, afternoon tiredness, pallor, anorexia, \downarrow libido (can be due to many illnesses and \uparrow PRL), impotence, amenorrhoea, no menarche by 16, depression, hypothyroidism, reduced body hair in males (due to hypogonadism – is also normal in older age – but not frontal baldness – that's due to androgens), intolerance of intercurrent illness and postural hypotension (hypocortisone), mild fluid retention (myxoedema and \downarrow cortisol \rightarrow water retention), mild anaemia, pallor (yellow of myxoedema, and anaemia), also marked behavioural changes
 - Space occupying effects: headache (unusual as usually small adenomas), visual loss (visual field loss but normal acuity \rightarrow patient may not notice)

- Signs: breast atrophy, small testes, ↓muscle to fat ratio, ↓hair, thin flaky wrinkled skin, postural hypotension, *visual field defect*
- The age of presentation makes a difference:
 - Prepubertal failure slows growth, delays puberty
 - Post-pubertal failure reduces gonadal activity
 - Post-menopausal women: High FSH and LH would be normal. If FSH within normal range then → very sensitive test of early pituitary failure
 - Craniopharyngiomas are the commonest cause of pituitary failure in children, but can be found at any age
- Types of lesion:
 - Mostly hypopituitarism comes from non-functioning pituitary adenomas (adenomata)
 - But also craniopharyngioma, GH or prolactin secreting tumours
 - 2nd to surgery or radiation
 - Most other causes are rare: pituitary apoplexy (a pituitary haemorrhage, mostly into a pre-existing tumour) and pituitary infarction (occasionally during delivery)
 - Numerous genetic lesions eg KAL mutation → ↓FSH and LH
- Sites of tumour extension from the fossa
 - Suprasellar affects optic nerve
 - Parasellar affects III, IV and VI nerves
 - Infrassellar shows xray changes
- Treatment:
 - Hydrocortisone – adrenal is intact and K will drive mineralocorticoids. Start steroids before T4 – otherwise ↑metabolic rate may precipitate an Addisonian crisis
 - Thyroxine – *follow T4 not TSH*
 - Testosterone in men (see page 87), Oestrogen for pre-menopausal women till 45, then HRT till 55 – unless history of prostate or bowel cancer
 - Maybe GH – only funded for kids, but likely to improve the cardiovascular risk profile and well being in adults
- Supportive Treatment:
 - IHD risk management
 - Monitor for steroid side-effects: DEXA, fasting BSL, cataracts, ocular pressure
- Pituitary Apoplexy:
 - Acute gland failure – an emergency
 - Usually due to sudden haemorrhage into the pituitary following complicated childbirth, trauma or an enlarging adenoma
 - Presents with headache +/- neuropraxias (eye signs, ↓visual fields), maybe Addison's

Pituitary Tumours

- Symptoms caused by local pressure, hormone secretion or hypopituitarism
- Effects of pressure: headache (unusual as usually small tumours, felt anywhere over head, local or general), bilateral hemianopia (initially of superior quadrants), III, IV or VI palsy, CSF rhinorrhoea (erosion through floor of sellae)
- Almost always benign adenomas
 - 30% are non-functional (null cell or non-secretory) – PRL is often elevated due to stalk pressure
 - 30% are prolactinomas
 - Surgery usually necessary for diagnosis and debulking
- Histological classification:
 - Chromophobe (70%): half produce PRL, some non-secretory, a few produce ACTH or GH
 - Acidophil (15%): Secrete GH or PRL
 - Basophil (15%): secrete ACTH
- Investigations:
 - Pituitary imaging
 - Visual field tests
 - Prolactinoma: Serum PRL (exclude medications)
 - Pituitary Function
 - Water deprivation test if diabetes insipidous is suspected
 - Acromegaly: elevated serum IGF-1 (cf to age and gender matched controls), oral glucose tolerance test should suppress GH

- Cushing's disease: 24 hour urinary free cortisol or 1 mg Dexamethasone at 12 pm and fasting cortisol at 8 am – normally should suppress, then ACTH assay
- Treatment:
 - Trans-sphenoidal surgery with prior medical stabilisation. Risk of post op DI, hypopituitarism, meningitis, CSF leak, visual deterioration
 - Trans-frontal surgery: for large tumours, craniopharyngioma
 - Radiotherapy (but side-effects common, most commonly hypopituitarism): external beam or stereotactic "gamma knife"
 - Hormone replacement. Bromocriptine for PRL secreting tumours

Pituitary Incidentaloma

- 10 – 25% autopsies
- 10% found on MRI
- In the absence of focal neurology, never image the pituitary without documenting a hormonal abnormality
- Natural history:
 - Microadenomas unlikely to change in size (<10%)
 - Macroadenomas may enlarge (~30%)
- Investigation:
 - Exclude hormone hypersecretion
 - Detect hypopituitarism

Prolactinaemia

- Physiology: see page 84
- Most common pituitary presentation. Presents early in women (amenorrhoea), late in men
- Symptoms: *Most 2nd to hypogonadism*
 - Women: ↓libido, weight gain, apathy, vaginal dryness (due to hypoestrogen), amenorrhoea (very sensitive to ↑PRL, infertility due to ↑PRL → ↓LH peak, ↑PRL suppresses progesterone), galactorrhoea (will need to differentiate from breast inflammatory exudate – clear or green). If infertility, always check the man (cause of 1/3 of problems of infertility)
 - Men: impotence, ↓libido, reduced facial hair, local pressure effects, galactorrhoea (30%), mildly ↓testosterone (but asymptomatic), ↓muscle mass. Not gynaecomastia (usually only in ↓testosterone or ↑oestrogen)
 - Osteopenia
- Investigations: basal prolactin between 10.00 – 12.00 h (repeat 2 – 3 times), MRI, assess pituitary function
- Management:
 - MRI and exclude hypothyroidism and pregnancy
 - If tumour < 10 mm. *Microadenomas rarely progress to macroadenomas:*
 - Cabergoline weekly: D2 agonist – suppresses PRL for 14 days with one dose. Generally better tolerated than bromocriptine. Less evidence on safety in pregnancy
 - Bromocriptine daily to restore fertility, avoids complications of ↓oestrogen due to ↑PRL (could take pill instead). May → postural hypotension. Commence slowly otherwise nausea. Good prognosis. No known teratogenic effects of bromocriptine – but still withdrawn on becoming pregnant if possible
 - If a patient becomes pregnant, withdraw treatment and monitor
 - Treat macroadenoma with surgery if bromocriptine fails to reduce size of PRL (nearly always do). But if pressure effects or pregnancy is contemplated then surgery. Monitor PRL
- Prolactin deficiency causes failure of lactation but has no other known ill effects. Deficiency is very rare

Acromegaly

- = autonomous growth hormone release
- Growth Hormone:
 - Secreted by acidophilic somatotroph
 - Highly variable – normally undetectable, spikes 10 times a day, mainly during deep sleep – useless for measurement
 - Induced by GHRH & oestrogen, also in sleep, with sepsis (along with ACTH and PRL), exercise and consumption of a protein meal
 - Inhibited by:

- ↑glucose
- Somatostatin (SRIF – Somatotropin-release inhibiting factor) – also found in pancreas where it inhibits islet hormone secretion
- Chronic glucocorticoid excess
- Induces IGF-1 in the liver (which feeds back to inhibit GHRH release from the hypothalamus)
- Usually presents between 30 – 50 years. Rare (3/million/year)
- Causes:
 - > 95% caused by somatotroph adenoma, majority are macroadenomas > 1 cm
 - ↑GRH secretion – hypothalamic or ectopic
- Symptoms: insidious onset (look at old photos), coarse oily skin, large tongue, bossing of supraorbital ridge, ↑shoe size and teeth spacing, spade-like hands, carpal tunnel syndrome, progressive heart failure and/or HTN, goitre, headache, cranial nerve palsies, T2DM, OSA
- Symptoms due to: **periosteal growth** (gigantism if the condition starts before closure of the bony epiphyses), **fibrous tissue growth** (→ skin thickening), **organomegaly** (eg cardiomegaly, hepatomegaly, splenomegaly, testicular enlargement), **cartilaginous growth** (↑ears, nose, costochondral junctions), **neurological overgrowth** (→ peripheral neuropathy, exacerbated by the soft tissue swelling)
- Complications: DM, ↑BP, cardiomyopathy, ↑lipids, hypopituitarism, ↑risk of bowel cancer
- Tests:
 - NOT random GH
 - Screening: ↑IGF-1 (insulin like growth factor) indicates GH secretion over the previous 24 hrs.
 - Confirmation: Oral glucose tolerance test – 75 gm glucose. If GH doesn't fall then acromegaly (also anorexia nervosa, poorly controlled DM, or Cushing's)
 - MRI
 - Tests as for pituitary tumour. Some tumours will co-secrete prolactin
- Treatment:
 - Trans-sphenoidal surgery if young (50 – 80% success depending on size)
 - External irradiation for elderly
 - Somatostatin analogues (Octreotide) sc if patient is not a good operative risk (at least some response in 90%, SE ↓gastric motility, gallstones)
 - Dopamine agonists (eg Bromocriptine) may be helpful where IGF-1 increase is modest, and adenoma is co-secreting PRL (approx 40%)
 - GH receptor antagonists (not available in Aust/NZ): eg Pegvisomant → ↓IGF-1. Normalises IGF-1 but raises GH – long term data needed (?→ tumour enlargement). Very expensive
- GH deficiency in children → growth retardation. One high GH level excludes deficiency. Take after sleep or exercise

Vasopressin/Antidiuretic Hormone

- =Arginine vasopressin
- Release mediated by osmoreceptors in the hypothalamus. Sensitive to sodium but not urea or glucose
- Polyuria = > 3500 ml/day (50 ml/kg). Normal urine osmolality > 300 mosmol/L

Diabetes Insipidus/ADH deficit

- Central Diabetes Insipidus:
 - ↓Water resorption in kidney due to ↓ADH secretion from posterior pituitary → low urine osmolality (eg 150 mosmol/kg) despite dehydration. > 5l per day urine requires hypothalamic damage as well as posterior lobe
 - Causes of central DI: idiopathic (50%), head injury, tumour, metastasis, TB, sarcoidosis, vascular lesion, inherited, drugs (eg phenytoin)
- Nephrogenic DI:
 - Reduced response by kidney to ADH. See Water Handling, page 105
 - Causes of nephrogenic DI: ↓K, ↑Ca, *drugs (lithium)*, pyelonephritis, congenital, loss of medullary hypertonicity (eg renal interstitial disease)
- Primary polydipsia:
 - Psychogenic: schizophrenia, OCD
 - Dipsogenic (abnormal thirst): infections, trauma, MS, Drugs (lithium, carbamazepine), idiopathic
- Tests:
 - U&E, Ca, glucose, plasma and urine osmolalities

- Water deprivation test. Stop drinking then measure urine for 8 hours. Aiming to induce plasma osmolarity > 300. If urine osmolality > 500 – 600 mosmol/kg then DI excluded. If diuresis continues, give nasal desmopressin and continue measuring. It is central if ddAVP raises urine OSM to > 600

Excess ADH

- Causes:
 - Ectopic production: malignancies of lung, bronchus, brain, kidney, duodenum
 - Head trauma
 - Infections: multiple
 - Cerebrovascular occlusions/haemorrhages
 - Metabolic: porphyria, asthma, pneumothorax, PP ventilation
 - Drugs: Vincristine, Carbamazepine, cyclophosphamide, TCAs, MAOIs, SSRIs
- For treatment of Hyponatraemia see page 107

Adrenal Cortex

- Produces:
 - Zonula fasciculata and zonula reticularis: Glucocorticoids: eg Cortisol, regulated by ACTH (also IL-1, IL-6, TNF and neuropeptides)
 - Zonula glomerulosa: Mineralocorticoids eg aldosterone, regulated by angiotensin II and K (also ACTH)
 - Zonula reticularis: Androgens and oestrogens
 - All embryologically derived from the mesoderm
- Enzymes:
 - Progesterone is a precursor for aldosterone, cortisone and androgens
 - 21 and 11 β hydroxylase necessary for aldosterone and cortisone production (not testosterone)
 - Aromatase converts testosterone to oestrogen

Cortisol

- Corticotrophin releasing factor (CRF from the hypothalamus) → ACTH (from pituitary) → cortisol
- Postulated that Cortisol inhibits a general or uncontrolled inflammatory response to tissue damage following insult. Raised in trauma, infection, severe psychiatric disease. Specific anti-inflammatory effects include
 - ↓PG and leukotrienes synthesis
 - ↓cyclo-oxygenase in inflammatory cells
 - ↓capillary permeability
- ACTH production is inhibited potently by betamethasone and dexamethasone, prednisone has intermediate potency and hydrocortisone (ie cortisol) has the lowest potency of these agents
- Morning level (2am – 8 am) is twice evening. Remember: *Helps you get up in the morning*. Severe stress can override diurnal pattern
- Transported on cortisol-binding globulin (high affinity) and albumin (low affinity)
- All assays measure total not free cortisol
- Long term ↑ACTH → adrenal hyperplasia, ↓ACTH → atrophy
- Cortisol is conjugated to glucuronide in the liver and excreted. Some free cortisol is filtered at the glomerulus and appears as free cortisol (used in urinary testing). 20% of cortisol is converted to cortisone
- An intracellular enzyme in the kidney, 11 β -hydroxysteroid dehydrogenase type 2, metabolises cortisol so that it doesn't bind to the mineralocorticoid receptor (which has equal sensitivity for corticosteroids). This enzyme is overwhelmed in Cushing's → ↑mineralocorticoid effects. The liver can reactivate this metabolite (cortisone) to cortisol via the 11 β -hydroxysteroid dehydrogenase type 1 enzyme
- Summary of best tests:

↑Cortisol	↓Cortisol
24 hour urine/evening saliva	↓Renin
Low dose dexamethasone	Short Synacthen test

Cushing's Syndrome

- = Chronic glucocorticoid excess, either exogenous or endogenous (adrenal or pituitary neoplasm, or ectopic ACTH secretion)

- Can resemble metabolic syndrome
- Signs:
 - General: Obesity, HTN
 - Metabolic: water retention, hyperglycaemia (30%), ↑lipids, nephrolithiasis, polyuria
 - Skin: plethora, acne, *thin skin*, purple abdominal striae, easy *bruising*, hirsutism
 - Musculoskeletal: Tissue wasting, *proximal myopathy*, osteoporosis, supraclavicular fat-pad (“buffalo hump”),
 - Neuropsychiatric: depression, cognitive impairment, psychosis
 - Gonadal: amenorrhoea, impotence, decrease libido
 - Immune Suppression: predisposition to infection
- Tests:
 - Confirm source biochemically before looking radiologically. CT adrenal ‘incidentalomas’ are common ⇒ does not prove adrenal source of cortisol excess
 - Tests for raised cortisol:
 - Outpatient tests:
 - “next test”: 24h urinary free cortisol (normal < 280 nmol/24 hr). Sensitivity and specificity ~ 70%. If positive then high dose dexamethasone suppression test. Some recent concerns about negative predictive value (some false negatives reports)
 - Overnight dexamethasone suppression test: give 1 mg po at midnight, check cortisol at 8 am (normal 450 – 700 nmol/L). False positives with depression, obesity and drugs affecting metabolism of dexamethasone (eg phenytoin, phenobarbitone). Assumes ACTH secreting adenoma is not sensitive to dexamethasone suppression (but some are a little)
 - 2 day low-dose dexamethasone suppression test: 0.5 mg oral dexamethasone 6 hourly for 48 hours then serum cortisol. Reported sensitivity 79%, specificity 74% with mild Cushing’s – so a bit dodgy in that context.
 - *Midnight salivary cortisol* – new assays are reported to be 93% sensitive and 100% specific
 - Inpatient tests:
 - “best test”: Midnight cortisol: but must do as an inpatient (need to wake to do it and be unstressed) – midnight is low point of diurnal cycle, if high then diurnal cycle depressed
 - Measure ACTH to differentiate adrenal or ACTH secreting tumour (measure on 2 separate days)
 - CT is the preferred way to image adrenals. If ectopic production, start with a high resolution chest CT
- Causes and treatment:
 - Pseudo-Cushing’s Syndrome: Obesity, chronic alcoholism and depression may partially mimic Cushing’s in terms of high cortisol
 - ACTH-dependent (ie due to high levels of ACTH) – ~ 80%:
 - Cushing’s Disease: (adrenal hyperplasia secondary to pituitary tumour, F > M, peak age 30 – 50). Some, but not normal, suppression of cortisol with high dose dexamethasone. May have low glucose (↓GH) and signs of ↓testosterone/amenorrhea (mass effect). Untreated 30 – 50% 5 year mortality. *MRI is frequently normal, and this is more common than ectopic ACTH.* Treatment: Transsphenoidal resection of pituitary adenoma
 - Ectopic ACTH production: especially small cell carcinoma of the lung and carcinoid. No suppression of cortisol with high dose dexamethasone. Plasma ACTH generally >250 ng/L. Hypokalaemic alkalosis is common. CT relevant areas (lung, pancreas, mediastinum, thyroid)
 - To differentiate these there are a variety of tests:
 - High dose dexamethasone Suppression Test: 2 mg QID 48 hours, pituitary origin if cortisol < 50 nmol/L. Alternatively 8 mg overnight dexamethasone suppression test. Assumes pituitary will ↓ACTH production and an adrenal or ectopic tumour won’t – about 80% sensitive
 - MRI + gadolinium – but complicated by high rates of incidentalomas
 - Inferior Petrosal Sinus Sampling: catheterise each sinus and sample blood after iv CRH. Can also help localise to the left or right
 - ↓K suggestive of ectopic focus
 - ACTH-independent:
 - Exogenous corticosteroid administration: reduce as much as possible. In asthma, use inhaled steroids
 - Adrenal gland adenoma, hyperplasia (usually specific genetic defect) or carcinoma: No suppression of cortisol with high dose. Undetectable ACTH. Treatment: surgical removal

- Can block adrenal cortisol production with ketoconazole. SE ↑transaminases, gynaecomastia, impotence, GI upset

Addison's Disease

- See Lancet review, 2003
- Adrenal insufficiency after > 90% cortex lost (ie lots of functional reserve – unilateral loss not sufficient to → insufficiency)
- Primary adrenal failure: Failure of gluco- and mineralo-corticoids – both have similar hypotensive and electrolyte effects (different mechanisms but additive)
- Causes:
 - 80% idiopathic (autoimmune). Associated with Graves, Hashimoto's, IDDM, pernicious anaemia... Peaks 4th decade. In first 2 decades M > F, lifelong incidence M = F. 50% have another autoimmune endocrine disorder. See Polyglandular Autoimmune Syndrome, page 76
 - Metastases from other sites: lymphoma
 - Haemorrhagic infarction: 2nd to thrombosis, sepsis (meningococcal, pseudomonas, etc), anticoagulation treatment
 - Infection:
 - Tb (used to be 90% of cases, now ↓↓)
 - Fungal in immunocompromised
 - CMV, AIDs (→ CMV, MAC, Cryptococcus)
 - Drugs: rifampicin, phenytoin, ketoconazole, opioids may potentiate insufficiency
 - Secondary Adrenal insufficiency – peaks 6th decade
 - Critically ill patients: no consensus on how to interpret or treat low cortisol in these patients. If pre-existing suspected deficiency then give dexamethasone and do short Synacthen test
 - Genetic:
 - Congenital Adrenal Hyperplasia: Recessive partial deficiency of 21, 11B or 17A hydroxylase. ↓Cortisol → ↑ACTH → normal cortisol but ↑androgens. Huge spectrum of disease, from completely deficient to partial (anovulation and mild hair loss in late teens – 2nd to ↑testosterone). Measure 17-hydroxyprogesterone (precursor in the pathway). Treat with cortisone, fludrocortisone and anti-androgens
 - Adrenoleukodystrophy: X linked (affects only males), mutation in ABCD1 gene, progressive neurological dysfunction and adrenal deficiency due to defective beta oxidation of fatty acids → *young males with Addison's should have the TGs checked*. Treatment: diet
 - Others
- With suspected Addison's, need to check for features of:
 - Mineralocorticoid deficit (few, but relate to salt depletion)
 - ACTH excess (hyperpigmentation – patchy pigmentation of the buccal mucosa, freckles become darker, hair and nails darker, pre-existing scars pigmented)
 - A pituitary lesion (space occupying effects)
 - Hypopituitarism (gonadal, thyroid, prolactin or GH deficiency, PRL excess, ADH/vasopressin)
 - History of glucocorticoid medication
- Symptoms: very non-specific, weakness the cardinal sign, abdominal pain, depression, 'viral illness', anorexia, D&V, nausea, pigmentation in palmar creases and buccal mucosa (takes ↑↑ACTH), arthralgia, myalgia, weight loss, nocturia, confusion, irritability, constipation, dehydration, dizziness (eg due to Na depletion → postural hypotension), hypoglycaemia (reduced gluconeogenesis). Lack of cortisol will obscure adrenergic effects of hypoglycaemia, diarrhoea, ↓libido, vitiligo (autoimmune mediated depigmentation of patches of skin). ↑Ca. Not constipation or dehydration in pure cortisol deficiency
- Addisonian Crisis: tachycardia, fever, shock, coma, ↓Na (in 85 – 90%), ↑K. Also nausea, abdo pain, fever, confusion. Precipitated by mineralocorticoid deficiency
- Diagnostic tests:
 - 8 am plasma cortisol < 83 nmol/L (everyone has a different cut-off) diagnostic, random cortisol > 500 rules it out, everything in between requires a stimulation test
 - ↑Plasma renin (most sensitive indicator of mineralo-corticoid insufficiency)
 - Short ACTH stimulation test (250 mcg Synacthen)
 - Better than 24 hr urine Cortisol (midnight cortisol test is equivalent to 24 hour urine)
 - Usually test at 0 and 30 minutes
 - Negative if cortisol is above 550 (ie absolute level, not measuring the rise)

- If Cortisol doesn't rise then do prolonged ACTH stimulation test over 3 days (eg to differentiate between Addison's and prednisone suppression)
- If abnormal response, retest the same samples for aldosterone – if due to adrenal insufficiency then aldosterone will not rise, if pituitary it will
- 8 plasma ACTH will determine gland or origin (if high then primary, if low then secondary)
- Test for adrenal antibodies and check for signs of Tb (eg calcification on Xray)
- Anti-adrenal antibodies are non-specific – most common is antibody to 21 hydroxylase
- Screen for TSH and IFG for Autoimmune Polyendocrine Syndrome (see page 76)
- Also test for: hyperkalaemia, hyponatraemia, hypoglycaemia, uraemia, mild acidosis, hypercalcaemia (?from pre-renal failure), normocytic anaemia, abnormal LFTs, ↑eosinophilia, ↓neutropenia

Secondary Hypoadrenalism: Pituitary Failure

- Short Synacthen test: measures adrenal atrophy
- Insulin tolerance test: check for ACTH and cortisol release. Little data to judge normal range → not often used clinically
- *Will have preserved mineralocorticoid function – this will be driven by K so the loss of ACTH won't affect angiotensin II production*

Treatment for Steroid Deficiency

- Treatment:
 - Hydrocortisone (20 – 30 mg/d, given as 20/5/5, or Cortisone Acetate 25/12.5 mg) + gastric protection (may ↑gastric acid) + Fludrocortisone 0.05 – 0.1 mg per day (for aldosterone replacement) + ample salt intake +/- DHEA replacement in women (improved quality of life and bone mineral density). Don't need bone surveillance with physiological doses
 - Hydrocortisone: have to take 3 times a day due to short T_{1/2}, and to avoid plasma peaks (→ side effects, eg osteoporosis)
 - Prednisone: 7 mg per day (5mg mane, 2.5 nocte to replicate diurnal variation). Longer T_{1/2} and fewer mineralocorticoid effects than hydrocortisone
 - Adjust by measuring cortisol (ie 24 hour urine cortisol). Replacement therapy does not usually suppress elevated ACTH. Measure postural BP. Plasma renin may stay high
- Double hydrocortisone/prednisone in intercurrent illness
- If adrenal crisis, don't need mineralocorticoid as high dose glucocorticoid has maximal mineralocorticoid effect. If vomiting then iv dose
- Thyroxine increases cortisol clearance, so if deficient in both, replace cortisol first otherwise may → crisis

Mineralocorticoids

- See Renin-Angiotensin pathway, page 20
- Glucocorticoids and mineralocorticoids bind with nearly equal affinity to the mineralocorticoid receptor (MR)
- Mineralocorticoid deficiency only occurs in primary adrenal disease
- Renin:
 - ↓Circulating blood volume → ↓renal perfusion pressure → juxtaglomerular cells +/- catecholamines +/- macula densa “feedback” due to filtered sodium in the distal tubule +/- decreased dietary potassium intake → ↑renin release
 - Decreased by (→ false positive ARR)
 - β-blockers, methyl dopa, clonidine, NSAIDs
 - Renal failure
 - Increased by: (→ false negative ARR)
 - Diuretics, calcium antagonists, ACE and ARD due to ↓renal perfusion
 - Pregnancy
- Pathway:
 - Renin catalyses Angiotensinogen (made in the liver) to angiotensin I
 - ACE converts Angiotensin I to angiotensin II (particularly in pulmonary vasculature endothelium)
 - Angiotensin II:
 - → potent systemic vasoconstriction (acts on arteriolar smooth muscle → maintaining renal blood flow), ↑renal Na reabsorption, and ↑ thirst

- → ↑aldosterone by the adrenal cortex → ↑Na reabsorption. Also causes thirst. *Aldosterone is also released in response to potassium, ACTH and others. 75% of Aldosterone inactivated in one pass through the liver*
- Aminopeptidase converts angiotensin II to angiotensin III
- Tests: several days of sodium restriction should ↑aldosterone. Also 2 – 3 hours of upright posture → ↑

Hyperaldosteronism

- Excess of aldosterone independent of renin-angiotensin system → ↑Na → ↑volume → ↓renin
- Signs: headaches, diastolic hypertension, ↓K (not common PC, → muscle weakness), ↓Mg, alkalosis, Na is normal or slightly raised, U waves on ECG
- Primary hyperaldosteronism is found in 11% of patients with treatment resistant HTN (ie still HTN despite 3 drugs) Lancet 7 June 2008
- Primary hyperaldosteronism:
 - Causes: 65% due to unilateral adrenocortical adenoma ([Jerome] Conn's Syndrome). Other causes include bilateral adrenal hyperplasia (30%), carcinoma (rare), genetic defect (Familial hyperaldosteronism FH-I and FH-2 – type 1 suppressed by steroids, type 2 not)
 - Screening tests:
 - Test K 3 times on salt replete diet (no diuretics [verapamil, prazosin, hydralazine don't affect the ratio], etc for 4 weeks). If < 3.7 mmol, test seated in the morning for aldosterone and ARR
 - Renin will be low and aldosterone high (with no correction with volume expansion). But suppressed renin activity occurs in 25% of patients with essential hypertension
 - *High Aldosterone/Renin ratio (ARR) ⇒ aldosterone autonomy (used as a screening test in all hypokalaemic, treatment resistant hypertension). Autonomy is only with respect to volume expansion – may respond normally to K loading or ACTH. The appropriate cut-off for the ARR is debated – varies depending on posture and time of day. Normal 4 – 5, high is > 20. Test invalid if on spironolactone*
 - Can also do 24 hour urinary aldosterone level
 - Diagnostic tests:
 - Principle is to see if aldosterone can be suppressed
 - Salt suppression test – salt load for 1 week, test supine ARR, Aldosterone and 18-hydroxy-cortisol – normally renin and aldosterone would fall – or saline infusion test
 - Fludrocortisone suppression test: fludrocortisone and salt tablets for 4 days to see if upright aldosterone suppressed
 - Then CT for ?adenoma. Only 50 – 70% adenomas evident (Imaging is fraught in any endocrine condition – don't look unless there is localising biochemistry)
 - Adrenal vein sampling (looking for 10:1 ratio of plasma aldosterone on the affected side)
 - Treatment: surgery and/or spironolactone (SE in men of gynaecomastia, impotence). See Treatment of Heart Failure, page 34. Eplerenone is more expensive but fewer endocrine side effects. Surgery improves hypokalaemia, HTN, and avoids other consequences of high aldosterone independent of BP effects
- Secondary hyperaldosteronism: Aldosterone high because renin is high
 - Physiological in pregnancy
 - Essential hypertension
 - Severe arteriolar nephrosclerosis (malignant hypertension)
 - Renal artery stenosis (→↑BP and ↓K+)
 - Coarctation of the aorta
 - In many forms of oedema, eg secondary to hepatic failure, cirrhosis, CHF – 2nd to arterial hypovolaemia. Can be exaggerated by thiazides and frusemide
 - Renin secreting tumour
- If HTN and ↓K, but ↓renin and ↓aldosterone the consider causes of excess glucocorticoid (adrenal hyperplasia, exogenous, Cushing's, etc)

Adrenal Incidentalomas

- ~ 5 % incidental finding on CT (more if older)
- Detected more often in females on the right side (they have more RUQ ultrasounds)
- Most are benign and non-secreting
- Most common secreting mass found is Cushing's (5%). Malignancy < 5%
- CT characteristics:

- If > 6 cm then excise (although 80% will still be non-functional), if < 4 cm likely benign, otherwise ?additional imaging
- Benign are usually solitary and smooth
- If Hounsfield units < 10 the likely an adenoma
- Vascular is bad, rapid washout of contrast is good (benign are not vascular, so not much contrast got in to start with)
- Re-image in 6 – 12 months
- History of prior malignancy ⇒ 50% risk of metastasis
- Screening tests:
 - Overnight 1 mg po dexamethasone test for preclinical Cushing’s Syndrome
 - DHEAS: Females with virilisation or males with feminisation: test sex steroids
 - ARR if hypertensive, ↓K
 - Exclude pheochromocytoma before FNA performed by measuring plasma free metanephrines (highly sensitive ⇒ good rule out test, not commercially available, also urine metanephrines, otherwise urine catecholamines)
- Adrenal malignancy rare – CT suggestive (large, low fat content, irregular), FNA not helpful, need resection, poor prognosis (50 – 70% of cancers are secretory, 20% 5 years survival)

Adrenal Medulla

- Sympathetic system:
 - Adrenergic neurons synthesize noradrenaline and small amounts of dopamine (from which adrenaline and noradrenaline are synthesised)
 - Adrenaline is synthesized in the adrenal medulla, secretory cells are modified post-ganglionic neurons
- Receptor subtypes:
 - Adrenaline and noradrenaline are agonist for all adrenergic receptor subtypes, but with varying affinities
 - α -receptors:
 - $\alpha 1$: on postsynaptic cells in smooth muscle → vasoconstriction
 - $\alpha 2$: on pre-synaptic membranes of postganglionic nerve terminals that synthesize noradrenaline. Act as negative feedback inhibiting further noradrenaline release (ie antihypertensives can either inhibit $\alpha 1$ or stimulate $\alpha 2$)
 - β -receptors:
 - $\beta 1$: stimulate rate and strength of myocardial contraction (→ ↑CO) and ↑renin
 - $\beta 2$: relaxes vascular smooth muscle → vasodilation
- Effect on vascular smooth muscle depends on the concentration of each type of receptor

	Adrenaline	Noradrenaline
Acts on	Mainly β (a little α)	Mainly α (a little β)
HR	↑	↓
BP	Small ↑	↑↑
CO	↑	↓
TPR	↓	↑
	Hyperglycaemia & lipolysis	Hyperglycaemia only (α receptors in liver → gluconeogenesis)

Pheochromocytoma

- = Benign (usually) unilateral tumour in adrenal medulla producing catecholamines (mostly noradrenaline, some adrenaline, very rarely dopamine). 2 – 8 per million. Mean age is 40
- 10% are bilateral, 10% are extra-adrenal, 10% are malignant
- 25% are inherited germ-line mutations – anticipate these – look (especially if < 40):
 - MEN 2A and 2B, Neurofibromatosis type 1, Von Hippel-Lindau. See page 76
 - Familial Paragangliomas:
 - Paraganglioma = catecholamine producing tumours of head or neck, or those arising in the parasympathetic system (may secrete little or no catecholamines)
 - Mutations in succinate dehydrogenase subunits B, C and D – tumour suppressor gene
 - Type D: multiple pheo’s common, 70% by 40. Autosomal dominant but maternal imprinting
 - Type B: Multiple pheo’s common, 70% by 60, malignancy a feature

- Signs: *headache, episodic hypertension, palpitations, profuse sweating* (specific and sensitive), plus restlessness, anxiety, weight loss, tremor, cold feet, extensive heart investigations. ↑BSL
- Test:
 - HMMA (breakdown products) in urine for initial testing, with no bananas, coffee, peppers, stress, many medications
 - Plasma metanephrines measurements detect O-methylated metabolites leaking from the tumour and less sensitive to stress. Borderline positives likely to be false-positive
 - CT with contrast (ionic contrast contraindicated)
 - MRI T2 the most sensitive
 - PET with 6-18 flourodopamine
- Differential:
 - Essential Hypertension
 - Anxiety attacks
 - Cocaine/amphetamines
 - Carcinoid syndrome
 - Clonidine withdrawal
 - Autonomic epilepsy
 - Factitious crises
- Treatment:
 - Surgery – careful management of BP before and after surgery. Don't use β-blockade alone to control pulse, also need α-blockage (*start this first*) otherwise may → hypertensive crisis. Post op they can crash (↓BP and ↓BSL) or remain hypertensive
 - If malignant, 44% 5 years survival, chemo with cyclophosphamide, adriamycin, vincristine

Poly Endocrine Cancers and Syndromes

	PTH	Pancreas	Pituitary	MTC	Pheo	Other
MEN1	↑	↑	↑			?↑gastrin
MEN2A	↑			↑	↑	
MEN2B				↑	↑	Mucosal neuromas
VHL		↑				Clear Cell Ca

- Multiple Endocrine Neoplasia (MEN):
 - MEN 1: Wermer's Syndrome:
 - Triad:
 - Hyperparathyroidism (hyperplasia or adenoma) – main presentation. Occurs in 95% by age 40. Problematic to diagnose (best with tissue sample) and manage
 - Pancreas (Islet cell hyperplasia, adenoma or carcinoma – 25% malignant) and duodenal tumours in > 40%
 - Pituitary (hyperplasia or adenoma of any hormone) in > 30%, usually PRL
 - Maybe gastric hypersecretion and peptic ulcer disease (Zollinger-Ellison Syndrome, 35%, due to ↑gastrin)
 - Adrenocortical hyperplasia (33%)
 - Also skin manifestations: 1 – 2mm erythematous lumps on face
 - > 90% have mutations in MEN1 gene encoding the protein MENIN, on chromosome 11q13. A tumour suppressor gene. 260 known mutations. Hereditary syndrome consists of inheriting one defective gene. A somatic mutation in the other then leads to disease
 - Peak onset in 20 – 30s. Test for MEN1 in hyperparathyroidism presenting < 30
 - Type 2A and 2B:
 - Mutations in RET gene – a proto-oncogene on 10q11. Genotype of mutation influences timing of prophylactic thyroidectomy. Mutation in RET is also one cause of Hirschsprung's Disease
 - 2A (Sipple Syndrome): Medullary thyroid carcinoma (MTC) in 95%, phaeochromocytoma in 50% and hyperparathyroidism (10 – 50%)
 - 2B: Aggressive MTC, phaeochromocytoma in 50%, multiple mucosal neuromas. HyperPTH rare
- Von Hippel-Lindau Syndrome (VHL): See page 400
 - AD

- VHL gene is a tumour suppressor gene on 3p and plays a role in the regulation of angiogenesis. Regulates level of HIF-1 α . Loss of heterozygosity \rightarrow \uparrow levels \rightarrow transcription of growth factors for angiogenesis, cell proliferation and survival
- Leads to:
 - Pheo, pancreatic islet cell tumours
 - Retinal, cerebellar and spinal haemangioblastomas (slow growing cystic tumours)
 - Renal cysts occur in the majority of cases
 - Renal clear cell carcinoma in 40 – 70%, often multifocal. Yearly CT screening recommended
- *Neurofibromatosis type 1 (NF1)*:
 - NF1 gene is a tumour suppressor regulating the RAS cascade
 - Features: multiple neurofibromas, 6 or more café au lait macules (light brown, 1 – 10 cm, normal people have them too), axillary freckling of the skin, Lisch nodules of the iris
 - Causes pheochromocytoma

- Autoimmune Polyendocrine Syndrome (APS) :

	PTH	Adrenal	Thyroid	Other
APS1	\downarrow	\downarrow		Candida
APS2		\downarrow	$\uparrow\downarrow$	T1DM coeliac, other
APS3		-	$\uparrow\downarrow$	

- Aka Polyglandular Autoimmune Syndrome: **Adrenal insufficiency plus**:
 - APS1: Hypoparathyroidism, Chronic Mucocutaneous Candidiasis, onset childhood. Recessive mutation in AIRE gene chromosome 21q22.3. Aka Autoimmune Polyendocrinopathy candidiasis ectodermal dystrophy (APECED) \rightarrow failure to express tissue-specific antigens in the thymus \rightarrow don't delete self-sensing T cells \rightarrow autoreactive T cells released into the periphery
 - APS2: (most common) Autoimmune thyroid disease – may also have T1DM, vitiligo, coeliac disease, chronic atrophic gastritis, primary gonadal failure. Dominant, incomplete penetrance associated with HLA-DR3 and CTLA-4. No gene test. Usually family history
 - APS3: autoimmune thyroid disease but no adrenal insufficiency
 - APS4: other autoimmune disease but no thyroid disease

Endocrine Tumours of the GI Tract and Pancreas

- Share general neuroendocrine cell markers, and generally slow growing (although can be aggressive) and have similarities in the genetic abnormalities
- Gastrointestinal Neuroendocrine Tumours (NET) divided into:
 - Carcinoid Tumours:
 - Classified according to anatomic area of origin (foregut, midgut, hindgut)
 - Occur in bronchus, jejunum/ileum, colon/rectum
 - Most commonly secrete serotonin, but may also contain wide range of other GI peptides that may or may not be secreted in sufficient quantities to cause symptoms (including insulin, gastrin, glucagon, ACTH, AVP)
 - May present with diarrhoea, bronchoconstriction, cardiac heart lesions and flushing (Carcinoid Syndrome) – diagnosis relies on measurement of urinary or plasma serotonin or urinary metabolites
 - Medical treatment: serotonin receptor antagonists, somatostatin analogues (eg Octreotide). Surgery is the only potentially curative therapy. Usually chemo resistant
 - Metastatic disease is bad (usually to the liver)
 - Pancreatic Endocrine Tumours: 9 functional syndromes secreting gastrin, insulin (insulinoma), glucagon, somatostatin, ACTH, etc

Thyroid

- For thyroid disease in pregnancy see page 462

Background

- Components:
 - TPO = Thyroid peroxidase: iodine oxidised to form reactive iodine then added to tyrosyl residues within Tg. *Inhibited by carbimazole*
 - T4 = thyroxine – 4 iodine atoms. Secreted in 20 fold excess over T3. Half life 7 days

- T3 = triiodothyronine – 3 iodine atoms. Half life $\frac{3}{4}$ of a day. Potency 3 * T4 due to tighter binding to nuclear receptors
- Deiodinase enzyme 1 or 2 converts T4 to T3. Enzyme 3 converts T4 to rT3 (reverse T3). Deiodinase found in thyroid, liver, kidney, pituitary, brain, brown fat
- T3 & T4 bound with high affinity to Thyroxine Binding Globulin (TBG, increased by oestrogen) and with lesser affinity to albumin
- Variety of genetic disorders along the production pathway
- Axis:
 - TSH (*longish half life ~ 50 minutes*) binds to TSH-R causing Tg (thyroglobulin) reabsorption from the follicular lumen, proteolysis within the cell then release of hormones (mainly T4)
 - T4 and T3 inhibit TRH and TSH production
 - Dopamine, glucocorticoids and somatostatin suppress TSH but only significant in pharmacological doses
- Thyroid gland:
 - Normal gland = 12 – 20 gm
 - Developing gland migrates along the thyroglossal tract – can leave ectopic gland in its track
 - Medullary C cells produce calcium lowering calcitonin – neural crest cells
 - IGF-1 also produced in gland with trophic effect (which is why acromegaly → goitre)
- Exam:
 - Swallow water and feel gland move
 - Bruit ⇒ ↑vascularity
 - Pemberton’s Sign: Retrosternal goitre → compression → venous distension and difficulty breathing when arms raised (draws thyroid into thoracic inlet)
 - Assess supraclavicular and cervical nodes
 - Check eyes
- Labs:
 - fT4 normal in 2 – 5% patients with thyrotoxicosis so need to measure fT3 then as well
 - TSH low in first trimester (due to HCG secretion) and in response to steroids or dopamine
 - TSH is the best marker, except for hypopituitarism, sick euthyroid, non-steady state
 - Don’t use TSH to assess thyroid function in pituitary disease – it is highly variable in 2ndary hypothyroidism
 - Antibodies:
 - Against TPO and Tg. Most patients with autoimmune hypothyroidism and 80% Graves have high levels of TPO antibodies
 - TSI (thyroid stimulating immunoglobulin) – antibodies that stimulate TSH-R in Graves’ disease – not measured often

	TSHRAb (%)	hTgAb (%)	hTPOAb (%)
General population	0	5 – 20	8 – 27
Grave’s	80 – 95	50 – 70	50 – 80
Autoimmune thyroiditis	10 – 20	80 – 90	90 – 100
Relatives of patients	0	40 – 50	40 – 50
IDDM	0	40	40
Pregnant Women	0	14	14

- Serum Tg – follow up in cancer patients following thyroidectomy and radioablation (should be undetectable)
- Ultrasound:
 - Is seldom indicated to screen for thyroid Ca and *never indicated to investigate thyroid dysfunction*
 - Detects nodules and cysts > 3 mm (ie it is used for neck masses), monitors size, guides aspiration/FNA and Doppler assessed vascularity
- Scanning:
 - Thyroid uptakes 123I, 125I, 131I and 99mTc Pertechnetate
 - Graves: enlarged gland and homogenous uptake
 - Toxic adenoma: focal area(s) or increased uptake, with reduced uptake elsewhere
 - Multinodular Goitre: enlarged gland, distorted architecture, multiple areas of increased and decreased uptake
 - Thyroiditis: very low uptake because of follicular cell damage and TSH suppression
 - Cold nodules: 5 – 10 % risk malignancy. Hot nodules hardly ever malignant

Autoimmune Hypothyroidism

- = Hashimoto's
- Can cause a goitre – or later in the disease with atrophic thyroiditis
- Initially subclinical then overt hypothyroidism
- Mean age = 60, F > M
- Symptoms (↓order of frequency): tiredness, weakness, feeling cold, hair loss, poor concentration, constipation, weight gain with poor appetite, dyspnoea, hoarse voice (oedema of vocal chords), menorrhagia (later oligomenorrhoea), conductive deafness (due to fluid in middle ear)
- Signs:
 - Dry coarse skin, cool peripheral extremities, puffy face hands and feet (myxoedema), diffuse alopecia, bradycardia, delayed tendon reflex relaxation, carpal tunnel
 - PRL levels may be increased (→ galactorrhoea)
 - Pericardial effusions in 30%
 - Myopathy:
 - Stiffness, myalgia and cramps in 75%, proximal weakness in 25%, myxoedema in 30%
 - Elevated CK in most hypothyroid patients, up to 10 x normal if overt myopathy. EMG normal
 - Prognosis: recover slowly and incompletely
 - Histology: lymphocytic infiltration, atrophy of follicles, fibrosis
 - Genetic risk from HLA DR3, DR4, DR5 (in common with T1DM, Addison's, pernicious anaemia vitiligo)
 - Cell destruction primarily mediated by CD8+ cytotoxic T cells. Transplacental passage of Tg or TPO antibodies had no effect on fetal thyroid ⇒ T cell mediated injury
- Labs:
 - Measure TPO. May also have associated anaemia, elevated lipids
 - fT3 normal in 25% due to adaptive Deiodinase response → T3 measurement not indicated
 - 20% have antibodies to TSH-R which prevent binding of TSH (unlike stimulatory effect of TSI)
 - ↑PRL – if you find raised PRL think thyroid before pituitary
- Treatment:
 - Complete replacement totals about 100 – 150 µg thyroxine
 - If elderly and heart disease, start low (eg 25) with increments every 2 – 3 months
 - Measure TSH ~ 2 months later
 - May not experience relief of symptoms until 3 – 6 months after TSH normal
 - Adherence an issue once recovered
 - A number of drugs interfere with absorption: Cholestyramine, Fe sulphate, Ca, rifampicin, amiodarone, carbamazepine, phenytoin
 - No consensus on treatment of subclinical hypothyroidism, usually not treated with TSH < 10
- Myxoedema coma: poor compliance with thyroxine + precipitant → ↓LOC, hypothermia. Loading dose of thyroxine, hydrocortisone (impaired adrenal reserves in hypothyroidism) + supportive care

Other Causes of Hypothyroidism

- Iatrogenic:
 - Lithium (inhibits T4 production and secretion, treat with thyroxine to normalise TSH)
 - Amiodarone
 - IFNα: not well understood, stirs up immune system in conjunction with primary disease
- Secondary: diagnosed in workup of pituitary

Hyperthyroidism/Thyrotoxicosis

- See Lancet Review 2002, NEJM 12 June 2008
- Hyperthyroidism = excess thyroid function. Thyrotoxicosis = too much hormone. Not the same thing
- Causes of thyrotoxicosis:
 - Primary hyperthyroidism:
 - Circulating Thyroid Stimulators: Graves'
 - Autonomy: TMG, Toxic adenoma, functioning thyroid carcinoma mets, iodine introduction where previously iodine depleted or large doses of iodine eg drugs or contrast (Jod-Basedow Phenomenon – may reflect underlying pre-existing autonomy – consider investigation for MNG or Graves), genetic defects
 - Without hyperthyroidism: Subacute thyroiditis, thyroid destruction (amiodarone, radiation...)
 - Secondary: TSH secreting pituitary adenoma, gestational...

- Factitious (taking thyroxine)

Graves Disease

- 60 – 80% thyrotoxicosis
- Usual age 20 – 50
- Presentation:
 - Irritable, insomnia, impaired concentration (differential: depression), muscle wasting, proximal myopathy without fasciculation, tachycardia, tremor, goitre, polyuria, diffuse alopecia, osteopenia if long standing
 - Periodic paralysis: seen in Asians, due to transient severe hypokalaemia, often following high-carbohydrate meal or severe exercise. Mechanism not well understood
- Risks:
 - Genetic susceptibility: concordance in monozygotic twins = 30%, dizygotic < 5%. Ask about family history
 - Smoking a minor risk factor for Graves, a major risk factor for ophthalmopathy
 - 3 times risk post partum
 - Iodine exposure (eg CAT scan with contrast)
- Caused by TSH-R antibodies (aka TSI). TPO antibodies usually present
- Exam:
 - Diffusely enlarged thyroid, 2 – 3 times normal size
 - Maybe bruit 2nd to hyperdynamic circulation
 - Lid retraction, eye grittiness, excess tears, diplopia in 10%, rarely visual field defects (compression of optic nerve)
 - If severe (always eye problems first) then pretibial myxoedema and thyroid acropachy (a form of clubbing)
- Labs:
 - Measure fT3 as in 2 – 5% only T3 is increased
 - Don't usually measure antibodies (although present in > 90%) as diagnosis apparent
 - Homogenous uptake on Tc99 scan
 - ALP is ↑, LDL is ↓
- Ophthalmopathy (See Internal Medicine Review 2004):
 - TSH-R also found on ocular muscles
 - Two types (60% have both):
 - Congestive ophthalmopathy: inflammation of orbital connective tissues with relative sparing of the EOM
 - Ocular myopathy: inflammation and dysfunction of EOM – especially difficulty of upward gaze
 - Pathophysiology:
 - Infiltration of tissues by activated T cells
 - Activated fibroblasts → fibrosis and ↑ glycosaminoglycans trap water → swelling
 - Worsens over 3 – 6 months, plateaus for 12 – 18 months. Can get worse as thyroid gets better
 - Blindness can result from corneal scarring (inability to oppose eyelids) and compression of optic nerve
 - Smoking and radioiodine are risk factors for progression
 - Treatment: stop smoking, artificial tears, if severe high dose steroids (and/or radiotherapy or decompressive surgery)
 - Novel treatments: anticytokine therapy, T-cell modulation, SOM 230 – somatostatin that binds to orbital fibroblasts
- Treatment (drugs in Europe, radioiodine in US – no approach optimal):
 - Antithyroid drugs: Inhibit TPO so stop organification of iodine
 - Thionamides such as:
 - Carbimazole at 10 – 20 mg tds (once daily possible once euthyroid)
 - Propylthiouracil (PTU) – bd, preferred in pregnancy/breast feeding
 - Remeasure T4 after 4 weeks and titrate. May take 6 – 8 weeks. TSH suppressed longer – be guided by T4
 - Two strategies: Titration and block-replace (not used much now)
 - Treat for a year after suppressive dose found. Remission rates of 30 – 50% within 2 years – usually within 6 months

- SE: rash, urticaria, fever, arthralgia. Rarely hepatitis, SLE-like syndrome, agranulocytosis (< 1%, symptoms sore throat, fever, mouth ulcers) – don't monitor FBC – onset abrupt and idiosyncratic, pANCA +ive in up to 10% (frank vasculitis rare)
- Supportive: propranolol (20 – 40 mg QID), warfarin if AF. Increased doses of digoxin needed in hyperthyroidism
- Radioiodine:
 - → progressive destruction of thyroid cells
 - Treatment leads to small risk of initial thyrotoxic crisis – pretreat with propranolol and, if elderly, with antithyroid drugs to deplete Tg. But stop carbimazole 3 days prior to ensure good I uptake
 - May be mild pain 2nd to radiation thyroiditis 1 – 2 weeks after treatment
 - No hard data in young women re teratogenicity
 - Hyperthyroidism can persist for 2 – 3 months after treatment
 - Risk of hypothyroidism depends on dose
- Beta-blockers: longer half life ones better: Propranolol (β_1 and β_2 selective), metoprolol, atenolol
- Surgery: near total thyroidectomy. 2% Hypoparathyroidism and 2% recurrent laryngeal nerve injury
- Not steroids unless ophthalmopathy
- Graves in Pregnancy:
 - Not common as Graves → ↓fertility
 - Diagnose with TSHr, not Tc99
 - Use PTU, particularly approaching term (carbimazole expressed in breast milk)
 - Risk of passive Graves in the foetus of around 1%

Thyroid Crisis/Thyroid Storm

- 2nd to acute illness, thyroid surgery, radioiodine treatment
- Presentation: fever, delirium, seizures, vomiting, diarrhoea, jaundice – rarely a straightforward diagnosis
- High mortality
- Treatment:
 - Large doses of propylthiouracil – as it also inhibits T4 → T3 conversion (as does propranolol)
 - Dexamethasone 2 mg qid (also blocks T4 → T3)
 - Cholestyramine (blocks enterohepatic circulation of T3 – small effect)
 - Thyroidectomy
 - β -blockade

Thyroiditis

- Presentation:
 - Thyroid pain and goitre, fever, dysphagia, overlying erythema
 - Only 25% have a hard painful gland
- Causes:
 - Acute: Bacterial (staph, strep, enterobacter), fungal, radiation after 131I
 - Subacute: viral, *postpartum* (see page 462), TB
 - Chronic: autoimmune (eg early stage Hashimotos), parasitic, traumatic
 - Differential: haemorrhage into a cyst, malignancy, amyloidosis, amiodarone
- Subacute thyroiditis: de Quervains:
 - Viral: mumps, coxsackie, influenza, adenoviruses...
 - Patchy inflammatory infiltrate → granulomas and fibrosis
 - Destructive phase releases hormones, then depleted. No radioactive iodine uptake, until TSH rises 2nd to depletion then may return to normal
- Treatment:
 - Large doses of aspirin or NSAIDs. Steroids if necessary
 - Propranolol if necessary
 - PTU/CBZ ineffectual: not a case of ↑ production but release of preformed hormone 2nd to gland destruction
- Silent thyroiditis (usually post-partum). More common in T1DM. Distinguished from Subacute by presence of a normal ESR and TPO antibodies

Sick Euthyroid

- Usually presumptive diagnosis
- Any acute illness can → variations in TSH and T3/4 so don't test in an ill patient unless thyroid disease suspected
- Most common pattern is low T3 with normal T4 and TSH 2nd to impaired peripheral conversion with increased rT3 (likely due to decreased clearance)
- If very sick, may also drop T4 – poor prognosis
- Acute liver disease → release of TBG and rise in total but not free T3/4
- HIV: transient rise in T3 & T4

Goitre & Nodular disease

- Goitre = enlarged thyroid – lateral lobe larger than the patients thumb
- Small nodules present in ~25%
- Diffuse non-toxic goitre: no nodules – usually iodine deficiency. Usually regression with treatment in 3 – 6 months unless fibrosis. 131I can reduce size
- Non-toxic Multinodular Goitre:
 - Wide variation in nodule size. Hyperplastic not monoclonal
 - Develop over years
 - Sudden pain usually haemorrhage into a nodule (but may be malignancy)
 - Pulmonary function tests to check for compression
 - Ultrasound for sinister characteristics (microcalcifications, hypoechogenicity, increased vascularity)
 - T4 suppression usually ineffective
 - Avoid contrast agents
 - Radioiodine often decreases goitre size and reduces any underlying autonomy
- Toxic Multinodular Goitre:
 - Main difference to non-toxic MNG is presence of functional autonomy in at least two nodules
 - Nodules develop high sensitivity to TSH through mutations in the TSH-R. Very rarely malignant
 - Usually elderly
 - Antithyroid drugs + β -blockers normalise thyroid function (but often stimulate the size of the goitre) first to prevent storm (not as long term treatment – spontaneous remission rare)
 - Then trial of radioiodine before surgery. Radioiodine preferentially taken up by the nodules (the rest are suppressed), remainder of the gland then normalises
- Toxic Adenoma (Solitary toxic Nodule)
 - = hyperfunctioning solitary nodule
 - Most have acquired somatic, activating mutations in the TSH-R
 - Less commonly, somatic mutations in $GS\alpha$
 - Mild symptoms, palpable node
 - Focal uptake on thyroid scan
 - Radioiodine the treatment of choice – corrects thyrotoxicosis in 75% in ~ 3 months. Hypothyroidism in 10% over next 5 years
 - Ethanol injection sometimes used – may take repeat injections
- Thyroid cysts – about 1/3 of palpable nodes. Easily recognised on US

Subclinical Thyroid Disease

- Abnormal TSH with normal fT3 and fT4
- Differential: sick euthyroid
- Subclinical hyperthyroidism:
 - Concerns are osteoporosis and AF
 - If these are present, do a Tc99 scan and treat (eg radioiodine)
 - Also if TSH < 0.1
 - For TSH 0.1 – 0.4 observe (DEXA or Holter if at risk)
- Subclinical hypothyroidism: Treat if TSH > 10 or symptoms

Amiodarone

- Contains 39% iodine by weight. Usual doses → ↑↑ levels of iodine intake which can cause inhibitory or thyrotoxic effects
- Effects:
 - Inhibits T4 → T3 by inhibiting 5' monodeiodinase (→ initial ↑T4 and ↓T3)

- Direct toxic effect on follicular cells → thyroiditis
- High 126.0 I content → Wolff-Chaikoff Effect (if chronic autoimmune thyroiditis inhibits I transport and hormone synthesis – “Stuns” the gland) or profoundly thyrotoxic if any degree of autonomy
- Hypothyroidism in 13% – high TPO antibodies a risk factor
- Amiodarone Induced Thyrotoxicosis (AIT) in 10% – increased rate in I deplete areas:
 - Type 1: associated with underlying abnormality/autonomy – Graves or nodular goitre → excess synthesis. Uptake on scan. Increased vascularity on doppler. Treat with carbimazole
 - Type 2: destructive thyroiditis – may lead to hypothyroidism. No uptake on scan. Decreased vascularity on Doppler. Steroids have variable effect
- Management:
 - Discontinuation has no acute effect due to long half life
 - PTU/CBZ if hyperthyroid
 - Tc99 not often helpful
 - RAI not helpful – lots of iodine already in the body, not taken up. Surgery if desperate. Cholestyramine blocks enterohepatic circulation of T3 but small effect

Assessment of a Thyroid nodule

- Up to 5% of nodules > 10 mm contain carcinoma
- If < 1 cm, don't need FNA unless other concerning features
- Evaluation:
 - Risk factors: < 20, > 50, men, past neck irradiation, family history (including MEN, see page 76)
 - Symptoms suggestive of malignancy: Pain, dysphagia, hoarse voice, nodes, brachial plexus, rapid growth, tethered, other endocrine involvement (eg MEN)
- Investigations:
 - TFT: Also consider calcitonin for MTC and maybe antibodies (but may co-exist with cancer)
 - If ↓TSH then a scinit scan as a hot nodule is almost never malignant
 - FNA otherwise, sensitivity and specificity of 95%, however often non-diagnostic, haematoma only complication. Malignant potential of follicular lesions (less common) can't be determined by FNA – need surgery
 - US in most patients – palpation pretty poor at picking up nodules. Higher risk if calcification
- Management:
 - Macrofollicular nodules: GP follow up, re-refer if they grow
 - Microfollicular nodules: Resect non-autonomous adenomas. Treat autonomous adenomas with carbimazole, then radioiodine and surgery if required

Thyroid Cancer

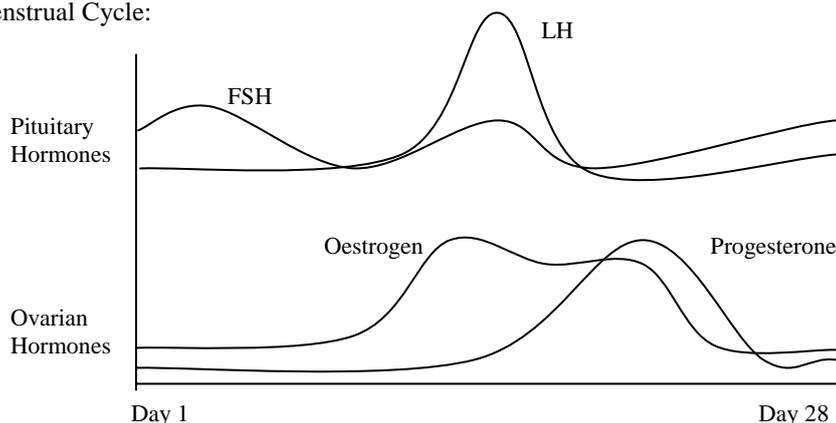
- Types:
 - Follicular Epithelial Cell:
 - *Papillary* carcinomas – 70 – 90%. Histology: psammoma bodies and papillary structure. Mainly lymphatic spread → often multicentric. Also to bone and lung
 - *Follicular* carcinomas: 5 – 10%. Difficult to diagnose on FNA – looking for evidence of invasion. Spreads by blood to bone, lung, brain. Differential of cannon ball mets
 - *Undifferentiated/anaplastic* carcinoma: dead in 6 months regardless
 - C Cell (calcitonin-producing): Medullary thyroid cancer: 10 %, *nasty*, includes familial forms of MEN2A and 2B. Elevated serum calcitonin a marker of residual or recurrent disease. Surgery. Family screening. Prophylactic thyroidectomy before age 20 for carriers of RET mutations (see Polyendocrine Syndromes, page 76)
 - Other: Mainly Lymphomas: 2%: Often on background of Hashimoto's. Most common is diffuse large-cell lymphoma. Highly sensitive to external radiation. Chemotherapy. Avoid initial surgery – may spread disease
- Good points of thyroid cancer:
 - Nodule palpable (found early) and accessible for FNA
 - Radioiodine is specific and effective treatment – as many differentiated cancers express TSH – allowing T4 suppression & 131I treatment
 - Serum markers allow monitoring of residual disease
- Risks:
 - young (<20) or older (>45) associated with worse prognosis
 - Male is worse, although more common in women

- Prior head/neck irradiation
- Large size (> 4cm), local fixation, lymphatic invasion and metastases all bad
- Treatment:
 - Always surgery +/- lymph node dissection
 - Lifelong T4 suppression (ie run them mildly thyrotoxic – 0.2 – 0.4)
 - 131I ablation – reduces recurrence but only small impact on mortality – controversial in low risk patients. Enables monitoring of recurrence with thyroglobulin (also measure Tg antibodies, if present can't rely on Tg level)
 - Do a whole body unsuppressed scan 6 months later (take of T4 for 6 weeks – or use recombinant TSH – an expensive alternative to feeling rotten for 6 weeks). Cure likely if 2 consecutive scans clear
 - High dose I131 if recurrence

Reproductive

Reproductive Physiology

- GnRH:
 - 10 amino acids – only lasts seconds \Rightarrow requires portal circulation
 - Pulsatile release
 - Stimulates release of FSH + LH
 - Inhibited by progesterone (strongest inhibitor), PRL, inhibin, testosterone, oestrogen, stress
- FSH: acts on germ cells
- LH: acts on supporting tissue:
 - Male: Leydig cells \rightarrow testosterone
 - Female: Thecal cells \rightarrow testosterone \rightarrow acted on by aromatase (produced by granulosa cells) \rightarrow oestradiol
- Oestrogen: three types:
 - Oestradiol: ovary
 - Produced by follicles
 - \rightarrow \uparrow Mucus, \rightarrow \uparrow acidity \rightarrow \downarrow other bacteria
 - -ive feedback on FSH
 - Above a threshold \rightarrow \uparrow LH
 - Unopposed oestradiol causes endometrial hyperplasia – growth without the maturing effect of progesterone
 - Oestriol: placenta
 - Oestrone: metabolised from androgens (eg testosterone) by adipose tissue
- Menstrual Cycle:



- Inhibin from developing follicle suppresses FSH compared with LH \rightarrow LH surge
- Phases for uterus endothelium:
 - Menstrual: triggered by falling progesterone
 - Proliferative/follicular: Rising FSH promote follicles \rightarrow oestrogen \rightarrow proliferative endometrium. Once oestrogen reaches a threshold \rightarrow LH surge \rightarrow release off egg
 - Secretory/ progestational/Luteal: Progesterone from the corpus *luteum* stimulates endometrial maturation

- Human Chorionic Gonadotrophin (hCG) from implanted zygote signals corpus luteum to continue progesterone production
- Pregnancy: ↑PRL (lactation is common in later pregnancy) → ↓↓ FSH and LH, ↑oestrogen (differentiated from prolactinoma in that oestrogen is not low 2nd to ↓FSH and LH)
- Prolactin:
 - PRL has pulsatile and diurnal pattern: rises dramatically during REM sleep, peaks 4 – 6 am
 - Dopamine type D2 receptors inhibit prolactin
 - PRL is raised by:
 - Hypothyroidism → ↑TRH → ↑PRL – *a slightly raised PRL is more likely to be thyroid than pituitary*
 - Oestrogen → slightly ↑PRL (ie women higher than men)
 - TRH → slightly ↑PRL (used in pituitary stimulation test)
 - T5 Dermatome stimulation → ↑PRL (but breastfeeding won't increase the size of a prolactinoma)
 - PRL rises 10 fold through pregnancy, stays high if breastfeeding
 - Drugs: most major tranquillisers (ie antipsychotics), metoclopramide → ↓dopamine → ↑PRL. Aldomet (alpha-methylDOPA) is the only hypotensive agent which increases prolactin (via dopamine depletion)
 - Can rise due to emotional or physical stress (including stressful venipuncture → artefact)
 - High in chronic renal failure
 - Sarcoidosis
 - Post-pill amenorrhoea (if due to other causes usually resolves < 1 year)
 - PRL level is not effected by progesterone or nausea
- Adrenal Androgens
 - Main adrenal androgen is DHEA (Dehydroepiandrosterone) and its ester (DHEAS)
 - Always occurs in primary adrenal insufficiency
 - Have minimal effect in males – sex characteristics predominantly determined by testosterone
 - In females, sexual hair largely mediated by adrenal androgens. ↑DHEA → ↑testosterone

Amenorrhoea

- Primary: lack of secondary sexual characteristics by 14, absence of menses at age 16
- Secondary: No period for > 3 months
- Causes:
 - Disorders of the tract (US to see what's inside)
 - Ovarian:
 - Failure: Turner's, autoimmune, chemotherapy
 - Abnormal follicular development: PCOS, obesity, thyroid
 - Pituitary: prolactinoma
 - Hypothalamus: stress, anorexia, exercise, craniopharyngioma, Kallman's Syndrome (absence of GnRH – also no sense of smell)
- Investigations:
 - βHCG, PRL, LH, FSH, oestradiol (no ovarian function in Turner's). If no FSH, LH or oestrogen then on pill or pituitary failure
 - Testosterone, SHBG and DHEA-S if clinically warranted
 - TFT
 - Karyotype XO, XX, XY
 - US pelvis: presence and structure of pelvic organs, ovarian follicles, endometrial hyperplasia
 - Imaging the pituitary if indicated
- Turner's Syndrome:
 - 45XO
 - Nearly always short stature, rarely classic webbed neck and cubitus valgus, also widely spaced nipples
 - Diagnosis: ↑FSH, ↓oestrogen, karyotype, gonadal streak on US (underdeveloped gonadal structures)
 - 5% menstruate, 2% spontaneously conceive
 - Treatment: oestrogen and GH
 - Associations: 90% sensorineural deafness, CVS 30%, 20% Hashimoto's, coarctation of the aorta

Polycystic Ovary Syndrome (PCOS)

- See NEJM Review, 2005
- Seek help for: infertility (anovulation), menstrual irregularity and androgen excess. 5 – 10% women
- Usually presents early – if presenting in late 30s think of differentials:
 - Idiopathic hirsutism: normal ovaries and androgens
 - Cushing's: high 24 hour urinary free cortisol
 - Non-classic congenital adrenal hyperplasia: rare, 17-OHP ↑ in the follicular phase
 - Androgen secreting tumour: very rare, rapid progression, no association with menses, very high testosterone or DHEAS
 - HAIRAN: very insulin resistant, Acanthosis nigricans and lipodystrophy
- At least two of:
 - Oligomenorrhoea (<9 menses a year)
 - Hyperandrogenism (hirsutism, acne, male pattern baldness) **or** elevated total or free testosterone
 - Polycystic Ovaries on ultrasound (Can have PCOS without polycystic ovaries and visa-versa)
- If rapid virilisation then look for tumour – not PCOS
- Associated with:
 - Obesity in 30 – 75% – not the underlying cause but does exacerbate the features
 - Type 2 diabetes: insulin resistance → hyperinsulinaemia. 40% have IGT and 10% T2DM ⇒ most women are able to compensate for insulin resistance by ↑ insulin. Attenuation of insulin resistance with weight loss or medication improves most of the metabolic aberrations
 - Lipid abnormalities → vascular disease (eg 7 times risk of MI)
 - HTN and OSA is higher than expected and not explained by obesity alone
 - Increased endometrial, breast and ovarian cancer – but also associated with obesity – ?is it an independent risk factor
 - Some consider it a sex specific form of the Metabolic Syndrome
- Pathogenesis:
 - Complex multigenic inheritance
 - ?Primarily a disorder of LH hypersecretion
 - ↑Non-cyclical oestrogen (including from adrenal androgens and obesity) leads to:
 - ↑LH → ovarian hyperplasia → ↑theca cell synthesis of androgens → perpetuates the cycle + excess androgens converted to testosterone (by 17B-HSD) or estrone (by aromatase in granulosa cells)
 - ↓FSH → ↓follicular maturation → ↓cyclical oestrogen → chronic anovulation → ↓progesterone → no menses
 - ↑LH:FSH ratio → ovaries preferentially synthesizing androgen rather than oestrogen
 - Hyperinsulinaemia acts synergistically with LH to enhance androgen production
 - Hormonal cycling is disrupted and ovaries enlarged by follicles with have failed to rupture
- Investigations:
 - Serum Testosterone, LH and FSH. Testosterone and LH high
 - Sex hormone binding globulin (decreased)
 - Fasting HDL, LDL, cholesterol
 - Glucose tolerance test (if pregnant do at beginning of pregnancy)
 - Ultrasound: > 10 follicles
 - Risk of endometrial cancer increased if amenorrhoea for lengthy periods – may need endometrial biopsy
 - Rarely:
 - DHEAS for adrenal androgen tumour
 - 17-hydroxyprogesterone for congenital adrenal hyperplasia
 - PRL for prolactinoma (normal in PCOS)
 - Consider Cushing's, Acromegaly
- Treatment:
 - Diet and exercise → ↓weight → ↓peripheral oestrogen and androgens, ↓insulin resistance
 - Combined pill (Diane 35):
 - Drug of choice if not wanting to get pregnant
 - To control bleeding and ↓risks of unopposed oestrogen on endometrium. But ?negative effects on coagulability and insulin resistance
 - Oestrogen → ↓LH → ↓androgens + ↑hepatic production of sex hormone binding globulin
 - Induce ovulation with Clomifene → ↑FSH

- Metformin → ↑insulin sensitivity, ↓menstrual disturbance and ↑ovulatory function (not glitazones as not assessed in pregnancy)
- Prevention of risks of diabetes and ischaemic heart disease
- Antiandrogens:
 - For treatment of hirsutism and acne. Cyproterone (antiandrogen) or high dose spironolactone (binds to testosterone receptors and stops testosterone itself binding. Not if wanting to get pregnant)
 - Established facial hair won't go away when hormones corrects (require cosmetic treatment)
- Differential: Tumours of the ovary (eg granulosa and thecal cells) → chronic anovulation

Premature Ovarian Failure

- 1% < 40
- ↑FSH and ↓oestrogen
- Causes: idiopathic, chemotherapy, 30% autoimmune, Turner's
- Treatment: HRT

Menopause

- See Lancet 2008:371
- Up to last period and 2 years following
- Primary ovarian failure → ↓ oestrogen feedback → ↑↑FSH (perimenopausally)
- Usually age 50 – 51. Cycles start to slow from 47 – 48. Usually follows pattern of her mother
- Test for high TSH if wanting to exclude thyroid and psychiatric problems
- Proven therapies for vasomotor instability: oestrogen (2.6 less hot flushes per day), gabapentin (~ 2 less per day), paroxetine (at least one per day) and Clonidine (mixed results, average about 1 less per day)
- Studies have not consistency found a relationship with depression
- Bone mineral density falls 3 – 5% for 3 years, then 1% thereafter

Hormone Replacement Therapy

- Replacing normal physiological dose of oestrogen (cf CoC which is much higher)
- If intact uterus then combined with progesterone to stop unopposed endometrial hyperplasia (which may → cancer). If no uterus can take oestrogen only
- Women's Health Initiative (see Osteoporosis, page 93):
 - Risks of CVD higher for combined HRT – but not for oestrogen alone
 - Secondary analysis showed women starting HRT > 10 years after menopause had a greater risk of CVD than those who start early
- Up to 5 years of therapy
- Small increase in VTE and Breast Ca. 8 – 12 additional CVA events per 10,000/year, 8 CVS events per 10,000 per year. Major surplus events ~1 in 1,000
- Benefits: fracture prevention, ↓colorectal cancer, no effect on Alzheimer's
- Contraindications:
 - History of breast or endometrial cancer (not ovarian or cervical)
 - Undiagnosed vaginal bleeding
 - Liver disease (it's metabolised in the liver)
 - Pregnancy or breast-feeding!
 - Past PE
 - DVT is a relative contra-indication (whereas OC dose of oestrogen is bad for clots) – 18 excess VTEs per 1,000
 - High cholesterol is NOT a contra-indication – it's protective (compared with OC dose of progesterone which is bad)
 - Smoking is NOT a contra-indication – it's protective

Testosterone

- 95% secreted by Leydig cell under stimulation by LH & FSH, 5% from adrenal DHEAS
- 2% free in plasma, 60% SHBG bound (secreted by the liver), 38% albumin bound
- Effects:
 - Direct effect on muscle
 - Via metabolism:
 - 5α reductase to DHT: effect on prostate and bone
 - Aromatase to oestradiol: effect on brain and bone

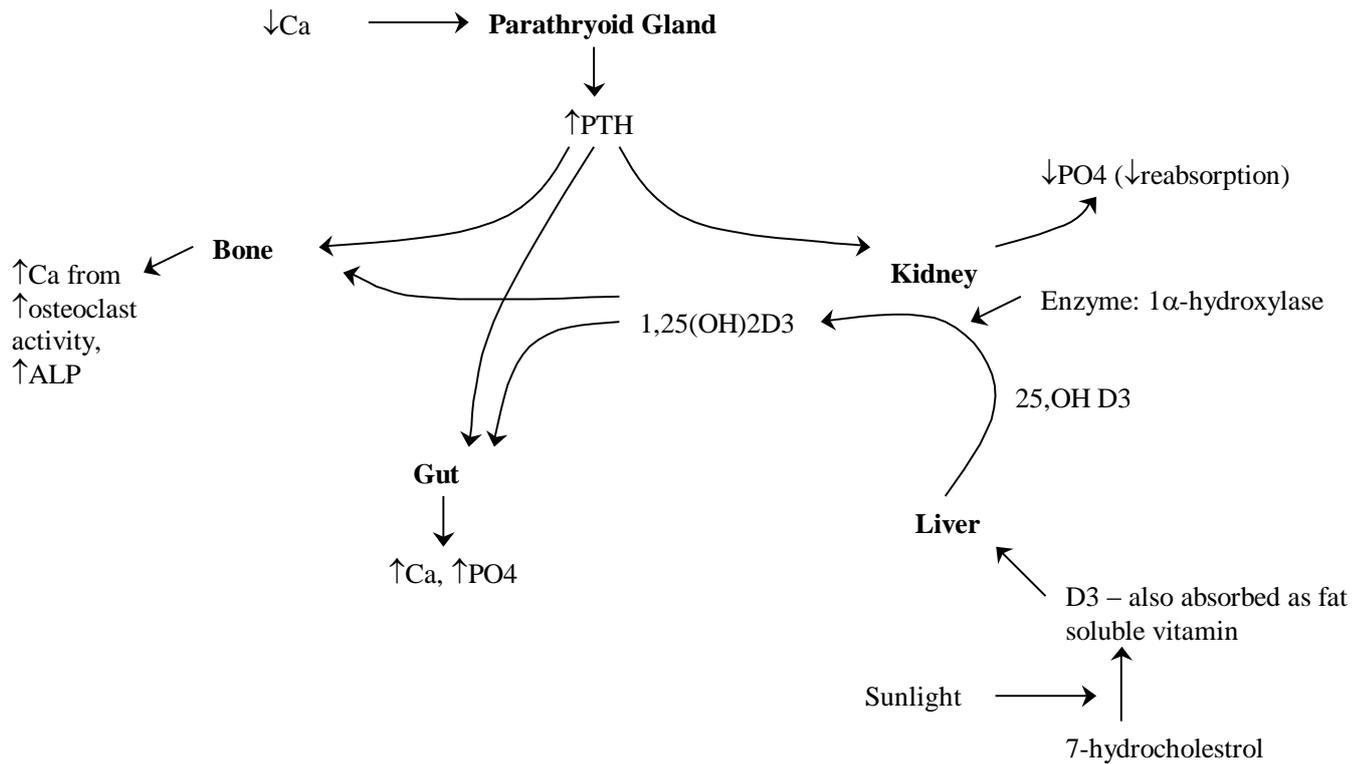
- Symptoms (in order): ↓energy, ↓motivation, ↓libido, cantankerous mood, sleepy after lunch...
- Causes of deficiency:
 - Primary Testicular Failure:
 - Normal adult male testes: 4 – 7 cm in length, 20 – 25 ml in volume
 - Congenital:
 - Klinefelter's Syndrome (XXY) and mosaic variants: Tall, poor beard growth, minor breast development, testicular atrophy, female pubic hair pattern, ↓libido, osteoporosis. Only 25% during their life
 - Cryptorchidism and defects of testis development
 - Others...
 - Acquired:
 - Orchitis: mumps, leprosy, AIDS, other
 - Trauma, torsion, surgery
 - Radiation/chemotherapy
 - Idiopathic
 - Secondary (Hypogonadotropic) hypogonadism/Pituitary:
 - Due to gonadotrophin or GnRH deficiency:
 - Pituitary tumour/surgery/irradiation
 - Kallman's Syndrome: Mutations in the KAL1 or FGFR1 (fibroblast growth factor receptor 1) genes, associated with midline cranial defects and anosmia (no smell)
 - Other genetic causes
 - Sleep apnoea
 - Chronic illness: T2DM, CHF, liver disease, haemochromatosis
 - Opioids, glucocorticoids, anabolic steroids
- Testosterone Replacement:
 - Levels below 8 nmol/L should be replaced, > 12 not required
 - Poorly absorbed orally (tds medication)
 - Replacement options:
 - Daily Transdermal patches: but SE skin reactions
 - 3 weekly deep IM depot: but → fluctuating levels (SE polycythaemia), newer 3 monthly depot
 - Implants, sc every 5 – 6 months
 - Topical daily testogel
 - Contraindicated in metastatic prostate cancer and breast cancer, higher risk in unexplained PSA elevation, obstructive symptoms with BPH, severe CHF
 - Monitoring at 1, 6 and 12 months then annually: voiding history, DRE, sleep apnoea, gynaecomastia, bloods for testosterone, haemoglobin and PSA

Erectile Dysfunction

- Rarely hormonal. Can be psychogenic, neurogenic, impaired veno-occlusion and arterial flow, drugs, depression, age related, diabetes....
- Treatment:
 - Type 5 phosphodiesterase inhibitor (PDE-5 inhibitors) – Sildenafil (Viagra – NB also used for pulmonary hypertension), Tadalafil (Cialis), vardenafil (Levitra)
 - Absolute contraindications: nitrates used within 24 hours or frequent need, exercise induced angina
 - Side effects: headache, flushing, SOB, nasal congestion, visual disturbance

Parathyroid

Calcium metabolism



- Normal value of Ca: 2.12 – 2.65 mmol/L. Take sample uncuffed
- Renal handling of Ca:
 - 8 – 10 g/d of ca filtered by the glomeruli, of which 2 – 3 % appears in the urine
 - Most filtered ca is reabsorbed passively via a non-regulated paracellular route in the proximal tubules
 - Thick ascending loop of Henle reabsorbs 20%
- Causes of discrepancy between total and ionized calcium:
 - Hypoalbuminaemia. 40% of calcium is bound to albumin. Adjust Ca for changes in albumin (0.025 per 1g of Albumin)
 - Paraproteinaemia
 - Citrate-complexed calcium (blood products)
 - Gadolinium (lowers Ca)
 - Acid-base disturbances: Acidosis → H displaces Ca on albumin → ↑free Ca
- Ionised calcium is a more sensitive measure than corrected calcium
- **PTH:**
 - Released from parathyroid in response to ↓Ca
 - If low Mg, then no ↑ in PTH in response to ↓Ca
 - ↑rate of dissolution of bone mineral → ↑Ca into blood
 - ↑renal absorption of Ca
 - ↑renal production of 1,25(OH)2D → ↑Ca absorption from gut and ↑Ca flux from bone and kidney into circulation
 - Calcium sensing receptor (CaSR):
 - G-protein coupled receptor on the surface of the parathyroid cell
 - ↑Ca → ↓PTH secretion
 - Inactivation or activation mediated both by genetic causes and autoimmune causes
 - Familial Hypocalciuric Hypercalcaemia: AD (ie heterozygous inactivating mutation): Life long mild hypercalcaemia. Normal urinary Ca. PTH normal or mildly ↑
 - Familial Hypocalcaemic Hypercalciuria: AD activating mutation of the CaSR (parathyroid and kidney) → excessive Ca-induced inhibition of PTH → mild hypocalcaemia
 - Calcimetic agents:
 - Make CaR more sensitive to extracellular Ca
 - → ↓PTH → ↓Ca in patients with primary hyperparathyroidism and dialysis patients

- PTHrP:
 - Secreted by the foetal parathyroid and increases placental Ca transport
 - Is a local growth factor secreted in many tissues
 - Has same 1 – 14 sequence as PTH → binds to PTH/PTHrP receptor
- Calcitonin: antagonist of limited physiologic significance to humans
- **Vitamin D:**
 - Found in fish oils and egg yolks
 - Metabolism:
 - Vit D2 and D3 from diet incorporated into chylomicrons and transported to the venous circulation via the lymphatic system
 - Bound to vitamin D-binding protein to be transported to liver
 - Converted in liver to 25(OH)D (by 25-hydroxylase). This is the circulating form but is biologically inactive
 - Converted to 1,25(OH)2D by 25-hydroxyvitamin D-1 α hydroxylase found in convoluted tubule, induced by PTH and hypophosphatemia, suppressed by Ca and 1,25(OH)2D
 - 1,25(OH)2D →
 - ↑Ca and ↑PO4 absorption from small intestine
 - ↑Ca release from bone
 - ↓its own synthesis via negative feedback
 - ↓PTH synthesis
 - Effect mediated by vitamin D receptor (VDR)
 - Affinity for VDR for 1,25(OH)2D three orders of magnitude greater than other metabolites
 - Toxic dose may be as high as 40,000 iu per day (ie large safety margin with dosing)
 - Causes of impaired Vitamin D action:
 - Deficiency: impaired cutaneous production, dietary insufficiency, malabsorption
 - Increased loss:
 - Increased metabolism: phenytoin, rifampicin
 - Impaired enterohepatic circulation
 - Impaired 25-hydroxylation: liver disease, isoniazid
 - Impaired 1 α -hydroxylation: hypoparathyroidism, renal failure, ketoconazole, genetic
 - Target organ resistance: VDR mutation, phenytoin
 - Vitamin D prevents falls – a meta-analysis showed vitamin D reduced odds of falling by 20%, with NNT of 15. Mechanism ?↑muscle strength not stronger bones (JAMA 2004;291:1999-2006)

Calcium Summary

- Low:
 - Hypoparathyroidism: abscess/gland destruction, ↓Mg, resistance to PTH (pseudo)
 - ↓Vit D: renal failure, malnutrition
- High:
 - ↑PTH: primary, secondary or tertiary
 - Paraneoplastic: PTHrH, bone metastasis
 - ↑Vitamin D: nutritional, ↑conversion (sarcoid)

Hypercalcaemia

- Signs: “Bones, stones, groans and psychic moans”. Also abdominal pain, vomiting, constipation, polyuria (Ca potentiates ADH effect), depression, anorexia, weakness, ↑BP, renal stones, short QT, cardiac arrest
- Most commonly (90%):
 - Primary hyperPTH in the community
 - Malignancy in hospital
- If albumin raised:
 - Urea raised → dehydration
 - Urea normal → cuffed specimen
- Causes:
 - PTH related:
 - Primary hyper PTH: adenomas or MEN. Ectopic PTH tumours extraordinarily rare
 - Lithium
 - Genetic

- Malignancy related:
 - Solid tumour with metastases (breast) – local production of PTHrP in bony metastases gives high RANKL:OPG ratio, stimulating osteoclasts and releasing TGFβ that was laid down in bone with stimulates further PTHrP
 - Solid tumour with PTHrP – humoral excess: non-metastatic squamous cell and renal (note small-cell and lung adenocarcinoma most likely to produce mets, but less ↑Ca). PTH will be very low, high osteoclastic markers, low osteoblastic markers, but PTHrP does not stimulate 1-OHylation of 25OHVitD
 - Haematological malignancies:
 - Multiple Myeloma – doesn't ↑ ALP so can't diagnose on bone scan. Hepatocyte growth factor induces osteoblast to secrete IL-11 which stimulates osteoclast production
 - Lymphoma, leukaemia: ↑1,25(OH)2VitD
- Vitamin-D related:
 - Intoxication
 - Sarcoidosis and other granulomatous diseases (Tb, fungal). Tb, sarcoid, leprosy → ↑macrophages which ↑ 1,25D3. Try suppression with Prednisone for 10 days
 - High Bone turnover: hyperthyroidism (bone resorption > bone formation), *immobilization*, thiazides (can unmask primary Hyper PTH), ↑Vitamin A
 - Renal failure: severe 2ndary Hyper PTH, aluminium intoxication
 - *Thiazides: ↑Ca reabsorption*
 - Milk Alkali Syndrome: Excessive ingestion of calcium (eg milk, antacids or calcium carbonate) causing hypercalcaemia → ↑Na excretion and depletion of total body water, together with ↓PTH → bicarbonate retention → alkalosis → renal calcium retention → worse hypercalcaemia. Can → nephrocalcinosis and renal insufficiency (Burnett's syndrome)
- Treatment: if Ca > 3.5 mmol/l or severe symptoms:
 - Note – hypercalcaemia is nephrotoxic
 - Mild: treat the cause and avoid thiazides
 - Moderate: above plus rehydrate and correct any hypokalaemia and hypomagnesaemia
 - Severe:
 - Diuretics once rehydrated (frusemide, avoid thiazides)
 - Bisphosphonates (eg pamidronate): lower Ca over 2-3 days by inhibiting osteoclasts
 - In haematological malignancy of granulomatous, glucocorticoids → ↑urinary Ca excretion and ↓absorption, but also negative skeletal Ca balance
 - If renal failure: dialysis. Although large quantities of phosphate lost in dialysis which will aggravate ↑Ca if not replaced

Hypocalcaemia

- Symptoms:
 - Tetany, depression, carpo-pedal spasm (wrist flexion and fingers drawn together)
 - Neuromuscular excitability:
 - Chvostek's sign: eg tapping over parotid causes facial muscles to twitch
 - Trousseau's sign: BP cuff inflated on arm to > systolic pressure for 3 minutes → painful carpal spasm
 - Prolonged QTc
- Causes of hypocalcaemia:
 - Spurious: hypoalbuminaemia
 - PTH absent:
 - hypo PTH: idiopathic (autoimmune)
 - ↓Mg (chronic alcoholism, Gittelman's syndrome) → ↓PTH → hypocalcaemia
 - Thyroid or parathyroid surgery
 - PTH ineffective:
 - Chronic renal failure (+/- failure of Vitamin D conversion)
 - Pseudo hypoPTH
 - Severe Vitamin D deficiency: nutritional or medications (phenytoin, carbamazepine, isoniazid, rifampicin)
 - Genetic: Ca sensing receptor abnormalities
 - Acute pancreatitis
 - Excess blood transfusion (citrate)

- If PO₄ normal or ↓ then osteomalacia (↑ALP), over hydration or pancreatitis
- Treatment: Ca supplementation. If acidotic and ↓Ca, correcting the acidosis first could dangerously reduce ionised Ca. Give Ca gluconate 10%, 10 ml over 4 minutes then 100 ml in 900ml D5 at 50 ml/hour, titrated to serum Ca

Hyperparathyroidism

- If prolonged → osteitis fibrosa cystica: High turnover, bone pain and proximal myopathy, subperiosteal erosions esp on phalanges and brown tumours. Xray changes include resorption of the phalangeal tufts. Now fairly rare (seen in prolonged renal failure)
- Causes:
 - Primary: ↑PTH → ↑Ca²⁺, ↓PO₄
 - Usually detected as incidental finding. If symptoms: pain/fracture, renal stones, constipation, abdominal pain, depression. Also maybe dehydration, ↑BP, thirst, nocturia, stiff joints, myopathy
 - Sporadic causes: Single (90%) or multiple adenoma, carcinoma (1%), hyperplasia
 - Familial causes: Familial isolated primary hyperparathyroidism, MEN I and IIA, familial Hypocalciuric hypercalcaemia. Associations: endocrine neoplasia (eg pancreas, pituitary, pheochromocytoma and thyroid). See Polyendocrine Syndromes, page 76
 - Tests: ↑Ca, ↓PO₄ (unless renal failure), ↑ALP, PTH raised or normal. ↑Urinary Ca (cf low in familial Hypocalciuric hypercalcaemia). CXR for ‘pepper pot skull’ and pelvis.
 - Treatment: surgery if Ca > 3.0, marked hypercalcaemia, renal impairment/stones, young (< 50) or T score < -2.5, otherwise monitoring
 - PTH related protein (PTHrH): produced by some tumours (normally produced by lots of different cells) – causes some of the hypercalcaemia seen in malignancy. See Hypercalcaemia, page 90
 - Secondary Hyperparathyroidism: ↓Ca → ↑PTH. Causes: ↓Vitamin D and chronic renal failure (see Renal Osteodystrophy, page 114). Treatment: restrict dietary phosphate. **Lithium → ↑PTH**
 - Tertiary Hyperparathyroidism: continued secretion of PTH after prolonged secondary hyperPTH

Hypoparathyroidism

- See NEJM 24 July 2008
- Primary HypoPTH
 - After thyroidectomy or neck surgery. → ↓Ca and ↑PO₄, normal ALP.
 - Autoimmune: Associations with pernicious anaemia, Addison’s, hypothyroidism, hypogonadism. See Polyendocrine Syndromes, page 76
 - Also infiltration in haemochromatosis and Wilson’s disease
 - ↓ or ↑Mg → functional hypoPTH (Mg can activate calcium-sensing receptors)
 - A number of genetic mutations characterised eg Di George Syndrome
- PseudohypoPTH: Genetic disorder → failure of target cell response to PTH. Round face, short metacarpals and metatarsals. Variations have hypo- or normo-calcaemia. Parental imprinting of the gene
- Test: Ca, albumin, PO₄, Mg, Cr, PTH, 25(OH)D₃
- Treatment:
 - No hormone replacement therapy available
 - Ca gluconate iv if acute (irritating if extravasated – take care)
 - Calcium carbonate: best absorbed with meals and acid present, SE constipation
 - Calcium citrate: if taking PPI or achlorhydria

Bone Disease

- Bone: solid mineral in close association with an organic matrix – 90 – 95% of which is type 1 collagen
- 99% of the 1 – 2 kg of calcium in the body is in the bones
- Structure:
 - Cortical bone: peak loading in long bones
 - Trabecular bone: flexibility favoured over peak loading, eg vertebral bodies
 - Bone strength is a combination of:
 - Structural properties: geometry, microarchitecture, cortical thickness, etc
 - Material properties: mineral, collagen
- Mesenchymal precursor differentiates to osteoblasts (and then to osteocyte), adipocytes, and chondrocytes via signalling pathways

- Osteoblasts:
 - Synthesize and secrete organic matrix, which is then mineralised with Ca (initially 70% over 3 months, completed over years)
 - Produce RANKL – binds to osteoclast RANK (Receptor Activator of NFκB) receptor to promote (via NF-κB ligand) osteoclast differentiation, activation and survival. ↑production 2nd to ↓oestrogen
 - Osteoprotegerin (OPG) expression is induced by factors that block bone catabolism and binds to RANKL acting as a decoy receptor → inhibits osteoclast differentiation → ↓ resorption (?potential as a therapeutic target)
 - Control osteoclast differentiation through RANKL:osteoprotegerin ratio
- Osteocyte:
 - Osteoblast now buried in the bone, connected to blood supply through canaliculi
 - Senses strain. Apoptosis with microfractures which initiates osteoclast remodelling. Become more sensitive in the absence of oestrogen (ie post menopause) → ↑turnover
- Osteoclasts: multinucleated cells derived from the common precursor of macrophages and osteoclasts. Resorption of bone by dissolving mineral and osteoid. Releases Transforming Growth Factor beta (TGF beta) that was laid down with bone which stimulates osteoblasts to begin work
- PTH increases the number of bone remodelling units
- Bone Biochemical Markers: Research tool. Clinical use not well established
 - Formation: ALP, Osteocalcin, Type 2 procollagen amino terminal propeptide (PINP)....
 - Resorption: N or C telopeptide

Osteomalacia

- ↓Vitamin D (see Calcium Metabolism, page 88) → ↓Ca and ↓PO₄ → impaired mineralization of bone matrix → osteomalacia (in kids associated with growth retardation)
- Causes:
 - ↓Vit D, or defects in Vit D metabolism, malabsorption in Coeliac, chronic liver disease, ↓sun
 - Phosphate deficiency or wasting: Aluminium, type 1 or 2 tubular defects, Fanconi syndrome
 - Drugs: bisphosphonates, aluminium, fluoride, phenytoin, rifampicin, glucocorticoids
 - Osteogenesis imperfecta: AD defect of collagen type 1, blue sclera, various types ranging from mild to severe
- Three levels of bone disturbance:
 - Mild, with secondary hyperparathyroidism → increased bone turnover (with osteoid proportionate to osteoblast and osteoclast number): a high turnover osteoporosis
 - Moderate, with low phosphate. ↑PTH increases conversion of 25 to 1,25 Vitamin D which is more potent, which holds things for a bit. Impaired mineralization (ie osteomalacia), normal plasma calcium
 - Severe, with all skeletal surfaces covered with unmineralised osteoid and hypocalcaemia
- Features:
 - Proximal myopathy (2nd to Vitamin D deficiency)
 - Bone pain
 - Prone to bowing of weight-bearing extremities
 - Skeletal fractures
- Investigations:
 - Ionised calcium (low or normal)
 - PTH (high, due to 2ndary hyperPTH) or normal
 - Vitamin D: low (<50), very low (<30)
 - ALP can be raised
 - Xray: pseudo-fractures or Looser's zones: radiolucent lines resulting from ?pulsations of overlying arteries
- Treatment of Vitamin D deficiency:
 - Also with Ca – 1.5 – 2.0 g/d of elemental calcium
 - Calcitriol if hydroxylation the problem
 - Monitor by looking at urinary calcium excretion (normal 100 – 250 mg/d). Low = not enough, high = risk of nephrolithiasis

Osteoporosis

- See NEJM 2005:353
- Low bone mass and microarchitectural deterioration of bone tissue

- Epidemiology:
 - Approx 30% > 50 have one or more vertebral fractures
 - Approx 20% of men over the age of 50 will have an osteoporosis-related fracture in their remaining lifetime
 - One year after a hip fracture: 20% are dead, 30% have permanent disability and 40% are unable to walk independently
 - Bone loss is greater in women because they gain less bone, not because they lose more → more cortical thinning in women
- Pathophysiology: Due to bone resorption > bone formation (occurs from age ~35). Mediated by RANKL
- DEXA:
 - T score compares to normal young woman
 - Z score compared to age matched cohort – mainly for use in kids
 - NIH definition = WHO definition = T score < -2.5
- Risk factors for a fracture: (see calculator at www.shef.ac.uk/FRAX)
 - Advancing age
 - Low body weight
 - Low peak bone mass
 - Maternal history of osteoporosis. Linkage studies implicate 5 genetic loci (NEJM May 2008):
 - ESR1: Estrogen receptor
 - OPG (Osteoprotegerin gene) and RANKL (receptor activator of nuclear factor- κ B ligand gene) major regulators of osteoclast activity
 - Two others
 - Not clinically useful in individual risk assessment, but may in future guide targeted therapy (eg when to use oestrogen or Denosumab [RANKL monoclonal antibody])
 - Direction of fall (backwards is worse)
 - Previous fracture (ie one vertebral fracture predicts the next)
 - Female
 - Current cigarette smoking
 - Alcoholism
 - Steroids (likely cause of ↑fractures post transplant)
 - Propensity to fall: eyesight, frailty etc
 - Many diseases: hypogonadal states, endocrine disorders, nutritional deficiencies, RA, malignancies, COPD, amyloid....
- Secondary causes to exclude:
 - Primary hyperparathyroidism
 - Vitamin D deficiency due to low intake, low sunlight or malabsorption
 - Multiple Myeloma
- Testing:
 - FBC, renal and hepatic function (ALP), ?urinary calcium, ?Vitamin D, consider BJP and SPE, TFTs, cortisol testing, PTH, testosterone in men
 - DEXA. High Resolution peripheral Quantitative CT (HR-pQT) is a new, low radiation dose assessment tool
- Intervention thresholds:
 - Primary prevention if T > -2.5
 - Secondary prevention if previous fracture and/or markedly decreased BMD
 - Approximately 50% of fragility fractures occur in women with a T score greater than -2.5
- Presentation: Vertebral fractures: only 25 – 30% present with sudden onset back pain. Usually lasts 6 – 10 weeks

Osteoporosis in Men

- Causes:
 - Primary osteoporosis:
 - Idiopathic osteoporosis
 - Age-related osteoporosis
 - Secondary osteoporosis:
 - Alcohol
 - Hormonal disorders: hypogonadism, Cushing's, hyperthyroidism, primary and 2ndary hyperPTH

- GI disorders: Malabsorption syndromes, inflammatory bowel disease, primary biliary cirrhosis, post gastrectomy
- Hypercalciuria
- COPD
- Transplantation osteoporosis
- Neuromuscular disorders
- Systemic illnesses: RA, multiple myeloma, malignancy
- Medication: glucocorticoids, anticonvulsants, thyroid hormone, chemotherapy
- Treatment with Alendronate: ↑lumbar spine and femoral neck BMD and ↓ vertebral fractures (0.8% vs 7.1%)

Non-Pharmacological Treatment of Osteoporosis

- Avoid smoking and excess alcohol
- Weight bearing exercise works
- Hip protectors: new evidence shows no effect (randomised trial of wearing them on the left or the right)
- Back strengthening exercises
- Analgesia for existing vertebral fractures
- Adequate nutrition
- Exercise: meta-analysis shows exercise prevents bone loss, but no gain in bone mass
- Vertebroplasty: injection of cement into the vertebra. Non-randomised study shows analgesic effect. Needs RCTs for effect and safety

Medication for Osteoporosis

- No currently well-accepted guidelines for monitoring treatment
- Calcium:
 - Calcium supplementation – recommended intake 800 – 1000 mg pre-menopausal, 1200-1500 for post-menopausal women. Meta-analysis showed increase of 2% in spine bone mineral density after 2 years, but risk of fracture not reduced to statistically significant levels
 - Usual intake inadequate. take < 600 mg at a time as calcium absorption fraction decreases at higher doses
 - CO₃ formulations – need to take with food as require acid to be soluble
 - If history of kidney stones, 24 hour urinary Ca first
- Vitamin D:
 - Multivitamins usually contain 400 iu. > 1000 iu/d may be required in elderly and chronically ill
 - Vitamin D: ?Best to use D₃ (cholecalciferol) over D₂. Variable data. Calcitriol [1,25(OH)₂D] variable evidence. Can cause hypercalcaemia. Not for normal osteoporosis. Use in renal disease
 - Strong evidence that it enhances muscle strength and reduces risk of falling
- Vitamin D and Calcium combined:
 - Meta-analysis: RR 0.88 from Ca + Vit D (Lancet 2007;25:657)
 - Women's Health Initiative tested supplemental Ca and Vit D on healthy postmenopausal women – found no difference in fracture rate but ↑kidney stones. But the cohort were healthy, and had good baseline dietary levels
- Cochrane 2009:
 - Vit D + Ca together in institutionalised people → ↓hip and other non-vertebral fractures. The effectiveness in community dwellers is unclear but may be marginal reduction
 - Vit D alone (in currently used doses) is unlikely to be effective in any group. There is no evidence that analogues (eg calcitriol) are better than Vit D, and calcitriol has ↑ SE (eg hypercalcaemia)
- Bisphosphonates: see page 96
- HRT (ie various forms of oestrogen):
 - Decreased hip fracture ~ 50% reduction. No residual effect > 10 years after stopping
 - *Women's Health Initiative* (WHI) (>16,000 post menopausal women, mean age 67, 70% overweight, stopped after 5.2 years because of ↑risk of breast cancer):
 - ↓Risk of hip and clinical spine fracture by 34%. But MI risk 29%, 40% ↑CVA, 26% ↑breast cancer, and 100% ↑VTE
 - Improved hot flushes (treatment usually only required short term), sweats, mood swings,.... (although most women >15 years post menopausal and trial not designed to test post-menopausal symptoms)
 - Impact (Harrison's pg 2404): for each 10,000 women treated for 1 year: 8 excess MIs, 8 excess breast cancers (although those who had not taken it before the trial had no ↑risk – consistent

with previous trials showing no risk if taken for < 5 years), 18 excess VTEs (risk attenuates with time), 5 fewer hip fractures (ie NNT 1,700!), 44 fewer clinical fractures, 6 fewer colorectal cancers

- Bottom line: HRT should be used for no more than 2 – 5 years for treatment of postmenopausal symptoms only. Avoid if high risk for VTE, MI and stroke. There are better options for bone protection
- PTH (1-34):
 - Once daily sc injection
 - Stimulates bone remodelling by increasing bone formation – ↑ number and activity of osteoblasts → new bone formation on periosteal bone surfaces (cf anti-resorptive drugs which increase mineral content of existing bone)
 - Reduced vertebral and non-vertebral fracture by 50%
 - Concern about osteogenic sarcoma so not recommended for more than 2 years
 - Would be ideal in patients with multiple fractures to restore bone mass but not funded and very expensive
 - Only mild side effects. No impact on plasma Ca (once daily injection with half life in minutes – just acting as an osteoblastic stimulator)
 - Contraindicated in high bone turnover states (eg Paget's) and severe renal impairment
 - Previous bisphosphonates (which linger in the bone for years) may attenuate its action. Future may be to give PTH to restore bone then bisphosphonates to keep it
- Estrogen related agents:
 - Selective Oestrogen Receptor Modulators (SERMs): inhibits bone resorption through same pathway as oestrogens, reduces breast cancer, increases BMD and ↓vertebral fracture risk only by 30 – 50%. Eg Raloxifene and Tamoxifen (same class but all different receptor-drug conformation). MORE Study of Raloxifene: ↓vertebral fractures, no effect on hip fractures (not as potent as bisphosphonates), SE: DVT, hot flushes
 - Selective Tissue Estrogenic Activity Regulators (STEAR): eg Tibolone – differential effect in different tissues. LIFT study – ↓fractures and ↓breast ca but ↑stroke, trial stopped early
- Other:
 - Calcitonin: partially inhibits osteoclast bone resorption. Nasal and sc preparations approved for post-menopausal osteoporosis. Most trials used salmon calcitonin (50 times more potent than human). Poorer quality trial evidence. Only use if unable to take more effective treatments
 - Anabolic agents: Sodium fluoride stimulates formation of new bone but increased risk of non-vertebral #
 - Small studies of Growth Hormone have not shown consistent or substantial effects on bone mass
 - Phase II trial of Denosumab (monoclonal antibody inhibiting the RANKL-RANK pathway) showed similar effectiveness to alendronate. Mimics action of osteoprotegerin. 3 or 6 monthly sc for 12 months. ↑BMD. Fracture data awaited
 - Strontium: substitutes for Ca, trials show ↓ fractures, ? → DEXA overestimating BMD
- Cortico-steroid induced bone loss: STOP Trial (NEJM 2006) showed Alendronate better than calcitriol for prevention of bone loss in 201 patients with RA. BMD increased 2.1% vs loss of 1.9%. Heterogeneous sample. No difference in fracture rate at 48 weeks. RCT showing ↓fracture rate with Risedronate

Bisphosphonates

- Generations:
 - 1st generation: etidronate (potency = 1). Could inhibit formation as well as blocking resorption so given cyclically to prevent osteomalacia. No evidence in non-vertebral fractures
 - 2nd generation:
 - Aldendronate (potency 100 – 1000)
 - Pamidronate: given IV (30 – 90 mg) over 30 – 90 minutes. ↑spine and femoral neck BMD by 4 – 6%. No good fracture data
 - 3rd generation: Zoledronate (potency 10,000+), risedronate (RCT evidence of ↓fracture), ibandronate
- Unknown effect over decades of treatment
- Powerful inhibitors of bone resorption: uptake by osteoclasts → inhibits farnesyl pyrophosphate synthase → inhibits osteoclast action and monocyte-macrophage differentiation into osteoclasts → ↑bone mass. Promotes osteoclast apoptosis
- Alendronate:

- Reduce relative risk of hip and vertebral fracture by 50% (Fracture Intervention Trial). ↑spine BMD vs placebo 6 – 8% at 3 years. Conflicting results when tested in osteopenia (T score < -1, > -2.5) – if no previous fracture then ?↑ in forearm fractures, if previous clinical or radiological fracture then ↓fracture rates
- Equivalence of once daily 10 mg vs 70 mg once weekly shown in trials. Take before food as *poorly absorbed*. Oesophageal complications reported (so take upright), but in trials GI symptoms no different to placebo
- Recent trial (JAMA 2006) shows little clinical difference between 5 and 10 years therapy. Slight loss of BMD in the former, but no difference in fracture rate. It's laid down in bone and inhibits osteoclasts when they later remodel the bone
- Zoledronic acid: IV infusion of 5 mg annually. Recently approved for osteoporosis. In a study of > 700 post menopausal women with previous fracture treated with 5 mg iv annually, significant reduction in fractures. Increased rate of AF ? cause. Infusion within 90 days of a low-trauma hip fracture reduces new clinical fractures by 35% (8.6 vs 13.9%) and *mortality* by 28% (9.6 vs 13.3%) (NEJM 2007;357:1799)
- Replace vitamin D – if deficient they will become hypocalcaemic
- Osteonecrosis of the Jaw– definitions vary “an area of exposed bone that persists for more than 6 weeks”. Especially after dental surgery, and mainly in cancer patients treated with multiple doses of the more potent bisphosphonates. Incidence ranges from 1 in 2,000 to 10,000. Evidence that rates higher are first year of treatment – so get major dental work done early

Paget's Disease

- See Lancet 12 July 2008
- Overactive focal osteoclastic bone resorption followed by increased osteoblastic formation that is structurally disorganised (woven bone, rather than lamellar bone) and more susceptible to fractures
- Osteoclasts are hypersensitive to vitamin D and RANKL
- Cause unknown. Both genetic and viral aetiologies. SQSTM1 mutation associated with severe disease
- Approx 4% people > 55 years
- Presentation:
 - ↑ALP and/or pain from bowing, fractures, etc
 - Ca and PO₄ normal. Do Vitamin D. Can confirm with isotope bone scan
 - ↑↑blood flow through vascular pagetic bone may rarely → high output heart failure (usually existing heart disease)
 - May be deafness (?small bones of ears or nerve canal)
 - Complication in < 1% (5 – 10 % of severe): osteosarcoma
- Treatment if pain, deformity or risk of fracture: bisphosphonates → restoration of normal bone architecture. Alendronate 30 mg/d (ie high dose) for 2 months usually leads to remission (normal ALP) – but usually continued. Pamidronate, Risedronate and Zoledronic Acid (single infusion) also have evidence of effect. Lytic lesions become sclerotic with treatment

Causes of Osteosclerosis

- = high bone density
- Paget's
- Sclerotic secondaries: breast, prostate
- Osteoma
- Myelofibrosis
- Renal osteodystrophy
- OA
- Ank Spond
- Rare complication of Hep C
- Genetic forms: Osteopetrosis: LPR5 gain of function, CICN7....

Causes of Bone Pain

- Differential: OA, myalgia, synovitis, bursitis, enthesitis, fibromyalgia, periostitis/trauma
- Stress fracture
- Paget's disease
- Malignancy: breast, thyroid, prostate, osteosarcoma
- Osteomyelitis
- Osteomalacia

- Renal osteodystrophy
- Genetic bone disease
- Regional or local osteoporosis (ie Xray finding): variety....

Other Electrolytes

Phosphate

- Normal uptake 800 – 1400 mg/day, 60 – 80% absorbed
- Freely filtered in glomerulus
- 80% resorbed in proximal tubule – acute and chronic adaptations alter resorption according to intake
- \uparrow PTH \rightarrow \uparrow PO₄ into urine (inhibits Na-P co-transporter) but there is resistance to this effect when there is phosphate deficiency
- Hypophosphatemia:
 - Symptoms: proximal myopathy, dysphagia, ileus....
 - Causes of hypophosphatemia:
 - \downarrow renal tubular reabsorption:
 - Hyperparathyroidism
 - Fanconi's syndrome
 - Other: renal disease, drugs, alcohol, genetic
 - \downarrow Vit D synthesis or effect
 - Decreased absorption 2nd to antacids, diarrhoea, steatorrhoea
 - Dietary restriction
 - Shift of extracellular phosphate into cells: IV glucose, insulin, respiratory acidosis
 - Accelerated bone formation: eg post parathyroidectomy
 - Severe if < 0.75 mmol/l – seizures likely < 0.25 mmol/L. Correct low Ca first
 - Treatment: IV replacement can \rightarrow severe hypocalcaemia. Oral supplements (1000 mg/day) the safest
- Refeeding Syndrome: Calories reintroduced into a system that has been metabolising fat stores \rightarrow \uparrow insulin and \uparrow metabolism \rightarrow \downarrow PO₄ (most important – key component of ATP and 2,3-DPG) and \downarrow Mg along with cardiac instability. \downarrow K also occurs, in part due to intracellular shift following \uparrow insulin. Watch for it in alcoholics, anorexia, long post-op course... Avoid with gradual refeeding
- Hyperphosphatemia:
 - Causes:
 - Impaired renal excretion:
 - Renal insufficiency
 - Hypoparathyroidism
 - Pseudo-hypoparathyroidism
 - Acromegaly
 - Heparin therapy
 - Massive extracellular loads:
 - Extensive cellular injury/necrosis: tumour lysis, rhabdomyolysis, severe haemolysis
 - Acidosis
 - Exogenous: administration, Vit D overdose
 - Pseudohyperphosphataemia: myeloma interferes with assay, extreme \uparrow TGs
 - Causes \downarrow Ca (because of CaPO₄ deposition, also \uparrow PO₄ \rightarrow \downarrow 1 α hydroxylase \rightarrow \downarrow 1,25D₃ \rightarrow \downarrow Ca absorption
 - Treatment: phosphate binders. \downarrow Dietary intake may help but rarely sufficient alone. Parathyroidectomy curative

Potassium

- Normal value of K: 3.5 – 5 mmol/L
- Standard western diet contains ~ 70 mmol/day
- Shifts from ICF to ECF in response to:
 - Insulin deficiency
 - β -blockers
 - Acidosis
 - Cell necrosis

- Excreted in the distal tubule (K and H swapped for Na) under the influence of aldosterone. High HCO₃ excretion also → ↑ K loss (eg alkalosis)
- Investigations:
 - H⁺
 - HCO₃⁻: usually ↑ when K ↓ and visa-versa except when there is acidosis (eg renal tubular necrosis, diarrhoea)
 - Creatinine
 - Urinary K: > 20 mmol/L ⇒ renal K loss
 - Na: ↓ in hyperkalaemia, consider renal tubule disorder, ↓mineralocorticoid
 - Glucose
 - ECG (if widened QRS complexes give Ca)
- Key differentials: Diabetic ketoacidosis, renal failure

Hyperkalaemia

- Causes:
 - Usually ↓ renal excretion
 - Shift from ICF (eg acidosis, massive cell lysis)
 - Low aldosterone: *ACE inhibitors* (instead use spironolactone), ↓renin (renal disease, NSAIDs, diabetes), poor adrenal function (eg Addison's)
 - Renal unresponsive to aldosterone: interstitial nephritis, K sparing diuretics
 - Renal failure: hyperkalaemia once GFR < 25 ml/min
- Signs: myocardial depression, peaked T wave, flat P wave, wide QRS, VF, diarrhoea, abdominal pain, muscle excitability
- Treatment:
 - If severe (> 6.5 mmol/L) consider:
 - Glucose 50 g + soluble insulin 10 U over 15 mins
 - IV calcium gluconate – stabilises myocytes but doesn't change K
 - β₂ agonist (salbutamol)
 - Dialysis if extreme
 - If moderate (5.5 – 6.5 mmol/L): Calcium resonium 15 g po (calcium binding resins), ↑renal loss through diuretics, mineralocorticoids

Hypokalaemia

- Causes:
 - GI losses (ECF volume contraction):
 - Vomiting, NG suction → alkalosis → ↑HCO₃ in urine and ↑aldosterone → renal loss of K
 - Diarrhoea: → K loss and metabolic acidosis
 - Urinary losses:
 - Diuretics: thiazides or loop
 - Alkalosis (also shift to ICF if significant alkalosis)
 - ECF normal or high: high aldosterone or hypermineralocorticoid (eg Cushing's)
 - K shift into cells: metabolic alkalosis, insulin, β-adrenergics
 - ↓Intake (starvation, surgery)
- Symptoms:
 - Muscle weakness, cramps
 - GI: constipation, ileus
 - Polyuria, nocturia
 - Urine – if ↑ volume then diuretics or osmotic diuresis, if not consider aldosterone action
- Signs: arrhythmias, PR prolonged, inverted T waves, U waves, VF, GI ileus, muscle weakness, hypotonicity, digoxin toxicity, alkalosis
- Treatment: May have large total body deficit (eg DKA). Replacement KCl up to 40 mmol/hour

Magnesium

- Stored 65% in bone, 35% in cells
- Concentration generally follows Ca and K
- Excess:
 - Usually in renal failure ⇒ treat renal failure not magnesium
 - Symptoms: neuromuscular depression → ↓BP → CNS depression
- Deficiency:

- Causes: severe diarrhoea, ketoacidosis, alcohol, TPN, with ↓Ca or ↓K (especially diuretics)
- Symptoms: tetany (same as ↓Ca, ↓K gives weakness), fits, arrhythmia
- Treatment: Mg salts either po or iv

- For Renovascular disease, see page 21

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Measurement of Renal Function

- Anatomy:
 - Efferent vessel of the glomeruli supplies the proximal tubule, loop of Henle, and the distal convoluted tubule
 - Glomeruli filter ~ 180 litres/day
 - If the proximal tubule is non-functional, it signals the afferent to close off → ↓filtration → stops dehydration

Urinalysis

- **Dipstick:**
 - Blood: indicates bleeding in the urinary tract or free haemoglobin or myoglobin
 - Proteinuria:
 - Dipstick tests for albumin
 - Transient proteinuria can be caused by fever, exercise, obesity, sleep apnoea, emotional stress and CHF
 - Hyaline and granular casts and Bence Jones Proteins and Igs **don't** test +ive for protein
 - Glucose: diabetes, pregnancy, sepsis, tubular damage or low renal threshold
- **Microscopy:**
 - Blood: should be less than 8×10^6 cells per litre
 - Normal morphology: bleeding from the lower urinary tract: calculi, infection, neoplasia, BPH, papillary necrosis, renal stones, cystic kidney disease
 - Dysmorphic cells: glomerular bleeding: glomerulonephritis and vasculitis (including endocarditis), interstitial disease and diabetic renal disease (ie non-specific)
 - Microhaematuria can be either nephrotic or nephritic. Macro haematuria is normally nephritic
 - WBCs indicate infection, less commonly renal tuberculosis, renal stones and papillary necrosis
 - Eosinophils > 5% urine leukocytes ⇒ interstitial nephritis (usually drug induced)
 - Casts:
 - Hyaline casts: just protein, acellular and may be normal (especially concentrated urine) or pre-renal ARF– aka “benign” or “inactive”.
 - Granular casts: Degenerative cellular material – usually tubular cells ⇒ usually ATN (but not present in 20 – 30%). Muddy brown. Usually in association with mild proteinuria < 1 g/d (impaired reabsorption. > 1 g/d ⇒ glomerular injury or myeloma light chains)
 - Red cell casts: glomerular bleeding → usually active GN (probably the *most specific urine test for glomerulonephritis*), otherwise tubulointerstitial nephritis
 - White cell casts: pyelonephritis, interstitial nephritis or glomerulonephritis
- Proteinuria:
 - Damage via hyperfiltration, tubular toxicity from resorbing certain proteins (?Fe containing), ↑tubular work, mesangial toxicity
 - Thought to be ↓ by ↓ intraglomerular pressure – hence ACEI
 - Albuminuria:
 - 24 hour urine is “gold standard” – but imprecise due to patient compliance
 - Albumin to creatinine ratio in the morning correlates reasonably well – *best screening test*. Normalises to creatinine to compensate for hydration, allowing for variations in concentration

Imaging

- Ultrasound: useful. Good for obstruction. Check for presence of two kidneys, size, can rule out masses and obstruction. It takes time for kidneys to shrink in renal failure, so small kidneys = longstanding disease (except early diabetic nephropathy, amyloidosis and HIV where kidney's may be enlarged). Can check for reflux nephropathy – but if kidney's small repair does not improve renal function
- CT: preferred modality for flank pain and possible urolithiasis

Indices

- Age related decline of ~ 1 mL/min per 1.73 m² per year. Many “normal” people > 90 have a GFR < 60 ml/min
- Risks for progression:
 - GFR < 90 is the best predictor of development of renal failure (better predictor than age, smoking, HTN, obesity..). If it's bad now, it is more likely to get worse
 - Proteinuria is also strongly predictive in both diabetics and non-diabetics

- Cr:
 - Is both secreted and filtered
 - Useful for measuring *changing* GFR, but is a poor predictor of GFR itself
 - Normal range has not been validated in NZ ethnic groups and may include up to 25% of individuals with a GFR < 60
 - Absorbed in proximal tubule, so for low Cr reabsorption may mask ↓GFR. This is saturated by about Cr of 150 μmol/L, so above this an ↑ in Cr reflects ↑GFR
 - Some drugs interfere with measurement (eg cephalosporins), trimethoprim (and others) can impair tubular secretion
 - Muscle wasting → ↓ Cr → overestimation of the GFR
- GFR:
 - Varies with muscle mass and ingested cooked meat protein
 - Estimated from Modification of Diet in Renal Disease Study (MDRD):
 - $GFR (ml/min \text{ per } 1.73 \text{ m}^2) = 1.86 * PCrE - 1.154 * AgeE - 0.203$ (ie no weight adjustment)
 - Better the CG equation in renal impairment, neither is brilliant in near normal renal function – above GFR 60 +/- 30%, above GFR 100 +/- 100%
 - Not validated in children, pregnancy or age > 70, ethnic groups (there is an adjustment for Afro-American)
 - Cockcroft Gault equation: (ml/min): needs to be based on lean body weight
 - Urine Output. Causes of ↓: shock, bilateral urinary track obstruction, renal cortical necrosis, bilateral vascular occlusion (dissecting aneurysm or TTP/HUS)
 - Under investigation as biomarkers of ARF: Serum Cystatin C, Urinary IL 18, others...

Salt and Water Handling

Sodium Handling

- Overall:
 - Daily 25,000 mmol of Na is filtered, only 150 mmol is excreted
 - Requires lots of energy
 - Kidney's take 25% of cardiac output
- Proximal tubule:
 - 60 – 65% of Na reabsorbed
 - Minimal hormonal influence – relatively fixed
 - Site of HCO₃, Cl, amino acid, glucose and solute absorption
 - Cl, amino acid, glucose and solute absorption dependent on Na, which in turn is driven by Na-K ATPase on the capillary membrane (ie pumps 3 Na ions out, 2 K ions in, creates intracellular gradient for Na compared with lumen)
 - HCO₃ absorption dependant on luminal and intracellular carbonic anhydrase – site of action of carbonic anhydrase inhibitors (eg *acetazolamide* – not powerful diuretics)
 - Lithium absorption follows Na – so if dry then ↑ reabsorption → toxicity
- Loop of Henle:
 - 25 – 30% of Na resorption
 - Water absorbed from the *thin* descending loop, *thick* ascending limb is impermeable to water, only Na absorbed via Na/K/2CL co-transporter (inhibited by *Furosemide* – also ↑Ca and Mg losses, co-transporter also found in ear → ototoxicity)
- Distal tubule:
 - Reabsorbs 5% of total NaCl via Na-Cl co-transporter (thiazide sensitive channel) – independent of aldosterone
 - Ca reabsorption, ↑ by PTH. Blocking the *thiazide* sensitive channel also ↑Ca reabsorption (prevent renal calculi)
- Cortical collecting duct:
 - 2 cell types responsible for fine tuning of net salt balance under direct control of renin-angiotensin system:
 - Principle cells: Na and K channels (also have ADH dependent H₂O channels)
 - Intercalated cells: pH balance
 - Na reabsorbed and creates a electronegative lumen which promotes K and H excretion
 - Aldosterone → ↑ number of Na channels and ↑ activity of Na-K-ATPase pumps → ↑Na reabsorption and ↑K excretion

- Diuretics:
 - *Amiloride* (and high dose trimethoprim): close luminal Na channels directly → ↑K (also inhibits Li entry into cells)
 - *Spironolactone* and Eplerenone (less anti-testosterone side effects): Competitively antagonises intracellular aldosterone receptor
- Syndrome of Apparent Mineralocorticoid Excess (SAME):
 - HTN, ↓K, metabolic acidosis, ↓renin and ↓aldosterone
 - Mineralocorticoid receptor is activated by cortisol
 - Cortisol → cortisone by 11β-hydroxysteroid dehydrogenase (11βHSD) in the principle cell. Cortisone can't act on the receptor. So if no enzyme, or it is overwhelmed, then ↑cortisol → ↑mineralocorticoid effect
 - Liquorice inhibits 11βHSD. Adrenal deficiencies of 17α-hydroxylase, 11β-hydroxylase and 21-hydroxylase ↑production of steroids → activate the mineralocorticoid receptor
- Hypokalaemic metabolic alkalosis:

Hypertension	↑renin, ↑aldosterone	Renovascular Renin Tumour Diuretics
	↓renin, ↑aldosterone	Primary Hyperaldosteronism
	↓renin, ↓aldosterone	Liddle's SAME Liquorice Anything that ↑cortisol
No Hypertension	Urinary chloride low (<20)	Vomiting, diuretics
	Urinary chloride N (>40)	Bartter's and Gitelman's (can't reabsorb Cl) Diuretics

- See also Renin-Aldosterone System, page 20, and Primary Aldosteronism, page 73

Syndromes

Bartter's Syndrome

- AR genetic defect in salt transport in thick ascending loop → *similar effect to continue loop diuretics*
- Neonates with profound ↓K, polyuria, ↓concentrating ability, hypotension, alkalosis, *hypercalciuria* (cf Gitelman's) +/- hypomagnesaemia
- Activation of RAA system to stop Na loss → excretion of K
- Rare variant associated with deafness

Gitelman's Syndrome

- Mutations of the thiazide sensitive Na-Cl co-transporter in the distal tubule → *like continuous thiazide diuretics*
- More benign than Bartter's – presents later
- Normal renal function, normal concentrating ability, low Cl, alkalosis, ↓K, ↓Mg, *hypocalciuria*, ↑aldosterone

Liddle's Syndrome

- Rare, AD
- Abnormal collecting tubule Na channel results in ↑Na reabsorption → HTN, ↓K
- Family Hx of early HTN. Hypokalaemic metabolic alkalosis, ↓aldosterone. Presentation similar to apparent mineralocorticoid excess
- Treat with amiloride – closes channel directly. Not spironolactone – doesn't act on the problem

Fanconi Syndrome

- Damage to proximal tubular reabsorption of glucose, amino acids, phosphate, bicarbonate and urate. Causes (amongst other things) a type 2 renal tubular acidosis
- Causes:
 - Familial: AD, AR, X linked. Part of other inherited conditions (eg **Wilson's**)
 - Acquired: **multiple myeloma** (toxic effect of proteins), amyloidosis, heavy metal toxicity, chemotherapy, hyperparathyroidism, post-transplant rejection
- Effects:
 - Renal tubular acidosis type 2 (proximal)

- Glucosuria despite normal serum glucose
- Proteinuria and aminoaciduria
- Salt wasting and polyuria
- Hypophosphataemia causing rickets and osteomalacia. Calcitriol may be low
- Hypouricaemia and hypokalaemia
- Treatment: phosphate and calcitriol supplements, alkali for RTA, liberal salt and water intake

Various

- Mineralocorticoid excess: ↓K and metabolic alkalosis, directly stimulates H secretion
- Mineralocorticoid deficiency: ↓serum Na with hypovolaemia and urine Na > 20, especially if ↑K
- Liquorice: active ingredient is glycyrrhetic acid. Inhibits renal 11βOH steroid dehydrogenase → allows mineralocorticoid effects of glucocorticoids
- Surreptitious vomiting: ↓HCL, hypovolaemia, ↓↓ urine Cl, urine Na not as low as usual because of obligate loss, ↓K due to 2ndary hyperaldosteronism
- Cerebral Salt Wasting: Any cerebral irritation (especially SAH) → ↑ADH. May be important not to fluid restrict if SAH given risk of vasospasm

Water Handling

- See also Vasopressin, page 69
- Normal urine osmolality 50 – 1200 mosmol/L, mainly determined by urea concentration
- Principles:
 - Osmo-regulation is sensed in the hypothalamus, using ADH and thirst to control water intake and excretion
 - Volume regulation is monitoring tissue perfusion, sensing this in the glomerula, carotid sinus and atria, and using the RAA system and ANP to alter urine sodium
- Salt and Water balance:
 - Oedema = too much salt. Normal response → ↑ Na excretion ⇒ ↑ urinary Na (> 20 mmol)
 - Volume depletion = too little salt. Normal response → ↑Na retention ⇒ urinary Na < 20
 - Hyponatraemia = too much water. So ↓ADH → ↑water excretion ⇒ low urine osmolality (< 100)
 - Hypernatraemia = too little water. So ↑ADH and thirst ⇒ high urine osmolality (> 100)
- ADH receptor (V2 Receptor) found on the basolateral side of the principal cell
- Actions of ADH:
 - ↑aquaporin 2 (AQP2) channels in the cortical and medullary collecting ducts
 - ↑activity of the Na/K/2Cl co-transporter in the thick ascending limb
 - Thirst

Hyponatraemia

Key Points

- Hyponatraemia is not a diagnosis – it is found in diverse conditions. Body Na may be low, normal or high. Relative water retention is a common factor
- Treatment must be slow and monitored closely. Treatment can range from water restriction or diuresis to sodium restriction or normal saline. Need to know underlying cause
- Don't use hypotonic fluids post-op unless Na is high. Eg dextrose saline – glucose absorbed very quickly post surgery → hypotonic

Symptoms

- The big boogie is underlying cerebral oedema. Bigger problem if abrupt onset. Rapid correction can cause central pontine melanosis. Greater risk in pre-menopausal females, liver disease and malnourished. Delayed presentation (1 – 7 days) ?apoptosis
- Symptoms don't correlate well with [Na]
- Early: anorexia, headache, nausea, vomiting, muscle cramps, weakness
- Advanced: mutism, dysarthria, impaired response to verbal or painful stimuli, bizarre behaviour, hallucinations, asterixis (ie Liver flap – but not due to liver), incontinence, respiratory insufficiency, spastic quadriparesis in 90%
- Far advanced: (too late to do much) decorticate or decerebrate posturing, bradycardia, hypo or hypertension, dilated pupils, seizures, respiratory arrest, coma, polyuria (central diabetes insipidous)
- Should always be a differential in post-operative coma

Aetiology

- Either Na depletion or water gain (usually water gain)
- Inappropriate water retention: eg drugs (most common – eg antiepileptics), ↑ADH, kidney or thyroid problems
- May be borderline hyponatraemic before (eg long term use of diuretics)
- Normal ADH will ↑ if ↑osmolality or ↓blood volume
- Operative stress or serious illness → syndrome of inappropriate ADH (in most people) → water retention (especially in women, smaller starting fluid volume). NB it's not really inappropriate – the body is making a justifiable physiological response: I'm stressed so conserve water rather than throwing it out
- Ageing impairs fluid homeostasis → wider swings happen easily
- Worse symptoms for the same level of Na in premenopausal women due to an oestrogen effect
- Exercise induced hyponatraemia (eg marathon runners): effectively consumption of hypotonic fluid with NaCl sweat loss. Vomiting a distinguishing feature. Hypovolaemia in 6 – 30% of “collapsed athletes”

Assessment

- History: fluid losses, *diuretics*, other medications
- Clinical findings: pulse, blood pressure, volume assessment, oedema, thirst, skin, input/output
- Laboratory:
 - Creatinine, urea, glucose, HCO₃, K, plasma osmolality, urine Na and Osmolarity
 - Severe hyponatraemia is < 125 mmol/l: nausea, malaise, headache
 - < 115 mmol/l: convulsions
- Look for:
 - 1: Low Na
 - 2: ↓ serum osmolality. If:
 - Low then true hyponatraemia
 - Not then false hyponatraemia:
 - If plasma osmolality is high then measure glucose. Hyperglycaemia → shift of water out of muscle cells: Na ↓ 1 mmol/L for every 4 mmol/L ↑ in glucose
 - If osmolality is normal then pseudo-hyponatraemia (eg hyperlipidaemia, hyperproteinaemia eg ↑urea). An artefact: Na has been incorrectly measured in plasma volume rather than plasma water
 - 3: Urine osmolality higher than expected (>200 and usually > serum osmolality). If Urinary osmol < 100 then this is appropriate – they've got too much water and are trying to lose it ⇒ primary polydipsia
 - 4: Urinary sodium higher than expected (> 30). If < 15 then volume depletion. If > 40 then normovolaemia and SIADH or other renal salt wasting
 - Normal pituitary, adrenal, cardiac, and renal function
- Clinically useful grouping (⇒ volume assessment critical):
 - Hyponatraemia with oedema: heart failure + diuretic, cirrhosis, nephrosis (impairment of water loss via increased ADH +/- Na loss) – ↑NaCl, ↑↑water
 - Hyponatraemia with dehydration:
 - Urine [Na] > 20 mmol/l: Diuretics, Addison's Disease, salt losing nephritis
 - Urine [Na] < 20 mmol/l: Vomiting, diarrhoea, skin loss
 - Usually rehydrate slowly with normal saline
 - Hyponatraemia with euvoemia and reduced plasma osmolality:
 - Urine [Na] > 20 mmol/l: Chronic water overload eg primary polydipsia, chronic SIADH:
 - CNS disorders
 - Malignancy: especially SCLC, pancreas, kidney, lymphoma
 - Drugs: SSRIs (especially in elderly), carbamazepine, bromocriptine, thiazides
 - Adrenal insufficiency
 - Hypothyroidism
 - Urine [Na] < 20 mmol/l: Acute water overload – conserving more water than they should = SIADH
 - Pulmonary infections
 - Oxytocin for induced labour, etc
 - Treat with fluid restriction < 1000 ml/day, and treat underlying cause

Treatment of hyponatraemia

- Acute hyponatraemia:
 - Principles:
 - Base treatment on the symptoms not the sodium
 - Raise the sodium at a safe rate
 - Treat the cause
 - Basic regimes:
 - If *volume depleted* (Renal/GI losses, diuretics, adrenal insufficiency): saline isotonic to the patient or normal saline. Extra Na will have a small effect but \uparrow volume \rightarrow \downarrow ADH \rightarrow excess water excreted \rightarrow rapid correction
 - *Normovolaemic or oedematous* (SIADH, renal failure, polydypsia, oedema): Water restriction
 - If severe symptoms or if sodium < 110 then ?hypertonic saline. *Giving normal saline with ADH \rightarrow excretion of the Na as can maximally concentrate urine but retention of the water \rightarrow giving a free water load.* \uparrow Na by no more than 12 mmol per 24 hours: keep rate smooth. Key judgement is speed of infusion. No front loading. Animal studies show correction by > 14 /mmol/24 hours \rightarrow lesions in 71% of dogs. If no symptoms – maybe go slower
 - Monitor 2 hourly. Manage in high dependency unit. Detect and treat hypoxia
 - Adverse neurological consequences of rapid correction: myelin breakdown in the pons, patchy symmetrical lesions elsewhere in the brain. But risk of not treating acute cerebral oedema far exceeds the small risk of osmotic demyelination
 - Maybe frusemide to \uparrow free water excretion
 - Chronic hyponatraemia:
 - Range 120 – 130 mmol/L
 - ??impaired long term cognitive function and \uparrow risk of falls
 - SALT 1 and SALT 2 trials – may improve neuro-cognition when Na raised to > 130 mmol/L
 - ??Role of vasopressin receptor blockers

Dehydration or Volume Depletion

- Dehydration:
 - Often used loosely to describe a volume depleted patient
 - Correctly it refers to \downarrow intracellular water, following fluid shifts from ICF to ECF
 - Water is lost (either as pure water or as hypotonic fluid) \rightarrow \uparrow osmolality and thirst
 - Treatment is water replacement (dextrose)
- Volume depletion:
 - Losses from the ECF (isotonic sodium) \rightarrow \downarrow circulating volume
 - \downarrow BP, \uparrow tachycardia, \downarrow tissue turgor
 - Treatment is replacement of NaCl
- Dehydration and volume depletion can co-exist

Vaptans

- New class of drug targeting the three arginine-vasopressin receptor subtypes:
 - V1a receptor antagonist: Relcovaptan – initial positive results in the treatment of Raynaud's disease, dysmenorrhoea, and tocolysis
 - V1b receptor antagonist: SSR-149415 being assessed for psych disorders
 - V2 receptor antagonists: \rightarrow Highly hypotonic diuresis without effecting electrolytes (cf diuretics). Effective in euvolaemic hyponatraemia (licensed indication)
 - Conivaptan: V1a/V2 non-selective antagonists approved by the FDA for IV treatment of hyponatraemia
- Don't inhibit the thirst of ADH
- Potential uses:
 - Cardiac failure: EVERST Trial – no effect on long term mortality, \uparrow short term loss of weight, \uparrow Na – currently not recommended
 - Cirrhosis: potential risk of variceal bleeding with V1a. ?benefit from V2R
 - Polycystic Kidney Disease. ?Inhibit V2 \rightarrow small cysts. Phase 3 trials underway
 - Benefit in some forms of x-linked nephrogenic diabetes insipidous – normal ADH but dud V2 receptor (some forms have loss of function of aquaporin – has no effect on this)

Hypernatraemia

- Indicates ICF volume contraction
- Usually **not** due to \uparrow total body sodium – total sodium is low, normal or high. Kidney is good at excreting excess Na (except if swamped – eg near drowning)
- Always means the patient is hyperosmolar
- Thirst and \uparrow ADH protect against hyperosmolality \Rightarrow don't see hypernatraemia where the thirst mechanism is normal and there is access to water
- Cellular dehydration \rightarrow neurologic symptoms: lethargy, weakness, irritability, seizures, etc. Cerebral oedema if it is rapidly corrected
- Classification:
 - Water and sodium deficiency with water loss $>$ sodium loss (ie lost hypotonic fluid), eg vomit, diarrhoea, sweat, osmotic diuresis (urine osmolarity not low), burns
 - With normal total body sodium (pure water depletion): unable to drink (old, babies, sick, etc), central or nephrogenic diabetes insipidus
 - With increased total body sodium: excess iv hypertonic saline, ingestion of sea water, mineralocorticoid excess (low sodium output) (\Rightarrow expanded ECF)
- Treatment:
 - Chronic: may be asymptomatic even at 170 – 180 mmol/l due to adaptation by brain \Rightarrow gradual correction
 - If water deficit then:
 - Stop the water loss: give ADH, prevent osmotic diuresis, etc
 - SLOWLY give oral water or iv dextrose (Watch for hyperglycaemia, rate \sim 300 ml/hr. Add sodium if history suggests loss of sodium containing fluid and patient is not polyuric)
 - Aim for Na reduction of 1 mmol/L/hr and no more than 12 mmol/24 hours
 - If \uparrow Na: diuretics and give free water
 - Oral replacement is best if feasible

Acid-Base balance

Acid Base Physiology

- Metabolism produces two acids:
 - Volatile: carbonic
 - Non-volatile: eg lactic
 - Produce approx 50 – 100 meq H ions daily
- Kidney uses four mechanisms to “mop up” the excess acid produced by the body:
 - Proton excretion in the proximal tubule and collecting duct (via H^+ ATPase in the intercalated cells)
 - Reabsorbing (technically regenerating) the pool of HCO_3^- via the carbonic anhydrase reaction:
 - $H_2O + CO_2 \rightarrow HCO_3^- + H^+$: H^+ lost in urine, HCO_3^- reabsorbed in the blood
 - 85% in the proximal tubule, 10% in the thick ascending loop
 - But can only acidify urine so much, and that's not enough
 - Buffers which bind H^+ in the urine, allowing further generation/secretion of H^+ without lowering pH
 - Ammonium: Glutamine \rightarrow 2 NH_3 (into the lumen) + 2 HCO_3^- + glucose (into the plasma) in the proximal tubule. Binds with H^+ \rightarrow NH_4^+ (but only if urine is sufficiently acidic to start with). Process stimulated by acidosis
 - Phosphate (not a major contributor): $H^+ + HPO_4^{2-} \rightarrow H_2PO_4^-$
- Lowest possible urine pH is \sim 4.5
- In renal impairment:
 - Gradual loss of H pumps with progressive loss of nephrons
 - Once GRF $<$ 25 L/min organic acids accumulate
 - If kidney buffering is insufficient, buffers from bone are used ($CaPO_4$ and $CaHCO_3$)
- CO_3 Buffer systems:
 - $H^+ + HCO_3^- \leftrightarrow H_2CO_3$ ($H_2O + CO_2$)
 - Henderson Hasselbach Equation:

$$\text{pH} = 6.1(\text{pKa}) + \log \frac{[\text{HCO}_3]}{0.03 * [\text{PCO}_2]}, \text{ or}$$

$$\text{pH} = 6.1(\text{pKa}) + \log \frac{\text{Kidney Production of HCO}_3}{\text{Respiratory Regulation of CO}_2}$$

- Normal range for pH is 7.35 – 7.45 (= 45 – 35 nmol/L of H⁺ ion)
- Range of pH compatible with life is about 6.8 – 7.8 = H⁺ concentration of 160 – 16 nmol/l
- Lots of other buffering systems
- Compensation:
 - Never complete
 - Respiratory: pH measured in the brain medulla. Compensates rapidly
 - Renal:
 - Alter bicarbonate reabsorption
 - Titratable acid excretion: organic buffers in tubules acidifies urine. Excretes 30 – 50% of acid produced each day
 - NH₄ excretion: formed in tubules, ↑ takes days. Excretes 50 – 70% of acid

Anion Gap

- Anions = negative charge, cation = positive charge
- Anion Gap
 - AG = Na + K – (Cl + HCO₃) – Usually 8 – 16 milliequivalent/l (measure of charge)
 - Alternatively, AG = Na – (Cl + HCO₃) – normal range 10 – 14
 - Unmeasured anions include anionic proteins (esp albumin), phosphate, sulfate, and organic anions (eg acetoacetate and lactate)
 - ↑ AG usually due to ↑ in unmeasured anions, not a ↓ in unmeasured cations
 - **High Anion Gap:**
 - Ketoacidosis: Diabetic, starvation, alcoholic (on withdrawal against a background of poor nutrition, with vomiting and volume depletion. With fluid hydration, preferential accumulation of β-hydroxybutyrate shifts to acetoacetate. Dipsticks for ketones measure the later – nitroprusside reaction – so dipsticks can show more ketones as the patient actually improves)
 - Lactic acidosis:
 - Poor tissue perfusion (type A): circulatory insufficiency (shock, cardiac failure), severe anaemia, carbon monoxide
 - Aerobic disorders (type B): Malignancies, NRTI, DM, renal or hepatic failure, severe infections, seizures, drugs/toxins
 - Renal failure (acute and chronic): Hyperchloraemic acidosis of moderate renal insufficiency → high-AG acidosis of advanced renal failure due to reduction in nephrons → can't keep pace with net acid production with NH₄ production
 - Poisoning: salicylate, methanol, ethanol, ethylene glycol (check urine for oxalate crystals)
 - **Normal anion Gap:**
 - GI or GI loss of HCO₃: Diarrhoea, drugs (eg Cholestyramine)
 - Renal acidosis:
 - With ↓K: Renal Tubular Acidosis types 1 and 2
 - With ↑K: Renal Tubular Acidosis type 4 (including chronic renal insufficiency)
 - Drug induced ↑K with renal insufficiency: *K-sparing diuretics, Trimethoprim, ACEI, ARBs, NSAIDS, cyclosporine and Tacrolimus*
 - Other:
 - Acid loads: ingestion of HCl or NH₄Cl eg elementary feeds
 - Expansion acidosis (rapid saline administration)
 - Li intoxication (a cation)
 - ↓albumin in nephrotic syndrome
 - Hyperviscosity or severe hyperlipidaemia which → underestimation of Na and Cl
 - Practical use limited – cause of metabolic acidosis obvious from history and observation
 - Most labs have deleted it from electrolyte profile

- Cl normally tracks Na except in metabolic acidosis. Eg severe vomiting: ↓HCl (→ hypochloreaemic metabolic alkalosis) and volume depletion (→ kidney retains Na → generation of HCO₃ and K depletion). Correction of alkalosis requires correction of volume, chloride and K

Respiratory Alkalosis

- Hyperventilation. Causes:
 - Hypoxia
 - Lung disease: PE, asthma
 - Anxiety
 - Fever, sepsis
 - Salicylate overdose: stimulates respiration, will subsequently develop metabolic acidosis
- ↓PaCO₂, ↑pH, initial alterations in [HCO₃] are minimal, if it persists then kidneys compensate

Respiratory Acidosis

- Hypoventilation. Causes:
 - PCO₂ excretion lags production – eg severe asthma (initially asthmatics hyperventilate)
 - Pulmonary disease, muscular diseases, etc
 - CNS depression: primary or drugs/toxins
 - Asphyxia, smoke inhalation
- As PCO₂↑ then CO₂ + H₂O → H⁺ + HCO₃⁻
- ↑PaCO₂ → ↓pH, initial alterations in [HCO₃] are minimal, if it persists then kidneys compensate (↑HCO₃ reabsorption, ↑NH₃ formation and excretion)

Metabolic acidosis

- Net gain of acid. Causes:
 - Accumulation of acid (anion gap > 18 mmol/L): ↑H⁺ (ketoacidosis, lactic acidosis, ingestion of salicylates, methanol), renal failure (failure to excrete H⁺)
 - ↓HCO₃ (anion gap < 18 mmol): GI tract loss (eg diarrhoea), renal loss (eg ↓carbonic anhydrase), hypoaldosteronism
- K sparing diuretics: reduced Na resorption means lumen is less electronegative, reducing K & H excretion

Metabolic alkalosis

- Net loss of acid. Causes:
 - Loss of H⁺:
 - Vomiting (suspect surreptitious if low Cl)
 - NG suction
 - Renal loss (hyperaldosteronism)
 - Increase in HCO₃ reabsorption:
 - K depletion (Conn's, Cushing's, drugs, diuretics).
 - Volume depletion, eg ↑Aldosteronism → ↑Na/H exchange
 - Gain in alkali: eg NaHCO₃ administration
- Loop and thiazide diuretics: ↓ECF → ↑aldosterone + high distal flow rates and Na delivery → K reabsorption and H loss

Summary of compensation rules

		Change in HCO ₃ per 10 CO ₂	
		Acute	Chronic
	CO ₂		
Acidosis	↑	↑1	↑ further 2.5 (total 3.5)
Alkalosis	↓	↓2	↓ further 3 (total 5)
		Change in PCO ₂ for each HCO ₃	
Alkalosis	↑	↑0.6	
Acidosis	↓	↓1.2	

Mixed Acid/Base disorders

- Suspect if:
 - Clinical grounds
 - Compensation rules not obeyed
 - Normal pH but abnormal PCO₂ and HCO₃
- Examples:
 - Respiratory + Metabolic Acidosis: Pulmonary oedema + cardiac arrest
 - Respiratory + Metabolic Alkalosis: Over-ventilation + Nasogastric suction
 - Respiratory Alkalosis + Metabolic Acidosis: Septic shock or Salicylate OD
 - Respiratory Acidosis + Metabolic Alkalosis: CORD + Diuretic
 - Metabolic Acidosis + Metabolic Alkalosis: Renal failure + vomiting

Interpreting Blood Gas Results

- Look at PCO₂. If < 36 then hyperventilation. If > 44 then hypoventilation.
- Look at HCO₃. If < 22 then metabolic acidosis. If > 26 then metabolic alkalosis. But HCO₃ depends on PCO₂. So (to work out if its just compensation, or there is a metabolic problem as well as a respiratory one):
 - For acute changes (hours): a fall in PaCO₂ → a normal HCO₃ 2 less for every 10 mmHg ↓ in PaCO₂. A rise in PaCO₂ → normal HCO₃ 1 greater for every 10 mmHg ↑ in PaCO₂
 - For chronic changes (days): a rise in PaCO₂ results in a normal HCO₃ 4 greater for every 10 change in PaCO₂

Base Excess

- Given on all arterial blood gas results
- = Concentration of titratable base when titrating blood or plasma with a strong acid or base to a plasma pH of 7.40 at PCO₂ of 40 mmHg at 37C
- Intent is to remove the impact of the respiratory component leaving just the metabolic component:
 - If +ive: metabolic alkalosis → deficit of non-carbonic acid
 - If -ive: metabolic acidosis → excess of non-carbonic acid
- BUT recognises normal compensation as an extra disturbance. May be useful for an anaesthetist (eg simple and acute disturbances)

Acute Renal Failure

- = Rapid decline in GRF → ↑plasma and urea and (usually) ↓urine volume, acidosis and ↑K common
- If both kidneys were removed, Cr would rise by ~ 200/day – ie rises slowly
- RIFLE Criteria:
 - Risk: Cr ↑ 1.5 times baseline levels or UO < 0.5 ml/kg/hr for > 6 hrs
 - Injury: Cr ↑ 2.0 times baseline or UO < 0.5 ml for 12 hrs
 - Failure: Cr ↑ 3.0 times baseline (or Cr = 355 when there was an acute rise of > 44) or UO < 0.3 ml/kg/hr for > 24 hours of anuria > 12 hours
 - Loss: persistent loss of kidney function for > 4 weeks
- Indications for dialysis:
 - Refractory fluid overload
 - K > 7 mmol/l
 - Uraemic encephalopathy (usually > 45 mmol/L)
 - Resistant metabolic abnormalities (pH < 7.1, HCO₃ < 12 mmol/l)
 - Pericarditis
- Frusemide has no clinical benefit in the prevention and treatment of acute renal failure in adults, and high doses → ↑risk of ototoxicity (Meta-analysis reported in Ann Intern Med 2008 148:49). Has been used for improving fluid and electrolyte balance, and thought it may serve as an anti-ischaemic agent by inhibiting the energy-dependent Na-K-Cl pump in the medullary thick loop of Henle. This meta-analysis suggests not
- Acute renal failure patients have a much higher mortality for the same degree of renal impairment as do chronic renal failure

Pre-renal Failure

- 2nd to hypovolaemia or hypoperfusion
- Renal parenchyma may not be damaged initially, may → ischaemic injury (ATN)

- Mild hypoperfusion:
 - Compensatory afferent arteriolar vasodilation (a local myogenic reflex – autoregulation)
 - Angiotensin II → ↑prostaglandin E2 and prostacyclin → afferent arteriolar vasodilation
 - Angiotensin II → efferent vasoconstriction
- With ↑ hypoperfusion, these compensatory mechanisms are overwhelmed
- Drugs can also tip the balance: NSAIDs, ACEI and ARBs
- In bilateral renal artery stenosis or unilateral stenosis in a solitary functioning kidney, perfusion may be exquisitely dependent on angiotensin II → acute problems with ACEI or ARBs
- Hepato-renal syndrome: See page 371

Intrinsic Renal Failure

- Usually complicated by metabolic acidosis with ↑anion gap
- No proven benefit from a variety of treatments (ANP, dopamine, loop diuretics, CCB, antioxidants....)
- Diseases of large renal vessels: Renal artery thrombosis, atheroembolic disease (livedo reticularis and “trash toes”, renal vein thrombosis)
- Diseases of small vessels and glomeruli:
 - Glomerulonephritis (see page 124)
 - Thrombotic Microangiopathy (see page 131)
- Ischaemic Acute Tubular Necrosis:
 - Initiation phase: Reduced GRF 2nd to ↓renal blood flow → ↓ glomerular filtration, and tubular obstruction 2nd to casts of epithelial cells and necrotic debris. Most prominent in S3 segment of proximal tubule and the medullary portion of the thick ascending limb – sensitive because of high rates of ATP dependent transport, and low partial pressure of O₂ in outer medulla
 - Extension phase: Ischaemic injury and inflammation
 - Maintenance phase (1 – 2 weeks): GFR bottoms out, maybe uraemic complications
 - Recovery phase: regeneration and diuresis
- Pathology: patchy and focal necrosis of tubular epithelium and occlusion with casts. Glomeruli and renal vasculature normal
- Nephrotoxic ARF:
 - Pathology: Less pronounced cellular necrosis, morphologic changes in convoluted and straight portions of proximal tubule
 - Causing *intrarenal vasoconstriction* → ↓GFR, benign urinary sediment and low fractional excretion of sodium:
 - Radiocontrast: see page 511
 - Cyclosporin and Tacrolimus
 - Antibiotics and chemotherapy → *direct toxicity*. Eg aminoglycosides accumulate in proximal renal tubular epithelial cells → slowly rising toxicity→ oxidative stress. Cisplatin and carboplatin → ARF after 7 – 10 days of exposure
 - Amphotericin B → *vasoconstriction and direct toxicity* to proximal tubule
 - *Endogenous nephrotoxins*:
 - Ca, myoglobin from rhabdomyolysis (↑K, ↓Ca, ↑uric acid, ↑creatin kinase-MM isoenzyme), haemoglobin from haemolysis (eg recent blood transfusion reaction), urate, oxalate, myeloma light chains
 - Acute uric acid nephropathy after chemotherapy for lympho- or myelo-proliferative disorders: see page 386
 - Urate: net reabsorption in the proximal tubule – blocked by probenecid
 - Nephrotic Syndrome: Gold, NDAIS, penicillamine
- Disease of the tubulointerstitium:
 - Omeprazole
 - Allergic Interstitial Nephritis: Infiltration of the tubulointerstitium by granulocytes (typically but not invariably eosinophils), macrophages, lymphocytes and oedema. Usually NSAIDs or antibiotics (penicillins, cephalosporins, quinolones, sulphonamides, rifampin)
 - Acute bilateral bacteria pyelonephritis
- Other drug effects on the kidney:
 - Interfere with Cr secretion from tubules: cimetidine, trimethoprim
 - Interfere with lab assessment of Cr: Vit C, L-Dopa, Cefoxitin
 - NSAIDs: Inhibitors of PG synthesis:
 - Inhibiting PGE₂ → ↑Na retention, oedema, HTN
 - Inhibiting PGI₂ blocks vasodilation

- Cause of acute interstitial nephritis and nephrotic syndrome

Postrenal Renal Failure

- Commonly prostatic disease, neurogenic bladder, anticholinergic drugs
- Also blood clots, calculi, urethritis with spasm, sloughed renal papillae, infiltration of ureter or external compression

Investigations in Acute Renal Failure

	Pre-renal	ATN	RPGN	AIN
Urine Osmolality	>500	<350	300-400	300-400
Urine Na	<20	>40	20-40	20-40
Urine/Plasma urea	>10	<10	Intermediate	Intermediate
Urine/Plasma creatinine	>40	<20	Intermediate	Intermediate
Fractional excretion of Na	<1	>3	<1	>1
Urine Sediment				
RBC	Occasional	+	+++	Occasional
WBC	Occasional	Occasional	++	+++
Granular casts	Occasional	++	++	+
Epithelial casts		+++	++	
RBC casts			+++	
WBC casts				Occasional

- Fractional excretion of Na = $\frac{\text{Urine Na} * \text{Plasma Cr} * 100}{\text{Plasma Na} * \text{Urine Cr}}$
 - Relates Na clearance to creatinine clearance (which is not affected in either ATN or prerenal failure). In prerenal ARF, Na is avidly reabsorbed → low ratio (also in some forms of nephrotoxic ATN eg contrast, but not if diuretics, adrenal insufficiency...). High in ATN
- Management:
 - Treat cause: hypovolaemia, stop toxic drugs, etc
 - Acidosis: unable to maintain serum HCO₃ > 15 or arterial pH < 7.2. Usually means they're going to need emergency dialysis
 - HyperPO₄: dietary restriction (but maintain calories) or phosphate binding agents (eg Ca Carbonate)
 - Anaemia: transfuse – EPO is too slow and bone marrow resistance is common
 - Dialysis if uraemic, ?empirically if urea > 100 (but not validated in RCTs)
 - Low dose dopamine: does not help protect kidney's in ARF (Meta-analysis in Ann Int Med 2005;142:510)
 - ANP: no proven benefit
 - Diuretics: no proven benefit

Chronic Kidney Disease

- Chronic renal failure = Chronic Kidney Disease (CKD) stages 3 – 5
 - Stage 3: GRF 30 – 59
 - Stage 4: GFR 15 – 29
 - Stage 5: < 15 or on dialysis
- Up to a half due to diabetes, a quarter due to HTN and renovascular disease, the rest GN
- Much more likely to die from CVD than renal failure. CKD is a risk factor equivalent to diabetes
- If kidney's small on ultrasound, no point in biopsy: it's technically difficult, pathology will be difficult to determine due to fibrosis, and disease specific therapy is too late

Pathophysiology of Progressive Renal Disease

- Loss of one kidney → compensation in the other:
 - One kidney returns to GFR of 80% of both via process of compensatory renal hypertrophy – ↑size of each cell along a nephron, little cellular proliferation
 - Signalled via angiotensin II, transforming growth factor β and epidermal growth factor (EGF)
- After a certain loss of nephron mass, maladaptive deterioration → renal progression:
 - Hyperfiltration: ↑single-nephron glomerular filtration 2nd to loss of autoregulation – angiotensin II selectively increases efferent arteriolar vasoconstriction relative to afferent arteriole (transmits hypertension to the glomeruli)

- Increasing proteinuria → tubular damage → cytokines → ↑chemokines (eg TGFβ, platelet derived growth factor B and fibroblast growth factor 2 FGF-2) → tubular atrophy and tissue fibrosis (→ less sensitive to ADH)
- Progressive loss of capacity to dilute or concentrate urine – urine osmolality relatively fixed at around 350 mosmol/L → Nocturia, easily volume depletion if ↓oral intake, hypotonic if they drink too much
- Potassium:
 - Kidney excretes 90% of daily load. Colon can increase excretion from 10 to up to 30% if needed
 - ↑K → ↑aldosterone (not just in response to renin-angiotensin) → increased excretion of K from collecting duct
- Risk factors for progression:
 - HTN: activation of R-A-A system
 - Diabetes
 - Cigarette smoking accelerates nephron loss
 - Lipid oxidation in obesity or central adiposity → progressive renal damage
 - Low birth weight → relative deficit in the total number of nephrons → more HTN and renal failure as an adult
 - Lots of as yet unknown genetic factors

Chronic Renal Failure after Other Organ Transplant

- Within 5 years, CFR is < 30 ml/min in:
 - 18% of liver transplants
 - 15% of lung transplants
 - 10% of lung transplants
- Mainly due to calcineurin inhibitors + other comorbidities

Renal Osteodystrophy

- = All skeletal changes resulting from chronic renal disease, including:
 - ↑Osteoclast resorption (mimicking hyperPTH) → bone pain and fragility
 - Delayed matrix mineralisation (osteomalacia)
 - Osteosclerosis
 - Growth retardation
 - Osteoporosis
 - Dialysis related amyloid (Aβ₂M Amyloid), see page 273
 - Alternatively a risk of Adynamic Bone Disease – reduced bone mass from depression of PTH 2nd to Vitamin D supplements, Al toxicity and *excess calcium from calcium containing phosphate binders*. More common in diabetics
- Due to:
 - PO₄ retention → :
 - ↑PTH (Secondary HyperPTH) → ↑Osteoclast activity (including osteitis fibrosa cystica, see page 92) → ↑Ca and ↑tubular PO₄ excretion. May → tertiary hyperparathyroidism where PTH hypersecretion has become autonomous → ↑Ca
 - ↓Conversion of α₁-hydroxylase → ↓calcitriol and ↓Ca absorption from the gut and ↑PTH
 - So, serum PO₄ and Ca normalise (in the short term) but at the expense of bones and extra-osseous CaPO₄ deposition
 - As well as ↑PTH, the mass of parathyroid cells increases with diffuse (polyclonal) or nodular (monoclonal) hyperplasia – the later a risk for tertiary autonomous hyperPTH
 - Metabolic acidosis → bone reabsorption
 - Aluminium deposition (from antacids, dialysis fluid) at the site of mineralisation → ↓mineralisation
 - Uraemia and steroids → osteopenia
 - Similar impact to osteomalacia: ↑PTH → osteoclastic bone resorption
- Investigations:
 - X-ray and bone densitometry
 - Bloods: Ca, albumin, phosphate, PTH, ALP, Vitamin D3 levels
 - Urine Ca usually low and faecal Ca high
- Treatment:
 - ↓GI PO₄ absorption:
 - Dietary advice to ↓PO₄

- PO4 binders with Ca(CO₃)₂ (but Ca leads to calcification), Mg(OH)₂ (but it's useless), Al(OH)₃ (but Al leads to bone toxicity and anaemia)
- Other binders awaiting hard data: Sevelamer (Renagel) – non absorbable cationic polymer
- ↓PTH with:
 - Vitamin D: Calcitriol (1,25(OH)Vit D₃) – aim for PTH 1.5 – 3.5 times normal (ie once PO₄ normalised, control ↑ PTH with vitamin D)
 - or calcimimetics: cinacalcet/Sensipar – stimulates Ca sensing receptor to alter the set point for Ca stimulated PTH secretion – tricks the gland into thinking Ca is higher than it needs to be so → ↓PTH. Studies show good control of Ca/PO₄, no outcome data on mortality
 - or parathyroidectomy if persistent hypercalcaemia (> 3 mmol/L), PTH > 10 * normal, falling BMD, bone pain/fractures....
- Bicarbonate: aim for HCO₃ > 22 mmol/L
- Calciphylaxis:
 - Patches of ischaemic necrosis on the skin ?2nd to vascular calcification of subcutaneous penetrating arteries
 - Treatment difficult, includes hyperbaric O₂ and reductions in calcium and phosphate
 - Risk with concurrent warfarin (decreases Vitamin K dependent regeneration of matrix GLA protein which prevents vascular calcification)

Uraemic Syndrome

- End stage renal disease = uraemic syndrome, usually GFR < 20
- Accumulation of 100s of toxins, impairment of metabolic and endocrine functions (lipids, protein, PTH, insulin, sex hormones, prolactin...), anaemia and worsening inflammation (eg ↑CRP and consequent fall in negative acute-phase reactants such as albumin)
- Fatigue, restless legs, anorexia, nausea, bleeding, tenacious pruritis, pigmentation, impotence, uraemic pericarditis....
- Cardiovascular risk: dramatically increased risk
 - Little evidence of benefit of CVD risk modification in kidney patients (eg statins)
 - Nephrotic syndrome → atherogenic lipid profile and hypercoagulability
- Monitoring:
 - Cr and Urea affected by malnutrition
 - Cr may be falsely elevated at low levels due to some tubular excretion
 - Anaemia, Albumin, HCO₃

Anaemia in Chronic Renal Disease

- Normocytic normochromic anaemia as early as stage 3 disease (GFR 30 – 59) and near universal by stage 4 (GFR 15 – 29)
- Due to ↓EPO, Fe deficiency, inflammation → impaired iron utilisation, bone marrow fibrosis 2nd to severe hyperPTH, shortened red cell life 2nd to uraemia. Also check B12, folate and TFT
- Can treat anaemia with blood transfusions but only temporary benefit and complicated by Fe overload and development of antibodies (problem if future renal transplant)
- Check iron status:
 - Reduced ability to access Fe stores in ESRF – an inflammatory condition
 - Haemodialysis patients loose 2 gm of iron per year
 - Want ferritin > 200 and transferrin saturation > 25%
 - If deficient give Fe iv (oral only 1% bioavailable – next to useless)
- Commence EPO once Hb < 100 g/l (RR of death and hospitalisation ↑ below this level)
- EPO/Erythropoietin:
 - 90% made by kidneys in response to hypoxia (10% from liver)
 - Replacement options: various modifications to recombinant EPO to lengthen half life (CERA – Continuous Erythropoietin Receptor Activator is the longest)
 - → ↑Fe uptake and Hb synthesis in erythroblasts. Binds to receptor on CFU-E (colony forming unit – erythroid) promoting proliferation, also growing evidence for local paracrine actions, including renal protection and enhanced recovery
 - Aim for Hb < 120, and avoid HCT > 36%. No benefit and possibly harm from trying to normalised haemoglobin, rather than aiming for 105 – 115 (Ann Int Med 20 Nov 2007, p723) – too much EPO toxic?
 - Check Hb in 4 weeks. If Hb response poor then consider iron and ↑EPO dose by 50%. If no response by 8 weeks then non-responsive

- SE: ↑BP in 5 – 10%
- Trials show no effect on renal function

Other Complications

- *Hyperphosphataemia is likely the best predictor of CV disease*
- Prolonged bleeding time: often corrected by dialysis. Value of warfarin for AF? Use unfractionated heparin rather than LMWH as you can monitor APPT
- Neuropathy: Sensory affected before motor. Also autonomic neuropathy
- GI: uraemic fetor (urine like odour on the breath from breakdown of urea to ammonia in saliva). Prone to ulcers and constipation (worsened by Fe and Ca supplements). Protein restriction can help nausea
- Endocrine:
 - Fasting glucose usually normal. Insulin levels slightly higher second to reduced renal clearance. Metformin contraindicated
 - Estrogen levels low in women. If GRF < 40 very high rate of spontaneous abortion. Reduced testosterone in men
- Diabetic nephropathy doesn't usually cause haematuria or white blood cell casts

General Management of Chronic Renal Disease

- See Internal Medicine Journal 2004; 34:50 – 57
- Quitting smoking is good for proteinuria and renal function
- Proteinuria:
 - Aggressive BP control → reduced proteinuria
 - If proteinuria > 1 g/d then BP should be **125/75**, salt restriction (too much salt blunts ACEI effect), diuretics
 - ACEI and ARBs:
 - Have been shown to slow progression in diabetic and non-diabetic nephropathy in terms of time to doubling of creatinine, proteinuria and cardiovascular death
 - Are probably equivalent
 - Renal protection exceeds their anti-HTN effect, especially if:
 - Chronic Kidney disease stage 3 or higher
 - Proteinuria, especially > 3 gm/day
 - Do not withdraw if Cr rises by up to 30% but stabilises within the first 2 months as these are likely to have most benefit. If Cr rise exceeds 30% then investigate for bilateral renal artery stenosis
 - Average rise in K is 0.5 mmol/L. ACEI should be withdrawn if K > 6 mmol/L despite dose reduction, dietary K restriction and diuretic therapy. Concurrent metolazone may improve K excretion
 - Double blockade:
 - ACEI + ARB → better ↓HTN and ↓proteinuria than either alone in both diabetics and non-diabetics (Ann Int Med 2008;148:30)
 - Long term benefit in terms of avoiding RRT has not (yet) been demonstrated
 - Some concern that it may cause excessive ↑K and in some cases worse renal failure (ONTARGET trial – telmisartan and ramipril in patients with vascular disease or high risk DM – more hypotension and renal impairment without ↑ benefits)
 - Triple blockade: preliminary data with addition of spironolactone suggests ↑GFR, ↓proteinuria and ↑LV Fn, but limited by ↑K. Larger trials awaited
 - In advanced nondiabetic renal disease (Cr > 274) benazepril has been shown to slow progression of disease, excluding those with K > 5.6 or rise of Cr of 30% on ACEI (previously no data about ACEIs in advanced disease). Ann Internal Medicine 2008;148:51
 - Amongst CCBs, diltiazem and verapamil superior to dihydropyridines – but no benefit beyond antihypertensive effect
- Salt/Water Homeostasis: Thiazides of limited use. Loop diuretics usually needed in stages 3 – 5. May need high doses. Supplement with metolazone (inhibits Na-Cl co-transporter in distal convoluted tubule)
- Control of blood sugar in type 1 and type 2. Test for microalbuminuria at least annually. In terms of effect on nephropathy, control of BP more important than control of glucose
- Potassium. Dietary restriction, watch for K-retaining medications (esp ACEI or ARB) and K binding resins (eg Ca resonium)

- Metabolic acidosis: Common. Produce less ammonia. pH rarely < 7.35, usually corrected with oral NaHCO₃ supplementation (except watch for the increased sodium load)
- Protein restriction:
 - Epidemiology studies suggest association between high-protein diets and progression, although Modification of Diet in Renal Disease Trial did not show conclusively that protein restriction retarded progression – several meta-analyses do
 - but watch for malnutrition (renal failure is a catabolic disease)
 - ACEI may remove impact of protein restriction as most in protein restriction studies not on an ACEI (Cochrane 2006)
- Statins: Small RCT trial evidence that statins trend towards reducing proteinuria in non-diabetic patients with renal impairment (Ann Int Med 15 March 2005). Effect on progression unknown. Benefit in cardiovascular risk reduction
- Atherosclerotic renal artery stenosis: see page 21

Renal Replacement Therapy

- When to treat: Unclear
 - Commonly accepted:
 - Pericarditis (strongest indication) or other serositis
 - Overload refractory to diuretics
 - Severe hyperkalaemia and/or acidosis refractory to medical treatment (stop ACE, low K diet, resonium)
 - Uraemic syndrome (eg encephalopathy)
 - Additional considerations:
 - Malnutrition without other overt cause
 - No absolute Cr (Cr on it's own is never an indication for dialysis), GFR or urea cut-off – but most symptoms and complications develop with GFR < 10 ml/min
- Recommendations of the National Kidney Foundation in KDOQI Guidelines: delaying dialysis until patients uraemic or malnourished leads to a worse outcome than with dialysis or transplantation
- Underlying cause:
 - Diabetic nephropathy: 32% Australia, 41% NZ
 - Glomerulonephritis: 24% Australia, 22% NZ – Mesangio IgA by far the most common

Dialysis

- Annual mortality 20%, 5 year survival 30 – 35%
- Significant increase in numbers on treatment is partly driven by accepting older patients for treatment
- Death due to CVD (50%) and infection (15%)
- Most common cause is diabetes, followed by HTN
- Most ESRD patients require 9 – 12 hours per week
- No head to head trials of haemodialysis or peritoneal
- Measure of adequacy – volume of body fluid completely cleared of urea in a single dialysis: Dialysis dose – KT/V per treatment (usual target 1.2) where:
 - K = urea clearance rate of the dialyzer
 - T = time spent on dialysis
 - V = volume of body water (volume of distribution of urea)
- Other measures of haemodialysis:
 - Are you keeping PO₄ under control
 - With peritoneal dialysis, fluid is harder to remove – monitor this as well
- Albumin (↓in inflammatory states) and hyperphosphataemia predicts CVS mortality in a dialysis patient
- Decision about whether to use peritoneal or haemo-dialysis is multifactorial:
 - PD not so good (probably) in diabetics and the elderly
 - CHF and haemodialysis tricky
 - Need to consider capacity to learn, manual dexterity, vision, social circumstances

Peritoneal Dialysis

- One or both of:
 - Continuous ambulatory peritoneal dialysis (CAPD): 4 – 5 bags every day, or
 - Continuous cyclic peritoneal dialysis (CCPD) – machine overnight with faster cycles

- Works well when they retain some residual kidney function and more independence and flexibility. Once renal function gone then less effective
- Dialysate is an osmotic agent – usually glucose (problem for diabetic control as some will be absorbed. The search is on for other agents). Variable concentrations → removal of different amounts of saline
- Initial prescription: 2L of 1.5% dextrose concentration for 2.5 H with 3 daytime exchanges and 1 overnight. Aim for KT/V > 2.0 per week and Cr clearance > 65L/week/1.73m²
- Do peritoneal equilibrium test in 2 months: Categorized from low to high “transporters”. High transporters lose efficiency of ultrafiltration with long dwells due to loss of larger quantities of albumin across peritoneal membrane
- Can give insulin to diabetics in dialysis fluid. Can contain heparin to stop obstruction of the catheter
- Requires Tenckhoff catheter. Prior abdominal surgery may complicate/prevent this (adhesions → ↓surface area). *Contraindicated in previous perforated diverticulum/appendix*
- Pros:
 - Smooth removal of fluid and solute
 - Cardiac friendly
 - No heparin
 - Independence
- Complications:
 - Catheter infection
 - Peritonitis – Leukocyte count > 100/mm³ with < 50% polymorphs
 - Initial therapy: 1st or 4th generation cephalosporins or gentamicin, some use vancomycin. Need G+ ive and G-ive cover
 - Skin source: S Aureus common. Most cases managed with intraperitoneal or oral ABs
 - Gut source: Gram negatives – needs laparotomy (especially if 2 or more bugs), diverticular disease, ischaemic gut (there’s a hole in the gut and you need to fix it)
 - If pseudomonas, fungal or yeast, catheter removal usually required (unusual)
 - Recurrent peritonitis can → sclerosing peritonitis which is nasty
 - Weight gain and hyperglycaemia (from absorption of dextrose) and metabolic disturbance
 - Loss of albumin → may need higher protein diet
 - Inefficient. Residual uraemia (if no residual kidney function)
 - Splints diaphragm → ↓FVC

Haemodialysis

- Types:
 - Intermittent haemodialysis: 3 – 4 hours per day, 3 – 4 times per week
 - Slow low-efficiency dialysis: 6 – 12 hours per day, 3 – 6 times per week
 - Continuous renal replacement therapy (CRRT) – usually in ICU, especially if haemodynamically unstable (less effective than dialysis at ↓K)
 - Arteriovenous modalities: Arteriovenous haemofiltration (CAVH), Haemodialysis (CAVHD), haemodiafiltration (CAVHDF)
 - Venovenous Modalities (needs a blood pump): Venovenous haemodialysis (CWH), venovenous haemofiltration (CWH), venovenous haemodiafiltration (CWHDF)
 - In acute renal failure in ICU patients, more dialysis is not necessarily better than standard (NEJM 20 May 2008)
- Pros and cons:
 - Efficient solute removal, reasonable fluid removal
 - Intermittent → fluctuation in solute, fluid and BP
 - Requires good cardiac function
 - Access problems
 - Heparin exposure can → immune response
 - Still have to pay strict attention to fluid and solute intake
- Access:
 - Native arteriovenous fistula (preferred): usually at the wrist (“Brescia-Cimino” fistula). Most fail in 3 years
 - Synthetic graft
 - Tunnelled line
- Dialysate:
 - K concentration varied from 0 to 4 depending on predialysis plasma concentration. Usually 1.25
 - Na usually 140

- Adjust concentrations of other solutes depending in what you want your result to be – eg HCO₃, Ca, Phosphate (can increase or decrease plasma levels by adjusting dialysate concentration)
- Adjust the amount of fluid taken off by adjusting dialysate *pressure*
- Efficiency largely dependent on duration, blood flow rate, dialysate flow rate and surface area of the dialyzer. Small molecules (eg urea 60 Da) much better cleared than larger (eg Creatinine 113 Da)
- Prognosis:
 - Patient survival is critically dependent on hours per week on dialysis, after adjustment for Kt/V (dialysis dose)
 - Low albumin predicts poor prognosis
 - Old age → ↓ survival (50% 12 month mortality for > 85 years)
- Complications:
 - Hypotension (especially in diabetics given autonomic neuropathy), compounded by high output failure in those with arteriovenous fistulas
 - Muscle cramps: cause unknown
 - Anaphylactoid reactions to the dialyzer (especially on first use, and to older cellulose-containing membranes rather than newer biocompatible synthetic ones)
 - Access thrombosis
 - Catheter sepsis
 - Dialysis related *amyloidosis* – deposition of β₂ microglobulin as amyloid deposits in bone and synovial tissues – cysts at the end of long bones, also common in metacarpal, carpal and tarsal bones (→ carpal tunnel syndrome). See page 273
 - Dialysis Disequilibrium Syndrome: headache, confusion, rarely seizures, due to rapid solute removal, early in dialysis history before adaptation to the procedure

Cardiovascular Disease in Dialysis Patients

- Traditional risk factors do not apply!
- ESRD has an odds ratio for cardiovascular disease of 20 – 1000 – the younger the person the higher the relative risk
- Risk on dialysis > transplant
- Role of statins in dialysis patients:
 - Controversial
 - Very low cholesterol (< 2.6) → ↑ mortality
 - 4-D study (20 mg atorvastatin vs placebo) showed no difference
 - Is it stenotic calcific disease rather than rupturing lipid rich plaques causing CVD? Arterial calcification predicts cardiovascular mortality
 - Treat Ca and phosphate for the heart – not the bones – need to ↓ phosphate (and PTH, and calcium)
- LVH correlates with renal failure, and predicts survival in ESRD
- High BMI seems protective of mortality in dialysis – no one understands this....
- BP:
 - Both high and low values associated with mortality. Don't really know what BP targets to aim for. Benefits of treatment not clear. Standard target is 140/90
 - Blood pressure falling post haemodialysis is good in terms of mortality, compared to staying the same or rising
 - Blood pressure control should be possible in 90% of patients by fluid removal alone (depends on compliance with fluid restriction)
 - Beta-blockers best at mortality reduction in HTN on dialysis – better than CCB and ACEI
- IL-6 proposed as a biomarker for cardiovascular disease, greater predictive power than CRP

Kidney Transplantation

- Demand is growing and exceeds supply
- Mortality rates after transplantation increase with age and with diabetes
- Transplantation better than dialysis for life expectancy (although mortality higher immediately post-transplant)
- Living donors:
 - Do well with just one kidney, even after 20 years (NEJM 29 Jan 2008 – 20 – 30 year follow-up study of donors, average age at donation 41. Rates of ESRF lower than general population – although a very healthy group to start with)
 - Risk of BP rise of ~ 5 mmHg over > 5 years (Meta-analysis reported in Ann Internal Medicine 2008:148:54)

- Problems only arise if another condition is superimposed (eg HTN or diabetes)
- Don't want the donor to get T1DM after the event – screen for anti-insulin and anti-islet cell antibodies if family history
- Exclude polycystic disease (see page 133)
- Factors affecting success:
 - Living related donor > living unrelated donor > cadaver donor
 - Related 5 – 7% higher survival than unrelated
 - Living > cadaver because of reduced warm ischaemic time and no cold-ischaemic time
 - Female donor's show poorer outcome (?due to lower nephron mass). Male donor in a female also worse than female to female -?due to antibodies to Y chromosome (Lancet 5 July 2008)
- Recipient selection:
 - Should have a life expectancy > 5 years to go on a waiting list
 - Screen for indolent infection: HIV, Hep B, Hep C, Tb, CMV
 - Screen for neoplasm in both donor and recipient
 - Organ placed in inguinal fossa outside the peritoneal cavity
- Tissue Typing:
 - ABO blood (can transplant a type O donor into an A, AB or B recipient)
 - HLA matching (live related donor): HLAs expressed by all nucleated cells to define self. Recipient will react to anything they have never seen before. No lower limit – just need more immunosuppression
 - 1 year graft survival: 92.7 % for 6/6 HLA mismatch vs 96.7% for 0/6 mismatch
 - 5 year graft survival: 57.7 % for 6/6 HLA mismatch vs 92.7% for 0/6 mismatch
 - Screen for antibodies:
 - HLA class I and II (5% of fully matched organs still rejected, often within weeks). Testing for pre-existing antibodies to other HLA types (eg because of blood transfusion, prior transplant or pregnancy) → acute rejection
 - WBCs contaminating transfused RBCs → recipient sensitisation. Cyclosporin with transfusion reduces the development of these – but they're often sick so this is not ideal. Ideal is WBC depleted transfusions
 - Direct cross-matching of recipient serum with T lymphocytes (anti HLA class 1) of donor:
 - If there is a reaction, don't transplant
 - Prevents hyperacute rejection. Avoiding this is the minimal purpose of cross-matching
- Post-transplant management:
 - Initially avoid NSAIDs and ACEI
 - ATN may → oliguria, especially if long warm ischaemic time or under perfused cadaver
 - Calcineurin inhibitors → afferent arteriolar constriction → prolong ATN
 - Superimposed rejection is common. See page 122
 - US/MRI can exclude vascular problem (eg clot) or urinary obstruction

Immunosuppressive treatment

- For Immunosuppressive treatment see also page 227 (Immunology) and page 241 (treatment of rheumatology conditions)
- 3 steps in immune activation and proliferation:
 - 1: Presentation of antigen on an APC MHC molecule to the TCR of a T cell. CsA, FK506 and AEB block the intra-cellular pathway of the TCR which would otherwise drive ↑IL2 secretion
 - 2: Co-stimulation via B7/CD28, CD40/CD40L system. CTLA4 Ig (belatacept) blocks costimulation which would also otherwise ↑IL2 secretion
 - 3: ↑IL2 which drives other T cells via IL2 receptor (CD25). Receptor blocked by Anti-CD25 (Basiliximab), and intracellular pathway blocked by PSIs and JAK3
- Principles:
 - Multiple agents: ↑efficiency, ↓toxicity
 - Taylor immunosuppression to risk of acute rejection (highest in first 6 months) so *start high and taper – as it contributes to CAN* (Chronic Allograft Nephropathy, especially CsA)
 - Clinical and pharmacokinetic monitoring: CsA is nephrotoxic
 - Prophylaxis for predictable side effects: osteoporosis and valgacyclovir
 - Nearly all immunosuppressants are substrates of CYP3A4 – lots of interactions
 - Acknowledge uncertain effects on chronic rejection
- More selective to primary than to memory immune responses

- Triple therapy the norm: CsA or Tacrolimus for 3 – 6 months *and* an antiproliferative (AZA or MMF, usually ongoing with downwards titration) *and* prednisone (titrate down over 3 – 6 months) [*and* Basiliximab (anti CD25/IL2R) up front]

Agent	Pharmacology & Mechanism	SE	Notes
Glucocorticoids	Blocks transcription of IL 1,2,3,6, TNF α and IFN γ . \uparrow Bioavailability with \downarrow albumin. 300mg prior to transplant then 30 mg for a week, taper over months	HTN, IFG, \uparrow lipids, osteoporosis	Pulses effective for acute rejection. Maintenance dose for chronic rejection. Alternate days \rightarrow \downarrow SE
Cyclosporin A (CsA)	Calcineurin inhibitor. Inhibits PK-C stimulation in T cell \rightarrow blocks cytokine production (eg IL2) and T cell activation, stimulates TGF β . Variable absorption	Main problem is nephrotoxicity (vasoconstriction, tubular injury, microthrombotic angiopathy, \uparrow uric acid, can look similar to rejection on biopsy – not glomerular injury). Also HTN, \uparrow lipids, IFG, <i>hirsutism</i> , <i>hyperplasia of gums</i> , \downarrow Mg	More effective with MMF or prednisone. See below re interactions. Measure peak 2 hours post dose
Tacrolimus (FK506)	Macrolide, well absorbed. Complex with calcineurin. Blocks cytokine production (eg IL2), stimulates TGF β	Nephrotoxic (more than CsA), neurotoxicity, HTN, more diabetes, less hirsutism and hyperplasia of gums, rare cardiomyopathy, \downarrow Mg, lipids less of a problem	See below re interactions. Measure trough
Azathioprine	Mercaptopurine analogue. Hepatic metabolites inhibits purine synthesis \rightarrow impairs DNA/RNA synthesis \rightarrow inhibits mitosis of lymphoid cells and antigen processing. 1.5 – 2.0 mg/kg	Marrow suppression (WBC > RBC > platelets). Jaundice and alopecia if excessive amounts	Generally overtaken by newer drugs. Added to cyclosporin to reduce it's dose. OK in renal impairment. Xanthine oxidase inhibits degradation \Rightarrow not with allopurinol
Mycophenolate mofetil (MMF)	Metabolised to mycophenolic acid. Inhibits purine synthesis via inosine monophosphate dehydrogenase \rightarrow antiproliferative	Diarrhoea/cramps. Uncommon dose related liver and marrow suppression	Has generally replaced azathioprine. Allopurinol OK. Don't measure levels. Levels high with Tacrolimus
Sirolimus	Macrolide, poor oral bioavailability. Blocks p70 S6 kinase on the IL-2 receptor pathway (and others)	\uparrow Lipids, thrombocytopenia, poor wound healing, anaemia, mouth ulcers, interstitial pneumonitis	

- CsA, Tacrolimus and Sirolimus all metabolized through P450-3A4:
 - \downarrow metabolism if: conazoles, macrolides, CCBs
 - \uparrow metabolism if anticonvulsants, rifampicin, isoniazid
- Antibodies to lymphocytes:
 - OKT3: antibody to CD3 on T cells. Given for 7 – 10 days in acute rejection. Try and avoid it now
 - Antilymphocyte globulin (ALG): serum from animals made immune to host lymphocytes and then injected into the recipient causing selective suppression of cell mediated immunity
 - CTLA-4 IG: Belatacept/Abatacept: Fusion protein (Fc portion of Ig prolongs half life). Co-stimulatory blockade. Equal efficacy to CsA in *preventing* acute rejection in phase 2 trial (NEJM 2005), phase 3 underway. Not grunty enough in *treating* acute rejection – need depleting ABs for that. Chief advantage may be avoidance of nephrotoxicity

- IL2 receptor antibodies: basiliximab (currently in 60% of Aussi transplants) or daclizumab (in trial) – used for prophylaxis for acute post-transplant rejection. Duration 2 months. Only targets activated T cells and doesn't kill them
- mTOR inhibitors: Rapamycin/sirolimus, Everolimus: bind to FKBP which binds mTOR, inhibiting IL-2/co-stimulatory triggered cell signalling, leading to G1 arrest. Not grunty enough for initial use, but switch to them, ↓ risk of cancer, problems with bad proteinuria if recurrent glomerular disease or poor graft
- JAAK3 and PKC inhibitors in trial – novel T cell pathways
- The future?: Combined bone marrow and kidney transplant: 4 of 5 patients were able to discontinue all immunosuppressive treatment after ~ 1 years, and renal function remained stable. 1 suffered acute humoral rejection (NEJM 24 Jan 2008)

Rejection

- Mediated by lymphocytes responding to HLA antigen in the organ: Class II incompatibility → CD4+ proliferation. Class 1 incompatibility → CD8+ response (proliferate into cytotoxic T cells)
- Signs:
 - Rise in serum Cr – most sensitive indicator
 - HTN
 - Reduced urine output
 - Fever, tenderness and swelling over graft is rare
- Workup:
 - Difficult to differentiate. May only present with ↑ Cr and no change in urine volume
 - Measure drug levels to exclude toxicity
 - Arteriography, nuclear scans to check vasculature and blood flow
 - Ultrasound: rule out obstruction
 - Biopsy to confirm diagnosis – look for endothelial injury and deposition of C4d
- Can be:
 - *Hyperacute*: immediately due to presensitisation. Due to ABO or HLA class 1 pre-formed antibodies. Vascular thrombosis occurs very rapidly. Now rare
 - *Acute*: sudden change in renal function within weeks to months (but occurs at any stage if not sufficiently immunosuppressed)
 - Occurs in 1 in 4 or 5 kidney transplants and 1 in 10 livers
 - Most commonly cellular rejection:
 - Biopsy: interstitial cellular infiltrate with lymphocytes under the basement membrane (tubulitis) – mildest form of rejection
 - Treat with 3 pulses of steroids (90% effective), OKT3 or ALG if severe (non-depleting antibodies like antiCD25 not useful), and switch to Tacrolimus/MMF/Prednisone
 - Occasionally vascular (humoral) rejection (worse prognosis):
 - Antibody mediated
 - Biopsy: interstitial haemorrhage
 - Vascular inflammation, C4d staining on peritubular capillaries, microthrombi
 - Treat with plasmapheresis, IVIg, tacrolimus, ?*Rituximab*
 - *Chronic allograft nephropathy (CAN)*: progressive dysfunction after 6 – 12 months. Entirely different process. Not well understood. Scarring – fibrosis + sclerosis. Immune plus non-immune. Progressive renal dysfunction, proteinuria, HTN
- In general, 5% grafts lost in 1st year, with 3 -4 % loss per year thereafter

Pregnancy in transplant recipients

- Optimal timing ~ 2 years post transplant
- Preeclampsia in 30% – difficult to diagnose
- Preterm deliver (<36 weeks) in 50%, low birth weight in 50%
- Most experience with azathioprine, cyclosporin and steroids. Case reports with Tacrolimus. MMF and sirolimus contraindicated. Breast feeding controversial
- Impact on kidney:
 - If serum creatinine < 125 µmol/L then most studies show no little effect of pregnancy on long term renal function
 - If Cr 125 – 250 µmol/L then 30% have irreversible decline

Long Term Complications

- Summary:

	Early	Late
Infection	Bacterial, viral, CMV	Viral – warts/zoster. BK
Rejection	Acute	Chronic allograft nephropathy
Drugs	ARF, GI, mood & bone (steroids)	Hair, skin, kidney, bone (steroids), CVS
Tumours	PTLD	Carcinoma (skin, cervix), lymphoma
General	Surgical complications	CVS disease

- Prophylaxis: valgancyclovir for CMV + co-trimoxazole for PCP + calcitriol + Ca (1993 study on asthma patients on steroids) or pamidronate iv before and 1 month after transplant
- Chronic vascular changes common → slow decline
- > 50% mortality due to CVD
- Failure due to disease recurrence:
 - GN:
 - Overall types, 1 in 10 risk it will cause your graft to fail in 10 years
 - Primary FGS 50% (risk highest in those with an original rapid course – does the same to the graft)
 - IgA 35%, but often doesn't lead to graft failure
 - Lupus < 10%
 - Vasculitis < 10%
 - Diabetes – graft loss common after 10 years
- HTN: due to native kidney disease, rejection, renal artery stenosis from surgery, renal calcineurin inhibitor toxicity. Treatment – usually start with CCBs then ACEI
- Anaemia 2nd to bone marrow suppression
- Tumours:
 - Incidence of tumours 100 times higher than age matched controls
 - Also common: non-melanoma skin (7% at 3 years, universal after 30 years, SCC > BCC), lips, cervix. Also melanoma, Kaposi's (9 fold risk)
 - Common solid organ cancers: approx twofold higher
 - Risk proportionate to duration and dose of immunosuppressants
 - Post Transplant Lymphoproliferative Disease (PTLD):
 - Most occur < 2 yrs post transplant
 - Especially in those who are EBV + or who receive polyclonal (ALG) or monoclonal AB therapy
 - 90% are non-Hodgkin's B-cell lymphoma with most associated with EBV. Extra nodal disease common (eg gut)
 - Treatment: reduction in immunosuppression, Rituximab, CHOP
- Opportunistic Infections:
 - Peritransplant (< 1 month): usually **bacterial**, wound infections, herpesvirus, oral candida, UTI
 - Early (1 – 6 months): **CMV**, PJP, Legionella, listeria, Hep B and C
 - Late (>6 months):
 - **Fungal** (eg aspergillus – especially if not able to taper prednisone), Nocardia
 - **BK polymavirus**:
 - A DNA polyoma virus – cousin of JC virus (which causes progressive multifocal leukoencephalopathy in AIDS). Primary infection in childhood with no clinical consequence, persistence for life in urinary tract epithelial cells → reactivation
 - Highest risk with Tacrolimus
 - Diagnosed with immunohistochemistry, EM, serology, PCR. Urine shows decoy cells – tubular cells with funny morphology
 - Treat with reduction in immunosuppression, a material proportion loose graft
- CMV infection:
 - Most common opportunistic infection in renal transplant
 - Infection most common 1 – 4 months after transplant or post prophylaxis
 - Highest risk: D+, R-. With no treatment 70 – 90% will get infection, 30% get pneumonitis, 15% will die
 - 70% of population IgG positive
 - Post OKT3 also high risk

- Most common presentation: fever, malaise, myalgia, ↓WCC with atypical lymphocytes. Possibly colitis, pneumonitis, hepatitis. Rarely chorioretinitis, encephalopathy
- Diagnosis: Serology: IgG, IgM, culture, PCR, histology
- Treatment:
 - Prophylaxis: oral Valganciclovir/valacyclovir (5% have hallucinations, lots of pills) for 3 months
 - Infection: IV ganciclovir for 2 weeks and reduction in immunosuppression: particularly AZA and MMF
- Diabetes:
 - 10% get T2DM within a year of transplant as a combination of:
 - Insulin resistance: steroids, calcineurin inhibitors, inflammation, CMV, obesity, inactivity
 - Insulin deficiency: tacrolimus > CsA (calcineurin is in insulin production pathway), mTOR (eg sirolimus), age, insulin degradation in new, better functioning kidney
 - Main impact is on death with a functioning graft (ie ↑risk of CVD) – diabetes is a bigger risk for IHD events post transplant than high cholesterol, HTN or smoking
- Other:
 - Tertiary hyperPTH → ↑Ca
 - Avascular necrosis of head of femur 2nd to steroids on background of hyperPTH
 - *Hepatitis B*: persistent surface antigen positive especially high risk

Glomerular Diseases

- For conservative/supportive treatment, see page 116

Glomerulonephritis Background

- Diseases typically affect one cell:
 - Mesangial: controls glomerular structure. Damage spills blood and protein
 - Endothelial cell → haematuria
 - Epithelial cell: interferes with slit filtration → proteinuria
- Renal failure best correlates with tubulointerstitial nephritis – not type of glomerular injury
- Either:
 - Primary: limited to the kidney
 - Secondary: part of a more widely disseminated immune process
- Systemic diseases that may present as GN:
 - Lupus nephritis: deposits of immune complexes everywhere within the glomerulus
 - Arteritis: Microscopic polyarteritis
 - Amyloid: Nephrotic Syndrome or renal failure. Histology with congo red stain
 - Diabetes
 - Hypertension
- Genetic causes:
 - Congenital Nephrotic Syndrome: mutations in NPHS1 and NPHS2
 - Partial Lipodystrophy: lamin A/C and PPAR γ genes → metabolic syndrome associated with MPGN
 - **Alport's Syndrome**: mutations in genes for the α 5 chain of collagen IV → split basement membrane with glomerulosclerosis + sensorineural deafness. Usually X linked. Haematuria in the first decade. ESRF between 15 – 35 years. Female carriers may have haematuria but ESRF rare
 - Lysosomal Storage Diseases: eg Fabry's Disease → FSGS
 - **Thin Basement Membrane Disease**: AD, probably minor mutations in the collagens of the GBM. Relatively common. Reported in up to 5 – 9% of kidney donors. *Cause of benign (usually microscopic) haematuria*. Minimal proteinuria. Renal function normal. EM: thin GBM
- Terminology:
 - Proliferative: proliferation of endogenous glomeruli cells
 - Exudative: infiltration by polymorphs – usually post-infectious
 - Necrotising: cell destruction
 - Diffuse: involves > 50% glomeruli
 - Focal: involves < 50% glomeruli
 - Global: involves the whole glomerular tuft
 - Segmental: involves only part of the glomerular tuft
 - Endocapillary: cells proliferate in the tuft only
 - Extracapillary: cellular proliferation extends into the Bowman's space

- Sclerosis: glomeruli have acellular material throughout the tuft but normal mesangium. Age-related glomerulosclerosis is common in adults
- Diagnosis:
 - Urine biochemistry: urine sodium > 20 mmol/L (if pre-renal failure then < 20, ie frantically trying to reabsorb Na)
 - Urine analysis: Blood morphology and casts, protein (usually mild).
 - Ultrasound: exclude obstruction, looking for normal or slightly enlarged kidneys, echogenic (dark on US => ↑fluid)
 - CXR: look for Goodpastures Syndrome, Wegener's Granulomatosis
 - Bloods: ANA (connective tissue disorders), ANCA (Anti-neutrophil cytoplasmic antigen => Wegener's Granulomatosis), Anti-dsDNA (=> SLE), anti-GBM
- Histology using a variety of stains. May see:
 - Glomerula epithelial cells usually have interdigitating foot processes. If they swell, ↓ gaps between them → proteinuria
 - Mesangial cells (supporting framework) are the first to react to injury and the last to return to normal

Summary of Glomerulonephritis

- Nephritic: think immune complex mediated, Anti-GBM disease, pauci immune
- Nephrotic: think membranous, minimal change, FSGN
- Microscopic haematuria: think IgA, thin basement membrane, Alport's

	Proteinuria		Haematuria		Nephritic	Cell affected	Anti-GBM	↓C3	Anti-strep	Anti IgA
	Asymptomatic	Nephrotic	Macro	Micro						
Minimal Change		++++		+		Epithelial				
FSGN	+++	++++		++++		Epithelial				
Membranous	+++	+++	+	+++		Epithelial				
Post-Infectious	+	+	+	++++	++++	Endothelial		+++	+++	
RPGN		+	+	++++	+++		++			
IgA	+++	++	+++	++++	+	Mesangial				++
Mesangio-capillary	+	+++	+	++++	+++	Endothelial		+++	+	

Nephritic Syndrome

- ~ Proliferative glomerulonephritis
- Presentation:
 - Hypertension
 - Haematuria: often macroscopic. Can present with "clot colic"
 - Urinary sediment: dysmorphic red cells and red cell casts, granular and cellular casts
 - Oliguria (< 400 mls/day) → fluid retention and oedema
 - Renal impairment → ↑Cr, electrolyte disturbance
 - Oedema: ↓GFR but tubular function OK so Na/H₂O reabsorbed → oedema. Including periorbital oedema (cf dependent in nephrotic)
 - Varying degrees of proteinuria (eg 1 – 2 g/d)
 - Also headache, nausea, malaise
 - Swelling of renal capsule can cause flank or back pain
- Histology: Large glomeruli (diffuse changes of predominantly mesangial cells), polymorphs and black deposits on epithelial side of BM, can occasionally lead to crescents (ie lots of cell proliferation compared with Nephrotic Syndrome => rapidly progressive glomerulonephritis)

- **Immune complex mediated present with nephritic syndrome**

- Possible causes: Usually proliferative GN
 - Post-infectious GN
 - Rapidly progressive GN
 - Mesangio-capillary GN
 - Maybe IgA GN

Rapidly Progressive Glomerulonephritis

- What is it:
 - A description not a diagnosis
 - = Acute renal failure secondary to glomerula disease *generally with a nephritic presentation*
 - Any form of GN can present in a rapidly progressive form. Generally caused by immune mediated diseases
- ~ Crescentic glomerulonephritis (marker for *severe* RPGN)
 - = Cellular proliferation in glomeruli, and crescent formation
 - Pathogenesis of crescents: rupture of the basement membrane → fibrin leaks into Bowman's space, macrophages recruited, epithelioid cells form a crescent. Leads to scarring and fibrosis of glomeruli
 - Light Microscope: Extensive proliferation of cells, numerous crescents, generally without polymorphs
- Due to:
 - *Immune complex mediated GN*:
 - **Granular** IgG and C3
 - Post-infectious GN: e.g. post-streptococcal (rarely crescents, dialysis rarely needed) also staph. Has *granular* IgG plus neutrophils
 - Lupus Nephritis. 40%, Has *granular* IgG (plus IgA, IgE, etc). See page 258
 - IgA, mesangiocapillary, also vasculitis
 - *Anti-glomerular-basement membrane diseases* (Goodpasture's syndrome): 10%, **Linear** IgG ⇒ Goodpastures, as attacking the BM itself rather than depositing on it
 - *Pauci-immune*: (ie *no* evidence of immune deposits, probably cell mediated immune rather than humoral problem): 50%, Wegner's, microscopic polyangiitis, and Churg-Strauss Syndrome (See page 272)
- Prognosis dependent on % of crescents
- Management:
 - Urgent diagnosis: biopsy, serology for SLE, ANCA, anti-GBM
 - Immunosuppressive:
 - Prednisone pulsed * 3 then high dose oral + cyclophosphamide +/- adjunctive plasmapheresis in Anti-GBM and ANCA, no proven benefit in SLE

Nephrotic Syndrome

- ~ Non-proliferative glomerulonephritis
- Presentation:
 - *Marked proteinuria* (may make urine frothy) > 3 g/day (On it's own is "nephrotic range proteinuria" – need other features to be "nephrotic syndrome")
 - Minimal haematuria
 - *Hypoalbuminaemia* → *oedema*: generalised, dependent, insidious onset, may be peri-orbital in the morning, legs in the afternoon. If gross then ascites and pleural effusion. Treatment: diuretics
 - *Hypercholesterolaemia* (treat with statins – liver goes into overdrive to replace albumin and produces more of everything, including coagulation cascade proteins → hypercoagulable). Mainly ↑LDL, not TGs
 - Renal function is relatively preserved. With sustained hyperfiltration → nephron loss
 - If polyuria then ⇒ tubular and interstitial damage as well
- Pathogenesis: common end point of a variety of disease processes that alter the permeability of the basement membrane
- Possible causes (first 3 reasonably common in adults, membranous is perhaps the most common):
 - Minimal change GN
 - Membranous GN
 - Focal Segmental GN
 - Maybe IgA and mesangiocapillary
 - Also diabetes, amyloidosis (eg from multiple myeloma), drugs

- Management:
 - Minimal change: very responsive to steroids. The rest need something stronger (eg cyclophosphamide) and commonly → renal failure over time
 - Fluid restrict
 - Monitor and treat BP
 - Salt restricted, high protein diet
 - Oral diuretics + K (beware hypovolaemia → pre-renal failure)
 - Statins
 - ACEI or ARB
 - Pneumovax
 - Albumin infusions ineffective – lose it in urine within 48 hours
- Complications:
 - Loose antithrombin protein as well as albumin → renal vein (and other) thrombosis. ?Prophylactic anticoagulation. Eg Warfarin if severe proteinuria only
 - Loss of various serum binding proteins (eg thyroid binding globulin) → alterations in tests

Glomerulonephritis with generally Nephritic Presentation

Post-Infectious Glomerulonephritis

- Following Group A β -haemolytic M type strep infection of throat (2 – 6 weeks after) or skin (1 – 3 weeks after), also SBE, osteomyelitis, etc. Mainly kids, but 10% > 40
- Cultures usually negative, strep serology may be helpful (ASO in 30%)
- Presentation: Usually **nephritic** with acute endocapillary proliferative glomerulonephritis, *not relapsing*
- May be rapidly progressing → acute renal failure
- Bloods: Anti-DNAase-B +ive, RF +ive (30 – 40%), pANCA (10%), ↓C3, maybe ↓C4
- Biopsy: usually in adults to rule out a crescentic rapidly progressive GN:
 - LM: mesangial and endothelial cell proliferation + *neutrophils*. Crescents if severe
 - IF: Usually +ive for granular IgG and C3 deposition, as well as IgM, C4, C 5- 9
 - EM: deposits on epithelial (ie Bowman’s capsule) side of BM
- Treatment: supportive (which may include dialysis), *not* immunosuppressive. Treat culture positive family members with penicillin
- Prognosis: slow recovery, mild residual impairment in a few, renal failure in 1 – 3%

Lupus Nephritis

- See SLE, page 258
- Nephritic syndrome with proteinuria and active sediment
- Usually immune complex in the glomerular capillary wall, but may be due to thrombotic microangiopathy (see page 131) if antiphospholipid syndrome
- Bloods: ↓complement, ANA +ive, dsDNA correlates with activity
- Renal biopsy to classify from Class I to Class VI ranging from mesangial deposits to global sclerosis. Guides prognosis and treatment
- Treatment:
 - Induce remission with steroids plus either cyclophosphamide (**IV** – only GN for which IV is used rather than oral) or MMF, with maintenance of lower dose steroids and MMF or azathioprine
 - Cyclosporin and plasmapheresis also used but not good data

Goodpasture’s Syndrome

- If only kidney affected = *Anti-GBM disease*
- If lung and kidney affected = *Goodpasture’s Syndrome*
- **Not** generally relapsing
- GN +/- pulmonary involvement (ranging from pulmonary infiltrate on x-ray to life threatening frank haemoptysis [mainly smokers]). If pulmonary disease present it usually predates renal disease by weeks to months. Raised DLCO (separates it from eg CHF). **Lower** respiratory tract only
- Pathogenesis: antibodies against $\alpha 3$ NC1 domain of type IV collagen in the glomerular basement membrane and pulmonary tissue. Exacerbated by infection, smoking, oxidants and solvents
- Biopsy: Crescents + linear (“ribbon like”) immunofluorescence on the basement membrane staining for IgG + focal or segmental necrosis
- Can measure serum anti-GBM antibody (> 90%). pANCA in 10 – 15%

- Treatment:
 - Immunosuppression (steroids, cyclophosphamide)
 - +/- plasmapheresis for 1 – 2 weeks to get rid of antibodies (lung haemorrhage responds better to this than renal problems)
 - If you have to start dialysis, rarely get off it
 - 1 year survival > 90% if treatment started before Cr > 442

Mesangial IgA disease (Berger's Disease)

- *Most common form of GN.* Common cause of recurrent haematuria in young men. Usually more benign. Differential is Thin Basement Membrane Disease, see page 124
- Presentation, either:
 - Macroscopic haematuria 24-48 hours after (or even the same day) as a (usually viral) URTI (= Spharyngeal haematuria), also after GI infection, vaccination or strenuous exercise
 - HTN and ↓GFR
 - Asymptomatic microscopic haematuria picked up on dipstick testing
 - Nephrotic levels of proteinuria are rare
 - *Recurrent*
 - IgA raised in 50% – not sensitive
 - Associated with Coeliac disease and chronic liver disease (esp alcohol related)
- Biopsy:
 - LM: **Mesangial** cell proliferation + ↑ matrix formation, rarely crescents
 - IF: Mesangial deposits of **IgA** (same as HSP) and C3 (may also be IgM, IgG, light chains). IgA1 not IgA2 (blood derived not secretory). Note: Lupus can also stain positive for IgA
- *C3 normal (also in HSP)*
- Prognosis: Only 25 – 30% progress to end-stage renal failure over 20 – 25 years. Urine red cell count best predictor of developing ESRF. Also more likely to have proteinuria (bad sign), hypertension and impaired renal function at presentation
- No agreement on treatment. Consider ACEI, and immunosuppressive treatment if rapidly progressive. Steroids and fish oil both shown to be beneficial in some trials only
- Same renal lesion as Henoch-Scholein Purpura – but HSP is more widespread, causing purpura (especially buttocks and ankles) and abdominal pain (which may → GI bleeding). 1% progress to ESRF. In adults can cause RPGN. IgA staining on skin biopsy

Mesangioproliferative GN

- Sometimes used as synonymous with Mesangial IgA disease – Harrison's lists it separately
- Expansion of the mesangium and mesangial immune deposits (IgM, C1q and C3)
- Commonly haematuria, also proteinuria
- Can be caused by:
 - IgA nephropathy (usually cause)
 - *P falciparum*
 - Post-infectious glomerulonephritis
 - Class II Lupus
 - Idiopathic in < 15%
- Little agreement on treatment

ANCA Small Vessel Disease

- All **pauci-immune** – few immune complexes
- Features:
 - RPGN more common presentation than acute nephritic syndrome
 - Necrotising GN with crescents in > 50% glomeruli
- Generally treated similarly: induction with plasmapheresis (uncertain benefit), prednisone pulses and cyclophosphamide (1-2 mg/kg/day)
- Wegener's Granulomatosis:
 - Causes fever, purulent rhinorrhoea, nasal ulcers, sinus pain, arthralgia, cough, SOB, haemoptysis, non-caseating granuloma (ie **Upper** and lower respiratory tract involvement)
 - Microscopic haematuria, 0.5 – 1 g/d proteinuria
 - cANCA is highly specific (anti-PR3), present in 80 – 90%
 - Renal biopsy: -ive immunofluorescence, segmental necrotizing glomerulonephritis
 - Typically older patients. Nodules and infiltrates on CXR

- Microscopic polyarteritis (also joints) – pANCA more common. Like Wegner’s, but no lung disease or destructive sinusitis. See page 271
- Churg-Strauss: pANCA more common. Small-vessel vasculitis, mononeuritis, asthma, allergic rhinitis. Eosinophilia. Focal segmental necrotizing GN. See page 272

Mesangiocapillary or Membranoproliferative GN

- ↓incidence ?due to ↓Hep C
- Proteinuria, haematuria, pyuria (30%), malaise, **nephritic** picture with RPGN in 25%
- **Persistent reduction in serum C3**
- Biopsy:
 - LM: cellular expansion of the mesangium. ‘Twin track’ or ‘tram track’ BM. Protein casts in tubules
 - EM: Subendothelial deposits *or* deposits within the BM – a split appearance – “bubbles” within the BM
- Type 1 Disease (most common): Nephrotic presentation. Due to idiopathic, persistent **Hep C**, autoimmune diseases (eg **SLE**) or cancer of the lung, breast and ovary
- Type 2: Usually nephrotic presentation, also nephritic, RPGN or recurrent haematuria. Due to: Idiopathic or C3 nephritic factor-associated (See page 232). (Maybe profoundly) low C3 and dense deposits in GBM
- Type 3: Idiopathic or complement receptor deficiency
- Treatment:
 - Kids: prednisone
 - Adults: Aspirin + dipyridamole → ↓ proteinuria, but probably no effect on GFR. ACEI

Glomerulonephritis with Generally Nephrotic Presentation

Minimal Change Disease

- Presentation:
 - Usually nephrotic syndrome, with severe oedema, uncommonly have hypertension and 10% have microscopic haematuria
 - Commonly after an URTI, also immunisation and atopic attacks
 - 90% of childhood nephrotic syndrome, 20 – 30% of adult nephrotic syndrome
 - **Renal function normal** (only GN in which this is the case), unless it deteriorates secondary to hypovolaemia
 - Weak association with Hodgkin’s Disease and NSAIDs
 - **Relapse common.** Representation with oedema. Give them some dipsticks to self-test if they’re concerned
- Investigations:
 - Light Microscopy (LM): glomeruli are normal
 - Immunofluorescence (IF): **Negative**
 - Electron Microscopy (EM): fusion of foot processes. Many other causes have this, but normal LM eliminates the rest
- Management:
 - Kids: natural history unpredictable:
 - 90% of kids respond to 8 weeks of steroids. If they relapse, respond to steroids again (eg triggered by intercurrent illness). No renal failure but complications of treatment
 - 10% become steroid dependent or resistant → use cyclosporin
 - Steroids less effective in adults, take longer, but still reasonable response rate. May need cyclophosphamide. May have haematuria, ↓GFR and HTN

Focal and Segmental Glomerulosclerosis (FSGS)

- Hypothesised that this is on a spectrum with minimal change disease at the “benign” end
- Presentation:
 - Usually **young adults**
 - Usually nephrotic, can be nephritic
 - Usually microscopic haematuria
 - Accounts for 10 – 20% of nephrotic syndrome in adults
 - Can be relapsing/remitting
 - Can be HTN and ↓GFR

- Differential:
 - Primary/idiopathic – *the majority*
 - Associated with systemic disease: HIV, Hep B, HTN, drugs, lymphoma, genetic, others...
 - As a consequence of sustained glomerular capillary HTN: Sickle cell disease, reflux nephropathy, radiation nephritis, GN, heroin use...
- Investigations:
 - Portions (ie segmental) of fewer than 50% of glomeruli (ie focal)
 - LM: segmental sclerosis of the glomerular tufts. Because it's patchy may have false negative biopsy. May be ↑mesangial matrix, interstitial fibrosis and tubular atrophy – especially in glomeruli located at the corticomedullary junction (ie a superficial biopsy may miss it)
 - IF: Weakly positive for IgM and C3 (?artefact)
- Management:
 - Poor prognosis: 50% have a five year renal survival. Degree of proteinuria at presentation is prognostic. If remission then good outcome
 - 50% remission to prednisone 1 – 2 mg/kg for 3/12 then taper, but frequent relapse – if response then cyclophosphamide and cyclosporine (NB nephrotoxic) can be used (try anything!)
 - 25% of Primary FSGS who get a kidney transplant develop FSGS in the allograft

Membranous Glomerulonephritis

- Presentation:
 - Nephrotic syndrome, also asymptomatic proteinuria
 - Microscopic haematuria, hypertension, renal impairment
 - 30% of adult nephrotic syndrome, most commonly **middle-aged** (30 – 50) with male: female of 2:1
- Usually idiopathic, but 25% of it is secondary to underlying disease, including:
 - Lung, breast or colon cancer (< 10% of adults presenting with Membranous GN)
 - Infections: hepatitis B and C, malaria, schistosomiasis, leprosy, syphilis, *not TB*
 - SLE, more rarely RA
 - Drugs: penicillamine, gold, high dose captopril, NSAIDs
- Investigations:
 - Is autoimmune – but there is no antibody you can measure
 - LM: diffusely thickened BM (best seen with PAS stain), irregular capillary loops, *spikes in BM with silver stain* (intra-membranous protein deposits)
 - IF: granular deposition of IgG and C3
 - EM: Subepithelial deposits
- Prognosis:
 - Variable – 30% progress to end-stage, 30% improve, and the rest retain stable renal function but with ongoing proteinuria (ie wobble along)
 - Highest reported incidence of renal vein thrombosis, pulmonary embolism, DVT
- Treatment:
 - Secondary, treat cause
 - Steroids don't work (controlled trials). 6 months steroids and eg cyclophosphamide or cyclosporin for the progressive group – so only initially treat the poor prognostic people (HTN, ↓GFR, > 50, male)
 - Anticoagulation if albumin < 20 (marginal benefit above that)

Diabetic Nephropathy

- Thickening of the GBM sensitive for the presence of diabetes. Loss of negative charge
- Increase filtration of serum proteins, predominately negatively charged albumin
- Expansion of mesangium due to accumulation of extracellular matrix → mesangial sclerosis
- Microalbuminuria appears 5 – 10 years after the onset of diabetes
- > 90% of T1DM with nephropathy have retinopathy – so if no retinopathy think about additional causes of renal impairment
- Kidneys often initially enlarged, not small
- Survival on dialysis shorter than for other indications

Glomerular Deposition Diseases

- Deposition within the glomeruli, but not termed glomerulonephritis
- Not common
- Either:

- Cast nephropathy but not heavy proteinuria (amyloidosis), or
- Nephrotic syndrome with renal failure (Light Chain Disease) with kappa light chains (can't form fibrils). Light chains don't stain with Congo Red, but do with anti-light-chain antibody on immunofluorescence
- Renal amyloidosis (see Amyloidosis, page 273):
 - Amyloid L (AL, primary amyloidosis): Fibrillar deposits of Ig light chains. About 10% have overt myeloma
 - AA Amyloid (secondary amyloidosis): deposition of amyloid A protein – acute phase reactant. 40% have RA, another 10% have Ankylosing Spondylitis or Psoriatic arthritis
 - Amyloid deposits are distributed along blood vessels and in the mesangial regions

Glomerular-Vascular Syndromes

- Vasculitis
- Eclampsia: vasospasm and endothelial injury in multiple organs
- **Thrombotic Microangiopathy:**
 - → **microangiopathic haemolytic anaemia**, fever, **low platelets**, renal failure with haematuria and proteinuria
 - Blood film → fragmented red cells, Combs' negative
 - 90% response to plasmapheresis
 - Pathology: platelet thrombi within small vessels, especially glomeruli, fibrin deposition, and intimal thickening during healing
 - Causes:
 - *Haemolytic-Uraemic syndrome*: recent E. Coli GI infection producing Shiga toxin (EHEC; O157:H7). Mainly kids, some adults (usually non-shiga toxin associated), follows bloody diarrhoea. Toxin attaches to endothelium → inflammation and DIC. Treatment usually supportive
 - *Thrombotic Thrombocytopenia Purpura*: see page 445
 - HELLP in pregnancy: see page 460
 - Antiphospholipid Syndrome: see page 262
 - Microvascular thrombotic crisis in SLE
 - Drugs: oral contraceptives, quinine, treatment of transplant patients with OKT3, calcineurin inhibitors, clopidogrel, chemotherapy (mitomycin C, cisplatin, gemcitabine)
 - Diseases: adenocarcinoma, HIV
 - Treatment: untreated leads to irreversible renal failure and death in 90%. Plasma exchange (not always in post-diarrhoea HUS). Continue until platelets have normalised and haemolysis ceased. Platelet transfusion may worsen disease
- Atherosclerosis: chronic nephrosclerosis
- Cholesterol emboli: Shower of cholesterol crystals – especially after endovascular procedure (especially on aorta) → emboli trapped in microcirculation → ischaemia → focal glomerulosclerosis
- Hypertension:
 - Histologic changes: intimal fibrosis, hyaline deposition, downstream infarction → progressive scarring, granular surface
 - Risk factors for progression include low birth weight, pre-existing renal injury, duration of HTN
 - Usually history sufficient for diagnosis without biopsy
 - Treatment: ACEI and thiazide initially
 - In malignant hypertension, kidney's characterised by a "flea-bitten" appearance resulting from haemorrhages in surface capillaries
- Sickle cell anaemia: SA-haemoglobin. Homozygotes develop widespread vaso-occlusive disease → glomeruli HTN, FSGS, interstitial nephritis and renal infarction

Infectious Diseases damaging the Glomerulus

- Subacute bacterial endocarditis. Unusual in acute bacterial endocarditis as it takes 10 – 14 days to develop immune-complex mediated injury. Focal proliferation around foci of necrosis with immune deposits of IgG, IgM, C3. Maybe emboli infarcts or septic abscesses. Treatment: 4 – 6 weeks ABs
- Malaria: GN 2nd to immune complexes containing malarial antigens that are implanted in the glomerulus
- Schistosomiasis: primarily involves urinary and GI tracts. *S. mansoni* most commonly associated with renal disease

- HIV: usually 2.5 years after diagnosis, affecting 10% of HIV infected patients. Biopsy shows FSGS followed by MPGN. Present with nephrotic range proteinuria but without HTN, oedema or high lipids
- Hepatitis B and C (up to 30%): may present with microscopic haematuria, proteinuria and HTN. Hep B also associated with polyarteritis nodosa
- Syphilis
- Leprosy

Renal Tubular Diseases

Renal Tubular Acidosis

- A group of acquired or genetic disorders causing a *non-anion gap (hyperchloraemic)* metabolic acidosis resulting from proximal tubular HCO₃ wasting (failure to reabsorb) or impaired distal net acid excretion
- The degree of acidosis is out of proportion to the reduction in GFR (ie metabolic acidosis from CRF is not included in this group [and usually has a high anion gap] although may coexist)
- Untreated acidosis → osteomalacia. Retained acid is buffered by alkaline salts from bone (esp CaCO₃) → ↑Ca excretion and risk of stones
- Can be primary (inherited or sporadic) or acquired secondary to other conditions
- **Summary:**

	Type 1 – distal	Type 2 – Proximal	Type 4	GI HCO ₃ loss
Urine pH	> 5.5	< 5.5	< 5.5	5 – 6
Serum K	↓	↓/normal	↑	↓
Nephrocalcinosis	Yes			
Fanconi syndrome		Yes		
Daily acid secretion	↓	normal	↓	↑
Urine anion gap	+	+/?-	+	Normal (ie ↑Cl)
Daily HCO ₃ replacement	< 4 mmol/kg	<4 mmol/kg (? More)	>4 mmol/kg	variable

- **Type 1** (distal) Renal Tubular Acidosis (dRTA) – was discovered first (hence type 1 even though distal):
 - ↓K (can't get rid of H, so ditch K)
 - Is the worst in terms of acidosis – it's distal – nothing to mop up after it. Most acidotic of the RTAs – HCO₃ may be < 10
 - Unable to maximally acidify urine in the presence of systemic acidosis
 - Categories:
 - Acquired (the majority): **Sjogren's**, SLE, hypogammaglobulinaemia, chronic active hepatitis, drugs (eg amphotericin B toxicity), damage to renal medulla from a variety of causes (pyelonephritis, hyperparathyroidism, urinary tract obstruction...)
 - Primary AR with or without deafness, AD and sporadic forms, deficiency of carbonic anhydrase II (rare), or part of other hereditary disorders (eg Ehlers-Danlos, Wilson's)
 - **Impaired H secretion** or HCO₃ reabsorption in the **distal nephron**:
 - Affects H⁺-ATPase proton pump on luminal surface (associated with sensori-neural hearing loss) or chloride-HCO₃ exchange on apical membrane (exit point for HCO₃ into the blood) of the intercalated cell of the collecting duct
 - Urine can't be acidified
 - Ammonia excretion then affected as urine pH can't be lowered enough
 - Complications:
 - ↑Ca (released from bone to buffer acid) combined with alkali urine in the absence of citrate (normally inhibits stones, acidosis and ↓K cause citrate reabsorption) → **CaPO₄ stones**
 - Bone loss
 - Inability to concentrate urine (→ polyuria)
 - Potassium wasting: ↓H in tubule → ↑K loss in exchange for distal luminal Na which is reabsorbed. Also **2ndary hyperaldosteronism** because overall distal Na reabsorption is impaired
 - Acidosis and hypokalaemia can be life threatening with an intercurrent illness
 - Diagnosis: Normal anion gap acidosis with ↓K and urine pH > 5.5. Test by acid loading with ammonium chloride or calcium chloride and urine pH should normally drop < 5.5. Bicarbonaturia does not occur when alkali is given (unlike RTA 2)

- Treatment:
 - Acute: May present with muscle weakness with severe ↓K, acidosis +/- hypocalcaemia. Correct the hypokalaemia first (otherwise dangerous hypokalaemia as the acidosis reverses with K-H intracellular exchange)
 - Then alkali supplements. *Relatively low doses of alkali are sufficient: 1 – 3 mmol/kg/day.* Aim to maintain serum HCO₃ in the normal range. Ongoing K replacement usually unnecessary as fixing acidosis reverses K losses
- **Type 2** (proximal) RTA (pRTA):
 - ↓K
 - Impaired **HCO₃ reabsorption** and H secretion in the **proximal tubule** (bulk of filtered HCO₃ is recovered here). Distal HCO₃ reabsorption is overwhelmed. Acidosis is milder than type 1, HCO₃ is usually 12 – 20 mmol/L
 - Can still acidify urine down to ~ pH 4.5 as the distal tubule has a “2nd chance” to get it right
 - Diagnosis: HCO₃ in the urine (pH > 6.5 after an HCO₃ load) when plasma HCO₃ is low (< 22)
 - ↑Urinary HCO₃ leads to ↑K excretion. Need K⁺ and vitamin D as well. ↑Ca excretion but normal citrate so stones not so common as dRTA
 - Most often secondary to:
 - Autoimmune, drug-induced, infiltrative (eg myeloma), nephrotic syndrome, heavy metals, hyperPTH
 - One of several abnormalities that constitutes Fanconi Syndrome (see page 104)
 - Inherited diseases in which toxic metabolites produce tubular injury: eg Wilson’s disease, glycogen storage disease...
 - Drugs which cause inhibition of carbonic anhydrase eg acetazolamide
 - Rare primary genetic
 - Treatment:
 - Significant oral alkaline loads unlikely to restore acid base balance due to HCO₃ urinary loss
 - K⁺ supplements (K doesn’t resolve with correction of the acidosis), vitamin D
 - Thiazides enhance proximal reabsorption of Na and HCO₃ will follow
- **Type 3:** AR with features of type 1 and 2
- **Type 4:**
 - Acquired disorder on a background of moderate renal impairment – most commonly diabetic nephropathy. Usually not apparent until 80% of nephrons lost (diabetes, interstitial nephritis, obstructive nephropathy)
 - Leads to distal tubular ammoniogenesis
 - ↑K and acid urine (pH < 5.5)
 - Hypoaldosteronism or ↓aldosterone effect
 - Features:
 - Impaired secretion of K and H in the distal tubule
 - Hyperkalaemia → ↓NH₃ production. Inadequate secretion of daily acid load, but urine still acidic as there isn’t enough ammonia to act as a buffer
 - Causes:
 - **Aldosterone deficiency** (eg due to ↓renin in renal impairment or adrenal insufficiency) **or resistance** (eg Sickle Cell disease or obstruction)
 - Drugs which reduce aldosterone or its effect: spironolactone, NSAIDs, ACEI, trimethoprim, heparin
 - Genetic defects
 - Treatment:
 - Reduce hyperkalaemia as this will allow ↑NH₃ production
 - Low potassium diet (but not very effective). K binding resins usually not tolerated long term
 - Discontinue aldosterone inhibiting medications
 - Mineralocorticoid supplements (eg **Fludrocortisone**) if no concerns about HTN or CHF, otherwise loop diuretics with liberal salt intake

Cystic Renal Disease

Adult Polycystic Kidney

- Autosomal dominant. 10% sporadic: PKD1 loci on chromosome 16 (85%, worse, codes for polycystin-1, receptor molecule), PKD2 on chromosome 4 (15%, milder, later onset, codes for polycystin-2, ion channel). ESRF by average 54 and 70 years respectively

- NB: Autosomal recessive PCKD is more severe, presents in infancy, 1 in 20,000, mutation of the PKHD1 gene
- 1 in 500. 4% of ESRF in the US
- Pathogenesis:
 - Epithelial de-differentiation and proliferation
 - Whole nephron blows up → squashes other nephrons → progressive renal failure
 - Cystic lesions in other organs: *liver* (40% over 60), pancreas, lung, diverticular disease
 - Mitral valve prolapse in 25%. Also higher rates of AR and TR
 - 4 fold risk of intracerebral aneurysm
- Presentation:
 - Present with hypertension around 50 → IHD (most common cause of death), CVA
 - Vary in severity and onset
 - Usually only moderate proteinuria
 - Kidney's can get very large → impair respiration
 - If infected may be blood culture positive and urine negative if cyst doesn't communicate with the ureter
- Diagnosis:
 - With US (at least 3 – 5 cysts per kidney) or CT. Sensitivity over the age of 30 is 100% if positive family history. A negative US after age 30 excludes PKD1 in 100% (cysts “always” present by then). For PKD2, it's less sensitive and an age at which it has a high NPV hasn't been found.
 - In equivocal cases on imaging (eg and considering live kidney donation):
 - Mutation analysis: lots of allelic heterogeneity so consequently mutation analysis only identifies a mutation in around 60%
 - Linkage analysis may be the best option if an index family member can be tested
- Treatment: slow progression through aggressive blood pressure control. No evidence for low protein diet. Lipid soluble ABs (eg co-trimoxazole and quinolones) for infections (get into cysts)

Other Cystic Diseases

- Simple Cortical Cyst:
 - Dilation of a single nephron, usually to 5 mm – 1 cm. Most people usually have 3 or 4
 - Usually asymptomatic
 - If large and rupture → urinary peritonitis
- Infection: Tb and hydatids can present as cystic dilation on US
- Medullary Sponge Kidney: Rare. Sporadic > AD. Dilated collecting ducts. Best diagnosed with IVP. Can get TRA type 1. Renal function usually normal. Watch for stones
- Medullary Cystic Disease: AD, polyuria, anaemia and progressive renal failure presenting in 3rd – 4th decade. No specific therapy
- Tuberous Sclerosis: kidney's affected in 80% – renal cysts (like PCKD)
- Von Hippel-Lindau Syndrome: AD. Renal cysts occur in the majority of cases. Renal cell carcinoma in 40 – 70%, often multifocal. See page 76

Nephrolithiasis

- Most commonly due to idiopathic hypercalciuria
- Most stones are either calcium oxalate or calcium phosphate. Uric acid stones in 5 – 10%
- Hyperphosphaturia; In 20% of patients with stones and normal PTH, excess phosphate excretion may be to blame → ↑ 1,25 Vit D → ↑ intestinal Ca and PO₄ absorption. ?Associated with mutations in renal phosphate transporters (eg NHERF1 gene). NEJM 11 Sept 2008
- Hyperoxaluria:
 - Dietary: high levels of oxalate in chocolate, tea, rhubarb, asparagus, spinach
 - Enteric: stones more common in fat malabsorption
- Uric acid stones: Gout, idiopathic, dehydration, Lesch-Nyhan syndrome, malignant tumours
- Investigations: 24 hr urine, serum Ca, uric acid, electrolytes, Cr, pH
- Treatment:
 - High water intake
 - In 20%, oxalate stones are due to ↑ uric acid → allopurinol
 - Hypercalciuria: ↓ dietary Ca may → ↑ stones. Low Na, low protein diet better. Thiazides effect. Monitor and treat ↓ K (as ↓ urine citrate → ↑ Ca crystallisation)
 - Alkalisiation in RTA

- Oral α 1-adrenergic blockers relax ureteral muscle – shown to reduce time to stone passage

Infections of the Renal Tract

- In symptomatic patients, colony counts of 10^2 – 10^4 may signify infection. If obtained by in-out catheter or SPA then infection
- Types:
 - Non-catheter associated/community acquired:
 - 80% are G-ive bacilli E coli
 - Also G-ive rods: Proteus, Klebsiella, occasionally Enterobacter
 - Proteus and Klebsiella predispose to stones and are isolated more frequently if canuli present
 - Catheter associated/nosocomial:
 - The above plus pseudomonas and Serratia, S epidermidis. Much more likely to be resistant
 - If catheterised or diabetics, colonisation with candida or other fungi may lead to invasive infection
 - If urine is “sterile” consider Chlamydia trachomatis, Neisseria gonorrhoeae and HSV. Generally gradual onset, no haematuria, no suprapubic pain and > 7 days of symptoms
 - Also consider M Tb if sterile
- Pathophysiology:
 - Urea and high osmolarity of urine kill many bacteria
 - Bacterial virulence: most infecting E Coli are type O, K or H. Have fimbriae which mediate attachment to endothelium
 - Bladder epithelial cells secrete IL 6 and 8 → attracts polymorphs
 - Apoptosis of epithelium sloughs of cells and bacteria
- Risk factors for urinary tract infection:
 - Loss of normally dominant H₂O₂ producing lactobacilli from vaginal flora → colonisation by E coli
 - Spermicidal compounds → ↑risk of vaginal E coli colonisation
 - Pregnancy
 - Obstruction of any cause
 - Diabetes
 - Neurogenic dysfunction: spinal cord injury, tabes dorsalis, MS, diabetes...
 - Vesicoureteral reflux: retrograde flow during voiding
 - Men: prostatic hypertrophy
- Catheter associated UTI:
 - Risk of 3 – 5% per day
 - No benefit of treatment of asymptomatic infection (unless immunocompromised). Change catheter if treatment needed
- Treatment:
 - Uncomplicated UTI: stat dose as effective at clearing infection, but more frequent recurrence and doesn't eliminate vaginal colonisation as effectively as longer regimes
 - Chlamydia: azithromycin 1 gm stat or doxycycline 100 mg bd for 7 days
- Pyelonephritis:
 - Respond with ABs within 48 – 72 hours, unless papillary necrosis, abscess or obstruction. Treat for 7 – 14 days
 - Papillary necrosis: Infection of renal pyramids in association with kidney vascular disease or obstruction may → papillary necrosis. Can → acute renal failure
 - Emphysematous pyelonephritis: rapid course, unwell patient, accumulation of fermentative gases in perinephric tissues
- Acute Prostatitis: tense, boggy and extremely tender prostate. Prostatic massage usually → purulent secretions on subsequent urine, but may also cause bacteraemia. In uncomplicated cases generally due to common E Coli

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Chronic Fatigue Syndrome 182

Glossary

- Abulia: loss of will power, initiative or drive – inability to make decision
- Acalculia: inability to do mathematical calculations
- Anosognosia: lack of awareness that a deficit exists
- Apraxia: inability to perform a familiar task despite normal sensory and motor function
- Ataxia: inability to coordinate movement
- Finger agnosia: loss of ability to indicate one's own or another's fingers
- Eyes:
 - Ptosis: drooping of upper eye lid
 - Exophthalmos: protrusion of the eye
 - Mydriasis: dilation of the pupil
 - Miosis: contraction of the pupil
- Movement problems:
 - Akathisia: motor restlessness, as seen in reactions to phenothiazines
 - Athetoid: slow writhing movements
 - Chorea: Ceaseless rapid, jerky, involuntary movements
 - Dyskinesia: impairment of voluntary movement
 - Dystonia: impairment of muscle tone – sustained muscle contractions causing twisting movements of abnormal posture

Neuroimaging

- Blood:
 - Initially clots, fibrin contracts and squeezes out serum → more dense than surrounding tissue. As haemoglobin is lysed, ↑osmotically active particles → water drawn in

	Bone	Fluid	Acute Blood	Chronic Blood
T1 MRI	Black	Black (hypo-intense)	Grey	White
T2 MRI	Black	White (hyper-intense)	Black	White
CT	White	White (hyper-dense)	White	Black

- MRI more sensitive than CT for detecting lesions – esp spinal chord, cranial nerves and posterior fossa
- Diffusion MR – detects microscopic motion of water – *most sensitive technique for ischemic stroke*, also good for encephalitis, abscess and prion diseases
- Perfusion weighted MR – looks for perfusion – useful for distinguishing irreversible infarct from reversible ischaemic penumbra
- CT is better when you need it quickly (eg screening for bleed, infection), and for fine osseous detail – bone, trauma and conductive hearing loss. 3 – 5 cGy per study
- Contrast with CT: detects defects in BBB (tumours, infarcts, infection) and structures lacking a BBB (pituitary, choroid plexus and dura)

Cerebrovascular Disease/Stroke

- See Lancet 10 May 2008
- Pathophysiology:
 - No glycogen → neurologic symptoms in seconds
 - If very widespread → global hypoxic-ischaemic encephalopathy
 - Haemorrhage → mass effect + toxic effect of blood
 - Tumours → haemorrhage, seizure, hydrocephalus
 - Ischaemic penumbra – area of reversible ischaemia around the stroke – goal of thrombolysis is to save this
 - Oedema peaks on 2 to 3rd day. Watch in cerebellar CVA → raised ICP in the posterior fossa → brainstem compression → sudden respiratory arrest. Only signs may be gait unsteadiness, headache, dizziness, nausea and vomiting
- Prognosis: ¼ dead in a month, 1/3 by 6 months and a half by a year
- Ischaemic penumbra:
 - Abnormal brain tissue consistent with cellular dysfunction but not death – salvage of this tissue related to better clinical outcome (eg through thrombolysis)

- Assessed with MRI with DWI and PWI looking for DWI:PWI mismatch – still lots of technical issues associated with it's use in a clinical setting

Differentials of Stroke

- Stroke:
 - Ischemic 85% (Cardioembolic 17%, Carotid atherosclerosis 4%, other 64%)
 - Haemorrhage 15% (aneurysmal SAH 4%, Hypertensive ICH 7%, other 4%)
 - Can't differentiate on clinical grounds although more depressed LOC and higher BP favour bleed, remitting deficit favours ischaemia
- TIA: Most true TIAs (ie no permanent damage) last < 15 minutes. Infarcts often occur without signs. Risk of stroke in following 3 months is 10 – 20%, with most occurring in the following 2 days.
- Amaurosis fugax (Transient monocular blindness) occurs from emboli to the central retinal artery of one eye – think carotid stenosis
- Embolic stroke:
 - See AF, page 3, for risks in AF
 - Paradoxical embolisation: venous thrombi migrate through patent foramen ovale or atrial septal defect, detected by bubble-contrast echo. Has been debated – but evidence generally supports PFO and stroke link. Systematic reviews of small trials favour closure over medical treatment (Warfarin better than aspirin). PFO closure is an independent risk factor for AF
 - Artery – artery embolism: carotid bifurcation the most common site
 - Aortic Arch Atheroma: plaque thickness > 4 mm has hazard ratio of 13.8 for stroke. Embolic or just marker of atherosclerosis?
 - Dissection: internal carotid or vertebral arteries a common source of emboli in the young (< 60). Dissection is painful and precedes the stroke by hours/days. Associated with Marfan's, cystic medial necrosis, fibromuscular dysplasia, and spinal manipulative therapy. Conventionally treated with anticoagulation for 3 – 6 months
- Less common causes:
 - Watershed infarcts: lead initially to ischaemic of layers 4 and 6 giving laminar necrosis (seen on MRI). If severe ischaemia then deeper necrosis
 - Hypercoagulable disorders: Usually venous clots (ie venous sinus thrombosis). Protein S deficiency and homocysteinemia also arterial clots. SLE with Libman-Sacks endocarditis can cause embolic stroke
 - Venous sinus thrombosis: see page 146
 - Fibromuscular dysplasia – affects cervical arteries in women. See page 22
 - Temporal/Giant Cell arteritis: subacute, granulomatous inflammation with giant cells. Usually spares internal carotid (so little association with stroke)
 - Necrotizing arteritis – alone or in association with polyarteritis nodosa or Wegener's, small ischaemic infarcts of brain, optic nerve and spinal cord
 - Drugs: amphetamines and perhaps cocaine → acute HTN and drug induced vasculitis
 - Binswanger's Disease: rare. Subacute white matter infarction
 - Cephalgic migraine (without pain): can occur for first time after age 65, sensory disturbance predominates, crosses vascular boundaries, visual symptoms (eg scintillating scotomata)
 - Syphilis

Transient Ischaemic Attack

- ABCD2 Score:

• Age > 60 years	1
• First BP > 140 systolic or > 90 diastolic	1
• Clinical features:	
• Unilateral weakness	2
• Speech impairment without weakness	1
• Duration:	
• > 60 mins	2
• 10 – 59 mins	1
• Diabetes:	1
• Score > 4 admission or urgent evaluation, 30 day stroke risk 5 – 15%. If score 6 or 7 then 8% stroke in 2 days	
- TIA assessment:

- EXPRESS Study: Compared protocol for TIA assessment – delayed vs rapid (1 day) assessment: 90 day risk of recurrent stroke 10.3 vs 2.1 %
- Admission → ↓ risk of early stroke. No difference in events occurring after 1 month ie if haven't had it by then, unlikely to have it (NSW study)

Management of Stroke

- Imaging:
 - CT: with contrast can detect deficits in perfusion and SAH. CTA detects intracranial aneurysms. At least within 48 hours. More urgently if deterioration, SAH is suspected, trauma, anticoagulant therapy or hydrocephalus 2nd to ICH suspected
 - MRI is less sensitive than CT for detecting acute blood. Diffusion and FLAIR are more sensitive than standard MR for early infarction
 - No CXR unless specifically indicated
 - Consider TTE where it may lead to a change in management
- Proven Acute Treatments:

Acute Strategy	ARR	NNT	Benefit per 1000 strokes in Australia
TPA within 0 – 3 hours	11	9	11
Aspirin	1.2	83	6
Stroke Care Unit	5.6	18	46

 - Common measure of functional state is modified Rankin Score (mRS): 0 = OK, 5 = bad
 - Stroke Units:
 - Reduces mortality by about 20%, likely 2nd to improved BP control, early mobilisation, and adherence to best practice
 - Prevent death or disability in 50 out of a 1000 strokes (cf 6 per 1000 with tPA and 4 per 1000 with aspirin)
 - Thrombolysis (see NEJM 25 Sept:2008):
 - NINDS Trial (National Institute of Neurological Disorders and Stroke):
 - Showed clear benefit of rtPA 0.9 mg/kg to 90 kg max, 10% bolus, rest over 60 mins to patients treated *within 3 hours of onset* – most favourable effect if within 90 mins
 - Mortality reduction non-significant (21% vs 17%), significant reduction in disability (32% vs 44% ⇒ NNT ~ 10 [Wgtn Guidelines quote NNT of 7]), increase in bleeds (6.4% vs 0.6%) with higher risk with increased age, high BP, very severe deficits, severe hyperglycaemia, and (possibly) early ischaemic changes on CT
 - Only used for CVA covering less than 1/3 of MCA territory (5% risk of catastrophic bleed after large stroke). However subgroup analysis showed very old patients with very severe strokes still had better outcome with treatment (but absolute value of benefit was small)
 - ECASS III trial enrolled patients between 3 and 4.5 hours (also severe strokes excluded, fewer diabetics, so placebo arm did better than NINDS). Treatment with alteplase. Showed benefit in disability at 90 days, and non-significant ↓ in deaths. NNT 14 for favourable outcome. Same underlying rate of ICH as in NINDS (after adjustment for different measures)
 - Contraindicated if elevated INR
 - rtPA is a recombinant human tissue plasminogen activator causing fibrinolysis. Half life is 5 minutes
 - No other antiplatelet/anticoagulant within 24 hours. Repeat CT
 - Trials up to 6 hours showed no difference, as did higher dose of rtPA (1.2 mg/kg)
 - Streptokinase worse than placebo
 - Differences in drug dose and trial decision → efficacy remains unclear
 - If patient wakes with a stroke → onset considered the time they went to bed
 - Trials underway of intra-arterial thrombolysis (↓ systemic bleeding)
 - Aspirin. Only antiplatelet studied prospectively. International Stroke Trial (IST) and Chinese Acute Stroke Trial (CAST) showed benefit within 48 hours in ischaemic stroke: deaths at 14 days 9.0 vs 9.4%, fewer recurrent strokes (2.8 vs 3.9%), no excess of haemorrhagic stroke. Doses studied are 160 – 300 mg. No data for use < 48 hours. Meta-analysis: ARR of 1.4% any vascular event per year. Absolute excess intracranial bleeding of < 1 per 1000 per year. No difference in bleeding risk from 75 to 325 mg
 - Decompressive Surgery: Hemispheric decompression in young patients (18 – 60) with malignant middle-cerebral-artery-territory infarction and space occupying brain oedema within 45 hours of onset supported by evidence. NNT = 4 (but appropriate treatment in very few strokes, saves lives)

but ↑ number of moderate to moderately severe functionally impaired survivors). Usually arises 2 – 5 days after event. Difficult to predict

- Other Acute Treatments:
 - Anticoagulation:
 - Trials of glycoprotein IIb/IIIa (abciximab) underway
 - TOAST trial: no benefit of LMWH over aspirin acutely (although heparin often used for crescendo TIAs)
 - DVT prophylaxis: Grade A evidence for Aspirin. PREVAIL trial showed superiority of enoxaparin compared with unfractionated low-dose heparin
 - BP management: No RCT trial evidence to guide BP management after stroke. Treat cautiously for the first week (Grade C). Don't let systolic fall below 100-110. Lower malignant BP (220/12), or a BP >185/110 if thrombolysis anticipated. Treat DBP > 130
 - Association between hyperglycaemia and poor outcome, but no evidence about how to treat it. European Stroke guidelines recommend BSL < 10, Americans say intervene if > 16.7. Avoid glucose containing IVF. Reduce normal oral antihyperglycaemics and insulin while reduced eating. Measure BSL 4 hourly
 - Fever worsens ischaemia
 - Supportive care: infections, pressure areas,
 - Mood disorders (in excess of normal grief reaction) common. Assess with Hospital Anxiety and Depression Scale or Geriatric Depression Scale + clinical assessment. Antidepressant treatment for symptoms persisting at 6 weeks more effective than placebo. If good response then continue for at least 6 months – although optimal duration after stroke unknown
 - Driving: Patient may overestimate their skill. Signs predicting poor on road performance: homonymous hemianopia (absolute contraindication to driving), visuospatial and attentional deficits, reduced speed of motor processing, motor impairment, right cerebral hemisphere lesion. Minimum 1 month stand-down for TIA or stroke (with full recovery and no significant disabilities...)
- Acute treatments under evaluation: sonothrombolysis (low frequency ultrasound + thrombolysis to improve clot mobilisation), thrombectomy devices, BP reduction
- Neuroprotective strategies:
 - Drugs haven't shown benefit yet (benefit in animal models, no benefit in stage 3 trials in humans)
 - Induced hypothermia: promising treatment. Evidence suggests needs to be applied soon after injury (1 – 2 hours). Fever (irrespective of cause) adversely affects various neurologic injuries. Affects a range of temperature dependent cellular response to ischaemia and reperfusion (↓ apoptosis, ↓ free radical production, ↓ oedema, ↓ metabolism, ↓ seizure activity). Hypothermia has been proven to ↓ intracerebral oedema irrespective of cause. Many animal studies in stroke, small non-controlled studies in humans, only one with thrombolysis and cooling (safe but small numbers so no conclusions). Lancet 7 June 2008

Prevention of Stroke

- Primary Prevention:
 - Manage risks: Usual risks, especially HTN, previous stroke, also OCP, recent MI, hypercoagulable states
 - HTN: TIAs fall by 1/3 for every 10 mmHg SBP reduction. No lower threshold. Benefit from lowering below traditional definitions, particularly strong evidence for ACEI and ARBs. More related to level than agent – although PROGRESS trial showed combination of perindopril and indapamide more beneficial
 - Aspirin in women > 45 years old but not men proven
 - Statins: studies with patients *with cardiovascular risk factors* (including dyslipidaemia) → 20 – 30% relative risk reduction. Reduce risk even in patients with normal cholesterol. Studies specific to secondary prevention in progress. Optimal levels are total cholesterol < 4.0 and LDL < 2.5
 - Tight control of blood sugar in diabetes not proven to reduce stroke
 - Smoking cessation: no evidence from RCTs post stroke – but observational studies suggest risk reduction

Secondary Prevention:

2 nd prevention Strategy	ARR	NNT	Benefit per 1000 strokes in Australia
Antiplatelet	23	1	100
BP lowering	28	2.2	45
Carotid Endarterectomy	44	3.8	26

- Antiplatelet:

- Aspirin: RRR of ~ 13%
- Clopidogrel: see page 25
 - CAPRIE Trial (Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events) showed it was only marginally more effective than aspirin in preventing stroke – and this margin was accounted for by the subgroup with peripheral vascular disease
 - CURE Trial: Aspirin and Clopidogrel together → more effective but more bleeds. Need to treat 108 patients for 2 years to avoid one event
- Dipyridamole:
 - Antiplatelet that inhibits uptake of adenosine by a variety of cells, including the vascular endothelium → inhibits aggregation
 - Trials in early 90s showed questionable benefit from addition to aspirin
 - ESPS-2 Trial (Effective in European Stroke Prevention Study-2). Controversial (eg dosing of Aspirin 50 mg and Dipyridamole 200 mg BD). But combination better
 - ESPRIT Trial: 2763 patients (mean age 63 years) with past TIA or non disabling stroke given aspirin 30 to 325 mg/d (median 75 mg) +/- extended release dipyridamole 200 mg bd, treatment group had fewer primary outcome events 13% vs 16% over 3.5 years median follow up. NNT for dipyridamole over aspirin = 70. No increase in bleeding. Lancet 2006;367:1665-73
 - SE: headache, plus requires BD dosing
 - Caution in hypotension (can cause orthostatic hypotension, exacerbate AS), can exacerbate myasthenia gravis, caution in heart failure and migraine history
- PRoFESS Trial (Prevention Regimen for Effectively Avoiding Secondary Strokes, NEJM 18 Sept 2008): enrolled 20,000. Failed to show superiority of aspirin + dipyridamole over clopidogrel. More serious bleeding complications with aspirin + dipyridamole than clopidogrel
- Pooling data from these trials in a network analysis ⇒ aspirin + dipyridamole better than clopidogrel better than aspirin
- IIb/IIIa antagonists associated with increased mortality
- Anticoagulation:
 - AF proven, rheumatic heart disease assumed. With prosthetic heart valves, aspirin adds benefit to warfarin. Otherwise increased bleeding without benefit
 - SPIRT Trial – used INR 3.0 – 4.5 and found not to be worth the bleeding
 - WVARSS Trial found 1.4 – 1.8 no benefit compared to aspirin
 - If stroke and significant mitral valve disease or an MI in the preceding 3 months should start warfarin. Timing uncertain – usually after 14 days
 - 0.3 – 0.6% per year risk of major bleeding (mainly ICH, risk rises with age, BP and INR)
- ACEI:
 - HOPE trial: 10 mg ramapril in patients with vascular disease or diabetes plus one other risk factor reduced combined endpoints (stroke/MI/vascular death) by 22%
 - PPARS trial showed peridopril plus indapamide reduced stroke (?ACEI or just effect of ↓BP)
 - PRoFESS Trial: No difference in recurrent stroke, major cardiovascular events or diabetes from an ARB (telmisartan, vs placebo) initiated early after a stroke, in a trial of 20,332, median follow up 2.5 years
- Cholesterol:
 - Weak risk factor for ischaemic stroke
 - Fatal and non-fatal stroke reduced with statins, independent of baseline cholesterol (ie is it a non-cholesterol mediated effect??)
 - Heart Protection Study: 40 mg Simvastatin in patients with TIA or stroke lead to ↓cardiac events but not ↓stroke recurrence
 - SPARCL Trial (Stroke Prevention by Aggressive Reduction in Cholesterol Level): atorvastatin 80mg vs placebo starting ~ 3 months following stroke or TIA and no history of IHD → ↓fatal and non-fatal stroke: 11.2% vs 13.1% for any stroke (ie NNT 50)
 - Avoid in haemorrhagic stroke unless compelling reasons – combining CARE, LIPID, SPARCL and HPS shows RR of haemorrhagic stroke of 1.73. Disputed...
- Endarterectomy:
 - Symptomatic carotid disease: patient has experienced an event within the vascular distribution of the artery within the last 4 (NASCET) or 6 (ECST) months
 - Treatment studied in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and European Carotid Surgery Trial (ECST). If stenosis > 70% then 2 year stroke

risk dropped from 26 to 9% with *early* revascularisation (NNT for 5 years to prevent 1 stroke = 6.3). Smaller benefit for 50 – 70% stenosis. Harm if < 30% or near occlusion (>99%)

- *Asymptomatic* Carotid Atherosclerosis Study (ACAS), > 60% stenosis, surgery lead to a 1.2% annual risk reduction, *in patients < 75 years*. Benefit on both contralateral and ipsilateral sides
- Most inappropriate endarterectomies are with asymptomatic patients with excessive comorbidities or low-grade (<60%) stenosis
- Balloon angioplasty and stenting: SAPHIRE trial (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy, NEJM 2008:358): Endarterectomy = Stenting at 3 years (although greater proportion of stenting people lost to follow-up (30%))
- Patient PFO: No trials. Put < 55 years on aspirin and device close those older or anticoagulate
- Physiotherapy: movement re-education, positioning, mobilisation, no monkey bars (→ learned non-use of the affected side), management of spasticity.
- Moderate exercise (30 – 60 minutes of brisk aerobic activity 3 times per week) – Grade A

Stroke Syndromes

- Four classes:
 - Total anterior circulation infarction (TACI. Anterior = Carotid artery ⇒ anterior *and* middle cerebral arteries): language or visuospatial disorder (depending on side) + homonymous hemianopia + motor deficit in two or more of face, arm or leg. Can have cerebral oedema and ↓LOC. Mortality at one month = 40%
 - Partial anterior circulation infarction (PACI): 2 of 3 of TACI criteria (ACA occlusion: Flaccid paralysis and sensory loss of leg). Mortality at one month = 5%
 - Small vessel stroke (preferred term for lacunar infarct – LACI):
 - 30 – 300 µm diameter arteries. 20% of strokes. HTN and age main risks. Manifestations:
 - Pure motor stroke: posterior limb of internal capsule – usually involving face, arm and leg
 - Mixed motor/sensory hemiplegic stroke
 - Ataxic hemiparesis – infarct in the base of the pons
 - Motor hemiparesis with Broca’s aphasia due to lenticulostriate branch to the genu and anterior internal capsule and adjacent white matter
 - Pure sensory stroke – ventrolateral thalamus (uncommon)
 - Mortality at 1 month = 2%
 - Posterior circulation infarction (POCI. Posterior = Basilar artery ⇒ posterior cerebral artery): variety of presentations, including ipsilateral cranial nerve palsy with contralateral motor and/or sensory deficit, isolated cerebellar dysfunction, isolated homonymous visual field defect, may also have dysconjugate eye movements, Horner’s syndrome, dysarthria and/or dysphagia
- Signs of brain stem involvement:
 - Diplopia, bilateral weakness or numbness, vertigo, ataxia
 - Brain stem syndromes:

Syndrome	Structures Affected	Symptoms
Medial Medullary due to Ant. Spinal or Vertebral artery	Hypoglossal nerve (12)	Atrophy and paresis of tongue, deviates to ipsilateral side
	Medial lemniscus	Contralateral loss of discriminative touch and proprioception
	Pyramid	Contralateral hemiparesis
Lateral Medullary, due to Vertebral, PICA, maybe AICA	Spinal trigeminal n. & tract	Ipsilateral loss of pain/temperature on face
	Spinothalamic tract	Contralateral loss of pain/temperature on body
	N. ambiguous	Loss of gag reflex, dysphagia, dysarthria, swallowing problems
	Inferior cerebellar peduncle	Ipsilateral ataxia
	Vestibular n.	Nystagmus, vertigo
	Dorsal motor n.	Vomiting
Basal Pontine Syndrome, due to Basilar and pontine	Descending sympathetic fibres	Ipsilateral Horner’s syndrome
	Abducens	Ipsilateral medial deviation of the eye
	Facial	Ipsilateral paralysis of face

arteries	Medial lemniscus	Contralateral loss of discriminative touch and position sense
	Corticospinal tract	Contralateral hemiparesis
Mediobasal mesencephalic syndrome due to aneurysm of posterior Circle of Willis or Basilar	Oculomotor Edinger-Westphal	Ipsilateral outward deviation of eye Ipsilateral dilated pupil, no light reflex
	Corticospinal tract Red nucleus	Contralateral hemiparesis Contralateral cerebellar ataxia

- Anton's Syndrome: cortical blindness but the patient is adamant they can see. May also be confused. Requires bilateral occipital infarcts

Intracranial Haemorrhage

- CT more sensitive than MRI acutely for blood
- 1 month mortality approaches 50%
- **Subarachnoid Haemorrhage:**
 - Bleed in the subarachnoid space (ie anywhere you'd get CSF)
 - 5% of all strokes
 - Most common cause: rupture of saccular ("Berry") aneurysm. Probably 2% of people have them. Surgical risk far exceeds bleeding rate if asymptomatic
 - Most common sites for giant aneurysms (> 2.5cm) is terminal internal carotid artery, MCA bifurcation and top of the basilar artery. 6% annual rupture risk
 - In cases of rupture, survival of those that arrive at hospital is ~45%. Rebleeding rate high
 - Rupture → sudden ↑ICP and ↓LOC. Headache +++, vomiting, neck stiffness
 - LP: Blood in 95%. Xanthochromia: Lysis to bilirubin within 6 – 12 hours, peaks at 48 hours, lasts 1 – 4 weeks
 - May be ST segment and T wave changes on ECG due to circulating catecholamines
 - Differential: Thunderclap migraine
 - Delayed deficits due to:
 - Rerupture
 - Hydrocephalus
 - Vasospasm → symptomatic ischaemia/infarction in 30% over 4 – 14 days with preceding ↓ in mental status. ?Due to blood surrounding the artery. Detected by TCD ultrasound or CT angiography. Treatment with nimodipine 60 mg QID – a cerebroselective CCB which reduces vasospasm (as opposed to acute BP lowering) – routinely used but not a lot of evidence
 - Hyponatraemia: Over first two weeks, 2nd to inappropriate secretion of vasopressin. Don't fluid restrict as this → ↑stroke risk due to decreased perfusion. Give N saline
- Management:
 - If SAH, then keep BP below 170/110 (American Heart Assoc guidelines) with nicardipine, labetalol, nitrate patch...
 - If ↓LOC (GCS <14) or haematoma > 3 cm then neurosurgical referral. Surgical evacuation or decompressive craniectomy in patients with supratentorial haematomas has not been shown to be of benefit
 - If comatose then treat for presumed ↑ICP with hyperventilation, mannitol and head elevation
 - Stool softeners to avoid straining till repaired
 - Pneumatic compression stockings
- Antiplatelet/Anticoagulation issues:
 - Proximal DVT/PE management: Risk of recurrent ICH in someone anticoagulated for 3 months is 3 – 5% (Hart, 2004), with the risk highest in the first 2 weeks, cf risk of 25% of fatal PE in someone with proximal DVT or PE without anticoagulation (Barrit and Jordan, 1960 – likely that the risk is not this high). Consider vena cava filter in the first two weeks – anticoagulation after that
 - Aspirin for vascular prevention? No (especially if likely amyloid pathology). Aspirin increases the risk of recurrent ICH by 40%, absolute increase of 0.8% per year. Balance favours aspirin for 1 month after MI (3.6% absolute benefit from aspirin). Also perhaps for recent TIA/stroke
 - If AF: Warfarin only if annual absolute risk of ischaemic stroke is > 7% (Eckman, 2003)
 - Mechanical valve: withhold anticoagulation for up to 10 – 21 days following ICH (Phan, 2000)

- Also bleeding from a vascular anomaly and extension in the subarachnoid space from a intravertebral haemorrhage. Also mycotic aneurysms from bacterial endocarditis
- **Intraparenchymal haemorrhage:**
 - Most common type of intracranial haemorrhage
 - Hypertensive haemorrhage: spontaneous rupture of a small penetrating artery. Presents usually while awake, abrupt onset focal signs, seizures uncommon. Deficits worsen over 30 – 90 minutes maybe with ↓LOC
 - Associated with anticoagulant therapy may develop over 24 – 48 hours
 - Risks of mortality: low GCS, > 30 ml volume, intra-ventricular or infra-tentorial extension, age > 80. Other poor prognostic factors: haematoma growth, early deterioration, warfarin
 - STICH trial for surgery vs conservative management: not significantly different, greater benefit if haematoma < 1 cm from the surface
 - rFVIIa within 4 hours of onset decreased haematoma volume at 24 hours but no difference in clinical outcome (NEJM 2008;358(2):2127)
 - INTERACT Trial: Spontaneous ICH with SBP 150 – 220. Target BP 180 (standard) vs 140 (intense) treatment. Mean haematoma growth in 24 hours 36% vs 14% but ?no translation into clinical difference
- Other causes of intracerebral haemorrhage:
 - Extradural Haemorrhage: bleed into the potential space between the inner table of the skull and the dura. Lentiform shaped bleed on CT. eg rupture of middle meningeal artery
 - Subdural Haemorrhage: bleed into the potential space between the dura and arachnoid mater. Crescentic shaped collection. Extension limited by the falx and the tentorium
 - Cerebral amyloid angiopathy → arteriolar degeneration. Common cause of *lobar* haemorrhage in the elderly. Especially if recurrent haemorrhages and after thrombolysis. Seen with congo red stain of vessels. No treatment
 - Due to anticoagulant therapy
 - Haemorrhage into a brain tumour: Choriocarcinoma, melanoma, renal cell, bronchogenic
 - Hypertensive encephalopathy → headache, nausea, vomiting, seizures, ↓LOC. Usually no localising signs. Retinal haemorrhages, exudates, papilloedema. ICP and CSF proteins elevated. Lower BP – but stroke if too quickly
 - Vasculitis (eg polyarteritis nodosa or SLE) haemorrhage into any area of the brain
 - Arterial Venous malformations: bleeding most common from age 10 – 30. Half of AVMs become evident as intracerebral haemorrhages. Treatment: surgery or stereotaxic radiation. If asymptomatic, 2% per year of bleeding. Mortality risk with bleed ~ 15%
- Rebleeding:
 - Deep hemispheric “hypertensive” bleeds: recurrence 2 – 3 % per year
 - Lobar haemorrhages: Risk as high as 28% over 20 months (Greenberg, 2004)

Venous Sinus Thrombosis

- Lateral or Sagittal sinus thrombosis. Thrombus or external compression → occlusion → cortical venous infarction (commonly haemorrhagic at the white-grey matter junction)
- Due to:
 - Pregnancy/postpartum, sepsis, dehydration, elderly and intracranial infection
 - Hypercoagulable: thrombophilia polycythaemia, sickle cell, protein C&S deficiency, Factor V (resistance to activated protein C), antithrombin III deficiency, homocysteinemia
- PC: non-specific, headaches, focal signs, nausea, vomiting, possible seizures, possible psych presentation
- Signs: maybe papilloedema, forehead and skin oedema, proptosis, CN 3, 4 & 6 compromise 2nd to cavernous sinus thrombosis
- Imaging. CT usual normal. Diagnosis with MR Venography. May be subtle signs on CT. Variants of venous anatomy are common. Hypoplastic sinus or prominent arachnoid granulations may simulate venous thrombosis
- Treatment: IV Heparin improves outcome, even if intracranial haemorrhage

Headache

- Source: Diagnosis and Treatment of Headache, ICSI.org
- Check: family history, current treatment
- Warning signs:
 - Worsening over months

- New of different headache
- Any headache with maximum severity at onset
- New onset > 50
- Headache precipitated by a valsalva
- Suggestion of a systemic disorder, neurologic signs or seizures
- Migraine (Lancet Jan 31, 2004)
 - Prevalence peaks at age 40
 - Unilateral, throbbing, severe, nausea/vomiting, photophobia, aggravated by normal activities
 - Aura: does not last more than 60 minutes and attack follows within 60 minutes
 - Best criteria for differentiating migraine from other headaches: presence of nausea/vomiting with 2 out of three of: photophobia, phonophobia, osmophobia
 - Pathophysiology:
 - Some genetic forms: Familial hemiplegic migraine mapped to chromosome 19
 - Aura occurs during phase of spreading reduction in cortical blood flow (spreading oligoemia), but is due to neuronal dysfunction
 - Headache 2nd to cortical spreading which ↑NO, K⁺, H⁺ and cytokine release affecting the dura → depolarise perivascular trigeminal terminals → activation of trigeminal nucleus → ↑middle meningeal artery blood flow & proinflammatory peptides in the meninges
 - Treatment: treat early
 - Adjuvant therapy:
 - Dark, quiet room, IV rehydration, caffeine
 - Dopamine antagonists/antiemetics: metoclopramide, prochlorperazine (Stemetil), chlorpromazine (Largactil)
 - Mild:
 - Aspirin 900 mg
 - Paracetamol 1000 mg
 - Ibuprofen 400 – 800 mg
 - 5HT agonists (triptans)
 - More severe:
 - DHE
 - Chlorpromazine
 - Valproate
 - Magnesium IV
 - Serotonin (5-hydroxytryptamine or 5-HT):
 - 7 classes of 5-HT receptors in the body: 5-HT_{1to7}. The 5-HT_{1B} receptor is located on intracranial blood vessels and CNS neurons. 5-HT_{1D} on CNS neurons and trigeminal nerve endings, 5-HT_{1F} on trigeminal nerve endings
 - Ergots (eg Ergotamine) and Triptans are agonists at the 5-HT_{1B}, 5-HT_{1D} and in part at 5-HT_{1F}. They act to constrict extra-cerebral intracranial vessels, inhibit trigeminal neurons and block transmission in the trigeminal nucleus. No evidence of benefit during the aura phase of an attack. Ergots have greater affinity at 5-HT₂, adrenergic and dopaminergic receptors → ↑ adverse events
 - Can't use ergots and triptans concurrently, or if IHD/Prinzmetal's angina, PVD (they minimally constrict coronary arteries), not in pregnancy or ? hemiplegic or basilar-type migraine (basilar = 3 of diplopia, dysarthria, tinnitus, vertigo, transient hearing loss or mental confusion)
 - Sumatriptan was the first of the triptans – the other 6 are more centrally penetrant but sumatriptan is the only one that can be given sc (97% bioavailability cf ~15% orally, nasally or PR). Metabolised by MAO-A so contraindicated if MAOIs. 1 hour response in 69%
 - DHE (dihydroergotamine mesylate – only IV ergot preparation) protocol:
 - Test dose: 0.5 mg IV over 2 -3 minutes + metoclopramide
 - Then infusion at 0.125 mg/hr
 - Prophylaxis:
 - Keep a symptom diary
 - Score severity with MIDAS – Migraine disability assessment scale
 - Avoid triggers: alcohol, hunger, irregular sleep, relationship with menstrual cycle

- β -blocker (several proven effective), Amitriptyline (only antidepressant with limited support for effectiveness, in combination with beta-blocker if needed), AEDs (Topiramate, Gabapentin), Verapamil (not in migraine with aura, SE constipation)
- Several natural products (eg Riboflavin) have shown effectiveness in blinded RCTs
- Women with migraines with aura should avoid use of oestrogen containing OC
- Patent foramen ovale: high prevalence (38%) of moderate to large patent foramen ovale in migraine sufferers. MIST trial (shunt procedure) found closure had no significant advantage
- Episodic Tension Headache:
 - Less than 15 days/month, lasting 30 minutes to 7 days
 - Tight, non-pulsating, bilateral, not aggregated by normal activities
 - No nausea/vomiting/photophobia
 - Adjuvant Treatment: stress management, physiotherapy
 - Prophylaxis: amitriptyline, venlafaxine
- Chronic Tension Headache (diverse cluster of symptomatology):
 - As for episodic, but > 15 days per month
 - Control of analgesia primary aim: often taking too much and getting rebound
- Cluster Headache
 - Severe, unilateral, orbital, supraorbital and/or temporal pain lasting 15 to 180 minutes untreated
 - Associated with at least one of (on the side of the pain): conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, forehead/ facial swelling, miosis, ptosis, eyelid oedema, agitation/ unable to lie down
 - Frequency up to 8/day
 - Acute Treatment: O₂, sumatriptan, DHE
 - Prophylactic Treatment: Avoid alcohol during cluster cycle, verapamil (first line), lithium
- Sinus headache:
 - Migraines often misdiagnosed as sinus headaches
 - Sinus headache = purulent nasal discharge, pathologic sinus finding by imaging, simultaneous onset of headache and sinusitis, and headache localised to facial areas of the sinuses
- Other headaches:
 - CADASIL – 22% have migraine with aura
 - Brain tumour – headache in 30%, dull ache, worsens with exertion or change in position. Vomiting preceding headache by weeks → posterior fossa tumour
 - Temporal arteritis: headache may involve any part of the cranium, also PMR, jaw claudication, fever, weight loss
 - Glaucoma – headache in association with painful eye
 - Coital headache – abrupt in onset, fades over minutes

Dementia

- For Delirium see page 470
- = an acquired deterioration without reversible cause in memory and at least one of:
 - Impairment of abstract thinking
 - Impairment in judgement
 - Personality change
 - Other disturbance of higher cortical thinking
- that impairs the successful performance of ADLs or relationships
- Memory is the most common ability lost

Memory

- Working memory: lasts < 30 s and has limited storage capacity. Holds ~ 7 bits of information. Highly vulnerable to distraction – requires attention. Tested by spelling words backwards. Involves reticular activating system and prefrontal and parietal lobes
- Episodic memory – last minutes to years. Tested by 3 to 5 minute recall. Involves hippocampal complex. Vulnerable to metabolic and degenerative processes. “what”, “where”, and “when” information.
- Remote or long term memory. Contains personal experiences and knowledge. Facts stored in left anterior temporal cortex. Rest unknown

- Cholinergic system important – anticholinergic agents (eg atropine) interfere with memory. Choline acetyltransferase (catalyzes the formation of Ach) and cholinergic receptors deficient in AD.
- Progression:
 - Benign forgetfulness of the elderly
 - Mild cognitive impairment (MCI):
 - Condition between normal cognition and dementia. Trades under many names
 - MMSE often normal – memory impairment but preserved general cognitive function and intact ADLs
 - Risk factors: family history of dementia, presence of an apolipoprotein $\epsilon 4$ allele, small hippocampal volumes, education
 - Annual conversion to dementia of 0 – 34% (average 16%) depending on definition and population studied. Age is the strongest predictor. PET shows extensive amyloid in those who subsequently convert
 - 20% remain stable after many years, some revert to normal
 - No intervention proven beneficial

Pathology

- Major degenerative dementias associated with the abnormal aggregation of a specific protein:
 - α -synuclein:
 - Multiple System Atrophy (early urinary incontinence, postural hypotension, and dysarthria)
 - Parkinson's
 - Dementia with Lewy Bodies (but early hallucinations – especially drug induced – and disturbances of behaviour)
 - Tauopathies
 - Progressive Supranuclear Palsy (early imbalance and falls)
 - Frontotemporal dementia. 3 repeat Tau (Pick bodies) in Pick's variant
 - Amyloidopathies: Alzheimer's – plaques of amyloid (A β 42), also tangles (Tau) and Lewy bodies (α -synuclein)
 - Prion related protein: CJD

Workup

- History:
 - Change in personality, disinhibition, weight gain, apathy, abnormalities in speech – favour FTD not AD
 - Early presence of visual hallucinations, parkinsonism, delirium, Capgras syndrome (delusion that a familiar person has been replaced by an impostor) – favour DLB
 - Rapid progression with motor rigidity and myoclonus suggests a prion disease
 - Gait disturbance: consider vascular dementia, Parkinson's disease, normal-pressure hydrocephalus
 - Occupations: lead exposure
 - Unexplained falls, axial rigidity and gaze deficits: progressive supranuclear palsy
- Exam:
 - MMSE \leq 24:
 - In AD has poor sensitivity (63%) but good specificity (96%)
 - Not good for other dementias – all short tests approximately equal
 - AD: deficits in episodic memory and category generation (eg naming 4 legged animals)
- Testing:
 - Multiple screening tests for less common reversible causes: each with a low yield
 - Routine: TFTs, Vitamin B12, CBC, Electrolytes, VDRL (controversial)
 - Imaging:
 - On CT (rule out)/MRI (rule in): no specific pattern for DLB (although tend to have less hippocampal atrophy than seen in AD). Diffusion-weighted MRI detects basal ganglia abnormalities in most CJD
 - Must image when age $<$ 60, rapid ($<$ 2 months) decline, significant head trauma, unexplained neurological symptoms, anticoagulants, unexplained urinary incontinence/gait problems (?normal pressure hydrocephalus)
 - PET increasingly used to rule in Alzheimer's
 - LP shows increased Tau and decreased A β 42 in AD, but sensitivity and specificity not high
 - ApoE4 testing not recommended

Differential

- Common:
 - Alzheimer's
 - Vascular dementia
 - Alcoholism
 - Parkinson's Disease
- Less common:
 - Vitamin Deficiencies: Thiamine (B1), B12 (pernicious anaemia)
 - Endocrine & Organ Failure: Hypothyroidism, Adrenal insufficiency, Hypo and Hyper-PTH, renal failure, liver failure, pulmonary failure
 - Chronic infections: HIV, Neurosyphilis, Papovavirus (progressive multifocal leukoencephalopathy), Prion diseases, TB, fungal and protozoa
 - Head Trauma: Subdural haematoma, normal pressure hydrocephalus
 - Neoplastic: tumours, sarcoidosis
 - Toxic: drugs, heavy metals, dialysis dementia
 - Psychiatric: Depression, schizophrenia, conversion reaction
 - Degenerative: Huntington's, Pick's, Lewy Body Dementia, Progressive Supranuclear Palsy (Steel-Richardson syndrome), Multisystem Degeneration (Shy-Drager syndrome), Motor Neuron Disease, MS, Adult Down's
 - Miscellaneous: Vasculitis, CADASIL, recurrent non-convulsive seizures
- Most common reversible causes: depression, hydrocephalus and alcohol

Alzheimer's Dementia

- Most common cause
- Begins in entorhinal cortex, spreads to hippocampus then posterior temporal and parietal neocortex, eventually diffuse
- Diffuse atrophy and secondary enlargement of ventricular system, atrophy of the *hippocampus* most closely correlates with memory loss. On PET scan decreased activity in the parietal lobes
- Microscopically: neuritic plaques ("senile" plaques) containing **A β 42 amyloid** (derived from a larger transmembrane protein amyloid precursor protein APP), silver staining neurofibrillary tangles (NFTs) in the neuronal cytoplasm and A β amyloid accumulation in arterial walls
- Reduction in acetylcholine may result from degeneration of cholinergic neurons in the nucleus of Meynert
- Presentation: memory impairment spreading to language and visuospatial deficits. Rapid forgetting prominent in testing. Advanced ADLs (finances, shopping, etc). Social graces and superficial conversation retained. Anosognosia = unaware of difficulties. Delusions (eg theft, infidelity)
- Prognosis: life expectancy 8 – 10 yrs, range 1 – 25 years
- Risk factors: *age*, family history, female
- Genetics:
 - Familial forms < 1% of all Alzheimer's
 - Point mutations in APP on chromosome 21 produce early onset, autosomal dominant AD. Very rare. (Note: 3 chromosome 21's in Down's Syndrome – relationship with Down's dementia?)
 - Numerous mutations in Presenilin-1 (PS-1, chromosome 14) and PS-2 (chromosome 1) lead to familial AD
 - Apo ϵ (chromosome 19) – late onset familial and sporadic AD. Involved in cholesterol transport – alleles 2, 3 and 4. Type 4 associated with AD in the general population. ?Dose dependent modifier of the age of onset. E4 the strongest risk factor – but neither necessary nor sufficient
- Prevention: numerous epidemiological associations (Vitamin E, NSAIDs, Statins, Moderate alcohol, social/physical activities), no prospective trials show evidence

Treatments for Alzheimer's

- Acetylcholinesterase inhibitors:
 - Tacrine (liver toxicity – withdrawn), donepezil, rivastigmine and galantamine
 - Modestly efficacious, but clinically discernable benefit in 10 – 33%, peak efficacy at 3 months, maximum difference cf placebo at 6 months, decline proceeds but at a later time. Failure to decline also a response
 - Minimum 12 weeks trial. Stop if poor compliance or continued decline
 - Maximum benefit in retention of ADLs, changes in adverse behaviour more controversial
 - No change in late stages

- 3 of 6 RCTs and 2 meta-analyses have shown significant differences, the magnitude of the difference is small
- Cochrane Review 2007 of 10 trials: improvement of 2.7 in 70 point scale, more side effects of nausea, diarrhoea, vomiting. Another meta-analysis shows no difference in terms of institutionalisation
- One head to head trial of donepezil vs rivastigmine showed equivalence, but fewer adverse events on donepezil
- SE:
 - Nausea, loose stools and disturbed sleep +/- vivid dreams
 - SE dose related and minimized by gradual titration from donepezil 5mg/d to 10 mg/d over 4 weeks
 - *Bradycardia*
 - Caution in poorly controlled asthma and peptic acid disease (cholinomimetic properties)
 - Possibly less with Rivastigmine patch (coming...)
 - No established evidence in other dementias (?useful in Lewy Body)
- Memantine: Neuroprotective NDMA antagonist (blocks glutamate-induced excitotoxicity). Studies in moderate-severe Alzheimer's. Listed in Australia for MMSE 10 – 14 and monotherapy
- Vaccination against A β protein effective in animal models – risk of meningoencephalitis in humans. Vaccination with 6 year follow up showed reduced amyloid burden, but no significant improvement in cognitive function (Lancet 19 July 2008). Raises the question of whether A β -amyloid initiates the process but that it is perpetuated by other factors (eg continued accumulation of Tau, inflammatory injury, etc)
- Dimebon found effective in a RCT of 183 patients in Russia (Lancet 19 July 2008)
- Not established/doubtful:
 - Antioxidant selegiline slowed institutionalisation – vitamin E cheaper and often used – possible modest benefit
 - Huperzine A (Chinese club moss extract, an anticholinesterase) improved cognitive function – meta-analysis of 6 trials of 454 patients (Cochrane Review 2008)
 - Anti-inflammatories: Small studies suggested NSAIDs: not confirmed in larger prospective studies. \uparrow vascular events. Not effective as therapy
 - HRT: Early indications of the benefit of estrogen-progesterone replacement subsequently disproved. Possible protective effective but unlikely treatment benefit
- **Supportive:**
 - Carer training: 1 year of training leads to sustained benefit and \downarrow depression in caregivers. OR of patient remaining at home = 5
 - Make life comfortable, uncomplicated and safe
 - Memory aids – note books, lists
 - Stress familiar routines, short term tasks, walks
 - In a trial in dementia patients, collaborative care including a nurse manager led to reduced neuropsychiatric symptoms and lower carer stress at 12 months, increased use of cholinesterase inhibitors and antidepressants (JAMA 2006;295:2148)
- PEG feeding: Doesn't stop aspiration and they don't prolong life

Vascular Dementia

- Next most common cause after AD (unless poor country with poorly controlled cardiovascular risk factors in which case it tops the list)
- Clinical features:
 - History of discrete episodes of sudden neurologic deterioration, onset of dementia within 3 months of symptomatic stroke
 - Early deficits involve attention, executive function and self monitoring. Memory may be only mildly affected
 - Often early disturbance of gait (frontal parts of the brain affect gait)
- MMSE is a poor screening tool for vascular dementia – better to target executive function
- Two types:
 - Subcortical or cortical multi-infarct – or a single strategically placed infarct
 - Diffuse white matter disease (subcortical arteriosclerotic encephalopathy = Binswanger's disease). A dominantly inherited form is Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy – CADASIL. Dementia from 5th decade with migraine and recurrent stroke but not HTN. Mutation in Notch 3 gene

Frontotemporal Dementia and Related Dementias

- A diverse group characterised by tauopathies

Fronto-temporal Lobar Degeneration

- M = F, onset between 50 and 70
- Behavioural symptoms initially predominate – spare memory but involve planning, judgement, language, apathy, disinhibition, weight gain, fetishes
- Asymmetric left sided: speech problems. Right frontal or temporal: changes in social conduct
- Differential is a frontal presentation of Alzheimer's
- Sporadic or familial (including point mutations in tau gene on chromosome 17)
- 15% go onto develop motor neuron disease
- CT/MRI: marked atrophy of temporal and frontal lobes
- Micro: gliosis and neuronal loss, ballooned neurons with cytoplasmic inclusions staining for tau
- Pick's Disease: a type of frontal temporal dementia with fluent aphasia. Increasingly Pick's disease is used to classify the subset of FTD cases that show Pick's bodies at autopsy.

Progressive Supranuclear Palsy

- See page 167

Dementia with Lewy Bodies

- PC:
 - Visual hallucinations, parkinsonism, sleep disorder, fluctuating alertness and falls. May present in someone with longstanding Parkinson's
 - Highly sensitive to metabolic disturbance → delirium
 - Delirium may be triggered by giving L-dopa for presumed Parkinson's
- Diagnosis:
 - Progressive cognitive impairment: impaired memory, deficits in attention, executive function, visuospatial ability
 - Plus (2 = probable, 1 = possible):
 - Fluctuating cognition, attention, alertness
 - Recurrent visual hallucinations (often animals)
 - Spontaneous motor parkinsonism not preceding other features
 - Supportive features: recurrent falls, syncope, transient LOC, neuroleptic sensitivity (→ Parkinson's), systematised delusions, sleep disturbance, depression
- PET can be useful to differentiate
- Pathophysiology:
 - Usually also have Alzheimer's pathology
 - Micro: presence of Lewy bodies throughout cortex, amygdale, cingulated cortex and substantia nigra
 - Lewy bodies: intraneuronal cytoplasmic inclusions that stain with periodic acid-Schiff (PAS) and ubiquitin. Usually found in the Substantia Nigra of Parkinson's patients. But also found in Alzheimer's
 - Amyloid protein frequently found but few neurofibrillary tangles compared with Alzheimer's
 - Defects in ACh, dopamine and serotonin systems identified.
- Important to diagnose given differences in management. Overlap with Parkinson's disease with dementia
- Treatment:
 - Anticholinergics (as in AD). May be more effective than Alzheimer's
 - Exercise programmes to maintain motor function
 - Antidepressants for accompanying depression
 - Low dose atypical antipsychotics to alleviate psychosis (but may exacerbate extrapyramidal syndromes – can be very sensitive)
 - Extremely sensitive to dopaminergic medications. For anti-nausea use domperidone – doesn't cross BBB

Other Dementias

Huntington's Disease

- Autosomal dominant CAG triplet repeat of the Huntington gene (IT15) on chromosome 4 (function unknown)
- Demonstrates anticipation
- Mutation is more unstable inherited from a father than a mother
- Pathology: cerebral atrophy, initially in the caudate
- Onset age 4 – 80, mean age 40. Big range in onset for same repeat size. Invariably fatal. Diagnosis to death averages 15 years
- Prevalence 1:10,000
- PC:
 - Initially chorea is focal then spreads. Peaks at 10 years then replaced by bradykinesia, rigidity and dystonia (may → contractures)
 - Early eye movement disorders (smooth pursuit interrupted by saccadic intrusions)
 - Behavioural (often early) and cognitive disturbances: affective disorders, intermittent explosive disorder, substance abuse problems, antisocial personality traits, depression
 - Memory preserved. Depression and apathy common
- Predictive testing: much concern about safety – but the suicide and self harm rate low in counselled group – and survivor guilt, uptake less than anticipated
- Treatment:
 - Supportive: movement and behavioural changes may be helped by haloperidol or BZDs
 - Dopamine antagonists may help psych symptoms but may make movement disorder worse. Variable evidence of the benefit for valproate and clonazepam
- Differential of chorea:
 - Huntington's disease
 - Sydenham's Rheumatic fever
 - Vasculitis: SLE, APS
 - Cerebrovascular events: Hemiballismus
 - Drug induced: neuroleptics, levodopa, amphetamines, phenytoin, OCP, anticholinergics
 - Wilson's disease
 - Neuroanthocytosis
 - Thyrotoxicosis, Polycythaemia
 - Pregnancy

Normal-Pressure Hydrocephalus

- Rare: Abnormal gait, mild dementia, urinary retention
- Imaging: communicating hydrocephalus with patent aqueduct of Sylvius. Periventricular oedema
- LP: Opening pressure in high-normal range and normal chemistry. To treat take off 30 mls CSF
- Cause: presumed obstruction to CSF flow and/or delayed absorption
- May have history of meningitis, SAH, or head trauma

Prion Diseases

- Normal alpha protein in the brain (PrP^c) converts to beta helix formation protein (PrP^{sc}) which forms fibrils and leads to apoptosis
- Human prion diseases (process the same, different locations in the brain):
 - Kuru – ritualistic cannibalism
 - Iatrogenic CJD: prion containing hGH and dura mater grafts
 - Variant CJD: infection from bovine proteins. Less rapid progression, more sensory and psychiatric features (often first manifestation). MRI different. EEG much less useful. Can't detect the protein in CSF. PrP^{sc} in tonsillar tissue. Don't know incubation period
 - Familial CJD: germ line mutation
 - Sporadic CJD: sporadic somatic mutation or spontaneous conversion of c to sc
- Presentation: rapidly progressive dementia, myoclonus (90%), rigidity, choreoathetoid movements
- EEG becomes abnormal (periodic synchronous sharp wave complexes)
- Imaging: cortical and basal ganglia abnormalities

Thiamine/Vitamin B1 Deficiency

- Wernicke's Encephalopathy
- PC: Malnourished, confusion, ataxia, diplopia
- Treat promptly with IV thiamine in the first several days otherwise → irreversible Korsakoff's Syndrome

Vitamin B12 Deficiency

- See page 340
- Most common presentation: spinal cord syndrome affecting the posterior columns (loss of position and vibratory sense) and corticospinal tracts (hyperactive tendon reflexes with Babinski response).
- Damages peripheral nerves → sensory loss with depressed reflexes
- Damage to cerebral myelinated fibres → dementia

Other

- Infections:
 - 20 – 30% of advanced HIV have dementia with psychomotor retardation, apathy, impaired memory due to HIV infection itself or secondary infection. See page 305
 - Neurosyphilis: see page 321
- Neoplasm: Limbic encephalitis – paraneoplastic dementing syndrome associated with occult carcinoma (often small cell lung cancer): confusion, agitation, seizures, movement disorders, sensory neuropathy
- Complex partial status epilepticus
- Isolated vasculitis of the CNS – may → chronic encephalitis. Cerebral angiogram → multifocal stenosis (although may only affect small vessels). See page 272
- Chronic metal exposure:
 - Lead: fatigue, depression, confusion, episodic abdominal pain, peripheral neuropathy. Anaemia with basophilic stippling of red cells. May resemble acute intermittent porphyria. Treatment: chelation with EDTA
 - Mercury
 - Arsenic: signs include pigmentation and scaling of the skin, transverse white lines on finger nails (Mee's Lines)
 - Aluminium: dialysis – severe and generalised EEG changes
- Recurrent Head Trauma
- Fugue states: amnesia for personal identity and events closely associated with personal past (cf other dementias)

Drug treatment of Neuropsychiatric Symptoms of Dementia

- See JAMA 2 Feb 2005
- Symptoms: agitation, aggression, delusions, hallucinations, wandering, repetitive vocalisations
- Present in over 90% of dementia patients – usually later stages. Frequent precipitant of institutionalization
- Before medicating, check medications, physical problems (eg constipation and pain) and depression contributing to mood disturbance
- Bottom line: assess for medical and environmental causes first, then consider behavioural interventions, drugs last. Treat depression/anxiety with antidepressants. Consider atypical antipsychotics. Reasonable to consider a cholinesterase inhibitor. Small trial evidence for familiar music
- Trials don't include Lewy Body dementia – risk of sensitivity to antipsychotics, extra-pyramidal SE and Neuroleptic Malignant Syndrome (see below)
- Choices:
 - Antipsychotics: see below. Widely used to treat behavioural and psychological symptoms of dementia although little evidence for the use with most symptoms
 - Antidepressants: well tolerated and effective. Only Citalopram ever shown to have benefit for other symptoms (more effective than placebo in reducing irritability, not restlessness, in Alzheimer's)
 - BZDs are more effective than placebo (but less than antipsychotics) with risks of over sedation, falls, ataxia, worsening cognitive impairment and sleep disordered breathing
 - Cholinesterase Inhibitors: See page 150
 - Mood stabilisers: Valproate not effective. Carbamazepine effective for agitation in one small trial
 - NMDA antagonists: Memantine recently approved by FDA. Didn't improve scores, but placebo scores dropped....

Antipsychotics

- Block D2 receptors in ventral striatum (→ extrapyramidal side effects and ↑PRL). Also may effect cholinergic, α -adrenergic, histamine and serotonin receptors
- Antipsychotics differ in the potencies and have wide variation in side-effects – there is nothing that clearly distinguishes the “typicals” from the “atypicals” (except price!). As a group they are no more efficacious, and don’t have clearly different side effect profiles (Lancet 3 Jan 2009). Many trials of 2nd generation compared with haloperidol – which had a recognised high EPS rate
- Typical/“1st generation”:
 - Phenothiazines: eg chlorpromazine, prochlorperazine
 - Butyrophenones eg haloperidol
 - Cochrane review comparing haloperidol to placebo only found benefit for aggression (not agitation). SE somnolence and extra-pyramidal. No clear evidence for use
- Atypicals/“2nd generation”:
 - Atypicals may involve NMDA receptor blockade, α 1 and α 2 activity, effects on neuroplasticity....
 - Bottom line: risperidone probably the “cleanest” in terms of side effect profile (especially anticholinergic effects)
 - All 4 atypicals have the potential to cause sedation and hypotension. Probably worse in diabetes, independent of weight gain
 - All RCTs drug company sponsored and among nursing home residents with moderate – severe symptoms. In Alzheimer’s, Risperidone → 50% in rating scale cf placebo. 2 mg no better than 1 mg and more SE. Olanzapine 5 mg and 10 mg (not 15mg) → improvement. But no better than placebo for psychosis. Atypicals may ↑risk of stroke and MI
 - Clozapine: (an old drug) greater potency in blocking 5HT2 than D2, and higher affinity for D4 than D2. Unlike other antipsychotics doesn’t ↑PRL. 1% risk of blood dyscrasias and 10% of seizures. Worst for anticholinergic side effects
 - Risperidone: greater potency at 5HT2 than D2, significant α 2 antagonism
 - Risperidone or olanzapine for upsetting hallucinations or delusions
- Classic Side Effects:
 - Caution in Long QT
 - *Extrapyramidal side effects* are:
 - Dystonia (abnormal face and body movements): more common in young adults after only a few doses
 - Akathisia: restlessness, usually after large initial doses, onset over days. May resemble condition being treated. May respond to β -blockers
 - Parkinsonian symptoms: eg tremour, occurring more commonly in the elderly with gradual onset, over weeks to months. Anticholinergic and parkinsonian symptoms respond well to benzotropine 1 – 2 mg bd
 - Quetiapine has lower incidence of EPSE than other atypicals, but less data on the use in the elderly
 - *Tardive dyskinesia*: usually with long term therapy of first generation. Earliest sign is find vermicular movements of the tongue. May be irreversible
 - *Sedation*
 - *Anticholinergic effects*
- Other side effects:
 - Hypotension and interference with temperature: dose related
 - *Neuroleptic Malignant Syndrome*:
 - In 1 – 2% of treated individuals, mortality up to 20%
 - Evolve over days, usually shortly after introduction of the drug
 - Hyperthermia, fluctuating LOC, catatonia, *rigidity* with myonecrosis and ↑CK, autonomic dysfunction – hyperthermia, pallor, tachycardia, sweating, labile BP, urinary incontinence
 - No proven therapy: withdraw offending agent, dopamine agonists/ bromocriptine or levodopa, cooling, amantadine, BZDs. ?Dantrolene. Lasts 5 – 7 days
 - Apparent increased risk of diabetes – estimates vary
 - Also apathy, agitation, insomnia, seizures, confusion, GI disturbance, ECG changes, menstrual disturbance, blood dyscrasias
- Considerations in the elderly:
 - Reduced renal clearance: issue for some metabolites of antipsychotics
 - Progressive loss of D2 receptors → ↑risk of tardive dyskinesia and extrapyramidal side effects

- Psychosis with Parkinson's:
 - First attempt to reduce the dose of the antiparkinson drug
 - If antipsychotic needed, use atypical as less sensitive to EPSE eg low dose Quetiapine or clozapine

Epilepsy

- See NEJM 10 July 2008 (good drug comparisons)
- = recurrent seizures due to a chronic underlying process
- Epilepsy Syndrome – distinctive clinical and pathological features suggesting a specific etiology, usually with a specific age of onset. Syndrome identification allows accurate prognosis, proper family and genetic counselling and specific treatment
- Syndromes are either:
 - Idiopathic: no extraneous cause, no evidence of brain damage, usually easily treatable
 - Symptomatic/cryptogenic: identified cause, often evidence of brain damage, often difficult to control
- Prevalence 0.5 – 1%
- Classification of seizures:
 - Partial: simple (motor, sensory, vision, autonomic), complex partial (temporal or frontal involvement may give changes in hearing, smell, auditory) or with secondary generalisation (in which case the “simple” stage is an aura). 70% of adults with new onset epilepsy have partial seizures
 - Generalised: (arise from both hemispheres simultaneously):
 - Absence (brief and no post-ictal confusion) – usually childhood onset. 3 Hz spike and wave discharge. Provoked by hyperventilation
 - Tonic-Clonic: 10% of all seizures. Sympathetic tone → ↑HR, BP and pupillary size. Post-ictal period: muscular flaccidity, excessive saliva, incontinence
 - Atonic: sudden loss of postural muscle tone lasting 1 – 2 secs
 - Myoclonic: sudden brief local or generalised muscle contraction. Most commonly seen in metabolic disorders, degenerative CNS and anoxic brain injury

Basic Mechanism

- Influx Ca → influx Na → long depolarisation → Hyperpolarising after-potential mediated by GABA or K channels
- Glutamate (principal excitatory neurotransmitter in the brain) in OD causes seizures
- Penicillin lowers seizure threshold by antagonizing effects of GABA
- Genetics:
 - Majority of genetic epilepsies are polygenic
 - Voltage gated channelopathies: defects in sodium, K and Cl
 - Ligand-gate channelopathies: defects in GABA and nicotinic receptors found

Syndromes

- Juvenile Myoclonic Epilepsy – onset early adolescence. Myoclonic jerks on waking. Usually simple. Also TC and absence seizures (often preceding other seizures and beginning towards the end of the first decade). Responsive to treatment. Polygenic cause
- Lennox-Gastaut Syndrome: Multiple seizure types, abnormal EEG, usually impaired cognitively. Poor control
- Mesial Temporal Lobe Epilepsy Syndrome (MTLES): most common cause of complex partial seizures. Hippocampal sclerosis on high resolution MRI. Refractory to drugs, responds well to surgery. Aura common, post-ictal disorientation, anterior temporal spikes on EEG
- Head injury: severe penetrating head injury – 50% risk of subsequent epilepsy

Differential of Epilepsy in Adult

- Syncope: Anticipatory symptoms (sweating, nausea, tunnel vision), brief but not prolonged convulsive motor activity, relatively brief LOC
- Psychogenic seizures: Look for side-to-side turning of the head, asymmetric large-amplitude shaking of limbs, pelvic thrusting. Test prolactin – rises in most generalised and complex partial seizures in the 30 mins following
- Trauma
- Genetic disorders (adolescent)
- Metabolic (uremia, hepatic failure, hypoglycaemia, electrolyte disturbance)

- Infection
- Brain Tumour
- Toxic: Alcohol intoxication or withdrawal, drug overdose
- CVD (approx 50% cases in > 65 years – seen more with embolic than haemorrhagic or thrombotic stroke)
- CNS degenerative diseases (eg Alzheimer's)
- Idiopathic
- Transient Global Amnesia: Sudden onset of severe episode memory deficit, usually age > 50. Often emotional stimulus. Retained CGS and communication. Settles in hours. Cause unknown – ?epilepsy, ?CVA, ?migrainous

Workup

- Was it an epileptic seizure → what sort of seizure → what is the likely syndrome

Exam Tips

- Skin: neurocutaneous disorders (tuberous sclerosis or neurofibromatosis), liver or renal disease
- Organomegaly: metabolic storage disease
- Signs of head trauma, alcohol or drug use

Tests

- Bloods: electrolytes, Ca, Mg, Glucose, LFTs usually normal. However, LFTs and electrolytes important as baselines for AED treatment. Fraction of unbound drug for highly protein bound drugs (eg phenytoin and valproate) higher if hypoalbuminaemia
- ECG
- Urine Tox screen

Imaging

- MRI more sensitive – yield of ~ 15%. FLAIR sequence for Mesial Temporal Sclerosis. Particularly important if adult or focal onset. Can do without only if you can confidently diagnose on EEG (eg Benign Rolandic and idiopathic generalized epilepsies)
- CT for infection or lesion when MRI not immediately available – misses half the lesions seen on MRI
- Emerging role for SPECT and PET in refractory epilepsy, fMRI (functional MRI) has an emerging role

Electroencephalography (EEG)

- Records post-synaptic potentials of vertically orientated pyramidal cells in the cortex. Doesn't pick up deeper activity
- How useful is it:
 - Specific, not sensitive (~ 40%) test
 - Interictal EEG normal 60% of the time. Can't exclude epilepsy
 - Sleep deprivation, hyperventilation and photic stimulation used to increase yield
 - Early EEG (within 24 hours) better than late EEG (51% vs 34%)
 - Not useful for determining who will get epilepsy in those at risk (eg head injury)
- Epileptiform activity includes interictal epileptiform discharges (IEDs – common in Rolandic and Medial Temporal Lobe Epilepsy, rare in people without a seizure history), periodic lateralized epileptiform discharges (PLEDs), and generalized periodic epileptiform discharges (GPEDs) eg spikes and sharp waves
- Nonepileptiform abnormalities:
 - Include non-specific slow waves (but also seen in partial and symptomatic epilepsies, which may be diffuse, regional, or localized; amplitude changes or asymmetries)
 - Are abnormal but rarely helpful. Wide spectrum of change
- Waves:
 - Delta — 0 to 4 Hz – abnormal in an awake person, common in encephalopathy
 - Theta — 4 to 8 Hz – normal in stage I sleep, abnormal in an awake person
 - Alpha — 8 to 12 Hz – observed posteriorly in normal awake individuals with their eyes closed
 - Beta — More than 12 Hz – increased by sedatives or centrally active drugs
- *Diagnostic in liver failure (Triphasic waves), herpes encephalitis (focal periodic complexes), CJD*

Treatment

- Acute Therapy: Benzodiazepines: midazolam can be IM, diazepam can't be
- New Onset:

- First seizure has a recurrence risk of over 50%, generally in the first 6 months
- “First seizures” are frequently not epileptic
- “First seizures” are often not the first
- Multimodal:
 - Education and demystification
 - Psychological factors
 - Lifestyle advice: Avoid driving, operating high risk equipment, working at heights, or swimming alone, avoidance of precipitating factors,
 - Prophylactic therapy with AEDs
- When to treat with AEDs (usually after 2nd seizure):
 - If precipitated by infection, tumour or trauma – treat with first seizure
 - If unprovoked, risk of recurrence is 25% in 12 months. Higher if:
 - Abnormal neuro exam
 - Presented as Status
 - Postictal Todd’s paralysis
 - Strong family history
 - Abnormal EEG
 - Seizures do not beget seizures at onset (Lancet 2005: 365:2007) – deferred or immediate treatment has no difference in 5 year remission (but more seizures)
- Withdraw treatment: consider after 1 year seizure-free if good prognostic indicators: single seizure type, normal EEG, normal exam, normal intelligence. Withdraw over 2 – 3 months, reverse last dosage reduction if relapse
- Surgical Treatment: for refractory partial epilepsy

Anti Epileptic Drugs (AED)

- Monotherapy preferred
- Modify activity or ion channels or neurotransmitters
 - Inhibition of Na dependent action potentials: Phenytoin, carbamazepine, lamotrigine
 - Inhibition of Ca channels: Phenytoin
 - Decrease glutamate release: Lamotrigine
 - Potentiation of GABA receptors: BZDs and Barbiturates
 - Increase in GABA: Valproic acid, gabapentin
- Initiation: Start at lowest dose and titrate up slowly (at least after steady state achieved) until control achieved. Minor side effects usually resolve in a few days
- Drug Monitoring: usually unhelpful – assays usually measure free and bound drug, whereas free correlates with efficacy. Check levels for compliance or ?toxicity
- Changing drugs: Start new one slowly, then withdraw old one slowly. Combination required long term in 1/3 patients
- First Line: Older drugs – phenytoin, valproic acid, carbamazepine and ethosuximide effective and cheap
- Common side effects: sedation, ataxia, diplopia
- Common rarer effects: rash, blurred vision, bone marrow suppression, hepatotoxicity (monitor FBC and LFTs before and during titration)
- Indications:
 - Partial Seizures: Carbamazepine, phenytoin (now less favoured), valproate of some value or lamotrigine
 - Generalised Seizures: Valproate (especially in mixed seizure types). Also Lamotrigine (not first line for funding reasons), followed by carbamazepine and phenytoin (these two can worsen absence, myoclonic, tonic and atonic seizures)
 - Absence: Also ethosuximide
 - Clonazepam for myoclonus and other seizure types
- Specific Drugs:
 - Phenytoin: long T_{1/2} so OD or BD dosing. Saturated metabolism so small increases can → marked side effects. Long term → Hirsutism, gingival hypertrophy. Effect on bone metabolism (so not good for younger patients). 70% of dose if given IV compared with oral
 - Carbamazepine: Initial dose 200 mg/day, target 400 – 600 mg/day. *Level increased by erythromycin, fluoxetine. Induces it’s own metabolism* SE: weight gain, hyponatraemia
 - Lamotrigine: broad spectrum, few interactions, no enzyme induction, good cognitive profile. Blocks voltage dependent Na channels. Start at 25 mg/day, titrate slowly to 100 – 200 mg/day.

Skin rash during titration (esp with valproate) – stop immediately. Risk of Stevens-Johnson Syndrome. Risk reduced by slow titration. *Valproic acid inhibits its metabolism (caution if combined)*. Dizziness and double vision with carbamazepine. Teratogenicity looks positive? Better than valproate in obese

- Valproate: Reversible bone marrow suppression and hepatotoxicity. Least excreted in breast milk. Clotting studies pre surgery (↓ vitamin K factors). SE nausea, alopecia, tremour, dyspepsia, somnolence, *worst for weight gain* (not visual SEs)
- Gabapentin: Well tolerated, no interactions/induction, but variable absorption, wide dose range, tds dosing, only moderate efficacy, unknown teratogenicity. Only in partial seizures. Uncertain mechanism (?binds to Ca channel)
- Topiramate: broad spectrum, multiple mechanisms, potent, few interactions, no induction but neurotoxic, renal stones, weight loss, very slow titration, rodent teratogen. Use it for partial or symptomatic seizures as an add on
- Vigabatrin: prevents breakdown of GABA (not widely used now). *Monitor visual fields*
- Tiagabine: blocks reuptake of GABA → ↑synaptic levels
- Levetiracetam: binds to synaptic vesicular protein → influences release of neurotransmitters
- Choosing between new AEDs: no head-to-head comparisons, trials are aimed at licensing, clinical experience....
- Monitoring: Every 2 – 5 years on enzyme inducers (Carbamazepine, Phenytoin, Topiramate, Phenobarbitone) do FBC, U&E, LFTs, Vit D

Women

- Catamenial Epilepsy: increased seizures at time of menses. ?Acetazolamide (↓CSF production) as adjuvant over menstruation
- Contraception (enzyme inducers metabolise OC quicker):
 - POP and progesterone implant not recommended
 - COCP: minimum 50 mcg oestrogen
 - Depot Progesterone: 10 week cycle instead of 12
 - Emergency contraception: levonorgestrel 1.5 mg and 750 mcg 12 hours apart
- In pregnancy: Pregnancy has little effect on epilepsy. Incidence of fetal abnormalities higher, in part due to teratogenic effect of drugs (normal risk 1 – 2%, monotherapy risk 4 – 6%) – however seizures more harmful so should continue drugs – ?valproate the worst. Take folate 5 mg/day. Vitamin K for newborn due to effect of drugs

Other

- Depression common: SSRIs OK (fluoxetine interacts with carbamazepine), TCAs lower seizure threshold
- Death 2 – 3 times more common, mainly due to underlying etiology (eg tumour, stroke). SUDEP (Sudden unexpected death in epileptic patients) usually affects young people with convulsive seizures at night – cause unknown

Multiple Sclerosis

- See BMJ, 4 March 2006,, Lancet 25 Oct 2008

Pathology

- = Inflammation and selective destruction of CNS myelin (and axonal degeneration) with gliosis (scarring)
- Anatomy: lesions vary from 1 mm to 2 cm containing predominantly T cells and *macrophages*. BBB is disrupted but vessel wall is preserved. Surviving or new oligodendrocytes may partially remyelinate surviving naked axons, producing shadow plaques. Axonal loss in demyelinated foci and possibly neuronal loss. Heterogeneity in these processes observed
- Recent evidence suggests grey as well as white matter change, and axonal damage may be better correlated with progression
- Causes conduction block in fast axons, then slower conduction as sodium channels redistribute. Variable conduction block can occur with raised body temperatures (ie exacerbation with a fever)
- Normal appearing white matter is not disease free: diffuse axonal injury and Wallerian degeneration with diffuse dense lymphocytic infiltration
- Immunological basis:
 - Myelin basic proteins likely a T cell antigen in human MS

- Autoantibodies against myelin oligodendrocyte glycoprotein
- Mediated by proinflammatory Th1 cytokines IL2, TNF α and IFN γ
- Triggers. MRI shows frequent subclinical disease activity even when asymptomatic. ?viral trigger

Epidemiology

- Increasing global incidence
- Epidemiology: F = 2 * M, onset between 20 and 40, ethnic variation, UK lifetime risk 1:1000
- Genetic basis: polymorphic susceptibility: siblings have 2 – 5% lifetime risk, 25% monozygotic concordance (70% MRI concordance), HLA DR2 (DRb1*1501) confers 3- 4 times risk
- Latitudinal gradient for where they lived for first 15 years of life, but cause is unclear

Clinically Isolated Syndromes (CIS) or First Demyelinating Events (FDE)

- = First presentation
- Types of presentation:
 - Transverse Myelitis (30%):
 - Symptoms evolve over hours up to 1 – 2 weeks, rarely stuttering, improve over weeks/months
 - Differential:
 - Parainfectious (40%): CMV, EBV, mycoplasma, HTLV, HIV. Infection often not found
 - Cord ischaemia (12%)
 - MS associated (20 – 30%)
 - Idiopathic (20 – 60%)
 - Optic Neuritis (40%):
 - Acute or subacute unilateral eye pain on movement → varying degrees of visual loss (esp central scotoma) + colour desaturation (esp red)
 - +/- afferent pupil defect
 - +/- disc oedema – but usually fundus is normal as it's a retrobulbar defect (ie patient sees nothing and you see nothing)
 - Simultaneous bilateral involvement is rare. Rarely progresses after 2 weeks
 - 90% regain vision over 2 – 6 months
 - Uhthoff's Phenomenon: Rare. Heat and exercise intolerance. Reversible decrements in physical (eg walking) or cognitive (memory) function due to increased ambient body temperature or exercise, 2nd to nerve conduction block
 - Early treatment after CIS with IFN β delays the onset of definite MS
- Symptoms:
 - Initial symptoms in order of prevalence: sensory loss, optic neuritis (36%, ↓ visual acuity or ↓ colour saturation), weakness (35%, esp exercise induced), paresthesias (pain, prickling, numbness), diplopia (15%, from internuclear ophthalmoplegia affecting medial longitudinal fasciculus – very suggestive if bilateral, 6th nerve palsy or pendular nystagmus), ataxia (cerebella tremors), vertigo
 - Also spasticity, bladder and bowel (constipation or incontinence) dysfunction
 - Significant cognitive dysfunction is rare
 - Depression – 50 – 60% – reactive, endogenous, disease related
 - Fatigue in > 90% may precede neuro signs by several months
 - Sexual dysfunction
 - Neuropathic pain
 - Paroxysmal – frequent, brief symptoms due to discharges at the edge of the plaque – treat with anticonvulsants
 - Lhermitte's Syndrome – flex your neck (or other movement) → electric shock type symptoms

Diagnosis of MS

- Tests:
 - MRI: gadolinium leaks through BBB into parenchyma and is visible in a lesion up to 3 months old (ie active disease), plaques visible indefinitely on spin-echo (T2 weighted). Various types of lesions have differing sensitivity and specificity for the development of MS
 - Evoked potentials: Most useful in clinically uninvolved pathways. Not specific but a marked delay in latency is suggestive of demyelination
 - CSF:
 - Mildly raised mononuclear cells (pleocytosis) in 25% (usually young patients with RRMS), > 5 cells/ μ L, but not > 75 cells (esp if polymorphs present)

- Increased level of protein 2nd to increased intrathecally synthesized IgG (but not greater than 1.0 g/L) – *but often normal*. Also assess by oligoclonal bands in the CSF (2 or more bands in 75 to 90%) – need also to do paired serum protein electrophoresis to exclude a peripheral source. 40 – 60% +ive in MS. If positive doubles the risk of MS. Positive with other CNS inflammatory conditions (vasculitis, infection, malignancy)
- Diagnostic criteria: symptoms last for > 24 hours, with at least 2 distinct episodes separated by a month or more. Neurological signs must be present in at least one episode. New criteria: McDonald Criteria – allow earlier diagnosis – allows MRI diagnosis of the 2nd site or 2nd episode (inclusion of MRI well validated), as can evoked potentials. The predictive power is for the rate of development of a second clinical attack, not for future severity

Differentials of MS

- Consider differential especially if:
 - Symptoms localised to one region of CNS
 - Age < 15 or > 60
 - Progressive from the onset
 - Never had visual, sensory or bladder symptoms
 - Always do ESR, B12, ANA, VDRL to check for differentials
- Acute Disseminated Encephalomyelitis (ADEM):
 - Usually younger (mean age 15)
 - Encephalopathy with behavioural changes, multifocal, polysymptomatic neurological deficit (motor signs predominate). Low grade fever, headaches, seizures
 - Associated with prior immunization or infection: EBV, mycoplasma, strep pyogenes or pneumoniae, CMV, HIV, Varicella, anything...
 - Widely scattered small foci of perivenular inflammation and demyelination
 - MRI: large fluffy lesions, white and gray matter involved, basal ganglia often involved (rare in MS), Gadolinium enhancing
 - Monophasic course. If severe, onset is abrupt and progressive (hours to days)
 - Most severe form: acute haemorrhagic leukoencephalitis
 - Treatment: IV methyl pred, after infection ruled out
- Devic's Disease: Relapsing/remitting involvement of optic nerves and/or spinal cord with long cord lesions, without oligoclonal CSF bands, can be clinically severe, anti-aquaporin 4 autoantibody is 73% specific and 91% sensitive, directed against a water channel predominant in CNS (also renal medulla and gastric parietal cells)
- Progressive Multifocal Leukoencephalopathy: see page 313. Reactivation of JC-virus – 2nd to AIDs in 85%. Also associated with humanised monoclonal antibodies: Natalizumab, Rituximab, Alemtuzumab
- Infection: HIV, Lyme disease, Syphilis
- Ischemic optic neuropathy
- Neoplasms (eg lymphoma, glioma, meningioma)
- Sarcoid
- Connective tissue disease: Sjogren's syndrome, Vasculitis, Antiphospholipid Syndrome, SLE
- CVD
- Vitamin B deficiency

Progression

- Disease course:
 - Relapsing Remitting MS (RRMS, initially 85%): discrete attacks – otherwise neurologically stable. After 15 years 50% progress to SPMS. 15% never have progress – called Benign MS
 - Secondary progressive MS (SPMS): Initially RRMS then change to steady deterioration. Discrete attacks continue in 1/3, stop in 2/3
 - Primary Progressive MS (PPMS, 15%): steady functional decline from the outset (like SPMS)
 - Progressive/Relapsing MS (PRMS, 5%): steady decline with superimposed flares
- Two ways of getting more disabled:
 - Attacks with increased sustained disability. An uncommon type of progression – usually in the early stages. Improved with IFN
 - Slowly progressive paraplegia/hemiplegia/ataxia. Important in primary and secondary progressive disease. Possibly not autoimmune. Not helped by IFN
- Assessment with EDSS – Expanded Disability Status Score: 0 = normal, 6 = walking stick, 10 = dead
- Progression is *extremely* variable:

- Progression to MS from a CIS is *highly* predicted by the number of T2 lesions on baseline MRI
- High attack rates and short attack intervals predict poorer prognosis
- 50% require a walking stick at 15 years
- Inflammation (demyelination → incomplete remyelination and scarring [gliosis]) appear to sensitize surviving axons to subsequent insults. ⇒ ?benefits from earlier treatment when the majority of inflammatory activity is subclinical
- Death by complication or suicide – death due primarily to MS is rare

Treatment of MS

- Outcome measures used in trials: relapses, disability scales, and MRI changes. No one biomarker for disease outcome
- Acute Attacks:
 - Exclude pseudo-exacerbation from fever, infection or hot showers/bath
 - Methyl Pred 1.0 gm for 3 days. +/-oral prednisone tapered over 2 weeks (probably no extra benefit) – generally for motor attacks, not sensory attacks unless painful
 - Causes closure (restoration) of the BBB, ↓oedema, suppression of inflammation (induction of T-cell apoptosis, down regulation of endothelial adhesion molecules)
 - Effect on long term prognosis not demonstrated
 - SE: fluid retention, K loss, weight gain, acne, emotional lability. Cover with PPI if PUD
 - Refractory relapses: repeat pulse after 4 – 8 weeks or plasma exchange (7 exchanges every other day for 14 days) if fulminant and unresponsive to steroids
- Disease Modifying Agents for Relapsing Forms (less convincing in SPMS, not established in PPMS)
 - Overview:
 - First line: IFN β and Glatiramer, reduce disease activity only modestly
 - Second line: Mitoxantrone and Natalizumab, more potent but more serious adverse effects
 - Interferon:
 - Generally equivalent: reduce relapse rate by 30%
 - IFN- β 1a (Avonex or Rebif)
 - IFN- β 1b (Betaferon)
 - CI in severe depressive illness, poorly controlled epilepsy or decompensated liver disease
 - SE of IFN:
 - Flu-like symptoms (wane over 1 – 3 months – give at night, give panadol/brufen)
 - Injection site irritation (ice first)
 - Mild LFT rise, mild lymphopenia. Rare: severe hepatotoxicity
 - Screening bloods at 1 and 6 months. If ALT > 400 stop and recommence at lower dose once LFTs normal
 - A portion will develop neutralising antibodies from 18 months → then completely ineffective. Test at 12 and 24 months. If positive, repeat at 3 – 6 months (can go negative again). If sustained high titre then discontinue
 - Glatiramer acetate (Copaxone). Daily injection. Synthetic polypeptide containing myelin basic protein (MBP). May promote proliferation of Th2 cytokines, alters macrophage function. Reduces relapse rate, ↓disease severity less well established. ~30% fewer exacerbations and fewer new plaques on MRI cf placebo. Equivalent to IFN in 2 head to head trials
- Persistent Relapses on Treatment:
 - Azathioprine – double the number of relapse free patients at 1, 2 and 3 years. No change in disability progression
 - Mitoxantrone – chemo agent – for progressive forms if failed other treatment, continued rise in EDSS and ongoing activity on MRI. Not in primary progressive MS. Cardiac complications in 2% (anthracycline – do echo first). Also nausea, uncommon cytopenia, LFT abnormalities, APML in 0.25%. Using less now but the most powerful drug
 - RCT of Natalizumab (α 4 integrin adhesion molecule antagonist) reduced disease progression NNT 10, RRR 67%, with SE of fatigue and allergic reaction. NEJM, 7 March 2006. Also more effective in combination than Beta-1a alone. Case reports of PML on combination treatment
 - Rituximab (monoclonal antibody which depletes CD20+ B lymphocytes): Stage 2 trial showed 2 doses 14 days apart reduced MRI detected lesions and relapses to week 48. Provides further evidence of B cell involvement (NEJM 14 Feb 2008). Trial in PPMS negative
 - Others in trial:
 - An oral formulation of dimethyl fumarate (Lancet Oct 25 2008)
 - Phase III trials underway of:

- Teriflunomide: active metabolite of leflunomide
- Cladribine: purine nucleoside analogue, used in treatment of Hairy Cell Leukaemia
- Laquinimod: oral drug (an advantage compared to other treatments), 0.6 mg reduced surrogate endpoint of MRI gadolinium-enhanced lesions (Lancet 21 June 2008)
- Alemtuzumab: lysing anti-CD52 Ab, depletes CD4 and CD8 T cells, NK cells and monocytes, infusion for 5 days once a year, 75% RRR, 65% reduction in disability progression, trialled early in disease, significantly better than IFN, SE ITP (including a fatality), Graves in 25%. Is effective but toxic. Postulate benefits from early treatment
- T-cell therapies: all negative
- TNF inhibitors: Worse, no effect on MRI, ↑relapse rate, ↓time to 1st attack
- IL-2 antibody (Daclizumab): reduced lesions but ↓relapse rate not significant
- What we've learnt from the drugs:
 - B-cells and antibodies are important
 - T cells are (probably) not that important
 - TNF is good
 - IL-12 is not important
 - IL-2 is bad
- No treatments for primary or secondary progressive disease
- No neuronal restoring agents
- Other treatments:
 - Methotrexate – ? slows upper extremity dysfunction
 - Cyclophosphamide?
 - IV Ig monthly – probably reduces relapse rates
- Supportive Treatment:
 - Tremour: Clonazepam, propranolol, ondaneztron
 - Spasticity and spasms: physiotherapy, OT, baclofen, diazepam, ...
 - Pain: anticonvulsants (carbamazepine, phenytoin, gabapentin – also effective for Paroxysmal symptoms), antidepressants (Amitriptyline, venlafazine)
 - Bladder:
 - Detrusor hyperreflexia: anticholinergic to relax bladder: oxybutinin, imipramine
 - Retention: intermittent self catheterisation
 - Fatigue: organise tasks with intermittent rest. Consider amantadine 100 mg bd (limited efficacy)
 - Depression: SSRIs + psychiatrist
 - ¾ patients visit alternative practitioners more times than their doctor
- Exercise: Cochrane Review 2007: Strong evidence in favour of exercise therapy in terms of muscle power, exercise tolerance and mobility related activities. Moderate effect on mood. No impact on fatigue or perception of disability
- On going research: neuroprotection and repair mechanisms

Movement Disorders

- See also:
 - Huntington's Disease page 153
 - Neuroleptic Malignant Syndrome page 155

Parkinson's Disease

- Epidemiology: ~1% over 55, onset in 60s, familial clusters account for ~5% (earlier onset)
- 2nd most common neurodegenerative disease after Alzheimer's
- Risk factors: positive family history (10%), head injury
- Exogenous factors from case control studies: exposure to pesticides, well water and rural living. Protective factors: coffee, ?NSAIDs and ?HRT

Pathology

- Where: Degeneration of the dopaminergic cells of the substantia nigra pars compacta and elsewhere → gradual denervation of the striatum → reduction of dopaminergic transmission in the basal ganglia
- Starts with: oxidative stress, mitochondrial dysfunction, excitotoxic damage, protein mishandling
- Leading to: accumulation of presynaptic protein α -synuclein with the presence of Lewy Bodies
- End result: Lots of things going on with the final stage being signal induced apoptosis

- Is now considered a multisystem disease, and actually begins with neuronal loss outside the motor system (eg lower brainstem, Raphe nucleus, etc)
- Genetics: >90% cases are sporadic. 10% have a genetic cause, we understand about half of these. 4 genes linked to familial forms PARK1 – PARK10, dominant and recessive
- Overlaps with Dementia with Lewy Bodies:
 - Parkinson's patients can have lots of Lewy Bodies without impairment
 - ?Spectrum of the same disease. Controversial
 - Features of DLB: fluctuating cognition (50 – 70%), visual hallucinations (70%), motor Parkinson's (50% at presentation, 95% eventually)
 - If they had the Parkinson's for > 12 months first, then Parkinson's Disease with dementia (a line in the sand for research purposes, pathology is identical)

Symptoms

- Cardinal signs:
 - Bradykinesia: paucity and slowness of movement, difficulty initiating movement and with concurrent movements
 - Tremor at rest: 25% never get it, 25% lose tremour
 - Rigidity – especially unilateral onset
 - Postural instability late in the disease course, profound effect on functional disability
- Also masked facies, decreased eye blinking, decreased arm swing, shuffling gait (rare early in the disease), festinating gait (accelerate to catch up with centre of gravity), flexed posture, decreased manual dexterity (→ micrographia), soft speech (hypophonia)
- Later effects:
 - Dopamine related symptoms (weren't seen in Parkinson's prior to Levodopa):
 - Motor fluctuations:
 - 80% by 10 years
 - “On” and “Off” – random, brittle, sudden, not linked to dose
 - Associated involuntary movements (“over flow” of movements to other parts of the body)
 - Reduced response: “Wearing off” at end of dose period – don't lose response, just get worse
 - Dyskinesias: variable disability but consistent for each patient, eg “off” phase dystonia
 - Neuropsychiatric toxicity (60%): spectrum. eg visual hallucinations. Major dose limiting effect. May or may not have insight. Correlates with LB density in the amygdala, parahippocampus, inferior temporal cortex
 - Non-dopamine related symptoms: significant impact on quality of life, institutional placement, poorly recognised and difficult to treat
 - Disorders of balance and gait
 - Swallowing, speech
 - Mood (eg depression)
 - Sleep disturbance: primary REM sleep disorder, plus 2nd to rigidity, and vivid dreams from dopaminomimetic therapy
 - Cognitive impairment:
 - Early changes: 30% of newly diagnosed. Attention, working memory, ↓processing speed – ie more frontal than Alzheimer's – not primarily a memory problem
 - May be 2nd to medication, but rate of dementia 6 times that of age matched controls – definition of dementia depends on impairment of ADLS – difficult to disentangle from motor disorder
 - Autonomic

Differential

- Red flags for another disorder:
 - Wide based gait
 - Rapid decline
 - Early falls and instability, autonomic signs, marked speech and swallowing dysfunction
 - Early cognitive decline
 - Absence of rest tremour, presence of postural tremour
 - No response to levodopa
- Other neurodegenerative disorders: see page 149
- Genetically mediated with parkinsonian features:
 - Wilson's disease

- Huntington's disease
- Miscellaneous:
 - Essential tremour – but bilateral, faster, postural dependency and better with alcohol
 - Prion disease
 - Normal pressure hydrocephalus – abnormal gait, urinary retention, mild dementia
 - Cerebral Palsy
 - Vascular disease
 - Mass lesions
- Infectious: Neurosyphilis and post-encephalitic
- Drugs:
 - Neuroleptics (typical antipsychotics)
 - Antiemetics (eg metoclopramide)
 - Lithium
 - Valproic acid
 - Fluoxetine
- Toxins: cyanide, methanol, carbon monoxide

Treatment

- Can use response to L-dopa as a diagnostic test. Failure to respond in < 10% PD
- Education and support groups (may have severe cases → rude shock to recently diagnosed) – course over decades
- RCTs of exercise: maintains function and QoL but doesn't affect progression
- Motor symptoms initially respond well to symptomatic treatment. Cognitive and autonomic symptoms don't
- Initiate dopaminomimetic therapy as soon as ↓quality of life. Slow titration
- Start with dopamine receptor agonists:
 - Primarily act on postsynaptic D2 receptors – longer acting than levodopa
 - Less potent than levodopa at controlling motor symptoms – 25% at 3 years happy with response
 - However, ↓ risk of later treatment-related complications: inter-dose motor fluctuations and dyskinesias (choreiform and dystonic movements, developed by 50% after 5 years of levodopa)
 - So aim is to save the limited duration of Levodopa for later
 - SE: more neuropsychiatric side effects but fewer motor side effects than Levodopa. Hallucinations (avoid in dementia), nausea, postural hypotension, sedation. May be helped by domperidone (peripheral dopamine blocker)
 - Non-ergot alkaloids preferred (occasional sleep attacks), not funded in Australia or NZ yet:
 - Pramipexole: renal metabolism, reduce in renal failure, SE *sleep attacks* in 25%, dizziness, hypotension, 6% *impulse control disorders*
 - Ropinirole: hepatic metabolism, drug interactions, mainly in Restless Legs
 - Ergot alkaloids:
 - Pergolide and Cabergoline (long half life 65 hours, sole treatment in de novo disease in the young): rare valve disease – 5-HT_{2B} expressed in heart valves. 1 in 5 get subclinical disease. So used as 2nd line
 - Bromocriptine: rare pulmonary and retroperitoneal fibrosis
- Cochrane Review 2008: Dopamine agonists as a class decrease motor symptoms but have side effects
- As an adjunct to levodopa they improve motor control, reduce “off” time and limit the need for levodopa
- Impulse Control Disorders: related to excessive dopamine receptor stimulation eg gambling, eating, punding (repetitive handling, sorting), addictive medication use, disinhibition. Cause unclear: behavioural sensitization of the dopaminergic behaviour/reward system (??D3) mesolimbic projections. Associated with certain pre-morbid behaviours and family history
- Most require addition of levodopa in 1 – 3 years. It is the most effective treatment for motor symptoms:
 - “Gold standard”: strongest dopaminergic agent with 95% response rate
 - Amino-acid precursor of dopamine
 - Honeymoon period for 5 – 10 years
 - No effect on progression of disease. No change to non-motor features (ie postural instability)
 - Generally mild side effects: a little nausea, a little postural hypotension. Cause urinary retention

- Carbidopa (in Sinemet, Benserazide in Madopar) blocks peripheral levodopa decarboxylation into dopamine before the levodopa can reach the brain. Peripheral dopamine → nausea, vomiting, postural hypotension
- Initially with meals → ↓ nausea. Later on empty stomach → more predictable absorption
- Should reach at least 1000 mg a day. If no response then no other intervention is likely to be beneficial
- No evidence controlled release is better
- Abrupt withdrawal can → neuroleptic malignant syndrome
- Levodopa Augmentation:
 - Selegiline: Selective, irreversible MAO-B inhibitor with weak symptomatic effect. At low dose no need for dietary restrictions. SE: insomnia. [MAOI block enzymatic degradation of monoamines: dopamine, serotonin, noradrenaline...]
 - Catechol O-methyltransferase (COMT) inhibitors (entacapone [available in NZ] and tolcapone) block extracerebral degradation of levodopa and dopamine, ↑ area under the curve by 30%, longer “on” time. Greater effect than slow release formulations. SE gastrointestinal and dyskinesias
 - Anticholinergics: control unresponsive rest tremor and dystonia (little evidence). Not if > 75 and contraindicated in dementia. [ACh receptors have an inhibitory effect on dopamine neurons]
 - Amantadine: reduces drug induced dyskinesias, mechanism unknown ?weak glutamate antagonist properties. SE nausea, headaches, oedema, erythema
 - Apomorphine: potent dopamine agonist in advanced disease for severe “on” “off” symptoms. Only available subcut. Highly emetogenic, need domperidone cover
- Non-motor symptoms:
 - Dopamine agonist nocte for restless legs and urinary urgency
 - Depression: SSRIs and TCAs (note rare serotonin syndrome with Selegiline and SSRI), or ECT
 - Psychotic symptoms:
 - Exclude other causes eg intercurrent illness
 - Stop anticholinergics and amantadine first
 - Reduce dopaminergic agents: but ↓ motor mobility
 - Simple sedation: benzodiazepines
 - Consider an antipsychotic with low incidence of extrapyramidal side effects (eg Quetiapine or clozapine – not risperidone and Olanzapine as may → Parkinsonism). Often allow ↑ in levodopa dose without recurrent of neuropsychiatric toxicity
- Neuroprotective strategies: Watch this space. ?NSAIDs, ?oestrogen in epidemiological studies. DATATOP study: ?slower motor decline on Selegiline. Coenzyme Q10 ?delays decline
- Surgery: After > 5 years drug induced motor fluctuations and dyskinesias. Not for atypical Parkinson’s. Must have had a clear response to Levodopa. Either Deep Brain Stimulation or ablation (pallidotomy or thalamotomy)
- Disappointing results so far with fetal cell transplantation – despite grafting the dopamine replacement had not effect over Levodopa

Secondary Parkinsonism

- Tremour less prominent
- Drugs (usually dose dependent response):
 - Neuroleptics, some atypical antipsychotics
 - Lithium Carbonate
 - Antiemetics (especially metoclopramide)
- Less common:
 - Valproate
 - Fluoxetine
 - Antihypertensives: reserpine, α -methyl dopa
 - Manganese, CO, cyanide, methanol

Multiple System Atrophy

- Varying degrees of parkinsonism (60% at onset, >90% eventually), and cerebellar, corticospinal and autonomic dysfunction – hallmark is *α -synuclein positive inclusions* in various brain regions (substantia nigra, putamen, pontine nuclei, brainstem, cerebellum, cf Parkinson’s the Lewy Bodies are in the brainstem, in DLB they’re in the brainstem, cortex and hippocampus, etc)
- Average onset at 50, median survival 6 – 9 years

- With progression: parkinsonian signs, autonomic failure (orthostatic hypotension, leg swelling, changed sweating, autonomic storms with diaphoresis and flushing, urinary urgency/retention/incontinence, and impotence), upper motor neuron signs (spasticity and pseudobulbar palsy). Symmetric tremour (cf Parkinson's). Poorly responsive to dopaminergic therapy
- Pathology: neuronal loss, astrogliosis. Oligodendroglial cytoplasmic inclusions > neuronal cytoplasmic inclusions > intranuclear inclusions. Widely distributed and poor correlation with cell loss
- Three categories (MRI may help differentiate – where is the atrophy?):
 - Striatonigral degeneration (SND): akinetic rigid parkinsonism with limited response to levodopa
 - Olivopontocerebellar atrophy (OPCA): ataxia, upper motor, myoclonus, oculomotor, peripheral neuropathy and deafness (sporadic and hereditary forms)
 - Progressive Autonomic Failure: Shy-Drager syndrome when associated with Parkinson features
- Often initially misdiagnosed as PD

Progressive Supranuclear Palsy

- Aka Steele-Richardson-Olszewski Syndrome
- Motor sub-type of Fronto-temporal Lobar Degeneration
- Often confused with Parkinson's
- Associated with Tau pathology: neurofibrillary tangles positive for tau (mostly 4-repeat tau), negative for amyloid or α -synuclein
- Presents 6th – 7th decade, faster progression than Parkinson's, death in 5 – 10 years
- PC: heterogeneity – falls 2nd to unstable posture and eye signs:
 - Akinetic rigid parkinsonism, dizziness, unsteadiness, slowness, falls, pseudobulbar dysarthria, eventually frontal-type cognitive dysfunction
 - Eye signs: vertical supranuclear gaze paresis (difficulty with downward gaze but retained doll's eye – vestibular ocular reflex – which suggests the lesion is above the ocular motor nuclei), then upward and horizontal movement
- MRI: midbrain atrophy

Corticobasal Degeneration

- PC: asymmetric progressive apraxia, rigidity, dystonia, myoclonic jerks, alien limb, bilateral over 2 – 5 years, to paraplegia in flexion with frontotemporal dementia or progressive aphasia
- A tauopathy with focal cortical degeneration in the parietal and frontal regions

Restless Legs Syndrome

- = Ekbom Syndrome
- Commonest movement disorder
- Symptoms always worse at rest, relieved by walking. Usually associated with periodic limb movements during sleep (although this is also associated with other things such as sleep apnoea) → reduced total sleep and sleep efficiency
- A dopamine deficiency disease
- Classification:
 - Primary/idiopathic:
 - Natural clinical course is to worsen with age
 - More likely to be familial if onset before 40 – 50
 - Secondary:
 - Fe deficiency: Associated with Fe deficiency probably because Fe is a cofactor for the enzyme tyrosine hydroxylase which makes dopamine from tyrosine
 - Very common on dialysis (25 – 50%)
 - Pregnancy (25%)
 - Peripheral neuropathy in diabetes
 - RA
 - ??Parkinson's Disease
- Treatment:
 - Fe if deficient
 - Improve sleep hygiene
 - Avoid exacerbating factors: caffeine, alcohol, SSRIs, dopamine receptor blockers, TCAs
 - Small dose of a dopamine agonist (Levodopa, bromocriptine proven in RCT. SE insomnia, nasal congestion, swelling of hands and feet, bloating, nausea, vomiting. Long term use may lead to worse symptoms, including during the day), or Ropinirole

- Alternatives: opiates (eg oxycodone), clonazepam, gabapentin

Essential Tremour

- PC: 6 – 12 Hz postural and kinetic tremour predominantly affecting the arms, initially bilateral (cf Parkinson's)
- Often autosomally dominant
- Partially response to alcohol, exacerbated by stress
- Aggravated by: Valproate, lithium, thyroxin, glucocorticoids, TCAs, SSRIs, β -adrenergic agonists
- Propranolol and Primidone proven in RCTs, effective in 50%
- Surgery: thalamotomy or deep brain stimulation of the central intermediate nucleus of the thalamus

Hemiballismus / Hemichorea

- Hemiballismus – acute onset, ranging from mild chorea to wild flinging movements. Lesion of the subthalamic nucleus usually 2nd to lacunar stroke
- Drugs may help: haloperidol, propranolol, phenytoin, baclofen, clonazepam
- Supportive care of injuries, exhaustion and dehydration

Dystonias

- Involuntary muscular contractions → twisting, repetitive movements, abnormal postures, involving agonist and antagonist muscles
- Heterogeneous group of disorders
- Present during attempted voluntary movement
- Focal primary dystonias: Blephrospasm (involuntarily closing eyelids), cervical dystonia, torticollis, also can affect jaw and larynx
- Secondary dystonias: levodopa induced, cerebral palsy (athetoid form), trauma, nerve injury....
- Treatment: anticholinergics for primary dystonia (trihexyphenidyl) +/- BZDs +/- baclofen (similar to GABA) +/- botulinum (blocks release of acetylcholine)

Ataxic Disorders

- Gait impairment, unclear (“scanning”) speech, visual blurring due to nystagmus, hand incoordination, tremor with movement
- Problem with cerebellum and afferent and efferent pathways
- No dizziness or perception of movement (cf vestibular/labyrinth disease)
- Symmetric ataxia:
 - Acute: drugs, intoxication, rare infections (eg polio)
 - Subacute: alcoholism + malnutrition, paraneoplastic (breast, ovarian, small cell lung, Hodgkin's)
 - Chronic: inherited ataxia, metabolic disorder, chronic infection, hypothyroidism
- Focal ataxia: usually ischaemic, ipsilateral symptoms, bleed, abscess, tumour, MS, AIDs related
- Examples:
 - Friedrich's Ataxia: presents before 25, progressive staggering gait, frequent falling. PC can be dysarthria, nystagmus, cardiomyopathy. Also 20% with diabetes. Loss of tendon reflexes, vibration and proprioception. Dead by 35. Men do worse. Deformities: pes cavus, scoliosis. Spinal chord atrophy on MRI. Loss of peripheral myelinated fibres. A triplet repeat expansion genetic defect
 - Ataxia Telangiectasia:
 - AR, chromosome 11, DNA repair mechanism
 - PC:
 - First decade with telangiectatic lesions, nystagmus and abnormal gait (ataxia), neurologic deficits
 - ↑tumours: 100% lifetime risk of NHL, also breast, ovarian and GI, radiation sensitivity
 - Immunodeficiency (most commonly ↓IgA and IgG2)

Motor Neuron Diseases

Amyotrophic Lateral Sclerosis (ALS)

- Most common form of Motor Neuron Disease
- Median survival 3 – 5 years, incidence 1 – 3 per 100,000, onset 45 – 65, M > F

- Due to death of lower motor neurons (anterior horn cells in the spinal cord and brainstem nerves innervating bulbar muscles) **AND** upper (cortico-spinal) motor neurons (originating in layer 5 of the motor cortex)
- Affected motor neurons undergo shrinkage, accumulation of p106 and disruption to neuron cytoskeleton. Astroglia and microglia proliferate (as in all degenerative CNS processes)
- →Denervation, atrophy (hence amyotrophy) and fasciculation of muscle fibres
- Does NOT affect sensory, extrapyramidal or cognitive function neurons (although some familiar forms also have a fronto-temporal dementia). Oculomotor and sacral parasympathetic motor neurons (bladder and bowel) spared (at least until late in the illness)
- Presentation: variable
 - Insidious development of asymmetric limb weakness (flexor > extensor) initially 40% upper, 40% lower. Spasticity, exaggeration of motor expressions of emotion (weeping or laughing), early wasting, cramps
 - In about 20%, initial symptoms are related to bulbar weakness: swallowing or chewing problems, dysarthria, coughing, breathing. OE drooping palate, depressed gag reflex, weak cough, wasted and fasciculating tongue
 - Worst prognosis is from involvement of respiratory muscles. Death is usually by pulmonary infection
- Disease can't be completely diagnosed until bulbar, cervical, thoracic and lumbosacral motor neurons all involved
- 5 – 10 % inherited as autosomal dominant (= Familial ALS)
- Diagnosis:
 - UMN/LMN findings in 3 spinal, or bulbar and 2 spinal regions
 - EMG: active/chronic denervation in ≥ 3 regions. CSF normal. MRI ↑T2 in motor tracks
- Differential Diagnosis:
 - Look elsewhere if:
 - Restricted to either upper OR lower motor neurons
 - Other than motor neurons involved
 - Evidence of motor neuronal conduction block
 - Exclude:
 - High cervical lesion (tumour, osteophytes) – would spare cranial nerves
 - Infection (tetanus, Lyme, polio, herpes zoster, retroviral myelopathy)
 - Intoxication, eg lead, aluminium
 - Autoimmune processes
 - Paraneoplastic (eg in lymphoma)
 - Metabolic: hypoglycaemia, hyperPTH, hyperthyroidism, Folate, B12 deficiency, malabsorption
- Treatment:
 - Survival benefits from Riluzole (slightly extends survival), BiPAP, PEG feeding
 - Celecoxib showed promise
 - Rehab measures: foot drop splints, finger extension splints, cough assist devices, gastrostomy
 - Spasticity: Baclofen, diazepam
- Variants of MND besides ALS:
 - Progressive muscular atrophy
 - Primary Lateral Sclerosis: Very rare – progressive spasticity of the limbs. Fasciculations, muscle wasting and sensory changes absent
 - Progressive bulbar palsy

Selected Lower Motor Neuron Disorders

- No evidence of involvement of corticospinal motor systems (eg no spasticity)
- Multifocal Motor Neuropathy with Conduction Block: regional and chronic disruption in conduction. May respond to IV Ig or chemotherapy – need to consider as differential to ALS
- Kennedy's Disease (Spinal and Bulbar Muscular Atrophy): X-linked. SMN1 deletion in > 95%. A symmetrical pure proximal motor neuron disease. One of nine neurodegenerative disorders caused by a polyglutamine repeat expansion affecting an androgen receptor. Onset 30 – 50. . Phenotypes vary by age of onset. PC: muscle cramping, fasciculations, tremour 2nd to loss of anterior horn motor cells. May be mistaken for ALS

Selected Upper Motor Neuron Disorders

- Familial Spastic Paraplegia: dominantly inherited. Spastic weakness of lower extremities begins in the 3rd or 4th decade

Spinal Chord Diseases

- Anatomy:
 - Cervical roots exist above their numbered vertebra, thoracic below (there are 8 cervical roots and only 7 cervical vertebrae)
 - Spinal chord enlarges at cervical and lumbar regions
 - Most tracts are ipsilateral except pain and temperature which ascend on the contralateral side
- Clinical Signs:
 - Initially spinal shock (arreflexia), then hyperreflexia, spasticity
 - Level of the lesion: Sensory level – identify pinprick or cold stimulus starting at the bottom and moving up on each side. Detects damage to spinothalamic tract. Lesion is located one or two segments above the perceived level if unilateral, or at that level if bilateral
 - At the lesion there may be a band of altered sensation, fasciculations, muscle atrophy, diminished or absent deep tendon reflexes (ie LMN signs)
 - Patterns:
 - Brown-Sequard Hemicord Syndrome: ipsilateral weakness (corticospinal tract) and loss of joint position and vibration (posterior columns) with contralateral loss of pain and temperature (spinothalamic) one or two levels below the lesion
 - Central cord syndrome: damage to grey matter nerve bodies and crossing spinothalamic tracts near the central canal. In cervical cord: arm weakness greater than leg, and sensation loss of pain and temperature
- Differential:
 - **Compressive:** If radicular symptoms and no evidence of myelopathy, safe to defer imaging for 24 – 48 hours
 - Neoplasm: Epidural (the majority – breast, lung, kidney, lymphoma frequently go to thoracic vertebrae, ovarian and prostate more often to lumbar/sacral), intradural (usually slow growing meningiomas and neurofibromas) or intramedullary. Acute management of epidural: dexamethasone till radiotherapy +/- biopsy. Motor deficits > 12 hours don't usually improve. Bone scan + xray miss 15 – 20% – MRI best
 - Epidural abscess: Pain (usually < 2 weeks), fever and rapidly progressive weakness. 2/3rds blood spread (IV drug use, skin infections, dental, endocarditis...), 1/3rd from local infections (eg vertebral). Most Staph aureus. Consider TB. Treatment: Abs +/- decompressive laminectomy
 - Epidural haemorrhage or haematomyelia (haemorrhage into the substance of the chord)
 - Cervical spondylosis (less thoracic, so if thoracic pain think ?neoplasm). Cervical spine impingement and impingement of nerve roots → early neck and shoulder pain (radicular pain) paraesthesia of feet and hands, wasting of hands → spasticity. Needs MRI and surgical laminectomy. Most often C5/C6 distribution → reduced biceps reflex
 - Herniated disc
 - Post-traumatic 2nd to displaced vertebrae or haemorrhage
 - Vascular:
 - AV malformation – usually posterior, detected with MRI + contrast
 - Antiphospholipid syndrome (or other hypercoagulable state) → infarction. Also 2nd to systemic hypotension (greatest risk at T3-T4 and at boundary between anterior and posterior zones → weakness and spasticity with little sensory change), aortic atherosclerosis, dissecting aortic aneurysm (chest/back pain with diminished leg pulses)
 - Anterior spinal artery syndrome: loss of sphincter control, motor, sensory and autonomic below the level of the lesion except vibration and position sensation (posterior columns)
 - Inflammatory:
 - MS
 - Idiopathic Transverse Myelitis (ie can't find the cause, ~ 25% cases of ATM)
 - Sarcoidosis
 - Vasculitis (Acute Transverse Myelopathy in 1% of SLE)
 - Infectious:
 - Viral: Polio, VZ, HSV-1 and HSV-2, CMV, HIV...

- Bacteria: *Borrelia* (Lyme disease), *Listeria*, syphilis, TB
- *Mycoplasma Pneumonia*
- Parasitic: schistosomiasis, toxoplasmosis
- Post-infectious or post-vaccination myelitis (like ADEM)
- Human T-cell lymphotropic virus type-1 (HTLV-1) – retrovirus → slowly progressive spastic paralysis with variable sensory/bladder disturbance). ELISA for HTLV-1 specific antibodies available. Treatment: symptomatic. See page 314
- Developmental:
 - Syringomyelia – slowly enlarging cavity of the cervical cord, symptoms in early adulthood, cervical-thoracic scoliosis common. Associated with Chiari type 1 malformations (cerebellar tonsils protrude through foramen magnum). PC: sensory loss and areflexive weakness of upper arms. Treatment generally unsatisfactory
 - Meningomyelocele
 - Tethered cord
- Metabolic:
 - Vitamin B12 deficiency: Parasthesias in hands and feet, early loss of vibration and position sense, progressive spastic and ataxic weakness. Generally symmetric. Check homocysteine
 - Adrenomyeloneuropathy (X-linked)
- Familial: familial spastic paraplegia – progressive weakness and spasticity in legs
- Investigations:
 - MRI with contrast – exclude compressive causes
 - CSF: cell count, protein, glucose, oligoclonal bands, VDRL, gram stain, AFB, India ink stains, PCR for VZ, HSV-2, HSV-1, EBV, CMV, enteroviruses, HIV, bacterial viral and fungal cultures
 - Blood for infection: HIV, IgM Mumps, measles, rubella, schistosomal antibody
 - Immune mediated: ESR, Connective tissue screen,
 - Sarcoidosis: Serum ACE (+ive in 25%), serum Ca, 24 hour urine Ca, CT chest, lymph node biopsy
 - Demyelinating disease: Brain MRI
 - Vascular causes: Spinal angiogram
- Acute Management of Spinal Cord disorders:
 - Somatic and visceral pain may be missing – fever, worse spasticity or ↓mental status → think infection (UTI, lung, skin, bone), intra-abdominal pathology.... Loss of thermo regulation may → recurrent quadriplegic fever
 - Dramatic paroxysmal autonomic hyperreflexia may occur for lesions above the major splanchnic sympathetic outflow at T6 → headache, flushing, diaphoresis above the level of the lesion, HTN and brady or tachy cardia. Trigger is usually a noxious stimuli below the level of the lesion
 - Bladder dysfunction:
 - Detrusor Spasticity – treat with anticholinergics (oxybutinin) or TCAs with anticholinergic properties (imipramine)
 - Failure of sphincter to relax (Urinary Dyssynergia): α-adrenergic blockers: terazosin
 - Intermittent catheter, condom or permanent IDC
 - Don't treat asymptomatic bacteruria
 - Bowel cares
 - Respiratory function for high lesion
 - Management of VTE risk – initially calf compression +/- anticoagulation
 - Skin care
 - Spasticity prevention: Baclofen and Diazepam → GABA mediated inhibition of motor reflex arcs

Lumbar Spinal Stenosis

- NEJM, 21 Feb 2008
- Caused by symptomatic compression of spinal nerve roots
- Causes neurogenic claudication: radiation into buttocks and thighs
- Symptoms typically better on forward flexion
- May have wide based gait and be Romberg positive due to involvement of proprioception
- Categories:
 - Congenital: shortened pedicles, onset 20 – 40, or achondroplastic
 - Acquired Degenerative:
 - Central canal: disk degeneration, facet osteoarthritis, ligamentum flavum hypertrophy
 - Peripheral canal

- Spondylolisthesis (forward movement of a vertebrae on the one below): back pain may predominate
- Iatrogenic: post-laminectomy or post-fusion
- Miscellaneous: Corticosteroid excess (endogenous or exogenous), Paget's, Acromegaly
- Differential:
 - Hip osteoarthritis pain: typically in groin provoked by internal rotation
 - Trochanteric bursitis – associated with superficial tenderness
 - Vascular claudication: not influenced by lumbar extension or standing still
- CT/MRI each have pros and cons
- Conservative treatment limited. Data on epidural injections sparse and mixed
- Surgery: decompression +/- fusion → demonstrated improvement

Cranial Nerve Disorders

Eye Movement Disorders

- Adduction: Medial Rectus, 3rd nerve
- Abduction: Lateral Rectus, 6th nerve
- With eye abducted:
 - Elevation: Superior rectus, 3rd nerve
 - Depression: Inferior rectus, 3rd nerve
- With eye adducted:
 - Elevation: Inferior oblique, 3rd nerve
 - Depression: Superior oblique, 4th nerve
- If diplopia:
 - If images side by side: either medial or lateral rectus
 - If images above each other then either obliques or superior or inferior recti responsible
- Nerve lesions:
 - Third nerve lesion: ptosis, divergent strabismus (eye “down and out”), dilated unreactive pupil. Causes include posterior communicating artery aneurysm (ie “surgical 3rd nerve” – needs a surgeon)
 - Isolated 4th nerve palsy rare – can't look in and down
 - Isolate 6th nerve palsy – can't look laterally. Causes: mononeuritis multiplex, ↑ICP, trauma, diabetes, Wernicke's if bilateral
- Abnormalities of conjugate gaze:
 - Centres for conjugate gaze:
 - Frontal lobe: saccadic movements
 - Occipital lobe: pursuit movements
 - Conjugate movement to the right is controlled from the left side of the brain
 - Supranuclear palsy: loss of vertical or horizontal gaze or both. Both eyes are affected, usually no diplopia, reflex eye movements are intact. Causes include Progressive Supranuclear Palsy and Oculogyric crises (involuntary upward deviation, eg 2nd to L-Dopa)
- Nystagmus: due to disturbance in tone between opposing muscles. The slow phase (drift) is abnormal, a quick saccadic movement brings it back:
 - Jerky horizontal nystagmus can be due to:
 - Vestibular and cerebellar lesions or toxicity (phenytoin, alcohol)
 - Internuclear ophthalmoplegia: nystagmus in the abducting eye and failure of adduction on the other (affected) side. Lesion in the medial longitudinal fasciculus. If bilateral and young then MS, if old consider vascular cause
 - Jerky vertical nystagmus: brainstem lesions, alcohol, phenytoin
 - Pendular nystagmus: phases equal. Retinal (eg ↓macular vision) or congenital

Trigeminal Nerve (V)

- Sensation to the skin of the face and anterior half of the head. Innervates masseter and pterygoids masticatory muscles
- Differential of trigeminal disorders:
 - Nuclear (brainstem) Lesions: MS, stroke, syringobulbia, glioma, lymphoma
 - Preganglionic lesions: Acoustic neuroma, meningioma, metastasis, cavernous carotid aneurysm
 - Gasserian ganglion lesions: Trigeminal neuroma, Herpes Zoster, infection (eg from otitis media)

- Peripheral nerve lesions: nasopharyngeal carcinoma, trauma, GBS, connective tissue diseases, sarcoidosis, leprosy
- Trigeminal Neuralgia (Tic Douloureux):
 - Excruciating paroxysms of shock like pain in lips, gums, cheek, chin (less so in V1) lasting for several weeks at a time
 - No objective signs of sensory loss. Corneal reflex always present
 - May be due to compression of nerve → hyper-excitability
 - If young and bilateral think MS
 - Treatment: Carbamazepine

Facial Nerve (VII)

- Supplies muscles of facial expression, sensory for taste on anterior 2/3rds of tongue and anterior wall of auditory canal
- Travels with acoustic nerve then the facial canal and exits skull at stylomastoid foramen
- Bell's Palsy (see Lancet 31 May 2008):
 - Lifetime incidence 1 in 60, 62% of acute facial paralysis
 - Abrupt onset, maximal weakness at 48 hours. Pain behind the ear may precede paralysis by a day or two. May be unilateral taste loss
 - 80% recover fully in weeks/months
 - Pathophysiology:
 - May be entrapment or swelling of facial nerve and geniculate ganglion
 - Herpes Simplex (HSV-1) found more common in Bell's Palsy patients than matched controls
 - Reactivation of latent Varicella Zoster (Ramsay-Hunt Syndrome) implicated in 8 – 28% – often complicated by painful ear and vestibulocochlear dysfunction
 - Differential:
 - Tumour: insidious onset
 - Compression from acoustic neuroma
 - Bilateral facial paralysis in GBS
 - Infection: Lyme disease & Leprosy
 - Supranuclear palsy is less likely to involve orbicularis oculi – upper facial muscles have bilateral innervation
 - Treatment: prednisone (proven) +/- acyclovir (studies vary – was dose big enough to cover possible Varicella – needs bigger dose), paper tape to close eyes at night

Peripheral Neuropathies

- See Peripheral Neuropathy Seminar, Lancet, June 26, 2004

Electrodiagnosis (EDX)

- For testing nerve, muscle and neuromuscular junction pathology
- Will *not* show pain syndromes, small fibre neuropathy (tests fast/large fibres only) and minor nerve injury
- Nerve Conduction Studies (NCS):
 - Can test motor and sensory nerves
 - Reference ranges are used to gauge normality for standard nerves, can also compare side to side, and proximal to distal
 - Cannot test proximal nerves/muscles – can't get superficial access to the nerves
 - Demyelination → slowing of nerve conduction velocity (NCV, normal ~ 50 m/s, upper extremity < 32 m/s very slow), dispersion of action potentials, conduction block (decreased amplitude)
 - Axonal neuropathies → low amplitude, velocity preserved, positive sharp waves and complex repetitive discharges
 - F waves: reflected potential in motor nerves. Latency and dispersion useful
 - For root lesions, motor nerves are affected (nerve cell body is in the dorsal horn), sensory nerves are not (cell body is in the dorsal root ganglion, peripheral to the spinal foramen)
- Electromyography (EMG):
 - Recording electrical potentials from a needle in a muscle at rest and during voluntary contraction – for distinguishing between myopathic and neurological disorders. Testing motor unit recruitment
 - Neuropathic disorders:
 - Denervation: fewer motor units but more frequent firing → large polyphasic potentials

- Fibrillation ⇒ muscle fibres have lost innervation – last 2 –3 weeks
- Reinnervation over months: broader, more chaotic muscle waveform
- Myopathy: low amplitude, short duration, fragmented, polyphasic
- Repetitive stimulation: either normal (no change over train of stimuli), decremental responses (↓neuromuscular transmission) or facilitation (marked increase post-exercise or high frequency stimulation)

Assessment

- Exam:
 - Small fibres (pain/temperature and peripheral autonomic fibres): diminished pin prick, temperature sensation, painful burning dysesthesias, autonomic dysfunction. Eg *diabetes, amyloid and HIV*
 - Large fibres (all motor fibres apart from γ efferents, as well as vibration and proprioception fibres are large fibres): areflexia, sensory ataxia, motor dysfunction, fasciculation
- Bloods: FBC, ESR, glucose, B12, TFT, protein electrophoresis, autoantibodies, serum CK may be elevated in motor neuropathy, maybe heavy metals
- EMG
- Nerve Biopsy: sural nerve at ankle. Few indications – vasculitis, multifocal demyelinating neuropathies, amyloidosis, leprosy, occasionally sarcoidosis

Types of Peripheral Neuropathy

- By pathology:
 - Axonopathy:
 - Commonest type. Often metabolic or toxic cause. Usually chronic
 - Pattern: sensory loss and weakness legs > arms. Vibration loss > proprioception. Early muscle wasting. Paresthesias. Tendon reflexes absent or reduced distal > proximal
 - Myelinopathy:
 - Weakness is proximal and distal, wasting not prominent, sensory loss mild, tendon reflexes diffusely absent or reduced
 - It is not conduction slowing that causes disability but secondary axonal loss
 - Differential:
 - Inflammatory: GBS, CIDP, PEOMS
 - Metabolic: storage disorders, mitochondrial
 - Drugs/Toxins: chloroquine, perhexiline, amiodarone, gold, diphtheria
 - Mononeuropathy: single nerve trunk → focal cause eg trauma, compression, entrapment. Conservative management if sudden onset, no evidence of axonal degeneration
 - Polyneuropathy:
 - Most common is distal symmetrical polyneuropathy
 - Usually acquired toxic or metabolic states causing and axonopathy. Nerve fibres affected according to axon length
 - Present initially with sensory loss of lower limbs and absent ankle jerks. Later foot drop and loss of knee jerk. At this point symptoms in finger tips

Axonal	Acute (days to weeks)	Porphyria, Intoxication (eg arsenic), GBS axonal form
	Subacute (weeks to months)	Mostly toxic or metabolic < 5 years toxic/metabolic, > 5 years hereditary, diabetes
	Chronic (months to years)	
Demyelinating	Acute (days to weeks)	GBS
	Subacute (weeks to months)	Relapsing form of CIDP
	Chronic (months to years)	Hereditary, autoimmune, dysproteinemias

- Assessment of Polyneuropathy:
 - Check for recent viral illness, other systemic symptoms, new medications, exposures (solvents, pesticides, heavy metals), alcohol
 - Palpate nerve trunk – enlargement, tenderness, neurofibromas
 - Associations with systemic illness (only some of the long list....) S = sensory, M = motor:
 - DM: axonal and demyelinating, rarely only M
 - Sepsis: axonal, M > S
 - Chronic liver disease: demyelinating, S
 - Malabsorption (eg celiac): axonal, S or SM

- Carcinoma (late): axonal, S > M (eg anti-Hu)
- HIV: axonal S >>M
- Multiple Myeloma and MGUS
- Sjogren's: S
- Drugs: amiodarone, cisplatin, disulfiram (Antabuse), hydralazine, isoniazid, metronidazole, nitrofurantoin, anti-retrovirals, phenytoin, pyridoxine, statins, vincristine
- Toxins: arsenic, diphtheria, solvents, inorganic lead, organophosphates, thallium (rat poison), mercury, lead
- Mononeuropathy Multiplex (Multifocal neuropathy):
 - Simultaneous or sequential non contiguous nerve trunks involved, more confluent with time
 - Causes: Vasculitis (eg RA, Sjogren's). Also Sarcoid, lymphoma, carcinoma, amyloid, leprosy, HIV

Single Nerve Lesions

Upper Limb

- Motor:
 - Shoulder abduction: deltoid, C5, axillary nerve
 - Elbow flexion: biceps, brachialis, C5-6, musculocutaneous nerve
 - Elbow extension: triceps, C7, radial
 - Wrist extension: Extensor carpi ulnaris and radialis, C6-7, radial nerve
 - Finger extension: extensor digitorum, C7
 - Finger flexion: flexor digitorum, C8
 - Abduction of index finger: ulnar nerve, T1, dorsal interosseus
 - Abduction of thumb: median nerve, T1, abductor pollicis (Try and push raised thumb down into palm)
- Reflexes:
 - Biceps: C5, C6
 - Triceps: C7, C8
 - Supinator/Brachioradialis: C5,C6. Normally contraction of the brachioradialis causes flexion of the elbow. If finger flexion is the only response then it's "inverted" ⇒ spinal chord lesion at C5 or C6 with a lower motor neurone lesion at C5 and C6 with an upper motor neurone lesion affecting reflexes below this level
 - Finger jerks: C8 (often normally absent)
- Shoulder abduction:
 - To 45° due to scapular rotation
 - 45 – 90° due to rotator cuff
 - 90 – 180° due to deltoid
- Common Lesions:
 - **Ulnar neuropathy:** Claw-hand deformity. Elbow compression → weakness of finger but not thumb abduction. Thumb adduction weak (paper test). Weakness of long flexors of 4th and 5th fingers – hyperextension of MCP joints and flexion of IP joints (esp 4th and 5th). Wasting of interossei. Sensory loss on little finger. Often pressure palsy at elbow
 - **Median nerve compression in Carpal Tunnel Syndrome:** Due to entrapment of the median nerve at the wrist or to infiltration/inflammation (eg connective tissue disease, amyloid). Less common finding in hypothyroidism, RA and DM. Weakness and wasting of abductor pollicis brevis (thenar eminence), with numbness of palmar surface of fingers 1,2,3 and lateral 4. Tingling/pain which wakes at night
 - **C7 Radiculopathy:** pain from neck, shoulder, arm and forearm. Weakness of elbow, wrist and finger extension
 - **C6 Radiculopathy:** Weakens elbow flexion and wrist extension. Sensory loss of dorsolateral forearm, thumb and index finger
 - **Radial nerve (Saturday night Palsy):** Unable to dorsiflex the wrist or extend fingers or thumb.
- Less Common Lesions:
 - Peripheral neuropathy: weakens small muscles of the hand, glove sensory loss
 - T1 root lesion: Weakness of small hand muscles, sensory loss on medial arm and often Horner's syndrome
 - Brachial Plexus Lesions:
 - Upper Trunk (Erb, C5/C6): ↓shoulder movement, ↓elbow flexion (→ waiter's tip position), ↓sensation lateral arm and forearm

- Lower Trunk (Klumpke, C8/T1): claw hand (↓all intrinsic muscles), ↓sensation medial arm and forearm, Horner's

Lower Limb

- Motor:
 - Hip flexion: ilio-psoas, L1-2, lumbar plexus
 - Hip extension: gluteus maximus, sciatic nerve, L5-S1
 - Knee Extension: quadriceps, femoral n, L3-4
 - Knee Flexion: hamstrings, sciatic nerve, L5 – S1
 - Ankle dorsiflexion: tibialis ant, peroneal n, L4 – 5
 - Ankle plantarflexion: gastrocnemius, sciatic nerve, S1 – 2
 - Ankle inversion: tibialis ant & Post, peroneal and tibial n, L4 –5
 - Ankle eversion: peronei, peroneal nerve, L5 – S1
- Reflexes:
 - Patella: L3/L4
 - Ankle: S1
- Rapid tests:
 - Walk on heels ⇒ no foot drop or L5 lesion
 - Walk on toes ⇒ no S1 lesion
- Common Lesions:
 - **Tarsal Tunnel Syndrome:** Just posterior to medial malleolus from ankle sprain, ill fitting footwear, etc. Pain on sole of foot when walking, weakness of toe plantars
 - **S1 Radiculopathy:** Pain in back, buttock, thigh, leg, and foot, numbness of the lateral border of the foot. Mild weakness of eversion and dorsiflexion, depressed ankle jerk
 - **L5 Radiculopathy:** Pain in back, buttock, thigh, leg, and foot, numbness of medial border of the foot and big toe, weakness of inversion and dorsiflexion. No reflex change
 - **Common peroneal nerve lesion from compression at the fibula head:** Painless, severe weakness of dorsiflexion and eversion, with normal inversion, and numbness on the lateral foot and dorsum of the foot. Maybe sudden onset with severe footdrop. Ankle jerk normal. 80% of nerve palsies causing foot drop recover over 3 – 4 months. Differentiating foot drop:

	Common Peroneal Lesion	L5 Lesion
Ankle jerk	OK	May be depressed (normally S1)
Inversion	OK	Weak
Eversion	Weak	OK

Special Categories

Diabetic Neuropathy

- Types:
 - Symmetric:
 - Distal, primarily sensory (most common)
 - Diabetic symmetric sensorimotor polyneuropathy
 - Autonomic (also common): orthostatic symptoms, impotence, gastroparesis, diarrhoea, retention, sudomotor abnormalities (eg sweating)
 - Chronically evolving proximal motor neuropathy. Can be asymmetric, painful, relapsing (?immune mechanism)
 - Asymmetric:
 - Acute or subacute proximal motor neuropathy
 - Cranial mononeuropathy – usually 6th or 3rd nerve (usually sparing the pupil) + headache
 - Truncal neuropathy
 - Entrapment neuropathy

HIV

- GBS or CIDP (Chronic inflammatory demyelinating polyneuropathy) following seroconversion
- Symptomatic stages:
 - subacute axonal mononeuritis multiplex
 - Distal, symmetric S > M polyneuropathy – often with symptomatic encephalopathy
- Distinguish from toxic polyneuropathy from nucleoside analogues – more rapid, severe with lactic acidemia

- CMV infection of nerve roots: subacute asymmetric polyradiculopathy involving the cauda equine – treatment: Ganciclovir

Lyme Disease

- Usually sensory radiculoneuropathy
- Following infection with tick-borne spirochete *Borrelia Burgdorferi*

Herpes Zoster

- Acute inflammation of dorsal root ganglia → sensory neuritis
- Inflammation may affect surrounding motor roots
- Postherpetic neuralgia – intense, burning pain. Blunted with carbamazepine or gabapentin, or TCA. May be persisting infection and ?response to IV antivirals

Leprous Neuritis

- *Mycobacterium Leprae* invade Schwann cells in cutaneous nerves, especially unmyelinated

Autonomic Neuropathy

- Usually a more generalised polyneuropathy: eg diabetes, GBS or alcohol
- Mainly negative symptoms: postural hypotension, anhidrosis, hypothermia, bladder atony, dry mouth/eyes, blurred vision (loss of pupillary and ciliary regulation) and impotence

Pure Motor Neuropathy

- Differential:
 - Spinal muscular atrophy: infantile, childhood, juvenile and adult onset
 - Poliomyelitis
 - Motor Neuron Disease (see page 168)
 - Adult variant hexosaminidase A deficiency
 - Lead intoxication
 - Porphyria
- Neuromuscular junction disorders (eg Lambert-Eaton Syndrome) and other toxic neuromuscular blockades are localised with EMG

Plexopathy

- Affecting brachial or lumbosacral plexus
- Eg trauma, infiltration, radiation

Cold Effects

- Axonal degeneration of myelinated fibres following cold

Tumours

- Usually benign – neurilemmoma (schwannoma) and neurofibroma

Charcot Marie Tooth Disease and other Inherited Neuropathies

- Heterogeneous group on inherited peripheral nerve disorders
- Usually autosomal dominant – also recessive or X-linked
- 1 in 2,500 people
- History: muscle weakness, initially feet/legs then hands. Prior high stepping gait with frequent falls. Sensory fibres involved but symptoms rarer. Often first or second decade of life
- Exclude other causes before considering genetic tests for CMT
- Treatment supportive. Avoid Vincristine
- Types:
 - CMT1 – demyelinating, however wasting is due to cumulative axonal loss. Reduced conduction velocities (< 38 – 40 m/s). Findings of hypertrophic demyelinating neuropathy (“onion bulbs”). Two variants: CMT1A and CMT1B – different proteins affected by mutations
 - CMT2 – axonal. Near normal NCV. Less common. Later onset
 - Dejerine-Sottas Disease (CMT3): Severe, infantile, hypertrophic demyelinating diseases. Overlap with severe CMT1
 - X linked and rarer forms (autosomal recessive) – lots....
- Other inherited neuropathies:
 - Hereditary Neuropathy with Liability to Pressure Palsies: episodic

- Sensory disorders – heterogeneous group
- Familial amyloid neuropathy: Autosomal dominant, with sensory and autonomic neuropathy with cardiomyopathy

Immune-Mediated Neuropathies

Guillain-Barre Syndrome

- PC: ascending paralysis, initially “rubbery legs”, evolving over hours to days, maybe tingling in the extremities. Face diparesis in 50%. Lower cranial nerves may be involved → bulbar weakness and difficulty with secretions. If severe, autonomic involvement (BP problems and arrhythmias). Deep aching pain in weakened muscles
- Signs: deep tendon reflexes disappear in first few days and ↓ proprioception (both fast sensory fibres)
- Antecedents: 75% preceded by acute infection 1 – 3 weeks ago. Especially *campylobacter jejuni* (neuronal gangliosides are similar in structure to an antigen in the outer core layer of *C. jejuni*), also HIV, CMV, EBV, Mycoplasma pneumonia, vaccination. *C. jejuni* and CMV predict delayed recovery
- Increased risk in lymphoma, HIV and SLE
- Differential:
 - Fever: unlikely in Guillain Barre
 - Bladder dysfunction → consider spinal chord disease
 - Acute myelopathies: esp with back pain and sphincter problems
 - Infectious causes:
 - Botulism: pupillary activity lost early
 - Diphtheria: early oropharyngeal disturbance
 - Lyme and other tick-born paralyses
 - Poliomyelitis: fever and meningism common
 - CMV polyradiculitis if immuno-suppressed
 - Porphyria: abdominal pain, seizures, psychosis
 - Vasculitic neuropathy: check ESR. Fever, anorexia, weight loss, malaise, non-specific pains
 - Neuromuscular disorders: eg MG (usually begins with bulbar symptoms)
 - Poisonings: organophosphates, thallium, arsenic
- Immunopathogenesis:
 - T cell activation: IL2 in serum, IL6, TNF α and IFN γ in CSF
 - Humoral response: cross reactive antibodies to gangliosides (present in nerves, including nodes of Ranvier)
 - Demyelination → conduction block → flaccid paralysis and sensory disturbance. If demyelination severe then also axonal degeneration
 - No consistent HLA or other genetic associations have been found
- Investigations:
 - CSF shows raised protein (may have to wait 48 hours, maybe longer) without cells in 80% – as spinal roots are affected
 - Findings in nerve conduction studies lag clinical features (may be normal in first couple of days):
 - Demyelination: prolonged distal latencies, conduction slowing, conduction block, temporal dispersion of compound action potential
 - Primary axonal pathology: reduced amplitude without slowing
- Types:

Type	Characteristics	Pathology	
Acute Inflammatory Demyelinating Polyneuropathy (AIDP)	> 90% cases. Rapid recovery. Anti-GM1 antibodies in < 50%. GM2 in sensory > motor	Demyelinating	Attack Schwann cell. Variable 2ndary axonal damage
Acute Motor axonal neuropathy (AMAN)	Children & young adults. China & Mexico. Recovery rapid. GD1a antibodies	Axonal	Attacks nodes of Ranvier. Extent of damage highly variable
Acute motor sensory axonal neuropathy (AMSAN)	Uncommon. Slow, incomplete recovery	Axonal	Damage usually severe

M. Fisher Syndrome (MFS)	Uncommon (<5% cases). Ophthalmoplegia, ataxia, arreflexia, anti-GQ1b antibodies in 90%	Demyelinating	Resembles AIDP
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- Poorer prognosis if: older age, rapid onset, need for respiratory support, low amplitude CMAP, complete arreflexia acutely, diarrhoea prodrome, slower onset of improvement
- Treatment:
 - Treat on suspicion – each day counts. Immunotherapy no longer effective after 2 weeks
 - High dose IV Ig or plasmapheresis equally effective in RCTs (1985 – 1997), both not significantly better than one (although exchange studied up to 4 weeks, IV Ig only to 2 weeks). IV Ig: 5 daily infusions totalling 2 gm/kg body weight. Plasmapheresis: ~40 to 50 mL/kg plasma exchange 4 times over a week
 - Mechanism of IV Ig likely multifactorial: blockade of Fc receptors, anti-idiotypic antibodies, interference of complement etc
 - Treatment halves proportion requiring ventilation after 4 weeks
 - If treated early may relapse in 2nd or 3rd week, brief course of original treatment
 - Glucocorticoids NOT effective
 - Watch vital capacity (25% need ventilatory support), BP and arrhythmias (autonomic instability), skin care, range of motion movements to all joints, DVT prophylaxis
- Recovery complete in 85% within a year (although may have ongoing fatigue/residual weakness 2nd to loss of motor units). 5% mortality

Myasthenia Gravis

- Caused by antibodies to the acetylcholine receptor on the post-synaptic junction. ACh is released normally but produces small muscle potentials. Normally repeat firing leads to reduced ACh release. In MG this is exacerbated by poor action potential response at the postsynaptic receptors to produce myasthenic fatigue
- PC:
 - 1:7500. Women 20 – 30s, men 50 – 60s.
 - *Painless* weakness especially with repeated use. No numbness. May relapse and remit. Remissions rarely complete. Worse with intercurrent illness, may → myasthenia crisis
 - Early involvement of extraocular muscles (→ diplopia and ptosis, maybe for years). Weakness in chewing, speaking and swallowing. Asymmetric involvement of proximal limbs. Reflexes preserved
 - Susceptible to muscle relaxants: exacerbated or detected during anaesthetic
 - No wasting, normal reflexes
 - Exacerbated by infection, stress, pregnancy, hyperthyroidism and drugs (mycin ABs, prednisone, β -blockers....)
- Exam: Test forward arm abduction time (5 mins), forced vital capacity, range of eye movements and time to development of ptosis on upward gaze
- Types: ocular, bulbar, generalised
- Testing (nothing has brilliant sensitivity):
 - Anticholinesterase test: give drugs that inhibit acetylcholinesterase → improved strength
 - “Tensilon Test”: Edrophonium – onset 30 sec, duration 5 mins. Initial IV dose of 2 mg. Test arm abduction. If improvement then positive. If no change give 8 mg iv (staged to avoid SE of nausea, diarrhoea, salivation, fasciculations, rarely syncope or bradycardia – have 0.6 mg atropine available in case). False positives in motor neuron, and placebo
 - Neostigmine 15 mg oral, longer action, more time to evaluate
 - AntiAChR radioimmunoassay, ~85% positive in generalised GM (40% of non-responders have antiMuSK antibodies), ~50% in ocular MG. False negatives possible
 - Repetitive nerve stimulation: decrement of >15% at 3 Hz ⇒ MG highly probable
 - Single fibre EMG
 - For ocular or cranial MG exclude intracranial lesions by CT/MRI
 - CT/MRI of mediastinum for ↑thymus
 - Test of other autoimmune diseases + TFTs + fasting glucose
 - Pulmonary Function tests
 - Bone protection baseline
- Differential:

- Inherited myasthenic syndromes – heterogeneous group of disorders affecting any component of the neuromuscular junction
- Drug-induced myasthenia
- Lambert Eaton Myasthenic Syndrome (LEMS): Usually proximal lower limbs, depressed or absent reflexes, autonomic changes (dry mouth, impotence), incremental not decremental responses on repetitive nerve stimulation. Caused by autoantibodies against P/Q type voltage-gated Ca channels at the motor nerve terminal → presynaptic blockade → ↓ ACh release. 50% have *small-cell carcinoma of the lung*, also associated with autoimmune disease. Treatment initially prednisone
- Hyperthyroidism
- Botulism: *C. botulinum* infection. Oculo-bulbar weakness with descending limb/trunk weakness and dilated pupils. Risk of aspiration, respiratory failure. Treatment antitoxin, ?ICU support
- Intracranial mass
- Motor Neuron
- Muscular Dystrophy
- SE of Penicillamine or aminoglycosides antibiotics (exacerbation in MG patients, de novo in high doses)
- Non-organic disorders: jerky release or “give-away” weakness
- Progressive external ophthalmoplegia → ?mitochondrial disorders, rare
- Associated disorders:
 - Thymus: thymoma (usually benign) in 10%, hyperplasia in 65%, more in early than late (>40) onset
 - Other autoimmune disorders
 - Exacerbated by: hyper or hypothyroidism, occult infection
- Treatment:
 - According to severity:
 - Ocular: pyridostigmine (anticholinesterase) → immunosuppression
 - Generalised: pyridostigmine → assess for thymectomy in all patients age puberty to 55 years (85% get improvement) → immunosuppression
 - Crisis (diaphragmatic and intercostal muscle weakness, 2nd to excess anticholinesterase medication [so stop these] or precipitating infection): ICU + plasmapheresis/IVIg +/- neostigmine IV → immunosuppression. Also antibiotic therapy (immunosuppressed protocols) and chest physio
 - Anticholinesterase medications: pyridostigmine – acts in 15 – 30 mins, lasts 4 hours. Titrate up from 60 mg tds. Can cause a cholinergic crisis
 - Immunosuppression if not well controlled on anticholinesterase:
 - Glucocorticoids: improvement within 1 – 3 months. Start at low dose (~20 mg/d) to avoid early weakening that occurs in 1/3 treated straight off with a high dose. Titrate up till improvement or 60 mg/d reached. Maintain for 1 – 3 months then decrease
 - Azathioprine: improvement over 3 – 6 months, up to a year. Used due to relatively safety. Intolerable in 10% due to flu-like symptoms, bone marrow depression or abnormal LFTs. Initial dose of 50 mg/d. Titrate (typically to 2 – 3 mg/kg) till WBC falls to 3 – 4 (unless concurrent steroids). Avoid allopurinol (common degradation pathway)
 - Cyclosporin if refractory to above: improvement in 1 – 3 months. 3 – 4 mg/kg in 2 divided doses. SE: HTN and nephrotoxicity. High dose course in refractory cases – “reboots” immune system by eliminating mature lymphocytes (with haematopoietic precursors spared as they express the enzyme aldehyde dehydrogenase which hydrolyzes cyclophosphamide)
 - Mycophenolate Mofetil: 1 – 1.5 g bd. Expensive. Inhibits purine synthesis by the de novo pathway. Lymphocytes lack the alternative pathway (present in other cells) so this inhibits proliferation of lymphocytes only. Have to wait for existing lymphocytes to die (may take months) before effect. SE rare diarrhoea and leukopenia

Other

Chronic Inflammatory Demyelinating Polyneuropathy

- Incidence less than GBS, but protracted so prevalence higher
- PC: initially may look the same as GBS, symptoms both motor and sensory. Sometime chronic progressive, sometime relapsing remitting (like MS). Some have tremour or cranial nerve findings
- Ameliorates over time with treatment. 75% have reasonable function after years
- Tests: Raised acellular protein in CSF. Demyelination with axonal loss in >50% on NCS. MRI may show nerve root hypertrophy and enhancement. Nerve biopsy: inflammation + atrophy

- Exclude MGUS (occurs in 25%, IgM type worse prognosis) with electrophoresis, connective tissue disease (esp SLE), chronic hepatitis, HIV and diabetes mellitus
- Pathogenesis unclear
- Treatment may wait until walking compromised. Initially treated with IVIg or plasmapheresis. Responds to corticosteroids. ~ Half respond initially. May also consider immunosuppressive therapy

Multifocal Motor Neuropathy

- Uncommon – slowly progressive motor weakness over years in selected nerve trunks, with persistent focal conduction block. Arms > legs
- Confused with peripheral forms of Motor Neuron
- 50% have high titres of polyclonal IgM antibody to ganglioside GM1
- Respond to high dose IVIg

Multiple Myeloma and Monoclonal Gammopathy of Uncertain Significance

- See page 441
- Not certain it's the paraproteins that are the problem....
- Sensorimotor neuropathies in ~5% typical multiple myeloma (= with lytic bone lesions, kappa light chains) – often irreversible axonal degeneration
- In atypical myeloma with osteosclerotic features (~3% cases, lambda light chains), polyneuropathy in ~50%. Demyelinating. Respond to radiation to primary lesion. May occur in association with POEMS (Polyneuropathy, Organomegaly, Endocrinopathy [eg hypothyroid], M protein and Skin changes)
- MGUS: Neuropathies occur in association with IgG, IgA and IgM, indistinguishable from CIDP

Vasculitic Neuropathy

- Peripheral neuropathy common (~50%) in Polyarteritis Nodosa. Usually multifocal asymmetric motor-sensory neuropathy (Mononeuroitis Multiplex) due to ischaemic lesions of nerve trunk and roots. NCS show axonal loss
- 1/3rd cases not systemic – affecting only peripheral nerve
- Seen in other connective tissue diseases: RA, mixed cryoglobulinaemia, Sjogren's syndrome, Wegener's, Hypersensitivity Angiitis, and Progressive Systemic Sclerosis

Anti-Hu Paraneoplastic Neuropathy

- Sensory 2nd to selective damage to dorsal root ganglia, 25% cases are 2nd to Small Cell Lung Cancer

Muscle Disease

- See Polymyositis, page 266
- Most myopathies → muscle replaced by connective tissue and fat → same size
- Watch for the combination of fibrates, statins and cyclosporine (cumulative toxicity)
- Investigations:
 - Serum MM-CK – can be elevated after activity or seizure
 - LDH and AST both present in muscle
 - EMG: myopathies → excessively recruited compound action potentials
 - Muscle biopsy
 - DNA analysis for common defects
- Drugs causing myalgia or myopathy:
 - Statins/fibrates, vincristine, cyclosporin, gold, labetalol, nifedipine, methadone, prednisone, d-penicillamine, amiodarone, chloroquine, colchicines, zidovudine (AZT)...
 - Statin Myopathy: see page 63
 - AZT Myopathy: see page 309

Muscular Dystrophies

- Duchenne *Muscular* dystrophy:
 - X-linked recessive, 30 per 100,000 males
 - Obvious from 3 – 5 years, Gower's sign, contractures from age 6, wheel chair by 12 with scoliosis
 - Also cardiomyopathy and sometimes mental retardation
 - Defect of dystrophin gene → dystrophin deficiency
 - CK levels 20 to 100 times normal
 - Prednisone at 0.75 mg/kg slows progression up to 3 years, SE weight gain

- Becker Muscular Dystrophy
 - Same gene as Duchenne (but the “in-frame” deletion allows for some dystrophin production), less severe, less common (3 per 100,000)
 - Proximal weakness onset from 5 to 15
- Limb girdle muscular dystrophy: several disorders, onset up to the 4th decade
- Numerous others....AD, AR and XL, including:
 - Limb girdle muscular dystrophies
 - *Myotonic* Dystrophy: Most common is Steinert’s Disease – AD CTG repeat disorder. Myotonin protein kinase also expressed in heart (ie multisystem disease...)

Other muscle disorders

- Of energy production:
 - Glycogen diseases:
 - Causing progressive weakness: Acid maltase deficiency, Debranching Enzyme Deficiency
 - Disorders of Glycolysis causing exercise intolerance: five conditions with onset in adolescence
 - Lipid disorders
- Mitochondrial myopathies:
 - Often chronic progressive external ophthalmoplegia is the presenting symptom (usually no diplopia, cf myasthenia). Many of them...
 - Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS)
 - Myoclonus, Epilepsy, Ragged Red Fibres (MERRF): cerebellar ataxia, peripheral neuropathy, SN deafness, lipomas
 - Investigations: serum/CSF lactate and pyruvate, CK and muscle biopsy (with histochemistry), and electrophysiology
- Disorders of muscle membrane excitability: various channelopathies
- Endocrine myopathies: thyroid, parathyroid, adrenal, pituitary, diabetes, Vitamin D deficiency

Chronic Fatigue Syndrome

- Diverse names reflect controversial hypotheses about etiology. Various clusters reported over the 20th century
- Common themes: often post-infectious, commonly accompanied by neuropsychological complaints
- CDC diagnostic criteria:
 - *Unexplained* persistent or relapsing fatigue
 - Four or more of the following persisting or recurring during > 6 months:
 - Impaired short term memory or concentration
 - Sore throat
 - Tender cervical or axillary nodes
 - Muscle pain
 - Multi-joint pain without redness or swelling
 - New headaches
 - Un-refreshing sleep
 - Post exertional malaise lasting > 24 hours
- Changes in numerous immune parameters have been reported, none is seen in most patients and they do not correlate with severity
- Some evidence of disturbances in hypothalamic-pituitary-adrenal axis
- Mild to moderate depression in > 50%, higher rate than other chronic illnesses
- Treatment:
 - Education and monitoring
 - NSAIDS for headache
 - Treat depression. Trials of CBT showed benefit
 - Graded exercise (bed rest → deconditioning)
 - No benefit from trials of acyclovir, fludrocortisone, IV Ig (among others)

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Chest Radiology

Plain Films

- Chest Xray sensitivities:
 - Normal in 10% with infiltrative lung disease
 - Normal in 30% with bronchiectasis
 - Normal in 50% with emphysema
- Reading a plain film:
 - Demographics
 - How was it taken: PA, AP, erect, supine, etc
 - Quality: exposure, centering, inflation, breasts, diaphragm (and air under)
 - Lungs: tracheal position, apices, upper, mid, lower, behind heart, CP angles
 - Mediastinum:
 - Heart size
 - RUQ: paratracheal stripe, azygous vein
 - LUQ: L subclavian, aortic knuckle, L edge of aorta, pulmonary artery, AP window (always convex)
 - RLQ: RA
 - LLQ: LA appendage (below bronchus), LV, behind the heart
 - Scanning: compare side to side not top to bottom
 - Bones and soft tissues, including neck
 - Spine, scapulae, humerus
 - Review areas: apices, hilar, behind heart, CP angles, pneumothorax, surgical emphysema
 - Lateral: Retrosternal space same density as inferior lung
- Anatomy:
 - Upper lobe segments: apex, anterior, posterior
 - Lower lobe segments: apex, then along the diaphragm: anterior (most lateral), lateral, posterior, medial
 - L pulmonary artery goes over top of the bronchus – higher than on the R
- Collapse:
 - Major criteria: fissure shift, ↑density
 - Minor criteria: elevation of diaphragm, mediastinum, crowding of ribs
- Pulmonary oedema:
 - Heart enlargement, then
 - Upper lobe vessels (upper lobe vessels normally < lower zone along a vertical line), then
 - Interstitial oedema with peribronchial cuffing and Kerley B lines
- MRI not good for lung parenchyma – not enough water – it's all air
- Criteria for determining benign or malignant:
 - Growth: doubling time of a tumour between 25 and 450 days (less *or* more then unlikely to be a tumour)
 - Calcification: Benign patterns – dense central, laminated, diffuse or popcorn (conglomerate). Anything else not benign
 - Margin: From benign to malignant: Smooth and regular, smooth and irregular, speculated (spiky), corona radiate (radiating spikes)
 - Enhancement: More enhancement is bad

High Resolution Chest CT

- More radiation than a Chest CT (does thick slices), same as a CTPA (can now reprocess as a HRCT – can't with a normal chest CT)
- HRCT: does a sampling of thin slices (1mm thickness or less), optimises the exposure and uses an edge enhancing algorithm
- Smallest pulmonary unit you can see on CT is the 2ndary pulmonary nodule – has central bronchiole and artery, and peripheral lymphatic drainage adjacent to the interstium
- Diagnostic approach:
 - What is the pattern:
 - Airways:

- Size: usually same calibre as adjacent artery. Enlarged airway with normal sized artery → signet ring sign
- Wall thickness: bronchiectasis progresses from tubular to varicose
- Patency: mucus plug = bronchocele. If terminal bronchiectasis (bronchiolectasis) then fibrotic lung disease
- Interstitium: interlobular, peribronchovascular, intralobular. Any of these can be thickened with fluid, cells or collagen (fibrosis). Pattern can be linear or reticular
- Nodules:
 - Small: uniform – miliary, metastases, patchy – sarcoid, lymphangitis
 - Medium/large: metastasis, infection, inflammation
- Airspace:
 - Opacity: if can see vessels through it then ground glass, if no vessels visible then consolidation
 - Lucency: if no walls then emphysema, if walls visible then cysts
- What is the distribution:
 - Central: sarcoid, ABPA
 - Peripheral: eosinophilic pneumonia, COP
 - Upper: granulomatous, emphysema
 - Lower: IFP, asbestosis
- Associated features:
 - Lymph nodes
 - Pleural effusion
 - Pleural thickening
- Correlation with clinical history: acute, sub-acute, chronic, drug and dust exposures etc

Differentials of findings

- Solitary circumscribed density: nodule < 3 cm, mass > 3cm
 - Sarcoid: usually small peribronchial nodules
 - Primary or metastatic neoplasm
 - Localised infection (bacterial abscess, Tb, fungal). Fungi:
 - Aspergillus → cavities
 - Cryptococcus → mass
 - Wegener's granulomatosis (one or several nodules)
 - Rheumatoid nodule (one or several nodules)
 - Vascular malformation
 - Bronchogenic cyst
 - If no old films, or new nodule then CT. If stable for > 2 years then stop
- Multiple nodules:
 - Infection
 - Well defined → mets: breast, thyroid, kidney, GI, renal
 - Poorly defined, uniform size and distribution: inflammatory (eg sarcoid)
 - Cavitation: septic emboli, TB, sarcoid, Wegner's
 - Haematogenous spread of infection (bacterial, Tb, fungal)
 - Pneumoconiosis
 - Langerhans cell histiocytosis
- Localised opacification (infiltrate)
 - Pneumonia (bacterial, atypical, TB or fungi)
 - Neoplasm
 - Radiation pneumonitis
 - BOOP
 - Bronchocentric granulomatosis
 - Pulmonary infarction
- Diffuse interstitial disease:
 - Idiopathic pulmonary fibrosis
 - Pulmonary fibrosis with systemic rheumatic disease
 - Sarcoidosis
 - Drug-induced lung disease
 - Pneumoconiosis

- Hypersensitivity pneumonitis
- Infection: PJP, viral
- Langerhans cell histiocytosis
- Diffuse alveolar disease:
 - CHF
 - Acute respiratory distress syndrome
 - Diffuse alveolar haemorrhage
 - Infection: PJP, viral or bacterial pneumonia
 - Sarcoidosis
- Differential of honeycomb lung on xray:
 - Idiopathic Pulmonary Fibrosis
 - Drugs
 - Toxins (including asbestos)
 - Connective Tissue Disease
- Mediastinal masses:
 - Anterior: thymomas, lymphomas, thyroid masses
 - Middle: vascular masses, ↑lymph nodes from metastases or granulomatous disease
 - Posterior: neurogenic tumours, meningoceles, oesophageal diverticula

Lung Function Tests

- Obstructive diseases:
 - Asthma, COPD, bronchiectasis, CF, bronchiolitis
 - Slight decrease in static lung volumes seen with obesity (BMI > 35)
 - TLC not effort depend – can be helpful
- Restrictive:
 - Parenchymal: Sarcoidosis, IPF, pneumoconiosis, drug or radiation induced interstitial lung disease
 - Extraparenchymal:
 - Neuromuscular: diaphragmatic weakness/paralysis, myasthenia gravis, GBS, muscular dystrophy, cervical spine injury
 - Chest wall: kyphoscoliosis, obesity, ankylosing spondylitis
- DLco (gas exchange capacity of lung as a whole):
 - = VA (Alveolar volume – the number of contributing alveolar units) * kCO (efficiency of individual units)
 - Loss of DLCO that is less than a loss of volume (ie ↓DLCO but ↑DLCO/VA) suggests extraparenchymal abnormality (eg pneumonectomy or chest wall restriction)
 - Loss of DLCO that is greater than the loss of volume (ie ↓DLCO and ↓DLCO/VA) suggests parenchymal abnormalities
 - ↑DLco: consider pulmonary haemorrhage (eg Goodpastures Syndrome)
 - Normal gas transfer:
 - Normal lung volumes: asthma (DLCO may be high)
 - Decreased lung volumes (with DLCO corrected for lung volumes): Mechanical restriction (eg scoliosis), chronic PE, primary pulmonary HTN
 - Decreased gas transfer:
 - Normal lung volumes: anaemia, PE, early ILD, early emphysema
 - Increased lung volumes: emphysema
 - Decreased lung volumes: interstitial lung disease (eg asbestosis, sarcoidosis)
 - And obstructive pattern: emphysema, also LAM
- Flow volume loops:
 - Obstructive: large volume (ie shifted to left)
 - Extra-parenchymal restrictive disease: TLC < normal, RV > normal
 - Parenchymal restrictive disease: RV < normal (ie shifted to right)
 - Poor effort: upslope of expiration gentler slope and end of expiration is truncated
 - Extra-thoracic restriction (eg vocal chord paralysis or tumour): mid-inspiratory flow markedly reduced/flattened, expiratory flow minimally reduced
- A-a gradient:
 - = PAO₂ – PaO₂. Normal is 5 – 15
 - PAO₂
 - = PIO₂ – PaCO₂/R

- = $(PB - PH_2O) * FIO_2 - PaCO_2/R$
- = $707 * FIO_2 - PaCO_2/0.8$
- = $150 - PaCO_2/R$ at room air

Asthma

- See Lancet 26 October 2002

Natural History

- In chronic asthma there may be a degree of irreversible airflow obstruction
- If persistent or severe childhood asthma, may remit during adolescence and return as an adult
- Adults with asthma rarely become permanently asymptomatic

Etiology

- Overall: a dynamic disease best viewed as a set of interacting subsystems (inflammatory, immunological, and mechanical)
- Atopy: non-atopic individuals have a very low risk of asthma
- Genetic: high degree of twin concordance. Polygenic. Most frequent associations are polymorphisms on chromosome 5q, including TH2 cells, IL4, 5, 9, 13 (associated with atopy)
- Hygiene hypothesis: allergic sensitisation and asthma less common in kids with older siblings → ?lack of early childhood infections maintains the TH2 bias present at birth
- Diet: interventional studies have not supported a role for antioxidants, omega's, magnesium. Exclusion diets unsuccessful
- Air pollution: can trigger asthma but unclear role in etiology
- Allergens: Common triggers and implicated in allergic sensitisation. No evidence that allergen avoidance → ↓incidence. Most common trigger is Dermatophagoides (dust mite)
- Intrinsic asthma: ~ 10% have negative skin test to common inhalant allergens and normal serum concentrations of IgE
- Occupational exposure: ~10% of asthma. Approx 200 sensitising agents identified

Pathogenesis

- Improved knowledge of mechanisms has led to a recognition of different asthma phenotypes that might reflect distinct types of inflammation (eg adult onset vs child onset)
- Airway mucosa infiltrated with activated eosinophils, mast cells (IgE mediated, role in bronchoconstriction) and T lymphocytes. Inflammation poorly correlated with disease severity
- Changes in FEV1 after allergen exposure:
 - Early reaction: 1 – 2 hours – mast cell reaction, stabilised by β-agonist
 - Late reaction: 2 – 8 hours – eosinophilic mediated, improved by steroids
- This specific pattern of inflammation → *airways hyperresponsiveness* (AHR):
 - Excessive bronchoconstriction to triggers that would not have affected normal airways.
 - May be contributed to by epithelial damage (loss of barrier function to antigens, loss of enzymes)
 - Measured by methacholine or histamine challenge – measure concentration that reduces FEV1 by 20% (PC20)
- Vasodilation and angiogenesis (↑ number of blood vessels)
- Fibrosis of the basement membrane with collagen III and V
- Leads to chronic bronchitis with mucus gland hypertrophy and chronic airway limitation
- A common finding in fatal asthma is a mucous plug
- Cytokines:
 - TH2 release Il-5 → eosinophilic inflammation and release of Il-4 and 13 → ↑IgE formation
 - But blocking Il-5 → ↓circulating eosinophils but not change in asthma symptoms
 - TNFα and Il-1β amplify the inflammatory response – ?role in more severe disease
 - Il-10 and 12 are anti-inflammatory – ?deficient in asthma
- Smooth muscle abnormalities:
 - eg ↓responsiveness to β-agonists, ?2nd to chronic inflammation
 - Reflex activated bronchoconstriction via acetylcholine activated muscarinic receptors
- Drugs:
 - ACEI theoretically detrimental as they inhibit breakdown of kinins which are bronchoconstrictors – but in practice little difference. ACEI cough as common in non-asthmatics as asthmatics

- Aspirin: 1% of asthmatics worse with aspirin (and other COX inhibitors. COX2 safe). Well defined subtype of asthma presenting with Samter's Triad: rhinorrhoea, wheezing and nasal polyposis. Also conjunctival irritation and facial flushing. Low-grade trials suggest desensitisation may help symptoms. Can be due to a functional polymorphism of cys-leukotriene synthase. If persistent, consider asthma inhalers (especially leukotriene antagonists), nasal steroids, polyp removal
- Exercise: Hyperventilation → ↑osmolality in airway fluids → mast cell mediator release → bronchoconstriction. Usually after exercise has ended
- Pre-menstrual exacerbation: related to fall in progesterone. Can treat with progesterone
- Hyper and hypo thyroidism can worsen asthma, mechanism unknown

Differential

- COPD: less variability of symptoms, less response to bronchodilators
- Upper airway obstruction: tumour or laryngeal oedema. But stridor predominates. Flow volume loop shows reduction in inspiration as well as expiration
- Persistent wheezing in a specific area of the lung: endobronchial obstruction or foreign body
- Left ventricular failure
- Eosinophilic pneumonias and systemic vasculitis (eg Churg-Strauss and PAN) can cause wheezing
- Exclude mycoplasma or chlamydia
- Vocal chord dysfunction → wheezing/stridor
- Conversion disorder

Severity Assessment

- Diagnosis:
 - Methacholine challenge (PC20) is the most sensitive test – so useful if you want to rule out ?asthma in chronic cough. But rarely useful in practice. A measure of airways responsiveness
 - ↑FEV1 following bronchodilators is the most specific test – while COPD, bronchiectasis and CF can give results > 12%, an increase of > 15 – 20% is only seen in asthma
- Chronic severity:
 - Hospital admission in last 12 months (15 fold risk of mortality)
 - Ever had an ICU admission
 - Smoker
 - ↑risk if ↓ICS therapy
- Acute severity:
 - Rapid onset (<24 hours)
 - Puffs β agonist in last 24 hours
- Clinical (poor evidence basis): < 1 complete sentence, > 25 breaths per minute
- Only ABG if life threatening
- Peak Flow more effort determined than FEV1
- Symptoms at night a marker of instability
- Spirometry or serial peak-flow measurements are neither sensitive nor specific, especially in mild disease
- Trials of short-term treatment will be complicated by other acute conditions that mimic asthma (eg post-viral hyperresponsiveness, anxiety, vocal chord dysfunction, COPD, bronchiectasis...), by observer biases, compliance....
- Can measure sputum eosinophils
- So it would be nice to have better measures of underlying inflammation. Eg Nitrogen Oxide (NO):
 - Produced particularly by airway epithelial cells and macrophages. Expired NO higher in asthmatics. Related to eosinophilic inflammation.
 - Can be used in diagnosis and monitoring asthmatic inflammation. Levels > 50 and < 25 ppb can identify patients who do, and do not, require long term steroids. Benefits of long term ICS occur predominantly in patients with evidence of eosinophilic airway inflammation (Lancet 20 Sept 2008)
 - RCT of using fraction of exhaled NO to guide treatment showed no difference over usual guideline treatment (Lancet 20 Sept 2008) – it was hoped it would be a helpful biomarker...

Chronic Treatment

- A good example of evidence not translating into everyday practice.... Major surveys show a high level of uncontrolled symptoms, significant tolerated limitation in ADLs and excess emergency visits
- Initially symptom and peak flow diary for 2 weeks (NZ guidelines)

- Level 1 evidence that optimal self-management education (regular review, education, written action plan) results in better outcomes (days off work, better lung function, fewer out of hours presentations)
- Inhaled Corticosteroids:
 - ↓number of inflammatory cells in the airways by switching off transcription of multiple activated genes for inflammatory proteins. Inhibits transcription factors NFκB and AP-1
 - Prevent symptoms (eg exercise induced and nocturnal exacerbations) and severe exacerbations
 - Estimates of peak effect range from a dose equivalent to fluticasone 200 mcg daily to 600 mcg – don't know if some have relative steroid insensitivity – not much research
 - Response is heterogeneous
 - Time to response: 1 month to no night symptoms, up to 6 months for FEV1 to reach maximal improvement, a year for no SABA use, AHR even longer – may take a year on ICS to significantly ↓ exacerbations
 - SE: Hoarseness (dysphonia) most common, oral candidiasis (↓ with spacer)
 - ~1% of asthmatics require maintenance treatment with oral corticosteroids
 - Cochrane Review (2008): no difference between Fluticasone/salmeterol and budesonide/formoterol – although confidence intervals wide so may be meaningful differences
- Bronchodilators:
 - Act on smooth muscle. Little or no effect on underlying inflammation
 - β₂ agonists activate β₂ adrenergic receptors. Also inhibit mast cell mediator release, ↓plasma exudation, ↓sensory nerve activation
 - Short acting: duration of 3 – 6 hours
 - Long acting (salmeterol and formoterol): duration > 12 hours. Don't give without ICS. *First choice as add on to ICS if not adequately controlled on ICS alone.* Improve asthma control and ↓exacerbations when given with ICS, over and above ICS effect. The slight excess of mortality with the use of LABAs is due to lack of concomitant ICS use
 - SE: tremour, palpitations, small fall in plasma K
 - Causes β-receptor down regulation, but there is sufficient receptor reserve for this to have no clinical consequence
 - Formoterol onset is 1 – 3 minutes, salmeterol is 10 – 30 minutes (ie too slow to be used as an acute reliever). Given there is a slow, progressive worsening of symptoms before an exacerbation, patients instinctively self-medicate with their SABA. In this setting, if they were to use a quick acting LABA that also had steroid (eg symbicort – budesonide + formoterol, 100/6 not 200/6 otherwise reach the ceiling too quickly, max 12 per day) evidence is that it can slow the onset of an exacerbation
- Anticholinergics:
 - Muscarinic receptor antagonists (eg ipratropium bromide) → ↓cholinergic nerve-induced bronchoconstriction and mucus secretion. Have a slower onset (ie if acute give β-agonists first). Little or no systemic absorption. SE dry mouth, and urinary retention/glaucoma in elderly
 - If irreversible airway narrowing, tiotropium (long acting anticholinergic) can be tried
- Theophylline: Inhibits phosphodiesterases in airways smooth muscle. Doses required for bronchodilation commonly cause SE (nausea, vomiting and headaches, also diuresis and palpitations, at high concentrations arrhythmias, seizures). At lower dose ?anti-inflammatory effect. Need plasma concentrations of 10-20 mg/L. Small additive to ICS in severe asthma. Metabolised by erythromycin and allopurinol
- Antileukotrienes:
 - Cysteinyl-leukotrienes: mainly produced by mast cells. Potent bronchoconstrictors, cause microvascular leakage, activate cyc-LT₁-receptors → ↑eosinophils
 - Antileukotrienes (eg montelukast and zafirlucast) block cys-LT₁-receptors → modest clinical benefit. Used as add on
- Cromones (eg cromolyn sodium) inhibit mast cells. Use limited by short duration (required QID). No significant side effects
- Anti-IgE (Omalizumab, sc every 2- 4 weeks, no significant side effects): neutralises circulating IgE. ↓exacerbations in severe asthma. Expensive. Only useful in very selected patients. *The only monoclonal antibody to have an effect in asthma*
- A variety of novel anti-inflammatory treatments are in development
- Pregnancy: ICSs and theophylline safe. Less safety information about LABAs, antileukotrienes and anti-IgE. Use prednisone rather than prednisolone as it can't be converted to the active prednisolone metabolite by the fetal liver
- What doesn't work:

- Steroid sparing treatments: Methotrexate, cyclosporine, azathioprine, gold and IV gammaglobulin have all been tried without long term benefit
- Immunotherapy: desensitisation with pollens or house dust mite – lack of evidence of clinical efficacy
- Alternative therapies: No efficiency in RCTs of hypnosis, acupuncture, chiropraxy, breathing control, and yoga

Future Directions

- See Lancet 20 Sept 2008
- Better delivery – fast onset, once daily formulations, pro-drug steroids with reduce systemic absorption, etc
- Drugs targeting specific pathways, eg
 - Inhaled p38 MAPK inhibitors and anti-oxidants
 - Transcription factor and/or kinase inhibitors
 - Adhesion blockers
 - Mediator antagonists
 - In combination, and to reduce corticosteroid insensitivity
- Immunoregulation: anti-IL13 and modulators of T helper cell function, cytokine inhibitors and agonists
- Development of ability to discriminate between different asthma subtypes, better biomarkers for disease progression or treatment response

Acute Treatment

- 6 litres O₂
- Salbutamol:
 - 2.5 mg salbutamol twice as often better than 5.0 mg
 - 5 puffs via a spacer the same as 2.5 mg neb
- Systemic corticosteroids:
 - 100 mg hydrocortisone (no more, 50 mg may be OK) onset 6 hours
 - Oral prednisone, 6.5 hours onset
- Acute Severe Asthma: Add MgSO₄
- CPAP/BiPAP: controversial. Small trials suggest ↓work of breathing and ↓intubation, but risk of barotrauma

Refractory Asthma

- Most common cause is poor compliance. Try combination ICS and LABA – combine something that works with something that has a symptomatic effect
- Also consider adding theophylline or maintenance oral steroids
- Resistance of corticosteroids: 1 in 1000. ?Excess transcription factor AP-1, or an alternative form of glucocorticoid receptor GR-β, or a defect in IL-10 production....
- Brittle Asthma: Chaotic variations in lung function despite maximal therapy. Sc adrenaline if not bronchodilator responsive

Work related asthma

- = *Made worse* by work related agents (as opposed to “occupational asthma” which is *caused* by work agents)
- Eg: bakers, latex, lab animal workers (animal urine), detergents, spray painters (esp cars), circuit boards.... Need high dose of antigen – won’t get enough at home to cause symptoms
- History:
 - Rhinitis, eczema and asthma
 - Takes time to be sensitised (3 – 6 months)
 - Symptoms relationship with work
 - Doesn’t respond well to asthma treatment

Eosinophilic Bronchitis

- No longer synonymous with asthma
- Diagnosed by > 2.5% eosinophils in induced sputum
- Airways hyper-responsiveness absent
- Atopy at the same frequency as the general population
- Responds to ICS and oral steroids

Allergic Bronchopulmonary Aspergillosis (ABPA)

- See Aspergillosis Mycotic Infections, page 297
- Characterised by Type-I (\uparrow IgE, blood eosinophilia, immediate skin test reactivity) and type-III immune reactions to Aspergillus
- In pre-existing, steroid dependent asthma (also CF) who develop worsening bronchospasm, fleeting pulmonary infiltrates, eosinophilia
- Presentation:
 - Airways blocked with mucoid plugs rich in eosinophils – cough up brown plugs and have haemoptysis. May \rightarrow central bronchiectasis and transient, recurrent infiltrates on CXR
 - Intermittent wheezing, infiltrates due to bronchial plugging, *eosinophilia*, sputum, episodic fever and pulmonary infiltrates, thick tenacious secretions
- No single diagnostic test. A negative skin prick test virtually excludes the diagnosis. \uparrow IgE and \uparrow IgG Aspergillus precipitins on serology
- Treatment:
 - Steroids suppress the immune response and induce remission. No evidence that long term prednisone prevents exacerbations
 - Small trial evidence of selective benefit of itraconazole (if older and no bronchiectasis)
- Progression:
 - Usually remits
 - May \rightarrow saccular bronchiectasis and fibrotic lung disease
 - Small risk of developing invasive aspergillosis

Chronic Obstructive Pulmonary Disease/COPD

- See BMJ 19 March 2005
- GOLD (Global Initiative for Chronic Obstructive Lung Disease) definition: includes:
 - Emphysema: destruction and enlargement of the alveoli
 - Chronic bronchitis: chronic cough and phlegm
 - Small airways disease: narrowing of small bronchioles (need this – bronchitis without small airways disease is not included in COPD)
- Risk factors:
 - Dose-response relationship with smoking – but only 15% of the variability in FEV1 is explained by pack years. Less compelling association with cigar and pipe smoking
 - \uparrow Airways hyperresponsiveness: a predictor of subsequent decline in pulmonary function
 - Biomass smoke a significant risk factor for COPD among women in the third world
 - Low birth weight (ie poor lung growth)
 - Asthma: (RR 12.5 times): reversible \rightarrow fixed airflow obstruction
 - Less certain association:
 - Infections cause exacerbation, but association between infection and progression not proven
 - Occupational dust as a risk factor in addition to smoking is uncertain
 - Ambient air pollution unproven
 - Passive smoke is associated with reductions in pulmonary function, it's importance as a risk factor for COPD is uncertain
- Genetic associations:
 - Severe α 1-antitrypsin deficiency:
 - Proven risk factor for COPD
 - M allele associated with normal α 1-antitrypsin deficiency, S is slightly reduced, Z is markedly reduced. Two ZZ alleles (1 in 2,000), or one Z and one null allele are the most common form of severe deficiency. Found in 1 – 2 % of COPD. The risk with MZ individuals (who have ~ 60% of MM individuals) is controversial – ?an excess amongst COPD patients in case-control studies
 - Diagnosis by \downarrow serum α 1AT then α 1AT genotype
 - Liver disease: can be found in those with SZ in addition to ZZ. Liver biopsy shows PAS-positive diastase-resistant globules in the periphery of the hepatic lobule
 - Treatment supportive. Liver transplant curative
 - Other genetic factors likely, none identified
- Pathophysiology:
 - FEV1 seldom shows large responses to inhaled bronchodilators – although improvements up to 15% common

- Airflow during forced expiration reflects the balance between elastic recoil (→ promotes airflow) and resistance of the airways (limits flow)
- Loss of elastin → ↓recoil at the same volume
- COPD → “air trapping” (↑ residual volume) and hyperinflation (↑total lung capacity). The later is adaptive: preserves maximum expiratory airflow due to ↑elastic recoil and ↑airway size. But flattens diaphragm – which ↓ventilation
- Tidal volume is at much higher lung volumes – requires more work to expand lung when it’s already full
- Gas exchange: PaO₂ normal until FEV₁ ~ < 50% predicted, PaCO₂ doesn’t rise until ~ < 25% predicted
- Ventilation-perfusion mismatches characteristic (not shunting) due to heterogeneous distribution of disease. Can be demonstrated by delayed wash out of nitrogen when breathing 100% O₂. Explains effectiveness of small increases in inspired O₂
- Pathology:
 - Cigarette smoking:
 - Mucous gland enlargement and goblet cell hyperplasia
 - In small airways, replacement of surfactant-secreting Clara cells with mucus-secreting cells and infiltrating mononuclear inflammatory cells → luminal narrowing
 - Fibrosis → small airway narrowing
 - Proteolytic destruction of elastic fibres in the bronchioles and alveoli
 - Accumulation of macrophages, ↑ inflammatory cytokines (eg TNFα)
 - Cigarette smoke-induced loss of cilia → bacterial infection with neutrophilia
 - Patterns:
 - Centriacinar emphysema: commonly in smokers, enlarged airspaces in association with bronchioles, often quite focal, upper lobes and upper segments of superior lobes
 - Panacinar emphysema: usually α₁-antitrypsin, predilection for the lower lobes
 - Vulnerable to IHD and cancer – smoking can kill you in other ways

Assessment

- Presentation:
 - Cough, sputum and exertional dyspnoea
 - Pink puffers: emphysema – thin, prominent use of accessory muscles
 - Blue bloaters: Chronic bronchitis – heavy and cyanotic – but stereotypes usually much more mixed
 - Advanced disease → weight loss
 - No clubbing
 - ?α₁-antitrypsin measurement in all new diagnosis. If low need type determination to then be helpful
- Pulse oximetry (SpO₂):
 - Percentage of arterial haemoglobin that is oxygenated
 - Unreliable if: variant haemoglobins (HbS, HbF), shocked, anaemic, CO poisoning, poor probe contact, nail polish...
 - O₂ sats of 98% is not normal if RR 24/min and pulse 110 – what would it be without these compensatory mechanisms?
- Lung Function:
 - Airflow obstruction = FEV₁ < 80% predicted and FEV₁/FVC < 0.7. Reversibility not usually necessary for COPD (NICE guidelines)
 - ↓diffusing capacity
 - Degree of airflow obstruction of prognostic value – basis of Gold classification (Stage 0 – IV based on FEV₁ and FEV₁/FVC):
 - Mild: FEV₁ 50 – 80%
 - Moderate: FEV₁ 30 – 49%
 - Severe: FEV₁ < 30%
 - LFT is poorly correlated with patient-centred outcomes such as SOB and exercise capacity
 - Better predictor is based on airflow obstruction, exercise performance, dyspnoea and BMI (BMI < 20 has relative risk of 1.5 compared with 20 – 25)
 - CT: doesn’t change management (except for differential diagnosis) unless considering surgery
- Blood gas assessment: In acute COPD, pH is the best marker of severity (not PCO₂). pH < 7.26 (<7.3 in some trials) ⇒ poor prognosis in this exacerbation
- Other prognostic factors:
 - ↑CO₂ during an exacerbation is not related to survival, chronically it confers a small risk

- An acute exacerbation requiring admission confers a significant adverse prognosis, with 1 year mortality at 43%, independent of other risk factors (eg BMI and FEV1)
- Differential: consider asthma if > 400 ml response to bronchodilators, significant diurnal or day-to-day variability on serial PEFr or if > 400 ml response to 30 mg prednisone for 2 weeks. Chronic productive cough uncommon in asthma

Treatment

- Natural history only demonstrated to be affected by smoking cessation, O2 therapy in chronically hypoxemic patients and lung volume reduction surgery (LVRS) in selected patients
- Treatment progression: PRN SABA → PRN SABA + LABA/Anticholinergic → PRN SABA + LABA/Anticholinergic + ICS
- **Pulmonary rehab** (always mention it):
 - Package of education and cardiovascular conditioning has been shown to improve health related quality of life, dyspnoea and exercise capacity and ↓hospitalisation and LOS
 - May ↓mortality, may ↓exacerbations, certainly ↑ QoL and exercise capacity
 - Benefits persist for up to 18 months
 - Should be considered for GOLD stage II to IV
 - Many skeletal changes in COPD – quads more than arms, ↓oxidative capacity. Combination of diffuse systemic inflammatory state, disuse, steroids, hypoxia, nutrition
- Details:
 - β-agonists and anticholinergic agents:
 - Start before ICS
 - Symptomatic relief, no influence on decline in lung function
 - Long acting bronchodilators improve exercise capacity, dyspnoea and quality of life more than ipratropium.
 - Combination of LABA and long acting anticholinergic only tested in one small study and showed additive benefit over either alone
 - SE: dry mouth in 6 – 16%, maybe constipation
 - Tiotropium:
 - Qualify if FEV1 < 60% predicted
 - M1/M3 muscarinic receptor antagonist. Doesn't block M2 receptor like Ipratropium
 - Reduced time to first exacerbation cf placebo, and ↓lung volume
 - UPLIFT study (NEJM 9 Oct 2008) [Understanding Potential Long-Term Impacts on Function with Tiotropium]:
 - Study in 6000 of Tiotropium vs placebo (and no other anticholinergics allowed)
 - Initial improvement in FEV1 maintained, but after that no difference in the rate of decline of FEV between arms – the Holy Grail of COPD treatment is to slow the rate of decline in FEV1 – this didn't do it
 - Improvements in quality of life and reduced exacerbations [vs both placebo *and* LABA in other studies]
 - Adding LABA and LABA + Steroid (Seretide) to Tiotropium ↑disease specific QoL, Rate of all cause hospitalisations, lung function (OPTIMAL study, funded by Canadian Govt)
 - Inhaled Corticosteroids:
 - Ineffective as treatment for mild to moderate COPD. Prolonged therapy with high dose ICS required to achieve modest effects (eg Lung Health Study)
 - *No benefit on disease progression*
 - Use if an FEV1 < 50% predicted who have had 2 or more exacerbations requiring ABs or corticosteroids in 12 month period (NICE guidelines). Reduce the rate of exacerbations and improvements in HRQL. *May* slow rate of decline in FEV1. Dose response relationships and long term toxicity unknown
 - Reduce exacerbations (RR = 0.70) but at the risk of oral candidiasis (RR =2.1) and skin bruising (RR = 2.1), and no improvement in mortality
 - Largest study is TORCH study (Towards a Reduction in COPD Health, NEJM 2007;356:775) in severe COPD: treatment with Seretide – LABA (Salmeterol) and ICS (Fluticasone) – better than either alone (increased risk of pneumonia in patients on fluticasone, no significant osteopenia), symptomatic improvement, ↓exacerbations but ↓mortality at 3 years didn't reach significance (P = 0.052) with an absolute reduction of 2.6% (equivalent to statins in CHD)
 - Theophylline: modest incremental benefit in lung function

- Mucolytic drugs: PEACE trial (Lancet 14 June 2008) showed ↓exacerbations with carbocisteine: 1.01 vs 1.35 exacerbations per year (although less inhaled bronchodilator and corticosteroid use than other large studies)
- Supplemental O₂:
 - 4 Trials – the 2 done on those with severe resting hypoxaemia (PO₂ < 60 mmHg) showed mortality benefit
 - Mortality benefit proportional to number of hours/day on O₂.
 - Current criteria: pO₂ < 55 mmHg or < 60 mmHg and evidence of cor pulmonale (pulmonary HTN or RHF)
- Blood-product derived α1AT supplementation in those who are deficient, biochemical efficacy demonstrated but no RCT trials measuring decline in lung function
- Influenza vaccine annually. Also pneumococcal recommended but no definitive proof of efficacy. Zanamivir and oseltamivir are recommended for at-risk patients who present with influenza-like illness within 48 hours of onset of symptoms (NICE guidelines)
- Lung Volume Reduction Surgery: Symptomatic benefit and mortality benefit in certain patients only (upper lobe predominant emphysema and low exercise capacity). If FEV₁ < 20%, diffuse disease or DLCO < 20% then ↑mortality with LVRS (NEJM 22 May 2003)
- Lung transplant: failure of medical treatment, < 65 years, no other comorbidities
- If flying with COPD and sats 92 – 95 then require further assessment to determine if they need supplemental O₂ in flight (see Air Travel Advice, page 220)

Exacerbations

- Average 1 – 2 per year, frequency increases as disease progresses
- No evidence that combining SABA and anticholinergics is more effective than either alone. No evidence for IV theophylline
- Measuring lung function has not been demonstrated to be helpful in the diagnosis or management of exacerbations of COPD
- Infections (see NEJM 27 November 2008):
 - New evidence that infection is the predominant cause of exacerbations and is a likely contributor to the pathogenesis of COPD. About 50% of exacerbations caused by bacteria
 - Purulent sputum during an attack is highly correlated with the presence of bacteria in the lower respiratory tract
 - Acquisition of new bacteria more important to an exacerbation than change in bacterial load
 - Most common bacteria: Haemophilus influenzae (20 – 30% of exacerbations, see page 288), then Moraxella catarrhalis, then Strep pneumoniae. Amoxicillin is inactive against 40% of Haemophilus influenzae and 95% of Moraxella catarrhalis strains (Ann Intern Med 2006:144:49-56)
 - Mycoplasma or chlamydia in 5 – 10%
 - Viral infections in 1/3rd, no precipitant found in 1/3rd
 - Antibiotics have only been shown to be effective if ↑SOB, ↑sputum volume and ↑sputum purulence are all present (Wgtn antibiotic guidelines). Empiric treatment with amoxicillin 500 mg po q 8 h or doxycycline po 100 mg q 12 h. Augmentin if severe
 - Chronic suppressive antibiotics not beneficial
- Steroids in hospitalised patients have been shown to ↓ length of admission and ↓relapse
- Supplemental O₂:
 - Has been demonstrated to be of benefit in both acute and chronic ↑CO₂. A modest ↑in CO₂ is likely to be due to alteration of ventilation-perfusion and is OK
 - Maintaining SpO₂ 85 – 92% minimises the risk of acidosis (Thorax 2000)
 - SpO₂ > 92% associated with acidosis in 33 – 50% of hypercapnic COPD patients (↓hypoxic drive → respiratory acidosis) (Thorax 1999)
- Respiratory stimulants:
 - Most common is Doxapram
 - Minor, short term improvement in blood gas tensions (Cochrane Review 2000)
 - Compared with NIV, benefit of doxapram lost at 4 hours, NIV benefit maintained
 - Confine use to patients awaiting NIV, if NIV unavailable or poorly tolerated, for those with reduced drive (eg due to sedation)

Ventilation

- Respiratory Failure:

- Type 1 failure: $PO_2 < 60$ mmHg (8 kPa) with a normal or low pCO_2 . Problem is gas exchange (PE, asthma, pneumonia, LVF)
- Type 2 failure: $pO_2 < 60$ mmHg and $pCO_2 > 49$ mmHg (6.5 kPa). Problem is gas exchange and ventilation (COPD, obesity hypoventilation, musculo skeletal)
- Ventilation Terminology:
 - Trigger: what starts inspiration: patient, ventilator time
 - Limit: what limits flow of gas into lungs: fixed flow, fixed pressure
 - Cycling: what starts expiration: volume, time, flow, pressure
- CPAP: Continuous positive airway pressure:
 - *Not* ventilation: splints airways open and recruits alveoli. Just delivering $\uparrow FiO_2$. \downarrow Shunting, \downarrow preload, \downarrow auto PEEP. Best in type I respiratory failure (pneumonia, LVF). Use if hypoxic on rebreather. For LVF start at 5 cm H₂O (cf 15 for OSA). For asthmatics, they should be in ICU.
 - Not good in type 2 failure – it's not ventilating the patients, doesn't blow off CO₂
- NIPPV (ie BIPAP):
 - BIPAP = bilevel inspiratory positive airway pressure: patient triggered, pressure limited, pressure cycling
 - Indications: failure of usual management (ie must try other things first) and $pH < 7.35$ (BTS guidelines 7.25 – 7.35)
 - Bullae not a contraindication, pneumothorax is. High aspiration risk and massive obesity are relative contraindications (use if ceiling of treatment). \uparrow risk of aspiration (especially if \downarrow LOC or vomiting)
 - Major risk: delay in intubation when this was warranted
 - Settings:
 - IPAP (inspiratory positive airway pressure): determines tidal volume and thus CO₂. \uparrow IPAP \rightarrow \uparrow volume \rightarrow \uparrow more CO₂ blown off
 - EPAP (Expiratory positive airway pressure): recruits more alveoli at end of expiration \rightarrow improves oxygenation in COPD
 - BPM = back up breaths per minute = $60 \text{ secs} / (T_i + T_e)$. Not good for apnoea – doesn't alarm. S/T = extra breaths if too slow
 - Start at 10 – 12 / 4 – 5. Difference between IPAP and EPAP needs to be at least 5 – the difference is the amount of ventilating you're doing. Add enough O₂ to get sats $> 85 - 90\%$ (may need 5 – 6 litres). Do an AGB at 1 hour. Titrate IPAP up to 20 as needed (although usually improve on 12 if they're going to)
 - Biggest cause of failure is insufficient pressure support (IPAP – EPAP) – put up IPAP
 - Effects of BIPAP:
 - \uparrow tidal volume and \downarrow respiratory rate \rightarrow \uparrow alveolar ventilation \rightarrow \downarrow CO₂ and \uparrow O₂
 - Improved ventilation without change in V/Q mismatch
 - Reduces work of breathing
 - Allows high inspired O₂ in patients who would otherwise develop progressive CO₂ retention
 - Outcomes:
 - Significant reduction in mortality, need for intubation and length of stay with bi-level. Pooled results of RCT shows NIV averts the need for intubation in 50 – 75% of patients
 - Predictors of success (within 4 hours): rapid improvement, improved PCO₂ and pH on ABG
 - Predictors of failure: severe illness, excessive secretions, no improvement over 48 hours
 - No benefit in mild exacerbations – improved dyspnoea score but no difference in intubation rates or LOS
- Intubation: mortality is 17 – 30%. If over 65, ICU admission carries 60% mortality

Smoking cessation

- Epidemiology:
 - Relapse is high – consider as a chronic disorder
 - Passive smoking: all cause mortality $\uparrow 15\%$ in lifetime non-smokers who live with smokers
 - Stopping smoking \rightarrow slowed decline in lung function. Lifelong smokers die, on average, 10 years younger. Cessation at age 60, 50, 40 and 30 gains about 3, 6, 9 or 10 years of life expectancy (BMJ 2004;328:1519)
 - Decrease by 50% does not improve all cause mortality and \rightarrow only $\downarrow 30\%$ reduction in toxin marker (eg compensate by deeper inhalation)
 - Smoking cessation at any age extends life expectancy (age 30 years by 10 years, at 60 by 3 years)
- Pathophysiology:

- Nicotine addiction mediated through nicotinic ACh receptors in the brain. Different receptor configurations predict dependence
- Smoking persistence is 50 – 80% genetically determined (twin studies)
- Persistence of smoking → up regulation of receptors → stimulation with reward and ↑ withdrawal symptoms (including first thing in the morning). Associated learning → anticipation of reward → cravings
- Smokers titrate the number of cigarettes to reduce withdrawal symptoms from ↓ nicotine (thus filters don't work – they just smoke more)
- Evidence for different approaches:
 - Tapering as likely as cold turkey to be associated with nicotine withdrawal symptoms
 - 'Cold Turkey' has the worst quit rate – success < 5% at one year
 - Brief advice results in a 1.74 OR of quitting. Absolute difference of 2.5%. More intensive advice of marginal increased benefit. The five A's of brief advice:
 - Ask about tobacco use
 - Advise to quit
 - Assess willingness to make a cessation attempt
 - Assist in cessation attempt
 - Arrange follow-up
 - Individual and group counselling: OR 1.5
 - Community approaches: no evidence for effect
 - Advice and pharmacotherapy better than either alone
 - Clinic-based smoking status identification system has OR of 3.1
 - Smoke Free legislation: 17% ↓ in admissions for ACS (NEJM 2008;359:482)
- Bottom line: everyone attempting to quit should use NRT and have the personalised assistance of a health care provider. See http://www.quit.org.nz/file/quitcards/QC_FlowChart.pdf
- No evidence of hypnotherapy, psychotherapy, stress management, and acupuncture – but RCTs difficult. No evidence for weaning either number of cigarettes or weaning NRT dose
- Pharmacotherapy:
 - Nicotine replacement therapy:
 - NRT (of any sort) improves chances of smoking cessation by 50 – 70% (12% vs 6% at 2 years). No benefit beyond 8 weeks
 - Effect independent (and additive) to other levels of support
 - No increased in MIs (Cochrane Review 2008)
 - Allows time for down regulation of nicotine receptors → ↓ withdrawal symptoms
 - Patch is slowly absorbed (2 -3 hours to peak) so put it on at night to wake in the morning without craving. 21 mg patch sustains blood level 40 – 50% of smoking 30/day. Some evidence that higher doses in heavy smokers → better quit rates (quit rates of 26% for 44 mg vs 20% for 21 mg)
 - Not recommended in pregnancy (fetus doesn't metabolise nicotine well) but is still safer than smoking
 - May be benefit from additional forms of NRT (eg add in gum or nasal spray for breakthrough craving)
 - Is still of benefit in smokers not ready or willing to quit and still smoking, without ↑ side effects
 - Other tips with NRT: eat breakfast (sugar helps reduce cravings), carry jelly beans for cravings, no alcohol for first 2 weeks and reduce intake generally
 - Non-nicotine:
 - Bupropion (Zyban): Noradrenergic and dopaminergic enhancer. OR 1.94 (Cochrane 2008), longer than 8 weeks doesn't increase quit rates. Increases 1 year quit rate: placebo 16% (higher than other studies), Zyban 30%, Zyban + patches 35% (?significance). Not subsidised. Costs same as smoking. Contraindicated in seizure disorders, or at risk of (alcohol abuse or other drugs lowering seizure threshold)
 - Varenicline (Chantix in the US, Champix in Canada): new therapy in smoking cessation. Competitively blocks the nicotine acetylcholine receptor and only partially activates it, good CNS penetration. Take for 1 week whilst continuing to smoke (no "hit" from smoking). Smoking cessation at 1 year (OR 3.2) better than bupropion (Zyban – OR 1.7) or placebo. SE nausea in 30%, insomnia, abnormal dreams, headache. Contraindicated following acute MI (data is lacking...). Available but not subsidised in NZ
 - Topiramate: small 12 week study in alcohol-dependent smokers showed benefit
- Second line:

- Nortriptyline: subsidised, treatment for 12 weeks in combination with NRT, Cochrane review (4 trials) OR 2.34
- Clonidine – some evidence, role unclear
- New Treatments:
 - Rimonabant: Cannabinoid receptor antagonist
 - Nicotine vaccine: frequent injections. Only 1/3rd develop sufficient antibody levels to produce abstinence
- Risks of stopping:
 - Weight gain: average 4.5 kg, 10% will gain \geq 13 kg. Benefits of quitting > harm of weight gain. Advice to control calories may \rightarrow \downarrow abstinence and does not control weight. NRT, antidepressants and varenicline all reduce weight gain in the short term but long term benefit unclear (Cochrane 2009)
 - Mild depression: If history of depression, then higher risk of relapse over first 6 months

Pneumonia

- Pathogenesis:
 - Small volume aspiration occurs commonly in sleep
 - Alveolar macrophages are extremely efficient at clearing pathogens
 - Assisted by local proteins (eg surfactant proteins A and D) that have intrinsic opsonizing or antibacterial activity
 - Phases of pneumonia:
 - Oedema
 - Red hepatisation: neutrophils plus erythrocytes
 - Gray hepatisation: erythrocytes degraded, prominent neutrophils and fibrin deposition
 - Resolution: macrophages
 - Host factors are important
- Diagnosis:
 - For every ED diagnosis of pneumonia, 67 – 75% don't have it (ie over diagnosed)
 - Clinical and radiological features are not predictive of microbiological cause \rightarrow empiric therapy
 - In 20% of early pneumonia CXR is normal
 - Sputum: main purpose of gram stain is to ensure it's adequate for culture – must have > 25 neutrophils and < 10 squamous epithelial cells per low power field
 - Sputum Culture: even in blood culture proven pneumococcal pneumonia, the positive yield from sputum culture is < 50%
 - Blood culture: only positive in 5 – 14% of hospitalised CAP, and most show *S pneumoniae* – which you've treated for empirically. Don't culture routinely – only if high risk – those with neutropenia, asplenia, complement deficiencies, chronic liver disease, or severe CAP
 - Antigen tests: Positive even after ABs commenced
 - Legionella urine antigen test: detects serogroup 1 (eg legionella haemophyla) – but this accounts for most cases of Legionella CAP. 90% sensitivity and 99% specificity
 - Pneumococcal urine antigen test: 80% sensitive, > 90% specific (ie reasonable rule out test)
- Treatment:
 - Monotherapy: if you have time to trial one approach
 - Dual therapy: if you have to get it right first time

Community Acquired Pneumonia

- Pathogens:
 - Polymicrobial infections are common
 - Typical: *S pneumoniae*, *H influenzae*, *S aureus*, and G –ive bacilli (eg *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*)
 - Atypical: *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella*
 - Cannot be cultured on standard media, nor seen on G stain
 - Intrinsically resistant to all β -lactams \Rightarrow treat with a macrolide, fluoroquinolone or a tetracycline
 - Viruses: Influenza, adenoviruses, respiratory syncytial viruses – *viruses are a more common cause than St pneumoniae* (18% vs 13.9% in one Australian study)
 - *S aureus*: complicates influenza infection
 - Anaerobes:
 - If aspiration days to weeks previously

- Unprotected airway and significant gingivitis are the major risk factors
- Often complicated by abscess formation, empyemas or parapneumonic effusions
- Complications:
 - Parapneumonic effusion in 40%
 - Empyema
 - Abscess
 - Severe CAP who are hypotensive despite fluids:
 - May have adrenal insufficiency → ?response to glucocorticoids
 - Activated protein C (drotrecogin alfa) if persistent shock and APACHE II score ≥ 25
- Two sets of criteria for risk stratification:
 - CURB-AGE score (Confusion, Urea > 7 , RR > 30 , Systolic BP < 90 , Age > 65). 30 day mortality of score 0 = 1.5%, 2 = 9.2%, $\geq 3 = 22\%$. Poor ability to predict safety for home care or need for ICU
 - Pneumonia Severity Index (Developed by Fine et al NEJM 1997 → sometimes called Fine Score): 20 variables sorting patients into 5 classes, with mortality ranging from 0.1% to 29.2%. ?too complicated for routine ED use. Heavily weighted to age and co-morbidities – thus predicts who was already about to die, rather than “unexpected deaths”
- Treatment:
 - Antibiotics for pneumonia within 4 hours of arrival at hospital reduces inpatient mortality (6.8% vs 7.4% if later), and 30 day mortality (11.6% vs 12.7%) (Ann Intern Med 2006;144:49-56)
 - Apart from ICU admissions, no data to suggest treatment directed at a specific pathogen is statistically superior to empiric treatment
 - Treatment duration:
 - 5 day course sufficient for CAP treated with flouroquinolones and telithromycin
 - Longer course if bacteraemia, metastatic infection, or virulent (eg P aeruginosa or CA-MRSA)
 - 3 day course of IV followed by orals equivalent to 7 day IV course, and has shorter hospital stay (BMJ, 2006;333:1193)
 - Failure to respond after 72 hours:
 - Atypical or unusual bug
 - Virulence factors (common)
 - Pharmacological
 - Complications (NB you’ll get liver and renal impairment in any severe pneumonia)
 - Resistance of macrolides: US data: 59% of penicillin-resistant S pneumoniae are also resistant to macrolides through several mechanisms:
 - Target site modification: ribosomal methylation in 23S rRNA encoded by the ermB gene → highly resistant
 - Efflux mechanism encoded by the mef gene → lower level resistance
 - Moxifloxacin and gatifloxacin: 3rd generation “respiratory” quinolones. Designer drugs to target atypical (mycoplasma, chlamydia, pseudomonas) and pneumococci (*ciprofloxacin doesn't cover strep*)
 - CPAP: Mixed results. CPAP → ↑ oxygenation, ↓RR and dyspnoea. May delay intubation → ↑complications. ?No mortality difference – but may be for COPD patients
- Aspiration Pneumonia: Study in rest home residents with risks for aspiration found causative bug was aerobic G-ive enteric bacilli (49%), S aureus (12%), and anaerobic bacilli (16%). Aerobic G-ive bacilli were present in 55% of anaerobic samples. Ie most don’t have an anaerobe and most with them responded to usual antibiotics (Ann Int Med 15 Feb 2005)
- Pneumococcal Vaccination:
 - Vaccinate with capsular polysaccharide from 23 most prevalent serotypes (different from paediatric conjugate vaccine which covers 7 serotypes)
 - Level and duration of protection decreases with age. The very high risk (chronic lung disease, impaired Ig response) may not respond at all (Cochrane review 2008) in terms of all cause pneumonia. Protective against invasive pneumococcal disease
 - Revaccinate every 5 years (no consensus about this)

Health-Care Associated Pneumonia

- Multi drug resistant G-ives an important pathogen in this group: E Coli, Klebsiella pneumoniae, Enterobacter spp, Pseudomonas aeruginosa, Acinetobacter spp
- Hospital Acquired Pneumonia: develops 48 hours after admission. Highest risk factor for HAP is mechanical ventilation. Others include:

- Hospitalisation for \geq 48 hours, or hospitalisation for $>$ 2 days in prior 3 months
- Nursing home resident
- Antibiotic therapy in last 3 months
- Chronic dialysis
- Home infusion therapy
- Antacid therapy
- Ventilator Acquired Pneumonia:
 - Develops 48 – 72 hours after ventilation
 - ET tube still permits aspiration of oropharyngeal or gastric pathogens
 - Associated with significant mortality
 - Difficult diagnosis. Clinical Pulmonary Infection Score (CPIS) used to stratify risk
 - If risk factors for multi-drug resistance (associated with frequent use of cephalosporins) then treat with a β -lactam (eg ceftazidime) + an agent active against G-ives (eg gentamicin or ciprofloxacin) + agent active against G +ive pathogens (eg Vancomycin or Linezolid)
- Mixed evidence of value of oropharyngeal and gastric decontamination to prevent VAP

Pneumonia in Immunocompromised Host

- Multiple simultaneous infections are common
- Diagnosis should include CT scan and tissue diagnosis (histopathology and culture)
- Treat empirically early
- Humoral defect (asplenia, haematopoietic malignancy, transplantation, Ig deficiency) \Rightarrow biggest risk is encapsulated bacteria with \downarrow opsonizing capacity
- Cell mediated or macrophage defect \Rightarrow risk from intracellular organisms: mycobacteria, legionella, nocardia, strongyloides
- Disseminated disease more likely. Consider head scan, LP, bone scan
- Patterns:
 - Community acquired: consider respiratory viruses, CMV, atypicals
 - Nosocomial: Neutropenia predisposes to bacteraemia from lines etc
 - Environmental: Endemic G-ives – Legionella pneumonia, Pseudomonas aeruginosa, fungi (Aspergillus, Cryptococcus, histoplasma). Candida invasion very rare – if found on sputum don't treat. However can get fungaemia from lines and catheters
 - Reactivation: Tb, toxoplasmosis, herpes, cryptococcosis, strongyloidiasis

Bronchiectasis

- Classification:
 - Global or diffuse
 - Shape: cylindrical, varicose or saccular/cystic
- Pathophysiology:
 - Destructive inflammation and fibrosis of medium-sized airways
 - Primarily mediated by neutrophils through enzymes eg elastase
 - Resulting airways often occluded by purulent sputum
- CT: airway $>$ adjacent blood vessel \Rightarrow dilated
- Infectious causes:
 - Childhood: infection, measles, pertussis
 - Haemophilus and pseudomonas produce toxins \rightarrow immune mediated epithelial injury and reduced mucociliary clearance
 - Adenovirus and influenza
 - Necrotising bacteria: S. Aureus, Klebsiella, anaerobes
 - TB
 - Non-TB mycobacterium often colonise, may infect
 - ABPA (affects central airways)
 - Impairment of host defences:
 - Ig deficiency
 - Primary ciliary disorders: eg primary ciliary dyskinesia in 10% of bronchiectasis \rightarrow sinusitis, otitis media and bronchiectasis, infertile males, abnormal visceral rotation during development \rightarrow random placement of lateralised organs (Kartagener's syndrome)
 - Cystic Fibrosis
 - \Rightarrow in unexplained bronchiectasis measure Ig, do a sweat test, and test cilia

- Non-infectious causes:
 - Slow growing endobronchial neoplasms (eg carcinoid)
 - Foreign body aspiration
 - Toxic substances: eg ammonia inhalation, aspiration of gastric contents (compounded by aspiration of bacteria)
 - α 1-antitrypsin deficiency – usually Panacinar emphysema but also bronchiectasis
- Presentation: Haemoptysis, second to friable mucosa or rupture of hypertrophied bronchial arteries
- Imaging: saccular bronchiectasis may be hard to differentiated from bullous emphysema or honeycombing
- Sputum: lots of neutrophils + colonising bacteria
- LFT: obstructive pattern, often with some reversibility
- Management:
 - Treat infection. Infection with pseudomonas associated with faster deterioration – treat with quinolone, 3rd generation cephalosporin, aminoglycoside
 - Improve clearance of secretions: likely to be beneficial, not well studied. Mucolytic agents controversial. Aerosolized DNase only of benefit in CF – may be harmful in other bronchiectasis
 - Reduce inflammation
 - Treat any underlying cause
 - Surgery if localised
 - Embolisation of refractory haemoptysis

Lung Abscess

- Cause:
 - Aspiration, 2nd to oesophageal dysmotility, seizure disorders, bulbar dysfunction
 - Risk factors: periodontal disease and alcoholism
- Infectious agents:
 - Anaerobes most common – but difficult to isolate
 - S. Aureus, Klebsiella pneumoniae, Nocardia, Pseudomonas (higher mortality with these)
- Differential:
 - Tb
 - Malignancy
 - Pulmonary infarction
 - Infected bulla
- Presentation:
 - With anaerobes may be an indolent course or asymptomatic
 - Acute infections more likely to be aerobes
 - Exam: check fetid breath, poor dentition, clubbing, hypertrophic pulmonary osteoarthropathy if chronic
- CXR: may see air fluid level
- BAL controversial: low yield, and risk of rupture with spillage into airways
- Management:
 - Given \uparrow resistance to penicillin, clindamycin often used
 - Metronidazole alone associated with high treatment failure
 - Surgery only for failed medical management, refractory haemoptysis or if tissue diagnosis required

Cystic Fibrosis

- See Lancet 2003: 361;681-89
- Genetics:
 - AR mutation of the CF transmembrane conductance regulator (CFTR) on chromosome 7:
 - Cyclic AMP-regulated Cl channel, also regulates other ion channels. Abnormalities in Na absorption and Cl secretion \rightarrow “dehydrated” epithelial surface \rightarrow thickened mucus with low O₂ tension (?favours pseudomonas)
 - \rightarrow raised transepithelial electric potential difference
 - There is another Cl channel (Ca activated) – ? potential therapeutic target
 - Approximately 1,400 mutations identified
 - Class I – III mutations: “severe” – as indexed by pancreatic insufficiency and high sweat NaCl:

- Class I: Defective protein production with complete absence of protein. Eg mutations encode for premature stop codons – potential therapeutic target with agents that promote “read through” of the stop codon
- Class II: protein doesn’t make it to the cell membrane (ie assembly defect). Eg $\Delta F508$ (most common mutation)
- Class III: Defective regulation
- Class IV – V: “mild” – pancreas OK
 - Class IV: Defective channel conduction – ion flow and duration of channel opening reduced
 - Class V: reduced number of active CFTR
- 1 in 3000 Caucasian live births, 1 in 90,000 of Asian Hawaiians
- Presentation:
 - Neonatal testing: test for immune-reactive trypsin on dried blood spot, confirm with DNA analysis
 - ~5% present after age 18
 - Abnormal sweat gland function: Can’t reabsorb NaCl from sweat as it moves through the gland. < 40 meq/L Cl- normal, > 80 diagnostic, > 140 then error
 - Chronic infection of airways
 - → bronchiectasis
 - Exacerbations → ↑sputum, mild fever, ↓pulmonary function
 - Sinusitis, nasal polyps in 25%
 - Haemophilus and S Aureus commonly isolated. Pseudomonas (often mucoid and AB resistant) comes later. Burkholderia (formerly Pseudomonas cepacia) is pathogenic. Other G-ive rods. 50% have aspergillus, 10% have ABPA. Tb is rare. 10 – 20% have non-TB mycobacterium
 - Clubbing eventually universal
 - Exocrine pancreatic insufficiency. 90%. → failure to secrete NaHCO₃ and water → retention of enzymes (lipase) → destruction of virtually all pancreatic tissue. Starts before birth. Protein and fat malabsorption, including Vit E and K. Also osteopenia 2nd to Vit D malabsorption. β cell function declines with age → hypoinsulinaemia
 - Intestinal dysfunction: fails to flush secreted mucins from intestinal crypts → malabsorption and obstruction. Distal Intestinal Obstruction Syndrome in young adults (like meconium ileus) – treatment radiocontrast via enema to terminal ileum. No increase in appendicitis
 - Hepatobiliary system: thickened biliary secretions → focal biliary cirrhosis, cholelithiasis (10%). 1/3 have abnormal liver function tests
 - Urogenital dysfunction. Late onset puberty. 95% males azoospermic. 20% women infertile (thick cervical mucus, tube damage)
- CXR: hyperinflation (small airways obstruction) → luminal mucus impaction → bronchiectasis. Pneumothorax > 10% of patients
- Treatment:
 - Secretion clearance:
 - Breathing exercises, flutter valves, chest percussion – effective in preserving lung function.
 - Inhaled hypertonic saline (7%) reduces exacerbations (studied to 1 year). (NEJM 2006)
 - DNase increases time between exacerbations (breaks down long bacterial DNA molecules in sputum). \$20,000 per year, requires a therapeutic trial
 - Treat reversible airflow obstruction
 - Antibiotics: note – lab culture conditions don’t mimic CF lung (hypoxia).
 - Exacerbations: prompt treatment with cefepime
 - If Pseudomonas:
 - Initial colonization with non-mucoid strains, then chronic infection with mucoid strains which cannot be eradicated
 - European consensus statement recommends regular IV abs every 3 months regardless of symptoms but no good trials
 - Macrolides (eg azithromycin) – may inhibit biofilm formation → more susceptible to other ABs
 - Ciprofloxacin limited by rapid emergence of resistance. Use in combination
 - Inhaled tobramycin: after 1 year showed delay of chronic infection
 - Haemoptysis: treatment of infection, test coagulation, if massive haemoptysis then embolisation
 - GI:
 - Adequate nutrition
 - Pancreatic enzymes (now protected microspheres) but not too much otherwise *fibrosing colonopathy*.

- Vit A, D, E and K replacement (esp E and K). A, D and E in multivit 6 (2 tabs od)
- Watch for diabetes
- Long term prednisone: improved lung function but benefits out-weighted by side effects
- Transplant:
 - 2 year survival > 60%
 - Indication: risk of 2 year mortality > 50%, indicated by FEV1 < 30%, PaO2 < 55 mmHg, PaCO2 > 50 mmHg
 - Death from:
 - Acute: surgical, acute rejection
 - Medium term: fungal infection
 - Long term: chronic rejection, often involving obliterative bronchiolitis

Acute Lung Injury/ Acute Respiratory Distress Syndrome

- See Lancet 5 May 2007
- Causes:
 - Direct injury: pneumonia, gastric aspiration, drowning, fat and amniotic fluid embolism, pulmonary contusion, alveolar haemorrhage, smoke/gas inhalation, reperfusion (eg after pleural effusion drainage), unilateral lung re-implantation
 - Indirect injury: severe sepsis, transfusions (TRALI), shock, salicylate or narcotic overdose, pancreatitis
 - Is similar to Infant Respiratory Distress Syndrome
- Definition:
 - Must be a precipitating event
 - Acute onset (< 7 days)
 - Severe hypoxaemia (PaO2/FiO2 < 300 for Acute Lung Injury and < 200 for Acute Respiratory Distress Syndrome)
 - Diffuse bilateral pulmonary infiltrates on frontal CXR consistent with pulmonary oedema (can be patchy and asymmetric, and pleural effusions can be present)
 - Absence of left atrial hypertension (pulmonary-artery wedge pressure < 18 mmHg if measured – but usually rule heart failure out clinically or with echo)
 - Hyaline membranes on autopsy
- Differential (ARDS is a diagnosis of exclusion):
 - LV failure
 - Intravascular volume overload
 - Mitral stenosis
 - Venous-occlusive disease
 - Lymphangitic carcinoma
 - Interstitial and airway diseases: hypersensitivity pneumonitis, acute eosinophilic pneumonia, COPD
- Pathology:
 - Acute exudative phase → fibrosing alveolitis (including big bullae) → recovery (although on going diffusion problems if you look for them). Mortality > 50%
 - Endothelial injury → permeability and alveolar oedema
 - Epithelial injury → oedema, ↓surfactant, fibrosis
- Treatment:
 - Treat other causes
 - Supportive: Prevention of DVT, GI bleeding, pressure ulcers, head raised to 30° (↓hospital acquired pneumonia), glucose control, appropriate nutrition
 - Ventilation settings: Used to do whatever was needed to achieve target PaO2 – but that puts high pressures into a small amount of compliant lung. tending toward lower tidal volumes (eg down from 12 to 6 ml/kg – ?reduction in barotraumas – variable smaller studies, one large study – ARDSnet), PEEP to aid alveolar recruitment (less evidence)
 - What is unlikely to work:
 - Prone positioning (better gas exchange but no change in mortality and logistically difficult)
 - *Steroids*
 - Vasodilators (eg Nitric Oxide)
 - Anti-inflammatories, inhaled surfactant, prostacyclin

Pneumonitis

Hypersensitivity Pneumonitis

- Aka extrinsic allergic alveolitis
- *Cell-mediated hypersensitivity* of the alveolar walls and terminal airways induced in a susceptible host by repeated inhalation of a variety of organic agents
- Neutrophils in alveoli and small airways → influx of mononuclear cells → **formation of granulomas**
- TH1 mediated immune response to antigen with IFN γ , IL-12 and maybe IL-18 contributing
- Presentation:
 - Interstitial pneumonitis
 - Acute: cough, fever, chills, SOB 6 – 8 hours after exposure. Clears over a couple of days
 - Sub-acute: insidious onset cough and SOB, may become severe
 - Chronic: looks like pulmonary fibrosis. May be clubbing
- Diagnosis:
 - ↑Inflammatory markers, rheumatoid factor, serum Igs
 - *Not eosinophilia*
 - Suspected serum antigens (but also found in exposed people with no disease). False negatives due to difficulty of testing
 - CXR/CT:
 - Pleural effusion or hilar adenopathy unusual
 - Acute may have confluent alveolar opacification
 - Subacute: poorly defined, patchy or diffuse infiltrates or with discrete nodular infiltrates. Ground glass in lower lobes
 - Chronic: Diffuse reticulonodular infiltrate. Eventually honeycombing. Patchy emphysematous change
 - LFTs: restrictive or obstructive, ↓ volumes, impaired diffusion. Generally reversible when exposure stops
 - BAL: lymphocytic alveolitis. Mastocytosis
 - Lung biopsy: alveolar infiltrate consisting of plasma cells, lymphocytes, occasional neutrophils
- Differential:
 - Idiopathic pulmonary fibrosis: can have neutrophils on BAL
 - Sarcoidosis: can have predominance of CD4+lymphocytes + hilar lymphadenopathy
- Treatment:
 - Avoid the antigen – finding it is therefore important
 - Progressive sub-acute form may need steroids
- Types of Hypersensitivity Pneumonitis
 - Farmer's lung: proteins from thermophilic bacteria and fungal spores from mouldy hay
 - Bird fancier's lung: proteins from feathers and droppings

Pulmonary Infiltrates with Eosinophilia

- A number of syndromes with eosinophilic pulmonary infiltrates and, usually, peripheral blood eosinophilia
- Causes:
 - Fungal infections: aspergillus (see page 191), or more rarely, Penicillium, Candida, etc
 - Parasite-associated disorders: filarial infection (eg Wuchereria bancrofti), Ascaris, Ancylostoma, Toxocara, Stongyloides
 - Drug-induced: Nitrofurantoin – symptoms 2 hours – 10 days after drug started with dry cough, fever, chills, SOB. Also sulphonamides, penicillin, thiazides, TCAs, hydralazine, gold salts, isoniazid, indomethacin....
 - Idiopathic Eosinophilic Pneumonias:
 - Acute: idiopathic acute febrile illness of < 7 days
 - Chronic: fever, chills, night sweats, cough, anorexia and weight loss of weeks to months duration. Often dramatic resolution with glucocorticoids
 - Associated with T cell lymphoma and also following lung and bone marrow transplant
 - Hypereosinophilic syndromes:
 - See page 430
 - > 1500 eosinophils per microlitre of peripheral blood for > 6 months, lack of allergic or parasitic causes and signs of multi system dysfunction

- May have cardiac infiltration with restrictive fibrosis or tricuspid valve involvement. Maybe also lungs, liver, spleen, skin and CNS
- Treatment: steroids and/or hydroxyurea

Environmental Lung Disease

- 15 – 20% of the burden of asthma and COPD estimated to be due to occupational factors
- Particle size important: > 10 – 15 μm in diameter \Rightarrow deposited in upper airways only
- History:
 - Temporal association of symptoms with work
 - Work practices: specific contaminants, respiratory protection, workspace ventilation, co-workers with similar problems
 - Other possible sources: hobbies, home, second-hand smoke, proximity to traffic or industrial sites
- Diagnosis:
 - Restrictive pattern on LFT
 - Measure FEV1 before and after a Monday shift
 - CXR:
 - Small rounded opacities in silicosis or coal work's pneumoconiosis
 - Small, linear opacities in asbestosis
 - Evaluation of heavy metal concentrations in urine: cadmium
 - Skin prick testing or specific IgE antibody titres for evidence of immediate hypersensitivity to agents capable of inducing occupational asthma (eg flour)
- Removal of the patient from the harmful exposure is often the only useful intervention
- "Portal of entry". Not lung diseases but nasties that affect other parts of the body, gaining entry via the lung:
 - Benzene \rightarrow bone marrow
 - Cadmium \rightarrow kidney
 - Mercury \rightarrow kidney, CNS

Inorganic dust

- Usually cause fibrotic change
- PMF = Progressive massive fibrosis: large non-segmental conglomerates of irregular masses, may be progressive in the absence of further exposure
- Asbestos:
 - \rightarrow Fibrosis: **Asbestosis** – diffuse interstitial fibrosing disease, related to intensity and length of exposure – usually at least 10 years to any asbestiform fibre, restrictive pattern and \downarrow diffusion. CXR: Can have plaques, benign effusions and/or ground glass. Virtually no risk from non-occupational exposure to undisturbed sources of asbestos-containing building materials
 - Also causes pleural plaques (sign of exposure – benign), pleural thickening, benign pleural effusion, mesothelioma
 - All forms of lung cancer are the most common cancer with asbestos exposure – latency of at least 15 years, $\uparrow\uparrow$ risk with smoking
 - **Mesothelioma:**
 - See Lancet 2005;366:397-408
 - Pleural and peritoneal
 - Not associated with smoking but tobacco with asbestos \rightarrow 10 – 20 times risk
 - Long latency: time from exposure typically 30 years, can be as low as 15 years, exposure may have been short
 - Presentation: pleural effusion (which obscures the underlying tumour) +/- chest wall pain. Maybe fatigue and weight loss
 - Diagnosis. Needs a biopsy. Can resemble adenocarcinoma. Immunohistochemistry important. Serum mesothelin-related protein (SMRP) a potential tumour marker, elevated in > 60% at diagnosis
 - Universally fatal. ~50% metastasize but death usually by extension. Median survival 9 – 12 months. No effective treatment
 - Palliation chemotherapy: pemetrexed + cisplatin or gemcitabine + cisplatin
- **Silicosis:** SiO₂ or crystalline quartz \rightarrow fibrosis (silicosis), PMF, cancer, silicotuberculosis, COPD. Can develop disease with < 1 years exposure. HRCT pattern of "crazy paving". With less intense exposure can develop small rounded opacities in the upper lobes, with calcification of the hilar nodes. \uparrow risk of infections requiring cell-mediated response (Tb, fungi)

- Coal dust: → fibrosis (**Coal Workers' Pneumoconiosis**), PMF, COPD. After 15+ years, small rounded opacities as in silicosis.
- Beryllium: light weight metal used in electronics industry → chronic granulomatous disease. Differentiate from silicosis with test for delayed hypersensitivity to beryllium: beryllium lymphocyte proliferation test (BeLPT). Highly associated with HLA-DP alleles
- Many other metals eg cobalt exposure in diamond polishing

Organic dust

- Often cause mucous hypersecretion (chronic bronchitis)
- Cotton dust: Byssinosis (asthma like syndrome), chronic bronchitis, COPD
- Grain dust: asthma, chronic bronchitis, COPD – identical findings to smokers – cough, mucus, wheeze, obstructive LFTs
- Agricultural dusts: hypersensitivity pneumonitis
- Toxic chemicals: chronic bronchitis, COPD, hypersensitivity pneumonitis, pneumoconiosis, cancer
- Others: Smoke inhalation, synthetic polymers and paints, nylon (→lymphocytic bronchiolitis) and diacetyl (butter flavour in popcorn → BOOP)
- Biomass smoke from indoor cooking: globally the second leading environmental hazard behind unsafe water

Diffuse Parenchymal Lung Disease (DPLD)

- Classification:
 - Idiopathic Interstitial Pneumonias: (aka Interstitial Lung Disease – old term) occurs between epithelial and endothelial basement membranes

<i>Diagnosis</i>	<i>Histological pattern</i>
Idiopathic pulmonary fibrosis (IPF) – 55%	Usual interstitial pneumonia
Non-specific interstitial pneumonia (provisional) NSIP 25%	Non-specific interstitial pneumonia
Acute Interstitial pneumonia (AIP) < 1%	Diffuse alveolar damage
Cryptogenic organising pneumonia (COP) 3%	Organising pneumonia
Smoking Related:	
Desquamative interstitial pneumonia	Desquamative interstitial pneumonia
Respiratory bronchiolitis interstitial lung disease	Respiratory bronchiolitis
Lymphocytic interstitial pneumonia	Lymphoid interstitial pneumonia

- DPLD of known cause: drugs, connective tissue disease, etc
- Granulomatous DPLD: Sarcoid, inorganic dust
- Other forms: lymphangioleiomyomatosis (LAM), HX
- General presentation:
 - Progressive exertional dyspnoea and/or persistent, non-productive cough. Wheezing and chest pain uncommon (can have either in sarcoid)
 - Pneumothorax in tuberous sclerosis, LAM, neurofibromatosis
 - Acute: unusual. Allergy (drugs, fungi, helminths), AIP, eosinophilic pneumonia, hypersensitivity pneumonitis
 - Subacute: may occur in all DPLD but especially sarcoidosis, drug-induced, alveolar haemorrhage syndromes, COP and SLE/polymyositis
 - Chronic: most
 - Episodic: unusual. Maybe eosinophilic pneumonia, hypersensitivity, COP, vasculitides
- Little consensus on the best management
- Pathogenesis:
 - A variety of non-infectious inflammatory processes initially affecting the alveolar walls and air spaces, spreading to adjacent interstitium and vasculature and leading to fibrosis
 - Granulomatous disease: T lymphocytes, macrophages and epithelioid cells organising into granuloma
- UIP is a bad prognosis vs non-UIP. Bottom line: Steroids don't work in IPF – immunosuppression should be considered in others

Assessment and Management

- Key points on history:
 - Time course
 - Non-respiratory symptoms

- Connective tissue symptoms: joints, oesophagus, Raynaud's, rashes, eyes, mouth ulcers
- Malignancy
- Occupational/environmental exposure
- Drugs/radiation
- Bloods: ANA, RF, ACE in sarcoid, serum precipitins in hypersensitivity. ↑LDH is a non-specific common finding
- CXR: correlates poorly with the clinical or histopathologic stage of the disease
- HRCT: *can be sufficiently specific to exclude the need for biopsy or BAL in IPF*, sarcoid, hypersensitivity pneumonitis, asbestosis, lymphangitic carcinoma and pulmonary Langerhan's cell histiocytosis (PLCH)
- LFTs:
 - Usually restrictive. Prognostic value in IPF and NSIP. Obstructive if airway involvement
 - Usually ↓DLco – usually due to V/Q mismatch. Severity doesn't correlate with disease stage
- Exercise testing:
 - ABG more sensitive following exercise. Serial measurements may help determine responsiveness to treatment
 - 6 minute walk: distance and desaturation – global evaluation of function
- Bronchoscopy:
 - Often helpful in infections, neoplasm, sarcoid only
 - Bronchoalveolar Lavage (BAL): neutrophils ↑ in IPF, ↑lymphocytes in some. Doesn't diagnose fibrotic conditions. Only has sufficient positive predictive power in alveolar proteinosis, Langerhan's cell histiocytosis, cancer, eosinophilic pneumonia and infection (eg PCP)
- Does the patient need a tissue biopsy:
 - An area of controversy
 - Do need to separate fibrosis from CTD, drug induced fibrosis, vasculitis, hypersensitivity – but this is usually evident on a good history, blood tests, and CT
 - Clinical and radiological diagnosis of UIP is right about 2/3rds of the time
 - Aim is to achieve a confident diagnosis of UIP where steroid therapy is accepted to be futile (it's fibrotic not inflammatory), compared to all other categories where it is reasonable to consider immunosuppressive treatment
 - Via bronchoscope has low accuracy (don't get good tissue, need multiple sites – video assisted surgical or open thoracotomy underutilised – but patients often elderly and hypoxic...)
- Treatment:
 - When to treat:
 - Watch and wait for 3 months – is there a change in symptoms or PFT
 - The more ground glass the more likely to respond to treatment (inflammation rather than fibrosis)
 - Supplemental O2 if hypoxic
 - Diuretics, maybe phlebotomy, if cor pulmonale develops
 - There have been no placebo controlled trials of glucocorticoids in ILD, but it is recommended for symptomatic eosinophilic pneumonia, COP, CTD, sarcoidosis, acute inorganic dust exposure, acute radiation pneumonitis, DAH, and drug-induced ILD. Optimum dose and duration unknown. Highish dose for 4 – 12 weeks then tapering course over 4 – 12 weeks common
 - Cyclophosphamide and azathioprine tried with varying success in IPF, vasculitis, and other ILDs

Idiopathic Interstitial Pneumonias/Interstitial Lung Disease

Idiopathic Pulmonary Fibrosis (IPF)

- Most common IIP
- Age > 50, coughing and SOB for > 3 months, maybe clubbing, fine-end inspiratory crackles
- CXR: basal and peripheral fibrosis
- LFT: restrictive, ↓DLco and PaO₂
- HCRT: patchy, predominantly basilar, subpleural reticular opacities, often traction bronchiectasis and honeycombing. Consider alternative diagnosis if extensive ground-glass abnormality, nodular opacities, upper or mid-zone prominence, prominent hilar or mediastinal lymphadenopathy
- Histology: UIP pattern: *alternating areas* of normal lung, interstitial inflammation, foci of proliferating fibroblasts, honeycombing. Peripheral parenchyma affected most ⇒ transbronchial biopsy usually not helpful, need surgical biopsy
- Distinctly poor response to therapy and bad prognosis

- Monitor with 6 Minute Walk – desaturate early in the disease (compared with COPD where this happens later)
- Treatment: No substantial evidence to support any particular treatment
 - Immunosuppressive: steroids and azathioprine standard but no RCTs. Cochrane review says little evidence to justify use of any non-corticosteroid agent. Prednisone 0.5 mg/kg + azathioprine 2 mg/kg + NAD 600 oral tds the best regime (level C evidence – BTS guidelines). No evidence that early treatment delays progression
 - Anti-oxidant: High dose acetylcysteine (NEJM 2005) preserves VC and DLco
 - Anti-fibrogenic:
 - IFN γ disappointing (NEJM 2004) – probably the therapy with best evidence in IPF at present
 - Pirfenidone (novel anti-inflammatory): RCT with encouraging results (AJRCCM 2005)
 - Anti-TNF, anti-endothelial – trials underway
- Consider lung transplant (although often referred too late and die on the waiting list)

Non-specific Interstitial Pneumonia (NSIP)

- A histologic pattern that can occur in the context of a CTD, drug induced or chronic hypersensitivity disorder
- Usually younger, typically women who have never smoked, slower onset, maybe clubbing (less than IPF)
- HRCT: bilateral, subpleural ground-glass opacities. Honeycombing unusual
- Histology: *uniform* cellular or fibrosing interstitial involvement
- Treatment: steroids, azathioprine
- Good prognosis: 5 year mortality < 15%, maybe relapse

Acute Interstitial Pneumonia

- = idiopathic ARDS
- Rare, fulminant
- Presentation: 7 – 14 days prodrome with fever, cough, SOB
- CXR: diffuse airspace opacification
- CT: diffuse ground glass with areas of consolidation
- Histology required for diagnosis: diffuse alveolar damage (DAD) indistinguishable from ARDS
- Prognosis: 60% mortality within 6 months

Cryptogenic Organising Pneumonia (COP)

- Aka BOOP
- 5th and 6th decade, flu-like illness for < 3 months with cough, fever, fatigue. Inspiratory crackles
- CXR: bilateral migratory patchy alveolar opacities, *normal lung volume*
- HRCT: peripheral and lower zone air-space consolidation, ground-glass opacities, small nodular opacities
- Histology: granulation tissue within small airways and alveolar ducts
- Treatment: steroids → recovery in 2/3rds after a long course

ILD Associated with Smoking

- Both: Smoking related
- Insidious onset over weeks/months
- Good clinical course especially if stop smoking + steroids
- ***Desquamative Interstitial Pneumonia (DIP):***
 - Also related to heavy dust inhalation in addition to smoking
 - Accumulation of macrophages in alveolar spaces with minimal interstitial fibrosis
 - CXR: diffuse hazy opacities
 - HRCT: diffuse ground glass
- ***Respiratory Bronchiolitis (RBILD):***
 - A subset of DIP
 - Macrophages in the peribronchial alveoli
 - HRCT: centrilobular nodules, ground-glass opacity, emphysema with air trapping
- ***Pulmonary Langerhan's Cell Histiocytosis (PLCH):***
 - Rare, mainly smoking men aged 20 – 40
 - Ill-defined or stellate nodules, reticular or nodular opacities, upper zone cysts, preservation of lung volume

- Markedly reduced DLco

DPLD of Known Cause

Drug Induced Lung Disease

- Always consider drugs with DPLD – many agents implicated (see www.pneumotox.com)
- May take drug for several years before reaction (eg amiodarone)
- Many radiological patterns:
 - Organising pneumonia: amiodarone, bleomycin, interferons, statins
 - NSIP: methotrexate, chemotherapy, amiodarone
 - Eosinophilic pneumonia: antibiotics, NSAID, ACEI
 - AIP/DAD: chemotherapy, methotrexate, gold

Connective Tissue Related ILD

- See Connective Tissues Diseases, page 258
- May be difficult to exclude as pulmonary manifestations may precede systemic signs by months or years
- **Scleroderma:** (PSS):
 - Extrapulmonary and pulmonary manifestations don't correlate
 - 70 – 80% have pulmonary abnormalities, 1/3 have clinically significant disease
 - Pulmonary is the main cause of death
 - Anti-topoisomerase (Scl-70) in ILD
 - Anti-centromere associated with pulmonary vascular disease (and not ILD)
 - Mainly NSIP, rest UIP
- **SLE:** Thoracic involvement common: Pleuritis +/- effusion most common, pneumonitis and pulmonary haemorrhage, fibrosis not common
- **Rheumatoid Arthritis:**
 - ILD in up to 20%
 - NSIP, UIP, OP, LIP, necrotic nodules (essentially pulmonary rheumatoid nodules)
 - PHT
 - Prognosis depends on histological variant
 - Caplan's Syndrome: rheumatoid pneumoconiosis
- Polymyositis and Dermatomyositis:
 - More common in the subgroup with anti-Jo-1 antibody to histidyl tRNA synthetase
 - Histology: OP, NSIP, UIP, DAD, also vasculitis, PHT
- Sjogren's Syndrome:
 - Lymphoproliferative (eg LIP), also NSIP, UIP, OP
 - General dryness and cough 2nd to ↓secretions

Granulomatous DPLD

- Sarcoidosis: see page 209. HRCT has very specific signs (eg nodules on interlobular fissures)
- Extrinsic Allergic Alveolitis
- Bronchocentric granulomatosis: variant of Aspergillus hypersensitivity
- Other: Inorganic pneumonitis: beryllium, silica

Other DPLD

- Eosinophilic Pneumonia: See page 203
- Pulmonary Alveolar Proteinosis (PAP):
 - Strictly not an ILD – but a defect of macrophage function
 - Accumulation of lipoproteinaceous material in distal air spaces with little or no lung inflammation
 - ?autoimmune disease with and Ig neutralizing antibody against granulocyte-macrophage CSF (GM-CSF)
- Pulmonary Lymphangiomyomatosis (LAM)
 - Rare condition affecting premenopausal women, accelerates during pregnancy
 - Presents with “emphysema”, pneumothorax (in 50%), chylous pleural effusion
 - Proliferation of atypical smooth muscle cells
 - Associated with tuberous sclerosis (characteristic findings of meningioma and renal angiomyolipomas – hamartomas)

- Treatment: ?progesterone or LHRH, not oophorectomy any more, discontinue oestrogen containing drugs. Lung transplantation
- Progression common with median survival 8 – 10 years
- Syndromes of ILD with Diffuse Alveolar Haemorrhage: disruption of alveolar-capillary basement membrane → bleeding into alveolar. Consider:
 - Goodpasture's (linear deposition)
 - Wegner's (pauci-immune)
 - Isolated pulmonary capillaritis
 - SLE (granular deposition)
- Lymphocytic Interstitial Pneumonitis: rare, slow onset in women

Sarcoidosis

- Inflammatory disease characterised by non-caseating granulomas, with evidence of Th1 predominant inflammation at involved sites and hypergammaglobulinaemia. An acute onset usually predicts a self-limiting course, an insidious onset (esp with multiple extra-pulmonary lesions) may predict a relentless progressive lung fibrosis (failure to remit in 2 years = chronic sarcoid)
- Cause unknown: environmental agent triggering an inflammatory response in a genetically susceptible host.... Possible triggers:
 - Propionibacter acnes (found disproportionately in the lymph nodes of patients)
 - A mycobacterial protein mKatG which is resistant to degradation
 - Or a host response to multiple agents
 - Clusters noted – ?person to person transmission or shared exposure...
- 20 – 60 per 100,000. Appears to be two age peaks – young otherwise healthy adults and around 60 (usually females). 5% have a family member with Sarcoid (HLA-A1, B8 and DR3 associations)
- Pathology: influx of T helper cells (if no T helper cells in HIV then Sarcoid rare) + accumulation of activated monocytes + release of IL-2, IFN γ and TNF α . However, cyclosporine (which ↓ T helper cell responses) makes little difference
- Presentation and findings:
 - From asymptomatic to organ failure
 - Fatigue, fever, night sweats, weight loss, myalgia, arthralgia (especially swollen knees)
 - Lungs:
 - Cough and dyspnoea most common
 - On CXR hilar adenopathy +/- infiltrates may → fibrosis. Differential of upper lobe disease: hypersensitivity pneumonitis, silicosis, Tb, PCP
 - HRCT: peribronchovascular involvement, subpleural, interlobular septa are specific
 - DLCO most sensitive test for interstitial lung disease. Can be restrictive or obstructive (either obstructive or airway hyperreactivity which may respond to bronchodilators)
 - 5% have PAH – more common in end stage fibrosis than other fibrotic lung diseases
 - Skin:
 - In 1/3 of patients
 - Erythema nodosum: transient rash
 - Maculopapular lesions: most common lesion in chronic disease – 1 – 3 cm, may become confluent
 - Subcutaneous nodules
 - Lupus pernio: nodular red-brown skin lesions over the hard palate, nose and ear lobes
 - Eye: lesions in 20% anterior uveitis or posterior inflammation. Sicca. Can be asymptomatic and still → blindness. Always get an ophthalmology review
 - Liver: lesions in over half, but only 20% will have ↑LFTs (initially ↑ALP). Avoid IFN treatment in Hep C if concurrent Sarcoid – will make Sarcoid worse
 - Bones (1/3 patients) and spleen (detected in 5 – 10%, but in 60% on biopsy): → lymphopenia, anaemia in 20%
 - ↑Ca:
 - 10% due to ↑1,25 OH Vitamin D by macrophages in lungs and lymph nodes → ↑Ca absorption, ↓PTH
 - Treat with restriction of Ca intake, stop Vitamin D supplements, avoid sunlight
 - Thiazides contra-indicated: usually used to inhibit hypercalciuria related renal stones, but inhibition of hypercalciuria → ↑hypercalcaemia

- Low-dose glucocorticoid therapy: inhibits mononuclear cells and inhibition of Ca absorption, serum Ca falls within 2 days
- If history of stones then 24 hour urine
- Kidneys: in <5% – most likely due to ↑ Ca
- Nervous system: 5 – 10%, MRI can be negative (especially if on steroids). CSF shows ↑lymphocytes, mild ↑protein and normal or low glucose. Often cranial nerves, maybe optic neuritis (can be difficult to differentiate from MS)
- Cardiac: either CHF or arrhythmias (including SCD). Ablation not helpful (diffuse), consider ICD
- Spares breast, testes, ovary, stomach – consider neoplasm
- Investigations:
 - CXR
 - Serum angiotensin-converting enzyme (ACE). Elevated in 60% active disease and 20% chronic disease. Elevations > 50% upper limit only seen in Sarcoid, leprosy, hyperthyroidism and disseminated granulomatous diseases (eg miliary Tb). ACE in lymphoma is usually ↓. ↓↓ If concurrent ACE
 - Biopsy: skin or bronchoscope. BAL may show high CD4/CD8 ratio. In the absence of symptoms or progressive gland enlargement, observation without mediastinal biopsy is safe (ie the number of missed alternative diagnoses < biopsy morbidity)
- Differential:
 - Tb and fungal infections
 - Malignancy
 - Toxins: beryllium
- Natural history:
 - Many resolve in 2 – 5 years: acute, self-limiting sarcoid
 - 20% – chronic course – associated with ↑IL-8, and lung fibrosis, bone cysts, cardiac or neurological disease on presentation. Generally indolent – but lung fibrosis common
- Treatment:
 - Based on symptoms. Probably no benefit from treating asymptomatic patient with ↑LFTs or lung fibrosis. Cough only then ICS
 - Glucocorticoids first line – most trials in pulmonary disease, remain controversial, failing these then methotrexate (works in approx 2/3rds), azathioprine, etc
 - Hydroxychloroquine for skin disease, topical steroids (also for eyes)
 - Infliximab works, etanercept doesn't (same as in Crohn's disease)

Pulmonary Hypertension

- Presentation: dyspnoea, angina, syncope, peripheral oedema... Non-specific → delayed diagnosis
- Causes (WHO 2004 classification – groupings reflect different treatment and different prognosis):
 - Pulmonary Arterial Hypertension
 - Idiopathic (5 year survival 35%). Formerly known as Primary Pulmonary Hypertension. Typically women of child bearing years
 - Familial: 6 – 10%. AD, incomplete penetrance (~25 % ⇒ other cofactors). PPH1 gene on 2q33 → defective morphogenetic protein receptor type II (BMPRII) in 50%. Normal protein inhibits muscle proliferation, abnormal protein → vascular remodelling
 - Associated disease (much more common):
 - HIV: HIV infected macrophages → release cytokines → endothelial damage. Improves with HAART and epoprostenol
 - Connective tissue disease eg scleroderma
 - Portal hypertension → Hepatopulmonary syndrome
 - Drugs eg cocaine (OR 2.8), anorexic drugs (OR 23 with > 3/12 use)
 - Pulmonary HTN with Left Heart Disease: ASD/VSD or left sided valvular heart disease
 - Due to respiratory disease: COPD, ILD
 - Chronic thromboembolic hypertension
 - Disorders affecting pulmonary vasculature: sarcoid, histiocytosis,
- Definition:
 - Most commonly used: Mean pulmonary artery pressure > 25 mmHg at rest [Severe = > 50 mmHg] or 30 with exercise (if you exercise people you find more) AND the absence of significant parenchymal lung disease, chronic thromboembolic disease, LH valve or myocardial disease, congenital heart disease or systemic connective tissue disease

- Alternative threshold: WHO 1998 systolic peak pulmonary pressure > 40 mmHg, corresponds to tricuspid regurgitant velocity on Doppler of 3.0 to 3.5 m/sec
- Investigations to exclude other causes:
 - Echo/ECG for heart problems
 - CXR/PFTs: emphysema, fibrosis
 - Sleep study (low yield)
 - CTPA: VTE
 - Autoantibodies: Scleroderma, SLE, RA, vasculitis
 - HIV
 - LFTs and signs of liver disease
 - Then – exercise test, RH catheterisation, vasodilator test
- Biomarkers (all predict prognosis):
 - Pro-BNP – correlated with degree of RV dysfunction
 - Uric acid: sign of tissue hypoperfusion
 - Trop
- Pathogenesis: vasoconstriction 2nd to endothelial dysfunction, remodelling (chronically ↓NO, ↓prostacyclin, ↑endothelin 1 – a vasopressor), thrombosis in situ
- Key prognostic measure is *pulmonary vascular resistance* – higher is a worse prognosis
- “Responders”: reduction in pulmonary arterial pressure of > 10 mmHg in response to iv adenosine, inhaled nitric oxide, iv epoprostenol or other vasodilators (with no change in cardiac output or systemic BP) – only 10 – 25% of patients – usually not in CTD
- Drugs typically don’t help PAH 2nd to Eisenmenger’s Syndrome
- Medications:

Drug	Action	Evidence	Route	Side Effect
CCB	CCB	↑5 yr survival	PO	
Epoprostenol	Prostacyclin	↓PAP (pulmonary artery pressure), ↓PVR (Pulmonary vascular resistance), ↑ <i>survival</i> , ↑6 minute walk	Iv	Jaw pain/arthritis
Treprostinil	Epoprostenol analogue	↑6 minute walk, ↓symptoms	Sc	Injection site pain
Iloprost	Prostacyclin analogue	↑6 minute walk/HYHA class	inhaled	
Bosentan	Endothelin receptor antagonist	↓PAP, ↓PVR, ↑6 minute walk, ↑CO, ↑ <i>survival</i>	PO	Significant liver enzyme ↑
Sildenafil	PDE5 inhibitor	↓PAP, ↓PVR, ↑6 min walk	PO	Double whammy with GTN and/or Viagra

- Ca antagonists can cause sustained improvement (use amlodipine or diltiazem – may need high doses – eg 120 – 900 mg diltiazem). Improved survival in responders only. Evidence only idiopathic PAH – no evidence in CTD
- Prostacyclins: → Prostaglandin I₂ → cAMP mediated vasodilation and antiproliferation. Improved haemodynamics, 6 minute walk time
 - *Epoprostenol* (Prostacyclin) – potent vasodilator, inhibits platelet aggregation and smooth muscle proliferation. Continuous IV infusion via pump. For both responders and non-responders. Improved survival demonstrated in RCT. SE Jaw pain, arthralgias, diarrhoea
 - Treprostinil is an epoprostenol analogue that can be used continuously sc but problems with injection site pain
 - *Iloprost* – PGI₂, vasodilator. *Inhaled* prostacycline analogue 6 – 12 times daily – aim to reduce systemic affects with “topical” (ie lung) application. Small studies. ?only works for a minority
- Endothelin Receptor Antagonists: Endothelin – binds to ET-A and ET-B receptors within pulmonary circulation
 - *Bosentan* is a non-selective IV or oral ET-receptor antagonist – a small study shows benefit, SE ↑aminotransferase levels. Inhibits endothelial proliferation. EARLY study (Lancet 21 June 2008) showed benefit in stage II disease (previously used for stage III or IV). Very expensive. Benefits in idiopathic and CTD associated PAH. Improved survival demonstrated against historical controls

- Sitaxentan (a selective endothelin-A antagonist) considered equivalent but no head to head studies. If toxicity to one, try the other (SEs not a class effect)
- Sildenafil: *oral* cyclic GMP phosphodiesterase (PDE) type 5 inhibitor – enhances NO mediated vasodilation and inhibits proliferation of vascular smooth muscle cells. Numerous studies show improvement
- Some evidence of incremental benefit with combination treatment
- Anticoagulation: consider warfarin given ↑ risk of intrapulmonary thrombus – only data in primary idiopathic PAT – ?→bleeding in CTD
- Atrial septostomy: creates R → L shunt to ↓RHF. Last resort
- Heart-Lung Transplant for patients with class III-IV symptoms not responsive to medical treatment

Venous Thromboembolism

- See BTS Guidelines for the management of suspected acute PE
- See Lancet 2204:363;1295-305, NEJM 6 March 2008 and BMJ review article 2007
- Risks:
 - Genetic predisposition: see Hypercoagulable States, page 444. Only a minority of VTE patients have genetic factors, and most with genetic factors do not develop clinical evidence of clotting
 - Antiphospholipid syndrome (<1%), more severe effect [usually low platelets]
 - OCP:
 - POP: no increased risk
 - 2nd generation: 2 – 4 times risk
 - 3rd generation: 6 – 8 times risk
 - Greatest risk in the first year (also with HRT)
 - Travel:
 - If flying more than 8 – 10 hours, rate of DVT on US is 2 – 10% (most below knee). 85% in non-aisle seats
 - Aspirin makes no difference to DVT rates. One ?underpowered study
 - No study evidence to guide dose/duration or LMWH prophylaxis or above or below knee stockings in high risk (prior VTE, varicose veins, cancer, thrombophilia)
 - Seated thromboembolism
 - Cycling and weight lifting – ?damage to popliteal vein in the back of the knee
- Epidemiology:
 - About half of those with proximal deep vein or pelvic DVT develop PE
 - Isolated calf DVT have a much lower risk – but are most common source of paradoxical embolism (via small patent foramen ovale or atrial septal defect)
 - Arm DVT rarely embolise and cause PE
 - Recurrence of VTE is 30% after 8 years → it's a chronic disease
 - 25% of symptomatic PE present as sudden death, 5% further 7 day mortality (old data, don't really know)
 - 3 month mortality of PE ~ 17%. Death rate ↑ with age > 70, cancer, CHF, COPD, hypotension, tachypnoea, RV hypokinesis
 - Case-fatality of recurrent PE is 4 – 9%
 - Subsegmental PE may be asymptomatic, is predictive of future symptomatic PE. Role of anticoagulation is still uncertain
- Pathophysiology:
 - PE causes hypoxia out of proportion to clot – vasoactive mediators → V/Q mismatch remote to the embolus
 - Pulmonary infarction rare given dual circulation (pulmonary and bronchial)
 - RV dysfunction: the usual cause of death. Septum bulges into the LV with impaired diastolic filling
 - Non-thrombotic embolic can be caused by: fat (after blunt trauma and long bone fractures), tumour, bone marrow, amniotic fluid or air embolism
- Presentation:
 - DVT: most frequent symptom is cramp. Also tenderness along distribution of deep veins
 - PE: most frequent symptoms is unexplained SOB. Tachycardia the most frequent sign. Also low grade fever, neck vein distension, loud P2. Chest pain, cough and haemoptysis more common with small, peripheral emboli. 65 – 80% have DVT found
- Complications:
 - Major adverse outcome of DVT is post-phlebotic syndrome:

- Permanent damage to venous valves of the leg → incompetent → ↑exudation of fluid from veins
- Chronic ankle and calf swelling and aching, maybe ulceration
- In up to 10% of symptomatic DVT
- Prevent with daily use of below-knee 30 – 40 mmHg vascular compression stockings
- Complication of PE: chronic thromboembolic pulmonary HTN in 4% who have PE

Investigation of PE

- Revised Geneva score: no blood gas, no xray, and doesn't have the "alternative diagnosis" score that makes the Well's score subjective:

Risk Factors

Age > 65 years	+1
Previous DVT or PE	+3
Surgery or fracture within 1 month	+2
Active malignancy	+2

Symptoms

Unilateral leg pain	+3
Haemoptysis	+2

Clinical signs

Heart rate 75 – 94	+3
Heart rate => 95	+5
Pain on leg deep-vein palpation and unilateral oedema	+4

Probability: Low 0 – 3, Intermediate 4 – 10, High >= 11

- Modified Wells Criteria for PE:

Clinical symptoms of DVT (swelling, pain with palpation)	3.0
Other diagnosis less likely than PE	-3.0
Pulse > 100	1.5
Immobilisation (>= 3 days) or surgery in the last 4 weeks	1.5
Previous PE/DVT	1.5
Haemoptysis	1.0
Malignancy	1.0

Probability: Low < 2, Intermediate 2 – 6, High > 6

- D-dimer: derivative of cross-linked fibrin
 - Sensitivity for DVT > 80% (smaller thrombus than PE), > 95% for PE – only 50% if subsegmental PE
 - Up to 75% of hospital patients without PE have an elevated d-dimer
 - Should not be performed (level B evidence) in those with a high clinical probability of PE as a negative d-dimer only reliably excludes those with a low and moderate clinical probability
 - If D-dimer > 4000:

Clinical Probability	Specificity
20%	65%
50%	90%
80%	97%

All for the same D-dimer result...

- ABG: Neither PaO₂ or Aa gradient reliably differentiate patients with PE at angiography
- ↑Trop in RV micro-infarction (proposed as a marker for more aggressive treatment – 44% mortality) and ↑BNP 2nd to myocardial stretch
- ECG:
 - S1Q3T3 specific but insensitive, most frequent abnormality is TWI in V1 – V4
 - RBBB, P wave pulmonale and/or RAD if massive embolism
 - Helps exclude MI and pericarditis
- Ultrasound for DVT:
 - Looking for compressibility of deep veins, augmentation of flow on doppler with compression and loss of normal respiratory variation. MR venography with gadolinium contrast (not nephrotoxic) is good

- False positive in 3%, a DVT is not found in 70% of patients with confirmed PE (ie absence of a DVT unhelpful)
 - CXR: most are normal
 - CTPA: principal test for non-massive PE (level B evidence)
 - PIOPED II study, 824 patients (not all patients had angiogram as gold standard):
 - Sensitivity: 83% for PE, specificity 96% without PE had a negative CTPA
- | | PPV with +ive CTPA | NPV with -ive CTPA |
|----------------------------------|--------------------|--------------------|
| High Pretest Probability | 96% | 96% |
| Intermediate Pretest Probability | 92% | 89% |
| Low Pretest Probability | 58% | 60% |
- D-Dimmer + CTPA is as sensitive and specific as D-Dimmer + Leg US + CTPA for excluding PE. The 3-month thrombotic risk in people negative for each is 0.3%. Leg US was positive in < 1/3rd positive PEs (Lancet, 19 April 2008)
 - RV enlargement ⇒ 5 fold risk of death in next 30 days
 - A good quality negative CTPA does not require further investigation (level A). They have a low risk of a subsequent symptomatic PE
 - Lung scanning (VQ Scan):
 - Used when renal insufficiency or allergy to contrast
 - Less radiation than CTPA
 - Perfusion scan with radionuclide labelled albumin. Ventilation scan with radiolabelled gas
 - Looking for perfusion filling defects not matched by ventilation defects (requires 2 or more for high probability scan)
 - < half patients with PE have a high probability scan. Up to 40% with a high clinical suspicion but low probability scan have a PE
 - High clinical probability and high probability VQ have 95% chance of PE
 - Intermediate probability scan and intermediate probability have 28% chance of PE (PIOPED study)
 - Normal scan rules out acute PE
 - Echo: most with PE have normal echos. Don't usually see thrombus. Look for hypokinesis of RV free wall with normal motion of the RV apex. Useful for differentials: Acute MI, pericardial tamponade, aortic dissection
 - Pulmonary angiography: replaced by CTPA. Only useful if considering catheter-directed thrombolysis (but has the greatest sensitivity)
 - Thrombophilia screen should be considered in patients aged under 50 with recurrent PE, or those with a strong family history of proven VTE (level C evidence BTS guidelines), or development of a clot at an atypical site (eg mesentery). Don't test when they have a clot – will be consuming their own clotting factors

Treatment

- Risk stratification:
 - Predictors of adverse outcome in PE: cancer, heart failure, hypoxia, hypotension, DVT on USS and previous DVT. Also high troponin on admission
 - Symptomatic below knee DVT is beneficial for treatment (6 – 12 weeks). 1/3 of PEs only had a below knee clot
 - 10 – 20% of all patients > 65 have underlying malignancy, more aggressive clotting, may respond better to heparin than warfarin
- Anticoagulation:
 - See also page 445
 - After 5 – 7 days anticoagulation, residual thrombus becomes endothelialised → ↓ risk of embolisation. Anticoagulants do not dissolve existing clot
 - Heparin:
 - See Anticoagulation, page 445
 - Unfractionated Heparin: accelerates the activity of antithrombin III → ↓ further clot formation. Short half life → can be quickly switched off. Risk of heparin induced thrombocytopenia
 - LMWH (eg enoxaparin): less binding to plasma proteins → greater bioavailability, more predictable dose-response, longer half life than heparin. Generally preferable to unfractionated (level A evidence). Reverse with protamine sulphate. Monitor by measuring the activity against activated factor X
 - Equivalence of heparin and LMWH in treatment of PE is established, with no difference in safety (Ann Int Med 2004;140:175)

- Warfarin:
 - See MJA 1 November 2004
 - See Anticoagulation, page 445
- New treatments:
 - Fondaparinux: anti-Xa pentasaccharide, sc od. Not in renal failure (renally excreted). Not available in NZ. Not licensed in Australia for prophylaxis but Grade 1A evidence
 - Activated factor X (factor Xa) inhibitors:
 - Rivaroxaban: dose 10 mg, high oral bioavailability, half life of 5 – 9 hours and predictable anticoagulant response (so no monitoring required)
 - 4 large phase 3 trials have compared it with enoxaparin for prevention of DVT in hip and knee arthroplasty. Rivaroxaban is superior, with no increase in bleeding (Lancet 5 July 2008, NEJM 26 June 2008)
 - Trials underway for treatment of DVT and AF
 - Once daily, oral unmonitored dabigatran etexilate (a direct thrombin inhibitor) is non-inferior to enoxaparin for prevention of DVT after total hip arthroplasty – resurfacing after non-registration of first generation drugs
- In patients with cancer and VTE (most commonly lung, also GI, prostate, ovary, pancreas), LMW Heparin (Dalteparin) is better than Warfarin for ongoing treatment (CLOT Trial, 8 vs 16% recurrence or major bleed, major bleeds the same ~5%). There is insufficient evidence to treat people prophylactically with cancer for VTE (despite an increased risk, especially in metastatic disease)
- Duration:
 - Provoked (trauma, surgery): 4 – 6 weeks
 - Unprovoked (includes long haul travel): recurrence common, American College of Chest Physicians recommends long term. BTS guidelines recommend 3 months for first unprovoked (level A), and at least 6 months for second (level C)
 - Circumstances of occurrence more relevant to recurrence risk than underlying thrombophilia
 - PROLONG Trial: tested D-dimer in 619 patients 1 month after at least 3 months effective anticoagulation after a first, unprovoked VTE. Randomised those with an abnormal d-dimer (37%) to go back on anticoagulation. At mean follow-up of 1.4 years, further VTE rates in the high d-dimer group were 15% vs 3%. High d-dimer had a hazard ratio of 2.27 from recurrence. NEJM 2006;355:1780-0
- IVC filters: if active bleeding prevents anticoagulation or recurrent VTE despite maximal treatment. May let small-medium sized clots through, or may clot itself causing bilateral leg swelling. *Double the risk of DVT over the following 2 years*
- Thrombolysis:
 - Be aware of too much fluid for hypotension – exacerbates RV wall stress and ↓LV filling
 - Thrombolysis: 100 mg tPA (Alteplase) as infusion over 2 hours. 10% total bleeding risk, 1 – 3 % ICH, also retroperitoneal and GI haemorrhage. Study in Chest 1999: Risk of ICH 1.2%, fatal ICH 0.6%. Risks greater for > 55
 - Massive PE (ie hypotensive): Meta-analysis with conflicting results. No trial has been big enough to conclusively demonstrate a reduction in mortality. Thrombolysis is a reasonable option for patients who are hypotensive. Cochrane review: ?no difference from heparin in terms of mortality, recurrence, or bleeding. But... Thrombolysis may ↓incidence of pulmonary HTN and complications from DVT
 - “Submassive” PE: (ie RV dysfunction or pulmonary hypertension, but no shock), thrombolyse if low risk of bleed (ie young). Trial of 256 patients with submassive PE, heparin vs heparin + alteplase, much less “treatment escalation” (cross over to the alteplase treatment!) in alteplase group, 30 day mortality the same

In-hospital VTE

- See Prevention of VTE, Chest, 7th ACCP Conference on Antithrombotic and Thrombolytic Therapy, 2004
- Why worry:
 - 2/3rds of symptomatic VTE events are hospital acquired – up to 70% in patients from medical wards
 - The majority of symptomatic VTE associated with hospital occur after discharge
 - Hospital acquired DVT and PE are usually clinically silent
 - PE is the most preventable cause of in-hospital death
 - 10% of inpatient deaths are due to PE, and in 80% of these VTE had not been considered

- Only 40% of at risk medical patients receive the recommended prophylaxis (Lancet 2 Feb 2008) compared with 59% of at risk surgical patients
- Risks in surgical patients:
 - Specific indications for different sorts of surgery vary, and can mix and match graduated compression stockings, intermittent pneumatic compression devices and thromboprophylaxis
 - In general, hip and knee replacement and major gynaecology surgery worst. Low risk patients with laproscopic surgery need only routine mobilisation
 - Risks without prophylaxis in surgical patients are:

	Calf DVT%	Proximal DVT%	Clinical PE%	Fatal PE%
Low risk: minor surgery in patients < 40 with no additional risk factors	2	0.4	0.2	< 0.01
Moderate risk: minor surgery with additional risk factors, surgery in patients 40 – 60 with no other risk factors	10 – 20	2 – 4	1 – 2	0.1 – 0.4
High risk: Surgery in patients > 60, or age 40 – 60 with additional risk factors (prior VTE, cancer, molecular hypercoagulability)	20 – 40	4 – 8	2 – 4	0.4 – 1.0
Highest risk: Multiple risk factors (age > 40, cancer, prior VTE), hip or knee arthroplasty, hip fracture surgery	40 – 80	10 – 20	4 – 10	0.2 – 5

- VTE prophylaxis in general surgical patients is safe (ie a low risk of ↑major bleeding is outweighed by risks of VTE) Ann of Int Med 20 Nov 2007
- Medical patients:
 - Risks for medical patients:
 - Class III or IV heart failure
 - COPD exacerbations
 - Sepsis
 - Plus other standard risk factors: age, history of VTE, cancer, stroke with lower leg weakness, bed rest
 - No studies of mechanical devices in medical patients
 - LMWH at high prophylactic doses reduces DVT by 70% with no increased risk of bleeding (20 mg clexane same as placebo)
- Cost effectiveness of prophylaxis has been repeatedly demonstrated
- Little or no increase in clinically significant bleeding with prophylactic doses of heparin

Pleura and Mediastinum

Pleural Effusion

- Types:
 - Transudate (hydrostatic pressure > clearance):
 - Due to systemic factors affecting formation and absorption of pleural fluid
 - CHF, cirrhosis, nephrotic syndrome...
 - Exudate:
 - Caused by local factors → ↑vascular permeability
 - Bacterial pneumonia, malignancy (75% are mets of lung, breast or lymphoma), viral infection, PE
 - Exudate if any one of (Light's Criteria):
 - Pleural protein/serum protein > 0.5
 - Pleural LDH/serum LDH > 0.6
 - Pleural LDH > 2/3rd upper limit of normal serum
- Can also test pleural fluid for:
 - Cell differential:
 - Lymphocytosis: TB, lymphoma, sarcoid, RA, chylothorax

- Eosinophilia: Pneumothorax (most common cause), haemothorax, benign asbestos, PE/infarction, parasitic/fungal disease, Hodgkin's Lymphoma...
- Amylase: elevated in oesophageal rupture, pancreatic pleural effusion, malignancy
- Glucose: low (eg < 3.33) in malignancy, bacteria infections, rheumatoid pleuritis (often pH and glucose drop together), TB, SLE, oesophageal rupture
- Cytology:
 - 100 ml sample → 60 – 70% sensitivity. With second sample this increases to 80 – 90%
 - Lymphocytic exudate: TB or cancer
 - Eosinophils: cancer
- Fibrinous septations are better seen on US than CT. CT better than US for pleural thickening
- Differentials:
 - Consider CTPA for PE
 - Massive effusions usually due to malignancy
 - Tb: most common in primary TB – ?hypersensitivity reaction to Tb protein
 - Pleural fluid not good for culturing Tb – guided pleural biopsy better
 - Culture fluid, or test for TB markers: adenosine deaminase > 40 iu/l, IFN γ > 140 pg/ml or PCR. See Presentation of TB, page 299
 - Mesothelioma: (see page 204). Usually requires a tissue biopsy. If mesothelioma biopsy then the site should be irradiated to stop tumour invasion (level A evidence)
 - AIDS: effusion uncommon. Consider Kaposi's sarcoma
 - Chylothorax: disruption to the thoracic duct. Usually cause trauma. Also mediastinal tumours. TG level exceeds 1.2 mmol/L. Also microscopy for cholesterol crystals and chylomicrons
- Intrapleural fibrinolytic drugs (eg streptokinase 250 000 iu bd for 3/7) improves radiological outcome but mortality impact not yet know

Pleurodesis (BTS guidelines)

- CXR to confirm fluid drainage and lung expansion first (failure of either → ↑risk of pleurodesis failure)
- Lignocaine (3mg/kg, max 250 mg) given intrapleurally just prior to sclerosant administration. Consider premedication for anxiety/pain
- Talc (2 – 5 gm) is the most effective (90%) sclerosant but < 1 % develop acute respiratory failure following administration
- Tetracycline (1 – 1.5 gm) is modestly effective (65%) with few side-effects, and is the preferred sclerosant to minimise adverse event rates. Bleomycin (60 units) has a modest efficacy (61%) and is more expensive. Doxycycline also used (500 mg, 76%)
- Pleuretic chest pain and fever most common side effects
- Patient rotation unnecessary
- Clamp the tube for 1 hour, then unclamp. As long as fluid drainage < 250 ml/day, tube should be removed within 12 – 72 hours of sclerosant administration
- Chest tube removal: no statistical difference in post-removal pneumothorax with removing at end-inspiration or end-expiration

Pneumothorax

- Primary Spontaneous Pneumothorax: Risk factors:
 - Smoking: RR in a male smoker cf non-smoker: 7 times for < 12/day, 102 times for > 22/day
 - Family history +ive in ~ 10%
 - Marfan's syndrome
 - Homocystinuria
 - Thoracic endometriosis
- Secondary Spontaneous Pneumothorax: risk factors:
 - COPD: responsible for 70%. ↑risk with ↑obstruction
 - PJP: 30% will develop SSP
 - AIDS: most had a prior PJP infection
 - CF: 6% will have a SSP
 - TB: 3% will have a SSP
 - Secondary usually more dangerous than primary given already ↓ pulmonary reserve
- “Large” is greater than 2 cm visible rim (previous classifications have tended to underestimate size)
- Management (BTS guidelines):

- Small (< 2cm), closed pneumothoraces without significant SOB should be observed. Outpatient review. If admitted, high flow O₂
- Breathless patients should have some intervention regardless of size. Then, if uncomplicated, observe for 4 – 6 hours and DC
- First line treatment for all pneumothoraces should be simple aspiration
- Repeated aspiration is reasonable if the patient is still breathless and less than 2.5 litres aspirated
- There is no evidence that large tubes are better than small tubes
- High volume, low pressure (-10 – -20 cm H₂O) suction can be added after 48 hours for persistent leak or failure to re-expand
- HIV: early aggressive treatment – tube drainage and early surgical referral
- Future advice:
 - Don't fly until a CXR has shown complete resolution
 - Avoid diving permanently unless surgical pleurectomy

Sleep

- Normal Sleep architecture:
 - Start with non-REM. Persistence of vigilance for first 20 minutes or so
 - More deep sleep in 1st 1/3 of night
 - Periodic limb movements > in deep sleep

	% of sleep period	Aging
Wake	5	↑
Stage 1	2 – 5	↑
Stage 2	45 – 55	-
Stage 3	3 – 8	-
Stage 4	10 – 15	↓
REM	20 – 25	-

- REM sleep occurs in 90 – 110 minute cycles with 4 – 6 episodes per night, associated with dreaming. REM is reduced on TCAs and SSRIs without apparent consequence
- Compared to non-REM sleep, REM sleep is more metabolically active, HR irregular and ↑, RR irregular and ↑, muscle tone reduced (intercostals ↓, more reliance on diaphragm, problems if that's damaged)
- Melatonin increases in evening/night – not soporific on its own but adjusting sleep phase
- Differential of a teenager sleeping in all the time:
 - Normal
 - Drugs/alcohol
 - Depression
 - Narcolepsy
 - Sleep phase disorder
 - Sleep deprivation
 - Investigate using a sleep diary: when do they go to bed, go to sleep, waking
 - Treatment for sleep phase delay: bright light in early morning → suppresses melatonin over a 2 -3 week period

Obstructive Sleep Apnoea

- See Internal Medicine Journal 2004; 34: 420-426 and Lancet 20 July 2002
- = unexplained excessive daytime sleepiness *and* at least 5 obstructed breathing events per hour of sleep
- Caused by upper-airway dilating muscles (which relax during sleep) being sucked in on inspiration due to ↑intrathoracic pressure. When awake increased tone maintains airway patency
- Predisposing factors:
 - Obesity (BMI > 30 in 50%)
 - Shortening of the mandible and /or maxilla (may be familial)
 - Hypothyroidism and acromegaly (narrowing of the airway 2nd to infiltration)
 - Other features ↓airway size
 - Drugs: alcohol, BZD
- Causes: impaired vigilance, driving accidents, depression, HTN (2nd to current nocturnal hypoxia)
- Complications:
 - Somnolence, mood effects, ↓performance

- HTN: 2.89 ↑ risk for those with AHI > 15 compared to AHI < 1.4 (relationships doesn't hold for those over 65)
- Mild pulmonary artery HTN
- Mild ↑ in Hb
- Evidence suggests ↑risk of MI (?2nd to HTN) and stroke (which causes which, some association observed, various mechanisms hypothesised)
- Associated with insulin resistance independent of obesity
- Hepatic dysfunction
- ↑Perioperative risk: harder to tube and obstruction during recovery
- Relative risk of a car accident if you have untreated OSA is 2 – 7 times (normalises with CPAP)
- Differential:
 - PAIN
 - Insufficient sleep
 - Shift work
 - Depression
 - Hypothyroidism
 - Stimulant and sedative drugs
 - Narcolepsy
 - Periodic Limb Movements of Sleep
 - Idiopathic hypersomnolence
 - Phase alteration syndromes
 - Central Sleep Apnoea:
 - Instability of respiratory control
 - Idiopathic: treatment with nocturnal ventilation or diaphragm pacing
 - 2ndary to Cheyne-Stokes Respiration: Cyclic pattern of crescendo/decrecendo breathing in:
 - CHF (mechanism unclear, worse prognosis, CPAP improves cardiac function, improves QoL, ?survival effect). In a study of patients with EF < 40%, 10 % had OSA and 40% had Cheyne Stokes – CPAP improves sleep but not mortality in CHF even if it's central
 - Neurologic disease (esp stroke, motor neuron, muscular dystrophy)
 - Also 2nd to High Altitude and drugs
- Epworth Sleepiness Score > 11 (usual referral threshold) may not capture some people who constantly fight sleepiness but don't actually nod off
- Assessment: Apnoea + Hypoxia Index (AHI) < 20 mild, > 60 severe
- Progression:
 - With ↑age and ↑weight, AHI increases
 - Untreated, AHI < 20 4% mortality at 8 years, > 20 37% mortality at 8 years
- Treatment:
 - Conservative: ↓weight, ↓alcohol, ↓sedatives, don't drive, treat nasal obstruction
 - CPAP: → pneumatic splint
 - RCTs demonstrate ↑sleep quality, improved BP (decreased by 3.3 – 9.9 mmHg – probably only in those with severe OSA), vigilance, driving ability, improved LV fn in those with CHF. In CHF, improves 6 minute walk but doesn't extend survival (NEJM 10 Nov 2005)
 - Halves the recurrence of AF in the 12 months following successful cardioversion
 - Need to find most comfortable mask (usually nasal). Airway drying can be alleviated by heated humidifier. Can also ↑bloating/burping
 - No evidence for BIPAP (consider in restrictive chest wall disease or nocturnal hypoventilation)
 - Mandibular Reposition Splint (MRS): hold lower jaw and tongue forward, widening the pharyngeal airway. Effective in RCTs. Not as good as CPAP, but should consider if not tolerant of CPAP or mild OSA
 - Surgery only in specific cases (eg jaw advancement). No robust evidence for uvulopalatopharyngoplasty – reduces the uvula but it's usually the posterior tongue that's the problem – Snoring cure in 90%, apnoea cure in < 50% (with lower weight and milder OSA)
- NZ LTSA driving restrictions. Driving must cease if:
 - OSA suspected and there is a high level of concern about sleepiness while driving
 - Complain of severe daytime sleepiness and a history of sleep related MVA
 - Confirmed severe OSA that is not treated for whatever reason

Sleep Related Disorders

Periodic Limb Movements of Sleep

- Repetitive flexion of limbs in sleep, periodicity of 20 – 30 secs
- Causes: Apnoea, TCAs, SSRI, Age, Restless Limb Syndrome, neurodegenerative disorders, spinal cord disorders, narcolepsy, idiopathic

Restless Legs Syndrome

- See page 167
- Compelling urge to move, worse with rest
- Causes:
 - Primary
 - Secondary: iron deficiency, neurological disorders, pregnancy, uraemia, drug induced (TCA, SSRI, lithium, dopamine agonists, caffeine)
- Treatment: Dopamine agonists (sinemet, perfolide, ropinirole). ?benefit from clonazepam, codeine, carbamazepine

Narcolepsy/Cataplexy

- Daytime intrusion of overwhelming REM + muscle weakness 2nd to REM inhibition (→ fall over – cataplexy)
- Variable onset – usually late teens. PLMS (Periodic Limb Movement) in 40%
- Sleep study – very short sleep latency and early REM (eg 3 – 4 minutes, usually ~ 90)
- Causes: ?deficiency of hypocretin/orexin (same thing)
- Treatment: Cataplexy: TCA, SSRI. Sleepiness: dexamphetamine, methylphenidate (Ritalin), modafinil

Obesity Hypoventilation Syndrome

- BMI > 30, PaCO₂ > 45
- Small volume lungs (cf high volume in COPD)
- Progression:
 - Hypoxia – first at night then daytime
 - Pulmonary vasoconstriction
 - Pulmonary HTN
 - RHF
- In 10 – 20% of OSA
- Worse outcomes: LOS, mortality
- Managed with CPAP +/- BiPAP

Lung Transplantation

- Common indications: COPD, IPF, CF, α 1AT deficiency, primary pulmonary HTN
- Common exclusions: HIV, Hep B and C, other uncontrolled infection, malignancy, smoker, comorbidities
- Matched for blood group, and to some degree size
- Bilateral transplant better the unilateral for COPD and α 1AT, not demonstrated in other indications
- Post transplant maintenance immunosuppression usually:
 - Calcineurin inhibitor: cyclosporine or tacrolimus
 - Purine synthesis antagonist: azathioprine or MMF
 - Prednisone
 - Prophylaxis for PJP, and maybe CMV
- 5 year survival ~ 50%, worse for primary pulmonary HTN

Other

Air Travel Advice

- Aircraft cabins are pressurised to a maximum altitude of 8000 ft – the equivalent of breathing 15.1% O₂ at sea level. In a normal person PaO₂ falls to 53 – 64 mmHg. Can exacerbate hypoxic conditions, especially severe COPD

- Can do a pre-flight “hypoxic challenge test” to test for the need for in-flight O₂ if sats 92 – 95%. If < 92% then need supplemental investigation
- Transmission of respiratory infections during air travel:
 - Cabin air is essentially sterile, and exchanges at least 20 times/hour
 - Droplet spread: coughing and sneezing, direct contact with mucous membrane of recipients, < 1m for risk of transmission: common cold virus, SARS, meningococcal
 - Airborne transmission: droplet nuclei (1 – 10 μm) disperse rapidly and widely within closed environments and via ventilation systems
 - Tb spread uncommon even with highly infectious cases. WHO guidelines: contact tracing if infectious, flight > 8 hours, within 2 rows

Altitude Sickness

- Hypoxic stress outstrips acclimatisation (mainly ↑ ventilation) → poorly understood hypoventilation for the degree of hypoxia
- Presentation: headache → anorexia, nausea, insomnia, fatigue
- Prophylaxis:
 - Acetazolamide 5 mg/kg/day in divided doses (also effective in early treatment). Carbonic anhydrase inhibitor → metabolic acidosis → respiratory compensation → hyperventilation
 - Gradual acclimatisation
- Treatment: O₂ + immediate descent
- Spectrum:
 - Acute Mountain Sickness
 - Occasional high-altitude pulmonary oedema (2nd to ↑pulmonary artery pressure and hypoxic pulmonary vasoconstriction): SOB, wheeze, maybe haemoptysis. Salmeterol prophylaxis of benefit if at risk. Add Nifedipine for treatment
 - Rarely High altitude cerebral oedema: altered consciousness and ataxic gait. O₂ + dexamethasone 4 – 8 mg/6 hourly

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Cells of the Immune System

Principles

- See NEJM July 6 and 13, 2000 and following editions
- Antigenes:
 - Haptens: small, non-immunogenic antigens. Must be coupled to larger immunogenic molecules to stimulate a response
 - Epitopes: parts of large proteins that are recognised by an antigen receptor (antibody or T-cell receptor)
 - Superantigens: usually antigens bind to the $\alpha\beta$ groove in MHC1 and 2 molecules, and to the V region of TCR α and β chains, activating < 1 in 10,000 T cells. Superantigens bind to the lateral portion of the TCR β , independent of the D, J and V α sequences, triggering up to 20% of the T cell population. Eg staph enterotoxins \rightarrow toxic shock syndrome
- Innate (natural):
 - Occur to the same extent however many times the infectious agent is encountered
 - Use phagocytic cells (neutrophils, monocytes, macrophages), cells that release inflammatory mediators (basophils, mast cells, and eosinophils) and natural killer cells
- Acquired (adaptive):
 - Increase on repeated exposure
 - Involve proliferation of antigen-specific B and T cells. Antigen presenting cells display the antigen to lymphocytes
- Cytotoxicity:
 - IgG mediated cytotoxicity: NK cells, monocytes, macrophages and neutrophils
 - IgE mediated cytotoxicity: Macrophages, eosinophils and platelets
- Lymphoid tissues:
 - Secondary lymphoid tissues: lymph nodes (including palatine tonsils and adenoids), spleen, mucosa-associated lymphoid tissue (MALT)
 - Germinal centres appear in lymphoid tissue during an immune response. Hypermutation and class switching of Igs occurs, and memory B cells and plasma-cell precursors are generated. Contain follicular dendritic cells, rapidly dividing B cells, CD4 T cells and macrophages – a microenvironment where all the necessary cells for rapid antibody production are in close contact
- Flow cytometry: uses monoclonal antibodies with fluoro-chromes attached to interrogate the phenotype of cells – “stains” for different cell wall markers and counts them

Innate Immune Cells

Macrophages

- Derived from blood born monocytes
- Main role is phagocytosis of self-cells containing intra-cellular antigen
- Present throughout connective tissue: alveolar macrophages (lung), Kupffer cells (liver), mesangial cells (kidney), microglia (brain), osteoclasts (bone)
- Also act as APCs (along with dendritic cells – the main APC)
- Has two relevant receptors:
 - Receptors for carbohydrates not normally found on the cells of vertebrates (eg mannose)
 - Receptors for antibodies and complement (as do neutrophils) so that coating of microbes with antibodies and/or complement enhances phagocytosis
- Apoptotic cells (programmed cell death resulting in the digestion of DNA by caspase mediated endonucleases) express molecules on their surface that mark them as targets for phagocytosis [cf necrotic cells which release substances that trigger an inflammatory response]

Natural Killer (NK) cells

- Aka Large Granular Lymphocytes, CD 16, 56, 57 +ive
- ~10 – 15% of lymphocytes
- Bone marrow derived (ie non-thymic)
- Don't express specific receptors
- Innate response cell that recognises and kills cells:
 - With a “suspicious” surface protein (activates the killer activating receptor) *and* without MHC1 molecules (MHC1 stimulates the NK cell's “Killer inhibitory receptor”) – viral or tumour cells – or

- ADCC (antibody-Dependent Cell-mediated Cytotoxicity): When the IgG of coated microbes binds to the NK cells IgG Fc receptors (Fc ϵ RIII)
- Injects cells with cytotoxic granzymes which initiate apoptosis
- IL12 \rightarrow NK cells produce INF γ \rightarrow stimulates macrophages and favours Th1 differentiation
- Major cell of the pregnant uterus: protect from viral infection, don't attach foreign (paternal) MHC

Granulocytes

- Neutrophils: phagocytose and kill pyogenic bacteria, produce antimicrobial peptides
- Eosinophils:
 - Only weakly phagocytic, and release various cytokines
 - Once activated, kill parasites by releasing cationic proteins and reactive oxygen metabolites into the extra-cellular fluid
- Basophils and tissue mast cells: important in parasitic defence. Multiple TLR on their surface. High affinity receptors for IgE (FcRI). Release mediators of immediate hypersensitivity responses

Interdigitating dendritic cell

- Role:
 - No clonal selection nor memory, no risk of allergy or autoimmunity
 - Live at antigen rich sites
 - Collect antigen and migrate to the local draining lymph node (lymph nodes, spleen, MALT) where the antigen (which has been processed intracellularly into short peptides) is presented to a T cell via TCR. B cells recognise intact "whole" antigen via surface immunoglobulin
 - Initiate or "prime" adaptive immune responses for which there is no prior immunologic memory by activating "naïve" T cells
 - So, links innate and adaptive immunity
 - Activates macrophages (which can also act as antigen presenting cells)
- Three types:
 - Myeloid: interstitial (lymphoid organs, blood, lung, heart, kidney) and Langerhans (lymph nodes, skin, thymus, blood). Produce IL-12 and IL-10
 - Plasmacytoid: lymphoid organs and blood. Produce IFN α
- Antigen recognition – how does an APC know it's an antigen?
 - When pattern-recognition receptors (PRRs) on their surface recognise distinctive, highly conserved pathogen-associated molecular patterns (PAMPs) on the surface of microbes they are activated and acts as antigen presenting cells (APCs)
 - Pattern-recognition receptors include:
 - C-type lectin receptors (CLRs)
 - NOD-like receptors (NLRs): structures within the cell which recognise inflammatory producing stimuli, activate caspases 1, 4 or 5 \rightarrow IL-1 β and IL-18
 - Toll-like Receptor Proteins (TLR):
 - TLRs (currently numbered 1 – 10). Major role is to activate NF κ B transcription factor which drives gene transcription \rightarrow inflammatory cytokines \rightarrow TH1 or TH2 response
 - TLR4: Associated with lipopolysaccharide [LPS – present on all G-ive bacteria] binding protein which transfers LPS to the macrophage LPS receptor, CD14. Signalling by large amounts of LPS via the TLR4 mediates LPS induced shock
 - TLR3 detects dsRNA (eg Herpes Simplex)
 - Some TLRs are intracellular receptors
 - Originally studied in the *Drosophila* fruit fly...
 - Mannose binding lectin: an acute phase protein which binds a wide spectrum of oligosaccharides (a "universal AB"), recognising G-ive and G+ive bacteria, yeast, fungi, parasites, some viruses) \rightarrow turns on a particular part of the complement cascade (see page 232)

Cell Transport

- Adhesion Cascade:
 - L-Selectins: ligands on immune cells that bind Lewis-X expressed on endothelial cells – keeps the cell "rolling" along the periphery of the blood vessel lumen as it circulates
 - Integrins: ligands on immune cells that bind IgSF structures (eg E-selectin) on endothelial wall causing *adhesion* and *arrest*. The IgSF structures are expressed on the endothelium in response to cytokines in the underlying tissues

- Diapedesis: cells “squeeze” through the endothelial cell junctions and migrate along the concentration gradient created by C3a, C5a, chemokines, histamine, prostaglandins and leukotrienes
- Related illnesses: Leukocyte Adhesion Deficiency 1 and 2: see page 234
- Chemokines:
 - Chemotactic cytokines. Released in tissues to create a concentration gradient directing leukocyte migration – at least 45 described. Different combinations of chemokines attract different cells by acting on chemokines receptors (eg eosinophil, basophil, neutrophil, activated T cell, resting T cell, monocytes, dendritic cells, NK cells etc)
 - Of relevance to HIV: R5 strains use CCR5 (a chemokine) receptor for macrophage and T cell entry – less aggressive virus. X4 strains use CXCR4 receptor for CD4 entry only. Homozygotes to CCR5 Δ 32 → CCR5 not expressed on cell surface → resistant to HIV infection

Adaptive Immune Cells

- Slugs and worms don't have T & B cells – they just have innate mechanisms

Major Histocompatibility Complexes

- Molecules whose role is to present antigen to T cells
- On chromosome 6p
- MHC/HLA Class 1:
 - Are present on all nucleated cells (ie everything except RBC) – but this expression can be lost as a result of microbial interference in its expression (eg herpes virus infection) or as a result of malignancy
 - 100,000 – 200,000 copies of the MCH1 on any given cell, binding several hundred to several thousand peptides
 - MHC Class 1 pathway is continually “sampling” the inside of the cell and putting proteins on the MHC1 receptors on the cell surface for “routine surveillance”:
 - Cytoplasmic peptides are degraded by proteosomes (multicatalytic proteinase complex) expressed in all cells
 - Free cytoplasmic peptides are transported into the endoplasmic reticulum (ER) by specific transporters – TAP-1 and TAP-2 (Transporters Associated with Ag Processing)
 - Bind to MHC1 molecules and are transported to the cell surface via the Golgi complex
 - Expression is upregulated by IFN γ
 - Most common source of peptides presented by MHC1 are viruses, also other intracellular infectious agents (eg Listeria, plasmodium), and tumour antigens – role in intracellular infection
 - Mainly presents self-antigen to the TCR on CD8 T cells (can hold 8 – 11 amino acids)
 - Consists of single 3-domain chain and β 2 microglobulin
 - Three main classes/loci: HLA-A, B and C. Is highly polymorphic – 100s of different alleles have been identified for each locus. Allow presentation of a wide variety of different peptides derived from any given antigen
 - There are 3 further class Ib MHC molecules – HLA –E, F and G. HLA-E is the major self recognition target for NK cells. HLA-G is expressed selectively in fetal tissues in contact with maternal tissues. The function of HLA-F is unknown
- MHC/HLA Class 2:
 - Are present on APCs and present antigen to the TCR on CD4 T cells – can hold peptides up to 30 amino acids
 - Are inducible on most endothelial and epithelial cells in response to cytokines (eg IFN γ)
 - Presentation:
 - Antigen is imported into the cell in an endosome and broken into fragments by splisosomes
 - Peptides are transported into the ER
 - MHC molecules synthesised in the ER and bind peptides in their groove
 - Whole complex is transported to the cell surface
 - Three main regions of the MHC2 genome, each with multiple genes: HLA-DP, DQ and DR.
 - Nomenclature: Each region has an A locus and a B locus that code for the α and β chains of the MHC2 molecule. Eg DQA1 and DQB1 genes encode the HLA-DQ molecule. There are usually multiple B loci. DRBZ*XXYY = DRXX gene, coded at the BZ locus, allele number YY

Antigen receptors

- Lymphocytes are capable of producing 10E15 different antibody variable regions (B cells) and T-cell-receptor variable regions

- Achieved by recombination processes that cut, splice and modify variable-region genes (clusters of gene segments: V (variable), D (diversity), and J (joining) genes for each component of the antibody complex and the T-receptor) – one from each region is chosen at random for the finished product – there are ~50 V genes, ~25 D genes, ~6 J genes in B cells, more complex in T cells
- Each lymphocyte uses a different combination of the relevant gene segments to form the genetic code of its antigen receptor
- Along with splicing errors and added nucleotides, each B and T cell clone has a molecularly unique receptor
- There will only be a few thousand lymphocytes for each antigen
- These lymphocytes are involved in an immune response by a process called “clonal selection” if they can bind a relevant antigen → rapid proliferation. If all cells possess identical VDJ re-arrangement, this proves clonality. Most responses are polyclonal as even a simple antigen has several different epitopes
- B-cell receptors undergo further refinement in a process of hypermutation during B-cell proliferation within germinal centres of secondary lymphoid tissue. Fine tunes the antibody – better “fits” → better chance of B cell survival → better overall antigen affinity and memory (see page 228)

T Cells

- Stem cells continuously migrate to the thymus where they develop into T cells – continue to develop there throughout life (ie they leave marrow very early in their development)
- Receptors are mainly α/β (recognise short segments of processed antigen + MHC complexes) and a few γ/δ (recognise antigen directly) transmembrane molecules which have structural similarities to Ig heavy and light chains
- “Thymic education”: process of:
 - VDJ receptor rearrangement of the TCR (T Cell Receptor – very different from Ig on B cells – which is the same as soluble Ig)
 - Negative selection of T cells that can recognise self MHC molecules but are not auto-reactive (only a minority of T cells can do this subsequent to T-cell-receptor gene rearrangements). Triggers apoptosis in any T cell that expresses a T-cell receptor for a self-peptide plus a self-MHC complex (ie binds MHC strongly)
 - Positive selection involves switching off the apoptosis that is otherwise triggered in all T cells
 - AIRE gene (Autoimmune regulator) controls expression of tissue specific antigens at low levels in the thymus as a substrate for this “education” process. Mutation → Autoimmune Polyendocrine Syndrome Type 1 (see Polyendocrine Syndromes, page 76)
 - 98% of T cells are self reacting or non-functional – lots of censoring to be done – the result are T cells that bind MHC weakly
- Peripheral T-cell Tolerance:
 - Central tolerance of T cells is induced in the thymus and for B cells in the bone marrow – removes cells that recognise self as antigen. However, most tissue-specific self-antigens aren’t present in the thymus or marrow
 - Peripheral tolerance supplements central tolerance – incomplete signals (ie antigen presented without co-stimulatory signals) given to cells when they encounter peripheral self-antigens → apoptosis
 - Some degree of peripheral autoreactivity is necessary for the survival of T and B cells.
- T-cell Activation:
 - Requires presentation by an APC of peptide in an MHC *and* co-stimulation (otherwise → tolerance)
 - Costimulation is mediated by:
 - B7.1 (CD80) and B7.2 (CD86) binds with CD 28 on T cell. Important for initial activation
 - B7.2 (CD86) binds with CTLA-4 (cytotoxic T-Lymphocyte Antigen-4) on T-cell. CTLA-4 is induced slowly on T cells following activation and binds B7 more strongly. Generates a negative signal → dampens response in due course
 - CTLA-4.Ig (extracellular portion of CTLA-4 fused to Fc portion of IgG) binds to B7 – acts as a decoy so the B7 can’t bind to CD28 and activate the T cell. Used for diseases caused by excessive T cell activation (RA, IBD, psoriasis, in trial for prevention of graft rejection)
 - Anti-CTLA-4 up-regulates T cells – uses in cancer but ↑ autoimmune disease
 - IL-2:
 - T-cell growth factor → drives resting T-cell division and generation of Tregs which in turn control lymphocyte activation
 - Acts on IL-2R receptor – CD 25 is the IL-2 receptor (genetic defect of the γ chain of this receptor → SCID – no T cells)

- Clinical applications: see immunosuppression in kidney transplant, page 120. and Biologic DMARDS, page 242
- **Regulatory T cells** (previously called Suppressor T cells):
 - Stimulated by TGF- β and IL-10
 - Suppress mature self-reactive lymphocytes. Role in maintenance of self-tolerance in peripheral tissues
 - Represent approx 1-5% of CD4+ cells (the rest being mainly Th1 or Th2)
 - Various overlapping subtypes, eg CD4+ CD25+ foxp3+ (= forkhead box P3) T-cells. Also CD8+
 - Bind to MHCII on T-cells and require costimulation (B7, CD80 and 81). Produce large amounts of IL-10 \rightarrow immunosuppressive effect via inhibition of other T cells
 - Interest in manipulating regulatory T cells to treat disease
 - IPEX: Immune dysfunction, Polyendocrinopathy, enteropathy, rare X-linked disease
 - Lack of foxp3 \rightarrow global overactivity of immune function, especially T-cell mediated autoimmune disease
 - Present during first few months with autoimmunity, atopic features, lymphadenopathy
- **Helper T cell:**
 - Usually CD4+, secretes various cytokines that regulate other immune cells. Differentiate from Th0 cells
 - CD4 binds to the MHC class II molecule on APCs
 - Most antigens can't stimulate B cells without costimulation from a CD-4 cell = "T-cell dependent antigens". B cell processes the antigen and expresses it on a MHC2 receptor. A neighbouring CD4+ recognises the complex and expresses co-stimulatory molecules (eg CD154 aka CD40 ligand) which stimulate the B cell to begin hypermutation and class switching
 - Depending on the predominating cytokines, will develop into:
 - IL-2, IL-12 and IFN γ \rightarrow **Type 1 helper T cell**: secretes IL-2 and IFN γ (but not IL-4, 5 or 6), inhibits type 2 helper cells and activates cell-mediated immunity (ie activated macrophages and cytotoxic T cells) in the presence of intracellular bacteria or viruses
 - IL-4 \rightarrow **Type 2 helper T cell**:
 - Secretes IL-4, 5, 6 and 13 (but not IL-2 or IFN γ), inhibits type 1 helper cells and stimulates humoral immunity (production of antibody by B2 cells) against parasites and extracellular encapsulated bacteria
 - Evolutional role in defence again helminths? [Mice can survive without TH2 response]
 - IL-6, TGF β , IL-23, IL-23 \rightarrow **Type 17 helper T cell**: secretes IL-17, IL-22, IL-26, IFN- γ and TNF- α \rightarrow stimulates many cells types to release cytokines that attract neutrophils (\rightarrow chronic inflammation). Role in defence against candida, staph, others (they are absent in hyper IgM disease characterised by these infections) ?Role in autoimmune disease
 - CD45RA is expressed on native T helper cells, CD45RO is expressed on T helper cells that have become memory cells (which are more rapidly triggered \rightarrow quicker secondary than primary immune response)
- **Cytotoxic T cells:**
 - Usually CD 8+ which binds to MHC class I molecule
 - Also undergo positive and negative selection in the thymus
 - If a CD8 + cell recognises complexes of "internal" antigenic peptides and MHC1 molecules on the target cell membrane it then kills the cell (usually virally infected) – the only way to deal with intracellular infection
 - Either:
 - Injects perforin-granzymes into the cell \rightarrow activates caspase enzymes \rightarrow triggers apoptosis, or
 - Binds Fas ligand (the "self-destruct button" on all cells) \rightarrow activates caspase enzymes \rightarrow triggers apoptosis
 - Releases virus into the extracellular environment where antibody can bind it
 - Also produces cytokines, including TNF α and IFN γ . IFN γ , together with IFN α and IFN β secreted directly by infected cells, makes neighbouring cells more resistant to viral infection (stimulates a "viral resistance phenotype" – cell stops working so well \rightarrow \downarrow any viral replication that may be happening inside itself)

B cells

- Early B cells distinguished by CD 10 and 34 +ive
- Develop in the bone marrow: B-lineage cells undergo:
 - Antigen receptor (VDJ) rearrangement

- Negative selection for autoreactivity:
 - Highly cross-linking self-Ag → deletion
 - Minimally cross-linking self-Ag → anergy
 - Doesn't always work – ANAs are Ig's from B cells to self antigen that are still functioning
- Then becomes a naive B-cell which matures in the periphery – naïve B-cells in the spleen, LN, MALT and GLAT await specific Ag (and T cell help) before differentiating further
- Surface IgM characterises all B cells (and IgD in mature cells as well)
- B1 cells: a minor population of B lymphocytes that secrete polyclonal low-affinity IgM antibodies (“natural antibody”). Most express CD5 on their cell surface
- B2 cells: arise from stem cells in the bone marrow, do not express CD5, and secrete highly specific antibody within the secondary lymphoid tissue
- Differentiation post-antigen exposure:
 - B-cells encounter antigen in lymphoid tissue – engulf it and present it on MHC2 to T-cells
 - Receive T-cell help: CD40 (activated by CD40L on T cells) activates B cells and initiates:
 - Activation
 - Somatic hypermutation → higher affinity antibody. Occurs in germinal centre *after* activation. Mutation of Ig genes during B cell proliferation
 - Positive selection: affinity tested on follicular dendritic cells for better affinity for antigen. If reduced affinity → die by apoptosis
 - Differentiation into:
 - Memory B cells, surface Ig-expressing (usually isotype-switched). Long lived (turn neoplastic in myeloma). Able to respond to secondary challenge with minimal T cell help and already-isotype-switched Ab (often IgG)
 - Antibody forming cells: lymphoblasts, plasmablasts, plasma cells. Migrate to bone marrow where they secrete Ab for a long time
 - Class switching eg from IgM to IgG (which also then requires the B cell to divide). Class switching requires T cell help. Can have T cell independent class switching to some antigens, eg pneumococcal
- Antibodies:
 - = Immunoglobulins
 - Structure:
 - Consist of two identical light chains and heavy chains
 - N terminal of each chain has a highly variable domain that binds antigen through 3 hyper-variable regions. Variable region coded by VDJ
 - C terminal domains are constant, define the class of the antibody, and whether the light chain is the κ or λ type
 - There are 4 subclasses of IgG and two if IgA
 - Can be produced as a circulating molecule, or planted in B-cell membrane where it functions as a B-cell receptor (triggering this receptor → clonal expansion)
 - First Ab made is IgM, low affinity but 10 effective binding sites per antibody
 - Later, IgG response, has higher affinity
 - With subsequent exposure there is the same IgM response but a faster and better IgG response

Acute Phase Response

- T-cells that have been primed in lymphoid tissue circulate in peripheral tissue and respond to antigen presented locally
- Release cytokines to engage B cell help, activate NK cells, macrophages etc
- Th-1 cells release IFN γ which activates macrophages
- Macrophages release IL-1, IL-6, TNF
- Act on hepatocytes to release acute phase reactants: CRP, α 1antitrypsin, fibrinogen (measured in ESR), ferritin

Various Cytokines

Cytokine	Source	Major activity	Clinical Relevance (old source)
TNF α	Macrophages, NK cells, T cells, B cells, mast cells	Promote inflammation	Treatment with TNF α antibodies in RA, etc

TNF β (lymphotoxin)	Th1 cells and B cells	Promote inflammation	Implicated in MS and T1DM
Transforming Growth Factor β	T cells, macrophages, B cells, mast cells	Immunosuppression	?useful in MS and myasthenia gravis
Granulocyte Macrophage CSF	T cells, macrophages, NK cells, B cells	Promotion of granulocytes and monocytes	Reduce neutropenia after chemo, stimulate cell production after BMT
IFN α	Virally infected cells	Induction of resistance to viral infection. \uparrow MHC1 expression	Treat Kaposi's sarcoma, chronic Hep B and C
IFN β	Virally infected cells	Induction of resistance to viral infection. \uparrow MHC1 expression	Reduce relapses in MS
IFN γ	Th1 and NK cells. Production stimulated by IL-12	Activation of macrophages and neutrophils, inhibition of Th2 cells	Enhance the killing of phagocytosed bacteria in chronic granulomatous disease

Mast cells and IgE disorders

- Little evidence that blood basophils develop into tissue mast cells
- Both have high affinity IgE receptors (Fc ϵ R)
- Binding of IgE to mast cells and basophils (sensitisation) prepares these cells for subsequent antigen specific activation
- Activated mast cell:
 - eg C3a and C4a can trigger activation
 - Activated cell produces:
 - Lipid mediators: LTB4, LTC4, PAF (platelet activating factor), PGD2 (Prostaglandin)
 - Secretory granule preformed mediators: Histamine, proteoglycans, tryptase and chymase, carboxypeptidase A
 - Cytokines: IL-1, 3, 4, 5, 6, 13, GM-CSF (Granulocyte-Macrophage CSF)
- These lead to:
 - Leukocyte responses: adherence, arrest, diapedesis (squeezing through endothelial junctions), chemotaxis, IgE production, mast cell proliferation, eosinophil activation
 - Fibroblast responses: proliferation, vacuolation, collagen production
 - Substrate responses: activation of coagulation cascade
 - Microvascular responses: augmented vascular permeability, leukocyte adherence, constriction, dilation

Anaphylaxis

- Life threatening response in seconds to minutes in a sensitized human to a specific antigen, causing respiratory distress, laryngeal oedema, and/or intense bronchospasm, followed by vascular collapse. Pruritis and urticaria with or without angioedema
- Atopy does not predispose individuals to anaphylaxis from penicillin or venom, but is a risk factor for food or latex
- Elevated tryptase implies mast cell activation
- Exclude:
 - Complement-mediated immune complex reaction
 - Idiosyncratic reaction to a NSAID (eg aspirin and indomethacin). Associated with nasal polyposis. Not associated with the presence of specific IgE. Due to inhibition of PGHS-1
 - Direct effect of mast cell-degranulating agents (iv opiate derivatives, contrast media)
 - Transfusion reaction in congenital IgA deficiency, anti-IgA \rightarrow complement activation \rightarrow mast cell activation
- Treatment:
 - Pruritis and urticaria 0.3 – 0.5 ml of 1:1000 sc or im adrenaline, repeated at 5 – 20 min intervals
 - Adrenaline infusion if prolonged
 - Vasopressors (eg dopamine) if intractable hypotension
 - Volume expanders (N saline)
 - O2 plus nebulised salbutamol if necessary for bronchospasm
 - Antihistamines, plus steroids to alleviate later reaction

- If on β -blockers, and not responsive to adrenaline and fluids, give glucagons 1 – 5 mg iv \rightarrow \uparrow cAMP by by-passing β -receptor activation (also used in β -blocker overdose)
- Prevention:
 - β -blockers relatively contraindicated
 - Scratch skin test should precede an intradermal skin test
 - Skin testing of no value for non-IgE mediated eruptions
 - Desensitisation
 - Avoidance (eg of bees)
 - Medic alert bracelet
 - Unexpired auto-injectable adrenaline

Atopy

- \uparrow propensity to develop IgE mediated reactions to common environmental allergens
- Includes allergic rhinitis, atopic asthma, atopic dermatitis, food allergy, but *not* necessarily bee-sting allergy, drug allergy, chronic urticaria
- Dominated by a Th2 response: IL-4 and 13 \rightarrow IgE switching by B cells. IL-5 \rightarrow eosinophils
- Hygiene Hypothesis: \downarrow serious childhood infections, widespread use of ABs, urban environment \rightarrow altered Th1-Th2 balance in favour of Th2
- IgE Receptors:
 - Role: ?Ag presentation
 - Fc ϵ RI: high affinity IgE receptors expressed on mast cells and basophils
 - Fc ϵ RII (CD23): low affinity IgE receptors expressed on mature B cells, macrophages, monocytes, dendritic cells, eosinophils
- IgE-allergen complex triggers Fc ϵ RI causing mast cell degranulation \rightarrow :
 - Histamine and leukotrienes release \rightarrow early phase acute inflammation, marked and steroid resistant
 - Chemokines + cytokines release \rightarrow last phase acute inflammation – influx of eosinophils and neutrophils, steroid responsive
- Eosinophils release mediators which cause epithelial damage
- Desensitisation:
 - Effective for:
 - Insect sting anaphylaxis (96% protective)
 - Allergic rhinitis: of benefit but ?better than medical therapy
 - Asthma: ?risks outweigh benefits
 - Mechanism debated: injection favour Th1 response? Induction of allergen-specific IgG (?prevents allergen from reaching mast cell)
- Maternal avoidance of allergenic foods during pregnancy and lactation have been shown not to significantly reduce the incidence of allergenic disease in offspring

Urticaria

- Urticaria = superficial portion of the dermis
- Angioedema = deeper levels of the dermis and subcutaneous tissue
- Causes:
 - IgE dependent:
 - Specific antigen sensitivity: pollens, foods, drugs, venom
 - Physical: dermatographism, cold, solar
 - Autoimmune – 40% of chronic urticaria patient's have autoantibodies to IgE
 - Bradykinin-mediated:
 - Hereditary and acquired angioedema: c1 inhibitor deficiency. See Complement, page 232
 - ACEIs – attenuated degradation of bradykinins
 - Complement-mediated:
 - Necrotizing vasculitis
 - Serum sickness
 - Reaction to blood products
 - Non-immunologic:
 - Direct mast cell-releasing agents: opiates, antibiotics, contrast
 - Agents that alter arachidonic metabolism: aspirin, NSAIDs
- Treatment:
 - H1 antihistamines: loratadine, cetirizine. Older H1 blockers were sedating and had anti-cholinergic (muscarinic) effects. Newer ones don't cross BBB

- H2 antihistamines: cimetidine, ranitidine may add benefit
- Doxepin has H1 and H2 action

Other

- Systemic Macrocystosis
 - Clonal expansion of mast cells that is usually indolent and non-neoplastic
 - Presentation: pruritis, flushing, palpitations, gastric distress, lower abdo crampy pain
 - Urticaria pigmentosa: cutaneous lesions, reddish brown macules or papules that respond to trauma with urtication and erythema
- Allergic rhinitis:
 - Antihistamines for itching and tearing
 - For congestion need α -adrenergic agonist decongestants (eg pseudoephedrine) – contraindicated in narrow angle glaucoma, urinary retention, severe hypertension, marked CVD or 1st trimester

Complement

- 30 plasma and membrane proteins that provide innate defence and an adjunct to humeral immunity (~15% of globulin fraction of plasma)
- Works by self-amplifying cascade
- Links the innate and adaptive immune system
- Named in order of discovery – not sequence. Activated in this sequence: C1 → C4 → C2 → C3 (cleaved into C3a and C3b) → C5....
- Three pathways:
 - Classical pathway: activated when IgM or IgG antibodies bind to antigens, then C1 binds to the antibody-antigen complex and initiates activation:
 - C1 is made up of C1q, C1r and C1s. When C1 binds to antibody-antigen complex, C1s is released → cleaves C4 in C4a and C4b...C4bC2a is a C3 convertase → cleaves C3 into active C3a and C3b particles
 - C1q binds to CRP (part of the innate pathway). CRP binds phosphocholine residues on bacterial polysaccharides (eg pneumococcal C polysaccharide – hence the name C-reactive protein) and apoptotic cells
 - Alternative pathway: does not require specific antibodies to function. Triggered by microbial cell walls. C3b + Factor B (alternative pathway protein) bind to microbe, Factor D cleaves B into Ba + Bb which triggers MAC
 - Lectin pathway: Mannose-binding protein (MBP, homologous in structure to C1q) binds to carbohydrates on the surface of a pathogen, and activates C4 and C2. ?Particular role in the period between loss of maternal antibody immunity and development of one's own antibody responses...
 - All 3 pathways converge on C3
- Complement function:
 - Activated complement components deposit in large numbers on microbes (“opsonization” by C3b and C4b). Phagocytes bind to these ligands. Efficient uptake by APC
 - Clearance of immune complexes and apoptotic cells (C1q; fragments of C3 and C4)
 - Promotes inflammation (eg the “anaphylatoxins” C3a, C4a and C5a – cleaved particles): mast cell degranulation, smooth muscle contraction, dilation of blood vessels, activation of macrophages and epithelial cells, chemotaxis of granulocytes
 - Augmentation of antibody responses: C3b and C4b bound to immune complexes and to antigen, C3 receptors on B cells and APCs
 - Forms the membrane attack complex (MAC – C5b to C9) which perturbs the cell membrane and can cause lysis (the problem in autoimmune haemolytic anaemia)
- Testing:
 - CH50 – tests the entire classical pathway (C1 – C9) – all are required to give a normal result. Screens for any deficiency in the classical pathway. Poor serum handling can → depressed result
 - AH50 – same but measures alternative pathway (factors B, C, P etc)
 - C3, C4 – decreases in SLE flare, used as markers
 - Tissue deposition measured with immunofluorescence for C1q, C4, and C3
 - Classical pathway activation measured by ↓C4 and C3, and normal factor B
 - Alternative pathway activation measured by ↓factor B and C3, and normal C4
 - Presence of C3 fragments on erythrocytes in haemolytic anaemias assessed by agglutination with antibodies to C3 (Combes test)

- Pyogenic infections as a result of complement deficiency:
 - Deficiency of C3 (milder effects from deficiency of C2 and C4): Increases susceptibility to pyogenic bacteria such as *H. Influenzae* and *Strep pneumoniae*. Normal process is opsonization with antibody → activation of complement → phagocytosis → intracellular killing
 - Deficiencies in the alternative pathway (eg of properdin and factor D) → ↑pyogenic infections
 - Deficiency of the MAC → ↑*Neisseria meningitidis* and *Neisseria gonorrhoeae* infection – as extracellular lysis is a major mechanism of killing them as they can survive intracellularly
- The bugs fight back:
 - EBV, HIV, pathogenic Mycobacteria and intracellular bacteria use receptors (usually a complement receptor on an immune cell) to enter target cells
 - Group A strep produces an M protein that binds factor H → ↑catabolism of C3b → ↓formation of C3 convertase enzymes
- Clinical associations of inherited deficiencies:

Deficiency	Consequence	Association
C3	Low opsonisation and no activation of MAC	Pyogenic infections Membranoproliferative GN
C3, properdin, MAC proteins	Failure to form MAC	Neisserial infection
C1 inhibitor	Loss of regulation of C1	Angioedema
CD59	No formation of MAC on autologous cells	Haemolysis, thrombosis
Factors H and I	Failure to regulate the activation of C3 → severe C3 deficiency	Haemolytic-uraemic syndrome, Membranoproliferative GN
C1q, C1r, C1s, C4, C2	Failure to activate classical pathway	SLE

- C3 Nephritic factor: an autoantibody that stabilises C3 convertase (C3bBb) leading to constant complement mediated activation. Associated with mesangiocapillary glomerulonephritis type 2. See page 129
- C1 Inhibitor Deficiency:
 - C1 inhibitor is the primary inhibitor of the classical complement pathway, as well as involvement in coagulation, fibrinolytic and kinin-generating pathways. Deficiency → uninhibited activation of the complement cascade
 - → clinical syndrome of angioedema (not “allergic” angioedema). Oedematous lesions of the upper respiratory tract and GI tract lasts several days, *without* urticaria
 - Can be either a deficiency of the inhibitor (type 1 – 85%) or non-functional (type 2 – 15% – which have normal to high levels when tested...)
 - Either acquired (autoantibody to C1-inh or excessive utilisation, usually in the setting of malignancy) or autosomal dominant inheritance (ie need both alleles working to be normal) – Hereditary Angioedema
 - Precipitated by minor trauma (eg dental work), also pregnancy, oestrogen, ACEI, stress, cold...
 - Causes severe illness if gut affected or death if severe bronchoconstriction
 - Treatment: FFP (C1 inhibitor concentrate not available in Australasia)
 - C1 inhibitor also inhibits the enzyme catalysing the formation of bradykinin, so deficiency → ↑bradykinin (a potent vasodilator)
 - ACE (aka kininase 2) breaks down bradykinin, so ACEI deficiency also → ↑bradykinin, so ACEI absolutely contraindicated in C1 inhibitor deficiency
 - Leads to chronically reduced levels of C4 and C2 (substrates of C1)
- Therapeutic applications:
 - sCR1 (soluble version of complement receptor 1[CR1] – the C3b receptor) is effective in animal models of ischemia, transplantation rejection and ARDS – in clinical trials. The “cluster of differentiation” (CD) assignment: CR1 = CD35
 - Monoclonal antibody to C5

Immunodeficiency

- Overview:
 - Primary Immunodeficiency:
 - Defects in innate immunity
 - Defects in lymphocyte maturation
 - Defects in lymphocyte function and activation

- Associated with other inherited disorders
- Secondary immunodeficiency: HIV, chemotherapy, cancer, splenectomy...
- What deficit leads to what:
 - Lack of antibody response leads to:
 - Recurrent sinopulmonary and gut infections: sinus, OM, tonsils, pneumonia, skin infections, diarrhoea
 - With infections by: polysaccharide-encapsulated pyogenic organisms (Strep pneumonia, HIB, Strep pyogenes, Branhamella catarrhalis), Staph aureus, Giardia lamblia, Campylobacter – ie not opportunistic infections – just every day ones
 - Lack of T-cells: infection with intracellular organisms (as in AIDS): fungi (mucosal candida), viruses (CMV, VZV, HSV, Protozoa, Listeria), mycobacteria
 - Lack of neutrophils/monocytes: High grade bacterial infections (Staph Aureus, G-ive bacteria) and fungi (invasive aspergillus, systemic candidiasis)
 - Complement: C1-4 deficit → G –ive and pyogenic infections, C5 – C9 → Neisseria meningitidis and gonorrhoeae

Defects in Innate Immunity

- *Chronic Granulomatous Disease*: Rare, 2/3rds X linked, 1/3rd AR. Impaired superoxide formation to kill phagocytosed bacteria so form granulomas to encase cells with live bacteria (as in Tb). Recurrent intracellular bacterial and fungal infections, esp S Aureus, Aspergillus. Treatment IFN γ and prophylactic ABs and antifungals
- *Leukocyte Adhesion Deficiency*: LAD 1 & 2. Rare AR. Impaired binding of leukocytes to endothelium. Recurrent bacterial and fungal infections. Absent or deficient expression of the β 2 integrins
- *Chediak-Higashi Syndrome*: AR. Mutation of the lysosomal trafficking regulator gene LYST → giant cytoplasmic granules in neutrophils, monocytes and lymphocytes → ↓function, also ↑bleeding, seizures, albinism, nerve defects, ↓platelets, developmental problems. NK function impaired. Increased infections,
- *Job's Syndrome*: Sporadic. Hyper IgE, defective production of IFN- γ (major activator of neutrophils), recurrent skin and sino-pulmonary abscesses, pruritic dermatitis in the first weeks of life, retained primary dentition. Mutation in STAT3 (signal transducer and activator of transcription) (NEJM Oct 18 2007)
- Inherited defects in TLR pathways: Mutation in NF kB essential modulator NEMO – anhidrotic ectodermal dysplasia with immunodeficiency – prevents activation of NF kB
- IFN γ receptor deficiency: failure to form mature granulomas in response to mycobacterium (→ disseminated infection), opportunistic infections, immune dysregulation (asthma, atopy, GN, vasculitis, RF +ive as TH2 not suppressed). IFN γ secreted by NK and Macrophages, stimulated by IL12, activated macrophages, class switching, ↑TH1, ↓TH2, ↑MHC2 on APCs
- Complement deficiencies: see page 232

Defects in Lymphocyte Maturation

- *Severe Combined Immunodeficiency*:
 - Affects cell mediated and humoral systems
 - Infant presentation with failure to thrive, chronic diarrhoea, opportunistic infections, variable severity, autoimmunity and malignancy risk
 - Caused by any defect in a component essential for T-cell function
 - X linked (60%):
 - Gene mutation of γ chain common to several receptors → abnormal IL2 and IL7 receptor (→ defective T cell maturation) and IL5 receptor (→ defective NK proliferation)
 - Markedly decreased T cells and NK cells, normal or increased B cells, ↓serum Ig as no T cell help ⇒ combined deficiency
 - Treatment: bone marrow or stem cell transplant
 - AR types (40%):
 - Phenotypically similar to X linked version
 - Mutations in the IL-7 receptor (α chain) or a signalling protein JAK3 kinase: Defective maturation of T and B cells
 - Mutations in the RAG1, RAG2, and Artemis genes – encode components of VDJ recombinase: absence of mature B and T cells

- ADA deficiency (Adenosine deaminase, purine catabolism): accumulation of deoxyadenosine → toxic → inhibits DNA synthesis, reduced number of B and T cells (T and B cells more sensitive to this toxicity than other cells)
- PNP (Purine nucleoside phosphorylase) deficiency: toxic effects on immature lymphocytes, mainly T cells
- B cell immunodeficiencies:
 - *X-linked Agammaglobulinaemia*: aka Bruton's Syndrome. Neonatal onset (when maternal IgG runs out at 6 – 9 months, cf CVID which is later). Mutation in B cell tyrosine kinase gene, blocks maturation beyond pre-B cell. No B cells. ↓ in all serum Ig isotypes. Autoimmune disorders develop in almost 20%. Family history in 50%. Treatment: Intragam
- T cell immunodeficiencies:
 - *DiGeorge* (CATCH22): deletion on 22q11, anomalous development of 3rd and 4th branchial pouches leading to thymic hypoplasia (deficient T cell maturation), absent parathyroid, abnormal great vessels. FISH test. Improves as they get older ⇒ ?another site of T cell help
 - Chronic Mucocutaneous Candidiasis: See Autoimmune Polyglandular Syndrome 1, page 76. Defect in AIRE gene → defective thymic education of T cells
- Autoimmune Lymphoproliferative Syndrome (ALPS): genetic defect of Fas or Fas ligand – failure of apoptosis, including during thymic education

Defects in Lymphocyte Function and Activation

- *Combined Variable Immunodeficiencies*:
 - Variable reductions in multiple Ig isotypes with normal or decreased B cells due to defect in terminal differentiation of B cells with absent plasma cells
 - Genetic basis unclear, 1:80,000, most common cause of panhypogammaglobulinaemia. In a small proportion there is a genetic cause identified
 - Impaired antibody responses to infection (pneumonia, bronchiectasis, OM, diarrhoea) and immunisation (useful for testing)
 - Associated with autoimmune disorders (pernicious anaemia, RA – can't make AB to foreign organisms, but can make them to self) and malignant tumours (eg B-cell neoplasia)
 - Diagnosis: ↓IgG, and one or both of IgA and IgM also ↓ (tested with protein electrophoresis and quantitative Ig). Normal B cell numbers, impaired vaccination response
 - Exclude: Drugs (carbamazepine, sulfasalazine; captopril, gold, valproate, NSAIDs can cause low IgA), *myeloma*, *lymphoma*, *nephrotic syndrome*, GI protein loss
 - Treatment: Intragam P, early antibiotics, avoid live vaccines
- *Hyper-IgM syndrome*:
 - Mutation in CD40 ligand on T cell (*X-linked*) or CD40 on B cell (AR rarer) → defective switching of B cells to IgG and IgA, and impairment of APC:T cell interaction
 - Uracil-N-glycosylase (UNG) mutations (AR) – remove uracil residues from Ig genes
 - More severe end of spectrum – present 1 – 2 years with recurrent bacterial infections
 - Diagnosis: flow cytometry (detects CD40L). Normal or ↑ IgM, ↓↓ other Ig's. Normal circulating B cells but no memory cells. Impaired antibody to T cell dependent antigens
 - Treatment: IVIG, bactrim prophylaxis, ?bone marrow transplant
- Selective Ig deficiencies: eg
 - Test with vaccination studies
 - IgA Deficiency (most common genetic deficiency, 1 in 700):
 - Respiratory and GI infections
 - Defect in Ig isotype class switching during B cell activation
 - Sometimes familial, can be 2nd to intrauterine TORCH infection
 - Associated with atopic disease, cow's milk allergy, IBD, Coeliac, Autoimmune
 - Diagnosis: Electrophoresis normal, Ig levels → absent IgA, B-cell count normal
 - Risk of anaphylaxis or serum sickness to unwashed blood products due to anti-IgA to exogenous IgA
 - Treatment: prompt antibiotics. Don't treat with Ig (only has traces of IgA so won't achieve anything)
 - IgG3 deficiency most common subtype deficiency: susceptibility to bacterial infections or no clinical problems. Do vaccination studies to see if they respond. Controversial – what is normal?
- T cell activation defects:
 - Mutations in CD3 and ZAP 70 → ↓T cells or abnormal ratios of CD4:CD8 (normally CD4 > CD8)

- **Idiopathic CD4 T-cell Lymphopenia:** Presents like AIDS. Persisting low CD4 count and repeatedly HIV negative
- **X-linked Lymphoproliferative Syndrome:** unable to eliminate EBV → fulminant disease, development of B cell tumours
- **Bare Lymphocyte Syndrome:** MHC II deficiency: numerous mutations → lack of class II expression, impaired CD4+ development, defective cell-mediated immunity and T cell-dependent humoral immunity. Die in infancy
- **TAP deficiency:** AR, lack of class I MHC expression, mutation in TAP genes → usually transports molecules into the endoplasmic reticulum to bind to MHC1 before expression on cell surface → no MHC1 expression on all cells

Associated with other Inherited disorders

- **Wiskott Aldrich Syndrome:** X-linked, presents with eczema, thrombocytopenia and susceptibility to bacterial infection with polysaccharide antigens (ie encapsulated infection), more severe immunodeficiency with age
- **Ataxia Telangiectasia:** see page 168

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Radiology

- Looking for:
 - Morphologic change in an individual joint
 - The skeletal distribution
- Features:
 - Joint space narrowing, either localised or uniform
 - Erosions: if at the margin then periarticular erosions
 - Marginal osteophytes: bony lip at edge of joint – an adaptive change to ↑ surface area of the joint and therefore ↓ pressure per unit area of joint
 - Subchondral cysts: formed by synovium getting through fissures in the cartilage
 - Subchondral sclerosis: micro-fractures in the subchondral bone → attempted repair → dense white band
 - Periarticular osteopenia: cytokine mediated thinning of the surrounding bone (check other joints)
 - Periarticular soft tissue swelling:
 - Fusiform: in inflammatory
 - Asymmetric: in gout
- Features of different arthropathies:

	Rheumatoid	Primary Osteoarthritis	Gout
Signs	<ul style="list-style-type: none"> Uniform joint space narrowing Erosions Periarticular osteopenia Fusiform soft tissue swelling Can get cysts (call geods in RA) 	<ul style="list-style-type: none"> Localised joint space narrowing (ie not whole joint space). Usually weight bearing portion Subchondral cysts Marginal osteophytes Subchondral sclerosis 	<ul style="list-style-type: none"> Erosions (often para-articular or long way from the joint, may have cave like opening with overhanging margins) Relative preservation of joint space and bone density until late in the disease Asymmetric soft tissue swelling
Distribution	<ul style="list-style-type: none"> Hand: proximal joints All large joints <i>Symmetric</i> Pencilling of distal end of clavicle 	<ul style="list-style-type: none"> Weight bearing joints: hip, knee, C5-C6 (fulcrum for flexing the neck) Distal Hand: DIP, PIP and 1st carpo-metacarpal joint <i>Asymmetric</i> 	<ul style="list-style-type: none"> Any small joints of hands and feet Elbows and knees <i>Asymmetric</i>

- Other arthropathies are variations on this:
 - Secondary osteoarthritis:
 - Looks like OA but not standard (eg uniform joint space)
 - Eg due to anything that weakens cartilage eg previous trauma or infection, metabolic disease (Haemochromatosis – typically MCP joint of 2nd and 3rd finger, Wilson’s disease)
 - If inflammatory but wrong distribution → ?sero-negative
 - Unilateral sacroiliitis: always exclude infection
- Idiot’s rule of thumb for hand arthritis:
 - Rheumatoid: MCP and MTP joints
 - Psoriasis: PIP joints (also DIP)
 - Osteoarthritis: DIP
- DIP joints:
 - Spared in RA and SLE (but ligamentous laxity can given RA like deformity – but normal joints on Xray)
 - Not spared in Gout, OA and Psoriatic arthritis

Blood tests in Inflammatory Arthritis

- Role: diagnosis and some prognostic information
- Gout and seronegative arthritis are not normally positive for rheumatoid factor and auto-antibodies

- Rheumatoid Factor:
 - IgM against Fc portion of IgG
 - Can be tested with the Rose-Waaler titre
 - Positive in:
 - 70 – 90% of RA
 - 75 – 100% of Primary Sjogren's
 - 40 – 100% Cryoglobulinaemia
 - < 40% of SLE
 - 30% of PSS
 - Anti-CCP: See page 247
 - Also in liver disease, sarcoidosis, IPF, *Hep B and C*, TB, leprosy, syphilis, SBE, malaria, *viral infection*...
 - Also found in 5% healthy people, increases with age
- ANA: Antinuclear Antigens
 - Screening test of SLE: present in > 95% at titre > 1:200 – but not specific
 - Present in RA (30%), Sjogren's (68%), PSS (64%), and normal (0 – 2%)
 - Also ↑ with age, other autoimmune diseases, drugs, infections
 - Patterns:
 - Diffuse ANA suggests anti-histone may be +ive (ie drug induced lupus or lupus)
 - Peripheral ANA suggests anti-dsDNA may be +ive (ie lupus)
 - Speckled ANA suggests an ENA may be +ive
 - Nucleolar ANA: suggests RNA polymerase 1 (or others) positive. 40% of PSS (primary Sjogren's Syndrome)
 - Centromere ANA: Anti-centromere: suggests Limited Scleroderma or CREST (rather than diffuse systemic sclerosis)
 - Anti-dsDNA: Present in 70% with SLE and 0.5% without. Specific (ssDNA is not)
 - ENA: Extractable Nuclear Antigens (not all speckled ANA results are due to ENAs):
 - Titres correspond to clinical activity and risk of nephritis
 - Anti-histone: Most common in drug lupus. In 95% of drug SLE (but in this case dsDNA usually negative)
 - Anti-Ro (SSA): Primary Sjogren's, SLE (30%). Associated with 4 % risk of congenital heart block in pregnancy (as is anti-La)
 - Anti-La (SSB): Primary Sjogren's. Always associated with SSA. Found in only 15% of SLE. Usually negative in secondary Sjogren's (ie RA with Sjogren's). if Ro and La positive then ↑risk of renal failure
 - Anti-Sm: 10 – 30% of SLE. Specific. Association with cerebral lupus
 - Anti-RNP: SLE (40%), polymyositis, scleroderma, > 90% in Mixed Connective Tissue Disease – contentious diagnosis – ?just an overlap syndrome involving SLE
 - Anti Jo-1: 25% of polymyositis and dermatomyositis (can occur in interstitial lung disease without myositis)
 - Anti Scl 70 (anti Topoisomerase-1): specific but not sensitive for diffuse systemic sclerosis (rather than limited scleroderma or CREST)
 - Antiphospholipid antibodies (attacks phospholipid on platelets)
 - Occurs in 50% of SLE. Do Lupus anti-coagulopathy test
 - Lupus anticoagulant: More specific. Causes ↑APTT, but causes thrombosis in vivo. Includes dilute Russell Viper Venom Time test (dRVVT)
 - Anti-cardiolipin. More sensitive.
 - Also antibodies against β2-microglobulin – but not commercially available
 - Associated with false positive VDRL test
 - ANCA: Antineutrophil Cytoplasmic Antibodies – directed against certain proteins in the cytoplasmic granules of neutrophils and monocytes. *Associated with some small vessel vasculitis*. Can divide arteritis into ANCA +ive and –ive (although pANCA may also be found in 20% of polyarteritis nodosa):
 - Cytoplasmic anti-neutrophil cytoplasmic antiproteinase-3 antibody (**cANCA anti-PR3**): Diffuse, granular cytoplasmic staining pattern. Specific but not sensitive for Wegener's disease, if active disease > 90% +ive. Not useful for monitoring treatment
 - Perinuclear anti-neutrophil cytoplasmic antibody (**pANCA**): More localised perinuclear or nuclear staining pattern. Main antigen target is myeloperoxidase (**anti-MPO**). Microscopic polyangitis ~ 75% (vasculitis in kidney and lung) and PAN (can occur in RA)

- ANCA negative small vessel vasculitises include Henoch-Schonlein Purpura, cryoglobulinaemic vasculitis, and cutaneous leukocytoclastic vasculitis
- CD4+:CD8+ ratio (normally ~3) ↑ in Polymyalgia Rheumatica

Pharmacology

NSAIDS

- Action: Many! Inhibit PG synthesis by inhibiting cyclo-oxygenase (converts arachidonic acid to PGG₂ and PGH₂):
 - COX-1: present in blood vessels, stomach, kidney (eg might actually help in heart disease – eg aspirin)
 - COX-2: induced during inflammation → PGs (eg Celecoxib/Celebrix – ↑MI risk). Rofecoxib/Vioxx withdrawn due to ↑MI risk
- Effects:
 - Analgesic: Effective against pain where PGs sensitise nociceptors
 - Anti-inflammatory: Reduce vasodilation, oedema, pain. Effect may not be clinically obvious for 2 – 3 weeks
 - Antipyretic: acts in hypothalamus
- Pharmacokinetics: well absorbed, no first pass metabolism (except aspirin), highly protein bound
- Side effects:
 - ↑ Risk in elderly
 - GI: dyspepsia, mucosal irritation, ulceration (relative risk 5 times, ↑↑ if on warfarin, etc). See page 334
 - Renal: Little effect on renal function in normal people. If chronic renal impairment, CHF, gout, or longer T_{1/2} NSAIDs then Na retention and oedema in 3 – 5%
 - Skin: rashes, urticaria, photosensitivity and erythema multiform
 - Other: headache, ↓platelet function → ↑bleeding time, blood dyscrasias (aplastic anaemia with indomethacin and phenylbutazone)
 - Not in pregnancy beyond 20 – 22 weeks (closes ductus). Can ↓follicular rupture and make conception more difficult
- Interactions:
 - ↓ Antihypertensive effect of ACE inhibitors
 - ↓Diuretic action of frusemide and thiazide diuretics
 - ↑Methotrexate levels
 - Not if on anti-coagulants → GI bleed
- Commonly used NSAIDs:
 - Salicylates: Aspirin (not in kids) and diflunisal
 - Propionic Acids (better tolerated and more sensitive for COX-2): Ibuprofen, naproxen (likely no ↑CV risk)
 - Pyrazoles: Phenylbutazone
 - Acetic Acids: Indomethacin (potent, CNS side effects), sulindac
 - Paracetamol (no anti-inflammatory or GI effects)

Other Pain relief

- Amitriptyline: a TCA which in low dose has pain modifying effects
- Colchicine good for lots of inflammatory conditions – gout, pericarditis, etc

Immune Suppressive Drugs

- Glucocorticoids:
 - Prednisone and methylprednisolone
 - Used to induce remission. RCT in RA have shown ↓erosions and ↑long term outcome
 - Trial of controlled release prednisone, taken at bedtime and aimed to achieve peak steroid concentration at the time of the normal circadian peak showed shorted morning stiffness, NEJM 19 Jan 2008
 - When tapering, alternate day dosing → ↓SE
 - SE:
 - Osteoporosis:
 - Dose dependent ↑risk of vertebral fracture and ↑risk of fracture at a higher T score
 - MP pulses may have less BMD reduction

- Weight gain: significant at all doses, 4 – 8% over two years
- Ulcer risk: small risk alone (RR 1.8), RR 12 with NSAID
- Cataracts, glaucoma, DM, metabolic and electrolyte abnormalities, immune suppression → opportunistic infections (dose related ↑risk of pneumonia), HTN, avascular necrosis of bone, myopathy (very rare with doses < 7.5 mg), alterations in mood, psychosis (RR 1.3% at 40 mg), peptic ulcers, thin skin
- Impact on MI risk unknown (although dose ↑lipids and glucose, but ↓inflammation), confounded by indication. RR 2.6 for > 7.5 mg (Ann Int Med 2004; 141:764)
- Cyclophosphamide:
 - An alkylating agent – damages DNA → impairs replication
 - Induction regime eg 2 mg/kg orally
 - Monitor WBC to maintain it above 3 (generally maintains neutrophils above 1.5)
 - SE:
 - Cystitis in ~ 30%, bladder cancer in 6% (may be years after stopping treatment) with > 2mg/kg/d for > 1 year, caused by metabolite acrolein. Drink lots of fluid (dilutes urine). Prophylactic mesna (binds acrolein) may help haemorrhagic cystitis with iv dosing
 - Myelodysplasia (2%) and Leukaemia
 - Gonadal suppression, high risk of permanent infertility in both men and women
 - GI intolerance, hypogammaglobulinaemia, pulmonary fibrosis, oncogenesis, teratogenicity, opportunistic infections, shingles, alopecia
- Mycophenolate mofetil: See page 260. Not in pregnancy
- Azathioprine:
 - Azathioprine → 6-MP → 6-TIMP →
 - 6-TGN → T-cell apoptosis and Rac-1 blockade (level correlates with clinical response, so keen to drive metabolism down this path)
 - 6-MMPR → hepatotoxicity
 - Inhibits purine synthesis and cell proliferation
 - Monitor FBC weekly (catching the rare profound myelosuppression) for 4 weeks then 3 monthly. hepatic and renal impairment
 - SE:
 - Dizziness, vomiting, fever, myalgia, rash, dose related bone marrow suppression, hair loss, infections (including shingles), hepatitis, pancreatitis in 3 – 4 %, risk of lymphoma but still net benefit...
 - Phase 2 metabolism by Thiopurine S-methyltransferase (TPMT): inactivates 6-mercaptopurine (formed non-enzymatically from azathioprine). Homozygotes for inactive TPMT (about 1 in 300) → severe or fatal pancytopenia. Homozygotes for fully functioning alleles → reduced effect. Investigation for TPMT or drug level monitoring not well established
 - *OK in pregnancy, not in breast feeding*
 - 6MP also metabolised by xanthine oxidase – *potently inhibited by allopurinol* (so avoid it) → toxic levels of 6MP and azathioprine. Experimental interest in allopurinol to shunt to 6-TGN

Disease Modifying Anti-Rheumatic Drugs (DMARDs)

- Aim: to suppress inflammatory activity → ↓destructive changes (NSAIDs reduce inflammation but don't act on the pathway that leads to joint destruction)
- Indicated for patients at an early stage with high markers of disease activity ⇒ don't wait for nodules or erosions
- Combination therapy is usually better
- Effect:
 - Suppress inflammatory activity
 - Reduce the need for NSAIDs and corticosteroids which have greater potential toxicity
- First line agents (high efficacy especially in combination, low toxicity, trials have demonstrated a clear batting order):
 - Methotrexate
 - An “antimetabolite”. Inhibits dihydrofolate reductase, impairing folate pathway and causing DNA damage, especially in the S phase of the cell cycle.
 - Action: ↓IL-1, ↑IL-10, ↓neutrophil chemotaxis
 - Start at 7.5, titrate up to 20 mg weekly: Can give sc to avoid GI effects
 - SE: nausea, bone marrow suppression, GI ulceration, teratogenic, stomatitis, reversible dose related LFT impairment, nodules. Rare: pneumonitis (much greater risk if concurrent

leflunomide, was it rheumatoid lung disease rather than drug SE?), irreversible liver toxin (→ fibrosis or cirrhosis – biopsy if persistent LFT derangement). *No increased infection risk*. Also mood disturbance (tearful, nightmares)

- Not with cotrimoxazole (folate antagonist too)
- Give folic acid 5 – 10 mg/wkly – reduces mouth ulceration (no conclusive evidence that it reduces effectiveness)
- Monitor CBC, LFTs, Cr
- Cleared by glomerular filtration and tubular excretion → ↑SE in renal failure. At high dose (ie oncology not rheumatology) → crystallises in renal tubules → renal damage, alleviated by urine alkalinization
- Rescue treatment if pancytopenia: folinic acid (a derivative of tetrahydrofolic acid) which occurs in the folate pathway after the step inhibited by methotrexate
- Leflunomide:
 - Metabolised to an active metabolite that inhibits dihydroorotate dehydrogenase – essential in the pyrimidine pathway. Inhibits proliferation of T lymphocytes
 - Most common immunosuppressive agent in RA (according to Harrison's), can be used in conjunction with Methotrexate
 - SE: renal impairment, bone marrow suppression, hepatotoxicity mainly in first 6 months, paresthesias, rashes, HTN, ↑lipids. Not in liver impairment or pregnancy
 - Effective contraception essential (including for men up to 3 months following cessation). Protective against pneumonia.
 - Detectable in the body for years after cessation. Enterohepatic circulation. If adverse effects or pregnancy planned then “wash-out” with cholestyramine (8 gm tds for 11 days)
 - A lot like methotrexate in terms of efficacy and toxicity
- Sulphasalazine (Salazopyrin): Pro-drug for mezasalazine (Pentasa). Poorly absorbed. ↓synthesis of inflammatory mediators. Start low, increase to 2-3g per day. Best tolerated and most often used. Effect after 3 – 6 months. SE: nausea, rashes, ↓sperm count, hepatitis, oral ulcers, rarely: blood dyscrasia, Stevens-Johnson, neutropenia, monitor CBC and LFTs. OK in pregnancy
- Antimalarials: Hydroxychloroquine: weak disease modifying drug, doesn't stop periarticular osteopenia. SE: nausea, rash, headache, tinnitus. Rarely: bone marrow suppression, corneal & retinal damage. Monitor: Cr and 6 – 12 monthly ophthalmological review. Chloroquine more toxic. OK in pregnancy
- Others:
 - Gold: Sodium Aurothiomalate / Myocrisin. Similar efficacy to Sulphasalazine/methotrexate but more toxic. When it works it works well. Action: accumulates in macrophages. SE: rash, thrombocytopenia, nephrotic syndrome, proteinuria. Not with allopurinol, SLE, breast feeding, liver/renal disease. Monitor CBC, Cr, Urine dipstick for protein
 - D-Penicillamine (antifibrotic – prevents collagen cross linking): Some benefit but don't alter progression of radiological changes. Older drug with poorer evidence. SE: ↓marrow, proteinuria, ↓taste, oral ulcers, myasthenia, Goodpasture's

Biologic DMARDs

- See Internal Medicine Journal 2004: 687-693
- Don't combine biologics: no ↑ in effect but ↑toxicity
- General nomenclature:
 - imab = chimeric antibody (eg humanised constant region, mouse variable region, aim to reduce antibodies to the drug and can use it many times)
 - umab = humanised antibody
 - cept = fusion protein
- Tumour Necrosis Factor Inhibitors:
 - TNFα generally produced by macrophages 2nd to lymphocyte stimulation → ↑proinflammatory cytokines, adhesion molecules, acute phase response, fibroblast response, ↑epithelial permeability
 - Randomised trial evidence in RA, Crohn's, Psoriatic arthritis, psoriasis, juvenile inflammatory arthritis and Ankylosing Spondylitis. No RCT evidence in SLE (and negative case series) nor vasculitis
 - Agents:
 - Infliximab and Adalimumab bind to membrane bound TNFα on the lymphocyte. This induces apoptosis of activated T lymphocytes

- **Infliximab:** recombinant chimeric mouse/human (75% human) monoclonal Ab to TNF α . Binds to both soluble TNF and cell bound TNF (which \rightarrow cytolysis). 3-5 mg/kg *iv infusion* given at 0, 2, 6 weeks, then 2 monthly. Antibodies to infliximab form in 15% \rightarrow infusion site reactions and \downarrow response (?significance). Incidence of antibodies reduced with regular q8w infusions, and pre-medication with hydrocortisone 200 mg
- **Adalimumab** (100% human MAb) 40 mg **sc** biweekly. *Only one funded in NZ.* Annual treatment cost \$25,000. For RA, must have severe disease and have failed all other medical therapy, including methotrexate, triple therapy, cyclosporin or leflunomide
- **Etanercept:** soluble human TNF receptor fused to IgG1 – TNF receptor antagonist, blocks TNF α and β , doesn't cause cell destruction as it doesn't bind to cell bound TNF – only soluble TNF (?the reason it's not effective in IBD), 25 mg twice weekly by subcutaneous injection
- Toxicity:
 - Injection site or infusion related reactions
 - Infection: Not as bad as corticosteroids (hazard ratio 2.0 vs 1.4)
 - Don't initiate if active infection (including chronic such as bronchiectasis)
 - Common infections the most common (more than TB): Staph, strep, E coli. Alters the presentation of infections – such as masking systemic features \rightarrow late presentation. Use standard empirical treatment (ie don't treat with immunosuppressed regimes)
 - Reactivation of Tb: Most in the first few months, infliximab > etanercept, relative risk 4.1, not associated with primary Tb. Often early and often extra-pulmonary. Screen with a good history, tuberculin skin test, CXR. If latent TB (strong history or screening test positive) then isoniazid for 4 – 6 weeks first then for 9 months (ie latent TB is not a contraindication – it is unrecognised TB that's the problem). If active TB then standard chemotherapy for 2 months first
 - Also Listeriosis, aspergillosis, candida, CMV, PCP, cryptococcus, Nocardia, atypical mycobacteria – especially with prolonged T cell suppression (> 12 months) – an HIV like state
 - Combination with methotrexate increases the risk
 - No live vaccines. Consider antifungal prophylaxis and screening (CMV)
 - If HBV positive (ie HBsAg and HBcAg but low viral load) then possible reactivation. *Treat pre-emptively with Lamivudine*
 - Infliximab NNH for serious infection = 59.
 - Non-melanoma skin cancer? No definite increase in solid tumours observed but prefer not to prescribe if history of malignancy within the last 5 years. Lymphoma possibly related to RA itself, not the TNF blockers
 - Rare hepato-splenic T cell lymphoma
 - Rare demyelinating disease (eg optic neuritis)
 - CHF (doesn't worsen existing CHF?)
 - Pancytopenia
- Issues:
 - Efficacy: fail to achieve substantial improvement in 50% – blocking TNF α is not the whole story
 - Multiple Sclerosis: Lenercept (like etanercept) was used in an MS trial and made them worse
 - Induction of ANA: Infliximab and etanercept associated with induction of ANA but drug lupus rare. Discontinue treatment and it resolves. Doesn't trigger full blown SLE. Avoid in SLE
 - Antibodies: Anti-chimeric molecule antibodies (HACA) develop to Infliximab in 40% RA and 61% Crohn's. Predisposes to transfusion reactions. *Is associated with \checkmark efficacy* – but not in RA. Largely prevented by concurrent use of methotrexate
- Paradoxical effects of TNF:
 - TNF in psoriatic arthritis can precipitate psoriasis
 - Frequency of flares of iritis may increase, especially for Etanercept
 - Low but variable incidence of IBD flare (Etanercept not effective for treatment of IBD)
- B cell depleting agents: **Rituximab:**
 - Chimeric human-mouse monoclonal antibody to CD20 (present on all pre-plasma B cells). Depletes 90% of mature B cells in 3 months – leaves plasma cells and pre-B cells
 - Leads to antibody dependent cell mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) \rightarrow induction of apoptosis
 - B cells are a key driver in the immune response, act as APCs to T cells, costimulation, etc
 - Primary use thus far is TNF failure with concurrent methotrexate – may develop first line use

- Treat at 0, 2, weeks, 6, 12, 24 months. SE transfusion reactions that can be controlled with steroids
- No material increase in infections. Little long term data, treatment protocols unclear
- Ustekinumab: monoclonal antibody against IL 12 and 13 effective in treating moderate to severe psoriasis (not arthritis) with 75% improvement in 67% (45 mg) vs 3% placebo (PHOENIX1 trial, Lancet 17 May 2008). 12 weekly dosing
- Coming: IL 15, IL 12, IL 32....

Vaccination

- Infectious disease common cause of morbidity: infection kills as many as SLE disease itself in the first 5 years (often have functional asplenism), RA infection deaths 2 – 5 times matched controls, infection causes 1/3 deaths in vasculitis
- Usual infections rather than opportunistic
- DMARDs – no increased risk except steroids and leflunomide (in respiratory infections)
- Vaccine safety:
 - Generally safe: ??↑risk of flare following Hep B
 - Avoid live vaccines if steroids > 10 mg or > 1 month or if HIV (MMR and Varicella if CD4 > 200, never polio or BCG)
- Efficacy (small studies only):
 - Methotrexate may modestly impair pneumococcal response
 - TNF may impair influenza modestly
 - In SLE, slight decrease in response to influenza and pneumonia, good response to HIB and Meningococcal
- Varicella: check immune status before starting on immunosuppression, vaccinate patient and family members prior to initiation
- Measles: Iv Ig if contact with an infected person

Differentials for Arthritis

- Assessment:
 - Disease Activity Score (common in European trials)
 - Health Assessment Questionnaire (common in US trials)

Causes of Monoarthritis

- Acute Monoarthritis:
 - Septic arthritis:
 - Either haematogenous or following penetrating injury
 - Usually G +ive staph. Consider Neisseria gonorrhoeae, (tenosynovitis, dermatitis and polyarthralgias without purulent arthritis), Mycoplasma hominis, ureaplasma urealyticum, mycobacteria including Tb
 - Aspirated WBC is commonly > 100,000 but can be as low as 25,000 (cf crystal arthropathy where it's ~ 15 – 30,000)
 - Gram stain is 50 – 70 sensitive, except for gonococcal where it is < 10%
 - The “best” approach for knee aspiration is the medial side, directly under the middle of the patella
 - Traumatic
 - Gout, pseudogout
 - Haemarthrosis (eg haemophilia)
 - Sometimes seronegative spondyloarthritis
- Chronic monoarthritis:
 - Chronic infection (eg Tb)
 - Osteoarthritis
 - Seronegative spondyloarthritis
 - Metastasis

Causes of Polyarthritis

- Acute polyarthritis
 - Infection: viral (mumps, rubella, EBV, etc), bacterial
 - Rheumatic fever
 - Onset of chronic polyarthritis
 - Drug allergies

- Chronic polyarthritis:
 - Rheumatoid arthritis
 - Seronegative spondyloarthritis
 - Primary osteoarthritis
 - Gout, pseudogout or hydroxyapatite arthropathy
 - Connective tissue disease (eg SLE)
 - Infection (eg Tb)

Differential by Distribution

- Inflammatory:
 - Peripheral, symmetrical, small joint polyarthritis:
 - RA
 - Lupus and Connective Tissue Diseases (non-deforming and non-nodular)
 - Psoriatic arthritis (including but not limited to Arthritis Mutilans)
 - Asymmetrical, large joint, oligoarthritis, possibly with spinal disease: Sero-negative spondyloarthropathies:
 - Ankylosing Spondylitis
 - Reactive Arthritis and Reiter's Disease
 - Psoriatic Arthritis
 - Arthritis of IBD
 - Acute inflammatory mono or oligo arthritis: septic arthritis or gout
- Non-inflammatory:
 - Osteoarthritis: weight bearing joints or hands
 - Soft tissue or locomotor pain syndromes
- Sacroilitis: occurs in Ankylosing Spondylitis, Reiter's Syndrome, Crohn's Disease, Chronic Polyarthritis

Causes of Arthritis and Nodules

- Rheumatoid arthritis
- SLE (rare)
- Rheumatic fever (very rare)
- Granulomas, eg sarcoid (very rare)

Raynaud's Syndrome

- Episodic digital ischaemia, precipitated by cold or emotion
- Fingers ache and go pale → blue → red/purple (pain most severe in this stage, during reperfusion)
- May be:
 - Idiopathic: Raynaud's disease
 - Associated with underlying cause (Raynaud's phenomenon): Scleroderma, SLE, RA, arteriosclerosis, leukaemia, drugs, etc. *Not* polyarteritis nodosa
- Keep warm, stop smoking, try Ca channel blockers (eg diltiazem), nitrate pastes,
- If severe (ie ischaemic ulcers) then bosentan and iloprost may have value, surgical sympathectomy
- On xray may have terminal osteolysis second to ischaemia
- Positive anti-centromere indicates highest risk of development of a Raynaud's related disease

Rheumatoid Arthritis

- See BMJ 21 Jan 2006
- Persistent, symmetrical, deforming, peripheral arthropathy
- Epidemiology:
 - Peak onset: 4th decade. Usually more aggressive if over 60 at onset
 - Prevalence: 1 – 3%
 - Female:male = 3:1
 - After 10 years 50% are unemployed due to disability
 - Average life expectancy reduced by 3 – 7 years (mainly due to ↑atherosclerosis)
 - Smoking associated with worse outcome (if CCP positive)

Pathogenesis

- Microbial agent initiates the disease: a suspect is EBV, plus other "classic" arthritogenic viruses

- Genetic predisposition:
 - ↑monozygotic twin concordance, HLA DR4 or *DRB1 0404* association, HLA β1 alleles
 - *PTPN22* (gene on tyrosine kinase involved in activation of T and B cells). Lymphoid specific phosphatase – potent inhibitor of T cell activation. Missense mutations of *PTPN22* leading to ↓function are strong predictors of RA
 - PADI: together with smoking → ↑citrullination
 - STAT4 (as opposed to STAT3 in IBD, Ank Spond, and Job Syndrome): on the JAK-STAT proinflammatory pathway
- Presentation of (unknown) antigen to CD4+ T-helper cells + plasma cells + macrophages + Toll like receptors (amplifying the response) → adhesion + trafficking of leucocytes → cytokine-mediated synovial neutrophilic exudate (including *IL 17*) + ↑vascularity → cartilage-degrading enzymes (including *aggrecanase*) + fibrosis + panus formation (inflamed synovium + fibroblasts → collagenase) + ↑osteoclastic (via RANKL) and chondrocytes activity + demineralisation + ligament and tendon laxity/damage
- Inflammatory cells in panus: dendritic cells, T cell, plasma cell, B cell, osteoclast, fibroblast, mast cell (everything drives everything)
- Polymorphs mainly in synovial fluid
- Erosions:
 - Caused by osteoclasts
 - Fibroblast and T cells secrete RANKL (in normal bone it's osteoblasts that do this)
 - This is recognised by RANK (a receptor) on osteocyte precursors. Activating the receptor causes osteoclast maturation
 - OPG (osteoprotegerin): is a natural inhibitor of RANK – it binds to RANKL and prevents activation of RANK
- → Painful, unstable, disrupted joint (eg subluxed, deformed, etc)
- Systemic symptoms from ↑IL-1, TNF and IL-6 (monocyte derived). Anti-inflammatory counter regulatory cytokines are also present (soluble TNF receptor, IL-10, IL-1 receptor antagonist) – but proinflammatory predominate
- Autoimmunity to type 2 collagen can be demonstrated in most patients with RA
- Implicated mediators are cytokines: TNF, IL-1, IL-6, IL-15, interferon-α, growth factors, proteases, elastases

Presentation

- Diagnosis: American College of Rheumatology Guidelines (1987): 4 or more of 7 criteria:
 - Morning Stiffness: > 1 hour before maximal improvement
 - Arthritis of 3 or more of 14 joint areas observed simultaneously: Left or Right PIPs, MCPs, MTPs, wrist, elbow, knee, ankle
 - Arthritis of hand joints: wrist, MCP or PIPs
 - Symmetric arthritis: involvement of the same joints on both sides of the body
 - Rheumatoid nodules
 - Positive RF (ie *don't* have to be RF positive)
 - Radiographic changes typical of RA on posterior hand and wrist films
- Presentation:
 - Common: Swollen, painful, stiff hands and feet, especially in the morning. Progresses to larger joints
 - Less common:
 - Palindromic: relapsing and remitting monoarthritis of different large joints
 - Persistent monoarthritis (especially the knee)
 - Systemic illness: ↓weight, pericarditis, pleurisy
 - Vague limb girdle aches
 - Sudden-onset widespread arthritis
- Pattern of involvement:
 - Usually symmetrical
 - Most RA involves:
 - PIP and MCP joints and wrists (DIP spared) in the hands
 - Tarsal and MTP joints in the foot. Hallus valgus and lateral deviation and dorsal subluxation of the toes
 - Also involves:
 - Elbows

- Shoulders (eg Pencilling – erosion of distal end of the clavicle)
- Small joints of upper cervical spine: Atlanto-Axial instability: anterior subluxation of C1 on C2 with cervical flexion due to erosion of the transverse atlantal ligament → threatens spinal cord
- Lumbo-sacral region usually spared
- Hips
- Knees
- **Not:** DIP joints or thoracolumbar spine
- Deformities:
 - Initially sausage-shaped fingers and MCP joint swelling
 - Ulnar deviation and volar subluxation (partial dislocation) of the fingers
 - Fingers: Swan Neck and boutonniere (buttonhole)
 - Z deformity of the thumb: hyperextension of the IP joint and fixed flexion and subluxation of the MCP joint
 - Subluxation of the wrist, with prominent radial head
- Extra-articular involvement:
 - Nodules: subcutaneous central zone of fibrinoid necrosis surrounded by palisading histiocytes and fibroblasts. May occur in viscera, including heart, lung and GI. May ↑ with methotrexate
 - Anaemia
 - Lymphadenopathy
 - Vasculitis affecting nearly any organ
 - Carpel Tunnel Syndrome (early manifestation)
 - Multifocal neuropathies (= Mononeuritis Multiplex): Sequential, multifocal, random involvement of non-contiguous peripheral nerve trunks (there are other causes besides RA – See page 174 and 181)
 - Splenomegaly
 - Eyes (< 1%): episcleritis, scleritis, keratoconjunctivitis sicca
 - Pericarditis. May → chronic constrictive pericarditis
 - Pulmonary fibrosis (common in men), pleural disease (usually asymptomatic)
 - Amyloidosis
 - Osteoporosis: common, and aggravated by steroids
 - **Not** glomerulonephritis

Investigations

- Bloods (see also page 238):
 - No tests are specific
 - Rheumatoid factor
 - +ive in 75%. Likelihood ratio +ive 4.8
 - Poor PPV – however high titres have prognostic significance in association with nodules and extra-articular manifestations
 - Anti-CCP (Cyclic citrullinated peptides):
 - Generated within the synovium – immune response to self peptides which have been citrullinated
 - Predicts development of RA in early undifferentiated arthritis
 - Correlated with aggressive/erosive disease
 - More specific than RF, 4% less sensitive than RF (ie it misses some genuine RA). Likelihood ratio +ive 15
 - Usually in RF +ive patients (although sometimes in RF negative)
 - Found in ~1.5 % of normal individuals – most of whom won't develop RA
 - May be present for up to 10 years before symptoms
 - A new CCP2 test coming – more sensitive
- X-ray:
 - 80% normal at presentation. MRI can detect changes in over 80%.
 - High resolution US can detect synovitis and erosions in 7 times more patients than xray
 - Erosions are typically “moth-eaten” – scruffy and subtle, compared to the sharply demarcated erosions seen in gout

Progression

- Greatest damage occurs in first 4 – 5 years
- Predictors of structural damage/severity:

- MRI score of the wrist, assessing erosions, bone oedema, synovitis and tendonitis. High score → significantly higher risk or erosions at xray after 2 years
- High CRP and ESR
- RF (correlated with extra-articular manifestations) and anti-CCP
- Swollen joint count (> 20 inflamed joints)
- High disability score at presentation
- Presence of HLA-DR1 or DR4
- Indicators of (current) activity:
 - High CRP and ESR
 - Swollen joint count

Treatment

- Treatment: Interdisciplinary
 - Regular exercise
 - Physiotherapy to maintain muscle strength and joint mobility
 - Occupational therapy
 - Household and personal aids (eg wrist splints)
 - Intra-lesional steroids
 - Surgery: hips, knees, shoulders *for relief of pain and reduction in disability*
 - CVD risk factor modification
 - Some evidence of symptomatic relief from substituting omega-6s with omega-3s
- Other drug treatment:
 - Bone protection
 - CVS risk management – they're most likely to die from CV causes. RA is an independent risk factor

Drug Treatment

- Early treatment → less destructive disease course. Tight Control for RA Study (TICORA) showed marked improvement in signs and symptoms in the aggressive intervention arm
- Up to 30% are not adequately controlled with currently available DMARDs and TNF α inhibitors
- Need to risk stratify:
 - Less aggressive course likely – start with methotrexate monotherapy
 - More aggressive course likely:
 - Aggressive early disease, failed DMARDs, can't tolerate DMARDs, persistently elevated swollen joint count
 - Start on triple therapy with a view to early biologics
- NSAIDs (eg ibuprofen, naprosyn): To control inflammation/pain. Inhibit COX → ↓prostaglandins. Don't affect cytokines ⇒ no impact on progression. COX-2 → ↓GI side effects but ↑CV risk
- DMARDs: Disease modifying drugs:
 - See Disease Modifying Anti-Rheumatic Drugs (DMARDs), page 241
 - Combination more effective than single agent. All have side effects, monitoring essential. All can cause rash
 - Methotrexate: Gold standard
 - Probably drug of choice if risk factors for bony destruction in RA
 - Takes several months to work but more rapid onset than other DMARDs – maximal improvement by 6 months
 - Lower drop out rate in RA
 - Effective in 75% with reduction in joint counts
 - Flare with discontinuation
 - Improved clinical activity, function status, radiological progression and mortality
 - Usual drug to be combined with biologics
 - Leflunomide (Arava): Effective alone or in combination with sulphasalazine and hydroxychloroquine, with methotrexate, with cyclosporin (less commonly used)
 - Triple Therapy: Methotrexate in combination with two of: sulphasalazine, prednisone, azathioprine, gold or hydroxychloroquine. “Step up” approach – add them one at a time. “Step down” approach – start with everything (the most common)
- Glucocorticoid Therapy: To control flare-ups. Can reduce erosions if given in early disease. Need to keep dose low (ie 7.5 mg/day) – but due to symptomatic improvement patients often want more.

Pulses to induce remission. SE: ↓bony density, cataract, fluid retention, peptic ulcers. ↑effect of methotrexate

- Biologics (see page 242):
 - TNF α antagonists (monoclonal antibodies and receptor fusion proteins):
 - 60% of patients respond
 - Rapid onset 1 – 2 weeks (cf minimum 6 weeks with DMARDS)
 - No difference in efficacy between the different agents
 - Acceptable toxicity
 - Dramatically inhibit structural damage. ?prevents activation of RANK ligand → ↓bony damage
 - Compared to methotrexate, causes a similar reduction in signs and symptoms but halves structural progression. Combined therapy → 80%↓ in damage cf methotrexate alone. ?because patients on DMARDs alone still have measurable inflammation even when in remission
 - Recent study showed clear benefit in using biologics and high dose steroids as initial therapy
 - Methotrexate + etanercept better than methotrexate alone for early RA (Lancet 2 August 2008) – but in patients with a high disease burden. No long term outcomes available (ie would the difference be maintained at 10 years)
 - If no benefit from TNF blockade then anti-B cell therapy (Rituximab) may have benefit (principally used in SLE) in conjunction with methotrexate. Approved for RA if failed TNF blockers. Optimal regime not established. Currently repeated at 6 monthly intervals when B cells return
 - Modulating T cell activation: **Abatacept**/Belatacept (CTLA-Ig):
 - Fusion protein of CTLA4 and Fc portion of IgG1 – (see page 227)
 - 14 infusions per year
 - Inhibits T cell co-stimulatory pathways resulting from T-Cell expressed CD28 and the CD 80/86 on APCs
 - Used in TNF failures in RA with concurrent methotrexate. ATTAIN Study. Similar outcomes to Rituximab. No added benefit and more serious infections in combination with TNF blockers
 - FDA approved but not in use in NZ or Australia. No long term data
 - If TNF blockers have been tried and failed, rituximab preferred by NICE on the grounds of cost (£12,000 per QALY as opposed to £37,000 for abatacept – Lancet, 3 May 2008)
 - **IL-6** receptor inhibition with **tocilizumab**:
 - Charisma trial: Phase 3 trial in RA over 16 weeks – symptomatic improvement in 59% patients compared with 26% in placebo arm. ↓MRI progression. NEJM 22 March 2008
 - IL-6 drives many inflammatory processes. Produced by monocytes, T and B cells, fibroblasts. Receptors on megakaryocytes, haematopoietic stem cells, osteoclast, B cells, hepatocytes, T cells, mesangial cells, etc
 - Levels proportional to CRP and disease severity
 - Used for multiple DMARD failures – not fully tested yet
 - SE: significant transaminitis (11% have ↑LFTs). ↑Total and HDL cholesterol – net effect unknown (?offset by ↓↓CRP)
 - **IL-1**-neutralising agents: **Anakinra**. Recombinant. Blocks binding of IL-1 β and IL-1 α to IL-1 receptor. Improves signs and symptoms, ↓disability, slow radiological progression SE: injection site reactions, more serious infections. Less effective than TNF blockers and rarely effective if TNF blockers ineffective (Cochrane 2009). No added benefit in combination with TNF blockers. Good for Juvenile RA and Still's Disease (driven by IL-1)
 - RANKL Blockade: Denosumab: significant reduction in erosions but no effect on clinical disease (ie get inflammation but bones don't dissolve). Safe as placebo. Not yet in clinical use
 - What doesn't work: CD4 T cell depletion – they're very important in the pathogenesis but while depletion reduces CD4 cells in the serum, ?it doesn't affect CD4 cells in the synovium
- Immunosuppressive Therapy:
 - Cyclosporin (SE nephrotoxicity) and cyclophosphamide (SE malignancy)
 - Shown to be effective in RA, similar to DMARDs but more toxic
 - May be necessary in RA vasculitis
 - Use if clearly failed DMARD
- Gold occasionally used, cyclophosphamide and penicillamine are now rarely used
- Treatment in Pregnancy:
 - Aim for well controlled remission before trying to get pregnant
 - Hydroxychloroquine OK. Azathioprine OK – but less effective – great for lupus, less so for synovitis
 - Oral steroids OK – but minimise dose to ↓gestational diabetes

- Salazopyrin OK but may ↓fertility
- Intra-articular steroids useful
- No methotrexate or Leflunomide in pregnancy or breast feeding
- No evidence for biologics in pregnancy – only case series saying it's OK (but only the positive ones get written up and published)

Juvenile Rheumatoid Arthritis

- = Arthritis beginning at or before 16 years of age (usually early childhood)
- = Still's Disease
- Signs: High, swinging, early evening fever, pink maculo-papular rash, arthralgia, arthritis, myalgia, generalised lymphadenopathy
- Number of different types:
 - Oligoarthritis (persistent): asymmetrical, affecting 4 or fewer joints, especially wrist, knees, ankles. Usually remission in 4 – 5 years
 - Oligoarthritis (extended): Oligoarticular onset progressing to > 4 joints
 - Polyarticular JRA: Usually in teenagers progressing to widespread joint destruction, especially hands (less so the DIPs)
 - Extra-articular involvement can include: pericarditis, myocarditis, pulmonary fibrosis, glomerulonephritis, uveitis and growth retardation
- Differences from Adult RA:
 - Oligoarthritis is more common
 - Systemic onset is more frequent
 - Large joints affected more than small joints
 - Rheumatoid nodules and rheumatoid factor are usually absent
 - ANAs often positive
- Treatment:
 - Low dose NSAIDs/paracetamol (Aspirin: beware of Reyes Syndrome)
 - Corticosteroids
- Prognosis: variable: up to 50% have long term disability
- Completely different disease entity to Juvenile Spondyloarthropathies – although clinically may overlap. Enthesitis common

Spondyloarthropathies (Seronegative Arthritis)

- Rheumatoid factor is negative – but exclude seronegative RA
- Clinical overlap between the conditions
- Have in common:
 - Inflammatory back pain: Defined by at least two of the following:
 - Morning stiffness > 30 minutes
 - Improvement with exercise not by rest
 - Awakening with pain only in the 2nd half of the night
 - Alternating buttock pain
 - Involvement of spine and sacroiliac joints (= axial arthritis): true synovial joint is the anterior-inferior half, projecting over the lower 1/3rd on an AP xray of the pelvis. Graded from 0 (Normal) to 4 (advanced). *Radiologic progression is very slow* (ie don't xray any more frequently than every 2 years)
 - Usually asymmetrical large joint mono or oligo-arthritis:
 - 4 or fewer inflamed joints
 - Asymmetric
 - Disease activity assessed by number of tender/swollen joints and acute phase reactants (ESR, CRP)
 - Inflammation then calcification of tendon insertions (enthesopathy). Scoring systems (eg Maastricht Enthesitis Score tests tenderness at 13 sites) – pain doesn't correlate well with objective disease
 - Dactylitis: Diffuse fusiform swelling of a toe or finger due to inflammation of the flexor tendon sheath. Most common in psoriatic arthritis and reactive arthritis, also in sarcoidosis and gout
 - Extra-articular manifestations:
 - Uveitis: unilateral, acute, eye pain, photophobia, blurring of vision with redness at the scleral-corneal junction

- Skin: psoriasiform lesion: keratoderma blenorrhagica, circinate balanitis
- Enteric mucosal lesions: up to 60% have a colonic lesion, only 10% have clinical disease
- Aortic regurgitation
- Upper zone pulmonary fibrosis
- Familial tendency: HLA-B27 +ive predisposition (8% in the general Caucasian population)
- If type not clear then classified as ‘*Undifferentiated spondyloarthropathy*’. Also called axial arthritis. More than 50% will evolve into AS. Infliximab has shown efficacy in early disease

	AS	Reactive	Psoriatic	Enteropathic
Sex	<i>M > F</i>	M = F	<i>F > M</i>	F = M
Age of onset	~ 20	Any	Any	Any
Uveitis	++	+	+	+
Conjunctivitis	-	+	-	-
Peripheral joints	Lower>Upper	Lower>upper	<i>Upper>lower</i>	Lower>upper
Sacroiliitis	<i>Always</i>	Often	Often	Often
HLA-B27	95%	80%	20 – 50%	50%
Onset	Gradual	<i>Sudden</i>	Variable	Gradual
Symmetry spinal	+	-	-	+

Back Pain Red Flags

- Age > 50 years
- History of cancer
- Temperature > 37.8
- Constant pain: day and night
- Weight loss
- Significant trauma
- Features of spondyloarthropathy
- Neurological deficit
- Drug or alcohol abuse
- Anticoagulants
- Corticosteroids
- No improvement over 1 month
- Possible cauda-equina syndrome (saddle anaesthesia, recent onset bladder dysfunction, severe or progressive neurological deficit)

Ankylosing Spondylitis

- = Chronic systemic inflammatory disorder of the axial skeleton, affecting SI joints and spine
- Ankylosing = fibrous replacement of the joint → bony fusion
- Epidemiology:
 - Prevalence: 2 – 5 per 1,000 males. Men have more progressive disease
 - Men more common and present earlier (6:1 at 16 years, 2:1 at 30 years)
 - Onset usually between 15 – 40 years. If you’re going to get it, you’ll have symptoms by 45
- Clinical presentation:
 - 75% first present with insidious onset of dull back ache, worse at night, improved by exercise
 - Morning stiffness, backache, sacroiliac pain, loss of spinal movement
 - Leading to flattening of lumbar spine, thoracic kyphosis, neck hyperextension
 - Fatigue common
 - Average delay in diagnosis is 5 – 8 years, females longer than males
 - Most common pattern is persisting symptoms with superimposed flares (46%), some have no symptoms between flares (21%), and some have complete loss of inflammation in time (7%)
- Modified New York Criteria for Definite AS (eg used for original TNF studies):
 - Radiographic findings of bilateral sacroiliitis ≥ grade 2, or unilateral ≥ grade 3, and at least one of
 - Inflammatory back pain
 - Reduced spinal mobility in 2 planes
 - Reduced chest expansion
- Distribution:
 - Sacroiliac joints and spine (lumbar to start with, C-spine later):
 - Bilateral sacro-iliac joint tenderness
 - Tenderness of the lumbar vertebrae

- Loss of thoracic kyphosis and lumbar lordosis
- Hips (30%), also knees and shoulders
- Peripheral arthritis infrequent
- Other features:
 - Commonly:
 - Enthesitis secondary to inflammatory granulation tissue
 - ↓Bone mineral density of the spine and proximal femur
 - Iritis/Anterior Uveitis (25 – 30%): unilateral, acute, painful, with photophobia and blurred vision. To test: shining light in opposite eye causes pain in the affected eye
 - Costochondriasis + chest pain referred from thoracic vertebrae
 - Chest wall rigidity → ↓VC (↓chest expansion)
 - Plantar fasciitis
 - Inflammation in colon/ileum. Frank IBD in 5 – 10%
 - Psoriasis in 10%
 - Osteoporosis – half of AS patients have a T score < -1.0 SD, mainly affecting thoracic spine, with RR for vertebral fractures increased 6 – 8 fold. Fracture risk of lower limbs normal
 - Rare:
 - Neurological involvement: secondary to spinal fracture (eg C-spine), atlanto-axial subluxation, cauda equina syndrome. 10% lifetime risk of fracture
 - Amyloidosis
 - Carditis and aortic regurgitation due to fibrosis of the aortic valve (can also affect AV bundle → arrhythmias)
 - Apical lung fibrosis (rare)
- Pathogenesis:
 - No specific event or exogenous trigger identified – ?enteric bacteria
 - Antibody complexes cause synovitis, enthesopathy (including tendon attachment calcification) → capsular ossification, ankylosis (bony fusion) of the sacroiliac joint, inflammatory arthritis of the synovial joints in the spine and ossification of spinal ligaments
- Predictors of severe disease:
 - Juvenile onset
 - Poor response to NSAIDs
 - Dactylitis, oligoarthritis
 - Poor social supports
 - Smoking
 - *Hip arthritis*
- Assessment:
 - BASDI: Bath Ankylosing Spondylitis Disease Activity Index – patient self-report questionnaire
 - Measuring spinal mobility:
 - Early restriction in lateral flexion of the spine – test by seeing how far they can slide their hand down the side of their leg without bending forward. Measure fingers to floor when upright, and with maximal lateral flexion. Normal > 10 cm difference
 - Schober test: mark spine 10 cm above and 5 cm below lumbosacral junction (ie L5 spinus process). Distance between should increase by > 5 cm (ie > 20 cm total) on maximal forward flexion
 - With back to wall, measure gap between occiput and wall – any gap is abnormal
 - Reduced chest expansion
 - X-rays:
 - ‘bamboo’ or ‘railroad’ spine, squaring of vertebrae, syndesmophytes (due to enthesitis of the annulus fibrosis of vertebral discs), erosions of the apophyseal joints (between rib tuberosities and spinal processes), eventually bony ankylosis of the SI joints (also seen in Reiter’s and Crohn’s diseases)
 - Quantify with Modified SASSS (AS Spinal Score): score of changes in anterior vertebral edge of cervical and lumbar spine – maximum score is 72. Early syndesmophytes occur commonly in the thoracic spine – but these are not seen well on lateral xray
 - CT/MRI more sensitive and specific in early disease.
 - Inflammatory change (ie subchondral osteitis) shows in fat suppressed (eg STIR images) on MRI
 - MRI T1 weighted images show structural change: cartilage, subchondral bone, erosions
 - If no sacroiliac inflammation (white spots) on MR then Ank Spond unlikely

- Sacroiliac change on MRI has a PPV of 60% of xray change in 3 years
- Bloods:
 - FBC (mild normochromic anaemia in 15%)
 - ↑ESR and CRP in fewer than half, elevation typically modest, but higher if peripheral arthritis, hip involvement, and/or IBD
 - ↑ALP if severe disease
- Treatment:
 - Disease course highly variable – but want to treat before irreversible deformity. Diagnostic delay due to the frequency of low back pain
 - Physiotherapy/Exercise (not rest) to maintain posture and mobility – main aim is to prevent kyphosis, so exercises for hyperextension of the spine
 - NSAIDs to relieve pain and stiffness. 70 – 80% will derive benefit; no apparent difference between different NSAIDs. Recent RCT showed daily NSAIDs reduced progression over 2 years compared with NSAIDs for symptomatic relief only. Mean difference of 1.1 out of 72 – ?clinical benefit. General sentiment is that they have no or little disease modifying benefit
 - Prednisone for flares – ?more effective when injected into a joint
 - DMARDS (used often but hasn't been shown to benefit in RCT):
 - Sulphasalazine 2 -3 g/d of modest benefit – ?mainly used if peripheral arthritis
 - Methotrexate – ?less effective
 - If severe: dramatic response to TNF- α inhibitors in RCT on measures of spinal mobility, bone oedema on MRI, quality of life, extra-articular features: Infliximab, etanercept, adalimumab (although impact on radiologic disease progression not yet definitively established, cost and lack of long term safety data). Response in 2 – 6 weeks. Recurrence within 3 – 12 months of stopping TNF inhibitors
 - Local corticosteroids for uveitis, enthesitis, peripheral synovitis
- Monitoring: distance from fingers to floor when bending forward, measure chest expansion

HLA-B27

- Class 1a MHC molecule
- Occurs in 8% of the Caucasian population
- Strong ethnic variances in HLA prevalence: present in Caucasians, absent in indigenous people of South America and Australia, high prevalence in Eskimos....
- 30 HLA subtypes identified with different disease susceptibilities. Some (eg HLA-B*27 06 and 09 are not associated with AS)

Disorder	HLA-B27 %
AS	90
Psoriatic Arthritis	40 – 50
Reactive Arthritis	40 – 80
Spondyloarthropathy of IBD	40 – 60
Undifferentiated Spondyloarthropathy	40 – 60
Acute anterior uveitis	50

- In AS:
 - Accounts for 30 – 40% of genetic predisposition
 - 2 – 20% risk for positive individual, depending on pretest probability (ie random find vs known 1st degree relative, etc)
 - No formal role in diagnosis – but helps if clinical features suggest AS but no xray change

Differentials for Ankylosing Spondylitis

- Differential from RA:
 - Spine rarely affected in RA
 - Small peripheral joints rarely affected in AS
 - In AS there are no subcutaneous nodules and no RF (but there may not be in RA either)
- Osteitis Condensans Iliis (OCI):
 - Multiparous women
 - Usually bilateral
 - Triangular area of dense sclerosis on iliac side, adjacent to lower ½ of SIJ
 - Does not involve the SI joint
- Diffuse Idiopathic Skeletal Hyperostosis (aka Forestier's Disease)
 - Calcification and ossification of the anterior longitudinal ligament

- The “railway tracks” are thicker than AS
- Associated with males older than 50, T2DM in 20%, and not HLA B27
- Treatment: simple analgesics, NSAIDs

Psoriatic Arthritis

- See also psoriasis, page 456
- Epidemiology: occurs in 5 – 30% of psoriasis patients, age 35 – 45, male = female
- Pathology:
 - Genetics: concordance in monozygotic twins for psoriasis is > 65%, for PsA > 30%. Associated with B27+, DR7, DQ3, B57...
 - Can have a reactive type presentation due to a host of possible infective/inflammatory agents
 - Primary lesion = synovitis (similar to RA but less hyperplasia and cellularity and ↑vascularity): hypertrophic villi, T-cell infiltration, aggregates of T cells. But usually only minimal joint impairment. Articular destruction in a subset with panus formation, cartilage erosion, etc = Arthritis Mutilans
- Clinical presentation:
 - Usually psoriasis develops first, then arthritis, but 15% go the other way
 - Usually insidious but can present acutely
 - Nails: check for pitting, transverse ridging, onycholysis
 - Extra-articular manifestations are uncommon (except for conjunctivitis and iritis)
- Types (Moll and Wright Classification):
 - Arthritis with DIP joint involvement predominant (and usually nail changes)
 - Arthritis Mutilans
 - Symmetric polyarthritis (indistinguishable from RA)
 - Asymmetric Oligoarticular arthritis
 - Predominant spondylitis (looks like AS) – asymmetric involvement common, syndesmophytes less common, cervical spine involvement in up to 70 – 75%
- Other signs:
 - DIP joints in hands and feet especially affected – unique to PA. Terminal osteolysis on xray
 - Inflammation of digital tendon sheaths → sausage finger (dactylitis) – usually one not many (also in gout, Tb and rarely sarcoid). Don’t confuse with sclerodactyly in scleroderma
 - Enthesitis: Achilles tendonitis and plantar fasciitis
- Diagnosis: Psoriasis (exclude seborrhoeic dermatitis and fungal infections) or psoriatic nail involvement + sero-negative arthritis. Increased likelihood in B27 +ive
- Investigations:
 - Bony proliferation and osteolysis (together making “pencil in cup” deformity) key differentials from other arthritis
 - X-ray of hands → DIP involvement + resorption of the terminal phalanges
 - US and MRI sensitive for enthesitis
- Differentiating from RA:
 - Presence of skin rash
 - Asymmetric
 - DIP and PIP involvement
 - Can overlap with RA and present as a symmetrical, destructive arthritis. *Look for psoriasis and nail changes*
- Treatment:
 - NSAIDs for pain – but may worsen skin lesions (no change in progression, compared with RA where they have been shown to slow progression)
 - Corticosteroid injections for local synovitis
 - Dermatologists don’t like systemic steroids for psoriatic arthritis – can precipitate a flare of psoriasis after cessation
 - DMARDS:
 - Much less data
 - Methotrexate and sulphasalazine have clinical efficacy but don’t halt disease progression
 - Leflunomide shown in a RCT to be effective
 - All 3 TNFα inhibitors: Prompt improvement and delayed progression (first treatment to show this) shown in large RCTs – more dramatic response than in RA

Reactive Arthritis

- Previously = Fiessenger-Leroy-Reiter Syndrome or Reiter's Syndrome
- Original classic triad: urethritis, conjunctivitis and acute onset seronegative arthritis, with new joints affected over days to 1 – 2 weeks. Recurrence in 50%, attacks can last several months – a year. Destructive arthritis in 5%. HLA-B27 associated with more severe course
- Caused by sterile synovitis (T-Cells showing predominantly Th1 phenotype cf Th2 in RA) and enthesitis (with ↑vascularity and macrophage infiltration of fibrocartilage) following infection 1 – 4 weeks previously with:
 - Enteric infection: shigella, salmonella, yersinia, campylobacter, maybe also clostridium difficile (M = F)
 - Genital infection: chlamydia trachomatis (mainly men)
 - Viable organisms or bacterial fragments reach the joint via circulation from the gut or urogenital tracts
 - Also in leukaemia, endocarditis, acne, acromegaly, Wilson's disease, sarcoid, sickle cell, haemochromatosis
- Presentation:
 - Most common type of inflammatory arthritis affecting young men
 - Acute asymmetrical polyarthritis 1-2 weeks post infection lasting for 3 – 6 months. Can be florid, confused with gout or septic arthritis. Distribution:
 - Sacroiliac joints and spine
 - Hips
 - Knees (maybe with tense effusion)
 - Ankles and most of the joints of the feet
 - Can become chronic with relapsing and remitting course
 - Other features:
 - Enthesitis is common (eg → plantar fasciitis or Achilles tendonitis)
 - Fever, malaise, weight loss
 - Iritis
 - Mouth ulcers
 - Nail dystrophy
 - Keratoderma blenorrhagica (brown, aseptic abscesses on soles and palms). Severe if HIV
 - Circinate balanitis (painless serpiginous penile rash) +/- prostatitis
 - Rarely: cardiac conduction defects, aortic insufficiency, pleuropulmonary infiltrates
- Investigations:
 - ↑ESR
 - Causative agent: Blood culture/serology for antibodies/stool culture
 - Chlamydia: First of 2 glass urine test shows more debris in the first glass in urethritis (cf prostatitis where there is more in the 2nd). Urine PCR. Anti-chlamydial antibodies
 - Joint aspiration for septic arthritis
 - X-rays: periosteitis at ligamentous insertions. Rheumatoid like changes if chronic
- Differential:
 - Exclude disseminated gonococcal disease – which can also be associated with urethritis
 - Psoriatic arthritis: usually gradual in onset, primarily affects upper extremities
- Management:
 - Treat causal agent if still present (esp tetracyclines if Chlamydia). In RCTs, no benefit from treatment once arthritis presents
 - NSAIDs (indomethacin 75 – 150 mg/d in divided doses), steroid injections, recovery may be slow
 - Persisting symptoms may respond (off licence use and no RCTs) to sulphasalazine (up to 3 g/d in divided doses), azathioprine (1-2 mg/kg/day) or methotrexate
 - No trials of anti-TNF α

Enteropathic Arthropathies/Arthritis of Inflammatory Bowel Disease

- Associations:
 - Inflammatory bowel disease (15% of Crohn's and UC get arthritis)
 - Also associated with intestinal bypass surgery and Whipple's Disease (See page 341)
- Asymmetrical lower large joint mono- or oligo arthropathy
- No joint destruction
- Sacroiliitis or Spondylitis in 5% (70% of these have HLA-B27)

- Manage underlying condition:
 - Sulphasalazine for both bowel disease and arthritis
 - Total proctocolectomy results in remission of peripheral arthritis in UC only
 - NSAIDs and steroid injections for monoarthritis
 - Infliximab (Remicade) and Adalimumab (Humira) for peripheral and axial disease. Etanercept has no efficacy

Crystal Arthropathy

Gouty Arthritis

- See Postgrad Med Journal, 2005:81:572
- Prevalence:
 - ½ – 1%, male:female = 5:1. Uncommon pre-menopause in women. Common in Maori and Polynesian populations (14% in Maori males)
 - Incidence ↑ in NZ and US, ↓ in UK (?wonky data)
 - Most people with hyperuricaemia don't have gout
- Family history common
- Types:
 - Acute Gout:
 - Severe pain, redness and swelling, may be febrile
 - Differential of acute gout: septic arthritis or haemarthrosis
 - Chronic Recurrent Gout:
 - Urate deposits with inflammatory cells surrounding them (tophi) in avascular areas: pinna, infrapatella and Achilles tendons, joints, eye, etc ⇒ chronic tophaceous gout = gouty tophi
 - Bone erosion and loss of cartilage
- Distribution:
 - Acute gouty arthritis is usually monoarticular
 - Affects MTP joint of the great toe in 75% of cases (septic arthritis of this joint uncommon)
 - Ankles and knees involved after recurrent attacks
 - Fingers, wrists and elbows affected late
 - Fever is common, more likely with poly-articular episodes
- Exclude: septic arthritis, other crystalline-associated arthropathies, palindromic RA, psoriatic arthritis
- Classifications:
 - Primary – innate cause
 - Secondary – acquired cause
- Pathogenesis:
 - Uric acid is the last step in the breakdown of purines (adenine and guanine)
 - Hyperuricaemia (uric acid > 0.41 mmol/L, if > 535 then annual incidence of ~ 5%) → deposition of monosodium urate crystals (MSU) in joints (and viscera, especially the kidney) → chemotactic to leukocytes and activate complement → accumulation of neutrophils and macrophages → erosion, inflammation, secondary OA.
 - Uric acid may be in the normal range during an attack – it is a change (either up or down) that correlates with an attack
 - May be precipitated by trauma, surgery, starvation, infection and diuretics
 - Causes of ↓ excretion (90%) or ↑ reabsorption of MSU: Gouty individuals excrete 40% less urate for the same serum concentration
 - Primary gout
 - Renal failure → hyperuricaemia which rarely → gout
 - Hypertension, DM
 - Primary hypoparathyroidism
 - Hypothyroidism
 - ↑ Lactic acid production (eg from ETOH)
 - Drugs: aspirin, diuretics (frusemide & thiazides), alcohol, cyclosporin – compete with urate for excretion
 - Causes of ↑ Production (10%) of MSU:
 - ↑ Cell turnover (→ ↑ turnover of purines): Lymphoma, leukaemia, severe psoriasis, haemolysis, polycythaemia, Paget's, muscle necrosis, extreme exercise, obesity

- Disorders of purine synthesis (eg Lesch-Nyhan syndrome: X linked, a deficiency of HGPRT enzyme which normally “recycles”/salvages purines for reuse, also causes spasticity and mental retardation)
- Inflammasomes: Structures within the cell which recognise inflammatory producing stimuli. MSU activates NALP3 inflammasome → activates caspase 1 → release IL-1 β → acute inflammation
- Complications:
 - Nephrolithiasis: urate calculi
 - Urate nephropathy – crystals deposit in the kidneys → giant cell inflammation (now rare)
 - Uric acid nephropathy: causes reversible acute renal failure. Precipitation of uric acid in renal tubules causing obstruction. Requires marked hyperuricaemia, eg leukaemia, cytotoxic treatment (tumour lysis), following epileptic seizure or prolonged exercise with heat stress. Ratio of uric acid to Cr in 24 hour urine is > 1
- Diagnosis:
 - *Needle shaped, negatively birefringent* urate crystals in tissues and synovial fluid (serum urate not always \uparrow) – also neutrophils (+ ingested crystals) from 2,000 to 60,000/ μ L
 - \uparrow ESR
 - Serum uric acid or 24 hour urine collection for uric acid (likely to be low)
 - Check renal function and BP
 - X-rays: in early stages may only show soft tissue swelling. Later, cystic changes, well-defined erosions with sclerotic margins and soft tissue masses
- Treatment:
 - No treatment for asymptomatic hyperuricaemia (other than acute uric acid nephropathy)
 - No aspirin: salicylates competes with uric acid for excretion → \uparrow serum urate
 - Acute:
 - DON'T STOP ALLOPURINOL – changing uric acid levels (either up or down) → attack
 - No head to head trials – but NSAIDs most common and probably quickest
 - NSAID (eg ibuprofen, naproxen [naprosyn/synflex], indomethacin, not aspirin): short half-life is better – but problematic in renal failure and heart failure (→ fluid retention). Also caution – if on anticoagulants (→ GI bleed)
 - Colchicine. uncouples MSU from inflammasome activation in neutrophils → \downarrow cytokines (but doesn't stop bacteria doing the same thing). It also inhibits microtubule formation and adhesion thus decreasing migration. Likely as effective as NSAIDs, able to be used in CHF and in patients on anticoagulants, toxicity at high doses and in renal impairment. Can be used IV but life threatening toxicity if > 4 mg/day. Contraindicated in pregnancy. SE mainly GI. Rare rashes, renal and hepatic impairment, peripheral neuritis, myopathy
 - Prednisone and naproxen were equivalent treatments in a Netherlands trial of 120 patients (excluding those with history of upper GI disease) with crystal proven gout (Lancet 31 May 2008)
 - Glucocorticoids – injected if one joint, oral if multiple joints (40 – 40 – 20 – 20 – stop)
 - ACTH (Synacthen) 40-80 iu every 12 hours for 1 – 2 days useful if NSAIDs/colchicine contraindicated
 - Prevention: *life long*
 - Poor compliance with prophylaxis → treatment failure
 - Stop smoking
 - Avoid purine-rich foods (offal, oily fish eg anchovy), \downarrow obesity and excess alcohol (\uparrow synthesis and \downarrow excretion, beer worse than spirits worse than wine). Strict diet can \downarrow uric acid by 60 μ mol/L
 - Long term ('interval') treatment if multiple attacks, tophi and raised uric acid: Allopurinol:
 - Xanthine-oxidase inhibitor → \downarrow serum urate (xanthine oxidase is the last step in purine metabolism in the liver and small intestine)
 - 100 – 300 mg/d (up to 800 mg/day if needed). *Titrate up till urate < 360 μ m/L – 100 for 2/52, 200 for 2/52, then 300*
 - Supposed toxicity in renal failure based on one study (Hande K et al, Am J Med 1984,76:47 – 56, poor study) which showed an \uparrow risk of idiosyncratic reaction in renal failure. \uparrow Cr alone is not a good reason to \downarrow allopurinol (and certainly not suddenly)
 - But not during an acute attack – wait three weeks. Mobilises gouty tophi → \uparrow systemic urate → precipitates acute gout. Use with colchicine cover. Avoid thiazides
 - SE: rash (can → toxic epidermal necrolysis), fever, \downarrow WCC. Rarely systemic vasculitis, bone marrow suppression, hepatitis, renal failure

- Allopurinol can also be used during chemotherapy for leukaemia/lymphoma/myeloma to prevent gout from ↑purines
- Also uricosuric drugs (→ ↑excretion): probenecid or sulphinpyrazone. C/I if previous urate calculi
- Other drugs:
 - Rasburicase: given by IV infusion for hyperuricaemia 2nd to tumour lysis syndrome in haematological malignancy. ?Place in gout
 - Benzbromerone (?spelling): section 29 drug, ↑ uric acid secretion (better than probenecid), rare liver failure reported, \$100 per month

Pseudogout

- = Calcium Pyrophosphate Deposition (CPPD)
- Onset in 30s
- Deposition of chalky white crystalline material – usually calcium pyrophosphate
- → Chondrocalcinosis: deposition in articular cartilage → calcification on x-ray
- Predominantly large joints (especially the knees)
- Aspirate: *positively birefringent rhomboid shaped* crystals
- In some there are signs of hyperparathyroidism and haemochromatosis
- Treatment: symptomatic. May be value in low dose colchicine prophylaxis

CaOx Deposition Disease

- Primary oxalosis: Rare hereditary disorder → deposition of calcium oxalate crystals in tissues with death by age 20
- Secondary oxalosis: More common. Complication of ESRF on dialysis. Deposition in visceral organs, blood vessels, bones, and cause of arthritis. End product of ascorbic acid metabolism

Connective Tissue Diseases

Systemic Lupus Erythematosus

- See NEJM 28 Feb 2008 and BMJ 15 April 2006
- Epidemiology:
 - Peak age of diagnosis: 30 – 40
 - Female:male = 9:1
 - Prevalence: 0.2%
 - Commoner in pregnancy, Afro-Caribbeans, Asians
 - Genetic predisposition: HLA A1, B8, DR3
 - 15% 15 year mortality – mainly due to renal failure

Presentation (OHCM p 672)

- Gradual or sudden onset
- General: Fever (77%), splenomegaly, lymphadenopathy, *extreme fatigue* (common, and persists between flares. Exclude hypothyroidism and anaemia)
- Musculo-skeletal symptoms (95%): joint/muscle pain, non-erosive *small joint* polyarthritis, bone necrosis, rare joint deformity due to capsular laxity. Joint deformity may be due to ligament and capsular laxity, without erosions, can manipulate it to a normal position (unlike RA), similar to Jaccoud's arthropathy (seen rarely in Rheumatic Fever)
- Skin (81%): photosensitive butterfly rash, Raynaud's, purpura, oral ulcers, discoid lupus (= skin involvement only: 3 stage rash: erythema → pigmented hyperkeratotic oedematous papules → atrophic depressed lesions), nail-fold vasculitis, livedo reticularis, subacute cutaneous lupus erythematosus (limited form of lupus rash in sun exposed areas only)
- Alopecia: bald patches – not hair fall. Often appears after a flare. Common – but not a criteria as not sufficiently discriminative
- Renal (<75%): proteinuria, casts, oedema, uraemia, glomerulonephritis.
- Pulmonary (<48%): Pleurisy (+/- effusion – try NSAIDs or steroid course if severe), fibrosing alveolitis, BOOP
- CVS (38%): ↑BP, pericarditis, Libman-Sacks endocarditis (fibrinous endocarditis)
- CNS (<18%): Anything! Depression, psychosis, fits, cranial nerve lesions, retinal exudates, severe headache (not relieved by opioids), ataxia, dementia, SAH, cranial neuropathy, peripheral neuropathy, Guillain-Barre. Exclude steroid psychosis. ?role of antibodies against NMDA receptor

- Eyes: Sicca Syndrome common and rarely threatens vision. Retinal vasculitis and optic neuritis are serious → blindness over days/weeks
- Blood: Normocytic anaemia (75%), Coombs +ive haemolysis, ↓WCC, ↑INR, ↓platelets, ↑ESR, normal CRP
- Vascular occlusions: Stroke, MI
 - Antiphospholipid antibodies associated with thrombotic events
 - Accelerated atherosclerosis is associated with chronic disease. Also steroids → IFG, HTN, obesity and deranged lipids
- **Formal criteria** – American College of Rheumatology: 4 of the following 11 simultaneously or serially:
 - Skin features (note each is a criteria on its own):
 - Malar rash: erythema tending to spare the nasolabial folds
 - Discoid rash: erythematous raised patches with keratotic scaling, atrophic scarring in older lesions
 - Photosensitivity: skin rash in response to sun light
 - Oral or nasopharyngeal ulcers: usually *painless*, observed by a physician. If painful think Behcet's
 - Arthritis: *non-erosive* arthritis of 2 or more peripheral joints with swelling or effusion. Ie differential of symmetrical polyarthritis
 - Serositis: pleuritis or pericarditis
 - Renal disorder: persistent proteinuria > 0.5 gm/day or cellular casts
 - Neurologic disorder: Seizures or psychosis
 - Haematologic disorder (one criteria even if you have them all): haemolytic anaemia, leukopenia (< 4 on 2 occasions) or lymphopenia (< 1.5 on 2 occasions) or thrombocytopenia (< 100) in the absence of offending drugs
 - Immunologic disorders: Positive antiphospholipid antibody, Anti-DNA, Anti-Sm, or false positive VDRL (confirmed by Treponema pallidum immobilisation or fluorescent treponemal antibody absorption test)
 - Antinuclear antibody in the absence of drugs causing drug lupus

Lupus Nephritis

- Most common serious manifestation
- Asymptomatic – monitor urine and Cr
- Proliferative glomerular damage common → haematuria and proteinuria, nephrotic syndrome and HTN
- Only biopsy if expecting class 4
- Class: Can only differentiate on histology
 - 1: mesangial immune deposits without hypercellularity. Don't treat. Why did you biopsy?
 - 2: mesangial immune deposits with hypercellularity
 - 3: focal proliferative, < 50% glomeruli
 - 4: diffuse proliferative, > 50% glomeruli – the worst – poor prognosis – always treat with cyclophosphamide or MMF
 - 5: membranous. No evidence for treatment. Note ↑lipids and ↓albumin. Can try MMF and stop if no effect
 - 6: advanced sclerosing lesions
- Benefit of immunosuppressive therapy is established in class 3 and 4
- Histology:
 - IF: lots of everything
 - EM: subepithelial, mesangial ⇒ multi site deposition
- Proposed that either:
 - Anti-dsDNA autoantibodies bind to nucleosomes that have “escaped” into the blood stream, these settle in the glomerulus and activate complement → glomerulonephritis
 - Auto-antibodies cross react with kidney proteins → direct pathogenic effect
- Tubular interstitial disease and vascular disease important to outcomes, but glomerulus is the focus

Pathology

- Environmental triggers on a genetically susceptible background
- Female excess: oestrogen binds to receptors on T and B lymphocytes → ↑activation and survival → prolonged immune response (although 2 RCTs have shown no impact from OCP)
- Ultraviolet light → flare in 70%. ?↑Apoptosis of skin cells

- Immune dysregulation featuring:
 - Activation of innate immunity (dendritic cells) by DNA and RNA self-antigens
 - Lowered activation thresholds of adaptive immunity cells (antigen specific T and B lymphocytes)
 - Abnormal clearance of apoptotic cells due to ineffective phagocytosis → nuclear antigens persist in the blood → ↑inflammation
- Only occurs in B lymphocytes being stimulated by T lymphocytes as well as antigen (ie “T-cell help”)
- Leads to:
 - ↑proinflammatory TNF α , IL-1 and IL-2, B-cell driving cytokines B lymphocyte stimulator (BLyS) and IL-10 (which is persistently high in SLE and stimulates polyclonal populations of B-cells)
 - T and natural killer cells fail to produce enough IL-2 and TGF (transforming growth factor) to induce regulatory CD4+ and CD8+ cells so unchecked proliferation of helper T cells
- Homozygous deficiencies of C1, C2 and C4 (rare) → strong deposition to SLE. Suggests low complement important in sustaining SLE. Anti-C1q present in 40 – 50% of SLE

Investigations

- FBC – usually anaemia of chronic disease
- ESR > 20, CRP often low
- Antibodies:
 - Most have antibodies for ~ 3 years before symptoms develop
 - 80 – 95% are ANA +ive: useful “rule-out” test. Repeat if negative but symptoms persist
 - High dsDNA ANA (but not ssDNA) almost exclusive to SLE (+ive in 40 – 60%)
 - 30% are anti-Sm positive – highly specific to SLE
 - 40% are RF +ive
 - Lupus anti-coagulopathy test (not specific to SLE): see page 262
 - Antibodies to Ro (SS-A), La (SS-B) and anti-RNP (ribonuclear protein) help define overlap syndromes
- VDRL false positive in 30%. See page 321
- Lupus band test: Igs and complement at the dermo-epidermal junction in normal skin in a patient with active SLE – not sensitive but specific
- Organ/skin biopsy
- Cerebral lupus:
 - Abnormal EEG
 - LP: most common finding is raised CSF to serum Ig (called Ig index). Also do oligoclonal bands. Normal doesn’t exclude CNS lupus. Also to exclude infection if immunosuppressed
 - MRI: sensitive. Typical lesion is T2 hyperintensity (normal is up to one per decade of life). Stroke can be a manifestation. MRI may or may not improve with symptomatic improvement. May be reported as a vasculitis – but it’s not – it’s parenchymal inflammation
- Pain disproportionate to radiological damage on X-ray
- Monitoring:
 - BP
 - Urinalysis
 - FBC, U&E, Complement (C3, C4 – better than ESR)
 - dsDNA ANA titres
 - AST and ALT commonly elevated during a flare

Treatment

- Aim to control flares, limit chronic symptoms and prevent organ damage
- Conservative treatment for non-life threatening (generally = kidney’s OK)
 - Sun block creams
 - Analgesics: joint pain, swelling, fever
 - Hydroxychloroquine for skin and joint pain – the mainstay of treatment for mild SLE. RCT showing ↓flares. SE: retinopathy – check eyes annually. Also Mepacrine on its own or in combination (an anti-giardia and antimalarial drug). Sometimes used as primary treatment in discoid lupus)
 - NSAIDs: but SLE patients at greater risk for ↑LFTs, HTN, renal dysfunction. Weigh risk of ↑MI risk from COX-2 inhibition
 - Topical glucocorticoids and anti-malarials for dermatitis
 - Supervised exercise has been shown to be beneficial

- Oral contraceptives are not contraindicated unless antiphospholipid antibodies and do not increase flares. Use lowest oestrogen pill possible
- HRT increases the risk of mild to moderate, but not severe flares, and no effect on renal failure or death
- Consider bone protection
- Atheroma: SLE strongly associated with premature atheroma – in older age others catch up. Odds ratio of vascular death = 1.7. Risks due to inflammation, and steroid side effects (obesity, DM, HTN)
- Vaccination: Lupus has no effect on vaccine effectiveness and vaccines don't cause flares
- Prednisone:
 - 0.25 mg/kg: skin, joints, musculoskeletal
 - 0.5 mg/kg: serosal, moderate haematological
 - 1 mg/kg: CNS, renal, significant haematological
 - Prednisolone: higher dose or pulses (RCT show shortens time to maximal improvement but no improvement in renal function) for exacerbations, lower dose for chronic disease – mainstay of treatment. Effect within 24 hours
- Proliferative Lupus Nephritis:
 - All immunosuppressive trials have been on patients with lupus nephritis – treatment in other settings is by extrapolation
 - MMF preferred over cyclophosphamide unless significant renal failure at the start of therapy. Cyclophosphamide has been shown to work, whereas MMF trials excluded people with significant renal impairment
 - Mycophenolate mofetil (a relatively lymphocyte-specific inhibitor of inosine monophosphatase and therefore of purine synthesis): for Class 4 GN, or if Azathioprine intolerant. Probably better than cyclophosphamide in conjunction with prednisone in a flare, and safer in maintenance phase. Small numbers in trials. Better for fertility and bladder cancer
 - Cyclophosphamide (an alkylating agent): monthly or quarterly IV pulse for severe proliferative GN, and for treatment failure (various regimes have supporting data, in conjunction with or followed by azathioprine or mycophenolate). Evidence that lower dose as good as higher dose. Helps renal function more than steroids. *Short course then Azathioprine*. SE ovarian failure (reduce risk with GRH agonist prior to each dose) – effect within 3 – 16 weeks
 - Azathioprine (a purine analogue) 1.5 – 2.5 mg/kg: Reduces flares and steroid requirements. Inferior to cyclosporine for induction therapy (in class 4) but equivalent in maintenance. Use for GN other than class 4
 - Methotrexate – may have a role in treatment of arthritis and dermatitis, but probably not in life threatening disease
 - Leflunomide: watch this space
 - IV Ig increasingly used in resistant SLE, but no large RCTs
- CNS Lupus: IV cyclophosphamide superior to IV methylprednisone
- Biologics:
 - Rituximab: antibody against CD 20 (found on all mature B cells) → depletes mature B cells. Doesn't ↓ ANAs (made by plasma cells). Evidence of benefit from *case series only* on CNS disease, activity, proteinuria, dsDNA. Probably works on B-T cell interaction, not IgG production. If they don't deplete (some don't and we don't know why) then no benefit. Dose 1 g IV 2 weeks apart (same as in RA)
 - Also anti-CD22 antibody under trial
 - Anti-TNF associated with ↑ANA and drug lupus. No RCT evidence – *not effective* in follow-up of case series
 - Abetimus sodium: 4 strand dsDNA – soaks up anti-dsDNA antibodies. Reduces dsDNA titres but doesn't affect disease activity – designed to deplete only B lymphocytes producing anti-dsDNA antibodies
- Some trials showing benefit in DHEA treatment in cerebral lupus (not available in NZ) – evidence marginal
- Can cause avascular necrosis of the femoral head (especially if antiphospholipid Syndrome) 2nd to vasculitis of the ligamentum teres. Also associated with steroid use. Donut like uptake in bone scan – high uptake in femoral head with low uptake in necrotic central portion
- Microvascular Thrombotic Crisis
 - ~ Thrombotic Thrombocytopenic Purpura, Haemolytic Uraemic Syndrome
 - Haemolysis, thrombocytopenia and microvascular thrombosis in kidneys, brain, etc

- Most commonly in young SLE patients with nephritis
- High mortality
- Tests: schistocytes on peripheral blood smears and ↑ lactate dehydrogenase
- Treatment: plasma exchange

Pregnancy with Lupus

- Fertility rates probably normal
- Hydroxychloroquine safe
- Prednisone safer for fetus (placental 11-β-dehydrogenase deactivates it) than fluorinated glucocorticoids (dexamethasone, betamethasone)
- Higher fetal loss if disease flare (especially at the time of conception), antiphospholipid antibodies, or nephritis
- Pregnancy complications: pre-eclampsia, IUGR, pre-term delivery, maternal thrombosis

Drug Lupus

- Caused by isoniazid, hydralazine, procainamide, chlorpromazine, anticonvulsants (lithium, carbamazepine, phenytoin), some ACEIs and β-blockers
- Lung and skin effects greater than renal and CNS
- ENA anti-histone more likely to be positive. Not usually anti-dsDNA positive
- Remits if drug stopped

Antiphospholipid Syndrome (Hughes Syndrome)

- See NEJM 7 March 2002
- Occurs alone (primary) or with other autoimmune diseases (secondary), including SLE
- Presentation:
 - DVT most common presenting feature, with up to half of these having a PE
 - Arterial clots: 50 % in brain (stroke or TIA), 23% in coronary arteries. May also be caused by emboli from valve (?↑incidence of abnormality)
 - Microvascular complications: may be slow progressive loss of organ function 2nd to thrombotic microangiopathy (non-specific histology)
 - Thrombocytopenia in 40 – 50%
 - Haemolytic anaemia in 14 – 23 %
 - Livedo reticularis (a reddish blue netlike mottling of the skin) in 11 – 22%
- Pathogenesis: unclear
 - Antibodies to anionic phospholipids, particularly β2 glycoprotein 1. Activation or damage to endothelium, interferes with phospholipid-binding proteins in the regulation of coagulation....
 - Antiphospholipid antibodies can interfere with both anticoagulant and procoagulant pathways (can have a normal APPT)
- Diagnosis requires (Sapporo Criteria):
 - Arterial or venous clotting and/or repeated fetal loss (3 losses at < 10 weeks or 1 > 10 weeks or preeclampsia < 34 weeks) and/or thrombocytopenia
 - 2 positive tests for aPL 12 weeks apart: IgG anticardiolipin (more sensitive) and lupus anticoagulant (more specific). May also be positive for β2-glycoprotein I antibodies (strongly associated with thrombosis, but not formally in diagnostic criteria)
- In pregnancy:
 - RCT have shown ↓↓ fetal loss with heparin and low dose aspirin with antibodies and prior fetal loss. But if no history of SLE or thrombosis, despite presence of antibodies and prior fetal loss, then treatment equal placebo. Currently, heparin is generally treatment of choice
 - Anti-Ro antibodies associated with neonatal lupus (rash and congenital heart block)
 - Plasma exchange, steroids, immunoglobulin used in treatment. Cyclophosphamide increases mortality
 - Catastrophic Antiphospholipid Syndrome: Multiple simultaneous clots. Rare. Digital infarcts progressing to proximal clotting
 - *Long term anticoagulation indicated after a thrombotic event* (less clear if no prior clot):
 - INR 2 – 3 if one episode of venous clotting
 - INR 3.0 – 3.5 if recurring clots or arterial clotting, especially in the CNS

Sjogren's Syndrome

- See Lancet, 23 July 2005
- = Dry eyes, dry mouth and associated with rheumatoid arthritis

- Epidemiology: onset 15 – 65 years, more common in women
- Types:
 - Primary (ie no other connective tissue disease) – slow benign course. Parotid enlargement common (cf not in secondary)
 - Secondary: associated with other connective tissue diseases: Rheumatoid (50% of Sjogren's have RA), SLE, Scleroderma, polymyositis, primary biliary cirrhosis (ie autoimmune disorders), graft-verses host disease, AIDS
- Presentation:
 - Gritty, sore eyes: keratoconjunctivitis sicca (↓lacrimation → dry eyes)
 - Dry mouth: xerostomia (↓salivation) – can't swallow, need sips of water at night, enlarged tender parotids (less likely in secondary disease)
 - Also dry nose, vagina
 - Less frequent involvement of other exocrine glands: ↓mucosal secretions in respiratory tract, atrophic gastritis, subclinical pancreatitis. Only in primary disease, not with RA
 - Tiredness/depression
 - Myalgia (attributed to associated fibromyalgia)
 - Arthritis (as in SLE) – at least one episode of non-erosive arthritis in primary Sjogren's
 - Raynaud's
 - Other extra-glandular manifestations (very rare in Sjogren's with RA):
 - Hypothyroidism is common
 - Cranial neuropathies: especially VII (Bell's palsy), VIII (sensorineural hearing loss) and eye movements
 - Peripheral neuropathy in 20%
 - Pulmonary fibrosis, pleurisy, PAH
 - Interstitial nephritis → tubular dysfunction with or without acidosis. If acidosis then may → nephrocalcinosis. Pauci immune GN rare and only if mixed cryoglobulinaemia or SLE overlapping with Sjogren's
 - Vasculitis: small and medium vessels → purpura, urticaria, skin ulceration, GN and mononeuritis multiplex
 - Primary biliary cirrhosis or chronic hepatitis
- Formal diagnosis by 4 of 6 criteria
- Compared to RA:
 - ANA is more strongly positive in Sjogren's
 - Arthritis is not destructive
- Investigations:
 - Schirmer test: < 10 mm of filter paper under the lower eye lid is wet after 5 minutes
 - Slit-lamp examination of the cornea with rose Bengal staining → punctuate ulcerations
 - Lacrimal gland biopsy – or small piece of oral mucosa on inside of lip – contains salivary glands
 - ↑ESR & CRP. May have normal CRP (can get this in most CTDs, but not RA)
 - 100% have RF
 - ANA positive in 60 – 70%
 - Anti-Ro (SSA) and Anti-La (SSB) present in 70% of primary, and 10% of secondary. Associated with worse prognosis. NB Ro and La antibodies cross the placenta causing congenital heart block
- Pathology:
 - T-cells infiltrate secretory glands (also skin, lungs and liver) and B lymphocyte hyperreactivity (B cell activating factor BAFF high) causing apoptosis and fibrosis. Macrophages and natural killer cells rarely detected
 - ?Triggered by persistent enteroviral infection (?Coxsackie)
 - HLA B8, DR3 and DRw52 association
- Treatment:
 - Symptomatic relief: Artificial tears and saliva
 - Avoid drugs that reduce secretions: diuretics, antihypertensives, anticholinergics and antidepressants
 - Hydroxychloroquine (good for arthralgia and lymphadenopathy)
 - Visceral involvement:
 - More problems with steroids (periodontal disease/candidiasis)
 - Azathioprine ?better than methotrexate
 - Mycophenolate being looked at as a replacement for cyclophosphamide in severe disease

- Differentials:
 - Exclude Hep C (can look like SS except for serological tests), head/neck radiotherapy, sarcoidosis, graft vs host disease, HIV, Human T-lymphotropic virus type 1 (HTLV-1)
 - Bilateral parotid gland enlargement:
 - Viral infection: mumps, influenza, Epstein-Barr, Coxsackie, CMV, HIV
 - Sarcoidosis
 - Amyloidosis
 - Endocrine: acromegaly, gonadal hypofunction
 - Metabolic: DM, chronic pancreatitis, hepatic cirrhosis
 - Alcohol
- Small but significant number develop malignant lymphoma (~ 6%), suggested by persistent parotid gland enlargement, purpura, leukopenia, cryoglobulinaemia, ↓C4. Most are extra-nodal, low-grade marginal zone B cell lymphomas

Systemic Sclerosis and Scleroderma

- See Clinical Medicine, May/June 2005
- Connective tissue disease with inflammation, vasculitis and fibrotic changes in skin and viscera
- Epidemiology: female = 3 * male. Any age, but peak is 30 – 50 years. Incidence 1 – 2/100,000. Highly heterogeneous
- Pathology:
 - Small genetic contribution: twin concordance low (4.7%). Environmental causes suspected but unclear
 - Small vessel damage + oedema → collagen laid down → fibrosis and contraction of skin and viscera + obliterative vasculopathy of small vessels. Inflammation only detected early in disease
 - Dilation of other vessels → telangiectasia
- Presentation:
 - “Always” Raynaud’s (90%) may precede other signs by years
 - Then swelling of fingers and hands (sclerodactyly *not* dactylitis – that’s psoriasis)
 - Then skin gets tight, itchy, waxy and tethered (eg fingers – pointy fingers, forearms, face – no wrinkles, pointy nose)
 - Other: telangiectasia, *nail bed spots*, symmetrical polyarthritis, distal ischaemia
 - Carpel tunnel
 - True inflammatory arthritis is uncommon
 - Also large bowel diverticular

Types

- **Diffuse/Generalised Cutaneous Systemic Sclerosis (dcSSc)**: widespread skin involvement (chest, abdomen, upper arm and shoulders) with early visceral involvement → kidney (proteinuria, sediment, maybe crisis ↑↑BP), polyarthritis, *myopathy* (especially proximal), lung fibrosis (↓expansion + ↓gas transfer → SOB) and GI fibrosis
- **Limited Cutaneous Scleroderma (lcSSc)**:
 - Scleroderma = thickening of skin
 - Raynaud’s precedes onset (cf dcSSC where it is contemporaneous)
 - Tightening and fibrosis of the skin on hands face and neck:
 - Proximal skin scleroderma (eg face – can they open their mouth wide, any wrinkles – if so then no involvement). Limited mouth opening (= microstomia) or any 2 of sclerodactyly (can they make a fist, Prayer sign: can they oppose palmar MCP joints), *digital pitting scars* (healed necrosis), pulp loss
 - Hands go through oedematous phase (puffy, not yet fibrotic, differential psoriasis), then indurated (oedema and early thickening) to sclerodactyly (sclerosis of the digits). Claw hand is not caused by joint erosion but by skin tightening
 - Late stages may include PAH, hypothyroidism and primary biliary cirrhosis
- CREST Syndrome (probably very different disease entity to Diffuse):
 - Calcinosis (subcutaneous calcium deposits on hands)
 - Raynaud’s phenomenon
 - Disordered distal oesophageal motility (heart burn and dysphagia 2nd to involuntary muscle involvement – fibrosis or some argue neuropathic – can also get anal sphincter involvement with faecal incontinence) → Barrett’s oesophagus (and prior to PPI then strictures)
 - sclerodactyly (Scleroderma of the hands)

- telangiectasia (apply pressure to check). If on tongue then may also be in the gut – risk of internal bleeding – scope and laser them
- Scleroderma limited to the hands and maybe face (‘Limited Scleroderma’) is probably a presenting symptom of CREST syndrome even if the other features aren’t present
- CREST is part of the Limited spectrum of disease – similar and very small risk of the nasty visceral effects
- Scleroderma Spectrum disorders
 - Morphea (localised skin sclerosis) rarely, if ever, progresses to SS. Associations with vinyl chloride, some evidence of silica (eg in mining)
 - Eosinophilic Fasciitis: ↑IgG, ↑ESR, Woody induration of arms and legs, sparing face and hands. Highly responsive to steroids

Investigations

- No known severity markers
- FBC: normocytic anaemia, haemolytic anaemia
- ↑ESR
- ANA positive in 75%. May have antibodies to:
 - Anti-centromere. Anti-centromere (ACA) in **lcSSc** and **CREST**
 - Topoisomerase-1 (Scl-70) in **diffuse**
 - RNA polymerases: usually extensive skin involvement and renal crisis
- RF +ive in 30%
- 24 hour urine
- Hand x-ray. Can get distal phalanges resorption
- Barium swallow, CT of lung, and PFTs. Echo if heart problems or PAH

Pulmonary disease

- No advantage from doing bronchoalveolar lavage for PMN% – doesn’t help predict treatment response. Do HRCT and PFPs. On HRCT looking for progression – poor correlation between CT findings and histology with respect to inflammation (ground glass) and fibrosis
- Interstitial lung disease: aka fibrosing alveolitis or pulmonary fibrosis. 75% have some degree of this. SOBOE, non-productive cough and fine velcro creps. ↓FVC and ↓DLCO. DLCO < 40% ⇒ 9% 5 year survival, 75% if > 40%. Cyclophosphamide → ↑survival from interstitial lung disease. Small treatment effect but nothing else works. Skin disease may also improve – but don’t use it just for skin – toxicity not worth it
- Pulmonary Hypertension:
 - 10 – 40%
 - ↓DLCO but no change in FVC
 - If no significant interstitial disease then resembles idiopathic pulmonary HTN
 - More common in lcSSc than dcSSc
 - Usually a late and progressive feature. 6 minutes walk often used as a clinical measure. Gold standard test is R heart catheter
 - Treatment:
 - Medication as for primary pulmonary hypertension (Bosentan, Sitaxentan, Sildenafil) – see page 210. If also fibrosis, then you don’t know which came first. Trial of treatment, stop if echo doesn’t improve
 - No evidence for use of steroids in lung disease – but trials had them on a bit of steroid so this is replicated in treatment. Doses > 15 mg prednisone are a risk factor for scleroderma renal crisis
 - Long term O2, consider diuretics, digoxin and anticoagulation
- Lung Cancer: incidence is approx 5 times higher than age matched controls

Renal disease

- Some proteinuria, mild ↑Cr and/or HTN common
- Scleroderma renal crisis:
 - Always measure BP
 - Severe and life threatening renal disease most often in patients with early dcSSc with rapid skin progression: acute renal failure, only mild proteinuria with few cells or casts, abrupt onset of marked HTN with headache and blurred vision (although BP may not be markedly elevated)
 - Obliteration of renal cortical arteries → ↓renal flow → ↑renin

- Predictors of risk of renal crisis: pericardial effusion, palpable tendon rub, new anaemia/thrombocytopenia
- *Aggressive ACEI* (don't stop even if ↑Cr)
- May regain renal function after up to 18 months on dialysis

Other Treatment

- Requires accurate disease subsetting, staging within each subset
- Nothing found which alters natural history of SSc. Focus is symptom alleviation and slowing progressive organ damage
- Education, support groups, etc
- Raynaud's: warmth and vasodilators (Ca blocker). For severe Raynaud's with tissue at risk: Prostacycline/Iloprost (infusions for 3 – 5 days, drug has half life of minutes but effect can last months), Bosentan and Sildenafil beneficial. *Bosentan prevented but didn't heal ulcers.*
- Myopathy, if present, needs steroids
- Oesophageal motility: omeprazole, cisapride (prolongs QT), reflux prevention. Vascular lesions may → anaemia. If mid gut disease then ?prokinetic agents, subcut octreotide, pancreatic enzyme supplements. Large bowel – may find small frequent low fibre meals useful. ↓motility may → bacterial overgrowth → ↓B12 and folate absorption 2nd to bacterial consumption. Treat with intermittent erythromycin (works both as antibiotic and ↑motility)
- Scleroderma:
 - D-penicillamine (antifibrotic, no efficacy in RCT) or immunosuppressants (little efficacy from steroids)
 - Anti-TNFβ aimed to stop fibrosis but had no effect on skin
 - Methotrexate has shown statistical (not clinical) benefit in clinical trials
- **Prognosis:** Limited disease has 70% 10-year survival; diffuse has 55% 10-year survival. Death from lung/renal effects

Mixed Connective Tissue Disease

- Features of SLE, PSS, polymyositis, and RA – is it a separate disease or just an overlap syndrome? – loosing favour as a diagnosis
- Anti-RNP (antibodies to U1-RNP ribonuclear protein) +ive without other types of ANA (no SSc-specific antibodies)
- Characteristic presentation: Raynaud's → sclerodactyly, calcinosis and cutaneous telangiectases (lcSSc features) → skin rashes suggestive of SLE (malar rash, photosensitivity) or dermatomyositis (heliotrope rash on the eyelids, erythematous on knuckles) → arthralgia +/- erosive polyarthritis. Maybe pulmonary fibrosis and/or PAH
- Good response to glucocorticoids (unlike SSc) and long term better prognosis

Polymyositis, Dermatomyositis and Inclusion Body Myositis

- See Lancet 20 Sept 2003

	Polymyositis	Dermatomyositis	Inclusion Body Myositis
Age at onset	> 18	Any	> 50
Familial Association	No	No	In some cases
Extramuscular	Yes	Yes	Yes
Manifestations			
<i>Associated conditions:</i>			
CTD	Usually	Usually alone, but can occur with SSc and MCTD → overlap syndromes	All, in 20%
Systemic Autoimmune diseases	Frequent	Infrequent	Infrequent
Malignancy	No	Up to 15%	No
Viruses			HIV & HTLV-I
Drugs	Penicillamine, zidovudine		

- Peaks in age 10-14 (mainly dermatomyositis, most common) and 45 – 60 years (mainly polymyositis, least common, over-diagnosed). Rare (1 in 100,000)
- Presentation:

- Voluntary muscle inflammation → *insidious*, symmetrical, proximal muscle weakness (shoulders, hips, trunk, neck – compared to polymyalgia rheumatica which just has stiffness). *No facial involvement* (maybe in IBM only). Dysphagia. Rarely and severely: Respiratory muscles. May → atrophy and contractures (mainly DM). Myalgia affects less than 10%
- DM: skin is the presenting complaint → diagnosed earlier. Gottron's lesions: erythematous plaques or macules over MCP joints, extensor knees, wrist and elbows. Heliotrope rash (blue-purple) on upper eyelids often with oedema. Rash over upper chest, neck. Subcutaneous calcifications. *Dilated capillary loops at the base of the fingernails*. Rough cracked skin on palmar and lateral surfaces of fingers resembling *mechanics hands*
- PM: Do *not* have a rash. Over diagnosed
- Inclusion Body Myositis:
 - Most common of the inflammatory myopathies – usually misdiagnosed as PM until patient doesn't respond to treatment. Maybe misdiagnosed as motor neuron
 - May be asymmetric, *early fine motor involvement*, weakness and atrophy of foot extensors and *deep finger flexors*, *mild facial weakness* (spared in PM and DM)
 - Falling common because of early involvement of quadriceps
 - Other symptoms: Fatigue, malaise, weight loss, fever
 - Causes dysphagia, dysphonia, facial oedema, respiratory weakness
 - Also Raynaud's, lung involvement (interstitial fibrosis), polyarthritis, retinitis, myocardial involvement (arrhythmias)
 - Never affects extraocular muscles
 - Normal sensation and reflexes
- Diagnosis of exclusion
- Differential diagnosis:
 - Infection
 - Muscular dystrophy
 - Endocrine: thyroid, PTH, ↑Ca, ↓K
 - Neurology: motor neurone, Guillian Barre, myasthenia gravis
 - Drugs
 - Skin: SLE
 - Hereditary myopathies
- Pathogenesis:
 - DM: humoral mechanism via complement activation: Activated C3 → membrane attack complexes → deposited on endothelial cell wall → destruction of capillaries and ischaemia in skin, gut, muscle
 - PM and IBM: Cytotoxic T-cell mediated. Antigen specific CD8 cells complex with MHC-1 molecules aberrantly expressed on healthy muscle → necrosis
 - IBM: autoimmune disease in 15%, some hereditary forms
- Investigations:
 - ↑ESR, CRP, CK (elevated by up to 50 times, can be normal in IBM), maybe ↑AST and LD
 - RF positive in 50%
 - ANA may be +ive, as well as myositis specific antibodies (eg Anti Jo-1 – linked to HLA DR3 – positive in < 25%, can occur in patients with interstitial lung disease without myositis, anti-Scl in overlap syndromes)
 - EMG → denervation and myopathy: voluntary motor units have low amplitude units of short duration. ↑Spontaneous activity with fibrillations and positive sharp waves
 - Biopsy:
 - DM: inflammation is predominantly perivascular
 - PM: CD8+ infiltrates surrounding and invading healthy muscle fibres expressing MHC1. Can be stained for CD8/MHC1 complexes
 - IBM: rimmed vacuoles, eosinophilic inclusions, myofibre atrophy, *amyloid*, abnormal mitochondria
- Associations:
 - Other autoimmune rheumatological diseases
 - DM: Malignancy in 10 – 15% – ovary, GIT, lung, breast and non-Hodgkin's lymphoma. No benefit from asymptomatic CT screening
 - Coxsackie virus, rubella & influenzae
- Treatment (treat patient not the CK):
 - Active graded exercise between attacks
 - Steroids: High dose tapering over 10 weeks. May cause steroid myopathy

- Immunosuppressive drugs if severe or unable to taper steroids (never tested in RCTs): Usually azathioprine or methotrexate. Cyclosporin (mild benefit), mycophenolate and cyclophosphamide (limited benefit and significant toxicity) are alternatives
- Rituximab shown in a small trial to benefit DM
- IV Ig (short lived benefit → may require 8 weekly infusions) or plasmapheresis – third line but may → rapid improvement
- Prognosis: IBM generally resistant to immunosuppressive drugs and least favourable prognosis (walker or wheel chair in 5 – 10 years)

Polymyalgia Rheumatica

- See Lancet 19 July 2008
- Old ladies with morning stiffness in proximal muscles +/- mild polyarthritis, depression, fever, anorexia, maybe angina, hypopituitarism, *not* weakness
- May be features related to underlying CTDs (arthritis if superimposed RA, headache in GCA ⇒ ask about headaches, visual disturbance etc)
- ?Syndrome with many underlying causes (eg variety of connective tissue diseases)
- Differential:
 - RA with onset of central joints
 - Frozen shoulder
 - Carcinomas: breast, thyroid, prostate
 - Myeloma
 - Polymyositis
 - Bacterial endocarditis
- Investigations: ↑ESR, anaemia, no abnormality on X-ray, usually RF and ANA negative, CK *not* usually raised, liver involvement → ↑ ALP
- Treatment: dramatic response to low dose steroids (eg 15 mg/day)
- 10 – 20% go on to develop giant cell arteritis – strong relationship – ?spectrum of the same disease. PET scan uptake in subclavian arteries on 30% of isolated PMR

Vasculitis

- Associations:
 - Occurs in non-organ specific autoimmune diseases (eg RA, SLE)
 - Principal feature of other connective tissue diseases that may or may not be autoimmune
 - Also occurs in conditions not usually included in connective tissue diseases (eg drug reactions)
- Types:
 - Great deal of overlap
 - Large vessel vasculitis: Giant cell arteritis, Takayasu's arteritis
 - Medium sized vessels: Polyarteritis Nodosa (PAN), Kawasaki's disease
 - Small vessel vasculitis: Wegener's Granulomatosis, Microscopic Polyarteritis, Henoch-Schonlein purpura, Churg-Strauss, Cryoglobulinaemic Vasculitis, Cutaneous Leukocytoclastic vasculitis
- Mechanisms of vessel damage:
 - Immune-complex formation and/or deposition (probably in all of them): HSP, Serum sickness, Hep C cryoglobulinaemia, Hep B associated PAN → complement activation (esp C5a) → strongly chemotactic for neutrophils → immune mediated damage → compromise of vessel lumen → ischaemia
 - Production of anti-neutrophilic cytoplasmic antibodies: Wegener's, Churg Strauss, microscopic polyangitis
 - Pathogenic T lymphocyte responses and granuloma formation: Giant cell, Takayasu's, Wegener's, Churg-Strauss
- Granuloma: either due to delayed hypersensitivity and cell-mediated damage, or response triggered directly by endothelial cells
- General approach:
 - Diagnosis suggested by: palpable purpura, pulmonary infiltrates, microscopic haematuria, inflammatory sinusitis, mononeuritis multiplex, unexplained ischaemic events
 - Exclude:
 - Infectious diseases: endocarditis, EBV, HIV, gonococcal infection, syphilis, Lyme disease...
 - Coagulopathies: antiphospholipid syndrome
 - Neoplasm: lymphoma, carcinomatosis (Hairy cell leukaemia with PAN)

- Drugs: cocaine, amphetamines, ergot alkaloids, arsenic
- Sarcoidosis
- Atheroembolic disease
- Goodpasture's syndrome
- Amyloidosis
- Migraine
- Formal diagnosis usually requires biopsy

Summary of distinguishing features

	Vessels	Signs/Symptoms	Investigations	Treatment
Giant Cell	Extracranial and carotid branches	Jaw claudication, visual loss	ESR, biopsy showing granuloma, giant cells	Pred
Takayasu's	Aorta and large branches (esp subclavian)	Arm claudication, HTN (renal artery stenosis)	ESR, angiography showing stenosis	Pred +/- MTX
PAN	Medium (not small)	Renal artery stenosis, neuropathy, abdo pain. Not lungs	ESR, beaded pattern on angiography, necrotizing vasculitis without granuloma, no GN. 30% Hep B	CycloP + Pred
Wegner's	Small	Upper & lower Resp tract. Renal	cANCA, granulomatous, pauci-immune focal segmental GN	CycloP + Pred. AZA maintenance, MTX if intolerant
Microscopic polyangiitis	Small	Renal, haemoptysis, neuropathy (like Wegner's but no URT or pulmonary nodules)	pANCA, necrotising vasculitis without granuloma, pauci immune	CycloP + Pred. AZA maintenance, MTX if intolerant
Churg-Strauss	Small	Asthma, rhinitis, neuropathy	ANCA 50%, marked eosinophilia	Pred
HSP	Small	Purpura, arthritis, abdo pain, renal	Skin biopsy: IgA deposition	Pred for GI/arthritis symptoms only
Cryoglobulinaemia	Small	Purpura, arthritis, neuropathy	Cryoglobulins, Hep C, Myeloma. Biopsy: immune complexes. Renal: membranoproliferative	Underlying disease
Leukocytoclastic Vasculitis/ Hypersensitivity Angiitis	Small	Purpura, necrotic papules, ulcers, urticaria	Skin Biopsy. Drugs, SLE, Hep B related	NSAIDS, antihistamine, dapson, colchicine, thalidomide
Behcet's	Large-small	Oral + genital ulcers, eyes, acquired blindness	Pathergy test (sterile pustules at phlebotomy sites in some)	NSAIDS, antihistamine, dapson, colchicine, thalidomide

Differential of Small Vessel Vasculitis by Investigations

	HSP	Cryoglobulinaemia	Microscopic Polyangiitis	Wegner's	Churg Strauss
IgA deposits	+				
Cryoglobulins		+			
Serum ANCA			+	+	+
Granulomas				+	+
Asthma & Eosinophils					+

Immunosuppression in Vasculitis

- Anti-TNF:
 - Infliximab: small open label studies with short term remission seen. No effect over steroids in GCA
 - Etanercept: RCT showed no effect on remission or maintenance and ↑cancer risk (had usually previously been on cyclophosphamide – so double whammy)
- Lower grade evidence for methotrexate and leflunomide in ANCA+
- Emerging evidence of MMF in ANCA+ vasculitis induction
- Rituximab: in Wegner's open label study in salvage therapy shows benefit
- If all else fails in ANCA+ use plasmapheresis (small data)

Giant Cell Arteritis/Temporal Arteritis

- Large and median muscular arteries – aortic, subclavian, external carotid and branches (usually one or more branches of the carotid artery, especially temporal arteries → medical emergency – affects retinal arteries).
- Almost exclusively > 50 years, peaking at 75
- Genetic associations: HLA-DR4 and DRB1 locus
- Clinical: Initially persistent headache, then superficial pain and tenderness over temporal arteries +/- decreased pulsations, unilateral visual disturbance, arthritic pain, jaw claudication (the most specific symptom), fever, malaise, ↑ESR (age and ESR both over 60 in 3/4 cases). Associated with risk of aortic aneurysm
- Immune reaction with internal elastic lamina (? antigen in arterial wall) which causes swelling into the lumina and stenosis. *CD4+ most important cell in it's pathogenesis*
- Diagnosed by biopsy showing giant cells engulfing the IEL and inflamed media. May be segmental involvement so yield improved by 3 – 5 cm section. Biopsy is critical as treatment should continue for 2 years and therefore want to be sure of diagnosis
- Treatment:
 - Steroids:
 - Presumptive treatment with steroids starting at 40 mg/day – equivalent to 60 or 80 (biopsy still positive for up to 14 days afterwards)
 - Initial pulsed methylprednisone at 15 mg/kg for 3 days → lower overall relapse rate and reduced cumulative steroid dose (2006 study)
 - Immediate risk is blindness, but longer-term morbidity is due to steroid treatment!
 - Aspirin to ↓stroke risk
 - Methotrexate vs steroids trialled with conflicting results
- Relapse 60 – 85%
- Overlaps with Polymyalgia Rheumatica in 25% of cases (→ stiff proximal muscles in the morning). See Polymyalgia Rheumatica, page 268

Polyarteritis Nodosa

- Affects young adults. M:F = 4:1. Very uncommon
- Presents with non-specific symptoms – fever malaise, abdominal pain, renal failure, purpura.
- Immune complex mediated arteritis (type 3 hypersensitivity)
- 30% associated with Hep B, and also hairy cell leukaemia
- Necrotising vasculitis of medium sized arteries (not arterioles, nor venules – if so consider microscopic polyangiitis). Involves smaller arteries – kidney (arteritis without glomerulonephritis → HTN and ↑Cr), heart, liver, GI, *not* usually lungs. Often patchy distribution. Macroscopic: small nodules. Microscopic: fibrinoid necrosis, intimal proliferation, media destruction, inflammation of adventitia, scarring if chronic
- Aneurysmal dilatations up to 1 cm are characteristic (may be seen on angiography). Not granulomas nor ↑eosinophils
- Investigations: FBC, biopsy of affected organ, ECG, ANCA rarely +ive
- Treatment: steroids/immunosuppressives (azathioprine/cyclophosphamide). ?Anti-retrovirals for Hep B
- Poor prognosis if untreated – death from bowel infarct/perforation or CVD. Relapse in 10%

Kawasaki Disease

- = Mucocutaneous Lymph Node Syndrome ~ Childhood Polyarteritis Nodosa
- Immune mediated injury to vascular endothelium, including coronary artery arteritis
- ?post viral
- Fever in kids (usually < 5) for > 5 days with bilateral, non-purulent conjunctival infection, oral mucosal changes, cervical lymphadenopathy, changes in the extremities (eg swelling of hands), and generalised rash
- Investigations: Echo for coronary aneurysm, FBC (↑WBC, ↑platelets), ↑CRP
- Differential: Scarlet fever, EBV
- Complications: pancarditis, aneurysms or dilatation
- Treatment: none, or high dose IgG/steroids

Wegener's Granulomatosis

- Wegner's triad: aseptic necrosis of the lower and upper respiratory tract and focal glomerulonephritis of the kidney
- Generalised necrotising arteritis of small-medium sized arteries of the respiratory tract and kidney with non-caseating intra-vascular or extra-vascular granuloma formation. Inflammation of the sinuses and nasopharynx (and any other organ, including eyes, skin and more rarely heart)
- 3 per 100,000, M = F, mean onset 40, extremely rare in black Americans
- Presentation:
 - Upper airways disease (chronic rhinitis/epistaxis/sinusitis/mouth ulcers) unresponsive to therapy. CXR shows spots. May have haemoptysis. Progresses to ulceration of nasal mucosa, perforation of the septum, heavy nose bleeds, granulomatous invasion of large bronchi → bronchial stenosis
 - Glomerulonephritis. If untreated then slow progression to end stage renal failure
 - Systemic: fever, night sweats, weight loss
 - Non-deforming arthritis and arthralgia
 - ↑incidence of thrombotic events
- Progression highly variable
- Pathology: ↑IFN-γ, TNFα, CD4+ cells, but not IL-4, IL-5, or IL-10. Th1 type cytokine pattern
- Investigations:
 - ↑ESR, cANCA positive, ↑ IgA, CXR (nodular masses, cavitation)
 - Renal biopsy: necrotising glomerulonephritis: may be focal and crescentic. Immunofluorescence is –ive ⇒ pauci-immune
- Differential: lymphomatoid granulomatosis, EBV +ive B cell proliferation with 50% → malignant lymphoma
- Treatment:
 - Prior to treatment universally fatal, usually within a few months of renal disease
 - Remission induction with cyclophosphamide + steroids → 90% remission but frequent relapse. Continue for a year then taper off
 - Could swap to methotrexate or azathioprine for remission maintenance, or use methotrexate for induction if not severe
 - Biologics:
 - Etanercept (TNF blocker): made no difference when added to standard regime
 - Favourable preliminary results with rituximab
- Relapse in 50%

Microscopic Polyarteritis

- Mean age onset 57
- Necrotising vasculitis of small-medium sized vessels, including venules, with no immune complexes
- Multisystem involvement including glomerulonephritis and lungs (ie rapidly progressive renal failure and haemoptysis)
- Differentiate from Wegener's by absence of granuloma
- Kidney involvement: crescentic rapidly progressive GN common, no immune deposits on immunofluorescence (ie pauci immune)
- Biopsy: fibrinoid necrosis and cellular proliferation within capillaries
- 75% +ive for pANCA
- Treatment: similar to Wegener's – little trial evidence
- Poor prognosis (74% 5 year survival in treated patients) – death from bowel infarcts/perforation or from CVD. Relapse in 34%

Henoch-Schonlein Purpura

- Leukocytoclastic vasculitis of small vessels with deposition of C3 and IgA immune complexes in the skin, gut and kidney
- Usually in young children, associated with URTIs
- Palpable purpuric rash over the buttocks and ankles, abdominal pain and arthralgia
- Renal involvement: macroscopic or microscopic vasculitis, mesangioproliferative glomerulonephritis (variant of Mesangial IgA disease, see page 128), maybe crescentic, IF +ive for mesangial IgA deposition
- Usually self-limiting, otherwise steroids for symptoms – but not shown to change natural history

Other Vasculitis

- **Hypersensitivity angiitis/(Leukocytoclastic vasculitis):** Type 3 immune injury presenting with purpura, necrotic papules, ulcers and urticaria. Associated with medicines, lupus, HBV. Diagnosis: biopsy. Microscopically: neutrophils, fibrinoid necrosis
- **Churg-Strauss Syndrome:** aka allergic angiitis and granulomatosis: asthma, striking peripheral and tissue eosinophilia, extravascular granuloma, and vasculitis of multiple organ systems. Mononeuritis multiplex in 72%, pANCA +ive in approx ~50%. Steroids alone effective in many patients
- **Idiopathic Cutaneous Vasculitis:** Inflammation of the blood vessels of the dermis – usually secondary or as part of a vasculitis syndrome. Palpable purpura, papules, vesicles, bullae, ulcers, urticaria. Generally treatment resistant
- **Essential Mixed Cryoglobulinaemia:** Present with purpura, arthritis, neuropathy, renal failure. Cryoglobulins are cold-precipitable monoclonal or polyclonal immunoglobulins. Mostly an aberrant immune response to Hep C (in 5% of Hep C patients). Rarely in lymphoproliferative disorders (eg myeloma), CTD and infection. Skin involvement and proliferative glomerulonephritis (not focal segmental), also arthritis and peripheral neuropathy. Bloods: circulating cryoprecipitates, RF +ive, hypocomplementaemia in 90%, usually Hep C +ive. Treat Hep C if possible. Fairly treatment resistant – treat underlying disease. Kidney involvement → poorer prognosis
- **Takayasu's arteritis:**
 - Aka Pulseless Disease
 - Aortic thickening (and aortic branches, especially subclavian) with autoimmune granulomas → chronic thickening of the wall
 - Rare. Typically young adult women in Asia/Japan
 - Initial presentation: fatigue, low grade fever, night sweats, weight loss, hypertension, pain of affected artery. Discrepancies in blood pressure, arterial bruits. ↑ inflammatory markers
 - Do angiogram – biopsy difficult: focal stenosis on multiple major arteries (may require bypass or stenting)
 - Treatment uncertain – steroids +/- methotrexate. Chronic, relapse common
 - Complications: eventual stenosis, occasional aneurysms
- **Thromboangiitis Obliterans** = Buerger's disease. Neurovascular bundles – mainly in legs and arms of young/middle aged smokers – become inflamed and thrombosed
- **Behcet's Disease:** Named after the Turkish dermatologist who first described it. Systemic vasculitis, commoner in Turkey and Japan (the "Silk route"), oral (no scars) and genital ulcers sparing glans (→ scrotal scarring) lasting 1 -2 weeks, erythema nodosum like lesions but they ulcerate, eye lesions, arthritis of knee, ankles, wrists and elbows. HLA-B5 association. Antibodies to ACSA (also found in Crohn's disease). Superficial or DVT in 25%. Treatment: topical steroids, thalidomide if severe, aspirin, maybe colchicine
- **Isolated Vasculitis of the CNS:** Small vessel arteritis, presenting with headache, altered mental function or focal deficits. Diagnostically difficult – MRI, LP, angiography or brain/meninges biopsy. Treatment prednisone +/- cyclophosphamide
- **Relapsing Polychondritis:** rare inflammatory disorder of unknown cause affecting the cartilage of the ears, nose and laryngotracheobronchial tree. Associated with a number of CTDs and Vasculitis?. Treatment – initially higher dose steroids

Osteoarthritis

- See BMJ 18 March 2006
- Caused by aberrant local mechanical factors (misalignment, muscle weakness, loading) in the context of systemic susceptibility (especially older age, also female sex, polygenic genetic predisposition – no genes identified)
- Presentation:

- Pain (usually exacerbated by exercise, initially relieved at rest, eventually painful also at rest), stiffness, reduced movement, swelling, crepitus, maybe bony swelling and age > 40 in the absence of systemic features (eg fever)
- Knee OA most commonly presents initially in the medial compartment
- If effusion, it should be non-inflammatory (<2000/mm white cells, clear, viscous)
- Involves entire joint:
 - Bone remodelling and sclerosis, osteophyte formation
 - Cartilage breakdown
 - Meniscal damage
 - Synovial hypertrophy
- Results in structural and functional failure of synovial joints
- Marked change must be present to detect changes on xray (ie not sensitive)
- Management:
 - Assess in the context of the individual's function, quality of life, occupation, mood, relationships and leisure activities
 - Education
 - Low impact exercise: including local muscle strengthening and general aerobic fitness
 - Physical therapy: range of motion exercises, muscle strengthening, muscle stretching (anything to do with the knee → refer to physio)
 - Weight loss if overweight if knee or hip arthritis
 - Use of supportive footwear (shock absorbing)
 - Adjunct therapies: TENS, braces, joint supports (eg valgus bracing of the knee), insoles, assist devices (eg walking stick)
- Drug treatment ladder (NICE guidelines):
 - Paracetamol
 - For knee and hand consider topical NSAIDs
 - Oral NSAIDs or opioid
 - If NSAID then use at lowest dose for shortest period, and use a PPI with NSAID or COX-2
 - Intra-articular cortico-steroid injections for the relief of moderate/severe pain – short term relief (ie 1 week)
- Acupuncture, glucosamine (Cochrane 2009 – variable quality trials, the best ones show no benefit) and chondroitin have been shown to be ineffective in RCT (same as placebo)
- Surgical referral:
 - Don't refer for arthroscopic lavage and debridement unless knee arthritis with a clear history of mechanical locking, giving way or xray evidence of loose bodies. Almost all knee arthritis has meniscal tears – but these are not necessarily the cause of symptoms
 - Meniscal tears are common in the general population. Arthroscopic surgery of OA of the knee provides no additional benefit to optimised physical and medical therapy (NEJM 11 Sept 2008)
 - Refer for joint replacement if pain, stiffness and reduced function that substantially affect their quality of life and are refractory to non-surgical treatment. With proper selection, excellent results in 95% with implant survival expected to be 95% at 15 years

Amyloidosis

- Extracellular deposition of insoluble polymeric protein fibrils, caused by misfolding of proteins (usually α -helical folding)
- All have a common β -pleated sheet structure that stains with Congo Red stain
- *All amyloid contains serum amyloid P at a concentration of ~ 15%*
- Diagnosis:
 - Biopsy: if systemic then any organ will show deposits – fat is 80% sensitive and easy to FNA. Used to use rectal biopsies
 - Once amyloid found on staining, needs to be typed
 - Non-specific findings on blood tests. Hypoalbuminaemia if proteinuria. \uparrow BNP if cardiac involvement. \uparrow ALP with cholestasis 2nd to liver involvement. Hypothyroidism if gland infiltration, etc
- AL Amyloid (L for Light chain):
 - = Primary systemic amyloidosis
 - 4.5 per 100,000
 - Kappa or Lambda Lights chains of Ig immunoglobulins from a clonal B cell marrow disorder

- Like myeloma – except those proteins are properly folded
- Occurs in multiple myeloma (20%), Non-Hodgkins lymphoma, Waldenstrom’s macroglobulinaemia
- Presentation:
 - Kidney’s: proteinuria, often in nephrotic range. Test urine – but usually not sufficient quantity to detect on electrophoresis
 - Cardiac involvement: low voltage ECG, concentrically thickened ventricles
 - Neurology: peripheral sensory neuropathy, carpal tunnel syndrome (25%)
 - Macroglossia in 10%
 - Hepatomegaly and splenomegaly
 - Cutaneous ecchymoses – especially around the eyes (“raccoon-eyes”)
- Rapidly fatal if not treated
- Screen for cardiac, renal, hepatic and autonomic involvement and factor X deficiency
- Treatment:
 - As for multiple myeloma. Cyclic oral melphalan + prednisone or dexamethasone. Autologous cell transplant but peritransplant mortality higher than for other indications because of impaired organ function
 - Supportive: diuretics and stockings for oedema, no evidence of effect of ACEIs, diuretics for CHF (CCB and β -blockers relatively contraindicated). Amiodarone for arrhythmias
- AA Amyloid:
 - = Secondary amyloidosis
 - Composed of the acute phase reactant serum amyloid A protein (SAA) produced in the liver – occurs in chronic inflammatory or infectious diseases. Now rarer given better anti-inflammatory treatment. Consider if inflammatory condition and multiple organ dysfunction
 - Screen for renal and hepatic involvement
 - Recent RCT showed eprodisate → delays progression (binds amyloid fibrils and destabilises them). No benefit from colchicine
 - Familial Mediterranean Fever: a group of recessively inherited diseases with recurrent fever and serosal, synovial or cutaneous inflammation and, in some, the eventual development of systemic AA amyloidosis. Colchicine prophylaxis reduces recurrence and progression to amyloidosis
- AF Amyloid:
 - Familial ATTR Amyloidosis is the most common
 - Transthyretin is the most commonly implicated precursor protein
 - Onset in midlife
 - Screen for neuropathy, heart, screen relatives
 - Liver transplant removes the major source of variant TTR production
- A β 2M Amyloid:
 - Occurs in *end stage renal failure* (eg on dialysis for many years – too big to dialyse → accumulation), levels elevated in ESRF due to ↓excretion by the kidney
 - Presents with most commonly with carpal tunnel and shoulder pain, also persistent joint effusions (can test synovial fluid), spondyloarthropathy, bone cysts...
 - Should be a thing of the past with newer, less inflammatory dialysis membranes
- A β Amyloid:
 - Alzheimer’s Disease – the most common localised amyloidosis
 - Abnormal proteolytic processing of the amyloid precursor protein APP

Arthritis Associated with Systemic Disease

- Arthropathy of acromegaly:
 - → OA, back pain, muscle weakness and carpal tunnel
 - Arthritis clinically resembling OA: disorganised cartilage overgrowth which then breaks down, ligament laxity
- Arthropathy of haemochromatosis:
 - From age 50, 2nd to iron damage to cartilage
 - OA like, affecting small joints (*initially 2nd and 3rd MCP joint*) then large joints. Stiffness and pain, brief morning stiffness
 - Xray: irregular narrowing of the joint space, subchondral sclerosis and subchondral cysts, hook-like osteophytes
 - Non-inflammatory synovial fluid

- In half there is evidence of CPPD
- May progress despite phlebotomy
- Treatment: NSAIDs
- Haemophilic arthropathy:
 - 2nd to haemarthrosis
 - Knees, ankles, elbows, shoulder's hips from age of 1 when they start to walk
 - With repeated bleeding →swollen joints and flexion deformities
 - Muscle bleeds (eg into psoas) can also cause pain → flexion deformities
 - Hard to distinguish acute bleed from septic arthritis – always aspirate and treat for both
 - Xray changes like OA: early on capsular distension, later marginal erosions and subchondral cysts, joint space narrowing
 - Studies have shown ibuprofen OK for a short period, COX-2 have no platelet effect so presumed safe
 - Synovectomy may help if recurrent
- Associated with haemoglobinopathies:
 - Sickle cell disease: sickle cell crisis associated with periarticular pain and joint effusions, osteomyelitis of the long bones, bone infarction 2nd to thrombosis 2nd to sickling of red cells, avascular necrosis in ~5%
 - Thalassaemia symmetric ankle arthropathy in 2nd or 3rd decade (mainly thalassaemia major and intermedia)
- Familial hypercholesterolaemia: recurrent migratory polyarthritis, Achilles tendonitis (may → xanthomas)
- Neuropathic Joint Disease (Charcot's joint): loss of pain, proprioception or both. Most commonly DM, also leprosy, syringomyelia, meningomyelocele, Charcot-Marie-Tooth and amyloidosis
- Hypertrophic osteoarthropathy and clubbing (HOA) or Hypertrophic Pulmonary Osteoarthropathy (HPOA):
 - Clubbing always a feature (and early stage of HOA): loss of the normal 15o angle between nail bed and cuticle, enlargement of the distal volar pad, base of the nail feels spongy, and the nail can be rocked on its bed. Marked periungal erythema
 - May experience joint pain, most often in the ankles, wrist, knees
 - Primary/familial: onset in early teenage years – clubbing and periostitis
 - Secondary/Acquired: associated with intrathoracic malignancies (most commonly bronchogenic carcinoma, infrequently metastases), suppurative lung disease, congenital heart disease, thyroid acropachy (Graves disease – treated or untreated – with clubbing and periostitis)
 - On xray – a thick wavy periosteal reaction. Bilateral and symmetric. Leads to thickened cortical bone

Heritable Disorders of Connective Tissue

- Osteogenesis Imperfecta: various genetic defects giving decreased bone mass (osteopenia). Progressively associated with blue sclera, dental abnormalities, progressive hearing loss and a positive family history. Range from mild to severe
- Ehlers-Danlos Syndrome: hyper-elasticity and easy scaring of the skin (described as velvety) and hyper-mobile joints. A variety of genetic mutations, inheritance patterns, and affected proteins (including Collagen V and III). Also mitral valve prolapse
- **Marfan Syndrome:**
 - Prevalence of 1:5,000
 - Long thin extremities, loose joints, chest deformities, reduced vision (a result of lens dislocation) and aortic aneurysms.
 - Progressive aortic root dilation with associated AR and ascending aortic rupture/dissection. The primary cause of mortality in Marfan's
 - 90% have autosomal dominant mutation of fibrillin-1 gene (FBN1) making fibrillin-1
 - Little correlation between severity of disease and Marfan symptoms
 - If > aortic root size:
 - Annual echo follow-ups
 - Attenuate dilation with β -blockers
 - Replace aortic root when > 5 cm
 - ↑Risk in pregnancy/post partum – so consider surgery in women considering pregnancy

Pain Syndromes

Chronic/Complex Regional Pain Syndrome (Type 1)

- = Reflex Sympathetic Dystrophy
- =Algodystrophy
- Can develop as a consequence of trauma affecting the limbs with or without obvious nerve lesion
- Cause: ?peripheral sympathetic over-activity, pathological interaction of sympathetic and afferent systems
- Presentation:
 - Pain
 - Abnormal blood flow (cold or hot) and sweating (including distal to the trauma)
 - Structural changes eg muscle wasting (over months to years can → contractures)
- Treatment: difficult: pain relief, rehabilitation, physio, early refer to pain management clinic

Fibromyalgia

- Aetiology: unknown
- Presentation:
 - Diffuse musculoskeletal pain (over all 4 quadrants and axial) but normal muscle power
 - Morning stiffness
 - Paraesthesia
 - Tender points over the body
 - Skin fold tenderness
 - Sleep disturbance, fatigue and vertigo
- ESR usually normal
- Associations: Raynaud's phenomenon, anxiety/depression, IBS
- Diagnosis: based on finding a number of separate, defined tender points
- Treatment: analgesics and exercise

Infectious Diseases

- For Pneumonia, see page 195
- For Hepatitis B & C, see page 350
- For Infection in Pregnancy, see page 464

- Golden Rules of Infectious Diseases (Patrick Charles, Melbourne Course);
 - Sepsis:
 - Recurrent rigors are most likely due to bacterial infection (therefore rigors = admit)
 - Severe muscle pain may be a symptom of sepsis, even without fever
 - When suspecting bacteraemia, don't wait for a fever to do cultures
 - The older, the colder: don't assume an afebrile elderly person is not septic
 - Sepsis with hypothermia has worse prognosis than sepsis with fever
 - Fever in the elderly is rarely caused by viral infections
 - Early meningococcal rash may resemble a non-specific viral rash
 - Think of vertebral osteomyelitis or epidural abscess in a patient with fever and back pain
 - When a patient has a post-op fever it is usually related to the surgical procedure
 - An elderly patient from a TB-endemic area with fever and multi-system disease has disseminated TB until proven otherwise
 - Staph aureus in the urine is a sign of staph bacteraemia until proven otherwise
 - A moveable joint does not exclude septic arthritis
 - Infection in a diabetic will flourish until the diabetes is controlled
 - If treating for HSV encephalitis, also treat for Listeria meningoenephalitis
 - Pus should be sent to the lab in a specimen jar or in a syringe rather than by swab
 - The great mimics are:
 - TB
 - HIV
 - Syphilis
 - Lyme disease in returned travellers
 - Whipple's disease

Antibiotics

- Issues:
 - Empiric verses directed therapy
 - Use of as narrow a spectrum AB as possible
 - Use a single agent unless good reason to do otherwise
- Wgtn Antibiotic Guidelines:
 - Ceftriaxone the only reliable AB for N gonorrhoeae
 - N Meningitidis, S pyogenes and S agalactiae are sensitive to penicillin
 - Acute osteomyelitis/septic arthritis: Flucloxacillin, alternative Cefazolin
 - Cellulitis/Erysipelas:
 - Outpatient: Flucloxacillin po 1 g q 8 h for 3/7 then 500 mg q 8h for 7/7 or erythromycin po 400 mg q6h
 - Admitted: Flucloxacillin iv 1g q6h or Cefazolin iv 1g q8h (1st generation)
 - Necrotising Cellulitis/Fasciitis: Benzylpenicillin iv 4 mu (2.4 gm) q4h and clindamycin iv 600mg q6h
 - Diabetic foot infections:
 - Mild: oral augmentin or oral cefaclor and metronidazole
 - Severe: augmentin iv or cefuroxime and metronidazole iv
 - Mastitis: Breastfeeding: Flucloxacillin or cefaclor, non-breast feeding: augmentin or cefaclor and metronidazole
 - Prostatitis: Ciprofloxacin
 - Surgical prophylaxis: Cefazolin (+/- metronidazole if abdominal): broader spectrum and less reactions than flucloxacillin

Mechanisms of Antibiotic Action and Resistance

Overview of Mechanisms Of Resistance

- Types of Resistance:
 - Intrinsic resistance: it's always been there eg *Gram negative's resistance to vancomycin* (ie spectrum), Klebsiella and amoxycillin
 - Acquired: mutation of resident genes or acquisition of new genes in the face of antibiotic pressure:
 - Spontaneous DNA mutation, eg S aureus and rifampicin
 - Acquisition of new DNA:

- Bacteriophages
- Transduction: a virus infecting a bacteria can pick up and pass on some bacterial DNA
- Plasmid: circular dsDNA separate from the chromosome that replicates autonomously
- Integron: site specific recombination which allows for horizontal transfer of gene cassettes
- Transposon: “jumping genes” that jump from chromosomes to other chromosomes and plasmids, replicating as they do. Not site specific \Rightarrow can cause mutations. 45% of the human genome is made up of transposons or their remnants
- Mechanisms of resistance:
 - Antibiotic inactivation:
 - β -lactamases
 - Pneumococcus to macrolides (erm – erythromycin methylation gene)
 - Enzymatic modification of aminoglycosides
 - Alteration of antibiotic target:
 - Pneumococcus and penicillin
 - S aureus and methicillin-like antibiotics
 - Decreased uptake:
 - Reduced penetration: Porins – pseudomonas and carbapenems
 - Antibiotic efflux: Pneumococcus and macrolides (mef – macrolide efflux gene)

Resistance Mechanisms to Common Antibiotics

- Beta-Lactams:
 - Beta-lactamase:
 - Most common mechanism of bacterial resistance to beta-lactams is destruction of the drug by beta-lactamases
 - Can combine an antibiotic with a beta-lactamase inhibitor (eg clavulanic acid) – however none has been produced that can resist all of the many beta-lactamases identified
 - Beta-lactamase enzyme classes:
 - A: Penicillinases (TEM, SHV, CTX-M)
 - B: Metalloenzymes (VIM, IMP)
 - C: Cephalosporinases (AmpC)
 - D: Oxacillinases (OXA)
 - Alteration in PBP (penicillin binding protein) reduces affinity for the drug
 - *Not* a beta-lactamase
 - Eg Staph, strep, gono and meningo resistance to penicillin
 - *Most common mechanism in pneumococcal resistance*
 - β -lactam resistance is typically associated with erythromycin, chloramphenicol, tetracycline and co-trimoxazole resistance
- Cephalosporins (β -lactams as are penicillins):
 - Penetrate CSF poorly unless the meninges are inflamed (ceftriaxone OK)
 - Cefuroxime: less susceptible to inactivation by beta-lactamases, and greater activity against H influenzae, and N gonorrhoeae
 - Third generation (Cefotaxime, ceftazidime and ceftriaxone) greater activity against G-ive but less active against G positive – especially Staph Aureus
 - Ceftazidime (3rd generation) has good activity against pseudomonas (better than ceftriaxone)
 - Cefoxitin: active against bowel flora including bacteroides fragilis \Rightarrow used in abdominal sepsis
 - Cefaclor: skin reactions, esp in kids
- Carbapenems: are β -lactams
- Vancomycin:
 - See also VRSA and VRE, page 282
 - Inhibits bacterial cell wall synthesis by binding to the D-alanine-D-alanine, inhibiting addition of further subunits to the peptidoglycan backbone. Genes encoding resistance carried on plasmids that can transfer from cell to cell \rightarrow vancomycin unable to bind to cell wall (Enterococcus resistance). Also new resistance in S aureus and S epidermidis due to markedly thickened cell walls
 - Avoid rapid infusion. Risk of anaphylactoid reaction
 - SE nephrotoxicity, ototoxicity, neutropenia
 - Vancomycin monitoring (Wgtn AB guidelines):
 - Usual dose: Vancomycin iv 1g infused over 100 minutes q12h, if CrCl > 50 ml. If elderly start at 500 mg

- Monitoring: trough level before the third dose of vancomycin, target trough levels to be within the range 10 – 20 mg/L
- If normal renal function, monitor once a week. More often if elderly, rapidly changing renal function, prolonged or high dose treatment, on other nephrotoxic drugs (eg gentamicin)
- Quinolones:
 - eg nalidixic acid, and fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin)
 - Inhibit the activity of the bacterial enzymes DNA gyrase and topoisomerase IV – responsible for negative supercoiling of DNA. Most common mechanism of resistance is point mutations in the target enzymes (need mutations in both enzymes for resistance). Also mechanisms that reduce permeability or promote efflux. *S. Aureus* only uses topoisomerase and *Pseudomonas* only uses DNA gyrase – so resistance to these is easier to acquire as only needs one mutation, and then a resistant strain is quickly selected
 - Ciprofloxacin is only moderately active against strep pneumoniae (hence the development of the “respiratory quinolones” levofloxacin and moxifloxacin). Is active against chlamydia and gonorrhoea
 - SE: tendon inflammation and damage (eg rare ↑risk of Achilles tendon rupture, esp with steroids)
 - Caution: seizures, G6PD deficiency, myasthenia, renal impairment, pregnancy and breast feeding, photosensitivity, children (risk of arthropathy in animal studies)
- Aminoglycosides:
 - Bactericidal, bind to bacterial ribosome blocking protein synthesis. Works via “post-antibiotic effect” – it is peak dose not maintenance of MIC that is key
 - Bacterial uptake is an aerobic, energy dependent process ⇒ activity markedly reduced in anaerobic conditions. Poor CNS penetration
 - Most common mechanism of resistance is inactivation of the antibiotic by adding groups to it (eg hydroxyl group), also ↓permeability through outer wall membrane and active efflux
- Metronidazole
 - A synthetic imidazole. Is active only against anaerobic bacteria and protozoa
 - Causes bacterial DNA damage. Little resistance
 - Also Carbapenems and chloramphenicol for anaerobes. Not aminoglycosides, trimethoprim, or β-lactams
 - Don't use metronidazole for aspiration – this habit is based on old bad studies. Most – even with anaerobes – get better without it. Only needed if effusion or really bad gums
- Trimethoprim and sulphonamides: most common mechanism is acquisition of plasmid encoded genes – insensitive dihydrofolate reductase for trimethoprim and an altered dihydropteroate synthetase for sulphonamides

New Gram Positive Antibiotics

- Linezolid:
 - Inhibits protein synthesis at the 50S ribosome – unique mechanism of action so no cross-resistance
 - First agent of the new class of oxazolidones
 - Activity:
 - Bacteriostatic, slowly bactericidal for staph and strep
 - Active against most G+ive (incl *E. faecalis*)
 - Active against mycobacteria and *Nocardia*
 - Not gram –ive (resistant due to efflux pumps)
 - Use: equivalent to vancomycin in the treatment of MRSA in skin/soft tissue, pneumonia and urinary infection (but ↑SE) – unclear in osteomyelitis, meningitis and endocarditis
 - IV = oral (~100% bioavailable). Penetrates well in bone, fat and muscle
 - Dose unchanged in renal and hepatic impairment. No effect on cytochrome P450 isoforms
 - Possible antagonism with other antibiotics (eg vancomycin and gentamicin – very unclear)
 - SE:
 - Nausea, headache and diarrhoea
 - Marrow suppression (thrombocytopenia, anaemia) common → stop therapy
 - Peripheral neuropathy rarer, also lactic acidosis, ocular toxicity, serotonin toxicity (weak MAO inhibitor), avoid tramadol (seizures)
- Quinupristin-dalfopristin:
 - Binds to 50S ribosomal subunit → inhibits protein synthesis
 - Bactericidal in combination
 - Active against more Gram +ives, not *E. faecalis*

- IV only – preferably with central access (makes it less attractive than Linezolid)
- Inhibits CYP 3A4
- SE: Myalgia, arthralgia, infusion site reactions, ↓Na, anaemia, nausea, diarrhoea, rash
- Daptomycin:
 - Potent bactericidal activity against most G +ives
 - ~ equivalent to vancomycin
 - Probably not useful for S Aureus with reduced vancomycin sensitivity
 - Inhibited by surfactant – not use for pneumonia
- Tigecycline:
 - Bacteriostatic protein synthesis inhibitor
 - Low MICs for MRSA, MSSA, VISA, VRE
 - Active against many G –ives – not pseudomonas (efflux)
- Ceftobiprole:
 - A novel cephalosporin, active against MRSA, VRE E faecalis (not E faecium)
 - Similar to cefepime for G –ives (ie not for ESBLs)

New Gram Negative Antibiotics

- Colistin (c1959):
 - Salvage therapy only
 - Aka Polymyxin E (aka detergent!)
 - Replaced in 1970's when "safe" aminoglycosides arrived
 - Not orally absorbed. Can be used for bowel sterilisation in neutropenic patients
 - Binds to lipopolysaccharides and phospholipids in outer cell membrane → disruption, leakage and death
 - Renal and neurotoxicity
- Ertapenem:
 - New, once daily iv carbapenem
 - Looses pseudomonas cover
 - Role uncertain: hospital in the home for polymicrobial infections or some ESBL infections
- Moxifloxacin:
 - Very broad spectrum: MSSA, NORSA, Streps, many G –ives, anaerobes, Legionella, leprosy, TB
 - No data for mycoplasma, chlamydothila, poor for pseudomonas
 - Good tissue penetration and bioavailability
 - Two step resistance (cf 1 for ciprofloxacin)
 - Effect on QT interval

Gram Positive Antibiotic Resistance

Penicillin-non-susceptible S pneumoniae

- Altered PBPs (not beta-lactamase)
- Definitions:
 - Penicillin Sensitive S. Pneumoniae (PSSP): MIC < 2 µg/mL
 - Penicillin Intermediate S Pneumoniae (PISP): MIC = 4 µg/mL
 - Penicillin Resistant S Pneumonia (PRSP): MIC > 8 µg/mL
 - If meningitis the PSSP is < 0.06 and PRSP > 0.12 (lower due to ↓BBB penetration)
- Risk factors: children, day care centres, recent antibiotic exposure (eg azithromycin)
- Penicillin resistance often linked with resistance to other agents (macrolides, cephalosporins, quinolones). Rates of PISP/PRSP vary around the world and correlate to the overall amount of antibiotics used
- Only really significant for meningitis (and otitis media) but pushed by drug companies to market newer ABs

MRSA

- See also page 286
- Defined as an oxacillin MIC ≥ 4 mg/mL
- Confusing nomenclature:
 - CA (community acquired) vs HA (hospital acquired)
 - NORSA (Non-multiply resistant SA) vs MRSA. NORSA frequently susceptible to clindamycin, co-trimoxazole, macrolides, gentamicin

- Resistance to oxacillin or methicillin \Rightarrow resistant to all β -lactams *including cephalosporins*
- Must have a mec gene to be MRSA. MecA encodes penicillin binding protein 2a – an abnormal binding protein
- Mec gene is part of a mobile chromosome element called Staph Cassette Chromosome (SCCmec):
 - Hospital acquired strains: SCCmec types I, II, III:
 - Often multi-resistant (eg macrolides, tetracyclines, chloramphenicol, cotrimoxazole, quinolones, gentamicin)
 - Treatment options eg fusidic acid + rifampicin (not good for pneumonia), linezolid. Meropenem has no action against MRSA
 - Infection control effective – hard to eradicate in a hospital once established
 - Community acquired strains: SCCmec types IV and V:
 - Usually sensitive to trimethoprim-sulphamethoxazole, clindamycin, ciprofloxacin
 - Associated with Aborigines in West Australia, Polynesian ethnicity, eg pyoderma ('school sores'), prisoners, athletes
 - Erythromycin resistance usually predicts clindamycin resistance (both act on 50S portion of bacterial ribosome inhibiting chain elongation)
 - Usually low transmissibility in hospital
 - 3 main strains in Australia: WA (Western Australia), WPSS (Western Pacific), Queensland
 - E-MRSA15 (e for epidemic) – a community strain from the UK, very infectious. Resistance to ciprofloxacin, clindamycin and erythromycin. Cotrimoxazole (a good 2nd line in cMRSA after flucloxacillin) and doxycycline effective, vancomycin if sick
 - Pantan-Valentine Leukocidin (PVL) is a virulence gene associated with some c-MRSA, causing necrotizing skin infections – kills white cells
- Detection:
 - Oxacillin-salt agar screening plates
 - PCR for mecA gene and latex agglutination tests for the protein product of mecA PBP2a most accurate
- Control (for Hospital acquired, data on community-acquired limited):
 - Hospital-acquired MRSA most commonly spread on hands of health care workers
 - Surveillance cultures of high risk patients from anterior nares (sensitivity 73 – 93%) and open lesions (surgical wounds, ulcers) [High Grade evidence]. Patients colonised on admission have a 10 – 30% risk of developing in-hospital or post-discharge MRSA infection
 - Insufficient evidence to support topical or systemic ABs to eradicate MRSA carriage. Data on the efficacy of decolonization with intranasal mupirocin and chlorhexidine baths is limited. May be appropriate if multiple documented infections, household transmission, or colonized healthcare workers linked to an outbreak
- Treatment: vancomycin. Most clinical experience with this drug for invasive syndromes including pneumonia, endocarditis, meningitis, and osteomyelitis

Vancomycin Resistant Staph Aureus

- Staph aureus with reduced vancomycin susceptibility (SA-RVS):
 - Definitions:
 - MRSA/VSSA: MIC < 2 μ g/mL
 - VISA: MIC 4 – 8 μ g/mL (in reality, > 4 is resistant)
 - VRSA: MIC > 16 μ g/mL
 - Vancomycin-intermediate S. aureus (VISA):
 - Japan, USA, Europe: small number reported
 - ?Mechanism thick cell wall – overproduce target (D-Ala-D-ala) for vancomycin, which then gets trapped in the G +ive cell wall and doesn't make it to the target on the cell membrane
 - Risk factors: dialysis, prolonged vancomycin, infected but non-removable foreign bodies (eg LV assist devices, joint replacements)
 - Heteroresistance: resistance subpopulations reported NZ & Australia
 - In theory high dose vancomycin will work – but you may have a mixed culture and just be selecting resistant strains by vancomycin treatment
 - VRSA:
 - VanA gene complex, originally from VRE, very rare (case reports in Japan and US)
 - Alternative Treatments:
 - IV: Teicoplanin (not available in US, better tolerated) and linezolid. Also Daptomycin, quinupristin, dalfapristin, tigecycline?

- Oral: Rifampicin + fusidic acid, cotrimoxazole, pristinamycin

Vancomycin-Resistant Enterococci (VRE)

- Normal enterococci are resistant to all cephalosporins and flucloxacillin, and are inhibited (not killed) by penicillins and vancomycin → use gentamicin
- Some VRE in Australia
- Enterococcal clinical isolates: *E faecalis* 70 – 90%, *E faecium* 10 – 20%
- VRE Phenotypes (mostly *E faecium*):
 - VanA: resistant to vancomycin and teicoplanin (similar to vancomycin)
 - VanB: moderate resistance to vancomycin only
 - VanC: low level resistance to vancomycin only
- Mechanism:
 - Multi-gene cluster on plasmid/transposable element
 - Multiple mechanisms → altered vancomycin target:
 - D-alanine-D-alanine usually allows peptidoglycan cross-linking in the cell wall
 - Change D-ala-D-ala to D-ala-D-lac so vancomycin can't bind (but can still cross link)
 - Eliminate any D-ala-D-ala that does get made
 - Dipeptidase to cleave D-ala-D-ala
 - Can transfer resistance genes to Staph in vitro
 - Associated with avoparcin in animal feeds
- Epidemiology:
 - Immunosuppressed, ICU, dialysis patients
 - Antibiotic exposed: eg oral vancomycin, 3rd generation cephalosporins
 - Most patients colonised, minority infected
 - Outbreaks difficult to control
- Treatment:
 - Infection: Main agents are linezolid, tigecycline, daptomycin
 - Colonisation: avoid anti-anaerobic antibiotics (99.9% bowel commensals are anaerobes) – makes spread more likely

Gram Negative Antibiotic Resistance

Inducible beta-lactamase

- ESCAPP(P)M: *Enterobacter*, *Serratia marcescens*, *Citrobacter freundii*, *Acinetobacter*, *Providencia*, *Proteus*, (some *Pseudomonas*), *Morganella*
- Exposure to β -lactams can induce β -lactamase hyperproduction – due to a gene that's always been there but induced by cephalosporin use → resistance
- Cephalosporin sensitive in vitro but not clinically reliable

Extended spectrum Betalactamases

- Arise by:
 - Mutation in existing beta-lactamase genes (eg TEM, SHV, OXA)
 - Plasmid mediated transfer
- Epidemiology:
 - Highly transmissible
 - Increasing community-acquired infections – mainly UTIs
 - May appear sensitive to 3rd generation cephalosporins in vitro (eg MIC 2 – 8)
 - But associated with the failure of cephalosporins and with extensive use of 3rd generation cephalosporins (particularly ceftazidime)
- Types:
 - *Broad*-spectrum β -lactamases, resistant to many penicillins and first generation cephalosporins, are frequently expressed in enteric G-ive bacilli. These can be inhibited by clavulanic acid
 - *Extended* spectrum β -lactamases hydrolyse virtually all penicillins and cephalosporins, even including cefepime. Inhibitors (such as clavulanic acid and tazobactam) don't bind all β -lactamases so can't be relied upon. May also possess porin mutations that → ↓ uptake of cephalosporins and β -lactam/ β -lactamase inhibitor combinations
- Types:
 - *Klebsiella*: mainly clonal, consider health care facility acquired (TEM1/2, SHV1, KPC, CTX-M...)
 - *E. Coli*: mainly community acquired (ampC gene) – hydrolyses all cephalosporins

- Management:
 - Contact isolation precautions
 - Don't eradicate if colonisation on rectal swab – is likely to come back if ever treated with antibiotics (not cultured on swab doesn't mean it's gone)
 - Nitrofurantoin effective for most
 - Treat with *carbapenems* (eg *meropenem*, best in head to head trials), colistin, tigecycline

Acinetobacter Baumannii

- For the ID geeks
- Becoming a major nosocomial infective agent – traced from Iraq/Afghanistan via wounded US military personnel
- Amazing acquisition of resistant genes (most coded on the “resistance island”) but few virulence factors (so far). Resistance includes:
 - Multiple types of β -lactamase production
 - AmpC + promoter gene
 - OXA: carbapenemase
 - ADC: Acinetobacter Derived Cephalosporinase
 - Altered PBPs
 - Outer membrane Proteins (OMP): altered transport of antibiotics
 - Aminoglycoside Modifying Enzymes (AME)
 - Fluoroquinolone efflux pumps: *gyrA*, *parC*
 - Other efflux pumps: including tigecycline

Multisystem infections

- Systemic Inflammatory Response Syndrome (SIRS): Consider if 2 or more of:
 - Temp > 38 or < 36
 - HR > 90
 - RR > 20 or PaCO₂ < 32
 - WBC > 12 or < 4 or > 10% immature (band) forms
- Definitions:
 - Sepsis = SIRS + evidence of infection
 - Severe sepsis = Sepsis + organ dysfunction/hypoperfusion: 1 of oliguria, acutely altered mental state, lactic acidosis
 - Septic shock = Severe sepsis + Hypotension unresponsive to IV fluids: SBP < 90 or a fall of > 40 from baseline – vasoconstriction can mask hypotension
- Principal pathogens: *S. Aureus*, Streptococci, Meningococcus
- Bacterial components involved in severe sepsis:

Structural cell wall constituent	Outer cell wall, all G-ives	Endotoxin (LPS, lipid A), Peptidoglycan
Pore-forming exotoxins	Cell wall of all bacteria	Lipoteichoic acid
	<i>S aureus</i>	α -Hemolysin
	<i>Strep pyogenes</i>	Streptolysin-O
Superantigens	<i>E Coli</i>	<i>E coli</i> hemolysin
	<i>Aeromonas spp</i>	Aerolysin
Enzymes	<i>S aureus</i>	Toxic shock syndrome toxin 1, enterotoxins A – F
	<i>Strep pyogenes</i>	SPEA, SPEC, SMEZ
	<i>Strep pyogenes</i>	IL-1 β convertase
	<i>Clostridium perfringens</i>	Proteases, phospholipase C

- Clinical features:
 - Fever often absent in the elderly
 - Delirium common in the elderly
 - Check skin, iv lines, wounds, pressure sores
 - LFTs * 2 – 3 common from sepsis
 - Check Cr and CPK
 - Acute lung injury lasts 8 – 10 days, shock last only 1 day
- Mortality predictors:
 - Key elements: hypotension, hypoxia, underlying diseases, delirium, other organ dysfunction

- Mortality scores: APACHE for sepsis, Fine for pneumonia (see page 197)
- Interventions:
 - Good or some evidence of benefit:
 - Replacement corticosteroids if low cortisol
 - Dexamethasone in meningitis: if pneumococcal then pre-Abs
 - Noradrenaline as vasopressor (vs dopamine)
 - Early nutrition
 - Avoiding high FiO₂ (>55%)
 - Clindamycin: toxic shock, fasciitis
 - Activated Protein C? if Apache II > 25
 - Limited or no benefit:
 - Albumin (vs crystalloid IV)
 - Correction of acidosis
 - Immune enhancing diet
 - Anti-TNF

Fever of Unknown Origin

- Differential (see also Hospital Acquired Infections, page 325):
 - Neoplasm: lymphoma, leukaemia (check lymph nodes), other (hepatic, renal, other)
 - Infection:
 - Bacterial: Tb, abscess (subphrenic, hepatic, pelvic, renal – look for ↑ neutrophils), endocarditis, pericarditis, osteomyelitis, cholangitis, pyelonephritis, PID, syphilis, cystitis
 - Viral: EBV, CMV, HBV, HCV, HIV, Varicella-Zoster
 - Parasitic: malaria, toxoplasmosis
 - Fungal
 - Autoimmune: RA, SLE, vasculitis, inflammatory bowel disease
 - Endocrine: hyperthyroidism
 - Miscellaneous: drug fever (especially penicillins, sulphonamides), rheumatic fever, granulomatous disease (eg Sarcoid), fictitious/Munchausen's (eg injecting themselves with saliva), gout, alcohol withdrawal

Bacterial Infections

- Gram positive:
 - Cocci: Strep, Staph, Enterococcus
 - Rods: Actinomyces, Bacillus (incl anthrax), Clostridium, Corynebacterium, Listeria (facultative anaerobe)
- Gram negative:
 - Cocci: Moraxella, Neisseria
 - Rods: Acinetobacter, Bacteroides, Bartonella (incl Cat Scratch, Trench Fever), Brucella, Campylobacter, Enterobacter, E Coli, Haemophilus, Helicobacter, Klebsiella, Legionella, Proteus, Pseudomonas, Salmonella, Serratia, Shigella, Vibrio, Yersinia (incl plague)
- Acid Fast rods: Mycobacterium Tb, leprae, avium complex, kansasii
- Mycoplasmas
- Chlamydiae: trachomatis, pneumoniae, psittaci (obligate intracellular bacteria – needs high intracellular concentration of antibiotic)

Streptococci

Lancefield Group	Example	Haemolytic pattern	Typical infection
A	<i>S pyogenes</i>	β	Pharyngitis, impetigo, cellulitis, scarlet fever, necrotising fasciitis (also <i>S Aureus</i> , <i>C perfringens</i>)
B	<i>S agalactiae</i>	β	Neonatal sepsis, UTI, diabetic ulcers, endocarditis
C, G	<i>S dysglactiae</i>	β	Cellulitis, bacteraemia, endocarditis
D	Enterococci, <i>S bovis</i>	None	UTI, bacteraemia, endocarditis. Vancomycin resistance occurs
Variable	Viridans (<i>S sanguis</i> , <i>S mitis</i>)	α	Native valve endocarditis, dental abscess,

milleri group	Variable	brain abscess Brain abscess, visceral abscess
S pneumoniae	α	Otitis media, sinusitis, pneumonia, meningitis

- Streptococcal toxic shock:
 - Usually strep pyogenes. Primary infection is wound or skin
 - 2nd to erythrotoxin, treatment: β -lactam + clindamycin (potent inhibitor of toxin production)
- Group A β haemolytic: Not normal skin flora. Strep pyogenes \rightarrow pharyngitis. Erythrogenic toxin producers \rightarrow scarlet fever. Rheumatic fever
- Pneumoniae: Increasing penicillin resistance (resistant = MIC > 1 mcg/ml, highly resistant > 4) 2nd to decreases affinity PBP
- Strep Bovis: associated with bowel cancer

Staphylococci

- Staph aureus:
 - Either infection or toxin mediated (\rightarrow scalded skin syndrome in kids, toxic shock, and enterotoxin food poisoning)
 - Toxic Shock Syndrome:
 - Presentation: fever, vomiting and diarrhoea, shock within 24 hours, diffuse maculo-erythematous rash
 - Blood culture usually negative. Treat with flucloxacillin +/- clindamycin
 - Caused by a superantigen. Usually 1 in 10,000 T cells will bind to an antigen, a superantigen binds to all of them by cross linking MHC2 to a T cell receptor, regardless of the T cell receptor shape. Most people develop antibodies to toxic shock antigens
 - Some have a polymorphism that means they don't produce this antibody \rightarrow recurrent toxic shock – treat with Intragam
- Coagulase-negative staphylococci: important cause of infection of intravascular and prosthetic devices. β -lactam resistance common
- Staph saprophyticus (honey mooners UTI): treat with amoxicillin
- For MRSA see Antibiotic Resistance, page 281

Meningococcus

- Capsular antigens: A, B, C, X, Y, W-135, L. B, C and Y most common in developed countries
- Nasopharyngeal colonisation (carrier state) \rightarrow invasive disease (trigger unknown)
- Short course antibiotic therapy is effective: 3 days iv benzylpenicillin had mortality 7% (all on treatment at death)
- Chemoprophylaxis: aim to eradicate asymptomatic carriage (with transmission to someone else): ceftriaxone, ciprofloxacin, rifampicin
- If recurrent infection consider terminal complement deficiency states (C6 – 9)
- Vaccination:
 - Group C Conjugate: for type C, long term immunity, no booster required. Reduced colonisation contributes to herd immunity
 - Polysaccharide: covers A, C, Y, W-135. Not immunogenic in young children, duration of protective immunity short (booster required), minimal or no effect on carriage and therefore transmission
 - Group B: in 2003 in NZ 72% of meningococcal disease was due to Group B (little in Australia). Needs 3 dose schedule to improve immunogenicity in children

Disseminated Gonococcaemia

- See page 326
- In ~ 1 – 2 % of infected patients
- Presentation: fever, polyarthritis, *tenosynovitis*, rash (papules, pustules, haemorrhagic, mainly on extremities)
- Differential in young adult arthritis – can look fairly well. Also consider meningococcaemia, septic arthritis, reactive arthritis
- Diagnosis: blood culture, gram-stain and culture of pustular lesions, genital and pharyngeal swabs. Initially synovial fluid culture negative

- Treatment: Ceftriaxone

Clostridium

- Clostridial *myonecrosis* (*Gas Gangrene*): Pain and oedema around a wound with prostration and systemic toxicity, red fluid-filled vesicles. Gas in the tissue by palpation or radiograph. Gram-positive rods in culture or smear. Caused by many clostridial species including *C. perfringens*. High dose penicillin, surgical debridement, ?hyperbaric O₂
- **Tetanus**: History of wound and possible contamination, jaw stiffness followed by spasms of jaw muscles → stiffness of neck and other muscles, dysphagia → painful convulsions. Caused by neurotoxin tetanospasmin from *C. tetani*. Incubation 8 – 12 days. Ubiquitous in soil. Clinical diagnosis. Treatment: passive immunisation if immunisation status uncertain with tetanus immune globulin, and active immunisation with tetanus toxoid. Penicillin
- **Botulism**: *Clostridium botulinum*. Ubiquitous, strictly anaerobic spore forming bacillus. Toxins A, B, and E bind to pre-synaptic nerves blocking acetylcholine release. No sympathetic or sensory involvement. Diplopia, fixed dilated pupils, dry mouth, dysphagia, dysphonia → paralysis and respiratory failure. Normal temperature. It's the toxin, not the bug, that's the problem
 - Food-borne: ingestion of preformed toxin in canned, smoked or vacuum packed foods
 - Wound-borne: usually IVDU with toxin produced in vivo
 - Differential: Miller Fisher variant of GBS, myasthenia gravis or basilar meningitis
 - Treatment: antitoxin, penicillin
- ***Clostridium difficile*** causing pseudomembranous colitis:
 - See Postgrad Med J 2005; 81:367-369, Lancet 3 May 2008
 - Causes CDAD (*C. Difficile* Associated Disease)
 - Pathogenesis:
 - Gram positive, spore forming anaerobic bacillus that is *not* a normal commensal. Over 400 subspecies. Discovered in 1935 and named *Bacillus difficilis* because of its difficult anaerobic isolation from faeces
 - Infection requires disruption of normal flora, and an exogenous source (associated with prolonged hospital stay)
 - Toxins:
 - Only toxin producing strains cause disease, non-toxin producing don't
 - Toxin A: enterotoxin
 - Toxin B: cytotoxin; disrupts intercellular tight junctions
 - Toxin B 1000 times more cytotoxic than Toxin A
 - Incidence has increased since the appearance of a hypervirulent strain in 2000 – NAP1/027, causing problems in USA, Canada, Europe and Japan – produces high levels of both toxins
 - Recent (2003 – 2005) outbreaks in the US (REA BI and NAP1 strain) and Europe (toxintype III and PCR ribotype 027)
 - Potential virulence factors: hypertoxin production, hypersporulation, antimicrobial resistance (quinolone resistance is a classic finding, but don't use quinolones to treat anyway)
 - Asymptomatic carriage in 1 – 3% of healthy adults, and 40 – 60% of neonates (esp if born in hospital)
 - Presentation:
 - Maybe bloody diarrhoea and fever
 - Most common cause of nosocomial diarrhoea
 - Severe disease WBC > 15 or > 50% rise in Cr, also associated with fever, ↓albumin, ↑CRP (these criteria not prospectively validated)
 - Complications: CDAD has mortality of 5 – 10%, causes severe colitis, toxic megacolon, perforation, multiorgan failure
 - Precipitating antibiotics: clindamycin probably the most common (methodological differences in studies make conclusions soft), ciprofloxacin also increased risk
 - Diagnosis:
 - Culture doesn't differentiate carriers from disease, nor identify toxin producers, and is hard to culture
 - Toxin-B Tissue culture assay the gold standard. But ELIZAs for toxins fast and cheaper, with sensitivity and specificity 60 – 85%
 - Treatment:
 - Mild disease. Placebo as good as treatment (Cochrane Review July 2007). Oral rehydration: avoid antibiotics if possible

- Oral metronidazole for 10 – 14 days first line therapy if severe (it's cheap, as effective as anything else, well tolerated and ↓vancomycin resistance – however ~ 30% failure in complicated severe disease), then oral vancomycin (iv doesn't work) after metronidazole treatment failure. If severe and complicated disease, ID Society of America recommends vancomycin 2 gm/day. Some evidence that teicoplanin better than vancomycin
- Treatment failures due to:
 - Neither antibiotic eliminates the spores
 - Development of virulence factors (resistance to both vancomycin and metronidazole very rare)
 - Recurrence usually within a week – no standard, uniformly effective treatment. Long tapering doses or pulse treated used
- Prevention:
 - Antibiotic stewardship
 - Hand-washing: requires mechanical action (soap and water), not alcohol
 - Spores can survive in the environment for up to 5 months → isolation and hand washing around infected patients
 - Small trial evidence of probiotics with general antibiotic therapy

Pseudomonas aeruginosa

- G+ive aerobic bacilli
- Management: if detected remove all infected catheters/lines, look for and drain all abscesses
- Treatment:
 - Options:
 - Penicillins: ticarcillin, piperacillin
 - Third generation cephalosporins: ceftazidime
 - Fourth generation cephalosporin: cefepime
 - Carbapenems: Imipenem (resistance to monotherapy common), meropenem
 - Fluoroquinolones: ciprofloxacin, levofloxacin
 - Inhaled tobramycin in CF
 - Controversy about monotherapy or combination therapy in suspected infection given risk of drug resistance – no conclusive evidence of benefit of the latter, but recommended in (with aminoglycoside adjunctive therapy):
 - Pneumonia
 - Meningitis
 - Bacteraemia in neutropenia
 - Septic Shock
 - No response in 48 hours to monotherapy
 - High incidence of resistance
 - Resistance due to degrading enzymes (eg plasmid mediated PER-1), reduced permeability and active efflux
 - If severe, multi-drug resistant disease: colistin – but nephrotoxicity and ototoxicity

Anthrax

- Bacillus anthracis, G +ive rod
- Transmission through contact with spores in soil/animals – carcasses return bacteria to soil. No human to human transmission
- Outbreaks in Africa, India, Thailand
- Infection:
 - Usually skin (painless black cutaneous eschar with surrounding erythema) → lymph nodes → bloodstream → flu-like symptoms and pleural effusion, oedema
 - If pulmonary infection: inhale spores → onset in 10 days – 6 weeks, fever, sweats, cough, nausea for 2 days → meningitis in 50%. CXR: mediastinal lymph nodes, bloody pleural effusion, haemorrhagic mediastinitis →widened mediastinum on CXR, pneumonia in the minority
 - Maybe GI: ingestion of contaminated meat → severe abdo pain, haemorrhagic ascites, melaena
- Labs: culture of blood, ?sputum, nasal swab, CSF. Capsule on Gram stain
- Treatment: Ciprofloxacin or doxycycline (although penicillins may be OK). If severe then 2nd AB. Duration 60 days (persistent spores)

Others

- Legionella:

- Legionnaires' Disease: pneumonia cause by these species. Prominent GI symptoms
- Pontiac fever: acute, febrile, self-limited illness serologically linked to Legionella
- Water born
- Intracellular \Rightarrow requires cell mediated immunity. Minimal involvement of neutrophils
- Diagnosis: Culture best, urinary antigen testing more sensitive than antibody serology
- Treatment: needs AB reaching MIC intracellularly. Newer macrolides (eg azithromycin) better at this than older (eg erythromycin). Also quinolones (esp in transplant patients as macrolides and rifampicin interact with cyclosporine and Tacrolimus). Gentamicin ineffective
- NB: Legionella longbeachae in potting mix
- Haemophilus Influenzae: G-ive coccobacilli. Clinically relevant serotype are:
 - Serotype b (Hib): Encapsulated. Causes meningitis and invasive infection by haematogenous spread in unimmunised children, generally age < 6 years. Capsule prevents opsonization. Maternal antibodies protective till about 6 months of age. Treatment of meningitis: cephalosporin + dexamethasone
 - Nontypeable strains: have no capsule (so can't be typed!), causing mucosal infections: otitis media in children, sinusitis, LRTI in adults with chronic bronchitis. Little invasive disease. No vaccine. Immune response is strain-specific, so recurrent infection possible. 20 – 30% produce β -lactamase. Augmentin has good cover
- Diphtheria: Corynebacterium diphtheriae: tenacious grey membrane in pharynx. Sore throat, malaise, fever. Toxin \rightarrow myocarditis and neuropathy. Treatment: antitoxin + penicillin
- Listeriosis: Listeria monocytogenes
 - Anaerobic G+ ive rod. Intracellular infection.
 - Neonatal infection, gastroenteritis, bacteraemia or meningitis (slower course than meningococcal, mainly very young or old, HIV or TNF therapy, neutrophilic CSF). 5 – 10 % of community acquired pneumonia in the US
 - If pregnant, 70 – 90% of fetal infection with mortality up to 50%
 - Food borne – coleslaw, milk, soft cheeses, delicatessen meat. Can grow at refrigerator temperatures
 - Treatment: ampicillin, penicillin. Cephalosporins ineffective
- Brucellosis: Various Brucella bacteria species (eg Brucella abortus – cattle). Direct contact with cattle, pigs, sheep, goats, *unpasteurised milk*. Insidious onset, continuous or intermittent fever and malaise, may last for months, lymphadenopathy, HSM. Diagnosis: blood culture, positive serology. Relapse common \Rightarrow combination drug regimes (eg doxycycline + rifampicin). Not in NZ for a while
- Yersinia pestis: Plague. Rodent infection transmitted by fleas or contact. Incubation 1 – 6 days. Fulminant fever, headache, delirium, suppurative lymphadenopathy, bilateral pneumonia, purpuric rash (black plague). Treatment streptomycin + prophylaxis + respiratory isolation. Also doxycycline, ciprofloxacin
- Bartonella:
 - B quintana: Trench Fever. Louse borne. Self remitting relapsing fever, weakness, pain behind the eyes and back of legs
 - B henslae and quintana: Cat-scratch disease. Papule or ulcer at site of inoculation \rightarrow 1 – 3 weeks later fever & malaise. Lymphadenopathy. Self-limited. Treatment: none, macrolides, tetracyclines, rifampicin
- Mycobacterium Leprae: Leprosy. Chronic disease following prolonged exposure in childhood. Pale, anaesthetic macular skin lesions. Superficial nerve thickening. Acid fast bacilli in skin lesions, nasal scarring, or characteristic histologic nerve changes. Can't be cultured in vitro. WHO treatment: Dapsone, rifampicin, clofazimine

Meningitis

Testing CSF

- CT before LP if papilloedema, seizures or focal neurology
- ABs given within 4 hours prior to LP probably don't affect culture results
- Bacterial infection suggested by excess polymorphonuclear neutrophils on LP:
 - Glucose < 2.2 , CSF/serum glucose < 0.4 , (normal > 0.6)
 - Gram stain smear: positive in 60 – 90%
 - CSF culture: positive in over 90%
- Viral Infection:
 - CSF: May be normal. \uparrow Lymphocytes. Normal glucose

- PCR better than viral cultures – certainly for HSV, Enterovirus, CMV, EBV VZV. Serology useful for others when there is low general prevalence (ie not HSV, VZV, CMV and EBV) – need acute and convalescent serology showing ↑IgM
- PCR used for Herpes simplex and Varicella-zoster. Can also detect *S pneumoniae*, *H influenzae*, *N meningitidis*, *M Tb*, *B burgdorferi*, *Tropheryma whippelii*, CMV, EBV, enteroviruses but only in reference labs and probably no more sensitive than culture (but are faster)
- Latex agglutination tests can detect antigens of encapsulated organisms but usually only used for *Cryptococcus neoformans*

Purulent/Bacterial Meningitis

- Infection of the subarachnoid space

Population	Common bugs
18 – 50 years	<i>S pneumoniae</i> , <i>N meningitidis</i>
> 50 years	<i>S pneumoniae</i> , <i>N meningitidis</i> , <i>L monocytogenes</i> , Gram-negative bacilli, maybe <i>S agalactiae</i>
Impaired cellular immunity	<i>L monocytogenes</i> , gram-negative bacilli, <i>S pneumoniae</i>
Post-surgical, post traumatic	<i>St aureus</i> (<i>rare cause other than post-surgical/trauma</i>), <i>S pneumoniae</i> , gram negative bacilli

- Duration of treatment:
 - *H influenzae* 7 days – getting rare 2nd to vaccination
 - *Neisseria meningitidis* 3 – 7 days
 - *S pneumoniae* 10 – 14 days. ↑ risk if pneumococcal pneumonia, also sinusitis, otitis media, alcoholism, diabetes, splenectomy, hypo-Ig, head trauma. Repeat LP after 36 hours to check CSF sterile (?resistance)
 - *Listeria monocytogenes* 14 – 21 days. Case fatality of 15 – 26% (hasn't changed much over time). Subacute presentation. Consider in all older or chronically ill adults with “aseptic” meningitis – neutrophil predominance and modest WBC counts on CSF. Can cause macroscopic brain abscess from bacterial seeding. Ampicillin active, as is penicillin. Cotrimoxazole iv if penicillin allergic. ?Gentamicin for synergy. Case reports of vancomycin, tetracycline and erythromycin success but also case reports of failure with each. Cephalosporins **not** effective
 - G –ive bacilli: 21 days
- Pathophysiology:
 - Polysaccharide capsule in *Neisseria*, *Streptococcus* and *Haemophilus* → avoid phagocytosis and classical complement mediated bactericidal activity
 - Bacteria multiple rapidly in CSF given few WBCs and only small amounts Ig and complement
 - TNF and IL-1 → ↑permeability of BBB → vasogenic oedema and protein influx
 - Obstruction of CSF outflow via arachnoid granulations → communicating and obstructive hydrocephalus
 - Neurological sequelae 2nd to inflammatory response, not the bug ⇒ can continue after CSF sterile
- Presentation:
 - Seizures in 20 – 40% during illness
 - Signs of ↑ICP: ↓LOC, papilloedema, dilated poorly reactive pupils, 6th nerve palsies, decerebrate posturing, Cushing's reflex (bradycardia, hypertension, and irregular respirations)
- Investigations:
 - MRI better than CT for cerebral oedema and ischaemia. Diffuse meningeal enhancement following gadolinium
 - CSF
- Differential:
 - Viral (see page 291)
 - Subdural and epidural empyema especially if focal findings
 - Subarachnoid bleed
 - Rocky Mountain Spotted Fever: Rickettsial, diffuse erythematous maculopapular rash within 96 hours → purpuric rash → necrosis. See Rickettsial Diseases, page 321
 - Chemical meningitis due to rupture of tumour contents into CSF (eg cystic glioma)
 - Inflammatory disorders: sarcoid, SLE, Behcet's, pituitary apoplexy, Wegner's
- Wgtn antibiotic guidelines:
 - Ceftriaxone 2 gm *Q12H*: Good coverage of susceptible pneumococcal, GBS, *H influenzae*, and OK for *Neisseria* (Penicillin G better – change if this is isolated)

- +/- vancomycin 1 gm Q 12H if: LP is not possible, prior to LP in critical patients, when LP shows gram positive cocci (Neisseria are G – ive cocci, Strep are G +ive cocci) or when meningococci are not seen on LP. If MIC < 0.125 then benzylpenicillin OK
- Steroids:
 - Dexamethasone 10 mg iv 6 hourly for 4 days (with S pneumoniae and as empiric treatment in case of S pneumoniae)
 - Inhibits synthesis of IL-1 and TNF by macrophages and microglia if given before they are activated by endotoxin, decreasing outflow resistance and stabilising the BBB. Little impact once activation is induced so give (ideally) prior to antibiotics. Unlikely to be of benefit if given > 6 hours after ABs
 - Mortality 7 vs 15%. May decrease penetration of vancomycin into CSF
 - Cochrane Review 2007 of Steroids in bacterial meningitis: RR of 0.57 for mortality in all comers, 0.59 in Strep Pneumonia, and non-significant favourable trend in meningococcal. Reduced short term neurological sequelae. Reduced hearing loss in kids with Haemophilus
- Acyclovir if HSV suspected. Doxycycline in tick season!
- Cefepime if Enterobacter or Pseudomonas
- Amoxicillin for Listeria (if <3 months, old, impaired cell mediated immunity)
- Supportive treatment for ↑ICP: elevation of head, intubation and hyperventilation (PaCO₂ 25 – 30 mmHg) and mannitol
- Nasopharyngeal eradication in contacts: Rifampicin prophylaxis 600 mg bd for 2/7 for index case and contacts (not in pregnancy or on pill), im ceftriaxone, ciprofloxacin (not in kids or pregnancy, theoretical cartilage damage). Penicillin takes 3 – 4 days to eradicate carriage

Viral Meningitis/Encephalitis

- Viral Meningitis:
 - Common:
 - Enteroviruses > 75% (seasonal) but this proportion declines with age (coxsackievirus, echovirus, enteroviruses 68 – 71)
 - HSV-2. See page 294
 - HIV: with primary infection in 5 – 10%, cranial nerve palsies of V, VII and VIII more common in HIV meningitis than other viral causes
 - Less common: Varicella Zoster, EBV, West Nile Virus
- Viral Encephalitis:
 - Common:
 - HSV-1 encephalitis:
 - Headache, fever, altered consciousness, focal deficit, seizures
 - CSF: lymphocytic pleocytosis, normal glucose
 - MRI: high signal intensity lesions in brain parenchyma within 48 hours
 - EEG: may be distinctive periodic pattern
 - Varicella, EBV
 - Less Common: Rabies, CMV, Enteroviruses (including coxsackie viruses and echoviruses), Flaviviruses (West Nile encephalitis, Japanese encephalitis + others), and mumps (previous document infection excludes this)
 - Retro-orbital headache, maybe pain on moving eyes. Altered LOC. Focal or generalised seizures. Involvement of hypothalamus or pituitary → SIADH, temperature dysregulation, DI
 - Considerable variation in neurological sequelae
 - Leptospiral infection: secondary syphilis and Lyme disease may be grouped here because of relatively benign course and lymphocytic response on CSF (rather than polymorphs)
 - In aseptic meningitis also consider:
 - TB, cryptococcus, leptospirosis, syphilis
 - Parameningeal focus
 - Non-infectious: sarcoid, vasculitis, CNS lymphoma
 - Treatment: usually symptomatic. Empirical acyclovir if unwell

Chronic or Subacute Meningitis

- Causative bugs:
 - M Tb
 - Atypical mycobacteria

- Fungi: Cryptococcus (polysaccharide antigen test highly sensitive and specific, treatment Amphotericin followed by long course of fluconazole), coccidioides, histoplasma
- Spirochetes (Treponema pallidum and Borrelia burgdorferi – Lyme disease). Syphilitic meningitis if ↑WBCs and protein on CSF, and a reactive serum treponemal test is positive or CSF VDRL is positive. Treatment penicillin G
- See Progressive Multifocal Leukoencephalopathy, page 313
- Subacute Sclerosing Panencephalitis (SSPE): rare, chronic demyelinating disease associate with chronic infection of the measles virus. Usually primary infection age < 2, latent phase and onset age 5 – 15

Other

- Partially treated Bacterial Meningitis: Previous antibiotic therapy for 12 – 24 hours will decrease CSF gram stain and culture sensitivities, but not change inflammatory results
- Neighbourhood reaction: adjacent purulent infection (eg abscess, osteomyelitis of the vertebrae, subdural empyema, epidural abscess, mastoiditis) spills some of the products of the inflammatory process into the CSF
- Non-infectious meningeal irritation: carcinomatous meningitis, sarcoid, SLE, drugs (eg NSAIDs, OKT3, TMP-SMZ, others) can give abnormal CSF like infections
- Brain abscess:
 - Risks: otitis media, mastoiditis, paranasal sinusitis, pyogenic infections in chest or elsewhere, penetrating head trauma, neurosurgery and dental infection
 - Presents more as a mass lesion than an infectious process. Vomiting, fever in only 50%, altered mental state, focal neurology, seizure
 - Do a CT, if abscess don't LP – doesn't usually give useful results. MRI better than CT
 - Usually polymicrobial: S aureus, gram-negative bacilli, streptococcus, anaerobes. If immunocompromised: Nocardia, toxoplasma, aspergillus, candida, C neoformans
 - Treatment: drainage (excision or aspiration) + 3 – 4 weeks ABs – metronidazole + ceftriaxone as empiric therapy
- Amoebic meningoencephalitis: identified by culture of wet mount of CSF. No effective treatment

Viral Infections

Influenza

- Greater morbidity in > 60, chronic respiratory or cardiac disease
- Virus Characteristics:
 - Segmented RNA genome with high mutation rate
 - **H**aemagglutinin (HA): attachment. H1 – H15 (capsule proteins). Binds to sialic acid on respiratory epithelial cells for viral entry. Main target for neutralising antibodies
 - **N**euraminidase (NA): penetration and release of daughter virions. N1 – N9. Antibodies are not neutralising but prevent cell to cell spread and reduce severity of illness
- Subtypes:
 - Human infection with H1, H2, H3 and N1 and N2 combinations
 - Influenza A: pandemics of severe disease, zoonotic infection
 - Influenza B: epidemics, less strain variation
- Antigenic drift and shift:
 - Drift: HA antigen changes “shape” due to poor RNA proof reading and repair so pre-existing antibodies are ineffective → annual adjustment to vaccinations
 - Shift: Generation of a novel virus from combination of two viruses (eg avian and human) in a host (eg a pig). No immunity in the community to such a virus. → Pandemic
- Diagnosis: almost always with PCR – few labs do cultures. Nose and throat swabs easier than NPA
- Two available class of antiviral drugs:
 - Adamantanes (target M2 ion-channel): amantadine, rimantadine (resistance in some countries) – Influenza A only
 - Neuraminidase inhibitors (target neuraminidase): Oseltamivir (Tamiflu), zanamivir, peramivir –for Influenza A and B
- Treatment: Oseltamivir (Tamiflu), Neuraminidase inhibitor (sialic acid analogue), reduced symptoms by 1 – 2 days, best if started early, more effective for Flu A than Flu B, resistance has been seen already, prophylactic use amongst close contacts reduces cases, SE nausea and vomiting
- Vaccination:

- Reduces risk of hospitalisation and death amongst the elderly
- Usually poor match between vaccines and circulating virus
- Contraindicated in egg allergy
- Inactivated vaccine and live attenuated vaccines have difference efficacies against different classes (NEJM 2006;355(24):2513). Usual is inactivated – safe in immunocompromise

H5N1 Influenza Virus

- See Lancet, 26 April, 2006, NEJM 17 January 2008
- Highly pathogenic H5N1 influenza virus = Bird Flu = Avian Influenza
- First seen in Hong Kong in 1997, re-emerged in 2003. Human infection in > 300 people since 2003 with 60% mortality
- Transmission:
 - Large amounts of virus in bird faeces – inactivated after 24 hours at room temperature
 - Inefficient transmission to humans – probably respiratory (droplet), direct contact, maybe GI
 - Most significant risk factor: handling sick or dead poultry in the previous week
 - Human to human transmission have all involved lengthy, close, unprotected contact – low risk for health care workers if isolation measures used (gowns and gloves, N95 masks)
 - Can also infect cats and dogs
- Presentation:
 - First symptoms after 2 – 4 days (maximum 9) → infectious prior to symptoms → difficult to control. Median age 18
 - High fever (median 39.2), cough, SOB (mean RR 52), radiological evidence of pneumonia – often bilateral fulminant pneumonia → rapidly progressive to requiring ventilation, ARDS, renal dysfunction, multiorgan failure
 - Early onset lymphopenia
 - Primary CNS involvement in one case
 - Asymptomatic or mild illness rare
- Diagnosis:
 - Pharyngeal rather than nasal swabs. LRTI samples best
 - Difficult – requires lab facilities of biosafety level 3
 - Specific antibodies may not be detected till day 14
 - Reverse transcriptase PCR used for rapid subtype specific diagnosis in 4 – 6 hours in level 2 labs
 - Requires frequent updating of primers and probes
- Pathogenesis:
 - Target cells for replication include type 2 alveolar pneumocytes and macrophages
 - Continued antigenic evolution of hemagglutinin (capsule protein) impairs protective immunity
 - Amongst the virulence factors of the virus is an NS1 protein which acts as an interferon-antagonist – resistant to antiviral effects of interferon and inducing high concentrations of TNF α
 - Death by cytokinetic storm
- Management:
 - Generally supportive
 - Little evidence of effectiveness of antivirals (see page 292) – ?less effective because of late initiation, ?under-dosing, ?rapid resistance
 - No evidence of benefit of steroids
- Vaccine:
 - Would take 6 months to produce and would require big doses to get an antibody response
 - Debate over whether to target humoral or cell-mediated immunity (humoral is faster in action, but vaccinated individuals can mount a T-cell response 2 days faster...)
 - A two dose vaccine of hemagglutinin antigen without adjuvant induced neutralizing antibodies against diverse H5N1 strains (clades 1, 2 and 3) ⇒ potentially useful as a vaccine (NEJM 12 June 2008)

SARS

- Coronavirus
- Transmission through direct or indirect contact of mucous membranes with infectious droplets, amplified by nebulisers, bronchoscopy, etc
- ?Horseshoe bat the natural reservoir
- WHO Case definition:
 - Suspect case:

- High fever (>38) and cough/difficulty breathing and one of:
 - Close contact with a suspected or probable case
 - Travel to an area with SARS
- Probably case = suspect case +
 - Pneumonia on CXR
 - Positive test for SARS coronavirus
- Diagnosis: antibody testing (highest detection in stools) or isolation of virus – PCR low in first week
- No specific treatment found to be effective: mortality up to 10%. Treat as severe CAP. Isolation. Steroids in severely ill patients with increasing O2 requirements. Ribavirin not recommended (no evidence from in vitro studies). ?use of IFN β

Human Herpes Viruses

Herpes Simplex Viruses

- Linear dsDNA viruses
- Infection via mucosa, broken skin → enters sensory or autonomic neuronal cells → transported to nerve cell bodies in ganglia → latent infection → possible future reactivation → reappearance on mucosal surfaces
- Humoral and cell-mediated immunity important (CD8+)
- Incubation 1 – 26 days
- After primary infection, active viral shedding occurs up to 50% of days in initial few years, even if asymptomatic
- Both subtypes 1 and 2 can cause oral and genital lesions (clinically indistinguishable)
- Oral-facial infections:
 - Primary infection: gingivostomatitis and pharyngitis, child and young adults, up to 2 weeks of fever, malaise, myalgia, adenopathy, oral lesions, maybe exudative pharyngitis
 - Reactivation: latent virus in trigeminal ganglia → mucosal ulceration, vermillion border, facial skin, viral excretion in saliva
 - Immunocompromised patients: eczema herpeticum if atopic eczema. Erythema multiforme (target lesions): HSV infection the precipitating event in 75% of cases
 - Bell's palsy: associated with HSV and VZV. Short course steroids may help
- Genital infections:
 - Primary infection: fever, malaise, myalgia, vesicles, pustules or painful erythematous ulcers, dysuria, vaginal discharge. Associated with other clinical syndromes – urethritis, meningitis, etc
 - Reactivation: Often subclinical. Perianal lesions from the sacral dermatome. Proctitis → anorectal pain, tenesmus, constipation
- Herpetic Whitlow: HSV infection on the finger – often with fever and lymphadenitis. Confused with pyogenic infection
- Eye Infections:
 - Keratitis – acute onset pain, blurred vision, conjunctivitis and dendritic lesions of the cornea. Topical antiviral +/- interferon therapy. Topical glucocorticoids may exacerbate
 - Chorioretinitis: usually seen with disseminated infection in immunocompromised
- Central and Peripheral Nervous System Infections:
 - Encephalitis:
 - 10 – 23 % of sporadic viral encephalitis, 95% HSV-1
 - Fever + focal neurologic symptoms, especially temporal lobe. Neurologic sequelae common, especially patients > 50 years of age
 - IV antivirals until CSF levels of viral DNA are reduced or undetectable
 - Aseptic Meningitis:
 - HSV DNA found in 3 – 15 % of CSFs, usually in association with primary genital infection
 - Acute, self-limited disease without sequelae, fever, headache, photophobia
 - Lymphocytic pleocytosis in CSF
 - No studies on whether treatment is effective. HSV most common cause of recurrent lymphocytic meningitis (Mollaret's Meningitis) → oral acyclovir long term
 - Autonomic and Motor/Sensory dysfunction: HSV and VZV, most commonly sacral area, numbness/tingling, retention, constipation, impotence. Rarely, transverse myelitis or GBS follows HSV infection
- Visceral infections:
 - Oesophagitis

- Pneumonitis – rare. Either by extension or haematogenous dissemination
- Diagnosis:
 - Staining of ulcer scrapings → giant cells and intra-nuclear inclusions
 - Culture: positive in 48 – 96 hours
 - HSV antigen staining → diagnosis in < 24 hours
 - PCR detection of HSV DNA most sensitive
- Treatment:
 - Acyclovir, valacyclovir and famciclovir are nucleotide analogues that interfere with DNA polymerase, specific to HSV and Varicella Zoster. Only effective during viral replication (ie need to start early)
 - Acyclovir. IV associated with transient renal insufficiency (crystallization in the renal parenchyma). CSF levels are 30 – 50% of plasma, so double in CNS infection
 - Valacyclovir and Famciclovir – better bioavailability
 - HSV-2: valacyclovir has been shown to reduce transmission to a non-infected, immunocompetent heterosexual partner (Ann Intern Med 2006:144:49-56). Could have a role in reducing HIV transmission, given it's association with HSV-induced ulcers
 - Biggest risk factor for acyclovir resistance is the degree of immunosuppression

Human Herpes Virus 6

- Possible cause of bone marrow suppression, meningoencephalitis, interstitial pneumonitis
- Ubiquitous, reactivation in immunosuppression
- Diagnosis: culture, PCR (?significant – infected or chronic)
- Management: ganciclovir

Human Herpes Virus 8

- Associated with Kaposi Sarcoma in HIV. Pathogenesis unclear

Parvovirus B19

- Erythroid-specific virus: cellular receptor on erythroid progenitors
- Infection leads to acute and self-limited cessation of RBC production
- Other manifestations likely immune-complex mediated: rash and polyarthropathy
- Disease manifestation depends on host:
 - Normal child: “Fifth Disease” – erythema infectiosum, slapped cheek rash 2 – 5 days after prodromal symptoms
 - Normal adults: polyarthropathy syndrome: women, small joints, symmetric, lasts 1 – 3 weeks
 - Patients with increased erythropoiesis: Transient aplastic crisis in hereditary spherocytosis, thalassaemia, AIHA
 - Immunocompromised: persistent anaemia in congenital immunodeficiency states, HIV, transplant
 - Pregnancy:
 - Fetus < 20 weeks: hydrops fetalis
 - Differential: Rubella, Enterovirus
 - Exposure risks: household 50% susceptibility, community 20%
 - Diagnosis: repeat serology at 2 – 4 weeks if IgG – and IgM – or +
 - Outcomes: 1% excess foetal loss in first 20/40, 3% hydrops 9 – 20/40, no teratogenicity
 - Ultrasound examination at 1 – 2 weekly intervals for 6 – 12 weeks after confirmed maternal infection. Foetal blood sampling if hydrops

Vaccine Preventable Viral Infections

- Measles:
 - Paramyxoviral infection transmitted by respiratory droplets
 - Exposure 10 – 14 days prior
 - Prodrome of fever, coryza, cough, conjunctivitis, photophobia, Koplik’s spots
 - Rash: irregular, brick-red, maculopapular, starts on face spreading down and out
 - Leukopenia
 - Post exposure prophylaxis: measles live attenuated virus
- Mumps:
 - Paramyxoviral infection transmitted by respiratory droplets
 - Exposure 14 – 21 days before onset
 - Painful, swollen salivary glands, usually parotid

- Frequent involvement of testes, pancreas, and meninges in unvaccinated individuals
- Vaccine: live attenuated virus
- Poliomyelitis:
 - Enterovirus with faecal-oral spread
 - Incubation 9 – 12 days
 - Muscle weakness, headache, stiff neck, fever, nausea, vomiting, sore throat
 - Lower motor neuron lesion (flaccid paralysis) with decreased deep tendon reflexes and muscle wasting
 - CSF: lymphocytic predominance
- Rubella:
 - Togavirus spread by respiratory droplets
 - Exposure 14 – 21 day before onset
 - Arthralgia, particularly in young women. Posterior cervical lymphadenopathy 5 – 10 days before rash. Mild prodrome coinciding with eruption or fine maculopapular rash of 3 days duration, face → trunk → extremities
- Varicella Zoster (Chicken Pox): ↑perinatal mortality. If maternal perinatal exposure and seronegative then immunoglobulin within 72 hours of exposure

Other

- EBV: infects B lymphocytes, T lymphocytes are often atypical

Mycotic Infections

Fungal and yeast infections

- For fungal skin infections see Infections in Dermatology, page 452
- Background:
 - Risks increase with declining neutrophil count and duration of low count
 - Good evidence for prophylaxis in stem cell transplants and AIDS
- Diagnosis:
 - Cryptococcal antigen (latex agglutination): has been around for years
 - Antigen tests for aspergillosis
 - PCR: Panfungal assays vs species specific. In trial. Not standardised
- Histoplasmosis: bird droppings and bats. Respiratory illness most common problem (atypical pneumonia), common in AIDS. ↑ALP, ↑↑LDH, ↑Fe, Itraconazole if indolent, amphotericin if severe
- Pneumocystis Jiroveci Pneumonia:
 - Asymptomatic infection in most by a young age
 - Clinical infection in malnourished, preterm neonates and cell-mediated immune compromised (80% of AIDS patients not on prophylaxis)
 - Airborne transmission
 - See AIDS related Illness, page 312
- Cryptococcosis: See AIDS related illnesses, page 311
- Zygomycosis:
 - Rare
 - Angio invasive, tissue necrosis++
 - Risk factors: acute leukaemia, organ transplant, diabetic ketoacidosis, iron overload, desferrioxamine therapy, burns
 - Involvement of paranasal sinuses, dissemination to brain and orbit
 - Treatment: debridement + amphotericin
- Many others....

Antifungal drugs

- No evidence for combination therapy, but active research in this area
- Polyene antifungals: not orally absorbed
 - Mechanism: insertion into fungal cytoplasmic membrane → ↑membrane permeability
 - Nystatin: for candida Albicans infections of the skin and mucous membranes
 - Amphotericin: iv for severe fungal infections, active against most fungi and yeasts. Highly protein bound and poor tissue penetration. SE many and common. Nephrotoxicity (pre-hydrate) and infusion reactions (dampen with steroids). Lipid formulations much better tolerated, more

expensive. Often *flucytosine* added in combination for synergistic effect, impairs DNA synthesis. SE bone marrow suppression (weekly blood counts), renal impairment resistance

- Azole antifungals:
 - Mechanism: inhibition of CYP450, required for cell membrane ergosterol synthesis by fungi
 - Lots of CYP450 drug interactions
 - Fluconazole: good oral and CSF absorption, active against *C. albicans*, well tolerated
 - Itraconazole: active against aspergillus, not in liver disease, renal toxicity, ?bioavailability
 - Voriconazole: broad spectrum antifungal for life threatening *Candida* and aspergillus infections, transient visual disturbances in 30%, asymptomatic ↑LFTs
 - Posaconazole: active against zygomycetes, recent evidence (NEJM 2007) of superiority against fluconazole for prophylaxis against high risk invasive fungal infection. Well tolerated
 - Clotrimazole: topical treatment of vaginal candidiasis and dermatophytoses (ringworm – tinea)
 - Ketoconazole: best oral absorption but associated with fatal hepatotoxicity
- Others:
- Echinocandins:
 - Inhibit glucan synthase → impairs cell wall synthesis. Fungicidal against *Candida*, stunts aspergillus
 - Caspofungin: for invasive aspergillosis unresponsive or intolerant to amphotericin or itraconazole. Empiric therapy in febrile neutropenia. Well tolerated. Not such good data
- Griseofulvin: generally superseded
- Terbinafine: drug of choice for fungal nail infections

Candidiasis

- A yeast. *Candida albicans* the most common
- Commensal on skin, GIT, female genital tract
- Mucosal
- Candidal Funguria, may indicate systematic infection
- Candidaemia: Fever +/- sepsis, following broad spectrum ABs, venous catheters, urinary catheters, TPN, renal impairment...
- Disseminated – blood cultures 50% sensitive. Seen with prolonged neutropenia. Infrequent if azole prophylaxis. Presents with fever *after* neutrophil recovery, abdominal pain, ↑ALP. Abscesses in liver, spleen, kidney, lungs, brain, eyes
- Endocarditis: post valve surgery or IVDU
- Treatment:
 - Systemic antifungal therapy for 14 days, removal of devices/abscesses
 - Drug options:
 - Amphotericin
 - Triazole: *C. krusei* resistant to fluconazole (voriconazole works)
 - Echinocandins

Aspergillosis

- *Fungi*
- Many species with wide spectrum of disease. *A. flavus* and *A. fumigatus* common
- All disease-causing aspergillus are common in the environment – colonisation common, disease rare
- 90% of patients with aspergilliosis have 2 of:
 - Neutropenia (< 500/ μ L)
 - Treatment with corticosteroids
 - Treatment with other immunosuppressive agents
- Primary infection in the lung with dissemination
- Presentations:
 - Allergic Bronchopulmonary Aspergillosis (see page 191)
 - Aspergillosis and HIV: usually pulmonary disease with fever, cough, dyspnoea
 - Aspergilloma: hyphal ball in pre-existing pulmonary cysts or cavity, usually upper lobe, *without* tissue invasion
 - Endobronchial saprophytic pulmonary aspergilliosis: chronic cough + haemoptysis due to endobronchial colonization
 - Cerebral: severely immunocompromised. Nasal lesions with rapid extension into Paranasal sinuses, orbit, face

- Invasive aspergilliosis: Rapidly progressive pulmonary infiltrate spreading via blood to lung, brain and other organs. Rarely necrotizing aspergillosis, hyphal invasion of blood vessels, thrombosis, necrosis, hemorrhagic infarction
- Diagnosis:
 - Repeated isolation from pulmonary secretions suggests colonisation or infection
 - Biopsy
 - IgE antibody to Aspergillus antigens seen in ABPA
 - CT: Halo sign, seen as a blush around the lesion. Indicative of haemorrhage, suggestive of infection with an angio-invasive fungal organism
- Treatment:
 - Endobronchial or endocavitary aspergilliosis: no benefit from antifungals
 - ABPA: short course corticosteroids. Prophylactic itraconazole may be of some use
 - Invasive disease: IV voriconazole, amphotericin. Itraconazole (200 mg bd) if indolent course
 - Surgical resection if haemoptysis or aspergilloma

Mycobacterium Tuberculosis

- See Lancet 15 December 2007

The bug

- Rod-shape aerobic bacterium
- Neutral on gram staining, can't be decolourised by acid alcohol → "acid fast", due to cell wall lipids
- Can survive within phagocytes (ie macrophages) – if phagocyte maturation arrested (complex reactions 2nd to cell wall) they can replicate. Intracellular survival due to resistance to reactive oxygen intermediates, and inhibition of phagosome fusion and acidification
- Epidemiology:
 - Estimated 8 – 9 million new cases per year, > 95% from developing countries
 - 1.6 million deaths / year
 - Western cases in immigrants and HIV
 - If untreated, fatal in 5 years in 50 – 60%
- Transmission:
 - Droplet nuclei, aerosolized by coughing, sneezing or speaking
 - 3000 infectious nuclei per cough
 - Crowding a significant risk factor
 - If sputum contains microscopically visible AFB → much more likely to transmit infection. Most common in patients with cavitating disease (and, rarely, laryngeal infection)
 - Sputum negative/culture positive much less infectious
 - Miliary: not so infectious (blood born, not bronchial)
 - HIV much less likely to have cavitating disease ⇒ less infectious

Host factors

- Risk factors for activating infection include (+ relative risk):
 - HIV infection (100) – incidence of 10% per year in high-burden communities, 30% per year in advanced illness in South Africa
 - Post-transplantation (20 – 70)
 - Jejunoileal bypass (30 – 60)
 - CRF/dialysis (10 – 25)
 - Recent infection < 1 year (12.9)
 - Immunosuppressive treatment (10) – prednisone > 15 mg for > 1 month
 - Gastrectomy (2 – 5)
 - Diabetes (2 – 4)
- Polymorphisms in multiple genes associated with susceptibility, including HLA, IFN γ , TGF- β ...
- Initial immune response:
 - Cell wall lipoproteins trigger TLRs present in dendritic cells (especially TR2 and TR9). TR1 and 2 ligation activates 1- α hydroxylase → \uparrow 1,25(OH) $_2$ Vit D. Vit D deficiency associated with Tb in immigrants to UK → ??role in treatment
 - Transported by macrophages to regional lymph nodes, then haematogenous spread
- 2 – 4 weeks after infection, two host responses develop:
 - Macrophage activating CMI – T-cell mediated

- Tissue damaging response: Delayed hypersensitivity reaction, destroys unactivated macrophages that contain bacilli causing caseous necrosis
- Activated macrophages (evolving toward giant cells) wall off this necrosis → granulomas. Tb inhibited (although not killed) due to low O₂ tension. May heal with subsequent calcification or continue to be inflamed

Presentation

- Either pulmonary, extrapulmonary or both, and either primary or secondary
- Primary Tuberculosis:
 - Common in children up to 4 and in immunocompromised
 - Not usually highly transmissible
 - Primary progressive Tb = infected pleural effusion and/or progressive cavitation
 - If acquired later in life, contained for a while with those who develop infection usually doing so in 1 – 2 years
 - Pulmonary findings:
 - Enlarged lymph nodes → obstruction → segmental collapse or distal bronchiectasis
 - Haematogenous spread common and often asymptomatic
- Secondary (post-primary) Tuberculosis:
 - Due to latent bacteria
 - Cavitating illness more likely → more infectious
 - In up to 10% of infected patients in their lifetime (higher in HIV) – peaks in adolescence/early adulthood and the elderly
 - Pulmonary findings:
 - Localized to apical and posterior segments of the upper lobe due to higher O₂ tension
 - Cavity formation → necrotic contents spill into airways → satellite lesions
 - If untreated → progressive infection (“galloping consumption”), spontaneous remission, or chronic course
 - Systemic symptoms: fever, night sweats, weight loss,
 - Cough: initially non-productive then productive +/- blood streaking
 - SOB only really if extensive disease
- Extra-pulmonary disease:
 - Lymph nodes (40% of USA cases): painless swelling, discrete nodes, most commonly posterior cervical and supraclavicular. FNA shows AFB on 50%, culture positive on 70 – 80%, granulomas on histology
 - Pleural (20% cases):
 - Pleural biopsy is most sensitive (> 90%)
 - Pleural fluid culture: 42 % sensitive
 - Pleural concentration of *Adenosine Deaminase* (ADA) a useful screening test – Tb virtually excluded if value is very low. Sensitivity 78 – 95%, specificity 95%. Useful as an aid to differential diagnosis
 - Upper airways: if hoarseness, dysphonia, dysphagia
 - Genitourinary (15% cases): urinary frequency, dysuria, nocturia, haematuria, flank or abdominal pain, or asymptomatic. Pyuria and haematuria on urinalysis. If culture negative then ?Tb. Culture of 3 morning urine specimens 90% sensitive
 - Skeletal (~10% cases): Spine in 40% (usually lower thoracic, upper lumbar), hips in 13%, knees in 10%
 - Meningitis:
 - Usually kids and HIV. Haematogenous spread
 - Prodrome of fever, malaise, night sweats, irritability, then headache and subtle mental changes, paresis of cranial nerves
 - Investigation of CSF:
 - High leukocytes (up to 1000/μL), protein (1 – 8g/L)
 - AFB in 1/3, repeated LP increases the yield. Yield improved to 50% by centrifugation
 - Culture diagnostic in 50 – 80% (Gold standard)
 - PCR has sensitivity up to 80%, but false-positive rates up to 10%
 - ADA concentration sensitive but not specific
 - May be subtle changes in CT/MRI (eg hydrocephalus)
 - Uniformly fatal if not treated
 - Neurologic sequelae in 25% of those treated (usually delayed diagnosis)

- Trails of dexamethasone show significantly enhanced survival but no reduction in neurological sequelae
- Pericardial: 40% mortality. Pericardial effusion common. Aspirate by pericardiocentesis. Higher yield from biopsy. ↑ADA and ↑IFN γ suggestive
- Miliary/Disseminated: Haematogenous spread → multiple yellowish granulomas 1 – 2 mm in diameter (resemble millet seeds, hence miliary). Eye exam → choroidal tubercles in 30%, pathognomonic. Sputum microscopy negative in 80%

Diagnosis

- High index of suspicion is key
- Sputum:
 - AFB on smears in 10 – 25%
 - AFB microscopy: sensitivity 40 – 60%. Improved by 3 consecutive early morning sputum samples
 - Sputum culture: sensitivity 20 – 50%, if parenchymal disease then 90%, if no parenchymal disease then 11%
 - HIV: sputum more likely to be negative than in non-HIV → diagnosis difficult
- Early morning gastric lavage if no sputum (often the case in kids)
- Culture: broth faster than solid medium
- Nucleic acid amplification: sensitivity and specificity approaching culture, most useful in confirming positive specimens. Expensive
- Isolates should be sensitivity tested for isoniazid, rifampicin and ethambutol
- Serologic tests not useful – especially if low pre-test probability
- Diagnosis of latent infection:
 - Tuberculin skin testing (TST)/Mantoux test: with tuberculin purified protein derivative (PPD).
 - Limitations:
 - Lack of mycobacterial species specificity (testing for highly conserved proteins) – tests positive for MAC
 - Subjective interpretation
 - Deterioration of product and batch-to-batch limitations
 - Can't differentiate between latent and active disease
 - False-negatives if immunocompromised and in overwhelming Tb
 - False-positives if vaccinated with BCG
 - Promotes T cell memory ⇒ bigger next time. Tb conversion = 10 mm bigger than last time
 - Quantiferon Gold Assay/IFN γ Release Assays (IGRAs):
 - Expose whole blood to highly specific Tb antigens
 - Measure T cell release of IFN γ in response. Also test response to mitogen and to nothing (+ive and -ive controls to check lymphocytes working OK)
 - Doesn't differentiate latent from active infection
 - More specific than TST due to less cross-reactivity with BCG and non-tuberculous mycobacteria
 - Better correlation than TST with exposure to contact investigations in low-incidence settings
 - Recent studies suggest it works OK in immune-compromised people (eg HIV)
- Contact tracing: do Mantoux. If positive then CXR. If -ive then repeat in 3 months

Treatment

- Combination therapy. Resistance invariably the result of monotherapy. No cross resistance amongst commonly used drugs
- Isolate for ~ 2/52 or as long as expectorated AFBs
- Long treatment due to intra-cellular survival and slow dividing bacteria. *Most common cause of treatment failure is poor compliance*
- Regimes: 2IRPE + 4IR
 - Initial, bactericidal phase, usually daily for 2 months: renders them non-infectious – all 4 first line agents (although can omit ethambutol if risk of isoniazid resistance is low – eg no prior treatment and no contact with resistant strains and not immunocompromised)
 - Longer, sterilizing phase, usually daily for 4 months: eliminates persisting mycobacteria and prevents relapse – standard course is isoniazid and rifampin
 - Longer course if big cavities, still smear +ive at 2 months, resistance, CNS, skeletal or disseminated disease
 - If compliance an issue, there are 2 and 3 times weekly directly observed/supervised regimes

- In HIV, potentially hazardous interactions

Drug	SE	Comment
Isoniazid	<ul style="list-style-type: none"> • Adverse effects in 5% • Rash (2%), fever (1.2%) • Hepatitis: transient ↑LFTs in 20%, active hepatitis in 1%, fulminant in << 0.01%. Risk ↑ with age, alcohol, concurrent Rifampicin and active Hep B. Only monitor LFTs if at ↑ risk or abnormal LFTs • Peripheral neuropathy. If at risk (diabetes, alcohol, renal failure, HIV) give prophylactic pyridoxine (vitamin B6) • Optic neuritis, seizures (give B6) • Rare psychosis 	<ul style="list-style-type: none"> • Inhibits cell wall synthesis. Bacteriostatic against resting bacilli and bactericidal against rapidly multiplying organisms • Cheap • Good CSF penetration • Not if active liver disease
Rifampicin (In US aka Rifampin)	<ul style="list-style-type: none"> • Rash (0.8%), mild GI symptoms • Flu-like symptoms (give twice weekly or ↓dose) • Transient mild ↑LFTs common. ↑risk of hepatitis with isoniazid or pyrazinamide • Haemolytic anaemia (< 1%) • Autoimmune thrombocytopenia (stop drug) 	<ul style="list-style-type: none"> • The main sterilising drug • Inhibits DNA dependent RNA polymerase • Red/orange urine – use as compliance check • Excretion: bile + renal • OK in renal impairment • Multiple interactions: ↓half life of OCP, prednisone, phenytoin, sulphonylureas, warfarin, digoxin, protease inhibitors and NNRTIs (can substitute with rifabutin but more expensive)
Pyrazinamide	<ul style="list-style-type: none"> • Liver toxicity (less so with current doses) • Hyperuricaemia and arthralgia (give aspirin). Monitor uric acid only in gout or renal failure. ?Reduced by rifampicin • Gouty arthritis (stop drug) 	<ul style="list-style-type: none"> • Only active against intracellular, dividing forms of Tb. Only active at pH < 6.0 (ie in phagocyte or granuloma). Not used for any other infectious agents • Good CSF penetration – useful in Tb meningitis
Ethambutol	<ul style="list-style-type: none"> • Reduce/avoid in renal disease • Asymptomatic hyperuricaemia • Axial or central neuritis • Optic neuritis (dose dependent, very unlikely if < 30 mg/kg) → ↓visual acuity, central scotoma, ↓green vision (usually after several months) 	<ul style="list-style-type: none"> • Snellen chart check and red-green vision (Ishihara Colour Book) before use. Monthly if high dose • Low levels in CSF

- Pregnancy: all first line drugs can be used and is the most effective treatment. Pyrazinamide can be omitted (lowest safety profile) in which case treat for 9 months
- First-line supplemental drugs (effective with acceptable toxicity):
 - Fluoroquinolones: generally third generation levofloxacin and moxifloxacin. Used in resistant regimes. ↓time to bacillary clearance in mouse models. Concerns about cross-resistance developing in pyogenic infections (Lancet, 29 March 2008)
 - Injectable aminoglycosides: Streptomycin (the first anti Tb agent, not in pregnancy). Not good CSF penetration. Ototoxicity and renal toxicity
- Second line drugs: Only when resistant or intolerant to first line:
 - Injectable aminoglycosides: kanamycin, amikacin
 - Capreomycin (injectable)
 - Oral agents: ethionamide, cycloserine, PAS (para-aminosalicylic acid)
- Paradoxical reactions – “Immune Reconstitution Reaction”: getting worse once treatment starts

- Seen in 2 – 23% of HIV –ive patients 20 – 150 days into treatment. More common in those with HIV, especially on commencing HAART
- Treatment with corticosteroids common but only proven in meningitis and maybe pericarditis (and adjuvant corticosteroids predisposes to Tb)
- Continue anti-TB therapy, aspirate any puss, excise any abscess
- Resistance:
 - If localised disease and sufficiency pulmonary reserve, then consider lobectomy
 - “Drug-resistant”: Resistant to one first line drug (isoniazid the most common – NZ 6.2% in 2001)
 - Multi-drug resistance: resistant to at least isoniazid and rifampin. > 10% in central Asia and Eastern Europe. Worldwide prevalence ~ 4%, 40% in those previously treated for Tb. Treatment longer, more costly, poorly tolerated and less effective
 - Extensively drug-resistant disease: resistant to at least rifampicin, isoniazid, any quinolone and at least one injectable 2nd line agent (Capreomycin, amikacin, kanamycin)
 - Trials of inhaled IFN γ underway
- Treatment of latent TB (aka Chemoprophylaxis):
 - Aim: prevent active disease. RCT show 6 – 12 month course reduces the risk of active disease by up to 90% in infected people. Optimal duration ?9 – 10 months
 - Cut-off for a positive TST reflects probably of actual infection, and risk that active disease will develop (ie treat if > 5 mm if HIV, > 15 mm if low risk person)
 - Esp if considering immunosuppressives (including cytotoxics, and possibly long term steroids)
 - Isoniazid for 9 months, rifampicin for 4 months if isoniazid intolerant or resistant
 - Risk of isoniazid resistance if inadvertently given to patients with subclinical or unrecognised Tb
- Monitoring: check sputum monthly until culture negative (> 80% after 2 months treatment)
- SEs:
 - Most common is hepatitis. Do baseline LFTs, get patients to watch for dark urine, loss of appetite. Worse with rifampicin and pyrazinamide than isoniazid. Only monitor LFTs if at higher risk (liver disease, alcohol) or if symptomatic
 - Hypersensitivity reactions: stop everything and rechallenge one at a time
 - All first line drugs safe in pregnancy
 - Not ethambutol in children given difficulty of eye testing (unless you have to because of isoniazid resistance)
- New drugs: moxifloxacin is bactericidal. Linezolid also effective but takes long course

Vaccination with BCG

- = bacilli Calmette-Guerin (the two blokes who developed it)
- Derived from an attenuated strain of *M bovis*. Disseminated BCG infection and death in < 1 per million (almost exclusively in immunocompromised)
- Efficacy ranges from 0 to 80% in RCT
- Higher efficacy in protection of young children from serious illness (eg miliary and meningitis)
- Now contraindicated in neonates with HIV given 417 per 100,000 affected by disseminated BCG disease (Lancet 6 Sept 2008). A problem in the 3rd world given access to HIV testing
- Not recommended for general use in developed world
- Research on modified BGC looks promising....

Human Immunodeficiency Virus

- See NEJM, 2005;353:1702-10

HIV Virus

- Virus of the Retroviridae subfamily Lentivirinae (slow viruses)
- History: Traced to a simian virus infecting chimpanzees in southern Cameroon. Independent transmission events in the early 20th century spawned three groups: M (major), N (only a few cases identified) and O (outlier – relatively rare – ?gorilla origin). Group M is the predominate HIV-1 virus. Spread along the Congo river. Found in a human blood sample from 1959
- Mechanisms which allow it to allude immune control:
 - Heavy glycosylation of the external glycoprotein (which protects epitopes)
 - Direct targeting of the CD4 molecule
 - Frequent mutation → “mutational escape” of immune response and drug therapy
- Rapid viral evolution due to:
 - Reverse transcriptase lacks proof reading ability: 3.5 * 10E-5 mutations per base pair replication

- Viral production of 10 billion virions per day throughout the course of the disease
- Viral recombination: if coinfecting with two different strains → circulating and unique (ie only found in index case) forms – CRFs and URFs. Lineages of these can be traced geographically
- Types:
 - HIV-1:
 - Current subtypes (called “clades”): A1, A2, A3, A4, B, C, D, F1, F2, G, H, J and K based on envelope sequences
 - Some evidence that some subtypes → more rapid disease progression
 - Type B most studied (predominates in Australia, USA, Europe), but represents only 12% of global infection. 50% of global infection is with subtype C. SE Asia subtype E predominates
 - Viral diversity → possible variations in progression, responses to treatment and vaccination
 - HIV-2 (largely West Africa and India) and HIV-1 type O possess intrinsic resistance to non-nucleoside RTI
- Replication:
 - Virus gp 120 protein binds to CD4+ cell
 - Membrane fusion with co-receptor: either CCR5 or CXCR4 and cell entry CCR5 (R5 viruses) are more frequently transmitted than CXCR4 co-receptor (X4 viruses). All subtypes can use both, but subtype D may be dualtropic (ie R5X4) most frequently
 - Cytoplasmic RNA coded to unintegrated linear DNA by *reverse transcriptase*
 - DNA integrated into cellular DNA by viral *integrase* enzyme → integrated proviral DNA
 - Cellular transcription → genomic RNA and mRNA for protein synthesis, processing and assembly
 - Virally encoded *protease* catalyzes the cleavage of the gag-pol precursor → budding of new virion
- Half life of a circulating virion is 30 – 60 mins and a productively infected cell is 1 day
- Progression: in ~40% transition from a predominant R5 virus to an X4 virus is associated with relatively rapid progression

Host Factors

- Dendritic cells express a receptor (DC-SIGN – a C-type lectin receptor) which has a high affinity for gp 120 and mediates CD4+ cell infection
- Homozygotes for CCR5 $\Delta 32$ are, with rare exceptions, protected from infection (1% Caucasians, rare in Africans and Asians). Heterozygotes for the deletion show slower progression. Other genes have been associated with slower progression
- HLA-B27 associated with ↑ viraemia. HLA-B57 associated with slow progression. Many other associations. ⇒ certain HLA molecules present HIV epitopes more effectively which enhances cell mediated immunity
- Coinfection with a range of viruses (eg HSV, EBV) upregulate expression
- Gut associated lymphoid tissue (GALT):
 - A common early reservoir of infection → widespread viraemia via lymphoid organs → massive depletion of CD4+ cells from the GIT following acute infection
 - Only 1 – 2 % of CD4+ cells are in the blood, 30% reside in mucosal sites – notably the gut
 - Express relatively high levels of CCR5
 - Cells die by direct infection and apoptosis of uninfected cells
 - HIV-1 is able to bind to the gut homing molecule $\alpha 4\beta 7$ (binds to an adhesion molecule on mesenteric lymph node endothelium) via gp120 (NEJM 22 May 2008)
- Monocytes are chronically infected and act as a reservoir. Tissue macrophages in the brain (glial cells) are infected – problems given it’s a sanctuary site
- Rapid rise in CD4 count after initiation of treatment may be due to redistribution of T cells as the viraemia abates
- Immunocompromise results from reduction in CD4 cells, and direct and indirect dysregulation of remaining cells
- CD4 count is the key predictor of mortality

Transmission

- Sex:
 - Worldwide, most infection is heterosexual
 - Anal intercourse more likely to lead to infection than vaginal intercourse due both to thinner rectal mucosa and greater risk of trauma: Estimated risk following a single exposure:
 - Receptive anal sex: < 3.0%
 - Receptive vaginal sex: < 0.1%

- Insertive anal or vaginal sex: < 0.1%
- Extremely low rate in oral sex (< 0.1%)
- Greater concentration of virions in seminal fluid in inflammatory states such as urethritis (associated with other STDs). Early treatment of STDs → ↓transmission (Tanzanian study). Randomised study of valacyclovir showed ↓genital and plasma HIV-1 RNA but ?↓transmission
- Greatest risk of infection is shortly after a sexual partner has seroconverted (0.8 transmissions per 100 coital acts). Further high risk period with partner in late stage disease
- No ↓ in transmission with diaphragm and lubricant gel
- Circumcision → ↓transmission by 70% in heterosexual contact
- Blood and blood products: needles, transfusion, semen for AI, organ donors. IVDU drives heterosexual spread in the US
- Occupational exposure:
 - Risks of transmission:
 - Percutaneous exposure to HIV infected blood: 0.3%
 - After a mucous membrane exposure 0.09%
 - After exposure to fluids or tissues other than blood probably considerably lower than for blood
 - Post-exposure prophylaxis as soon as possible:
 - Low risk exposure:
 - Mucous membranes, intact skin exposure, solid needles, low HIV viral load
 - 2 nucleoside/nucleotide reverse transcriptase inhibitors eg lamivudine + zidovudine for 4/52
 - High risk exposure:
 - Percutaneous injury with hollow-bore needle, high viral load
 - Add 3rd drug eg Lopinavir + ritonavir 4/52
- Fetal-Maternal Transmission: 23 – 30% is prior to birth, 50 – 65% during birth, 12 – 20% via breast feeding. Without prophylaxis transmission occurs in 20 – 30% of babies (risk correlates with viral load + other factors including prolonged rupture of membranes, ↓with elective caesar). Maternal CD4+ > 500 does not ↓risk (independent of viral load)
- No convincing evidence of transmission through saliva (virions are present at very low levels) or kissing
- Estimated ¼ of infected people in the US are unaware of their infection
- ↑diagnoses + ↓death from HAART → ↑prevalence

Diagnosis and monitoring

- Testing “normalised” in recent MoH directive. Opt out testing. Should test in all cases of:
 - Pregnancy
 - Shingles in < 40 yr old
 - All lymphomas
 - Any weird malignancy
 - Aseptic meningitis
 - Reactive arthritis or Uveitis (eg from syphilis)
 - Any unusual peripheral neuropathy
- Currently 250 diagnoses a year in NZ
- HIV ELISA and Western Blot:
 - Antibodies to HIV usually appear within 6 weeks, and always within 12 weeks of primary infection
 - ELISA: sensitivity of > 99.5%, most assays test for both HIV-1 and HIV-2. In low risk populations (eg blood donors), specificity of only 10%
 - Western Blot used as a highly specific follow-up test – positive if it demonstrates antibodies to all three of the major genes of HIV (gag, pol and env)
 - Current AIDs serology test tests for antibodies + one viral antigen ⇒ *window period only 10 – 11 days*
- HIV plasma viral load testing:
 - False positives in 4 – 26% of individuals → *not* for diagnosis
 - Used if high risk exposure to HIV and indeterminate Western Blot (eg early in seroconversion disorder)
- HIV RNA by PCR reliable to 40 copies/mL
- CD4 + count determined by flow cytometry
- Other methods...
- Recommended time for testing neonates is 4 – 6 weeks

- Resistance testing:
 - Genotypic assays: genome sequences from the patient compared with known resistance profiles
 - Phenotypic assays: Growth in vivo of patient virus compared with reference strains
- Baseline Bloods:
 - FBC, U&Es, fasting BSL and cholesterol
 - LFTs, CK, amylase
 - Syphilis, Hep A, B, C, Toxoplasmosis titre, CMV titre
 - Cervical smear, anal screening for HPV
 - Mantoux test, ECG, CXR, MMSE
 - CD4 cell count, Plasma HIV-1 RNA

Presentation

- Acute HIV syndrome (Seroconversion Syndrome):
 - ~ 50% experience acute HIV syndrome, which correlates with degree of viraemia, but level at this point has no prognostic significance
 - 3 – 6 weeks after primary infection
 - General: Fever, pharyngitis, lymphadenopathy, headache, arthralgias, myalgia, lethargy, nausea
 - Neurologic: meningitis, encephalitis, peripheral neuropathy, myelopathy
 - Skin: erythematous maculopapular rash, mucocutaneous ulceration
- Proceeds to chronic infection with latent infection and continual virus replication at some level for ~ 10 years untreated before progressing to AIDS. With treatment, “long term survival” is currently defined as > 20 years
- Long term non-progressors show little or no decline in CD4+ counts over extended periods of time – usually have low viral loads
- Some remain asymptomatic despite ongoing CD4+ decline
- Early HIV-induced disease (CD4 > 500) includes: Guillian Barre Syndrome, chronic demyelinating neuropathy, idiopathic thrombocytopenia, Reiter’s syndrome, polymyositis, Sjogren’s syndrome, Bell’s palsy
- Conditions listed in the AIDS surveillance case definition include: candidiasis of oesophagus or LRT, invasive cervical cancer, cryptococcosis, CMV disease (other than liver, spleen or nodes), HIV related encephalopathy, herpes simplex infection (if mouth ulcers, > 1 month), histoplasmosis, Kaposi’s sarcoma, Burkett’s, primary or brain lymphoma, extrapulmonary MAC, TB (any site), Pneumocystis jiroveci pneumonia (was PCP), recurrent pneumonia, progressive multifocal leukoencephalopathy, recurrent salmonella septicaemia, toxoplasmosis of the brain, wasting syndrome due to HIV
- US AIDS definition includes anyone with CD4 count < 200, but not included in Australian definition
- Symptomatic conditions not in the AIDS surveillance case definition include oral or vulvovaginal candidiasis, cervical dysplasia, fever or diarrhoea > 1 month, oral hairy leukoplakia, Herpes Zoster, ITP, Listeriosis, PID, peripheral neuropathy
- Advanced disease:
 - < 50% of deaths are as a direct result of an AIDS defining illness
 - Average CD4+ count at death is 300
 - Increased rates of non-HIV related infections: CVD, renal, liver

Complications of HIV

- Opportunistic Infections and malignancy by CD4 count:
 - 200 – 500 cells/μL: Herpes Zoster, pneumococcal pneumonia, oral candidiasis, TB
 - 50 – 200: PJP, CNS Toxoplasmosis (< 100), Cryptococcosis, Kaposi’s Sarcoma, NHL, PCNS Lymphoma
 - < 50: Disseminated MAC, CMV retinitis, Cryptosporidiosis
- Respiratory disease:
 - Acute bronchitis and sinusitis prevalent: increased infection with encapsulated bacteria such as H influenzae and Strep pneumoniae
 - Pneumonia:
 - S pneumoniae is by far the most common cause of community acquired pneumonia in HIV. Relative risk compared to CD4 count: > 500 = 2.3, 200 – 500 = 6.8, < 200 = 10.8. 100 fold ↑ risk of pneumococcal bacteraemia. Legionella is significantly less common
 - Unicellular fungus Pneumocystis jiroveci causing PCP – diagnosis needs sample – 95% have count < 200

- Tb: median CD count at presentation 326, 2/3 have pulmonary disease, 1/3 have extrapulmonary disease. 15% blood culture positive. Mantoux screening should be performed on all new cases and treated at a cut off of 5 mm. Treatment regime same as non-HIV patient – although may prefer to treat with 2 months rifampicin and pyrazinamide (despite liver toxicity) rather than 9 months isoniazid to simply drug regimes. Triple nucleoside regimes not so effective for HIV but safer in Tb as there are fewer liver SEs to compound liver effects of Tb treatment
- Other: fungal, relatively benign forms of interstitial pneumonia
- CVS:
 - As a result of HIV, treatment of lipodystrophy syndrome
 - Dilated cardiomyopathy second to myocarditis: late complication
- GI:
 - Oral: thrush due to candida, oral hairy leukoplakia (presumed due to EBV, not premalignant), aphthous ulcers (cause unknown, thalidomide may help)
 - Oesophagitis: 2nd to candida, CMV or HSV
 - Bacteria: Salmonella, Shigella, Campylobacter, C difficile
 - Fungal infection: histoplasmosis, coccidioidomycosis, penicilliosis
 - Protozoa: cryptosporidia, microsporidia and Isospora belli most common
 - CMV disease with low counts
- Hepatobiliary:
 - 1/3 of deaths related to liver disease, often coinfection with Hep B (IFN α less successful in HIV coinfection. Use Lamivudine etc) or Hep C (IFN α + ribavirin for 2 weeks, if no drop in Hep C load then stop)
 - Liver infection: Tb, fungal
 - Liver and pancreatic injury 2nd to HAART
- Renal: HIV associated nephropathy and UTIs. Syphilis increases rate of HIV transmission due to genital ulcers
- Endocrine: Osteoporosis, thyroid disturbance
- Haemopoietic:
 - Anaemia, leukopenia and/or thrombocytopenia common
 - Bone marrow suppression from: HIV, fungal and B19 parvovirus infections, lymphoma and medications
- Skin: Seborrheic dermatitis, folliculitis, opportunistic infections, shingles, molluscum...
- Neurologic:
 - Infections: *toxoplasmosis*, *Herpes simplex*, *cryptococcosis neoformans*, VZV, CMV, syphilis, MTb, HTLV-1, *progressive multifocal leukoencephalopathy* (JC Virus)
 - Neoplasm: *CNS lymphoma* (EBV in CSF), Kaposi's sarcoma
 - As a result of HIV-1 infection itself:
 - Aseptic meningitis
 - Cognitive impairment (including *AIDS encephalopathy* – seizures common – test HIV viral load in CSF). HIV dementia is a diagnosis of exclusion, focal neurology suggests another cause
 - Myelopathy (any spinal cord dysfunction)
 - Peripheral neuropathy (GBS, CIDP, mononeuritis multiplex). See page 176
- Eyes: cotton-wool spots common (no visual loss) and CMV retinitis, also HSV and varicella retinitis
- Generalized wasting: weight loss > 10%, fever, chronic diarrhoea, fatigue, lasting > 30 days. Indication for initiation of HAART
- Neoplastic: Kaposi's sarcoma (multiple vascular nodules, now rare 2nd to HAART, can occur at any CD4 count, associated with Human Herpesvirus-8), non-Hodgkin's lymphoma (immunoblastic, Burkitt's and primary CNS lymphoma), and a small increase in incidence of cervical cancer

Non-drug Treatment

- Education and counselling essential including:
 - On going infection risk even if viral load undetectable
 - Important of compliance once treatment initiated
- Should have a power-of-attorney
- Contact tracing
- Immunisation:
 - Hepatitis B, Hepatitis A, Influenza annually (not if egg allergy), Strep pneumoniae (before count < 200), HPV for females 9 – 26 years

- If starting HAART at time of diagnosis, wait 3 months to allow ↑CD4 count → better vaccine effectiveness
- Live vaccines: Never BCG or oral polio. ?Varicella and MMR if CD 4+ > 200

Principles of Drug Treatment

- Aims: suppression of HIV, increase in CD4 count, little resistance, low toxicity, CNS penetration (otherwise dementia) and simplicity (→adherence). Different regimes rank differently on these different criteria
- Never use monotherapy otherwise → ↑resistance
- HAART = Highly Active Anti-Retroviral Therapy
- Complex regimes with multiple daily doses → compliance an issue. Median compliance is 60 – 70%, a but a dramatic difference in treatment effect for compliance > 85%
- When to treat unclear:
 - ↑CD4 count doesn't necessarily translate into better outcomes than waiting to treat later
 - Intermittent treatment → ↑risks of HIV and non-HIV complications and mortality (eg MI, CVA). Once started, can't stop – no treatment holidays. (Shown in SMART Study). No virological or immunological benefit. Within days of stopping ↑IL6 and ↑d-dimer
 - Treatment → ↓non-AIDS related illnesses – CVD, malignancy, hepatitis
 - Current consensus: Initiate treatment if:
 - Acute severe HIV conversion syndrome – but duration (or long term benefit) of treatment unclear
 - All pregnant women
 - Symptomatic disease
 - Asymptomatic disease and CD count < 200 – 350/μL. “Generally recommend treatment” for 200 – 350. Not if > 350 as long-term toxicity and development of resistance outweigh benefits (although some recommend treatment if CD count falls consistently by > 100 in a year)
 - ??very high viral loads
 - ?6 week prophylactic course following high risk exposure
- What to start on:
 - Routine “starter pack” in New Zealand: Efavirenz (teratogenic), tenofovir and lamivudine – one tablet once a day, lowest metabolic toxicity
 - Other Regimes:
 - 2 nucleoside analogues (one of which is usually lamivudine) + non-nucleoside inhibitor (more convenient to dose than PI and no PI has been shown to be superior to Efavirenz)
 - 2 nucleoside analogues + protease inhibitor
 - Recent trial of NRTI-sparing regime (with Efavirenz + Lopinavir-ritonavir showed rough equivalence, NEJM 15 May 2008) – NRTI have a reasonable side effect burden....
 - If compliance or SE an issue then a od 3 * NRTI pill is available (AZT/3TC/ABC)
- Many later drugs only trialled in combination, or in situations of triple therapy failure, with a surrogate endpoint (eg viral load, CD count), not mortality
- On starting HAART:
 - Should be a brisk rise in CD of 100 -150/μL
 - There is an initial early rise in CD4 memory cells – probably redistributed from lymphoid tissue – and a slow recovery of naïve CD4 cells over months-years
 - Expect a 10 fold reduction in viral load in 1 – 2 months and eventually a decline to < 50 copies per ml
- Immune Reconstitution Syndrome:
 - From 2 weeks to 2 years after starting HAART, especially if initial count < 50
 - Prolonged fever, lymphadenitis, pulmonary infiltrates, uveitis and Grave's disease
 - May need steroids
 - Treat opportunistic infections for several weeks before starting HAART (clean them up a bit first) otherwise apparently worsening opportunistic infections as the immune system “wakes up” to their presence
- On going management:
 - Monitor RNA levels and CD4+ counts every 3 – 4 months, other bloods 6 monthly
 - Sorting out drug toxicity from HIV symptoms: stop everything for a while – drug reactions should improve within ~ 2 weeks
- Treatment failure:
 - Virologic failure:

- Incomplete virologic response: Detectable virus after 48 weeks
- Virologic rebound: repeated HIV RNA detection after viral suppression
- Immunologic failure: CD4 has not risen by > 25 – 50 on 12 months therapy
- Clinical failure: occurrence of HIV-related events after > 3 months on therapy
- Resistance:
 - Defined as a viral load repeatedly detectable during therapy. Exclude poor compliance
 - Due to:
 - Primary resistance: acquiring a resistant strain
 - Secondary or acquired resistance 2nd secondary to treatment over about 6 months – never use monotherapy. Maximal replication suppression → ↓risk of resistance
 - Role of resistance testing yet to be determined – ? use in areas of high resistance. May be useful if concerned about compliance
 - Drug resistance testing should be done while the patient is taking the failing regime. Genotype testing usually needs > 1000 copies/ml to perform test. Phenotype testing (not available in Australasia) tests the virus' ability to grow in different concentrations of different antiretrovirals

Reverse transcriptase inhibitors

- Block RNA dependent DNA synthesis
- Nucleoside and nucleotide analogues:
 - DNA chain terminators, bind more avidly to the active site of the reverse transcriptase
 - Inhibit a variety of DNA polymerization reactions in addition to HIV-1 reverse transcriptase → side effects, including *mitochondrial damage* due to inhibition of mitochondrial DNA polymerase (* below) → *hepatic steatosis and lactic acidosis*. Also *peripheral neuropathy, pancreatitis, and subcutaneous lipoatrophy* (especially d4T and ddI)
 - Most need adjustment in renal impairment
- Non-nucleoside reverse transcriptase inhibitors. No activity against HIV-2. Bind to regions outside the active site causing conformational change rendering it inactive. Don't have mitochondrial side effects. Frequent macular-papular rash on initiation usually fades. Exclude Stevens-Johnson (mucosal involvement, fever, painful lesions with desquamation). Also early hepatitis

Class	Drugs funded in NZ	SE (in addition to above)	Comments
<i>Nucleoside Reverse Transcriptase Inhibitors * = hepatic steatosis & lactic acidosis, ~ = used for Hep B</i>			
	Zidovudine (AZT)	Anaemia, granulocytopenia, myopathy in 17% with "ragged red cracked" fibres on muscle biopsy, distinct from HIV myositis (test CK), *	Initial fatigue, nausea may resolve Also in prevention of fetal transmission
	Didanosine (ddI)	Pancreatitis in 10% → stop drug, painful peripheral neuropathy, *	Not with Tenofovir. Need to take when fasted
	Stavudine (d4T)	Greater * toxicity	Discontinued in US – antagonistic with AZT
	Lamivudine (3TC) ~ (Etricitabine [FTC] ~ very similar)	Hepatotoxicity	Commonly first line drug. Better than AZT, well tolerated. Effective in Hep B. Excellent synergy with other NRTIs – strains resistant to lamivudine have ↑ susceptibility to other NRTIs
	Abacavir	Hypersensitivity (higher rate if HLA B57+), potentially fatal if rechallenged	Tested for B57 prior to treatment (as a result of Perth based research)
<i>Nucleotide Reverse Transcriptase Inhibitors</i>			
	Tenofovir ~	Renal toxicity – not in CRF (renally cleared)	Common first line drug. Effective in Hep B. No mitochondrial toxicity. ↑Didanosine levels in combination and ↓effectiveness
<i>Non-nucleoside Reverse Transcriptase inhibitors</i>			
	Nevirapine	Skin rash, life threatening hepatotoxicity, especially at higher CD counts	Can get Stevens Johnson.
	Efavirenz	Rash, dysphoria, drowsiness,	\$500 per month. Only once daily

Etravirine – not available in NZ	dreams, depression, teratogenic	NNRTI. Less toxic than Nevirapine. Induces its own metabolism – need to increase dose. Fetal harm in 1 st trimester. Interferes with methadone (ie problem in IVDU acquired HIV) Active against HIV resistant to the first 3 NNRTIs. Need > 3 mutations for resistance
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Protease Inhibitors

- Inhibit the HIV protease which lyses viral proteins into their active form following translation
- In combination with RTI, suppress viral load to < 50/ml for a minimum of 5 years
- Rapid resistance if monotherapy
- Ritonavir inhibits P450 degradation of all other PIs (*and may other drugs*, eg macrolides, warfarin, ondaneestron, CCB, steroids...). Used in combination at low dose (due to intolerance) to boost all other PI levels – which otherwise have to be dosed frequently due to short T_{1/2} → poor compliance...
- Cause fat redistribution, abnormal lipids and hyperglycaemia (# below) – **lipodystrophy**. Half will develop insulin resistance and up to 10% will get diabetes. ↑risk of MI

Drugs funded in NZ	SE	Comments
Ritonavir (RTV)	#	
Saquinavir mesylate (SQV)	#, well tolerated	Degraded by P450 – given with ritonavir
Indinavir sulfate	Nephrolithiasis in 4%, ↑bilirubin in 10%, #, ingrown toe nails	First protease inhibitor used with dual nucleoside treatment → profound effect on viral replication
Nelfinavir mesylate	#, may contain traces of carcinogen/teratogen	
Lopinavir (LPV)	Diarrhoea, #	Single capsule. Superior to nelfinavir
Atazanvir (ATV)	#, ↑bilirubin, PR prolongation	Less ↑lipids than others, once daily. Needs acid for absorption so not with PPI. ↑levels of CCB, macrolides, statins
Darunavir (DRV)		Shown to be effective in salvage therapy

Entry Inhibitors

- Interfere with the binding of HIV to its receptor or co-receptor, or by interfering with fusion
- CCR5 inhibitors: Maraviroc prevents binding of (only) the R5 tropic virus. Need to test first (only one lab in San Francisco does it). When added to optimised treatment in patients with R5 virus only, on a background of sustained HIV levels despite treatment with 3 classes, leads to a ↓ in viral load (NEJM 2 Oct 2008). No associated hepatotoxicity. Resistance can develop in R5 viruses. Usually CCR5 virus predominant in early illness, with X4 predominating later in illness. Concerns that CCR5 inhibition may select for x4 viruses not born out (so far)
- Fusion inhibitors: Enfuvirtide (only injectable drug)

Drugs funded in NZ	SE	Comments
Enfuvirtide (only funded if other treatment failure)	Injection reactions in nearly 100%, hypersensitivity, ↑bacterial pneumonia	\$2,300 per month. Twice weekly injection. Binds to gp41 subunit of the HIV-1 envelope
Maraviroc (not in NZ)	Allergic hepatotoxicity, postural hypotension, fever, arthralgia...	CCR5 blocker. Need to confirm R5 virus first

Integrase Inhibitors

- Block integration of HIV provirus into the host genome. Safe and potent. Raltegravir the only currently licensed one (NEJM 24 July 2008)

	SE	Comments
Raltegravir (not in NZ)	Nausea. Minimal side effects	Active against HIV1 and 2, including MDR strains. No CYP450 or other HAART interactions.

Complications of HIV Treatment

- Lipodystrophy:**
 - 33 – 75% receiving HAART develop:
 - Lipid abnormalities: ↑TG, ↑cholesterol, ↑apoprotein B,
 - Insulin resistance: ↑glucose
 - Lipoatrophy: sunken cheeks, peripheral wasting, prominent veins
 - Lipohypertrophy: fat redistribution with truncal obesity, breast enlargement, buffalo hump
 - Women, patients > 40, longer duration of therapy and CD count the main risks
 - NRTI → greater risk than NNRTI. Disfigurement → ↑risk of non-compliance
 - Do pre-treatment fasting glucose, monitor 3 – 4 monthly on therapy for the first year then annually thereafter if OK
 - Management:
 - Change ARV: modest reductions in lipids by exchanging PI for NNRTI (cease ritonavir if possible, atazanvir the best PI for lipids)
 - Statins: pravastatin best (not CYP450 dependent). Avoid simvastatin and caution with atorvastatin as ↑levels with PIs → ↑risk of rhabdomyolysis
 - Fibrates
 - No effect of rosiglitazone – promotes subcutaneous fat
- Myocardial Infarction:**
 - Generally from observational data, not RCTs
 - HAART doubles the risk over 5 years. No association with HIV VL or CD4 count
 - Risk higher with PIs than NNRTIs
 - Specific risks with Abacavir and Didanosine
- Hepatotoxicity:**
 - Liver disease is significant cause of death in the post-HAART era (partly because they're no longer dying of AIDS)
 - Nevirapine: early effect, dose titration reduces risk
 - PIs: any time during treatment course
 - HCV coinfection:
 - Highest in IVDU, also in haemophiliacs, lower in MSM
 - worse HCV progression and complications
 - Debate about which treatment to start first. HIV treatment is hepatotoxic, CD4 decreases with interferon
 - HBV coinfection:
 - HIV modifies the natural history of HBV: higher rate of chronic infection, ↓HBeAg seroconversion, ↓ALT levels but faster progression to cirrhosis
 - If HBV treatment indicated and HIV not, then PEG-IFN or adefovir
 - If HIV treatment indicated and HBV not, then avoid LMV, FTC and TDF
 - Higher rates of lamivudine resistance if HIV coinfection. Tenofovir resistance rare. Entecavir selects for HIV resistance
 - Causes of ↑LFTs: Immune reconstitution reacting to HBV, hepatotoxicity from ARV, development of HBV resistance, other liver disease
- Drug Interactions:**
 - Need to check if you ever add or change drugs in someone on HAART: www.hiv-druginteractions.org
 - P450 3A4 interactions:
 - PIs and NNRTI metabolised by P450 3A4
 - PIs also inhibit P450 3A4, ritonavir the most potent. Ritonavir also inhibits 2D6, 2C9, 2C19, Efavirenz induces and inhibits P450 3A4 – unpredictable reactions
 - NNRTI: nevirapine induces P450 3A4 enzymes

- Absolute contraindications:
 - Cisapride → Long QT
 - Lovastatin → rhabdomyolysis, use pravastatin
 - Midazolam → prolonged sedation, use propofol
- Caution:
 - Ritonavir: TCAs, CCBs
 - Fluticasone → Cushing's, osteoporosis, avascular necrosis
 - Oestradiol: 40% ↓
 - Methadone: Nevirapine results in withdrawal, stopping nevirapine → overdose

HIV Vaccine Development

- Difficulties:
 - Mutational escape over time from CD8+ cells and antibodies to original infection
 - Cross reactive responses to other viral subtypes are typically limited
 - Trials ineffective so far. Some progress in inducing T-cell mediated response that reduces viral load (but doesn't eliminate infection)
 - Need for development of effective mucosal immunity
 - Haven't established correlates of protective immunity to HIV

Prophylaxis

What	When (summarised)	First choice
PJP	Count < 200 or oral candidiasis	Cotrimoxazole (drug reactions common, may not need to stop), alternative dapsone
M Tb	Skin test > 5 mm, close contact	Isoniazid + pyridoxine (if not resistant)
M Avium	Count < 50	Azithromycin or clarithromycin
Toxoplasma	Toxo IgG antibody and count < 100	Cotrimoxazole, alternative dapsone
Varicella	Exposure and no previous infection/immunisation	PEP with Varicella immune globulin
Cryptococcus neoformans	Prior disease. Stop if ok for 6 months with count > 200	Fluconazole
Histoplasma capsulatum	Prior disease.	Itraconazole
Coccidioides	Prior disease or +ive serology and count < 250	Fluconazole
Penicillin marneffeii	Prior disease	Itraconazole
Salmonella	Prior bacteraemia	Ciprofloxacin for > 6 mths
Cytomegalovirus	Prior disease and count < 100	Ganciclovir
Bartonella	Prior infection	Doxycycline, azithromycin, clarithromycin

Prevention

- Individual-level behaviour interventions
- Structural interventions:
 - That affect factors shaping or constraining individual behaviour: poverty, gender (eg female powerlessness or violence), discrimination, age, policy and power. Must address the drivers of HIV risk and vulnerability at the individual, household, community and national level
 - Include physical, social, cultural, organisational, economic, legal or policy features of the environment in which HIV infection occurs

AIDS Related Infections

- See Aspergillus, page 297

Cryptococcus Neoformans

- Round *yeast* like cells with polysaccharide capsule
- Found in pigeon droppings
- Associated with HIV, and steroid or immunosuppressive treatment

- Infected via inhalation, with haematogenous spread to the brain
- Presentation:
 - Pulmonary: granulomatous reactions, often asymptomatic, otherwise chest pain or cough
 - Meningoencephalitis: Most common presentation. Headache, fever, irritability, confusion, staggering gait. Papilloedema in 1/3 and cranial nerve palsies in 1/4 at diagnosis
 - Skin lesions: in 10% associated with disseminated disease, enlarging papular lesions with central ulceration
- Diagnosis:
 - India ink smear of centrifuged CSF positive in > 50%. Lymphocyte predominant pleocytosis
 - Samples for staining and culture
 - Cryptococcal capsular antigen testing by latex agglutination of CSF, serum
- Treatment: Amphotericin B + flucytosine → fluconazole indefinitely when stable

Pneumocystis jiroveci

- Aka Pneumocystis Carinii – renamed as it's a fungi not a protozoa
- Risk ↑ dramatically with CD4+ count < 200 cells/μL
- Most common cause of pneumonia in AIDs (also occurs in SCID, malnourished infants, organ transplant, steroids)
- Propagate within the alveoli. With severe disease interstitial oedema, fibrosis and hyaline membrane formation
- Presentation:
 - SOB, fever, non-productive cough, lasting 1 – 2 weeks (longer in HIV – higher organism burden, more insidious onset). Chest often clear on exam
 - Disseminated disease mainly in patients taking prophylactic inhaled pentamidine (if intolerant to cotrimoxazole): Lymph nodes, spleen, liver, and bone marrow involvement
- Investigations:
 - ABG: ↑A-a gradient, ↓PaO₂, respiratory alkalosis
 - ↑LDH
 - CXR: bilateral diffuse infiltrates beginning in the perihilar regions
 - PCR most sensitive but don't know the specificity – can be PCR positive but don't know if it's colonisation (which is common) or disease
 - Induced sputum (otherwise BAL), various staining techniques
- Treatment:
 - Degree of hypoxia predicts outcome. Mortality 15 – 20% at 1 month, 50 – 55% at 1 year
 - Cotrimoxazole. IV pentamidine if severe but highly toxic. Adjunctive steroids may help if severe
- Prophylaxis: TMP-SMX, dapsone, pentamidine if HIV and CD4 < 200/mm³ (or non-HIV if on prednisone > 20 mg for > 1 month)

CMV

- Herpes virus, cells 2 – 4 times the size of surrounding cells
- Spread in breast milk, saliva, faeces, urine, semen, requires repeated or prolonged contact
- Latent infection in multiple organs and cell types persists throughout life, reactivated by depressed T cell immunity
- Presentation:
 - *Congenital*: petechiae, hepatosplenomegaly, jaundice, microcephaly, IUGR, chorioretinitis. Labs: ↑LFTs, thrombocytopenia, haemolysis, ↑CSF protein
 - *Perinatal infection*: most asymptomatic, maybe interstitial pneumonitis esp if prem
 - *CMV mononucleosis*: most common presentation in normal hosts. Incubation 20 – 60 days. Symptoms for 2 – 6 weeks: fevers, fatigue, myalgia, headache, splenomegaly. Pharyngitis and lymphadenopathy rare. Labs: > 10% atypical lymphocytes, ↑AST/ALT/ALP
 - *Immunocompromised Host*: Fever, malaise, night sweats, arthralgia/myalgia, tachypnoea, unproductive cough, GI disease (ulcers, hepatitis), CNS disease (encephalitis), retinitis
 - HIV patients: esp when CD4+ counts below 50 – 100/μL → *retinitis*, colitis, etc
 - Immune Recovery uveitis: inflammatory reaction to CMV after initiation of ART. Treatment steroids
 - Transplant recipients: Greatest risk is 1 – 4 months after transplantation. Retinitis can occur later
- Diagnosis:
 - Viral culture

- CMV antigens in peripheral-blood leukocytes or CMV DNA in blood or CSF
- Serology: antibodies may not be detected for > 4 weeks after primary infection and elevated for years. IgM may be useful for acute infection
- Treatment: Ganciclovir: 70 – 90% response in HIV infected patients, with ongoing maintenance treatment unless sustained ↑ in CD4 count > 100 – 150 on HAART. Valganciclovir replacing Ganciclovir (at least in CMV retinitis)
- Prophylactic or suppressive Ganciclovir to high risk transplant recipients (seropositive before transplantation or culture positive afterwards)

Non-Tuberculous Mycobacterium in HIV

- Mycobacterium Avium Complex (MAC):
 - Primarily in advanced HIV disease without HAART (usually CD4 < 50 cells/μL), also transplant patients and leukaemia (exp hairy cell leukaemia)
 - Presentation: fever, weakness, wasting, adenopathy. Consider in Immune Reconstitution if HAART has been started
 - Lab: anaemia, hypoalbuminaemia, ↑ALP, blood culture after 7 – 14 days. AFB of bone marrow or liver faster
 - Treatment: Macrolide (clarithromycin 500 mg bd) or azithromycin (500 mg/d) plus ethambutol. Long course – can stop after 12 months if CD4 + counts > 100 for > 6 months
 - Prophylaxis: azithromycin or clarithromycin if CD4+ < 50
- M kansasii: Disseminated disease in advanced AIDS, resembles MAC but more pulmonary findings. If receiving HAART, substitute rifabutin for rifampicin to avoid drug interactions

Toxoplasma Gondii

- Parasite
- Cats are definitive hosts. Transmission from ingested oocyst from contaminated soil, from tissue cysts from undercooked meat, or maternal-fetal transmission (in 1/3rd acute maternal infections)
- Presentation:
 - Immunocompetent: usually asymptomatic, maybe cervical lymphadenopathy
 - Immunocompromised: mainly due to reactivated latent infection. CNS principal site of infection, including mass lesions. Most common site brainstem, basal ganglia, pituitary, corticomedullary junction
 - Also pneumonia (may be confused with pneumocystis), chorioretinitis (most congenital). Also, GI tract, pancreas, heart, liver
- Diagnosis:
 - CSF not sensitive
 - Tachyzoites in tissue (eg brain biopsy) or concurrent presence of IgM and IgG antibodies
 - CT: multiple contrast enhancing lesions. Single lesion may be lymphoma
 - PET may help differentiate CT from Lymphoma
 - Congenital: PCR on amniotic fluid, or positive IgM or IgG after first week of life
- Treatment: pyrimethamine + sulfadiazine + leucovorin followed by chronic suppressive therapy. Glucocorticoids to treat intracerebral oedema
- Prophylaxis: If HIV and CD4+ < 100, then cotrimoxazole for both toxoplasmosis and pneumocystis. Reactivation of latent infection more important than primary infection (so recommendation of ↓cat contact less of an issue)

Progressive Multifocal Leucoencephalopathy

- Progressive multifocal demyelination throughout the CNS, plus change in astrocytes and oligodendrocytes
- A widespread papovavirus, infecting children, leading to latent infection in the kidneys and lymphoid organs. No recognised acute JC virus infection. Targets myelinating oligodendrocytes
- Presentation: progress, subacute, visual deficits (often homonymous hemianopia – not optic neuritis), dementia/confusion/personality change, eventually motor weakness, 60 – 80% have HIV, most others have an underlying immunosuppressive disorder (see Differentials of Multiple Sclerosis, page 161)
- CT often normal. MRI: always abnormal, coalescing white matter lesions periventricularly, parietal-occipital region and in the cerebellum
- CSF: Often normal, maybe mild pleocytosis
- CSF: PCR of JC virus DNA is diagnostic, PCR of urine not helpful. Brain biopsy gold standard

- No treatment. If HIV, then may improve with HAART (risk of Immune Reconstitution Syndrome PML)

Human T cell Lymphotropic Virus (HTLV)

- Not AIDs related – but the other reverse transcriptase virus affecting humans
- HTLV-1:
 - Infects CD4 cells. Associated with T cell lymphoma
 - Incubation 15 years
 - Chronic syndrome: diffuse lymphadenopathy, organomegaly, lytic bone lesions, hypercalcaemia, skin lesions, maybe myelopathy (HAM – HTLV Associated Myelopathy) and neuropathy (like MS but doesn't remit)
 - Predisposition to opportunistic infections, eg PJP
 - No benefit from antivirals. Management of lymphoma/leukaemia similar to non-Hodgkins lymphoma: combination chemotherapy + radiation
 - Donated blood is screened
- HTLV-2:
 - Reported association with hairy cell leukaemia not confirmed
 - Infects CD8 cells. Common in IVDU

Diarrhoea

- See also Clostridium, page 287 and Malabsorption, page 337
- Consider differentials: inflammatory bowel disease, malabsorption, hyperthyroidism, drugs
- Types of infectious diarrhoea:
 - Inflammatory diarrhoea:
 - Frequent bloody, small volume stools, associated fever, abdo cramps, tenesmus, faecal urgency
 - Suggests colonic involvement by invasive bacteria, parasites or toxin
 - Consider Shigella, Salmonella, Campylobacter, Yersinia, invasive E coli, E coli O157:H7, C difficile
 - Faecal leukocytes and lactoferrin (neutrophil marker) often positive
 - Non-inflammatory diarrhoea:
 - Milder – viruses or toxins affecting small bowel → large-volume water diarrhoea with nausea, vomiting, cramps
 - Consider viruses (rotavirus, enteric adenoviruses, coronavirus), vibriones (eg cholerae), enterotoxin producing E Coli, Giardia lamblia, cryptosporidia
- “Food poisoning”: caused by toxins.
 - If 1 – 6 hour incubation, toxin present in food. Vomiting without fever. Eg Staph aureus
 - If 8 – 16 hours, toxin produced after ingestion: less prominent vomiting, cramping, no fever: eg Clostridium perfringens
- Protozoans:
 - **Cryptosporidia**, cyclospora: Acid fast stain (not usually done unless requested). Profuse watery diarrhoea – prolonged but self-limiting. Can become chronic if immunocompromised. Treatment of cryptosporidia (if needed, eg in AIDs) is difficult. Paromomycin – non-absorbed aminoglycoside. Cyclospora with cotrimoxazole
 - **Giardia**: infection of the upper small intestine by the flagellate Giardia lamblia. Cyst form evades gastric acidity, trophozoites doesn't. Contaminated water. 50% have no symptoms. Incubation 1 – 3 weeks. Fever and vomiting uncommon. May become chronic. Diagnosis stool microscopy – ↑sensitivity with repeat specimens. Antigen assays available if giardia highly suspected. Treatment metronidazole 250 mg tds for 5/7, or Tinidazole stat
- **Norovirus**: transmitted by contact or non-cooked food. Persists in stool for 2 weeks after recovery. Virus can persist on surfaces for > 1 week. 30% of infected people show no symptoms but are asymptomatic carriers. (Ann Intern Med 2006:144:49-56)
- **Amoebiasis**
 - Main pathogen = Entamoeba histolytica. Humans the only host
 - Cysts remain viable for weeks-months in moist environments outside the body
 - Presentation:
 - Mild to moderate colitis: recurrent diarrhoea. Can be latent for years
 - Severe colitis: severe bloody diarrhoea with fever, abdo pain, progression to haemorrhage or perforation

- Hepatic abscess: fever, abdo pain, hepatomegaly + abscess on imaging
- Diagnostic tests (amoebic liver abscess, colitis):
 - Stool microscopy: 30 – 90% (non-specific for histolytica or dispar, which is not pathologic)
 - Stool antigen: > 90% and sensitive for histolytica
 - Blood serology: 70%, may rise later, higher sensitivity in liver abscess
 - Positive serologic tests with colitis or hepatic abscess, but may represent prior infections
- Treatment:
 - Tinidazole, metronidazole
 - Asymptomatic cysts passer: diloxanide furoate (“luminal agent”)
- General treatment:
 - Generally supportive
 - Shigella: treat as infecting dose very small so want to eradicate it from stool, shortens duration of symptoms by 2 – 3 days. Fluoroquinolones. Do not give opioids (or other antimotility agents)
 - Salmonella: Fluoroquinolones if high risk of systemic dissemination
 - Campylobacter: therapy within 4 days of onset shortens course. Treatment erythromycin (also azithromycin 1 gm stat, or ciprofloxacin, increasing fluoroquinolone resistance reported)
 - E Coli (not isolated from stools because no selective media):
 - Enterotoxigenic E coli (ETEC): Produce toxin. Fluoroquinolones shorten disease
 - Enteroinvasive E coli (EIEC): invade cells → bloody diarrhoea
 - Enterohaemorrhagic E coli (EHEC): Don’t treat E coli O157:H7 – doesn’t change course and increases risk of haemolytic uraemic syndrome (esp in kids)
 - Cholera: Vibrio cholerae. Toxin mediated, fever unusual. Stool is liquid, grey without odour, blood or pus (“rice water stool”). Fluid replacement. Positive stool culture. Tetracyclines shorten excretion of vibrios

Tropical Illnesses and Travel

- Protozoal diseases: Leishmaniasis, Malaria, Toxoplasmosis, Amoebiasis, Giardiasis, Cryptosporidiosis, Cyclosporiasis, Trichomoniasis

Vectors

- Aquatic snails: Schistosomiasis (bilharziasis)
- Blackflies: River Blindness (onchocerciasis)
- Fleas: plague (transmitted by fleas from rats to humans)
- Mosquitoes:
 - Aedes (bite during daylight hours): Dengue, Rift Valley fever, Yellow Fever, Chikungunya
 - Anopheles: lymphatic filariasis, malaria
 - Culex: Japanese encephalitis, lymphatic filariasis, West Nile fever
- Sandflies: Leishmaniasis
- Ticks: Lyme disease, rickettsial diseases

Travellers Diarrhoea

- See WHO website
- See Diarrhoea, page 314
- Bacteria cause 80%: Enterotoxigenic E coli (most common), Shigella, Campylobacter jejuni
- First line treatment: ciprofloxacin or levofloxacin – but increasing resistance especially amongst campylobacter
- Azithromycin if resistant, child or pregnant
- Self treatment: azithromycin 1 gm or norfloxacin 800 mg; +/- loperamide (not if bloody diarrhoea and fever)

Fever in Returned Traveller

- History: duration of travel, season, rural vs urban, animal contact, unprotected sex, untreated water or food, pre-travel immunizations, adherence to malaria prophylaxis
- Differential:
 - Most are common infections: viral illness (URTI, EBV), pneumonia, UTI, cellulitis
 - Malaria most common cause of hospitalisation, dengue next
 - Incubation < 21 days: Malaria (prophylaxis never 100% effective), dengue, typhoid (vaccine 70% effective), rickettsial infections, leptospirosis

- Incubation > 21 days: viral hepatitis, malaria, Tb, HIV seroconversion, schistosomiasis, amoebic liver abscess
- Hep A and B vaccines extremely effective
- Symptoms:
 - Fever, rash: dengue, typhoid, viral hemorrhagic fever, leptospirosis, meningococcaemia, yellow fever, typhus, Salmonella typhi, acute HIV
 - Fever alone: malaria, typhoid, HIV, rickettsial illness, visceral leishmaniasis, trypanosomiasis, dengue
 - Pulmonary infiltrates: Tb, ascaris, strongyloides
 - CNS involvement: N meningitidis, leptospirosis, arboviruses, rabies, cerebral malaria
 - Jaundice: Hepatitis A, Yellow Fever, haemorrhagic fever, leptospirosis, malaria
- Workup:
 - Most important to exclude are malaria and typhoid
 - If febrile then malaria smear and blood culture (repeat films in 8 – 12 hours if negative), if negative then FBC, if low platelets consider dengue and do daily platelets, if < 100 then admit
- No neutrophilia: malaria (often mild ↓platelets), typhoid, dengue (biphasic fever), rickettsias (eschar, rash)
- Ceftriaxone will treat typhoid as well as most common infections. If not ceftriaxone, make sure ciprofloxacin in the initial treatment regime

Traveller's Vaccinations

- ADT (toxoid): 5 – 10 years
- Hepatitis A
- Hepatitis B
- Meningococcal: 3 years
- Polio
- Typhoid
- Cholera: 6 months
- Yellow fever: 10 years
- Japanese B encephalitis: 3 years
- Rabies

Typhoid/Enteric Fever

- See NEJM 28 November 2002
- Salmonella enterica serotype typhi
- The bug:
 - Human-specific pathogen
 - Oral-faecal spread – especially poor water/sanitation, water/ice-cream from street vendors
 - 16 million new cases each year, 600,000 deaths
 - Gastric acid barrier important: PPIs etc lower the infective dose (normally 1,000 to 1 M bugs)
 - Can survive within phagocytes
 - Incubation 7- 14 days (range 3 to 60)
 - Produces a potent toxin
- Presentation:
 - Usually aged 5 – 25
 - Fever, malaise, chills, nausea, myalgia, HSM common
 - *Constipation* (although if HIV, then diarrhoea common)
 - Rose-spots: faint salmon-coloured maculopapular truncal distribution, pathognomic
 - Relative bradycardia, neuropsychiatric manifestations (5 – 10%)
 - Increasing fevers into the 2nd week
 - ↑LFTS, maybe ↓WBC
- Complications:
 - Initially: GI bleed, intestinal perforation, encephalopathy
 - Relapse after 2 – 3 weeks in 5 – 10%
 - Bone and joint pain, endocarditis, pericarditis, splenic or liver abscess, infected AAA grafts, aneurysms
 - Can excrete typhi in faeces for up to 3 months or longer
- Diagnosis:

- Leukopenia, anaemia, ↑LFTs, mild ↑CK
- Blood culture (take 15 mls) positive in 60 – 80%, higher in first week
- Bone marrow more sensitive
- Stool culture positive in 30%
- Widal's test (agglutinating antibodies to O and H antigens) controversial
- Differential: malaria, deep abscesses, TB, amoebic liver abscess, encephalitis, influenza, dengue, leptospirosis, EBV, endocarditis, brucellosis, typhus, visceral leishmaniasis, toxoplasmosis, lymphoproliferative disease, CTD
- Treatment:
 - Originally treated with chloramphenicol, then trimethoprim, sulphmethoxazole, and ampicillin, now often multi drug resistant. Require long treatment (2 – 3 weeks)
 - Fluoroquinolones (eg ciprofloxacin) for 3 – 5 days. Fever clearance takes longer (~ 7 days)
 - Multi-drug resistance in Asia not uncommon. Increasing concerns about fluoroquinolone resistance → azithromycin
 - Rare resistance to ceftriaxone
 - Treated fatality rate ~ 1%. Worse if delays in treatment
 - If shocked or neuropsychiatric symptoms dexamethasone
- Chronic carriers: persistence of salmonellae in stool or urine for > 1 year. Higher risk with gallstones or concurrent bladder infection with schistosoma. Associated with carcinoma of the gallbladder
- Vaccination:
 - Original whole cell vaccination → systemic side effects
 - Oral Ty21a vaccine: live attenuated virus (not if immunocompromised) efficacy from 50 – 95%
 - IM Vi based vaccine, efficacy 64 – 72%, no serious side effects

Flaviviruses

Disease	Geographic Distribution	Vaccine
Yellow Fever	Sub-Saharan Africa, South America	Available
Japanese Encephalitis	Asia	Available
Tick-borne encephalitis	Europe	Available
West Nile Fever	Africa, Middle East, Europe, North America	Under development
Dengue Fever	Asia, South America, Pacific, Africa	Under development

Dengue Fever/Enteric Fever

- See Lancet 10 November 2007, NEJM 1 September 2005
- 50 – 100 million infections per year, mortality 25,000 per year (mainly kids)
- A disease of urbanisation – vector breeds around human dwellings – uncovered water storage, tires
- Viruses – 4 types:
 - Family Flaviviridae: single stranded RNA viruses
 - Dengue 1 – became prevalent in Hawaii, transmitted by Aedes albopictus mosquito (inefficient vector → slow moving outbreak, compared with Aedes aegypti)
 - All 4 types sequentially through Tahiti
 - When DENV-2 was reintroduced into Cuba, only adults previously infected with DENV-1 became ill
 - Seems that infection with another virus type, or with the same virus after a long delay, is bad
- Pathogenesis:
 - Cross-reactive but non-neutralising antibodies from a previous infection bind to the new infecting serotype, enhancing uptake by phagocytes → cytokine cascade → endothelial dysfunction and hemorrhagic manifestations
 - ?Autoimmune component
- Presentation:
 - Can be asymptomatic
 - Onset usually 4 – 7 days after infection. Can rule out Dengue if > 14 days since exposure. Fever > 10 days usually rules out Dengue
 - Sudden onset fever lasting 5 – 7 days, *severe headache, retro-orbital pain, severe myalgia and arthralgia* (“*break-done fever*”), relative bradycardia (as in typhoid), splenomegaly, abdo distension, rash (usually generalised erythema) around the time of defervescence
 - Dengue haemorrhagic fever/Dengue shock syndrome: Fairly rare

- Main risk factor is secondary infection with another serotype in kids. Re-exposure doesn't seem so important in adults
- Usually around time of defervescence
- Abdo pain, vomiting, restlessness, ↓LOC, fever → hypothermia
- Rapid onset capillary leakage and sometime profound thrombocytopenia (bone marrow suppression, ↑destruction), and liver damage, haemorrhage (usually GI)
- Shock second to venous pooling from capillary leak, with raised diastolic pressure/reduced cardiac output → cardiovascular collapse.
- High levels of IFN α found after 1 – 2 days, and high levels of IL2 plus others as fever subsides and vascular permeability rises
- **Diagnosis:**
 - Haemorrhagic signs with capillary leakage (ie not just GI bleed), platelet count < 100, objective evidence of plasma leakage (↑packed cell volume, hypoproteinaemia)
 - Abdo and chest ultrasound → pleural effusion and ascites
 - Tourniquet test: inflate cuff midway between systolic and diastolic for 5 minutes, positive if > 20 petechiae per square inch on forearm
 - Stage 1: fever and viraemia with NS1 antigen in blood. No antibodies at this stage. Can detect viron (test not commonly available), RNA or dengue proteins. PCR useful (sensitivity declines through illness)
 - Stage 2: Early post-febrile period with Arbovirus IgM (false positives, including due to Rheumatoid Factor) and IgG. Many serologic studies hampered by cross-reactivity with other flaviviruses
- **Treatment:**
 - No specific therapy. Steroids and antivirals have no proven effect
 - Avoid aspirin/NSAIDs
 - Treat moderate disease with crystalloid, need colloid if severe
 - Blood and FFP if needed
 - Watch for fluid overload as things settle
- **Prevention:**
 - DEET insect repellents, protective clothing, insect repellents
 - Aedes mosquitoes bite during the day → limited effectiveness of bed nets

Yellow Fever

- Zoonotic flavivirus transmitted by Aedes mosquitoes in Africa and South America, not Asia
- Incubation 3 – 6 days
- Sudden onset of severe headache, aching in legs, and tachycardia. Brief remission followed by bradycardia, hypotension, jaundice, haemorrhagic tendency. Severe course in 15%, with 20 – 50% mortality. Supportive treatment
- Proteinuria, leukopenia, ↑bilirubin. IgM diagnosis, PCR becoming available

Tick-borne Encephalitis

- Flavivirus transmitted by Ixodes ticks in a vast area from West Europe to Japan (Lancet 31 May 2008)
- Morbidity worst in adults, half who develop encephalitis, with a third having long standing sequelae
- IgM and IgG serology sensitive in the 2nd stage of the illness
- No specific treatment, vaccination effective

Japanese Encephalitis

- Mosquito born (Culex tritaeniorhynchus) flavivirus causing encephalitis affecting children and older adults, occurs from May to September in SE Asia and China
- > 99% subclinical
- Diagnosis: serology. Leukocytosis, CSF pleocytosis (lymphocytic), diffuse delta-wave activity on EEG, MRI diffuse white matter oedema or haemorrhage often in thalamus
- Risk low, vaccination can have serious side-effects (generalised urticaria, disseminated encephalomyelitis) – so only vaccinate if benefits > risk

Rabies

- Transmitted mainly through the saliva of an infected dog – other animals also (cats, foxes), in USA mainly bats
- Infection by contact with respiratory secretions, viral replication in muscle, retrograde neural spread to CNS

- Signs (may be a month later): fever, headache, malaise in prodrome (4 – 10 days), tingling at the site of the bite, unsteady gait, autonomic dysfunction, sixth nerve palsy, labile mood, convulsions, paralysis, thick tenacious saliva
- No human-human transmission reported
- Vaccination:
 - Pre-exposure vaccination: at 0, 7 and 21 days. Later boosters not normally required unless very high risk of exposure
 - Post-exposure vaccination: Rabies Ig (½ into wound) + 5 doses of vaccine if not vaccinated (days 0, 3, 7, 14, 28), 2 doses if vaccinated (days 0, 3) and no Ig

Malaria

- See NEJM 12 Sept 1996, NEJM 14 April 2005
- In 50s and 60s strategy was prevention – including a lot of DDT. Enthusiasm for this waned → resurgence of disease. Counterfeit drugs a big problem in the third world
- Presentation:
 - Non-specific and irregular fevers – can't diagnose from pattern
 - Vomiting in 20%
 - Diarrhoea in 5%
 - → Enlarged spleen and anaemia
 - *Rash rare*
- Diagnosis:
 - Repeat blood film 12 hourly for 48 hours if negative – don't need to wait for fever
 - *Falciparum*: Normal sized RBCs, crescent-shaped gametocytes and ring-forms (chromatin)
 - *Vivax*: fewer infected RBC, infected RBC are swollen, fine eosinophilic 'dots', round/oval gametocyte
 - Bloods: anaemia rare in a traveller, common in children in endemic areas. WBC normal or low. *Platelets low in 60 – 80%. LFTs abnormal in 50%*
 - Finger prick antigen test strip (Immunochromatographic test – ITC) for *falciparum* has same sensitivity as microscopy (monoclonal ab) and not dependent on expertise. *Falciparum* sens 97%, spec 98%, PPV 78%, NPV 99.8%. *Vivax* Sens 90%, spec 98%, PPV 70%, NPV 99%. Remain positive after plasmid is cleared
 - If species uncertain, treat as *falciparum*
 - Anaemia uncommon, WBC low or normal, platelets low, LFTs abnormal in 50%
- Pathogenesis:
 - Humans are just a means of getting into the Anopheline mosquito where sexual recombination can occur
 - Distinct stages of the plasmodia → specific and different drug susceptibilities for each stage, eg liver hypnozoites, blood schizonticide and gametocytocide
 - Malaria burden in a symptomatic person is 10E8 to 10E13 parasites – drugs induce a constant fractional decline – higher burden requires a longer course. Acquired immunity reduces the parasite burden
 - Acidosis a poor prognostic sign
- Benign malarias:
 - *Vivax*, *malariae* (may persist in circulation for > 20 years), *ovale*: Treatment chloroquine for 3 days. SE pruritis in dark skinned people, rarely transient neuropsychiatric syndrome
 - *Vivax* and *ovale* need two week course of primaquine to eradicate hypnozoites parasites that survive in the liver (radical cure). Partial resistance common in Oceanic strain. Contraindicated in G6PD deficiency
 - *Vivax* resistance to chloroquine in Oceania (very common in PNG and Indonesia) – treat as for uncomplicated *P. falciparum*

Falciparum

- 1 – 3 million deaths per year, typically children in sub-Saharan Africa
- Incubation 7 – 28 days
- Infects RBCs of all ages → greater parasite load (cf *vivax* which prefers older RBCs)
- *P. falciparum* alters the surface of the RBC → adhesion to endothelial cells → organ sequestration → renal and cerebral complications
- If severe → acute renal failure, jaundice, pulmonary oedema, coma, hypoglycaemia, focal seizures, 2ndary bacterial infections

- Treatment:
 - Drugs affect P450 2C19
 - Uncomplicated:
 - Chloroquine if sensitive (not often!): North Africa, north of Panama Canal, Middle East
 - Quinine (first option – regardless of region):
 - For treatment (not prophylaxis) of uncomplicated malaria, for 3 – 7 days, in combination with another blood stage schizonticide (tetracycline or doxycycline)
 - Quinine (IV if too sick for orals) or quinidine not well tolerated → cinchonism (nausea, dysphoria, tinnitus, high tone deafness) – drugs from the bark of the cinchona tree. Poorer adherence due to side effects
 - Mefloquine (second option, don't use for treatment if used for prophylaxis) alone for 1 day. SE of mefloquine: nausea, giddiness, dissociation, nightmares, neuropsychiatric and neuropathies. Resistance in Thai/Cambodia/Myanmar border areas
 - Malarone (third option): proguanil (folate synthesis inhibitor) with atovaquone
 - Severe malaria (↓LOC, jaundice, oliguria, anaemia, pulmonary oedema ie multiorgan involvement):
 - IV artesunate followed by oral artemether + lumefantrine (Wgtn AB guidelines)
 - IV Quinine
 - Other:
 - Mefloquine, halofantrine or quinine with tetracycline (eg doxycycline) for multi-drug resistance
 - Most of Africa, parts of Asia and South America: Single dose combination sulphonamide (eg sulfadoxine) + pyrimethamine (acts synergistically against folate synthesis). Resistance on Thai/Cambodian border and East Africa
 - Primaquine: kills liver, asexual and sexual blood stages. Controversy over dosing and duration
 - Artemisinin derivatives (qinghaosu), developed in China, not registered outside China, used for drug-resistant falciparum. Developed by WHO. Potent in combination. Riamet: artemether with lumefantrine – for treatment of acute uncomplicated falciparum

Prophylaxis

- Mosquito avoidance
- Chloroquine sensitive malaria (central America north of Panama, Middle East): Chloroquine weekly commencing 1 week prior, and till 4 weeks after
- Chloroquine resistant malaria (Pacific, SE Asia, India, China, Africa, South America):
 - Daily atovaquone + proguanil (Malarone), from 1 – 2 days prior till 7 days after
 - Weekly mefloquine 250 mg shown in RCTs to be as well tolerated as other drugs. SE CI in neuropsychiatric disorders, epilepsy, cardiac conduction defects
 - Daily doxycycline 100 mg, if widespread mefloquine or chloroquine resistance. SE photosensitivity, vaginal thrush
- Mefloquine-resistant malaria (SE Asia): Doxycycline or atovaquone-proguanil
- Pregnancy:
 - Daily proguanil 100 mgs + weekly chloroquine (planquneil) 200 mgs – however, has become linked with higher risk of insomnia, fatigue and adverse neuropsychiatric effects
 - Sulfadoxine-pyrimethamine, given several times during pregnancy, is more effective at preventing infection of the placenta than chloroquine

Leishmaniasis

- Zoonotic parasite transmitted by sand flies
- 20 different species → variety of clinical syndromes
- ~ 2 million cases per year, 50,000 deaths
- Visceral leishmaniasis:
 - Mostly India, Bangladesh, Nepal, Sudan, Brazil
 - Incubation 4 – 6 months (up to 24)
 - Early treatment reduces 90% mortality to 2 – 5 %
 - Insidious or acute onset, fever, chills, weakness, anorexia, cough, diarrhoea
 - Progressive enlarged, firm, non-tender spleen. Enlarged liver. Lymphadenopathy. Hyperpigmentation (→ named Kala Azar “black fever”). Jaundice, oedema, ascites, wasting, death 2nd to secondary infections
 - Labs: FNA of spleen (generally safe and very sensitive), bone marrow (safer, less sensitive), looking for parasites

- Cutaneous leishmaniasis: single or multiple cutaneous swellings 2 weeks to several months after sand fly bite → chronic, painless, moist ulcers
- Mucocutaneous leishmaniasis: destructive nasopharyngeal lesions
- Labs: specific culture medium, PCR. Serology not particularly sensitive or specific
- Treatment: Long courses, toxicity problems. Pentavalent antimonials (resistance in India), liposomal Amphotericin B (less toxicity than conventional Amphotericin B deoxycholate), miltefosine (new oral agent)

Rickettsial Diseases

- Heterogenous group of small, obligately intracellular, G-ive bacilli
- Transmitted by tick, mite, flea or louse
- Except for louse-borne typhus, humans are an incidental host
- In general, serology has limitations and treat with doxycycline
- Typhus Group:
 - *Epidemic (Louse-Borne) Typhus*: due to infection with the parasite *Rickettsia prowzekii*. Extremely infectious. Headache → chills and fever → intractable headaches, prostration, macular rash on the 4th to 7th day, sparing face, palms and soles. Little travel association. Latent infection can reactivate. Diagnosis: antibody detection. Only transmitted via louse
 - *Endemic (murine) typhus*: flea born transfer of *Rickettsia typhi* in flea faeces, carried on rats. Slower onset and shorter duration. Rapidly fading maculopapular rash on the trunk. Antibody detection after 15 days. Doxycycline
- *Scrub Typhus* (Tsutsugamushi Fever):
 - Rodent parasite *Orientia tsutsugamushi* transmitted by mites in SE Asia, western Pacific (including Korea) and Australia. Mites live on vegetation
 - 1 – 3 week incubation. Black eschar at the site of the bite, with regional and generalized lymphadenopathy, conjunctivitis and a short-lived macular rash, malaise, chills, severe headache. Frequent pneumonitis, encephalitis, GI symptoms and cardiac failure
 - Diagnosis: serology and PCR. Reticulonodular infiltrate on CXR
 - Differential in tropical fever, also consider leptospirosis, typhoid, dengue, malaria, other rickettsial infections.
 - Treatment: doxycycline or chloramphenicol
- Spotted Fevers:
 - *Rocky Mountain Spotted Fever*: Tick born *Rickettsia*, in USA on Southern Atlantic seaboard (not Rocky Mountains!). Also central and south America. Influenza like prodrome followed by chills, fever, headache, myalgia, sometime delirium and coma. Red macular rash on wrist and ankles spreads centrally. Retrospective serologic confirmation. Doxycycline
 - Others: Tick typhus, Tick Typhus, Mediterranean Spotted Fever
 - *Q fever*: *Coxiella burnetti* transmitted by inhalation or ingestion. One organism can cause pneumonia. From sheep, goats, cattle. Incubation 1 – 3 weeks, febrile illness with prostration, myalgia. Pneumonia, also hepatitis and CNS disease. Can → chronic, culture negative endocarditis. Treatment initially doxycycline (maybe fluoroquinolones, very long course eg years for endocarditis)

Ebola

- Ebola and Marburg viruses present as a haemorrhagic fever with high mortality
- Family Filoviridae
- Outbreaks in recent years in Angola, Congo, Zaire
- Incubation 7 – 10 days → abrupt fever, headache, myalgia, nausea, vomiting → maculopapular rash and bleeding from any mucosal site in 50%
- Diagnosis: ELISA, PCR

Spirochetal Infections

Syphilis

- Spirochete *Treponema pallidum* (literally “pale twisted thread”)
- Infection through sexual contact, minor skin lesions (usually genital but also elsewhere), blood transfusion or congenital
- Stages:
 - Early/Infectious stage:

- Primary syphilis: chancre and regional lymphadenopathy after 2 – 6 weeks
- Secondary syphilis: skin and mucous membranes, occasionally bone, liver, CNS – have an abundance of spirochetes
- Treatment: im Penicillin stat + contact tracing + abstinence till cleared
- Then can be latent with relapses (1/3 latent for life). Treatment: course of im penicillin, to prevent late sequelae. Monitor for 24 months and worry if an increase in titres (don't expect them to fall)
- Late stage/Tertiary syphilis (1/3 of initial infections):
 - Lesions (gummas) involving skin, bones, liver, aortitis, eyes
 - Neuro-syphilis:
 - Asymptomatic but CSF changes: positive serology, ↑cell counts, maybe ↑protein
 - Meningovascular syphilis: Involvement of meninges or vasculature (or both): headache, irritability, cranial nerve palsies (basilar meningitis), unequal reflexes, irregular pupils, CVAs
 - Tabes dorsalis: chronic progressive degeneration of the posterior columns: impairment of proprioception, vibration, muscular hypotonia, hyporeflexia, shooting pains in muscles of the leg
 - General paresis: insidious involvement of cerebral cortex, personality change, tremour
 - Treatment: high dose penicillin (IV not IM). Titres unlikely to fall
 - Few demonstrable spirochetes, not contagious, tissue reactivity (vasculitis, necrosis)
- Labs:
 - Immunofluorescence or darkfield microscopy shows treponemes in 95% of chancres
 - Non-treponemal antigen tests: eg **RPR** (Rapid Plasma Reagin, easier) and **VDRL** (Venereal Diseases Research Laboratory, harder, standard in CSF testing – highly specific but less sensitive), positive 4 – 6 weeks after infection, false positives in CTD, EBV, malaria, leprosy, IVDU, old age, Hep C.... But cheap and good for screening. Titre reflects disease activity
 - Treponemal antibody tests: eg FTA-ABS (positive for life), now overtaken by T Pallidum particle agglutination test (**TPPA**) which is more sensitive for primary syphilis. Good as confirmatory tests, when used for screening have false-positive rates of 1 – 2 %
- Other Treponema infections: Yaws and Endemic (rather than venereal) syphilis

Leptospirosis

- Most widespread zoonotic disease in the world – *Leptospira interrogans* – 24 serogroups and over 200 serovars. Occurs in Queensland
- Transmission: direct contact with skin cuts/abrasions from a mammalian host (eg rats, dogs, cattle) or indirect from contaminated water or soil, especially after rainfall
- Occupational exposure in farmers
- Presentation: anything!
 - Fever, headache, vomiting, myalgia, jaundice, anaemia, sometimes a rash
 - Weil's disease: renal/hepatic failure, meningitis, respiratory distress. Jaundice a risk factor for mortality
- Clinical diagnosis with retrospective serology
- Treatment: doxycycline, penicillin G, ceftriaxone reduced days of hospitalisation, but not mortality. Jarisch-Herxheimer reactions may occur following treatment (release of toxins, ?TNF mediated – also occurs in syphilis)

Lyme Disease

- Tick-borne disease of the spirochete *Borrelia burgdorferi* (others in Europe and Asia). Named after the town of Old Lyme, Connecticut
- Serology is not standardised and manifestations vary
- Presentation (highly generalised):
 - Stage 1: flu-like symptoms with typical rash (erythema migrans) 7 – 10 days after tick bite
 - Stage 2: weeks or months later: neurology (eg Bell's palsy or meningitis), myocarditis
 - Stage 3: months to years later: arthritis (immunologic rather than persisting infection?)
- Treatment: Doxycycline (amoxicillin if pregnant)

Helminthic Infections

Schistosomiasis (Bilharzia)

- A type of trematode (fluke)

- Affects 200 million. 100,000 deaths annually
- Cercariae released by infected snails and penetrate skin/mucosa. Migrate to portal circulation, mature over 6 weeks, adult worms mate and migrate to terminal mesenteric or bladder venules where females deposit their eggs. Disease is primarily due to a host response to the eggs with granuloma formation and inflammation → fibrosis
- Presentation:
 - History of fresh water exposure in an endemic area
 - Cercarial dermatitis: Maculopapular rash at site of cercarial entry. In non-tropical areas can be caused by bird schistosomes that can't complete their life cycle in humans (swimmer's itch)
 - Acute schistosomiasis (Katayama fever): fever, prostration, HSM, lymphadenopathy, eosinophilia (especially in exposure naive traveller)
 - Neuroschistosomiasis: *S japonicum* (brain) > *S haematobium* (cord)
 - Chronic: Often light infections and only mildly symptomatic – but over years anorexia, anaemia, weight loss
 - Intestinal: *S Mansoni*, *japonicum*: Early – abdo pain, colonic polyps, fatigue, diarrhoea → late: portal fibrosis and portal hypertension and HSM
 - Bladder: *S haematobium*: early – haematuria, dysuria, bladder polyposis, late – hydronephrosis, UTI (rarely bladder cancer)
- Diagnosis:
 - Eggs in faeces or urine, biopsy of rectal or bladder mucosa
 - Positive serology (test reasonably sensitive). *Eosinophilia*
 - US looking for scarring, masses or inflammation of the bladder
- Types:
 - Main ones:
 - *S masoni*: Liver – Africa, eastern Mediterranean, Caribbean, South America
 - *S haematobium*: Liver, bladder – Africa, Eastern Mediterranean
 - Others:
 - *S japonicum* gp (incl *S mekongi*): liver, CNS – SE Asia, Western Pacific
 - *S intercalatum*: central Africa
- Treatment: praziquantel – stat dose, may need repeating

Cestode Infections

- Parasitic helminths. Cause of eosinophilia
- Tapeworms (Cestode infections): *Taenia saginata* and *T Solium* from undercooked beef, pork, faeces contaminated eggs. *Echinococcus granulosus* causes cystic hydatid disease. Also alveolar and CNS cysts

Nematode (Round Worm) Infections

- Nematode parasites transmitted in soil, dirty eggs, contaminated fruit and vegetables.
 - *Ascaris lumbricoides*: Ascariasis – infects ~ ¼ world's population, especially kids. Hatch in small intestine, migrate to lungs, then via airways back to GI tract. Up to 40 cm in length, live to 1 – 2 years. High loads → malnutrition, intestinal obstruction, cholangitis, obstructive jaundice. Eosinophilia marked during migration, may be absent during intestinal infection. Treatment albendazole, mebendazole
 - *Angiostrongylus Cantonensis* (Rat Lung Worm): from snails and slugs or vegetables → eosinophilic meningitis. Supportive treatment. Self limiting
 - *Hookworms*: especially *Necator* and *Ancylostoma* species. Contact with human/canine faeces. Larval forms penetrate the skin → migrate to alveoli → ciliary clearance to throat, swallowed. Mature in upper small bowel. Often asymptomatic. Pulmonary symptoms, anorexia, diarrhoea, abdo discomfort, Fe deficiency anaemia. Treatment: albendazole
 - Strongyloidiasis:
 - *Strongyloides stercoralis*
 - Less prevalent. But also endemic in North America, Japan, Europe, Australia.
 - Larvae from soil → penetrate skin → lungs → bronchial tree → gut. Can live for up to 5 years releasing eggs
 - Acute infection: pruritic rash (usually feet) → dry cough, sneezing, wheezing, eosinophilia → GI infections after some weeks
 - Can cause severe infection in immunocompromised (immunosuppressive medication especially corticosteroids, haematologic malignancy, alcoholism, low risk in HIV) due to its ability to

complete full lifecycle in humans. Hyperinfection syndrome – dissemination of large numbers of larvae to lungs and other tissues. Mortality 25% with treatment. Eggs in sputum. 2ndary bacteraemia 2nd to intestinal ulcerations.

- Eggs seldom found in faeces. Larvae in stool or duodenal contents. Serology 90% sensitive but cross reacts with other helminths
- Treatment: course of ivermectin or albendazole

Filariasis

- Lymphatic filariasis:
 - Wuchereria bancrofti (90% of the problems), Brugia malayi, Brugia timori
 - 120 million infected
 - Transmitted by Culex, aedes and anopheles mosquitoes
 - Larvae move from infected bite to lymphatics and lymph nodes → mature over months to thread-like adult worms. Release large numbers of microfilariae, especially at night
 - Disease 2nd to inflammatory response to mature and dying worms. Acute lymphangitis, fever, oedema, inflammation spreading *distally* from lymph nodes
 - Over time: pitting oedema → non-pitting oedema → sclerotic changes (Elephantitis)
 - Diagnosis: blood samples at midnight to look for microfilaraemia. Low strike rate. Eosinophilia with acute inflammation. Serology can't distinguish between current and past infection
 - Drug treatment controversial: can't reverse disease, treatment may cause inflammatory symptoms

Other

Immunocompromised Host

- Impaired humoral Immunity:
 - Eg Congenital, multiple myeloma, chronic lymphocytic leukaemia, splenectomy
 - Lack opsonizing antibodies
 - At risk from encapsulated organisms: Haemophilus influenzae, Neisseria meningitidis, Streptococcus pneumoniae
- Neutropenia:
 - Eg following stem cell transplant, in solid tumours with myelosuppressive chemotherapy, and in acute leukaemias
 - Risk increases with counts < 1000, and increases dramatically < 100
 - Susceptible to gram-negative enteric organisms, pseudomonas, gram-positive cocci (Staph aureus, S epidermidis, and viridans spp), Candida, Aspergillus
- Impaired cellular immunity:
 - Heterogeneous group: HIV, lymphoreticular malignancies (eg Hodgkin's disease), and immunosuppressive treatment (steroids, cyclosporine, cytotoxic drugs...)
 - Particularly susceptible to organisms that replicate intracellularly: listeria, legionella, salmonella, mycobacterium, viruses (herpes simplex, varicella, CMV), fungi (Cryptococcus, histoplasma, pneumocystis), protozoa (Toxoplasma)
- Haemopoietic Cell Transplant Recipients:
 - Day 1 – 21: severely neutropenic. At risk from gram positive (esp catheter related) and gram-negative infections, herpes simplex, RSV, candida, mucositis
 - 3 weeks – 3 months: CMV, adenovirus, aspergillus, candida, P jiroveci (esp in graft vs host disease treated with immunosuppression)
- Solid Organ Transplant Recipients:
 - Exclude transplant rejection, organ ischaemia, thrombophlebitis and lymphoma (post transplant lymphoproliferative diseases)
 - Postoperative infections: involve donated organ (eg pneumonia in lung, cholangitis in liver, UTI in kidney)
 - 2 – 4 weeks: Wound/catheter infection, hospital acquired
 - 1 – 6 months: immunosuppression:
 - Reactivated herpes simplex, varicella-zoster, CMV
 - Fungal: candida, aspergilla, Cryptococcus, pneumocystis
 - Listeria, Toxoplasmosis
 - After 6 months with maintenance levels of immunosuppression: more like the general population
- Prophylaxis:

- Wash ya bloody hands!
- Pneumocystis: Trimethoprim-sulphmethoxazole. If allergic then dapsone (not if G6PD deficiency)
- Herpes Simplex: acyclovir if seropositive for 4 – 12 weeks (if not receiving Ganciclovir for CMV prophylaxis)
- CMV: greatest risk is in sero-negative recipients from sero-positive donors. Various Ganciclovir regimes
- Fungal: to prevent invasive mould (primarily Aspergillus) and yeast (primarily Candida) – dose and duration not standardised. Eg low dose Amphotericin, itraconazole, etc
- Vaccination of the immunocompromised:
 - See also vaccination in HIV page 306
 - Avoid live vaccines (MMR, Varicella, BCG, oral polio)
 - Varicella vaccine: wait until 12 months following cessation of immunosuppression
 - Vaccinate pre-transplant
 - Splenectomy: vaccinate pre-operatively or > 2 weeks post surgery. CDC immunisation schedule says immunise people with functional or anatomic asplenia for meningococcal. No data for HIB vaccination over age 71 months but no contraindication
 - Post SCT/BMT: re-vaccinate at 6 months following autologous, 12 months following allogenic

Hospital Acquired Infections/Problems

- Wash ya bloody hands!
- Fever in Intensive Care Unit Patient:
 - Infections: catheter-associated, hospital-acquired, ventilator associated pneumonia, surgical site infections, UTIs, sepsis, line infections
 - Non-infectious: thromboembolic disease, adrenal insufficiency, thyroid storm, transfusion reaction, drug fever
- If fever in someone with a central line → take blood for culture from line and from new venipuncture site
- Post Operative patient:
 - Immediately:
 - Necrotising fasciitis due to group A streptococci
 - Malignant hyperthermia: rare, presents 30 minutes to several hours after halothane (plus other inhalational anaesthetics). High fever, muscle rigidity, rhabdomyolysis, hypotension
 - Aspiration of gastric contents → chemical pneumonitis (Mendelson’s Syndrome)
 - Within a week of surgery:
 - Infectious: hospital acquired or line infections
 - Non-infectious: alcohol withdrawal, gout, PE, pancreatitis. No good evidence atelectasis causes fever
 - > 1 week after surgery:
 - Surgical site infections
- Wgtn Antibiotic Guidelines if no obvious source:
 - Moderate illness (fever in a not particularly unwell patient): Cefuroxime iv 1.5 g QID (< 70kg use 750 mg) +/- metronidazole iv 500 mg q12h if suspicion of intra-abdominal source
 - Severe: Flucloxacillin iv 2 gm q6h and either ceftazidime iv 2g q 12h or gentamicin q 24 h
- Catheter Infections:
 - IV lines most common source of hospital acquired blood stream infections (BSI)
 - Prevention: “Bundle strategy”
 - Education
 - Maximal sterile barrier precautions for insertion
 - 2% chlorhexidine preparation for skin antisepsis
 - Avoid routine replacement of central venous catheters (CVC)
 - Antiseptic/antibiotic impregnated catheters if rate of infection is high despite the above strategies
 - Heparin + vancomycin locks: reduced rate of CR-BSI but concern re VRE ⇒ not routinely recommended
 - Diagnosis of catheter infections: If blood taken from a catheter and from peripheral blood both grow the same bug, the infection is likely to be catheter related if the time to positivity is > 2 hours for the catheter specimen (much less specific if IV ABs given through the catheter) Ann Int Med 2004;140:18
 - Staph Aureus catheter related infections:

- Endocarditis in 23%
- Nontunnelled CVCs should be removed
- TOE
- If endocarditis: treat for 4 – 6 weeks. If TOE negative, treat for 14 days
- Don't use vancomycin if not MRSA as it has poorer tissue penetrance and risks selecting resistant organisms. Use flucloxacillin (or cephazolin)
- Infection Control Precautions:
 - Respiratory:
 - Influenza, varicella, measles
 - Meningococcus until 24 hours post antibiotic
 - TB until negative sputum smears
 - Contact: VRE, MRSA, VISA, Scabies
 - Enteric: Hepatitis A, typhoid, gastro, C difficile

Bites

- Cat bites become infected 30 – 50% of cases, child bites rarely infected (too superficial), adult bits 15 – 30% and dog bites ~ 5%
- Polymicrobial – pasteruella (eg gram negative coccobacillus pasteruella multicicla) most common isolate in dogs and cats
- Prophylaxis in high risk bites: any cat bite, hand bits by animal or human (oral penicillin V) or bites not cleaned well > 3 hours. Wgtn guidelines: Augmentin or doxycycline and metronidazole
- Tetanus booster

IV Drug Users

- Skin infectious: Staph aureus
- Hepatitis: B & C
- Aspiration pneumonia (and it's complications – lung abscess, empyema, brain abscess) with mixed oral aerobes and anaerobes
- Pulmonary septic emboli from venous thrombi
- Right sided endocarditis: S aureus, candida, Enterococcus faecalis, other streptococci, gram –ive (esp Pseudomonas and Serratia marcescens). Treat empirically with Vancomycin (due to high rate of MRSA and/or Enterococcus) and gentamicin. TOE 90% sensitive for vegetations
- Osteomyelitis and septic arthritis: eg vertebral bodies, sternoclavicular joints, pubic symphysis, sacroiliac joints

Sexually Transmitted Diseases

- Gonorrhoea, syphilis (see page 321), Condyloma accuminatum, chlamydia, herpes virus, trichomonas vaginitis, chancroid (like chancre but painful), scabies, louse infestation, bacterial vaginosis
- Also Hep A, B, and C, amoebiasis, giardiasis, cryptosporidiosis, salmonellosis, and campylobacter
- Gonorrhoea:
 - See also page 286
 - Neisseria gonorrhoeae. G –ive intracellular diplococci. PCR largely replaced culture
 - Men: purulent urethral discharge, dysuria, epididymitis, prostatitis. Rectal infection in MSM
 - Women: cervicitis (may be asymptomatic), salpingitis
 - Disseminated disease: fever, rash, synovitis, arthritis, conjunctivitis (treatment: 1gm ceftriaxone stat). May mimic reactive arthritis. Rarely endocarditis or meningitis
 - Treatment: Ceftriaxone im 250 mg stat
- Chlamydia trachomatis:
 - Also C psittaci and Chlamydophila pneumoniae (formerly Chlamydia pneumoniae)
 - Large group of obligate intracellular parasites closely related to G –ive bacteria
 - Extra-genital symptoms:
 - Conjunctivitis, urethritis
 - Lymph node enlargement and suppuration with draining sinuses
 - Proctitis and rectal stricture
 - Positive complement fixation test
 - Treatment: azithromycin po 1 g stat for urethritis (OK in pregnancy, or on going if lymphatic involvement), also doxycycline (not in pregnancy) or erythromycin
- Treatment: PID: Ceftriaxone im/iv 250 mg stat AND azithromycin po 1 gm stat + 1 week later
- Trichomoniasis:

- Protozoan *Trichomonas vaginalis*
- Women: Incubation 5 days – 4 weeks → copious frothy yellow/green vaginal discharge, pruritis, dysuria. Inflammation of the vaginal wall with punctuate haemorrhages
- Men: usually asymptomatic. Scant urethral discharge
- Treatment: Metronidazole 2 g stat, tinidazole
- Post sexual assault:
 - Consider: chlamydia, gonorrhoea, hepatitis B, HIV, syphilis
 - Prophylaxis:
 - Ceftriaxone, azithromycin, tinidazole (for trichomoniasis)
 - HIV PEP efficacy unknown. Usually given if HIV exposure known or suspected
 - HBV vaccination and HBIG

Radiology

Plain Films

- Gas:
 - Bowel:
 - Small bowel: normally < 2.5 cm. Valvulae (plicae circularis) complete transverse bands
 - Colon:
 - Haustrations form incomplete bands (on the luminal surface they are interrupted by the teniae)
 - Contain faecal material (small bowel doesn't)
 - Caecum should be < 9 cm (cut off for abnormal lowers to < 6.5 cm in colitis)
 - Ectopic: intraperitoneal, retroperitoneal, renal tract (eg emphysematous pyelonephritis), biliary system or hernial orifices
- Stripes:
 - Psoas shadow: may be obscured by retroperitoneal inflammation/haemorrhage
 - Flank stripes: bowel should be right by it – if not then ?fluid in paracolic gutter
- Stones: any extraosseous calcification, eg chronic pancreatitis, 20% gallstones are radioopaque, renal calculi
- Bones: trauma, metastases, metabolic bone disease. Think laterally – eg check SI joint in colitis (normal SI joint has clear cortical margin on each side to be normal), check for syndesmophytes, etc

Other

- Strictures on barium enema:
 - Malignant: short segment with shouldering, not gradually tapered (as opposed to oesophagus where, rarely, tumour can spread submucosally and give a tapering appearance)
 - Focal-segmental contractions are normal bowel peristaltic action and can be confused with stricture
- Colitis
 - On barium enema: thumb printing – oedema of haustra
 - “collar stud” abscesses on single contrast enema – erosion down to and then along the muscularis
- Differential of uniform small bowel thickening: cancer, lymphoma, oedema, vascular, early infiltrates (Whipple's, eosinophilic, mastocytosis)
- US of cirrhosis: coarse texture, nodular surface

Oesophagus

- Heartburn = pyrosis. Symptom of reflux oesophagitis
- Odynophagia = painful swallowing. Characteristic of non-reflux oesophagitis. Causes:
 - Infection: candida, HSV, CMV, HIV
 - Drugs: doxycycline, bisphosphonates, NSAIDs, K
 - Radiation
- Oesophageal chest pain: due to reflux disease or motility disorders (eg oesophageal spasm)
- Regurgitation:
 - Tasteless: distal oesophagus
 - Bitter-tasting: associated with incompetence of both UES and LES
- Barium swallow with fluoroscopy used to evaluate structural and motor disorders
- Oesophageal motility studies helpful in motor disorders (eg achalasia, spasm and scleroderma)

Motor Disorders

- Achalasia:
 - Motor disorder of oesophageal smooth muscle: loses peristaltic contractions due to loss of inhibitory intramural neurons → LES does not relax normally (cf CREST which has a weak sphincter)
 - Presentation: dysphagia, chest pain and regurgitation
 - Diagnosis: absence of gastric air bubble, air fluid level in the mediastinum. Elevated oesophageal and LES resting pressure on manometry. Scope can usually be passed into the stomach with gentle pressure – unlike a stricture or constricting tumour
 - Treatment:
 - Soft foods, eat slowly

- Short term relief from nitrates and CCBs (eg nifedipine). Sildenafil. Botulinum toxin (median duration 12 months, similar effect to dilation)
- Good but short term response from balloon dilatation (response 65% at 5 years, perforation 5%, mortality 0.2%)
- Surgery: 85% response at 5 years. Mortality 0.3%
- Increased risk of oesophageal SCC. Average 14 years after diagnosis. Screening not recommended
- Diffuse oesophageal spasm:
 - Non-peristaltic contractions
 - Barium swallow shows uncoordinated contractions – the “cork screw” oesophagus
 - Treatment: nitrates or nifedipine
- CREST/Scleroderma:
 - Atrophy of smooth muscle → weakness of the lower 2/3rds and incompetence of the LES
 - Presentation: dysphagia to solids, heartburn, regurgitation
- Presbyoesophagus:
 - Progressive dysphagia for solids and liquids
 - Manometry: ↑ tertiary wave activity and ↓ amplitude of contractions

Gastroesophageal Reflux Disease

- Loss of gradient of pressure between stomach and LES due to ↑ frequency of transient lower oesophageal sphincter relaxation (TLESR)
- Symptoms of heartburn do not correlate well with endoscopic features – can have either and not the other
- Differential: cardiac, gallbladder, gastric or oesophageal cancer, peptic ulcer disease, motility disorders, and eosinophilic, infectious or pill oesophagitis
- Causes:
 - LES weakness without cause, or 2nd to gastric distension, alcohol, caffeine, fat, smoking
 - Scleroderma, pregnancy, smoking, anticholinergic drugs, smooth-muscle relaxants (β-adrenergic agents, aminophylline, nitrates, CCB)
 - Surgical damage
 - Role of H pylori in GORD is questionable (it causes gastric disease). H. Pylori causing atrophic gastritis may → low acid and be protective
- Spectrum of injury:
 - Erosive (Graded with LA classification system) and non-erosive disease
 - Oesophagitis – necrosis of surface layers of oesophageal mucosa
 - Strictures in 10%
 - Columnar metaplasia
 - Adenocarcinoma
 - Chronic cough: 43 – 47% of patients with GORD related cough have no reflux symptoms. May respond to antacid treatment. Up to 40% of cases of chronic cough are caused by GORD – either due to acid aspiration or vagus stimulation in the oesophagus triggering cough centre
- Scope is not diagnostic of GORD – it is normal in non-erosive disease
- Treatment:
 - Recommended but no robust RCTs: Weight reduction, raising head of the bed, not smoking, avoiding fatty foods, coffee, chocolate, alcohol and some drugs (CCB, anticholinergic drugs)
 - H2 receptor antagonists: RCTs show PPIs have the edge
 - PPIs: RCTs show quicker healing (a large meta-analysis shows 83% vs 52% for H2 blockers vs 8% placebo) and less relapse. B12 and Ca absorption impaired by treatment. Response of heartburn more variable than oesophagitis
 - Surgery: first establish reflux on pH monitoring and exclude achalasia on manometry. Fundoplication. RCTs of open vs closed show similar effect but less complications with closed. Mortality < 1%. 90% symptomatic improvement at 5 years. Dysphagia 6%. 10 – 65% still on PPI. Also some endoscopic procedures
- Barrett’s Oesophagus:
 - Metaplasia from squamous → columnar (intestinal) epithelium as a result of severe reflux oesophagitis
 - Prevalence increases with the duration of reflux symptoms
 - Occurs during healing – columnar is more resistant to acid-pepsin damage than squamous
 - Diagnosis: intestinal metaplasia with goblet cells. *Inflammation interferes with histology interpretation. If inflammation present, PPIs and repeat after 2/12*

- Arbitrarily divided into long segment (> 2 – 3 cm) and short segment
- Intestinal metaplasia → low grade dysplasia → high grade dysplasia (20% progression so surgery indicated) → adenocarcinoma
- Risk of progression from metaplasia to adenocarcinoma of 0.5% per year in long segment – risk 40 – 125 times general population
- Screening endoscopy recommended, interval not proven. Eg:
 - No dysplasia: endoscopy with biopsy every 3 years
 - Low-grade dysplasia: endoscopy with biopsy every year until no dysplasia
 - High-grade dysplasia: endoscopy with biopsy every 3 months
- Established metaplasia does not regress fully with acid suppression – but is likely to slow dysplastic transformation so treat with BD PPIs
- Oesophagectomy is the only treatment that removes all neoplastic endothelium, but has a mortality of 3 – 12%. Endoscopic ablation (regression of high grade dysplasia in 70%) or mucosal resection being evaluated
- See Oesophageal Cancer, page 393

Other oesophageal disorders

- Infective:
 - Viral:
 - HSV-1 in immunocompetent, and HSV 1 and 2 in immunosuppressed. Culture to test for acyclovir resistance, PCR more sensitive for diagnosis
 - Varicella-zoster
 - CMV
 - HIV: can be part of a seroconversion syndrome
 - Bacterial: unusual. In AIDs may see cryptosporidium, Pneumocystis carinii and TB
 - Candida: Normal commensals in the throat. Oesophagitis if immunosuppressed, or asthmatics who haven't rinsed. Confirm with culture or fungal stain of biopsy. Treat with fluconazole lozenges
- Eosinophilic Oesophagitis:
 - Eosinophilic inflammation and submucosal fibrosis
 - ?related to parasite infection
 - Histology like asthma
 - Presentation: intermittent dysphagia and food impaction
 - Diagnosis: eosinophils on histology
 - Treatment: 12 week course of swallowed Flixitde (not dilation). Maybe prednisone
- Radiation Oesophagitis: Treat with viscous lignocaine and/or indomethacin
- Corrosive oesophagitis: ingestion of caustic agents. Prednisone not helpful during healing. Heals with strictures
- Pill-induced: doxycycline, tetracycline, penicillin, clindamycin, also aspirin, Fe sulphate...
- Mallory Weiss
- Hiatal hernia: small sliding hiatal hernias probably produce no symptoms but contribute to GORD
- Structural problems (can be congenital): diverticula, webs, rings
- For varices, see page 369

Peptic Ulcer Disease

Physiology

- Cells:
 - G cells: in *gastric antrum*, release gastrin 2nd to stomach stretch and protein. A variety of gastrin peptides have different sizes and actions. Major role is to promote acid secretion. Causes of hypergastrinaemia:
 - Acid inhibition
 - Atrophic gastritis (parietal cells not working → ↑feedback → ↑production)
 - Vagotomy
 - Gastrin secreting tumours
 - Renal failure
 - Hypercalcaemia
 - Artfactual in hyperlipidaemia

- Parietal cell (aka oxyntic cell): secretes H via a H⁺K⁺ ATPase, stimulated by gastrin, histamine (via H₂ receptors), and acetylcholine (M₃ receptor), inhibited by prostaglandin and somatostatin. Also secretes intrinsic factor. Most acid secreted in fundus and body of the stomach
- Chief cell: secretes pepsinogen, which is cleaved in an acid environment to the proteolytic enzyme pepsin
- Enterochromaffin cell: stimulated by gastrin, inhibited by somatostatin, to produce histamine
- Epithelial cells secrete mucous and HCO₃, stimulated by prostaglandin. Epithelial cells can migrate to restore a damaged region (restitution), modulated by EGF, TGF α and fibroblast growth factor
- Acid stimulation:
 - Sight/smell/taste \rightarrow Vagus nerve \rightarrow cholinergic stimulation \rightarrow stimulates parietal cell (cephalic phase)
 - Amino acids in stomach \rightarrow G cell \rightarrow gastrin release \rightarrow stimulates parietal cell (gastric phase)
 - D cells release somatostatin \rightarrow inhibits parietal cell directly and also via inhibition of ECL cell (intestinal phase)
- Cyclooxygenase controls the rate limiting step in prostaglandin synthesis from arachidonic acid:
 - COX-1 expressed in stomach, platelets, kidneys, endothelial cells
 - COX-2 induced by inflammatory stimuli and expressed in macrophages, leukocytes, fibroblasts and synovial cells

Clinical

- Ulcers:
 - Duodenal: 90% in the first 3 cm. Malignant DU's extremely rare
 - Gastric: generally occur later in life than duodenal lesions. Greatest risk of malignancy is in the gastric body and fundus. Repeat endoscopy to document healing advised
 - Steroids don't produce bleeding, but prolong healing of existing ulcers
- Other risk factors for PUD:
 - Epidemiological evidence that smoking is bad
 - Genetic predisposition: 1st degree relatives \rightarrow 3 times the risk (?compounding by H pylori)
 - Psychological stress: conflicting results from studies
 - No evidence of correlation with specific diet (including alcohol and caffeine)
 - Strong association with chronic diseases: systemic mastocytosis, pulmonary disease, renal failure, cirrhosis, nephrolithiasis, α 1AT deficiency
- Presentation:
 - Abdominal pain: poor predictive value for presence of DU or GU
 - Pain typically 90 mins to 3 hours after food. Waking from midnight to 3 am is the most discriminating symptom (but also occurs in non-ulcer dyspepsia)
- Ulcer complications:
 - GI bleeding: in 15% of ulcers, more if > 60
 - Perforation, or penetration (tunnelling into an adjacent organ, eg pancreatitis)
 - Gastric outlet obstruction in 1 – 2 %

Helicobacter Pylori

- G –ive rod, found in the deeper layers of mucous gel
- Does not appear to invade cells
- Produces urease (produces ammonia from urea) – alkalizes the surrounding pH
- Infection associated with low SES, transmission is oral-oral or faecal-oral
- Leads to ulceration in 15% only (but most will have a gastritis). Effect is due to inflammatory response from host
- Patterns of H. Pylori gastritis due to different strains:
 - Antrum predominant: chronic inflammation, irritation of G cells \rightarrow \uparrow gastrin \rightarrow \uparrow acid, duodenal inflammation and ulcer
 - Pan-gastritis: chronic inflammation, atrophy, intestinal metaplasia, \downarrow acid, gastric ulcers
- Diagnosis (with sensitivity/specificity):
 - Invasive: rapid Urease test (80 – 95/ 95 – 100), Histology (80 – 90/ >95), culture (pretty tricky)
 - Non-invasive: serology (>80 / >90 – can be false positive in early follow up), urea breath test (>90 / >90), stool antigen (>90 / >90 – not established for confirming eradication)
- Cag A positivity:
 - More virulent strain: associated with VacA (Vacuolating cytotoxin)

- Clinically more duodenal ulcers, worse gastritis, higher risk of relapse (but still low ~ 1%)
- Treatment:
 - Only treat those with PUD – not asymptomatic carriage (consensus position)
 - 14 day triple therapy more effective than 7 day therapy
 - 4 day quadruple therapy as good as 7 day therapy
 - Antibiotic resistant strains the most common cause for treatment failure in compliant patients. But in vitro resistance does not predict outcome in patients. In USA, metronidazole 35% resistance, clarithromycin 10% resistance
 - Reinfection is rare (< 1% year)
 - Small benefit in eradication in non ulcer dyspepsia – but benefit mainly was reduced symptoms. Downside is risk of ↑ resistance. Ann Int Med 2005;143:347 – 354
 - No reduction in gastric cancer following eradication: RCT of 1630 patients followed for 7.5 years. Non-significant trend to ↓ cancer – ?study underpowered
 - Follow up > 4 weeks after treatment to confirm eradication if complicated ulcers
- Eradication has generally reduced ulcer recurrence (< 10 – 20% compared with 60 – 70% recurrence without eradication)

NSAID-induced Disease:

- 80% of patients with serious NSAID-related complications did not have preceding dyspepsia
- Prostaglandin depletion → ↑HCL, ↓Mucin, ↓HCO₃, ↓surface active phospholipid secretion, ↓epithelial cell proliferation
- Topical and systemic effect: they are weak acids that remain in a nonionised lipophilic form in an acid environment → can diffuse into the epithelial cells
- Systematic review of randomised trials have shown reduced NSAID induced ulcers from (but few head to head trials):
 - PPIs
 - Misoprostol
 - Double dose histamine receptor antagonists
 - COX2s
 - H pylori eradication
- Prophylaxis for NSAID induced ulcers (Lancet 4 Oct 2008):
 - Indicated in high risk patients (previous ulcer bleeding, age > 75, concurrent use of steroids, anticoagulants or aspirin)
 - Uncertain in average risk (1 – 2 % annual incidence of complications). Cost-effectiveness analysis suggest either histamine-receptor antagonists or test-and-treat for H pylori infection (depending on general incidence of H pylori). PPI not cost effective
 - With PPIs is not sufficient to prevent recurrent ulcer bleeding in NSAID users with previous ulcer bleeding

Treatment of ulcers

- Antacids:
 - Usually aluminium and magnesium hydroxide (avoids too much of either. Aluminium → constipation and PO₄ depletion, magnesium → diarrhoea. Neither good in renal failure)
 - Calcium carbonate → milk alkali syndrome with long term use (see page 90). Na carbonate can → alkalosis
- H₂ receptor agonists: Cimetidine was the first. Inhibits P450 (affecting warfarin, phenytoin, theophylline). Ranitidine more potent. Can develop tolerance
- PPIs:
 - Irreversibly inhibit HK-ATPase
 - Acid labile – in a capsule that dissolves in pH > 6 (ie duodenum)
 - Maximum inhibition 2 – 6 hours after dose, total duration of 72 – 96 h
 - Serum gastrin levels return to normal 1 – 2 weeks after cessation
 - Side effects:
 - Intrinsic factor production is inhibited but B12 deficiency rare
 - ↑pH interferes with absorption of iron, ketoconazole, digoxin
 - Omeprazole inhibits P450, later ones (eg pantoprazole) don't – effect unclear but caution with warfarin, diazepam, atazanvir, phenytoin

- Associated with higher incidence of community-acquired pneumonia (RR 1.89), bacterial gastro (RR 2.9), *C. difficile* (RR of 2), hip fracture (RR of 1.4 over 50 years, 2nd to ↓Ca or ↓Vit D absorption)
- For acute bleed: iv PPI → ↑pH → ↑stability of the clot
- *PPIs are effective in non-ulcer dyspepsia*. *Ann Int Med* 2005;143:347 – 354
- Sucralfate: aluminium containing sucrose salt, insoluble in water, that forms a paste coating ulcers. Toxicity is rare
- Surgical treatment:
 - Vagotomy: truncal and selective (preserves celiac and hepatic branches) approaches → ↓acid but also gastric atony
 - Billroth 1 and 2: removes antrum (removes most gastrin production). Billroth 1 preferred but can't do it if too much duodenal scarring. Complications:
 - Dumping syndromes: due to vagotomy and concurrent Billroth → cramping pain, nausea, diarrhoea, tachycardia, palpitations, sweating and rarely syncope:
 - Fast (early, within 30 mins) rapid delivery of hyperosmotic load to duodenum, fluid shift into the gut lumen → distension and hypovolaemia
 - Late (1 – 3 hours) non-digested CHO rich material in the duodenum → ↑insulin → hypoglycaemia (treat with Acarbose)
 - Billroth 2 leaves a blind loop of duodenum and is associated with bacterial overgrowth due to stasis → post prandial bloating and diarrhoea with fat and B12 malabsorption
 - Malabsorption/maldigestion: steatorrhoea, ↓B12, Fe, vitamin D, calcium

Zollinger-Ellison Syndrome

- Unregulated gastrin release → acid hypersecretion
- 0.1% of people with PUD, next most common symptom is diarrhoea
- Sporadic tumours more common, also 1/3 have MEN type 1 (gastrinomas in 25%)
- Suspect if multiple ulcers, family history, postoperative recurrence...
- Diagnosis: fasting gastrin level > 1000 pg/ml. But also high via negative feedback if acid suppression treatment, and due to *H Pylori* infection. Confirm suspicions with assessment of acid secretion (secretin provocation)
- Locate tumour with endoscopic ultrasound

Chronic Gastritis

- →Glandular destruction, atrophy and metaplasia
- Type A:
 - Less common
 - Fundus and body with antral sparing
 - Pernicious Anaemia:
 - Autoimmune
 - Antibodies to the HK-ATPase in parietal cells – not uncommon in the elderly. Also common in patients with vitiligo and Addison's disease. ~50% with parietal cell antibodies will also have thyroid antibodies
 - Anti-IF antibodies are more specific than parietal cell antibodies for Type A gastritis
 - See Pernicious Anaemia in Megaloblastic Anaemia, page 419
- Type B:
 - More common, antral-predominant
 - *H Pylori* the most common cause
- Lymphocytic gastritis: intense infiltration with lymphocytes. Etiology unknown
- Eosinophilic gastritis: treat with steroids

GI Bleeding

- Haematochezia: bright red rectal bleeding
- Occult bleeding: minute bleeding – can't see with scope
- Obscure bleeding: can't find the cause, ie not detected by common diagnostic procedures

Upper GI Bleeding

- See *NEJM* 28 August 2008, *Lancet* 3 Jan 2009
- Defined as bleeding proximal to the ligament of Treitz (duodenojejunal flexure)

- Majority are older: 68% > 60 years, 27% > 80 years
- Mortality 5 – 10% (altering case mix – more varices and less surgery)
- Exam: include orthostatic changes in fluid assessment. Do PR. FOB +ive doesn't change management so usually not indicated
- Causes of Upper GI bleed:
 - PUD – the majority
 - Varices: oesophageal, gastric (see page 369)
 - Mallory-Weiss tears. If pre-endoscopy Rockall score of 0 with consistent history, no melaena and normal Hb can be safely discharged without endoscopic follow up
 - Oesophagitis: peptic (reflux), drugs
 - Less commonly:
 - Haemorrhagic gastritis
 - OGD cancers
 - Cameron Ulcers in hiatus hernia
 - Dieulafoy lesion (weak walled vessel, bleeds easily), other AVMs (usually bleed slowly)
 - Aorto-enteric fistula in 3rd part of the duodenum
- Relative risk of Upper GI bleeding from NSAIDs:
 - Cox-2: 1.3 – 1.5 times
 - Aspirin: 1.5 – 2.5 times
 - NSAIDs: 4 – 7 times
 - NSAID + Warfarin: 12 times
- Management:
 - Hb < 100 or tachycardia > 100 then transfusion as a general rule
 - In non-variceal bleeding there is no difference in outcome (death/blood transfusion/surgery) between early (< 8 hours) and delayed (12 – 24 hours) endoscopy. Adequate resuscitation is the primary objective. The primary benefit of early endoscopy is to facilitate early discharge
 - Risk scoring:
 - Two validated scoring systems – Glasgow-Blatchford Score (clinical and lab values, 0 – 23, 23 is bad) and Rockall (composite of age, shock and co-morbidity, clinical presentation only, 0 – 11, 11 is bad, add ons following endoscopy). Pre-endoscopic Rockall predicts death but not rebleed. GBS may better predict who can be safely discharged for OP assessment
 - Appearance of a bleeding ulcer scored on Forrest classification – predicts risk of rebleeding
 - Omeprazole:
 - Effect of PPI while awaiting endoscopy is to downstage lesions, no apparent affect on outcome (rebleeding, surgery or death, so cost-effectiveness disputed). High dose infusion (80 mg bolus + 8 mg/hr infusion) vs placebo → 19% vs 28% of patients needing endoscopic haemostatic treatment. Economic analysis suggest an advantage. Only give if the patient requires transfusion or initial Rockall score >= 3
 - Best studied as infusion (eg Hong Kong trial): 1 mg/kg bolus followed by 8 mg/hr, but iv formulation only stable for 6 hours (a hassle!) so 40 mg QID iv used instead. Protocols for high risk recommend initial dose of 80mg. Continue iv for 72 hours
 - Mechanism: higher gastric pH favours platelet aggregation and stabilizes the clot
 - After endoscopy results in ↓transfusion requirement, shorter hospital stay, lower mortality (but only if high risk or Asian), ↓rebleed, may reduce rate of detection of H Pylori
 - Not used:
 - H2 blockers ineffective
 - Erythromycin promotes gastric motility and improves visualization at gastroscopy but doesn't improve diagnostic yield substantially nor outcomes
 - Somatostatin and its analogue octreotide inhibit acid and pepsin secretion and ↓mucosal blood flow but RCTs show no benefit
 - Restart oral fluids after 6 hours
 - Test for H Pylori and treat
 - Low risk lesions: early discharge with oral PPI
 - For non-variceal bleeds, “second look” endoscopy within 24 hours ↓ rates of rebleed and mortality but only limited reduction, and doubtful cost-effectiveness
 - Consider for surgery if < 60 and transfused 8 units or > 60 and transfused 4 units or re-bleed or spurting vessel at endoscopy not controlled by injection

Lower GI bleeding

- Causes of small intestinal bleeding:
 - Vascular (the main cause): angiodysplasia, telangiectasia, haemangiomas, Dieulafoy lesions
 - Ulceration: Crohn's, NSAIDs, K+, 6MP, Meckel's diverticulum, ZE syndrome, vasculitis, worms, TB
 - Tumours: stromal tumours, lymphomas, carcinoids, carcinoma
 - Aorto-enteric fistula
- Causes of colonic bleeding:
 - Carcinoma: chronic slow bleeding
 - Diverticular disease
 - Angiodysplasia
 - Polyps
 - IBD
 - Ischaemic colitis
 - Post-polypectomy bleed
 - Infections, NSAIDs, radiation colitis
 - Lower Rectal bleeding: haemorrhoids, polyps, rectal varices, ulcers, trauma, FB, Ca
- Investigations for mid to lower bowel bleeding:

Investigation	Rate for optimum detection (ml/min)
Tagged RBC scan (but must be actively bleeding)	0.1 – 0.5
Mesenteric angiography	1.0
Non-selective aortography	6
Colonoscopy	Any rate
Intraoperative endoscopy	Active bleeding
Capsule endoscopy	Small bowel lesions

 - Enteroscopy: endoscopic evaluation of the distal duodenum → part of the ileum: eg by Push enteroscopy, balloon assisted enteroscopy, intraoperative (highest yield)
 - Capsule endoscopy: Mouth-2-Anus (M2A) capsule enteroscopy
- Endoscopic haemostasis for colonic bleeding:
 - Injection: adrenaline (also has tamponade effect). For PUD also use fibrin glue, alcohol, sclerosants
 - Thermal: heater probed, gold probe, argon plasma coagulator (APC)
 - Mechanical: haemoclips, banding, endoloops, staples

Malabsorption

- For Pernicious Anaemia see Megaloblastic Anaemia, page 419
- Most syndromes are associated with steatorrhoea, an increase in stool fat excretion of > 6% of dietary fat intake. "Gold standard" is timed, quantitative stool fat determination
- Short chain fatty acids are not dietary lipids, but are synthesized by colonic bacterial enzymes from non-absorbed carbohydrate. They are rapidly absorbed in the colon. Most non-C difficile antibiotic associated diarrhoea is due to antibiotic suppression of colon flora → ↓SCFA production
- Investigations:
 - Normal stool: no WBCs or RBCs. Fat globules rare. pH alkaline (acid if CHO malabsorption)
 - Stool fat: 100 mg fat/day for 3 days before test. Normal people can eliminate all but 6 mg/day
 - Schilling test:
 - Expensive and time consuming
 - 1 mg ⁵⁸Co-labelled cobalamin given orally and urine collected for 24 hours
 - Excretion reflects absorption (as long as intrahepatic binding sites are fully occupied – give 1 mg im normal cobalamin 1 hour later to be sure)
 - Abnormally low excretion in pernicious anaemia, chronic pancreatitis, blind loop syndrome and ileal disease
 - Can sequentially add intrinsic factor, pancreatic enzymes, and antibiotics (to ↓bacterial overgrowth) to see where in the absorption pathway the problem is. Also test before and after gluten free diet
 - Urinary d-xylose test: absorbed almost exclusively from the small intestine. Check levels in urine collected for 5 hours after oral dose to exclude duodenal/jejunal mucosal disease
 - Pancreatic function tests: faecal elastase the most common. Many others but generally can't get the reagents any more
- Diseases diagnosed on small-intestine mucosal biopsy:

- Diffuse, specific:
 - Whipple's disease
 - Agammaglobulinaemia
 - Abetalipoproteinaemia
- Patchy, specific:
 - Intestinal lymphoma
 - Intestinal lymphangiectasia
 - Eosinophilic gastroenteritis
 - Amyloidosis
 - Crohn's disease
 - Infection
 - Mastocytosis (mast cell infiltration)
- Diffuse, non-specific:
 - Celiac
 - Tropical sprue
 - Bacterial overgrowth
 - Folate deficiency
 - Vitamin B12 deficiency
 - Radiation enteritis
 - Zollinger-Ellison syndrome
 - Drug induced
- Differentials:
 - Diarrhoea:
 - Biliary tract disease
 - Cancer
 - Infection, see page 314
 - Lactase deficiency
 - Laxative abuse
 - Malabsorption, eg coeliac
 - Hyperthyroidism
 - IBD
 - IBS
 - Constipation:
 - Drugs: antihypertensive, anticholinergic, antidepressant
 - Endocrine: hypothyroidism, hypoparathyroidism
 - Lead poisoning or porphyria if abdo pain

Coeliac Disease/Coeliac Sprue

- See Lancet 2 August 2003
- Gluten-sensitive enteropathy. T-cell activation → intestinal villous damage
- 1 in 300 in Europe, 1 in 22 if 1st degree relative
- Two peaks in diagnosis: infant and around 40
- Under diagnosed: random population studies have found 2 out of 3 with no previous diagnosis
- Gliaden in wheat, barley, rye. Theoretically able to eat oats but in practice people get into trouble (?contamination, ?related compound)
- Presentation:
 - Diarrhoea in only 70% (following progression to more distal small bowel). ↓Lactase → osmotic diarrhoea. ↓surface area → ↓fat absorption. ↓activation of pancreatic enzymes. Impaired salt and water absorption
 - *Anaemia (most common adult presentation)*
 - Steatorrhoea, 2ndary lactase deficiency
 - Malabsorption of Fe (folate and fat soluble vitamins also affected, but not as much). Worse proximally – so affects lactase, iron and folate before B12 (absorbed distally)
 - Also abnormal LFTs, clubbing, neurological symptoms
 - Adults generally have a milder presentation than kids (?sensitive to fewer gliaden variants)
- Pathogenesis:
 - ?Triggered by adenovirus type 12
 - Gluten peptide P31 induces IL-15

- Gluten peptide P37 is deaminated by tTG (transglutaminase), attaches to HLA DQ2 and DQ8 high affinity peptides
- Gluten specific CD4+ T cells recognize DQ2 and DB8 gluten peptide complexes → Cytotoxicity by T cells and intra epithelial lymphocytes
- Associated with (?subtle nutritional deficiency 2nd to malabsorption, ?autoimmune)
 - Dermatitis herpetiformis (mechanism unknown): Intensely pruritic papulovesicular lesions on extensor surface and natal cleft that respond to dapsone (but this doesn't help the gut). Few coeliacs have it. 50% with it have coeliac. Gluten free diet helps both gut and skin. *Diagnosed by IgA deposits at the dermal-epidermal junction on immunofluorescence*
 - Diabetes type 1 (3 – 8% have coeliac), RA, SLE, Sjogren's
 - IgA deficiency ~ 3%
 - Thyroid disease ~ 8%
 - Primary biliary cirrhosis (*always screen for coeliac*) and PSC
 - ↑risk of gastrointestinal (eg small bowel adenocarcinoma) and other cancers and intestinal lymphoma – risk ↓ with diet
 - Fertility: delayed menarche, premature menopause, amenorrhoea, recurrent abortions (9 fold increase)
 - Hyposplenism: mechanism unknown
 - Metabolic bone disease
 - Neuropsychiatric effects: migraines, ADHD, cognitive defects, ataxia, depression
 - Down Syndrome: 16%
- When to screen:
 - GI symptoms
 - Abnormal LFTs, short stature, delayed puberty, Fe deficiency, obstetric problems
 - Type 1 diabetes
 - First or 2nd degree relatives
 - Turner's syndrome, Down's syndrome
 - Infertility
 - Autoimmune liver disease: PBC < PSC, AIH
 - Not osteoporosis – it's so common that the yield is low
- Investigations:
 - Antibodies:
 - The main one: tTG: **IgA** anti-tissue-transglutaminase (tTG) – Highly sensitive, a bit less specific, easy test
 - AGA: Antigliadin antibodies:
 - IgG: 75% sensitive, 80% specific
 - IgA: 85% sensitive, 90% specific
 - EMA: **IgA** antiendomysial antibodies (90 – 95% sensitivity and specificity) – difficult test
 - But 3% of coeliacs have selective IgA deficiency → negative IgA-AGA, so test total IgA as well to check or use less reliable IgG tests
 - Will be negative after ~ 3 months on a gluten free diet
 - Absence of HLA-DQ2 (in 90 – 95%, but a very common genotype – 30%, few of them are coeliacs) and DQ8 (in ~ 5%) effectively excludes the diagnosis
 - ↓ D-xylose test, Schilling test normal
- Biopsy:
 - Both gluten free diets and prednisone → false negative biopsy. Do gluten challenge first
 - Should do it – has life long health impact and it's expensive (and if biopsy proven can prescribe gluten free products for free)
 - May stay abnormal even on gluten free diet. Titrate treatment to clinical not histological response (histology may take 2 years to improve)
 - Differential: acute gastro, giardia, tropical sprue, eosinophilic gastro, CVID, cows milk allergy, lymphoma, radiation
- Treatment:
 - Dietician → gluten free diet. Should → disappearance of antibodies over ~ 6 months. Compliance is difficult – even some medications contain gluten
 - Symptoms should improve in ~ 2 weeks, may linger for up to 12 months
 - Monitor ABs at 6 months (instead of re-biopsying)
 - ?Lactose restriction

- Screen for iron and folate deficiency
- Vitamin supplement
- Bone densitometry: test Vit D and PTH if osteoporotic
- Constipation management (↓fibre)
- Pneumococcal vaccine due to hyposplenism
- Consider serology on 1st degree relatives
- If refractory:
 - Fails to respond to diet
 - Variants: Collagenous, ulcerative, stricturing
 - Also consider: IBS, lactulose, bacterial overgrowth, Lymphoma
 - Consider steroids, infliximab, azathioprine, elemental feeds

Carbohydrates

- Monosaccharides:
 - Hexoses: glucose, fructose (fruit), galactose (milk), mannose (ivory nuts)
 - Pentoses: xylose, sorbitol (not absorbed, used in sweeteners, found in several fruits)
- Disaccharides:
 - Sucrose: glucose + fructose. Split by sucrase. High quantities in corn syrup
 - Maltose: glucose + glucose. Split by maltase
 - Lactose: glucose + galactose. Split by lactase. Use as diabetic sweetener and pill filler (NB occult source in lactose intolerance). 1 cup of milk has 12 gm of lactose. 2 gm lactose when burnt generates 22 litres of H₂
 - Lactulose: galactose + fructose. Humans have no enzyme to break it down. Split by bacteria in the colon → osmotic effect. Also acidifies the bowel, trapping NH₃ as non-absorbable NH₄ and therefore excreted → ↓encephalopathy

Lactose malabsorption

- The only clinically important disorder of carbohydrate absorption
- Lactose = disaccharide present in milk = glucose + galactose
- Is broken down by lactase in the brush border
- Primary lactase deficiency: a genetically determined decrease or absence of lactase. Common in adulthood in non-Caucasian groups
- Secondary lactase deficiency: occurs in small-intestinal mucosal disease which damages the brush border. Common in celiac disease
- Diagnosis: hydrogen breath test. Hydrogen comes from bacterial breakdown of CHO in the large bowel – also produces CO₂ but this is quickly absorbed. Do a baseline breath H₂ level. Give a 25 gm lactose load then measure every ½ hour. If it goes up straight away, ?proximal bacterial overgrowth. If goes up after 2 hours then lactase deficiency. Not available in Wellington
- Malabsorption is common, intolerance is less so
- Can look like irritable bowel – differentiate with a lactose free diet

Tropical Sprue

- Chronic diarrhoea, steatorrhoea, weight loss and nutritional deficiencies (including folate and cobalamin) and abnormal small intestine biopsy – with known infectious causes excluded
- Clinical pattern varies in different parts of the world
- Cause unknown, but ?infectious given it responds to antibiotics
- Treatment: tetracycline for up to 6 months + folate

Short Bowel Syndrome

- Following varying resections of small bowel
- Residual intestine undergoes adaptive change over 6 – 12 months (ie don't give up too soon)
- Removal of ileum and/or ileocaecal valve associated with more severe diarrhoea than jejunum
- Treatment: codeine to slow transit time and low-fat high carbohydrate diet to ↓steatorrhoea, monitor vitamins

Vitamin B12 Deficiency

- See Pernicious Anaemia, page 419
- Assess with Schilling's test
- Causes:

- Diet: Vegans
- Gastric: pernicious anaemia, atrophic gastritis, gastrectomy
- Small bowel: bacterial overgrowth, pancreatic insufficiency, Crohn's disease, blocking agents (eg neomycin)

Bacterial Overgrowth Syndrome

- Proliferation of colonic-type bacteria in the small intestine → diarrhoea, steatorrhoea and macrocytic anaemia (due to cobalamin, not folate, deficiency – all the cobalamin is used up by the bacteria → none to absorb, the bacteria frequently produce folate)
- Caused by impaired peristalsis or direct communication between small and large bowel (blind loop syndrome)
- Diagnose with Schilling test, with and without intrinsic factor, then give antibiotics and repeat (should see an improvement)
- Treatment: surgical correction or tetracycline (but ↑resistance), metronidazole, augmentin...

Whipple's Disease

- Presentation:
 - Insidious onset, diarrhoea, steatorrhoea, abdominal pain, weight loss, migratory large-joint arthropathy, fever, late development of dementia
 - Mainly middle aged Caucasian men
- Caused by *Tropheryma whipplei* – low virulence but high infectivity
- Diagnosis: tissue biopsy from affected organ (small intestine, liver, lymph nodes, heart, eyes, CNS, synovial membrane), and seeing extracellular bacilli. PCR. PAS-positive macrophages with intracellular bacilli suggestive, but can be confused with *M. avium*
- Treatment: high dose cotrimoxazole for 1 year. Relapse possible

Motility Disorders of the Gut

- Autonomic innervation of the GI tract:
 - Parasympathetic via the vagus nerve
 - Sympathetic via the thoracic and lumbar sympathetic chain
 - Enteric system intrinsic to the gut wall
 - Myenteric plexus has as many neurons as the CNS
 - Peristalsis controlled by 'pacemaker cells' – interstitial cells of Cajal
- Motility disorders associated with the loss of interstitial cells of Cajal:
 - Hirschsprung's disease
 - Chronic idiopathic constipation
 - Internal anal sphincter achalasia
 - Gastroparesis
 - Paraneoplastic dysmotility
 - Chagas' disease

Inflammatory Bowel Disease

- See Lancet 5 July 2008
- Peak onset age 15 to 30, second peak from age 60 to 80. Crohn's is doubling each decade
- Risks:
 - Smoking reduces risk in UC (Ulcerative Colitis), increases in CD (Crohn's Disease)
 - Odds ratio of 1.4 for OCP in CD
 - First degree relative: 10% lifetime risk of IBD. CD > UC
 - Association with Turner's Syndrome, hypogammaglobulinaemia, IgA deficiency...
- Genetics:
 - Polygenic → multiple clinical subgroups
 - Some loci associated with both UC and CD
 - Eg CARD15 (caspase-associated recruitment domain containing protein 15) on chromosome 16 (aka NOD2): a cytosolic molecule that senses a bacterial peptide and regulates intracellular signalling. On the transduction pathway for TLR4. Loss of function mutations are highly associated with CD (and occur in up to 10%) – allows excess NF-κβ activation or ↓ intestinal antimicrobial activity – correlates with younger onset, small bowel involvement and fibrostenosing disease
 - Polymorphism in the IL23 receptor recognized in 2006

- Pathogenesis:
 - Dysregulated immune function in a genetically predisposed individual
 - Possible infective etiology
 - Major life events/psychosocial stress are associated with ↑ symptoms
 - Loss of tolerance to normal flora. Mucosal immune system is normally unreactive to luminal contents – a process called oral tolerance, including deletion of antigen reactive T cells and activation of CD4 T cells that suppress inflammation
 - Altered balance between pro- and anti-inflammatory cytokines
 - CD: Likely TH1 cells inducing granulomatous inflammation
 - UC: TH2 and NK cells secreting IL13 (and IL-4 and 5) inducing superficial mucosal inflammation
- Serology: No role in clinical practice
 - pANCA (different from vasculitic pANCA) associated with UC (+ive in 60 – 70% of UC, 5 – 10% of CD and 2 – 3 % of the general population). In UC associated with more severe disease
 - ASCA (anti-Saccharomyces cerevisiae antibodies) +ive in 30 – 50% Crohn's
 - Other antigens: porin C (Omp C), I2, Cbir 1...
- In 10 – 15% of cases may not be able to differentiate between CD and UC
- Definitions will change as we get better ways of characterizing this disease spectrum

Differential

- Infection: campylobacter colitis, Tb (small bowel obstruction and mass), CMV or herpes simplex proctitis, HIV, protozoa, parasitic infections (hookworm, whipworm, strongyloides)
- Diverticular disease
- Chronic ischaemic colitis
- Radiotherapy: symptoms after 1 – 2 weeks with bloody, mucoid diarrhoea and tenesmus in distal disease, diarrhoea, malabsorption and weight loss with small bowel involvement
- Microscopic colitis:
 - See Int Med Journal 2003:33: 305 – 309
 - Present with chronic diarrhoea
 - Uncommon
 - Collagenous colitis: subepithelial collagen deposition, usually 6th to 7th decade
 - Lymphocytic colitis: ↑intraepithelial lymphocytes, associated with celiac disease
 - Colonoscopy normal. Diagnosed on biopsy. Spontaneous remissions occur
 - Treat as for inflammatory bowel

Ulcerative Colitis

- Diarrhoea, rectal bleeding, tenesmus, mucus, crampy abdominal pain. Distal disease → ↑proximal transit time → constipation. Proximal disease → ↓transit time → diarrhoea
- ↑CRP, ESR, ↓haemoglobin, ↓albumin. Faecal calprotectin correlates well with relapses (highly sensitive ⇒ good rule out test eg in IBS). Negative stool for C difficile, ova, parasites
- Endoscopy/barium enema better than CT
- Complications:
 - Rare massive haemorrhage
 - Toxic megacolon in 5% attacks, perforation rare but 15% mortality
 - Strictures in 5 – 10 % (exclude underlying malignancy)
 - Cancer with long duration (10% at 40 years) – annual screening from 10 – 15 years
- Pathology:
 - Proximal, continuous spread from the rectum, in 20% extending to a total colitis
 - In mild disease the mucosa has a fine granular appearance, if severe then mucosa is haemorrhagic, oedematous and ulcerated
 - Microscopic: Crypt architecture distorted and inflammatory infiltrate → crypt abscesses
 - If fulminant disease then toxic colitis with thin bowel wall, severe ulceration and possible perforation

Crohn's Disease

- Two patterns: fibrostenotic-obstructing pattern, or penetrating-fistulous pattern
- Predictors of severity: initial need for steroids, young age, peri-anal disease, fever at diagnosis, weight loss > 5 kgs at diagnosis
- Measures with Crohn's Disease Activity Index (CDAI)

- By 12 years 75% have had surgery at least once
- Most common site is terminal ileum – can have pain and an inflammatory mass resembling appendicitis
- Jejunoileitis: malabsorption and steatorrhea → vertebral fractures, niacin deficiency (→ pellagra) B12 deficiency
- Diarrhea 2nd to bacterial overgrowth 2nd to obstructive stasis or fistulisation, bile-acid malabsorption in distal ileum and ↓water absorption 2nd to inflamed intestine
- Pathology:
 - Any part of the GI tract, 30 – 40% have small-bowel disease alone, 20% have colitis alone
 - Rectum often spared, skip areas, “cobblestone appearance”, surpigenous ulcers, perirectal fistulas or abscesses, anal stenosis, transmural involvement → thickened wall, stenoses, fistulas
 - Microscopic: crypt abscesses, noncaseating granulomas, lymphoid aggregates
- Investigations: Imaging: Wireless capsule endoscopy (better than CT enterography – although this is reasonable at picking up small bowel abnormality). SE capsule retention. MRI may be better for rectal lesions – not proven
- Complications:
 - Weight loss
 - Abscess (consider if high spiking fever)
 - Perforation
 - Obstructive episodes
 - Gross bleeding not as common as in UC
 - Fistulas: to stomach, or duodenum, rectovaginal in 10% women
 - Cancer with long duration (> 10 years), ↑ risk with extensive disease, PSC. Also ? ↑ risk of lymphoma, leukaemia and myelodysplastic syndromes

Extraintestinal manifestations

- In up to one third:
 - Skin:
 - Erythema nodosum: in both UC and CD, correlates with bowel activity. Hot, red, tender nodules on anterior surface of legs and arms
 - Pyoderma gangrenosum: in 1 – 12% of UC, less commonly in CD. May occur years before bowel symptoms. On dorsal surface of feet and legs. Spreading pustule → ulcer with necrotic centre. Also occurs in monoclonal gammopathy, malignancy (eg CML), RA
 - Psoriasis in 5 – 10%, unrelated to bowel activity
 - Arthritis:
 - In 15 – 20%, more common in CD than UC, worsens with bowel activity
 - Asymmetric, polyarticular and migratory arthritis of large joints
 - Ankylosing spondylitis in 10% of IBD (CD > UC). Not related to bowel activity
 - Eyes: conjunctivitis, anterior uveitis/iritis and episcleritis
 - Liver/biliary:
 - Fatty liver from chronic illness, malnutrition and steroids
 - Gallstones (CD > UC)
 - Primary sclerosing cholangitis: in 1 – 5% of IBD, but 50 – 75% of PSC have IBD
 - Urologic: ureteral obstruction, fistulas, calcium oxalate stones (following small bowel resection → ↑oxalate absorption)
 - Metabolic bone disease: poor calcium absorption, inflammatory milieu, steroids, ↑risk with TPN
 - VTE

Drug Treatment

- Summary:

	Crohn's		Ulcerative Colitis	
	Induction	Maintenance-	Induction	Maintenance
Steroids	If high risk or small bowel	No	✓	No
5ASA	?Monotherapy for low risk colon	No	✓	✓
Antibiotics	maybe		in pouchitis only	
AZA	✓	✓		✓
Methotrexate	✓	✓		
Cyclosporin			Salvage	

Anti-TNF α

✓ (most evidence
in fistulizing)

Not funded

-
- 2 mistakes made: under treating severe disease and over treating minor disease \Rightarrow risk stratification important
 - Crohn's:
 - Smoking cessation
 - Low risk:
 - Little evidence for 5-ASAs – may consider for mild ileocolonic disease
 - Colonic: sulfasalazine oral and rectal (dose response relationship, so give more if needed). Taper steroids. If need steroids more than twice a year then ?azathioprine
 - Small intestine: steroids.
 - If response then taper. If relapse then steroids + AZA
 - If no initial response then AZA or methotrexate. If relapse then anti-TNF α
 - High risk:
 - < 18 years, non-inflammatory signs (strictures or fistula), extensive disease, early steroids needed, extra-intestinal manifestations, active smoker
 - Steroids + AZA. If response taper steroids. If no response then anti-TNF α .
 - No evidence from RCTs for sulphasalazine for fistulas. Evidence does not support metronidazole but it's frequently used
 - Fistulas: Infliximab, maintenance better than episodic txt to 1 years, not all on AZA and no correlation reported, incremental benefit to AZA in other trials) and AZA have established evidence. Cyclosporin and Tacrolimus not well studied
 - Current question: does early aggressive treatment (ie top-down) for high risk work better than Step-up therapy – ie can we alter the natural history of Crohn's – initial difference seems to wane with time
 - UC:
 - Start with:
 - Sulfasalazine: dose response \rightarrow give more. Oral and rectal
 - Tapering steroids. If needed more than twice a year then ?AZA
 - Severe:
 - IV hydrocortisone 100 mg qid + heparin for 5 – 7 days, if no response (predicted by CRP on day 3) then surgery or salvage therapy (cyclosporine, as a bridge to AZA. Infliximab effective in preventing surgery. Increasing interest in Tacrolimus)
 - Infliximab trialled in ACT 1 and 2 in refractory disease. Approx 65% response vs 30% for placebo at 26 – 48 weeks
 - Pouch surgery:
 - Pouchitis in 50%, most within the first 12 months. Disabling in 15%. Trials of ciprofloxacin, methotrexate, and probiotics show efficacy (?it's more a bug thing than an inflammation thing)
 - Reduced fertility (as much as 80%) – of critical important to young females
 - Glucocorticoids:
 - Oral, iv or enemas all of benefit
 - Effective in inducing remission, do not maintain remission (long term treatment does not prevent relapses)
 - Controlled ileal-release budesonide good for small bowel CD with fewer steroid side effects
 - Usually the first line treatment. However, combined immunosuppression with infliximab + azathioprine more effective than induction then maintenance with prednisone (60% vs 35% remission at 26 weeks, 61% vs 42% at 52 weeks) \Rightarrow suggests early immunosuppressive treatment better. Lancet 23 Feb 2008
 - 5-ASA agents (Aminosalicylates):
 - For remission induction in both UC and CD (although controversial in CD), *maintenance in UC*, not proven superior to placebo in maintenance of CD (well conducted negative studies – ie it's OK to stop if not helping)
 - Topical enemas in distal UC
 - Mezalazine = 5ASA
 - Sulphasalazine (Salazopyrin): antibacterial (sulfapyridine) + anti-inflammatory (5-ASA). Only partially absorbed and broken into constituent parts in the colon
 - Numerous other formulations with varying absorptive properties, eg Pentasa = 5ASA coated granules which release throughout the gut

- At higher doses, 30% experience allergic reactions (rash, fever, hepatitis, agranulocytosis, pneumonitis, pancreatitis...) or intolerable SE to the sulfapyridine moiety: headache, anorexia, nausea. Can impair folate absorption \Rightarrow give supplements
- PPAR- γ (Peroxisome proliferator activate receptor) may mediate 5-ASA activity by regulating NK- $\kappa\beta$
- Antibiotics: No role in UC. Few quality studies. Metronidazole effective in CD (peripheral neuropathy with prolonged administration) – week 8 remission 38% vs 33% for placebo
- Azathioprine and 6-mercaptopurine: See page 240 for mechanisms and side effects
 - Start low. Takes 3 – 6 months for effect
 - Used as a steroid sparing agent in UC and CD. Highly effective at maintaining remission (in 60%) of IBD, and effective at inducing remission in CD
- Methotrexate: See page 241
 - Oral, IM or SC
 - Effective in induction in steroid refractory CD
 - Maintains remission in CD
 - SE: leukopenia and hepatic fibrosis, rare pneumonitis
- Cyclosporin (CsA): see page 120
 - Binds to calcineurin (a cytoplasmic phosphatase involved in the activation of T cells)
 - Used IV in severe UC refractory to IV steroids. Not so effective orally long term – used with 6-MP/azathioprine to maintain remission
 - Blocks production of IL-2 by T-helper cells
 - SE: renal toxicity, HTN, gingival hyperplasia, paresthesias, tremours, headaches, electrolyte abnormalities, seizures (esp if \downarrow Mg or \downarrow cholesterol). Opportunistic infections
- Tacrolimus: Macrolide antibiotic, similar but much more potent than CsA and not dependent on bile or mucosal integrity for absorption (\Rightarrow good in small bowel CD)
- Tumour Necrosis Factor Inhibitors:
 - Not for fulminant disease – it's too slow
 - Not for pouchitis
 - Most effective in fistulizing Crohn's. Some but less efficacy in stenosing Crohn's. Up to 65% of CD patients refractory to the above agents will respond to infliximab (but remission in only 1/3rd), many will retain remission with 8 weekly infusions. 4 week remission in 48% vs 4%. 1/3rd don't respond at all
 - Also efficacy in UC (although not PBS approved in Aussi)
 - Development of antibodies to infliximab related to infusion reactions and \downarrow response. Concurrent steroids to \downarrow risk of antibody formation
 - Adalimumab also effective (100% humanized) ~ equivalent to Infliximab. Etanercept doesn't work in Crohn's
 - SE small \uparrow risk of lymphoma, infusion reactions, \uparrow infections (incl latent Tb), rarely optic neuritis, seizures, CNS demyelinating conditions, exacerbation of CHF
- Novel therapies:
 - Anti-p40 Antibodies:
 - IL-12 (activates Th1) and IL-23 (activates Th17) cytokine receptors share a common p40 subunit and β 1 receptor chain
 - P40 neutralizing antibodies therapeutic in human trials
 - Natalizumab (used in MS) effective in phase II trials. 3 cases of JC mediated progressive multifocal leukoencephalopathy
 - T-cell blockade with eg anti CD3+ and CD25+
 - Blockade of T cell differentiation or activation (as opposed to depleting a T-cell subset), eg directed at IL-6 or IFN γ
 - Targeting TNF signalling pathways
 - Blocking leucocyte migration to sites of inflammation by interfering with cell-adhesion molecules used in diapedesis – eg targeting α 4 integrins
- Nutritional: Active CD responds to bowel rest and TPN (equivalent to steroids for inducing remission). Elemental diets effective but not palatable
- Thalidomide: effective in fistulous CD but trials needed
- Surgery:
 - Indications: intractable or fulminant disease, perforation, stricture, abscess
 - UC: ileal pouch

Pregnancy

- Fertility:
 - Fallopian tubes can be scarred in CD
 - Sulfasalazine → temporary infertility in men
- Should be in remission for 6 months before conceiving otherwise ↑abortion and birth defects
- Disease state at conception predicts disease course during pregnancy. Key risk is active disease not drugs
- Consider Caesar to avoid scar which may become a fistula track
- Drugs in pregnancy:
 - Sulfasalazine OK in pregnancy and breast-feeding but need folate supplements
 - Steroids generally safe
 - Azathioprine safe (limited data)
 - Cyclosporin: avoid unless need to avoid surgery
 - Methotrexate **not** safe
 - No increased risk of problems found with infliximab

Irritable Bowel Syndrome

- Diagnostic criteria (Rome II & III, Manning Criteria): Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with two or more of the following:
 - Improvement with defecation
 - Onset associated with a change in frequency of stool
 - Onset associate with a change in form (appearance) of stool
- Pathogenesis poorly understood. Variety of mechanisms proposed: abnormal gut motor and sensory activity, serotonin imbalance/response, CNS dysfunction, psychological disturbance....
- Red flags: weight loss, fever, blood, older age, progressive course, persistent diarrhoea after a 48 hour fast, nocturnal diarrhoea, steatorrhoea
- Treatment:
 - Reassurance
 - Stool-bulking agents: variable results from controlled trials
 - Antispasmodics (eg anticholinergics)
 - Anti-diarrhoeal agents
 - Others... eg TCAs and 5-HT3 antagonists
- 5-HT3 receptors:
 - Controls sensation and contraction of intestinal muscle, release of fluid into the intestine
 - Alosetron: Selective 5-HT3 antagonist decreases intestinal transit and secretions → ↓stool frequency and pain. Used under a surveillance programme due to SE of ischaemic colitis
- 5-HT4 receptors:
 - Mediate relaxation and contraction of circular smooth muscle and bowel fluid secretion
 - Tegaserod (Zelmac) is a selective 5-HT4 antagonist that ↑transit time and water content. Withdrawn due to risk of acute MI

Liver Disease Overview

Background

- Cell types:
 - Hepatocytes
 - Kupffer cells – largest group of fixed macrophages in the body
 - Stellate (Ito or fat-storing) cells
 - Endothelial and blood vessel components
 - Bile duct cells
- Structure:
 - Hepatic arterial (20%) and portal (80%) blood enter the acinus from the portal areas (zone 1) and flow through the sinusoids to the terminal hepatic central veins (zone 3)
 - Bile flows from zone 3 to zone 1
 - Space of Disse is on the basolateral side of the hepatocyte
 - Bile is secreted through the cannicular membranes on the apical surface

History

- See Cirrhosis, page 369, for exam findings
- Constitutional symptoms: fatigue, weakness, nausea, poor appetite, malaise
- Liver specific symptoms:
 - Jaundice, dark urine, light stools, steatorrhoea, itching, abdo pain, bloating
 - Jaundice without dark urine → indirect/unconjugated hyperbilirubinaemia (eg haemolytic anaemia)
- Complications of cirrhosis and end stage disease: bruising, haematemesis
- Encephalopathy ≈ fulminant liver failure
- Risk factors:
 - Alcohol (see page 485), medications (including OCP and OTC), sexual activity, travel, exposure to high risk or jaundiced people, IVDU, recent surgery, past blood transfusion, needlestick exposure, family history of liver disease
 - Hepatitis risk factors:
 - Sexual transmission common with Hep B, rare with Hep C
 - Vertical transmission:
 - Hep C uncommon, no reliable means of prevention. More common in HIV co-infected mothers
 - Hep B prevented by passive and active immunisation at birth
 - Hep C:
 - IVDU the most common risk factor
 - Blood transfusions before 1992
 - Hep B: transfused blood started to be tested for anti-HBc in 1986
 - Hep E: more common in Asia, Africa
 - Tattooing and body piercing: transmission of Hep B and C very rare
 - Hep A: travel important, selfish transmission very rare

Investigations

- Liver Function Tests:
 - Most don't measure liver function at all, but liver damage. Each has poor sensitivity – use them as a battery
- Serum **Bilirubin**:
 - Breakdown product of the porphyrin ring
 - Conjugated in liver by UGT1A1 → via bile to duodenum. Either passed with stool or converted by bacteria to water soluble urobilinogen → reabsorbed → enterohepatic cycling. Some gets past hepatic metabolism and is excreted by the kidney
 - *Unconjugated* or *indirect* fraction:
 - Insoluble, bound to albumin in the blood, can't be excreted by the kidney
 - Isolated elevation hardly ever due to liver injury – think haemolysis (check for ↑reticulocytes) or Gilbert's syndrome
 - Decreased hepatocellular uptake: ?part of Gilbert's syndrome and reported with rifampicin
 - Crigler-Najjar Syndrome 1 and 2: absence or impaired UGT1A1 complex
 - Gilbert's Syndrome: mild unconjugated ↑bilirubin which ↑ with stress, alcohol, illness. 10% of population. Due to reduced UGT1A1 activity – various causes for the phenotype, eg primary genetic defect (AD) or defect of gene regulation (AR)
 - *Conjugated* bilirubin:
 - Elevation almost always implies liver or biliary disease
 - Rate limiting step is not conjugation, but transport into the bile canaliculi
 - In most liver disease, both conjugated and unconjugated elevated
 - Conjugated hyperbilirubinaemia: rare genetic defects of bile canalicular function
 - Urine bilirubin: any bilirubin in the urine will be conjugated, which implies liver disease. Urine dipstick can therefore give the same information as fractionation of the serum bilirubin
- Blood ammonia:
 - Liver converts ammonia to urea
 - Striated muscle converts ammonia to glutamine – but muscle wasting in liver disease → ↓metabolism via this route
 - Poor correlation with encephalopathy or hepatic function → not tested much
- Enzymes:

- Distributed in the plasma, but no known function outside the liver
- Probably cleared by reticuloendothelial cells, half life measured in days
- Damaged liver cells (not necessarily necrosis) → membrane permeability → ↑diffusion into serum
- Aminotransferases (transaminases):
 - Poor correlation between level and actual cell damage, so of little prognostic use in acute liver disease
 - Aminotransferase levels can be normal in Hep C despite moderate disease activity, and are unreliable in predicting severity in steatophepatitis
 - **Aspartate aminotransferase (AST)**: Found (in ↓ order of concentration) in liver, cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes and erythrocytes
 - **Alanine aminotransferase (ALT)**: Found primarily in the liver
 - Levels up to 300 found in any liver disorder. Levels > 1000 associated with extensive hepatocyte injury (eg viral, ischaemia, toxin or drug related)
 - Usually ALT > AST in acute disorders:
 - Viral
 - Medication
 - Ischaemia (dramatic rises and falls)
 - Autoimmune hepatitis
 - AST > ALT:
 - by 2:1 suggestive, and by 3:1 highly suggestive, of alcohol (contributed to by relative vitamin B6 deficiency). AST rarely > 300 in alcoholic disease, and ALT may be normal (due do alcohol induced deficiency of pyridoxal phosphatase)
 - Paracetamol
 - Underlying cirrhosis
 - Rarely raised in obstructive jaundice (except acute passage of a gallstone, may be 1000 – 2000)
- Cholestasis:
 - **Alkaline phosphatase (ALP)** and 5'-nucleotidase found near the bile canalicular membrane of hepatocytes:
 - Isoenzymes found in liver, bone, placenta and less commonly small intestine
 - Patients > 60 have a normal elevation of 1 – 1/5 times normal. Can also transiently increase after a fatty meal due to an influx of intestinal ALP into the blood
 - Also isolated elevation in late pregnancy, Hodgkin's disease, diabetes, hyperthyroidism, CHF, IBD
 - < 3 fold elevation can occur in any liver disease. > 4 fold elevations mainly in cholestasis, infiltration (cancer and amyloid) and rapid bone turnover. If it's > 2000 it's Paget's disease until proven otherwise
 - To isolate source, can test which isoenzyme with electrophoresis – but as GGT is specific for the liver, if that's raised as well, then assume ALP is of liver origin
 - Level of rise doesn't discriminate between intrahepatic and extrahepatic causes (eg stone or drug-induced hepatitis, primary biliary cirrhosis, etc)
 - **γ-glutamyl transpeptidase (GGP)**: found in the endoplasmic reticulum and bile duct epithelial cells – as it's found diffusely in the liver is less specific for cholestasis. Isolated rise in:
 - Alcohol (clue: ↑MCV)
 - Fatty liver
 - Medication: phenytoin, carbamazepine
 - ↑ALT and ↑GGT: mainly fatty liver, occasionally viral hepatitis, medication or congestion
 - ↑ALP and ↑GGT: biliary injury. Primary biliary cirrhosis (small bile ducts), Primary sclerosing cholangitis (large bile ducts), medications (injury to intrahepatic ducts): flucloxacillin, augmentin, allopurinol
 - ↑AST and ↑GGT: Alcohol
 - ↑ALT/AST + ↑ALP + ↑GGT: passed biliary stone (present with pain) or drug induced liver disease
 - Testing biosynthetic function:
 - **Albumin**:
 - Made exclusively by hepatocytes, half life ~ 20 days, ~ 4% degraded per day → not helpful acutely
 - Care in ascites: may be normal synthesis but ↑volume of distribution

- ↓in protein malnutrition, nephrotic syndrome, inflammation (prolonged ↑IL-1 and/or TNF → ↓synthesis)
- **Globulins:**
 - γ globulins produced by B cells, α and β globulins produced by liver
 - Liver disease → ↓clearance of intestinal bacterial antigen from hepatic circulation → ↑Ig
 - ↑IgG in autoimmune hepatitis, ↑IgM in primary biliary cirrhosis, and ↑IgA in alcoholic liver disease
- **Coagulation factors:** Because of rapid turnover (6 h for factor VII, 5 days for fibrinogen) serum prothrombin time is the best acute measure of synthetic function. Measures factors II, V, VII, and X. Can also be elevated in vitamin K deficiency (eg ↓fat absorption) affecting II, VII, and X. Test by giving IV vitamin K and seeing if it corrects
- Imaging:
 - US first test in ?cholestasis. Also able to differentiate between cystic and solid masses
 - US and CT have high sensitivity for detecting biliary duct dilatation and fatty liver
 - MCRP is more sensitive but less specific for choledocholithiasis
 - US and MRI for vasculature and haemodynamics
- Liver biopsy:
 - Best for diffuse conditions, sampling errors with focal disorders
 - If elevated INR can do trans-jugular biopsy more safely
 - Most important use is for assessing severity (grade), maybe if diagnostic uncertainty. Need a length of 1.5 – 2 cm for accurate assessment of fibrosis
 - Who to biopsy:
 - Hep B: commonly done – if not severe may not start treatment
 - Hep C: not routine – but may help treatment/no treatment decision
 - Value of knowing stage (ie degree of fibrosis – stage 3 = bridging fibrosis, stage 4 = nodular fibrosis) is you know when you've got cirrhosis and can manage accordingly (ie start screening of HCC)
 - Care with biopsying a potentially vascular lesion (eg haemangioma) – can do a labelled red cell scan
 - Typical histology:
 - Autoimmune hepatitis: plasma cells infiltrates
 - PBC: periportal fibrosis, lymphocytic and granulomatous infiltrates of bile ducts, ductopenia
 - PSC: fibrous obliterative cholangitis, ductopenia
 - Chronic viral hepatitis: Ground glass hepatocytes
 - α 1AT: intracytoplasmic globules
 - GVHD: lymphocytic and granulomatous infiltrates of bile ducts, ductopenia (note same as PBC)
 - Alcoholic steatohepatitis: steatosis; central inflammation and fibrosis
 - Non-alcoholic steatohepatitis: steatosis; central inflammation and fibrosis

Assessment of Liver Nodule(s)

- Normal liver and solitary nodule:
 - Simple cysts: smooth walls
 - Haemangioma: commonest benign tumour
 - Focal nodular hyperplasia (FNH): characteristic central artery, solitary circumscribed lesion, stellate “wagon wheel” scar on CT, contrast fills from the outside, static or slow growing, normal α FP
 - Nodular regenerative hyperplasia: benign nodules formed in response to vascular injury (eg after radiation)
- Adenomas:
 - Hypervascular with no true capsule → high risk of haemorrhage
 - Risk of malignant transformation so remove
 - Associated with high dose oestrogens and glycogen storage disorders
- Mets
- Cirrhosis and solitary nodule = HCC until proven otherwise
 - Rare to get a met in a cirrhotic liver – more likely to be shunted to the lung
 - Work up: US + CT +/- MRI → Guided biopsy
 - See Hepatocellular Carcinoma, page 398

Scoring

- Classification by grade:

- A histologic assessment of inflammatory activity, including periportal necrosis, piecemeal necrosis, degree of necrosis linking vascular structures (bridging necrosis), focal intra-lobular necrosis, etc
- Histologic Activity Index (HAI): score from 0 to 18
- Classification by stage:
 - Level of progression of disease
 - Degree of fibrosis from 0 to 6
- Child-Pugh-Turcotte (CPT) score for cirrhosis:
 - Reasonably reliable predictor of survival, predicts variceal bleeding and spontaneous bacterial peritonitis
 - Based on bilirubin, albumin, INR or prothrombin time, ascites and hepatic encephalopathy
 - Grade A (score 5 – 6), B (7 – 9) and C (10+), corresponding to 1 year mortality of 29%, 38%, and 88%
 - Only modifiable risk factor is albumin with better nutrition
- Model for End-stage Liver Disease (MELD):
 - INR, bilirubin and creatinine (NB CPT doesn't include renal function – renal impairment associated with worse prognosis) – used for liver transplant scoring in the US – accurately predicts short term survival independent of cause
 - Debate about whether it should include Na (NEJM 4 Sept 2008) as progressive cirrhosis often → hypervolaemic hyponatraemia via ADH acting on V2 receptors, with also increased risk at the time of transplant. But also a labile measure

Screening

- If cirrhosis, consider screening for oesophageal varices (consider β -blockers) and hepatocellular carcinoma (appropriate interval not established, consider annual US)
- Consider vaccination for Hep B and C, influenza and pneumococcal
- Avoid alcohol

Viral Hepatitis

- Distribution of cause of acute hepatitis (e.g. ALT > 1000) in Auckland: A – 25%, B – 25%, EBV – 25%, C – 5 – 10%, some CMV
- Worldwide, half a billion people infected with Hep B or C, killing 1.5 million annually (Lancet 17 May 2008)
- None of the hepatitis viruses are known to be directly cytotoxic to hepatocytes – damage relates to T cell immune responses and inflammatory cytokines

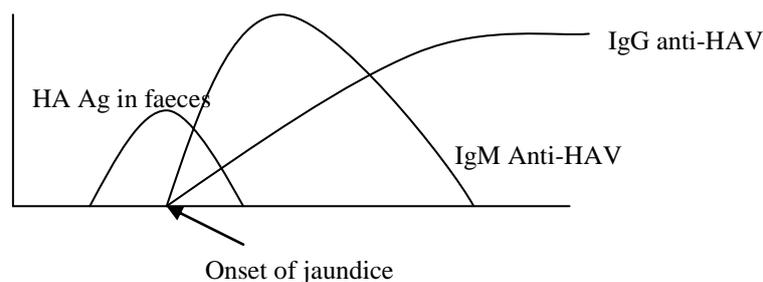
	Hep A	Hep B	Hep C	Hep D	Hep E
Type	RNA	DNA	ssRNA	RNA	RNA
Incubation	2 – 8 weeks (ave 4)	2 – 6 months (ave 6)	3 – 20 weeks (ave 7)	4 – 35 weeks (ave 8)	2 – 8 weeks (ave 6)
Symptoms	20 – 40%	40 – 60%	Mild		
Onset	Abrupt	Insidious			
Duration	1 – 3 weeks	1 – 4 weeks, sporadic			
Icterus (Jaundice)	30 – 35%	30 – 40%	10 %		
Route of Infection	Faecal/oral	Parenteral/sexual	Blood. STD related to HIV, other STIs and viral load	Close personal contact	Faecal-oral
Infectivity	Diminishes rapidly once jaundiced	Relates to HBV DNA level and presence of HBeAg	Related to viral load	Only in presence of Hep B	2ndary person-person spread rare
Chronic infection	None	10 – 15%	50 – 80%		None
Mortality	0.05 – 0.1%	1 – 2%			
Diagnosis	IgM anti-HAV IgG anti-HAV	IgM Anti-HBc, HBsAg, HBeAg	Exclusion. After 3 months Anti HVC. HVC RNA PCR earlier		

Treatment	None	Pegylated IFN or Lamivudine, Adefovir, Entecavir	Pegylated IFN and Ribavirin	IFN	None
Vaccination	Havrix: 99% cover	Engerix B: 90 – 95% cover	None	HBV vaccine	?IG – no evidence

- Indicators of severity:
 - Bilirubin > 300 $\mu\text{mol/L}$
 - Low/falling albumin
 - \uparrow INR
 - Hypoglycaemia
 - Advanced age
 - Serious comorbidity
- Fulminant hepatitis (massive hepatic necrosis): B is the most common cause. In 1 – 2% cases of E but 20% of cases when pregnant

Hepatitis A

- Especially in kids, normally mild
- Faecal-oral transmission by food (especially raw shell fish) or contaminated water
- Decreasing over time due to \uparrow hygiene and good vaccine
- Presentation:
 - Kids: gastro like illness
 - Adults: Jaundice and hepatitis. If testing for hepatitis, always do A, B and C
 - 1% mortality: very young and very old
 - Occasionally relapsing
- Viraemia lasts 7 days after onset of jaundice (ie infectivity declines rapidly once symptomatic \rightarrow standard infection control precautions only). Don't get virus in the blood (or only transiently). It's a gut bug
- Diagnosed by IgM Anti HAV during illness & ?exclusion of HBV. IgG anti-HAV persists
- Treatment: supportive, dietary restriction, rest, no alcohol. Notifiable disease
- Post exposure prophylaxis if not vaccinated with IgG for close contacts
- Vaccination:
 - Havrix 1440: 99% immunity after 1 month. One dose im. Booster after 6 – 12 months gives longer-term immunity. Inactivated HAV
 - Can't distinguish natural immunity from vaccine immunity (IgG Anti-HAV in both)



Hepatitis B

- See NEJM 2 October 2008 (good review article)
- 350 million with chronic infection, >75% of these Asian
- 30% of chronically infected die prematurely from the disease
- In NZ, approx. 50,000 carriers. Chinese 10%, Maori 5.4%, PI 4.4%, European 0.43%

Transmission

- Body fluids (blood, semen), including transfusion & contaminated needles
- Mother to baby (vertical transmission): 95% risk of infection – single dose of HBIG at birth and 3 doses of vaccine, first within 12 hours. Virtually no transmission from breast feeding
- Organ transplant
- Child to child (horizontal transmission). Must get into blood – e.g. grazes, stubbed toes. Very resilient virus

- Needlestick injury:
 - Risk of HBV infection related to source HbeAg status:
 - +ive: risk of HBV infection 37 – 62%, risk of clinical hepatitis 22 – 31%
 - -ive: risk of HBV infection 23 – 37%, risk of clinical hepatitis 1 – 6%
 - Efficacy of HBIG (Hepatitis B immune globulin) and/or Hep B vaccine not evaluated in occupational setting, but the increased efficacy of both (85 – 95%) in the perinatal setting, compared with HBIG alone, is presumed to apply
 - If past documented vaccine induced immunity, no action required following a needlestick, even if anti-HBs undetectable

Pathogenesis

- The virus:
 - 8 HBV genotypes – the differences are not sufficient to alter management, but:
 - Genotype A more likely to undergo interferon-induced HbeAg seroconversion
 - E antigen seroconversion more frequent in B than C
 - Relies on reverse transcription by a DNA polymerase – makes a pregenomic RNA intermediate from which it makes its replicated DNA. Thus the effect of lamivudine
- HBV hepatitis is caused by the immune system clearing infected hepatocytes. No immune activity → no hepatitis and lots of virus
- Ccc-DNA:
 - Covalently coiled closed DNA = super-coiled DNA
 - No way to get rid of it from the nucleus of some hepatocytes – it's there forever, even if anti-HBs +ive
 - Can be reactivated if immunosuppressed (eg rituximab) → high viral load → severe hepatitis when immune system reconstitutes. Treat prophylactically with lamivudine during any immunosuppressive treatment (eg chemo)
- **Mutations:**
 - Normal virus called 'wild type'. E protein is made simultaneously with core protein but not used in virion assembly, so its presence in the blood correlates with active replication
 - Pre-core mutant HBV virus: (essentially equivalent to Core-promoter mutant)
 - Doesn't produce E antigen (so won't produce HBeAg) but will still be HBV-DNA and HBeAb +ive (differentiate pre-core mutant infection from immune control of wild type by LFTs – will be ↑ in the former)
 - Single point mutation → stop codon at 1896 stopping the synthesis of HBeAg
 - Immune pressure is directed mainly at the e-antigen → selective pressure for pre-core mutant, and development of pre-core mutant means immune pressure then becomes less effective
 - Associated with more severe outcomes, higher HCC rates, fluctuating ALT levels, sustained response to IFN uncommon, usually responds to lamivudine but life long treatment probable
 - In NZ 60% of disease is HBeAg +ive, 40% is HBeAg -ive
 - YMDD/Nucleoside Analogue resistance mutations:
 - Reflects pressure of therapy on virus
 - Mutation in domain C with upstream compensatory mutation in polymerase domains A and B. Results from selective pressure of nucleoside (eg Lamivudine) treatment
 - Escape mutants: Change in HBsAg → loss of neutralising activity by anti-HBs. Rare

Diagnosis

- Viral Load: HBV DNA. Copies of HBV DNA per ml (cpm) = 5.82 IU [ie times copies by 5 to get IU]
- Diagnosis from bloods:
 - Acute HBV: IgM Anti-HBc (also in reactivation, false positives if high rheumatoid factor) and HBV DNA PCR
 - Chronic HBV: HBsAg – titre bears little relationship to severity. Clinical course is more dependent on immune response than viral load
 - Past infection: Anti-HBc
 - Vaccine immunity: Anti-HBs > 10 IU and not Anti-HBc
 - HBcAg is never found in the blood
- Chronic carriage infectivity:

	HBsAg	HBeAg	Anti-HBe
High	+	+	-
Intermediate	+	-	-

- Second stage: S antigen seroconversion
- *Immune control* (still latent infection eg due to ccc-DNA)
- *Immune escape*: in e antigen negative disease only. Inflammation and eventually fibrosis
- 20% of 'carriers' develop chronic active hepatitis → cirrhosis (mainly males), the remaining 80% remain immunotolerant
- Assessing progression:
 - Viral load:
 - The level of HBV DNA correlates with the level of liver injury and risk of progression
 - REVEAL study: observational study of 3774 HBsAg +ive people in Taiwan over 13 years without treatment (caution: does it apply to non-Asians – usually neonatal transmission, most in NZ is early horizontal transmission). Higher viral loads were associated with ↑rates or cirrhosis, HCC, ↑mortality
 - Lab features of chronic Hep B do not distinguish adequately between histologically mild and severe hepatitis
 - ALT tends to be higher than AST – can reverse once cirrhosis is established
- Complications:
 - Hepatocellular carcinoma peaking in the 5th decade
 - Nephritic syndrome with HBsAg, IgG and C3 deposition in glomerulus in chronic Hep B (Mesangiocapillary type 1 or membranous)
 - Association with polyarteritis nodosa: occurs in < 1% of those with HBV, but 20 – 30 % of patients with PAN are HBsAg +ive
 - Mixed cryoglobulinaemia: arthritis, cutaneous vasculitis (palpable purpura) with circulating cryoprecipitates – stronger association with Hep C

Vaccination

- Most effective means of control: vaccination: Engerix B. 85 – 90% efficacy
- Suspension of synthetic HBsAg
- Doses at 0, 1 and 6 months → immune levels of Anti-HBs in 92%
- Check for seroconversion 2 months later. If fail to seroconvert to vaccine, and high risk, give a further 3 doses
- Booster every 2 – 3 years if high risk (immunocompromised, *haemodialysis*), otherwise not indicated even if anti-HBs becomes negative
- OK in pregnancy

Treatment

- Should have liver biopsy – if normal may elect to wait
- Treatment aims:
 - Main aim is suppression of Hep B replication (measured by HBV DNA) – risk is highest for those with continued high levels of expression
 - HBeAg seroconversion to anti-HBe: if it occurs, this change is usually sustained, so may be used as a stopping point of therapy. If seroconversion doesn't happen then long term oral therapy (common) otherwise reactivation
 - Don't get HBeAg seroconversion in pre-core and core-promoter mutants – stopping is usually followed by reactivation → long term oral treatment
- Other treatment issues:
 - Sensitivity of tests for HBV DNA has improved since lamivudine trialled in the early 90s – bear this in mind when comparing with more recent trials
 - Serious outcomes of HBV arise over decades. Trials are usually for 1 – 2 years. So the trials usually rely on surrogate end points (eg E antigen seroconversion)
 - Treatment more likely to be effective if elevated ALT (ie need the immune system to assist with drug treatment)
 - Anti-virals → mutations; interferon does not
 - Risk of stopping treatment in cirrhosis is a post-treatment flare → decompensation
 - May be committing to life long treatment and 3 monthly blood tests (if ALT or HBV DNA going up then ↓compliance or resistance). Compliance is critical. *Education* is key
 - HBV carriers needing chemotherapy: immunosuppression → ↑HBV replication → rebound reactivation of hepatitis when chemo stops
- Treat if:
 - If ALT > 2 * normal or Viral load > 10E4 cpm

- Pre & post liver transplant
- Predictors of response: ↑ALT, ↓HBV, mild-moderate histological activity and stage, rapidity of fall on treatment
- HIV and HBV co-infection:
 - Durable responses rare → continued treatment the norm
 - Never use lamivudine as monotherapy → rapid HIV resistance
 - If need to treat the HIV → restore immune system → acute flare of HBV. Pre-emptive Lamivudine
 - If need to treat the HBV, and HIV doesn't need treatment, it's difficult. IFN OK, all the HBV antivirals at least theoretically promote HIV resistance → combination treatment often started
- **Nucleoside analogues:**
 - All target HBV polymerase. In theory no added potency with polytherapy, but....
 - Advantages:
 - Marked viral suppression (virtually 100%, more than IFN) → ↓necro-inflammatory activity and histologic improvement in fibrosis (frank cirrhosis not reversible) and improvement in liver function
 - After 2 years, HBeAg response (and even HBsAg response) is comparable to 1 year of PEG IFN
 - No side effects (ie better tolerated than IFN)
 - No risk of decompensating liver disease (cf interferon)
 - Better in older patients
 - Disadvantages:
 - Sustained responses are rarer ⇒ require long term therapy in most patients
 - Relapse if stop ⇒ indefinite therapy
 - Problems with resistance
 - Check viral load at 24 weeks, if not completely suppressed then high risk of resistance – need to add a 2nd agent
 - **Lamivudine:** \$140 per month
 - Purine L-nucleoside analogue: inhibits DNA polymerase. Potent inhibitor of HBV replications
 - As safe as placebo, no interactions, excreted unchanged
 - Safety data in pregnancy is best for lamivudine. Treatment in last month of pregnancy → ↓vertical transmission
 - Still the required first line treatment in NZ
 - In cirrhosis, treated with Lamivudine, progression is slower and hepatocellular carcinoma less common (less substantial but still significant if lamivudine resistance) (Ann Intern Med 2006;144:49-56).
 - Each year of treatment with lamivudine:
 - 17% HBe seroconversion (relapse still possible)
 - 15% – 30% get YMDD mutant (80% resistance by 5 years which then ↑risk of subsequent entecavir failure) → clinical deterioration, ↑ALT and ↑HBV DNA again (viral breakthrough => > 1 log over nadir, can have a fatal flare). Assays can detect the mutation, but usually a clinical judgement. **Check compliance.** Add in Adefovir (are supposed to just switch – combination only PHARMAC approved for cirrhosis, but combination better in all cases)
 - Probability is life long treatment. Don't stop unless viral load 0
 - Newer antivirals:
 - **Adefovir:** nucleotide analogue. \$670 per month. Requires Cr monitoring (nephrotoxic at HIV doses of 60 – 120 mg, dose in HBV is 10 mg). Not used as first line so only have data in lamivudine resistance. Effective in YMDD mutant. Does not suppress HBV DNA as much. In NZ, switching to Adefovir requires proven YMDD mutant. Adefovir prevents liver failure in Lamivudine resistance
 - **Entecavir:** an oral guanosine analogue nucleoside polymerase inhibitor. More potent and as well tolerated. Superior to Lamivudine. Much slower progression to resistance – 1.1% at 3 years (requires concurrent mutations at 2 if not 3 sites – but lamivudine resistant already have one or two of these). Active against lamivudine resistant HBV. Used first line in many other countries
 - In terms of fostering resistance, Lamivudine > adefovir > entecavir
 - No proven initial combination therapy. Current evidence is for monotherapy with add on if resistance
 - More in the pipeline
- **Interferon α:**

- Aim: get E antigen seroconversion in E antigen positive patients (ie HBeAg to anti-HBe)
- Advantages:
 - Definite term of therapy – 1 year
 - More likely to seroconvert than antivirals – however this later gain is only in 3 – 7% – is it worth subjecting everyone to IFN treatment for this gain?
 - Best for HBeAg +ive, ALT 2 * normal and non-cirrhotic, especially young woman (who won't want to take antivirals during a future pregnancy)
- Disadvantages:
 - Is given sc, associated with inconvenience, side effects and more expensive (\$100 a week)
 - Side effects: flu like symptoms, marrow suppression, emotional lability, autoimmune reactions (especially thyroiditis), alopecia, rashes, diarrhoea, numbness and tingling of the extremities
 - Is not as effective at suppressing HBV DNA
- Contraindications:
 - Major, uncontrolled depressive illness (history of, or well controlled, depression can be considered)
 - Renal, heart or lung transplant
 - Autoimmune hepatitis (exacerbated by interferon)
 - Untreated hyperthyroidism
 - No safety data in pregnancy
 - Not if cirrhosis
- Seroconversion → acute Hep B like elevation in ALT (?due to enhanced cytotoxic clearance of HBV-infected cells)
- PEG (pegylated) IFN has supplanted IFN (but only funded in NZ for Hep C):
 - PEG IFN- α 2b and α 2a
 - Once a week sc injection (as opposed to 3 times weekly for IFN) → less drug peaks → ?accounts for slightly better SE profile
 - But more neutropenia/thrombocytopenia
 - 10 – 20% seroconvert over the year of treatment, then a further 10 – 15% in the following year ⇒ 33% sustained response rate (ie remission, still suppressed 24 weeks after ceasing treatment. Can relapse if immunosuppressed)
- If they seroconvert then monitor. If not, consider starting Lamivudine
- “Consensus” Recommendations (eg from the American Association for the Study of Liver Diseases):
 - Immunotolerant:
 - For those with biochemical quiescence (ie normal ALT) the chance of serologic response is so low that antiviral therapy rarely achieves any near-term clinical benefit. Consider if risk factors for progression (eg age > 40, family history of HCC, etc)
 - Inactive “non-replicative” hepatitis B – undetectable HBeAg with normal ALT and HBV DNA < 10E4 copies/ml: No treatment
 - Active Flares/Immunoelimination phase (ie ↑ALT):
 - Detectable HBeAg, HBV DNA > 10E5 and ↑ALT (some say 2 * normal). Without therapy fibrosis progresses in approximately ¼ in a year. Such a clear cut indication that biopsy is optional
 - Undetectable HBeAg, HBV DNA > 10E4 and ↑ALT (some say 2 * normal) – ie lower threshold for HbeAg –ive (pre-core mutant)
 - PEG IFN, or Entecavir (better than Lamivudine) if IFN contraindicated
 - Early cirrhosis:
 - Compensated cirrhosis: some say treat regardless as it delays progression – some monitor those with HBV DNA < 10E4
 - Maybe IFN – but needs regular review – otherwise Entecavir
 - Decompensated cirrhosis: assess for transplant. Entecavir (Lamivudine in NZ), not IFN as treatment flair could → decompensation. Consider combination treatment – can't afford to develop resistant virus. Prevent reinfection post transplant with combined HBV immune globulin and an oral agent
 - Combined IFN and oral combined treatment suppresses HBV more profoundly during treatment, but no difference 6 months after stopping IFN, and more side effects ⇒ *no benefit from combined treatment*
 - Assess treatment after 12 weeks: if complete response (ie undetectable virus) continue treatment, if partial response (300 – 10,000 cpm) then keep same treatment and monitor closely, if inadequate response (>10,000 cpm) then alter treatment

- No value at any stage from prednisone – stimulates HBV – so pre-emptive treatment or close observation in transplant patients

Hepatitis C

- See Int Med Journal, 2004;34:324-37 (good article), Lancet 26 July 2008
- An enveloped ssRNA virus (used to be called non A non B). Does not integrate into host genome. 6 (?7) genotypes identified:
 - Genotype 1: 55%
 - Genotype 2 & 3: 35%
 - Genotype 4: Egyptians, Middle Eastern – endemic
 - Genotype 6,7: Vietnamese
- Genomic diversity and rapid mutation rate (envelop proteins are encoded by a hypervariable region) → neutralising antibodies short lived and vaccination so far ineffective
- Damage is caused by immune response – not virus
- Incidence peaked 1980 – 1990 in the US, has dropped by ~ 90% (mainly due to ↓IVDU infections)

Transmission

- Low infectivity: mainly transmitted by blood
- Transfusion (→ higher rates of cirrhosis from transfusion acquired disease ?2nd to bigger initial dose, rare since 1992)
- IV drugs (90% of cases)
- Sexual contact: 5% per high risk/year, 1.2% per monogamous/year (ie pretty rare)
- Maternal transmission to neonate in 5% of maternal infection (ie low risk), no risk from breast feeding
- Needle stick:
 - Transmission risk 1.8 – 3% for needlestick injuries
 - Highest risk if PCR positive source
 - PCR detects virus 10 days to 6 weeks after infection
 - ?immediate treatment (IFN α 2b) vs delayed (3 – 6 months)

Presentation

- Incubation to onset of symptoms average 7 weeks (range 3 – 20)
- Less than 1/3 have symptoms. Most diagnoses are incidental. Clinical illness (if any) lasts 2 – 12 weeks, never fulminant. Symptomatic patients have a higher likelihood of spontaneous clearance → monitor for 12 weeks before considering therapy
- ALT elevation to 300 – 800 with on going episodic fluctuation. > 1000 uncommon
- May present with end stage liver disease (e.g. may present for first time with variceal bleeding)
- Non-hepatic manifestations: arthritis, dry membranes, lichen planus (white plaques in mouth)
- Associations:
 - Increased incidence of T2DM by 11 fold
 - Essential mixed cryoglobulinaemia: circulating immune complexes containing HCV → arthritis, cutaneous vasculitis, occasionally membranous glomerulonephritis
 - Lymphoma: rare, usually B cell
 - HCC usually occurs after at least several decades, and usually only if cirrhosis. Test with ultrasound. ?Evidence that interferon for 6 months ↓risk of HCC
 - Porphyria cutanea tarda – blisters on skin (HCV precipitates most of this)

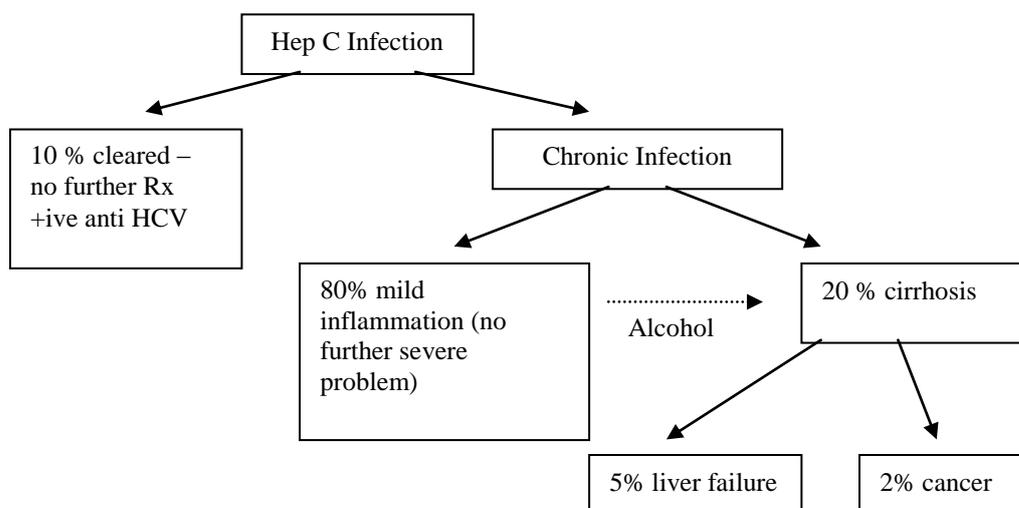
Viral Serology

- Acute HCV: Anti-HCV *doesn't appear for up to 3 months* – although newer generation assays become +ive during the acute hepatitis. May never be detectable in 5 – 10% of patients. False positives if rheumatoid factor. Exclude HAV, HBV, EBV, and CMV
- HCV RNA detectable by PCR within 1 – 3 weeks of exposure. Only way to diagnose acute infection. Rises rapidly to 10E6 – 10E8 per ml. Use if indeterminate Anti-HCV results, diagnosis in neonates and monitoring of interferon therapy
- 80% of chronically infected have persisting viraemia

Progression

- If self-limiting then HCV RNA undetectable and ALT back to normal in 1 – 3 months
- 75% go on to chronic infection (ie higher than adult acquired Hep B)

- Wide spectrum in chronic infection: 1/3 persistently normal ALT. Majority fluctuating ALT (\Rightarrow immune system active and causing hepatocyte death). ALT height doesn't correlate with histological severity. Acute – ALT 10 times normal
- Slow progression to cirrhosis occurs in ~ 20% over 10 – 20 years. Progression more likely in:
 - Longer duration of infection (probably the most important – other factors reflect this)
 - Alcohol
 - Older age
 - Advanced histologic stage and grade
 - Genotype of virus: effects interferon treatment. Type 1 and 4 (hyperendemic in Egypt) \rightarrow severe disease and poor response to interferon
 - More complex quasispecies diversity
 - Hepatic iron accumulation
 - Concomitant liver disorders: fatty liver, haemochromatosis
 - Level of ALT, level of HCV RNA, and severity of initial hepatitis do *not* predict eventual outcome
- Best prognostic indicator of progression to cirrhosis is histology (inflammation and fibrosis)



Management

- May have liver biopsy before commencing drug treatment to assist treat/don't treat decision – but often not
- Bottom line: can be cured in > 50%
- General:
 - Pre or post exposure prophylaxis (eg needlestick): none. Ig ineffective. Treat if established infection
 - No value at any stage from prednisone
 - \downarrow Alcohol
 - If severe pruritis, cholestyramine (bile salt-sequestering resin)
- Treatment indicated if:
 - Acute infection: Optimum drug regime and duration for acute HCV unclear, eg PEG IFN with ribavirin if type 1, or if virus fails to clear
 - Chronic infection:
 - Detectable HCV RNA and at least moderate grade and stage
 - Compensated cirrhosis can respond, although response rates lower. Survival benefit is controversial
 - Disease is more progressive with HIV coinfection, but response to treatment not so good
 - Intravenous drug users should have drug free urines (otherwise risk of reinfection)
- Higher sustained viral response if:
 - Genotype 2 and 3 (4 intermediate). 6 months as opposed to 1 years treatment is sufficient
 - Low viral load < 400,000 IU/ml
 - Younger < 40
 - Non-cirrhotic (cirrhosis is most predictive of a poor treatment outcome)

- Short duration of infection (< 5 years)
- Alcohol intake < 7 std drinks/week
- No other liver disease
- High ALT (although those with normal ALT respond just as well). Cirrhosis can ↓ALT so take care with it's relevance to treatment decisions
- ⇒ Those least likely to progress to cirrhosis are the ones most likely to benefit from treatment
- **Interferon α:**
 - *Contraindicated if on immunosuppressive treatment or decompensated liver disease*
 - PEG IFN has been shown to be twice as effective and ↓SE (↓flu-like symptoms and ↓depression) than IFN. Pegylation adds ethylene glycol → ↑molecular weight and slower absorption from the subcut site → longer half life. More expensive. Causes more profound neutropenia but no significant ↑ in infections. More injection site reactions
 - SE: more common with HCV than HBV (?viral response)
 - Common:
 - Flu like symptoms: fatigue (64%) ↓appetite, fever (46%), myalgia,, insomnia (40%), irritability (35%, warn family). Largely resolves after 1 – 2 weeks
 - Neutropenia: ↓dose. Not usually dangerous unless < 0.8
 - Thrombocytopenia: Reduce dose if < 50, stop if < 30
 - Serious:
 - Teratogenic
 - Depression (31%)/psychosis – care if prior history – not contra-indication – consider pre-emptive treatment
 - Given it up-regulates the immune system can also cause ↑autoimmune diseases (e.g. thyroid)
 - Exacerbation of IHD, epilepsy, diabetes
 - ~40% are PCR negative 6 months after completing treatment
- **Combination interferon/Ribavirin** (Purine nucleoside analogue)
 - Ribavirin ineffective on its own, but reduces likelihood of virologic relapse after achievement of an end-treatment response in combination
 - 800 mg od for genotypes 2 and 3, and 1000 – 1200 mg od for types 1 and 4
 - SE: teratogenic. Stored and transported in red cells. Dose dependent haemolysis ⇒ monitor HB and reticulocytes. Not in renal insufficiency. Nasal and chest congestion, pruritis, precipitation of gout
 - Combination therapy more difficult to tolerate than IFN monotherapy (high drop-out rates from combination arms of trials)
 - Regime:
 - Genotype 2 & 3: PEG IFNα and ribavirin for 24 weeks
 - Genotype 1, 4, 5, 6: Combination for 12 weeks, retest. If viral load ↓ to < 1 % (ie log 2 reduction) then treat for 48 weeks otherwise stop
 - Sustained virologic responses of ~ 55%. 46% SVR in genotype 1, 76% in genotype non-1
- Unlike Hep B, responses to treatment are not accompanied by ↑ALT
- Monitoring:
 - Viral response at 4 weeks predicts treatment
 - At 12 weeks:
 - Complete virological response = no HCV
 - Partial virological response = drop by log 2
 - No virological response → stop treatment
 - Most relapses occur within 6 weeks of stopping treatment. May still respond to re-treatment
 - Sustained viral clearance – also negative 6 months later
- Screening for HCC:
 - Unproven: most do it 6 – 12 monthly with USS. If abnormal then MRI or contrast CT
 - αFP lacks sufficient sensitivity and specificity so not recommended for screening (controversial)
 - Aim: detect HCC before lesions > 5 cm
 - Treatment: resection, transplantation or possible ablation
- Transplantation:
 - Hep C most common indication
 - Recurrent (usually mild) infection of graft. Treat only in the context of a trial
 - Survival: 65% at 5 years

- The future:
 - Protease (eg Teleprovir) and polymerase inhibitors in the pipeline
 - Very rapid resistance with monotherapy (eg 14 days)
 - Phase 3 trials underway of Teleprovir with IFN and ribavirin

Hepatitis D

- Defective virus that can only replicate in the presence of HBV infection (requires HBsAg as a viral coat – HBV doesn't need to be active)
- Common in Middle East, Pacific Islands
- Can co-infect or super-infect someone with hepatitis B
- Clinical:
 - Acute D on Acute B: eg super-infection in IV drug users. The main setting in which fulminant disease is seen
 - Chronic D on Chronic B: endemic in many parts of the world. Perinatal transmission
- Complications: Chronic hepatitis more common in HBV carriers who are also infected with HDV
- HBV vaccination also protects against HDV
- Treatment: ?efficacy of high dose long term IFN, experience with PEG IFN limited. HBV drugs don't work

Hepatitis E

- Faecally transmitted: contaminated food and water, but low viral load in faeces
- Epidemic in India, China, Russia, parts of Africa
- Usually young adults
- Higher mortality than HAV, up to 20% in pregnant women
- Usually jaundiced – may get FHF
- Test for IgM-specific antibody
- Does not progress to chronic hepatitis

Other Liver Disease

Non-alcoholic Fatty Liver Disease (Steatosis)

- Types:
 - NAFLD just fat – no hepatitis
 - NASH (Non-alcoholic steatohepatitis) does contain inflammation (fatty liver causing oxidative stress to hepatocytes and therefore damage). 30% → fibrosis (worse than Hep B & C)
 - Cryptogenic cirrhosis may have been NASH with the steatosis resolving once they became catabolic due to the cirrhosis
- Caused by:
 - Insulin resistance, obesity
 - Medications: glucocorticoids, estrogens, tamoxifen, amiodarone
 - Nutritional: starvation, protein deficiency (kwashiorkor)
 - Liver disease: Wilson disease, chronic HVC, jejunoileal bypass
- Pathology: adipocyte →
 - FFA → fat in hepatocytes
 - Proinflammatory cytokines → inflammation
 - Hyperinsulinaemia → fibrosis
- LFTs may be normal even in advanced NASH
- Exclude: alcohol, Hep B and C, iron studies and autoimmune diseases
- Liver biopsy: macrovesicular steatosis with mixed inflammatory infiltrate
- Treatment:
 - Weight loss (evidence mainly from post-bariatric patients) and exercise
 - Metformin: overall some benefit but limited evidence
 - Glitazones: conflicting results from trials
 - Bariatric surgery

Toxic and Drug-induced Hepatitis

- See NEJM 16 February 2006
- Principles of diagnosis:

- Latent period for onset after drug use is highly variable
- Other causes must be ruled out
- Injury may improve when drug stopped – but in severe cases falling enzymes may indicate impending liver failure, especially if declining function
- On rechallenge liver injury may occur more rapidly or not at all (adaptive tolerance)
- Rules of thumb:
 - Don't ignore vague symptoms (nausea, anorexia, malaise)
 - Jaundice that appears after drug induced hepatocellular injury is potentially serious
 - Report the injury
- Drug induced liver injury accounts for > 50% of fulminant liver failure:
 - ¾ due to paracetamol, anti-TB antibiotics also significant
 - 20% survival unless transplant

Types of reaction

- Direct toxic effect: dose dependent with early (eg 24 – 48 hours) clinical manifestations
- Idiosyncratic type:
 - Infrequent and unpredictable, not dose-dependent, and highly variable latency
 - If mild, may settle without withdrawal of the drug (ie liver “adaptation”)
 - Extrahepatic manifestations (rash, arthralgias, fever, leukocytosis, eosinophilia) in about 1/4
 - Used to be considered hypersensitivity reactions – but often now recognized as direct toxicity from metabolites. Eg mediated by polymorphisms in drug-metabolizing pathways
 - Immune mechanisms recognized through antibodies, eg anti-LKM2 to liver microsomes, or to metabolite-cellular component haptens
 - Prototypes are **halothane** (massive necrosis 7 – 10 days later) and **isoniazid** hepatotoxicity
- Some → chronic as well as acute liver injury (eg isoniazid → chronic hepatitis, methotrexate → cirrhosis)
- Zone 3 (perivenular – central vein) generally more sensitive to drug toxicity than zone 1 (periportal)

Mechanisms of injury

- Direct hepatotoxicity (hepatitis):
 - Eg free radical damage or membrane damage, activate apoptotic pathways, block biochemical pathways necessary for cellular integrity
 - Eg most drugs, which are water insoluble, undergo phase 1 reactions (P450 mediated oxidation or methylation reactions) followed by phase 2 reactions (glucuronidation or sulfation) to produce a water soluble form for biliary or renal excretion. Most drug hepatotoxicity is mediated by phase 1 metabolites
 - Eg:
 - Antibiotics: isoniazid, rifampicin
 - Anticonvulsants: phenytoin, carbamazepine
 - Antidepressants: fluoxetine, paroxetine
 - Anti-hypertensives: captopril, enalapril, losartan
 - Anti-inflammatory: indomethacin, diclofenac
 - Anti-psychotics: risperidone
 - **Isoniazid** (toxic and idiosyncratic reactions):
 - ~10% adults → ↑ aminotransferases over first few weeks (?an adaptive response)
 - ~1% adults → illness like viral hepatitis – possibly severe with up to 10% fatality (worse with ↑ age)
 - Enhanced by alcohol, rifampin, pyrazinamide, underlying Hepatitis B
 - ?worse in rapid acetylators
 - **Statins**:
 - Idiosyncratic mixed hepatocellular and cholestatic reaction
 - 1 – 2 % have asymptomatic, reversible elevations (> 3 fold) of aminotransferase activity
 - Larger proportion have lower and transitory increases
 - Some consensus groups say asymptomatic patients should not have LFT monitoring
- Hepatocellular Necrosis:
 - Yellow phosphorus, poisonous mushrooms
 - **Paracetamol/Acetaminophen overdose** (toxic reaction):
 - Usually requires > 15 – 25 gm
 - Usually AST > ALT (as with alcoholic hepatitis, but higher levels in paracetamol)

- Mainly metabolized by a phase 2 reaction → excreted in urine
- A small amount is metabolized by a phase I reaction (P450 CYP2E1) to toxic NAPQI, which is then bound to glutathione to become harmless. If ↑↑ levels, or glutathione deficient (eg overwhelmed or starvation) then ↑ toxic levels → oxidative injury → *centrilobular* inflammation
- Increased risk:
 - Enzyme induction (eg anticonvulsants)
 - Chronic alcohol (→ induces P450 2E1 ⇒ fraction of NAPQI produced is greater, and ↓glutathione due to chronic liver disease and malnutrition → toxicity with much lower doses especially with chronic paracetamol use). However, studies show *no significant increase in risk of chronic alcohol in single overdoses of paracetamol*. Appear to be at risk from multiple or supratherapeutic doses
 - Glutathione depletion: starvation, acute illness, chronic poisoning
 - Drugs inducing CYP 2E1 worsen prognosis: anticonvulsants (phenytoin and carbamazepine) and anti-TB drugs (isoniazid and rifampicin)
 - Malnutrition: in theory, but little evidence
- Decreased risk:
 - OCP
 - Probably acute alcohol in the absence of liver disease – possibly because alcohol competes with paracetamol for CYP2E1 (ie paracetamol for hangover OK)
 - Cimetidine inhibits P450s → ↓toxic metabolite [no evidence to support its use in treatment]
- No change in risk: Chronic liver disease in the absence of alcohol – doesn't accumulate with repeat administration ?protected by low P450 activity.
- Predictors of poor outcome: metabolic acidosis (Lactate > 3.5 mmol/L strong predictor of need for transplant), coagulopathy, encephalopathy, renal failure (also toxic to kidney). Not transaminases – if ALT is low it may be because they have run out of hepatocytes to kill
- Death occurs between 4 and 18 days post ingestion
- Treatment:
 - Intervention level: 150 mg/kg in acute ingestion (literature says 200 mg/kg, Auckland says 300 mg/kg)
 - NAC: donates sulphhydryl groups to bind NAPQI and stimulates glutathione production → ↓toxicity. If previous urticaria then slow infusion and premedicate with steroids and antihistamine – this is not a contraindication
 - Cochrane: activated charcoal best choice to reduce paracetamol absorption (but clinical benefit unclear). NAC seems preferable to placebo/supportive treatment (OR 0.65, CI 0.43 – 0.99). No evidence for haemoperfusion
- Cotrimoxazole:
 - Idiosyncratic reaction
 - Uniform latency of several weeks → hypersensitivity reaction
 - Attributable to the sulphamethoxazole component
- Steatohepatitis:
 - Most likely due to *mitochondrial toxicity*
 - Eg valproate (toxic and idiosyncratic)
 - **Reverse Transcriptase Inhibitors** and Protease Inhibitors:
 - Lots of reactions: mitochondrial toxicity (usually after > 6 months use), idiosyncratic steatosis, cholestatic
 - Indinavir: Inhibition of UDP-mediated conjugation → indirect hyperbilirubinaemia
 - Complicated to work out in coinfection with HIV and Hep B or C – HAART can affect natural history of both, and Hep B or C can affect drugs, etc
 - **Amiodarone**:
 - Toxic and idiosyncratic reactions
 - 50% have modest elevations of aminotransferases – may remain stable or diminish with continued use of the drug
- Sinusoidal lining cells → *venoocclusive disease*
 - Eg high dose cyclophosphamide, 5FU before SCT, Azathioprine
 - Presentation: hepatomegaly (acutely congested), weight gain, jaundice
 - Mortality 15 – 30%
- Cholestatic:

- Eg Interferes with bile salt exporting canalicular membrane transporters or canicular pump failure
- Mild: bland cholestasis eg estrogens (pruritis and jaundice after weeks to months, worse in those with recurrent idiopathic jaundice of pregnancy)
- Moderate: inflammatory cholestasis eg **augmentin**, erythromycin (idiosyncratic, over several weeks, resolve on withdrawal)
- More severe: sclerosing cholangitis or “Vanishing Bile Duct Syndrome”
- Severe: disappearance of bile ducts (ductopenic) eg carbamazepine, TCAs
- Also clopidogrel, cyclosporine, ezetimibe
- TPN: multifactorial cholestasis due to high carbohydrate load, lack of oral stimulation to bile flow, etc
- Others: flucloxacillin, ACEI, fluconazole, chlorpromazine
- 10 – 30% of cases continue for > 6 months. UDCA may control pruritis (no studies)
- Hypersensitivity: Rash, fever or eosinophilia. Eg Phenytoin

Treatment

- Withdrawal of agent (or observation)
- Supportive care
- Liver transplant
- Watch for other organ involvement (eg kidneys)
- Glucocorticoids or drugs for cholestatic toxicity are not effective

Autoimmune Liver Disease

Autoimmune Hepatitis (AIH)

- See NEJM 5 January 2006
- In the absence of autoimmune markers, is sometimes called idiopathic or cryptogenic chronic hepatitis. However, it’s increasingly recognized that non-alcoholic fatty liver (eg 2nd to ↑ rates of obesity) → cirrhosis, which → catatonic state with loss of steatosis on biopsy
- Cell mediated hepatocyte attack
- Presentation:
 - Typically either kid/adolescent with liver failure or a female aged 40 – 50 with ↑LFTs and fatigue
 - May be with recurrent bouts of acute hepatitis
 - Arthralgia involving the small joints
 - Aminotransferase levels in the thousands
 - Associated with thyroiditis, UC, T1DM, RA and coeliac
- Extrahepatic manifestations (eg arthritis, cutaneous vasculitis and glomerulonephritis) may be mediated by immune complex deposition
- Course:
 - 10 year survival is 80 – 90%
 - Mild disease or limited histologic lesions: progression to cirrhosis limited
 - Severe disease in 20%, with severe symptoms, aggressive histology
- Diagnosis:
 - Hypergammaglobulinaemia is common (2.5 g/l) – especially ↑**IgG** (most sensitive)
 - LFTs abnormal, but the level of rise does not correlate with the clinical severity of histology in individual cases
 - Antibodies absent in ~ 10%
 - Diagnosis of exclusion: exclude liver disease caused by genetic disorders, viral hepatitis, drug hepatotoxicity, alcohol
 - Typical histology: interface hepatitis, **plasma cells**
 - Likelihood increased by concurrent other autoimmune diseases
 - Response to treatment
- Patterns of disease:
 - Type 1:
 - Women (75%), marked hyperglobulinaemia, lupus features
 - Homogenous **ANAs** – **need at least 1:80**. Negative in 20% (ie ANAs don’t cause the disease)
 - Also autoantibodies against actin (**smooth muscle antibodies**) and atypical pANCAs
 - HLA DR3 and DR4 positive
 - ?Autoantigen is ASGPR
 - Treatment failure rare

- Type 2:
 - Most often children, female (95%), in Mediterranean populations
 - Linked to HLA-DRb1 and HLADQB1
 - **Anti-LKM1** (Anti-Liver Kidney Microsomal)– directed against P450 2D6 [Anti-LKM2 seen in drug-induced hepatitis and anti-LKM3 in hepatitis C]
 - ?Autoantigen is CYP-2D6
 - Treatment failure frequent, usually require maintenance treatment
- Type 3:
 - Neither ANA nor anti-LKM1
 - Antibodies to soluble liver antigen/pancreas antigen, directed against uracil-guanine-adenine transfer RNA suppressor protein
 - ?a severe form of type 1 (British combine them, Americans separate)
- Overlap with PBC
- Treatment:
 - Only demonstrated effect is for severe: eg AST > 10 times normal, or > 5 times normal with bridging necrosis or multilobular necrosis
 - RCTs show improvement with prednisone in 80% (some prefer prednisolone – the hepatic metabolite of prednisone)
 - Dose of eg 60 mg to achieve remission, tapering to 20 mg over 12 – 18 months. Can halve doses if concurrent azathioprine 50 -100 mg used (not effective in achieving remission on it's own)
 - Alternate day prednisone not effective
 - Improvement in symptoms in days to week, improvement in labs over weeks to months
 - Likelihood of relapse after stopping treatment ~ 50%. ?Continued azathioprine
 - Less treatment benefit in cirrhosis – as the inflammatory component has “burnt out” – unless continue elevated liver enzymes

Primary Biliary Cirrhosis

- See Lancet 5 July 2003
- Presentation:
 - Females 95%, median age ~ 50
 - Mostly asymptomatic finding on LFTs
 - **Fatigue** and pruritis prominent
 - Hyperpigmentation
 - Xanthelasma (xanthoma affecting the eye lids) and xanthomata (yellow nodule or papule made of foam cells): 2nd to disordered cholesterol metabolism
- Associations:
 - 75% have *Sjogren's syndrome*
 - 25% have serology of autoimmune thyroid disease
 - Other autoimmune associations, including CREST, RA, T1DM
- Labs:
 - ANA usually positive
 - **Antimitochondrial antibodies** > 1:40 present in about 90% (most sensitive marker), **M2** variant highly specific
 - ↑↑ALP and GGT, ↑ALT and AST. ↑Bilirubin once cirrhosis has developed. Bilirubin > 100 ⇒ < 2 year survival – refer for transplant
 - **IgM** typically raised
- Pathology:
 - Cause unknown. ? PDC-E2 auto-antigen
 - *Portal inflammation* and necrosis of cholangiocytes in **small and medium-sized bile ducts** – **intrahepatic** only
 - Progression from inflammation and lymphocytic infiltration of intrahepatic bile ducts → fewer ducts and proliferation of smaller bile ductules → fibrosis, starting with *periportal* and expansion to bridging fibrosis → cirrhosis
 - Liver biopsy probably not indicated – patchy disease so many not be helpful for staging
- Histologic features of chronic cholestasis: cholate stasis, copper deposition, xanthomatous transformation of hepatocytes and irregular biliary fibrosis. Patchy process so biopsy may misrepresent stage
- Treatment:

- Ursodeoxycholic acid (UDCA) 10 – 15 mg/kg. A secondary bile acid, usually produced in the bowel by action of bacteria → negative feedback on production of bile. No convincing trial evidence but considered to slow progression, best used early. SE in ~ 10%, worse pruritis, diarrhoea, headache
- Treat cholestatic pruritis with cholestyramine, narcotic receptor antagonists (naltrexone) and rifampin, gabapentin (itch is a pain pathway), plasmapheresis. Antihistamines not very helpful
- Bone protection: risk of osteoporosis (also osteomalacia, but less so despite the logic of vitamin D malabsorption)
- Decompensated liver failure → liver transplantation (better survival than for most other indications). Mild histologic recurrence common, clinically significant recurrence rare
- Dyslipidaemia
- ↑Cardiovascular risk

Primary Sclerosing Cholangitis

- Presentation: patient with UC presenting with cholestatic LFTs +/- pruritis (PSC can precede UC)
- Pathology:
 - Diffuse segmental *inflammation* of the entire biliary tree – **large bile ducts** (both **intra-** and **extra-**hepatic)
 - Bile duct proliferation, ductopenia and *fibrous* cholangitis (onion skinning in cross section)
 - Can overlap with Autoimmune Hepatitis
- Diagnosis:
 - No diagnostic serology, but pANCA is positive in ~ 65%, ANA common
 - Requires biliary tree imaging – usually MRCP (but less sensitive for small duct disease), also ERCP – shows multifocal stricturing involving both the intrahepatic and extrahepatic tree (“*beaded appearance*”). Stent dominant strictures, brushings to exclude cholangiocarcinoma. Gall bladder and cystic duct involved in 15%
 - Over 50% have UC – if PSC diagnosed should have a colonoscopy. Clinical course of UC and PSC are independent
- No proven treatment. Glucocorticoids, methotrexate, cyclosporin are not effective. Cholestyramine may help control itch. UDCA improves liver tests but no effect on survival demonstrated
- Median survival 10 – 12 years
- Complications:
 - Cancer: cholangiocarcinoma in 10% (↑ risk by 60 – 90 fold, usually in first 2 – 3 years, no evidence for surveillance but often done, difficult to diagnose, CA 19-9 and PET may be useful), 20 fold risk of pancreatic ca and 10 fold risk of colon cancer if colitis (⇒ annual screening)
 - Transplant if 2 or more episodes of cholangitis or end-stage disease. Normal liver transplant does duct to duct anastomosis. In PSC do duct to duodenum anastomosis

Alcoholic Liver Disease

- See Alcohol and Drug for other effects of alcohol and treatment of Alcohol Dependence, page 485
- Progression:
 - Fatty liver: present in > 90% of binge and chronic drinkers. Reversible with cessation. Progression beyond this stage requires poorly defined additional risk factors. Those known include:
 - Female sex
 - HCV
 - ↑↑alcohol consumption
 - Alcoholic Hepatitis/Steatohepatitis:
 - Presentation: Tender hepatomegaly, fever, jaundice +/- ascites +/- encephalopathy. Mortality ~40% – scoring systems predict mortality (eg Glasgow Alcoholic Hepatitis Score)
 - Labs: ↑↑bilirubin and GGT, modestly elevated AST > ALT (both less than 400)
 - Given difficulty of distinguishing from sepsis, transjugular liver biopsy may be helpful
 - Histology: hepatocyte injury with focal areas of hepatocyte necrosis, beginning around the *central vein*
 - Management: culture blood, urine, ascites, IV thiamine and vitamin K, IV cef and met, anti-TNF appears to protect against HRS, if HRS then albumin/terlipressin, nutrition, prednisone if culture negative...Pentoxifylline?
 - Potentially reversible with alcohol cessation
 - Cirrhosis (in only 6 – 10% of heavy drinkers):
 - Usually micronodular (nodules < 3 mm)

- Not apparent that this reverses with abstinence
- Portal hypertension (→ ascites) or esophagogastric varices ⇒ decompensated cirrhosis
- In most, a co-factor is required to develop advanced disease: genetic predisposition, haemochromatosis carrier, HCV, HIV, HBV, poor nutrition, obesity....
- Labs:
 - More modest AST and ALT rises than other causes of fatty liver
 - AST/ALT > 1, usually > 2
 - ↑TGS and ↑cholesterol
- Pathology is multifactorial – includes:
 - Toxic protein-aldehyde adducts
 - Oxidative stress
 - Immunologic activity
 - Pro-inflammatory cytokine release
- Prognosis of severe alcoholic liver disease is dismal – mortality of ~60% at 4 years
- Treatment:
 - Stop drinking. LFTs often worsen in first 2 – 3 weeks of withdrawal given loss of alcohol’s immunosuppressive effect
 - No proven benefit from different nutritional approaches
 - Limited paracetamol to < 2 g/day
 - Severe alcoholic hepatitis (prothrombin time > 5 s, anaemia, albumin < 25, bilirubin > 137, renal failure and ascites):
 - Restricted to a discriminating function (DF) > 32: calculated from total bilirubin + excess over normal prothrombin time * 4.6
 - Prednisone 40 mg for 4 weeks followed by tapering reduces 28 day mortality from 84 to 65%
 - TNF inhibitor → improved survival, mab specific for TNF → ↑infection.....
 - Transplantation:
 - Similar survival to other causes
 - After defined period of abstinence (? 6 months)
 - Child’s C + psychosocial stability
 - Recidivism rate 10 – 30%

Metabolic Liver Disease

- Cystic Fibrosis has liver effects – a small percentage have a form of biliary cirrhosis
- α1-antitrypsin Deficiency: Intracellular hepatocyte accumulation of α1AT → cirrhosis

Haemochromatosis

- See page 417 for Iron Metabolism
- Inappropriate Fe absorption → ↑tissue deposition → progressive Fe overload → end organ damage + fibrosis
- Presentation:
 - Classically 40s – 60s Caucasian male
 - 1 in 250
 - Women present later (?protective effect of menstrual blood loss and pregnancy)
 - Expression modified by comorbidities – eg alcohol, HCV, and possibly obesity
 - Major features: cirrhosis (usually affects liver first, hepatocellular carcinoma a late complication), DM (esp if family hx of DM), arthritis (usually after 50, see page 274), cardiomyopathy, hypogonadotropic hypogonadism, “bronzing” – slate grey hue to skin from ↑melanin and Fe
- Causes:
 - Genetic: AR
 - Most commonly HFE gene on chromosome 6:
 - Codes for a receptor on liver cells – detects ↓Fe and → ↑hepcidin → ↑intestinal uptake
 - Usually C282Y, very low penetrance – as little as 1% *homozygotes* may express significant iron overload, risk in heterozygotes is negligible. Some populations are up to 10% heterozygotes
 - Also H63D mutations, but little clinical significance
 - Several others found, all rare, eg transferrin receptor 2 (TfR2), hepcidin (HAMP) – net result of all the mutations is ↓hepcidin (which usually blocks ferroportin, a channel that allows iron efflux from iron storage sites) → ↑Fe absorption and ↑uptake by reticulo-endothelial cells
 - Secondary:

- Iron-loading anaemias: Thalassemia major, sideroblastic anaemia, chronic haemolytic anaemias, transfusional iron overload
- Dietary iron overload
- Chronic liver disease: Hep C, advanced alcohol cirrhosis, non-alcoholic steatophepatitis, porphyria cutanea tarda
- Ferritin can also be elevated in C282Y-H63D and C282Y-wild type heterozygotes, in fatty liver disease, alcohol and any inflammatory condition, but these rarely develop tissue iron overload. If high ferritin 2nd to ?alcohol, biopsy and stain for Fe in hepatocytes – pathognomic for haemochromatosis
- Diagnosis:
 - Iron studies: ↑↑ferritin (if mild ↑ monitor 6 – 12 monthly and do gene test if progressive rise), ↑transferrin saturation > 50%, ↑plasma iron, ↓total iron-binding capacity
 - Liver biopsy/MRI showing iron overload. Biopsy if > 40 years and ferritin > 1,000 – less than this associated with much reduced risk of cirrhosis
- Management:
 - *Family screening*
 - If < 45 years and normal ALT and ferritin < 500 then no biopsy, just phlebotomy. If ferritin > 1000 or significantly abnormal biopsy then biopsy for staging
 - Weekly phlebotomy of 500 ml blood until ferritin *normal* (make take 1 – 2 years) – ↑ 5 years survival from 33 to 89%
 - Support of damaged end organs
 - Role of Deferasirox (iron chelating agent) not established. Effective in thalassaemia and secondary iron overload

Wilson Disease

- AR disorder caused by mutation (> 200 found) to the ATP7B gene on chromosome 13, a membrane bound copper-transporting ATPase, eventually 100% penetrant
- 1 in 30 – 40,000
- Impairs biliary copper clearance → accumulation and toxicity – especially liver and brain
- Presentation:
 - Liver disease (eg presenting with hepatitis): *usually late teens, but up until 50s*. Mimics any liver disease
 - Neurologic: *onset in 20s (but up to 60s)* – Behavioural symptoms → Basal ganglia (Parkinson symptoms, dystonia) of any part of the body. Memory loss, migraines, seizures. MRI/CT shows basal ganglia and brainstem changes
 - Amenorrhea
 - Acute haemolytic anaemia
- Diagnosis:
 - Screening: normal LFTs in an adult give comfort
 - Consider if high bilirubin, relatively low ALP and AST >> ALT
 - *Low cerulo-plasmin and serum copper* – not overly sensitive – screening test – can be low in other liver diseases, and low-end normal in Wilson’s
 - Kayser-Fleisher ring: golden-brown copper pigment at the periphery of the cornea (best seen under slit lamp) – present in 99% with neurologic symptoms but only 30 – 50% with hepatic illness. May also be present in cholestatic liver disease
 - Raised 24 hour urine collection pretty good
 - Cu content of liver biopsy the gold standard
- Treatment:
 - “Decoppering”: penicillamine → ↑renal excretion, but side effects in 30%. Trientine (a chelating agent) also used
 - Maintenance: zinc in high dose (induces erythrocyte metallothionein which complexes ingested copper, then lost with intestinal cell shedding, etc) + low copper diet (low shell fish, nuts, liver, chocolate, mushrooms)
 - Emergency transplant (which corrects that metabolic defect) if acute liver failure or decompensating cirrhosis (otherwise high mortality)

Porphyria

- Genetic abnormalities in one of the eight enzymes in the biosynthetic pathway from glycine + succinyl-CoA to heme. Either AD or AR, but porphyria cutanea tarda (PCT, the most common) is usually sporadic
- Classified as either hepatic or erythropoietic depending on primary site of overproduction of their porphyrin precursors
- Presentation:
 - Hepatic porphyrias (notably PCT): latent before puberty with variable penetrance afterwards (?due to adult levels of steroids). Blistering cutaneous photosensitivity rash, neuropathic abdominal pain, peripheral motor neuropathy (axonal degeneration), mental disturbances. Symptoms can include ileus, hypertension, urinary retention, tachycardia, *not* fever. Precipitated by steroids, some drugs (heaps of them), and some foods
 - Erythropoietic porphyrias: birth or early childhood. Cutaneous, photosensitive rash
 - Also classified as acute or cutaneous depending on presentation
- Diagnosis: measurement of porphyrin precursors ALA and PBG or porphyrins in urine (or plasma, erythrocytes or faeces), followed by demonstration of the specific enzyme deficiency
- Examples:
 - Hepatic:
 - Acute Intermittent Porphyria
 - Porphyria Cutanea Tarda – deficient hepatic URO-decarboxylase. Blistering skin lesions on back of hands. Susceptibility factors: hepatitis C, HIB, excess alcohol, elevated iron levels, estrogens
 - Erythropoietic Porphyrias:
 - X-linked Sideroblastic Anaemia: signs of anaemia in childhood
- Various treatments

Cirrhosis

- See NEJM 15 April 2004, Lancet 8 March 2008
- See page 349 for assessment of liver biopsy and cirrhosis scores
- Pathogenesis:
 - With continuous injury, the usually quiescent hepatic stellate cells and portal or perivenular fibroblasts are activated
 - Myofibroblasts proliferate and produce excess extracellular matrix (ECM)
 - Initially this is counterbalanced by removal of ECM by enzymes, eg specific matrix metalloproteinases (MMPs). Chronic damage favours fibrogenesis over fibrolysis
 - A long list of targeted treatments to halt progression are being developed, eg antifibrotic drugs. However, progress is hampered by definition of validated endpoints for trials – no short-term surrogate markers for liver fibrosis
- Risks of cirrhosis increased if:
 - Regular, moderate alcohol consumption
 - Age > 50
 - Male gender
- Diagnosis:
 - US, CT and MRI not sensitive enough to detect cirrhosis → requires biopsy
 - Bilirubin rises later than GGT and ALP, an important predictor of mortality
 - ↑Prothrombin time
 - ↑IgG due to shunting of portal blood past the liver carrying intestinal antigens
 - ↓Na: ↑ADH (vasopressin 2 receptor effect)
- Complications of cirrhosis:
 - Portal Hypertension: Gastroesophageal varices, splenomegaly, ascites, spontaneous bacterial peritonitis – see page 369
 - Hepatorenal syndrome
 - Hepatic encephalopathy
 - Malnutrition
 - Coagulopathy: factor deficiency, fibrinolysis, thrombocytopenia, malabsorption of vitamin K → ↓factors 2, 7, 9, 10
 - Bone disease: ↓vitamin D and ↓Ca ingestion/absorption
 - Haematologic abnormalities:

- Anaemia: folate deficiency, hypersplenism, direct toxicity (alcohol), GI blood loss
- Thrombocytopenia: Hypersplenism, ↓hepatic thrombopoietin production
- Hepatocellular carcinoma:
 - Various screening guidelines – generally recommend one screening (US, CT, MRI) per year. αFP not recommended now because of poor sensitivity and specificity
 - See page 398

Clinical features

- Anorexia, fatigue, weight loss, muscle wasting: catabolic metabolism 2nd to anorexia
- Jaundice: due to ↓hepatocyte excretory function, when bilirubin > 20 mg/L → itch → excoriations, ↓fat soluble vitamins
- Hypertrophic osteoarthropathy/clubbing: due to hypoxaemia due to right to left-shunting or portopulmonary hypertension
- Vascular and fluid effects:
 - Caput medusae: Prominent veins radiating from the umbilicus in portal hypertension, due to reopening of the umbilical vein to shunt blood from the portal vein
 - Umbilical hernia
 - Hydrothorax
 - Widened pulse pressure and hyperdynamic circulation
 - Hepatic bruit and/or cachexia in metastatic or hepatocellular liver disease
- Endocrine effects:
 - Gynaecomastia: due to ↑ conversion of androstenedione to oestrogens and ↓degradation of these by the liver
 - Hypogonadism: direct toxic effect of alcohol or iron → signs of hyperestrogenaemia – gynaecomastia, testicular atrophy, loss of male pattern hair distribution
 - Spider angiomas (superficial tortuous arterioles occurring on the arms, face and upper torso filling from the centre outwards – unlike telangiectases) and palmar erythema: 2nd to raised oestradiol because of ↓liver degradation
 - T2DM: (in 15 – 30% with cirrhosis): abnormal glucose and insulin metabolism
- Skin:
 - White nails: hypoalbuminaemia
 - Hyperpigmentation in advanced chronic cholestatic disorders (eg PSC)
 - Slate-grey colour to skin in haemochromatosis
 - Xanthelasma and tendon xanthomata from ↑lipids
 - Mucocutaneous vasculitis with palpable purpura from Hep C cryoglobulinaemia
 - Kayser-Fleischer rings in Wilson's disease: see page 367
- Dupuytren's contracture: fibrosis of the palmar fascia
- Neurological:
 - Asterixis: flapping tremour of the body and tongue: disinhibition of motor neurons in hepatic encephalopathy
 - Encephalopathy: can be subtle – change in sleep patterns or personality, irritability, mental dullness – usually triggered by a medical complication – GI bleed, over-diuresis, uraemia, infection, constipation, narcotic analgesics. Test with trail-making test: connect numbers 1 – 25 in sequence, normal range 15 – 30 s
- Foetor hepaticus (sweat ammonia smell): volatile dimethylsulfide, especially in portosystemic shunting

Portal Hypertension

- Present in > 60% with cirrhosis
- Caused by:
 - Prehepatic: portal or splenic vein thrombosis (2nd to polycythaemia, essential thrombocytosis, deficiencies in Protein C and S, antithrombin, factor V Leiden), massive splenomegaly
 - Intrahepatic (95% of the total):
 - Presinusoidal: schistosomiasis, congenital hepatic fibrosis
 - Sinusoidal: cirrhosis, alcohol hepatitis
 - Postsinusoidal: venoocclusive syndrome
 - Post hepatic:
 - Budd-Chiari syndrome: Obstruction to hepatic veins → zone 3 sinusoidal distension. Associated 60% with myeloproliferative diseases, also SLE, coagulopathy
 - Inferior vena caval webs, cardiac causes (eg severe RHF, constrictive pericarditis)

- Diagnosis:
 - Wedge to free gradient. Pressure in hepatic vein via jugular vein, with and without balloon inflated, not used clinically. Portal HTN > 10 mmHg
 - Ultrasound suggestive: portal vein dilation or collaterals
- **Oesophageal Varices:**
 - 5 – 15% of cirrhosis patients develop varices per year. At risk if wedge-to-free gradient > 12 mmHg (normal ~ 5)
 - 1/3rd of those with varices develop bleeding, mortality of 15 – 20% per bleed → primary prophylaxis needed
 - Clinical entities:
 - Variceal: oesophageal, gastric, ectopic (duodenal)
 - Portal hypertensive gastropathy
 - Gastric Antral Vascular Ectasia (GAVE)
 - Treatment:
 - Routine screening. All cirrhotics should be scoped
 - No evidence for primary prevention (ie before varices seen) ⇒ Don't prescribe until varices
 - If identified then:
 - Non-selective beta blockade: RCTs of propranolol (rebleeding NNT = 5, mortality NNT 14) or nadolol. Lower risk of bleeding, decreased bleed related mortality, overall survival less clear cut. Aiming for a 25% heart rate reduction (or 60 – 70, whichever is higher). Nitrites reduce portal hypertension and ↓ episodes of bleeding compared to β-blockers but are associated with ↑ overall mortality for unknown cause
 - Endoscopic variceal ligation. Generally don't band asymptomatic varices – it just shifts the pressure and the varices to the fundus of the stomach. Sclerosing varices is less in favour due to complications (eg infection from injecting through unclear area)
 - Acute bleeding:
 - Avoid large volumes of crystalloid – blood and FFP are the priorities to correct coagulopathy. Platelets if platelet count < 60
 - Terlipressin (long acting analogue of vasopressin. RCT show is the best – ↓ mortality, others just ↓ transfusion requirement) or Octreotide: 50 µg bolus followed by 50 µg/h by infusion for 1 – 2 days if significant cardiovascular disease
 - Antibiotic prophylaxis in GI bleed 2nd to cirrhosis: Cefotaxime 1 gm or Ciprofloxacin. Not gentamicin, prone to hepato-renal syndrome. Culture blood, urine and ascetic fluid
 - Vitamin K 10 mg iv daily + thiamine 100 mg iv daily if alcoholic aetiology
 - Consider twice daily phosphate enemas to prevent/reduce encephalopathy
 - Prevention of rebleeding:
 - Band ligation + β-blockers the most effective treatment (similar to TIPS and nearly as good as shunt surgery). Banding alone better than β-blockers alone
 - If the varices extend into the proximal stomach then band ligation less successful. Consider transjugular intrahepatic portosystemic shunt (TIPS). SE encephalopathy in up to 20% (so contraindicated if pre-existing encephalopathy). Consider as a bridge to transplantation
 - Can also use a skin glue
- **Ascites:**
 - Clinically detected when > 1.5 litres fluid
 - Pathophysiology:
 - ↑intrahepatic resistance → portal HTN → ↑local production of vasodilators (mainly NO) → *splanchnic arterial vasodilation* → alters intestinal capillary pressure and permeability → retained abdominal fluid
 - In advanced cirrhosis, the splanchnic arterial vasodilation is so pronounced → under-filling of arterial circulation → activation of RRA system → sodium retention → ↑intra and extracellular fluid volume
 - Exclude malignant or infectious causes
 - Hypoalbuminaemia → ↓colloid pressure
 - → ↑splanchnic lymph
 - Assessment:
 - Paracentesis:
 - Serum to ascites albumin gradient (SAAG). If high then ascites (ie transudate), if low consider infection or malignancy (ie exudate)

- Cell count and culture
- Acid-fast smear and cytology
- Measure urinary sodium and protein
- Need to consider for liver transplant. 5 year survival with ascites is 30 – 40 %, compared with 70 – 80% with transplant
- Treatment: Don't want too fast a diuresis otherwise pre-renal failure
 - Sodium restriction: usual intake 6 – 8 gm, ideally restrict to 2 gm/day
 - Fluid restriction to 1 litre/day only if dilutional hyponatraemia
 - Spironolactone: 100 – 200 mg/day, can titrate up to 400 – 600 mg/day
 - Frusemide: 40 – 80 mg/d titrating up to 120 – 160 mg/day
 - In large volume ascites, RCTs show large-volume paracentesis followed by maintenance diuretics better than diuretics alone, but requires plasma expanders if removing > 5 litres to reduce recurrence of ascites, hepatorenal syndrome or dilutional hyponatraemia. Albumin probably the best plasma expander but controversial
- Complications:
 - Hepatic hydrothorax – usually right side. Fluid leaks through any hole in the diaphragm
 - Spontaneous Bacterial Peritonitis:
 - E. Coli, strep viridans, staph aureus, Enterococcus sp. Presumed caused by bacteria migrating to intra-abdominal lymphatics. If more than two consider perforation
 - Diagnosed if absolute neutrophil count > 250/mm³
 - Treat with albumin to prevent 30% risk of hepatorenal syndrome
 - Incidence significantly increased with variceal haemorrhage → prophylactic treatment with norfloxacin or co-trimoxazole

Other complications of Cirrhosis

- Hepatorenal Syndrome:
 - Normal kidneys but cirrhosis or liver failure
 - Functional kidney failure in 10% of people with advanced liver failure. 2nd to severe vasoconstriction in the renal arterial circulation → Kidney hypoperfusion 2nd to splanchnic vasodilation and arteriovenous shunting
 - No proteinuria or haematuria, no obstruction and urinary sodium < 10 mmol/l
 - Type 1 is acute (poor prognosis), Type 2 is chronic and stable
 - Phases of kidney dysfunction in cirrhosis:
 - Pre-ascitic: compensated Na retention
 - Ascites: Sodium reabsorption, mostly in distal convoluted tubule (so spironolactone good)
 - Full hepato-renal syndrome: proximal convoluted tubule Na retention
 - Treatment: stop diuretics, midodrine (oral α -agonist), noradrenaline (iv infusion), vasopressin analogues, octreotide and albumin (used but no RCTs). Not dopamine or prostaglandins
 - Kidney function recovers after liver transplant
- Hepatic Encephalopathy:
 - Due to gut derived neurotoxins not cleared by the liver due to vascular shunting and reduced hepatocyte mass. Includes ammonia, but little value in measuring given the poor correlation with severity
 - Check asterixis
 - Brain oedema often found on scanning
 - Acute episodes often triggered by precipitating events: hypokalaemia, other electrolyte disturbances, infection (including SBP), \uparrow dietary protein load, GI bleed, etc
 - Treatment:
 - Treat precipitants: infection, bleeding, electrolyte imbalance, sedatives
 - Not usually protein restriction (change to past practice) – downside of malnutrition outweighs benefit
 - Lactulose, aiming for 3 stools/day → colonic acidification → \uparrow nitrogenous elimination
- Hepatopulmonary Syndrome:
 - See NEJM 29 May 2008
 - \downarrow oxygenation 2nd to marked pulmonary vascular dilation in the setting of portal hypertension (with or without cirrhosis)
 - Most practical diagnostic test is an echo after injection of agitated saline into a peripheral vein. If the bubbles make it through to the left heart, then the lung vascular bed is abnormally dilated
 - No treatment other than transplant – consider if PO₂ < 60 mmHg

Liver Transplantation

- See also page 349 for scoring systems
- Terminology:
 - Orthotopic transplant: remove the old one and put the new one in the same place
 - Living donor transplant: transplant of right lobe (adults) or left lobe (children) – small proportion of cases. Not insignificant peri-operative risks to the living donor
 - Split liver grafts: divide a liver into two for an adult and a child, or to allow altruistic donation
 - All have cholecystectomy. Usually biliary anastomosis, Roux-en-Y for PSC or revision
- 1 year survival has improved from ~30% in the 1970s to 90% (3 year survival 80%) today due to:
 - Better donated organ procurement and preservation
 - Refinements in surgical treatment
 - Better immunosuppressive treatment
 - Better patient selection and timing (of critical importance – if you leave it too late the patients peri-operative risk rises)
- Indication:
 - Chronic or acute liver disease that is progressive, life threatening and unresponsive to medical therapy
 - Hep C: reinfection is universal, progressive and usually resistant to antivirals → cirrhosis in 20 – 30% at 5 years
 - Hep B: prophylactic use of HBV → success rates similar to non-viral indications
 - Hepatocellular carcinoma: for single tumours < 5 cm or three lesions < 3 cm
 - Emergency:
 - Liver failure from fulminant HBV (rarely HAV), seronegative hepatitis, drugs (eg paracetamol, isoniazid), Wilson's disease, hepatic artery thrombosis of graft, acute rejection of graft
 - King's criteria for fulminant Hepatic Failure:
 - Paracetamol induced: pH < 7.3 or INR > 6.5 and Cr > 300 and grade 3 or 4 encephalopathy
 - Non-paracetamol-induced: INR > 6.5 and 3 of: unfavourable aetiology (seronegative hepatitis, halothane, idiosyncratic drug reaction), bilirubin > 300, 10 > age > 40, PT > 50, time of jaundice to encephalopathy > 7 days
- Contraindications:
 - Absolute: basically about bad comorbidities (infection, CHD, pulmonary disease, metastatic cancer, etc), active drug or alcohol use
 - Relative contraindications: age > 70, portal vein thrombosis, HIV (can be successful if excellent control of infection), renal disease, previous extensive hepatobiliary surgery (→ fibrosis, and getting the old liver out is the hardest part)
- Organ matching: matched for ABO blood group and organ size. Not HLA matched and HLA antibodies don't preclude transplantation
- Difficult surgery: portal hypertension, coagulopathy, median duration 8 hours, during the anhepatic phase problems with hypoglycaemia, hypocalcaemia, hypothermia...
- Post-operative complications: infection, acute rejection (methylprednisolone), leaks, hepatic artery thrombosis (especially in PSC)....
- Immunosuppression:
 - Prednisone: used for 3 months, long term if autoimmune hepatitis caused the transplant
 - Cyclosporin:
 - The first breakthrough in the 1980s – little used now days
 - Calcineurin inhibitor blocking activation of T cells → ↓IL 2, 3, 4 and TNFα
 - SE: dose dependent renal tubular injury and renal artery vasospasm. Also HTN, ↑K, tremour, hirsutism, glucose intolerance and gum hyperplasia
 - Tacrolimus (originally FK506):
 - Isolated from a Japanese soil fungus, streptomyces tsukubaensis
 - Now preferred to cyclosporin:
 - Same mechanism but 10 – 100 times more potent
 - Reduced acute rejection, refractory rejection and chronic rejection. Patient and graft survival the same, but simplified management given ↓ rejection hassles
 - Oral absorption more predictable
 - More toxic, more likely to be discontinued for adverse events

- SE: nephro and neurotoxicity (ie similar to cyclosporin ⇒ not used together). HTN, dyslipidaemia, weight gain, T2DM. Less hirsutism and gingival hyperplasia. ↑risk of lymphoproliferative disease
- OKT3:
 - Monoclonal antibodies to T cells
 - Used if acute perioperative renal failure precludes tacrolimus or cyclosporin, or in acute rejection unresponsive to methylprednisone pulses
 - Increased infective risk
- Mycophenolate Mofetil:
 - Non-nucleoside purine metabolism inhibitor derived from *Penicillium* species
 - Given better performance over azathioprine in renal transplant, now used in liver transplant
 - SE: diarrhoea, leucopenia, anaemia
- Azathioprine:
 - May or may not be used depending on the transplant centre
 - SE: lymphopenia, allergic reaction, hepatitis, pancreatitis, photosensitivity, skin cancers with prolonged use
- Prophylaxis:
 - Valganciclovir for 6 – 12 weeks as CMV prophylaxis
 - Cotrimoxazole until prednisone < 10 mg as PJP prophylaxis
 - Lamivudine long term for HBV, along with intermittent HBIg
- Rejection: difficult to distinguish from recurrent hepatitis C, biliary obstruction, primary graft non-function, vascular compromise, CMV infection, drug hepatotoxicity, recurrent primary disease....

Pancreas

Acute Pancreatitis

- Inappropriate activation of trypsinogen to trypsin + delayed elimination from pancreas → autodigestion
- Causes:
 - Cholelithiasis and alcohol most common:
 - Markers with a high likelihood ratio > 10 of a stone in the common bile duct are cholangitis, jaundice, US evidence of common bile duct stones
 - Likelihood ratio of > 4 for: dilated common bile duct on US and ↑ bilirubin
 - Amongst others:
 - Post ERCP: meta-analysis of peri-procedural NSAID shows RR 0.36
 - Infection: mumps, viral hepatitis, coxsackie, opportunistic
 - Medications: azathioprine, sulphonamides, thiazides, frusemide, valproate...
 - Connective tissue disease
 - Penetrating peptic ulcer
 - Duct obstruction from tumour
 - Inherited pancreatitis:
 - Hereditary Pancreatitis: AD, 80% penetrance, recurrent mild attacks from 5 years, chromosome 7q35, mutation in trypsinogen gene PRSS1. Genetic test available
 - SPINK1 mutation: recently described in adolescents with chronic pancreatitis
 - CFTR gene mutations
 - Autoimmune pancreatitis: very rare. May present with a mass (differential cancer). Associated with Sjogren's, PBC, RA. Raised serum IgG4. Responds to steroids
- Signs include:
 - Erythematous skin nodules due to subcut fat necrosis
 - Cullen's sign: Blue discoloration in the periumbilical area due to haemoperitoneum
 - Turner's sign: Blue-red-purple or green-brown discoloration of the flanks due to tissue catabolism of haemoglobin
- Diagnosis includes:
 - Lipase: rises in parallel with amylase, both together ↑ diagnostic yield
 - Calcium: low in 25%
 - ↑TGs: may also cause spuriously normal amylase
 - USS: more sensitive than CT/MR for biliary/gallstones
 - MRI: may detect early duct disruption not seen on CT
 - EUS: may be most accurate test for biliary pathology

- Severity markers (Ransom criteria): Severe ≥ 3
 - At presentation:
 - Age > 55
 - WCC > 16
 - Glucose > 10
 - LDH > 350
 - AST > 250
 - During first 48 hours:
 - Urea rise > 10
 - Serum Ca < 2.0
 - Base excess > 4
 - PaO₂ < 60 mmHg
 - Albumin < 32
 - Estimated fluid sequestration $> 6L$
- Treatment:
 - Aggressive fluids, O₂, initially NBM, insulin if sugar high
 - No benefit from antibiotics in severe pancreatitis (although this could be a result of the antibiotic regime trialled....). Ann Int Med 2005;143:347 – 354
 - No evidence for octreotide
 - Analgesia: pethidine causes least spasm of sphincter of Oddi
 - ERCP in < 72 hours for gallstone disease
 - Necrosis: consider debridement – delay if possible. Antibiotics if infected (in 40 – 60%, typically after 1 – 2 weeks)
 - Pseudocysts develop in 15% after 1 – 4 weeks

Chronic Pancreatitis

- SAPE: sentinel acute pancreatitis event. Once initial event has occurred, higher risk of subsequent pancreatitis
- Smoking cessation at diagnosis of chronic pancreatitis reduces risk of calcification at 6 years (OR 0.56)

Background

- Epidemiology of cancer:
 - Age most significant risk factor – 2/3rds cancer over the age of 65
 - Relative incidence of different types (US figures):
 - Males: prostate (29%), Lung (15%), Colorectal (10%), Bladder (7%), Lymphoma (4%)
 - Females: breast (26%), Lung (15%), Colorectal (11%), Endometrial (6%)
 - Deaths due to cancer:
 - Male: Lung (31%), Prostate (9%), Colorectal (9%), Pancreas (6%), Leukaemia (4%)
 - Female: Lung (26%), Breast (15%), Colorectal (10%), Pancreas (6%), Ovary (6%)
- Cancer trials:
 - Phase I: Always in people with incurable cancer. Aiming to establish the maximum tolerated dose – looking at toxicity in humans not looking for tumour response
 - Phase II: Assess tumour response
 - Phase III: Endpoint is survival compared with standard treatment. Often use progression free survival as a surrogate for overall survival. Evidence for the correlation between PFS and OS in ovarian and colon cancer only
 - Phase IV: post marketing studies (new uses, treatment combinations)
- Staging Systems:
 - System of the International Union Against Cancer and the American Joint Committee on Cancer (AJCC)
 - T (Tumour): size of tumour
 - N (Nodal involvement): usually 0 or 1 – can be more elaborate
 - M (metastases): either 0 or 1
 - International Federation of Gynaecologists and Obstetricians uses FIGO
 - Ann Arbor originally for Hodgkin's disease
 - In addition to tumour burden, physiologic reserve of the patient is significant in terms of outcome – measured by:
 - Karnofsky Performance Status: 0 = dead, 100% = asymptomatic
 - Eastern Cooperative Oncology Group (ECOG): 0 = well, 4 = needs help with ADLs
- Tumour Markers:
 - CEA: Colorectal
 - CA-125: Ovarian
 - CA 19-9: Pancreatic
 - PSA: Prostate
 - CA 15-3 and 27.29: Breast
 - α FP: non-seminomatous germ cell tumours, hepatoma
 - β HCG: Seminoma (NOT NSGCTs)
 - LDH: Lymphoma, melanoma
- Screening: common biases are lead time, length-biased sampling and selection
- Prevention:
 - Physical activity \rightarrow \downarrow colon and breast Ca
 - High fat diets correlated in epidemiological studies with breast, colon, prostate and endometrium (not proven to be causative, Women's Health Initiative diet intervention group did not show \downarrow breast cancer over 8 years follow-up)
 - BMI associated (causality not proven) with cancers of colon, breast, endometrium, renal cell and oesophagus

Cancer Genetics

Cell Cycle

- M \rightarrow G1 [can exit and re-enter from G0] \rightarrow [Restriction point – past this committed to division] \rightarrow S \rightarrow G2 \rightarrow M
- Conserved from yeast to humans
- Interphase = G1, S and G2, Mitosis = M (spindle)
- G1 and G2 are intermediate phases: checking, a chance to grow, etc

- Each stage has check points – can arrest progression at any of these in response to an abnormal cellular state (eg DNA damage) as it is vital to ensure the genome is only replicated once and that chromosomes are equally divided between daughter cells
- Regulated by mammalian cyclin-dependent kinases (Cdk)
- G1 → S transition:
 - Preparation for synthesis
 - Minutes to hours long, depending on preparation index
 - Characterized by hyperphosphorylation of Rb and activation of E2F1 to E2F, and loss of activity of key cyclin dependent kinase (CDK) inhibitors. Rb normally stops progression. Inhibition of Rb (eg by 16Ey in cervical cancer) → “unintended” progression
 - 90% of human cancers have a defect affecting this pathway
 - Radiation and chemo lead to arrest in normal cells while they repair. Malignant cells continue to progress to S phase despite unrepaired damaged DNA and so die
 - ATM (Ataxia Telangiectasia Mutation) turns on p53 after damage (as do hypoxia, chemo agents, etc)→ turns off progression
 - p53 mediates G1 checkpoint via p21CIP1 and the S checkpoint via DADD45. It can also initiate apoptosis
- S Phase:
 - DNA synthesis from 5’ to 3’ end and repair of errors
 - Telomerases facilitate the net retention of tail end information
- G2 to M transition:
 - Initiated by accumulation of MPF and up-regulation of APC/C (→ destruction of CDK-1)
 - Chromosome condensation, spindle assembly, microtubule production and attachment, separation of the chromatids
 - Radiotherapy works on cells in this transition – therefore a good place for chemotherapy to arrest progression
 - Topoisomerase unwinds DNA. If it’s inhibited (eg by etoposide, irinotecan..) than arrest
- M Phase: checkpoint induced if chromosomes not being equally divided between daughter cells. The Spindle-checkpoint. Taxanes and Vinca Alkaloids active here
- DNA repair: Complex area. Many mechanisms. Potential therapeutic target. Eg if DNA damage is repaired by 2 different pathways, and one is knocked out in a cancer (egBRAC1 mutant → loss of homologous recombination) then blocking the other pathway (eg base excision repair with PARP) will kill that cell

Chromosomal Abnormalities in Cancer

- See NEJM 14 August 2008
- Two main classes: balanced and unbalanced chromosomal rearrangements
- Two functional consequences:
 - Formation of a chimeric fusion gene with new or altered activity
 - Deregulated expression of a structurally normal gene

Genetic Mutations in Cancer

- Epithelial cancers = carcinomas, non-epithelial (mesenchymal) cancers = sarcomas
- Clonal proliferation differentiates neoplasm from hyperplasia
- Multiple cumulative mutations are required for a fully malignant phenotype, including subversion of apoptotic pathways
- Somatic DNA mutations → unrestrained cellular proliferation
- Types of genetic mutations:
 - Oncogenes and Tumour-suppressor genes control cell division and apoptosis
 - **Oncogenes:**
 - Promote cell growth, become uncontrolled in cancer – takes single allele mutation (dominant)
 - 3 mechanisms of activation:
 - Point mutation: gain-of-function mutations of oncogenes are more unlikely
 - DNA sequence amplification: over-expression of gene product
 - Chromosomal rearrangement: eg translocations in myeloid and lymphoid tumours – especially lymphoid tumours – they normally rearrange their DNA to generate antigen receptors. Eg Philadelphia chromosome in CML: ABL oncogene on chromosome 9 translocated to be in proximity to the BCR on chromosome 22 → expression of ABL-

BCR gene product → activates signal transduction pathways for cell growth independent of normal external signals. Imatinib blocks the activity of BCR-ABL

- Multiple Endocrine Neoplasia type II: AD gain of function mutation in proto-oncogene RET on chromosome 10 (NB loss of function in this gene causes Hirschsprung's Aganglionic Megacolon). See page 76
- The products of oncogenes include transcription factors, growth factors, growth factor receptors, and signal transducers, and chromatin remodelers (chromatin is made up of histones – not just DNA packing proteins but involved in the regulation of gene expression)
- **Tumour-suppressor genes:**
 - Restrains cell growth – loss of function – takes mutations to both alleles – “two hit hypothesis” (recessive)
 - Mutations either point mutations or large deletions
 - Familial cancers have a pre-disposing loss-of-function mutation in one allele of a tumour-suppressor gene or a caretaker gene. Eg:
 - Colon Cancer (see page 394): Familial adenomatous polyposis and Hereditary non-polyposis colon cancer
 - In cervical Cancer, human papillomavirus proteins E6 and E7 inactivate tumour suppressor genes p53 and pRB
- Solid tumours are generally highly aneuploid – abnormal number of chromosomes
- Metastasis requires the acquisition of the ability to break through the basement membrane, migrate through the extracellular matrix and into the vascular compartment, repeat this process at a remote sign and generate new blood vessels
- Cancer cell growth:
 - Tumour growth is exponential in small tumours. Growth fraction starts at 100%, declines down to 1 – 4% with a tumour burden of $1 - 5 \times 10^9$ tumour cells
 - Larger tumours become very heterogeneous → treatment selects for drug-resistant variants of the original clone
 - Cancer cells often have defective cell cycle checkpoints → progression from one stage to the next of the cell cycle without waiting for the normal extra-cellular signalling events
 - Eg loss of p53:
 - Found in > 50% of cancers
 - Enables tumour cells to escape cell cycle arrest or apoptosis, despite the accumulation of DNA damage (eg then more resistant to radiotherapy)
 - Li-Fraumeni Familial Cancer Syndrome has a germline mutation of this gene (chromosome 17)
 - Telomerase:
 - DNA polymerase is unable to replicate the tips of chromosomes, resulting in a loss of telomeres with each replication cycle → growth arrest (replicative senescence) by p53 and pRB. In p53 and pRB defects cells bypass this growth arrest – but the cell still dies because of damage to DNA because the absence of protective telomeres leads to catastrophic DNA re-arrangements
 - Most tumours reactivate telomerase – can rebuild the telomere by adding TTAGGG repeats onto the 3' end of the chromosome → indefinite cell proliferation. This only happens normally in stem cells (eg haematopoietic, gut and skin epithelium and germ cells) which rely on extensive cell proliferation
- Signal transduction pathways:
 - Many tyrosine kinases act at the apex of signalling pathways, and are transmembrane proteins (receptor tyrosine kinases – RTK) – potential therapeutic targets eg Herceptin (see page 408)
 - Ras is a pathway “downstream” from RTK activation involved in cell cycle regulation

Epigenetic Changes

- Changes that alter the pattern of gene expression across at least one replication cycle, but aren't caused by changes in DNA – eg methylation, modification of histones
- DNA methylation is one of the layers of gene expression control
- Methylation occurs in Cytosines that precede Guanines, called CpGs. CpG-rich regions are known as CpG islands
- Hypermethylation of the CpG islands in the promoter regions of tumour-suppressor genes is a major event in the origin of many cancers
- Being potentially reversible, are therapeutic targets eg demethylation agents → re-expression of silenced genes and restoration of function

Immunology

- See NEJM 19 June 2008
- Immune system triggered by tumour specific antigens and tumour associated antigens (molecules expressed differentially by cancer cells and normal cells)
- Leads to “immuno-editing” with one of three results: eliminated cancer, selection of less immunogenic tumours and tumour escape
- Tumours evade immune response by:
 - Suppressing immunosuppressive cytokines (TGF- β , IL-4, IL-6, IL-10)
 - Cell signalling disruption (Loss of MHC 1, STAT-3 signalling loss in T cells, etc)
- A long term study of immunosuppressed solid organ transplant recipients showed incidence of cancer 7.1 times higher – but 26 times higher for leukaemias and lymphomas, 21 times for head and neck and 9 times for lung cancer
- Immunotherapy approaches:
 - Antibodies and T cells (ie passive immunity)
 - Vaccines: no cancer vaccine has had sufficient clinical activity to warrant its approval but research ongoing (including in combination with chemotherapy)

Treatment Modalities

- See PDQ (Physician Data Query) – database maintained by the National Cancer Institute – search CancerNet at www.icic.nci.nih.gov/health.htm for a vast range of protocols
- See www.adjuvantonline.com – very good calculator of the benefits of adjuvant treatment for a number of solid cancers
- Response to treatment: (RECIST criteria – Response Evaluation Criteria in Solid Tumours)
 - Complete response: disease gone
 - Partial response: > 50% reduction in the sum of the products of the perpendicular diameters of all measurable lesions
 - Progressive disease: any new lesion of > 25% in the sum of the products of the perpendicular diameters
 - Stable disease: everything else
- Modalities of treatment:
 - Surgery: about 40% of patients cured by surgery
 - Radiotherapy:
 - Cancer cells have a ↓ability to repair sublethal DNA and other damage
 - Radiation: breaks DNA and creates free radicals that do other damage
 - Hypoxic cells and non-dividing cells are more resistant to radiation damage
 - Rad (radiation absorbed dose) = 100 erg of energy per gram of tissue
 - 1 Gray (Gy) = 100 rad
 - Most curative regimes are delivered once a day, 5 days a week in 150 – 200 cGy fractions
 - Toxicities:
 - Thyroid failure, cataracts and retinal damage, damage to salivary glands, mediastinal radiation → 3 * risk of MI
 - Late effects: pericarditis, lung fibrosis, radiation enteritis, development of 2nd solid tumour (rate of about 1% per year from the 2nd decade after treatment. For mantle radiotherapy, the highest risk is subsequent breast cancer)
 - More fractions less quickly usually gives better control – bigger separation of dose-response curves for normal vs cancer tissue (normal tissue has time for DNA repair)
 - Adjuvant chemotherapy = what you give when you’re not sure there’s any cancer left. Improves survival by eradicating micro-metastases

Chemotherapy Agents and Other Drugs

- MTD = maximal tolerated dose, lower than the DLT (dose-limiting toxicity)
- Types:
 - Conventional chemotherapy agents: mainly target DNA or segregation of DNA as chromosome in mitosis
 - Targeted agents (biologicals): aimed at a particular molecular target
 - Hormonal therapies: target oestrogen and androgen function
 - Biologic therapies: alter host immune response

- Resistance occurs 2nd to cells not being in the appropriate phase of the cell cycle to allow drug lethality, or from ↓uptake, ↑efflux, metabolism of the drug or alteration of the target (mutation or over expression). Eg P-glycoprotein is an ATP dependent efflux pump (MDR1 = multidrug resistance)

Direct DNA interactive Agents

- Alkylating agents:
 - Presumed action: modify bases in DNA → broken or cross linked DNA which can't replicate and/or trigger apoptosis
 - Share similar SEs: myelosuppression, alopecia, gonadal dysfunction, mucositis, pulmonary fibrosis, late neoplasms (especially leukaemia)
 - **Cyclophosphamide:**
 - Liver dysfunction impairs drug activation, primarily renal excretion
 - Crosses BBB
 - Causes chemical haemorrhagic cystitis 2nd to acrolein, prevent with pre-hydration and mesna
 - SE include Pulmonary fibrosis, *alopecia, nausea, marrow* (relative platelet sparing), amenorrhoea, azospermia, ↑K, and in high doses cardiac toxicity. Gonadal failure is related to cumulative dose and age (the closer to menopause the worse)
 - **Chlorambucil:** SE: myelosuppression, azospermia, nausea, *pulmonary toxicity*
 - Also: mitomycin-C, Temoxolomide (used in GBM)
- Platinum Compounds
 - Form DNA adducts and crosslinks ("staple" the 2 strands together)
 - Renally cleared
 - Area-under-the-curve to guide dosing
 - **Cisplatin:**
 - Requires hydration plus forced diuresis with mannitol to prevent kidney damage – but still risk of ↓kidney function
 - Radiosensitiser
 - SE: *myelosuppression, nephrotoxicity*, ↓Mg → ↓Ca and tetany, stocking and glove *neuropathy*, *hearing loss, nausea +++*, alopecia
 - **Carboplatin:** used in ovarian cancer. Linear relationship between CrCl and elimination – dose according to GFR. *Very myelosuppressive. Less nausea than cisplatin*
 - **Oxaliplatin** (newer drug): used in colorectal cancer (both adjuvant and palliative), SE *neuropathy* (permanent and maybe painful, may not occur until after finishing treatment) and *cold-related dysaesthesia* (eg pseudolaryngopharyngeal dysaesthesia, no cold water or ice during infusion otherwise throat cramps, use gloves in the fridge). Less nausea, less nephrotoxic
- Antitumour antibiotics:
 - Bind to DNA directly and cause local free radical damage in any stage of cell cycle → arrest usually in S-phase or G2
 - **Bleomycin:** binds to DNA and Fe²⁺ → produces radicals. Little myelosuppression. Reduce in renal failure. SE fever, facial flushing, Raynaud's, rarely pulmonary fibrosis – *requires regular pulmonary function testing*
 - Anthracyclines (below) also sometimes classed as antitumour antibiotics – includes

Indirect DNA-Interacting Agents

- Antimetabolites:
 - Anti-intracellular metabolism → depletion of purine and pyrimidine pools for DNA/RNA processing
 - Methotrexate: inhibits dihydrofolate reductase. High-dose regimes with leucovorin rescue (calcium folinate – ie folinic acid) of normal marrow and mucosa used in osteosarcoma and haematopoietic neoplasms. ↑toxicity in renal failure. Collects in 3rd spaces and leeches back → prolonged *myelosuppression. Pulmonary toxicity, neurotoxicity, nephrotoxicity*
 - 5-fluorouracil (5FU). Inhibits thymidylate synthetase. Is incorporated into DNA and also RNA. Myelosuppression after short infusions, stomatitis after long infusions. Rare *CNS toxicity* (prominent cerebellar signs) and endothelial toxicity (thrombosis, including PE and MI), *diarrhoea. Can induce vasospasm – care in angina*
 - Capecitabine: an oral agent, metabolized to 5-FU. Enzyme for final of 3 steps is thymidine phosphorylase (present in higher concentrations in tumour cells) → higher concentration of active drug in malignant tissue → better SE profile. Dose limiting SE are hand-foot syndrome (palmar-plantar erythrodysesthesia – give a treatment break and restart on lower dose), mucositis, diarrhoea

- 6-Mercaptopurine (6MP): treatment of AML. Metabolized by xanthine oxidase → dose reduction with allopurinol
- Gemcitabine: NSCLC, bladder and ovarian cancer and mesothelioma in the palliative setting, down the list for breast ca. SE *pulmonary toxicity, thrombocytopenia*. Also itchy nodule rash
- Hydroxyurea: inhibits ribonucleotide reductase → S phase block
- Mitotic spindle inhibitors:
 - Damage the mitotic spindle and intra-cellular scaffolding tubulin proteins
 - Spindle assembly: Vinca alkaloids
 - **Vincristine**
 - Binds to tubulin: especially toxic in M phase
 - Metabolized by the liver.
 - SE: Powerful vesicant, frequent glove and stocking *neuropathy*, also other neuropathy (jaw pain, paralytic ileus, urinary retention, SIADH)
 - Vinblastine: SE *myelosuppression*
 - Spindle disassembly:
 - Paclitaxel and docetaxel (derived from the needles of the European Ewe tree) are **Taxanes**: “Stabilise” microtubules which then function abnormally – inhibits usual disassembly during cell cycle progression. Also inactivates bcl-2. Used in ovarian, breast, Kaposi’s, lung cancer. Premedication with dexamethasone and anti-histamines prevents common *hypersensitivity reactions* to a compound in the formulation. SE *alopecia, short duration myelosuppression*
- Topoisomerase interacting agents: stops DNA uncoiling or super-coiling ⇒ DNA polymerase can’t work
- Active against Topo I: **Irinotecan** (bowel cancer, SE *alopecia, myelosuppression, diarrhoea*) and Topotecan
- Active against Topo II:
 - **Etoposide**: plant derivative, sourced from the Mandrake root. SE nausea, vomiting, potentially severe diarrhoea, *myelosuppression* and *alopecia*
 - Actinomycin-C
 - **Doxorubicin (Adriamycin)**:
 - An **anthracycline** antibiotic, doesn’t cross BBB
 - SE *myelosuppression, alopecia, nausea, mucositis, acute arrhythmias or chronic CHF*
 - Powerful vesicant (causes blisters) – tissue necrosis 4 – 7 days after extravasation – give in a rapidly flowing line
 - Liver metabolism to an active metabolite, primary biliary elimination → ↓ in liver impairment
 - High peak plasma doses → 10% incidence of cardiomyopathy (worse with concurrent Trastuzumab/Herceptin)
 - Contraindications include: CHF, cardiomyopathy, irradiation of the heart. *Requires regular cardiac monitoring (baseline gated heart CT or echo to assess LVEF)*

Hormonal Agents

- Steroid hormone receptor-related molecules, alter gene transcription and in some tissues induce apoptosis
- Glucocorticoids: used in pulsed high dose in leukaemias and lymphomas → tumour apoptosis
- Tamoxifen and Aromatase inhibitors – page 407
- DES manipulation: see page 403

Targeted Therapies

- Represent a big change in oncology – treatment not just by damaging DNA, but:
 - Targeting mutated proteins
 - Assessing mutations to predict outcomes → different therapy or dose decisions
- Haematopoietic Neoplasms: Lots – see Haematology Chapter
- **Tumour angiogenesis** (see NEJM 8 May 2008):
 - Tumour growth requires recruitment of blood vessels and vascular endothelial cells to grow beyond 0.5 mm²
 - Stimulated by hypoxia, inflammation and altered gene expression in tumour cells. Numerous pro and anti angiogenesis factors – successful tumours tip the balance to pro-angiogenesis
 - One mediator is **VEGF** (vascular endothelial growth factor)
 - In normal adult restricted to placenta, endometrium and to wound healing

- Secreted by tumour cells → disrupts intercellular junctions. Binds VEGFR-2 receptor activating endothelial-cell proliferation.
- Many actions, many isoforms, at least 5 receptors. VEGFR1 and R2 are key in angiogenesis
- Two types of anti-VEGF:
 - Avastin/bevacizumab
 - Antibody inhibitor of VEGF, \$4,000 per dose twice monthly
 - Has had positive response in trials in colon, lung and breast cancer – but not in recurrent breast, nor pancreatic cancer
 - Not effective as a single agent (except perhaps renal cell)
 - Not used in squamous cell lung cancers due to haemoptysis
 - SE impairs wound healing (long T ½ of 3 weeks, need to delay surgery for 6 weeks), HTN, proteinuria (rarely → nephrotic syndrome), haemorrhage, →↑VTE, arterial thromboembolic events (CVA/MI), 1.5% GI perforation in colon ca (?2nd to tumour necrosis)
 - Contraindicated if uncontrolled HTN, proteinuria, history of bleeding, anticoagulants, bowel carcinomatosis
 - Oral small-molecule-receptor tyrosine kinase inhibitors (RTKIs): **sorafenib** (continuous BD dosing) and **sunitinib** (given 4 weeks on, 2 weeks off). Target multiple receptor tyrosine kinases, including VEGF receptors and platelet-derived growth factor (PDGF) receptors. Benefits in renal cell cancer and maybe hepatocellular cancer. Modest survival benefits. Costly and toxic side effects (HTN, cardiovascular complications, diarrhoea, weight loss, rash hand-foot skin reactions). US\$ 5,400 per month
 - SE: HTN (treat aggressively), reversible posterior leukoencephalopathy (rare, altered conscious state), proteinuria/renal dysfunction (usually just monitored), haemorrhage due to tumour disruption (eg lung and renal)
 - Emerging evidence of other angiogenic factors:
 - Motesanib diphosphate: oral inhibitor of VEGF and platelet derived growth factor receptors. Induced partial regression in phase II trials in progressive differentiated thyroid cancer
 - PlGF (placental growth factor) binds to VEGFR-1 resulting in recruitment of macrophages and other bone marrow-derived proangiogenic cells. Combination therapy with anti-VEGFR-2 and VEGFR-1 antibodies better than either alone
 - Angiopoietins: involved in endothelial cell differentiation and stabilisation
- **Epidermal growth factor receptor (EGFR) family:**
 - See NEJM 13 March 2008
 - Belongs to the HER family of protooncogenes (which also includes Her2/neu)
 - EGFR pathway leads to ↑angiogenesis, ↑cell proliferation, ↓apoptosis
 - Two types of agents block the EGFR signalling pathway:
 - Anti-EGFR antibodies block ligand-induced EGFR tyrosine kinase activation via the extracellular receptor, are highly selective. IV treatment. Eg cetuximab (Erbix) and panitumumab (Vectibix). SE acne-like rash – severity is correlated likelihood of efficacy – the worse it is the better it is
 - Small-molecule EGFR tyrosine kinase inhibitors block the intracellular tyrosine kinase pathway. Oral. Relatively selective. Eg Erlotinib (Tarceva), Gefitinib (Iressa):
 - 4 EGFR antagonists are currently available for the treatment of 4 metastatic epithelial cancers: non-small-cell lung, squamous-cell carcinoma of the head and neck, colorectal and pancreatic
 - Work in those with an activating mutation in the tyrosine kinase domain – but these cases are the minority
 - Secondary mutations in EGFR have been observed in those who develop resistance
- Ideally, need to be able to monitor the genetics tumour, but this is difficult (eg in lung cancer) due to access → developing technology to extract circulating tumour cells from blood to identify those with activating genes and with drug resistance (NEJM 24 July 2008)

Biologic Therapy

- See NEJM 19 June 2008
- Cancer represents a failure of the immune system
- Most require an active response (eg re-expression of genes or antigen expression) from tumour cell or host (as opposed to targeted treatments which just try to zap things)
- Cell mediated immunity:
 - Allogeneic T cell transferred to host – eg in bone marrow transplants

- Autologous T cells removed from the host, manipulated and given back. Enables T cells to recover from tumour-induced T cell defects
- Tumour vaccines to boost T cell immunity
- Antibodies: In general, antibodies are ineffective at killing cancers – many patients have antibodies to their tumours but these don't affect progression
- Cytokines:
 - IFN α : can induce partial responses in follicular lymphoma, hairy cell leukaemia, CML, melanoma, and Kaposi's. SE flu-like symptoms, myelosuppression, depression, induce autoimmune disease
 - IL-2: \uparrow growth and activity of T and NK cells. Melanoma and renal cell cancer. SE capillary leak, ARDS, hypotension, impaired liver and renal function...

Complications of treatment

- Incidence of depression ~ 25%. Evidence of benefit from complex psychosocial interventions (see Lancet 5 July 2008)
- Nutrition: chemotherapy more toxic if malnourished – but how to assess and intervene unclear
- Diarrhoea: eg with fluorouracil. Maintain hydration and electrolytes, and loperamide (4 mg initially then 2 mg every 2 hours until 12 hours without stool). Octreotide may help
- Mucositis: due to damage to the proliferating cells at the base of the mucosal squamous epithelia or intestinal crypts. Mild cases: topical anaesthetics and barrier preparation. Palifermin (keratinocyte growth factor) if severe
- Alopecia: cosmetic remedies
- Gonadal dysfunction:
 - Cessation of ovulation and azoospermia usual with alkylating agents and topoisomerase regimes. Amenorrhoea will usually recover if < 30, may not if > 35. Premature menopause common
 - Males with mechlorethamine and procarbazine containing regimes for Hodgkins are sterile
 - Fertility usually returns after regimes with cisplatin, vinblastine or bleomycin for testicular cancer
 - Pregnancy: most harmful in first trimester, most OK following this (except antimetabolites – especially antifolates)
- Recurrence: Studies of breast, melanoma, lung and colon cancer and lymphoma have not supported regular monitoring – asymptomatic relapses are not more salvageable than symptomatic relapses (Harrison's p 484)
- Leading causes of death: infection, respiratory failure, hepatic failure, renal failure

Alopecia

- Cyclophosphamide
- Irinotecan
- Cisplatin
- Adriamycin
- Taxanes
- Etoposide

Pulmonary Toxicity

- Busulfan
- Melphalan
- Chlorambucil
- Mitomycin-C
- Gemcitabine
- Methotrexate
- Bleomycin

Myelosuppression

- Highly myelosuppressive:
 - Methotrexate
 - Cyclophosphamide
 - Etoposide
 - Irinotecan
 - Cisplatin
 - Anthracyclines
 - Taxanes (short duration)

- Busulphan
- Vinblastine
- Thrombocytopenia: Busulfan, carboplatin, mitomycin-C (lifetime cumulative dose correlates to Haemolytic Uraemic Syndrome)
- Order of impact:
 - Polymorphonuclear leukocytes, half life 6 – 8 hours
 - Platelets, half life 5 – 7 days. Low levels uncommon 2nd to chemotherapy, but may be low in haematopoietic marrow infiltration. Can be increased with some cytokines (eg IL-6, IL-1, thrombopoietin) but clinical benefit not proven
 - Red blood cells, half life 120 days. Transfuse if < 80 g/L
- Maximal neutropenia after 6 – 14 days with anthracyclines, antifolates and antimetabolites

Other

- Neurotoxicity: Cisplatin, oxaliplatin, methotrexate, 5-FU, Vincristine
- Nephrotoxicity: Cisplatin, methotrexate (high dose, cf rheumatology dose OK)
- Diarrhoea: Irinotecan, 5-FU, Capecitabine
- Cardiac toxicity: 5-FU, anthracyclines

Infection

- Febrile neutropenia:
 - One temp > 38.5 or 3 readings > 38.0 in 24 hours
 - < 500 neutrophils the risk of death is markedly raised, little risk > 1000
 - Exam: check skin all over, catheter sites, dentition, mucosal surfaces, perirectal and genital orifices
 - AB with pseudomonas cover, eg ceftazidime
 - Wgtn Antibiotic Guidelines for neutropenic sepsis: Imipenem IV 1 gm q6h. There is no survival advantage over broad spectrum β -lactam with a narrower spectrum β -lactam combined with an aminoglycoside – which has higher adverse event rates, especially nephrotoxicity
 - If febrile after 4 – 7 days add an antifungal (eg Candida, aspergillus and occasionally fusarium)
 - G-CSF and GM (granulocyte – macrophage)-CSF (more restricted use) used preventatively and therapeutically (although no evidence of benefit in febrile neutropenic patients)
- Vaccination:
 - See page 324
 - Various regimes
 - Need to re-immunize for diphtheria, tetanus and polio after stem cell transplant

Hypercalcaemia of Malignancy

- Presentation: delirium, tiredness, anorexia
- Correct for albumin
- Causes:
 - Humoral effect from primary tumour from PTHrH: Lung Adenocarcinoma (*not* small cell), prostate, breast, myeloma
 - Vitamin D mediated in lymphoma, TB, sarcoid (steroids only help in this class)
- Severity:
 - Mild: < 3.0 mmol. Often don't require treatment. Monitor
 - Moderate: 3.0 – 3.5. Consider treatment if asymptomatic
 - Severe: > 3.5. Treat
- Biggest risk factor for renal impairment is from osmotic dehydration
- Treatment:
 - IV fluids: may require > 4 litres to rehydrate
 - Bisphosphonates
 - Calcitonin: short term effect only in resistant treatment
 - Avoid thiazides. No role for diuretics in malignant hypercalcaemia in multiple RCTs

Nausea with Chemotherapy

- See NEJM 5 June 2008 (good review article)
- Highly emetogenic drugs:
 - Cyclophosphamide
 - Ifosfamide
 - Busulfan (at high dose)

- Cisplatin
- Actinomycin-D
- Low emetogenic:
 - Gemcitabine
 - 5-FU
 - Capecitabine
- Moderately emetogenic: everything else
- Younger and female patients at greater risk. High alcohol consumption lowers risk
- Categories:
 - Acute: within 24 hours, most common
 - Delayed: 1 – 7 days after treatment (rare, but common with cisplatin). Complete control with ondansetron in 32% (no better than placebo), 40% for dexamethasone + ondansetron, 30% for dexamethasone + metoclopramide
 - Anticipatory: beforehand. Rates are reducing given better emesis control
- Management:
 - Mild: Eg taxanes. prochlorperazine 5 – 10 mg po (acts directly at the CTZ) or 25 mg PR or dexamethasone 10 – 20 mg IV (may enhance prochlorperazine). Haloperidol 0.5 – 1.0 mg im (dopamine antagonist) is also helpful
 - Moderate:
 - Eg carboplatin, anthracyclines, normal dose cyclophosphamide
 - Severe:
 - Eg cisplatin (rapid response lasting for up to 24 hours, then delayed response 48 to 72 hours later), high dose cyclophosphamide, dacarbazine...
 - Ondansetron (5HT3 antagonists) 8 mg Q 6hr from the day before + dexamethasone 20 mg IV + neurokine (NK1) receptor antagonists eg aprepitant
 - Delayed: often due to bowel inflammation (eg cisplatin, cyclophosphamide, carboplatin and anthracyclines). Oral dexamethasone + metoclopramide

Emetic Potential	Acute Emesis	Delayed emesis
High	5HT3 + Dex + NK1	Dex + NK1
Moderate	5HT3 + Dex	Dex
Low	Dex + MCP	nil
Minimal	nil	nil

- Drug details:
 - See Internal Medicine Journal 2005; 35:478-81
 - Corticosteroids:
 - Effective as sole agents in mild group
 - Effective for both delayed and acute
 - Mechanism poorly understood
 - 5HT3 antagonists:
 - Excellent control of acute emesis in over 80%, little effect on delayed emesis
 - SE: headache, constipation, transiently elevated LFTs
 - No evidence for IV over PO
 - No evidence for one 5HT3 antagonist over the other – however palonosetron is a new long-acting agent with higher receptor affinity...
 - NK1 receptor antagonists:
 - Substance P is a neuropeptide whose activities are mediated through the Neurokinin-1 receptor on vagal afferents (also central action)
 - Proven additive benefit to 5HT3 antagonists and dexamethasone in severe group, 1 trial in moderate group showed additive benefit (51 vs 42% complete response)
 - Toxicity similar to 5HT3, plus fatigue, dyspnoea and hiccups
 - Metabolized by 3A4, as is dexamethasone, so ↓dexamethasone dose with co-administration. Care with other chemo drugs. Weak inducer of warfarin pathway
 - Others:
 - Lower efficacy and less robust evidence
 - D2 antagonists: metoclopramide (activity similar to phenothiazines) more effect at higher doses ? 2nd to 5-HT inhibition, also stimulates appetite), phenothiazines (dopamine antagonists – block chemoreceptor trigger zone – prochlorperazine/Stemetil is less sedating than chlorpromazine – SE dystonic reactions) and haloperidol

- Antihistamines: Cyclizine: H1 antagonist, anti-muscarinic
- Domperidone: acts on chemotrigger receptor zone. Less likely than metoclopramide and phenothiazines to cause sedation and dystonic reactions, does not cross BBB (so good in Parkinson's)
- Synthetic cannabinoids: nabilone and dronabinol. SE postural hypotension and dysphoria
- Olanzapine: antagonizes dopamine and 5-HT. Effective in 2 phase 2 trials for acute and delayed nausea

Aside: Nausea in General

- Neurology of nausea:
 - Loosely organized neuronal areas in the medulla (an anatomically discrete vomiting centre is unlikely to exist) receives input from the chemoreceptor trigger zone (caudal end of 4th ventricle), and afferents from GI tract, cerebral cortex, and heart
 - Abdominal vagal afferents have the greatest importance. They have receptors in close proximity to enteroendocrine cells located in the gastrointestinal mucosa of the proximal small intestine. Chemo agents stimulate these cells to release mediators, including 5-HT (serotonin, also 5-HT receptors in CNS)
- Differential:
 - Infection
 - Brain mets
 - Drugs
 - Obstruction/ascites/gastric compression/constipation
 - Metabolic: ↑urea, ↑LFTs, ↑Ca
 - Pregnancy
 - Oral thrush
- Drugs use to treat nausea:
 - Histamine (H1) antagonists: *cyclizine*, promethazine and methotrimeprazine (Nozinan – multiple actions, more side effects eg drowsiness)
 - Dopamine (D2) antagonists:
 - Butyrophenone: *Haloperidol*
 - Phenothiazines: Chlorpromazine (Largactil), prochlorperazine (Stemetil), methotrimeprazine (Nozinan)
 - Prokinetics: *metoclopramide*, *domperidone* (Motilium), cisapride
 - Muscarinic Cholinergic (M1Ch) antagonists: scopolamine (Hyoscine), atropine, methotrimexprazine (Nozinan)
 - 5HT3 Receptor antagonists:
 - Ondansetron: licensed for post-chemo, post-radiotherapy, post-operative. SE constipation
 - Tropisetron, methotrimeprazine (Nozinan)
 - Corticosteroids: mode of action not established. ?reduced permeability of the BBB to emetogenic substances, ↓neuronal content of GABA, ↓ release of neurotransmitters in the emetic centre....

Tumour Lysis Syndrome

- Expect it to happen in SCLC and high grade lymphoma
- ↑urea and urate (from nitrogen metabolism):
 - Hyperuricaemia → acute urate nephropathy → ARF
 - ↑PO4 → ↓Ca (↑PO4 bind with serum Ca) which may be associated with tetany, ↓renal function, arrhythmia, seizure or sudden death
 - ↑K
- Prevention: pre-hydration and pre-treatment with allopurinol (or rasburicase)
- Treatment:
 - Fluids
 - Treat electrolyte abnormalities
 - Urinary alkalization (controversial): stops uric acid → urate
 - Maybe haemodialysis to get rid of urate
 - Rasburicase: iv infusion, recombinant urate-oxidase enzyme, catalyses oxidation of uric acid into a soluble metabolite, allantoin. SE: allergy

Lung Cancer

- See NICE Guidelines
- Epidemiology:
 - Incidence peaks 55 – 65
 - Responsible for more deaths than breast, colon and prostate combined
 - 85% are current or former cigarette smokers. Most non-smokers women
 - Adenocarcinoma the most common in non-smokers, or the young
 - 1st degree relatives have a 2 – 3 fold increase of lung or other cancers
 - Even a very good stage still has a poor prognosis

- Pathology:
 - Lung cancer = arises from respiratory epithelium. Doesn't include mesotheliomas, lymphomas and stromal tumours (sarcomas)
 - Need biopsy: different natural history's
 - Cancer stem cells: the < 1% of tumour cells responsible for the full malignant behaviour
 - Types:

	Frequency %	5 year survival (all stages) %
Adenocarcinoma & subtypes	32	17
Bronchioloalveolar carcinoma	3	42
Squamous cell	29	15
Small cell	18	5
Large cell	9	11

- So adenocarcinoma and squamous cell the most common types
- Also benign lesions: < 5% of all lesions, bronchial adenomas and hamartomas make up 90% of these
- Carcinoid tumours: see page 77
- Microscopy:
 - Small cell: scant cytoplasm, small nuclei
 - Non-small cell (NSCLC): abundant cytoplasm, pleomorphic nuclei
- Genetics (See NEJM 25 Sept 2008):
 - Small cell:
 - ACTH, AVP, GRP (gastrin releasing peptide) producing, RB mutations in 90%, p16 in 10% (inactivation of expression by methylation), never have EGFR
 - Methylation of the promoter region of four genes in stage I is associated with early recurrence (NEJM 13 March 2008)
 - NSCLC: RB mutations in 20%, p16 in 50%, EGFR in ~10%
 - Both: frequent p53 mutations and telomerase expression
 - Those with low activity of excision-repair-cross complementation group 1 (ERCC1), a DNA repair protein, do worse. However, when treated with cisplatin, they do better than people with high levels
 - Smokers and non-smokers have very different genetic changes, eg in non smokers p53, KRAS, EGFR and HER2
- Progression:
 - Tissue injury is associated with genetic and epigenetic changes – centrally in smokers, usually distally in non-smokers
 - Develops to 'clonal patches' – areas of clones with loss of heterozygosity, microsatellite instability and mutations
- Screening:
 - See NEJM 30 June 2005
 - Current controversy – not proven, not recommended even in high risk. Problems of lead time bias (CXR detects cancer without impacting on survival), length bias (favours detection of slow growing tumours) and over diagnosis. Most studies old – current studies in CT on going
 - CXR: hopeless. Mass must be > 1 cm before seen even in an easy place
 - Sputum: cancer cells in sputum come from proximal tree – they're not the ones you're going to cure
 - CT: many studies with different results. Detects more cancers, no change in mortality. Transitory non-cancerous small nodules common (ie false positives)
 - If solitary lung nodule in someone with a known primary elsewhere, treat it as a primary lung cancer (natural history worse than other tumours)
- Presentations:

- Clubbing: 30%, usually NSCLC, and hypertrophic pulmonary osteoarthropathy in 1 – 10% (usually adenocarcinoma)
- Phrenic nerve paralysis → elevation of hemidiaphragm and SOB
- Horner's Syndrome: sympathetic nerve paralysis: enophthalmos (backward displaced eyeball in orbit), ptosis (drooping eye lid), miosis (contraction of the pupil), and ipsilateral loss of sweating
- Neurologic-myopathic syndromes in 1%: Eaton-Lambert syndrome (antibodies to Ca channels) with small cell, and in all types peripheral neuropathies and polymyositis
- Thrombotic disease: Trousseau's syndrome (migratory venous thrombophlebitis)
- Causes of Pancoast's Syndrome:
 - NSCLC, commonest squamous cell Ca
 - Lymphoma
 - Tb
 - Primary chest wall tumours
 - Presentation: right shoulder pain +/- ulnar radiation the commonest first symptom. Horner's syndrome in 14 – 50%. Then neurological complication of the upper limbs from C8/T1 nerve root involvement. Maybe destruction of the 1st and 2nd ribs
 - Typically T3/T4 on presentation (involvement of surrounding solid organs)
 - Investigation: transthoracic FNA
- Paraneoplastic syndromes:
 - Squamous: PTH or PTHrH
 - Small cell: ADH or atrial natriuretic factor → hyponatraemia, ACTH
- Mets:
 - On biopsy found in > 50% with squamous cell, 80% of adenocarcinoma and large cell, and > 95% of small cell
 - To brain, bones, liver, lymph nodes, spine, adrenals (but rarely cause adrenal metastases)
- SVC obstruction occurs in 2 – 5 % of lung Ca patients:
 - Lymphoma: non-Hodgkins
 - Mediastinal metastasis: Germ cell cancer, metastatic breast Ca, thymoma
 - Non-malignant causes: mediastinal fibrosis, thrombosis of indwelling devices eg pacemaker
- Diagnosis:
 - Sputum helpful for differentiating TB
 - CT: diagnosis and staging – include liver and adrenals. Brain CT in small cell (10% have mets)
 - 18Fluro-deoxyglucose PET scan (FDG-PET) of mediastinal nodes in NSCLC: 85% sensitivity and specificity. A standardised uptake value (SUV) > 2.5 is highly suspicious. False negatives in diabetes, concurrent infections (eg Tb) and small lesions. *Primary function is to guide mediastinal biopsy for staging purposes.* Accurate in differentiating benign from malignant pulmonary lesions when a tissue diagnosis is not available. False positives in inflammation (eg sarcoid) and infection
 - LFT derangement with liver mets: ALP goes off first due to intra-hepatic obstruction (before hepatocyte destruction and ↓synthetic function)
 - MRI more sensitive than bone scan for bone mets – most likely spine and pelvis
 - ↑Ca: bony mets or squamous cell (PTHrP)
 - ↑Na: SCLC with exogenous ACTH
- Surgery:
 - Never know whether it's going to be a lobectomy or pneumonectomy till they're open
 - MI in last 3 months a contraindication – 20% fatality from perioperative MI
 - Poor pulmonary function or pulmonary HTN also a contraindication
 - 50 yr old well, non-smoker: 1 month mortality for lobectomy is 2 – 3 %, pneumonectomy is 10%
- Metastatic disease: in general chemo extends survival by 4 to 6 months over supportive care
- Supportive care: Grade I or II evidence in lung cancer for:
 - Efficacy of combined pharmacotherapy and psychotherapy for depression/anxiety
 - Improved quality of life from psychological interventions and early referral to palliative care services
 - Specialist palliative care services improve outcomes
 - Patients with advanced cancer and dyspnoea benefit from O2
 - Breathing retraining, relaxation, and coping skills can improve dyspnoea and functional capacity
 - Oral opioids are recommended for non-productive cough
 - Anti-depressants and anticonvulsants offer effective palliation for neuropathic pain
 - Bisphosphonates improve pain in symptomatic bony mets

Solitary Pulmonary Nodule

- See NEJM 19 June 2003. See differential of Xray nodule, page 185
- Definition:
 - Nodule is < 3 cm, surrounded by parenchyma, without other abnormalities
 - Masses are > 3cm, often malignant
- Risks of malignancy: older, smoker, size of lesion, shape of lesion (speculated worse), pattern of calcification, growth
- 35% of solitary incidental pulmonary nodules are malignant (although < 1% in non-smokers < 35 years). Only two radiological predictors are no growth over 2 years and pattern of calcification
- Management:
 - Very little evidence basis
 - Low risk: serial HRCT 3 monthly for a year, then 6 monthly for a year then stop
 - Intermediate risk:
 - PET if nodule > 1 cm (sensitivity 96%, specificity 77%)
 - Transthoracic FNA: sensitivity increases with size of lesions (60% if < 2 cm)
 - Bronchoscopy: sensitivity increases with size of lesion
 - If no malignancy then serial HRCTs as for low risk group
 - High risk: VATS or wedge resection with intra-operative frozen section with lobectomy if malignant

Small Cell Lung Cancer

- See Lancet, 15 October 2005
- Are usually inoperable by diagnosis
- Doesn't cause clubbing
- Present centrally with early dissemination
- 14% of new lung cancer cases, 95% will be due to smoking and 95% will die from it
- Poor prognostic factors: extensive stage, poor performance status, hyponatraemia, ↑ALP, ↑LDH
- Staging: Two type-staging:
 - Limited-stage disease: 30%, disease confined to one hemithorax and regional lymph nodes (all disease can fit in one radiotherapy field)
 - Extensive-stage disease: 70%, more than this, or involving cardiac tamponade, pleural effusion or bilateral lung parenchyma (not safe to give these radiotherapy)
- Treatment:
 - High mitotic rate → initially > 70% response to chemo, > 90% response to radiotherapy, most relapse, including prophylactic cerebral radiotherapy (but not concurrently with chemo)
 - Spinal tumour: intrathecal methotrexate
 - Limited stage:
 - Chemotherapy (platinum based: etoposide [Antitumour antibiotic] + cisplatin or carboplatin, every 3 – 4 weeks for 4 – 6 cycles) prolongs median survival from 12 weeks to 18 months, survival > 3 years 30 – 40%
 - Radiotherapy: small but significant survival benefit (5% at 3 years). Twice daily regimes better than once daily regimes but ↑oesophagitis and pulmonary toxicity
 - Occasionally appropriate for resection
 - If achieve a complete response after induction therapy, prophylactic cranial irradiation is associated with a reduction in brain mets and prolonged survival
 - Extensive disease: Offer multidrug platinum based chemo. At relapse, offer 2nd line chemo only if they responded to first line. Median survival without chemo 2 months, 10 – 12 months with chemo

Non-Small Cell Lung Cancer

- Process:
 - Stage the tumour
 - Assess operability: sufficient bronchial margin, nodal status, invasion of critical structures
 - Assess surgical fitness: PFTs, ?exercise test, cardiovascular disease (usually smokers)
- Types:
 - Stage for stage, histology of the various types of NSCLC makes little prognostic difference
 - Adenocarcinoma:
 - Most common type in non-smokers
 - Exclude other primary sites. Colon mets in the lung can be resected: wedge resection (as opposed to lobe resection for lung primary). All comers 5 year survival 10%

- Often peripheral (as are large cell)
- Bronchioloalveolar: a subtype of adenocarcinoma. Ground glass on CXR/CT
- Asymptomatic CT of brain of no value. Prophylactic brain radiotherapy of no value
- Squamous: present centrally
- Staging:
 - N1 = within visceral pleura, N2 = outside pleura on the same side, N3 = over the midline
 - Assessment: getting better methods for less invasive staging
 - Can do endobronchial ultrasound (EBUS) for intra-visceral and pre-tracheal/pre-carinal nodes
 - EUS (oesophageal ultrasound) is good for the mediastinum below the carina
 - Cervical mediastinoscopy gets at the pre-carinal and pre-tracheal nodes but not the anterior mediastinum and can't do lung biopsy
 - PET important for all patients prior to radical treatment – stage I – IIIA
 - Stage 2B: T3 N0 M0 or T2 N1 M0: (generally) > 3 cm, may involve chest wall but not mediastinum *or* hilar lymph nodes but not mediastinal lymph nodes
 - Stage 3A: Not mediastinal infiltration and peri-bronchial, hilar nodes or ipsilateral mediastinal nodes, nor malignant effusion
 - Stage 3B: Mediastinal infiltration or contra-lateral nodes
- Treatment:
 - See NICE Guidelines

	I	II	IIIA	IIIB	IV
Surgery	Yes	Yes			
Rx then surgery					
Surgery then Rx	Maybe	Maybe	Maybe		
Chemo then Surgery					
Surgery then chemo	Maybe	Maybe	Maybe		
Surgery then chemo & Rx					
Radical Rx	Maybe, if inoperable	Maybe	Maybe	Maybe	
Chemo and Radical Rx			Yes		
Chemo			Maybe	Yes	Maybe
Symptomatic (include Rx)					Probably

- Overall treatment stats: 30 – 50% response to radiotherapy, 20 – 35% response to chemo
- Stage 1A: surgery only is curative. Evidence is against chemo. High risk of recurrence. Surveillance for 5 years. Lobectomy has better survival than wedge resection. Full node dissection better than sampling. Pneumonectomy for proximal – a big operation – all cardiac output goes to one lung – need to be very fit. Unresectable if poor LFTs (FEV1 < 1 litre), frail, comorbidities...
- Stage I, II or some IIIA (about 1/3rd of NSCLC):
 - Can be cured with surgery +/- adjuvant chemo (stage II and III – incremental benefit modest – ↑5 year survival by 5 – 8%). LACE (Lung Adjuvant Cisplatin Evaluation) trial: post op cisplatin based chemotherapy for 4 months improves survival (absolute improvement of 5 – 15% in 5 year survival), significant toxicity
 - Consider post-operative radiotherapy if mediastinal nodes or if stage I or II and not-operative candidates (with curative intent, ~ 60 Gy [cf 30 – 45 for palliation] – about 20% survival)
 - If non-resectable and can get it all within a radiotherapy field then there's a role for chemotherapy
- A lot of controversy around stage IIIB – differs on whether it's bulky, effusion present, etc
- Stage IV and advanced stage III: treatment has quality of life advantage. Radiotherapy to symptomatic sites, palliative chemotherapy (eg cisplatin + taxane, improves quality of life and extends survival from ~4 – 6 months to 8 – 10 months), ?surgery of brain or adrenal mets. For 2nd line treatment (ie no response or remission to first line agents) docetaxel or Pemetrexed (antifolates) (response rate < 10%), latter with less side-effects
- Pancoast tumours: if no mediastinal involvement treat with preoperative radiotherapy and chemo, then surgery, with curative intent
- VEGF (Vascular endothelial growth factor): see page 381
 - Expression associated with poorer prognosis. Bevacizumab improves progression free survival and over all survival in advanced disease when combined with chemo. SE: Bleeding, HTN, proteinuria
 - Squamous cell: not appropriate for VEGF therapy given bleeding risk

- EGFR: see page 381
 - Adenocarcinoma: may be responsive to EGFR therapy (epidermal growth factor receptor – cell surface receptor with an intracellular tyrosine kinase domain). Up to 70% of NSCLCs has this gene amplified.
 - Erlotinib (Tarceva), Gefitinib (Iressa): oral inhibitor of EGFR tyrosine kinase. Big response in the small group with EGFR mutations. SE acneiform rash (correlates with effect), diarrhoea. No benefit combined with chemo
 - Cetuximab (Erbix): Monoclonal antibody: recent data showing improved survival combined with 1st line chemo
 - ?Presence of mutations to EGFR confers increased sensitivity to EGFR, and hence also to inhibitors. Next step is to be able to identify those who will benefit
- Complications:
 - Radiotherapy: oesophagitis (graded I – III, usually self limiting), radiation pneumonitis (can → fibrosis, treat with steroids), spinal cord injury (may be permanent)

CNS Tumours

General

- Presentation:
 - Elevated ICP suggested by papilloedema, impaired lateral gaze, early morning headache with increase if supine
 - Pre-frontal tumours or lesions in other clinically silent regions may mean the tumour is large at presentation
 - Diencephalic, frontal or temporal lobe tumours may present with psychiatric symptoms
- Evaluation:
 - No tumour markers for primary brain tumours
 - CSF: only for meningeal metastasis
- Treatment:
 - Symptomatic:
 - Dexamethasone 12 – 20 mg/day for oedema
 - Anticonvulsants: phenytoin, carbamazepine or valproate for tumours involving cortex or hippocampus
 - Prophylactic clexane if immobile
 - Curative: Surgery depending on site

Astrocytomas

- Graded with WHO or Anne/Mayo (USA) classification
- Range from low grade (I and II) to malignant astrocytoma (grade 3) to Glioblastoma Multiforme (GBM – approx 40% of brain tumour presentations)
- Most common glial tumours
- Presentation:
 - Low grade astrocytomas: Seizures in 90% (typically focal), headache (40%), hemiparesis (15%) – ie seizure presentation is better
 - Malignant astrocytoma: hemiparesis and mental state changes more common than low grade. Also more oedema and mass effect
- Diagnosis:
 - MRI +/- stereotactic biopsy (but grade varies from region to region so may not tell you about the grade)
 - Staging: worse with each of nuclear atypia, mitotic activity, endothelial proliferation, necrosis
- Management:
 - Debulking or attempt at curative resection, then radiotherapy
 - For high grade, chemo with Temozolomide (alkylating agent) enhances survival: 2 year survival from 10% to 26%. Median survival from 12 → 14.6 months Now standard treatment
 - Recurrent can be managed with further resection or stereotactic radio therapy (gamma knife)
 - Brainstem gliomas: inoperable. Use radiation and shunt if increased ICP
- Side effects of radiation:
 - ↑ICP
 - Alopecia, skin reaction, nausea

- After ~ 6 weeks: somnolence, ↓appetite
- Late: endocrine, cognitive (less common), necrosis (may look like recurrent tumour), optic chiasm necrosis (→blindness)
- Prognosis:
 - Low grade: 5 years – most die from progression to higher grade. Many of these are now being identified as low grade oligodendrogliomas with genetic testing
 - High grade: 3 years
 - GBM: 1 years

Ependymoma

- Major peak at 5 yrs, minor peak at 35 years
- 5% of intracranial neoplasms in adults
- Arise from ependymal cells lining ventricles and spinal canal
- Most are benign – younger patients have worse outcomes
- Most adult tumours in the lumbosacral regions, also supra and infratentorial regions
- Diagnosis with MRI: well demarcated, 50% have calcification. CSF cytology for metastases
- Management: Full gross excision with subsequent radiation – 80% 5 years survival. No role for chemo. Follow with MRI for recurrence

Oligodendrogliomas

- < 5% intracranial tumours, usually low grade, mean age 38 – 45 years
- Arise from oligodendroglial cells, responsible for axonal myelination
- Presentation: as for any CNS tumour, but can also haemorrhage easily
- Diagnosis: MRI. Calcification differentiates from astrocytoma
- Management: surgery, *chemotherapy* (not curative, but can induce remission) +/- radiotherapy. Median survival 16 years

Meningiomas

- Leptomeningeal origin. Arachnoid cap cells
- 20% of intracranial neoplasms
- Peak age 45
- Risk factors: history of breast ca, neurofibromatosis, cranial irradiation
- All meningiomas characterized by loss of C/S 22q
- Malignancy in 1 – 10% of cases, metastatic disease in < 0.1%
- Presentation: depends on location. Focal deficits common. Seizures > 50%
- Diagnosis: MRI – well circumscribed extra-axial lesions. Surrounding tumour and mass effect common
- Management: curative resection (base of skull unresectable) or stereotactic radiosurgery if small

CNS Lymphoma

- 1 – 3 % of intracranial tumours
- B cell malignancies of intermediate to high grade, without evidence of systemic lymphoma
- Peak in 6th to 7th decade
- Acquired or congenital immunosuppression → 100 to 1000 fold increase in risk
- Presentation includes uveitis in 15% (preceding cerebral symptoms by several months)
- Solitary lesion in 40% on presentation, usually becomes multifocal
- Diagnosis: MRI – usually periventricular with homogenous enhancement. Stereotactic biopsy for tissue diagnosis
- Treatment: Dramatic initial response to steroids but response quickly diminishes. High dose methotrexate. Radiotherapy post chemo (including orbit if retinal disease). Intrathecal methotrexate for leptomeningeal disease
- Prognosis: with chemotherapy and radiotherapy 5 year survival of 25%

Metastatic Lesions to the CNS

- Sites:
 - Haematogenous spread to the gray-white matter junction (cerebral flow greatest)
 - Spinal involvement 2nd to spread from vertebral metastases, direct invasion or retrograde spread via the vertebral venous plexus
- Brain Mets: Most common primaries:

- Lung
- Breast (especially ductal carcinoma)
- GI malignancies
- Melanoma
- Germ Cell tumours
- Thyroid cancer
- Presentation: usually progress rapidly
- Diagnosis: oedema out of proportion to the size of the lesion. MRI more sensitive than CT + contrast. CSF cytology rarely positive. 1/3rd patients have unknown primary
- Treatment: oedema very responsive to steroids. Anticonvulsants empirically as 1/3rd will develop seizures. Whole brain irradiation primary treatment (micro-mets common)
- Prognosis: untreated survival 1 month. Steroids and irradiation 3 – 6 month survival

Gastrointestinal Tumours

Oesophageal Tumours

- Peak incidence age 50 – 70
- Types: Barrett's is a greater risk than smoking
 - Squamous cell: associated with alcohol and tobacco, regions of China and SE Asia (radiosensitive)
 - Adenocarcinoma: most develop from Barrett's metaplasia (less radiosensitive). Also independently associated with obesity (mechanism unknown)
- Presentation with advanced disease 2nd to solid food dysphasia
- Diagnosis: Barium oesophagogram or endoscopy. Biopsy may be non-diagnostic if submucosal spread
- Staging: Endoscopic ultrasound for tumour depth. CT for pulmonary or liver metastases. PET for nodes if no distant disease. Maybe bronchoscopy if proximal lesion to exclude tracheo-bronchial extension
- Management:
 - Local tumour spread (T4) and metastases incurable – nothing prolongs survival. Palliative radiotherapy/chemo and/or stenting
 - Stage I, II, IIIA: surgery +/- adjuvant chemo or chemo + radiotherapy. Perioperative chemotherapy improves survival (Ann Int Med, 4 Dec 2007)

Gastric Tumours

- Adenocarcinoma (85%):
 - Tends to present with advanced disease, 5 year OS ~ 10 – 15%
 - Diffuse type (linitis plastica or “leather bottle” appearance, worse) or intestinal type
 - Associated with high concentrations of nitrates in dried, smoked and salted foods
 - Effect of H Pylori eradication under investigation
 - Associated with blood type A. Also known germline mutation in E-cadherin gene
 - Diagnosis: double contrast study
 - Treatment:
 - Radical surgical resection. High recurrence rates
 - Radioresistant – required dose exceeds tolerance of surrounding structures
 - Survival prolonged with palliative radiotherapy and 5-FU. Partial response to some chemo combinations
 - Perioperative chemotherapy is now standard in UK and Europe (5 year survival 23 vs 36% in MAGIC trial)
- Lymphoma (<15%, and 2% of lymphomas). Treatment of H Pylori alone → regression of 75% tumours. If high grade then subtotal gastrectomy + chemo [eg CHOP – cyclophosphamide, doxorubicin, Vincristine and prednisone – + rituximab]
- Gastrointestinal stromal tumours (GIST):
 - Very rare soft tissue sarcoma – usually in the stomach
 - Can have spindle cells on histology
 - Characterised by C-KIT activation
 - Median survival with metastatic disease 20 months
 - Imatinib:
 - Selective inhibitor of a number of protein tyrosine kinases:
 - ABL kinase

- CCR-ABL fusion oncoprotein of CML
- C-KIT (CD117)
- PDGF
- Stem Cell factor
- Benefit in phase II trials in GIST. In some cases PET negative in days

Small Intestine Tumours

- Rare (<3% of GI neoplasms) → delayed diagnosis
- Consider if:
 - Recurrent, cramping abdo pain
 - Intermittent bouts of intestinal obstruction, especially if no IBD or prior abdo surgery
 - Intussusception in an adult
 - Evidence of chronic intestinal bleeding if upper and lower scopes negative
- Diagnosis: small bowel barium study
- Differential:
 - Benign
 - Adenomas
 - Leiomyomas (smooth muscle derived)
 - Lipomas: mainly distal ileum
 - Angiomas (not true neoplasms): telangiectasia, or haemangiomas
 - Malignancy: in order of frequency: adenocarcinomas (50%), lymphomas (primary or secondary), carcinoid, leiomyosarcomas. More common in celiac, HIV

Colorectal Cancer

- Epidemiology: 2nd only to lung cancer as cause of cancer death. 1 in 25 women and 1 in 17 men will develop bowel Ca in their lifetime (Victoria, Australia)

Pathology

- Most arise from adenomatous polyps:
 - < 1% become malignant
 - Cancer more common in sessile than pedunculated, and in larger (10% if > 2.5 cm)
 - Villous (most of which are sessile) 3 times more likely to become malignant than tubular
 - Synchronous lesions in about 1/3rd → value of checking the whole bowel if one found by any means
 - Take longer than 5 years to grow to a clinically significant state → 5 yearly screening OK
- Genetics: stepwise progression often involving:
 - Point mutation of the K-ras protooncogene
 - Hypomethylation → DNA activation
 - Allelic loss of function of tumour suppressor genes: APC (Adenomatous polyposis coli, 5q21), DCC (Deleted in colon cancer, 18q), p53 (17p)
 - Somatic gene mutations found in a variety of genes → multistep process of carcinogenesis: APC, p53, DCC (“deleted in colon cancer”, 18q21), PPAR (proliferator-activating receptor gene – a family of nuclear receptors functioning as transcriptional regulators)

Risk factors

- Hereditary:
 - Familial Adenomatous Polyposis (FAP):
 - Rare **AD** cancer syndrome due to mutation in APC on 5q21
 - 30% are new mutations
 - Accounts for <1% of colon ca
 - 100% risk of colon ca. Polyps before 25 and cancer by 40
 - NSAIDs may temporarily decrease size and number of polyps
 - Treatment: Proctocolectomy with anal pouch in late teens
 - Screen for duodenal adenoma (especially around the sphincter) every 2 years
 - Screen family members with serum APC test then genetic typing to confirm. May take time. Once mutation known, much easier to screen family members
 - Gardner’s syndrome if also soft tissue and bony tumours (eg jaw), congenital hypertrophy of the retinal pigment epithelium, ampullary cancers
 - Turcot’s Syndrome: APC + CNS tumours
 - Hereditary non-polyposis colon cancer (HNPCC or Lynch Syndrome):

- **AD** mutations in one of at least 4 DNA mismatch repair genes (incl hMSH2 on chromosome 2 and hMLH1 on chromosome 3), 70% penetrance. All MMR proteins combine to form a complex, so any mutation causes similar phenotype
- One inherited defective allele – cancer happens after the other one knocked out in a cell → accumulation of replication errors
- Prior to genetic testing (which is still tricky), diagnosis was by Amsterdam criteria: presence of 3 or more relatives (including 1st degree) with colon cancer, at least one before age 50 (usual age is in 60s), 2 successive generations affected (these fairly tight criteria miss small families and ignore extra-colonic cancers (eg endometrial)
- Usually proximal large bowel, usually < 20 polyps but accelerated progression to cancer, ~ 4 – 5% of bowel cancer. Despite poorly differentiated histology, stage for stage they have a better prognosis than sporadic
- Endometrial (~40%) and ovarian (~10%) cancer (think HNPCC if in young women), other cancers rarer
- Screening if affected: colonoscopy every 2 years from age 25, gynae surveillance from 30 – 35 years
- Further 20% of cancers have a family history, but no gene found (?polygenic)
- Age: 90% are in patients > 50
- Diet: hypotheses about high animal fat (?→ ↑ anaerobes in gut flora), insulin resistance. RCTs of fibre have shown no difference
- Obesity (↑1.5 times risk), T2DM, low folate and alcohol are bad
- Tobacco: risk especially after 35 years smoking
- Inflammatory bowel disease: UC > Crohn's. Incidence grows with time – relatively rare in first 10 years, 8 – 30% by 25 years. Value of surveillance unknown
- Streptococcus bovis bacteraemia: high incidence of colon ca, cause unknown
- First degree relative → ↑risk 1.75 times, more if affected before age 60
- Controversial: calcium, red meat, “charred” meat

Prevention

- Regular aspirin → ↓incidence (but NNT = 1250 after 10 – 20 years)
- Oral folic acid and oral calcium → ↓risk in case control studies only
- HRT → ↓colon ca (?due to change in bile acid synthesis or ↓ IGF-1)
- Regular physical activity is preventative

Screening

- Early detection → better prognosis, so question of screening is relevant
- Recent ↓ in distal tumours (cause unknown) → sigmoidoscopy less sensitive
- Annual Faecal Occult Blood Testing FOBT could reduce mortality but:
 - Prospective trials of annual screening with FOBT → ↓incidence (even including dropouts) after 13 years follow up (maybe because they removed adenomatous polyps as they went), but
 - 1 – 5 % tests have positive test, and only 2 – 10% of these will have Ca (for 10 FOB +ive will get 1 cancer and 3 – 4 large polyps)
 - High false-positives → ↑↑ colonoscopies (→ poor compliance)
 - 50% with colon ca have negative FOBT
 - Specificity reduces over age 80
 - Newer immunological FOB is a quantitative test for human Hb – so don't need meat free diets etc and can set the sensitivity and specificity
 - Faecal DNA screening for mutations associated with cancer is more sensitive than FOB – but still pretty bad, and still negative in the majority of cancers
- CT colonoscopy detects 90% of adenomas or cancers > 10 mm diameter. Better than other screening tests (eg FOB). Sensitivity much less for smaller polyps, but whether such polyps are worth detecting is controversial. 17% required colonoscopy for polyps > 1 cm. 16% had extra-colonic findings trigger further testing/treatment – few extra-colonic findings can be treated effectively (other than aortic aneurysm). Cost of this screening test is high, but cost per year of life lost is not
- Colonoscopy (NEJM 18 Sept 2008):
 - 5 years after a normal colonoscopy in average risk people, repeat colonoscopy (only 52% follow up) showed < 0.2% have cancer and ~ 1 had advanced adenomas (but frequency and rate at which these → cancer is not known) → increasing evidence base to longer screening intervals

- Screening colonoscopy in persons 80 years of age or older results in only 15% of the gain in life expectancy compared to younger patients (50 – 54 yrs) (BMJ 2006;333:522)
- Colonoscopy detects ~ 25% more advanced lesions (pre or malignant) than FOB and sigmoidoscopy
- Screening recommendations (Australian NHMRC):
 - Average risk (~ 98%)
 - Asymptomatic, no history of ca or UC, no family history
 - FOBT every 2 years from age of 50, ?sigmoidoscopy every 5 years from 50
 - Moderately ↑ risk (~ 1 – 2 % of the population):
 - 1st degree relative with bowel ca < 55 years or 2 1st or 2nd degree relatives at any age (RR 3 – 6 fold)
 - Colonoscopy every 5 years from 50, or 10 years young than the age of 1st diagnosis in the family
 - High risk (< 1% of population):
 - >= 3 1st or 2nd degree relatives with bowel Ca (suspect HNPCC), or, >= 2 1st or 2nd degree relatives with CRC and (multiple CRCs in 1 person or CRC < 50 or 1 relative with endometrial or ovarian ca)
 - Genetic counselling +/- testing – then screen as per APC or HNPCC mutations above
 - Screening in NZ is funded if one family member < 55 years or any 2 family members. Start age 50 or 10 years younger than the earliest presentation, then every 5 years
- If previous adenoma (ie polyp) then screen every 3 years. Shown in National Polyp Study to ↓ incidence of bowel ca
- If had cancer, then 7% chance of a further “metachronous” cancer in their lifetime. Screen at 1 year then 3 yearly till old

Prognostic factors

- Staging – Modified Duke’s criteria:
 - For colon ca, CT chest/abdo/pelvis. For rectal, add in rectal MRI – want to look more carefully for local invasion
 - T = depth of tumour presentation: T1 – not submucosa, T2 – not muscularis propria, T3 – into muscularis, T4 on serosal surface
 - N0 = no nodes, N1 = 1 – 3 nodes, N2 = 4 – 7 nodes
 - Stage 1: T1-2N0M0
 - Stage 2: T3N0M0
 - Stage 3: TXN1M0
 - Stage 4: TXNXM1
 - Stage: in Australia and NZ use the Australasian Colon Pathological Staging (ACPS)
- Findings on histology:
 - Grade
 - Histologic variables (eg aneuploidy) especially in T3N0M0
 - Histologic type: mucinous slightly better
 - Serosal involvement is bad, independent of T stage
 - Number of nodes significant: 1 – 3 positive better than 4 or more. In stage 2 cancer the most important prognostic marker is the number of nodes collected (stops under staging by getting good sample size). Clinical significance of micro-metastases is uncertain (newer specific tests can find lymph node cancers down to ~ 1 mm)
 - Vascular invasion (within the primary): venous, lymphatic
 - VEGF level (high is bad)
 - Role of molecular markers is unclear
- Other:
 - Age (young is worse)
 - Gender (female better)
 - Tumour markers: CEA:
 - Preoperative elevation of plasma carcinoembryonic antigen (CEA) predicts recurrence and useful for monitoring recurrence
 - Raised in a number of other cancers, especially adenocarcinomas, and some non-malignant conditions (smoking, PUD, IDB, pancreatitis, hypothyroidism, cirrhosis)
 - Obstruction or perforation at diagnosis (→ micro metastasis)
 - Tumour location: rectum is worse
 - HNPCC is associated with improved survival independent of tumour stage

- Not influenced by the size of the primary lesion
- Predicting toxicity from treatment:
 - ECOG status > 2 → ↑chance of unsustainable toxicity
 - Albumin < 30 prospectively validated as predicting ↑ toxicity

Management

- Presentation:
 - Ascending colon: anaemia
 - Descending colon: impeded passage of stool → abdo cramping, obstruction
 - Rectosigmoid: haematochezia, tenesmus, narrowing of the calibre of stool
- Investigation:
 - Must have a whole bowel colonoscopy as 3 – 5% have synchronous ca
 - Colonoscopy the gold standard. Sensitivity for small polyps > 90%. Risks: perforation 1 in 2,000, 1 – 2% risk of bleeding from the base of a removed polyp, over sedation
 - CT colography: requires whole bowel preparation and air. Good sensitivity for large polyps but less specific. Not good for following up FOB, but a reasonable screening test for older people
 - Need biopsy to exclude SCC and lymphoma
- Metastasis:
 - Can't metastasise until its through the lamina propria
 - Liver most common, brain rare
 - Distal rectal ca can spread via paravertebral venous plexus (escaping the portal circulation) to the lungs and supraclavicular nodes

Treatment of Colon Cancer

- Surgery is definitive in stage 1 and 2
- Radiation ineffective in primary treatment of colon cancer
- Adjuvant chemotherapy for stage III, Duke's C disease:
 - Has progressed from single chemo to complex regimes with consequent extension of survival
 - Historically improvement in overall survival was the gold standard. 3 year disease free survival has been found to accurately predict this, so is now the surrogate end-point in trials
 - 5-FU + folinic acid was the stand or care for many years:
 - 6 month course in stage 3 disease → ↓ 40% in recurrence and ↑ 30% survival
 - If liver mets can infuse directly into hepatic artery with better tumour response – but costly, toxic and ?no prolongation of survival
 - Addition of folinic acid (leucovorin) if advanced (?enhances 5-FU binding). Better tumour response but marginal benefit for survival
 - Oxaliplatin-based regimes now the standard of care: Mosaic trial 5FU/Fa vs FOLFOX4 (5FU + Oxaliplatin + leucovorin) showed DFS of 73 vs 68% (not difference in stage II disease)
 - Capecitabine: Equivalent to 5FU/FA in the X-ACT trial. Now standard of care for elderly who won't tolerate FOLFOX
- Adjuvant chemotherapy for Stage II, Duke's B disease:
 - Controversial
 - Meta-analyses suggest 2 – 4 % ↑OS at the expense of toxicity
 - Might consider if features associated with ↑ recurrence risk: inadequate LN sampling, T4 disease, involvement of visceral peritoneum, peritumoural large vessel invasion (LVI), poorly differentiated histology
- For all stages of disease, patients > 80 derive as much benefit from adjuvant chemo as do younger people. But most trials exclude people > 70 so little data in the elderly
- Monoclonal ABs:
 - EGFR antibodies: cetuximab (Erbix) and panitumumab (Vectibix):
 - Benefit a small proportion of patients. Synergy with irinotecan and oxaliplatin
 - Indicated in metastatic disease with is EGFR+ and who have progressed on irinotecan
 - No correlation between presence or intensity of EGFR expression on immunohistochemistry and clinical response. So how do you predict who responds? K-ras is involved in the EGFR mitogen-activated protein kinase (MAPK) signalling pathway. Activating k-ras mutations found in 40 – 45% of CRC and are associated with *resistance* to EGFR agents. So test, and give to wild-type K-ras patients only (proven to be the only ones who benefit – NEJM 23 Oct 2008). In advanced colorectal cancer extend overall median survival from 4.8 to 9.5 months
 - SE acne-like rash – severity is correlated likelihood of efficacy – the worse it is the better it is

- VEGF antibodies: Bevacizumab (Avastin) improves survival from 16 to 20 months in addition to irinotecan and oxaliplatin. See page 381
- Metastatic disease:
 - 30 – 40% have metastatic disease at diagnosis
 - If liver or lung solitary nodules are resectable then 35% 5 year survival (ie a small subset are potentially curable) but only 20% of patients with isolated liver mets are suitable for resection. Induction chemotherapy may increase respectability rates
 - Median OS with best supportive care only is 5 – 6 months
 - If metastatic disease and asymptomatic, no benefit from early treatment vs observation (although no studies with newer agents in this setting)
 - Duration: unclear. Newer agents ↑survival but also ↑toxicity. Usually continue until toxicity or progression. ?role for intermittent vs continuous chemo to ↓SEs
 - Treatment options:
 - Capecitabine
 - 5-FU and leucovorin: ~ 1 year survival
 - Irinotecan, 5-FU and leucovorin: 16 months
 - FOLFOX or FOLFIRI infusions (5-FU, leucovorin oxaliplatin or irinotecan): 21 months – doesn't matter what order they are exposed to these agents, as long as the get them all over the course of their disease
 - SIRT – selective internal radiotherapy: microspheres into the hepatic artery, tumour response but little impact on 5 year survival – although sequential treatments extend survival
- Follow up:
 - Screening liver: some evidence of survival benefit from US/CT screening, interval unclear
 - Stage 1 & 2: 3 monthly CEA
 - Most recurrences following surgical recurrence occur within 4 years → all clear at 5 years
 - Probability of further cancer 3 – 5 % → 3 yearly screening

Treatment of Rectal Cancer

- Behaves differently because of embryology and fixed structure
- Pre-treatment staging:
 - Endorectal ultrasound
 - MRI pelvis: looking at perirectal lymph nodes and perirectal structure involvement
 - CT for liver/LN involvement
- T1 and T2: recurrence very low with optimal surgery. Can do anal saving surgery in ~ 80% (although requires 2 operations – need a temporary stoma as 10% anastomosis leak – so if old/comorbid reduce risk by just doing a one off AP resection)
- Preoperative 5-FU (radiation sensitising effect?) and radiation therapy reduces regional recurrence by 20 – 25% in fully resected stage 2 or 3 (especially if they've penetrated the serosa)
- Adjuvant chemo for 6 months recommended for LN disease, but no prospective trials (5FU and folinic acid, if more aggressive then FOLFOX, oxaliplatin, etc)
- Anal cancer: associated with HPV virus. Treatment: chemo/radiotherapy has replaced abdominoperineal resection

Hepatocellular Carcinoma

- See Lancet 2003; 362: 1907-17
- Globally one of the most common malignancies – but dramatic variations in incidence: white south Africans 1.2 per 100K, Mozambique 122 per 100k
- Risk factors:
 - Uncommon in non-cirrhotic livers – 20% of HCC don't have cirrhosis
 - Age, duration of cirrhosis, obesity, male gender all increase risk
 - Hepatitis B: 100 fold risk, half have cirrhosis, half have chronic active hepatitis. Viral load is proportionate to risk
 - Hepatitis C: 5% annual incidence of HCC if cirrhosis
 - Chemical carcinogens: eg Aflatoxin B1 – 3 fold increase, a product of aspergillus from grains stored in hot humid places
 - Cirrhosis from alcohol (4 times risk), α 1AT deficiency
 - Less commonly associated with primary biliary cirrhosis, autoimmune hepatitis and metabolic disease (haemochromatosis, Wilson's, etc)
- Typical presentations:

- Patient with previously well-compensated cirrhosis presenting with jaundice, ascites, encephalopathy or variceal bleeding
- Asymptomatic mass seen on screening ultrasound in a cirrhotic patient, with or without raised α FP
- Signs: hepatomegaly, abdominal bruits in 6 – 25%, ascites in 30 – 60%, weight loss, fever
- Tumour Markers:
 - α -Fetoprotein (AFP), increased in about 50% so not a good screening test (rely on imaging). Also in non-seminomatous germ cell tumours, gastric, biliary and pancreatic cancers, and in pregnancy, cirrhosis and hepatitis
 - des- γ -carboxy prothrombin (DCP), a protein induced by vitamin K absence. \uparrow in 80% with HCC, but also if vitamin K deficient or on warfarin
- Imaging: Ultrasound. Vascular abnormalities: hypervascularity of the tumour mass and thrombosis by tumour extension of otherwise normal portal veins. Light up in arterial phase on CT due to large arterial supply compared to partial supply to the rest of the liver
- Biopsy: Core biopsy preferred over FNA, but \uparrow bleeding risk (underlying pathology predisposes to bleeding)
- Lesions: vary from low grade dysplastic regenerative nodules to malignant disease
- Screening:
 - US more sensitive than \uparrow α FP. A typical protocol would be 6 monthly α FP and yearly US. But screening has not been shown to save lives
 - Recommended for:
 - All cirrhotic patients in whom treatment would be considered
 - In the following non-cirrhotic HBV carriers:
 - Asian males > 40 years and females > 50 years
 - Africans > 20 years
 - Family history of HCC
 - Those with persistent high viral titres or inflammatory scores
 - Mass < 1 cm is unreliably diagnosed by any means. Reimage in 3 months to assess growth
 - Lesion > 2 cm with α FP > 200 ng/ml or typical features on CT/MR are diagnostic and don't need biopsy, otherwise biopsy
- Staging: Cancer of the Liver Italian Program (CLIP) common. No consensus
- Treatment:
 - Usually managing 2 diseases: cirrhosis and HCC. Natural history of HCC highly variable
 - Intrinsic resistance to chemo (enhanced expression of transporters of the multidrug resistance protein family [MDR] which export intracellular chemo drugs) and many chemo agents are hepatotoxic
 - Stages 1 (< 2 cm) and 2 (> 2 cm):
 - < 30% have early stage disease
 - Surgical resection (treatment of choice if not cirrhotic, 5 year survival up to 90% but only 30% suitable, 50% 5 year new primary), local ablation (thermal or radiofrequency) superior to injection (eg ethanol, smaller lesions) and similar survival to surgery for small tumours. If cirrhosis, may not tolerate surgical loss of parenchyma
 - No clear advantage has been found for chemotherapy
 - Transplant:
 - If 3 lesions < 3 cm or 1 lesion < 5 cm (Milan criteria): survival approaches that for non-cancer transplant
 - Trans-arterial chemo-embolisation (TACE) or radio-frequency ablation upon listing to delay progression. TACE works on the principle that liver cancers are supplied by the hepatic artery, the rest of the liver predominantly by the portal vein, so arterial chemo (eg epirubicin) selects for the cancer
 - Early recurrence likely to be incomplete initial treatment. Later (> 2 years) likely due to new cancers
 - Stage 3 (bilobar, vascular invasion): No survival effect from chemotherapy. Varying reports from intra-hepatic artery regional chemotherapy (eg with TACE)
 - Advanced tumours: survival 4 months with or without treatment
 - Experimental:
 - Radiation: Selective internal radiation therapy (SIRT) with Yttrium-90 beads
 - Targeted agents (eg anti-angiogenesis): disease stabilisation rather than regression. SHARP trial showed sorafenib (Raf kinase inhibitor) \rightarrow modest but significant prolongation of survival (NEJM 24 July 2008)

- Paraneoplastic syndromes: Rare. Hypoglycaemia, ↑Ca, ↑cholesterol, carcinoid, changes in 2ndary sex characteristics (gynaecomastia, testicular atrophy)
- Prevention:
 - Hep B vaccination
 - Interferon for HBV → reduced hepatic failure, death and HCC rates
 - Interferon may lower rates in Hep C – unclear

Other GI Tumours

Benign Liver Tumours

- Predominantly in women
- Haemangiomas, adenomas (associated with OCP, can bleed or rupture, very low risk of malignant change), focal nodular hyperplasia (benign, no treatment)

Cholangiocarcinoma

- Mucin-producing adenocarcinoma arising for the bile ducts
- Risks: primary sclerosing cholangitis and liver fluke, chronic biliary inflammation and alcoholic liver disease, gall stones
- Presentation: painless jaundice
- Tumour markers non-specific
- ERCP to define tumour, biopsy, stent
- Treatment: consider palliative surgery. Liver transplant disappointing

Pancreatic Cancer

- Tumour marker cancer associated antigen 19-9 (CA 19-9):
 - 80 – 90% sensitivity and specificity for pancreatic cancer
 - 60 – 70% sensitivity for biliary tract cancer
 - Also in colon, oesophageal and hepatic cancers, and in cirrhosis, cholestasis, cholangitis and pancreatitis
- Ductal adenocarcinoma (see NEJM 24 April 2008):
 - Perhaps the most lethal cancer: median survival < 6 months, 5 year survival < 5%
 - Resistant to all available treatments
 - Mast cell infiltration around tumours may facilitate cancer growth → ?therapeutic target
- If it looks respectable, often operate prior to biopsy given theoretical concerns about biopsy seeding
- Screening: false positive rate too high
- Staging: limited value given poor prognosis
- Surgery for head of pancreas or uncinate process: Whipple's procedure – resection of head of pancreas, duodenum, first 15 cm of the jejunum, common bile duct and gallbladder, and partial gastrectomy. Perioperative mortality 5 % in experienced centres

Renal Tract Tumours

Renal Cell Carcinoma

- 90 – 95% of cancers arising from the kidney
- Annual incidence 3/100,000
- Risks:
 - Smoking accounts for 20 – 30%
 - Acquired cystic disease and end stage renal failure
 - Tuberous sclerosis
 - Von Hippel-Lindau Syndrome in 3%:
 - See page 76
 - 35% get renal ca
 - Mutation is a deletion of one VHL allele, also seen in 84 – 98% of sporadic clear cell RCC
 - In sporadic renal cell carcinoma there is either a mutation, a loss of heterozygosity and/or hypermethylation of the VHL promoter
 - Also obesity, hypertension, unopposed oestrogen
- Pathology: heterogenous. Includes clear cell carcinoma (60%), papillary tumours (5 – 15%),
- Presentation: haematuria, flank pain, flank mass, weight loss, anaemia, fever, hypertension... Often metastasised before diagnosis

- Histology:
 - Clear Cell Renal Cell Carcinoma – most common
 - Metastasise up the renal vein to the heart → emboli → cannon ball metastasis of the lung
 - Sheets of clear cells
 - 3 p25 deletion diagnostic feature
 - Papillary RCC: Better prognosis
 - Chromophobe RCC: Better prognosis, large cells, abundant cytoplasm, small dark nucleus
 - Sarcomatoid RCC: Highly malignant, highly anaplastic
- Staging: Robson classification and the American Joint Committee on Cancer staging system
- Treatment:
 - Previously bleak outlook – silent disease, presents late, no effective treatment other than resection
 - Localised: radical nephrectomy (includes ipsilateral adrenal)
 - Notable resistance to chemotherapy
 - Infrequently responsive to IL-2 and IFN α
 - Survival benefit from cytoreductive nephrectomy if metastatic disease and good performance status
 - *Antiangiogenic therapy with anti VEGF* agents where indicated by genetic studies recently demonstrated helpful:
 - See page 381
 - Sunitinib: Phase III trial vs IFN: Median PFS 11 months vs 5 months but OS not significantly different
 - Sorafenib: Small increase in DFS in previously treated patients
 - Bevacizumab: ↑RR and PFS over IFN alone, but no difference in OS
 - ?Role for sequential/combination treatments
 - mTOR inhibitors:
 - mTOR transduces extracellular signals that promote cell growth and survival – a master regulator of the cell
 - Temsirolimus: iv rapamycin analogue, competitive inhibitor of mTOR kinase. Improves OS
 - Everolimus: an oral inhibitor of rapamycin (mTOR inhibitors) showed benefit on people who had progressed on VEGF therapy (Lancet 9 August 2008)
- Prognosis: even metastatic disease shows variation – some have indolent course, even spontaneous remission (due to immune response). Can have recurrence after 10 – 15 years

Bladder Cancer

- Malignancy of the transitional cell epithelium (95% – some squamous)
- Associated with smoking, analgesic abuse, azo dyes
- 90% in the bladder, 8% in the renal pelvis, 2% in the ureter or urethra
- 5:1 incidence to mortality ⇒ predominance of superficial variants. 75% superficial, 20% invade muscle, 5% metastatic at presentation
- Tumour exhibits polychonotropism: recurrence over time in new locations. ?Field defect
- Risks:
 - Smoking accounts for about 50%
 - Radiation
 - Chronic cyclophosphamide
 - Schistosomiasis
- Presentation:
 - Painless haematuria in 80 – 90%. Can cause hydronephrosis, flank pain, and renal colic from clots
 - Peak in 6th – 7th decade, M > F
- Treatment:
 - Superficial disease: endoscopic resection +/- intravesical therapy (with BCG most commonly)
 - Invasive disease: radical cystectomy +/- chemotherapy with 2, 3, or 4 drug combinations prolongs survival

Blake's Cancers

Prostate Cancer

- See Lancet 17 May 2008
- Background:
 - Prostate-specific antigen (PSA):

- A serine protease produced in epithelial cells which liquefies seminal coagulum
- Age-related normal ranges ↑sensitivity for young men (more likely to die of the disease) and ↓frequency of detecting low-malignancy cancers in older men
- Most PSA is complexed to α 1-chymotrypsin. Most is bound. The level of free PSA is lower in men with cancer
- Screening with DRE:
 - > 4 ng/ml 20 – 30% PPV, > 10 ng/ml 50% PPV
 - Unbound PSA fraction < 10% PPV 55%
- PSA velocity – faster rise associated with cancer. At lower levels, a smaller rise is more significant
- Also raised in prostatitis, BPH, prostate trauma, after ejaculation
- PSA threshold at which to biopsy has not been defined
- Periurethral portion of the gland (the transition zone) undergoes benign hypertrophy from age 55
- Most cancers develop in the peripheral zone – can often be palpated on DRE
- Prostatic intraepithelial neoplasia is the precursor to cancer. 95% are adenocarcinomas
- 2nd leading cause of male cancer, but only 1 in 8 men with prostate ca die of the disease
- Risks:
 - 2 fold risk if one first degree relative affected
 - Asian men shifting to western environments show an ↑ risk (as with Asian women and breast ca)
 - Tomatoes (lycopene) and statins are protective!
 - Single-nucleotide polymorphisms in 5 chromosomal regions have a cumulative association with prostate ca (NEJM 28 Feb 2008)
- Screening:
 - Detects many early cancers, but limited ability to differentiate between those that are lethal but still curable, and those that are benign/clinically insignificant
 - 20 – 25% of men with an abnormal DRE have cancer
 - DRE and PSA together still miss more cancers than they find. 15% of men aged 62 – 91 with a PSA < 4 had prostate cancer (NEJM 2004;250:2239-46), 15% of these with a Gleason score > 7
 - No benefit for men with a life expectancy < 10 years
 - *Prospective RCTs have shown no survival advantage*
- Prevention (ie no cancer diagnosis):
 - 5- α -reductase inhibitors (eg Finasteride) block conversion of testosterone to dihydrotestosterone (DHT) – a potent stimulator of prostate cell proliferation. 7 years of treatment reduces incidence of prostate cancer from 5 – 9% to 4 – 6%, initially thought those with cancer have slightly higher risk of high grade tumour but this turned out to be a histologic artefact. Most cancers detected were clinically insignificant. (Cochrane Review 2008)
- Diagnosis:
 - TRUS-guided biopsy, minimum of 6 cores, 12 – 14 cores → ↑diagnostic yield. Gives Gleason score (2 good, 10 bad)
 - MRI with endorectal coil is better than CT for assessing extraprostatic extension
 - Bone scan sensitive but not specific for bony metastasis. Very rare if PSA < 8, uncommon if < 10
 - Urine de-oxypridinoline: a marker of increased bone turnover in bony mets
 - Bony mets from prostate cancer are usually sclerotic, compared to lytic lesions in other mets

Treatment approaches

- Difference between cure and “cancer control”. Frequently responds to treatment. Rate of tumour growth varies dramatically
- Local disease:
 - Prostate Cancer Prevention Trial: Radical prostatectomy slightly less mortality than “watchful waiting” – one life saved for every 18 – 20 mean given prostatectomy. SE incontinence, impotence. Advised if life expectancy > 10 years
 - For local disease radiation (either external beam or brachytherapy – implantation of radioactive capsules) ~ equal to radical prostatectomy, but more bowel problems from radiotherapy
 - Surgery vs radiotherapy vs nothing has nearly equivalent 5 year survival
 - Wouldn't normally consider radical prostatectomy if PSA > 10 – mets likely
 - No benefit from hormonal treatment in PSA relapse-free survival
 - Extra-capsular extension: can still be offered treatment with curative intent. Radiotherapy (including consideration of dose escalation to > 70 Gy), adjuvant hormonal therapy improves outcomes.

- Neoadjuvant therapy is controversial – androgen deprivation reduces resection margins but not LN metastases or OS. No studies with newer chemotherapy agents. Studies complicated by poorer pre-op staging, no good end-point, and questions about optimal regimens and duration
- Predictors of relapse:
 - Gleason score
 - PSA doubling time (< 10 or > 10 months)
- Adjuvant therapy for locally advanced disease:
 - Adjuvant hormonal therapy:
 - Little data. Probably benefit for high risk patients
 - Options of continuous vs intermittent and duration (recommended 2 years post radical treatment) have little data
 - Adjuvant radiotherapy: EBRT, conformal 3D or Intensity modulated XRT (higher doses delivered and less toxic). Post-op radiotherapy improves local control but ?impact on OS
 - Combined adjuvant treatment: trials awaited
 - Chemotherapy: Needs larger trials – some evidence for docetaxel
- Controversial question: when to treat an asymptomatic PSA-relapse (usual lead time over symptoms of 40 months). Aim is palliation not cure, so need to consider SE vs benefits. Early treatment → slightly longer survival but ↑SE. Interest in intermittent treatment with treatment holidays → ↓loss of bone mass, ?delay in emergence of androgen resistance and ↓toxicity in “off” times
- Non-castrate metastatic disease (ie non-castrate levels of testosterone) → chemical or surgical androgen depletion
- Castrate metastatic disease:
 - Become androgen independent 18 – 24 months after castration, median survival is then 10 – 12 months (= Hormone Refractory Prostate Cancer – HRPC)
 - Still often sensitive to 2nd or 3rd line hormonal treatment
 - Mitoxantrone + prednisone improves symptoms but no survival benefit
 - Docetaxel + estramustine (alkylating agent) or prednisone chemo – slightly longer survival but more side-effects (requires significant steroid premedication, myelosuppressive, alopecia but unlike paclitaxel has little neuropathy). Docetaxel + Prednisone the current standard of care. Useful for bone pain if hormone insensitive
- Bisphosphonates:
 - Role in preventing osteopenia in androgen blockade unclear
 - RCT suggests Zoledronic acid delays skeletal complications in bone mets
 - Pain responses only marginally improved
 - SEs include flare in pain, myalgia, worsening of pre-existing renal impairment, osteonecrosis

Androgen deprivation therapy (ADT)

- Mainstay of therapy for metastatic disease, may modestly prolong survival
- Reduces symptoms in about 70 – 80% of patients with advanced prostate cancer, but most tumours relapse to an incurable, androgen independent state within 2 years
- Castration: SE loss of libido, erectile dysfunction, hot flushes, gynaecomastia and breast pain, increased body fat, muscle wasting, anaemia, decreased bone mineral density
- Testosterone lowering agents:
 - Estrogens: Diethylstilbestrol (DES) acts at hypothalamus to ↓LH → ↓testosterone in the testes – but thrombosis and cardiovascular disease. SE: cardiovascular effects (MI, CVA, DVT, PE)
 - GnRH/LHRH agonists (eg leuprolide, other depot injections) have equivalent potency but ↓SE. → loss of normal pulsed LHRH → ↓LH → ↓testicular androgens (however there is an initial surge of testosterone → flare of disease, so contraindicated if significant obstructive symptoms)
 - SE: androgen-depletion syndrome: hot flushes, weakness, fatigue, impotence, loss of muscle mass, changed personality, anaemia, depression, ↓bone mineral density (2nd to LHRH → ↓oestrogen, treat with bisphosphonates), alteration in body composition, glucose intolerance
 - GnRH antagonists: avoid problems of testosterone surge
 - Still get adrenal androgens even if testes shut down
- Antiandrogens: Androgen receptor blockers:
 - Non-steroidal competitive antagonists, eg **Flutamide**. Fewer side effects (nipple tenderness, maybe gynaecomastia – can treat with Tamoxifen, also diarrhoea, liver toxicity, loss of libido) but less effective

- Steroidal competitive antagonists but side effects of oestrogen: eg Cyproterone Acetate → ↓testosterone via central inhibition and peripheral competition. SE rare, high mortality liver toxicity, less gynaecomastia, ↓libedo)
- Orchiectomy or leuprolide, plus flutamide, is called complete androgen blockage (CAB) – uncertain incremental benefit – conflicting trials, ↑SEs
- Ketoconazole: inhibits adrenal androgen synthesis
- Corticosteroids → ↓ACTH → ↓steroidogenesis

Testicular Cancer

- 95% primary germ cell tumours of the testes
- 95% of patients are cured
- Usually men aged 20 – 40. If over 50 then lymphoma till proven otherwise. 1 in 250 men develop a testicular cancer in their lifetime
- Risks: cryptorchidism
- Presentation: painless testicular mass. If metastatic then back pain. Raised LDH. If ↑hCG then gynaecomastia (acts on normal testicular Leydig cells → ↑oestrogen → gynaecomastia)
- *Never biopsy* a testicular mass
- Types:
 - All have radical inguinal orchiectomy
 - Non-seminomatous GCT:
 - 3rd decade – embryonal carcinoma (secretes αFP or hCG or both), teratoma, choriocarcinoma (secretes hCG), endodermal sinus (secretes αFP). Early metastasis
 - Treatment:
 - Lower stages: No difference between surveillance and retroperitoneal lymph node dissection for stage 1A, otherwise RPLND
 - Higher stages: Chemo. Must include cisplatin (only cancer where it's not equivalent to carboplatin) + etoposide +/- bleomycin 1 or 2 cycles. SE substantial nausea, vomiting, hair loss, myelosuppression, nephrotoxicity, ototoxicity, peripheral neuropathy, bleomycin pulmonary toxicity in 5%
 - Poor prognosis with mediastinal primary, non-pulmonary visceral mets, high αFP, βhCG or LDH
 - PET scan often useful
 - Seminoma:
 - Normal αFP. βHCG usually normal
 - 50%, presents in 4th decade, more indolent course – all highly treatable
 - Treatment of stage 1:
 - Active surveillance with CT. 15% recurrence. Salvage rates high if detected early *or*
 - Radiotherapy: SE 2 – 5 % 2nd testicular cancer, cardiac disease after 10 – 15 years, cause unknown *or*
 - Adjuvant chemo (eg single agent carboplatin) with PET scan to check response and resection of residual masses
 - Treatment of large nodes or metastasis: retroperitoneal lymph node dissection +/- neoadjuvant or adjuvant chemotherapy
 - Relapsed/Refractory disease: sequential high dose chemotherapy and mini-autografts. Chemo options include VIP (vinblastine + Ifosfamide + cisplatin) or TIP (paclitaxel + Ifosfamide + cisplatin)
- Significant risk of impaired fertility due to chemo or lymph node surgery → cryopreservation

Breast Cancer

Epidemiology

- Western disease higher in terms of incidence but 3rd world mortality higher. Maori have lower incidence but higher mortality
- 30% of women diagnosed go on to develop metastatic disease which is ultimately fatal
- It is hormone dependent – women who have never had functioning ovaries nor oestrogen replacement don't ever get breast cancer
- 2/3rds is post menopausal

- Breast cancer will affect 1 in 12 women (1 in 9 in Australia). 10% is associated with an inherited mutation in a tumour suppressor gene
- Male breast cancer 1% of all breast cancer
- Risks:
 - Age > 50 (relative risk of 10) – strongest general risk (although biology more aggressive in the young)
 - Family history one of the strongest risks:
 - 10 – 20% of women with breast cancer have a positive family history but only 5% attributable to BRAC1 and 2 (see below)
 - 2 first degree relatives = 4 – 6 times relative risk
 - Mother > 60 = 1.4 times relative risk
 - Prior irradiation = relative risk 75 times
 - Age at menarche – age 16 has only 50 – 60 % the risk of age 12
 - Age at first pregnancy: pregnant at 18 has 30 – 40% lower risk than nulliparous
 - Age at menopause: delay → ↑risk
 - Maternal nursing → ↓risk
 - Asian women in Asia have lower risk, rises when they live in the US. ?links with total calories or fat unproven
 - Little or no ↑risk from OCP, and protect against ovarian and endometrial cancer
 - HRT (Women’s Health Initiative): oestrogen + progesterone → ↑risk of breast cancer and CVD, ↓bone fractures and colorectal ca – in total more negative events with HRT. No increase in risk with women with hysterectomies on oestrogen only
 - Benign proliferative breast disease: atypical ductal hyperplasia (must be proliferative to ↑ risk)
 - Past history of breast Ca: pre-invasive lesion have 5% risk of cancer by 10 years. Risk of further primary if already had invasive disease ~ 1% pa. (Most follow up treatment after breast ca is not about local recurrence by detecting a further primary)
 - SES
 - ↑BMI post menopause
 - ↑height → ↑risk by 20%
- Regular physical exercise is protective for post-menopausal breast ca

Genetics

- Familial:
 - BRAC-1 and 2 account for 85% of detectable hereditary breast cancer (so far):
 - BRAC1 = 150 times relative risk
 - Several hundred mutations reported
 - Tumour suppressor genes with similar functions: maintain genomic integrity, transcription regulation, breakage repair
 - Both alleles need to be mutated for a tumour to develop (2 hit hypothesis)
 - BRAC-1 tumour suppressor gene on 17q21 – ?gene repair. AD with high penetrance. One mutated allele → 87 % risk of breast ca by age 70, 33% risk of **ovarian** ca. If male, ↑risk of **prostate** and **breast** ca
 - BRAC-2 on 13q12 → ↑risk of breast ca in men (6%) and women (85% lifetime risk), and risk of **ovarian** (10 – 20% – less than BRAC1)
 - Li-Fraumeni Syndrome: very rare, mutations in p53 tumour suppressor gene → ↑breast ca, osteogenic carcinomas + others
 - Ataxia Telangiectasia: 100% lifetime risk of NHL, also breast, ovarian and GI. See page 168
 - Hereditary breast cancer has an earlier age of onset (< 50), a higher incidence of bilateral tumours, an ↑ incidence in males, and an association with other tumours
 - Management of high risk women:
 - Complicated
 - Prophylactic bilateral risk reduction mastectomy: ↓ risk 90%. BSO ↓risk 90%
 - Screening:
 - Breast: self exam, 6/12 clinical breast exam, annual mammogram from 40 (or 5 years younger than relative), ?MRI – more sensitive but less specific so lots of false positives which are biopsied
 - Ovarian: TVUS and Ca 125 6 monthly from 35 (no evidence of benefit) – can be fast growing so can still get advanced disease with a short screening interval
 - OCP reduces ovarian risk but may increase breast risk

- Consider chemoprevention:
 - Primary Prevention in high risk women: IBIS 1 trial. 5 years of tamoxifen showed 32% risk reduction in breast ca but ↑ all cause mortality
 - Raloxifene: Compared with Tamoxifen in the STAR trial: equivalent in prevention, fewer DVTs and endometrial cancer, didn't reduce non-invasive cancers as much
- Acquired:
 - p53 mutation in 40% of breast ca
 - erbB2 (HER-2, neu): ↑ oncogene expression in ~25 % of breast ca

Screening

- Breast self-examination (leads to ↑ biopsy rate but no change in mortality), clinical breast-examination not tested in RCTs
- Screening mammogram:
 - Shown to be effective, but misses 10 – 20% of breast ca
 - For women aged 40 – 49, half will have a false positive, little benefit at 5 – 7 years, but small benefit at 10 – 12 years
 - For women aged 50 – 69, mortality benefit from 5 years after screening – 25 – 30% reduction in the chance of dying from breast cancer. Compared with 40 – 49 years, has higher incidence and less dense breast tissue
 - Less sensitive in BRC1 and 2 – ?affects younger women in whom screening is less sensitive
 - Not good for lobular invasive carcinoma, Paget's disease of the nipple, inflammatory carcinoma, peripheral small carcinomas
- MRI still being evaluated – but better in women at high genetic risk or with dense breast tissue (ie premenopausal), sensitive but not specific. Too sensitive for the general population

Diagnosis

- Process: mammography → ultrasound → biopsy
- If aspiration → non-bloody fluid then cyst
- Role of US – distinguish cysts from solid tumour
- Benign-feeling lump, negative mammogram and negative FNA → 1% risk of false negative
- Mammography: diagnostic mammography aimed at evaluating the rest of the breast before biopsy is performed – less about assessing a lump. Can't ignore a palpable mass even if mammography normal due to false negative rate
- MRI of contralateral breast at diagnosis detects more tumours than does mammography and clinical exam, but with many false positives
- In pregnancy:
 - Lactation is suppressed by progesterone suppressing prolactin. After delivery ↓ progesterone → unopposed prolactin
 - Development of a dominant mass cannot be attributed to pregnancy. Breast ca develops in 1 in 3000 – 4000 pregnancies
- Tumour markers: Ca 15.3 and 27.29. May have utility in detecting recurrence. One study shows highly sensitive for detecting preclinical mets
- Poor prognostic factors for a breast ca:
 - Stage
 - Increasing size
 - Positive axillary nodes
 - Higher grade tumours on histology
 - Genetics: HER-2/neu (but more likely to respond to doxorubicin) and P53 mutation worse
 - Lack of oestrogen and/or progesterone receptors → worse
 - Higher proportion of cells in S phase (via flow cytometry) → worse but greater effect from chemo
 - Half of all initial cancer recurrences occur > 5 years after initial therapy
- Inflammatory breast ca: a variant of epithelial cancer. Most lethal form of locally advanced breast cancer. A diffuse process – lower yield from mammography, need a biopsy
- Fibrocystic disease: histologic not clinical diagnosis. Small fluid-filled cysts and modest epithelial cell and fibrous tissue hyperplasia

Treatment

- Lumpectomy +/- radiation as good as mastectomy +/- radiation. Slightly higher recurrence with lumpectomy but 10 year survival the same. Tumours > 5cm, involve the nipple, multiple quadrants or

with extensive intraductal disease not suitable for lumpectomy. If no radiotherapy then 30% recurrence over 10 years. With radiotherapy then 10% recurrence over 10 years

- Now common for reconstruction at the time of mastectomy (ie TRAM)
- Oophorectomy → substantial survival benefit if ER positive – but not widely used
- Sentinel node biopsy now replacing need for axillary clearance:
 - Intradermal injection with blue dye or radioactive colloid
 - Negative predictive value 95% and decreased morbidity
 - Don't do it if palpable nodes or if had prior chemotherapy
 - If positive then axillary clearance (for prognostic purposes only)
- Stages:

Stage	10 yr overall survival	
I	80%	Tumour < 2cm, -ive nodes
II	55%	Tumour 2 – 5 cm, and/or +ive nodes
III	40%	Tumour > 5 cm and/or fixed nodes
IV	10%	Distant metastasis beyond ipsilateral axillary nodes

- Adjuvant treatment:

	Node negative		Node positive	
	HR+	HR-	HR+	HR- (nasty)
Pre-menopausal	Hormone ?chemo (?main benefit early menopause) ?Ov suppression (GnRH analogue)	Chemo 1 st – 2 nd generation	Chemo Hormone ?Ov Suppression (controversial)	Chemo: 2 nd – 3 rd generation
Post-menopausal	(best prognosis) Hormone	Chemo 1 st – 2 nd generation	Hormone ?chemo	Chemo: 2 nd – 3 rd generation

Adjuvant chemotherapy therapy

- 30% relative risk reduction:
 - High risk: 70% recurrence risk reduced to 49% – 21% ARR
 - Low risk: 10% recurrence risk reduced to 7% – 3% ARR for the same toxicities
- Unnecessary for tumour < 1 cm and no nodes
- Of most benefit in premenopausal, of positive but lesser benefit post-menopausal (may just use aromatase inhibitors/Tamoxifen)
- If node negative and ER positive, the recurrence score, derived from a multigene assay of 16 cancer related genes, identifies the subset of women most likely to benefit from adjuvant chemotherapy. For those with a low score, there is no difference between tamoxifen and tamoxifen + chemo (Ann Int Med, 4 Dec 2007). Test costs approx US\$3,000
- Usually dual regimes: anthracyclines (eg doxorubicin – Antitumour antibiotic) + taxanes (eg paclitaxel – an antimetabolic agent). Escalating doses or extra agents: need to weigh toxicities against absolute benefit
- 4 cycles of doxorubicin + cyclophosphamide then 4 cycles of taxane (eg weekly paclitaxel) are better than just the former (especially if ER negative)
- Neoadjuvant (ie before surgery) chemotherapy in stage III (locally advanced disease): No RCTs but use widespread. Chemo, then surgery, then radiation – allows many patients to be “down-staged” to breast conserving surgery. Disease-free survival in 30 – 50% (ER +ive better than ER –ive)

Adjuvant Hormone Therapy

- Aim is to ↓oestrogen activity in breast, uterus and ovary and ↑oestrogen activity in bone, brain and cardiovascular tissues
- ~40 % RRR for recurrence when used in early stage disease
- **Tamoxifen:**
 - A type of SERM (Selective Oestrogen Receptor Modulators): Modulate ER activity via epigenetic changes
 - An anti-oestrogen (competes with oestrogen binding) with partial oestrogen agonistic activity in endometrium and bone
 - 10 fold greater anti-tumour effect in ER positive over ER negative expression, but more modest if axillary node positive
 - Up-regulates TGF β (transforming growth factor) → ↓breast cell proliferation

- Mainly for women with post-menopausal disease (premenopausal treatment is ovarian suppression if ER positive eg GnRH analogue)
- Reduced the number of new cancers in the opposite breast by 1/3rd
- No benefit beyond 5 years. At 10 years, following 5 years treatment, disease free survival:
 - Node negative: 79 vs 64%
 - Node positive: 60 vs 45%
- Usual dose 20 mg daily, hepatic metabolism and biliary excretion
- Reduced bone fractures, ↓total cholesterol, ↓mortality from MI
- 2D6 metabolised. 5% are poor metabolisers so don't metabolise to the active metabolite → ↑risk of recurrence. Can assess clinically – if they get hot flushes then it's working. 2D6 inhibitors (eg paroxetine) are contraindicated
- SE:
 - Hot flushes: premenopausal 60%, post menopausal 10 – 20%
 - Small ↑ in endometrial cancer (0.75% after > 5 years use)
 - Stroke, PE and DVT, and *cataracts*
 - *Preserves bone density*
- **Aromatase inhibitors:**
 - Block the conversion of androgens to oestrogen in breast and subcutaneous fat
 - *In post-menopausal women only* – little role in pre-menopausal as ovaries produce the vast amount of oestrogen
 - *Must be ER +ive*
 - 3rd generation AIs:
 - Irreversible analogues (steroidal): **exemestane** (Aromasin)
 - Reversible inhibitors (non-steroidal): **anastrozole** (Arimidex) and **letrozole** (Femara)
 - Primary renal elimination
 - Can induce ovulation – so want menopause to be firmly established
 - SE: ↑*risk of osteoporosis*, diarrhoea, arthralgias, cataracts, ↓VTE and ↓uterine ca cf tamoxifen
 - No data for 5 year use – just based on tamoxifen data. Could have activity for life
- Aromatase inhibitors vs tamoxifen:
 - 7 reported studies with 3rd generation: 2 of initial therapy cf tamoxifen, 3 of “switch” therapy, 2 or late AI therapy (after tamoxifen)
 - Benefit unclear between Tamoxifen for 5 years then aromatase inhibitor, or the reverse, or Tamoxifen for 3 years then aromatase inhibitor (all better than Tamoxifen alone for 5 years – but took a head to head trial of 8000 women to show the difference) – improved disease free survival but not overall survival
 - Bottom line:
 - Premenopausal and ER +ive: 5 years tamoxifen then stop
 - Perimenopausal and ER +ive: tamoxifen till confident menopause past then change to AI
 - Post menopausal ER +ive: AI equivalent to AI followed by tamoxifen

Herceptin

- HER2/neu (Human Epidermal Growth Factor receptor 2, a member of the Epidermal growth factor receptor (EGFR) family) is amplified in ~15 – 25% of breast cancers, promotes DNA synthesis and cell growth, these are less responsive to chemotherapy and hormones, with reduced survival
- Measured with immunohistochemistry (protein expression) and FISH (measure gene amplification). IHC gives a score of 0/1+ (negative), 2+ (equivocal – do confirmatory genetic test), 3+ positive
- Trastuzumab (Herceptin) is a mab that binds HER2/neu on the surface of tumour cells and induces internalization of the receptor → ↓cell cycle progression and makes them more susceptible to apoptosis with concurrent chemotherapy
- 2 year disease free survival of 85 cf 77% without Herceptin (absolute treatment benefits at 2 years of 8%, reduced relative risk of recurrence by ~40%)
- Scant evidence in node negative disease
- Usually given following anthracyclines, concurrent with taxanes (synergistic effect)
- Given 3 weekly iv, 12 month cost of ~\$60,000 for drug alone
- SE: infusion related fevers/chills
- Inhibits cardiac function (usually reversible), especially if prior anthracyclines
- Trials with both concurrent and sequential addition to chemotherapy. PHARMAC disputes the evidence about sequential use (says there is selective publication of the data, Lancet 17 May 2008)

Metastatic Disease

- Can live a long time. Aim for symptom control, QoL, improved survival
- Sites: roughly equally spread between soft tissue, bone and visceral (lung/liver). Cerebral mets frequent
- If relapse then rebiopsy as in up to ~15% may have transformed from ER +ive → ER +ive and/or HER+ive → HER +ive
- Radiation +/- surgery for palliation of bone pain, spinal cord compression, cerebral mets
- Bone involvement → bisphosphonates
- Hormone therapy: Only if ER and/or PR +ive. Not if rapid response required (eg advanced liver disease). Aromatase inhibitors better than Tamoxifen, especially if ER and HER2 +ive. Combination therapy of no additional benefit – but sequential therapy may be
- Chemotherapy:
 - No additive survival benefit from chemotherapy on top of endocrine therapy – little effect on duration or survival if there is a tumour response
 - Consider for QoL if toxicities worth it. May active agents
 - If used, usually single agent (less toxicity): anthracycline or paclitaxel
- Targeted therapy:
 - Trastuzumab has further modest benefit. No CSF penetration (large molecule)
 - Lapatinib (Tykerb): oral small molecule tyrosine kinase inhibitor that target's the HER2 pathway. Benefit as single agent or with chemo. Appears to have activity against cerebral mets and in trastuzumab refractory disease
 - Bevacizumab: Small benefit in terms of time to progression in combination with chemotherapy
- Bisphosphonates: ↓risk of bone pain, fracture, hypercalcaemia and cord compression. Currently being studied for primary prevention for high risk

Non-Invasive Breast Cancer

- Ductal carcinoma in situ – now ductal intraepithelial neoplasia:
 - Cytologically malignant breast epithelial cells within the ducts – may be difficult to distinguish from atypical hyperplasia. If any invasion at all should do node biopsy
 - Clustered microcalcifications on mammogram
 - 1/3rd will develop invasive cancer within 5 years (but not sure – no ones left them in to see)
 - Treated with lumpectomy + radiation (reduces recurrence, equal survival, cf lumpectomy alone). Reduces recurrence to 10%, of which half will develop metastatic disease
 - Tamoxifen helps. No data for aromatase inhibitors
- Lobular Intraepithelial Neoplasia:
 - Not a pre-invasive lesion – but a marker of increase risk of developing breast cancer
 - Don't excise – doesn't make any difference
 - 30% who have had adequate local excision develop (usually infiltrating ductal carcinoma) over the next 15 – 20 years
 - Ipsilateral = contralateral recurrence ⇒ marker for risk rather than a form of malignancy itself
 - Treat with lumpectomy + Tamoxifen and annual mammography

Male Breast Cancer

- 1/150 as frequent in men as women
- Greater in men with gynecomastia
- Mastectomy + axillary node dissection
- Locally advanced disease or positive nodes → radiation
- 90% are ER +ive – no trials have evaluated adjuvant therapy

Gynaecologic Malignancies

Ovarian Cancer

- Use of oral contraceptives confers long term protection against ovarian cancer (Lancet 26 Jan 2008)
- Three types with different managements:
 - Germ cells
 - Stromal cells
 - Epithelial cells (85%): 50% benign, 33% frankly malignant (usually older), 16% low malignant potential (usually younger)

- Metastasises from breast, colon, gastric and pancreas
- Adnexal palpation, transvaginal ultrasound and serum Ca-125 assessed and not sufficient high sensitivity or specificity for screening purposes. No evidence screening saves lives (and lots of false positives from cysts)
- Diagnosis and staging from laparotomy
- Commonest cause of death is bowel obstruction
- Epithelial cell cancer:
 - Incidence increases until 8th decade
 - Presents late due to asymptomatic early stages with abdo pain, bloating and urinary symptoms
 - Familial Syndromes: Increased risk with BRAC-1 and BRAC-2, Lynch syndrome (non-polyposis colorectal, ovarian and endometrial cancer)
 - Reduced risk with more pregnancies, breast-feeding, oral contraceptives
 - Common oncogene abnormalities: c-myc, H-ras, k-ras and neu
 - Tumour markers: CA-125: decline after treatment correlates with prognosis but is not sufficiently accurate to guide individual decisions. Also in endometrial, breast, lung, oesophageal, gastric, hepatic, and pancreatic cancer, and in menses, pregnancy, fibroids, ovarian cysts, PID, cirrhosis, ascites, pleural/pericardial effusions, endometriosis
 - Treatment:
 - Stage 1: definitive surgery with 95% 5 year survival. If poorly differentiated tumour, small incremental survival from adjuvant chemo
 - More advanced disease: paclitaxel and carboplatin (better than paclitaxel and cisplatin – same survival, less SE). Place of intraperitoneal chemotherapy uncertain (more benefit, more toxicity)
 - 2nd look surgery no longer recommended
 - Progestational agents, Tamoxifen or aromatase inhibitors have response in 5 – 15%
 - Bevacizumab for VEGF has shown benefit in early trials
 - 20% express HER2/neu, response to trastuzumab

Uterine Cancer/Endometrial Cancer

- Most common female pelvic malignancy, primarily in post-menopausal women
- Presents early due to post-menopausal discharge/bleeding
- Risks: unopposed oestrogen from any cause – obesity, late menopause, chronic anovulation, exogenous, tamoxifen (twofold risk), also Lynch Syndrome
- ~ 80% are adenocarcinoma, further 10% are adenocarcinoma with squamous differentiation
- Staging via a total abdominal hysterectomy and bilateral salpingo-oophorectomy
- Treatment:
 - Stage 1: surgery
 - Nasty Stage I to stage III: surgery + radiation
 - Stage IIIC/IV: improved survival with platinum-based chemotherapy compared to whole-abdominal irradiation alone
 - Progestational agents → response in 10 – 20%

Cervical Cancer

- 70% caused by HPV 16 and 18, also caused by 31, 33, 52 and 58. In HPV 16 and 18, proteins E6 and E7 inactivate tumour suppressor genes p53 and pRB
- Vaccination: inactivated viral particles – non-infectious but highly immunogenic, and very effective in follow up to date (~ 5 years). Not all oncogenic HPVs are covered so screening is still necessary
- Pap smear is 90 – 95% accurate in early lesions such as CIN, less sensitive for frankly invasive cancer
- Treatment:
 - Carcinoma in situ: stage 0: cone biopsy
 - Stage 1: radical hysterectomy *or* radiation
 - Stages II – IV: surgery + combined external/intracavity radiation +/- chemo
 - Stage IIb – IVA: cisplatin + 5-FU with concurrent radiation better than radiation alone

Head and Neck Cancer

- See Lancet 17 May 2008, NEJM 11 Sept 2008
- Squamous cell carcinomas developing in the upper aerodigestive epithelium as a result of:
 - Tobacco and alcohol

- Human papillomavirus in some subsets
- Chemotherapy:
 - Eg cisplatin and taxanes, and targeted agents (eg EGFR inhibitors such as cetuximab), increasingly used alongside traditional surgery + radio therapy approaches. Eg neoadjuvant treatment for larynx preservation
 - Absolute benefit of 8% with concurrent chemoradiotherapy as opposed to radiotherapy alone
 - Prolonged survival demonstrated in stage III and IV tumours with docetaxel, cisplatin, and fluorouracil as induction chemo
- Emerging evidence of the value of PET scanning in staging and restaging after therapy
- Prognosis:
 - Stage 1: 90% survival
 - Stage 2: 70% survival

Carcinoma of Unknown Primary (CUP)

- Biopsy proven (eg from a lymph node) malignancy for which the primary can't be found after a CT of the chest, abdomen and pelvis
- Either primary has regressed, or it is too small to be found (ie malignant event that → ↑metastatic spread and survival relative to the primary)
- 3% of all cancers, 60% are adenocarcinoma, 5% squamous cell, the rest poorly differentiated
- Imaging and immunochemistry have a diagnostic yield of 20 – 30%
- Median survival is 6 – 10 months. Prognosis includes performance status, site and number of mets, response to chemo and LDH levels. Adenocarcinoma worse than SCC
- If liver, brain and adrenal mets then poor prognosis
- Possible tests:
 - Over-investigating has not been shown to alter survival!
 - Tumour markers: including CEA, CA-125, CA 19-9, CA 15-3, when elevated are non-specific
 - Women should have mammography, and MRI if anything suspicious
 - Colonoscopy has low yield unless symptoms (and they will already have had a abdo CT)
 - PET scan reveals primary in 20%
 - Cytogenetic studies rarely helpful, maybe if high suspicion of lymphoma
 - Immunohistochemical staining may give clues – but none are 100% specific. Prostate and thyroid stains are the most specific – but these rarely present as CUP. Estrogen and progesterone receptors suggest breast ca
 - Cytokeratin (CK): 20 different subtypes of filament with different expressions in different cancers – may help classify according to site of origin
 - The future: gene expression studies using quantitative reverse transcriptase PCR or DNA microarray
- Clues:
 - Poorly differentiated midline tumour in a male < 50 with ↑βhCG or AFP: extra-gonadal germ cell tumour. Cisplatin, etoposide and bleomycin → complete response in 25% and ~ 15% cure
 - Axillary adenopathy in a woman: treat as stage II or III breast ca. Unless ipsilateral breast is radiated, up to 50% will later develop a breast mass
 - Women with peritoneal carcinomatosis and ↑CA-125 (and maybe psammoma bodies): treat as ovarian – debulking surgery followed by paclitaxel + cisplatin or carboplatin, 20% response, 10% 2 year survival. Do TVUS
 - Neuroendocrine carcinoma: If low grade, may just treat with somatostatin. If high grade, treat as small cell lung cancer – a minority respond well to chemo
 - Skeletal metastases: if raised PSA think prostate, may respond well to hormonal therapy. Rule out lung
 - Cervical CUP (ie neck lymphadenopathy without known primary):
 - Direct laryngoscopy, bronchoscopy and upper endoscopy
 - PET scan may help identify primary tumour (in other settings controversial)
 - If squamous cell then radical dissection and radiation. Role of chemo unclear (but induction chemotherapy often used)
- Treatment:
 - Treat symptomatic lesions palliatively with radiotherapy
 - All-purpose chemotherapy regimes rarely produce responses but always produce toxicity

- Disseminated CUP: Platinum based chemo (eg carboplatin, paclitaxel & oral etoposide) extends survival. Role of second line chemo poorly defined

Paraneoplastic Syndromes

- If atypical clinical signs or symptoms in a cancer patient, consider paraneoplastic syndromes – they can add to both morbidity and mortality
- Neuroendocrine tumours (eg SCLC and carcinoids) produce lots of peptide hormones – common causes of paraneoplastic syndromes
- Mechanisms not completely understood:
 - Genetic rearrangements occur, but unusual (eg \uparrow PTH in some ovarian ca – PTH gene shifts to be under ovarian control)
 - Cellular de-differentiation \rightarrow expression of hormones from prior stages of development
- Lung cancers:
 - Small cell: SIADH, ectopic ACTH, Lambert-Eaton, SVCO
 - Squamous cell lung cancer: \uparrow Ca, HOPA, clubbing, Pancoast tumour (Horner's, wasting hand muscles)
- Typical syndromes (there are many others):

Syndrome	Ectopic Hormone	Typical Tumours
\uparrow Ca	PTHrP	Squamous cell (head, neck, lung, skin), breast, GI Lymphoma
	1,25DiVitD	Lung, ovary
	PTH (rare)	Renal, lung
	Prostaglandin E2 (rare)	
SIADH	Vasopressin	Lung (small cell, squamous), GI, genitourinary, ovary
Cushing's Syndrome	ACTH	Lung (small cell, bronchial carcinoid, adenocarcinoma, squamous), thymus, pancreatic islet, medullary thyroid
	Corticotropin-releasing hormone (CRH, rare)	Pancreatic islet, carcinoid, lung, prostate
Non-islet cell hypoglycaemia	Insulin-like growth factor	Mesenchymal tumours, sarcomas, adrenal, hepatic, GI, kidney, prostate

- PTHrH:
 - See hypercalcaemia, page 90, and hypercalcaemia in malignancy, page 384
 - In addition to circulating hormone, bone mets (eg breast, myeloma) may produce this with local effect. PTHrH binds to the PTH receptor
 - Clinical manifestations: usually incidental finding in malignancy workup. If very high (> 3.5 mg/dl) then fatigue, mental status changes, dehydration, nephrolithiasis
 - Measure PTH (to exclude primary hyperPTH), PTHrH and Vit D
 - Treatment: oral phosphorus. If acute then saline rehydration with forced diuresis if this is not sufficient. Bisphosphonates take several days to work. \uparrow Ca associated with lymphoma, myeloma or leukaemia may respond to glucocorticoids
- SIADH/Vasopressin:
 - At least 50% of SCLC. May compensate with \downarrow thirst, \downarrow aldosterone, \uparrow atrial natriuretic hormone (ANP)
 - Can't diagnose it if under or over loaded (eg if postural drop)
 - Measure urine sodium, glucose, exclude renal, adrenal and thyroid causes, exclude CHF, cirrhosis and medications
 - Treatment: correct gradually with fluid restriction. V2-receptor antagonists may be helpful
- Cushing's Syndrome:
 - 50% from SCLC, 15% from thymic, 10% from islet cell tumours, 10% bronchial carcinoid, 2% from pheo
 - Usually less weight gain and truncal obesity given short history and background cachexia. Can have very high levels \rightarrow marked metabolic changes: fluid retention, HTN, hypokalaemia, metabolic alkalosis, glucose intolerance, steroid psychosis
 - Adrenalectomy often not practical. Medical suppression with ketoconazole or metyrapone with steroid replacement

Paraneoplastic Neurologic Syndromes

- Remote effects of cancer, not caused by mets, stroke or metabolic derangements
- 0.5 – 1%, but 2 – 3 % of SCLC and 30 – 50% of thymoma or sclerotic myeloma
- Cross reactive antibodies to onconeural antigens expressed by tumours
- Can affect brain, brainstem, spinal chord, dorsal root ganglia (ie → sensory neuropathy), peripheral nerves, neuromuscular junction, muscle, visual system (eg retinopathy or uveitis)
- Generally respond poorly to treatment, roles of plasma exchange, IVIg and immunosuppression are not established
- Eg:
 - Anti-Hu → paraneoplastic encephalomyelitis (an inflammatory process with multifocal involvement of the nervous system), associated with SCLC and other neuroendocrine tumours
 - Anti-Yo → paraneoplastic cerebellar degeneration, associated with ovary and breast. In reality, it's a 6 week wait while it's done in the USA...
 - Thymoma → myasthenia gravis

Glossary

- Sideroblasts: developing erythroblasts
- Reticulocytes: need to stain before you can formally call them reticulocytes. “Polychromasia” is code for unstained bluish rbc that are assumed to be reticulocytes
- Target cell: suggests hypo/asplenic, thalassaemia, liver disease
- Schistocytes: rbc fragments
- Spherocytes: either HbS or haemolytic anaemia
- Poikilocytes: abnormally shaped rbc
- Acanthocytes or Spur Cells: spiculated red cells with projections: seen in malnutrition states, hypothyroidism, and coeliac disease
- MCV = mean corpuscular volume
- Differential of massive splenomegaly:
 - Myelofibrosis
 - Lymphoma
 - CML
 - CLL
 - Hairy cell leukaemia
 - Polycythaemia
 - Sarcoid
 - Autoimmune haemolytic anaemia
 - Malaria

- Differentials:

- Decreased counts:

	↓Production	↑Destruction
Hb	Fe, B12, folate, BM disorder (Pure Red Cell Aplasia)	Haemolysis, thalassaemia
WCC	BM infiltration BM dyscrasias (MDS)	Immune, drugs, sepsis
Platelets	BM infiltration BM dyscrasia (MDS)	Immune, TTP, DIC
Pancytopenia	BM infiltration BM dyscrasia Aplastic anaemia	Immune, drugs, sepsis

- Increased counts:

	Reactive	Clonal
Hb	Hypoxia, ↑EPO	Polycythaemia Vera
WCC	Infection, inflammation	Eg CML, CLL
Platelets	↓Fe, infection, inflammation, splenectomy	Essential thrombocythaemia
Eosinophils	Vasculitis, drugs, parasites, lymphoma, malignancy	Chronic eosinophilic leukaemia

Anaemia

- For anaemia 2nd to renal failure, see page 115

Hypoproliferative Anaemias

- Differential:
 - Elevated EPO and shift reticulocytes on blood smear:
 - *Iron deficiency*
 - *Thalassaemia*: inherited defect in globin chain synthesis. Fe and transferrin levels usually increased
 - Myelodysplastic syndromes: may have impaired haemoglobin synthesis with mitochondrial dysfunction
 - Endogenous EPO production inadequate for degree of anaemia observed:
 - *Acute and chronic inflammation*
 - Renal disease
 - Hypometabolic states: protein malnutrition

- Endocrine deficiencies: ↓testosterone or ↑oestrogen in males → ↓erythropoiesis. Hypothyroidism and hypopituitarism. Iron and folate absorption may be affected in these disorders as well. Addison's disease: anaemia may be masked by ↓ plasma volume
- Liver disease: anaemia from nearly any cause. Blood smear may show spur cells and stomatocytes from ↑cholesterol due to ↓lecithin cholesterol acyltransferase
- Lead and aluminium toxicity

Iron Metabolism

- See also Haemochromatosis, page 366
- Iron absorption:
 - About 1 mg in males and 1.4 mg in females required to be absorbed each day
 - Requires acid environment in the stomach to maintain iron in solution. Fe deficiency more likely than B12, folate, Ca or Mg deficiency following distal gastrectomy
 - If iron deficient, can absorb up to 20% of dietary iron (only 5 – 10 % in a vegetarian diet)
 - DMT1 imports Fe into the enterocytes at the apical surface. ↑expression in Fe deficient anaemia
 - Iron is transported through the basolateral surface of the gut cell into the plasma via the iron exporter ferroportin (also present on hepatocytes)
 - Ferroportin's function is negatively regulated by hepcidin (aka LEAP-1: Liver expressed antimicrobial peptide) – the principal iron regulatory hormone – made by the liver and:
 - ↑IL-6 (in inflammation) → ↑hepcidin (→ ↓Fe absorption). Hepcidin is an acute phase protein which binds to ferroportin marking it for lysosomal degradation. So the net effect is to sequester iron in enterocytes, macrophages and the liver during the acute phase response. ?Survival advantage from limiting serum Fe to micro-organisms or malignant cells
 - ↓ in hypoxia and anaemia
 - Hepcidin deficiency is the cause of most forms of haemochromatosis (2nd to hepcidin gene mutations or dysregulation of synthesis). See page 366
 - If the iron is not exported from the duodenal enterocytes, it is lost when the cell is shed (primary mechanism of body iron regulation)
- Fe transport:
 - Iron circulates bound to transferrin – the iron transport protein (iron is toxic so the body has lots of mechanisms to handle it carefully)
 - Interacts with transferrin receptors on the surface of marrow erythroid cells (also receptors on many tissues, especially macrophages and hepatocytes). Truncated fragments of transferrin receptors are released into the serum and can be measured: sTfR. ↑ in Fe deficiency anaemia (RBCs are hungry for Fe...)
- Fe storage:
 - Intracellular iron, in excess of that required for haemoglobin, is bound to a storage protein apoferritin, forming ferritin
 - Protein aggregates of ferritin form haemosiderin
 - Total body iron ~ 3 – 4 gm – 2.5 gm in Hb, 400 mg in Fe containing proteins, 3 – 7 mg bound to transferrin in plasma, rest stored as ferritin or haemosiderin
- Old red cells are phagocytosed by the reticuloendothelial system. Iron is very efficiently recycled
- There is no regulated excretory pathway

Iron deficiency anaemia

- Differential:
 - GI bleeding: ulcers, gastritis, malignancy, diverticulitis
 - Menstruation
 - Diet: vegetarians, children on cows milk
 - Others: Coeliac, gastrectomy involving duodenum, ↑ demand (pregnancy), polycythaemia, bleeding disorders, haematuria, hookworm
- Blood loss in excess of 10 – 20 ml of red cells/day is more than the amount of iron the gut can absorb
- Lab measures:
 - Serum iron: amount of circulating iron bound to transferrin. Useless measure – only reflects last meal
 - Ferritin: Reflects body stores of iron. Specific but not sensitive (eg inflammation). Normal values depend on age and gender. Males ~ 100, females ~ 30, < 15 ⇒ depleted iron stores

- Serum Transferrin (serum transporter)/Transferrin Receptor Protein (fragments of transferrin receptors on cells released into blood): is released into blood and correlates with erythroid marrow mass. **↑ in iron deficiency, ↓ or normal in inflammation**
- Total iron-binding capacity (TIBC): indirect measure of circulating transferrin – sites available to bind. **↑ in Fe deficiency, ↓ in inflammation**
- Transferrin % saturation of transferrin with iron (opposite of TIBC). Saturation (normally 25 – 50%) = serum iron * 100 / TIBC. Mildly ↓ (ie 10 – 20%) in inflammation, very ↓ (ie < 10%) in Fe deficiency
- sTfR/log ferritin > 2 in chronic disease with Fe deficiency and < 1 in chronic disease alone
- Protoporphyrin: Intermediate in haem synthesis. Accumulates if haem synthesis is impaired (also ↑ in lead poisoning)
- ↑ Red Cell Distribution Width (RDW): lots of variation (cf with thalassaemia where it's normal)
- Stages of iron deficiency:
 - Negative iron balance – draw on iron stores
 - Iron deficient erythropoiesis: serum ferritin and transferrin saturation falls and TIBC increases
 - Iron deficiency anaemia: haemoglobin and haematocrit fall. Initially bone marrow is hypoproliferative, but with severe, sustained iron deficiency → erythroid hyperplasia
- Signs:
 - Cheilosis: fissures at the corner of the mouth
 - Koilonychia: spooning of the finger nails
- Treatment:
 - Oral iron. On an empty stomach – food may impair absorption. 200 – 300 mg elemental iron per day → 50 mg absorbed → supports red cell production 2 – 3 times normal. Need to treat for 6 months after anaemia corrected to replenish stores. Hb should ↑ 2 – 3 g/l per month. Reticulocytes after 1 – 2 weeks. SE abdo pain, nausea, vomiting, constipation → non-compliance
 - Parenteral iron therapy: eg to augment response to EPO in dialysis. Slow through large cannula. Anaphylaxis/hypersensitivity reactions
 - 1 unit RBC = 200 mg iron

Anaemia of Chronic Disease

- See NEJM 10 March 2005
- Usually normocytic and normochromic, low or low normal reticulocytes
- Dysregulation of Fe homeostasis:
 - IL-1 and TNF → ↓ EPO production, ↓ responsiveness of cells to EPO, and ↑ hepcidin (which blocks iron release from endothelial cells)
 - ↑ uptake and retention of Fe within cells of the RES (macrophages, etc)
 - ↓ erythropoiesis: cytokine mediated (eg INF-γ)
 - Increased RBC destruction
- Anaemia of Renal Failure:
 - See Anaemia in Chronic Renal Disease, page 115
 - Characterised by EPO deficiency
 - Contribution to EPO suppression and resistance by:
 - Inflammation
 - Uraemia:
 - A chronic inflammatory state, with elevated IL-6 (major inducer of acute phase proteins, ferritin, CRP, oxidative stress...)
 - Inflammation increases on dialysis
 - Iron deficiency
 - So possible treatment options with ?anti-TNF drugs, ?statins (reduced CRP in RA)
- Beware long term transfusions → Fe overload and HLA sensitization
- Avoid iron therapy unless they also have an absolute iron deficiency, consider if on EPO and non-responsive
- If chronic inflammation associated with chronic blood loss, either replace iron and see what happens, or bone marrow stained for iron stores to exclude deficiency
- EPO: Response rates variable: MDS 25%, myeloma 80%, CRF 95%

Sideroblastic Anaemia

- Heterogenous group of anaemias in which haemoglobin synthesis is reduced because of failure to incorporate heme into protoporphyrin

- Iron accumulates – particularly in mitochondria
- Prussian blue stain of bone marrow → ringed sideroblasts (cells with iron deposits encircling the red cell nucleus)
- Bone marrow: ineffective erythropoiesis (expansion of erythroid compartment but no ↑ in reticulocytes)
- Usually acquired:
 - Early myelodysplasia
 - Chronic alcohol
 - Lead poisoning (rbc show coarse basophilic stippling)
- Some genetic: eg see X-linked Sideroblastic Anaemia in Porphyria, page 368

Megaloblastic Anaemias

- Causes:
 - Cobalamin (Vitamin B12) deficiency
 - Folate deficiency
 - Genetic or acquired abnormalities affecting the metabolism of these vitamins
 - Drugs:
 - Antifolates: methotrexate, trimethoprim
 - Affecting DNA synthesis: hydroxyurea, 6-mercaptopurine, cyclophosphamide, nucleoside analogues (AZT), etc
 - Myelodysplasia or acute myeloid leukaemia
 - Liver disease
 - Cu deficiency
 - Toxins: arsenic poisoning
 - Down's syndrome
- All lead to reduced DNA synthesis in the rapidly dividing cells of the marrow by reducing the synthesis of DNA precursors: dGTP, dTTP, dCTP, dATP
- Presentation:
 - Raised MCV, oval macrocytes, hypersegmented neutrophils, leukopenia (↓granulocytes and lymphocytes), moderate ↓ in platelets
 - Anaemia: weight loss, diarrhoea, constipation
 - Neuro: subacute combined degeneration of the cord, symmetrical neuropathy with LL > UL
 - Pregnancy: neural tube defects
 - Glossitis, angular cheilosis
 - Unconjugated jaundice due to the death of nucleated RBCs, ↑ urobilinogen, ↓haptoglobins, positive urine haemosiderin, ↑LDH
 - Bruising from thrombocytopenia
 - Cobalamin deficiency → impaired bactericidal function of phagocytes
 - High homocystinuria associated with cardiovascular disease, but prospective trials of folic acid or vitamin B12 have not shown a reduction in cardiovascular events

Cobalamin

- All forms have a cobalt atom at the centre of a corrin ring
- Synthesised solely by microorganisms, and the only source for humans is food of animal origin (meat, fish, dairy products)
- Acts as a cofactor for methionine synthase – in the pathway converting folate into all the folate enzymes (including homocysteine to methionine). If cobalamin deficiency, folate precursors accumulate → ↑homocysteine
- Cobalamin absorption:
 - Acid releases cobalamin from meat
 - Initially bound by r-binding protein (produced in saliva and stomach)
 - Then cleaved from the r-protein by pancreatic trypsin
 - Then bound by gastric intrinsic factor, produced by gastric parietal cells
 - Absorption is active in the terminal ileum, where B12-IF binds to the cubilin receptor
 - Transported on 2 main plasma transport proteins (Transcobalamin 1 and 2). Isolated absence of Transcobalamin 1 doesn't cause deficiency
 - Liver stores are 2 – 3 mg, sufficient for 3 – 4 years
- Deficiency due to:
 - ↓dietary intake, eg Hindu/vegan diet

- Achlorhydria (or PPIs): acid required to release cobalamin from meat
- Pancreatic insufficiency → ↓trypsin
- **Pernicious anaemia:**
 - Autoimmune destruction of gastric mucosa → gastric atrophy → ↓intrinsic factor and achlorhydria. Associated with autoimmune diseases, also premature greying and blue eyes! Rare less than 40 years
 - Intrinsic factor antibodies: *Specific* (50% sensitive)
 - Parietal cell antibodies: Sensitive (non-specific, 15% in normal females)
- Gastrectomy
- Intestinal stagnant loop syndrome (sequestered by bacteria)
- Ileal resection and Crohn's disease
- Tropical sprue and fish tapeworm
- Congenital deficiency of enzymes for B12 metabolism or transport
- May occur but usually not severe: gastritis, PPIs, *coeliac*, HIV infection, radiotherapy, rarely drugs
- Diagnosis:
 - No consensus or gold standard
 - Tests:
 - Film: MCV > 95 (may be 120 – 140), hypersegmented neutrophils, oval macrocytes, low retics
 - Bone marrow: megaloblastic change
 - Holotranscobalamin II: measure the small fraction of B12 bound to TCII – the amount available to the tissues
 - Deficiency defined as:
 - Clinical manifestations and
 - Biochemical: ↑methylmalonate (MMA, urine, slow and expensive test) and homocysteine (both elevated in early deficiency). Homocysteine also ↑ in folate deficiency
 - Chance of biochemical deficiency (↑MMA) with:
 - B12 > 130 pmol/L < 10%
 - B12 is 70 – 130 pmol/L = 30%
 - B12 < 70 pmol/L = 70 – 90%
- Replacement: lifelong IM injections – loading regime followed by 3 monthly

Folate

- A water soluble B vitamin
- Most foods contain some folate, especially liver, yeast, spinach, other greens and nuts
- Absorbed rapidly in the upper small intestine
- About 1/3 loosely bound to albumin, the rest free
- Transported into cells by a high affinity folate receptor, and also a low-affinity carrier which also takes up methotrexate
- Stores can be depleted in months
- Action: act as coenzymes in the transfer of single carbon units (including production of purines and pyrimidines for DNA and RNA replication) and formation of heme – as well as many other actions
- Methotrexate, pyrimethamine and (mainly in bacteria) trimethoprim inhibit the pathway from dietary to active folate metabolites
- Deficiency due to:
 - Dietary: old age, poverty, alcoholism, associated with scurvy or Kwashiorkor (severe protein deficiency)
 - Malabsorption: Eg *coeliac*, Crohn's, Whipple's disease, surgery...
 - Excessive utilization: pregnancy, haematological, malignant, or malignant disease, chronic inflammation
 - Anti-folate drugs: methotrexate, trimethoprim, phenytoin, sulphasalazine, nitrofurantoin, tetracycline
 - Mixed causes: liver disease, alcoholism, ICU
- Measurement:
 - Red cell folate better than serum folate – less affected by recent diet and haemolysis. > 95% folate is in RBC. However B12 deficiency → ↑serum folate and ↓red cell folate (it disrupts folate uptake into cells)
 - Low in severe cobalamin deficiency
 - False normal following blood transfusion

- Replacement: oral doses, even if malabsorption. Correct cobalamin deficiency first, otherwise giving folate → cobalamin neuropathy

Haemoglobin Disorders

- Normal haemoglobins:
 - 4 polypeptide globin chains in 2 pairs protect haem from oxidation. Each globin has an iron containing porphyrin which carries the oxygen
 - HbA: Adult haemoglobin has structure $\alpha_2\beta_2$ – 96%
 - HbA2: Minor adult haemoglobin = $\alpha_2\delta_2$ – 3.5%
 - HbF (fetal) = $\alpha_2\gamma_2$. Profound erythroid stress (eg severe haemolytic anaemia, chemotherapy) can induce HbF – normally 0.5%. There are 4 γ genes so deficiency unlikely
 - Gower and Portland haemoglobins in fetus up to approx 14 weeks
- Test with HPLC (High Performance Liquid Chromatography):
 - Detects different haemoglobins
 - A2 band also covers Hb E ($\alpha\alpha/EE$), in addition to $\alpha_2\delta_2$
 - β Thalassemia → high HbA2 and HbF
 - In Fe deficiency can get ↓HbA2 – so need to exclude Fe deficiency before testing for thalassaemia
- Types of haemoglobin disorders:
 - Structural haemoglobinopathies:
 - Altered amino acid sequences that result in altered function, shape or chemical properties
 - Haemoglobinopathy = synthesis of *abnormal* Hb
 - Thalassaemia = *reduced rate* of synthesis of normal Hb
 - Altered O₂ affinity (high and low affinity variants) → polycythaemia or cyanosis
 - Haemoglobins that are unstable or oxidise easily, eg methemoglobinemia (failure of reduction)
- Oxygen Dissociation Curve:
 - PO₂ on X axis, Oxyhaemoglobin on Y axis
 - Shifts R (→ increased O₂ available to tissues) with ↑temperature, ↑2,3-DPG, ↑CO₂, acidosis, adult Hb
 - Shifts L with CO (higher affinity for Hb than O₂)

Thalasseмииas

- Defective biosynthesis of either α or β globin chains (eg mRNA translation). Synthesis of the other chain unaffected – excess of this one forms deposits which cause the problem
- α -Thalassemia:
 - Far east and Asia
 - Due to gene *deletions*. Inherit 2 chains from each parent
 - ↓ α chains → ↓A, A2 & F → excess δ and γ chains which form tetramers (Hb Barts and Hb H)
 - Types:
 - Silent thalassaemia: $-\alpha/\alpha\alpha$ (ie one of the four loci deleted). May have ↓MCV
 - Thalassaemia trait: $-\alpha/-\alpha$ or $--/\alpha\alpha$. Normal HPLC. Not dramatically anaemic
 - Haemoglobin H disease/ α Thalassaemia Major: $--/-\alpha$. Mild, chronic, haemolytic microcytic anaemia (Hb 60 – 100). See **H bodies** in cells – tetramers of β -haemoglobin – speckled cell like a golf ball + bizarre shaped cells. May not be transfusion dependent. May have splenomegaly
 - Hydrops: $--/--$ fatal
- β -Thalassemia:
 - Mediterranean
 - Due to gene *mutations* – so can have a phenotypic spectrum: β^+ = reduced or defective, β^0 = none
 - Inherit one β chain from each parent
 - ↓ β chains → ↓A (not A2 or F) → precipitation of excess α chains → rbc destruction within the marrow (ineffective erythropoiesis)
 - Phenotypically described on the spectrum:
 - β -thalassaemia major: β^+/β^+ , β^0/β^0 , E/ β^+ or E/ β^0
 - Massive bone marrow expansion → “chipmunk” facies (maxillary marrow hyperplasia and frontal bossing), fracture of long bones, hepatosplenomegaly (extramedullary haematopoiesis), gallstones, high output congestive heart failure, iron overload → endocrinopathies, skin pigmentation, etc
 - HPLC shows ↓↓HbA ($\alpha\alpha\beta\beta$), ↑ HbF ($\alpha\alpha\gamma\gamma$) and maybe ↑HbA2 ($\alpha\alpha\delta\delta$)
 - Treatment: blood transfusion, iron chelation, SCT (80% survival)

- Trait (often misdiagnosed as iron deficiency): β/β^+ or β/β^0 . Hypochromia and microcytosis but no anaemia. IDA can \downarrow
- Splenectomy if \uparrow transfusion requirement, Pneumovax vaccine
- Monitor for infection, leg ulcers, biliary tract disease
- HbE:
 - β globulin variation common in SE Asia
 - Heterozygotes: asymptomatic
 - Homozygotes: mild hypochromic microcytic anaemia
 - HbE/ β^0 = thalassaemia major

Sickle Cell Anaemia

- Central Africa, pockets elsewhere
- C, D, O and S are all point mutations in the β chain
- HbS: Mutation in 6th amino acid of β -globulin gene (Glu \rightarrow Val). Polymerizes reversibly when deoxygenated \rightarrow stiffens RBC membrane and \uparrow viscosity
- Sickling disorders include: HbSS, HbSD, HbSC, HbSO, HbS/ β thal
- Diagnosis: blood film characteristic, HPLC, electrophoresis for HbS and HbA
- Sickle Cell Trait: $\beta\beta^S$. Normal FBC. Sickling *may* be precipitated by right shift in the oxygen dissociation curve (fever, hypoxia, acidosis, GA)
- Sickle cell disease: homozygous $\beta^S\beta^S$
 - Severe haemolytic anaemia with crises. Anaemia usually Hb 6 – 10 g/L (well tolerated)
 - Abnormally adherent to endothelium of small venules \rightarrow unpredictable micro-vascular occlusion (\rightarrow tissue ischaemia, pain and end organ damage) and RBC destruction of the abnormal cells by the spleen. Micro infarctions can destroy the spleen early in life \rightarrow susceptibility to infection
 - White count can fluctuate substantially
- Complications:
 - Failure to thrive
 - Painful vaso-occlusive crises precipitated by acidosis, fever, cold, stress, dehydration, etc: rigid rbc block capillaries. Acute pain and tenderness (with fever and tachycardia) anywhere in the body secondary to ischaemia, lasting hours to 2 weeks. Sites include muscles, retina, kidney, osteonecrosis (\rightarrow osteomyelitis)
 - Acute Chest Syndrome: chest pain, \uparrow RR, fever, cough, \downarrow sats – sickling in the lung
 - Temporary aplastic crises after eg parvovirus B19
 - Hyposplenism – slowly gets infarcted away \rightarrow Howell-Jolly inclusions (sign of splenectomy) – vaccinate
 - Retinopathy, leg ulcers, gallstones
 - Opiate addiction
- Treatment
 - Of crises: hydration, analgesia, exclude infection, exchange transfusion
 - Hydroxyurea if severe \rightarrow \uparrow fetal haemoglobin
 - Bone marrow transplantation only safe and effective in children – 80% DFS from HLA matched sibling

Complications of Haemolytic Anaemia

- Iron overload: independent of transfusion – due to ineffective erythropoiesis. Treatment desferoxamine – sc infusion 5 nights a week for 8 hours a time – awful compliance but survival benefit if compliance. Usually start age 4 – 6 (once ferritin reaches ~ 1000). Prior to chelation, died in their 20s from overload. Oral chelators now available [Exjade]
- Transfusional Haemosiderosis: Iron from 2 transfused units = 1 – 2 years dietary intake. Develop haemosiderosis with $>$ 100 units transfused \rightarrow iron overload \rightarrow endocrine dysfunction (glucose intolerance, delayed puberty) 2nd to gland infiltration, cirrhosis, cardiomyopathy. Use iron-chelating agents eg desferoxamine – start early.
- Bone marrow suppression occurs in anyone during acute inflammatory illness. Can lead to more dramatic fall in RBC in people with haemoglobinopathies
- Aplastic crisis: profound cessation of erythroid activity in people with chronic anaemia. Usually self limited. May be due to parvovirus B19

Haemolytic Anaemias

- Haemolysis = shortened red cell survival ($<$ 120 days)

- Presentation: Signs of haemolysis: pallor, jaundice, urobilinogen, splenomegaly (preferred site of extravascular haemolysis), if congenital then skeletal changes (but not as severe as thalassaemia)
- Complications:
 - Folate deficiency
 - Iron deficiency (if intravascular)
 - Iron overload (ineffective erythropoiesis)
 - Gallstones
 - Red cell aplasia after parvovirus
 - Leg ulcers
- Site of haemolysis:
 - Extravascular: usually ↑ destruction by the spleen
 - Intravascular: mechanical, chemical or complement mediated
- Labs:
 - The 5 basics: blood film, reticulocytes, LDH, haptoglobin, Bilirubin/LFTs. Also Coomb's
 - Signs of haemolysis:
 - ↑ unconjugated bilirubin, ↑ LDH (an intracellular enzyme, released with rbc lysis), ↑ AST, ↓ haptoglobin, ↑ urobilinogen in both urine and stool
 - If haemolysis is intravascular then also haemoglobinuria (and ↑ serum haemoglobin), and, over time, ↓ Fe (if it's extravascular in the spleen then Fe is efficiently recycled and possible Fe overload)
 - If persistent then gallstones
 - If splenomegaly then neutropenia and/or thrombocytopenia
 - Signs of erythropoiesis: ↑ reticulocytes – both percentage and absolute count → ↑ MCV. Macrocytes and nucleated red cells on blood film
 - Free serum Hb binds first to haptoglobin (which therefore ↓ in haemolytic anaemia, especially in intravascular), then to haemopexin, then to albumin (→ methaalbumin)
 - Haemosiderin: free haemoglobin is filtered and then absorbed into renal tubular cells, converted into haemosiderin. These cells are sloughed off and haemosiderin is detected in the urine. With intravascular haemolysis only. Same clinical significance as haemoglobinuria
- Red blood cell physiology:
 - Mature cells lack capacity to make proteins (no ribosomes) or undertake aerobic metabolism (no mitochondria) – susceptible to any stress
 - Gold standard for showing reduced survival is red cell survival study – measuring residual radioactivity over time are an injection of labelled red cells (now little used)
 - After acute blood loss, reticulocytes increase in the blood from day 2 – 3 and peak at day 7 – 10
- Intravascular causes:
 - Red cell fragmentation syndromes: microangiopathic haemolytic anaemia (TTP – see page 447 – and HUS), mechanical, damage by heat, etc
 - Paroxysmal nocturnal haemoglobinuria
 - Paroxysmal cold haemoglobinuria
- Extravascular causes:
 - Immune mediated: autoimmune or alloimmune
 - RBC membrane defects: Inherited or acquired
 - RBC enzyme defects: G6PD, PK, etc
 - Haemoglobinopathies
 - Metabolic defects (eg Wilson's)
 - Bacterial and parasitic infections (eg malaria)

Inherited Haemolytic Anaemias

- *Abnormalities of the membrane-cytoskeleton complex:*
 - Main cytoskeleton protein is spectrin
 - Abnormality of any component → structural instability → loss of rbc membrane in spleen and eventual haemolysis
 - **Hereditary Spherocytosis:**
 - 1 in 5000. Varying severity. Worsened by intercurrent illness
 - Originally a phenotypic diagnosis, now a number of mutations identified with diverse spectrum of disease
 - Defect in a rbc membrane structural protein eg ankyrin, band 3, α-spectrin, β-spectrin or protein 4.2

- Increased membrane fragility → membrane loss and spherical rbc. Spherocytes destroyed in the spleen
- Only condition in which an increased mean corpuscular haemoglobin concentration (MCHC) is seen
- Investigations: Spherocytes and polychromasia (same as for AIHA) but Coomb's negative. Gold standard: flow cytometry for abnormal protein
- Treatment: Can be mild. Splenectomy (major site of destruction) – but not if mild and wait till age > 4 (past the biggest risk of severe sepsis). Folate supplements
- NB: severe burns causes microspherocytosis of rbc
- Hereditary elliptocytosis: heterogeneous cluster of mutations including α or β spectrin...
- *Enzyme Abnormalities:*
 - RBCs rely exclusively on anaerobic metabolism (they have no mitochondria) for energy dependent cation transport
 - **G6PD deficiency:** Glucose 6-phosphate dehydrogenase
 - Most common human enzyme defect (400 million)
 - No effect on life expectancy
 - **X linked.** ~ 140 mutations found so far. Homozygous females affected. Female heterozygotes have ?resistance to falciparum malaria
 - G6PD is a housekeeping enzyme in the redox pathway – in RBCs it is the only source of NADPH which reduces oxidative stress
 - Morphology: “**bite and blister cells**”, with appropriate staining can see **Heinz bodies** (a type of inclusion body) – clumps of oxidized denatured haemoglobin – seen in all oxidative anaemias (also in dapsone)
 - Haemolyses easily 2nd to an exogenous stress – 3 types of triggers:
 - Fava beans (= broad beans)
 - Infections
 - Drug associations with anti-malarials (primaquine), nitrofurantoin, aspirin, co-trimoxazole (sulphamethoxazole), ciprofloxacin, dapsone ... See Lancet 2008:371
 - Causes neonatal jaundice and acute haemolytic anaemia (usually triggered by an exogenous agent), can cause chronic anaemia
 - Treatment: supportive (hydration/transfusion during haemolysis) and avoid relevant drugs
 - Pyruvate kinase deficiency: the least rare abnormality of the glycolytic pathway

Acquired Haemolytic Anaemia

- **Autoimmune (AIHA):**
 - Caused by red cell antibodies
 - Destruction via macrophages in spleen, liver, bone marrow (ie extravascular). May involve complement activation and MAC (ie intravascular)
 - Combes test: detects antibody on the cell itself. Coomb's reagent binds antibodies on rbc's (if present) → agglutination. False positive in 10 – 15% of elderly who have antibodies, but that's not the cause of any anaemia. The antibody may (but not always) be specific for a rhesus system antigen. Direct antiglobulin test = Direct Combes test:
 - **Warm – IgG**
 - **Cold – c3b** (IgM binds C3 then IgM falls off)
 - **Mixed (ie SLE) – IgG and c3b**
 - Can be isolated, or part of an autoimmune disease (eg SLE ⇒ must do full screen for autoimmune stuff)
 - **Warm AIHA:** ~ 37o
 - RBC coated antibodies taken up by macrophages or RES that have receptors for Ig Fc fragment → extravascular haemolysis
 - Idiopathic
 - Secondary to:
 - Autoimmune disease
 - Lymphoproliferative disease
 - Infections
 - Drugs: penicillins, cephalosporins, L-dopa
 - Rarely cancers
 - Diagnosis:
 - Haemolysis, spherocytes, splenomegaly

- Coomb's test positive
- Treatment (little evidence base):
 - Transfusion – but if the antibody is not specific may attack the new blood too. Difficult to get cross matched blood as this uses a test similar to Coomb's, so not sure if it matches or not
 - Prednisone → remission in 50%, relapse common
 - May require longer term immunosuppression: prednisone, azathioprine, cyclosporine
 - Splenectomy if persistent
 - Folate supplements
 - Maybe rituximab
- **Cold AIHA: < 37°C**
 - Paroxysmal Cold Haemoglobinuria: rare, self-limited, *usually children* or 2ndary syphilis. Donath-Landsteiner antibody. Biphasic **IgG** anti-P autoantibodies bind at low temperatures only, haemolyses 2nd to complement when warmed. *Intravascular* haemolysis → ↑haemosiderin
 - Primary Cold Haemagglutinin Disease aka Cold Agglutinin Disease:
 - Usually elderly. Chronic haemolytic anaemia aggravated by cold
 - **IgM** (cf PCH which is IgG)
 - Produced by a clone of B cells, may be enough to cause a spike on electrophoresis. IgM antibody is related to Waldenstrom macroglobulinaemia – ie a sort of low grade mature B-cell lymphoma. If mild, avoiding the cold may be sufficient
 - Treatment: Blood transfusions not effective as they are haemolysed too (I-antigen present on all RBCs). Immunosuppression not very effective. Plasma exchange is laborious. Rituximab promising
 - Secondary to infection: mycoplasma, EBV, syphilis
 - Autoantibodies:
 - Anti-I (adult antibody): mycoplasma, *lymphoma*, idiopathic cold HA disease
 - Anti-i (fetal antibody – serum reacts to cord rather than adult RBC): EBV, lymphoma
 - Blood film: clumps of red cells (may → artifactual ↑MCV). Cf cryoglobulinaemia – a *protein* that clumps together in the cold in the lab – doesn't involve red cells
 - Treatment:
 - Avoid cold
 - Treat any underlying disease
 - Steroids don't work. Splenectomy not effective (haemolysis mainly intravascular and associated with thrombosis)
 - Warmed blood transfusion (cold would get haemolysed)
 - Folate supplements
- **Non-autoimmune:**
 - Mechanical destruction:
 - March haemoglobinuria: marathon runners, barefoot dancers and vigorous bongo drumming!
 - Prosthetic heart valves
 - Toxic drugs:
 - 2nd to oxidative stress, cisplatin, dapsone
 - Via other mechanisms: copper, lead (basophilic stippling). Drugs can induce immune attack
 - Infection: malaria, shiga toxin-producing E Coli O157:H7, clostridium perfringens
 - 2nd to DIC or TTP
 - Paroxysmal Nocturnal Haemoglobinuria:
 - Rare, nocturnal dark urine (“Coca cola urine”), recurrent intravascular haemolysis, often pancytopenia and venous thrombosis. Rare. Median survival 10 years
 - Requires an acquired deficiency of PIG-A gene → deficiency of CD59 and CD55 makes RBCs susceptible to complement
 - Diagnosis: Hams test (old) – test for lysis in autologous serum. Flow cytometry gold standard – loss of CD 55 and 59 on neutrophils and rbc
 - Treatment:
 - 15% spontaneous remission, median survival 10 years
 - Transfusion + Iron/folate replacement
 - Anticoagulation for thrombosis

- Novel treatment with eculizumab – blocks complement C5 and downstream cascade →
↓transfusion requirement
- Allogenic SCT – but usually not sick enough to risk it

Bone Marrow Failure Syndromes

- Differential of pancytopenia:
 - With hypocellular marrow:
 - Acquired aplastic anaemia
 - Hereditary syndromes (eg Fanconi's anaemia)
 - Some myelodysplasia
 - Aleukaemic leukaemia (rare)
 - Some ALL and bone marrow lymphomas
 - Infection: Q fever, legionnaires, mycobacteria
 - Anorexia, starvation
 - With cellular bone marrow:
 - Primary bone marrow diseases:
 - Myelodysplasia
 - Myelofibrosis
 - Hairy cell leukaemia
 - Others
 - Systemic diseases:
 - SLE
 - Hypersplenism
 - B12, folate, infection
 - Overwhelming infection
 - Alcohol
 - Sarcoidosis
 - Infection: brucellosis, Tb, leishmaniasis

Aplastic Anaemia

- Excludes chemotherapy – which has a predictable dose-response bone marrow suppressive effect
- Abrupt onset of low blood counts in a previously well young adult
- Causes:
 - Rare inherited causes
 - Idiopathic – most cases
 - Secondary:
 - Radiation
 - Drugs/chemicals
 - Predictable – eg benzene
 - Idiosyncratic – rare and no dose-response relationship ⇒ complex and specific pathways with multiple susceptibility loci. Eg chloramphenicol (< 1 per 60,000 courses)
 - Viruses:
 - Seronegative hepatitis (non A B or C) – most common recent infection
 - EBV
 - Parvovirus B19 – transient only
 - HIV-1
 - Immune mediated: ↑numbers of activated cytotoxic T cells are detected in aplastic anaemia
 - Hypoimmunoglobulinaemia
 - Thymoma/thymic cancer
 - Graft vs Host in immunodeficiency – eg after transfusion of unirradiated blood products into an immunocompromised person
 - Paroxysmal nocturnal haemoglobinuria
 - Pregnancy – rare, resolves with delivery
- Presentation: bleeding/bruising, weakness, SOB. Not systemic complaints nor weight loss. Maybe retinal haemorrhages. Not lymphadenopathy
- Labs:
 - ↑MCV
 - Replacement of bone marrow with fat on aspirate (haematopoietic cells < 25%) and MRI of spine

- Reduced CD34 cells (marker of early haematopoietic cells), stem cell pool greatly reduced
- Differentials:
 - Immature myeloid forms – think leukaemia or MDS
 - Nucleated RBCs – think marrow fibrosis or tumour invasion
 - Abnormal platelets – think peripheral destruction or MDS
- Treatment:
 - Stem cell transplant: best for children with fully histocompatible sibling donor (survival 80 – 90%). Use leukocyte depleted transfusions and single donors to minimize alloimmunization
 - Immune suppression: Antithymocyte globulin or antilymphocyte globulin +/- cyclosporin (SE nephrotoxicity, HTN, seizures, infections including PJP). Relapse can occur
 - Little value from growth factors and no value from prednisone

Pure Red Cell Aplasia (PRCA)

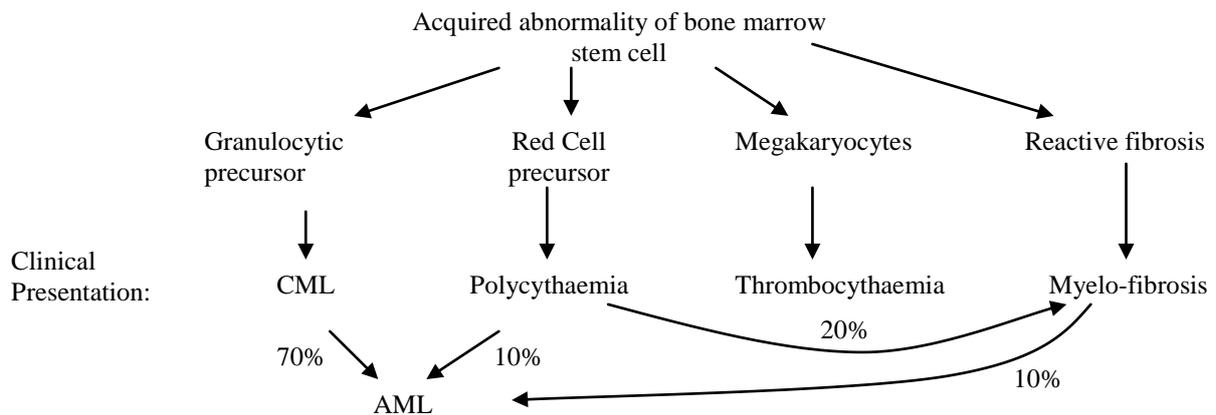
- Anaemia, reticulocytopenia and absent or rare erythroid precursor cells
- Other cell lines quantitatively normal
- Causes:
 - Idiopathic – respond favourable to immunosuppression with glucocorticoids +/- cyclosporin, azathioprine... daclizumab (antibody to IL-2)
 - Acquired:
 - Thymoma, lymphoid malignancy and paraneoplastic to solid tumours
 - Connective tissue disease: SLE, RA
 - Virus: Parvovirus B19 (IgG and IgM antibodies unlikely – detection requires PCR), hepatitis, EBV
 - Pregnancy
 - Drugs:
 - Phenytoin, azathioprine, chloramphenicol, isoniazid
 - **Erythropoietin** (eg Abs to administered erythropoietin)

Myelodysplasia

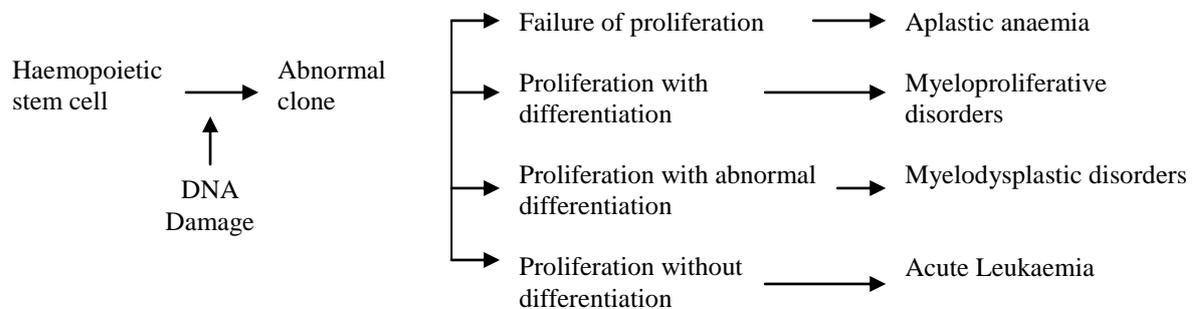
- Heterogeneous group of disorders with cytopenias, and dysmorphic, cellular bone marrow
- A disease of the elderly, as a late sequelae of combined treatment for cancer, in Down syndrome or rare hereditary causes
- A clonal disorder of cell proliferation and differentiation from the accumulation of genetic lesions, with increased apoptosis leading to bone marrow failure, rather than uncontrolled proliferation. Varying rates of leukaemic transformation amongst the subtypes (maximum 33%)
- Presentation: macrocytic anaemia, Neutropenia, thrombocytopenia. Fever and weight loss suggest a myeloproliferative not a myelodysplastic process. 20% have splenomegaly
- Blood film: macrocytosis, large platelets that lack granules and decreased function (→ bleeding), hypogranulated, hyposegmented neutrophils
- Bone marrow hypercellular
- Exclude B12 and folate deficiency, and B6 deficiency if ringed sideroblasts
- Types:
 - Refractory anaemia
 - Refractory anaemia with ringed Sideroblasts
 - Refractory anaemia with excess blasts
 - Refractory anaemia with excess blasts in transformation
 - Chronic myelomonocytic leukaemia
 - MDS with isolated del 5q (better prognosis)
- Therapy related MDS, regardless of type, usually progresses within months to AML
- Cytogenetics: -5, -7 21q-, 9q-, + 8. Higher blast count → higher risk
- Treatment:
 - Reasonably refractory, especially as they're often old
 - Supportive care: transfusion, G-CSF, erythropoietin
 - Cytotoxic therapy: azacitidine
 - Thalidomide, or lenalidomide (a derivative) – good in 5q-. SE: myelosuppression, DVT, PE
 - Consider alloBMT if progression or early poor cytogenetics

Myeloproliferative Diseases

- In addition to the sections below, some classifications include the following – which overlap with chronic myeloid leukaemias:
 - Chronic myelogenous leukaemia
 - Chronic neutrophilic leukaemia
 - These have a prognosis of years, with a high rate of transformation into acute myeloid leukaemia
- The following have prognosis of decades, and uncommon transformation to acute leukaemia
- PV (80%), IMF (50%) and ET (50%) are characterised by expression of *JAK2 mutation – V617F* – which causes activation of the tyrosine kinase essential for the function of erythropoietin and thrombopoietin receptors but not granulocyte CSF. Prognostic significance still uncertain – watch this space
- Primary, clonal proliferation of myeloid (marrow) cells
- Splenomegaly
- Arises at pluripotent stem cell level:



- Leads to mixed picture as diseases merge
- Variation is based on degree and type of proliferation:



- Leucoerythroblastosis:
 - Nucleated RBC and immature neutrophils in blood
 - Disturbance of blood/marrow barrier (normally stops immature cells getting out):
 - Immature barrier: common in new born
 - Toxic: septicaemia
 - Hypoxia: respiratory failure
 - ↑↑Marrow function
 - Mechanical damage: e.g. infiltration of metastatic cancer (breast, lung, prostate go to bones)
 - Extramedullary haematopoiesis:
 - Marrow cells outside marrow (e.g. spleen, liver, lymph nodes)
 - Common in MPD, especially myelofibrosis

Polycythaemia Vera

- Causes of erythrocytosis:
 - Relative: Exclude causes due to reduced plasma volume (dehydration, diuretics, androgens)
 - Absolute:

- PV
- Hypoxia: pulmonary, shunts, OSA, high altitude, high affinity haemoglobin
- Renal disease: renal artery stenosis, renal transplant
- Tumours: hepatoma + others
- Drugs: androgens, EPO
- Familial
- PV is EPO independent clonal disorder of a haematopoietic progenitor cell in which phenotypically normal red cells, granulocytes and platelets accumulate without physiologic stimulus
- Most common of the myeloproliferative disorders at 2 per 100,000
- Etiology unknown
- Presentation:
 - Usually incidental finding of high haemoglobin
 - Splenomegaly – which can → discomfort, portal hypertension and cachexia
 - Hyperviscosity → vertigo, tinnitus, headache, visual disturbance, TIAs
 - HTN
 - Venous or arterial thrombosis
 - High turnover of cells → ↑urea with gout and uric acid stones
 - Higher incidence of peptic ulcer disease and pruritis
 - ↓EPO
- Elevated erythropoietin excludes PV
- Little value from a bone marrow – may be normal, or indistinguishable from ET or IMF
- Treatment: indolent disorder
 - Phlebotomy if Hct > 55% to reduce thrombotic complications, induce Fe deficiency which stops re-expansion. Aim to keep Hb < 140 in males, 120 in females
 - Not prophylactic aspirin (Melbourne said use aspirin)
 - Allopurinol
 - Chemotherapy to ↓splenomegaly, leukocytosis or to treat pruritus. IFN-α reduces JAK2 expression. Hydroxyurea may help. If not then splenectomy
 - Alkylating agents are leukemogenic

Essential Thrombocytosis

- Aka essential thrombocythaemia, idiopathic thrombocytosis
- Clonal disorder of a multipotent haematopoietic progenitor cell → ↑platelets
- Uncommon, 1 – 2 in 100,000
- No clonal marker available
- Causes of thrombocytosis:
 - Tissue inflammation, malignancy, infection
 - Myeloproliferative causes: PV, IMF, ET, chronic myelogenous leukaemia
 - Myelodysplastic disorders
 - Post splenectomy
 - Fe deficient anaemia
 - Other...
- Platelet production from megakaryocytopoiesis depends on thrombopoietin (receptor is Mpl), produced in liver and kidneys
- Presentation:
 - Usually incidental finding
 - May have haemorrhagic or thrombotic tendencies
 - Mild splenomegaly only
 - *Not anaemia*, maybe mild neutrophilia
- Diagnosis:
 - Platelet count doesn't distinguish between benign and clonal causes
 - 50% express JAK2 V617F mutation. If absent, need cytogenetics to exclude CML or myelodysplastic disorder
- Treatment:
 - Survival no different to general population
 - Anticoagulation may make things worse. Can haemorrhage to due acquired deficiency of Von Willebrand factor – removed by the circulating platelets
 - If thrombosis: aspirin, or platelet reduction from IFN-α or hydroxyurea

- Risk of transformation from alkylating agents

Chronic Idiopathic Myelofibrosis

- Clonal disorder causing marrow fibrosis, extramedullary haematopoiesis and splenomegaly (often massive – as all blood production is extramedullary)
- Least common of the myeloproliferative disorders, and difficult to distinguish from PV and CML which also cause fibrosis and splenomegaly
- Differential:
 - Primary haematological disease: myelofibrosis or myeloid metaplasia
 - Secondary process: called myelophthisis, as a response to:
 - Invading tumour: usually breast, lung, prostate
 - Infection: MTb, MAC, fungi, HIV
 - Sarcoidosis
 - Late consequence of radiation
 - Other haematological conditions: eg CML, myeloma, lymphomas
- 3 features:
 - Polyclonal proliferation of fibroblasts in the marrow space (ie not part of the neoplastic clone)
 - Extension of haematopoiesis into the long bones and extramedullary sites (spleen, liver, lymph nodes) – myeloid metaplasia → tear drop cells, nucleated red cells, myelocytes, and promyelocytes
 - Ineffective erythropoiesis
- Presentation:
 - Maybe asymptomatic, or splenic enlargement or abnormal bloods
 - Night sweats, fatigue and weight loss (unlike PV and ET)
- Investigations:
 - Elevated ALP and LDH, markedly increased CD34+ cells
 - Marrow is often inaspirable due to myelofibrosis
 - Bone xrays may have Osteosclerosis
 - Cytogenetics to exclude CML
- Complications: 10% → aggressive acute leukaemia
- Treatment: No specific therapy. Splenectomy may be necessary. Allopurinol. Hydroxyurea to control splenomegaly. Allogenic bone marrow transplantation if young

Hypereosinophilic Syndromes

- Chronic eosinophilic leukaemia:
 - $> 1.5 \times 10^9/L$
 - Blast in marrow and clonal population
 - Mepolizumab has shown benefit (as a steroid sparing agent). It's an anti-IL-5 monoclonal antibody. IL 5 is a key cytokine in eosinophil maturation, proliferation and survival (NEJM 20 March 2008)
- Hypereosinophilic Syndrome: end-organ damage. t(1;4) and t(1;5) Imatinib sensitive
- Chronic Eosinophilia:
 - Idiopathic: asymptomatic, dermatitis (Gleich's Syndrome)
 - Secondary: infection, drugs, T cell clone

Chronic Myeloid Leukaemia

- Incidence 1.5 per 100K per year, most commonly from age 40 – 60
- A myeloproliferative disorder with increased numbers of the full spectrum of myeloid cells (both mature and immature)
- Presentation: may be asymptomatic, fatigue, weight loss, splenic enlargement (→ early satiety and LUQ pain). Lymphadenopathy unusual
- Labs:
 - ↑WBC (usually > 50 and maybe > 500) with ↑immature and mature granulocytes. Usually 5% circulating blasts and $< 10\%$ blasts and promyelocytes
 - ↑Platelets and anaemia
 - Low leukocyte alkaline phosphatase score in CML cells (cf chronic infections, haemolysis, etc where it is high). A score of stain uptake on light microscopy
 - Bone marrow: ↑cellularity. Normal or slightly elevated blast percentage (blast crisis = blood or marrow blasts $> 20\%$ ⇒ acute leukaemia)
- **Philadelphia chromosome:**
 - Clonal expansion of a haematopoietic stem cell with a t(9;22) translocation (in 90-95%)

- Combines breakpoint cluster region (BCR) on 22q11 with ABL (named after abelson murine leukaemia virus – normally produces a tyrosine kinase important in cell signalling) on 9q34
- Bcr-Abl gene results in production of abnormal tyrosine kinase (p210)
- Induces resistance to apoptosis and growth factor independence
- Now able to measure with quantitative PCR
- **Inevitable transition:** chronic phase → accelerated phase with increased resistance to therapy (definitions vary, 10 – 19% blast in peripheral WBC, > 20% basophils in peripheral blood) → blast phase (usually AML, sometimes ALL) with median time of 4 – 6 years, due to acquisition of additional genetic abnormalities
- Treatment history:
 - Original treatment: Hydroxyurea (ribonucleotide reductase inhibitor) for rapid disease control – still commonly used to control WCC in early stages of disease. Minimal impact on time to transformation
 - Then allogenic transplant: the only curative treatment but significant toxicity (10 – 20% mortality). Now used less given effectiveness of Imatinib. Outcome depends on:
 - The patient – age and phase of disease. Best in very young
 - Type of donor: syngeneic (monozygotic twins), HLA-compatible related or unrelated. Sex mismatch is bad. Marrow vs peripheral blood cells (higher relapse vs more chronic GVHD)
 - The preparative regime (myeloablative or reduced intensity) – eg cyclophosphamide + total body irradiation makes them sicker and more acute GVHD, but less chronic GVHD
 - GVHD: grade 1 decreases the risk of relapse, but grade II → high transplant related mortality. Risk increases over 40 yrs
 - Post-transplantation treatment
 - Best done in chronic rather than accelerated or acute phase
 - Then IFN- α . Mechanism unclear. Improves overall survival. Now rarely used
 - Chemo (eg cytosine arabinoside) now little used
 - Now **Imatinib**/Gleevec:
 - Competitive inhibition at the ATP binding site of Bcr-Abl kinase → inhibition of Bcr/Abl signal transduction
 - Complete haematologic remission at 18 months is 97%
 - Works best in chronic phase, with complete cytogenetic response of 30%
 - Monitor treatment with log₁₀ reduction of BCR/ABL transcript
 - Oral daily dose of 400 mg
 - SE usually mild: myelosuppression, fluid retention, nausea, muscle cramps, diarrhoea and skin rashes
 - Mechanisms of resistance: gene amplification, mutations in the kinase binding site, ↑ multidrug exporter genes, development of alternative signalling pathways
 - The future: high dose Imatinib, new Bcr-ABL inhibitors (eg Dasatinib and Nilotinib – useful in imatinib resistance), variations on SCT
 - Splenectomy only for symptom control in treatment resistant patients

Myeloid Leukaemia

- Infiltration of the blood, bone marrow and other tissues by haematopoietic neoplastic cells
- Normal myeloblasts differentiate into granulocytes, monocytes, erythroid cells and megakaryocytes
- Goals of treatment: haematologic remission → cytogenetic remission (test with eg FISH) → molecular remission (test with eg PCR)

Acute Myeloid Leukaemia

- Incidence 4 per 100K per year. Increases significantly with age. Median age 60. Commonest acute leukaemia in adults
- Major advances:
 - Better supportive care: good blood products, good ABs, etc
 - Better classification or subgroups
 - Better chemo
 - Transplant options
- Presentation:
 - Non-specific symptoms, fatigue, weight loss, fever, easy bruising, more rarely bone pain and lymphadenopathy or mass lesion of leukaemic cells (granulocytic sarcoma)

- Exam findings: splenomegaly, hepatomegaly, lymphadenopathy, sternal tenderness
- Some variants have gum and skin infiltration
- Labs:
 - Normocytic normochromic anaemia, ↓reticulocytes (reduced production, ↑destruction)
 - WBC counts can be low (<5) or very high (> 100). Morphology varies according to type
 - Often ↓platelets
 - Assess clotting
 - LP only if symptoms suggest CNS disease
 - Bone marrow, flow cytometry, cytogenetics and molecular studies
- Diagnosis:
 - Morphology: usually lacks specificity except for:
 - **Auer Rods**: pathognomonic for myeloid
 - Promyelocytic Leukaemia
 - Burkitt's
 - Flow cytometry: important for subtyping, and separating AML from ALL:
 - MPO (myeloperoxidase is the only marker completely specific for myeloid leukaemias), also CD33, CD13....
 - Myeloid markers:
 - Monocytic: CD14, CD64, CD11b
 - Megakaryocytic: CD41, CD61
 - B Lymphoid: CD 22, CD 79a, CD 19, CD 10
 - T Lymphoid: CD3, CD 2, CD 5, CD 8
 - Cytogenetics
- Classification:
 - WHO and French-American-British (FAB) classification schemes. Different thresholds: > 20% or 30% of nucleated bone marrow cells are blasts (normal < 4%)
 - Various types (M0 – M7 under WHO classification) depend on where in the natural ontogeny the problem is – eg M1, M2, M3 myeloid precursors, M6 red cells, M7 platelets
 - Small percentage are “**Secondary**” AML – arising from another haematological problems or secondary to chemotherapy:
 - Heredity: trisomy 21, defective DNA repair, others
 - Myeloproliferative syndromes
 - Radiotherapy with alkylating agents:
 - Alkylating agents: usually associated with abnormalities on chromosomes 5 & 7 – often preceded by a myelodysplastic phase after ~ 5 years
 - Topoisomerase 2 inhibitors: associated with MLL gene abnormalities on chromosome 11, arises de novo after 1 – 2 years
 - Chemicals: benzene, paints, herbicides
- Prognostic factors:
 - Untreated survival is 10 – 12 weeks. Overall cure 10 – 15%
 - Age – due to both ↓ ability to survive treatment, and leukaemia in older people more commonly expresses eg CD34 and the multidrug resistance 1 (MDR1) efflux pump (conveys resistance to eg anthracyclines)
 - Variety of chromosomal abnormalities – provide the most important prognostic information, treatment choices and relapse rates
 - T(15:17)(q22;q12) in APL – *All-trans-retinoic acid* (tretinoin) targets the fusion protein and promotes differentiation. Good prognosis (70 – 80% if young). *DIC common*
 - T(8:21)(q22;q22) associated with Auer rods
 - T(8;21) and t(15;17) associated with younger age
 - Complex karyotype t(6;9), inv(3), etc have a very poor prognosis (0% cure)
 - Molecular abnormalities in normal karyotype (ie cytogenetically normal AML) – used to be classed as intermediate prognosis – but some more specific markers now being used, and have the potential to guide eg decisions about SCT:
 - Class 1: mutations affecting signal transduction pathways eg FLT-3 (fms-related tyrosine kinase 3 mutation in 30% of AML, poor prognosis, inhibitors in phase III trials, consider for transplant)
 - Class 2: mutations leading to impaired differentiation
- Management:
 - Assess for infection
 - Replace blood components – if bleeding then platelet transfusion even if only moderately decreased

- Check urea (can → renal impairment). Allopurinol + hydration, or rasburicase if bad
- **Induction:** aim to achieve normal marrow
 - Cytarabine (Ara-C, Cytosine arabinoside – at standard or high dose), daunorubicin or idarubicin (anthracycline), intensified with etoposide
 - Cytarabine: s-phase-specific antimetabolite. SE at high dose: myelosuppression, pulmonary toxicity, significant and occasionally irreversible cerebellar toxicity
 - Then recheck marrow. If > 5% blasts with > 20% cellularity then repeat a version of induction therapy
 - 65 – 75% of adults < 60 with de novo AML achieve complete remission. Worse if older or prior myelodysplasia or myeloproliferative disorder
- Post-remission management:
 - **Consolidation** therapy. Without further treatment nearly all patients experience relapse. Relapse can only be cured by SCT. Aim is therefore to eradicate residual leukaemic cells. Maintenance treatment uncommon (cf ALL)
 - Sequential courses of high-dose cytarabine, autologous stem cell transplant (SCT), or high dose combination chemo with allogeneic SCT
 - Allogeneic SCT:
 - If younger, HLA-compatible donor and high risk cytogenetics
 - High toxicity: venoocclusive disease, GVHD and infections
 - Improved disease control offset by ↑fatal toxicity
 - Autogenic SCT: Usually only in clinical trial setting. Receive their own stem cells collected in remission. Lower toxicity (5% mortality) but higher relapse, and no benefit over conventional post-remission regimes
- Supportive care:
 - Several weeks of granulocytopenia and thrombocytopenia. G-CSF and granulocyte-macrophage CSF (GM-CSF) reduces median time to neutrophil recovery, but this hasn't translated into ↓infections or shorter hospital stays
 - Platelet transfusions if < 10. May benefit from HLA matched platelet donors. Blood products should be irradiated to prevent transfusion associated graft versus host disease. CMV-negative products or leuko-depleted products for CMV seronegative patients
 - Treat fevers with broad spectrum ABs (improved survival, even though only half go on to documented infection). Check lines and perirectal
 - Relapse bad: Gemtuzumab/Mylotarg is an antibody-targeted chemotherapy consisting of an antiCD33 antibody linked to calicheamicin (antitumour antibiotic) which leads to single agent complete remission in 30% of relapsed disease in the elderly (disappointing, ~ same as salvage). Effect limited by MDR1. SE infusional toxicity (fever, hypotension), cytopenias, veno-occlusive disease (hepatocytes express CD 33)
 - No maintenance treatment
- Definitions of response:
 - Complete response (CR): < 5% blasts by morphology and recovery of cell count
 - Partial response (PR): 5 – 15% blasts
 - Resistant disease (RD) > 15% blasts

Acute Promyelocytic Leukaemia/APL

- AML-M3 under FAB system. Malignant cell is a promyelocyte
- AML with t(15;17)(q22;q12) and variants. Retinoic acid receptor (RAR) translocates upstream of the promyelocytic (PML) gene
- Shows multiple Auer rods in blast cells
- Can present with DIC and pancytopenia
- Treatment:
 - All-trans-retinoic acid (ATRA) = tretinoin:
 - Discovered by Chinese
 - Targets the chromosome resulting from the 15,17 translocation in most forms of APL
 - Induces differentiation
 - Side effect: Retinoic Acid syndrome in ~25% after 2 days – 3 weeks: fevers, respiratory distress, lung infiltrates, effusions, heart failure (ARDS like), due to adhesion of differentiated cells to pulmonary vascular endothelium
 - Treatment: steroids (then restart ATRA). Use prophylactically if high white count (↑risk)
 - Cytarabine and daunorubicin → 10% incidence of DIC due to release of granules from dying cells

- Induction: tretinoin + anthracycline chemo. Arsenic trioxide as salvage treatment if refractory to tretinoin – promotes differentiation
- Consolidation/post-remission: daunorubicin followed by maintenance tretinoin
- Combined chemo → long term remission rates of 80 – 90%

Lymphoid Malignancy

- Malignant lymphoma = Clonal proliferation of lymphocytes *arising* in lymph nodes (or other lymphoid tissue). Minor exceptions – can get them in spleen, gut, etc
- Differentiating lymphoma from leukaemia: was its *origin* in the bone marrow or lymph nodes?
- Low (indolent) vs intermediate vs high (aggressive) grade
- Risks:
 - Inherited or acquired immune deficiency
 - Autoimmune disease: Sjogren's, RA, SLE
 - Chemical or drug exposures: phenytoin, radiation, prior chemotherapy or radiotherapy
- 75% of lymphoid leukaemias and 90% of lymphomas are B cell origin
- Stage of differentiation does not predict:
 - Its natural history. Burkitt's is the most aggressive lymphoid leukaemia but has the phenotype of a mature follicle centre IgM bearing B cell
 - The stage at which the genetic lesions developed. Eg follicular lymphoma has the phenotype of a follicular centre cell, but its characteristic translocation (t(14;18)) had to develop early in ontogeny as an error in the process of immunoglobulin gene rearrangement
- Cell differentiation:
 - B cells: Start in bone marrow with antigen-independent differentiation, committed to B cell development when it begins to rearrange its immunoglobulin genes, progresses to lymphoid follicle with antigen driven differentiation into follicular centre B cells and secretory B cells
 - T cells: Committed to T cell differentiation upon migration to the thymus and rearrangement of T cell antigen receptor genes. Differentiates through stage I, II and III in the thymus and then to peripheral and lymph node mature T helper cells and mature T cytotoxic cells
- Investigations:
 - Cell-surface phenotyping assists where lymphoid tumours appear similar under light microscope
 - Genetic abnormalities detected by:
 - Gross chromosomal changes (translocations, additions, deletions)
 - Rearrangement of specific genes
 - Over-expression, under-expression or mutation of specific oncogenes
 - The future: gene profiling using array technology – simultaneous assessment of the expression of thousands of genes
- Many lymphomas contain balanced translocations of the antigen receptor genes (Ig genes on 2, 14 and 22 in B cells, T cell antigen receptor genes on 7 and 14) which must therefore create a site of vulnerability to aberrant recombination

Acute Lymphoid Leukaemia

- Aka acute lymphoblastic or lymphocytic leukaemia
- See Lancet 22 March 2008
- Mainly kids (peak age 2 – 5) and young adults. 80% cure in kids, 20 – 30% in adults (biologically a different disease)
- More commonly associated with lymphadenopathy and splenomegaly, and 5 – 15% have leptomeningeal disease at presentation
- Risks:
 - Trisomy 21 → higher risk and maternal smoking during pregnancy for childhood ALL
 - Radiation exposure only other known risk factor
- Labs: FBC, chemistry for major organ function, bone marrow with genetic and immunologic studies *and LP to exclude CNS involvement*
- A number of common primary genetic lesions: BCR-ABL, MLL-AF4, TEL-AML1...
- Types:
 - Only subclassification with therapeutic importance is T-cell (associated with mediastinal mass), mature B-cell or B-cell precursor phenotypes. About half also show myeloid-associated antigen expression
 - Precursor B cell lymphoblastic Leukaemia (ALL)/Lymphoma: Most common childhood cancer

- T-ALL shows T cell antigens CD7 and CD 3
- B-ALL shows surface immunoglobulin and TdT
- Treatment:
 - Generally very responsive to chemo but high relapse rates. < 30% adults will be cured (> 75% kids cured)
 - Induction → consolidation → intensification → maintenance (→ +/- Allotransplant)
 - Complex and intensive rotating chemotherapy schedule for 12 – 24 months
 - Anthracycline, prednisone and vincristine induction
 - High dose methotrexate (CNS penetration)
 - If CNS involvement then intensified treatment, otherwise CNS prophylaxis. Cerebral irradiation
 - Low-dose oral chemo maintenance
 - SCT: only transplant those who are still chemosensitive, otherwise organ toxicity during ablation
 - PET scan emerging as useful if monitoring for remission/relapse in Hodgkin's disease and Diffuse Large B Cell Lymphoma. Can differentiate active disease from residual fibrous mass (CT can't). False negatives in uncontrolled diabetes
- Philadelphia-positive ALL:
 - Good CR rates, but early relapse and < 10% DFS at 3 years
 - Early data shows improved outcomes from Imatinib ? benefit in kids, not in adults (proven in CML)
- CNS relapse accounts for a significant portion of treatment failure, also testes (sanctuary sites)
- A long list of targeted therapies are in clinical trial

Burkitt's Lymphoma/Leukaemia

- ALL-L3 under FAB system – High grade non-Hodgkin's Lymphoma closely related to ALL
- <1% of NHLs but ~30% of childhood NHLs
- EBV associated with some types
- Diagnosed morphologically – may look a bit like diffuse large B cell – blue cytoplasm with *multiple vacuoles*
- High proliferative fraction, and usually t(8;14) (c-myc: myc oncogene translocates from 8 to the Ig heavy chain on chromosome 14)
- Rapidly progressive with propensity to metastasize to the CNS
- Treatment: prompt intensive chemo with high dose cyclophosphamide. High risk of tumour lysis syndrome. High response rate. Relapse quickly

Chronic Lymphoid Leukaemia (CLL)

- Most common form of leukaemia (25%), especially older adults, less common in Asians
- First degree relatives have 3 times the risk
- Only leukaemia *not* linked to cancer
- Mature B cell CLL/small lymphocytic lymphoma – can present as leukaemia or lymphoma (ie nodal vs bone marrow)
- Presents as asymptomatic finding, lymph nodes or immune problems
- Investigations:
 - Labs: FBC, chemistry for major organ function, bone marrow with genetic and immunologic studies and protein electrophoresis. Must have > 5 CLL cells. Lymphocytes may be > 300
 - Also consider serum Ig, Coombs test (AIHA in 15 – 30%, 5- 10% autoimmune thrombocytopenia), LDH, β 2macroglobulin, uric acid, calcium
 - **Smudge cells** on peripheral smear due to fragility of cells
 - Monoclonal CD5+ *and* CD 19+ B cells. Low expression of the B-cell receptor is a hallmark, as is high expression of ZAP70 (usually found in T cells). CD5 is normally a T cell marker and is aberrantly expressed in CLL
 - CT to exclude pathologic lymphadenopathy (worsens prognosis)
- Anaemia or thrombocytopenia may be due to:
 - Progressive marrow infiltration (further worsen prognosis)
 - Autoimmune phenomena (treat with steroids)
 - Hypersplenism (treat with splenectomy)
- Lymphoid disorders that can be confused with Typical B cell CLL:
 - Follicular lymphoma
 - Mantle cell lymphoma
 - Hairy cell leukaemia
 - Prolymphocytic leukaemia (B or T cell)

- Others
- Consider in a patient presenting with autoimmune haemolytic anaemia or thrombocytopenia
- Prognostic features: increasing ability to risk stratify:
 - Stage
 - Serum LDH and β 2macroglobulin
 - Unmutated IgH (bad) vs mutated
 - ZAP70 (bad) – strong predictor of need for treatment
 - CD38+ (bad)
 - Cytogenetics: translocations, deletions and trisomy
 - Genetic markers give some prognostic information, eg mutated IGHV is good, mutated 17p13 (p53) and 11q23 (ataxia-telangiectasia mutation – ATM) are bad
- Variable course:
 - 1/3 require no treatment and have long survival
 - 1/3 have initial indolent phase then disease progression
 - 1/3 aggressive from the outset
 - ~ 5% terminally progress to Richter’s Syndrome: diffuse T-cell Lymphoma with rapidly enlarging painful mass and rapid rise in LDH
- Rai and Binet staging systems: based on extent of disease, presence of anaemia and thrombocytopenia – predict outcome
- Management (similar to follicular lymphoma):
 - Treatment generally induces remission, but relapse the norm. Cure very rare. Early detection makes no difference to survival
 - If only marrow involvement and lymphocytosis: observation (in about 1/3rd). Median survival > 10 years
 - Lymphadenopathy and/or hepatosplenomegaly: as long as normal RBCs may still observe. Median survival 7 years – probably need treatment within several years. No benefit from pre-progression treatment – investigation on going. Initiate treatment if Rai stage III or IV, or “progressive disease”
 - Bone marrow failure (rather than autoimmune): require initial therapy otherwise median survival 1.5 years:
 - Chlorambucil for 2 – 4 months (ie low dose oral chemo) and/or fludarabine (a purine analogue, more effective but no difference in overall survival, PJP prophylaxis) +/- prednisone. Fludarabine + rituximab (CD20 more weakly expressed in CLL) + cyclophosphamide → complete response in 69% and molecular remission in 50%
 - Other regimes:
 - CHOP: cyclophosphamide, doxorubicin (hydroxydaunorubicin), vincristine (Oncovin), prednisone
 - CVP: cyclophosphamide, vincristine, prednisone
 - Rituximab: as single agent, response rate of 51% and complete remission rate of only 4%. Better with fludarabine
 - Consolidation treatment difficult. There is no characteristic chromosomal translocation to use to monitor treatment. Relapse common. SCT fraught given generally elderly patients – consider if young. Research ongoing
- Monoclonal B-cell lymphocytosis: < 5000 monoclonal B cells per mm³ without signs or symptoms. Higher rate of developing CLL than general population – ie a premalignant condition

Lymphoma

- Clinical features:
 - Painless lymphadenopathy: non-tender, rubbery
 - Hepatosplenomegaly
 - Systemic symptoms: fever, night sweats, weight loss, tiredness
 - Involvement of other areas: skin, CNS, GI, salivary glands
 - If bone involvement (fairly rare) then preference for bones with red marrow, and may present with bone pain
 - Ig heavy chain is on chromosome 14 – common gene affected in lymphoma
- Diagnosis: excision biopsy (not FNA)
- Hodgkin’s vs non-Hodgkin’s: histological diagnosis only. No clinical difference. Hodgkin’s responds better in general. In general, Hodgkin’s spreads node to node, non-Hodgkin’s spreads to any node in the body
- Evaluation:

- FBC, ESR, major organ function, uric acid, Ca, CT chest/abdo/pelvis, bone marrow biopsy, HIV
- Serum LDH (prognostic marker), β 2 microglobulin and protein electrophoresis
- Bone marrow – morphology and cytogenetics
- PET or a gallium scan can show persisting abnormalities after therapy (especially mediastinum) – more useful in aggressive NHL (eg diffuse Large B cell lymphoma) than in more indolent types (eg follicular)
- LVEF (prior to anthracyclines)
- Differential:
 - Reactive, atypical lymphoid hyperplasia (which can be disseminated and give systemic symptoms). Can be due to drug (phenytoin or carbamazepine), RA and SLE, CMV, EBV and cat-scratch disease
 - Castleman's disease: localized or disseminated lymphadenopathy associated with \uparrow IL-6, ?due to Herpes virus 8
- Autologous Stem Cell Transplant in Lymphoma
 - Definite indications: relapsed HL or NHL, incomplete response to primary therapy in NHL
 - Under investigation: up-front use
 - Can't do it in refractory disease – needs to be chemotherapy responsive to give induction chemo

Hodgkin's Lymphoma

- Characterised by Reed-Sternberg cells in a reactive cellular background. Derived from B lymphocytes of germinal centre origin
- Types:
 - Nodular sclerosis
 - Lymphocyte rich
 - Lymphocyte depleted
 - Mixed cellularity
- Bimodal peaks in 20s and 80s
- HIV a risk factor
- Presentation:
 - Non-tender, palpable lymphadenopathy, usually in the neck, supraclavicular area and axilla
 - 1/3 with fevers, night sweats and/or weight loss (B symptoms) – can present as a FUO
 - > 50% have mediastinal lymphadenopathy at diagnosis
 - Odd presentations: severe itching, erythema nodosum, paraneoplastic cerebellar degeneration, nephrotic syndrome, hypercalcaemia, immune haemolytic anaemia
- Staging: Ann Arbor Staging System (Ann Arbor is a place in the USA):
 - 1: one lymph node area only
 - 2: 2 or more lymph node areas on the same side of diaphragm
 - 3: 2 or more lymph node areas on different sides of the diaphragm
 - 4: disease in liver, bone marrow or other extra-nodal sites
 - Symptom status:
 - A = absence of fevers, sweats, weight loss
 - B = one of unexplained fever $>$ 38.5 C, weight loss $>$ 10 % in preceding 6 months, drenching night sweats [Unusual to include symptom status in cancer staging]
 - E = localized solitary involvement of extralymphatic tissue, excluding liver and marrow
 - Compared with leukaemia: if its in your bone marrow its everywhere
- Treatment:
 - Localized: High cure rate ($>$ 90%). Brief chemo then radiotherapy
 - Advanced: long term disease free survival in $>$ 75% if no systemic symptoms and 60 – 70% with
 - Chemo regimes:
 - ABVD (main one): doxorubicin, bleomycin, vinblastine, dacarbazine
 - MOPP: mechlorethamine, vincristine, procarbazine and prednisone
 - BEACOPP: more intensive – for high risk – cure rate high but high rate of myelodysplasia and infertility
 - Relapse:
 - If only radiotherapy initially then chemo (good prognosis)
 - If they had chemo then reasonable response from autologous SCT
- Complications (lots of data given good long term survival):
 - Radiotherapy \rightarrow premature CHD and solid tumours ($>$ 10 years later). Regular mammograms, stop smoking and aggressive treatment of cardiac risk factors

- Radiotherapy → hypothyroidism
- Thoracic radiotherapy: 15% get Lhermitte's syndrome – electric shock down spine and into lower extremities on flexion of the neck (also in cervical spondylosis, MS, spinal chord tumours or syringomyelia)
- Alkylating agents + radiotherapy → acute leukaemias
- Infertility: risk increases with age

Non-Hodgkin's Lymphoma

- See Lancet Oncology, June 2004
- International Prognostic Index (IPI): based on five clinical risk factors:
 - Age > 60 years
 - ↑serum LDH
 - Performance status > 2 (ECOG) or < 80 (Karnofsky)
 - Ann Arbor III or IV
 - > 1 site of extranodal involvement
- Risks: infectious (eg HTLV-1 virus), chemical exposures and medical treatments
- *Presence of kappa light chains best differentiates between B and T Lymphomas*
- Classification:
 - Now much more pathologically driven than clinical: WHO and REAL (Revised European American Lymphoma) classifications
 - WHO classification takes into account morphologic, clinical, immunologic and genetic information and attempts to divide non-Hodgkin's lymphoma's into entities that have clinical and therapeutic relevance...
 - 80 – 85% are B cells, 15% from T cells, < 1 % from NK cells
- Monoclonal Antibody Therapy for B-Cell NHL:
 - See NEJM 7 August 2008
 - Kill via complement mediated cytotoxicity, antibody dependent cellular cytotoxicity (both → lysis) and induction of apoptosis
 - Currently commercially available:
 - Alemtuzumab: CD52 for CLL – response in ~ 30% with relapse after alkylating chemo
 - Rituximab: CD20
 - Anti CD20 antibody – expressed on pre-B cells, absent on terminally differentiated plasma cells
 - Optimal dose has never been established
 - Generally low toxicity
 - Infusion related fever, chills, nausea, headache in up to 50%. Bronchospasm and hypotension in 1% (ie anaphylaxis) due to immune activation
 - Tumour lysis syndrome
 - Reactivation of hepatitis B while immunosuppressed, then as immune system returns → hepatic necrosis and possibly fulminant course
- **Follicular (Non-Hodgkin) Lymphoma:**
 - ~22% of NHL
 - Presentation: fevers, sweats and weight loss unusual
 - Diagnosed on histology: small and large cells in a follicular pattern. Confirm with confirmation of B type, existence of t(14;18) in 85% and abnormal expression of BCL-2 (part of apoptosis pathway – a survival signal, anti-apoptotic). Shifts BCL-2 under the transcriptional control of Ig heavy chain locus → ↑BCL-2
 - Low grade/indolent – median survival 8 – 10 years
 - Major differential is reactive follicular hyperplasia
 - 5 – 7% per year transformation to diffuse large B cell lymphoma (bad)
 - Treatment:
 - Up to 25% may undergo spontaneous temporary remission. If old and low stage, may just observe
 - For limited stage (I and II) involved field radiotherapy is well established, with long-term disease free survival in 35 – 50%. Total lymphoid RT is controversial and under investigation. Addition of chemotherapy shows promise but is yet to be conclusively established
 - Chemo: Chlorambucil (ie single agent), cyclophosphamide, CVP or CHOP → complete remission in 50 – 75% with median relapse after 2 years (although 20% > 10 years)
 - Rituximab starting to show prolonged survival with both induction and maintenance therapy

- IFN- α also used (being replaced by Rituximab), as is SCT
- The future: tumour vaccines
- **Diffuse Large B Cell Lymphoma:**
 - *Most common NHL*
 - Aggressive or intermediate, curable in ~60% – so treat or die
 - Median age 55 – 60
 - Diagnosed on morphology. Micro-array analysis progressively developing. Germinal centre B-like lymphoma 5 year OS 76%, activated B-like lymphoma 5 year OS 16%
 - 50% will have extranodal sites at diagnosis (most commonly GI tract and bone marrow – even pancreas – so biopsy needed as better prognosis than cancer)
 - Treatment: CHOP (alkylator-based) * 6 + rituximab (now proven) +/- involved field radiotherapy if localized. Increasingly tailored regimes (eg 2 or 3 cycles then CT, biopsy or FDG-PET to reassess)
 - Depending on IPI score, 70 – 80% of patients achieve complete remission, 50 – 70 % of these will be cured. Rituximab has improved these outcomes by ~ 15%
 - Autologous SCT superior to salvage chemotherapy
- **Extranodal Marginal Zone B cell Lymphoma of MALT type:**
 - ~ 8% of NHL
 - Indolent
 - Driven by antigen stimulation, eg helicobacter in the stomach, Hep C in spleen, Borrelia with skin
 - Small cell lymphoma in extranodal sites
 - Gastric (most common) associated with H Pylori, often responds to H Pylori treatment
 - Also orbit, intestine, lung, thyroid, salivary, skin.....
 - Distant metastases occur especially with transformation to diffuse large B cell lymphoma
 - Treatment: if localized surgery/radiotherapy can cure, otherwise single agent chemo (Chlorambucil)
- **Mantle Cell Lymphoma:**
 - ~6% of NHL
 - GIT involvement common
 - CD5+ positive
 - Characteristic t(11;14) involving bcl-1
 - Current therapy unsatisfactory: if young then chemo followed by SCT. Modest effect from rituximab
- Hairy cell leukaemia: rare, older males. Massive splenomegaly. Dry BM tap. Prone to unusual infections (eg MAC) and vasculitic disorders. Chemotherapy with cladribine.... Usually curative. Historically important – first one to be treated with immune modulators
- T Cell Lymphomas:
 - Mycosis Fungoides: cutaneous T cell lymphoma. Can spread to lymph nodes and visceral organs. Treat palliatively with topical steroids, PUVA, radiation, IFN
 - Adult T cell Lymphoma/Leukaemia: One manifestation of infection with HTLV-1. Check CD4+ and serum antibodies to HTLV-1
 - Anaplastic Large T/Null cell lymphoma: Aggressive but reasonable survival
 - Peripheral T cell Lymphoma: heterogeneous group of aggressive lymphomas – most are CD4+, some are CD8+, some both

HIV Lymphoma

- EBV associated
- B cell: CNS, Burkitt's, Diffuse Large Cell
- Some increase in low grade NHL, CLL, myeloma, Hodgkin's disease
- Treatment:
 - As for standard NHL
 - Cytopenias more common, increased infection
 - Growth factors needed
 - Dose-reduction often required
 - Higher relapse rate

Haematopoietic Cell Transplantation

- Chemotherapy dosing:
 - Palliation: minor toxicity
 - Standard doses: up to marrow toxicity – the rate limiting factor

- High dose + SCT: can increase up to the level of other organ toxicity (gut, liver, lung and heart). Requires steep dose-response curve of the tumour to the chemo – which is the case in blood malignancies but not usually in epithelial cancers
- Stem cell transplant possible because of:
 - Remarkable regenerative capacity – one cell can regenerate the whole marrow of a mouse, humans need just a few % of their normal marrow
 - Ability to home to the marrow
 - Ability to be cryopreserved
- 3 sources of stem cells (CD34+):
 - Cord blood
 - Marrow
 - Mobilised stem cells on peripheral blood following 5 days of CSF. Graft quicker but more graft verses host disease
- Variations:
 - Autogenic: 2.5 – 5% mortality
 - Allogenic:
 - Related: 100 day mortality for HLA identical sibling transplant ~ 20%
 - MUD (matched unrelated donor): mortality 20 – 40%
 - Mini-SCT: not myeloablative but ↑GVHD. Reduced conditioning (eg in the elderly) and get the new immune system to kill the tumour
 - ABO incompatibility between donor and recipient of little relevance, will acquire the blood type of the donor
- Conditioning regime:
 - Aims to:
 - Eradicate tumour
 - Immunosuppress the host to permit allogenic engraftment
 - Usually cyclophosphamide 120 mg/kg (high dose) + total body irradiation (12 Gray). The cyclophosphamide “spreads out” tumour lysis and avoids acute renal failure
- Complications of preparatory regime (eg high dose cyclophosphamide):
 - Early direct chemoradiotoxicities:
 - Oral mucositis after 5 – 7 days, hair loss from 5 – 6 days and profoundly neutropenic
 - 10% develop venoocclusive disease of the liver (2nd to endothelial injury) → tender hepatomegaly, ascites, jaundice and fluid retention. Peak incidence 16 days. Mortality is 30%
 - Late direct chemoradiotoxicities:
 - Reduced growth velocity in kids, delayed puberty
 - Gonadal failure
 - Thyroid dysfunction
 - Cataracts in 10 – 20%
 - Aseptic necrosis of the femoral head in 10% – especially those receiving chronic glucocorticoid therapy
- Graft verses host disease:
 - Is inversely proportional to relapse
 - Allogenic T cells (either transferred with stem cells or developed from them) attacking host cells
 - Acute GVHD (first 3 months):
 - From 2 – 4 weeks: erythematous maculopapular rash, persistent anorexia, diarrhoea, ↑LFTs
 - Mimics other problems – need biopsy to confirm – endothelial damage and lymphocytic infiltrates
 - Arises in 30% of matched sibling donors, and up to 60% of unrelated donors
 - Treatment: steroids, anti-thymocyte globulin, anti-T monoclonal antibodies
 - Prevention:
 - Immunosuppressive drugs early after transplant: methotrexate and either cyclosporine or tacrolimus. Also prednisone, anti-T cell antibodies, mycophenolate
 - T cell depletion of graft inoculum: reduces GVHD but ↑risk of graft failure and tumour recurrence (ie absence of graft vs tumour effect)
 - Chronic GVHD (later than 6 months):
 - Resembles an autoimmune disease: malar rash, sicca symptoms, arthritis, BOOP, bile duct degeneration (→ cholestasis)
 - Usually resolves over several years

- Treatment: single agent prednisone or cyclosporine
- Host vs graft: rarer, implies insufficient conditioning
- Graft vs tumour: a positive effect, and the benefit of allograft over autograft
- Graft failure: can be associated with CMV or herpes virus 6 or rejection by immunocompetent host cells
- Infection:
 - Prophylaxis usual with neutrophils < 500 – ABs and antifungals. Acyclovir if HSV seropositive
 - Pre-engraftment 1- 4 weeks: HSV, G +ive bacteria, G –ive bacteria, fungi (aspergillus, candida), viruses including respiratory
 - Post-engraftment: CMV (ganciclovir prophylaxis), BK virus, toxoplasma Gondii
 - Late risk period (12 – 52 weeks): VZV, streptococcus pneumoniae (vaccinate), Haemophilus influenzae (vaccinate), Neisseria meningitidis
 - At any stage: PJP (cotrimoxazole prophylaxis common), adenovirus, HHV-6, EBV, Nocardia, Legionella, Mycobacterium spp, Listeria

Plasma Cell Disorders

- All develop from common progenitors in the B lymphocyte lineage
- M component (for Monoclonal) – usually in the γ -globulin region of serum electrophoresis – is a reliable measure of tumour burden – but not specific. Can be raised in CML, breast and colon cancer, cirrhosis, sarcoidosis, parasitic diseases, RA, myasthenia gravis...
- Paraproteins/Monoclonal band in:
 - MGUS (68%)
 - Myeloma (14%) and Waldenstrom's (IgM, 2%)
 - Primary amyloidosis (9%)
 - Lymphoma and CLL (both rare)
 - Rarely in autoimmune disease, chronic infection, hepatitis C, neuropathies..
- Incurable except by autotransplant (but high transplant mortality and relapse)

Multiple Myeloma

- Proliferation of marrow plasma cells ($> 20\%$ of cells) – mature B cells. Arises in lymph nodes and disseminates to marrow
- A variety of chromosomal alterations found
- Hard to differentiate benign from malignant plasma cells on morphology
- Incidence around 4 per 100K
- Clinical features:
 - Hypercalcaemia (> 2.75 mmol/l), lytic lesions and bone pain: due to production of osteoclast activating factor by tumour cells and osteoblast inhibitory factors. Bone/back pain: precipitated by movement (cf metastatic pain which is often worse at night). May be a pathological fracture. Lesions are lytic. *Doesn't show up on bone scan* (as don't involve osteoblasts). May palpate mass lesions in skull and sternum
 - Renal failure (Cr > 173): Mainly due to high calcium, also light chain deposition in proximal tubule (\rightarrow Fanconi's syndrome), amyloidosis, urate nephropathy, NSAIDs for bone pain, recurrent infections. Glomerular function often normal so little albumin in the urine
 - Fatigue/anaemia (< 10 g/L): marrow infiltration
 - Recurrent infections: hypogammaglobulinaemia (normal Ig is broken down more rapidly), may be low CD4 count, deficits in complement function \rightarrow pneumonia and pyelonephritis
 - Neurologic symptoms: in 5% of usual myeloma, 50% of sclerotic myeloma (3% of total), hyperviscosity, amyloid, \uparrow Ca, nerve compression, POEMs syndrome – see page 181
 - Nausea and vomiting: renal failure, \uparrow Ca
 - Bleeding/clotting: interference with clotting factors
 - Rarely causes enlargement of the spleen or lymph nodes
 - CRAB: Calcium high, Renal insufficiency, Anaemia, Bone lesions – all define progressive disease that therefore needs treatment
- Pathogenesis:
 - MM cells bind via adhesion molecules to bone marrow stromal cells and extracellular matrix \rightarrow triggers intra MM-cell signalling promoting proliferation (Raf), drug resistance and anti-apoptosis (JAK \rightarrow STAT3), cell growth and migration into the bone marrow (protein Kinase C)
 - IL6 an important growth factor, also the case with Kaposi's Sarcoma (?link)

- Hyperviscosity: normal serum viscosity is 1.8 compared to water. Hyperviscosity occurs at a level of 5 – 6, which requires > 40 g/L of IgM, > 50 g/l of IgG3 and > 70 g/L of IgA. [With white cells, worry about hyperviscosity over 150 – 250]
- Diagnosis:
 - Urine: dip stick normal unless nephritic (BJP don't show up on dipstick, only albumin)
 - Protein electrophoresis and measurement of serum immunoglobulins – can be negative in non-secretory, or if IgD and IgE (don't label for these on PEP)
 - Bone marrow: plasmacytosis, monoclonal and CD138+. Cytogenetics is helpful for prognosis
 - MRI good for bony infiltration – or skeletal survey with plain film
 - *ALP usually normal* as little osteoblast involvement. Bone scan may be normal
 - Serum Free Light Chains: sensitive assay that identifies most patients producing monoclonal SFLC (saves doing marrows) – previously didn't have a test that differentiated SFLC from intact Ig – so had to test for them in the urine
 - Place of PET not established
- Prognostic markers:
 - Serum β 2-microglobulin: single most powerful predictor of survival and can substitute for staging
 - Albumin
 - Cytogenetics: chromosome 13 del – bad, hypodiploidy – bad, T(4:14) – bad, T(11:14) – good
 - LDH
 - High CRP correlates with disease (reflects IL-6)
- M component is usually IgG, next most common in IgA
- Treatment:
 - 10% have indolent course that only requires treatment when they become symptomatic
 - Different regimes:
 - Melphalan (alkylating agent – toxic to stem cells and renal failure – don't give if considering SCT – damage stem cells making autologous transplant harder) + Prednisone: either normal dose or high dose with stem cell support
 - Thalidamide + dexamethasone:
 - Gives effective cyto-reduction in 2/3rds while still allowing for harvest of transplant cells
 - As monotherapy for maintenance ~ 30% response rate
 - Initially thought it was an anti-angiogenic effect, now multiple mechanisms recognized (including T cell effects)
 - SE: somnolence, constipation, painful neuropathy (up to 90 % after 1 year), DVT (up to 35% with concurrent chemo)
 - Lenalidomide (thalidomide derivative) also used
 - Bortezomib is a proteasome inhibitor with efficacy in stage 3 trials of initial and salvage therapy with prednisone + melphalan that shows benefit (better than dexamethasone alone). No head to head trials with thalidamide
 - SCT if under 65 – but most diagnoses over the age of 70 – doubles survival but doesn't cure:
 - Induction: VAD (vincristine, doxorubicin, dexamethasone) –
 - Autologous transplant (Allogeneic transplant only suitable for 5%, high mortality but ?curative – there is a graft vs myeloma effect but doesn't increase cure rate)
 - Maintenance: Prednisone (eg alternate day) +/- IFN α (rarely used, can help)
 - Responders usually have prompt reduction in pain; fall in the M component lags symptomatic improvement
 - No standard maintenance treatment
 - Supportive care:
 - Pamidronate/Zoledronic acid decrease skeletal progression, bone pain and improve QOL. Zoledronic acid better than pamidronate. Calcium and vitamin D suggested but not proven.
 - Radiotherapy
 - If renal failure plasmapheresis effective but place in treatment controversial
 - Pneumococcal vaccines are indicated but may not elicit a response
- Median survival: 5 – 6 years
- Variations:
 - Subtypes: smouldering or asymptomatic myeloma (found on testing but no organ damage) or non-secretory myeloma (as opposed to myeloma-ROTI – Myeloma-related organ or tissue impairment)
 - Solitary bone plasmacytoma: single lytic bone lesion without marrow plasmacytosis. Highly responsive to local radiotherapy
 - Extraosseous plasmacytoma

- Light Chain Deposition Disease: light chains deposited largely in the kidneys – as opposed to Primary Amyloidosis (AL) where light chain deposition occurs in a wide range of organs (diagnosis on biopsy of rectal mucosa or subcutaneous fat pad aspiration). See page 273
- POEMS Syndrome: Severe polyneuropathy, organomegaly, endocrinopathy (amenorrhoea, gynaecomastia), multiple myeloma and skin changes. See page 181

Monoclonal Gammopathy of Uncertain Significance (MGUS)

- More common than MM: 1% of over 50s and 10% of over 75s
- Survival is 2 years shorter than age matched controls
- Diagnostic criteria:
 - M protein (= monoclonal protein) in serum < 30 g/L
 - Bone marrow clonal plasma cells < 10%
 - No myeloma-related organ or tissue damage (including no bony lesions)
- Can differentiate from MM by exposing bone marrow cells to radioactive thymidine to quantitate dividing cells. < 1% labelled in MGUS, > 1 % labelled in MM
- About 1% per year go on to develop MM – size of M band correlates with risk of progression, as is IgM or IgA (vs IgG)
- Monitor paraprotein q 6 – 12 months. Therapy if doubling of M protein in < 1 yr or bone lesions

Waldenstrom's Macroglobulinaemia

- Weakness and recurrent infections as with MM, but epistaxis, *visual disturbances* and neurologic symptoms (*peripheral neuropathy*, dizziness, headache, TIAs) more common
- Resembles CLL, MM and lymphocytic lymphoma
- Originates from a post-germinal centre B cell with characteristics of an IgM-bearing memory B cell
- Increased IgM band on serum protein electrophoresis, 75% of IgM kappa light chain type
- Interference of IgM with clotting factors → ↑INR and APPT
- Bone marrow: aspirate is frequently hypocellular, biopsy is hypercellular, lymphoid and plasmacytosis
- Involves marrow, but doesn't cause bony lesions or hypercalcaemia
- Size of IgM paraprotein means it's not excreted, so causes little renal impairment
- Treatment like CLL. Fludarabine or cladribine as single agents, +/- rituximab. Can treat *hyperviscosity* acutely with plasmapheresis

Disorders of Haemostasis

Coagulation

- "Cellular model": not just cascades in the serum – takes place on cell surfaces (eg of activated platelets) with endothelial, platelet and plasma protein interactions
- Initiation → amplification → clot formation → propagation → confinement
- Soluble fibrinogen → fibrin, catalysed by thrombin (factor IIa, prothrombin = II) formed from the products of the intrinsic (APPT) and extrinsic (Prothrombin time ~ INR) cascade. Thrombin is the most powerful activator of platelets
- Antithrombin localizes a clot by inhibiting thrombin and factors Xa and IXa
- Role of liver:
 - Production of coagulation factors, coagulation inhibitors (eg antithrombin), fibrinolytic factors
 - Vitamin K carboxylation
 - Clearance
- 3 causes of clotting problems:
 - Factor deficiency
 - Factor dysfunction
 - Inhibitors: eg autoantibodies, usually against factor VIII
 - To test, mix 1:1 with normal plasma. If it was a deficiency, the normal plasma will fix it. If an inhibitor, it will inhibit the normal plasma as well
 - Treat with recombinant activated VIIa to bypass inhibitors

Haemophilia

- Prolongs aPPT but not prothrombin time
- Severe (< 1% activity) and moderate (1 – 5% activity) are associated with spontaneous bleeds
- Mild (5 – 30% activity) have little spontaneous bleeding
- Inhibiting antibodies to FVIII form in 20% of severe

- In an acute setting: try high doses of FVIII, but may require activated VIIa
- To eradicate the ABs: immunosuppression ineffective. Use immune tolerance – daily infusion of FVIII till AB disappears (> 1 yr) +/- rituximab
- Acquired haemophilia:
 - Rare, but suspect in an elderly person without previous bleeding disorder
 - Acquired antibodies to factor VIII (FVIII inhibitor), about half of cases 2nd to pregnancy, malignancy, drugs, autoimmune diseases
 - Differential of a prolonged aPPT is anti-phospholipid syndrome – but these present with clotting

Acquired disorders of coagulation

- Liver disease
- Vitamin K deficiency
- Massive blood transfusion
- Uraemia: → platelet dysfunction. Responds to desmopressin/DDAVP (improves platelet adhesion) or red cell transfusion (with ↓large RBCs platelets flow centrally)
- DIC:
 - Pathogenesis:
 - Always 2nd to an underlying cause: sepsis, trauma, malignancy, pancreatitis, obstetric (amniotic fluid embolus, abruption, HELPP), liver failure, snake bite, transplant rejection
 - Release of thromboplastin (a lipoprotein in cell membranes) from eg tumour cells breaking down, massive injury, septicaemia, endotoxins
 - Activation of XII from damage to endothelium – which doesn't like anoxia, acidosis, sepsis...
 - Direct activation of II (prothrombin) and X: amniotic fluid embolism, acute pancreatitis
 - Diagnosis: ↑APPT and INR, ↓fibrinogen and platelets, ↑FDPs
 - Treatment:
 - If bleeding: platelets, to replace fibrinogen, give cryoprecipitate. To replace clotting factors give FFP
 - If thrombosis: heparin
 - Restore natural anticoagulants: recombinant activated protein C

Hypercoagulable States

Primary Causes

- Factor V Leiden:
 - Most common primary cause
 - Point mutation on factor V prevents breakdown by aPC → ↑levels of Va → hypercoagulable
 - Heterozygous are 5 – 8% of Europeans, and have lifetime risk of 30 – 40% of thrombotic event, homozygous then 50 – 60%
 - In thrombotic patients, 20 – 40% have factor V Leiden, mainly in Caucasians
 - Don't screen family. Clotting history of more clinical utility
- Activated Protein C resistance without factor V Leiden
- Prothrombin gene mutation
- Antithrombin deficiency:
 - 20210G → A mutation leads to reduced breakdown of thrombin
 - More severe effect (<1%) – the only one in which to consider family screening
 - Heparin co-factor, α₂ globulin
 - Autosomal dominant, 1: 2-5000 in Caucasian
 - Found in 2 – 3 % of DVTs
 - Can also cause mesenteric or brachial thrombosis. These are rare so → ↑index of suspicion
- Protein C or S deficiency
- Homocysteinaemia
- Lupus anticoagulant (most don't have lupus, but one of the antiphospholipid antibodies) inhibits a number of clotting factors, but paradoxically causes clotting. See page 262
- Acute thrombosis lowers antithrombin, and protein C and S. If these are normal despite the presence of thrombosis, then they're not deficient

Medication for Preventing Blood Loss

- See NEJM 31 may 2007

- Definitive data lacking for all haemostatic agents – trials of therapeutic efficacy but less on toxicity. Most studies in peri-operative blood loss, especially surgery
- Aprotinin: bovine-derived protease inhibitor. Most studied. Renal and cardiovascular adverse effects
- Antifibrinolytic lysine analogues:
 - Action: Plasminogen binds to plasminogen activator, which then binds to and fragments fibrin, creating fibrin degradation products. Lysine analogues prevent the binding of the plasminogen-plasminogen activator complex to fibrin
 - Aminocaproic acid and tranexamic acid (↓69% reduction in red-cell transfusions in acute peri-operative bleeding)
- Desmopressin/DDAVP: synthetic analogue of ADH that → ↑factor VIII and vWF. Little evidence of efficacy in conditions other than mild haemophilia A and vWD
- Activated factor VII. Originally licensed for haemophiliacs with antibodies to factor VIII or IX. Mixed results in surgical setting depending on indication. Trialled in intracerebral haemorrhage – smaller bleed size but no difference in clinical outcomes. Maybe decreased bleeding in variceal bleed in severe cirrhosis. Little evidence of ↑thrombotic risk – but most trials in people with impaired coagulation

Anticoagulation

- See also Anticoagulation in AF, page 3, DVT, page 214, and Stroke, page 141
- **Heparin:**
 - Derived from porcine intestinal mucosa, which is rich in mast cells (the source)
 - INR mainly measures the top end of the extrinsic pathway, so may not be affected by heparin, even though it affects the common pathway. APPT more sensitive to ↓common pathway
 - Activates antithrombin (previously antithrombin 3) → accelerates rate at which antithrombin inhibits clotting enzymes – especially Xa and II (prothrombin)
 - Heparin bound to antithrombin → conformational change in antithrombin → ↑ rate at which it inhibits Xa but no change in rate of II inhibition. Effect on II is mediated by the long chain of unfractionated heparin which promotes more stable binding of thrombin and antithrombin
 - Is unable to inactivate thrombin that is bound to fibrin, and factor Xa that is bound to activated platelets by thrombus
 - Highly variable pharmacokinetic person to person (necessitates monitoring):
 - At low dose, half life is short as it binds rapidly to endothelium. At higher doses, these binding sites are saturated → longer half life
 - Heparin is inactivated by being bound to a number of serum proteins, including PF4 released by activated platelets → ↓anticoagulant effect near platelet rich thrombi
 - Mainly clearance is by degradation by macrophages
 - Factor II and VIII are acute phase reactants → ↑ in inflammation → ↓APPT but factor Xa levels may be sufficiently low to be therapeutic
 - Different APPT reagents vary in their sensitivity to heparin → the therapeutic range will vary from lab to lab
 - Reversal: protamine sulphate, a mixture of basic polypeptides (isolated from salmon sperm!) binds heparin with high affinity
- **Low Molecular Weight Heparin:**
 - Eg enoxaparin (Clexane), dalteparin (Fragmin)
 - Derived from heparin, by removing some/all of the pentascarrharide-containing chains (→ reduces molecular weight to about a third)
 - Catalyses antithrombin inhibition of Xa much more than of II (4:1 rather than 1:1 as in heparin)
 - Less rapid binding to endothelial cells → eliminates the rapid, dose-dependent and saturable clearance mechanism of heparin → much more predictable dose response
 - Cleared by the kidneys
 - *Must be monitored by checking activated Xa levels, as it has little effect on APPT*
 - Dosing not extensively evaluated in morbid obesity
 - Risk of thrombocytopenia and osteoporosis lower than with heparin
- Fondaparinux:
 - Synthetic analogue of the antithrombin-binding pentasaccharide sequence of heparin (ie no chain at all), given sc
 - Has no effect on thrombin – ie only a Xa effect
 - 17 hour half life (cf 4 for LMWH)
 - Clearance is dose-independent, renally excreted

- As effective as LMWH for the initial management of DVT/PE with similar bleeding rates
- Initial studies show same efficacy and reduced bleeding in ACS (?not dose equivalent in the studies)
- Doesn't bind to PF4 → can be used in heparin-induced thrombocytopenia
- Longer acting forms in development (eg once weekly)
- **Warfarin**
 - Mechanism:
 - Vitamin K is a cofactor for the formation of γ -carboxyglutamic acid residues on coagulation proteins
 - Warfarin blocks the action of vitamin K epoxide reductase → impaired regeneration of reduced vitamin K
 - Prevents carboxylation activation of factors 2, 7, 9, 10. Also ↓synthesis of anticoagulant proteins C and S (which are also vitamin K dependent – so → initial hypercoagulable)
 - Pharmacokinetics:
 - Mean half life is 40 hours (range 20 to 60), maximum effect of a dose is 48 hours after administration (ie after pre-existing inhibited factors are cleared)
 - Narrow therapeutic index
 - Interactions: antibiotics, amiodarone, statins, anticonvulsants, St John's Wort, spinach/broccoli have lots of vitamin K – probably not significant unless you eat truck loads
 - Elimination entirely by metabolism – especially P450 CYP2C9. Two common variants have ↓activity → need lower doses
 - 5 polymorphisms of the vitamin K receptor gene + allelic variants of P450 2C9 explain 35% of the variability in dose-response to warfarin – ?future profiling to determine warfarin dose. (NEJM 2008, 358:10) Variants in the promoter region of vitamin K epoxide reductase (VKORC1) predict warfarin doses. Can't do these tests in real time, and no evidence that testing is better than dose titration
 - Clinical effect:
 - No effect on an established thrombus
 - Initial paradoxical exacerbation of hypercoagulability can increase the likelihood of thrombosis. Cover with heparin for at least 5 days. Wait several hours after LMWH for first dose
 - Initial increase (24 – 36 hours) in the INR is related to early clearance of factor VII (half life 6 hours). However this does not correlate to antithrombotic effect, which occurs mainly through ↓factor II (prothrombin – half life 60 – 72 hours – so little effect until this is cleared) and factor X
 - Loading and monitoring:
 - Loading doses not recommended – start with expected maintenance dose (5 mg). Avoid frequent dose adjustments
 - Self-monitoring with home point-of-care finger prick machine better in meta-analysis than anticoagulation clinic care
 - Reversal:
 - INR 5.0 – 9.0 and no bleeding: stop warfarin
 - INR 5.0 – 9.0 and high risk of bleeding: Vitamin K (1 – 2 mg orally or 0.5 – 1.0 mg iv)
 - INR > 9.0 and low risk of bleeding: 2.5 – 5.0 mg oral vitamin K or 1.0 mg iv
 - INR > 9.0 and high risk of bleeding: 1.0 mg vitamin K iv, Prothrombinex-HT (25 – 50 iu/kg) and FFP (150 – 300 ml)
 - ProthrombinX contains factors II, IX and X, but only low levels of factor VII. Use FFP as an adjunctive source of factor VII
 - Vitamin K takes ~ 6 – 12 hours for effect, full effect in 24 hours
 - If using FFP or ProthrombinX, need vitamin K to sustain its effect
 - Side Effects:
 - Risk of bleeding (in observational studies) related to age, history of past bleeding, specific comorbid conditions (HTN, renal insufficiency, excessive alcohol intake)
 - Non-bleeding side effects:
 - Alopecia
 - Rarely skin necrosis. Well demarcated erythematous lesions with progressively necrotic centre. Seen in congenital or acquired protein C or protein S deficiency. Warfarin → ↓protein C and S (→ procoagulant state) before ↓clotting factors kicks in → thrombosis in microvasculature of fatty tissues. Stop warfarin. Prevent by covering with heparin while titrating warfarin (?is this the same as Calciphylaxis, ↑risk with renal failure)

- Teratogenic, especially 6th – 12th week (→ fetal chondrodysplasia punctata), also 2nd and 3rd trimester (optic atrophy and mental retardation). Anticoagulant effect in foetus dangerous at delivery (eg intracerebral bleeds). Safe in breast-feeding
- Antiphospholipid syndrome: Lupus anticoagulant can → ↑INR – making monitoring problematic
- **Fibrinolytic drugs:** All work by converting the proenzyme plasminogen to plasmin, which degrades fibrin to fibrin degradation products
- **The future:**
 - *Direct Thrombin inhibitors:* Heparin and fondaparinux work via antithrombin – so they can't inactivate clot bound thrombin. This emerging class of drugs binds thrombin directly (and so are also effective in anti-thrombin deficiency)
 - Sc drugs already approved, eg bivalirudin, lepirudin (a recombinant hirudin, originally extracted from the salivary gland of the medicinal leech!), argatroban.
 - Oral ones in trial, eg Dabigatran. Ximelagatran not approved due to hepatotoxicity
 - Oral Direct Xa inhibitors. Rivaroxaban approved (see Treatment of PE, page 214), others in trial
 - Others being investigated: Tissue factor inhibitors, targeting factor V and VIII

Thrombocytopenia

- Exclude pseudothrombocytopenia: platelet agglutination via antibodies when Ca content is lowered by EDTA
- Differential:
 - Decreased production:
 - Inherited (rare)
 - Acquired: Bone marrow damage due to drugs, MDS, chronic hepatitis C, PNH, alcohol
 - Increased destruction/consumption
 - Immune: ITP, alloimmune (eg transplant or platelet transfusion), Drugs (eg HIT), HIV, CMV, Hep C, mycoplasma, EBV
 - DIC
 - TTP
- Workup:
 - Check spleen and liver
 - Must review blood film
 - If young, ↓production will result from marrow disorders also affecting RBC and/or WBC
- **Infection induced** thrombocytopenia:
 - Caused by many viral (more common in kids) and bacterial infections
 - DIC – usually G –ive bacteria
- **Drug induced** thrombocytopenia:
 - Eg acyclovir, amiodarone, carbamazepine, diclofenac, digoxin, ibuprofen, phenytoin
 - Drug-dependent antibodies – ie only bind platelet in the presence of the drug – eg quinine and sulphonamides
- **Heparin-induced** thrombocytopenia:
 - See Anticoagulation, page 445
 - Usually 5 – 10 days into exposure – ie can occur in a hospital-in-the-home setting – can nurses spot it?
 - Two differences to other drug thrombocytopenias:
 - Not so severe – platelets don't usually drop below 20
 - Marked increased risk of *thrombosis* (ie not bleeding)
 - 10 times more common with unfractionated than with fractionated
 - Results from antibody to a complex of platelet-specific protein platelet factor (PF4) and heparin, which then activates platelets. Only a fraction of those developing this antibody develop thrombocytopenia (ie the assay for the antibody is not specific)
 - Clinical diagnosis – the current tests are not available in real time and don't have sufficient sensitivity or specificity
 - Treatment: stop heparin. If anticoagulation required then switch to eg the antithrombin-binding fondaparinux (used to use Danaparoid)
- **Immune Thrombocytopenic Purpura (ITP):**
 - Acute and self-limiting in kids, chronic in adults (F>>M, 15 – 60 years)
 - Accelerated platelet destruction *and* ↓production
 - Mucosal bleeding, low (maybe very low) platelet count and otherwise normal FBC and blood film. Check retina

- IgG attaches to platelets as they pass through the spleen and liver, encounter macrophages with an Fc receptor and are engulfed
- Associated with AIHA, CLL, RA, SLE, drugs (quinine, antibiotics, antiepileptics)
- Workup:
 - Antibody testing not helpful
 - Bone marrow only in older patients (> 60) or with other abnormalities not explained by ITP
 - Exclude HIV, Hepatitis C, SLE, do protein electrophoresis and Ig levels, and, if anaemia, do Coombs test to exclude autoimmune haemolytic anaemia with ITP
- Treatment
 - Aim: platelets high enough to avoid significant bleeding – often just observe
 - Avoid platelet transfusion unless life threatening haemorrhage
 - Prednisone (>80% respond)
 - If severe: IVIg. Rituximab has efficacy. Splenectomy if needed (vaccinate prior). Additional immuno suppression (azathioprine...), Platelet stimulating drugs in trial (eg Romiplostim, a thrombopoiesis-stimulating protein, Lancet 2 Feb 2008)
- **Thrombotic Thrombocytopenia Purpura (TTP):**
 - See NEJM 4 May 2006
 - *Haemolytic anaemia*, renal failure (may just be proteinuria), fever, ↓↓ platelets, neurologic manifestations (may be just a headache, seizures, fluctuating focal deficits – NB HUS has no neurology), vague pains
 - Due to deficiency of, or antibodies to (ie hereditary or more commonly acquired autoimmune) ADAMTS13 (ADAM = a disintegrin and metalloproteinase domain), a metalloprotease that cleaves ultra-large vWF multimers → persistence of ultra-large vWF multimers → pathogenic platelet adhesion and aggregation in capillaries → endothelial damage → microangiopathic haemolysis
 - Provoking factors uncertain, include drugs (cyclosporin, chemotherapy), infection, HIV, pregnancy
 - Labs:
 - Similar degree of anaemia and thrombocytopenia
 - Blood film will show schistocytes (fragmented RBCs) and polychromia (due to reticulocytes)
 - ↑LDH, bilirubin and ↓haptoglobin 2nd to intravascular haemolysis
 - Coombs negative
 - *Coagulation and fibrinogen normal* (cf DIC which is the other microangiopathic anaemia, or a mechanical valve which has no thrombocytopenia)
 - 90% mortality without treatment, 10% with treatment. Plasma exchange or infusion of 3 litres FFP/day until platelets > 150 (may take months). Sometimes immunosuppression (rituximab, steroids controversial)
- **Haemolytic Uraemic Syndrome:** see page 131
- **DIC:** see page 444
- **HELLP Syndrome:** see page 460

Disorders of Platelet Function

- PFA100 (PFA = platelet function analyzer) has superseded bleeding time test
- Gum bleeding can be caused by platelet dysfunction, correlates with internal bleeding
- Acquired disorders:
 - Iatrogenic:
 - Antiplatelet therapy
 - High dose penicillins
 - Uraemia – treat with dialysis, DDAVP or conjugated estrogens
 - Paraproteinaemias
 - Cardiac bypass
- Von Willebrand Disease:
 - vWF has two purposes:
 - Tethers the platelet to exposed subendothelium. vWF binds to platelet glycoprotein 1b-IX-V. Binds platelets to endothelial surface – arrests flow by rolling then activation and aggregation
 - Acts as a binding protein for factor FVIII → significantly prolongs the half life of FVIII
 - Presents with mucosal bleeding, excessive bruising and epistaxis (rare in infancy). Menorrhagia
 - Treatment (especially pre-procedure):
 - DDAVP/desmopressin (1-deamino-8-D-arginine vasopressin) either IV or intranasal spray. SE hyponatraemia, so fluid restrict for 24 hours
 - vWF replacement

Blood Product Transfusion

- Leuco-depletion → ↓CMV, ↓immunisation to HLA and ↓febrile non-haemolytic reaction
- Indications for irradiated products in adults (↓risk of graft vs host and ↓CMV if CMV negative blood not available):
 - Exchange transfusions
 - Congenital immune deficiencies
 - Lymphoma
 - Recipients of stem cell or bone marrow transplants
 - Aplastic anaemia
- Cryoprecipitate: source of fibrinogen, not other clotting factors
- Transfusion reactions:
 - Immune:
 - Immediate haemolytic: the worst, usually ABO
 - Febrile non-haemolytic: 1% of all transfusions → ↑ of at least 1°C without chills or rigours. Donor WBC being lysed and cytokine accumulation during storage (esp IL-1, → PGE2 production in the hypothalamus). Significantly reduced by leucodepletion
 - Allergy/Anaphylaxis from transfusion, rare (eg to IgA in IgA deficient people)
 - Transfusion Related Acute Lung Injury (TRALI):
 - 1 in 5,000 plasma containing transfusions
 - Due to donor antibodies in 85%. Eg female donors who have made antibodies to fetal white blood cells when they had children, at risk if recipient has same antibodies
 - Acute respiratory distress 1 – 6 hours post transfusion. Fever, hypotension. CXR looks like ARDS. Mortality up to 15%
 - Treatment: supportive. Exclude LVF, steroids (not proven). Identify donor – should never donate again
 - Transfusion related GVHD: proliferation of donor T-cells – rare, most commonly in haematological malignancy or immunodeficiency (not AIDS). Onset 8 – 10 days. > 90% fatal. Investigations: biopsy, tissue typing, PCR for donor DNA. Stopped by irradiation, only reduced by filtration
 - Non-immune:
 - Volume overload
 - Infectious (bacteria, viral, protozoal) – consider bacterial in all severe febrile reactions
 - Other: Air embolism, citrate toxicity, hypothermia, iron loading, hyperkalaemia
- Transfusion related transmissible infections:
 - Bacteria – *most common in platelets* (1 in 1000 – 2000). Common bugs: S Aureus, coagulase negative staph, Yersinia, Serratia, Pseudomonas (ie often donor skin commensals). Empiric treatment. But much of the problem is endotoxin in the blood, not the bug itself
 - Viral: HIV, Hep B & C, HTLV1, CMV – all rare

- See dermnet.org.nz
- Definitions:
 - Macule: pure colour change
 - Papule = < 5 mm
 - Nodule = > 5 mm
- Approach:
 - What layer is the pathology in:
 - Epidermal: typified by scale, crusting (think infection), blistering, lichenification (accentuated skin lines like wrinkles, due to chronic rubbing)
 - Dermal: erythema (due to blood – vessels are in the dermal layer), induration
 - Or subcuticular
 - What colour is it: red (blood, inflammation), black (melanin eg melanoma)
 - Other clues: infection → lymph node spread
 - If in doubt, biopsy
- Steroids:
 - Weak: Hydrocortisone 1%
 - Stronger: Betamethasone 0.1% or Hydrocortisone butyrate
 - Strongest: Dermol
- Random stuff:
 - Sunburn: dermal erythema → epidermis exfoliation. Can treat with strong steroids (eg dermol)
 - Differential of itching: also consider fungal infection, uraemia, Fe deficiency, lymphoma, primary biliary sclerosis
 - ‘Allergic’ rashes: consider bugs, drugs and connective tissue disease
 - Dermographism: weal with skin scraping, mast cell instability, treat with antihistamines

Infections

- Cellulitis:
 - *always* look for athlete’s foot, and treat if found
 - S Aureus. Consider risk factors for other bugs:
 - Pasteurella: dog/cat bite with puncture wound
 - Aeromonas spp: freshwater, esp male and cirrhosis/cancer
 - Vibrio spp: seawater, esp male and cirrhosis
 - Clostridia spp (G –ive): immunocompromised
 - Mycobacteria marinum: water exposure, some specific areas of Aussie
 - Erisipelothrix: shell fish
- Impetigo:
 - β-haemolytic streps, also group B, C, G streptococci
 - Erythematous papule → vesicle → pustule → yellow crust and purulent discharge
 - Spread to close contacts
 - Associated with scabies
 - Management: saline, soap, penicillin
- Scabies:
 - Norwegian: in institutionalized patients. Have millions of the critters. Treat with oral ivermectin
 - Standard variety: ~20 females. Treat twice with permethrin(incubation 5 or 6 weeks), all household members, from the neck down. Wash linen (dies after about 24 hours away from host)
- Fungal infections:
 - Nystatin – for yeasts. Not for tinea – need an azole – see page 296
 - Common pathogens: Microsporium canis (from cats, fluoresce under Wood’s light), others
 - For fungal infection, do a skin scraping – 2 days for microscopy, 30 days for culture. Need to treat for 30 days – takes that long for the skin to grow out
 - Tinea Cruris: groin. If feet involved as well may need systemic treatment
 - Tinea Capis: Scalp → alopecia. Needs systemic treatment (topical doesn’t penetrate hair shaft)
 - Tinea Pedis (Athlete’s foot): usually lateral toes (cf eczema in medial)
 - Tinea corpus: May not itch
 - Tinea: Magnum: hand. Almost always a pre-existing foot infection
 - Onychomycosis: fungal (distal, spreads proximally), trauma, psoriasis (proximal, spreads distally), thyroid, drugs... Treatment oral terbinafine or itraconazole

- Tinea incognito: fungal infection treated with steroids. Itch stops but fungus spreads → follicular pustules
- Tinea Versicolor: due to a yeast, not a fungus. Hypo and hyper pigmented macules with powdery scale. Treatment Imidazole cream or oral itraconazole
- Necrotising fasciitis:
 - Presentation: acutely swollen and painful lower limb or abdominal wall, severe pain >> clinical signs, high fever
 - Usually Group A Strep, often polymicrobial, esp in diabetes
 - Odd cases:
 - Clostridial myonecrosis: gas gangrene
 - Vibrio vulnificus: salt water wound especially if immunocompromised
 - Rhabdomyolysis
 - Mycobacterium ulcerans: Some areas in Australia, treat with moxifloxacin, rifampicin + surgery
 - Treatment:
 - Surgery
 - Penicillin for strep, clindamycin (for “antitoxin” role), meropenem or gentamicin just in case of G-ives
 - IVIG: improved mortality in Group A streptococcal infection

Other Skin Lesions

- Erythema nodosum:
 - Commonest on shins – firm, tender, erythematous lesions 2 – 4 cm, 2 – 50 lesions
 - Erupt over 10 days and subside within 3 – 6 weeks, regress with bruise like discoloration
 - Can also have fever, aching, malaise
 - Associated with:
 - Children: strep infection
 - IBD, Sarcoidosis, TB, cat scratch disease, Yersinia, mycoses, some drugs
 - Erythema multiforme:
 - Definitions:
 - Over lap of definitions and significant confusion over terminology: major, minor, Stephens-Johnson, Toxic Epidermal Necrolysis
 - Bullous erythema multiforme: < 10 % body area blistering, plus target lesions
 - SJS: < 10% blistered + widespread red or purpuric macules or flat atypical targets
 - TEN with spots: > 30% blistered, plus rash
 - TEN without spots: < 10% blisters, in large epidermal sheets
 - Erythema multiforme:
 - Think bugs and drugs
 - Minor = no mucosal involvement, major = mucosal involvement
 - If due to an infection, usually herpes simplex, occasionally mycoplasma, rarely others. Treat with acyclovir for 1 year or more, otherwise the rash will recur with subsequent outbreaks. The current rash will resolve in 5 – 6 weeks and will require no further treatment
 - Classical targets (cyanotic or blistered centre, surrounded by pure halo, then erythematous ring), acral distribution
- | Herpes Simplex (~ EM) | Drug Reaction (~ SJS) |
|-------------------------------|-----------------------|
| Worse acraly (ie palms/soles) | no acral predominance |
| Typical targets | not typical targets |
| A little or a lot of rash | A lot of rash |
- Possible drugs: anticonvulsants, sulfonamides, other antibiotics, NSAIDs, allopurinol
 - Toxic Epidermal Necrolysis:
 - Reserved for widespread blistering or skin coming off in sheets (as opposed to erythroderma), with mucosal involvement, may also be renal impairment, anaemia or neutropenia
 - High mortality, 1 per million per year
 - Treatment:
 - Huge controversy
 - Remove offending drugs, if severe treat as for burns
 - ABs if infected
 - Emollient
 - NOT Steroids: likely to be harmful. Death is usually due to infection and steroids increase that risk

- IgG or IV cyclosporin advocated
 - Can be neutropenic (? GCSF)
- Erythroderma (=Exfoliative dermatitis in the USA):
 - 90% or more of body surface involved = generalised skin failure
 - Presentation:
 - Hypoalbuminaemia common
 - Oedema common – ↑capillary permeability
 - Fatal in 20 – 40%, especially elderly (from pneumonia, septicaemia, cardiac failure...)
 - Causes:
 - Eczema – 40%
 - Psoriasis – 25%
 - Lymphoma, leukaemia – 15%
 - Drug reaction – 10%
 - Unknown – 10%
 - Treatment:
 - Monitor fluid balance
 - Emollient. Avoid irritating topicals, UB
 - Rest, good diet
 - Steroids – avoid in psoriasis (otherwise rebound)
 - Other immunosuppressant agents
- Urticaria:
 - Transient erythematous/oedematous swellings of the dermis or subcutis, usually lasting < 24 hours, some may look target like (ie confused with erythema multiforme – but this is predominantly acral [hands and feet], doesn't itch, and doesn't change rapidly)
 - 50% are not allergic
 - Can be physical (eg due to pressure), cholinergic, hereditary angioedema, allergic IgE or IgG mediated, idiopathic or autoimmune
 - Foods causing urticaria: eggs, peanuts, fish and shellfish, wheat, legumes, tomatoes, pork, strawberries, dairy, soy
 - Most chronic urticaria (> 2 months) is not allergic
- Acanthosis nigricans:
 - Brown and velvety. Sides of neck, axillae, groin. Progressive in malignancy
 - Differential:
 - Obesity, insulin resistance
 - Drugs: nicotinic acid
 - Malignancy: especially adenocarcinoma
- Pyoderma Gangrenosum:
 - Associated with
 - Inflammatory bowel disease
 - Monoclonal gammopathy
 - Malignancy (esp haematological, eg CML)
 - Connective tissue disease (eg RA)
 - Biopsy shows just an ulcer
- Porphyria cutanea tarda: see page 368
 - Bullae on hands in summer. Hyperpigmentation, scleroderma changes, fragile skin
 - Familial and sporadic forms
 - Enzyme defect of uroporphyrinogen decarboxylase in the liver. Incomplete penetrance
 - Various agents trigger symptoms: alcohol, estrogens, chemicals, Hep C
- Sweets Syndrome:
 - Explosive onset of tender red plaques on the face or limbs, with leukocytosis, fever, raised ESR. Usually middle aged, F >> M
 - Histology characteristic
 - Numerous associations, including IBD, haematologic disease, post infectious or drugs
 - Responds to systemic steroids, dapsone
- Peutz Jeghers:
 - Pigmented macules on the oral mucosa, incl lower lip, +/- face and hands
 - Develops in infancy of childhood usually
 - Associated with intestinal polyposis

- Relative risk for breast or gynae cancer is 20: need screening for breast, bowel and gynae cancer
- Pseudoxanthoma elasticum:
 - Yellowish papules in linear or reticulate array developing before age 30. May look like “chicken skin”
 - Elastic fibre calcification. Also visual field loss and occasionally cardiovascular complications
 - Skin biopsy
 - Mainly sporadic, but AD and AR patterns exist. Screen family members
 - Can get similar lesions in patients with β -thalassaemia
- Seborrheic Dermatitis: erythema with greasy yellow-brown scale of scalp, eyebrows and perinasal areas

Tuberous Sclerosis

- Classically (but not invariably) seen with epilepsy and mental retardation (‘zits, fits and nit-twits’)
- Disorder of haematoma formation: especially in eye, brain, skin, kidney and heart
- Skin lesion:
 - Angiofibromas: appear from 3 – 10, firm, discrete red/brown telangiectatic papules, 1 – 10 mm, cheeks and chin
 - Periungual fibromas: smooth skin coloured excrescences emerging from the nail folds
 - Shagreen patch: skin coloured plaque in lumbosacral region
 - Oval white macules (Ash-leaf-macules) seen under Woods light. But also similar lesions common in normal kids
- Autosomal dominant with variable penetrance, 50% are new mutations
- Prevalence ?1/10,000

Neurofibromatosis

- Look like intradermal naevi but soft
- Neurofibromas: benign peripheral nerve tumours comprised of Schwann cells. Compressive if in enclosed spaces
- Type 1:
 - Commonest, 1/3000, Autosomal dominant, 30% new mutations
 - At increased risk of nervous system neoplasms
 - Café au lait spots, freckling in non-sun-exposed areas such as the axilla, hamartomas of the iris (Lisch nodules)
- Type 2: 2 or more of:
 - >90% have bilateral vestibular schwannomas → progressive unilateral deafness in 3rd decade. Also ↑risk of CNS tumours
 - Multiple café au lait spots occur rarely
- May lead to short stature, macrocephaly, kyphoscoliosis, intellectual handicap, endocrine problems (precocious puberty, acromegaly, Addison’s), neuro tumours (optic nerve glioma, astrocytomas), etc

Chronic wounds/Ulcers

- See Lancet 29 Nov 2008
- Venous ulcer:
 - Due to deep venous insufficiency, post-thrombotic syndrome, primary varicosis
 - Treatment: graduated compression bandaging effective (if ABI > 0.6, Cochrane 2009), physical activity, elevation
- Arterial ulcer:
 - Due to: macroangiopathy
 - Treatment: Angioplasty, vascular surgery, drugs to improve blood flow, physical activity, ↑risk factors
- Diabetic ulcer:
 - Due to neuropathy, small vessel disease
 - Treatment: glycaemic control, off-loading or orthopaedic footwear

Pressure Ulcers

- Risks:
 - ↓sensation or response to discomfort: neurological disease, CVA, depression, ↓LOC (eg 2nd to drugs)
 - Alterations in mobility: neurological disease, fractures, pain, restraints

- Significant changes in weight: malnutrition, oedema
- Incontinence
- Increases mortality by 4 fold
- ABI < 0.4 is associated with a low likelihood of wound healing
- Staging:
 - 1: non-blanchable erythema of intact skin – heal in days to weeks
 - 2: partial thickness skin loss – abrasion, blister or shallow crater
 - 3: full thickness skin loss, with damage down to the fascia – a deep crater – heal in months
 - 4: full thickness skin loss with damage down to supporting structures (bone, muscle, tendon, etc)
 - Can progress from stage 1 to 4 in as little as a day or two
 - Ulcer can't be staged until necrotic material is removed
- Management:
 - Debridement: surgical or chemical
 - Cleansing: usually normal saline, bactericidal agents can impair fibroblast repair
 - Dressing
 - Reposition – timing of turns depends on location and severity of the pressure area
 - No RCTs for nutritional supplementation
 - Incontinence is a risk factor, but no evidence for catheterisation

Inflammatory Skin Lesions

- Psoriasis:
 - 70% concurrence in identical twins, 20% in non-identical
 - Treatment if severe:
 - UVB – broad band or narrow band
 - PUVA: psoralens + UVA (increased risk of skin cancer if immunosuppressants)
 - Methotrexate
 - Neotigason
 - Azathioprine
 - Calcineurin inhibitors effective, eg cyclosporin. However, nephrotoxic
 - Not systemic steroids → rebound, possibly severe pustular psoriasis
 - Approved biologics: Anti TNF α , Anti CD2 and Anti CD 11a
 - Infliximab is effective but is expensive, inconvenient to administer, and little data on long term safety
 - ISA247 is a new calcineurin inhibitor for the treatment of autoimmune diseases and transplant recipients. Better side effect profile and tighter receptor binding. Effective in reducing plaque psoriasis – 75% reduction achieved in 47% compared with 4% (placebo) over 12 weeks. NEJM 19 April 2008
 - Weaker steroids for up to 4 weeks for flexural and facial psoriasis (no more than 1% hydrocortisone on the face). More potent Ok for scalp psoriasis (eg betamethasone)
- Other papulosquamous disorders besides psoriasis:
 - Lichen planus: flat topped papules and plaques, discrete or coalescing. Network of grey lines (Wickham's striae). Looks like everything else. Treatment steroids. Generally resolves in 18 months
 - Pityriasis Rosea: Herald patch (2 – 6 cm annular lesion) → smaller annular or papular lesions mainly on the trunk (like secondary syphilis but usually nothing on hands and feet, which is common in syphilis)
- Pemphigoid:
 - More common
 - Bullae, maybe initially localized
 - Epidermis splits from the dermis at the dermo-epidermal junction ⇒ blisters have intact epidermis overlying them so are sturdy and grow large, the blister base is raw, sore dermis
 - Immunofluorescence is linear, eosinophil infiltration
 - May also have circulating bullous Pemphigoid antigen (BP180) to the transmembrane hemidesmosomal glycoprotein of the basal keratinocytes
 - Causes: Usually autoimmune, very rarely a drug (eg vancomycin)
 - Treatment: prednisone 40 mg, dermol cream, azathioprine, tetracyclines, methotrexate, dapsone...
- Pemphigus:
 - Rare, intra-epidermal
 - Flaccid blisters, often starting with oral lesions becoming generalised over several months, erosions

- Patients appear ill. Untreated mortality 100%
- Net-like pattern on immunofluorescence due to antibody deposition in:
 - The superficial epidermis in Pemphigus foliaceus acantholysis. May respond to topical steroids
 - Full thickness in Pemphigus vulgaris – bullae are fragile – just fall apart. Treatment prednisone 80 mg
- Eczema related conditions:
 - Dyshidrotic eczema: deep vesicles of the palms, soles, sides of fingers and toes
 - Discoid eczema: In kids often atopic, in adults cause unknown
 - Asteatotic Eczema: superficial fissures, usually on legs, usually diuretics, excessive washing or hypothyroidism
 - Intertrigo: generic term for inflammatory dermatosis in skin folds – may be a form of atopic or seborrheic dermatitis, can be secondarily infected with candida or staph
- Other inflammatory lesions:
 - Discoid Lupus: Erythematous plaques with adherent scale and pitted surface. Mild end of lupus spectrum, skin rash and ANAs/ENAs normal
 - Morphea: localized cutaneous scleroderma

Skin Cancer

- Benign:
 - Seborrheic Keratosis: stuck on appearance, velvety, bleeds easily. Proliferation of squamous basaloid cells. Treatment: Liquid nitrogen for cosmetic reasons
- Premalignant:
 - Actinic keratosis (= solar keratosis):
 - Dysplastic squamous cells
 - Adherent scale, difficult to pick off, not well circumscribed, erythematous base
 - Recede or progress (very low rate of malignant transformation)
 - No evidence that removal → ↓risk of cancer
 - Treat: nitrogen if a few. Short course of 5FU cream
 - Bowen's Disease:
 - 75% are on the leg. Erythematous, well circumscribed, 1 cm or more, not as shiny as BCC
 - = "SCC in situ". If growing or bleeding remove. SCC arises in 3%
- Non-melanoma skin cancer:
 - See NEJM 24 Nov 2005
 - Surgery is first choice, margins of 3 mm
 - Radiation if incomplete margins
 - Cryotherapy is 2nd line for BCC (lower cure rates, and contraindicated if infiltrative), 1st line for solar keratosis (very small chance that it will develop into SCC, although it's very likely that an SCC has arisen from solar keratosis)
 - Squamous Cell Cancer:
 - Occur in heavily sun exposed sites. Skin coloured or purplish nodule/plaque +/- ulceration. Margins less well defined than SCC. May be cutaneous horn
 - Of the scalp, ear and vermilion have the highest rate of recurrent and metastasis
 - Do invade, 4% metastasize
 - Basal Cell Carcinoma:
 - Found on back, chest, legs, sometimes upper limb, 'never' on the dorsum of the hands – in sites of indirect sun exposure
 - Nodular: flat and paler than surrounding skin → 'rodent' ulcer (raised, rolled edges)
 - Superficial: red plaque
 - Sclerosing: scarring reaction
 - Don't metastasize, but do invade
- Melanoma:
 - See Lancet 19 Feb 2005
 - UVB is directly mutagenic to DNA
 - Pathology:
 - Mutations in R/RAF and N/RAS common (on the pathway from C-Kit [receptor] to MITF → growth and survival factors). This pathway being targeted in drug development
 - Can also have an activating mutation in Kit
 - So starting to categorize melanoma by causative mutation

- Assessment:
 - Size is not a good discriminator – lots of benign pigmented lesions are > 6 mm
 - Asymmetry, border irregularity, colour variability, diameter > 6 mm, elevation or enlargement
 - Look for lesions that are different to all the others – the odd one out. Ask about change (patient report typically very unreliable), bleeding
- Types:
 - Superficial spreading: commonly back in men and lower legs in women
 - Lentigo maligna melanoma: face in older patients
 - Acral lentiginous melanoma: hands, feet and mucous membranes, not related to being fair skinned (ie get them in blacks)
 - Nodular: grow vertically rather than spreading radially
- Histology: Breslow thickness = microscopic tumour depth, Clark level – anatomic level of invasion ie which layer had it penetrated (not so accurate)
- Staging:
 - T: T1 < 1.0 mm deep, T2 1 – 2 mm, T3 2 – 4 mm, T4 > 4 mm
 - N: N1 = 1 node, N2 = 2 – 3 nodes, N3 > 4 nodes
 - Metastasis to unusual sites (small bowel, kidney, spleen, heart)
 - Sentinel node biopsy for staging only (a good prognostic test) – but resection of oligonodal disease only has a small impact on OS
 - Routine CXR very low yield of mets
 - FDG-PET and MRI brain is useful for staging metastatic melanoma
- Survival is correlated with:
 - Melanoma depth
 - Sentinel node status
 - Ulceration
 - Distant mets have worse prognosis if ↑LDH
- Treatment: Wide local excision for stage 1 and 2. Follow-up to detect the next one (double the risk) not to detect recurrence
- Adjuvant therapy:
 - IFN α in high doses delays time to distant metastasis (recurrence free survival) but doesn't alter overall survival and SE++. Response in approx 15%. Greatest benefit in N1 (sentinel node only) disease compared with N2/3 (palpable node). (Lancet 12 July 2008)
 - In vitro expansion of CD4+ T cells clones specific to melanoma-associated antigen NY-ESO-1 lead to a durable remission in a case study (NEJM 19 June 2008). MAGE-1 is a tumour-specific antigen that stimulates T cells in vitro
 - Melanoma vaccines → inducible antibodies but few have tumour regression
 - Role of radiotherapy not well established
- No RCT of screening, but screening now so common that couldn't do the trial

Chorionic Gonadotropin and Diagnosis

- See page 84 for Reproductive Hormones
- Produced by trophoblast cells of the placenta
- α subunit the same for all glycoprotein hormones, so test for the β subunit
- Urine CG positive 1 week post missed menses (early morning urine best – more concentrated)
- In the first 8 weeks it rises exponential, with a doubling time of 2 days, declines from week 10 to third trimester
- Ectopic pregnancy: hCG fails to double over two days
- Gestational trophoblastic disease (GTC):
 - Arises from fetal, no maternal tissue
 - Very high levels of hCG
 - Benign course: Complete and partial hydatidiform mole
 - Malignant: Invasive mole, choriocarcinoma, placental site trophoblastic tumours
- False positives: pituitary can produce small amounts of hCG, can become detectable post menopause. Give OCP for 14 days, should reverse, otherwise ?tumour
- Aside: Fetal fibronectin (sampled via vaginal swab) predicts premature delivery within 7 – 10 days – enables steroids to be given

Physiological Changes in Pregnancy

- See also Pharmacology, Effects of Disease, page 497
- \uparrow Vd by $\sim 20\%$
- \downarrow Albumin – only clinically relevant if protein binding $> 80\%$ (phenytoin, valproate, TCAs)
- \uparrow Plasma volume probably outweighs effect of \downarrow binding
- Lipophilic molecules rapidly cross the placenta
- Fetal elimination slow due to fetus swallowing it's own urine
- Serum TGs \uparrow by 300% and cholesterol by 50%

Hypertension

- Normal changes in pregnancy:
 - \uparrow O₂ consumption from 300 to 350 ml per minute
 - \uparrow CO from 5 to 6.5 – 7 litres per minute due to \uparrow Stroke volume (10%) and \uparrow HR (15 bpm)
 - Peripheral resistance falls (by 35% due to hormonal changes)
 - MAP \downarrow by 10%
 - \downarrow PCO₂ to 31 mm Hg to increase gradient for shifting CO₂ from fetus
 - \uparrow Red cell mass (although anaemia as \uparrow in plasma volume is greater, peaks at 30 – 34 weeks)
 - \uparrow Blood volume by 40% from early pregnancy to delivery
 - \uparrow Ventilation
 - \uparrow Glomerular filtration \rightarrow \uparrow urination
- During first and second trimesters, BP (especially diastolic) falls by 10 – 20 mmHg, return to booking BP by 3rd trimester (partly due to hypotension \rightarrow \uparrow aldosterone)
- BP $> 140/90$ associated with \uparrow perinatal complications
- Treatment of chronic hypertension: α -methyldopa (centrally acting; drug of choice, stop post partum 2nd to risk of depression, contraindications depression, active liver disease, porphyria), labetalol, nifedipine (monitor renal function to exclude preeclampsia)

Preeclampsia

- New onset of BP $> 140/90$ and proteinuria > 300 mg/day after 20 weeks gestation
- Risk factors: nulliparity, DM, renal disease or chronic HTN, extremes of maternal age, obesity, factor V Leiden, antiphospholipid syndrome, multiple gestation (twins = twofold risk), new partner, prior preeclampsia (7 fold), long birth interval (2 – 3 fold if 10 years)
- Associated with antigenic material in semen – immune tolerance develops (eg with \uparrow length of cohabitation) \rightarrow \downarrow risk
- Presentation: maybe asymptomatic, headache, visual disturbance, epigastric and RUQ pain, progressive oedema
- Investigations: proteinuria, platelets, renal function, plasma urate, LFTs, coags, Doppler USS
- Pathophysiology
 - Abnormal trophoblast invasion \rightarrow poor placental perfusion

- ? contributed to by excessive placental secretion of an fms-like tyrosine kinase (vascular endothelial growth factor agonists) and ↓ placental growth factor
- → vasospasm and endothelial injury in multiple organs, abnormal cerebral autoregulation
- Renal biopsy shows characteristic endothelial injury
- Severe pre-eclampsia: BP > 160/110, proteinuria and CNS dysfunction (headaches, blurred vision, seizures, coma), renal failure, pulmonary oedema, hepatocellular injury (ALT > 2 * normal), platelets < 100,000 or DIC. 30% of severe, early onset pre-eclampsia may have aPL
- HELPP (haemolysis, elevated liver enzymes, low platelets):
 - Is a special subgroup, 15% present with placental abruption. 30% arise post partum
 - Also ↑LDH, ↑bilirubin and ↓haptoglobins, ↑reticulocyte count. May have renal failure in context of DIC. Raised PT, APTT, low factor V & VIII.
 - Differential from HUS or TTP by prolongation of prothrombin time
 - Initial treatment with plasma exchange
 - Treated by delivery, BP control, platelet transfusion and supportive care.
 - Also rituximab, vincristine, cyclophosphamide and splenectomy have clinical efficacy
 - Substantial risk in next pregnancy
- Treatment of eclampsia:
 - If severe then delivery (especially if ≥ 34 weeks)
 - IV labetalol or hydralazine (?more problems with hypotension) for ↓BP, also CCB. Decrease BP slowly. *NOT ACEI or ARBs in 2nd and 3rd trimester* → ↓fetal renal function → oligohydramnios
 - Mg sulphate for prevention and treatment of eclamptic seizures (demonstrated in RCT to be superior to phenytoin and diazepam)
- Prophylaxis: aspirin for all women doesn't prevent pre-eclampsia, but some evidence for protection in high risk women (Previous PET, antiphospholipid, diabetes or renal disease with HTN, NNT 90). CLASP trial suggests it may help prevent the onset of early pre-eclampsia. It is safe

Heart Disease

- Pulmonary Hypertension of any cause, including Eisenmenger's syndrome: contraindication to pregnancy. High mortality (30 – 50%), susceptible to preeclampsia, postpartum haemorrhage, preterm delivery and fetal growth retardation. Only 15 – 25% pregnancies progress to term. Vaginal delivery less stressful haemodynamically than caesarean
- Valvular heart disease:
 - Mitral stenosis: Most likely to cause death during pregnancy. ↑CO during pregnancy → pulmonary oedema or pulmonary HTN or both. Requires careful control of heart rate especially during labour (tachycardia is bad). ↑risk of AF (treat with digoxin and β-blockers) or other tachyarrhythmias. In general increase by one NYHA gradient in pregnancy
 - MR, AR: generally well tolerated. AS: Variable
- Congenital Heart Disease: ↑risk of congenital cardiac lesion in the baby. Atrial or ventricular septal defect generally well tolerated as long as there is no pulmonary hypertension. Use air filters on IV sets
- Supraventricular tachycardia: treat as in non-pregnant. Adenosine + CCBs acceptable risk. Electrical cardioversion well tolerated by mother and fetus
- Cardiomyopathy: uncommon myocarditis. Etiology unknown. Treat as per normal cardiomyopathy. May recover, may have a progressive dilated cardiomyopathy. Avoid future pregnancy. May occur in the last month or up to 5 months post-partum. Causes about 25% of cardiac deaths in pregnancy, but 95% 5 year survival
- Marfan Syndrome: 15% develop a cardiac complication during pregnancy. Aortic root < 4 cm favourable

DVT/PE

- See NEJM 6 Nov 2008
- DVT in 1 in 2,000 pregnancies. 4 times the risk of non-pregnant population. Evenly distributed over all trimesters
- PE is the commonest direct cause of death in pregnancy and post-partum (in the UK) – 1/3rd of all maternal deaths. Most PEs in the puerperium
- More common in the left than the right leg due to compression of the left iliac vein
- 20 fold increase in PE in ELSCS than in vaginal delivery
- Risks: Homozygous Factor V Leiden > antithrombin deficiency > Heterozygous Factor V Leiden > Antiphospholipid syndrome

- Activated protein C resistance caused by factor V Leiden → ↑ risk – 25% of pregnancy related DVTs have factor V Leiden (also ↑ risk preeclampsia).
- Data on impact of inherited thrombophilias and their impact on pregnancy is messy with lots of publication bias
- Treatment:
 - Only treat high risk: a high risk mutation plus a strong family or personal history
 - Heparin. Doesn't cross the placenta. Isn't found in breast milk. Can change to IV heparin before delivery. Risk of haematoma with epidural. Continue for 6 weeks post delivery
 - Warfarin: contraindicated. Fetal chondrodysplasia punctata in first trimester, in 2nd and 3rd trimesters may cause optic atrophy and mental retardation. OK in breast feeding
 - Heparin and warfarin OK with breastfeeding

Gestational Diabetes

- Insulin resistance in later pregnancy. Insulin production increases 2 – 2.5 times in pregnancy so relative deficit
- Diagnosis after 20 weeks – usually 28:
 - Screening: 50 gm oral glucose load with 1 hour glucose < 7.8 is normal
 - Diagnosis: 75 gm fasting oral glucose with any of baseline > 5.8, 1 hr > 10.5, 2 hr > 9.1 (Australia 8), 3 hr > 8.0 (some have more aggressive criteria)
- Risk of congenital abnormalities is related to the degree of peri-conceptual diabetic control
- Associations:
 - Macrosomia, pre-eclampsia, induction of delivery, caesarean, neonatal hypoglycaemia
 - 40% risk of the mother having DM within 10 years
 - Associated with T2DM in the child (macrosomia without diabetes is not)
- Treatment:
 - Dietary followed by insulin
 - Oral hypoglycaemia glyburide in widespread use – more safety data needed
 - MIG trial (NEJM May 08) reported Metformin was not inferior to insulin (in terms of perinatal complications) and better tolerated (although 46% needed additional insulin). Need longer term study to confirm safety

Thyroid Disease

- Effect of thyroid function on reproduction:
 - Hyperthyroidism → ↑ Sex Hormone Binding Globulin can → ↑ bound oestrogen and ↓ free oestrogen → loss of LH surge and anovulation
 - Hypothyroidism → ↑ TRH → ↑ TSH and ↑ PRL
- Thyroid hormones during pregnancy:
 - Rise in HCG during first trimester → ↓ TSH (βHCG shares the same α subunit so can stimulate the TSHR. TSH therefore no use for screening. fT3 and fT4 reference ranges often not available or validated for pregnancy
 - Thyroid hormones cross the placenta
 - Pregnancy is a state of relative iodine deficiency due to fetal needs and ↑ urinary excretion
 - Dose of thyroxine may need to be increased by > 50% during pregnancy
 - ↑ Hepatic synthesis of thyroid binding globulin → ↑ total and bound thyroid hormones but normal free level. Free T4 falls in the 2nd and 3rd trimester
 - Goitre often evident – especially in I deplete areas. Resolves
- Hyperthyroidism: see page 77
 - In 2 per 1000, 95% is Graves disease
 - Most discriminating features (eg from hyperemesis gravidarum) are weight loss, tremour and eye disease
 - Associated with spontaneous abortion and premature labour
 - Treatment:
 - Carbimazole or propylthiouracil – cross the placenta so use smallest possible dose
 - Betablockers for short periods but are associated with IUGR
 - Not radioiodine (for scanning or treatment) as it affects the fetal thyroid
 - Monitor neonate for thyrotoxicosis due to transfer of TSIg
- Hypothyroidism:
 - ↑ miscarriage, anaemia, pre-eclampsia and low birth weight
 - Hypothyroidism affects neural development – ensure euthyroid before getting pregnancy

- Treatment:
 - Thyroxine to avoid risk of impaired cognitive function (associated with hypothyroid mother). Only a small amount crosses the placenta, so fetus is not at risk of thyrotoxicosis from maternal thyroxine replacement
 - Increased requirement from 5th week – so if already on thyroxine increase by 30% as soon as pregnant and monitor TSH
- Postpartum Thyroiditis: see thyroiditis, page 81
 - Risks: FHx of hypothyroidism, thyroid peroxidase antibodies and T1DM
 - Presentation usually 3 – 4 months post partum, small painless goitre in 50%
 - 40% hypo, 40% hyper
 - Caused by a destructive lymphocytic thyroiditis
 - Most recover without treatment. If they are treated, withdraw 6 – 8 months later to test for spontaneous recovery
 - Significant risk of long term hypothyroidism
- Hyperemesis Gravidarum: may be associated with high levels of free T4 and suppressed TSH. Due to ↑ hCG which is structurally similar to TSH. HCG has a TSH like action

Other Pregnancy Related Conditions

- Haematological disease:
 - Anaemia: dilutional, watch for iron or folate deficient
 - Thrombocytopenia. Usually benign gestational, but watch for immune thrombocytopenia and preeclampsia
- Neurological disorders:
 - Increased migraine. However if visual blurring, then ?eclampsia or pseudotumor cerebri (benign intracranial HTN, esp if diplopia 2nd to 6th nerve palsy)
 - Chorea gravidarum: new movement disorder, associated with rheumatic fever
 - MS: lower risk during pregnancy, higher risk following. Treat with glucocorticoids, not IFN
 - Bells palsy and entrapment neuropathies (eg carpal tunnel) more common
 - Epilepsy: ↑ in seizures common. Multifactorial. Changes in drug concentrations probably most significant. Total concentrations of all first line AEDs (carbamazepine, phenytoin, valproic acid) fall during pregnancy, but free/unbound drug concentrations don't (valproate actually ↑ by 25%)
 - Imaging in pregnancy:
 - No known risk from MRI – ?some risk in rodent studies
 - CT brain OK if abdo shielded. Avoid contrast media
- GI:
 - Crohn's exacerbations in the 2nd and 3rd trimester. UC during the first trimester and post-partum
 - Exacerbation of gall stone disease
 - Acute fatty liver of pregnancy – can be confused with HELLP
 - Hepatitis B: give IgG after birth and vaccinate promptly
- Renal Disease:
 - GFR increases by 50% in pregnancy, ↑renal blood flow by 80%. Glomerula hyperfiltration but no ↑ in glomerular capillary pressure
 - In chronic renal disease, risk of acceleration of decline in renal function, and worsening HTN and proteinuria
 - Risk to mother and baby ↑ with ↑ Cr
- Liver Disease:
 - Dilutional fall of 30 – 40% in albumin, ALP rises 2 – 4 fold (produced by placenta), rest unchanged
 - Obstetric cholestasis:
 - Seen in 0.5 – 1%
 - Usually starts around week 37 with rapid onset pruritus, nausea, vomiting
 - Diagnosis of exclusion: pruritus without rash, ↑transaminases
 - Workup: Liver USS, Hep A, B, C, E serology, EBV and CMV and liver antibodies
 - Management: weekly fetal monitoring and LFTs, Vitamin K 10 mg daily from 32 weeks, UDCA for itch
 - Deliver 37 – 38 weeks. Undiagnosed mortality rates up to 20%
 - Risk in future pregnancies: 90%
 - Acute Fatty Liver of Pregnancy:
 - Rare. Potentially lethal

- Markedly raised bilirubin, hypoglycaemia, DIC
- Marked liver dysfunction with vomiting and abdo pain
- Treatment: delivery
- Hypoparathyroidism: usually due to prior surgery. ↑need for vitamin D in pregnancy → hypocalcaemia → 2nd trimester loss, neonatal rickets. Treat with Vitamin D and calcium supplements till delivery
- Addison's Disease: Deficiency of both cortisol and aldosterone. Increase corticosteroid during hyperemesis or infection. Watch for hypotension with the physiological diuresis following delivery

Connective Tissue Disease in Pregnancy

- Shift from cell-mediated (Th 1 response) to humoral immunity (Th2 response)
- RA:
 - 75% experience an improvement (but post-partum flare common), 25% have substantial disability
 - No effect on pregnancy, except anti-Ro antibodies may → neonatal lupus
 - Drugs:
 - Paracetamol safe
 - NSAIDs – usually avoided, especially in 3rd trimester (affect fetal kidney and ductus)
 - Corticosteroids OK
 - Azathioprine OK – do not discontinue. Fetal liver lacks the enzyme to convert it to active metabolites. Avoid in breast feeding
 - Antimalarials: Hydroxychloroquine: high doses may accumulate and cause retinopathy
 - Mycophenolate: avoided as no data
 - Penicillamine: teratogenic
 - Gold salts: avoid if possible
 - Sulfasalazine: safe in pregnancy and breastfeeding, but take folate
 - Cyclophosphamide, methotrexate and chlorambucil all contraindicated
- SLE:
 - Increased risk of a flare
 - Flares not prevented by increased steroids
 - → ↑miscarriage, fetal death, pre-eclampsia, IUGR
 - Ro positive mothers → 5% risk of transient neonatal cutaneous lupus and 2% risk of congenital heart block

Infection in Pregnancy

- 75% of pregnancy-associated pyelonephritis is the result of untreated asymptomatic bacteruria ⇒ treat
- Abdo pain and fever: consider amniotic infection – most commonly caused by E coli and GBS
- Post-partum endomyometritis, especially following emergency Caesar after prolonged ROM – usually polymicrobial
- CMV: primary CMV infection → risk of congenital CMV (petechiae, HSM, jaundice, microcephaly, hepatitis...). No agreed treatment for maternal infection
- Rubella:
 - Routine antenatal screening with rubella IgG
 - Differential: parvovirus, enterovirus
 - Testing in pregnancy if contact with rubella or rubella like illness (fever, erythema, arthralgia):
 - IgG +, IgM +: repeat to confirm
 - IgG -, IgM -: repeat if < 3/52 since infection
 - IgG -, IgM +: possible recent infection
 - If reinfection, risk of foetal damage < 5%
 - If primary infection, risk of Congenital Rubella Syndrome related to gestation:
 - <8/40: 90 – 100%
 - 8 – 12/40: 50%
 - 12 – 20/40: 20%
 - > 20/40, < 1%
 - Foetal infection diagnosed by per cutaneous umbilical blood sampling for IgM antibodies
- Varicella Zoster: Incubation 10 – 21 days, prodrome 24 – 48 hours. Risk of preterm labour. Congenital varicella syndrome rare. If maternal exposure, check varicella IgG Ab. If non-immune then IG within 96 hours. Acyclovir if exposure > 96 hours and in second half of pregnancy or other risk factors (underlying lung disease, smoker, immunocompromised)

- Active genital herpes: prescribe acyclovir for 4 weeks pre-delivery. Neonatal infection can be devastating
- HIV: ↑vertical transmission from: vaginal delivery, preterm delivery, fetal trauma, high maternal load, low maternal CD4+ count, prolonged labour, prolonged ROM, presence of other genital tract infections. Transmission also via breast milk. Treatment: perinatal zidovudine + caesar (esp if viral load > 1000 copies/ml)

- For Pre-operative assessment of the elderly see page 503
- For Dementia, see page 148
- Demographics:
 - Women outlive men – Also life expectancy at birth 84 for female, 79 for male
 - Men remarry more frequently than women, so women are more likely to be alone
 - Women spend a greater portion of their surviving years disabled
 - Dependency ratio: ratio of > 65 to 15 – 65 year olds. Currently 22% in Europe and 6% in Africa. Will be 50% in Europe by 2050
 - Life expectancy is often underestimated. The average at:
 - 75 is 11 years
 - 80 is 9.3 years
 - 85 is 6 years
 - 90 is 4.5 years
 - Twin studies: ⇒ 30% of variation in longevity can be attributed to genetic factors
 - Age adjusted incidence of cancer is 10 times higher in > 65 than < 65, and cancer mortality is 15-fold higher
 - Caring for a disabled spouse or parent is associated with ↑ risk depression
- Segmental progerias: single gene defects leading to premature aging (onset in childhood, mean survival 13 years)
- Frailty:
 - Defined as a syndrome where 3 or more of the following are present:
 - Unintentional weight loss of > 4.5 kg in the past year
 - Feeling exhausted (poor endurance)
 - Poor grip strength (weakness)
 - Slow walking speed
 - Low physical activity
 - Associated with a high risk of falls, disability and death
- Complex interventions (Lancet 1 March 2008):
 - Can reduce nursing-home admissions (RR 0.87), hospital admissions (RR 0.94), falls (RR 0.9) but not death
 - Interventions covered in this meta-analysis included geriatric assessment (either in the general population or in subgroups identified as frail), community based care after discharge, fall prevention and group education or counselling

Age related changes

- Aging is not related to replication: tissues with the highest turnover (gut lining and blood precursors) are not the ones to pack up
- Cardiovascular changes:
 - Decreased responsiveness to β stimulation (?due to sympathetic over-activity → desensitization) – best established pharmacodynamic change in the elderly
 - No change in response to α stimulation (?due to ↑ receptor density)
 - ↑ Atrial natriuretic peptide secretion
 - Maximum work capacity and oxygen consumption (VO₂max) decreased by 10% per decade, the cardiac element of this decline is driven by an age related *decline in the maximum heart rate*
 - Autonomic reflex dysfunction
- Heart changes:
 - Heart rate decreases, striking decrease in heart rate and contractile response to exercise, stroke volume in exercise maintained by increases in end diastolic volume (and thus ejection fraction falls) → reduced or absent functional reserve → ↑ susceptibility to heart failure
 - Stroke volume increases in males, not in females
 - Cardiac output at rest doesn't change in males, decreases in females
 - Stroke work increases
 - Early diastolic filling decreases (~ 50%)
- Respiratory changes:
 - ↑ chest wall rigidity, ↑ work of breathing, ↓ respiratory muscle strength and endurance
 - ↓ functional alveolar surface area, ↓ vital capacity, ↑ residual volume, 20% ↓ in size due to loss of elastic recoil
 - V/Q mismatching ↑ with rise in physiological dead space

- Blunted response to low O₂ or high CO₂
- Renal/urinary:
 - ↓number of nephrons, reduced GFR (30 – 50% by 70 years)
 - ↓renal blood flow, ↓urine concentrating ability, ↓total body water, ↓thirst perception
 - More salt sensitive, *lower* renin levels (but ACEI still work). Aldosterone secretion falls with age
 - Result: reduction in sodium conservation
 - Reduced functional bladder capacity: 600 → 200 – 300 mls. 100 – 200 ml residual volume a “grey” area with lack of normative data
 - ↑detrusor hyperactivity, ↓outflow resistance in women, ↑ in men
- Hepatic:
 - ↓hepatic mass (40% decrease by 80 years)
 - ↓hepatic blood flow (40% by 80 years) → ↓clearance (not related to changes in metabolism)
 - No change in LFTs or albumin with well elderly
- Muscle mass:
 - ↓skeletal mass and ↑fat mass
 - Sarcopenia = age related decrease in muscle mass (?contributed to by decreased exercise and nutrition). Best evidence for reversal is weight training
 - Greater loss of type 2 muscle fibres (endurance) than type 1 (fast)
- Immune system:
 - Diminished AB response (both peak and duration), more IgM, less IgG, autoantibodies more common
 - Thymus involution, T cell numbers constant but impaired T cell response (?explains reactivation of Tb, Zoster)
- Hormones:
 - ↑FSH/LH in both sexes
 - Vaginal changes → ↓lactobacilli secreting peroxide → more UTIs
- Other:
 - No change in TSH and T₄
 - PTH levels are slightly higher
 - Melatonin secretion is lower in older patients. Small doses given before bed improve sleep in older patients
 - ↓number of neurons (15% by 80 years)
 - ↓adrenal mass, ↓cortisol secretion (15% by 80 years)
 - ↓in thermoregulatory vasoconstriction (→ predisposes to perioperative hypothermia)

Pharmacology

- Complicated due to altered pharmacokinetics, pharmacodynamics, multidrug regimes, under compliance and comorbid disease
- Absorption: essentially unaltered despite ↓gastric acid
- Renal:
 - ↓renal clearance due to ↓renal mass, ↓blood flow and ↓GFR
 - Reduced muscle mass → Cr clearance may overstate renal function
 - Renally excreted drugs also tend to have narrow therapeutic index (eg digoxin, gentamicin, etc) so ↑problems
- Hepatic clearance:
 - ↓clearance
 - ↑bioavailability of first-pass metabolised drugs due to ↓*hepatic blood flow*. No change in effectiveness of hepatic enzymes
- Volume of distribution: ↓lean body weight and total body water, ↑ in adipose
 - Water soluble: ↓V_d → ↑concentration → ↑effect from single dose (eg morphine, digoxin, ETOH)
 - Lipid soluble: ↑V_d → ↓plasma clearance → longer T_{1/2} → accumulation (eg BZDs)
- NSAIDs (NB raise BP) and BZDs are the drug classes with the most potential problems
- Risk of underutilization especially antiHTN, statins after MI or stroke and ACEI in diabetics
- Pharmacodynamic changes:
 - Impaired homeostatic response → more sensitive to eg antiHTN
 - Alterations in receptor function – impaired response to β blockers most studied – reduced density of β-receptors is the cause
 - Idiosyncratic reactions more common

- Drug efficacy:
 - Most clinical trials omit patients with comorbidities – making results difficult to extrapolate
 - No drug that is effective in younger people has proven lack of efficacy in > 70 year olds (⇒ can usually extrapolate)
 - Adverse drug reactions 2 – 3 times higher in the elderly, likely due to ↓ physiological reserve of most organ systems → impaired homeostatic response
- Strategies to reduce polypharmacy:
 - Single prescriber, single dispenser
 - Medication Reviews (Cochrane 2006):
 - Clinical pharmacist review: RCT showed reduction in medications without change in outcome
 - Pharmacist education

Functional Assessment

- Functional status (how well a person is able to provide for their own daily needs) is the best indicator of prognosis and longevity:
 - ADLs: essential for physical independence – dressing, bathing, feeding, toileting, transferring and ambulating
 - Instrumental ADLs: money management, medication administration, using transportation, telephone usage, shopping, housekeeping and meal preparation
- Screening strategies for functional status:
 - Cognition: Dementia:
 - MMSE with cut-off < 24 (sensitivity 79 – 100%, specificity 46 – 100%)
 - Mini-Cog: ?better in culturally diverse settings. Remember three words, draw a clock at 11:10 (2 marks), remember words (1 point each), total of 0 – 2 positive for dementia. Sensitivity 94 – 100%, specificity 37 – 46%
 - Gait and balance: Timed Get Up and Go Test: rise from a chair, walk 3 m, turn around, return and sit. Normal < 10 sec. Validated measure. Difficulty with this associated with ↑ falls
 - Visual acuity: Snellen chart. Not associated with falls risk, but deficits in binocular vision, depth perception and contrast sensitivity are
 - Nutrition: Weight loss > 4.5 kg in 6 months, or weight < 45 kg. Associated with ↑ mortality, morbidity and rest home admission

Assessing Competence

- Definition: ability to make an autonomous informed decision that is consistent with the person's lifestyle and attitudes, and to take the necessary action to put this decision into effect
- Covered by the Protection of Personal and Property Rights Act (1988). Aim is to protect a person who is no longer competent. It can't be used to stop person from making a decision that is simply unwise. If no EPOA, the court can appoint a welfare guardian, a property manager, or make other kinds of personal orders. The court is required to make the least restrictive intervention possible
- Thresholds for competence vary depending on the seriousness of the consequences
- Is a clinical judgment – no formal test can answer the question
- Issues in assessing competence:
 - Why has the issue arisen at this stage
 - Does the patient know what his circumstances are, as they relate to the question of competence
 - Does the patient know what his or her options are
 - Does the patient know the consequences of each of the available choices
 - What is the patient's reason for making a particular choice – which should include an awareness of professional advice and the ability to balance their own motivation against the motivation for the advice
 - Is the patient consistent in his or her decisions
 - Is there any particular pressure on the patient to make one particular choice
 - Is the patient able to take the appropriate action to execute the choice he/she has made

Delirium in the Elderly

- See Int Med Journal 2004;34:115
- Diagnosis: A confusional state with
 - *Acute* onset and fluctuating course
 - *Inattention* (eg counting 20 → 1)
 - And either:

- Disorganised thinking
- Altered LOC (anything other than alert, can include hypervigilant)
- Other features: visual hallucinations are uncommon in dementia, alterations in psychomotor behaviour
- Confusion Assessment Method: sens > 95%, specificity 90 – 95%
- By definition, is the direct physiological consequence of a general medical condition
- Exclude: infection, electrolyte abnormalities, vitamin deficiency, thyroid disease, substance abuse, medication and psychiatric illness (esp depression)
- 80% of terminally ill patients develop delirium near death, 50% develop it postoperatively
- Those with delirium have an increased in-hospital mortality. ½ – 1/3rd are missed by the treating physician
- Risk factors
 - In order: dementia (RR 2.8), medical illness, alcohol abuse, depression, diminished ADLs, male, abnormal sodium, hearing impairment, visual impairment (RR 3.5), dehydration
 - Also:
 - Infection: often urine and chest, but think about sinusitis, OM, gallbladder, diverticular
 - Metabolic disturbances
 - Polypharmacy or addition of > 3 medicines in last 24 hours
 - No cause found in 10%
 - Can be multifactorial – *don't stop at the first abnormality*
 - Have a multiplicative impact
- Pathophysiology:
 - Reduced reserve: ↓blood flow, neuronal loss, ↓levels of neurotransmitters, cortical and subcortical involvement
 - ?reduced cerebral oxidative metabolism →:
 - ?↑endogenous anticholinergic activity from cholinergic antagonists (which cause deficits in information processing, arousal and attention) – but no benefit from cholinesterase inhibitors (eg donepezil) in RCTs
 - ?↑dopamine, with ?beneficial effect from D2 antagonists
 - ?↓serotonin
 - ?GABA involvement – BZDs a risk factor...
- CT scan:
 - Low yield for causal condition unless focal neurology
 - High yield for underlying structural abnormality
- Consequences:
 - 2.2 times the length of stay cf age matched patients
 - 2.3 times the risk of hospital acquired complications
 - 3 – 7 times the risk of admission to residential care
 - Only 4% completely resolve by discharge, 31% relapse post discharge, 31% still met DSM criteria at 6 months (?may actually damage the brain)
 - 12 month mortality greatest where delirium not associated with dementia
- Prevention:
 - RCT evidence that attention to the following ↓risk of post-operative delirium: adequate O2, fluid/electrolyte balance, treatment of severe pain, eliminating unnecessary medications, regulation of bowel/bladder, adequate nutrition, early mobilization, appropriate environmental stimuli
 - RCT evidence that improving post-operative sleep-wake cycles with BZDs/opioids reduces delirium (but be very careful with BZDs except in withdrawal)
- Management: manage underlying cause, use glasses and hearing aids, avoid dehydration, malnutrition, pressure areas, constipation. NO role for restraints
- Treatment:
 - RCT: no difference at 8 weeks between usual care or geriatric consult!
 - Unclear whether early detection is of benefit
 - Evidence for symptomatic treatment strongest with haloperidol and chlorpromazine
- Drug choices: no evidence one is more effective than the other, so based on side effect profile
 - Haloperidol first choice due to minimal anticholinergic and hypotensive effects
 - Clozapine and Olanzapine are antagonists of muscarinic receptors so potential to worsen delirium
 - Risperidone lacks significant anticholinergic activity, but might cause postural hypotension, and EPSE at doses as low as 5 mg/day

- BZDs potentially worsen cognitive impairment, behavioural disinhibition
- See also Drug Treatment of Dementia, page 154
- Typically resolves over 10 – 12 days

Visual Impairment

- Cataracts in 30% over 65. Main risk factors are age, DM and UV light
- Macular degeneration in 6.5%. Leading cause of blindness in the elderly. Risk factors: smoking and genetics. Dry and Wet types. Limited evidence for antioxidants and zinc
- Glaucoma occurs in 4% – only 10% of people with a raised intra-ocular pressure (greater than 22 mmHg) have glaucoma
- Diabetic retinopathy occurs in ~ 0.5%

Urinary Incontinence

- < 80 twice as common in women than men, over 80 the same. 45% in institutionalized elderly
- An independent risk factor for rest home placement
- Associated with advanced age, functional impairment, dementia, obesity, smoking, affective disorder, constipation, some illnesses (eg COPD and CHF) and a history of pelvic surgery
- Evaluation:
 - Voiding diary
 - Exam, including checking for vaginal prolapse and cough stress test (watch for discharge of urine with coughing)
 - Always measure post-void volume (scan preferred to catheter)
- Types:
 - Stress incontinence:
 - History is sensitive (90%) but not specific (50%). Rare in men
 - Involuntary urinary leakage on exertion, sneezing, or coughing
 - Occurs when bladder pressure exceeds urethral resistance given increased abdominal pressure
 - Risk factors: obesity, pregnancy, vaginal delivery
 - Urge incontinence (= detrusor instability):
 - More than 50% of old people have an overactive detrusor → uncontrolled detrusor contractions that overcome urethral resistance
 - *Most common form of incontinence*
 - Presentation: frequency and nocturnal incontinence, urgency, and associated with loss of large urine volumes (> 100 mls)
 - Mixed: both stress and urge
 - Overflow: either outlet obstruction (eg BPH) or atonic bladder (spinal chord disease, autonomic neuropathy in DM, alcoholism, B12 deficiency, Parkinson's)
- Reversible causes:
 - D: delirium
 - R: Restricted mobility
 - I: impaction, inflammation, infection
 - P: pharmaceuticals, polyuria
- Management:
 - Review drugs: sedatives, hypnotics, antipsychotics, antidepressants, antiemetics. Usually only cause incontinence in patients already susceptible but can do so in small doses:
 - Anticholinergics: ↓flow rate and ↑residual
 - Cholinergics: worsen urge symptoms
 - α-blockers: decreased outflow resistance eg labetalol
 - TCAs: ↑outflow resistance, occasionally retention
 - Worsen constipation: anticholinergics (gut peristalsis), Ca antagonists (smooth muscle), diuretics (dehydration)
 - Promote diuresis: diuretics, lithium
 - Pads
 - Weight loss: RCT evidence (NEJM 29 Jan 2009)
 - Devices: Pessaries – RCTs in exercise incontinence
 - Surgery: Newer tension free vaginal tape (a minimally invasive mid-urethral sling procedure) equivalent to Burch colposuspension (one of the “gold standard” procedures)
 - Begin with behavioural therapy:

- Bladder retraining (gradually extend period between voids to ↑ bladder capacity) and pelvic muscle exercises (for genuine stress incontinence). Systematic review supports this for urge incontinence, but insufficient data to compare with other treatments
- Evidence for scheduled toileting and prompted voiding
- Medication:
 - Urge: anticholinergic drugs: oxybutinin → bladder relaxation, use limited by retention, confusion, constipation and dry mouth
 - Stress: Duloxetine hydrochloride (serotonin-reuptake inhibitor) for stress incontinence – shown in meta-analysis. SE nausea
 - Alpha agonists: not supported by rigorous studies
 - Treat BPH with an α blocker (terazosin/Hytrin, doxazosin) +/- 5α -reductase inhibitor (if prostate volume > 25 ml). If not well controlled an antimuscarinic may have additional benefit (as an overactive bladder can cause frequency or incontinence in men). JAMA 2006;296:2319
- Urinary condom in men is better than indwelling catheter if a urinary collection device is needed (excl retention), in terms of reduced infection and better patient comfort (J Am Geriatric Soc 2006;54:1055)
- Difficult to monitor given lack of objective, standardized assessment, normal symptom variability, and all drugs have for treatment have multiple side effects
- Urinary Retention: Caused by anti-cholinergic drugs. Implicated drugs include TCAs, oxybutinin, antipsychotics, levodopa

Constipation

- Food spends 1 – 2 hours in the small intestine but 2 – 3 days in the colon (↑ with age)
- Causes: poor mobility, ↓ fluids, ↓ fibre, drugs (esp iron, opiates, CCB)
- Assessment: PR, U&E, Ca, TFTs if indicated
- Usual management: Laxatives
 - Stimulants: Stimulate mesenteric plexuses to produce peristalsis. Includes anthracenes (eg Senna) and polyphenolics (eg bisacodyl/Dulcolax which undergo hepatic cycling → prolonged action)
 - Softeners:
 - Lubricants (eg Liquid Paraffin, but care if taking oral drugs → ↓ absorption). Starting dose 10 ml daily, latency of action 1 – 3 days. May cause anal leakage
 - Surfactants (detergent action): eg Docusate. Latency of action 1 – 3 days
 - Osmotic laxatives:
 - Lactulose and duphalac: osmotic and stimulatory (from effect of ↓ pH) action. latency 1 – 2 days. Degraded in colon. Osmotic effect does not extend throughout the colon
 - Magnesium Sulphate, etc: 2 – 4 gm daily, latency 1 – 6 hours. Osmotic influence throughout the gut
 - Hydrophilic bulk forming agents: Bran, Psyllium (Metamucil), Ispaghula (Isogel): ↑ stool bulk. Not in palliative care (to unwell to eat it). Useful if diarrhoea from radiation colitis
 - Rectal laxatives for faecal impaction:
 - Glycerine suppositories: soften stool by lubrication and osmosis
 - Bisacodyl (Dulcolax) suppositories: stimulate peristalsis. Must reach mucosal wall. Onset 15 – 60 minutes
 - Sodium phosphate enemas: Stimulate peristalsis
 - Oil Enema (eg glycerine, milk speeds it up):
- Prucalopride: a prokinetic 5-HT₄ agonist just completed phase 3 trials for chronic constipation. Similar in function to cisapride (removed from the market after problems with long QT). NEJM 29 May 2008
- Methylnaltrexone: a μ -opioid-receptor antagonist, with reduced ability to cross the blood-brain-barrier. Phase 3 trials showed benefit (48% vs 15% placebo) in opioid-induced constipation, without impact on analgesia or precipitating opioid withdrawal. NEJM 29 May 2008

Elder Abuse

- 5% of older adults have been subject to some form of abuse – most likely from a spouse or a child
- May be active (conscious and intentional deprivation) or passive (failure to provide necessities)

Hypertension and Vascular Risk Factors

- See also Hypertension, page 17

- Problems with trials: they often exclude the chronologically or biologically elderly. Eg little statin evidence over 80
- Stroke risk: leading cause of severe acquired adult disability. > 65 1% risk per year, > 80 2 – 3% per year
- Main causes of HTN in the elderly:
 - Stiffer arteries due to connective tissue deposition and atherosclerosis
 - Reduced β 2-mediated vasodilation
- Often there is a reluctance to treat because:
 - Concerns about medication adherence (but some studies show \uparrow compliance > 85 years). Determining factors for adherence are cognitive impairment and doctor-patient relationship
 - Underestimation of average life span
 - Concerns about \uparrow rate of adverse events
 - Concerns about medicalisation of older age
- Lifestyle treatment:
 - Salt restriction is helpful as the elderly are more salt sensitive
 - Weight loss and exercise all have been shown to work in older adults
- Evidence:
 - SHEP study: median age 72, n = 4376, 8.2% vs 5.2% reduction in stroke over 4.5 years, benefits seen in subgroup over 80. RRR of 35% for stroke, 15% for coronary events. NNT over 5 years of 9 – 18 for one major CV event, 43 for one CVA, 61 for one coronary event, 16 – 40 for one CV death
 - STOP Study: published 1991, n = 1627, patients 70 – 84, incidence of CVS events: 5.5% vs 3.4% over 26 months, RRR CVA by 40%, MIs by 40%
 - Lancet meta analysis 1999 of trials recruiting patients > 80 years suggested \downarrow CVA but \uparrow mortality \rightarrow establishment of HYET
 - Treatment in the elderly: HYVET trial (Hypertension in the Very Elderly Trial, NEJM 2008:358): Trial of 1933 patients > 80 years (all relatively well...), 11.8% with history of cardiovascular disease. Treated with indapamide +/- perindopril. Trial stopped at 2 years due to \downarrow mortality. Mean fall 15/ 6 mmHg. 21% reduction in death from any cause, 64% reduction in CHF, non-significant reduction in stroke. Trial criticised as most patients were Eastern European – who have a very much higher baseline risk of stroke. Number of patients excluded (eg for dementia) not reported but presumed high so the trial only assessed treatment in the very well. NNT for 1 year to avoid one death was 80
 - *General consensus: Unequivocal evidence of benefit for stroke risk, probably mortality and maybe MI*
 - Treatment for HTN has been shown in RCTs to reduce risk of CHF
- Treatment approach:
 - BP in older people is more labile – in young people take 3 readings, in older people take 6
 - Trigger for treatment: 160. Aim for 140/90 but lower if other comorbidities
 - If under 85, there is no unsafe lower limit. Over 85 is debated
 - Thiazides are first line
 - Some evidence β -blockers are not as effective in older people. ? Older people have reduced β -2 mediated vasodilation
 - No substantive difference between other major classes (CCB, ACEI)
 - Only needs investigation for renal artery stenosis if resistant to treatment. This is the most common cause of hard to treat HTN of the elderly, but if it's atherosclerotic then there is no evidence of benefit from intervention

Falls

- See Int Med Journal 2004;24:557
- Epidemiology:
 - Risk for all > 65 years is 30% per year. If previous falls, risk over the next year approaches 100%
 - Only 2% falls result in a # NOF (but 40% of NOFs are from rest homes), 5% cause any #. 40% have soft tissue injury. 25% reported to a doctor
 - Are an independent risk factor for rest home placement
 - Fear of falling is the greatest fear for older people
 - Most falls are poorly investigated with no risk factor assessment
- Contributed to by:

- Aged related changes, including ↓proprioception, ↑postural sway, ↓baroreflex sensitivity (→ postural drop), and by poor health
- Environment (activity related risks). Encouraging activity/independence vs risk avoidance
- Medications: especially psychoactive
- Risk factor model and a threshold model are more useful than a single etiology model
- Risk factors:
 - Age
 - Female
 - Past history of a fall
 - Cognitive impairment
 - Lower extremity weakness
 - Balance problems
 - Taking 4 or more medications or taking *psychotropic* drugs (more significant than antihypertensive drugs causing orthostatic hypotension). Lots of the drug evidence comes from Canadian databases of paired prescription and hospital admissions. No evidence for the impact of NSAIDs
 - Arthritis
 - History of stroke
 - Orthostatic hypotension
 - Dizziness
 - Anaemia
 - Physical restraint use (strong risk), and associated with serious injury with a fall
 - Insomnia
 - Fear of falling
 - Lab measures associated with ↑risk: ↓GFR, ↑PTH, ↓Vitamin D
 - Environment is probably not a strong risk factor for falling (although fallers often rationalize why they fell by blaming an environmental hazard)
 - Osteoporosis is a major contributor to risk of injury from falls
 - No evidence for reduced vestibular function as a contributor
- Prevention: beneficial interventions include:
 - Best evidence is for multiple risk factor interventions. But no study has shown multiple strategies more effective than single strategy
 - A supervised program of muscle strengthening and balance retraining exercises (exercise program is the best single intervention, also transfer training and aerobic fitness)
 - 15 week Tai Chi group exercise intervention
 - Home hazard assessment by a trained person (only for those with a history of falling – no evidence if no history of falls, and no evidence for self or family assessment. Little evidence that removal of home hazards alone makes a difference)
 - Vitamin D supplementation, with or without calcium – soft RCT evidence. More conclusive that Vit D → ↓fractures and ↑strength
 - Cochrane 2004 suggests the best intervention → ↓ 20% relative risk, ↓ 9% absolute risk reduction and NNT to prevent one fall of 11
 - Stopping psychotropic drugs: John Campbell's trial in Dunedin – only RCT of medication stopping – 66% reduction in falls in the intervention group, 46% had resumed psychotropics after one month. In this study, exercise and balance programme not effective
- Interventions of unknown effectiveness:
 - Group delivered exercise interventions
 - Nutritional supplementation
 - Individual lower limb strength training
 - Interventions using a cognitive/behavioural approach alone
 - Hormone replacement
 - Correction of visual deficiency
 - Provision of a walking stick (no RCT)
 - Providing a list of exercises for the patients to do themselves is associated with more falls
- No evidence that:
 - Repairing cataracts prevents falls (more related to depth perception not acuity)
 - Anything ↓falls in an acute medical ward or rest home
 - Reducing falls prevents fractures

- Hip protectors: Initial cluster trials in rest homes positive, but more a recent RCT (randomized to L and R hips) showed no benefit
- Assessment:
 - History: identify syncope (*although many don't remember it*), risk factors
 - Exam: neuro, cardiac, musculoskeletal systems, esp postural signs, vision, gait, balance, strength, joint stability and range of motion
 - Target interventions: geriatric bloods, ECG, CT if indicated
 - After a prolonged lie after a fall, consider CK, check for hypothermia, pressure areas may take several days to appear
- Practice points:
 - ACEI are epidemiologically associated with ↑falls, but hard to tell if it's the cause in a specific individual
 - No difference between TCAs and SSRIs in terms of falls
 - There is no such thing as “no residual symptoms” from a CVA. Any person with any stroke will fall at least once in the following year
 - Giving a patient a list of exercises → ↑falls. Need a supervised initial programme to benefit
 - If xray NAD but still immobile then either:
 - Bone scan: usually positive if a #, and can see other bone disease, pelvic fractures, etc
 - MRI: more sensitive for a specific #
- Walking aids:
 - Walking stick: always on the contralateral side and always move with affected leg (whether hip or knee is the problem)
 - Crutches on stairs:
 - Going down: SAG: sticks, affected leg, good leg
 - Going up: GAS rises: good leg, affected leg, sticks

Prevention

- Adequate nutrition
- Functional decline:
 - Exercise improves body composition, psychological well-being, disease outcomes and ↓ risk of falls
 - Includes resistance, cardiovascular, flexibility and balance training
- Accident prevention: falls assessment, seatbelt use (per mile driven, older adults at greatest risk of serious injury in MVA), ability to drive assessment, modest alcohol intake
- Vaccination: influenza and pneumococcal
- Bone Health
- Cancer Screening:
 - Effect of cancer screening not evident until 3 – 5 years – so no use unless going to live this long
 - Breast cancer: > 25 % deaths occur in > 80 years. Benefit of mammography over 70 years inconsistent between trials
 - Prostate cancer: Insufficient evidence for or against screening
 - Colorectal cancer: see page 395
- Risk factor modification: Longitudinal studies suggest smoking cessation and ↓ HTN, especially from mid life, but up to age 75, gives greater gains in life-years than medical or surgical therapies

Other

- Subclinical hypothyroidism is not associated cognitive impairment or depression. This weakens the case for treating it (Ann Int Med 2006;145:573). In fact there is some data suggesting mild elevation in TSH correlates with a survival benefit
- Androgen replacement (eg DHEA tablets or testosterone for men) in elderly people with subclinical deficiency made no difference to measures of physical performance or insulin sensitivity. Testosterone increased fat-free mass and a slight increase in only femoral neck bone density. No clinically relevant benefit observed (NEJM 2006;355:1647)
- B-complex supplements do not improve cognitive function (although they normalize high homocysteine levels) NEJM 2006;354:2764

- See Palliative care section of the BNF
- See www.palliativedrugs.com
- Analgesia :
 - Bone Pain: NSAIDs (including rectal indomethacin, no RCTs), bisphosphonates (proven to reduce fractures, will also ↓Ca, less evidence of ↓pain but well worth a try), also morphine and radiotherapy. Think of metastatic bone pain as nerve pain – infiltration of nerve endings in bone cortex ?role for TCAs, etc)
 - Liver capsule distension, intracranial hypertension, tumour compression, nerve infiltration: corticosteroids (eg dexamethasone 12 – 16 mg/d)
 - Intestinal or urinary muscle spasms: Buscopan
 - Neuropathic pain: Anticonvulsants (eg gabapentin), antidepressants (amitriptyline)
- Opioid analgesics:
 - See page 487 for Opioid Overdose
 - Dextropropoxyphen has additive benefit with codeine
 - Alternatives to morphine 10 mg (eg if allergic, constipated, nausea, ↓GFR) are:
 - Codeine 60 mg = oral morphine 10 mg
 - Hydromorphone 1.3 mg
 - Diamorphine 3 mg im: preferred as is more water soluble → given in lower volume
 - Methadone: dose titration can be difficult but good maintenance drug, OK in renal failure, prolongs QTc
 - Oxycodone oral 5 mg
 - Transdermal fentanyl (90 mg orally daily = ‘25’ patch)
 - Morphine and oxycodone can be given rectally
 - Initially standard release to titrate level then convert to slow release (starting dose usually 10 – 20 mg bd if no other analgesia taken previously)
 - If breakthrough pain on regular dosing then “rescue” PRN dosing, including fentanyl lozenges
 - Antiemetic with morphine (eg haloperidol or metoclopramide) for 4 or 5 days then try and withdraw
 - Little association between higher final opioid dose and shorter survival
 - Half lives:
 - Morphine Elixir/Sevredol: peak effect 2 hours, duration 3 – 5hours, bioavailability 40%
 - Morphine Sulphate: duration 8 – 12 hours
 - Kapanol: duration of action 24 hours
- Neuropathic pain: not a lot of RCTs but lots of clinical evidence
 - High dose steroids: reduction of oedema if compression
 - TCAs (eg amitriptyline). Action via serotonin antagonism of descending inhibitory pathway
 - Carbamazepine/Valproate: membrane stabilisers – dampen uncontrolled neuronal firing
 - Faster onset with gabapentin
 - Can also use flecainide 50 mg tds as a membrane stabiliser
 - Iv lignocaine also effective in RCTs
- GI Pain: Colic – loperamide 2-4 mg qid
- Muscle spasm: diazepam 5 – 10 mg daily or baclofen 5 – 10 mg tds
- Raised ICP: dexamethasone 16 mg for 4 – 5 days then reduce to 4 – 6 mg if possible. Don’t give in evening otherwise → insomnia
- Dyspnoea: morphine (start at 5 mg tds) or diazepam 5 – 10 mg daily if anxiety. Perhaps dexamethasone
- Bowel Obstruction:
 - Octreotide somatostatin analogue → ↓secretion of every gut hormone → ↓secretions and peristalsis, reduces peri-tumour inflammation and blood supply
 - Hyoscine butylbromide (Buscopan): antimuscarinic used for GI smooth muscle spasm. No RCTs. Less lipid soluble → less likely to cross the BBB (⇒ less sedation/delirium)
- Respiratory secretions: Hyoscine hydrobromide 400 – 600 mcg every 4 – 8 hours (can be given sl) for respiratory secretions which causes sedation, sometimes paradoxical agitation. Causes dry mouth
- Restlessness: haloperidol 1 – 3 mg QID, or if severe then midazolam sc (can’t give diazepam sc)
- Nausea:

- Octreotide: stimulates water and electrolyte absorption and inhibits water secretion in the small bowel. Given by subcut infusion
- Metoclopramide: prokinetic, use for gastritis, gastric stasis and function bowel obstruction
- Haloperidol for chemical causes of vomiting (eg hypercalcaemia, renal failure)
- Cyclizine: for mechanical bowel obstruction, raised ICP, motion sickness
- Dexamethasone as an adjunct
- Greater resource utilization (ie ICU) near the end of life is not associated with perceptions of better quality of care. Areas of higher utilisation are associated with less assistance with pain control, dyspnoea relief and emotional support, not knowing what to expect, poorer communication (J Am Geriatric Soc 2005;53:1905)

- Genetics:
 - Heredity plays a major role in risk of major psychiatric disorders. Eg schizophrenia: general risk 1%, 1st degree relative 9%, monozygotic twin 50%
 - Difficulty due to polygenetic nature and interaction with non-genetic factors, and no objective diagnostic measures or biological markers – do the syndromes reflected in DSM correlate well with distinguishable neurobiologic factors?
 - No Mendelian form of a psych condition has been identified
- Neuro imaging:
 - Schizophrenia: may be disease-specific patterns of gray matter loss in the frontal and temporal cerebral cortex, volume losses in the amygdale and hippocampus....
 - Depression: some patients have abnormal activity in Brodman area 25 – the subgenual prefrontal cortex. PET scanning shows ↓metabolic activity in the caudate nuclei and frontal lobes in depressed patients that returns to normal with recovery
- Drugs: all were found from empirical observation, not from understanding the pathophysiology

Schizophrenia

- Genetics: some potential gene candidates for schizophrenia (eg disrupted in schizophrenia DISC1)
- Environmental risk factors for schizophrenia: maternal famine (found in the Netherlands during WW2), urban birth, migration, ↑paternal age, intrauterine vial infection
- Presentation:
 - Positive symptoms: hallucinations, delusions
 - Negative symptoms: social withdrawal, impoverished speech, lack of motivation
 - Cognitive symptoms: poor executive function
 - Subtypes:
 - Catatonic: profound changes in motor activity
 - Paranoid: prominent preoccupation with a specific delusional system
 - Disorganised: disorganised speech and behaviour
 - Residual: residual negative symptoms without delusions, hallucinations or motor disturbance
- Treatment:
 - See Antipsychotics in Dementia, page 155
 - All drugs block or diminish the activity of D2 receptors
 - All drugs have similar efficacy, but different side effect profiles. General more effect on positive symptoms. Clozapine (and maybe other atypicals) have some effect on negative symptoms
 - Effective in 70% of patients with a first episode, full remission taking 6 – 8 weeks
- Comorbidities:
 - Physical comorbidity accounts for ~ 60% of premature deaths not related to suicide
 - Many barriers to care, both doctor/system and patient/illness factors
 - Higher rate of preventable risk factors: smoking, alcohol consumption, poor diet, lack of exercise
 - Diabetes: higher native risk, and all antipsychotic agents (atypicals > typicals) increase the risk of diabetes
 - Hyperlipidaemia:
 - Antipsychotics associated with ↑lipids, both related to and independent of weight gain
 - Clozapine and olanzapine (dibenzodiazepine-derived) have ↑ levels of fasting glucose and lipids compared with risperidone. Long term differences between agents in terms of weight gain are less clear
 - Mortality due to IHD and arrhythmias is higher in people with mental illness
 - Risk of cancer is not greater, but risk of mortality in the event of cancer is 50% higher
 - Increased risk of HIV and Hep C than the general population (likely related to IVDU and unsafe sex)
 - ↑Osteoporosis: attributed to antipsychotic driven ↓ in oestrogen and testosterone, ↓ Ca due to smoking and alcohol, and polydypsia
 - ↑PRL in typicals and in risperidone → galactorrhoea, amenorrhoea, sexual dysfunction and ↓bone mineral density
 - Odds ratio for H pylori infection is 3.0

Depression

- see NEJM 3 Jan 2008:
- Much lower heritability than bipolar disorder or schizophrenia
- Biological theories:
 - Monoamine-Deficiency hypothesis: deficiency in serotonin (synthesized from tryptophan) or noradrenaline (synthesized from tyrosine) neurotransmission
 - Hypothalamic-Pituitary-Cortisol system hypothesis: patients with depression sometimes have cortisol levels increased in severe depression, the size of the anterior pituitary and adrenal cortex is increased, and CRH levels in the cerebrospinal fluid and CRH expression in the limbic brain regions are increased
 - Many other pathophysiological theories
 - Consistent findings of disordered REM sleep, and sometimes ↓stage 4 delta slow wave sleep
- Diagnostic criteria for major depressive episode:
 - Requires a distinct change of mood: 5 or more of the following nearly every day during the same 2 week period (with at least one being depressed mood or diminished interest):
 - Depressed mood most of the day nearly every day
 - Markedly diminished interest or pleasure in all or almost all activities
 - Clinically significant weight loss (eg >5% in a month) or decrease in appetite
 - Insomnia or hypersomnia
 - Observable psychomotor agitation or retardation
 - Fatigue or loss of energy
 - Feelings of worthlessness or excessive or inappropriate guilt
 - Diminished ability to think or concentrate, or indecisiveness
 - Recurrent thoughts of death, suicidal ideation with or without a plan, or a suicide attempt
 - Impairment in social or occupational functioning
 - Not due to a general medication condition or substance abuse
 - Not better accounted for by grief – unless persistent (normal grief arbitrarily defined somewhere around 6 – 12 months), associated with marked functional impairment, feelings of worthlessness, suicidal ideation, psychotic symptoms or psychomotor retardation
 - If the mood disorder is not episodic, but more associated with “normal” for that person then dysthymic disorder
- Hopelessness and suicidal ideation are better predictors of suicide than depression per se
- 50 – 60% of patients who have a first episode have at least one or two recurrences
- Cognitive Behavioural Therapy:
 - Shown in RCT to be effective
 - Also effective in anxiety disorders and OCD
- Medication:
 - Only 40 – 65% have an adequate response to any antidepressant medication, if given in a sufficient dose for 6 – 8 weeks
 - Approx 40% discontinue treatment if no improvement in a month. Outcome improves with ↑frequency of review within the first month or supplemental education materials given
 - Should be continued for at least 6 to 12 months. Relapse after early discontinuation up to 70% (regular follow up important)
 - Increase synaptic levels of serotonin, noradrenaline or, less commonly, dopamine
 - Also useful in anxiety disorders (panic disorder and generalized anxiety disorder), and SSRIs in high dose for OCD
 - SSRIs used as first line. Most common SE is dyspepsia or nausea which usually resolves over 7 – 10 days
- ECT at least as effective as medication, but reserved for treatment resistant and delusional patients
- Psychotic depression: ECT helpful – the combination of TCA and antipsychotic that has efficacy in young and middle aged may have lesser efficacy in the elderly

Depression in Association with Medical Illness

- Depressive symptoms can be caused by:
 - The disease itself
 - Reaction to the illness
 - Medication: eg β-blockers and CCBs, steroids, antiparkinsonian medications, anticonvulsants
- Specific settings in which depression is common:

- Following MI or cardiac surgery: impair rehab and are associated with higher morbidity and mortality
- Cancer: prevalence 25%. Treatment has been shown to improve quality of life and mood
- Neurological disorders: CVAs (including 1 in 5 with L hemisphere stroke affecting the dorsolateral frontal cortex), Parkinson's, dementia, MS, traumatic brain injury
- Diabetes: severity of depression correlates with hyperglycaemia
- HIV: estimated lifetime prevalence is 22 – 45%. Multifactorial
- Hepatitis C: IFN α may worsen it
- Antidepressants in diabetes:
 - SSRIs may \downarrow serum glucose and cause weight loss. Fluoxetine may increase the risk of hypoglycaemia, especially in non-insulin dependant diabetics
 - TCAs are more likely to impair diabetes control and increase serum glucose – but are safe unless diabetes is poorly controlled and complicated by renal and cardiac disease
 - Antidepressants such as amitriptyline, imipramine and citalopram are used to treat painful diabetic neuropathy
 - Lithium can be safely used as a mood stabilizer in patients without renal disease
 - Sodium valproate might give false positive urine tests for glucose
 - MAOIs can cause hypoglycaemia and weight gain

Late-life depression

- See NEJM 29 Nov 2007
- Risk factors: female, chronic medical conditions, persistent insomnia, stressful life events (eg death of a spouse), functional decline or social isolation
- Often undetected, especially in men and minority groups
- If untreated is associated with poor quality of life, poor adherence to treatment, worsening of chronic medical problems, and increased mortality from suicide and other causes
- Management:
 - Measure thyroids if symptoms of hypothyroidism, but the value of routine thyroid screening in patients with depression is not established
 - Antidepressant medications and structured psychotherapies (eg CBT, interpersonal psychotherapy and problem-solving therapy) have roughly equivalent efficacies in older adults. A combination is recommended for severe or chronic depression
 - Also good evidence for ECT (if severe, efficacy rates 60 – 80%) and physical-exercise programs (eg 12 week supervised group based physical exercise programs involving walking or other forms of aerobic exercise)

Tricyclic Antidepressants

- Inhibit reuptake of 5-HT (eg imipramine, amitriptyline) and/or NA (eg desipramine)
- Sedating: amitriptyline, dothiepin, doxepin
- Less sedating: imipramine, nortriptyline
- Narrow therapeutic index. The steady state plasma level can vary up to 10-fold between individuals, some ethnic groups require lower doses
- Not first line, but consider if previous good response or refractory to other medications
- Side effects (?lead to higher drop out rate than SSRIs):
 - Imipramine and amitriptyline: well established but more marked antimuscarinic and cardiac side-effects than others
 - Cardiac: Uncommon at therapeutic doses. Arrhythmias and heart block (esp cardiac disease). They are type 1 antiarrhythmic agents blocking sodium and K channels. Contraindicated within 2 weeks of an MI, if conduction defects, orthostatic hypotension, narrow angle glaucoma, urinary retention, BPH or cognitive impairment
 - Receptor profile – blocks:
 - Central and peripheral cholinergic receptors (antimuscarinic effects): Drowsiness, dry mouth, blurred vision, constipation, urinary retention. Persist as tolerance may develop
 - Histamine receptors: sedation and weight gain
 - α receptors: orthostatic hypotension
 - Associated with seizures: caution in epilepsy
 - Hyponatraemia
 - Neuroleptic malignant syndrome
 - Withdraw slowly

- Overdose:
 - Presentation: arrhythmias (inhibit fast Na channels in the His system), hypotension (main cause of mortality), anticholinergic toxicity (hyperthermia, flushing, dilated pupils, ileus, urinary retention, tachycardia, hallucinations)
 - Treatment: fluids for hypotension, bicarbonate for cardiovascular toxicity, alpha adrenergic vasopressors (eg noradrenaline) for refractory hypotension, charcoal (unless ileus), BZD for seizures (not phenytoin)

Selective Serotonin Reuptake Inhibitors

- Inhibit reuptake of serotonin
- No more effective, but less sedating, fewer antimuscarinic side effects and less cardiotoxic in overdose than the older TCAs, but more GI SEs
- Preferred over TCAs in diabetes
- Caution in epilepsy
- SEs related to serotonin reuptake inhibition (usually within 2 – 6 weeks):
 - GI: upset, anorexia and weight loss, flatus, diarrhoea in 20 – 30%
 - CNS dysfunction: insomnia, apathy, nervousness, restlessness (5%), tremor, headaches
 - Sexual dysfunction: usually occurs later – ↓libido (1 – 10%), anorgasmia, impotence (1 – 7%). Lower the dose or have weekend drug holidays
 - Mania and suicidal ideation in < 1%
 - Also rash, arthralgia, dry mouth, urinary retention, bleeding problems reported
- Hyponatraemia (2nd to SIADH – most in the first month, reported more frequently with SSRIs than TCAs)
- Long half life (2 months steady state)
- Nonlinear kinetics – increase dose 10 mg at a time
- Start fluoxetine and citalopram at 10 mg od and titrate up (max 60 mg for either). Withdraw slowly otherwise discontinuation syndrome (irritability, agitation, emotional lability affecting 60% following abrupt cessation). Paroxetine has reputedly more anticholinergic side effects

Other Antidepressants

- MAO Inhibitors:
 - Inhibit an enzyme that oxidizes 5-HT and NA in the pre-synaptic terminal
 - Not with SSRIs otherwise serotonin syndrome
 - Not with tyramine-containing food or sympathomimetic drugs otherwise risk of hypertensive crisis
- Venlafaxine:
 - Serotonin and noradrenaline reuptake inhibitor
 - No cholinergic, histaminergic and α-adrenergic affinity
 - Few head-to-head comparisons in the elderly, but SNRIs probably not so well tolerated by the frail elderly
 - May be particularly helpful if co-existing pain (esp neuropathic)
 - Doesn't have flat dose response of the SSRIs therefore higher dose better
 - SEs: nausea, agitation, somnolence, dry mouth, dizziness, constipation, sexual dysfunction. HTN esp at high doses – monitor diastolic BP
- Clonidine: stimulates 5-HT receptor on the post-synaptic neuron

Lithium

- Possible mechanisms:
 - Blocks inositol monophosphatase
 - Blocks glycogen synthase kinase 3 β
- Effective in acute mania in 70 – 80% within 1 – 2 weeks (may need BZD cover), and prophylactic effect (although compliance an issue)
- Pharmacokinetics:
 - Unbound in plasma and tissues
 - T_{1/2} = 19 hours ⇒ don't retest until 5 days after a change in dose (if you test at all)
 - Renal excretion:
 - 95% excreted unchanged via the kidneys within 24 hours – reduce in renal impairment
 - Most filtered lithium is reabsorbed in the proximal tubule, approx 20% excreted in the urine

- Reabsorption follows that of sodium – so anything that increases proximal resorption will ↑ Li levels, including any cause of volume depletion (GI losses, CHF, diuretics, ACEIs, NSAIDs – except sulindac and aspirin)
- Relative risks of toxicity:
 - Frusemide 5.5, ACEI 7.6
 - Thiazides, β-blockers, nitrates and CCBs not directly associated with Li toxicity (J Am Ger Soc 2004;52(5): 794-798)
- Narrow therapeutic index. Adjust dose to achieve trough serum concentration 0.4 – 1 mmol/L. May have mild toxicity from 1.5
- Reduce dose in diarrhoea/vomiting or intercurrent infection
- Toxicity:
 - Signs: tremor, ataxia, dysarthria, nystagmus, renal impairment and seizures
 - Toxicity worsened by sodium depletion (eg concurrent thiazides/frusemide should be avoided)
 - Serum lithium level is not an accurate predictor of toxicity – in chronic toxicity modest elevations may be symptomatic, in acute toxicity there may be high levels without any symptoms
 - Rarely causes ↑PTH → ↑Ca
 - Lithium Nephrotoxicity:
 - Nephrogenic diabetes insipidus: Hypernatraemia and low urine osmolality < 200 mosmol. Li enters the collecting tubule cells via the luminal Na channels and interferes with ADH action. Stop Li. Give amiloride to ↓entry into cells
 - Interstitial nephritis
 - Can cause mild hypermagnesaemia, and hypercalcaemia
- SE:
 - GI disturbance, fine tremour, polyuria, polydypsia, leucocytosis, weight gain
 - More serious effects: poor concentration, ataxia, dysarthria, incoordination
 - Suggestive evidence that it's teratogenic in 1st trimester (cardiac malformations)
- Monitoring: Li level every 3 months, TFTs every 6 – 12 months. Don't use a lithium-heparin (green top) tube → markedly elevated levels
- Valproate and olanzapine also effective in acute mania, as is lamotrigine in the depressed phase
- Overdose:
 - Intoxication often from accumulation, especially in renal impairment
 - Presentation: neuromuscular irritability, confusion, nausea, vomiting, bradycardia, hypotension
 - Treatment: rehydration (watch for hypernatraemia given nephrogenic diabetes insipidus – use half-normal saline), haemodialysis (most dialyzable toxin known – low molecular weight, no protein binding and Vd similar to that of water)

Anxiety Disorders

- Panic attack: appears to be associated with ↑noradrenergic discharges in the locus coreuleus. Treatment: antidepressants + CBT
- Agoraphobia: Anxiety about being in places or situations from which escape might be difficult, and the situation is avoided
- Generalised Anxiety Disorder: persistent, excessive and/or unrealistic worry with impaired concentration, autonomic arousal, insomnia... Onset usually before age 20
- Phobic disorders: marked and persistent fear or objects of situations with avoidance that affects occupational and social functioning
- Stress disorders: Anxiety developing after an extreme or traumatic event (high rate of comorbid depression)
- Anxiolytic agents:
 - BZDs bind 2 separate GABA-A receptor sites – accounting for their different effect profiles:
 - Type 1: broadly distributed
 - Type 2: concentrated in the hippocampus, striatum and neocortex
 - Longer acting (diazepam T_{1/2} 20 – 70 hrs, clonazepam T_{1/2} 18 – 50 hours) tend to accumulate active metabolites → sedation, impaired cognition and psychomotor retardation
 - Shorter acting (oxazepam T_{1/2} 5 – 15 hrs) → rebound anxiety and insomnia. Lorazepam (T_{1/2} 10 – 20 hrs)
- Anticonvulsants with GABAergic properties may also be effective against anxiety

Random Psych

- Somatoform disorders:
 - Somatization Disorder: multiple physical complaints. Symptoms not intentionally produced
 - Conversion disorder: mono-symptomatic
 - Factitious Disorders: Consciously and voluntarily produces physical symptoms of illness. Motivation is to assume the sick role
 - Malingering: External incentive for behaviour (eg economic gain)
- Personality disorders: inflexible patterns of behaviour causing functional impairment or subjective distress
 - Cluster A: odd, eccentric, emotionally distant. Paranoid, schizoid, schizotypal
 - Cluster B: impulsive, excessively emotional, erratic: antisocial, borderline, histrionic, narcissistic
 - Cluster C: anxiety and fear: avoidant, dependent, obsessive-compulsive
- Psychological adjustment to chronic disease (see Lancet 19 July 2008): to promote psychological adjustment, patients should remain as active as is reasonably possible, acknowledge and express their emotions in a way that enables them to take control of their lives, engage in self-management, and try to focus on potential positive outcomes of their illness

Alcohol

- See also Alcoholic Liver Disease, page 365
- Blood levels: 100 mg/dL = 0.1 g/dL
- 1 unit gives a blood level of ~ 15 – 20 mg/dL
- Driving limit: 80 mg/100 ml = 17.4 mmol/L = 400 mcg/L breath
- Absorption:
 - Modest amounts from stomach and large bowel
 - Major site: small intestine
 - Increased by rapid gastric emptying (promoted by carbonated beverages)
- Metabolism:
 - By alcohol dehydrogenase (ADH) to acetaldehyde, which is rapidly metabolised by aldehyde dehydrogenase (ALDH)
 - A 2nd pathway in the smooth endoplasmic reticulum (the MEOS system) accounts for ~ 10% at high blood concentrations
 - Metabolise at 15 – 20 mg/hour – even if tolerant no more than 30
 - Has modest effects on the storage of folate, pyridoxine (B6), thiamine (B1), nicotinic acid (niacin, B3) and vitamin A
- Action:
 - Enhances GABA-A and inhibits NMDA
 - Tolerance develops quickly (→ withdrawal on rapid cessation) with 3 compensatory mechanisms:
 - ↑hepatic metabolism over 1 – 2 weeks
 - Cellular tolerance – maintaining normal function despite ↑ alcohol
 - Behavioural tolerance – adapt behaviour to cope with its effects
- Side Effects:
 - Early: Depression (treat the alcohol before SSRIs), anxiety, insomnia, GORD, gout, HTN, AF, trauma
 - CNS:
 - Blackouts common – temporary anterograde amnesia
 - Disturbed sleep
 - Relaxed pharynx muscles → OSA
 - Impaired judgment and coordination → ↑risk of injury
 - Peripheral neuropathy with chronic high doses
 - Cerebellar degeneration or atrophy: unsteady gait and mild nystagmus
 - Only ~ 1 in 500 develop Wernicke's (ophthalmoparesis, ataxia and encephalopathy) and Korsakoff's (retrograde and anterograde amnesia) syndromes. Due to thiamine deficiency in predisposed individuals. NB nystagmus can occur with high levels of ETOH alone
 - Comorbid drug dependence, depression, and anxiety disorders
 - Alcohol induced mood, anxiety or psychotic disorder – can't assess these as primary disorders (eg depression) while still drinking
 - GI:
 - Haemorrhagic gastritis
 - Acute pancreatitis: 3 fold risk in alcoholics
 - Liver:
 - Little clear evidence for predicting which heavy drinkers get advanced disease
 - Fatty liver (90%): 2nd to ↓glucose from glycogen, ↑lactate, and ↓oxidation of fatty acids
 - Steatohepatitis (10 – 30%)
 - Cirrhosis (5 – 20%)
 - Cancer: ↑breast cancer, ↑ oral and oesophageal cancers with > 4 drinks/day
 - Blood: ↑MCV, ↓WBC, mild thrombocytopenia, if malnourished then folic acid deficiency and sideroblastic changes
 - CVS:
 - Dose dependent ↑ in BP
 - Risk of CAD and ↑risk of cardiomyopathy
 - Atrial or ventricular arrhythmias especially after a binge
 - Genitourinary: testicular atrophy, amenorrhoea

- Other: alcoholic myopathy (acute skeletal muscle weakness), lower bone density, ↑cortisol, ↓T3
- Assessment (See NEJM 2005;352:596-607):
 - Shrouded in denial
 - Alcohol history: missing meals, typical week, \$/week, solitary, amnesic episodes, corroborative information, family history
 - Differential of drowsiness: alcohol, other sedatives, head injury, post-ictal, hypoglycaemia, hepatic encephalopathy, Wernicke's
 - CAGE questions:
 - Have you ever felt you ought to cut down on your drinking
 - Have people annoyed you by criticizing your drinking
 - Have you ever felt guilty or bad about your drinking
 - Have you ever had a drink first thing in the morning (an eye-opener) to steady your nerves or get rid of a hangover
 - AUDIT Questions (WHO): Alcohol Use Disorders Identifications Test (1989) – Like an extended CAGE questionnaire
 - Classified as:
 - Alcohol dependence (requires 12 month history and includes tolerance and withdrawal, use of greater amounts than intended, use despite consequences, unsuccessful in controlling), or
 - Alcohol abuse: adverse effects on social, family, occupational or health status
- Lab assessment:
 - GGT > 35 U and *carbohydrate-deficient transferrin (CDT)* > 20 U/L both have > 70% sensitivity and specificity for heavy alcohol consumption – useful for monitoring. CDT less sensitive in women
 - Also high normal MCV (> 91) and uric acid > 416 mmol/L
 - ↓Platelets
 - ↑TGs
 - AST > ALT (< 300 u/l)
 - Blood alcohol underutilized
 - As an aside, muscle biopsy is frequently abnormal
- When to do a liver biopsy? Correlation of clinical assessment and histology is not good
 - Will confirm diagnosis and degree of liver damage
 - Exclude co-existing other liver disease
 - Prognostic/treatment issues
 - Persisting raised transaminases after 3 months abstinence
 - New fibrosis markers are beginning to replace biopsy.... Still require validation
- Prognosis: 5 year survival with cirrhosis: 34% if still drinking, 70% if stop
- Treatment:
 - Intoxication: exclude other drugs, screen for BZD and opioids, exclude hypoglycaemia, DKA or liver failure. BZDs for agitation. Also haloperidol – but lowers seizure threshold
 - Rehabilitation: motivation towards abstinence → adjust to life without alcohol → relapse prevention
 - Brief interventions and motivational interviewing – both proven effective
 - Between half and 2/3rds of alcoholics maintain abstinence for years after treatment – positive predictors are high levels of life stability and higher levels of functioning
 - Medications (supportive role only – no studies have reported ↓mortality):
 - Naltrexone: (see NEJM 14 August 2008) blocks μ-opioid receptor → antagonizes endogenous endorphin → ↓dopamine levels in the nucleus accumbens (ventral reward system). Mixed evidence. At 100 mg/day increases the number of days of abstinence. Contraindicated if liver enzymes > 4 – 5 times normal or on opiates for pain relief. Few side effects. Benefit of concurrent psychological intervention demonstrated in trials. T_{1/2} 48 hours. Mainly used in binge drinkers to ↓severity of binges
 - Acamprosate: inhibits NMDA receptors and blocks GABA. *Reduces craving*. Sustained benefit (cf naltrexone). Few side effects. Added benefit in combination with Naltrexone suggested in trials
 - Disulfiram: ALDH inhibitor → ↑acetaldehyde → unpleasant (and *potentially dangerous if CVD, CVA, DM or HTN*) reaction to alcohol with ↑pulse, vomiting and diarrhoea. No compelling evidence. Useful if observed treatment (eg by spouse) for high risk periods. Contraindications: IHD, severe hepatic disease, depression or psychosis
- Withdrawal:

- Presentation: symptoms the opposite for intoxication, caused by rapid withdrawal of a CNS depressant: tremour, agitation, anxiety, autonomic overactivity
- Generally begin within 5 – 10 hours of withdrawal and peak on day 2 – 3
- 2 – 5 % of alcoholics have at least one withdrawal seizure
- Delirium tremens: uncommon. Acute delirium in < 1% of withdrawals, usually if other severe medical problems
- Treatment: longer acting BZDs (eg diazepam – accumulates in hepatic disease) so there aren't short term fluctuations in blood levels. Haloperidol and phenytoin used but evidence base weak

Opioids

- See page 477 for dose equivalence and use in Palliative Care
- Types:
 - Derived from poppy: morphine, codeine
 - Semi-synthetic: diacetylmorphine (heroin), oxycodone
 - Synthetic: fentanyl, tramadol, methadone
- Together with endogenous opioids, act on μ , κ , δ receptors to produce analgesia, respiratory depression, sedation, constipation (due to \downarrow gut motility), euphoria, nausea, \downarrow cough reflex (useful as an antitussive)
- Abuse:
 - Genetic risk explains ~ 50% of dependence
 - Mortality 15-fold higher than general population
 - High risk groups:
 - Chronic pain
 - Doctors, nurses, pharmacists with easy access
 - Drug uses (also risk of HBV/HCV/HIV)
- Withdrawal:
 - Nausea, diarrhoea, coughing, fever, HTN, diffuse body pain, insomnia, yawning, intense drug craving
 - With shorter half life forms (heroin, morphine) starts 8 – 16 hours after last dose and peaks within 36 – 72 hours (7 – 10 days for methadone). Protracted abstinence phase of mild moodiness and disturbed sleep may persist for > 6 months
 - Treat acutely with graduated reduction (eg methadone), ibuprofen for pain, clonidine (α_2 agonist) to \downarrow sympathetic overactivity
- Maintenance:
 - Methadone or buprenorphine (used in 1/3 of maintenance patients in Australia, safer and more expensive, doesn't prolong QT)
 - Methadone prolongs the QT, is OK in renal impairment
 - Reduces heroin injection, HIV infection, mortality, criminality, but *not* HCV (the longer you're on methadone the higher your HCV incidence, reaching 90 – 95%)
- Overdose:
 - In overdose miosis (pupil contraction) \rightarrow mydriasis (dilation) once brain stem hypoxia develops, bradycardia, hypothermia, coma
 - Treatment: titrate naloxone so as not to provoke a withdrawal state. Repeat 0.4 – 2mg dose every 2 – 3 mins up to 10 mg. Wears off after several hours and may need repeating up to 72 hours with a long acting form such as methadone
- Lemon juice is often used to dissolve heroin for injection \rightarrow risk of candida infection \rightarrow panophthalmitis (must check eyes)

Other Drugs of Abuse

- Cocaine:
 - Stimulant, local anaesthetic, potent vasoconstrictor
 - Blocks reuptake of monoamine neurotransmitters (dopamine, noradrenaline, serotonin)
 - Effects of IV use rarely last > 1 hour
 - Mortality due to respiratory depression, arrhythmias, and seizures, ischaemic or haemorrhagic stroke and SAH. Severe pulmonary disease from chronic inhalation
 - Treatment: diazepam infusion to prevent seizures, propranolol for arrhythmias, check for other drugs
- Marijuana:
 - δ -9-tetrahydrocannabinol (THC)

- Converted in the liver to a psycho-active compound
- Slow clearance
- High density of cannabinoid receptors (CB1 and CB2) in the cerebral cortex, basal ganglia and hippocampus
- Presentation: conjunctival injection and tachycardia
- Rapid tolerance and ↓pulmonary vital capacity amongst regular users
- Methamphetamine:
 - → ↑release of monoamine neurotransmitters into the synaptic junction
 - SE: headache, ↓concentration, ↓ appetite, abdo pain, vomiting or diarrhoea, disordered sleep, paranoid or aggressive behaviour, psychosis
 - Life threatening: HTN, arrhythmias, CHF, SAH, ischaemic stroke, seizures
 - Treatment largely supportive. HTN may respond to nitroprusside or α antagonists
- Ecstasy
 - A derivative (NDMA – 3,4 methylenedioxymethamphetamine)
 - Rapid rise then depletion of serotonin, release of ADH
 - Onset 20 minutes, lasts 4 hours. Persisting abnormalities in the brains of ex-users
 - SE: Hyperthermia, seizures, DIC, rhabdomyolysis, renal/liver impairment
 - Treatment: Dantrolene of value in controlling body temperature (is drug of choice in malignant hyperthermia, not in heat stroke)
- Gamma-hydroxybutyrate (Fantasy):
 - Dizziness, blurred vision, hot/cold flushes, sweating, confusion, vomiting, LOC, tremours, blackouts
 - Serious withdrawal syndrome

Toxicology

Toxidromes

- **CNS depression:** cholinergic, hypnosedative, opioid
 - Cholinergic:
 - Signs: confusion, ↓LOC, weakness, salivation, urinary/faecal incontinence, GI cramping, sweating, muscle fasciculations, pulmonary oedema, miosis, hypotension, seizures [ie weeping, sweating, peeing, pooing]
 - Likely agents: organophosphate insecticides. Note these can be absorbed through the skin. Wear protective clothing. Remove patients clothing, wash exposed areas
 - Hypnosedative:
 - Signs: coma, CNS depression, nystagmus, hypotension, hypothermia, hyporeflexia
 - Likely agents: BZD, Zopiclone
 - Opioid:
 - Signs: Miosis (contracted pupils), coma, respiratory depression, hypotension, pulmonary oedema
 - Likely agents: heroin, methadone, morphine, codeine, dextropropoxyphene (is also cardiotoxic)
- **Stimulants:** Anticholinergic, serotonergic, sympathomimetic
 - Anticholinergic:
 - Signs: delirium, tachycardia, dry flushed skin, mydriasis (dilated pupils), myoclonus, urinary retention, ↓bowel sounds, (seizures, dysrhythmias) [ie blind, dry, mad and hot]
 - Agents: TCAs, datura, atropine, benztropine, antihistamines
 - Gastric stasis → delayed drug absorption
 - Serotonin Syndrome:
 - Excess of synaptic serotonin
 - Presentation: mental status changes, agitation, myoclonus, hyperreflexia, diaphoresis, tremour, diarrhoea, fever
 - Drug combinations causing it:
 - Inhibition of serotonin reuptake: SSRIs, TCAs, Tramadol, pethidine
 - MAOIs
 - St John's Wort
 - Partial serotonin agonists: LSD, buspirone (antianxiolytic)
 - ↑Serotonin release: amphetamines
 - Lithium
 - Serotonin precursors: Tryptophan (antidepressant adjunct)

- Sympathomimetic:
 - Signs: Delusions, paranoia, tachycardia, HTN, fever, diaphoresis, piloerection (erection of hair), mydriasis (dilated pupil)
 - Agents: amphetamines, decongestants, cocaine
- **Discordant:** Anion gap acidosis causing agents, eg ethylene glycol

Investigations

- Causes of anion gap acidosis:
 - Iron, isoniazid, ibuprofen
 - Lithium, lactate
 - Carbon monoxide, cyanide, caffeine
 - Respiratory dysfunction, β -blockers, benzyl alcohol
 - Methanol, metabolic dysfunction, metformin
 - Uraemia
 - DKA
 - Paraldehyde
 - Ethanol
 - Salicylates
- Elevated osmolal gap: ethanol, methanol, ethylene glycol, isopropyl alcohol, acetone
- ECGs:
 - Bradycardia: β -blockers
 - Broad QRS: type 1 anti-arrhythmics: TCAs, quinine, chloroquine
 - 2nd degree heart block: verapamil, diltiazem
 - Digoxin: any arrhythmia

Decontamination

- Activated Charcoal:
 - Decreases bioavailability
 - Given mixed in Sorbitol to increase transit time and avoid obstruction
 - Doesn't work for metals, strong acids or alkalis
- Gastric lavage:
 - Within one hour of ingestion (unless anticholinergic which \rightarrow delayed emptying)
 - Tablet has to be able to pass up the lumen of the NG tube
 - Protect airway, use small aliquots (otherwise may increase gastric emptying)
 - Follow with charcoal
- Whole bowel lavage:
 - Method of choice for metals (iron, lithium) and slow release preparations
 - 2,000 ml per hour in an adult
- Increase clearance:
 - Repeat dose activated charcoal
 - Forced alkaline diuresis
 - Dialysis for *aspirin, lithium, iron, methanol, ethylene glycol*

Antidotes for Poisons

- Aspirin:
 - Rapidly converted to salicylic acid
 - Activates chemoreceptor trigger zone (\rightarrow nausea) and respiratory centre (\rightarrow respiratory alkalosis, then superimposed metabolic acidosis 2nd to lactic acid)
 - Presentation: *tinnitus, fever* (induced mitochondrial defect), vertigo, nausea, diarrhoea, blurred vision
 - Treatment: activated charcoal (although aspirin is rapidly absorbed), supplemental glucose (CNS glucose levels < peripheral), treatment with bicarbonate (despite alkalosis) to leach the weak acid from the CNS and increasing urinary excretion. Haemodialysis
- β -blockers: glucagon, isoprenaline
- Benzodiazepines: flumazenil
- Chloroquine: diazepam
- Digoxin: fab, magnesium if torsades
- Iron: Rectal bleeding and haematemesis, cardiovascular collapse. Do CXR and AXR so see if pills still in the gut. Treatment: desferoxamine. Dialysis if bad

- Lithium: see page 482
- Methanol (wood alcohol) and ethylene glycol (antifreeze):
 - Symptoms and acidosis are due to toxic metabolites via alcohol dehydrogenase (methanol → formaldehyde)
 - Treatment: gastric lavage, sodium bicarbonate (may need large doses)
 - Fomepizole: inhibitor of alcohol dehydrogenase (better than ethanol)
 - Haemodialysis
- Opiates, clonidine: naloxone
- Organophosphate: atropine, pralidoxime
- Paraquat: fuller's earth
- Paracetamol: NAC. See Toxic and Drug Induced Hepatitis, page 361
- Tricyclic Antidepressants: See page 481
- Verapamil, diltiazem: calcium

- Pharmacokinetics: factors which determine drug delivery to and removal from molecular targets – absorption, distribution, elimination. What the body does to the drug. Describes the balance between accumulation and elimination
- Pharmacodynamics: processes that determine variability in drug response despite equivalent drug delivery to target sites. What the drug does to the body
- Pharmacogenetics: variability in drug responses due to polymorphisms

Enhancing Medication Adherence

- See Cochrane Review 2008
- Typical adherence rates are ~50%. 25 – 50% of patients make errors in the self-administration of prescribed medicines
- Most interventions aimed at long term compliance are complex and not amenable to meta-analysis
- Improved adherence does not necessarily imply improved clinical outcomes
- What's been tried:
 - More instructions for patients: verbal, written, visual
 - Education about the target disease, the role of therapy, possible side effects (found not to decrease adherence)
 - Automated or manual telephone follow-up
 - Family intervention
 - Simplified dosing, blister packing
 - Appointment and prescription refill reminders
 - Lay health monitoring, etc
- A pharmacist phone call midway between each medical assessment in patients taking 5 or more drugs and assessed as usually taking less than 80% of regular medication improved 2 year mortality (17% vs 11%), same number of admissions but fewer days in hospital (Hong Kong study, BMJ 2006;333:522)

Clinical Trials

- Preclinical trials: testing toxicity and potential therapeutic benefit
- Phase 1: Human pharmacology – in healthy subjects to define doses and effects. What is maximum tolerated dose. N = perhaps 20 – 30
- Phase 2: On diseased – focus is safety: dose level and frequency, unwanted effects, treatment duration. N = 50 – 200 or so
- Phase 3: Definitive trial in large group to compare with standard – designed to test efficacy (and to a lesser extent safety)
- Medicines licensed for use
- Phase 4: Post-market surveillance. Adverse reaction monitoring – rare effects only show up with widespread general use
- On average takes ~ \$US700 mill to get a drug from the lab to the bedside

Absorption

Bioavailability

- The fraction of the drug available to the systemic circulation after oral, sc, im, pr or sl administration, F mg.h/L
- Absolute oral bioavailability, $F = AUC_{oral}/AUC_{IV}$ (Curve of plasma concentration vs time)
- Oral bioavailability is affected by:
 - Food: can ↓absorption (↓bioavailability, eg rifampicin, glipizide) and ↓first pass effect (↑bioavailability) – but general affect is just a delay
 - Binding with aluminium-containing antacids or bile acid sequestrants
 - ↑gastric pH (eg with PPIs) → ↓solubility and hence absorption of weak bases (eg ketoconazole)
 - Drug solubility: Lipid-soluble → ↑absorption (+ distributes more widely)
 - First pass metabolism: is often significantly reduced in liver disease
- Relative bioavailability = the oral bioavailability of a test formulation (eg a generic) vs a reference formulation (eg the brand name drug)

First Pass Effect

- Extent to which a drug is removed by the liver of the gut prior to reaching the systemic circulation
- Due to biliary excretion and liver (and some gut enterocyte) metabolism
- Important in drugs with high hepatic extraction ratio

- ↓ with any form of hepatic obstruction (eg portal thrombosis), due to shunting via other routes (eg in advanced liver disease)
- Examples:
 - GTN can't be administered orally because of complete first pass metabolism
 - Verapamil: high pre-systemic metabolism. Iv dose is 1 – 5 mg, oral dose is 40 – 120 mg
 - Morphine: equivalent IV dose is about a third of oral due to first pass effect
 - Low dose aspirin: platelets affected in the portal vein, but systemic sparing because of first pass deacetylation in the liver

(Apparent) Volume of Distribution

- Distribution:
 - = volume into which the drug appears to be uniformly distributed with a concentration equal to that of plasma
 - **Vd (L) = Amount of drug in the body (Ab, mg) / it's plasma concentration (Cp, mg/L)**
 - Depends on drug solubility: lipid soluble → ↑Vd
 - Determines *loading dose*:
 - **Loading dose (mg) = Vd * desired Cp**
 - Allows Cp to quickly reach therapeutic levels and allows for immediate establishment of Cp_{ss} (steady state plasma concentration)
 - Rate of distribution: the rate at which a drug distributes is dependent on perfusion, lipid solubility, passive > active uptake. Can lead to a different therapeutic effect of the plasma concentration
 - Examples:
 - Digoxin: plasma level falls quickly after iv administration but takes hours to reach sufficient concentration at site of action. After 6 – 8 hours (when distribution is nearly complete) plasma concentration reflects therapeutic effect – that is the time to measure plasma levels. Vd = 500 litres
 - Gentamicin has an apparent Vd of extracellular H₂O (~ 15 litres)
 - Midazolam: Rapid uptake by the brain during distribution → quick sedation, with subsequent redistribution – so subsequently will have +ive blood concentration but no effect
 - Adenosine: very rapid elimination by uptake into erythrocytes and endothelial cells. Have to give it rapidly to have any left by the time it reaches the AV node
 - Fluoxetine: Vd = 3500 litres
 - Warfarin: Vd = 8 litres
- Protein Binding:
 - Drug response related to free rather than total circulating drug concentration
 - Only free drug is active
 - Only free drug is metabolised and/or renally excreted
 - Measured drug levels include both bound and unbound portions
 - Only of relevance for highly bound drugs (> 90%). Small changes in binding or a large change in plasma protein levels (uncommon) can make a big difference. Eg hypoalbuminaemia, liver disease, renal disease affecting drug binding, especially of acidic and neutral drugs like phenytoin. Displacement of drugs from plasma proteins is not usually clinically significant as the ↑free drug is rapidly cleared
 - Examples of highly protein bound drugs: propranolol, phenytoin, amiodarone
 - Binding of drugs in tissues is quantitatively more important in terms of drug distribution than binding to plasma proteins
 - Volume of distribution of drugs extensively bound to plasma proteins but not to tissue components approaches plasma volume (eg warfarin)
 - Drugs highly bound to tissues (eg digoxin and TCAs) have a volume of distribution of hundreds of litres. Not removed in overdose by haemodialysis
 - Drug interactions based on displacement from plasma binding sites alone are transient and not clinically significant
- Hysteresis Index:
 - Anticlockwise/Reverse: delayed distribution eg digoxin
 - Clockwise: rapid tolerance (tachyphylaxis) eg adrenaline

Elimination

- Clearance:
 - = Elimination

- = Metabolism (mainly liver) + Excretion (mainly kidney)
- Viewed as: concentration at the beginning and end of a period of time is unchanged, and a specific volume of the body has been cleared, ie measured in volume/time
- *Volume of plasma cleared of drug per unit time*
- May related to a single organ or the whole body
- Can't be greater than the blood flow to the eliminating organ
- **Cl (L/min) = Vd * K** (elimination constant) = **Vd * 0.693/T_{1/2}** [NB K is the proportion of drug eliminated per unit of time, 0.693 = log of 2]
- Determines *maintenance dose*: **Maintenance Dose = clearance * desired concentration** [ie for a given maintenance dose rate, clearance is the sole determinant of C_{ss}]
- Elimination **rate** (mg/hr, ie weight of drug per unit time) = Clearance (L/hour) * plasma drug concentration (mg/L) [NB elimination rate is very different at different concentrations]
- Initial rapid drop in drug concentration is not elimination but distribution into and out of peripheral tissues (also a first order process)
- Renal Excretion:
 - Fraction excreted unchanged (f_u):
 - = 1: totally renally excreted, eg digoxin
 - = 0: no renal excretion, eg phenytoin
 - Renal excretion is proportional to CrCl
 - Active and passive excretion
 - Highly susceptible to disease states
 - Examples:
 - Salicylate → ↓ renal clearance of methotrexate
 - Probenecid → ↓ renal clearance of penicillin (used for therapeutic effect)
 - Triple whammy: NSAIDs, diuretics and ACEI → renal failure (fatality rate of renal failure is 10%)
- Capacity limited metabolism/elimination:
 - First-order metabolism (= linear kinetics [except the graph is exponential not linear!]): Same proportion of the drug is eliminated per unit time. Rate of the process depends on the amount of drug present. Applies to most drugs
 - Zero-order metabolism (=Michaelis-Menten Kinetics):
 - Elimination becomes *saturated* at high doses, so elimination then happens at a fixed *amount* per unit time → plasma concentrations change disproportionately more than alteration in the dosing rate
 - Risk of toxicity or poor efficacy
 - Dose changes should be small and monitored carefully
 - Eg phenytoin, theophylline, alcohol, aspirin, perhexiline (CYP2D6 poor metabolisers)
 - Any drug at some dose will exceed the metabolic capacity, but this is unusual at the therapeutic dose
- **Half Life** (T_{1/2}):
 - The time taken for the plasma concentration to decrease by 50% – an exponential process. A constant proportion of the drug is eliminated per unit time
 - Is constant for drugs that follow first-order elimination kinetics
 - Composite of clearance and volume of distribution. Cl and Vd are independent variables, T_{1/2} is dependent on them. **T_{1/2} = 0.693 Vd / Cl**
 - Determines:
 - Duration of action of a single dose
 - The time to reach steady state with continuous dosing
 - Time course of elimination
 - Time course of accumulation
 - Choice of dose interval to avoid a large fluctuation in C_p
- Steady-State: drug administered per unit time = drug eliminated per unit time
 - C_{ss}: steady-state plasma concentration, is most determined by Vd
 - Magnitude of steady state is determined by clearance and dose alone:
 - C_{ss} = F (bioavailability, mg.h/L) * D (dose) / Cl * T (dose interval)
 - As Cl = (Vd * 0.693)/T_{1/2}, then
 - C_{ss} = (F * D * T_{1/2}) / (0.693 * Vd * T)
 - Is proportional to dose and inversely proportional to interval

- C_{ss} is reached in 4 to 5 half lives then stays constant
- C_{ss} is proportionately and predictably changed by changing dose and/or dosing interval
- Dosing regimes:
 - For drugs with T_{1/2} 8 – 24 hours, dosing interval = T_{1/2}
 - For drugs with a short T_{1/2} (and low therapeutic index), use slow release preparations
 - For drugs with a T_{1/2} > 24 hours, use once daily dosing
 - If dosing interval is equal to drug's half life, fluctuation is about twofold, which is usually acceptable
 - If drug is eliminated rapidly, it can still be given infrequently if it has a wide TI. Eg captopril has a half life of 2 hours, but can be given 12 hourly because it is safe to keep the plasma concentration well about the threshold for pharmacologic effect

Liver Metabolism

- Metabolism occurs mostly in the liver (other sites: kidney's, lungs, adrenals), mostly leading to inactivation of the drug, and increasing water solubility (→ renal excretion). Two phases:
 - Phase 1: oxidation, reduction, hydrolysis (eg via Cytochrome P450 [CYP] monooxygenase superfamily) – see below
 - Phase 2: conjugation via enzymes including: glucuronyl-, acetyl-, sulfo- and methyltransferases
- Active drug metabolites:
 - Prodrugs: require metabolism to generate active metabolites: eg many ACEIs, losartan, irinotecan, codeine (active metabolite morphine)
 - N-acetyl-procainamide (NAPA) is a major metabolite of procainamide, and accumulation → QT prolongation and torsades

Phase 1 Metabolism

- See NEJM 26 May 2005
- Phase 1/CYP Mono-oxygenase variants:
 - Mixed function oxidases in the liver, *also present in enterocytes of the intestinal epithelium*
 - P450 refers to a characteristic absorption peak at 450 nm when they bind in their reduced form to carbon monoxide
 - 13 CYP families – some involved in steroid and bile acid biosynthetic pathways, 4 families involved in xenobiotic metabolism. CYPs relevant to xenobiotic metabolism:

P450	No of subfamilies	No of forms
CYP1	1	2
CYP2	8	57
CYP3	2	10

- Causes of variation in metabolism:
 - Genetic variation in enzymes and their regulation:
 - Single nucleotide polymorphisms (SNP)
 - Insertion or deletion of one or more nucleotides – either exons (coding regions) or introns (non-coding regions)
 - Genetic variation leads to:
 - Poor metabolisers (PM): usually two loss of function alleles
 - Extensive metabolisers (EM), and
 - Ultra-rapid metabolisers (UM)
 - Inducers of CYP:
 - Lowers plasma levels over 2 – 3 weeks as gene expression of the eliminating enzyme increases
 - Toxicity can occur if inducing agent is stopped
 - Inhibitors of CYP:
 - Have rapid effect
 - Inhibition *will not affect PMs*, but will convert genotypic EMs to phenotypic PMs
 - Fluoxetine's inhibition with CYP2D6 takes weeks due to long half-life and slow generation of a CYP2D6-inhibiting metabolite
 - Inhibition can also occur competitively when two drugs metabolised by the same enzyme are given together
 - Some drugs have a non-specific effect on many enzymes:
 - Cimetidine (H₂ receptor antagonist for peptic ulcer disease) and ketoconazole are inhibitors → ↑levels of many drugs
 - Phenobarbitone and rifampicin are inducers

- Specific enzyme families:
 - CYP3A refers to both of:
 - CYP3A4: the most abundant hepatic and intestinal CYP and metabolises over half of all drugs. Activity varies by up to an order of magnitude between individuals but reasons not well understood
 - CYP3A5: closely related, shares substrates, and displays loss of function variants, especially in African populations
 - Note: cyclosporin is a substrate, azoles can augment it's affect in transplants via inhibition
 - CYP2D6:
 - Second to CYP3A in the number of common drugs it metabolises
 - UMs:
 - Have multiple functional copies
 - May need high doses of TCAs for clinical effect, may be euphoric or nauseous after codeine due to rapid production of morphine
 - SSRIs to treat tamoxifen related hot flushes → inhibition of CYP2D6 → Tamoxifen toxicity
 - CYP2C9: Loss of function variants → ↓warfarin doses, and if homozygous then ↑ bleeding risk.
 - CYP2C19: PM in 20% Asians, 3-5% Europeans. *Omeprazole* is a substrate: Ulcer cure rates with “standard doses” 29% in EM, 100% in PM. Clopidogrel is also a substrate, and is metabolised to the active drug by 2C19. Two PM alleles associated with poorer outcomes after PCI. Omeprazole and clopidogrel compete in PMs
 - CYP1A2: metabolises caffeine. TCAs. antipsychotics, theophylline, propranolol, verapamil
 - CYP2E1: metabolises ethanol. See page 360 for effects of acute and chronic alcohol on paracetamol metabolism
- For a more exhaustive list, see <http://medicine.iupui.edu/flockhart/table.htm> (a good table)

	Substrate	Inhibitor	Inducers
CYP3A4/5 No PM's identified Chromosome 7	CCB: diltiazem, felodipine, nifedipine, verapamil Antiarrhythmics: lidocaine, quinidine Carbamazepine (??) Statins: Simvastatin (?), atorvastatin (not pravastatin) Macrolides: clarithromycin, erythromycin Cyclosporin, tacrolimus NRTI and PIs Midazolam Losartan Sildenafil Warfarin (r-enantiomer – less clinical relevance) Oestrogen Methylprednisone Cisapride was withdrawn because of Torsade with concurrent inhibitors	CCB: Verapamil, Diltiazem (NB also substrates) Amiodarone Azoles: Ketoconazole & Itraconazole Macrolides: Erythromycin, clarithromycin NB also substrates (not azithromycin) Ritonavir Large quantities of grapefruit juice Fluoxetine (small effect, nil from paroxetine)	Rifampicin Anticonvulsants: Carbamazepine, Phenytoin ART: Efavirenz, nevirapine St John's Wort Chronic alcohol Dexamethasone Activate PXR (nuclear receptor) which binds to the CYP3A4 promoter
CYP2D6* PM in 7% Europeans & Africans 1% UM	Betablockers: Metoprolol, carvedilol, propranolol, timolol (→ systemic β blockade if inhibited) <i>Codeine</i> Flecainide (also renally excreted, so little impact) TCAs: Nortriptyline, amitriptyline (in part) Fluoxetine, paroxetine Simvastatin (note also 3A4)	Quinidine (even a ultra-low doses) TCAs: Clomipramine Fluoxetine, (larger effect, but ?clinical significance), trace from paroxetine, (NB also substrates) Neuroleptics: chlorpromazine & haloperidol	

	Haloperidol Venlafazine <i>Tamoxifen</i> (transformed to active metabolite)		
CYP2C9* 1 – 3% PM Little expression at birth Chromosome 10	<i>Warfarin</i> (S-enantiomer – which has the greatest anticoagulant effect – PM's require only ~ 1mg/d) Phenytoin Glipizide Losartan (transformed to active metabolite)	Amiodarone Fluconazole, miconazole Celecoxib Cimitidine and omeprazole impair R-enantiomer of warfarin → less effect	5' regulatory region has an PXR-RXR element, so CYP3A inducers also induce CYP2C9 (→ warfarin effect)

* = Clinical significant genetic variants described

Phase 2 Metabolism

- Phase 2/Transferase Variants:
 - Acetylation: N-acetyl transferase. Matures in infancy. Polymorphisms define slow and rapid acetylators (NAT1 expressed in virtually all individuals, NAT2 only in rapid acetylators, products of different genes). Caucasians 50% slow, 50% fast. Slow acetylators have higher risk of:
 - Drug lupus with procainamide and **hydralazine**
 - Hepatitis with **isoniazid** (peripheral neuropathy if rapid)
 - Aldehyde Dehydrogenase: deficient in 50% Mongoloids ⇒ unable to metabolise acetaldehyde from alcohol → disulfiram reaction (flushing)
 - TMPT – metabolises azathioprine – see page 241
- P-glycoprotein:
 - Most widely studied membrane drug-transport protein – an efflux pump
 - Product of the MDR1 gene
 - Expressed:
 - On apical aspect of the enterocyte (pumps back into the gut lumen)
 - On the canalicular aspect of the hepatocyte
 - In the kidney: is responsible for active excretion of some drugs in the kidney. *Major mediator of digoxin clearance* (excreted unchanged)
 - On the blood-brain barrier. Limited drug penetration of the blood-brain-barrier often due to a robust P-glycoprotein efflux process (?reason for poor CNS penetration of HIV protease inhibitors)
 - Also present in tumour cells
 - Can be affected by drug interactions or genetically determined variability in gene transcription
 - Quinidine, amiodarone, verapamil, cyclosporin, erythromycin and ketoconazole* inhibit MDR-1, affecting digoxin, cyclosporin, flouroquinolones, HIV protease inhibitors, lignocaine and ranitidine and many CYP3A substrates

Effects of disease

- For changes in the elderly, see page 468
- Renal disease:
 - Renal excretion by glomerular filtration and specific drug transporters
 - Examples:
 - Sotalol is renally excreted. ↓↓ dose in dialysis
 - Protein binding affected by uraemia eg phenytoin – measure free drugs
- Liver disease:
 - Effect on drug clearance much less predictable than with renal disease
 - Decreased drug metabolism due to ↓enzyme activity, ↓hepatic blood flow and intra/extra hepatic shunting
 - LFT's not useful in adjusting doses. Best measures are INR and albumin (synthetic function)
 - Oral availability of high-first pass drugs (eg morphine, midazolam, nifedipine, verapamil) much higher in cirrhosis
 - In general hepatic clearance in children is twice adult levels
- Heart failure/shock (changes don't all go the same way):
 - ↓hepatic drug flow (affects "high clearance" drugs)

- ↓renal blood flow (affects high fu drugs)
- ↓mesenteric blood flow → ↓absorption
- ↓tissue perfusion → drugs distributed into a smaller volume → ↑plasma concentration and tissues that are better perfused (heart and brain) will get ↑ concentrations
- Pregnancy: see page 460
 - Pharmacokinetic changes:
 - ↑Clearance: ↑cardiac output → ↑hepatic and renal blood flow, hormones → enzyme induction
 - ↑Vd by approx 20%
 - ↓Protein binding → lower measured drug levels but free levels are often unchanged
 - Pharmacodynamic changes:
 - All drugs cross the placenta to some effect
 - All drugs diffuse into breast milk to some extent
 - Categories:
 - A: no known risk
 - B: no known risk in animal studies but no human studies
 - C: risk in animal studies but not human studies
 - D: some risk
 - X: high risk, contraindicated

Pharmacodynamics

- Drugs usually interact with a protein receptor → linked to GTP binding proteins → intracytoplasmic 2nd messenger pathway → physiological effect
- Agonist:
 - Enhance the target receptor's usual action
 - Full or partial (unable to elicit the maximum response despite the maximum dose, usually have some antagonist effect)
- Antagonist:
 - Bind but do not activate the 2nd messenger pathway
 - Competitive: binds reversibly to the receptor, maximum effect still achievable with higher dose of the agonist
 - Non-competitive: binds irreversibly to the receptor, maximum effect is not achievable with an agonist
- Efficacy: height of the Cp/response curve regardless of dose. Defined by E_{max}
- Potency: gradient and lateral position of the dose/response curve. Defined by dose and E_{max} (maximum effect regardless of dose) and ED₅₀ (concentration required to give a half maximal effect – a measure of affinity of the drug for the receptor)
- Therapeutic range: Cp in which there is most therapeutic benefit without adverse effect
- Therapeutic index = LD₅₀ (Lethal dose) / ED₅₀ (is > 1)
- Narrow therapeutic index: dose response curves for desired and adverse effects are close, and the adverse effect curve is steep (small dose increments → sharply ↑ risk of toxicity)
- Drug effect may not be constant over time – external milieu may modulate effect, eg
 - Ion channel blockade (antiarrhythmics and anticonvulsants) affected by membrane potential, which varies with extracellular K⁺ or ischaemia
 - β-blockade may up-regulate β-receptors which may → severe agonist mediated effects on abrupt withdrawal

Adverse Drug Reactions

- If > 15 drugs given, likelihood of an adverse reaction in a hospitalized patient is > 40%
- Classification:
 - Medication incidents = problems associated with medications. Most do not cause harm to patients
 - Adverse Drug Events: (a type of medication incident) Harm to patients occurs. Includes prescribing error, non compliance
 - Adverse Drug Reactions:
 - A type of Adverse Drug Event – specifically related to the actions of the drugs
 - Type A: Exaggerated, **dose-dependent** pharmacological effect
 - Type B: **Idiosyncratic**, non dose-dependent, unpredictable, mostly immunological (eg rash).
Eg
 - Hepatotoxicity: halothane, valproic acid, augmentin, flucloxacillin
 - Aplastic anaemia: chloramphenicol, clozapine, sulphonamides, phenytoin, carbamazepine

- Erythema multiforme/Stevens-Johnson Syndrome: Phenytoin, carbamazepine, sulphonamides, NSAIDs, penicillin, amoxicillin, ampicillin
- Type C: associated with prolonged drug treatment, eg dependence or cumulative toxicity (eg analgesic nephropathy)
- Type D: delayed effects, eg carcinogenicity and teratogenicity
- Immunologic mechanisms of adverse reactions:
 - Most drugs are small molecules and therefore poor immunogens
 - Generation of an immune response usually requires covalent linkage to a protein, CHO or nucleic acid
 - Hypersensitivity types:
 - 1: Immediate, binds a specific IgE on mast cells and basophils → cell activation → anaphylaxis
 - 2: Cytotoxic/antibody mediated: IgM, IgG + drug-protein conjugate on a cell surface (eg rbc, platelets) → complement activation, Eg quinine, heparin-induced thrombocytopenia (see page 447) is caused by antibodies to platelet factor 4 and heparin
 - 3: Immune complex hypersensitivity: protein complexes + Igs → insoluble matrices which deposit in endothelium → complement activation → “serum sickness”. Rare. Presents 1 – 3 weeks after penicillin/sulphonamide treatment or foreign proteins (vaccines, streptokinase, therapeutic antibodies)
 - 4: delayed/cell mediated hypersensitivity: drug-protein complex + target cell → recognized by T-lymphocyte → direct cytotoxic/macrophage activation eg contact dermatitis due to chlorpromazine
- Therapeutic drug monitoring:
 - Generally drug concentration is not a good indicator of effect, eg:
 - ‘Hit and run’ drugs, eg Aspirin and MAOIs – does its work then the effect persists
 - Delayed distribution (eg digoxin)
 - Acute tolerance (eg P)
 - Active metabolites...
 - Characteristics of a suitable drug for therapeutic drug monitoring
 - Marked pharmacokinetic variability
 - Cp closely correlated with effects
 - Narrow therapeutic index
 - Defined therapeutic (target) concentration range
 - Take sample when Cp stable: after reaching steady state, when Cp least variable (ie trough) and after complete distribution. In reality efficacy and toxicity depend on many factors – may need to measure both trough and peak levels
- Risk factors for drug interactions:
 - Low Vd
 - Narrow therapeutic index
 - Capacity-limited hepatic clearance
 - Extensive metabolisers
 - High protein binding
 - Acidic drug
 - Active renal tubular excretion
 - IV administration

Random Drugs

- Random other interactions:
 - Amitriptyline → ↑ urinary retention
 - Imipramine acts in psych illness via noradrenaline
 - Doxycycline causes oesophageal ulceration
 - Lamotrigine and sodium valproate have a significant interaction – must adjust valproate dose
 - All antiepileptics are teratogenic, valproate > phenytoin
 - Cholestyramine → absorbs fat soluble vitamin K → ↑bleeding on warfarin
 - Indomethacin, and probably other NSAIDs (not aspirin), antagonize the antiHTN effects of β-blockers, diuretics and ACEI → ↑BP from trivial to severe
 - Diuretics → greater risk of ↓K → ↑risk of torsade from sotalol
 - Sildenafil inhibits phosphodiesterase 5 (which inactivates cyclic GMP). GTN → ↑GMP. So coadministration → profound hypotension

- Lower seizure threshold: antidepressants, antipsychotics, oral hypoglycaemics

Surviving Sepsis Guidelines

- See Crit Care Med 2004 32:3;858
- Shock → hypoperfusion → ↑lactate
- Principles (NEJM 28 Feb 2008):
 - Start early. Protocol driven fluids, inotropes and transfusion initiated in the ED → substantial reduction in in-hospital mortality
 - Antibiotics within 1 hour of hypotension → survival of 80% vs 42% for antibiotics after 6 hours hypotension (yet 49% not treated at 6 hours)
- Correct hypoperfusion by resuscitation aiming for:
 - CVP 8 – 12 mmHg (12 – 15 if mechanically ventilated due to ↑intrathoracic pressure)
 - MAP > 65
 - Urine output \geq 0.5 ml/kg/hr
 - Central venous oxygenation \geq 70%
- Take cultures from everywhere before Abs – 2 or more blood cultures
- Start Abs
- Source control, eg drain abscesses
- Fluids: no difference between crystalloids and colloids, except need more crystalloid given ↑Vd and more oedema. (Cochrane review 2007). This holds for albumin, hydroxyethyl starch, modified gelatine and dextran
- Vasopressors:
 - If fluid challenge doesn't ↑BP then vasopressors
 - Below a certain BP, autoregulation is lost and perfusion is linearly dependent on BP
 - Monitor lactate as well as BP
 - 1st: noradrenaline – vasoconstrictor → ↑MAP, and no change in HR and less ↑ in SV than dopamine
 - 2nd: dopamine: ↑HR and ↑SV → ↑MAP. Low dose for renal protection ineffective
 - Need ART line – cuff measurements ineffective at low BP
 - Vasopressin only in refractory ↓BP (may → ↓cardiac output). No better than noradrenaline in RCTs
- Inotropic therapy:
 - If low cardiac output despite adequate filling pressures then dobutamine
 - If measuring BP and CO use noradrenaline and dobutamine to target each
 - If only measuring BP use noradrenaline only (CO may be low, normal or high)
 - Don't use dobutamine to ↑O₂ over normal
- Steroids:
 - If requiring vasopressors for BP despite fluids then hydrocortisone (50 mg QID) + fludrocortisone (50 µg od) for 7 days. Only proven to ↓ mortality if adrenal insufficiency, no adverse events – do short Synacthen test and discontinue steroids if no relative adrenal insufficiency
 - Dexamethasone doesn't interfere with the cortisol assay (hydrocortisone dose)
 - Not in the absence of shock unless other indications.
- Recombinant human activated Protein C (rhAPC): if at high risk of death (APACHE II > 25). Stops pro-coagulant effect of early sepsis and is anti-inflammatory. Infusion for 96 hours. Mortality 25% vs 31% placebo. More bleeding in APC (3.5% vs 2.0%). Trial in APACHE II < 25 showed no difference
- Only transfuse if Hb < 70 unless other reasons
- Ventilation:
 - Aim for lower tidal volumes in ARDS (ie 6 ml/kg body weight) with end inspiratory pressures < 30 cm H₂O. ↑CO₂ ok to minimise pressures in ARDS (except if ↑intracranial pressure)
 - Ventilate semi-recumbent to ↓ pneumonia
 - Avoid neuromuscular blockade → prolonged weakness
- Insulin + glucose infusion aiming to keep hourly blood glucose < 8
- Haemofiltration preferred to haemodialysis given easier fluid management
- DVT prophylaxis
- Stress ulcer prophylaxis: H₂ blockers the only one studied
- Insulin treatment: Intensive treatment (aiming for glucose 4.4 – 6.1) decreases morbidity but not mortality over conventional treatment (infusion if > 12) if ICU stay longer than 3 days. More

hypoglycaemia and non-significant increase in mortality for those under 3 days. Recommendation – aim for glucose of 8.33 for first 3 days

Critical Illness Neuropathy

- Generalised weakness in the setting of sepsis, multiorgan failure, high dose steroid or neuromuscular blockers
- PC: failure to wean, proximal wasting
- Prognosis related to underlying disease
- Management: general, nutritional, respiratory support
- Variations of myopathy, neuropathy and mixed

Glucose Management

- Glucose control lowers the risk of deep sternal wound infection after cardiac surgery (Portland 1 Trial) – exponential increase with ↑glucose
- Intensive insulin therapy in critically ill patients:
 - Van den Berghe, NEJM 2001;345:1359
 - Intensive glucose control 8% vs 4.6% mortality (RRR 40%) – post cardiac surgery patients
- ADA targets:
 - ICU: 4.4 – 6.1 mmol/L
 - Other units: 6.1 – 10.0

Peri-operative

- Preoperative screening – risk factor assessment of:
 - Cardiac risk:
 - Combination of risk of the surgical procedure (vascular, intraabdominal or intrathoracic are high) and risk of heart disease (IHD, CHF, CVA, DM or CRF)
 - Can mitigate risk by preoperative medical management or prophylactic revascularisation (no perioperative mortality benefit unless L main stem or three vessel disease)
 - High rate of complications among patients who require cardiac surgery after PCI – ?associated with risks of discontinuing antiplatelet therapy (high risk of bleeding from dual aspirin and clopidogrel). Recent studies suggest a window of risk up to a year – delay elective surgery if possible
 - Perioperative cardiac testing (dobutamine stress echo) in intermediate risk patients on β blockers with tight heart rate control does affect outcomes and delays surgery
 - Pulmonary assessment: Risk is increased with intrathoracic, intraabdominal or prolonged surgery. If at high risk, should receive deep breathing exercises and/or incentive spirometry, and selective use of NG tube for postoperative nausea or abdominal distension. Routine spirometry and CXR don't help predict risk of pulmonary complications – but may be appropriate in COPD/Asthma
 - Prophylaxis for endocarditis if congenital or valvular heart disease (AHA guidelines)
 - Prophylaxis for DVT: heparins +/- graduated compression stockings or pneumatic compression devices
 - Major risk factors for post-op delirium are preoperative cognitive impairment and psychotropic drug use. See page 470
- Perioperative medication:
 - Perioperative medications: ACEIs should be stopped
 - Evidence for peri-operative statins is suggestive but incomplete
 - Perioperative prophylactic metoprolol:
 - Controversial
 - Is not indicated for heart rate control to prevent cardiac complications after vascular surgery, nor in diabetics undergoing non-cardiac surgery – no difference in cardiac complications and more intra-operative bradycardia and hypotension
 - Other evidence suggests titrating β blockers to achieve heart rates of 55 – 70 is cardioprotective
 - POISE study (Lancet 31 May 2008): prophylactic metoprolol reduced MI but increased total mortality and stroke. May be that beta-blocker naïve patients were given too high a dose, or should have been titrated up pre-surgery
 - But if on β blockers, should continue them
- Perioperative diabetes management:
 - Withhold oral agents on day of surgery, metformin ideally withhold for 48 hours
 - Optimising control → ↓infection, wound infection and metabolic complications

- Aim for BGL 4 – 8
- Patients on insulin should receive IV dextrose
- If fasting, give half the normal dose of insulin
- Evidence supports intraoperative tight glucose control via insulin infusion, over moderate glycaemic control
- Pre-operative fasting: no evidence that a shortened fluid fast results in increased risk of aspiration, regurgitation or related morbidity compared with “NBM from midnight” (Cochrane review 2003) [In fact, patients given a drink of water pre-operatively had lower gastric contents than those with standard fasting regimes]
- Respiratory complications:
 - Reduction in lung volumes with surgery is the main mechanism for post-op complications
 - Evidence for avoiding postoperative pulmonary complications is strongest for lung expansion manoeuvres (spirometry, deep breathing exercises, and CPAP). Evidence that laproscopic and epidural approaches reduce complications is inconclusive. While low albumin is a risk factor, there is no evidence that correcting this improves outcomes
 - Two weeks of preoperative inspiratory muscle training reduced post-operative pulmonary complications in patients undergoing CABG

Preoperative Screening of the Elderly

- Domains to assess:
 - Cognitive status: risk of delirium
 - Cardiovascular risk
 - Nutritional status: associated with poor outcomes, but no RCT evidence that improved nutrition prior to surgery improves risk
 - Musculo-skeletal status: Fixing their hip won't help mobility if the rest of their legs don't work!
 - Surgery specific risk
- Cardiac risk index with multifactorial predictors: first developed by Goldman. Modified in 1986 by Detsky. Weighting given to:
 - Age > 70 is bad
 - MI in the last 6 months worse than old MI
 - Current angina
 - Pulmonary oedema in the last week worse than historic pulmonary oedema
 - Arrhythmia: Other than SR or regular premature ventricular beats
- Clinical predictors of increased perioperative risk (British Journal of Anaesthesia, 2000: 85: 763-78):
 - Major predictors: unstable coronary syndromes, decompensated CHF, significant arrhythmias, severe valvular disease
 - Intermediate predictors: mild angina, previous MI > 30 days old, compensated or previous CHF, DM
 - Minor predictors: advanced age, abnormal ECG, rhythm other than sinus, low functional capacity, history of stroke, uncontrolled HTN
- American College of Cardiology/American Heart Association Guidelines:
 - Patients with minor clinical predictors of cardiac risk do not require further testing (eg non-invasive stress testing with subsequent treatment for risk factor modification – most can't do ETT so this means stress imaging or echo) unless their functional status is poor and a high-risk surgery is planned
 - Poor functional capacity (ie exercise tolerance in daily life) is one of the most important predictors of cardiac complications in non-cardiac surgery
- GA and epidural anaesthetic do not differ in terms of cardiac risk (some studies say yes, others no)
- Peri-operative β -blockers controversial. If they're on them continue, but no current compelling evidence to give them otherwise

- See also Cancer Genetics, page 376

General concepts

- Diploid = 46 chromosomes
- Haploid = 23 chromosomes (germ cells)
- Telomere: tips of chromosomes, gene rich, protect and stabilize chromosome
- DNA structure and copying:
 - Exons (*expressing regions*): coding regions, for 4 bases: adenine (A), cytosine (C), guanine (G) and thymidine (T). Genes are coded from the 5' to the 3' end. 2% of our genome encodes protein. Introns (*intervening regions*) may be involved in regulation. Transcription copies introns and exons (we don't know what terminates transcription)
 - DNA polymerase replicates DNA in the S phase of the cell cycle
 - DNA is *transcribed* to RNA (contains a uracil (U) instead of T) by RNA polymerase
 - Non-coding RNA: non-coding RNA represents 97% of RNA. Previously thought of as "junk" – now ncRNA recognized as a key regulator. The difference between a worm and a human is not the number of genes, but the amount of non-coding DNA, most of which is transcribed
 - RNA is *translated* to protein by ribosomes. Translation starts at a start codon (ATG) and ends at a STOP codon
 - Reverse transcriptase generates DNA from mRNA
- RNA Interference:
 - Small Interfering RNA (siRNA) (also called micro-RNA): dsRNA that modifies gene expression by increasing the RNA degradation rate (post transcriptional gene silencing)
 - Micro-RNA: a related class of ssRNA involved in gene expression via a post-transcriptional mechanism
- Single Gene Mutations:
 - Length mutations (frame-shifts, insertions, deletions) and nonsense point mutations (chain terminators – makes a stop codon which disrupt the production of protein): the biological activity of the protein is reduced in proportion to the reduction in the amount of protein
 - Missense mutations (amino acid substitution): a relatively normal amount of protein is produced
 - Silent mutations: the genetic code is redundant – there is more than one codon for most amino acids so a change in one base may result in no change in the amino acid sequence
 - Promoter mutations: mutations in the promoter region may lead to \uparrow or \downarrow transcription of a gene
 - Loss of function mutations can be AR or AD
- Different effects of dominant gene mutations:
 - Haploinsufficiency (eg tumour suppressor): abolish production from one copy \rightarrow \downarrow production of normal protein. Occurs when 50 percent decrease in the amount of functional protein is insufficient for normal function. Usually mild
 - Production of abnormal protein: eg Missense protein \rightarrow may be worse
 - Gain of function: protein product with increased activity or toxic effect
 - Usually less severe than recessive disorders (eg AD and AR Polycystic kidney disease) as disorder can't be so severe that it impairs ability to grow and reproduce
- Variation in the human genome:
 - Allele: one of several alternative forms of a gene or DNA sequence at a given locus
 - Hardy Weinberg equation: $p^2 + 2pq + q^2 = 1$ where $p + q = 1$
 - When the frequency of two or more alleles at a gene locus is greater than 1% in the population, the locus is polymorphic
 - Single Nucleotide polymorphisms: single nucleotide variations between unrelated individuals. Some SNP-phenotype variations occur as a direct result of the SNP. Some occur because of the SNP's proximity to the real genetic cause (linkage disequilibrium)
 - Copy Number Variations (CNVs): there is extensive variation of the genomic copy number between different individuals. Won't pick this up by sequencing a gene – that will just tell you if it's there or not. Awaiting new technology for this
- Chromosomal abnormalities:
 - Numerical abnormalities of whole chromosomes (aneuploidy):
 - Either trisomy or monosomy. Account for > half of all miscarriages
 - Only a minority of genes are dosage-critical eg genes involved in quantitative signalling, genes whose products compete with each other to determine a developmental switch
 - Sex chromosome aneuploidy:
 - 47 XXY (Klinefelter syndrome: tall stature, infertility, low testosterone, testicular atrophy, mild learning difficulties, germ cell tumours, MV prolapse) or 47 XYY
 - 45 XO (Turner's Syndrome): Short stature, ovarian dysgenesis, infertility, heart and renal defects, normal intellect. See page 85

- Tend to have less severe phenotype because most genes on X are subject to X inactivation – lyonisation happens at around 32 cell stage
- Numerical abnormalities of part of a chromosome: Deletions or duplication. Microdeletions – too small to be detected by standard cytogenetics, usually detected by FISH (Fluorescence in Situ Hybridisation) eg Di George 22q11 deletion
- Balanced structural rearrangements: does not usually result in problems unless a critical gene is interrupted:
 - Inversions
 - Translocations: 3 types
 - Reciprocal/Balanced don't usually cause phenotypic abnormalities, unless a breakpoint disrupts a gene or material is shifted from an X chromosome to an autosome or visa versa
 - Robertsonian/Unbalanced rearrangements result in partial trisomy or monosomy → congenital abnormalities. Involve 2 acrocentric chromosomes 13, 14, 15, 21, 22 (swap short and long ends). Everything that was there is still there, but problems arise at reproduction
 - Insertional (non-reciprocal): acquire a segment from a “donor” chromosome. Resulting zygotes may be normal, balanced, partially trisomic, or partially monosomic
- Causes of Heterogeneity:
 - Variable expressivity: the same gene may present with different severities in a family (this is different from penetrance, which concerns age of onset) – most common in dominant disorders
 - Incomplete penetrance: an individual carrying a mutation who does not express the phenotype (a feature of AD disorders)
 - Different mutations in the same gene may explain variability in expression between families
 - Pleiotropy: a mutation in one gene can result in seemingly unrelated effects for example, in unrelated tissues
 - Locus heterogeneity: mutations in different genes can lead to a similar phenotype (eg Long QT; loss of function in a hormone and it's receptor have a similar effect)
- Mosaicism:
 - Somatic mosaicism: one person carries more than one genetic cell line
 - Germ-line mosaicism: some of the germ cells, but few or no other cells, carry a mutation
- Imprinting:
 - For certain autosomal genes only the gene from one parent is transcriptionally active. So the same genetic material transmitted from a mother or father can result in a different phenotype
 - Approximately 100 – 200 imprinted genes are thought to exist – ensure development only proceeds when a full complement of the paternal and maternal genome is present
 - Only occurs in mammals
 - Net result of the defect is expression of 0 or 2 alleles rather than the usual 1
 - Maternal imprinting ⇒ *maternal*-derived allele is inactive and the *paternal* allele is expressed
 - Disease will result only if the mutated gene is expressed
 - Imprinting is reset for each generation at gametogenesis: it is consistent with the sex of the parent not the grandparent
 - Mechanisms:
 - One homologue could have a deletion or mutation
 - Uniparental disomy = inheritance of a pair of homologous chromosomes from 1 parent (and none of that chromosome from the other parent). Will result in disease if the chromosome involved has imprinted regions
 - Uniparental heterodisomy: inherit two different chromosomes from one parent
 - Uniparental isodisomy: inherit two of the same chromosomes from one parent
 - Prada Willi:
 - Failure to thrive, mental retardation, hyperphagia and obesity
 - 75% are deletion 15q11-q13 on the *paternal* chromosome, 25% are maternal UPD
 - Angelman Syndrome:
 - Ataxia, seizures, severe retardation, aphasia, inappropriate laughter
 - 75% are deletion 15q11-q13 on the *maternal* chromosome, 2% paternal UPD, 23% sporadic
- Mitochondrial inheritance:
 - Each mitochondrion contains several copies of a circular double stranded DNA
 - Mutations often affect neural and muscular tissues, optic neuropathy, deafness
 - Show matrilineal inheritance (transmission only by females) and heteroplasmy (single cells with some mutant and some normal mDNA)

- Mitochondria only has 13 genes. Most mitochondrial protein is drawn from cell DNA \Rightarrow lots of mitochondrial disorders are due to AR or AD inheritance – the minority are due to mitochondrial mutations

Testing

- Genetic tests are highly specific and varying sensitivity
- Positional cloning: identifying genes by location first then discovering the gene's function
- Southern Blot:
 - Main role: detecting large scale DNA changes: large deletions, duplications, expansions or rearrangements
 - DNA is digested with a restriction enzyme and separated by gel electrophoresis (larger fragments move slower). The DNA is denatured into single strands by NaOH
 - The DNA is transferred to a sheet of blotting paper. The fragments retain the same pattern of separation
 - The blot is incubated with copies of single stranded DNA that forms base pairs with complementary DNA sequences
 - The location of the probe is revealed by incubating it with a substrate that then becomes coloured or gives of light detected by xray film
 - Northern blot for RNA fragments, Western Blot for proteins
 - Gels now
- PCR:
 - dsDNA is heated to 94 – 96oC to separate the strands by breaking the H bonds that connect the two DNA strands (called denaturing)
 - Temperature is lowered so that primers can attach themselves to the single DNA strands (called annealing)
 - DNA polymerase copies the DNA strands, starting at the annealed primer (called elongation)
 - Sensitive, specific and reasonably robust technique. However, contamination a problem, need to know the sequence to make a primer, and primers can't be longer than several hundred nucleotides
- Reverse transcriptase PCR: messenger RNA \rightarrow complementary DNA using a DNA polymerase, which is then a template for PCR
- Fluorescence in situ hybridization (FISH): cell cultures are prepared from cultures of peripheral blood lymphocytes. Metaphase chromosomes are fixed on a slide, denatured and a labelled DNA probe added
- Indirect tests: Linkage Analysis
 - Principle: use inherited DNA sequence variation (polymorphisms) to track a mutation within a family
 - Two types:
 - Restriction fragment length polymorphisms (RFLPs) aka SNPs
 - Variable tandem repeat DNA length polymorphisms (VNTRs) – micro (1 – 6) and mini-satellites (9-25 repeats)
 - Used clinically if gene has been mapped but not cloned
 - Mutation tracking requires that the marker DNA used as a probe lies close to the faulty gene (ie is "linked")
 - Linkage disequilibrium: 2 alleles occur more commonly together than their gene frequencies (and their recombination fractions) would predict
 - Recombination fraction: determined by the distance between to genetic loci (usually an allele and a marker for that allele). Fraction is the likelihood that recombination has occurred between an allele and it's marker, disrupting the association. On average there are 52 cross overs per meiosis

Interpreting Family Trees

- Mitochondrial disease (transmitted only by females):
 - All the children of an affected female will be affected
 - An unaffected male cannot have an affected child
 - Variable expressivity is common
 - Eg Lebers Hereditary Optic Neuropathy
- X-Linked: An unaffected male cannot have an affected child (ie males can't be carriers)
 - Eg Haemophilia A, G6PD deficiency, Testicular feminization, Fragile X, colour blindness, Duchenne and Becker muscular dystrophy
 - X-linked dominant: all the female children of an affected father will be affected
- Autosomal recessive:

- If the carrier state is rare in the population then affected people are very unlikely to have affected children unless there is consanguinity or a founder effect (AR disorders more common in inbred populations)
- Eg Deafness, albinism, Wilson's, Sickle cell, Cystic fibrosis, Friedreich ataxia, Haemochromatosis, α 1AT deficiency
- Autosomal dominant with incomplete penetrance: If it looks like an autosomal recessive disease but the carrier state is rare in the population then it is much more likely to be autosomal dominant with incomplete penetrance
- Polygenic and autosomal recessive with incomplete penetrance: Too complicated and would require a massive family tree to work out. Conditions do cluster in families but do not follow predictable inheritance patterns

Triplet Repeat Disorders

- Trinucleotide repeats:
 - Repetition of three nucleotides
 - Normal part of the genome (used for DNA identification)
 - Disease causing beyond a certain threshold
 - Pre-mutation: repeat size which is unstable (ie increases at meiosis +/- mitosis) but does not result in a phenotype
 - Anticipation: severity of the disease increases as it is passed on through generations – usually triplicate repeat mutations (eg Huntington's [mutation is more unstable inherited from a father than a mother] and myotonic dystrophy)
 - Only expansion repeat that affects a protein is Huntington's
- Huntington Disease: see page 153
- Fredrick's Ataxia: see page 168
- Fragile X Syndrome:
 - Triplet repeat disorder
 - Old view was that the full mutation → mental retardation and those with the pre-mutation were healthy
 - But pre-mutation carriers (1/250 females, 1/400 males):
 - Females: 20% have premature (< 40) menopause
 - Males: ½ will develop a movement disorder in later life with tremour and ataxia – mental retardation in a grandson may be the only clue
 - But think before testing: all daughters of a pre-mutation bearing male will be obligate carriers, with their sons at risk of fragile X. Full informed consent important – it's not just about the patient in isolation
- Other triplet repeat diseases: spinobulbar muscular atrophy, myotonic dystrophy

Other Genetic Disorders

- Marfan Syndrome: See page 275
 - AD, 1 in 5,000, connective tissue disorder with variable clinical manifestations
 - Clinically diagnosed using the Ghent criteria
 - Due to FBN1 gene mutations on 15q21.1
 - Over 500 mutations reported, still no true genotype-phenotype correlations
 - ⇒ Testing a nightmare (negative test doesn't exclude the disease), clinical assessment better
- Long QT Syndrome: See page 10
 - AD, at least 7 genes implicated
 - High morbidity, treatable ⇒ compelling case for genetic testing?
 - But some genes unknown so negative test doesn't exclude the diagnosis
 - A positive test allows pre-emptive treatment and cascade screening
- Haemochromatosis: See page 366
 - Disparity between the rarity of the severe clinical phenotype and a common causative mutation
 - AR
 - Test is therefore a "susceptibility test" not a "diagnostic test"
- Cystic Fibrosis: See page 200
 - AR
 - "Milder" mutations can cause other conditions: isolated bronchiectasis, male infertility, idiopathic pancreatitis
 - Milder mutations are often non-coding and not examined for, therefore not found

- See:
 - Neuroimaging, page 139
 - Chest Radiology, page 183
 - Rheumatology Radiology, page 237

CT

- Hounsfield Units:
 - Relative measure of density: water = 0, air and fat are negative, everything else positive
 - When doing a CT you set:
 - Level: which Hounsfield unit do you want as mid grey, eg Liver = 40, lung = 750
 - Window: how wide do you want the range from white to black to do, eg do you want white to black to cover mid-grey +/- 50 or 500 Hounsfield units. When looking at contrast, have a narrow window
- Talk in terms of density: iso-dense, hypo-dense, hyper-dense
- Radiation exposure (see NEJM 29 Nov 2007):
 - Risks for each person small, but with increasing CT use, it is becoming a population issue
 - Dose for an adult abdo CT is 1,000 times a PA chest XR
 - Energy absorbed per unit of mass is measured in greys (Gy). One gray = 1 joule absorbed per Kg
 - Most estimates of radiation-induced cancer risk are derived from analysis of atomic bomb survivors
 - Reasonable evidence in adults and very convincing evidence in children that CT scans increase cancer risk. Risk decreases steadily from neonates through to mid 20s

Contrast

- Two types:
 - Ionic – cheap, more side effects and reactions
 - Non-ionic
- Timing: which phase do you want to capture
 - CTPA – time image capture so that contrast is maximally in the R side of the heart
 - CT aortogram – want contrast maximally in the aorta
- Severe allergic reactions in 0.04% due to direct mast cell degranulation (not IgE mediated)
- Contrast Nephropathy:
 - Acute rise in Cr of 85, *onset 1 – 2 days, peak 3 – 5 days, resolution in ~ 1 – 2 weeks* (unless poor kidney's to start with)
 - Risk factors: volume and type: hypo-osmolar > iso-osmolar
 - If at risk, non-ionic contrasts have been reported better, but difference dubious
 - Insufficient evidence for frusemide, mannitol, or dopamine prophylaxis
 - Unblinded RCT of 253 patients demonstrated strong benefit for NAC (1200 mg iv bolus before, 1200 mg oral bd for 2/7 following) with pre-hydration (1 mg/kg/hr for 12 hours)
 - Volume expansion with HCO₃ containing fluids superior to saline in one RCT (bolus of 3 ml/kg 1 hour before contrast, and 1 ml/kg/hr for 6 hours after) JAMA 2004;291:2328. One other study in favour if HCO₃, two other studies show no difference between saline and HCO₃
 - Management: supportive, pre- and post haemofiltration may help if already CRF (modest benefit in one RCT, not accepted into clinical practice)

MRI

- Earth's magnetic field is 0.05 Tesler. MRI magnet is usually 1.5 Tesler
- Talk in terms of signal intensity: iso-intense, hypo-intense, hyper-intense
- Hydrogen ions in a static magnetic field. Radiofrequency waves introduce energy
 - T1 weighted:
 - Return to equilibrium state of the protons (relaxation in the vertical plane) releases energy (the echo) which is detected
 - Fat and subacute haemorrhage have short T1 relaxation rates and therefore a high signal intensity on T1 images
 - T2 weighted: Initially electrons spin together in the perpendicular plane. With time they get out of synch. Measures loss of coherence in the induced current in the coil

- Different relaxation rates are measured by T1 (shorter – time for 63% to return to normal) and T2 (longer)
- Water laden structures – CSF and oedema have long T1 and T2 relaxation rates, so have low signal intensity on T1 and high on T2
- T2W better for oedema, demyelination, infarction and chronic haemorrhage
- Each plane obtained requires a separate sequence lasting 1 – 10 mins
- 5% experience severe claustrophobia in the MRI
- Types of sequences:
 - FLAIR: Fluid attenuated inversion recovery – T2W images with CSF suppressed (good for lesions around CSF)
 - Angiography: Fast flowing blood returns no signal (flow void) on T1 and T2. Using gradient echo sequences can pick out the fast flowing blood only
 - Diffusion Tract Imaging: detects preferential microscopic motion of water along white matter tracts – good for diseases affecting the integrity of white matter architecture
- MR Contrast:
 - Gadolinium: a heavy metal. Reduces relaxation times of adjacent protons → high signal on T1W and low on T2W. Safe renal excretion. Doesn't cross the BBB
 - Side effect in patients with renal failure of Nephrogenic Fibrosing Dermatopathy – thickening, induration and hardening of the skin

PET

- = Positron Emission Tomography
- Detects positrons from decay of injected radionuclide – a radiotracer attached to a metabolically active substance – usually 18-fluorodeoxyglucose (FDG), an analogue of glucose – but can use whatever is taken up by the tissue in question, or attaches to receptors (eg 6-18flurodopamine for a phaeo)
- Reveals areas of high glucose uptake (brain, liver and cancer)
- The radio-nucleotide has a short half life (2 hours for FDG) so the supply chain is often problematic
- False negatives in uncontrolled diabetes, false positives in granulomatous disease
- Increasingly concurrent CT is used to give anatomic definition as well as metabolic mapping
- Used mainly for the detection of extracranial metastatic disease – especially useful for lymphoma and lung cancer, also brain (eg Alzheimer's), heart scans for hibernating myocardium, etc

Levels of Evidence

- 1a – Systematic Review with homogeneity of RCTs
- 1b – RCT with narrow confidence interval, good follow-up, etc
- 2a – Systematic review of Cohort studies with homogeneity
- 2b – Individual cohort studies, retrospective studies, RCT with poor randomisation, etc
- 3 – Case control studies
- 4 – Case series or poor quality cohort or case-control studies
- 5 – Expert Opinion

Glossary

- A statistic is an estimate of an unknown quantity
- Standard deviation = Square Root (Variance). Variance = average of the sums of the squares of deviation from the mean
- Study Design for causation studies:
 - Experimental – RCT
 - Non-experimental, ie observational – no randomisation, can be descriptive (eg case series) or analytical (eg case-control studies).
- T test:
 - Unpaired t-test used to compare 2 independent groups or samples (eg birth weights of male and female children)
 - Paired t-test used to compare two dependent samples (ie same sample group – eg before and after measurements of blood pressure)
- Bias: systematic deviation of study results from true results due to the study design.
 - Selection bias: a bias in study design rather than chance when study and control groups differ in ways that may affect the outcome
 - Interviewer bias: systematic error due to interviewer's gathering of selective data.
 - Observation/Measurement bias: unreliable or invalid measurement (eg asking weights rather than measuring them)
 - Recall bias (a type of observation or measurement bias): systematic error due to differences in accuracy or completeness of recall. Referral filter bias – process of referral from primary to secondary \uparrow proportion of severe cases \rightarrow \uparrow unfavourable outcomes.
 - Lead time bias: if patients not enrolled at similar point in their illness, differences in outcome may only reflect differences in duration in illness. Eg Survival time is the time from diagnosis to death – which is longer in screened patients
 - Length Time Bias: Diseases with long lead time (pre-diagnosis) are more likely to be detected by screening. Longer survival then gives the impression that screening was beneficial
 - Publication Bias: results from studies with positive results are more likely to be published
- Study Analysis:
 - Confounding: a third variable is associated with both the exposure and the disease outcome. Unless it is possible to adjust for the confounding variables (eg stratification, multivariate analysis), their effects cannot be distinguished from those of the factors being studied
 - Intention to Treat Analysis: groups subjects according to the treatment they were randomised to, regardless of what actually happened, as opposed to per-protocol analysis (analyses according to what they actually got)
 - Efficacy: benefit of an intervention under ideal conditions (ie greater internal validity, less generalisability)
 - Effectiveness: benefit of intervention, including efficacy and acceptance (e.g. compliance, side effects – does it do more harm than good)
 - Precision: lack of random error. The range in which the best estimates of a true value approximate the true value
 - Statistical power: statistical chance of a study being able to detect a difference if one actually exists. Is the study big enough to answer the question? Done by predicting the likely differences between the groups being studied, which in terms determines the size of the study
 - Strength of inference: likelihood that an observed difference represents a real difference, rather than due to chance. Is weakened by bias and small sample sizes
 - Validity = Accuracy: Lack of systematic error. Results are unbiased and give true estimate of the measured effect. Extent to which a variable or intervention measures or accomplishes what it is

supposed to. Does it measure what it claims to measure – described by specificity and sensitivity, etc

- Internal validity: degree to which study results are correct for the sample studied
- External validity/generalisability: degree to which results hold true in other settings
- Multivariate Regression Analysis: multiple regression is used when the outcome is a continuous variable (eg blood pressure). Logistic regression is used when the outcome is dichotomous (eg alive or dead)

Type Errors

Trial Result	True Situation	
	Treatment works (ie null hypothesis false)	Doesn't work
Treatment works	Should use the new treatment	Type 1 error: start using new treatment
Treatment doesn't work	Type 2 error: keep using old treatment	Shouldn't use the new treatment

- The proportion of times we make a type 1 error is (all other things equal) governed by the significance level of the test
- Type 2 error rate is controlled by the true size of the difference, variability in the outcome measurement (ie SD) and the sample size
- Power = probability of making a correct decision that the new treatment doesn't work = 1 – type 1 error rate
- Power affected by sample size, variance, distribution of the sample, level of significance
- Confidence interval gives information about both the type 1 and 2 error rates

Risks and Odds

- Two commonly used measures of the strength of an association are relative risk and odds ratios
- NB: probability of rain in the next hour is 0.8, the odds in favour of rain in the next hour are 4:1

Exposure/Factor	Outcome/Disease	
	Yes	No
Yes	A	B
No	C	D

- Event Rate: proportion of patients in a group in whom an event is observed. Applied to Controls and Experimental groups → CER and EER
- Relative Risk = $(A/(A+B))/(C/(C+D)) = EER/CER$
- Relative Risk = probability of getting the disease when the factor is present/probability of getting the disease when the factor is absent
- Absolute Risk Reduction (ARR) = $C/(C+D) - A/(A+B) = CER - EER$
- Relative Risk Reduction: percent reduction in events in the treat group event rate compared to the control group = $(CER - EER)/CER * 100 = (C/(C+D) - A/(A+B))/(C/(C+D))$
- Risk Ratio = EER/CER
- Odds ratio (used in case-control studies as the incidence can't be calculated so an RR can't be calculated): odds of an experimental patient suffering an adverse event relative to a control patient = $(A/C)/(B/D)$. Odds in favour of the disease when the factor is present/odds in favour of the disease when the factor is absent
- Time frame: all measures (RR, RRR, ARR, OR) must be qualified by giving them a time frame (e.g. the length of the period of the study)
- When the probability of the disease is small, B and D tend to 1 and the OR is equivalent to the RR
- When RR and OR are around 1, there is no association between the factor and the disease
- Number needed to treat (NNT): number of patients needing treatment to achieve one favourable outcome = $1/ARR$ – always rounded up to the nearest whole number and accompanied by the 95% CI. Caution: NNT depends on the event rate in the control arm, the placebo rate may vary between trials
- Number needed to harm (NNH): number of patients who need to be treated to achieve one adverse outcome = $1/Absolute\ Risk\ Increase\ (ARI = EER - CER)$

- RRR and OR do not say anything about absolute risk. An RR of 30% can mean a risk reduction from 60% to 20%, or from 3% to 1%. The ARR and NNT varies dramatically
- Attributable risk is a measure of absolute risk, calculated by subtracting the incidence of a disease in non-exposed from the incidence in exposed

Evaluation of Diagnostic Tests

Sensitivity and Specificity

- Sensitivity: proportion of people with disease who have a positive test (i.e. true positive). How good is the test at picking up people who have the condition? SnNout = when a test has a high sensitivity, a negative result rules out the diagnosis
- Specificity: the proportion of people free of a disease who have a negative test (i.e. true negative). How good is this test at correctly excluding people without the condition? SpPin = When a test is highly specific, a positive test rules in the diagnosis

Pre-test Probability

- = $P(D+)$ = probability of target disorder before a diagnostic test result is known. Depends on patient (history and risk factors), setting (e.g. GP, A&E, etc) and signs/symptoms
- Is useful for:
 - Deciding whether to test at all (testing threshold)
 - Selecting diagnostic tests
 - Interpreting tests
 - Choosing whether to start treatment without further tests (treatment threshold) or while awaiting further tests

Likelihood Ratio

- Positive Likelihood Ratio = the likelihood that a positive test result would be expected in a patient with the target disorder compared to the likelihood that the same result would be expected in a patient without the target disorder
- Negative Likelihood Ratio = same but for negative result
- Less likely than sensitivity and specificity to change with the prevalence of a disorder
- Can be calculated for several levels of the symptom or test
- Can be used to calculate post-test odds if pre-test odds and LR known
- Impact of LR:
 - < 0.1 or > 10 : large changes in disease likelihood (i.e. large change to pre-test probability)
 - $0.2 - 0.5$ or $2 - 5$: small changes in disease likelihood
 - 1 : no change at all

Post-test Probability

- = Proportion of patients with a positive test result who have the target disorder
- Sensitivity and Specificity depend on setting. E.g. if screening for a disease occurring 1 in 10,000 in a population of 100,000 then a test with sensitivity of 99% and specificity of 99% will find 9.9 true positives and 999.9 false positives. But if the disease occurs 1 in 100 then you'll find 99.9 true positives and 99.9 false positives – far better strike rate
- Positive Predictive Value (+PV): proportion of people with a positive test who have disease. If the person tests positive, what is the probability that s/he has the disease? Determined by sensitivity and specificity, AND by the prevalence of the condition
- E.g., for a test with 99% sensitivity:

	Prevalence	Positive Predictive Value
	1	19
	2	33
	5	56
	10	73
	20	86

- So significance of test may vary between, say, hospital and GP

Formulas

		Diseased	Normal
Test	+ive	a	b
	-ive	c	d

Sensitivity = $a/(a+c)$

Specificity = $d/(b+d)$

LR + = sensitivity / (1-specificity) = $a/c * b/d$

LR - = (1-sensitivity)/specificity

Positive Predictive Value = $a/(a+b)$

Negative Predictive Value = $d/(c+d)$

Prevalence = $(a+c)/(a+b+c+d)$

Pre-test odds = prevalence / (1-prevalance)

Post-test odds = pre-test odds * LR

Post-test probability = post-test odds / (post-test odds+1)

Accuracy = $(a+d)/(a+b+c+d)$ = what proportion of results have given the correct result

Study design for researching a test

- Spectrum composition: what population was it tested on. Sensitivity and specificity may vary between populations with significant disease and the general population
- Are pertinent subgroups assessed separately? Condition for test use must be narrowly defined to avoid heterogeneity
- Avoidance of work-up bias: if there is bias in who is referred for the gold standard. All subjects given a test should receive either the gold standard test or be verified by follow-up
- Avoidance of Review Bias: is there objectivity in interpretation of results (e.g. blinding)
- Precision: are confidence intervals quoted?
- Should report all positive, negative and indeterminate results and say whether indeterminate ones were included in accuracy calculations
- Test reproducibility: is this tested in tests requiring interpretation

Screening

- Criteria:
 - Illness being screened for must be bad
 - There must be a pre-symptomatic phase detectable by the screening test
 - Intervention at this time should change the course of the illness to reduce morbidity and mortality
 - Test needs to be inexpensive, easy to administer and acceptable to patients, with high sensitivity
 - Screening programme should be feasible and effective
- If a condition is extremely prevalent, everyone is treated (eg iodised salt, fluoridated water, folate fortification, etc)

The Difficult Patient

- Notes from Mark O'Brien, MAS lecture 2006
- Difficult is a function of the patient, ourselves, the disease and the system
- Expectations:
 - All disappointment comes from unmet expectations – not ↓ quality. As complication rates ↓ then complaints ↑
 - The better we make the system the more we are disappointed by unmet expectations
 - People have little assessment of technical competence, so use interpersonal competence when things go wrong
 - “I remember the time he gave to my Dad. He would come around at the drop of a hat. He was a marvellous GP – apart from the fact that he killed my father” – Son of a patient of Harold Shipman
 - When something goes wrong, a patient asks “I though you were alright, was my original assessment correct”
 - Only 1 – 3 % of patients claim after a serious adverse outcome (ACC review of medical misadventure 2003). Approx 67% of claims related to adverse outcomes not associated with negligence
 - Mangels 1991: > 50% of patients who sued said they formed that intent prior to surgery
 - The closer your work is to a commodity, the more likely a client's expectations will align with a commodity
- Factors in ourselves:
 - Previous encounters with similar people
 - Degree of training in handling difficult situations
 - Our own emotional baggage
 - Our attitude to the sick role
 - Our belief about personal levels of responsibility
- As we become adults we learn:
 - The difference between truth and validity – just because its true does not make it valid to act that way
 - Good relationships are built on solving problems not avoiding them
- Difficult people are serial boundary violators. The irony of difficult people is that they've got the problem but you feel tense – they project their problems
- Normal people come with a problem and seek advice. Difficult people come and say “you've got a problem, what are you going to do about it”
- Skills for difficult interactions:
 - Acknowledge problems: “We've only been talking for a couple of minutes and we're already arguing – what's the problem”.
 - Don't prolong a difficult interaction. “This isn't going well, do you think it's worth carrying on? I don't want to leave you upset. I don't think I'll be able to meet your expectations.”
 - Setting boundaries: “I would love to be able to help you, but today is obviously not the day. I hope we can make it work another day”
 - Projecting your actions as being in the others bests interests
 - Problem solve rather than proving you're right – how many people say after you've proved yourself right “I appreciate that, I now respect you very much”
 - “Yes, but...” is the way we tell people they're wrong. If we're problem solving we say “and”
 - We need the maturity not to get sucked into arguments
- Most effective change takes high tension, high support
- Lots of empathy – “How can I help”, “what information do you need”, “that must be hard”, “What do you think you'll do and how can I support that”

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