**MRCP Part 1 Revision Sheet** Nigel Fong

*Juicy exam-friendly titbits for Part One - clinical utility sometimes debatable.*

*N.B. To maximise yield,*

* Things that you probably know from MBBS are left out
* Obviously useless and hard-to-remember facts have been left out too (spend your memory space on things that are easier to remember).
* Pharmacology questions are placed in the most relevant domain

Please let me know of any errors. Sources: uptodate, pastest, etc.

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## 1. Respiratory Medicine

**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 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).

**Interpretation of DLCO**

* Low DLCO, obstructive spiro: COPD, bronchiectasis
* Low DLCO, restrictive spiro: ILD, (sarcoid, TB)
* Low DLCO, normal spiro: vascular disease (PE, PH), extrapulmonary defect (pleural effusion, neuromuscular weakness, kyphoscoliosis), smoking, anaemia, pneumonia.
* High DLCO: increased capillary blood volume (pulmonary edema, polycythaemia, left to right shunt), pulmonary haemorrhage.
* Normal DLCO: asthma

**Upper vs lower lobe fibrosis**

* Upper lobe: all environmental causes (hypersensitivity pneumonitis, silicosis - eggshell CXR calcification, allergic bronchopulmonary aspergillosis, etc) except asbestosis, no systemic causes except ankylosing spondylitis; TB, sacroidosis, histiocytosis
* Lower lobe: all systemic causes (i.e. include scleroderma, dermatomyositis, RA, sjogrens) except ankylosing spondylitis; no environmental causes except asbestosis; drugs (bleomycin, amiodarone, methotrexate, busulfan)

**Sarcoidosis:** presents as bilateral hilar lymphadenopathy and miliary reticulonodular pulmonary infiltrates

**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 often 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*.

**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. IgG precipitins are present. However as this is not a type 1 reaction, reactions like wheeze, raised IgE, positive skinprick, eosinophilia are not present.

**Radiation pneumonitis** begins 1-6 months after high dose RT. Treatment is steroids +/- steroid sparing agents. Prognosis is good with early intervention.

**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.

**Cystic fibrosis:**

* **Men with cystic fibrosis** are infertile because of failure of development of vas deferens
* Pseudomonas eradication is with inhaled tobramycin.

**Bosentan** is a competitive antagonist at endothelin A and B receptors, leading to a fall in pulmonary and systemic vascular resistance. Adverse effects are flushing, hypotension, dyspepsia, hepatotoxicity (monitor LFTs). It is teratogenic.

**Theophylline toxicity** presents with nausea, vomiting, metabolic acidosis, and hypokalaemia. There can be seizures, myoclonus, hyperthermia, and AKI in severe toxicity. Drugs that may increase theophylline drug concentrations include

* Allopurinol
* Carbimazole
* Cipro, clarithro, erythromycin, fluconazole, isoniazid
* Diltiazem, verapamil

**Indication for LTOT**

* pO2 <55 mmHg or SpO2 <88%
* pO2 <60 mmHg or SpO2 <89%, with cor pulmonale, right heart failure, or erythrocytosis.

**BTS pneumothorax guidelines**

* Primary pneumothorax:
  + <2cm and asymptomatic: oxygen and observe (kiv discharge)
  + >2cm or symptomatic: aspirate, if fail, chest drain
* Secondary pneumothorax:
  + <1cm and asymptomatic: admit to observe
  + 1-2cm and asymptomatic: aspirate, if fail, chest drain
  + >2cm or symptomatic: chest drain

**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.

**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.

**Lung CA:** *squamous cell* CA is more frequently associated with hypercalcaemia.

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

**Doxapram** is a centrally acting respiratory stimulant which may be considered in patients who are deemed unsuitable for ventilatory support. It is contraindicated in heart disease, epilepsy, cerebral edema, status asthmaticus, HTN, phaeochromocytoma, and stroke.

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## 2. Neurology

**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 10 days after SAH
* Seizures

**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%

**Nystagmus variants:**

* **Midbrain:** limited upgaze in a dorsal midbrain lesion results in *convergence retraction* “nystagmus” (a misnomer) - on looking up, the eyes converge and retract
* **Pons:** *upbeat* nystagmus
* **Medulla** (craniocervical junction): *downbeat* nystagmus (e.g. worse reading, better looking up)
* **Cerebellum** (flocculus and nodulus)**:** *Oscillopsia***,** a periodic alternating nystagmus where the direction of the fast and slow components changes every 2 minutes.
* **Cerebello-pontine angle:** *Bruns nystagmus* - Ipsilateral slow, large amplitude nystagmus; contralateral rapid, small amplitude (vestibular) nystagmus.
* **Optic chiasm:** seesaw nystagmus

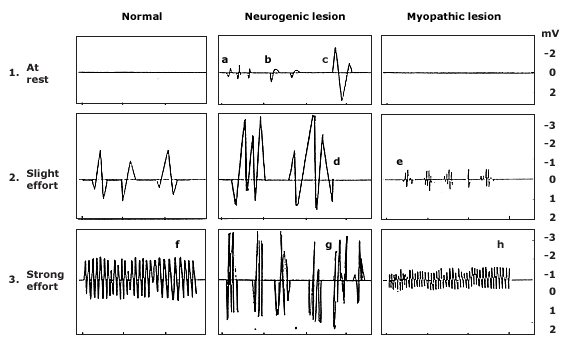
**Holmes-Adie pupil i**s an idiopathic condition, typically affecting young women, that presents with a unilateral dilated pupil that is poorly reactive to light and accomodates sluggishly, as well as absent ankle jerks.

**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:** 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)
* **Myopathy:** 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:



In **Guillain-Barre syndrome:** vital capacity is the most sensitive measure of resp muscle weakness.

**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-VG*K*C antibodies in limbic encephalitis)

**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.

**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

**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.

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

**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.

**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*.

**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*.

**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.

**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 MRCP question 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).

**Some seizure subtypes**

* **Juvenile myoclonic epilepsy:** absence seizures starting in *childhood*, *myoclonic jerks especially shortly after waking*, and GTCs.
* **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.

**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

**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 *basal ganglia and cortical hypointensities* on MRI later. CSF is normal but show elevated s100b and 14-3-3 breakdown proteins. There are typical EEG changes (1 Hz periodic discharges). **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.

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).

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## 3. Infectious Diseases

**Infections to treat with antitoxin:**

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

**TB treatment**

* **Latent TB:** H + pyridoxine *6 months*, or RH 3 months.
* **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; lepromatous leprosy is characterised by high bacterial load.

**HIV drug regimens**

* Treatment: dual nRTI backbone (tenofovir/emtricitabine or abacavir/lamivudine) 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

**Some HIV CNS syndromes**

* Cryptococcus - subacute meningitis, diagnosed on peripheral cryptococcal Ag +, CSF crypto Ag +, india ink stain +. Treatment with amphotericin + flucytosine, then consolidation fluconazole.
* Toxoplasma - focal mass lesions causing neuro deficits, seizures. Treatment is pyrimethamine + sulfadiazine + folinic acid; prophylaxis is bactrim
* Progressive multifocal leukoencephalopathy - demyelination due to JC virus. No specific treatment apart from HAART alone.
* CNS lymphoma - focal mass lesion

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

**Live vaccines:** These include BCG, MMR, oral polio, 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: Chlamydia trachomatis serovars L1-3 causes *painless* genital ulceration and regional lymphadenopathy
* Syphillis: painless chancre.

**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.

**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.

**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 (neurologic 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.

**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
* Treatment is with doxycycline, amoxicillin, or cefuroxime

**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 fever - fever, rash, myalgia, 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 strictures 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.

**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*, 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.

**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]

**Drug regimens for malaria:**

* Chloroquine sensitive (central america, mid east), falciparum and non falciparum: chloroquine or artemisinin combination therapy
* Falciparum, 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.

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## 4. Haematology

**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), arthralgia, BGIT, and membroproliferative glomerulonephritis. Type 2 and 3 CG both have IgM rheumatoid factor reactivity. 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. Biopsy shows apple green on congo red stain.

**Chronic lymphocytic leukaemia (CLL)** presents with hepatosplenomegaly, lymphadenopathy, and lymphocytosis with accumulation of small mature lymphocytes in marrow and blood. Most patients are asymptomatic; clinical manifestations, if present, include autoimmune hemolytic anaemia, hypogammaglobulinaemia causing repeated infections, membranoproliferative glomerulonephritis, and B symptoms. 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.

**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.

**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).

**Warm AIHA** is IgG positive, Cold AIHA is C3d positive. Steroids are urgent in warm AIHA but do not work in cold AIHA.

**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).

**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.*

**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.

**In B12 deficiency** macrocytic anaemia, bil and LDH can be raised due to hemolysis of erythroid precursors in bone marrow (ineffective erythropoiesis)

**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).

**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 inmunodeficiency, neonate (exchange transfusion, intrauterine transfusion)

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## 5. Nephrology

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

**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

* MPGN: Hep B, mixed cryoglobulinaemia
* Membranous: Hep B/C, malignancy, autoimmune (e.g RA), penicillaime. Anti phospholipase A2 receptor (Anti-PLA2R) antibodies positive in primary MN.
* MCD: Hodgkin lymphoma
* FSGS: HIV, lithium

**IgA nephropathy:** hypertension is the poorest prognostic factor.

**Management of lupus nephritis:**

* Class 1 (minimal change), 2 (mesangial): no specific Rx, background HCQ.
* Class 3 (focal segmental proliferative): high dose steroids + cyclophosphomide 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).

**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). 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.

**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. 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. 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)

**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.

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## 6. Rheumatology

**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). 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.

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

**Behcet’s syndrome** is a vasculitis affecting vessels of all sizes. It has r*ecurrent painful orogenital ulceration*, arthritis, uveitis, and skin lesions (erythema nodosum, papulo vesicular pustular eruptions). There is not much literature on treatment.

**Polyarteritis nodosa** is a medium vessel *ANCA negative* vasculitis which causes various skin lesions (livedo reticularis), mononeuritis multiplex, abdominal pain (mesenteritic vasculitis, testicular pain), and renal insufficiency, weight loss. Diagnosis is via biopsy.

**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)

**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. Mycophenolateis effective in and tends not to cause neutropenia (selective for B and T lymphocyte). Azathioprine is also effective but is non selective.

**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.

**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

**Lesinurad i**s a new uricosuric agent (URAT-1 inhibitor, inhibits urate reabsorption), used if there is inadequate decrease in uric acid with allopurinol.

**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).

**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
* 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

**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)

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## 7. Gastroenterology

**Digestive physiology**

* Amino acids stimulate gastrin
* Carbohydrate delivery into the small bowel stimulates incretin
* Fats stimulate pancreatic hormones and bile salt release

**Diagnosis of autoimmue liver diseases:**

* Autoimmune hepatitis: hepatocellular pattern of raised LFTs, +ve ANA / ASMA / LKM, elevated igG, histology.
* PBC: cholestatic pattern raised LFTs, +ve antimitochondrial Ab, histo
* 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 abscene 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.

**Hepatic encephalopathy:** **Lactulose** is 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.

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

**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.

**Glasgow score in pancreatitis:**

* P: PaO2 <60mmHg
* A: Age >55
* N: neutrophils - WCC > 15
* C: Calcium <2
* R: Renal - Urea > 16
* E: Enzymes - LDH >600 or AST >200
* A: Albumin <32
* S: Sugar - glucose > 10

**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.

**Stool tests:**

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

**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.

**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).

**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. Other side effects of azathioprine: pancreatitis, hypersensitivity, interstitial nephritis, liver disease.

**Mycophenolate** can cause diarrhoea due to an ulcerating colitis

## 8. Cardiovascular

**Systolic murmur differentiation**

* 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) or increased afterload (isometric exercise) increases chamber size; this and reduced inotropy (GTN, ca channel blockers) decreases obstruction and murmur intensity.

**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), or *embolism*, causing TIA/stroke (LA myxoma) or pulmonary infarcts (RA myxoma). 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.

**BP medicines** (UK guidelines): first choice is

* Over 55 or black: calcium channel agonist, 2nd line thiazide diuretic
* Under 55 and not black: ACE/ARB

**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.*

**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

**Nitrate tolerance** arises because of vascular oxidative stress, increasing degradation of NO.

**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.

**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.

**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.

**Antiarrhythmic drugs**

* **Amiodarone:** main action is on inward sodium and calcium channels, to prolong the action potential.
* First choice drug to **prevent recurrence of VT** is sotalol.
* Sotalol has risk of producing long QT and torsades de pointe

**Beta blocker overdose:** treat with atropine, then glucagon. If unresponsive, consider pacing.

**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

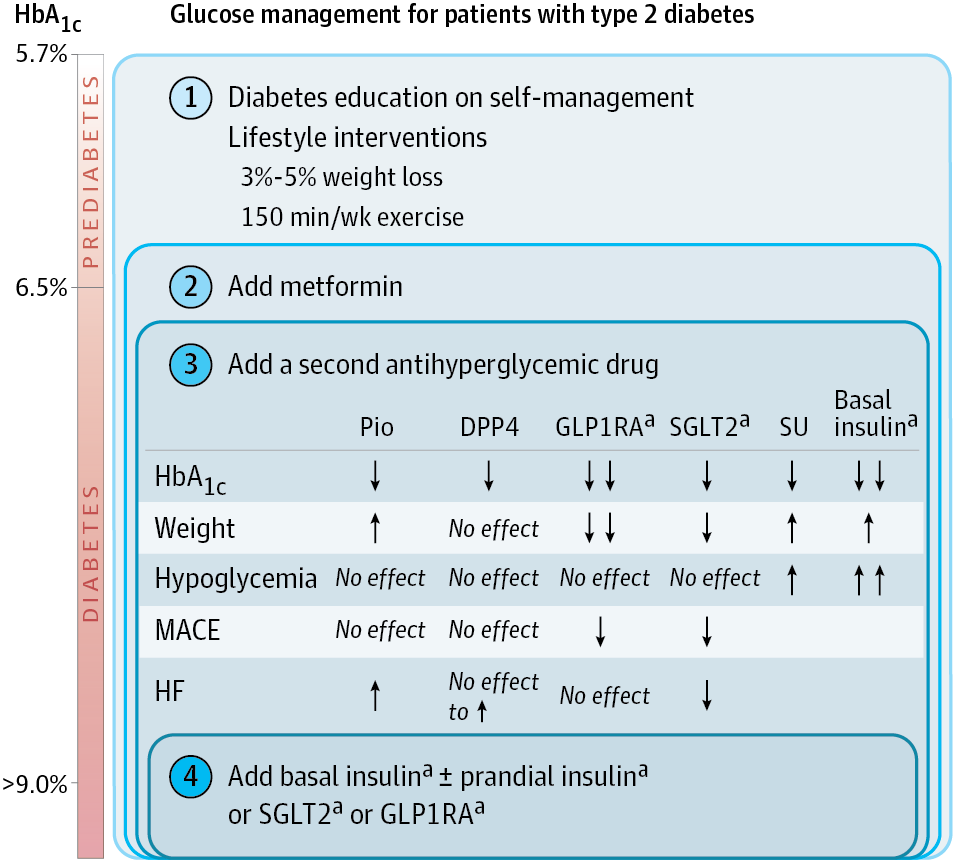
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## 9. Endocrinology

**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.
* **GLP1 agonists** have been linked with pancreatitis. Exenatide should not be used in renal insufficiency CrCl <30.
* **Pioglitazone** has increased risk of fluid overload, bone loss, bladder CA.
* **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

**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, 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.

**Post thyroidectomy,** RAI need not be used in tumors <1cm unifocal or multifocal, with no angioinvasion or capsular invasion on histology (Controversial)

**A large pituitary tumor** with prolactin >1000U/L is likely a prolactinoma, less marked elevations in prolactin can occur in a nonfunctional tumor.

**Diagnosis of acromegaly:** IGF1 is a good screen. OGTT showing failure to suppress GH secretion confirms (glucose suppresses GH).

While transsphenoidal resection of pituitary tumor is curative, Cushing’s syndromecan be treated medically with **metyrapone** and **ketoconazole**. Acromegaly can be treated with **dopamine** agonists (cabergoline) or somatostatin analogues.

**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
* MEN2 is associated with RET protooncogene mutation

**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 intefere 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.

**PseudohypoPTH:** maternal transmission of a G protein defectresults 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).

**Osteomalacia:** 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)

**Osteoporosis:** Recommended daily intake is 1500mg/day of calcium, 400-800 units/day of vitamin D

**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.

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## 10. Oncology

**Some environmental risk factors**

* Risk factor for NSCLC: isocyanates, polycyclic hydrocarbons, asbestos
* Risk factor for bladder CA: aromatic amines
* Risk factor for angiosarcoma of liver: vinyl chloride.

**Hormonal therapy for prostate CA**

* **GnRH agonist:** buserelin, goserelin leuprolide (initial increased gonadotropin release, afterwards levels fall)
* **Androgen receptor blocker:** flutamide, nilutamide, bicalutamide, enzalutamide.
* **GnRH antagonist:** degarelix

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

* **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 -- do not administer with warfarin.
  + DNA analogues: fludarabine, cytosine arabinoside (ara-C), gemcitabine -- SEs: myelosuppression, acute cerebellar syndrome (cytarabine).
* **Mitotic spindle poisons**
  + Vinca alkaloids: vincristine (leukaemia, *neurotoxic*), vinblastine (testicular cancer, lymphoma, myelosuppressive), vinorelbine (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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## 11. Dermatology

**Pemphigus vulgaris vs bullous pemphigoid:**

* 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).
* 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).

**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.

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## 12. Psychiatry

**Suicide risk factors:** between alcohol abuse and family situation, alcohol abuse is a stronger suicide risk factor

**History of violence** is the strongest predictor of future violence

**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.

**Stopping MAO-I:** after stopping selegilline, allow a washout of 2 weeks before starting SSRIs to reduce the risk of serotonin syndrome

**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.

**Lithium:**

* Leads to DI by downregulating aquaporin-2 gene expression
* HCTZ can cause a rise in lithium levels leading to toxicity

**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 *SIADH*, arrhythmia, *seizure, hypertension*. 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)

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## 13. Maternal medicine

**HELLP, Pre-eclampsia** are favourite questions.

**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 (vs obstetric cholestasis which usually runs a benign course). In contrast, **obstetric cholestasis** presents with puritus, raised bilirubin, but patients are otherwise well.

**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

## 14. Ophthalmology

**Band keratopathy** is due to calcium deposition in the cornea and can result from hypercalcemia or the degnerative phase of chronic eye diseases.

**Age related macular degeneration** presents as blurred central vision with choroidal neovascularization and macular leakage on fluorescein angiography. Smoking (most impt), HTN, previous cataract surgery are important risk factors.

**Retinitis pigmentosa** is a genetic condition (polygenic) presenting with gradual *loss of night and peripheral vision*. Ophthalmoscopy shows optic disc pallor, attenuated vessels, and *pigment deposits in a bone-spicule patter*n. Try a carbonic anyhdrase inhibitor but there is no cure.

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## 15. Misc & Syndromes

**Lead poisoning** can cause *abdominal pain*, RBC abnormalities (*basophilic stippling*, clover leaf morphology), peripheral motor *neuropathy*, interstitial nephritis, gingival blue-black/grey line.

**Acute intermittent porphyria** presents with abdominal pain, nausea/vomiting, neurological symptoms (neuropathy, seizures, coma, psychiatric disorder), with red/brown coloured urine. Porphyrin precursors urinary porphobilinogen and delta-aminolevulinic acid (ALA) are elevated. Urgent treatment with hemin / haem arginate is indicated; this downregulates heme biopsynthesis and decreases accumulation of heme precursors. If not available, treat with glucose loading.

**Porphyria cutanea tarda** (PCT) presents with chronic blistering photosensitivity +/- elevated LFTs. This arises from a defect in uroporphyrinogen decarboxylase, either inherited (AD) or due to susceptibility factors (estrogen, alcohol, hep C, haemochromatosis). Screen by measuring total plasma porphyrins, then identify subtype by fractionation. Treatment is with sun avoidance, modifying susceptibility factors, phlebotomy, and hydroxychloroquine.

**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*. 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.

**Yellow nail syndrome:** an abnormality of lymphatic drainage with recurrent bronchiectasis, small pleural effusions, lymphoedema, yellow nails.

**Klinefelter syndrome (XXY)** presents with 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.

**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.

**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

**Landmark for subclavian line insertion:** 1cm under and 0.5cm lateral to midpoint of clavicle in normal patients, 2cm under and 1cm lateral in obese.

**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

At high **sildenafil** doses (mainly a PDE-5 inhibitor), a PDE6 effect becomes prominent and patients complain of blue vision

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## 16. Statistics

**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.