## **MRCP Notes Compilation**

Nigel Fong Last updated 27 November 2017

**Introduction**

This is a personal compilation I assembled while preparing for the MRCP(UK) theory papers. It cobbles together short notes on the recognition and treatment of advanced conditions which are uncommonly encountered in day-to-day general medical clinical practice, but appear frequently on the exam, and may one day be important to recognize. To maximise yield, I have omitted conditions that should be familiar to most of us, that are well covered in an undergraduate syllabus, or that are supremely esoteric and an obvious waste of neurons. This will not cover everything on the exam but I hope that it will be a helpful start.

The same vignettes are useful for both the MRCP Part One and Two examinations. If you are preparing for the MRCP Part One, focus on recognizing conditions as much less emphasis is given to treatment. In addition, you will also need to pay attention to basic science, pharmacology, and statistics. On the other hand, for the Part Two, focus on diagnosis and treatment; there is little basic science weightage, except those most relevant to clinical practice (e.g. drug-drug interactions, drug toxicities etc).

Approaches covered in my notes on ‘approaches to symptoms of disease’ will not be repeated here, please refer to that set. I also strongly recommend “Rapid review of clinical medicine for MRCP” by Sanjay Sharma, above and beyond any question bank you might choose to do, for its high quality of questions and well-reasoned explanations. Finally, you may find that some topics are mentioned rather briefly here → it is helpful to read around the topic (e.g. on uptodate) if you find yourself unfamiliar with it.

**Note for part two -** I get the sense that the MRCP folks were deliberately focusing on clinical pattern recognition and reasoning, while downplaying advanced investigations. For instance, many questions in the question bank come with serological results. In contrast, a similar MRCP question would provide relatively more detailed history and examination, but no serological tests. It seems almost like the exam setters were making a statement against the current trend towards increasing reliance on specific investigations.

Please let me know if you spot any errors or have any feedback. The latest version of this notes, including any corrections, will always be available on my website (nigelfong.net) - try not to circulate downloaded copies as these may be old versions with errors.

All the best!

Nigel

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## **1. Cardiology**

### **a) Electrophysiology**

**LAFB & LPFB**

|  |  |  |
| --- | --- | --- |
|  | LAFB | LPFB |
| Axis | Left axis deviation | Right axis deviation |
| Vector | *Vector points to left*, so  - qR in I, aVL - rS in II, III, aVF | *Vector points down*, so  - rS in I, aVL - qR in II, III, aVF |
|  | Hemiblock + RBBB = bifascicular block Hemiblock + RBBB + 1st deg heart block = trifascicular block  Easy to degenerate into complete heart block | |

**2:1 AV block** can be localized to AV node vs His-Purkinje system by

* Vagal maneuver: increased vagal tone worsens AV nodal block but not infranodal block
* Atropine improves AV nodal block but worsens/ no effect on His-Purkinje system block
* Width of QRS - wider the more inferior the block.

**Long QT syndrome** can be congenital or acquired (drugs eg macrolides, antipsychotics, antiarrhythmics; electrolyte imbalance eg hypoCa, hypoMg). It causes bradycardia and polymorphic VT (torsades) which can present as apparent syncope, seizure, palpitations, or sudden cardiac death, and may be triggered by noise/exercise or drugs. Treatment of acute torsades - IV magnesium. Outside the acute setting, stop offending drugs; in congenital long QT, give beta blockers to blunt the sympathetic response, and consider ICD or cervical sympathectomy.

**Carotid sinus hypersensitivity** is a cause of syncope in which carotid sinus massage results in asystole >3s (cardioinhibitory type) and/or BP drop >50mmHg (vasodepressor type). As AV block can occur, ventricular pacing may be required.

**Commotio cordis:** VT/VF after being struck in the precordium by a high velocity projectile

**Catheter ablation for AF**

* After AF ablation, do not stop warfarin if indicated by CHADSVAsc score. Pulmonary vein stenosis is a complication and may present with dyspnoea.
* After successful cardioversion, continue warfarin 4/52 then reassess, kiv indefinite if high CHADSVASc or risk of recurrence.

**PVCs:** treat if symptomatic or frequent (>10k/24h or >10% of all beats) with beta blocker/CCB.

**Short notes on the antiarrhythmics**

* *Flecanide is contraindicated in structural heart disease*; it increases mortality.
* Sotalol is first choice to prevent recurrent VT. It has risk of producing long QT.
* Amiodarone toxicity: lung fibrosis, hyper/hypothyroidism, hepatitis, slate-grey skin pigmentation with photosensitivity

### **b) Ischaemic Cardiovascular Disease**

**Stress testing**

* Withhold beta blocker, nondihydropyridine CCB, digoxin, nitrates (unless stress testing to assess adequacy of current therapy)
* Not recommended in low-risk asymptomatic patients → high risk of false positive
* Adequate exercise test: 85% of age-predicted max heart rate and metabolic demand
* Positive stress test: >1mm ST depression in 2 contiguous leads (difficult to interpret if ST baseline abnormalities)
* If MIBI used in LBBB: use vasodilator rather than exercise study (perfusion defects unrelated to CAD can be seen in the septum with exercise)

**Stable angina**

* First line: beta blocker, nitrate
* Second line: CCB
* PCI if persistent symptoms or high risk on noninvasive stress testing (ST depression at low work load, ST elevation, hypotension)

**Complications post MI**

* Pericardial
  + Peri-infarction pericarditis (early): pleuritic chest pain, pericardial friction rub, widespread ST elevation, effusion → aspirin 650mg q6h + paracetamol (avoid NSAID).
  + Post cardiac injury syndrome / Dressler syndrome (weeks-months post MI): pleuritic chest pain, inflammation, diffuse ST elevation → colchicine, high-dose aspirin or other NSAIDs.
  + Pericardial effusion: may lead to tamponade (muffled heart sounds, elevated JVP, hypotension) → 2DE → pericardiocentesis.
* Mechanical
  + Free wall rupture: usually catestrophic right heart failure → pericardiocentesis, support, surgery
  + Septal rupture: biventricular failure, new PSM → surgical repair (early vs late)
  + Papillary muscle rupture / acute MR: haemodynamic compromise, new PSM → afterload reduction, surgery.
  + LV aneurysm: repair vs delay
* Arrhythmias
* Heart failure / cardiogenic shock.
* Reinfarction

**Familial hypercholesterolaemia** is an AD condition due to mutation in the apo B/E (LDL) receptor . It is characterised by high LDL, tendon xanthomas, and premature coronary artery disease. Target an LDL reduction of 50% or more with statins (cat X in pregnancy), KIV add other agents e.g. ezetimibe

**Indications for high intensity statin (AHA)**

* *Clinical ASCVD* and age <75
* *LDL >4.9*
* DM with *10 year cardiac risk >7.5%* (moderate intensity if risk <7.5%)
* Consider in others with 10 year cardiac risk >7.5%
* Moderate intensity if high risk for statin side effects.

### **c) Valvular & Congenital Heart Disease**

**Differentiating systolic murmurs**

* Increase in peripheral resistance (isometric exercise e.g. hand grip) and increase in afterload accentuates murmurs caused by backflow of blood (MR, AR, VSD).
* HOCM: LVOT obstruction and hence murmur increases when chamber size reduces. This occurs in *reduced preload* (*valsalva, supine to standing,* dehydration, diuretics), and *positive inotropy* (dobutamine). Conversely, increased preload (leg raise), increased afterload (isometric exercise), and reduced inotropy (GTN, ca channel blockers) decreases obstruction and murmur intensity.

**Interpretation of cardiac cath data**

* Left to right shunt: Step up in right heart saturations.
* Right to left shunt: Left heart saturations <96% or step down.
  + VSD with Eisenmengers: LV sats = aorta sats
  + Fallot’s tetrology: LV sats > aorta sats (as aorta receives blood from overriding RV)
* Pulm HTN: Pulm art systolic pressure > *35mmhg*
* AS / PS: Pressure *drop > 10 mmHg* across the valve
* AR: wide pulse pressure in aortic pressure
* MS: PCWP > LV end diastolic pressure
* MR: PCWP ‘v wave’ >20mmHg
* Pericardial constriction: RV diastolic = LV diastolic pressures, RA = LA pressures

**Pseudo-severe AS (low flow, low gradient):** Calculated *valve area can be falsely low if there is severe LV dysfunction* because low CO reduces the valve opening forces. Echo should be repeated with dobutamine infusion; patients with truly severe AS will show an increase in trans-aortic pressure gradient while the valve area remains the same, while those with falsely low calculated valve area manifest an increase in calculated valve surface area.

**Indications for valve replacement** (replacement for AS/AR, balloon valvotomy for MS, favour repair if MR if anatomy feasible)

* *Symptoms* attributed to valve disease
* Dysfunction
  + *EF* <50% (AS, AR) or <60% (MR)
  + *LV dilation* (AR, MR)
  + *Pulmonary hypertension* (MR)
  + New onset *AF* (MR)
* Other cardiac surgery with moderate-severe AS/AR/MS/MR
* Severe AS/MS before pregnancy
* Asymptomatic with very severe AS/MS

**HOCM**

* Dynamic LVOT obstruction is exacerbated by reduced preload (diuretics, squat to stand), reduced afterload (vasodilators, expiration), increase in contractility (e.g. digoxin)
* Treat symptoms
  + Avoid diuretics, vasodilators, ACE-I
  + *Reduce contractility:* beta blockers, CCB
  + Severe: surgical myomectomy vs alcohol septal ablation.
* Reduce risk: *ICD* if: >3cm hypertrophy, previous cardiac arrest, NSVT, hypotension during exercise, syncope, family history of sudden death
* Screening of first degree relatives: optional if <12 yrs (unless family history, symptomatic, competitive sports), 12-18 mths from 12-18 yrs, every 5 years after 18 yrs or if symptomatic.

**Patent foramen ovale** can present with platypnea-orthodeoxia syndrome (cyanosis and dyspnoea when sitting, resolve when supine), if the upright position results in deformation of the atrial septum and redirection of shunt flow.

**Atrial myxomas** present with a systolic *murmur* that changes with patient position (tumor flops in and out of the mitral orifice - can mimic MS), intracardiac *obstruction* (PND, orthopnea, platypnea - dyspnoea when upright, syncope), or *embolism*, causing TIA/stroke (LA myxoma) or pulmonary infarcts (RA myxoma). *Constitutional symptoms* (fever, raised inflammatory markers) and haemolysis can occur. Tumors are mostly benign and resection results in good outcomes. If there is also spotty skin pigmentation, or endocrine tumors, think of Carney complex which is an autosomal dominant genetic syndrome.

LMWH can be used as an anticoagulant during pregnancy, but for patients with a mechanical valve prosthesis, a weight-based regimen has been demonstrated to be inadequate. The LMWH dose must be adjusted to anti–factor Xa activity in order to provide adequate anticoagulation.

**Pregnancy risk** of ASD is minimal in the absence of pulmonary hypertension. In the presence of Eisenmenger syndrome, there is 40% maternal mortality and pregnancy should be avoided.

### **d) Other**

**Management of Pericarditis**

* Aspirin and NSAIDs usually, but *omit NSAIDs if MI* (impair myocardial healing)
* Constrictive pericarditis: can trial medical therapy to avoid surgical pericardiectomy.
* Judicious use of loop diuretics - higher filling pressures are needed to maintain stroke volume, overly aggressive diuresis can reduce cardiac output

**Constrictive pericarditis vs restrictive CMP**

* Similarity: elevated filling pressures, heart failure
* History / etiology
  + Favour CP: *pericarditis*, cardiac *surgery*, *malignancy,* TB, *connective tissue disease*
  + Favour restrictive: infiltrative disease (*amyloid, sarcoid*).
  + Prior radiation causes either.
* Examination: pericardial knock in CP, S3 in RCMP.
* ECG: BBB, LVH, q wave favours RCMP. Low voltage, ST abnormalities in either.
* BNP: constrictive pericarditis tends to be normal
* Echo: MR, TR, bright endocardium in restrictive CMP
* Cath: CP - end diastolic pressures equal in both ventricles, restrictive CMP - LVEDP slightly higher than RVEDP.

**[Basic Science for Part 1]**

**Antiplatelet agents**

* Aspirin: irreversible COX inhibitor, inhibits thromboxane A2 production
* Clopidogrel, ticlopidine: ADP receptor (P2Y12) antagonist
* Dipyridamole: phosphodiesterase inhibitor, increasing cellular cAMP
* Abciximab: GP2b/3a receptor inhibitor.

**Amiodarone:** main action is on inward sodium and calcium channels, to prolong the action potential.

## **2. Respiratory Medicine**

### **a) Testing & airway diseases**

**Interpretation of DLCO**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Low DLCO** | **Normal DLCO** | **High DLCO** |
| **Normal spiro** | Vascular (PE, PH, AVM)  Anaemia  Smoking |  | Increased capillary blood - Pulm edema - Polycythaemia - L to R shunt |
| **Restrictive spiro** | ILD | Thoracic cage deformity  Neuromuscular defect  Pneumonectomy | *Pulmonary haemorrhage (elevated DLCO an impt sign)* |
| **Obstructive spiro** | COPD  Bronchiectasis | Asthma |  |

**Spirometry interpretation**

* Obstructive disease: late expiratory peak, rapid early decline in exp flow resulting in flat exp flow curve after initial peak (no longer a triangle)
* Extrathoracic airway obstruction: squaring of inspiratory loop
* Intrathoracic airway obstruction: squaring of expiratory loop
* Restrictive disease: smaller lung volume.

**Asthma**

* Omalizumab useful if mod-severe asthma, inadequately controlled with ICS, allergens, IgE 30-700 U/ml
* Ddx: vocal cord dysfunction if (1) mid-chest tightness with exposure to particular triggers such as strong irritants or emotions, (2) difficulty breathing in, and (3) symptoms that only partially respond to asthma medications. Diagnosis - *adduction of vocal cords* during inspiration as seen on bronchoscopy, *flat inspiratory limb* on spirometry. Rx: speech therapy training exercise, treat GERD.

**COPD**

* Monitor with spiro alone, no need DLCO.
* *Indication for LTOT: pO2 <55 or SpO2 <88%; or pO2 <60 or SpO2 <89% with pulm HTN, right heart failure, or polycythaemia.*
* Refer for transplant if: exacerbations, pulmonary HTN, FEV1 <20% with DLCO <20% or homogeous emphysema
* Lung volume reduction surgery: if symptomatic despite max Rx and pulm rehab, mainly *upper lobe emphysema, FEV1 20%-45%*
* Roflumilast is a phosphodiesterase-4 inhibitor that is used as add-on therapy to reduce exacerbations in patients with severe COPD associated with chronic bronchitis and a history of recurrent exacerbations despite other therapies.

**Bronchiectasis syndromes**

* **Immotile ciliary syndrome -** sinusitis, nasal polyps, bronchiectasis, infertility, dextrocardia. **Kartagerner’s syndrome** (subgroup of immotile cilia syndrome) describes the triad of *dextrocardia, bronchiectasis, chronic sinusitis.*
* **Cystic fibrosis -** bronchiectasis, nasal polyp, short stature, biliary duct obstruction eventually cirrhosis, chronic pancreatitis and DM, infertile males and subfertile females.
* **Yellow nail syndrome:** an abnormality of lymphatic drainage with recurrent bronchiectasis, small pleural effusions, lymphoedema, *yellow nails.*
* **X-linked hypogammaglobulinaemia:** mimics cystic fibrosis, consider if there are low immunoglobulins (or low total protein with normal albumin).

### **b) Diffuse parenchymal lung diseases**

**Upper vs lower lobe fibrosis**

Upper lobe

* All *environmental causes* except asbestosis (hypersensitivity pneumonitis, silicosis - eggshell CXR calcification, allergic bronchopulmonary aspergillosis, etc)
* No systemic causes except *ankylosing spondylitis*
* Granulomatous disease: TB, sacroidosis, histiocytosis

Lower lobe

* All *systemic causes* except AS (i.e. scleroderma, dermatomyositis, RA, sjogrens)
* No environmental causes *except asbestosis*
* *Drugs* (bleomycin, amiodarone, methotrexate, busulfan)

**Allergic bronchopulmonary aspergillosis** (ABPA) is the result of a hypersensitivity reaction to aspergillus colonization in airways. It presents as *asthma* with recurrent exacerbations (i.e. asthma-plus), and also occurs in *cystic fibrosis*. Blood tests may show *eosinophilia* >0.5, *elevated IgE* >1000, *aspergillus precipitins*. CXR or HRCT shows *central bronchiectasis,* perihilar opacities due to mucus plugging. There is evidence of sensitisation to aspergillus (skin prick test or aspergillus-specific IgE). Treatment is oral steroids and antifungals.

**Tropical pulmonary eosinophilia** is an immune reaction to infection with filarial parasites (Wucheria bancrofti, Brugia malayi) -- fever, cough, wheeze, CXR infiltrates, eosinophilia.

**Hypersensitivity pneumonitis** is a type III/IV reaction to inhaled allergens. In the *acute form* it causes fever, cough, and SOB 4-6h after exposure. In the subacute form there is weight loss and fatigue. In the *chronic form* there is exertional SOB and *upper lobe pulmonary fibrosis*. CXR shows fine reticular or nodular shadowing, progressing to a fibrotic pattern with shrunken lungs (*NSIP pattern*). *IgG precipitins* are present. However as this is not a type 1 reaction, reactions like wheeze, raised IgE, positive skinprick, eosinophilia are not present. Exposure history is the key for diagnosis - can be mistaken as IPF.

**Radiation pneumonitis** begins *1-6 months after* high dose RT. There are ground glass opacities on CT, in a nonanatomic straight line demarcating involved versus uninvolved lung parenchyma. Usually resolve in 6 months but can become fibrotic. Treatment is steroids +/- steroid sparing agents.

**Cyclophosphamide indued lung fibrosis** presents *several years after* stopping cyclophosphamide. It *progresses relentlessly* to respiratory failure. CXR shows upper zone reticulonodular shadowing.

**Organizing pneumonia:** a/w collagen vascular diseases or certain drugs, but may be cryptogenic organizing pneumonia. Onset is typically over 4 to 6 weeks and symptoms rarely persist for longer than 6 months; its presentation may mimic community-acquired pneumonia. Chest imaging typically shows patchy airspace disease with consolidation and ground-glass opacities but no cystic changes.

**Respiratory bronchiolitis–**associated interstitial lung disease occurs primarily in smokers. It results in characteristic radiographic findings of *centrilobular nodules with air-trapping and scattered ground-glass attenuation.*

**LAM:** associated with tuberous sclerosis, thin walled cysts in lung. Treat with sirolimus (mTOR inhibitor)

**Pulmonary langerhans cell histiocytosis** presents with nonspecific respiratory symptoms, spontaneous pneumothorax. Extrapulmonary involvement includes rash, diabetes insipidus. Usually young adults, a/w smoking.

**Broncholitis obliterans** arises from excessive proliferation of granulation tissue in small airways, in association with inhalational injury, infection (mycoplasma), drugs, inflammatory disorders (RA), and GvHD post transplant. It presents as dyspnoea and cough. CXR is normal or hyperinflated. HRCT shows expiratory air trapping and bronchial wall thickening (*centrilobular nodules) +/- ground glass opacities.* Lung function tests show *obstruction* without bronchodilator reversibility and air trapping. DLCO is reduced. Treatment is with macrolides, ? steroids but response is variable.

**Sarcoidosis:**

* Classic presentation:
  + *Lofgren syndrome: hilar lymphadenopathy, erythema nodosum, polyarthralgia, fever*
  + Heerfordt syndrome: uveitis, parotid gland enlargement, facial nerve palsy, fever
  + Asymptomatic bilateral hilar lymphadenopathy
* Disease manifestations
  + Lung: *bilateral hilar LN* (stage 1) +/- *reticular opacities* (stage 2), reticular opacities mainly (stage 3 if with LN, 4 if without).
  + Other: skin (*EN*, papules), eye (*uveitis*), LN, MSK (*arthralgia*), *hypercalcemia,* *neuro* (mononeuritis multiplex, meningitis, psychosis)
* Diagnosis: biopsy except for classic presentations
* Treatment: steroids

### **c) Pleural diseases**

**BTS pneumothorax guidelines 2010**

* *Primary* pneumothorax:
  + <2cm and asymptomatic: consider discharge, review in 2-4 weeks
  + *>2cm or symptomatic: aspirate.* Discharge if successful, chest tube if fail.
* *Secondary* pneumothorax:
  + <1cm and asymptomatic: admit, high flow oxygen.
  + 1-2cm and asymptomatic: aspirate, if fail, chest drain
  + >2cm or symptomatic: chest drain

Small pneumothorax not apparent on CXR: a click synchronous with heart sounds is a sign of a small left apical pneumothorax - consider a lateral decubitus Xray.

**Rheumatoid pleural effusions** occur in 5% of RA patients, more common in men and may coexist with rheumatoid nodules and ILD. They are usually small and asymptomatic. Pleural fluid is *exudative* with low glucose, low pH, high LDH, *high RF +/- high cholesterol* levels. Effusions may be bilateral. Treatment is treatment of RA joint disease. But beware differentials

* Empyema if there are symptoms of infection.
* TB: there can also be a preceding inflammatory polyarthritis that mimics RA.

**Pleural effusion**

* Small bore tubes will do for drainage
* If suspicion for malignancy high but first pleural tap negative, repeat pleural tap once, then do thoracoscopic biopsy.
* If suspecting TB, most sensitive test is pleural fluid ADA. AFB smear and culture lacks sensitivity.

### **d) Others**

**CXR:** watch for left upper lobe collapse (*veil sign*) and left lower lobe collapse (*sail sign*) - these are not always obvious.

**Bronchial carcinoma with SVCO:** stenting superior to steroids.

**Bronchial carcinoid** presents in *young non-smokers* with gradual development of cough, wheeze, haemoptysis, recurrent postobstructive pneumonia, but no weight loss. Imaging shows a well-demarcated *centrally-located tumor*. There may be raised chromogranin A. Carcinoid syndrome is uncommon. These behave indolently and surgery is the treatment of choice.

**Carbon monoxide poisoning** causes tissue *hypoxaemia* in *brain* (AMS, seizures, coma, nausea, vomiting), *myocardial* ischaemia (with ECG changes), and *lactic acidosis*. Severe poisoning is associated with COHb concentrations *>30%* (vs <5% in healthy adults, 10% in smokers). Treatment is high flow oxygen, KIV hyperbaric oxygen.

**Methaemoglobinaemia** presents as clinical *cyanosis* and low SaO2 despite normal pO2, and dark-chocolate coloured blood. MetHb absorbs at pulse oximetry wavelengths, so SpO2 is inaccurate and *displays as approximately 85 percent*, regardless of the true hemoglobin oxygen saturation. Use a blood gas machine. This occurs due to oxidation of Fe2+ in Hb to Fe3+, usually by drugs (*dapsone*, topical anaesthetic agents, *nitrates*). Treatment is with *methylene blue* (ensure no G6PD deficiency).

**Pulmonary hypertension** (mean pulm art pressure >25mmHg)

* Right heart cath required for diagnosis of group 1 PAH, not necessary if presumptive group 3-4.
* Group 1: start Rx with oral meds - PDE-5 inhibitors (sildenafil, tadalafil), endothelin receptor antagonist (bosentan, ambrisentan). Prostanoids (IV epoprostenol, Neb iloprost) for patients with more advanced disease. CCB if positive vasoreactivity testing (decrease in pulm artery pressure >10mmHg without fall in CO/BP)
* Group 3 (PH due to lung disease); treat underlying lung disease, oxygen
* Avoid pregnancy.

**Indication for CT Chest surveillance (US guidelines):** age 55-79, 30 or more pack year history of smoking, currently smoking or quit within last 15 years.

**Management of pulmonary nodules**

* If long term stability from prior imaging - NFU
* Solid subcentimeter (<8mm) pulmonary nodules

- <4mm: no follow up

- 4-6mm: CT at 12 months then discharge

- 6-8mm: CT at 6-12 months then 18-24 months then discharge

- >8mm: CT at 3, 9, 24 months; PET, or biopsy

- If high risk (smoking, asbestosis, risk factors), move up one risk level

- Ground glass / semisolid nodule: KIV longer surveillance

* For 8mm-3cm nodules, assess malignancy risk;

- Low risk: CT at 3, 9, 24 months; PET, or biopsy

- Intermediate: PET/CT kiv biopsy

- High risk: surgery

**Pharyngitis -** if there are 3 or more Centor criteria (*fever, no cough, tonsillar exudates, tendercervical lymph nodes*) → test for group A strep using rapid antigen tests. If confirmed, treat with abx to reduce complications (glomerulonephritis, rheumatic fever).

## **3. Neurology**

### **a) Cerebrovascular**

**Complications after SAH**

* Hydrocephalus: drowsiness or drop GCS hours to days after
* Rebleeding: greatest risk within first 24-48h
* Delayed cerebral ischaemia: due to vasospasm, usually around *5-10 days after* SAH → do CT angio
* Seizures

**Nimodipine** is the favourite antihypertensive for hypertensive SAH or CVA as it reduces cerebral artery vasospasm.

**Asymptomatic aneurysm:** Consider surgery if >7mm in posterior circulation, >12mm in anterior circulation

**Guidelines for carotid endarterectomy**

* *Symptomatic* carotid stenosis (***ipsilateral*** ischaemic stroke/TIA), indicated if stenosis is 70-99%, possible if stenosis is 50-69% (do in a good centre with periop morbidity and mortality <6%)
* *Asymptomatic* carotid stenosis: controversial, can consider if stenosis 70-99%

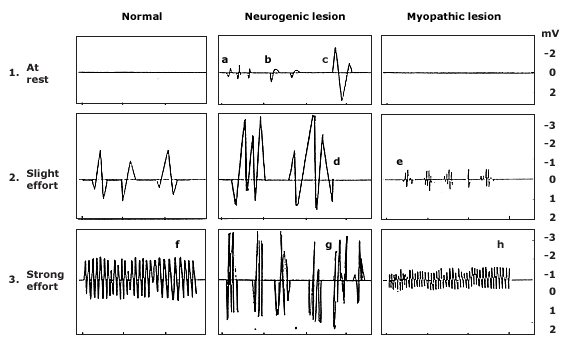
### **b) Neuromuscular Disease**

**Nerve conduction study**

* Demyelinating disease: decreased conduction *velocities* (e.g. AIDP, CIDP)
* Axonal neuropathy: reduce nerve amplitude *potentials.*
* Note if sensory or motor

**Electromyography:**

* **Neuropathy -- big complexes:** acutely, at rest there are denervation potentials, fibrillations (1a), positive sharp waves (1b), fasciculations (1c) and complex repetitive discharges. Reinnervation occurs - surviving motor neurons sprout to reinnervate many motor units, so motor unit action potentials (MUAP) are polyphasic potentials with increased duration and amplitude (2d). There are fewer motor units (3g). This can be an anterior horn cell or nerve problem.
* **Myopathy -- small complexes:** the number of motor units is normal, but there is loss of muscle fibres within each unit. Therefore, MUAPs are brief-small-abundant and polyphasic (2e), amplitude remains low even with strong effort (3h)
* Diagram from uptodate:

****

**Myasthenia gravis:** contraindicated drugs include

* Neuromuscular blocking agents
* Aminoglycosides, clindamycin, (fluoroquinolones)
* Beta blockers
* Quinine, chloroquine

**Lambert Eaton Syndrome:** key differences from myasthenia gravis are

1. Weakness *improves with exercise* (vs fatigable in MG)
2. *Reflexes are depressed* (vs normal in MG)
3. There is usually LL weakness (rare in MG)
4. *Ophthalmoplegia is less common* (common in MG)
5. There are often *autonomic symptoms* eg dry eyes, erectile dysfunction (rare in MG)
6. ***Anti-VGCC*** antibodies are found (vs anti AchR or MUSK antibodies in MG) (do not confuse with anti-VGKC antibodies in limbic encephalitis)
7. Treat with 3,4 - diaminopyridine and look for underlying CA.

**Variants of motor neuron disease:** while ALS classically presents as a mix of UMN and LMN signs, several variants have been identified

* Mainly LMN: progressive muscular atrophy
* Mainly UMN: primary lateral sclerosis
* Mainly CN: progressive bulbar palsy
* Mainly one limb: flail arm /leg
* ALS-plus syndromes

**Spinobulbar muscular atrophy** (Kennedy syndrome) is an X-linked recessive condition presenting as proximal weakness, cramps, and motor neuron signs (wasting, fasciculations, weakness, hyporeflexia). *Perioral fasciculations* are suggestive. There is also androgen insensitivity with *gynaecomastia and infertility.*

**Multifocal motor neuropathy** presents as subacute-onset asymmetric *patchy upper limb* LMN weakness, with wasting, fasciculations, *normal or depressed reflexes*, and sensory sparing. This mimics motor neuron disease. Nerve conduction shows *demyelination with conduction block* (vs axonal degeneration in MND). *Anti-GM1 antibodies* may be positive. Treatment is with IVIg.

**Idiopathic brachial plexopathy** (**Neuralgic amyotrophy**, Parsonage-Tuner syndrome, paralytic brachial neuritis) presents as acute/subacute onset of severe *pain* and patchy weakness in (usually) *C5-6,* unilateral or bilaterally, +/- sensory symptoms and muscle atrophy. EMG shows denervation. Recovery may take years and may be incomplete.

**Meralgia paraesthetica:** entrapment of the lateral cutaneous nerve beneath the inguinal ligament presents in an obese patient with parasthesia in the anterolateral thigh. Treatment is weight loss and wear looser pants.

**Polymyositis:** muscle biopsy shows fibre necrosis and regeneration; inflammatory cell infiltrate with lymphocytes. The associated antibody is anti-Jo1.

**Inclusion body myositis:** unlike polymyositis, this presents with insidious onset of *asymmetric* (vs symmetric), *proximal and distal* (vs proximal) muscle weakness especially affecting *finger flexors and quadriceps*. Dysphagia may develop but myalgia is minimal. On examination there is atrophy and hyporereflexia. *CK is <10x normal* and can be normal. EMG shows a mixed neuropathic (‘irritability’ - fibrillations, spontaneous activity) and myopathic (short-duration, small amplitude polyphasic units) picture. Biopsy is diagnostic.

**Myotonic dystrophy** is of two forms. Type 1 (DMPK gene / CTG repeat) may present in infancy (feeding and respiratory difficulty), in childhood (cognitive problems), or in 2nd-4th decade (classic presentation) - depending on the number of CTG repeats. Type 2 presents in the 2nd to 7th decade (less prominent manifestation). Features include

* Appearance: hangdog appearance, *frontal balding*
* Neurological:
  + *Myotonia:* percussion and grip myotonia,
  + *Weakness:* distal (T1) or proximal (T2, hip flexors) weakness, decreased grip strength, facial muscle wasting (hangdog appearance)
  + Muscle pain
* *Cardiac:* arrhythmias (AF, A flutter), cardiomyopathy
* Neurological complications
  + Respiratory weakness
  + Decreased GI motility, GI symptoms
* Endocrine: *insulin resistance, hypogonadism*
* Insomnia / excessive daytime sleepiness
* Cataracts

Workup: do NCS, EMG, 2DE, ECG; gene testing confirms diagnosis.

**L5 vs common peroneal lesion:** Peroneal L5

* **Hip abduction:** Preserved Weak
* **Foot inversion** (tib pos) Preserved Weak (supplied by L5 / tibial nerve)

**Subacute combined degeneration:** Unlike MS, ankle jerks can be absent (due to sensory peripheral neuropathy)

**Holmes-Adie pupil i**s an idiopathic condition, typically affecting young women, that presents with a *unilateral dilated pupil* that is poorly reactive to light and accommodates sluggishly, as well as *absent ankle jerks.*

### **c) Headache**

**Idiopathic intracranial hypertension (pseudotumor cerebrii):** usually an *obese* woman of childbearing age, presenting with *headaches*, visual changes (*transient visual obscuration* - transient loss of visual acuity when changing posture), and pulsatile tinnitus. Examination may find *papilloedema*, *visual field loss*, enlarged blind spot, and CN 6 palsy. MRI finds no other cause for raised ICP and LP confirms *increased opening pressure.* Patients are at risk of permanent visual loss. Treat with *weight loss*, then *acetazolamide*, diuretics, short-term steroids. Surgery (optic nerve sheath fenestration or shunting) is indicated if there is progressive visual loss or medical therapy fails.

**Giant cell arteritis:** Quite a favourite question (and important in clinical practice) so know it well. The most common eye finding is optic disk swelling. If there is visual loss, treat with IV steroids not oral steroids.

**Cluster headache:** acute treatment is with oxygen and sumatriptan (SC/intranasal). Prophylaxis is with verapamil or steroids (vs propranolol, TCAs, valproate in migraine).

**Paroxysmal hemicrania:** severe unilateral orbital pain with ipsilateral autonomic symptoms (conjunctival injection, tearing, nasal congestion, flushing, miosis). Attacks are *shorter* (<30min) and *more frequent* (>5/day) than cluster headache. This responds very well to *indomethacin.*

### **d) Seizures**

**Some seizure subtypes**

* **Juvenile myoclonic epilepsy:** absence seizures starting in childhood, myoclonic jerks especially shortly after waking, and GTCs. Treat with lamotrigine and levetiracetam. Valproate is effective but a/w congenital defects in pregnancy.
* **Mesial temporal lobe epilepsy with hippocampal sclerosis:** complex partial seizures with an aura followed by a spell of altered awareness with or without automatisms. Seizures are progressive.
* **Benign childhood epilepsy with centrotemporal spikes (benign rolandic epilepsy):** starts at 7-9 years as a simple focal motor seizure initially involving the face, then progressing to other areas of the body (Jacksonian march), or eventually a bilateral convulsive seizure. Seizures usually remit within 2 years.
* Absence seizure, use valproate or ethosuxamide.

**Antibiotics most likely to lower seizure threshold:** ertapenem, cefepime

**Adverse effects of antiseizure meds**

* **Phenytoin:** toxicity (nystagmus, ataxia, agitation, drowsiness, nausea/vomiting), skin (gum hyperplasia, dupuytrens contactures, acne), peripheral neuropathy, osteoporosis, benign lymphadenopathy. [no longer first line in UK due to side effects]
* **Valproate:** neuro (drowsiness, ataxia, tremor), gastro (hyperammonemia, *hepatitis*, pancreatitis), *blood dyscrasia*, weight gain, alopecia, teratogenicity
* **CBZ:** *SJS*, blood dyscrasia, neuro (drowsiness, ataxia, nystagmus)
* Lamotrigine: safest in pregnancy

The **tetrad of narcolepsy** includes chronic *daytime sleepiness*, *cataplexy, hypnogogic and hypnopompic hallucinations, and sleep paralysis*. This is associated with HLA DR2, HLA-DQB1. Multiple sleep latency test will demonstrate REM sleep at sleep onset. Treatment: sleep hygiene as first line, *stimulants* (modafinil, methylphenidate, amphetamines); in cataplexy, consider REM-sleep suppressing medication (venlafaxine, fluoxetine).

### **e) Dementia**

**Sporadic creutzfeldt-jakob disease** presents as *rapidly progressive dementia* (over weeks), focal neurology (*ataxia, myoclonus*). Peak incidence is in the 60s. Brain imaging may be initially normal but patients develop putamen and caudate head hyperintensities on *MRI* later. CSF is normal but show elevated s100b and 14-3-3 breakdown proteins. There are typical *EEG* changes (periodic synchronous bi- or triphasic sharp wave complexes). **New variant CJD** (due to bovine spongiform encephalopathy) presents *younger (*20-30s), with *psychiatric symptoms,* painful paresthesia (thalamic involvement), then *dementia, pyramidal signs, myoclonus,* and ataxia. MRI may show high T2 thalamic signal. EEG is usually normal. Tonsillar biopsy may show prion related protein.

**Biopsy finding in dementias:**

* AD: tau protein, beta amyloid, neurofibrillary tangles
* FTD: pick bodies

**CADASIL** (cerebral AD arteriopathy with subcortical infarcts and leukoencephalopathy) is the most common genetic form of vascular dementia. Characterised by *migraine with aura, young strokes, and early vascular dementia* with neuropsychiatric disturbance.

### **f) Others**

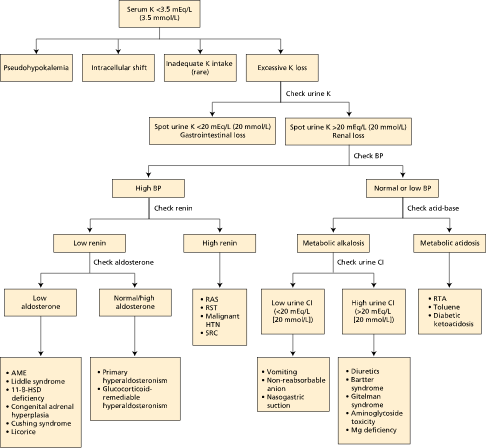
**Friedreich ataxia** is an AR condition presenting with neurological (dorsal column, spinocerebellar, and pyramidal tract dysfunction - predominant *ataxia*, *pyramidal* signs, and *peripheral neuropathy*), *skeletal* deformities (kyphoscoliosis, pes cavus, high arched palate), and *HOCM*. Some pt also have DM and optic atrophy.

**Tremors**

* Essential tremor 1st line: *primidone, propranolol*. Topiramate 2nd line. Botox if voice/head. DBS if severe medication-refractory.
* Focal dystonia - botox injection is most effective.
* Tics - clonidine
* Restless limb syndrome: dopamine agonists, gabapentin as treatment. Iron supplementation if ferritin is low or low-normal. iron replacement, dopamine agonist (pramipexole, ropinirole), gabapentin. Levodopa long term can cause augmentation (increase in severity with increasing doses of medications).

## **4. Nephrology**

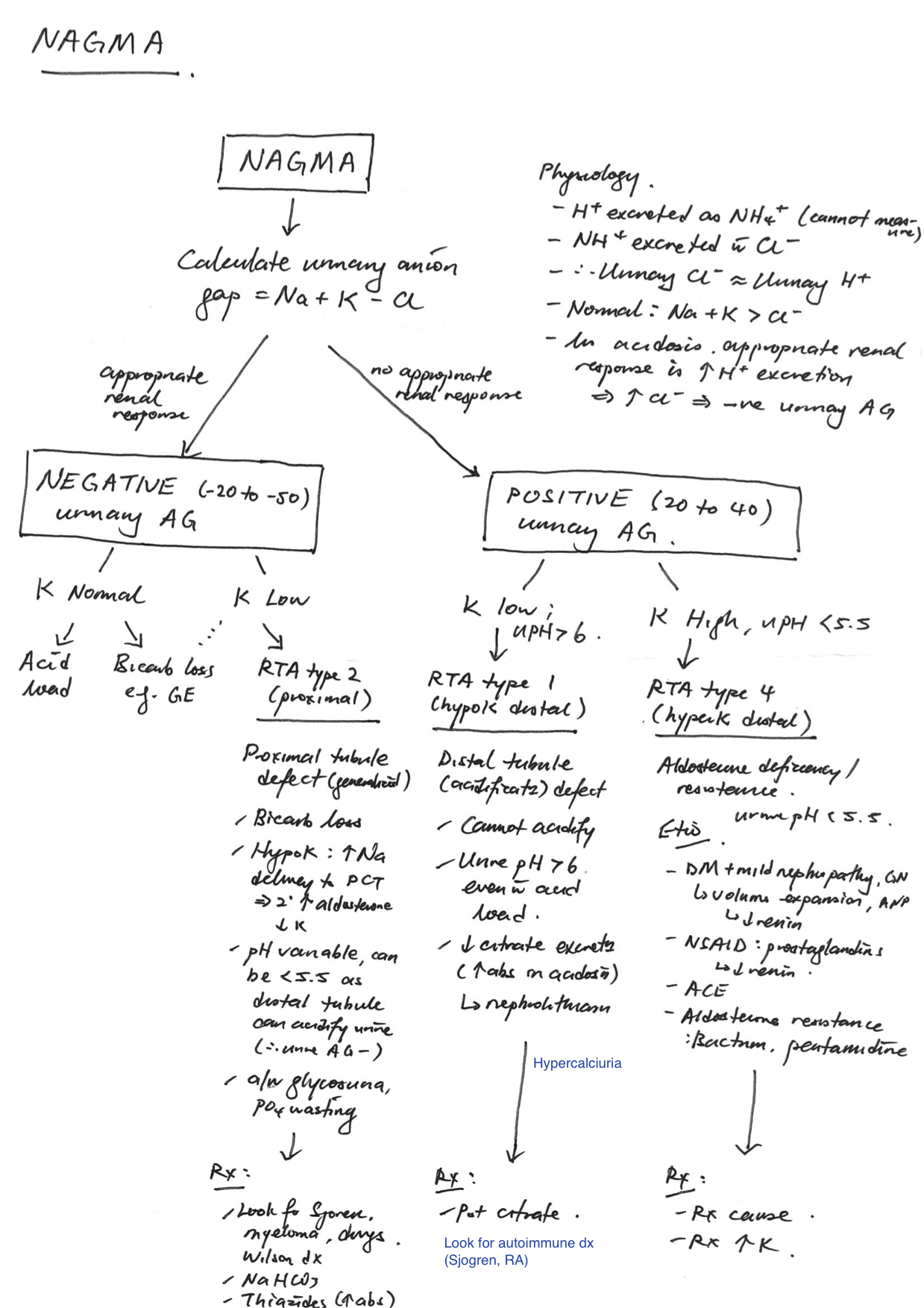
### **a) Electrolytes & Tubular Disorders**



Enhanced sodium / urine flow in CD

Approach to etiological diagnosis of hypokalaemia when it is not obvious

* Urine K >20 in hypokalaemia = inappropriate → renal loss.
* Suspect an aldosterone axis abnormality if there is hypertension, hypernatremia.
* Most causes of hypokalaemia cause alkalosis; acidosis with hypokalaemia happens only in renal tubular acidosis and DKA
* Hypokalaemia and alkalosis - urine chloride is a gauge of volume status. Low urine chloride = body attempting to conserve fluid → potassium loss somewhere. Exception is diuretics where K loss is high due to the effect of drug.

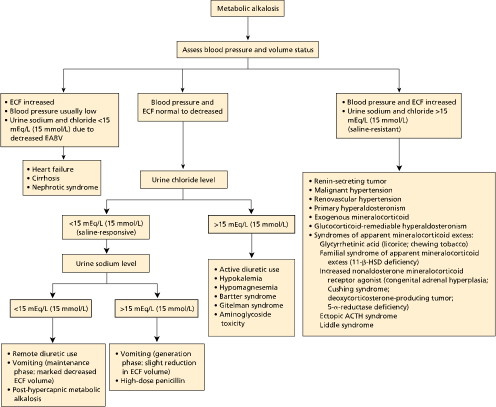


**Renal tubular acidosis:**

* Type 1 (distal RTA): impaired H+ secretion in the distal nephron results in absolute inability to acidify urine (urine pH >6 even with acid load). There is hypercalciuria and reduced citrate excretion, predisposing to *nephrolithiasis.* It usually presents in childhood with failure to thrive, or in adulthood with renal colic. A major etiology is autoimmune disease (Sjoren’s, RA). Treatment is with potassium citrate.
* Type 2 (proximal RTA): generalised proximal tubular defect leads to loss of bicarbonate, phosphate, glucose. Increased sodium delivery to distal nephron results in hypokalaemia (distal nephron tries to reabsorb sodium and in exchange has to excrete potassium to maintain charge balance). With acid load, however, the intact distal nephron is able to acidify urine to pH <5.5. This presents with acidosis, *polydipsia, polyuria, hypokalemia, rickets / osteomalacia*. Look for an underlying etiology - myeloma, lead, drugs (tenofovir, ifosfamide, aminoglycosides). Treat with sodium bicarb and thiazides.
* Type 4 (hyperkalemic RTA): *relative aldosterone deficiency* causes reduced potassium excretion and hyperkalaemic RTA (distinct from type 1 & 2). This occurs in (1) DM with mild nephropathy - mild volume expansion inhibits RAAS, (2) NSAIDS, which inhibit prostaglandin-dependent renin secretion, (3) ACE inhibitors, (4) aldosterone resistance (bactrim, pentamidine, spironolactone)

**Renal tubular genetic defects:** alphabetical order reflects nephron defect location - B (TAL), G (DCT), L (collecting ducts)

* **Bartter syndrome:** NKCC2 transporter mutation, mimics loop diuretics (hypoK, alkalosis, raised Ca excretion). This causes volume depletion - so patient has raised renin and aldosterone despite normotension (unlike Conn syndrome where there is HTN with raised renin and aldosterone). Tends to present in childhood. Hyperplasia of the JG apparatus is seen on renal bx.
* **Gitelman syndrome:** NCCT symporter mutation mimics thiazides, causing hypokalaemia, alkalosis, hypoMg; Ca excretion is not raised, unlike Bartter syndrome. BP is normal with raised renin and aldosterone.
* **Liddle syndrome** (pseudohyperaldosteronism): mutation in the epithelial sodium channel (ENaC) which mimics aldosterone action , causing hypertension, hypokalaemia, with suppressed renin and aldosterone.
* **Gordon syndrome** (pseudohypoaldosteronism): failure of response to aldosterone causing hyperK, acidosis, elevated renin and aldosterone
* Mimics
  + Laxative abuse: hypokalaemia and metabolic acidosis.
  + Diuretic abuse: can mimic bartter syndrome.



Chloride depletion Volume depletion without chloride depletion

### **b) Glomerulonephritis**

**Glomerulonephritis histology**

* MCD: light microscopy normal, EM fusion of foot processes
* FSGS: segmental areas of mesangial collapse in some but not all glomeruli (other variants - tip, perihilar, and cellular variants).
* Membranous: *basement membrane thickening* on light, *spikes or string of pearl* appearance on EM, granular staining for IgG
* Mesangiocapillary/membranoproliferative (MPGN)*: subendothelial immune complex* deposition, *splitting of basement membrane* giving a tramline / double contour effect, associated with C3 nephritic factor.
* Infection associated: diffuse proliferative changes, *subepithelial humps* of large electron dense deposit
* Goodpasture: linear immunoflorescence for IgG
* Thin basement membrane
* Lupus: full house immunostaining

**Glomerulonephritis disease associations:** each GN may be primary or secondary. Secondary causes:

* MCD: lymphoma & leukaemia (classically Hodgkin’s lymphoma), drugs (NSAIDs)
* FSGS: HIV associated nephropathy, CMV, EBV, parvovirus, drugs (heroin, pamidronate), adaptive (any cause of reduced nephron mass)
* Membranous: malignancy (often breast, lung, colon), hep B, drugs (gold, penicillaime), class V lupus nephritis. Primary membranous nephropathy is associated with positive anti phospholipase A2 receptor (Anti-PLA2R) antibodies.
* MPGN: Hep B, mixed cryoglobulinaemia

**Notes on nephrotic syndrome**

* **IgA nephropathy:** hypertension is the poorest prognostic factor.
* Renal vein thrombosis presents in nephrotic syndrome as flank pain, worsening creatinine and proteinuria.

**Management of lupus nephritis:**

* Class 1 (minimal change), 2 (mesangial): no specific Rx, background HCQ.
* Class 3 (focal segmental proliferative): high dose steroids + cyclophosphamide or mycophenolate
* Class 4 (diffuse proliferative): as with class 3, but may be too late to treat
* Class 5 (membraneous): treat if nephrotic / rise in creatinine / proliferative component, with mycophenolate.
* Adjuncts: control BP, control proteinuria (ACE).

### **c) Others**

**Acute Interstitial nephritis** present with a rise in creatinine, *fever, rash, eosinophilia* / eosinophiluria, and urine sediment showing white cells, red cells, white cell casts. Diagnosis is confirmed by renal biopsy (if pursued). Treat with steroids and stop the offending drug (NSAID, penicillins, sulphonamide, loop diuretics).

**Large kidneys** can be due to early DM nephropathy, hydronephrosis, acromegaly, renal vein thrombosis, amyloidosis, and ADPKD.

**Management of renal artery stenosis**

* Stent if short duration of high BP prior to diagnosis (likely to reverse HTN), failed or intolerant of medical therapy, recurrent flash APO or heart failure, and in bilateral RAS or unilateral functioning kidney, otherwise unexplained progressive CKD.
* Surgery if complex anatomy, otherwise stenting.
* Other patients - medical therapy.

**Screening in patients with family history of ADPKD**

* Ultrasound after 20 yrs (false positive if too young). Among pt 40 years of age or older, ultrasonographic evidence of zero or only one renal cyst excludes the disease.
* CTA or MRA for berry aneurysm only if high risk eg family hx of SAH, symptoms, previous SAH

**Other causes of CKD**

* Alport’s syndrome presents with hematuria progressing to renal failure, sensorineural hearing loss, retinitis pigmentosa and other ocular abnormalities. Transmission may be X-linked, AR or AD.

**Medullary sponge kidney:** pts are mostly asymptomatic. When patients with medullary sponge kidney do present with symptoms, the major clinical manifestations are kidney stones (which can cause flank pain and/or hematuria), hematuria, and urinary tract infections. In addition, flank pain may develop in the absence of an obstructing stone or urinary tract infection

**Risk factors for calcium oxalate urinary stones** include: increased colonic absorption (GI disease, short bowel syndrome), high oxlate diet, calcium restricted diet (less oxalate bound, greater oxalate absorption).

**Genitourinary TB**: Mycobacterial seeding may result in medullary granulomas, calyceal ulceration, scarring and calcification, and ureteric strictures, which can cause hydronephrosis and obstructive AKI. This presents as sterile pyuria, hematuria, and urinary tract symptoms. AFB are visualised in the urine. Repeated US scans should be done as strictures can form.

## **5. Haematology**

### **a) Malignant & proliferative disorders**

**Cryoglobulinaemia** is a syndrome of small to medium vessel vasculitis due to immune complexes which precipitate in the cold. This may be monoclonal Ig (Type 1 CG) in patients with multiple myeloma or waldenstom macroglobulinaemia, a polyclonal Ig with a monoclonal component (‘mixed’ - Type 2 CG) in chronic hep B / HIV, or a purely polyclonal CG (Type 3 CG) due to autoimmune disease. Type 1 CG is usually asymptomatic, or may present with *hyperviscosity complications* (neurologic s/s, peripheral arterial occlusion). Type 2/3 CG present as *cutaneous vasculitis* (palpable purpura, acrocyanosis - blue discolouration of fingertip and toes, raynaud’s, ear infarction), *arthralgia*, peripheral *neuropathy, BGIT, hepatosplenomegaly,* autoimmune *haemolysis,* membroproliferative *glomerulonephritis.* Type 2 and 3 CG both have *IgM rheumatoid factor* reactivity; complement is reduced. If biopsied, lesions are PAS-positive, congo red negative (vs apple green in amyloid), with amorphous or fibrillar appearance on EM. Treatment is that of the underlying disorder.

**Amyloidosis:** causes include myeloma, chronic disease (e.g. RA), hereditary (familial mediterranean fever etc). Can lead to nephropathy, restrictive cardiomyopathy, peripheral neuropathy, macroglossia, hepatomegaly, fatigue and weight loss. This is quite commonly asked so watch out for it.

**Waldenstom macrogloblunaemia** is a condition with *lymphoplasmacytic lymphoma* in the bone marrow (>10%) with an *IgM monoclonal gammopathy* in the blood. Symptoms may be due to *bone marrow involvement* (hepatosplenomegaly, cytopenias) or *IgM in blood* (hyperviscosity, neuropathy). There may be no symptoms (smouldering WM). It is clinically quite distinct from myeloma, with *no renal or bone involvement*. Treatment includes observation (asymptomatic pt), or rituximab based chemotherapy (symptomatic). In severe hyperviscosity (visual symptoms, retinal changes, impaired consciousness), IgM >50g/l, urgent plasmapheresis is indicated.

**POEMS** (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) syndrome presents in a plasma cell disorder (MGUS, otosclerotic myeloma) with neuropathy, otosclerotic bone lesions, elevated VEGF, endocrine abnormalities, volume overload, skin changes, organomegaly.

**Chronic lymphocytic leukaemia (CLL)** presents in the elderly. Most patients are asymptomatic. Others may present with *B symptoms* (night sweat, weight loss), lethargy, lymphadenopathy and *hepatosplenomegaly*, autoimmune *hemolytic anaemia,* hypogammaglobulinaemia causing *repeated infections*, and membranoproliferative glomerulonephritis. There is accumulation of small mature lymphocytes in marrow and blood. Treatment is indicated only if symptomatic, in advanced disease, or if there are complications. Consider FCR chemotherapy (fludarabine, cyclophosphamide, rituximab) in fit patients, or single agent chlorambucil in elderly/unfit.

**Paroxysmal nocturnal haemoglobinuria:** suspect in a patient with unexplained Coomb’s negative *haemolytic anaemia* +/- other cytopenias, +/- *venous thrombosis in atypical locations.* There may be episodes of jaundice and pink/red urine from *hemoglobinuria*. This is due to an acquired PIG-A gene mutation in a hematopoietic stem cell, resulting in a population of clonal PNH RBCs which lack a cell membrane protein (CD55, CD59). This results in increased susceptibility of RBCs to complement lysis. *Flow cytometry* to look for a mutated PIG-A gene is confirmatory (Ham’s test used to be done in the past). It may transform into AML.

**Causes of autoimmune hemolytic anaemia**

* **Warm AIHA** (IgG positive): SLE, lymphoma, CLL, methyldopa. Steroids are urgent
* **Cold IHA** (C3d positive): mycoplasma, EBV, paroxysmal cold hemoglobinuria, lymphoma. Steroids don’t work.

**G6PD** **deficiency** presents with acute haemolytic episodes triggered by food (fava bean) or drugs (e.g. primaquine, bactrim). PBF reveals RBC fragment, blister and bite cells, and heinz bodies (denatured Hb - contrast with Howell Jolly bodies)

**Hyposplenism:** Howell-Jolly bodies (DNA remnants) are associated with hyposplenism, whether anatomical (splenectomy) or functional (sickle cell dx). Remember to vaccinate these patients against encapsulated organisms (1 month pre-splenectomy).

**Some genetics**

* APML: t(15,17) PML RARA
* CML: t(9.22) BCR-ABL (philadelphia chromosome)

### **b) Coagulation disorders**

**Duration of anticoagulation for VTE**

* Distal leg: monitor if asymptomatic, treat 3 months if symptomatic
* Proximal leg DVT, PE:
  + Provoked: 3 months
  + Unprovoked: extended
* Cancer associated: as long as cancer is active, *preferably LMWH.*
* CTEPH: extended
* Thrombophilia testing usually not indicated unless it will influence length of treatment
* If there is superficial venous thrombosis, do US doppler for associated DVT.

**Warfarin**

* Reversal of warfarin with major bleeding: first choice is 4 factor PCC.
* If fluctuating INRs on warfarin, daily low dose vit K can stabilize INR
* INR <5 - withhold INR. INR 5-9 - 1-2.5mg oral vit K, INR >9 - 2.5 to 5mg vit K.

**Enzyme interactions with warfarin**

* Enzyme inducer: St John’s wort, Anti-epileptics (Phenytoin, carbamazepine, phenobarbitone), Rifampicin, griseofulvin, nnRTIs: Efavirenz & Nevirapine
* Enzyme inhibitor: many; including cranberry juice, flagyl, clarithromycin (more than ciprofloxacin)
* Decrease absorption: cholestyramine

**Heparin induced thrombocytopenia:** If suspected, calculate the 4Ts score (*Timing*: platelets drop *5-10 days after* starting heparin; *Thrombocytopenia* - drop by more than 50% but nadir >20k; *Thrombosis*; and nil other causes). Discontinue heparin and give another non-heparin anticoagulant (e.g. fondaparinux). Send anti-PF4 antibody and subsequently serotonin release assay.

**Warfarin induced skin necrosis** occurs on warfarin initiation. Clotting factors with shorter half lives eg protein C are depleted first, leading to procoagulant effect, vascular occlusion and tissue infarction followed by extravasation of blood. Underlying protein C deficiency or other procoagulant state may be associated.

**Immune thrombocytopenic purpura (ITP):** test Hep B/C/HIV and look for autoimmune conditions. *Treat if Plt < 30k or clinically significant bleeding.* First line treatment is prednisolone 40mg/day x 5 days, or IVIg + anti-Rh(D) if significant bleeding. Second line treatment includes splenectomy, rituximab, or thrombopoietin receptor agonists.

**Hemophilia A and B:** bleeding time is normal (as the predominant determinant of bleeding time is platelet aggregation). *Abnormal bleeding time leads to suspicion of severe von willebrand* disease (type 3).

### **c) Others**

**Mechanism of transfusion reactions:**

* TRALI: donor anti-HLA antibodies activate recipient neutrophils in lung
* Febrile nonhemolytic rxn: donor leukocytes generate cytokines during storage (traditionally, pt antibodies reacting against leukocytes in donor blood)
* Anaphylactic rxn: a recipient is IgA deficient and has anti-IgA Ab, encounters donor IgA
* Urticarial rxn: allergen in donor reacts with recipient’s pre-existing IgE Ab
* GvHD: donor lymphocytes attack recipient
* Hemolysis: ABO incompatibility (immediate), minor antigen incompatibility (delayed)

**Leukoreduction** *removes the majority of WBCs* from PCT transfusion, which may cause alloimmunization and subsequent transfusion reactions. Indications:

* High risk for alloimmunization and reaction: *previous febrile rxn*, *chronically transfused* pt
* Need to minimise alloimmunization: *transplant* pt, transplant candidate

**Irradiation** *kills all WBCs*, so as to prevent GVHD in at risk groups:

* Donor cells may not be recognized as foreign: *HLA matched* platelets, donations from *first or second degree relatives*
* *Severely immunocompromised:* hodgkin lymphoma, pts on fludarabine, stem cell transplant, t cell immunodeficiency, neonate (exchange transfusion, intrauterine transfusion)

Platelet refractoriness can be due to sepsis, fever, DIC, splenomegaly, alloimmunization. Treat with HLA-matched platelets. All HLA-matched platelets require irradiation (partial HLA matching results in receipient not recognizing donor lymphocytes as foreign and failing to mount immune response)

**Sickle cell disease**

* Transfuse only if: *symptomatic* (worse than usual), *end organ failure* (stroke, acute chest syndrome, organ failure), *major surgery*. No need for uncomplicated pregnancy, routine painful episodes, minor surgery, asymptomatic anaemia. Exchange transfusion if stroke, ACS with hypoxia, multiorgan failure, or if transfusion will raise Hb >10.
* Hydroxyurea if 1-2 vasoocclusive episodes a year

## **6. Rheumatology**

### **a) Multisystemic rheumatological diseases**

**ANCA Vasculitis** are favourite questions -recognize them. Remember the serology:

* pANCA = MPO = Churg Strauss (EGPA), microscopic polyangitis
* cANCA = PR3 = Wegeners (GPA)

**Adult-onset still’s disease** presents as daily *fevers*, *arthritis* (with DIPJ involvement), and salmon-coloured *rash* (can appear and disappear). Pharyngitis, lymphadenopathy, and hepatosplenomegaly may be present. *Ferritin is markedly elevated.* Treatment starts with NSAIDS then steroids.

**Pearls in SLE**

* A **significant ANA titre** is 1:100 or more.
* CRP is typically normal unless there is an infection, while ESR is elevated. Rheumatoid factor is often positive (not specific to RA - also positive in SLE, cryoglobulinaemia).
* **Drug induced lupus** may be caused by isoniazid, hydralazine, procainamide, chlorpromazine, antiepileptics, and antiTNF therapies. It is associated with ANA and anti-histone antibodies, but complement levels are normal. Renal and CNS involvement is rare. Treatment - stop the drug.
* **Treatment:** first choice is hydroxychloroquine. Azathioprine generally reserved for more severe manifestations of SLE not responsive to low-dose prednisone and hydroxychloroquine. Generally supplanted by mycophenolate**,** whichtends not to cause neutropenia (selective for B and T lymphocyte).

**Scleroderma**

* Antibodies: SCl-70 - diffuse SSC, RNA pol 3 - diffuse SSc, Anticentomere - CREST (note Anti-Jo-1 - dermatomyositis, not scleroderma)
* LcSSC associated with PAH, dcSSC associated with DPLD.
* Treatment:
  + Cyclophosphamide helpful for ILD
  + Biologics have not been shown to have benefit.
  + Treatment of scleroderma renal crisis: ACE-I (important to recognize renal crisis)
* Primary raynaud phenomenon may be idiopathic instead of CTD-related. Need not treat. If symptomatic, try nifedipine, sildenafil, endothelin-1 blockers.

**Antiphospholipid syndrome** is characterised by venous thromboembolism, recurrent miscarriages, livedo reticularis, prolonged aPTT and thrombocytopenia. Anti cardiolipin, lupus anticoagulant, and anti beta 2 glycoprotein 1 antibodies are positive. If patients wish to have a child they should be managed with clexane/heparin and aspirin.

**Felty’s syndrome** is the triad of longstanding RA, neutropenia, and splenomegaly. There may be recurrent infections. Distinguish from bone marrow causes of neutropenia, SLE. Treat with methotrexate (rather than another DMARD), add rituximab if unresponsive (not other TNF alpha inhibitors), and steroids as third line. GCSF may be considered.

**Behcet’s syndrome** is a vasculitis affecting vessels of all sizes. It has recurrent *painful orogenital ulceration (signature)*, arthritis, uveitis, and skin lesions (erythema nodosum, papulo vesicular pustular eruptions), LL thrombophlebitis, neurological complications. Treatment is empirical.

**Polyarteritis nodosa** is a medium vessel *ANCA negative* vasculitis characterised by microaneurysms, tissue infarction, haemorrhage. There is fever, various skin lesions (livedo reticularis), mononeuritis multiplex, abdominal pain (mesenteritic vasculitis, testicular pain), and renal insufficiency, weight loss. (Testicular pain and neuropathy is not seen in polymyalgia rheumatica). Diagnosis is made via *arteriography.*

**Thromboangiitis obliterans** (Buerger disease) presents with *distal arterial occlusion in young smokers* (e.g. digit ischemia, ulceraton, raynaud’s). Clinical features or serology of autoimmune disease is negative. Distinguish from atherosclerotic disease (involvement is distal and includes upper limbs, fewer risk factors). Imaging reveals *segmental occlusion interspersed between normal segments, and corkscrew collaterals*. Biopsy is not necessary for diagnosis but can be done if in doubt. Treatment is smoking cessation, ilioprost, calcium channel blockers. Immune suppression is not helpful.

**Fibromuscular dysplasia:** angiography shows abnormal appearance of vessels with areas of concentric stenosis (string of beads).

**Cholesterol atheroemboli** may complicate manipulation of atherosclerotic arteries e.g. during angiography, vascular surgery. Presents with fever, raised inflammatory markers, *eosinophilia,* hypocomplementemia, livedo reticularis / vasculitic rash, and *renal failure* (with white cells in urine and mild proteinuria).

**Familial mediterranean fever:**

* Episodes of fever, serositis, arthritis, rash, elevated acute phase reactants, lasting 1-3 days. Can get AA amyloidosis.
* MEFV1 mutation
* Treatment: *colchicine*, anakinra (IL-1 inhibitor)

**Relapsing polychondritis** presents with cartilaginous destruction (ear inflammation sparing lobes, pain over bridge of nose, airway structures causing OSA), arthritis, AR/MR, ear inflammation, skin findings. Treatment is mainly empiric, including steroids.

### **b) Arthritis**

**Gonococcal arthritis** may present with purulent arthritis, or as an *arthritis-dermatitis syndrome* with *tenosynovitis*, dermatitis (painless *vesiculopustular or pustular lesions*), and polyarthralgia. In contrast a **reactive arthritis** is usually an oligoarthritis without tenosynovitis, and may have a brown coloured rash on palms and soles (*keratoderma blenorrhagia*) or circinate balanitis on the penis.

**Poor prognostic factors in RA**

* Female sex
* Older age
* Gradual onset over few months
* Positive IgM rheumatoid factor
* Anti-CCP positive.
* Anaemia within 3 months of onset

**Gout**

* *Intra-articular steroids* if only 1-2 joints, no infection
* Avoid colchicine + clarithromycin, or colchicine + diltiazem.
* Allopurinol: 100mg/d and titrate upwards every 2-5 weeks, aim for serum urate <0.35mmol/L. *Continue flare prophylaxis if there are tophi*. Once target reached, continue for 3 months (if no tophi), or 6 months (after tophi resolve).
* Febuxostat (xanthine oxidase inhibitor) contraindicated in azathioprine use.
* Losartan helps with uricosuric effects.
* Lesinurad is a new uricosuric agent (URAT-1 inhibitor, inhibits urate reabsorption), used if there is inadequate decrease in uric acid with allopurinol.

In hemochromatosis, patients can develop gradual-onset OA-like joints, but characteristically 2nd/3rd MCPJ and wrist joints. Xrays show hook-shaped osteophytes. Systemic involvement includes cardiac, liver, and endocrine organ damage. If suspected, do *Tsat (>60% in men, >50% in women), ferritin.*

**Caution with anti-TNF treatment** (etanercept, infliximab, adalimumab, certolizumab, golimumab): TB reactivation, hep B/C, comorbid demyelinating disease (concern about inducing autoimmunity), ? heart failure (uncertain evidence).

**Scheuermann’s disease** affects normal ossification of ring epiphyses of thoracic vertebrae. It presents at 13-16 yrs old with kyphosis. X rays show irregular upper and lower vertebral endplates with loss of disk space, such that vertebrae deform forwards (as that is where the load is)

**McArdle syndrome** (type V glycogen storage disorder) presents with exercise-induced muscle pain and stiffness with contractures that subside at rest. CK is elevated. Myoglobubinuria can occur. In normal patients there is a sustained increase in serum lactate after exertion but this does not occur in this syndrome. Diagnosis is confirmed by muscle biopsy. No specific treatment but patients are instructed to avoid strenuous exercise.

### **c) Others**

**Hereditary angioedema**: C1 esterase inhibitor deficiency leads to intermittent attacks of complement activation and increased bradykinin, leading to vasodilation and angioedema. This presents as *recurrent episodes of cutaneous angioedema*, *laryngeal swelling*, or *bowel wall edema* (colic, nausea, vomiting, diarrhoea), often triggered by stress of mild trauma, and each lasting 2-4 days. Rule out anaphylaxis (*wheeze and urticaria is not seen* in HAE), and secondary causes (NSAIDs and ACE-I). Diagnosis is via low C4 and low C1INH. Treatment is with IV C1 inhibitor concentrate, or as per anaphylaxis if needed

**Scombroid poisoning** mimics anaphylaxis (flushing, rash, dizziness, headache, rarely bronchospasm), presenting rapidly after eating spoilt fish. IgE and mast cell tryptase are normal (mast cell tryptase is elevated in anaphylaxis). It arises from an excess in histamine in spoilt fish. Treatment is with antihistamines; or as for anaphylaxis if severe.

**Mastocytosis** is characterised by mast cell accumulation. It presents with *pruritus* on exposure to heat or irritation, urticaria pigmentosa, symptoms from *mediator release* (anaphylaxis, abdominal pain, nausea vomiting), organ or *marrow infiltration* (anaemia, eosinophilia, hepatosplenomegaly).

**[Misc basic science for Part 1]**

People with **latex allergy** often have allergic responses to banana, kiwi, avocado, chestnut, papaya, potato, tomato (which have similar proteins).

**Cytokine groups**

* Acute phase response: IL1, IL6, TNFalpha
* Antibody mediated: IL4, 5, 6, 10
* Cell mediated: IL2, INF-gamma

**HLA associations**

* HLA-A3: Haemochromatosis
* HLA-B5: Behcet syndrome
* HLA-B27: Seronegative spondyloarthropathies, erythema nodosum
* HLA-B57\*01: Abacavir hypersensitivity
* HLA-B58\*01: Allopurinol hypersensitivity
* HLA-Cw6: Psoriasis
* HLA-DR2: Goodpasture, MS, SLE
* HLA-DR3: Addisons disease, T1DM
* HLA-DR4: RA, SLE, T1DM, autoimmune hepatitis

## **7. Gastroenterology**

### **a) Hepatobiliary**

**Diagnosis of autoimmune liver diseases:**

* Autoimmune hepatitis: hepatocellular pattern of raised LFTs, +ve *ANA* & *ASMA* (Type 1) / *LKM* (Type 2) / soluble liver antibody (type 3) , elevated *igG*, histology.
* PBC: cholestatic pattern raised LFTs, +ve *antimitochondrial Ab*, histo → presents with puritus preceding onset of cholestatic jaundice, *xanthelasmas*, fat soluble vitamin malabsorption.
* PSC: cholestatic pattern raised LFTs, strictures on MRCP. Association with IBD.

**Genetic syndromes with hyperbilirubinaemia:**

* Conjugated hyperbilirubinaemia: (1) Dubin Johnson: defect in secretion of conjugated bil. Liver bx shows dark granular pigment. (2) Rotor syn: defect in storage of conjugated bil, normal liver biopsy.
* Unconjugated hyperbilirubinaemia: (3) Gilbert syndrome: reduced bilirubin glucuronyltransferase causing mild unconjugated hyperbilirubinaemia especially under conditions of stress, but no other significant consequence. In contrast, total absence of bilirubin glucuronyltransfase in (4) Crigler Najjar causes severe hyperbilirubinaemia, causing neonatal jaundice.

**Drugs that may cause liver injury**

* Cholestatic: chlorpromazine, azathioprine, captopril, cyclosporine, penicillamine, erythromycin, cloxacillin, OCP
* Hepatitic: paracetamol, phenytoin, ethanol, isoniazid (most impt among the TB meds), allopurinol.
* Mixed: augmentin, sulphonamide, sulfasalazine, carbamazepine.

**Hepatitis B risk of progression to cirrhosis:** most important factor is viral load.

**AIDS cholangiopathy** presents w cholestatic jaundice. Although infection is the most common cause of AIDS cholangiopathy, anti-infective treatment directed against C. parvum, Microsporidium, or CMV does not influence symptoms or cholangiographic abnormalities. Thus, *treatment of the cholangiographic abnormalities is primarily endoscopic*, and the approach varies with the anatomic abnormality.

**Interpretation of ascites tap**

* SAAG <11 - low protein (<25g/L) nephrotic, myxedema; high protein - infective, malignancy
* SAAG >11 - low protein (<25g/L) cirrhotic, high protein (>25g/L) budd chiari, cardiac.

**Cirrhosis**

(a) Consider Wilson disease in younger pt. Can present as acute liver failure with hemolytic anaemia. In a young patient with elevated liver test results, a *low ceruloplasmin* level, and *elevated urine copper excretion*, liver biopsy is typically obtained. *Genetic testing is complicated* as there are number of possible mutations. Treatment is with *penicillamine* or *trientine*. Patients with acute liver failure due to Wilson disease rarely recover and should be urgently referred for liver transplantation.

(b) Management of varices

* Primary prophylaxis (never bled): beta blocker if small, endoscopic variceal ligation (EVL) if big, either if medium.
* Secondary prophylaxis (already bled): EVL *PLUS* beta blocker
* No varices yet: no treatment.

(c) Management of AKI / HRS

* AKI: 1st treatment: albumin 1g/kg/d.
* If unresponsive → hepatorenal syndrome (Cr >1.5g/dL unresponsive to albumin x2 days, no other precipitant).
* Treatment for HRS: *terlipressin*, norE with albumin, midodrine/octreotide.

(d) **Hepatic encephalopathy:** Lactuloseis helpful, not just because of its effect as an osmotic laxative, but also because the acidic metabolites produced by lactulose breakdown promote ionization of ammonia into ammonium ions, which cannot diffuse back into the blood.

**Gallbladder polyps**: any larger than 1cm, offer cholecystectomy (malignancy risk).

**Pancreatitis:**

* Autoimmune pancreatitis can be diagnosed based on focal pancreatic enlargement with nondilated pancreatic duct, increased IgG, extrapancreatic involvement (sclerosing cholangitis). Treat with steroids.
* Gallstone pancreatitis: offer cholecystectomy prior to discharge.
* Chronic pancreatitis: offer pregabalin.

**Side effects of ribavirin**: hemolytic anaemia, teratogenicity (both male and female), GI (nausea, vomiting, stomatitis). Used less now with direct acting antivirals for hepatitis C.

**Acute fatty liver of pregnancy** presents in 3rd trimester with jaundice, elevated LFTs, abdo pain, nausea/vomiting, and the usual *complications of liver disease* (coagulopathy, renal impairment etc). Treatment is with stabilisation and delivery. In contrast, **obstetric cholestasis** presents with puritus, raised bilirubin, but patients are otherwise well → this runs a benign course and immediate delivery is not indicated.

### **b) Luminal**

**Colonoscopy intervals** (note: guidelines differ)

* Low risk adenoma (1-2, <10mm): 5-10 yrs
* High risk adenoma (>3, >10mm, villous histo, high grade dysplasia): 3 yr
* Serrated polyps: 5 yr (<10mm), 3 yr (>10mm or dysplastic), 1 yr (serrated polyposis syndrome)
* Post op colorectal CA: 1 yr, then 3 yr, then q5yr
* HNPCC: every 1-2 yr from 20-25 yr.
* FAP: every 1yr from 10-15 yr
* UC/Crohn: every 1-2 yr after 8-10 yr of disease

**Coeliac disease** presents with IBS-D symptoms (diarrhoea/steatorrhoea, abdo pain and bloating - not constipation), *malabsorption* (weight loss, fatigue, iron-deficiency *anaemia*, low *albumin*, neurological deficit from *B12 deficiency*). There may be other autoimmune disease (T1DM, hypothyroid), *dermatitis herpetiformis* (grouped puritic papules and vesicles), mild elevations in LFTs, and hyposplenism. Perform *anti-tissue transglutaminase (TTG) levels* with IgA levels (IgA deficiency results in false negative result), and duodenal biopsy for definitive diagnosis. Treatment is gluten avoidance. Dermatitis herpetiformis is treated with gluten avoidance and dapsone.

**Small bowel bacterial overgrowth** can arise in patients with slow GI motility (e.g. adhesions, IBD, scleroderma, strictures, gastric bypass). This presents as abdominal bloating, flatulence, or diarrhoea; there can be malabsorption including vitamin deficiencies. *Carbohydrate breath tests* (glucose/lactulose) confirms the diagnosis. Treatment includes prokinetic agents, rotating antibiotics (rifaximin, flagyl, cipro).

**Crohn disease**

* Little role for 5-ASA drugs
* Initial Rx: *steroids* (or controlled release budesonide for ileocolonic CD; not effective in left sided colitis), then *transition to AZA, 6-MP, or MTX* (steroids not effective for maintaining remission).
* Biologics (anti-TNF) if severe disease, and safe in pregnancy.

**UC**

* **Initial therapy:***5-ASA* first line, glucocorticoids 2nd line
* **Maintenance:** Prednisolone or MTX is not effective. Use azathioprine or 6-mercaptopurine (can’t give if low TPMT levels).
* Flare:
  + Colon <6cm: IV steroid as first treatment, then infliximab vs cyclosporin
  + Colon >6cm: colectomy (risk of perforation)

**Azathioprine** is second line for IBD.

* Before starting, some advocate *checking TPMT* (thiopurine S-methyltransferase) activity. Reduced TPMT activity leads to elevated levels of 6-mercaptopurine and more profound myelosuppression, so azathioprine should be avoided or used at reduced dose.
* Do not co-administer allopurinol as xanthine oxidase inhibition inhibits azathioprine metabolism, leading to toxic levels
* Other side effects of azathioprine: pancreatitis, hypersensitivity, interstitial nephritis, liver disease.

### **c) Others**

**Stool tests:**

* Alpha-1-antitrypsin: elevated in protein losing enteropathy (normally not secreted)
* Elastase: low in pancreatic insufficiency
* Calprotectin: high in inflammation - for IBD.

**Carcinoid tumors** may arise from GI tract (jejunum, ileum rather than colon) or lung. Carcinoid syndrome occurs when these tumors spread causing a high burden of liver mets such that vasoactive agents secreted cannot be catabolized. These cause flushing, bronchospasm, and fibrous depositions on right-sided heart valves (left sided is relatively spared: pulmonary inactivation of vasoactive agents), and can be detected by *urinary 5-HIAA*. These tumors are slow growing. Somatostatin analogues are useful for treating diarrhoea.

## **8. Infectious Diseases**

### **a) Systemic infections / sepsis**

**Infective endocarditis prophylaxis**

* Only for high risk patients (previous IE, cardiac transplant, prosthetic valve, unrepaired cyanotic congenital heart disease)
* going for high risk procedure (manipulation of gingival tissue. Not for scopes, hernia repair etc)

Indications for **early surgery in IE** (before completion of Abx)

* Complications: *Heart failure*, *heart block*, annular *abscess*
* *Failure of therapy*: bacteremia or fever 5-7 days after starting therapy
* Staph aureus, fungal, other *resistant organisms*
* KIV if vegetation >1cm, recurrent emboli.

**Antibiotic regimens for endocarditis** (simplified)[and prosthetic valve IE]

* Streptococcus (MIC <0.12): pen / amox / ampi / roc [PVE: same]
  + Allergic: Use vancomycin
  + Add gentamicin if relatively resistant (MIC 0.12-0.5)
  + Use enterococcus regimen if resistant (MIC >0.5)
* Enterococcus: *pen/ampi + genta* [PVE: same]  
   OR pen + roc
  + R/allergic: vanco + genta
* MSSA: Clox or cefazolin [PVE: + rifampicin + genta]
* MRSA: Vanco or daptomycin [PVE: + rifampicin + genta]

**Typhoid fever** presents as diarrhoea or constipation, fever with relative bradycardia, abdominal pain, maculopapular rose spots which blanch on pressure, headache, and hepatomegaly. Lab tests may revealed raised LFTs and neutropenia. Increasing resistance rates to ciprofloxacin has lead to azathioprine being the treatment of choice.

**C diff**

* Severe C diff (WBC >15k, Cr > 1.5 times the baseline) should be treated with PO vancomycin.
* Complicated C diff (toxic mega colon, ileus) should be treated with IV flagyl + PO vanco
* Second recurrence: PO vanco 6 weeks (first recurrence can treat with metronidazole or whatever was used initially)

**TB treatment**

* **Latent TB:** H + pyridoxine 6 months, or RH 3 months (better compliance).
* **TB meningitis:** treat with glucocorticoids and use RHZ plus either a fluoroquinolone or aminoglycoside (*ethambutol penetrates meninges poorly*).

**Leprosy:** Tuberculoid leprosy is characterised by strong T cell immune response with few bacilli detected (few well-demarcated lesions, granulomatous tissue ++); lepromatous leprosy is characterised by numerous lesions and high bacterial load.

**Infections to treat with antitoxin:**

* Diptheria
* Botulism
* Tetanus (use tetanus Ig); Abx (flagyl or penicillin); vaccination

**Fungal infections**

* Candidemia: echinocandins such as caspofungin, anidulafungin, and micafungin are the empiric therapy of choice. Invasive lines should be removed.
* Coccidioidal meningitis: fluconazole
* Aspergillus invasive rhinosinusitis: septate hyphae with acute angle branching. Voriconazole is treatment of choice

### **b) Atypical infections, parasites**

**Whipple’s disease:** the classic presentation of tropheryma whipplei infection is *migratory large joint arthralgia*, followed by intermittent diarrhoea and *abdominal* colic, malabsorption and weight loss. There may be other extraintestinal manifestation (*neuro*logic findings, hyperpigmentation, *endocarditis*). Diagnosis is by small bowel biopsy showing *PAS-positive macrophages*; vilous atrophy is also seen on endoscopy. A long course of antibiotics is required.

Suspect **Brucellosis** if there is a history of working with cattle or drinking unpasteurized milk. Symptoms include fever, hepatosplenomegaly, neuro s/s, arthralgia, endocarditis etc. Diagnosis is via serology or bone marrow culture (better). Treat w doxy/rifampin.

**Lyme disease** (bacteria: lyme borrelia; vector: ticks or lice) occurs in three stages

* Early localized disease: *erythema migrans* (vs erythema marginatum: rheumatic fever) +/- constitutional symptoms, within 1 month after the tick bite
* Early disseminated disease: *multiple* EM lesions, *neurologic* (meningitis, CN neuropathy, radiculoneuropathy) and *cardiac* (heart block, myopericarditis) manifestations weeks-months after infection. Serology is useful here but not elsewhere.
* Late disease: migratory or persistent *arthritis* +/- neurologic problems
* Diagnosis via EIA (sensitive but not specific), if positive, confirm with western blot (positive IgM without IgG in symptoms > 30 days is false positive). Laboratory testing insensitive at the early stage of infection, and not necessary when erythema migrans is present.
* Treatment is with doxycycline, amoxicillin, or cefuroxime (Doxy also treats southern tick–associated rash illness (STARI), which mimics lyme disease)

**Yellow fever** presents with a severe flu-like illness and pyrexia +/- epigastric pain and vomiting, and relative bradycardia. There is a transient well phase for a few days, after which severe illness with fever, jaundice, hepatomegaly, bleeding (brusing, BGIT) develops

**Rocky mountain spotted fever**: infection with rickettsia rickettsi, a tick-bourne illness in east, south, and west USA. Presents with *fever, headache, abdominal pain,* blanching erythematous rash with *macules that become petechial* over time (may slough). Sequelae may be *neurologic* (confusion, focal deficits, seizures, encephalitis), *cardiac* (arrhythmia, ARDS, pulm edema), or *haematological* (coagulopathy, BGIT). Antibiotic of choice is doxycycline, or chloramphenicol in pregnant patients.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **USA Fungi** | Location | Manifestation | Diagnosis | Treatment |
| Cryptococcus | California | Pulmonary infection  Meningoencephalitis  Skin, prostate, bone | Crypto antigen  Culture  LP all patients | Treat even if asymptomatic  Ampho + flucytosine  Then fluconazole 6-12m |
| Blastomyces | Great lakes  Ohio  Mississippi | Pneumonia  Skin  Bone, prostate | Yeast with broad based buds  Bone scan all pt  Urine c/s all pt | Ampho B + itraconazole |
| Histoplasma | Ohio  Mississippi | Asymptomatic  Nonspecific fever, wt loss, pancytopenia, pulmonary disease | Yeast forms within neutrophils | Itraconazole +/- ampho B |
| Coccidioido- mycosis | Southwest US desert | Pneumonia  Arthritis  Meningitis | Serology | Fluconazole |

**Schistosomiasis:** infection occurs from skin contact with infected freshwater (e.g. swimming) in Africa/Asia. An acute hypersensitivity reaction can occur *3-8 weeks* after infection (*Katayama feve*r - fever, rash, myalgia, *hepatosplenomegaly and pneumonitis*), but symptoms more commonly arise from chronic inflammatory response to migrating eggs. Genitourinary schistosomiasis (S. haematobium) presents with terminal *hematuria, dysuria*, bladder pseudopolyps and wall fibrosis, *SCC bladder*, and *urethral stricture*s which can lead to renal failure. Intestinal schistosomiasis (S. mansoni, others) causes intermittent *abdo pain*, diarrhoea (may be bloody), bowel *strictures*. Hepatosplenic schistosomiasis (S. mansoni, others) causes *hepatosplenomegaly, portal fibrosis*, portal hypertension. *Schistosome eggs may embolize* into the pulmonary circulation (pulmonary hypertension and dyspnoea), spinal cord (acute myelopathy), or brain (focal lesion, seizures). Diagnosis is via urine or stool microscopy, serology cannot distinguish past vs present infection. Treatment is with praziquantel (an antihelminthic).

**Cutaneous leishmaniasis** develops days-months after a sandfly bite. This begins as a pink papule that develops into an erythematous nodule. A golden crust forms then falls away, leaving a painless ulcer with an indurated border, which heals with scarring. **Visceral leishmaniasis** (Kala-Azar) presents with chronic malaise, fever, weight loss, hepatosplenomegaly.

**Chagas disease** is caused by Trypanosoma cruzi, in *latin american* countries. Chronic infection leads to *GI* and *cardiac* complications, including conduction defects and *achalasia-like* oesophageal dilation. There may be prothrombotic episodes. Diagnosis is via IgG antibody testing. Treat with benznidazole, nifurtimox.

**Hydatid liver cysts** (Echinococcus) present with mass effect, obstructive jaundice, and abdominal pain. Minor leaks lead to pain and a mild allergic reaction; rupture can cause anaphylaxis (aspiration is risky). CT (diagnostic modality of choice) demonstrates *daughter cysts* which distinguishes this from amoebic or bacterial abscess. Treatment includes albendazole alone (<5cm single cyst), puncture, aspiration, injection, and reaspiration (PAIR) technique (>5cm single cyst) or surgery (complicated cysts).

**Toxocariasis:**

* Visceral lava migrans: rash, lymphadenopathy, hepatosplenomegaly, eosinophilia -- diethylcarbamazine, thiabendazole.
* Ocular toxocariasis: granuloma formation in the eye. -- laser photocoagulation

**Parasites causing diarrhoea**

* Cryptosporidum: profuse watery diarrhoea +/- raised ALP. Oocytes seen on stool microscopy after *ZN staining*. Common in advanced HIV - treat with nitazoxanide.
* Microsporidia: chronic diarrhoea with malabsorption, stool sample shores spores - treat with albendazole.
* Giardia: *chronic bloating and explosive diarrhoea*, usually 1-3 weeks after exposure (later than e.g. e coli diarrhoea), stool sample shows trophozoites and cysts - treat with metronidazole, tinidazole, albendazole, etc.
* Entamoeba histolytica: amoebic *dysentry* (bloody) - treat with metronidazole.

**Drug regimens for malaria:**

* Chloroquine sensitive (central america, mid east), falciparum and non falciparum: chloroquine or artemisinin combination therapy
* Falciparum, or chloquine resistant: *artemisinin-based combination therapy.*
* Complicated falciparum (parasitemia >4%): IV artesunate or quinidine then artemisinin combination therapy
* Vivax and ovale: *add primaquine* to eradicate hypnozoite stage
* Patients on malaria prophylaxis should receive a different agent for treatment.
* N.B. falciparum malaria - cells are small and crenated (vs large in vivax), with high parasite count, and 2 chromatin dots (vivax has one)

### **c) HIV and STDs**

**Acute HIV**

* Acute HIV infection can cause aseptic meningitis; patients with meningitis and clinical signs HIV infection (pharyngitis, rash, and lymphadenopathy) should be tested.
* Differentiating infectious mononucleosis vs acute HIV infection:
* More often present in HIV: mouth ulcers, rash (unless ampicillin), diarrhoea
* More prominent in EBV: tonsillar exudates

**HIV drug regimens**

* Treatment: dual nRTI backbone (*tenofovir/emtricitabine* or abacavir/lamivudine - test HLAB5701 for abacavir) and a integrase inhibitor (raltegravir, dolutegravir, colbicistat boosted elvitegravir) or protease inhibitor (darunavir).
* Post exposure prophylaxis (PEP): tenofovir/emtricitabine, raltegravir (or a boosted PI) for 4/52
* Pre exposure prophylaxis (PrEP): tenofovir/emtricitabine
* Older HIV drugs have many side effects. For example, Zidovudine is associated with lipodystrophy and insulin resistance picture, Indinavir classically associated with indinavir renal stones, etc

**HIV CNS syndromes**

a) Contrast-enhancing MRI lesion

* Toxoplasma - focal *mass lesions* causing fever, headache, seizures, altered mental status, and focal neurology. Toxo Ab +ve. Usually *multiple*, frontoparietal/basal ganglia lesions with *ring enhancement* and surrounding edema. Treatment is pyrimethamine + sulfadiazine + folinic acid; prophylaxis is bactrim (higher dose than PCP prophylaxis).
* CNS lymphoma - focal mass lesion causing confusion, focal neurology, seizures, ‘B’ symptoms. Irregular/patchy ring enhancement (may *resemble toxo*). Associated with EBV. Can be difficult to tell from toxo (except that toxo Ab -ve) - can opt to treat for toxo first, with failure of radiological response prompting biopsy.
* Cryptococcus - subacute meningitis, diagnosed on peripheral cryptococcal Ag +, CSF crypto Ag +, india ink stain +. Treatment with amphotericin + flucytosine, then consolidation fluconazole.
* Cerebral abscesses

b) Not contrast enhancing MRI lesion

* Progressive multifocal leukoencephalopathy - demyelination due to JC virus. Rapidly progressive focal neurology, cognitive impairment. MRI bilateral, *asymmetric white matter demyelination* especially in periventricular & subcortical area. No specific treatment apart from HAART alone.
* HIV encephalopathy: dementia, depressive symptoms,motor (ataxia, generalized UMN weakness, incontinent), seizures over months. Multiple bilateral (*more symmetrical, less well demarcated*) lesions.

**EBV** is associated with oral hairy leukoplakia in HIV

**Live vaccines:** These include BCG, MMR, oral polio (injectable is not live), yellow fever, VZV, oral typhoid (injectable typhoid is not live). In HIV, do not give BCG, but the rest are ok if CD4 > 200.

**Genital ulcers**

* Chancroid: Haemophilus ducreyi causes a *tender* ulcer with ragged edges and contact bleeding, +/- lymphadenopathy
* Lymphogranuloma venereum (LGV): Chlamydia trachomatis serovars L1-3 causes *painless* genital ulceration and regional lymphadenopathy
* Syphillis: *painless* chancre.

**Rectal gonorrhoea** presents as tenderness and purulent rectal discharge. Rectal LGV presents as proctitis, rectal pain, PR bleeding, lymphadenopathy. It can cause fistulating disease which mimics crohns.

**Syphillis serology:** know how to interpret. Remember that VDRL may be false negative in late latent syphillis, while specific tests (TPPA, TPHA, etc) stay positive for life.

### **d) Other immunodeficiency**

**Complement deficiency**

* Early complement deficiencies (C1-4) lead to autoimmune disease e.g. SLE
* Late complement deficiencies (C5-8) predispose to encapsulated e.g. Neisseria infections.

**Infections in post transplant patients**

* First month: post-op surgical infections (wound, line sepsis, UTI, pneumonia)
* Months 2-6: immunocompromised infections e.g. CMV, PCP, listeria, TB.
* Month 6 onwards: community acquired infection

**Immunodeficiencies**

* **Common variable immunodeficiency** presents as recurrent respiratory tract infections, granulomas, and autoimmune phenomena.
* C3 deficiency and agammaglobulinaemia present with encapsulated bacterial infections.
* IgA deficiency presents as recurrent GI and respiratory infections.

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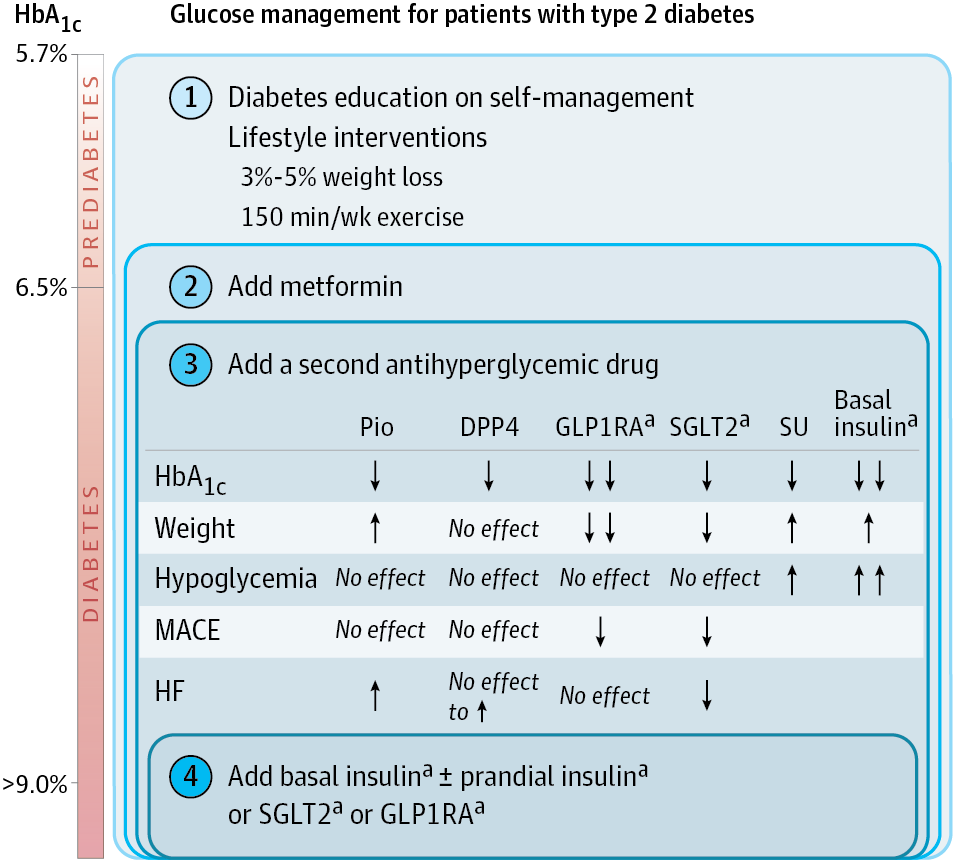
## **9. Endocrinology**

### **a) Diabetes**

**Maturity onset diabetes of the young** (MODY) is a genetic syndrome of various autosomal dominant genetic defects. It classically presents in a *non-obese* 10-30y with +ve family history (AD inheritance), *negative autoantibodies* (to anti islet cell, anti GAD, anti insulin - but note negative antibody does not rule out T1DM), high HDL and low renal threshold for glycosuria. Patients are insulin sensitive and often require only sulphonylureas.

**Diabetic drugs:**

* SGLT2 inhibitors (empagliflozin, etc) and GLP1 receptor agonists (subcutaneous drugs: -glutide, -natide etc) cause weight loss → SGLT2 inhibitors are in vogue as the 2nd line agent now.
* **GLP1 agonists** have been linked with pancreatitis. Exenatide should not be used in renal insufficiency CrCl <30. These are injectable so they aren’t popular.
* **Pioglitazone** has increased risk of fluid overload, bone loss, bladder CA. Avo
* **Saxagliptin** is associated with increased heart failure
* Chlorpropamide can cause hyponatremia by potentiating ADH effect on the renal collecting ducts.
* Rapid implementation of tight glycemic control is associated with worsening of DM retinopathy



**HHS** is defined using effective serum osmolality: 2 Na + glucose, *omitting urea*

### **b) Thyroid**

**Pearls in thyroid disease**

* If a patient has both hypocortisolism and hypothyroidism, replace cortisol first as thyroid replacement may precipitate an adrenal crisis
* When starting antithyroid drugs, counsel for agranulocytosis and hepatitis. If agranulocytosis develops, it is not appropriate to challenge with an alternative antithyroid drug (e.g. PTU instead of carbimazole); try cholestyramine and lithium until surgery or RAI.
* Both PTU and carbimazole inhibit organification of iodine. In addition, PTU also inhibits conversion of T4 to T3.
* If a thyrotoxic patient develops cardiac arrhythmias, don’t give amiodarone!
* Amiodarone induced thyrotoxicosis has two forms:
  + (1) In a patient with existing autoimmune hyperthyroid disorder (some clues: goitre, positive antibodies, increased uptake), amiodarone provides excess iodine substrate which feeds hormone production -- treat with antithyroid drug
  + (2) A thyroiditis -- treat with prednisolone
* Thyroid lymphoma is associated with Hashimoto thyroiditis.
* Thyroxine dose needs to be increased 25-50mcg in pregnancy. hCG has some TSH effect so TSH levels may be suppressed

### **c) Adrenal axis**

**Pituitary tumors**

* A large pituitary tumorwith *prolactin >1000U/L is likely a prolactinoma*, less marked elevations in prolactin can occur in a nonfunctional tumor (pit stalk compression).
* Diagnosing **acromegaly:** IGF1 is a good screen. OGTT showing failure to suppress GH secretion confirms (glucose suppresses GH).
* Treatment
  + Prolactinomas -- *dopamine agonists even if there is visual field defect* (tumor shrinks). Exception: tumor bleed
  + *All others - transsphenoidal resection as first line*
  + Cushing’s disease -- resection, *metyrapone and ketoconazole.*
  + Acromegaly -- First line: transsphenoidal surgery. Residual disease: *somatostatin receptor analogues,* GH agonist (pegvisomant), stereotactic RT.

Carcinoid tumors can produce GH also. If biochemically suspect acromegaly but MRI negative, search for carcinoid tumor.

**MEN syndromes**

* MEN1: the 3Ps - Pituitary, Parathyroid, Pancreas
* MEN2A: 2Ps and an M - Parathyroid, *Phaeochromocytoma,* Medullary thyroid
* MEN2B: 1P and 2 Ms - *Phaeochromocytoma,* Medullary thyroid, Marfanoid  
  [treat the phaeo first!\
* MEN2 is associated with RET protooncogene mutation

**Polyglandular autoimmune syndrome**

* Type 2: hypo*adrenal*, autoimmune *thyroid* disease.
* Type 1: mucocutaneous candidiasis, hypoparathyroid, hypoadrenal, gonads

**Adrenal adenoma**

* Benign adenomas usually low attenuation on CT scan, rapid washout of contrast (>50% in 10 min)
* All patients - evaluate cortisol, catecholamines. Those with HTN - test for aldosteronism. Do not biopsy prior to ruling out phaeochromocytoma.

**Glucagonoma** is characterised by impaired glucose tolerance, weight loss (due to protein catabolism), and *necrolytic migratory erythema* (erythematous rash which erodes).

**If doing aldosterone studies**, stop ACE/ARB and spironolactone. Thiazides (salt depletion stimulate renin release), calcium channel blockers may interfere but risk of stopping may outweigh risk of test. Beta blockers should be ok.

**Nonclassical congenital adrenal hyperplasia** arises due to defective 21-hydroxylation of 17-hydroxyprogesterone to 11-deoxycortisol, which shunts steroids to androgen production. While classical CAH presents in infancy with adrenal insufficiency and salt wasting, nonclassical CAH presents later with signs of *androgen excess and/or primary amenorrhoea*. Decreased cortisol synthesis stimulates *ACTH excess,* which allows maintenance of sufficient glucocorticoid and mineralocorticoids, at the expense of excess adrenal androgen production (vs classical CAH - unable to produce sufficient glucocorticoids and mineralocorticoids at all). Diagnosis is strongly suggested by a *high morning 17-hydroxyprogesterone* (>200), and confirmed by a *short synacthen test, which results in an exaggerated 17-OHP response* (>1500). The main differential is polycystic ovarian syndrome. Treatment is with oral

contraceptives or glucocorticoids.

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### **d) Calcium / Bone**

**PseudohypoPTH:** maternal transmission of a G protein defect results in pseudohypopara- thyroidism (end organ resistance to PTH causing *hypoCa, hyperPO4, but high PTH*) with features of albright’s hereditary osteodystrophy (*short stature, round facies, obesity, short forth metacarpal bones, developmental delay*), as well as *hypothyroidism and ovarian failure*. Paternal transmission of the same gene results in phenotypic features of albright’s hereditary osteodystrophy with no biochemical manifestation (*pseudo-pseudohypoPTH*).

**Osteoporosis**

* Newly diagnosed - look for secondary causes. Test FBC (malignancy), renal function, calcium, TSH, vit D, urine calcium (screen hypercalciuria)
* Treat if: *BMD -2.5*, BMD *1 to 2.5 and FRAX risk of major osteoporotic fracture >20% or hip fracture >3% in 10 years*
* Recommended daily intake is 1500mg/day of calcium, 400-800 units/day of vitamin D
* Drug holiday if bisphosphonates 3-5 years, no progression of disease, minimal risk factors for additional fracture.

**Paget’s disease** is a disorder of osteoclasts causing a localized or multifocal increase in bone turnover. This presents as *bone pain*, *fractures, deformities,* and consequence of bone overgrowth (*osteoarthritis*, *nerve impingement*, hearing impairment, *headache*). *ALP is elevated but calcium, phosphate, and PTH is normal* (ddx: hyperparathyroidism if Ca/PO4 abnormal). X-rays are diagnostic, revealing *osteolytic* (ddx: mets) and *osteoblastic lesions* (thickened cortices). There is an association with osteosarcoma. Treatment is with bisphosphonates.

**Osteomalacia / rickets -** can present with proximal myopathy, bone pain, *calcium is low/normal, PO4 is low/normal, ALP is high*, PTH can be elevated in secondary hyperparathyroidism. X ray may show *looser zones* (linear areas of low density surrounded by sclerotic borders). Etiologies -

1. Calcipenic rickets - a/w myopathy, raised PTH
   1. Nutritional calcium / vit D deficiency, or malabsorption
   2. Genetic - vit D dependent rickets
2. Phosphopenic rickets - no myopathy
   1. X linked hypophosphatemia - renal PO4 wasting
   2. Proximal (type 2) renal tubular acidosis.
3. CKD

**Hypercalcaemia**

* Hyperparathyroidism - Indication for parathyroidectomy: younger than 50, calcium > 1 SD from ULN, or complications (osteoporosis, CKD, renal stones).
* Familial hypocalciuric hypercalcaemia: diagnosis via 24h urine calcium <5, calcium-creatinine clearance ratio <0.01

### **e) Reproductive endocrinology**

**Contraindications to combined oral contraceptive pills** include (NICE)

* CVS risk: Age >35 y and smoking >15 cigs/day, HTN (BP >160/95), vascular disease
* VTE risk: SLE with APS, VTE, prolonged immobility
* Stroke risk: migraine with aura (increased risk ischaemic stroke)
* Breast CA

**Hypogonadism**

* Primary (*high LH FSH*)
  + *Klinefelter XXY* (male): tall stature, gynaecomastia, infertility due to azoospermia, and small testes. Sense of smell is intact (vs in Kallman’s syndrome where smell is impaired). Intellectual disability is not seen.
  + *Turner syndrome* XO (female)
  + Prader-Willi and other syndromes
  + Gonadal dysgenesis.
  + Testicular disease, ovarian disease: castration, mumps orchitis, rubella, cystic fibrosis, sickle cell anaemia, chemotherapy
* Secondary (*low* LH, FSH)
  + Kallman syndrome: a/w anosmia, cleft palate, colour blindness (absent olfactory bulb on MRI)
  + Hyperprolactinemia, steroids, critical illness, systemic illness, anorexia, DM, obesity, sleep apnoea
  + Pit tumor, infiltration, apoplexy.
* Secondary amenorrhoea - see approaches notes

**Polycystic ovarian syndrome**

* If do not desire fertililty: OCP first line treatment
* Distinction from nonclassical CAH - LH is usually high in PCOS but low normal in CAH
* Progestin withdrawal test: withdrawal bleeding (estrogen sufficient stage) vs no withdrawal bleeding (estrogen deficient state: hypothalamic amenorrhoea, uterine outflow blockage).

## **10. Oncology**

### **a) General notes**

**Short notes on chemotherapy** (characteristic side effects)

* **Platinum drugs** cross link DNA. Cisplatin is more *neuro-, oto-, and nephrotoxic*, while carboplatin more *myelosuppressive*.
* **Topoisomerase inhibitors** include
  + Anthracyclines (danorubicin): *Cardiotoxic.*
  + Irinotecan: Diarrhoea and immunosuppression
  + Podophyllotoxins (etoposide): hypotension during infusion, myelosuppression.
* **Antimetabolites**
  + Methotrexate
  + DNA analogues: 5FU (hand foot syndrome), capecitabine (caution: interaction with warfarin).
  + DNA analogues: fludarabine, cytosine arabinoside (ara-C), gemcitabine -- SEs: myelosuppression, *acute cerebellar syndrome* (cytarabine).
* **Mitotic spindle poisons**
  + Vinca alkaloids: vincristine (in leukaemia, *neurotoxic*), vinblastine (in testicular cancer, lymphoma, *myelosuppressive*), vinorelbine (in lung CA, neurotoxic and myelosuppressive).
  + Taxanes (paclitaxel, docetaxel): neurotoxic (paclitaxel), edema (docetaxel - capillary damage)
* **Bleomycin** is a free radical agent. Lung (*pulmonary fibrosis*) and skin toxicity. Unusually, there is no myelosuppression.
* **Thalidomide:** neuropathy, teratogenesis, constipation, drowsiness.
* **Alkylating agents**
  + Cyclophosphamide: *hemorrhagic cystitis* (give mesna to prevent)
  + Chlorambucil: myelosuppression, hepatotoxicity, azospermia
  + Melphalan: myelosuppression, SIADH, amenorrhoea, sterility, pulm infiltrates

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### **b) Specific cancers: notes on treatment**

*This field moves very rapidly - probably do not expect to know too much.*

**Breast CA**

* Chemoprophylaxis - offer *chemoprophylaxis* eg tamoxifen (premenopausal), exemestane (postmenopausal) *in high risk* including LCIS, atypical ductal hyperplasia.
* MRI breast cancer screening if: BRCA mutation, chest wall radiation between 10-30 yr old
* Staging: no need PET/bone scan if stage 0-2 without symptoms of mets
* *ER+ early breast cancer, use tamoxifen for at least 5 years*; 10 is better
* Mets: ER+ mets best managed with aromatase inhibitors, if fail, consider everolimus and other antiestrogen agents.
* In patients with aggressive breast cancer who develop severe arthralgia while on antiestrogen therapy due to an aromatase inhibitor, a second aromatase inhibitor should be tried; if the arthralgia fails to resolve, tamoxifen should be started.
* Most patients with recurrence outside the central nervous system should undergo biopsy. Discordance between the status of these molecular markers in the primary tumor and the metastatic site occurs in 10% to 15%, usually resulting in a change in treatment.

**Ovarian CA**

* CT-guided or ultrasound-guided *biopsy of a suspected ovarian mass is contraindicated*, as this may cause rupture and dissemination of cancer cells
* All patients with ovarian CA should undergo BRCA testing. If positive, risk-reducing bilateral salpingo-oophorectomies recommended between ages 35 and 40 years, once childbearing is complete.

**Treatment of cervical CA**

* 1A: microscopic disease - simple hysterectomy, cone biopsy
* I or IIA: cervix only or non bulky uterine invasion - radical hysterectomy vs radiation
* IIB, III, IVA: bulky disease, pelvic wall, vaginal, or ureteric involvement: chemoRT
* IVB distant mets: palliative chemo/RT

**Colorectal CA**

* Mutations in the K-ras or N-ras genes are associated with resistance to epidermal growth factor receptor–targeted agents (cetuximab, panitumumab).
* Postoperative surveillance: physical examination and CEA every 3 to 6 months, CT TAP annually for 3 to 5 years; colonoscopy 1 year after resection and then repeated at 3- to 5-year intervals.
* Surgical resection is the initial treatment for patients with stage I rectal cancer (defined as a tumor that invades into, but not fully through, the rectal wall, with no evidence of lymph node metastases). No need chemoRT.
* Anal CA: usually squamous cell origin, with chemoradiation the primary treatment modality - mitomycin plus 5-fluorouracil (5-FU)

**Pancreas**

* Multiagent systemic chemotherapy with 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) is appropriate treatment for metastatic recurrence of pancreatic cancer in patients with good performance status. Gemcitabine if poor performance status.

**Gastric CA**

* Determination of HER2 tumor status is indicated for patients with newly diagnosed metastatic gastric cancer, as the *anti-HER2 monoclonal antibody trastuzumab*, when added to a systemic chemotherapy regimen, is beneficial in treating patients whose tumors overexpress HER2.

**NSCLC**

* Stage I, II: curative surgery if fit, + adjuvant chemo in stage II (adjuvant cisplatin-based chemotherapy improves survival in patients who have undergone successful resection of stage II or stage III NSCLC)
* Stage III (mediastinal LN): chemoRT
* Stage IV (met or effusion): EGFR (erlotinib) or ALK/ROS (crizotinib) treatment if there is an activating mutation, if not platinum-based chemo

**SCLC**

* Surgery if very early stage
* Chemo RT for limited stage, + *Prophylactic cranial irradiation* if there is good response
* Platinum based chemotherapy for extensive stage

**Head and neck**

* Early stage (1 and 2, no LN) - surgical resection or definitive RT, except NPC (chemoRT for stage 2). Post surgery, consider adjuvant RT or chemoRT if positive margins, lymphovascular / perineural invasion, or T3/4 disease
* Locally advanced:
  + surgery (esp oral cancers) kiv adjuvant radiation or chemoRT (esp if positive margins)
  + combined therapy (RT + adjuvant cetuximab or cisplatin) - if residual cancer, then surgery / neck dissection
* Metastatic: chemotherapy (usually poor result)
* Surveillance: assessment of the primary site (for example, in this patient by direct oral examination) and periodic assessment of the remaining squamous mucosa of the head and neck via direct laryngoscopy.
* Test for HPV in all head and neck cancers (cure rate higher if HPV associated)

**Prostate CA**

* Imaging studies are currently not recommended for men with low-risk disease. Currently accepted parameters for imaging studies include a serum PSA level of 20 ng/mL (20 µg/L) or higher, a PSA level of 10 ng/mL (10 µg/L) or higher associated with a T2 tumor, a Gleason score of 8 or higher, or a T3 or T4 tumor.
* Early stage: surgery or RT. Following surgery, PSA should be undetectable <0.2 ng/ml. Higher values suggest residual/recurrent disease. If so, start androgen deprivation therapy.
* Identification of biochemical recurrence 2 or more years after surgery is more consistent with local recurrence → salvage radiotherapy beneficial. In contrast, radiotherapy does not seem to benefit men in whom a PSA level remains detectable following surgery
* Met: androgen deprivation therapy
  + **GnRH agonist:** buserelin, goserelin leuprolide (initial increased gonadotropin release, afterwards levels fall)
  + **Androgen receptor blocker:** flutamide, nilutamide, bicalutamide, enzalutamide.
  + **GnRH antagonist:** degarelix
* Note: Prostate nodule, asymmetry, or induration - all require prostate biopsy regardless of PSA

**Renal cell CA:** Close observation is the standard of care for patients following surgical resection for nonmetastatic renal cell carcinoma, as no studies to date have identified an adjuvant therapy that improves survival in these patients. Sunitinib can be helpful in met.

**Bladder CA:**

* Superficial bladder CA: TURBT
* Recurrence: usually managed with repeat TURBT and additional intravesical infusion. However, recurrence within 6 to 12 months of initial TURBT, or after one to two courses of BCG infusion should undergo cystectomy.
* For muscle invasive disease, neoadjuvant chemo then radical cystectomy

**Testicular CA:**

* Stage 1 (confined to testes): orchidectomy, then single agent carboplatin, or radiation, or retroperitoneal lymph node dissection (optional in seminoma, should do in nonseminoma)
* Stage II: retroperitoneal lymph node dissection or adjuvation chemoRT.

**Lymphoma**

* Mantle cell lymphoma: a/w t(11,14), cyclin D1 over expression.
* DLBCL: R-CHOP, involved field RT in bulky disease
* Autologous hematopoietic stem cell transplantation is indicated for patients with recurrent Hodgkin lymphoma, particularly patients who achieve a complete response to salvage chemotherapy.
* Mycosis fungoides: early stage (skin limited): topical glucocorticoids, retinoids, PUVA; advanced stage (3-4): RT, systemic therapy.
* Raised ICP with ?CNS lymphoma → steroids then brain biopsy.
* Follicular lymphoma: early treatment in grade 1-2 does not improve survival. IF symptomatic, then R-CHOP, R-CVP, or R-benda.

**Melanoma**

* Wide local excision
* Sentinel lymph node bx if thicker than 1mm or high risk, kiv lymphadenectomy
* Dascabazine for met melanoma
* If V600 BRAF mutation, targeted therapy with Vemurafenib
* Immunotherapy eg pembrolizumab, ipalimumab (CTLA-4 agent, T cell checkpoint agent; these agents can cause autoimmune-mediated side effects → treat SE with steroid)

**Cancer unknown primary**

* Women with abdominal carcinomatosis: assume ovarian CA → debulking with TAHBSO, platinum/taxane chemo
* Neuroendocrine: if low grade, use octreotide. If high grade, treat as SCLC with platinum based chemo

**Other onco**

* Malignant SVCO: histo diagnosis before therapy, use stenting rather than RT (except airway obstruction).

Histiocytosis X presents with rash, cytopenias, hepatosplenomegaly/lymphadenopathy, diabetes insipidus, bone involvement, lung cysts and nodules.

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## **11. Dermatology**

*There is no subsitute for looking at pictures!*

**Pemphigus vulgaris (PV) vs bullous pemphigoid (BP):**

* PV presents in a younger patient with intraepidermal (superficial) *flaccid blisters* (Nikolsky positive) and *mucosal involvement*; BP presents in an older patient with subepidermal tense blisters (Nikolsky negative) without mucosal involvement.
* Histology: In PV, there is intraepithelial cleavage with acantholysis (detached keratinocytes), resembling a ‘row of tombstones’. In BP, there is subepithelial cleavage and immunoflorescence shows linear IgG.
* Antibodies: desmoglein 3 in PV, BP180 & BP230 in BP.
* Treatment: for both, can use steroids and steroid sparing agents (azathioprine, MMF). Adjuncts in BP include doxycycline with nicotinamide and dapsone

**Erythema nodosum** presents as acute-onset tender nodules on bilateral shins. There should not be ulceration (erythema induratum), sclerosis (lipodermatosclerosis), atrophy (lupus), pus (infection), or trauma; underlying medical conditions of ESRF (calciphylaxis), pancreatitis (panniculitis), autoimmune disease (cutaneous PAN) prompt consideration of ddx. Etiologies include -

* Infective: strep throat, viral, mycoplasma, TB (and sarcoid)
* IBD
* OCPs: EN can develop as early as 2-3 cycles
* Lymphoma/leukaemia
* Drugs: sulphonamide, salicylates, NSAIDs

Management is symptomatic.

**Pyoderma gangrenosum** is associated with IBD, rheumatoid arthritis, haematological malignancies (leukaemias, myelomas). Treat with steroids, infliximab.

**Necrobiolysis lipoidica** presents in diabetics with a yellow-brown pretibial plaque (may be pruritic or painful) which atrophies. Treat with steroids.

**Granuloma annulare** presents as an asymptomatic, skin-coloured/erythematous annular plaque with a rope-like border and central clearing. This may be localized or generalized. There may be an association with HIV.

**Dermatitis herpetiformis:** see under gastroenterology

**Psoriasis** may be exacerbated by beta blockers, lithium, steroids, antimalarial drugs.

**Drug induced gingival hypertrophy:** phenytoin, cyclosporin, CCB (nifedipine, verapamil), erythromycin, hormones.

**Toxic shock syndrome:** S aureus exotoxin causes fever, hypotension, diffuse erythroderma with subsequent desquamation, and multiorgan involvement (GI, muscular, hyperemia of mucous membranes, renal, hepatic, CNS, haemato).

**Acanthosis nigricans** is most associated with gastric CA.

**Melasma** is a hormonally stimulated increase in melanogenesis. Typically appears as a symmetrical hyperpigmentation affecting the malar areas, upper lip, or forehead; worsening after sun or estrogen exposure

A solar lentigo that has variegation in colour (vs light tan) and progressively enlarges is suggestive of progression to **lentigo maligna**, a form of melanoma in situ.

**Darier’s disease** is an AD condition which presents in early adulthood with warty papules and plaques in seborrhoeic areas (scalp, chest, back), palmar pits and nail dystrophy.

### 

## **12. Miscellaneous**

### **a) The porphyrias**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Acute intermittent porphyria (AIP)** | **Lead poisoning** | **Arsenic poisoning** | **Porphyria cutanea tarda (PCT)** | **Hereditary coporphyria (HP)** |
| Defect | Porphobilinogen deaminase, AD.  Triggers: drugs, sepsis, fasting, alcohol | Inhibits haem biosynthesis  *Exposure hx* | Doesn’t inhibit haem synthesis  *Exposure hx* | Coproporphyrinogen oxidase, AD  Triggers: drugs, sepsis, fasting, alcohol | Uroporphyrinogen decarboxylase.  AD or ppt by alcohol, hep C, estrogen |
| Abdo symptoms | Abdo pain  Nausea vomit | Abdo pain  Nausea vomit | Abdo pain  Diarrhoea | - | Similar to AIP but less severe |
| Neuro s/s | Neuropathy  Seizures, coma  SIADH  Psychiatric dx | Neuropathy | Neuropathy | - | Similar to AIP but less severe |
| Skin | NIL | NIL | NIL | Chronic blistering photosensitivity | Photosensitivity |
| Haem | - | Microcytic anaemia  Basophilic stippling | Microcytic anaemia | - | - |
| Others | Red/brown urine | Proximal RTA  Interstitial nephritis  Gingival blue/black line | - | Elevated LFTs  Iron overload  DM | Elevated LFTs |
| ALA levels | High PBG, ALA | High ALA | - | - | High ALA, PBG |
| Coproporphyrins  (fecal, urine) | - | Elevated | - | N / elevated | Elevated |
| Treat | IV heme arginate  Glucose load | Stop exposure | Stop exposure | Sun avoidance  Chloroquine  Phlebotomy | Sun avoidance  Chloroquine  Stop alcohol/OCP |

PBG = urinary porphobilinogen

ALA = delta-aminolevulinic acid (ALA)

Haem arginate downregulates heme biosynthesis and decreases accumulation of heme precursors

The porphyrias are disorders of haem metabolism but unfortunately each presents rather differently. AIP is the prototypical acute porphyria with acute abdominal and neurological symptoms, but *no skin* involvement. ALA and PBG are elevated but not coporphyrins. PCT is the opposite - there is *skin* and hepatic involvement, but minimal abdominal or neurological symptoms; coporphyrins are elevated but not ALA and PBG. HP combined features of both AIP and PCT. There are other porphyrias - too many to remember. Lead poisoning mimics AIP but may also has exposure history, microcytic anaemia, renal involvement, and high coporphyrins.

### **b) Other syndromes**

**Marfan’s syndrome vs homocysteinuria**

|  |  |  |
| --- | --- | --- |
|  | Marfan’s syndrome | Homocystinuria |
| Skeletal changes | Yes in both: tall, kyphoscoliosis, arachnodactyly, high arched palate, pectus excavatus, lax ligaments | |
| Eye | Yes in both: ectopic lentis, glaucoma | |
| Aortic | Aortic dissection, regurgitation, MVP  *[requires monitoring!]* | Nil |
| Thromboembolism | - | Arterial and venous thromboses |
| Neuro | - | Epilepsy, low IQ |
| Bone | - | Osteoporosis |
| Diagnosis | Revised Ghent criteria | Homocystine levels |

**Fragile X syndrome:** A trinucleotide repeat disorder in the fragile X gene (FMR1) in the X chromosome. Causes *learning disability* and social disability (poor eye contact, hyperactivity, repetitive speech), dysmorphism (long thin face with large ears), large testicles, joint laxity, flat feet, mitral valve prolapse (*mimics marfan’s*). Diagnosis via karyotype.

**Leber’s hereditary optic neuropathy:** a young male presenting with *bilateral optic neuropathy and blindness in a short time*. There may be *tremor* and a MS-type illness. Diagnosis is made on muscle biopsy. This is a mitochondrial disorder (all male offspring of affected females are affected).

**Hereditary haemorrhagic telangiectasia** (Osler-Weber-Rendu syndrome) is an autosomal dominant disease characterised by multiple *telangiectasias* and AV malformations which lead to epistaxis, GI and cerebral *haemorrhage*, and haemoptysis. Pulmonary AVMs result in *paradoxical embolic stroke and brain abscess*, and hepatic AVMs can result in high output cardiac failure.

**Von-Hippel-Lindau** is characterised by

* CNS and retinal haemangioblastomas -- do yearly fluorescein angiography, MRI q3 yr
* Renal cysts and carcinomas
* Phaeochromocytoma - do yearly urinary metanephrines
* Pancreatic tumors

**Ehler-Danlos syndrome** is a disorder of collagen synthesis. Characterised by generalised hypermobility (recurrent dislocations), skin laxity, easy bruising, short stature with scoliosis, occular fragility.

**Xeroderma pigmentosum** is a disorder of nucleotide excision repair. Accumulated DNA damage and chromosome breakage lead to *sun damaged skin* (photosensitivity, severe sunburn, multiple freckles, solar keratosis), young onset *skin cancers*, and *neurologic disorders*.

**McCune-Albright syndrome** consists of

* Polyostotic fibrous dysplasia
* Cafe-au-lait pigmentation
* Autonomous endocrine hyperfunction (hyperthyroid, cushing’s, precocious puberty)
* Recurrent ovarian cyst / testicular abnormalities on US

### **c) Toxicology**

Some **Antidotes:**

* Neuroleptic malignant syndrome: dantrolene, bromocriptine
* Serotonin syndrome: cyproheptadine
* Malignant hyperthermia: stop anaesthetic agent, dantrolene
* TCA overdose: sodium bicarbonate.
* Cyanide poisoning: sodium thiosulphate, Dicobalt edetate, sodium nitrite
* Organophosphate: pralidoxine
* Digoxin: digitalis Fab (digibind)
* Beta blocker: atropine, then glucagon. If unresponsive, consider pacing.

**Methanol toxicity**

* Both methanol and ethylene glycol poisoning present with a high osmolar gap
* *Ocular signs and symptoms* (mydriasis, reduced visual reflexes, reduced acuity) more common in methanol
* *Flank pain and renal failure* occurs in ethylene glycol poisoning (due to crystallization of oxalic acid)
* Management: gastric decontamination within 4h, IV fomepizole, haemodialysis, folic acid in methanol toxicity, pyridoxine/thiamine in ethylene glycol toxicity

**Drug-related toxicity**

* Poor prognostic factors in paracetamol overdose are PT >20, pH < 7.3, Cr > 300
* **Acute ergotism** can develop in patients on ergotamine + CYP3A4 inhibitors (clarithromycin, ketoconazole, ritonavir), presenting with vasoconstriction and even amputation.
* **Theophylline**'s toxic effects arise from antagonism of adenosine receptors and indirect adrenergic activity. It includes metabolic abnormalities (eg, *hypokalemia*, hyperglycemia, metabolic *acidosis*), coarse muscle *tremor, vomiting,* and abdominal pain. *Seizures,* hypotension, and *arrhythmias* are the life-threatening symptoms. Drugs that may increase theophylline drug concentrations include
  + Allopurinol
  + Carbimazole
  + Cipro, clarithro, erythromycin, fluconazole, isoniazid
  + Diltiazem, verapamil
* **Digoxin toxicity** presents as arrhythmias, GI symptoms, neuro symptoms (confusion, weakness), and visual changes (classically a yellow discolouration of vision, but can be anything). Precipitating factors include:  
  - Inhibition of tubular secretion: verapamil, nifedipine, quinine  
  - Hypokalaemia, hypomagnesemia
* **Cheese reaction:** patients on MAO-I (selegiline, rasageline, moclobenmide) may suffer hypertensive crisis should they take tyramine rich foods (cheese, red wine, broad beans), as tyramine, normally broken down by MAO, accumulates and stimulates adrenaline release.
* **Lithium** leads to DI by downregulating aquaporin-2 gene expression. HCTZ can cause a rise in lithium levels leading to toxicity

**Differentiating NMS vs serotonin syndrome:** (1) NMS presents with confusion, fever, autonomic dysfunction, and *rigidity*; while serotonin syndrome presents as *tremor and hyperreflexia*, (2) NMS occur at any time during antipsychotic exposure, serotonin syndrome tends to occur in overdose or combination of serotoninergic agents. After stopping MAO-I, allow a washout of 2 weeks before starting SSRIs to reduce the risk of serotonin syndrome

**Drugs of abuse**

* **Cocaine** inhibits re-uptake of biogenic amines including dopamine (psychomotor *agitation*), noradrenaline (*sympathetic activity* - tachycardia, hypertension, sweating, hallucination, *seizures, acidosis*, rhabdomyolysis), and serotonin (*euphoria*). This may cause myocardial infarction, arrhythmias, premature coronary artery disease, dilated cardiomyopathy.
* **Ecstasy** is an amphetamine derivative which stimulates serotonin release and sympathetic nervous system activation. It may cause *sympathetic symptoms* (hyperpyrexia, sweating, tachycardia, hypertension, dilated pupils) *seizures*, *rhabdomyolysis, AMI*, arrhythmias, *SIADH*. Treatment: gastric lavage if within 1h, supportive mx (e.g. saline infusion), benzodiazepines, antihypertensives.

**Agents for smoking cessation:** bupropion (NDRI, risk seizures), varenicline (partial agonist of nicotinic receptors).

**Agents for alcohol cessation:** acamprosate (glutamate receptor), naltrexone (mu opoid receptor antagonist), disulfiram (aversive therapy).

### **d) Statistics [for part 1]**

**Which test to use**

* Comparing continuous outcome variables in independent data sets
  + Parametric data, 2 groups: unpaired T-test
  + Parametric data, >2 groups: ANOVA
  + Non-parametric data: 2 groups: Mann-Whitney U test (not normal, ratings 1-7)
  + Non-parametric data, >2 groups: Kruskal-Wallis test
* Comparing continuous outcome variables in PAIRED data sets
  + Parametric data, 2 groups: paired T test
  + Parametric data, >2 groups: ANOVA
  + Non-parametric data, 2 groups: Wilcoxon rank-sum test.
  + Non-parametric data, >2 groups: Kruskal-Wallis test
* Comparing CATEGORICAL outcome variables (e.g. frequencies) between two groups
  + Unpaired data: Chi square test, fisher exact test (more precise)
  + Paired data: McNemar test
* Survival time analysis: log rank test
* Correlation - ‘R’ (Pearson correlation coefficient) for continuous scale measurements, Spearman rank correlation coefficient for categorical variables (eg pain scores).

**Sensitivity & Specificity**

* +ve predictive value = of those who test +ve, how many have disease = A / (A+B)
* -ve predictive value = of those who test -ve, how many no disease = D / (C+D)
* Sensitivity = of those who have disease, how many test +ve = A / (A+C)
* Specificity = of those who have no disease, how many test -ve = D / (B+D)  
  The ability of the test to correctly identify those who have no disease.
* False negative rate is 1 - sensitivity.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Cancer | No cancer | Total |
| Test + | A | B | A+B |
| Test - | C | D | C+D |
| Total | A+C | B+D |  |

**Worked example:** Pretest probability for DVT 40%. If test sens = 90%, sp = 80%, what is post test probability if test is negative? > Generate this table --

|  |  |  |  |
| --- | --- | --- | --- |
|  | True +ve | True -ve |  |
| Test +ve | 36 | 12 | 48 |
| Test -ve | 4 | 48 | 52 |
|  | 40 | 60 | 100 |

Post test probability = 4 / 52

**Risk ratios**

* In a case control study, use ODDS RATIO = (A/B) / (C/D) = AD/BC
* In a cohort study, use RELATIVE RISK = [ A / (A+B) ] / [ C / (C+D) ]
* Distinguish absolute risk reduction vs relative risk reduction, number needed to treat is 1/ARR

|  |  |  |  |
| --- | --- | --- | --- |
|  | Cancer | No cancer | Total |
| Exposure | A | B | A+B |
| No exposure | C | D | C+D |
| Total | A+C | B+D |  |

A **type 1 statistical error** is the incorrect detection of an effect that is not present. A **type 2 error** is the failure to detect an effect that is present.

**Standard deviation** is the square root of variance. In a normal distribution, 66% of values lie within 1SD of the mean, 95% of values lie within 2SD of the mean.

**Levels of evidence** (simplified):

* 1a: systematic review / meta analysis of level 1 studies (i.e. RCTs)
* 1b: at least one well designed RCT
* 2a: systematic review / meta analysis of level 2 studies (Oxford), OR, at least one well designed controlled trial without randomization e.g. case control (USPTF)
* 2b: at least one well designed quasi experimental study (e.g. cohort study)
* 3: well designed descriptive study (e.g. comparative, case control, case series)
* 4: expert opinion.