5th Year
Pathology Swot Notes

Edited by David Tripp

Disclaimer: These are study notes I compiled for the 5th year pathology exam at the School of Medicine, University of Otago. I share them in the hope they may help others. However, this has not been peer reviewed in any way. I take no responsibilities for mistakes. Learn from them – don't repeat them!

I am very grateful to sources too numerous to name from which I have compiled, cut and pasted in order to learn everything I must know….

These notes are purely cut and pasted from the first edition of my medical school study notes – just extracting pathology material. Cross references to material elsewhere in the larger document were broken in this process (resulting in "Error!Bookmark not found"). These notes (including the revised 2nd edition of the medical school notes), and others I have compiled over the years, can be downloaded from www.sites.google.com/site/davidtrippsnotes.

Happy Hunting!

PUO

Pyrexia/Fever of Unknown Origin (PYO/FUO)

- Formal definition: > 38 C, > 3 weeks, no known cause (ie normal admission tests already done). However, often used to describe a temperature that that you haven't done any tests on yet.
- Usually an unusual presentation of a common disease
- History, exam, investigations, time course, urgency and likely cause depend on setting:
  - Community acquired (Classic PUO)
  - Nosocomial PUO (ie hospital acquired)
  - Immune-deficit or HIV related PUO
- Differential:
  - Neoplasm: lymphoma, leukaemia (check lymph nodes), other (hepatic, renal, other)
  - Infection:
    - Bacterial: Tb, abscess (subphrenic, hepatic, pelvic, renal – look for ↑ neutrophils), endocarditis (any dental work?), pericarditis, osteomyelitis, cholangitis, pyelonephritis, PID, syphilis, cystitis
    - Viral: EBV, CMV, HBV, HCV, HIV, Varicella-Zoster
    - Parasitic: malaria, toxoplasmosis
    - Fungal
    - See also Pyrexia of unknown origin if returning from 3rd world, page 21
  - Connective Tissue: RA, SLE, Vasculitis (eg polyarteritis nordosa – check for Raynaud's phenomena – abnormal response in fingers to cold)
  - Misc: drug fever (especially penicillins, sulphonamides), Rheumatic fever, inflammatory bowel disease, granulomatous disease (eg Sarcoid), Factitious/Maunchousens (eg injecting themselves with saliva)
- Clues:
  - Weight loss ⇒ chronic
  - Check eyes: iritis in connective tissue disease, jaundice, etc
  - Check tonsils, glands, ears for infection
- History:
  - Travel (eg malaria, did they have prophylaxis)
  - Exposure to others
  - Sexual history
  - Weight loss
  - Been to other doctors (had any antibiotics)
  - Ossupational exposure (eg cows)
- Exam:
  - Lymph nodes
  - Heart murmurs
  - Skin for rashes
  - Abdominal exam
- Possible investigations:
  - Blood count
  - Blood cultures
  - Urine microscopy & culture
  - Liver function (eg hepatitis)
  - Viral serology
  - Malaria film
  - Chest X-ray
-

Infectious Diseases

Blood Culture

- When to take them:
  - It takes 30 – 60 minutes for temperature to rise after introduction of bugs into the blood, but endothelial cels of the vascular system (spleen, kuppfler cells, etc) phagacytose cells in minutes
  - So when the temperature spikes, bugs may well be gone. So do *random* cultures in the hope of getting a hit
- Definitions:
  - Bacteraemia: no host response. Happens all the time (eg after cleaning teeth)
  - Scepticaemia: sustained bacteria in the blood stream – on going delivery of bugs into the blood stream from a replicating focus (don't multiply in blood). Leads to host response an disseminated loci of infection
  - Pyemia (older term): Spread of organisms via infected thrombi
- Infections associated with bacteraemia:
  - Community acquired pneumonia (treat strep pnumonia with penicillin, except in children where > 30% resistance so use cephalosporin)
  - Menningitis with petechial rash (treat menningitidis with pencillin)
  - Osteomyelitis (treat S Aureus with flucloxacilin or vancomycin if MRSA)
  - Leukaemia with infected Hickman line (Coag –ive staph, eg epidermidis, treat with vancomycin)
  - Pyelonephritis (treat E coli with Gentamycin)
  - Cellulitis (treat Strep pyogenes with Pencillin)
  - Perforated appendicitis (treat B Fragilis with Metronidazole)
  - Infective endocarditis (treat viridians Strep, eg S sanguis, with penicillin + maybe gentamycin
  - Epiglotitis (treat HIB with cephalosporin)
  - Premature baby with respiratory distress syndrome (treat Lancefield group B strep with pencillin)
- Procedure for blood culture:
  - Ensure everything sterile – contamination makes interpretation very difficult
  - 5 – 10 mls of blood in two bottles, one general purpose and the other anaerobic
  - For kids, use single 3 ml paediatric bottle
  - Choose vein (usually ante-cubital fossa)
  - Swab with betadine and wait 3 – 4 minutes to dry
  - Draw blood and inject into bottles
  - If already on antibiotics, notify lab
- Indications for blood cultures:
  - Infection of any degree of severity – especially if firm clinical diagnosis not possible
  - Absence of fever doesn't rule out infection, so is not a contra-indication (eg confusion, feeling off)
  - Specific indications:
    - Acute generalised infection: fever, rigors, sweating, shock
    - Febrile illness + congenital or acquired heart disease where infective endocarditis suspected
    - Diseases with a bacteraemic phase (pneumonia, meningitis, acute pyelonephritis, etc)
    - Shock (especially post-operative following abdominal surgery)
    - Intercurrent illness in patients with compromised imunity
  - Usually unnecessary to do more than 2 sets at the time bacteraemia is suspected, 20 minutes apart. If infective endocarditis, take 3 sets over 24 hours
- Bugs isolated in Wgtn Hospital:
  - Four most common G+ive: Staph aureus, Staph coag –ive (from lines), strep pneumonia, enerococcus faecalis
  - Four most common G-ive: E. Coli, Klebsiella, Other Coliforms, Pseudomonas aeruginosa
  - Most common is staph epidermidis (ie staph coag –ive): It's a common contaminant, but also the most common pathogen in catheter related infections, neonates and neutropenic patients. $\uparrow$resistance to Flucloxacillin $\rightarrow$ $\uparrow$use of vancomycin (expensive, side effects, etc)

Infections of the CNS

Bacterial Meningitis

Signs and Symptoms

- Signs & symptoms: Rapid onset of:
  - Meningism: Headaches, photophobia, stiff neck
  - ↑ICP: Headache, irritable, drowsy, vomiting, fits, ↓pulse, ↑↓BP, ↓LOC, pin-point pupils, papilloedema (late sign), tense fontanelle
  - Septicaemia: fever, arthritis, DIC, ↓BP, ↑pulse, tachycardia, rash (utimately 80% will have a purpuric rash, 10 – 15% will have a maculopapular or urticarial rash, 5 – 10% will have no rash)
- In different age groups:
  - Infants/toddlers: fever, lethargy, poor feeding, vomiting, toxic (drowsy, pallor), rash. Only 30 – 50% have signs of meningism ⇒ absence doesn't exclude. Bulging anterior fontanelle – but if vomiting may be normal or reduced
  - Children > 3: fever, headache, vomiting, photophobia, stiff neck, confusion (may be combative), non-blanching rash (initially blotchy macular rash that rapidly becomes petechial or purpuric)
  - Adolescents: may present as acute mania or appearance of drug induced psychosis

Pathogenesis

- Organisms:
  - Neonates: E. Coli, β-haemolytic streptococci Group B (eg streptococcus agalactiae – normal vaginal flora), rarely listeria
  - Children < 14 years: H. Influenza (if < 4 and not immunised), Neisseria Meningitidia, Strep Pneumoniae, Tb
  - Adults: Meningococcal, Strep Pneumoniae, maybe staph aureus or cryptococcus neoformans
  - Elderly, Immunocompromised: Pneumococcal, Listeria, Tb, G –ive, Cryptococcus Neoformans.
- Pathogenesis:
  - Pathology: inflammation of pia mater and arachnoid
  - Most common are N Meningitidis and S penumoniae
  - Nasopharynx→blood→subarachnoid space (via choroid plexus): N meningitides, HIB, S. pneumoniae
  - Middle ear→blood→subarachnoid space: S Penumoniae, HIB
  - Congential abnormalities (eg spina bifida): coliform bacillia, pseudomonas, Strep agalactiae
  - Trauma: Skull fracture + CSF leak, CNS surgery, shunts: Staph aureus
  - Depressed immunity: listeria monocytogenes, cryptococcus neoformans
  - Neonatal meningitis from vaginal flora (especially with prematurity, prolonged ROM, delayed 2nd stage): Strep agalactiae, coliforms (E coli), listeria monocytogenes
- If recurrent:
  - Consider immunosuppression (eg hypogammaglobulinaemia or complement deficiency)
  - Look for lumbrosacral defects, especially if enteric bacteria or S aureus

Investigations

- Do blood culture before presumptive treatment if possible, but NOTHING should delay presumptive treatment. Tell lab about antibiotics
- Must do:
  - Blood cultures
  - CSF via lumbar puncture unless contraindicated (see below)
  - Urine: subra-pubic aspiration or catheter
  - If antibiotics have already been administere:
    - Needle aspirate purpuric lesions for gram stain and culture
    - Throat swab
- Bloods:
  - Blood Glucose sample – may be hypoglycaemic[ABCDEF: DEFG = Don't Ever Forget Glucose]
  - FBC, electrolytes
- Lumbar puncture:

- Contraindicated if:
  - Signs of ↑ICP causing cerebral hernaiation (eg ↓LOC, *very* bad headache, focal signs including abnormal papillary reflexes, tonic seizures with decerebrate of decorticate posturing, irregular respirations, bradycardia, papilloedema, tense fontanelle). If in doubt then CT
  - Severe cardiovascular compromise with DIC/coagulopathy (eg fulminant sepsis)
  - Infection over the injection site
- Tests of CSF: Gram stain, Tb, cytology, virology, glucose, protein, India ink (Cryptococcus), culture (if clear then ? virus), antigen testing (especially if partially treated)
- May be normal, repeat if symptoms persist
- Typical CSF (lots of variation):

	Pyogenic	Tb/Fungal	Viral ('aseptic')	Normal
Main cell seen	Polymorphs	Mononuclear	Mononuclear	< 5 * 10E6 WBC/ml (< 20 in neonates)
Glucose	↓↓	↓	- or ↓	2.5 – 5.0 mmol/l
Protein	↑↑	↑	Mildly ↑ or ↓	< 0.4 g/l
Bugs seen	Yes	No	No	

  - NB: early viral meningitis may have predominantly polymorphs
  - RBCs: None. If there are then either traumatic (more in 1st of 3 tubes) or bleed (new if red, yellow if old – zathachromia)
- Appearance on Gram stain:
  - N Meningitidis: G –ive diplococci
  - H influenzae: Pleomorphic G –ive bacilli
  - S pneumoniae & S agalactiae: G +ive diplocci
  - Listeria: G +ive bacilli
  - TB: Acid fast bacilli very scant – take at least 5 mls of CSF
  - Cyptococcus neoformans: Indian ink stain shows capsules
- Imaging: To identify subdural collections, abscess, hydrocephalus, thrombosis and infarction. Only if LP contraindicated and suspected mass lesion or persistent or focal neuro signs

Management

- Management:
  - Standard infection control precautions plus surgical mask when examining throat, intubating etc
  - ICU if:
    - Coma
    - Circulatory collapse
    - Persistent, recurrent seizures
    - SIADH with cerebral oedema or seizures
  - Shock or ↑ICP is what kills
  - Maintain perfusion:
    - Colloid bolus (20 – 40 ml/kg 4% albumen iv), then colloid + glucose
    - Inotrope eg dobutamine (10 μg/kg/min
    - Watch for ↑ ADH secretion → hyponatraemia and cerebral oedema if too much fluid given
    - Check Na 6 – 12 hourly. If Na < 135 mmol/l then ↓iv rate. If Na > 145 then ↑rate
  - Respiratory support: O2, early elective intubation if persistent shock (but may exacerbate hypotension due to vasodilation and ↓sympathetic drive)
  - Correct abnormalities: anaemia, hypoglycaemia, coagulopathy (FFP), acidosis (NaHCO3), hypokalaemia
  - Seizures: anticonvulsants
  - Watch for ↑ICP:
    - ↓Conscious state, focal neuro signs, abnormal pupils, hypertension and relative bradycardia.
    - Treatment: ICU, ↓PCO2, diuretics (Mannitol, frusemide), headup, deep sedation, inotropes. But priority is to correct the shock (CBF = MAP – ICP)
  - Weight and measure head daily in an infant
  - Isolate patient, ensure analgesia
  - Dexamethasone treatment controversial (most benefit in Hib). Not routinely used. Reduces fever and gives misleading impression of clinical improvement

- Antibiotic regimes:
  - Empiric antibiotic treatment:
    - Neonate – 3 mths: Amoxycillin (for listeria) + Ceftriaxone. 2 weeks for G +ive, 3 weeks for G –ive.
    - Older child:
      - *Cefotaxime 50 mg/kg/6hr, max 2 g, iv for 7 – 10 days or*
      - *Ceftriaxone 50 mg/kg/12hr, max 2 g, iv for 7 – 10 days or*
      - *Penicillin G 50 mg/kg/4hr iv for 7 – 10 days*
    - If strep pneumonia suspected: *Vancomycin 15 mg/kg/6hr, max 500 mg, iv +* cefotaxime/ceftriaxone – synergistic, necessary due to ↑resistance to 3rd generation cephalosporins
  - Specific Treatment according to culture and susceptibility results:
    - N Meningitidis, S agalactiae: Penicillin (Cefotaxime if allergic to penicillin) for 5-7 days. For meningococcaemia only can use penicillin or cefotaxime
    - S pneumonia:
      - Penicillin susceptible: penicillin (but 20% are resistant) for 7 – 10 days
      - Penicillin resistant, 3rd generation susceptible: Cefotaxime
      - Penicillin and 3rd generation resistant: Cefotaxime + Vancomycin
    - H Influenza: Cefotaxime, Cetriaxone
    - L Monocytogenes: amoxycillin
    - Staph Aureus: Flucloxacillin
    - M Tuberculosis: Rifampicin, Isoniazid, Pyrazinamide, Ethambutol
    - Coliforms: 3rd generation Cephalosporin (ie Cefotaxime, Ceftazidime)
    - Pseduomonas: Ceftazidime
    - Cryptococcus Neoformans: fluconazole or amphotericin B
    - NB: Erythromycin and gentamycin don't have good CSF penetration
  - If not responding, or non-susceptible strain of pneumococci or receiving dexamethasone than repeat LP after 24 – 48 hours
- Complications:
  - Seizures:
    - First suspicion should be hyponatremia (also hypoglycaemia):
      - SIADH (Na < 130 and urine Na > 20) → exacerbates cerebral oedema.
      - Prevent by restricting fluids to 50% of maintenance
      - Treatment: severe fluid restriction (10 ml/kg/day), in an emergency consider hypertonic saline, Mannitol or frusemide
    - Hypoventilation can further ↑ ICP → hypoxia, hypercapnia, acidosis
    - Anticonvulsants can also exacerbate these metabolic changes
    - Management options: diazepam, Clonazepam, phenobarbitone, dextrose to control hypoglycaemia, intubation and ventilation
  - Major diability in 15%: Deafness, brain damage, peripheral necrosis, etc. All cases should have audiologist check within 6 – 8 weeks of discharge
  - Death in 5%, 10 –15% pneumococcal meningitis, 20% in fulminant meningococcaemia

Meningococcal Disease

- Cause: Neisseria Meningitidia
- Epidemiology:
  - 10 year epidemic started in 1990 with about 50 reported cases
  - 500 reported cases in 2000
  - Rates per 100,000 < 1 year olds:
    - Pacific Island: 427
    - Maori: 202
    - European: 80
- Healthy people can be carriers
- Transfer via respiratory secretions
- Kids and teenagers more susceptible than adults
- Notifiable to public health (as is Hib)
- Not a cause of Otitis media
- Pathogenesis: endotoxins (lipopolysaccharides in the cell wall) activate complement and release of PAF causing endothelial injury → immune activation and ↑vascular permeability
- Prophylaxis

- Rifampicin: 4 doses. Broad spectrum antibiotic
- Offer to index case (if only treated with penicillin), all intimate, household and daycare contacts
- Contraindications: pregnancy (use single dose ceftriaxone), liver disease.
- Side effects: nausea, vomiting, diarrhoea (GI effects), turns urine/tears/sweat orange/red (will stain contacts)
- Interactions: asthma, blood clotting and oral contraceptives (continue pill, use barrier method until 7 days after antibiotics finished)

TB Meningitis

- Rare
- Most common < 5 years
- Slow onset: malaise and fever progressing to drowsiness, neck stiffness and seizures over 2 weeks
- Mantoux testing may be normal, and CXR normal in ½ of cases
- Investigations:
  - Gastric lavage, urine and CSF for Acid fast stain and culture
  - CT
- Treatment: isoniazid, trifampicin, pyrazinamide
- Notifiable disease

Brain Abscess

- Aetiology:
  - Chronic otitis media sinusitis or dental sepsis
  - Trauma: foreign body, skull fracture, CNS surgery
  - Haematogenous spread (may be multiple abscess) from congenital heart disease (with R-L shunt), bronchiectasis, abdominal abscess, endocarditis, etc
- Bacteria:
  - Temporal lobe (from chronic otitis media):
    - Anaerobes: Bacteroides fragilis
    - Aerobes: Proteus mirabilis + HIB and E faecalis
  - Frontal lobe (from hronic sinusitis)
    - Anaerobes: Bacteroides melaninogenicus
    - Aerobes: Strep milleri
  - Traumatic: Staph aureus
  - Haematogenous spread: Staph aureus, Viridans Strep, Bacteroides fragilis, etc
- Treatment:
  - Surgery
  - Antibiotics:
    - Anaerobes: Metronidazole
    - Aerobes:
      - Strep: Amoxycillin
      - Coliforms: Cefotaxime
      - Staph aureus: Flucloxacillin

Viral CNS Infections

Viral Encephalitis

- Herpes Simplex:
  - Clinical: usually short history, fever headache, confusion, ataxia, focal convulsions → coma (if clouding of consciousness consider encephalitis in addition to meningitis)
  - CSF: raised leucocyte count, predominantly mononuclear
  - Diagnosis: PCR test of CSF for Herpes Simplex antigen
  - Treatment: Acyclovir 10 mg/kg iv 8 hourly for 10 days. Low threshold for treatment
- HIV:
  - Most AIDS patients have a subacute encephalitis caused by direct brain infection
  - Symptoms: mood changes, depression, lethargy, confusion, dementia
- Other viruses: Mosquito born (Murray Valley Encephalitis, Japanese Encephalitis), Rabies virus
- Management:
  - Full blood screen: Cr, electrolytes, glucose, LFT, ABG, urine drug & metabolic screen, blood and urine cultures, ammonia, cortisol, coagulation screen, ECG
  - Serology and viral cultures

    - LP if not contraindicated – may be normal in up to 50% of cases
    - Consider empiric acyclovir + cefotaxime – at least until HSV is excluded
    - CT (MRI better still) for focal lesions
- Consider differential:
    - Head injury
    - Toxic or metabolic encephalopathy
    - Hypoxic insult
- Supportive treatment:
    - Fluid restriction
    - Control of seizures
    - Cardio-respiratory support
    - Maintenance of nutrition

Viral Meningitis

- Causes:
    - Most due to non-polio enteroviruses:
        - Faecal $\rightarrow$ oral $\Rightarrow$ little kids at risk
        - ECHO viruses, Polio, Coxsackie A & B
    - Mumps
- Presentation: fever, headache, malaise, photophobia, abdominal pain and vomiting. Neck stiffness in older children. Maybe a macular or even patechial rash
- Differential diagnosis of lymphoctyic (aseptic) meningitis
    - Viral meningitis (eg ECHO, Mumps, Coxsackie)
    - Viral Encephalitis (eg Herpes Simplex, CMV, Varicella Zoster)
    - TB meningitis
    - Fungal meningitis (eg Cryptococcus neoformans)
    - Neurosyphilis
    - Acute Leptospirosis
    - Cerebral toxoplasmosis
    - Neoplasm
    - Cerebral sarcoid
- Lab tests:
    - CSF Culture: Enteroviruses, mumps, fungi, TB
    - Throat culture and Faeces for enteroviruses
    - CSF Antigen tests: PCR for Herpes Simplex, CMV, VZV, TB, Toxoplasmosis
    - Serology: antibodies to Treponema pallidum, Leptospira, Toxoplasma gondii
- Admit if:
    - Diagnosis in doubt
    - Antibiotics are being considered
    - IV Rehydration is needed
- Ensure good analgesia

Post-Infective Encephalitis

- Immune hypersensitivity reaction to host cells containing viral antigens
- Late onset – 7 – 10 days after acute illness
- Viruses involved: Morbilli (Measles), Mumps, Rubella, Varicella-Zoster

Other

- Spongiform encephalopathies:
    - Caused by Prions (Proteinaceous infectious particles)
    - Histology: vacuolation of brain tissue, deposition of amyloid plaques
    - Eg: Kuru (in PNG), Creutzfeldt-Jakob Disease (CJD), Variant CJD
    - Symptoms: Insidious onset of ataxia, dysarthria and dysphagia. Progressive dementia.
- Slow virus infections:
    - SSPE (Subacute sclerosing pan-encephalitis): Measles like virus affecting children and adolescents
    - PML (Progressive Multifocal Leucoencephalopathy): Affects adults from 40 – 70, Polymoa virus implicated.
- Neonatal Encephalitis:
    - TORCH complex: Toxoplasmosis, Rubella, CMV, Herpes Simplex

- Usually accompanied by disseminated disease
- Reye's Syndrome: post-infectious encephalopathy with associated acute liver failure. Most common antecedent infection is Influenza virus

Bacterial Disease

Streptococcus

Streptococcus Pyogenes (Group A, β Haemolytic)

- Causes:
  - Commonly: acute pharyngitis, cellulitis, impetigo (also caused by group C)
  - Uncommonly: necrotising fascitis (haemolytic strep gangrene), strep toxic shock syndrome, scarlet fever, erysipelas (= contagious skin infection with strep pyogenes) , acute otitis media
  - Rarely: pneumonia, infective endocarditis
- Has remained sensitive to penicillin
- Identical strep can lead to a variety of infections:
  - Sore throat
  - Impetigo/Cellulitis. See below
  - Toxic Shock Syndrome
  - Myositis
  - Necrotising Facitis
- Infection via throat (mainly) or via skin (impetigo/wound infection):
  - Supprative: tissue invasion
  - Non-supprative (after 2 – 8 weeks):
    - Rheumatic Fever
    - Glomerulonephritis
  - Super antigens: pyogenic exotoxins – ability to avoid classical antigen processing by APCs
- **Scarlet Fever**:
  - Direct response to Streptococcal toxins (cf virus rash which is autoimmune and therefore delayed)
  - Presentation: fever, exudative pharyngitis, scarlatina rash (fine punctate rash with perioral sparing), desquamation
  - Skin feels like sandpaper than desquamates. May get purpura in flexures
  - Tongue affected – white then strawberry red
- **Streptococcus Toxic Shock Syndrome**:
  - First described in children. Now associated with Tampon use
  - Early (1 – 7 days): vague, viral like illness: fever, chills, myalgia, diarrhoea
  - Later: abrupt onset of pain (not necessarily associated with findings), redness, hypotension, renal failure, ARDS, coagulopathy. May lead to necrotising faceitis. Also skin diffusely erythematous like sunburn, conjunctivitis
  - Desquamation a week later characteristic
  - Age group: 2- 50 year olds, no predisposing or underlying disease
  - Bacteriology:
    - Blood culture +ive in 60%
    - Swab or aspirate in 95%
    - M protein types 1 & 3: impedes phagocytosis by leucocytes, expressed on cell wall
  - Lab tests: Haematuria, ↑Cr, ↓albumin and ↓Ca, serum CK for deep tissue infections
  - Treatment: Ceftriaxone
- **Necrotising fascitis**:
  - Diffuse swelling and mild erythema, followed by bullae filled with clear fluid. Spreads along facial planes
  - Infection of subsutaneous tissue → progressive destruction of fascia and fat but may spare the skin itself.
  - 25 cases per year in NZ
  - Requires aggressive surgical debridement
  - Causative bacteria:
    - Group A strep most common
    - Staph Aureus
    - C. Perfringens
    - C. sceptica

- Predisposing factors:
  - Diabetes
  - Peripheral vascular disease
  - Chicken pox
  - Minor trauma/surgical procedures
- Use of NSAIDs masks inflammation and delays diagnosis

Impetigo (School Sores)

- = superficial infection involving the epidermis
- Most common in children during summer months
- Non-bullous impetigo:
  - = streptococcal impetigo
  - Vesicles on erythematous base → pustules (highly contagious) → yellow-brown scabs (CRUSTY), associated with regional lymphadenopathy
  - Ecthyma is deeper version – cut out edge
  - Commonly result of skin break such as insect bites or chicken pox. Especially if overcrowding and warmer climates
  - Goes for limbs and face
  - Fever uncommon. Check lymph nodes
  - Caused by Strep Pyogenes with or without co-infection with Staph Aureus (can → Scalded Skin Syndrome, see page **Error! Bookmark not defined.**)
  - Commonest cause of post-strep glomerulonephritis
- Bullous impetigo:
  - Due to Staph aureus of phage II (usually type 71).
  - Usually younger children
  - Lesions: begin as vesicles – turn into flaccid bullae in response to toxins. Following rupture of the bullae, a moist red surface remains and varnish like crust appears
- Neonatal Impetigo: Staph Aureus. Can spread to deeper tissues, umbilicus, bone and joints. If only one site, antiseptic bath once a day. If > 1 site then systemic antibiotics
- Treatment:
  - To relieve symptoms, stop new lesions, prevent complications (e.g. cellulitis, acute glomerulonephritis), and stop spread to others
  - Flucloxacillin, dicloxacillin, a cephalosporin, erythromycin or clindamycin are all effective
  - If MRSA: usually susceptible to co-trimoxazole (although not so good against S Pyogenes). Resistance to fusidic acid is also growing
  - Resistance is growing to topical agents (e.g. Mupirocin)

Cellulitis and Erysipelas

- Infection of subcutaneous layer by Strep Pyogenes
- Symptoms: inflammation, warmth, erythema, pain, fever
- Can → sepsis, bullae and small abscesses
- Also erythema around anus with puss and blood in stool
- May desquamate
- Impaired lymphatic drainage predisposes to recurrent cellulitis (e.g. pelvic, joint, breast surgery)
- Erysipelas is a distinctive superficial cellulitis, primarily involves dermis. Raised and well demarcated. Prominent lymphatic involvement. May → chills, fever and malaise
- Treatment: S Pyogenes still very susceptible to penicillin

Streptococcus Group B

- Eg Strep agalactiae: differential in neonatal meningitis

Streptococcus Pneumoniae

- Causes:
  - Commonly: actue otitis media, acute sinusitis, febrile convulsion in infants, community acquired pneumonia, infectious exacerbations of chronic bronchitis, meningitis (nasty type)
  - Uncommonly: peritonitis (2^{nd}ary to chronic hepatic/renal disease of to infected IUCD)
  - Rarely: infective endocarditis
- Antibiotic sensitivity:
  - Parenteral:
    - penicillin resistance in 1% blood isolates in adults and 11% in kids ⇒ Strep pneumonia penicillin resistance is not an issue in adults but is in kids

        - ceftriaxone
        - vancomycin (for penicillin resistant strains and MRSA)
    - Oral: amoxycillin, erythromycin, cefaclor, tetracycline (not kids or pregnant)
- Vaccination:
    - Pneumovax
    - Polysaccharide-based subunit vaccine containing 23 serotypes covering 90% of strains causing invasive pneumococcal disease
    - Contains T-cell independent antigents ⇒ non-immunogenic if < 2 years (and poor response for some serogroups up to age 6). Predominant IgM response without induction of memory. 5 yearly boosters recommended
    - Recommended for:
        - > 65 years
        - > 2 with asplenia, immunocompromised (including nephrotic syndrome) and chronic illness
    - Conjugate vaccines generating IgG response being worked on….

Viridans Steptococci (plus also Enterococcus faecalis)

- Causes UTI, abdominal wound sepsis, infective endocarditis (uncommon)

Staphlococcus

Staphlococcus Aureus

- Sources of bacteraemia:
    - Skin sepsis
    - Wound infection (esp hospital acquired)
    - Pneumonia (esp hospital acquired)
    - Osteomyelitis
    - Septic arthritis
    - Lines: Subclavian, IV drips (esp CVP)
    - Infective endocarditis

Staphlococcus coagulase negative (eg epidermidis)

- Sources of bacteraemia: IV lines – Hickman, CVP lines, premature neonates with IV lines

Haemophilus Influenzae

- Uncapsulated type (not type B which is capsulated)
- Causes:
    - Commonly: acute otitis media, acute sinusitis, acute infectious exacerbation of chronic bronchitis
    - Uncommonly: community acquired pneumonia (more CORD patients)
    - Rarely: meningitis
- Antibiotic sensitivity:
    - 5% of isolates produce penicillinase ⇒ resistant to amoxycillin
    - augmentin
    - cefaclor
    - tetracycline (not kids or pregnant)
    - cefuroxime (iv)
    - Is not sensitive to erythromycin

Branhamella Catarrhals

- Commonly causes: acute otitis media, acute sinusitis, acute infectious exacerbation of chronic bronchitis (same as Haemophilus Influenzae)
- Antibiotic sensitivity: 70% produce penicillinase, so use augmentin, cefaclor, tetracycline or cefuroxime (iv)

Other G-ives:

- Escherichia coli, klebsiella aerongenes, proteus mirabilis, other Coliform bacilli
- Cause: UTI, Pyelonephritis, abdominal wound sepsis, peritonitis, biliary tract infection (gallstones) or obstruction

Anaerobes

- Bacteroides fragilis, Clostridium perfringens, anaerobic streptococcis

- Cause: Abdominal wound sepsis, peritonitis, pelvic sepsis, septic abortion, puerperal sepsis

Mycobacteria

- Classification:
  - Tuberculosis complex: M. Tuberculosis and M. Bovis
  - Other mycobacteria: M. Avium-Intracellulare (MAC), M. Kansasii, M Marinum
  - Leprosy: M.Leprae
- Resulting Diseases:
  - Tuberculosis Complex
    - Immunocompetent: In descending frequency: lung, lymph nodes, kidney, genital tract, CNS
    - Immunodeficient: Lung in > 70%, but extra pulmonary involvement > 70% in blood (25 – 40%), lymph nodes, faeces, CNS due to ↓cell mediated immunity
  - MAC:
    - Immunocompetent: Kids – cervical lymphadenitis, adults: chronic destructive lung disease (uncommon)
    - Immunodeficient: Infection common. Initial colonisation of GI tract, then spread to blood, lymph nodes, liver, spleen, less lung involvement but invariably fatal
    - Most strains of MAC are resistant to standard anti-mycobacterial drugs
- Drug treatment:
  - Standard drugs: Rifampicin, Isoniazid, pyrazinamide, ethambutol. Normally first 3, except if from Pacific Islands where use all 4 due to ↑isoniazid resistance. Rifampicin is the best, if resistant to this then poor prognosis
  - Most strains of M Bovis are resistant to pyrazinamide
  - Many strains of M Tb from AIDS patients in the US (especially NY) are resistant to Rifampicin and Isoniazid
  - Other anti-mycobacterial drugs: ciprofloxacin, clarithromycin, amikacin, rifabutin, clofazimine
- Vaccination: BCG:
  - Live vaccine
  - Indicated for high risk infants: household has individuals from endemic areas of with past or current Tb
  - Neonatal BCG is 60 – 90% protective for extra-pulmonary Tb and 65% for pulmonary Tb. Protection lasts 10 – 15 years
  - Adverse effects: local abscess in 1%. Treated conservatively. Some require excision

Herpes Viruses

- All Herpes viruses exhibit latency

Herpes Simplex Virus (HSV)

- Manifestations: systemic (fever, sore throat), gingivotomatitis (ulcers with yellow slough – cold sores), meningitis (uncommon, self-limiting), encephalitis (fever, fits, headache, dysphagia, hemiparesis – do PCR on CSF sample – refer urgently)
- Incubation: 2 – 25 days. Chronic infection is due to the virus remaining in the sensory nerve ganglia. Infectious period indeterminate → contact isolation
- Symptoms:
  - Blisters which become shallow painful ulcers, often preceded by itching or tingling.
  - First episode may be accompanied by flu like illness, tender inguinal nodes and dysuria.
  - Recurrences can be brought on by stress, fatigue, depression, immunosuppression and concurrent illness. Recurrences usually less severe and become less frequent
- Diagnosis: clinical suspicion. Swab the base of an unroofed ulcer and refrigerate in viral medium. This will be painful. Culture negative doesn't exclude HSV as timing and collection technique important. Serology should not be routinely used
- Pathogenesis. There are two antigenic types of Herpes Simplex Virus:
  - Type 1 is associated with lesions on the face and fingers, and sometimes genital lesions. Treat with zovirax (topical cream). Prevalance: 70% of population
  - Type 2 is associated almost entirely with genital infections, and affects the genitalia, vagina, and cervix and may predispose to cervical dysplasia. 10% of oral lesions caused by type 2. Prevalance: 10 – 15% of population (depends on population – more in high risk)
- Children:

- May be hospitalised due to poor oral intake. May need NG tube.
- HSV1 the most common type in children.
- Dribbling can → perioral spread
- Auto-inoculation can → conjunctivitis, genital lesions, skin infection with eczema (eczema herpeticum) can be severe
- If neonate or immunocompromised can be life-threatening
- Treatment: Oral analagesics (eg ligoncane) and Paracetamol. Acyclovir

Type 1 Herpes Simplex Virus

- Infection of fingers or thumb leads to a whitlow (vesicles coalesce)
- Primary infection in childhood leads to gingivostomatitis – may lead to dehydration as child won't drink
- Can infect eczematous skin → eczema herpeticum

Genital Herpes (type 2)

- Description:
  - Painful, recurrent condition.
  - Male – anus or penis – small grouped vesicles and papules + pain, fever, dysuria. Dysuria may be severe enough to cause dysuria
  - 20% may have it, but 20% are asymptomatic and 60% mild or unrecognised
- 40% caused by type 1, 60% by type 2
- Transmission: spread through skin to skin contact, usually when skin is broken or lesions present, but asymptomatic viral shedding a possible route of transmission. Neonatal transmission is rare (1 in 10,000 live births), but carries risk of ophthalmic infection ⇒ caesarean section indicated if active blisters at delivery
- Prevention of genital herpes: Condoms with new partner (although doesn't eliminate risk). Avoid sex during an outbreak
- Can have extra genital lesions on thighs and buttocks.
- Treatment of Genital Herpes (type 1 or 2):
  - Acute: Acyclovir 200 mg 5 times daily for 5 days. Topical creams not effective. Symptomatic treatment: salt bathing, local anaesthetic creams, oral analgesia, oral fluids. Counselling and follow-up important – written information for patients and partners, Herpes Helpline (0508 11 12 13)
  - Suppressive Therapy: Where frequent outbreaks or psychological morbidity. Acyclovir 400 mg BD for up to a year. Can reduce viral shedding by up to 95%
  - Can be devastating. Refer to counselling at Sexual Health Service
- Complications:
  - ↑risk of AIDS transfer
  - Neonatal Herpes: 50% mortality
  - In pregnancy:
    - If first primary episode: miscarriage, prem labour
    - If recurrent, tiny risk for baby
    - If lesions at delivery then Caesarian

Varicella Zoster

- Primary infection: Chicken Pox.
  - Macules → papules → vesicles → crusts
  - Incubation 10 – 21 days (usually 14 – 16)
  - Infectious for 1 – 2 days before rash appears until it crusts over
  - Highly infectious, in hospital requires strict respiratory/contact isolation
  - Complications:
    - Commonly becomes super-infected (eg with scratching) with Staph aureus (or S Pyogenes) which leads to scarring
    - If immunocompromised → overwhelming infection, pneumonitis, hepatitis, encephalitis (treat with Ig and acyclovir)
    - Post-natal infection can be overwhelming
    - Immune response can → encephalopathy with cerebellar ataxia
    - Can lead to severe exacerbation of eczema
  - Then remains dormant in dorsal root ganglia
  - Treatment: Supportive, antipruritic lotion if itchy, cut fingernails short

    - Prevention: Live attenuated virus, or im Ig within 96 hours of exposure if at risk and susceptible (immunocompromised, pregnant, newborn, prem babies)
- Tests: culture – swab transported in viral medium
- Vaccination:
    - Live attenuated vaccine recently licensed for both children and adults
    - Not recommended for general use, but role in protecting non-immune adults (more severe illness)
    - Contra-indicated if immuno-suppressed or pregnant
- Shingles:
    - Reactivation of infection: affects 20% at some time. Elderly and immunocompromised are high risk
    - Symptoms: Dermatomal pain, then fever malaise for several days, then macule-papules + vesicles, especially in thoracic or ophthalmic division of trigeminal dermatomes. If sacral, then urinary retention may occur
    - If shingles around eye (especially end of nose), then are likely to have a dendritic ulcer on cornea. Stain with Fluorescein and shine on blue light, corneal abrasions will shine green. Don't give steroid → blindness. Urgent referral to an ophthalmologist
    - Recurrence suggests HIV
    - Treatment if needed: acyclovir as early as possible, 800mg 5 times a day for 5 days. Pain relief – analgesic or low-dose amitriptyline. Maybe prednisolone to reduce post-herpetic neuralgia. Report visual loss immediately

Epstein Barr Virus

- DNA virus
- One of Herpes Group
- Spread by respiratory secretions (e.g. sneeze, kiss)
- Pre-schoolers an important reservoir: usually just a non-specific URT infection. In later life (e.g. adolescent) get it more acutely plus hepatitis. 1 – 5% present as hepatitis
- Associated with Burkitt's lymphoma & nasopharyngeal carcinoma

Clinical

- Highly variable course. Often asymptomatic if < 5 years
- Sore throat (often exudative)
- Fever
- Lymph nodes up
- Tender liver (liver involvement → ↓appetite and ↑feeling unwell), maybe big spleen
- Rash in 10%
- Doesn't resolve (especially after antibiotics)
- Will be tired for weeks/months
- Incubation 30 – 50 days
- Association with symptoms:

	Sore Throat	Lymphadenopathy	Atypical Mononucleosis
EBV	+++	+++	+++
CMV	-	+	+++
HIV	++	++	++
Toxoplasmosis	+	+++	++
Viral Hepatitis	-	+	++

Investigations

- Throat swab
- FBC: may be ↑atypical mononuclear lymphocytes
- EBV serology

Treatment

- Symptomatic
- **Don't** give penicillin if risk of EBV: leads to rash which can be interpreted as penicillin allergy. (e.g. amoxycillin, rash in 80 – 90%)
- Infectious for months. No isolation required
- Steroids if upper airway obstruction in kids

Antibodies to EBV

- IgM Anti-VCA (Virus capsid antigen) and IgG Anti-VCA
  - Usually appear in blood 7 days after symptoms develop in acute primary EBV infection
  - IgM: usually persists for 2 – 4 months
  - IgG: usually persists for life
- Anti EBNA (Epstein-Barr nuclear antigen): Appears 2 months after primary infection and persists for life
- Profiles:

	IgM VCA	IgG VCA	EBNA
No infection	-	-	-
Acute Primary	+	+	-
Past Infection	-	+	+ (ie EBNA +ive rules out acute infection)

- Paul-Bunnell now largely obsolete. Negative in 10 – 15 % of cases

Associated diseases

- Burkitts lymphoma
- Nasopharyngeal carcinoma
- Hodgkins disease (EBV in 40 – 60% of cases)
- Chronic EBV may occur but is very uncommon (recurrent sore throat, cervical lymphadenopathy)

Chronic Fatigue Syndrome

- Unknown cause: but key differential to EBV

Diagnosis

- Severe chronic fatigue over 6 months or longer, with other known medical conditions excluded, **and**
- 4 of the following during 6 consecutive months:
  - ↓Short term memory or concentration
  - Sore throat
  - Tender lymph nodes
  - Muscle pain
  - Multi joint pain: without swelling or redness
  - Headaches of new type/pattern
  - Unrefreshing sleep
  - Post-exertional malaise lasting > 24 hours

Differential Diagnosis

- Depression
- Psycho-social stressors

Cytomegalovirus (CMV)

- Transmission:
  - Blood: transfusions, intra-uterine, perinatal, needle sharing
  - Cervical secretions and semen
  - Saliva (eg close contact with kids)
  - Urine (eg infants to adults)
  - Organ donation (transplantation)
- Immunocompetent:
  - Kids:
    - Common in preschoolers, usually asymptomatic
    - Prolonged excretion in saliva and urine common
  - Adults:
    - Usually asymptomatic, if not then usually self-limiting
    - May be fever (up to 2 weeks, ie a differential of PUO)
    - Sore throat, cervical lympadenopathy uncommon
    - Atypical mononucleosis on blood film
    - Differential: EBV, HIV, toxoplasmosis
  - Pregnancy:
    - Congenital infection (ie crosses placenta) in 20 – 40%

        - > 90% show no signs at birth, but long term neurological sequalae (eg sensoro-neural deafness, retardation)
        - Severe cases: respiratory distress, jaundice, microcephaly, etc
        - Part of TORCH complex: Toxoplasmosis, Rubella, Cmv, Hsv
    - Perinatal infection (eg during vaginal delivery):
        - Full term: usually mild
        - Pre-term: may be severe
- Immunodeficient:
    - AIDS: one of the most common infections → CMV retinitis (common), CMV encephalitis (rare), CMV colitis (rare)
    - Transplant: greatest risk if they're CMV negative and CMV positive organ → intersitial pneumonia and hepatitis (in liver transplant)
- Transfusion: blood is not routinely screened for CMV antibody. Should give CMV –ive blood to prem babies (<1500 g) and seronegative transplant recipients with seronegative transplants
- Lab diagnosis:
    - Serology:

	IgG	IgM
No infection	-	-
Past infection	+	-
Acute primary or reactivated infection	+	+

    - Cell culture – slow (>7 days). Culture lung biopsy or peripheral blood leucocytes
    - PCR for CMV DNA on peripheral leucocytes, amniotic fuild, CSF (very specific, less sensitive, very expensive)
- Treatment:
    - Ganciclovir: bone marrow toxicity
    - Foscarnet (nephrotoxic)
    - Ganciclovir prophylaxis used for –ive patients with +ive organs

Parasitology

Toxoplasmosis

- A protozoa/parasite
- Main source: cysts in meat. Also kitten faeces (eg oocyst in garden – pregnant gardeners should wear gloves)
- Presentation:
    - Immunocompetant:
        - Lymphadenopathy (eg unilateral)
        - Maybe: fever, myalgia, acute pharyngitis, hepatosplenomegally, atypical mononucleosis
        - Usually self-limiting – may take months to settle
        - If persistent/recurrent lympadenopathy → ?Need for treatment
    - Immunodeficient:
        - Acquired or reactivated
        - AIDS most common: CNS involvement (solitary space occupying lesion, encephalitis), also myocarditis, hepatitis
        - Less common in transplants and encephalitis
    - Ocular toxoplasmosis: most cases in adolescents and adults → reactivation infection.
      →Blurred vision, photophobia, multiple retinal lesions
    - Congential Toxoplasmosis:
        - 29% fetal infection if mother has primary CMV infection
        - Highest risk in 3rd trimester (1st trimester may miscarry)
        - Complications: spontaneous abortion, premature, still birth
        - Surviving neonates: bilateral choroido-retinitis. In sever cases, TORCH type symptoms
- Lab diagnosis:
    - PCR test for toxoplasmosis: amniotic fluid, CSF (AIDS patients)
    - Lymph node biopsy → characteristic histology
    - Serology:
        - IgM antibody after 5 – 14 days, peaks at 2 – 4 weeks, traces for up to a year
        - IgG: high levels for up to 6 months, declines slowly over years

    - Avidity test: can differentiate between acute phast ‘immature’ IgG and ‘mature’ IgG
- Treatment:
    - Pyrimethamine (Gold standard, but gies bone marrow suppression + give folate)) + sulphadiazine (not available in NZ)
    - Pyrimethamine + clindamycin (gives C.difficle diarrohea)
    - Spiramycin (only one safe in pregnancy)

Malaria

- Transmitted by mosquito and very rarely transfusion

Clinical

- Irregular fever – peaks on release of parasite from infected RBCs. May only be mild if person has immunity (ie previous exposure). Various strains have various periodicities
- Chills
- Headache
- Malaise
- Vomiting (20%)
- Diarrhoea (<5%)
- ie similar to Typhoid

History

- Travelled to a malaria country,
- What conditions did you stay in, rural/urban, etc
- Was chemoprophylaxis taken, how was compliance
- Diagnosed overseas
- When did you return to NZ (Plasmodium Falciparum usually in 1 month, P Vivax up to a year)
- Length of illness

Diagnosis

- Blood film for malaria parasite: a thick film is necessary as well as the standard thin film if parasites are scant (eg if have some immunity)
- Pointless if patient is afebrile
- If initially negative, repeat 12 hourly for 48 hours
- Critical that you find out which plasmodium species is present, eg:
    - Falciparum: common in Africa, can cause cerebral malaria (fatal)
    - Vivax: more common in Asia/Oceania
- Features of poor prognosis:
    - CNS signs: disturbed consciousness, repeated convulsions
    - Respiratory distress
    - Haemorrhage, shock
    - Biochemical markers: ↑Cr, ↓HCO3, ↑bilirubin, ↓glucose
    - High parasitic load

Prevention

- Assessment of risk:
    - Malaria geography: transmission rates vary by country (eg high in Sub-Sahara, PNG, Solomon Islands)
    - Likely extent of contact with mosquitos (eg standard of accommodation)
- Anti-mosquito measures: long sleeves & trousers, insect repellent/sprays, nets
- Chemoprophylaxis:
    - Start 1 week beforehand and continue till 4 weeks after leaving
    - Mefloquine (effective against chloroquine resistant P Falciparum).
        - 250 mg *weekly*
        - Side effects: nausea, diarrhoea, dizziness – usually self-limiting.
        - At higher doses (eg for treatment) convulsions and sinus bradycardia
        - Contraindications: drugs altering cardiac conduction, psychiatric disease, epilepsy, pregnant, kids < 5kg, or where fine CNS co-ordination required (eg airline pilots)
    - Doxycycline, 100 mg *daily*
        - After food otherwise gastritis
        - In rural areas of SE Asia, where mefloquine-resistant strains of P falciparum are reported
        - Contraindicated in pregnancy women and children

- Choloroquine + proguanil: Only one safe for first trimester. Low efficiacy against drug resistant falciparum
- Chloroquine weekly – countries without chloroquine-resistant P falciparum (Central America north of Panama)

Treatment

- P Vivax, P Ovale, P Malariae:
  - Acute treatment: 3 days of Chloroquine
  - For radical cure in P Vivax or P Ovale:
    - Primaquine for 2 weeks (screen for G6PD deficiency first)
    - Eradicates exo-erythrocytic liver cycle. If you don't, they will relapse
  - Relapse common (20%) – maybe several months later. If so, repeat 3 days of Chloroquine followed by 2 weeks of higher dose of Primaquine
- P Falciparum:
  - Quinine sulphate + Doxycycline for 7 days
  - No persisting cycle so relapse not a problem
  - Cerebral malaria: iv quinine: loading dose then maintenance infusion
- Drug resistance:
  - Chloroquine-resistent strains of plasmodium flaciparum are widespread
  - Chloroquine-resistant strains of P Vivax reported in Indonesia and PNG

Other

Amoebiasis (Entamoeba histolytica)

- Diagnosis:
  - Intestinal amoebiasis: stool sample * 3, 48 hours apart, in PVA fixative
  - Cysts: frequently present asymptomatically (carrier state)
  - Extra-intestinal amoebiasis (eg amoebic abscess of the liver) maybe months later. Serum antibody test
- Treatment:
  - Intestinal amoebiasis: metronidazole then diloxanide furoate
  - Extra-intestinal: metronidazole (surgical drainage may be necessary)
  - Asymptomatic: Diloxanide furoate

Giardiasis

- Diagnosis:
  - Stool examination for cysts, 3 samples 48 hours apart
  - Duodenal aspirate and direct examination for trophozoites
- Treatment:
  - Tinidazole 2g stat or Metronidaxole 400 mg 8 hourly for 7 days
  - Test for cure with repeat stool sample. Relapse not uncommon

Filariasis

- Commonest is Wuchereria bancrofit imported from Samoa
- Diagnosis: Blood sample
- Treatment:
  - Ivemectin
  - Most cases are asymptomatic or low grade pyrexia and don't require treatment
  - If severe, surgical relief of major lymphatic obstruction may be necessary

Intestinal Worms

- Hookworm
  - Ancylostoma duodenale, necator americanus
  - Diagnosis: stool sample * 3
- Roundworm
  - Ascaris Lumbricoides
  - Diagnosis: worms passed in faeces, or stool samples * 3 and examine for Ova
- Pinworm
  - Enterobius vermicularis
  - Diagnosis: sellotape swabs of anus
- Whipworm

    - Trichuris trichura
    - Diagnosis: stools * 3
- Treatment: medendazole 100mg BD for 3 days for Hookworm, Roundworm, Pinworm (treat whole family) and whipworm (only if severe)
- Strongyloides Stercoralis
    - Diagnosis: Stools * 3
    - Treatment: Thiabendazole
- Tapeworms
    - Taenia saginata, beef tapeworm
    - Diagnosis: Stools * 3, examin for worm segments
    - Treatment: niclosamide

Hydatid Disease

- Aetiology: Echinococcus granulosa (a flatworm). Infected from ova excreted in dog faeces. Dogs infected from eating raw sheep offal (ie liver) containing hydatid cysts
- Clinical: Often acquired in childhood, present in older age with solitary cysts (liver, lung, brain)
- Treatment: surgical drainage + aldendazole as adjunct
- Diagnosis: Serology: haemagglutination test + complement fixation test

Cryptosporidium

- Common protozoan parasite
- Profuse watery diarrhoea for 48 hours. Very common cause of diarrhoea.
- Severe and persisting cases in AIDS
- Diagnosis: Stool microscopy with ZN stain for acid fast cysts
- Treatment: Paromomycin (an oral, non-absorbable aminoglycoside) has some efficacy

Penumocystis Carinii

- Protozona parasite probably part of normal respiratory flora
- Causes interstitial pneumonitis in immuno-compromised patients (transplant, leukaemia, AIDS)
- Diagnosis: Bronchial lavage or open lung biopsy
- Treatment: Cotrimoxazole (alternatively pentamidine). Relapse in 25%

Travel Medicine

- Travel History:
    - Where are you going
    - How are you getting there
    - How long there
    - What will you be doing
    - Where are you staying
    - Have you been there before
- Examples:
    - 3 week package to Hong Kong, Singapore, Bangkok: Hep A and Tetanus up to date. Typhoid is overkill
    - 4 month Overland through from Thailand to Turkey (Vivax Malaria): Malaria, Hep A, Tetanus
    - 3 month TI in Tanzania: Hep A, Typhoid, Yellow fever (not Asia)
    - 3 year diplomatic posting in PNG: Malaria prophylaxis if going rural but not continuously

Vaccination

- Malaria chemo-prophlaxis: unnecessary if in a malarious country for < 7 days. Risk in main resort areas of Asia is low
- Typhoid:
    - Injectable: slamonella typhi antigen, 70% protection for 3 years
    - Oral vaccine: attenuated live strain, doses at 0, 3 and 5 days gives protection for one year. Useful at short notice
- Yellow fever:
    - Attenuated live strain ($\Rightarrow$ not if immunocompromised)
    - For travel to equatorial Africa and South America
    - Protection for 10 years
    - Requires special certificate, stamp, etc $\Rightarrow$ only done in designated centres
- Polio:

- OPV: Oral: 2 drops po (tiny risk of giving it to adults if no previous vaccine ⇒ use IPV)
- IPV: Inactivated polio vaccine: 0.5 mls sc
- Booster every 10 years

- Tetanus/Diphtheria Toxoid: booster every 10 years. 0.5 mls im into deltoid muscle
- Meningococcal Vaccine: For types A, C, W, Y – not B. sc injection gives 3 years protection. Indicated for travel to countries where epidemics occur – Nepal, West Africa, Brazil
- Hepatitis A: Formalin inactivated HAV. Im injection gives protection for one year. Booster dose 6 – 12 months later gives long term protection. If over 50, check immune status – may be immune and therefore won't need it (its expensive)
- Japanese Encephalitis Vaccine: Widespread through SE Asia. Rare for travellers to get it – but high mortality. Side effects from vaccine
- Rabies: Only for people intending to work longer term in rural/agricultural areas of Asia

Pyrexia of unknown origin if returning from 3rd world

- Diagnose on blood film/culture:
  - Malaria
  - Dengie
  - Typhoid (usually constipated, used to die of peritonitis, takes days for temperature to go down)
- Ross River
- Syphillus
- Filariasis (eg Samoa)
- Other imported infections from Pacific:
  - Leprosy (mycobacterium leprae)
  - Yaws (treponema pertenue)
  - Eosinophilic Mennigitis

Antibiotic Treatment

Summary

G +ive

Cocci	Strep pneumonia	Oral: Amoxycillin. IV: Penicillin G Allergy: Erythromycin. Resistant (eg kids): Ceftriaxone Resistant and Meningitis: Cefotaxime + Vancomycin (act synergistically) Resistant and Endocarditis: Vancomycin
	Strep faecalis	Trimethoprim
	Strep agalactiae	Penicillin. [β haemolytic. Normal vaginal flora)
	Strep pyogenes	Penicillin. Erythromycin if allergic. Also sensitive to flucloxacillin
	Strep sanguis	Penicillin [α haemolytic]
	Staph aureus	Flucloxacillin. Allergy: Ceftriaxone. MRSA (resistant to penicillins and cephalosporins): Vancomycin
	Staph epidermidis	Flucloxacillin. Resistant: Vancomycin
Bacilli	Listeria monocytogenes	Amoxycillin. Elderly/immunocompromised: ciprofloxacin (quinolone – not in kids)
	Clostridium difficile	Metronidazole
	Enterococcus faecalis	Amoxycillin
G –ive		
Bacilli	E Coli	Trimethoprim. Cotrimoxazole (trimethoprim + sulphmethoxazole), Norfloxacin (Quinolone). 48% resistant to amoxycillin. Augmentin resistance growing. Meningitis: Cefotaxime (good CSF penetration). Consider gentamycin or cotrimoxazole
	Campylobacter Jejuni	Erythromycin
	H Influenzae	Cefaclor, Augmentin, Tetracycline Resistant to penicillin, not sensitive to erythromycin
	Legionella	Erythromycin. Add rifampicin if severe
	Pseudomonas Aeruginosa	Ciprofloxacin. Maybe Tobramycin or piperacillin Meningitis: Ceftazidine

	Gardnerella Vaginalis	Metronidazole. Metronidazole is otherwise inactive against aerobes
	Bordetella Pertussis	Erythromycin
	Branhamella Catarrhalis	Augmentin, cefaclor, tetracycline, cefuroxime 70% penicillinase
Anaerobes	Bacteroides Fragilis	Metronidazole. *Not* penicillin or cephalosporins
	Helicobacter Pylori	Clarithromycin + metronidazole + omeprazole (7 days)
Cocci	Neisseria Meningitidis	Penicillin. Cefotaxime if allergic. Prophylaxis: Rifampicin, ceftriaxone if pregnant
	Neisseria Gonorrhoea	Stat: Amoxycillin + Probenicid Ciprofloxacin or tetracycline if penicillin allergy or resistant. Azithromycin if concurrent chlamydia or pregnant
Not G-ive	Chlamydia Trachomatis	Pneumonia: Erythromycin STD: Doxycycline, azithromycin, pregnancy: Erythromycin PID: Erythromycin + ornidazole NB: Obligate intracellular parasite. Cellular wall similar to G-ive but not actually a G-ive bacteria
Others		
	Mycoplasma	Erythromycin. 2nd line: Tetracyclines (eg doxycycline) except pregnant/kids
	TB	Rifampicin + isoniazid + pyrazinamide (also ethambutol if isoniazid resistant). Prophylaxis: rifampicin
	MAC	Clarithromycin
	Treponema pallidum	= Syphilis. Penicillin G. Resistant: Tetracyclines (eg doxycycline)
Yeasts		
	Aspergillus	Amphotericin B. Itraconazole prophylaxis
	Cryptococcus neoformans	Fluconazole (good CSF penetration), Amphotericin B
Virus		
	HSV	Acyclovir
	CMV	Ganciclovir
	Toxoplasmosis	Pyrimethamine + clindamycin. Pregnant: Spiramycin
Protozoa		
	Cryptosporidium	Nothing effective. Maybe Paromomycin (oral, non-absorbed aminoglycoside)
	Giardiasis	Tinidazole stat or metronidazole 7 days
	Trichomonas	Doxycycline, Metronidazole
	Pneumocystis Carinii Pneumonia	Cotrimoxazole
	Malaria Prophylaxis	Mefloquine weekly: good for chloroquine resistant falciparum. Not epilepsy, pregnant, babies Doxycycline daily: Exp Mefloquine resistant falciparum. Not kids or pregnant Chloroquine + Proguanil: if pregnant Chloroquine weekly: if no chloroquine resistant falciparum
	Plasmodium Falciparum	Quinine sulphate + doxycycline
	Plasmodium Vivax	Chloroquine 3 days then primaquine 2 weeks
	Amoebiasis	Metronidazole + diloxanide furoate
Worms		
	Filariasis	Ivermectin
	Intestinal worms	Hookworm, roundworm, pinworm: Medendazole Strongyloides Stercoralis: Thiabendazole Tapeworms: Niclosamide

Antibacterials

Penicillins

	Use for	Notes
Penicillin G (iv/im) (oral form: Pen V)	Streptococci	Not Enerococcus faecalis, resistance in kids to strep penumoniae
	Staphylococci	But 80% produce penicillinase
	N Gonorrhoeae	Some produce pencillinase
	N Meningitidis	
	T Pallidum	
	Leptospira	

	Syphillus Anaerobes	 Peptostreptococci, Clostridia, Fusobacteria, Bacteroides (not B fragilis), Actinomyces
Amoxycillin	As above plus: Enterococcus faecalis Listeria monocytogenes Haemophilus influenzae Some E coli Most Proteus mirabilis	 6 % produce penicillinase 48% resistant 20% produce penicillinase
Augmentin	 Haemophilus influenzae Branhamella Catarrhalis	Clavulanic acid inhibits penicillinase. Principle use is infectious exacerbations of chronic bronchitis Increasing E coli resistance
Flucloxacillin	Staph Aureus	Penicillinase producers. MRSA resistant to Flucloxacillin and cephalosporins
Piperacillin Tazocin	Pseudomonas aeruginosa Neutropenic cancer patients	Systemic infection only = Piperacillin + Tazobactam (a beta-lactamase inhibitor)

Cephalosporins

Gen	Examples	Use for
1	**Cefaxolin** Cephalothin (IV) Cephradine (IV & oral) Cephalexin (oral)	• Better for G+, poor for G- • Gram +ives: Streptococci (not E faecalis), Staphyloccoci, Anaerobes (Not B Fragilis) • Gram –ives: Some coliforms: E coli (20% resistant), Klebsiella • Inactive against: H Influenzae, Pseudomonas, Enterovoccus faecalis
2	**Cefuroxime** (IV+oral)Cefamandole (IV+IM) Cefaclor (Oral)	• G +ive: as for 1st generation • G -ive: Better against coliforms • Active against H influenzae • Inactive against: Pseudomonas, E Faecalis, B Fragilis
3	**Ceftriaxone** Cefotaxime Ceftazidime Cefpodoxime (oral)	• Good activity against most coliforms • Activity against G+ < 2nd generation • No activity against Bacteroides or Enterococcus • Ceftazidime good against pseudomonas aeruginosa • Ceftriaxone has long T½, can be given once daily • Good CSF penetration ⇒ first choice for meningitis caused by coliforms or HIB
4	**Cefipime** Cefpirome	• Highly stable against β-lactamases • Good against most aerobic G –ives (coliforms and *pseudomonas*) • Good against G +ive, incl staph aureus (similar to 1st generation) but not Enterococcus
	Cefotetan	• Broad spectrum cephamycin • Good against Bacteroides and Coliforms (not pseudomonas) • Indications: antibiotic prophylaxis for colonic and gynaecological surgery
	Aztreonam	• Active against G –ive bacteria only: including coliforms and to a lesser extent Pseudomonas • Indication: less toxic than aminoglycosides for G-ive infection
	Imipenem Meropenem	• A cabapenem (not cephalosporings) • Inhibit nearly all G+ and G- • Restricted as its so good • Indication: Empiric therapy in neutropenic cancer patients

Macrolides

- Effective against:

    - Staph aureus (up to 10% resistance in community strains)
    - Steptococci (not E faecalis)
    - Anaerobes (only moderately effective against B fragilis)
    - Mycoplasma pneumoniae
    - Chlamydia penumoniae
    - Chlamydia trachomatis (but tetracycline is the drug of choice)
    - Campylobacter jejuni
- Ineffective against:
    - H influenzae
    - No CSF penetration
- Indications:
    - Treatment of susceptible bacteria if penicillin allergy
    - Atypical pneumonia (eg Mycoplasma, Chlamydia or Legionella)
    - Campylobacter
    - Chlamydia infection in pregnancy women
- **Erythromycin**
- New analogues:
    - Roxithromycin (Rulide)
    - **Clarithromycin** (Klacid): Treatment of MAC, especially in AIDS patients
    - Azithromycin (Zithromax): Single dose treatment for STD's caused by Chlamydia trachomatis or N. gonorrhoeae (especially in pregnancy)

Vancomycin

- G+ive wonder drug – active against G+ive only
- Indications:
    - Systemic infections caused by MRSA or MRSE (Epidermidis), or infected Hickman lines in cancer patients
    - Infective Endocarditis due to Strep or Staph with penicillin allergy
    - Clostridium difficile colitis (by mouth). First line is metronidazole
- Otto and nephro toxic
- Teicolpanin: similar drug, active against some Vancomycin Resistent Enterococci (VRE)

Rifampicin

- Always used in combination (except meningitis prophylaxis)
- Active against M. Tb, Staph aureus, Leionella
- Indications:
    - TB (in combination)
    - Severe Staph aureus infections (eg infective endocarditis) in combination
    - Severe legionella pneumonia (in combination with erythromycin)
    - Prophylaxis against N meningitides or HIB

Aminoglycosides

- Active against all coliform bacilli (eg E Coli), pseudomonas, staphylococci
- Inactive against: streptococci, anaerobes
- Indications: G- sepsis, perforated appendix
- Drugs:
    - **Gentamicin**
    - **Tobramycin**: more active atainst pseudomonas
    - Amikacin: reserved for Gentamycin resistant bugs
    - Spectinomycin: N gonorrhoeae (penicillinase producers)
- Otto and nephro toxic

Cotrimoxazole

- = Trimethoprim + Sulphamethoxazole
- Broad spectrum: Staph, Strep, Many coliforms (not Pseudomonas), HIB, Pneumocystis, Brucella
- Indications: Acute infectious exacerbations of chronic bronchitis, PCP in AIDS
- **Trimethoprim** on its own is the standard treatment against community acquired UTI (E Coli, Klebsiella, Proteus, Strep faecalis)

Quinolones

- Broad spectrum oral antibiotic
- Active against: most coliforms, pseudomonas aeruginosa (main use), Staphs (including MRSE and MRSA), N gonorrhoeae, HIB, Branhamella catarrhalis (good), Salmonella, Shigella, Yersinia, Campylobacter
- Poor activity against Anaerobes, streptococci
- Can damage growth cartilage ⇒ not licensed for children
- Indications:
  - **Norfloxacin**: resistant UTIs
  - **Ciprofloxacin**: Mainly pseudomonas

Tetracyclines

- Eg **doxacycline** (once a day on full stomacy), very common in treatment of STIs
- Active against Staphs, Streps, Coliforms, HIB
- Other indications:
  - Syphilis and Gonorrhoea if pencillin allergy
  - Mycoplasma penumoniae
- Contraindications: young children, pregnancy, renal failure (except doxycyline)

Metronidazole

- Active against all anaerobes (eg B fragilis)
- Inactive against aerobes (excl Gardnerella vaginalis, causing bacterial vaginosis, where it is drug of choice)
- Active against Protozoa: Trichomonas vaginalis, Giardia lamblia

Other

- Fucidin: active against Staph Aureus, must be used in conjuction with, eg Flucloxacillin. Use in bone/joint infections
- Chloramphenicol: for infections caused by Burkholderia cepacia

Antifungals

- **Nystatin** (topical): vaginal or oral candida
- **Miconazole** (topical): Candida and dermatophytes (except scalp or nails)
- **Terbinafine** (oral) Dermatophyte infections of scalp or nails (has superceeded Griseofulvin)
- **Fluconazole** (Oral/IV): active against yeasts (candida, cryptococcus). Good CSF penetration (ef Cryptococcal meningitis)
- **Itraconazole** (oral): Dermatophyte infections of scalp or nails, prophylaxis in Candida and Aspergillus in immunocompromised
- **Amphotericin B** (IV): Very good but side effects, including nephrotoxicity
- See also **Error! Reference source not found.**, page **Error! Bookmark not defined.**

Antivirals

- **Acyclovir**: active against HSV and VZV (less active)
- **Ganciclovir**: CMV in immunocompromised patients. Bone marrow suppression → neutropenia
- Contraindications:
  - Acute illness or fever > 38 C: defer vaccine. Otherwise will blame the illness on the vaccine!
  - Living with an immune suppressed person: use IPV rather than OPV
  - Reaction to previous dose: encephalopathy with 7 days of DTP vaccines or immediate severe allergic reaction. If true anaphylaxis seek specialist advice
  - Immune suppression: don't give live vaccine. Likely to have reduced response to inactivated vaccines
  - Pregnancy: theoretical risk from live virus vaccines
  - If in doubt, refer to a paediatrician
- False contraindications:
  - Mild illness, URTI, fever < 38.5 C
  - Asthma, hay fever, eczema
  - Prematurity and low birth weight in an otherwise healthy child – these especially need vaccination
  - Previous clinical history of illness: no harm done from vaccinating and many clinically diagnosed cases of an illness are in fact something else
  - On antibiotics, inhaled or low dose steroids

- Stable neurological conditions (cerebral palsey, Down)

Currently Vaccine Schedule

- Current Vaccination Schedule:
  - Covers Hep B, Diphtheria (child dose = D, adult dose = d – smaller), Tetanus, Pertussis, Polio, HIB, Measles, Mumps, Rubella

	Hep B	DTPH	Oral Polio	MMR	Td
6 weeks	X	X	X		
3 months	X	X	X		
5 months	X	X	X		
15 months		X		X	
11 years			X	X	X

  - Will shortly change to Hep B + HIB, DTaP (acellular pertussis)
  - For unimmunised adults:
    - Give jabs over same timeframe
    - Don't need HIB, don't give paediatric dose of diphtheria (too big) and more inclined to use IPV
- Additional vaccination in specific age groups:
  - Neonates:
    - Babies of HbsAG +ive mothers: HBIG and vaccine at birth, vaccine at 6 weeks, 3 months and 5 months. Also offer vaccination to household and sexual contacts.
    - BCG if possible Tb exposure
  - Women of child bearing age who are susceptible to Rubella should be offered MMR
  - Adults: Td (10 yearly and after injury) + annual influenza
  - Elderly: annual influenza + pneumococcal (5 yearly)
- Specific exposure situations:
  - Splenectomy: Pneumococcal vaccine
  - Occupational: Health care workers (eg Hep B) or HAV to food workers
  - Travel: See Travel Medicine, page 20
- Future Developments:
  - Inclusion of Varicella Zoster and pneumococcal for children
  - Research into Group B meningococcal (currently 10 year epidemic, 250 cases per year), Rotavirus and RSV, non-infectious diseases including cancer

Vaccine Preventable Diseases

- Measles and Pertussis are the main ones still happening that we shouldn't have
- **Hepatitis B**:
- **Diphtheria**:
  - Corynebacterium diphtheriae $\rightarrow$ respiratory and cutaneous infection (grey membrane on throat). Exotoxin causes cardiac toxicity and ascending paralysis. Spread by nasal droplets
  - 1 imported case in last 20 years. Till 1945 killed 100 babies a year. High is USSR in 90s.
  - Vaccine: inactivated diphtheria toxoid, boosters every 10 years. > 80% efficacy
- **Tetanus**:
  - Clostridium tetani from soil and animal faeces $\rightarrow$ muscular rigidity due to neurone specific toxin, 10% mortality
  - 3 notifications per year (old ladies in the garden). Common in environment $\Rightarrow$ no herd immunity
  - Vaccine: Inactivated toxoid, boosters every 10 years, 100% efficacy
- **Pertussis**: See
- **Polio**:
  - Enterovirus spread by faeces and saliva
  - Presentation:
    - Usually asymptomatic or mild (fever, headache, nausea, vomiting
    - Only 1% of infected get severe clinical disease: severe muscle pain, neck and back stiffness $\rightarrow$ flaccid paralysis
  - Last wild virus infection in 1962. Occasional imported and vaccine associated cases
  - Vaccine:
    - Live oral polio (OPV) > 90% protection after 3 doses. < 1% of recipients develop diarrhoea, headache or muscle pains. 1 in 2.5 million recipients or close contacts develop

paralysis (more common in immunosuppressed) = Vaccine Associated Polio Paralysis (VAPP)
        - Inactivated polio vaccine (IPV) for immunocompromised (will be used more widely when it can be combined with other jabs)
- **Haemophilus influenzae type B** (HIB): See
- **Measles**: See
- **Mumps**: See
- **Rubella**:
    - Togavirus spread by nasal droplets
    - Presentation:
        - Incubation 2 – 3 weeks
        - Fever, headache, mild conjunctivitis, erythematous maculo-papular rash, lymphadenopathy (especially posterior triangle), arthritis, arthralgia
        - 50% develop the rash and lymphadenopathy
        - 50% of adolescents and adults have arthralgia or even frank arthritis
        - 1 in 5,000 have encephalitis
    - Complications:
        - Congenital rubella syndrome: 90% of embryos of mothers infected in 1st trimester will abort or have major abnormalities (severely retarded, seizures, deafness, cardiac defects). Frequent problems after birth
        - Rate of congenital rubella is 5 times the US rate
    - ~ 60 notifications per annum (1600 in 1995)
    - Vaccine:
        - 98 % protective
        - To protect the unborn child only – relies on herd immunity. Need to vaccinate guys as well otherwise they will maintain a population reservoir which women with vaccine failure will catch
        - 5% of adolescents and adults have arthralgia and 1% have non-infectious rash
        - Contra-indicated in pregnancy and immunosuppressed
- **Influenza**:
    - Virus types A (H3N2 and H1N1) and B
    - Causes Fever, rigors, headache, myalgia, protraction. Estimated 400 deaths per annum.
    - Vaccine: inactivated subunit vaccine for new strains (resulting from 'antigenic drift'). 60 – 90% effective. Contraindicated if egg allergy
    - Pandemics result from 'antigenic shift'
- Tb: **BCG**: See Mycobacteria, page 13
- **Pneumococcal Disease**: See Streptococcus Pneumoniae, page 11
- Varicella Zoster:

Chemical Pathology

Liver Function Tests

- Investigations:
  - Bloods:
    - Bilirubin
    - LFT: AST, ALT, ALP, GGT
    - Total protein, albumin
    - Tests can be widely variable for the same condition
    - Other: Coagulation studies, ammonia
    - Special tests: α1 antitrypsin, αfeta protein, hepatitis markers, specific autoantibodies, Igs, caeruloplasmin
    - Any liver disorder may $\rightarrow$ $\uparrow$ferritin (also an acute phase protein)
  - Also test for other causes of liver disease: HBV, HIV, iron studies (ferritin), immune liver disease ($\uparrow$Anti-nuclear Antibodies – ANA)
  - Imaging: ultrasound +/- CT, MRCP, ERCP. Ultrasound and CT have high false negatives for bilary
  - Percutaneous transhepatic cholangiogram – PCT
  - Liver biopsy the gold standard
- Aim to decide if liver disease is present, is progressing or is severe

- Normal values:
  - Bilirubin: 3 – 17 μmol/L
  - ALT and AST: 3 – 35 iu/L
  - ALP: 30 –300 iu/L (adults)

Aiming to answer three questions:

1) Is there liver cell death – inflammation and hepatonecrosis? Check:
   - Bilirubin: in acute hepatitis will be 50:50 direct and indirect
   - Raised aminotransferases predominate. If AST > ALT think severe cirrhosis, liver malignancy, alcohol. In normal hepatitis ALT > AST
   - Chronic damage: ALT > AST
   - Acute damage: AST > ALT
   - Common liver causes:
     - Non-alcoholic statohepatitis (fatty liver): probably the most common cause of mildly elevated LFTs, especially if obese, Type 2 diabetes and hyperlipideamia
     - Acute/chronic viral hepatitis
     - Genetic haemochromatosis
     - Autoimmune hepatitis
     - Less commonly: α1 antitrypsin deficiency and Wilson's disease
   - Causes of abnormal LFTs other than Liver disease:
     - Diseases of other organs affecting liver, e.g. RA
     - Medicines, alcohol, tonics, remedies, poisons
     - Congestive heart failure $\rightarrow$ hepatic congestion
   - AST: also produced by muscle. If normal ALT and $\uparrow$AST then do a CK for muscle breakdown
   -

2) Is there choleostasis (=impaired bile flow)? Liver can remove 5 * normal bilirubin from circulation (i.e. large functional reserve). Choleostasis usually refers to obstruction within the liver. 'Obstructive Jaundice' $\Rightarrow$ major ducts. Bile salts are 90% reabsorbed in the terminal ileum. They emulsify fats. Bile also contains cholesterol, phospholipids and bilirubin (reabsorbed $\rightarrow$ urobilinogen $\rightarrow$ urine)
   - If left <u>or</u> right hepatic duct blocked, other side of liver will be sufficient to keep bilirubin normal
   - GGT released in inflammation: usually in parallel with ALP in obstruction. If $\uparrow$GGT and $\uparrow$ALP then ALP is from the bilary tree
   - Raised ALP and GGT predominate in cholestatic diseases
   - Common:

        - Biliary obstruction: gallstones
        - Drug hepatotoxicity
        - Neoplasms (eg head of pancreas)
        - Primary biliary cirrhosis
        - Primary sclerosing cholangitis
    - Less Common:
        - Sarcoidosis
        - Autoimmune cholangiopathy
    - Other causes of ↑ALP:
        - ALP from bone and cholangiocytes (bilary epithelium). Excreted in urine, but saturated kinetics → ↑serum level
        - Physiological:
            - Bone: Growth and fractures. High in puberty
            - Pregnancy (placental)
            - Benign ↑ with age
        - Bone disease: Pagets, malignancy, renal failure, hyperparathyroidism, Rickets
        - GI tract can also produce ALP, eg Crohns
        - Miscellaneous: hyperthyroidism, familial benign, transient of infancy
    - GGT ↑ benignly with age and obesity
    -

3) Is liver function normal? Are detoxification, synthesis, and glucose management working? Has a large functional reserve. Check:
    - Bilirubin
    - Albumin. See below
    - Prothrombin time (INR): factors 2, 5, 7, 9, 10. Give parental Vitamin K to differentiate between malabsorption or poor liver function

- Tests in cirrhosis
    - Liver function tests very variable:
        - Quiescent phase: normal of minor ↑ in LFT
        - Active Phase: ↑ in ALT and AST when necrosis is dominant
    - Causes: idiopathic, alcohol, chronic active hepatitis, primary biliary cirrhosis, haemochromatosis, Wilson's disease, α1 antitypsin deficiency
- Other examples of Liver Function tests:
    - ↑↑ALT and ↑↑AST: viral hepatitis, Paracetamol OD
    - ↑ALP and ↑bilirubin in a 12 year old with vomiting: Gilbert's syndrome (↑bilirubin when fasting), ALP normally raised at this age
    - ↑Bilirubin, ↑ALP, ↓Albumin + neuro signs → ?Wilson's disease (very rare)
    - ↑Bilirubin, ↑ALP, ↓Albumin + abnormal electrophoresis → ? ↓α1 antitypsin

Total Protein

- Normal Ranges:

Total Protein	60 - 80
Albumin	34 – 46
ALP	40 - 110
Bilirubin	8 - 25

- Examples:
    - 55 year old man, ↓albumin, normal protein ⇒ ↑Ig (common in cirrhosis)
    - 14 year old, ↑cholesterol, ↓protein, ↓albumin ⇒ nephrotic syndrome (relevance of high cholesterol not understood)
    - 58 year old man with diabetes, protein 94, albumin 56 ⇒ dehydration (don't get albumin > 50 without dehydration)
    - 40year old post-op, protein 26, albumin 11 ⇒ dilution. Took blood downstream of iv line
    - 46 year old, enlarged nodes, protein 50, albumin 33 ⇒ ↓ globulin gap ⇒ ? immunocompromised/lymphoma
    - 60year old, pneumonia, protein 70, albumin 22 ⇒ actue phase + maybe ↑Ig
    - 50 year old, recurrent abdominal pain, protein 55, albumin 27 ⇒ pancreatitis → malabsorption
    - 38 year old, SOB, rash, protein 86, albumin 34 ⇒ sarcoidosis or SLE
- Differentials:
    - Hypoproteinaemia:

- Haemodilution: poor iv therapy, drip arm, SIADH, pregnancy
- ↓Albumin: ↓synthesis (liver disease, malabsorption, malnutrition), losses (renal, gut, skin), non-specific (eg illness)
- ↓Ig: primary or secondary immunodeficiencies. Only IgG deficiency is enough to show up as low protein or on electrophoresis

- Hyperproteinaemia:
  - Haemoconcentration: dehydration, haemostatsis
  - ↑Ig:
    - Monclonal: myeloma, lymphoma, macroglobulin, MGUS
    - Polyclonal: liver disease, infection, autoimmune, sarcoidosis
    - Oligoclonal

Aside: Electrophoresis

- Bands: albumin, α1 antitrypsin, haptaglobins (α2 band), transferring, complement, Igs
- Two indications:
  - α1 antitrypsin deficiency
  - Monocolonal antibody band
- Monoclonal Gammaglobulinaemia of Uncertain Significance (MGUS)
  - Benign, but potential for malignant transformation (eg to Myeloma): 5% at 5 years, 25% at 15 years
  - ⇒ need to follow up over time
  - See Aside: Conditions associated with Monoclonal proteins, page 30

Aside: Causes of Paraproteinaemia

- Benign monoclonal gammopathy: level < 30 g/L (low cf. MM), no light chains in urine. Other Ig's normal (cf. suppressed in MM). 15-20% go onto MM but may take 10 – 20 years
- Lymphoma or CLL
- Multiple myeloma
- Waldenstrom's Macroglobulinaemia: monoclonal proliferation of B cell lineage (half way between lymphocytes & plasma cell). Slowly progressive lymphoma. Monoclonal IgM paraprotein. Present with big glands/liver/spleen – no bone lesions

Aside: Conditions associated with Monoclonal proteins

- Associated with uncontrolled proliferation:
  - Multiple myeloma
  - Solitary plasmacytoma
  - Waldenstroms macroglobulinaemia
  - Lymphoma
  - Lymphocytic leukaemia
  - Heavy chain disease
  - Primary amyloidosis
- Associated with controlled proliferation
  - MGUS: difficult to distinguish from malignancy, especially in early stages. Tend towards malignancy if:
    - Serial M band levels are increasing
    - Bone lesions
    - IgG > 30 g/l or IgA > 20 g/l
    - Serum or urine light chains present
    - Normal Igs decreased
    - Marrow plasma cells > 10%
    - Renal failure
    - Hypercalcaemia
    - Anaemia
  - Chronic infections
  - Non-lymphoid malignancy
  - Connective tissue disorders
  - Transient (virus, drug reaction)
  - Peripheral neuropathy
  - Transplants

Hyponatraemia

Key Points

- Normal value of Na: 135 – 145 mmol/L
- Hyponatraemia is not a diagnosis – it is found in diverse conditions. Body Na may be low, normal or high. Relative water retention is a common factor.
- Condition and treatment can be hazardous
- Treatment must be slow and monitored closely. Treatment can range from water restriction or diuresis to sodium restriction or normal saline. Need to know underlying cause
- Don't use hypotonic fluids post-op unless Na is high. eg dextrose saline – glucose absorbed very quickly post surgery → hypotonic

Symptoms

- The big boggie is underlying cerebral oedema. Bigger problem if abrupt onset
- Symptoms don't correlate well with [Na]
- Early: anorexia, headache, nausea, vomitting, muscle cramps, weakness
- Advanced: mutism, dysarthria, impaired response to verbal or painful stimuli, bizarre behaviour, hallucinations, asterixis, incontinence, respiratory insufficiency, spastic quadriparesis in 90%
- Far advanced: (too late to do much) decorticate or decerebrate posturing, bradycardia, hypo or hypertension, dilated pupils, seizures, respiratory arrest, coma, polyuria (central diabetes insipidus)
- Should always be a differential in post-operative coma
- Pre-menopausal women more susceptible

Interpretation

- Clinical findings: pulse, blood pressure, volume assessment, oedema, thirst, skin, input/output
- History: fluid losses, diuretics, other medications
- Laboratory:
  - Creatinine, urea, glucose, HCO3, K, plasma osmolarity, urine Na and Osmolarity
  - Severe hyponatraemia is < 125 mmol/l: nausea, malaise, headache
  - < 115 mmol/l: convulsions

Aetiology

- May be borderline hyponatraemic before (eg long term use of diuretics)
- Normal ADH will ↑ if ↑osmolality or ↓blood volume
- Operative stress → syndrome of inappropriate ADH (in most people) → water retention (especially in women, smaller starting fluid volume)
- Ageing impairs fluid homeostasis → wider swings happen easily
- Inappropriate water retention: eg drugs (most common – eg antiepileptics), ↑ADH, kidney or thyroid problems
- Clinically useful grouping (⇒ volume assessment critical):
  - Hyponatraemia with oedema: heart failure + diuretic, cirrhosis, nephrosis (impairment of water loss via increased ADH +/- Na loss)
  - Hyponatraemia with dehydration:
    - Urine [Na] > 20 mmol/l: Diuretics, Addison's Disease, Salt losing nephritis
    - Urine [Na] < 20 mmol/l: Vomiting, Diarrhoea, Skin loss
  - Hyponatraemia with euvolaemia and reduced plasma osmolality:
    - Urine [Na] > 20 mmol/l: Chronic water overload (eg chronic SIADH, etc)
    - Urine [Na] < 20 mmol/l: Acute water overload (eg acute SIADH, etc)

Diagnostic Criteria

- Low Na and ↓ serum osmolality
- Urine osmolality higher than expected (>200 and usually > serum osmolality)
- Urinary sodium higher than expected (> 30)
- No evidence of hypovolaemia
- Normal pituitary, adrenal, cardiac, and renal function
- Not on diuretics
- Respond to water restriction with serum sodium and osmolality increase

Syndrome of Inappropriate ADH secretion

- = SIADH

- Ectopic Production (relatively rare): malignancies of lung, bronchus, brain, kidney, duodenum, pancreas
- Central production:
  - Cerebral infections, trauma, tumours, haemorrhage
  - Lung disease, eg pneumonia
  - Drugs, eg morphine, carbamazepine (anti-epileptic)
  - Can be seen in AIDS patients (?combination of above factors)

Common Scenarios

- Prolonged vomitting *and* rehydration with Gastrolyte – only contains 60 mmol/L Na
- If dehydrated (eg vomiting) and on diurectic, ADH still conserves water, but ↓Na retention so ↓[Na]. We preserve volume at the expense of osmolarity
- Also, ectopic ADH production from lung cancer
- Serious post-operative problem. Especially women after elective surgery (eg gynogology wards). Hypothesis: surgery → ↑ADH (eg due to pain), dextrose also given in belief that it slows catabolism and promotes healing – but together they lead to ↓[Na]
- Sample cases:

Case	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Na	130	126	125	125	125	128	128	128
K	3.7	3.5	3.5	3.5	3.5	6.5	2.1	5.7
Creat	130		56	56	56	700	200	220
HCO3						15	40	3.0
Uos/Sos			0.4	1.6				
Sos					285			
Alb		16						
	Heart Failure + diuretic: too dried out	Nephrosis	Water overload	SIADH	Pseudo hyponatraemia or something osmotically active (eg ↑glucose)	Renal failure	Severe vomiting	Ketoacidosis

Treatment

- Principles:
  - Raise the sodium at a safe rate
  - Treat the cause
- Basic regimes:
  - If volume depleted (Renal/GI losses, diuretics, adrenal insufficiency): isotonic saline. Extra Na will have a small effect but ↑volume → ↓ADH → excess water excreted
  - Normovolaemic or oedematous (SIADH, renal failure, polydypsia, oedema): Water restriction
  - If severe symptoms or if sodium < 110 then ?hypertonic saline. ↑Na by no more than 12 mmol per 24 hours: keep rate smooth. Key judgement is speed of infusion. No front loading. Animal studies show correction by > 14/mmol/24 hours → lesions in 71% of dogs. If no symptoms – maybe go slower
- Monitor 2 hourly. Manage in high dependency unit. Detect and treat hypoxia
- Adverse neurological consequences of rapid correction: myelin breakdown in the pons, patchy symmetrical lesions elsewhere in the brain. But risk of not treating acute cerebral oedema far exceeds the small risk of osmotic demyelination
- Maybe frusemide to ↑free water excretion

Dehydration or Volume Depletion

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

    - Treatment is replacement of NaCl
- Dehydration and volume depletion can co-exist

Hypernatraemia

- Usually **not** due to ↑ total body sodium – total sodium is low, normal or high
- Always means the patient is hyperosmolar
- Thirst and ↑ADM protect against hyperosmolarity ⇒ don't see hypernatraemia where the thirst mechanism is normal and there is access to water
- Cellular dehydration → neurologic symptoms: lethargy, weakness, irritability, seizures, etc
- Classification:
    - Water and sodium deficiency with water loss > sodium (ie lost hypotonic fluid), eg vomit, diarrhoea, sweat, osmotic diuresis, burns
    - With normal total body sodium (pure water depletion): unable to drink (old, babies, sick, etc), central or nephrogenic diabetes insipidus
    - With increased total body sodium: excess iv hypertonic saline, ingestion of sea water, mineralocorticoid excess (low sodium output)
- Treatment:
    - Chronic: may be asymptomatic even at 170 – 180 mmol/l due to adaptation by brain ⇒ gradual correction
    - Assess volume status> If water deficit then iv dextrose, or sodium if history suggest loss of sodium containing fluid
    - Oral replacement is best if feasible

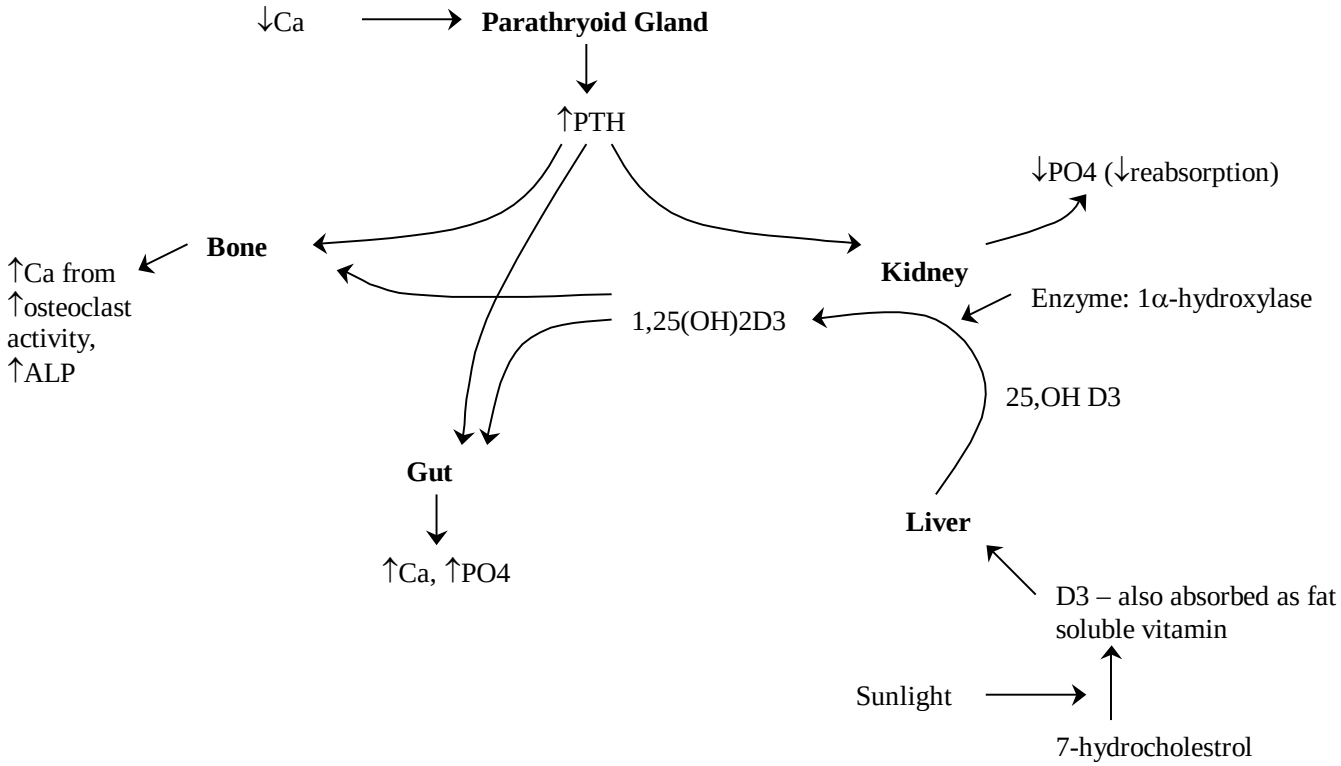
Other Metabolic Disturbances

- Arrest due to electrolyte abnormalities uncommon except for hyperkalaemia.

Abnormality	Common Cause	ECG	Emergency Treatment
↑ Potassium	Renal failure	Peaked T	Calcium chloride
	Addison's disease	Prolonged PR	Bicarbonate
		Small P	Insulin/Glucose
		Wide QRS	Beta agonists
		VT, VF, asystole	Dialysis
↓ Potassium	Diuretics	Wide, flat or inverted T	Potassium
	Hyperaldosteronism	Depressed ST segment	Magnesium
	Vomiting	Small QRS	
	Gastric aspiration	Prolonged PR	
		Prominent U wave	
		Large P wave	
↑ Magnesium	Renal Failure	Bradycardia	Calcium Chloride
		AV block	
		Asystole	
↓ Magnesium	Alcoholism	Long QT	Magnesium
	Starvation	Short QT	
	Urinary Loss	Broad T	
	Diuretics	VF, VT, asystole	
	GI loss		
	Malabsorption		
↓ Calcium	Hypoparathyroidism	Long QT	Calcium Chloride
	Acute pancreatitis	Elevated ST	
	Renal failure	Peaked or inverted T	
		AV block	
		Tachyarrhythmias	

Calcium

- Calcium metabolism:



- Hyperparathyroidism:
  - Primary: ↑PTH → ↑Ca2+.
    - Usually detected as incidental finding. If symptoms: pain/fracture, renal stones, constipation, abdominal pain, depression. Also maybe dehydration, ↑BP, thirst, nocturia, stuff joints, myopathy
    - Associations: endocrine neoplasia (eg pancreas, pituitary, phaeochromocytoma and thyroid)
    - Causes: Single (90%) or multiple adenoma, carcinoma, hyperplasia
    - Tests: ↑Ca, ↓PO4 (unless renal failure), ↑ALP, PTH raised or normal. CXR for 'pepper pot skull' and pelvis
    - Treatment: surgery
  - PTH related protein (PTHrH): produced by some tumours – causes some of the hypercalcaemia seen in malignancy
  - Secondary Hyperparathyroidism: ↓Ca → ↑PTH. Causes: chronic renal failure, ↓Vitamin D
  - Tertiary Hyperparathyroidism: continued secretion of PTH after prolonged secondary hyperPTH
- Hypoparathryoidism:
  - Primary HypoPTH. Eg after neck surgery. → ↓Ca and ↑PO4, normal ALP. Associations with pernicious anaemia, Addison's, hypothyroidism, hypogonadism
  - PseudohypoPTH: Failure of target cell response to PTH. Round face, short metacarpals and metatarsals

Hyperkalaemia

- Normal value of K: 3.5 – 5 mmol/L
- Signs: myocardial depression, peaked T wave flat P, wide QRS, VF, diarrhoea, abdominal pain, muscle excitability
- Treatment:
  - If severe (> 6.5 mmol/L): Glucose 50 g + soluble insulin 10 U over 15 mins or calcium gluconate or beta 2 agonist or dialysis
  - If moderate (5.5 – 6.5 mmol/L): Calcium resonium 15 g po

Hypokalaemia

- See also **Error! Reference source not found.**, page **Error! Bookmark not defined.**

- Signs: arrhythmias, PR prolonged, inverted T waves, U waves, VF, GI ileus, muscle weakness, hypotonicity, digoxin toxicity, alkalosis
- Treatment: Replacement KCl up to 40 mmol/hour

Hypocalcaemia

- Normal value of Ca: 2.12 – 2.65 mmol/L
- 40% of calcium is bound to albumin. Adjust Ca for changes in albumin (0.025 per 1g of Albumin). Take sample uncuffed
- Symptoms: Tetany, depression, carpo-pedal spasm (wrist flexion and fingers drawn together), neuromuscular excitability (eg tapping over parotid causes facial muscles to twitch – Chvostek's sign)
- Causes of hypocalcaemia:
  - ↓Mg → ↓PTH → hypocalcaemia
  - Thyroid or parathyroid surgery
  - If ↑PO4 then chronic renal failure (failure of Vitamin D conversion), hypoPTH or PseudohypoPTH
  - If PO4 normal or ↓ then osteomalacia (↑ALP), overhydration or pancreatitis

*Hypercalcaemia**

- Signs: Bones, stones, groans and psychic moans, abdominal pain, vomiting, constipation, polyuria, depression, anorexia, weakness, ↑BP, renal stones, cardiac arrest
- Most commonly:
  - Primary hyperPTH in the community
  - Malignancy in hospital
- NB: acidosis → H displaces Ca on albumin → ↑free Ca
- If albumin raised:
  - Urea raised → dehydration
  - Urea normal → cuffed specimen
- Albumin normal or low:
  - Phosphate low or normal (and urea normal): primary or tertiary hyperparathyroidism
  - Phosphate ↑ or normal:
    - ↑ALP: Bone metastases (most common primaries are breast, kidney, lung, thyroid, prostate, ovary, colon), sarcoidosis (↑Vitamin D conversion in the lungs), thyrotoxicosis
    - Normal ALP: myeloma, vitamin D excess, Ca supplements
- Treatment: if Ca > 3.5 mmol/l or sever symptoms:
  - Rehydrate and correct any hypokalaemia and hypomagnesaemia
  - Diuretics once rehydrated (frusemide, avoid thiazides)
  - Bisphosphonates (pamidronate): lower Ca over 2-3 days by inhibiting osteoclasts

Chloride

- Anion Gap = Na + K – (Cl + HCO3)
  - Usually 8 – 16 milliequivalent/l (measure of charge)
  - High Anion Gap: Ketoacidosis, lacticacidosis, renal failure, poisoning (salicylate, methanol, ethanol, ethylene glycol)
  - Low anion Gap: GI or GI loss of HCO3, therapy for diabetic ketoacidosis, ingestion of HCl or NH4Cl
  - Practical use limited – cause of metabolic acidosis obvious from history and observation
  - Most labs have deleted it from electrolyte profile
- Cl normally tracks Na except in metabolic acidosis. Eg severe vomiting: ↓HCl (→ hypochloraemic metabolic alkalosis) and volume depletion (→ kidney retains Na → generation of HCO3 and K depletion). Correction of alkalosis requires correction of volume, chloride and K

Porphyria

- Disorder of haem synthesis → toxic metabolites
- Many types, all due to genetic deficiency. Homozygous not viable. Heterozygotes can produce enough haem, but when the system is challenged → ↑ toxic metabolites
- Symptoms:
  - Uncommon, but differential in intermittent abdominal pain
  - Can be intermittent or constant
  - Can acutely cause psychotic symptoms
  - Sunsensitivity (acculumlation of metabolites in skin)

- Neuro-visceral symptoms (pain but no organ pathology)
- Rare types can cause sideroblastic anaemia

- Investigations:
  - Urine test for metabolites (porphyins)
  - Then specific test for which porphyria
- ALA synthase controls the rate limiting step at the beginning of the pathway:
  - Induced by: BZDs, alcohol, oestrogen and progesterone ($\rightarrow$ onset at puberty or on starting the OCP), sulfonamides, tetracycline, theophyllin
  - Inhibited by haem, glucose

Acid-Base balance

- Metabolism produces two acids:
  - Volatile: carbonic
  - Non-volatile: eg lactic
- Buffer systems:
  - H+ + HCO3- $\leftrightarrow$ H2CO3 (H2O + CO2)
  - pH = 6.1 (pKa) + log [HCO3-/(0.03 * PCO2)] (Henderson Hasselbach equation), or
  - pH = 6.1 + log (kidney production of HCO3)/(Respiratory regulation of CO2)
  - Normal range for pH is 7.35 – 7.45 (=45 – 35 nmol/L of H+ ion)
  - Range of pH compatible with life is about 6.8 – 7.8 = H+ concentration of 160 – 16 nmol/l

Acid/base disturbances

- Respiratory Alkalosis (hyperventilation):
  - $\downarrow$PaCO2, $\uparrow$pH, initial alterations in [HCO3] are minimal, if it persists then kidneys compensate
  - Compensation:
    - Acute: HCO3 $\downarrow$ by 2 for each 10 $\downarrow$ PCO2
    - Chronic: HCO3 $\downarrow$ by a further 3 (ie total of 5) for each 10 $\downarrow$ PCO2 [renal loss of HCO3]
- Respiratory Acidosis (hypoventilation):
  - PCO2 excretion lags production – eg severe asthma (initially asthmatics hyperventilate)
  - As PCO2$\uparrow$ then CO2 + H20 $\rightarrow$ H+ + HCO3-
  - $\uparrow$PaCO2 $\rightarrow$ $\downarrow$pH, initial alterations in [HCO3] are minimal, if it persists then kidneys compensate:
    - Acute: HCO3$\uparrow$ by 1 for each 10 $\uparrow$PCO2
    - Chronic: HCO3$\uparrow$ by a further 2.5 (ie 3.5 of total) for each 10 $\uparrow$PCO2
  - For example:

	PCO2	HCO3	pH
Uncompensated	80	24	7.10
Acute	80	28	7.17
Chronic	80	38	7.30

- Metabolic acidosis:
  - Accumulation of acid (anion gap > 18 mmol/L): $\uparrow$H+ (ketoacidosis, lactic acidosis), renal failure (failure to excrete H+)
  - $\downarrow$HCO3 (anion gap < 18 mmol): GI tract loss (eg diarrhoea), renal loss (eg $\downarrow$carbonic anhydrase)
  - Compensation: PCO2$\downarrow$ by 1.2 for each $\downarrow$1 in HCO3 (baseline = 24)
  - Final compensation is renal excretion of acid with regeneration of HCO3 ($\downarrow$PCO2 only temporary)
- Metabolic alkalosis:
  - Loss of H+/increase in HCO3:
    - GI or renal loss (hyperaldosteronism)
    - K depletion (Conns, Cushing's, drugs, diuretics)
    - Volume depletion
    - Gain in alkali: eg NaHCO3 administration
  - Compensation: PCO2 $\uparrow$ by 0.6 for each 1 $\downarrow$ in HCO3. Limited by hypoxia
  - Final compensation is by renal excretion of HCO3 – requires correction of Cl, K and volume
- Compensation:
  - $\downarrow$HCO3 $\rightarrow$ $\downarrow$PCO2

- ↓PCO2 → ↓HCO3

Mixed Acid/Base disorders

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

Interpreting Blood Gas Results

- Arterial blood taken in 2 ml syringe containing heparin (to stop clotting) and transported on ice
- Look at PCO2. If < 36 then hyperventilation. If > 44 then hypoventilation.
- Look at pH: 7.36 to 7.44 is normal
- Look at HCO3. If < 22 then metabolic acidosis. If > 26 then metabolic alkalosis. But HCO3 depends on PCO2. So (to work out if its just compensation, or there is a metabolic problem as well as a respiratory one):
  - For acute changes (hours): a fall in PaCO2 → a normal HCO3 2 less for every 10 mmHg ↓ in PaCO2. A rise in PaCO2 → normal HCO3 1 greater for every 10 mm Hg ↑ in PaCO2
  - For chronic changes (days): a rise in PaCO2 results in a normal HCO3 4 greater for every 10 change in PaCO2

Base Excess

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

Heart

- Old WHO definition: two out of three of: chest discomfort for > 30 minutes, enzyme rise and typical pattern of ECG involving the development of Q waves (ie normal ECG does not rule out infarction)
- New definition: Blood levels of sensitive and specific markers are raised in the clinical setting of acute ischaemia (ie ↑importance of biochemical tests).
- Troponins:
  - Increases highly specific for MI injury – but not synonymous with MI or ischaemia, but probably indicates irreversible injury
  - Increases above the 99th percentile are significant (lower than previously)
  - Prognosis related to degree of elevation
  - Rises no faster than CK (ie starts to rise within 3- 12 hours) and more expensive but substantial rise after MI (400 fold)
  - Causes besides MI:
    - Subendocardial injury from wall stress in left ventricular hypertrophy (eg heart failure)
    - Right ventricular injury in severe PE
    - Direct trauma (eg contusion)
    - Toxic injury by drugs or in septic shock
    - Myocarditis
    - Cardioversion
  - Troponin T
    - = Cardiac troponin T, cTnT, TnT): only available from Boehringer Mannheim
    - Normal < 0.1 ng/ml
    - Increases in renal failure due to ↓clearance (⇒ false positive)
  - Troponin I:
    - Everyone else's test. Normal value depends on which assay is used
    - I remains elevated for 5 – 9 days and T for 2 weeks. Better marker for recent MI than LDH. Harder to interpret in re-infarct – don't know whether it's the 1st or 2nd infarct
  - Test on admission to either see if already raised (poor prognosis) or to establish baseline

Blood

Myelodysplastic syndromes

- Description:
  - Heterogenous group of disorders
  - Clonal abnormality of haemopoeitic stem cells
  - Abnormal, ineffective haematopoiesis
  - Involves 1 or more lineages
  - Irreversible quantitative and qualitative defects (ie normal count but bad function)
  - Tendency to evolve to acute leukaemia
- Clinical
  - Usually elderly
  - Features of bone marrow failure: tired (anaemia), bleeding, infection, mild splenomegaly in 10 – 20%
  - Incidental finding on blood film in 20%
  - 4 – 12 per 100,000 per year (definitional problems)
- Variants:
  - Refractory anaemia +/- further features (eg excess blasts)
  - Chronic myelomonocytic leukaemia
- Differential diagnosis:
  - Megaloblastic anaemia
  - Acute leukaemia
  - Heavy metal toxicity (lead, arsenic)
  - Chronic infection
  - Immune deficiency (esp HIV)
  - Anticancer chemo/radio therapy
  - Myeloproliferative disorders
  - Bone marrow hypoplasia
- Progression:
  - 70 – 80% die of marrow failure
  - 20 – 30% die of progression to leukaemia
  - Median survival varies with subtype from 6 – 50 months
- Treatment:
  - Response rates to treatment poor
  - Supportive care
  - Maybe cytotoxic chemotherapy or stem cell transplants in the few young cases
  - Growth factors eg erythropoeitin
- Secondary myelodysplasia:
  - ↑incidence
  - Complication of former treatment: alkylating agents (including cyclophosphamide, widely used as an immunosuppressive, eg in Rheumatoid arthritis) and topoisomerase II agents
  - Risk related to cumulative dose and duration of exposure
  - Peak 5 years post treatment
  - Poor prognosis

Blood Transfusion Complications

- Risks:
  - Most common reaction to transfusion: febrile ½ an hour later:
    - Due to leukocytes contaminating red cells. If necessary, insert leucocyte filter on line (@$50) → leucocyte poor red cells
    - Febrile reaction more common if multiple blood transfusions or multiple children (more antigenically primed)
  - ABO incompatibility (eg due to incorrect labelling):
    - Hypotensive, rash, tachycardia
    - Symptoms of major intravascular haemolysis: nausea, vomiting, low back pain (renal reaction to free haemoglobin), feeling very unwell
  - If allergic to plasma proteins → washed red cells

- For immunocompromised: use irradiated red cells to stop leucocytes grafting into host & then attacking host
- Infection risks (depend on prevalence in population):
  - Bacteria:
    - Yersinia Enterocolitica: is cryophilic (likes cold) and blood is a great culture medium. Comes from transient bacteriaemia in infected donor.
    - Other bacteria: Brucella abortus, salmonella, M. Leprae
  - Viruses: HBV, HCV, HIV, HTLV-1, CMV, EBV
  - Parasites: Malaria, toxoplama gondii, Trypanasoma cruzi
  - Specific risks:
    - HIV infection via transfusion: 1 in 1 – 2 million
    - CJD: no documented case worldwide (although has been done in animals)
    - HBV: 1 in 200,000
    - HBC: 1 in 80,000
- Complications of massive blood transfusion:
  - Overtransfusion → Fluid overload and pulmonary oedema
  - Coagulation defects: dilutional thrombocytopaenia, ↓factors V, VII & X, DIC
  - Hypothermia (blood products are stored at 4 C)
  - Hyperkalaemia: K moves out of red cells in storage
  - Acidaemia: stored blood becomes acidotic with age
  - Hypocalcaemia & citrate toxicity → cardiac depression and alkalosis
  - Hypomagnesaemia
  - Transfusion haemosiderosis (ie iron overload) if on chronic transfusions (eg thalassaemia)
- Management of major reaction (either analphylaxis/haemolysis or sepsis)
  - If worried during the transfusion, stop it
  - Call blood bank for advice
  - Send back blood + samples from the patient
  - Check for errors
- Strategies to stop transmission of infection:
  - Donor screening – very effective
  - Blood screening:
    - But tests not 100% accurate & window periods
    - Move from serologic tests to PCR for viral antigens

Fever in a Neutropenic Patient

- Eg in patients undergoing chemotherapy
- Indicators of serious infection:
  - Signs and symptoms of infection are reduced – can't mount an inflammatory response
  - Temperature:
    - > 38.5 C
    - > 38 for 4 hours
    - Patient fells unwell but no temperature
  - Neutropenia:
    - Neutrophils < 0.5 * 10E9/L (less than 0.2 ⇒ serious concern)
    - Neutrophils falling
    - Prolonged neutropenia (> 7 days)
- Types of infection (drives focused history)
  - Respiratory: SOB, cough
  - Skin infection
  - Mouth and teeth
  - Perianal (pain on moving bowels and wiping0
  - Pain around central line
  - Less often: bowel & UTI
- Focused exam:
  - Signs of septic shock: Pulse, BP and peripheral circulation
  - Chest: percussion and ausciltation
  - Mouth: a good look around – abscesses will be sensitive to pain
  - Skin infections, especially lines

    - Quick abdominal
    - Exam perianal area – test for sensitivity to touch. Don't do PR (risk of minor trauma → bacteraemia)
- Investigations:
    - FBC
    - Blood culture (debate about whether to take it from the central line or not)
    - CXR
    - Swabs from anything that looks infected, including central line
    - Maybe CRP: ↑ in bacteraemia
- Normally don't find anything. Over half infections are low grade line infections
- If in doubt, treat empirically *now*. If infected will deteriorate quickly
    - Gentamycin + Ticarcillin (synthetic penicillin)
    - Monotherapy (eg imipenem)
    - +/- vancomycin (for staph line sepsis)
- Causes of infection:

	Frequency	Risk
First Fever		
Staph	+++	+
α haemolytic strep	+	++
G –ive bacilli	+	+++
Subsequent infections		
Staph	+++	+
Fungi	++	+++
Resistant G-ive	+	+++

    - Subsequent fevers: longer inhospital (↑hospital acquired infection), longer on antibiotics, etc
- If fever persists:
    - Repeat the above exam and investigations – but unlikely to add anything new
    - Choices:
        - Change antibiotics
        - Consider antifungal: Amphotericin. Watch for nephrotoxicity and the patient feels awful
- Obscure fevers:
    - Central venous line infection
    - Occult sinusitis (check with CT)
    - Hepatosplenic candidiasis (check with CT → abscess → biopsy)
    - Pulmonary/disseminated aspergillus (doesn't respond to amphotericin)
    - Viral
    - Drugs
- Prevention:
    - Avoid hospitalistaion
    - Strict handwashing
    - Avoid invasive procedures (beware interventionist surgeons!)
    - Care of IV devices
    - Consider prophylaxic antimicrobials
- Prophlaxis
    - Bacteria: selective gut decontamination (origin of many infections is bowed flora): Ciprofloxacin (fluorinated quinolone). Arguments for and against
    - Anti-fungal: Fluconazole, Itraconazole (OK for prophylaxis, not so good as amphotericin for established infection)
    - Anti-viral: acyclovir (for HSV), gancyclovir (for CMV)
    - Anti-pneumocystis: co-trimoxazole (but beware marrow suppression) or aerolised pentamidine
- Other possible treatments:
    - Granulocyte-CSF: try to ↑ marrow production of neutrophils
    - Maybe γ-globulin infusions
    - Transfuse granulocytes: emerging area

Hypercoagulable States

- Primary Causes:

    - Factor V Leiden:
        - Most common primary cause
        - Point mutation on factor V prevents breakdown → ↑levels of Va → hypercoagulable
        - Heterozygous have lifetime risk of 30 – 40% of thrombotic event, Homozygous then 50 – 60%
        - In thrombotic patients, 20 – 40% have factor V Leiden, mainly in Caucasians
    - Prothrombin gene mutation
    - Antithrombin 3 deficiency:
        - → reduced breakdown of thrombin
        - Heparin co-factor, $\alpha 2$ globulin
        - Autosomal dominant, 1:2-5000 in Caucasian
        - Found in 2 – 3 % of DVTs
        - Can also cause mesenteric or brachial thrombosis. These are rare to →↑index of suspicion
    - Protein C or S deficiency
    - Homocysteinaemia
- Secondary Causes:
    - Malignancy
    - Pregnancy and for 6 weeks afterwards: hypercoagulable, stasis, venous compression. If concurrent primary disorder then prophylaxis with subcut heparin (warfarin contra-indicated)
    - Stasis: immobilisation, surgery, local pressure
    - Age
    - Myeloproliferative disorders
    - Antiphospholipid Syndrome (acquired, aggressive)
    - Infection
    - Trauma

Possible Investigation for DVTs:

- Imaging:
    - CXR: most are normal
    - Dopler US for DVT
    - Ventilation-Perfusion Scan
    - Pulmonary arteriogram: gold standard but not often done
    - Spiral CT: pretty good and getting better
- ECG:
    - Small-medium PE: usually normal except for tachycardia. May be signs of AF or right ventricular strain
    - Massive PE: S1Q3T3 pattern: S wave in lead I, Q wave in lead III, inverted T wave in lead III. Tall peaked T waves in lead II.
- Bloods:
    - ABGs: Aa gradient
    - FBC - check Hb, WBCs, platelets (eg ↑ → hypercoagulable)
    - Clotting times: likely to be normal – tests of bleeding disorders, not clotting disorders
- D-dimmer test for fibrin degradation products → digested clot (cheap and easy):
    - +ive for cancer, trauma, post surgery, sepsis → lots of false positives
    - Don't use as first line test – only in the context of a complete algorithm
- Decision analysis:
    - If > 6% risk of a PE then test
    - If > 48% risk of a PE then treat
    - If risk > 6% but < 48% then further testing
    - Test sequence:
        - Chest X-ray and D-dimer: if d-dimer negative then no DVT/PE. Positive test doesn't change pre-test odds. If Chest X-ray normal then V/Q scan. If abnormal go straight to CT angiogram
        - V/Q Scan: if positive then treat. If negative, doesn't change pre-test odds
        - CT angiogram

Renal and Genitourinary

Notes to include:

- Normal Creatinine < 110
- Nephrotic syndrome = more than 3 g/day protein in urine, oedema, but still urinating
- Nephritic syndrome = maybe oedema, oligouria, ↑blood pressure, haematuria
- Normal urination: 1 ml/kg/hr (down to 0.5 ml/kg/hr OK)
- CVVHD = continuous veno-venous haemodialysis (used when BP too low for normal dialysis)
- Rhabdomyolysis:
  - Injury to membrane of skeletal muscle
  - → ↑↑ Ck
  - → renal failure due to combined effect of nephrotoxic effect of myoglobin, hypovolaemia and aciduria
- Copy in from OH p 371 for urine analysis

Kidney

Congenital Abnormalities

- Aplasia: absence of a kidney
- Hypoplasia: usually unilateral, secondary to obstruction of the ureter in utero
- Horseshoe kidney:
  - 1 in 500
  - Work normally
  - Disturbed renal flow: ureter has to flow over the kidney → recurrent UTI

Cystic Renal Disease

Adult Polycystic Kidney

- Autosomal dominant
- 1 in 500
- Vary in severity and onset
- Kidney's can get very large → impair respiration
- Cystic lesions in other organs: liver, pancreas, lung
- Diagnose with US
- Present with hypertension → IHD, CVA
- Whole nephron blows up → squashes other nephrons → progressive renal failure

Infantile Polycystic Kidney

- Autosomal recessive
- In mild forms that escape renal failure, is associated with congenital hepatic fibrosis

Cystic Renal Dysplasia

- Due to obstruction of urinary outflow tract prior to the union of metanephric blastema and the ascending ureteral bud
- → disordered kidney development. Contains bone, smooth muscle, etc but is not a tumour

Simple Cortical Cyst

- Dilation of a single nephron, usually to 5 mm – 1 cm, usually have 3 or 4
- Usually asymptomatic
- If large and rupture → urinary peritonitis

Other

- Infection: Tb and hydatids can present as cystic dilation on US
- Medullary Sponge Kidney: Rare. Dilated collecting ducts

Hydronephrosis

- Dilation of renal pelvis due to:
  - Obstruction of the pelvo-ureteric junction (often in kids)
  - Big prostates

    - Kidney stones
- Leads to renal failure due to:
    - chronic interstitial nephritis (as do other things) – leucocyte invasion.
    - atrophy of the collecting ducts and distal tubule (which are relatively hypoxic compared to the glomerulus). However, if the tubule goes, the glomeruli scleroses ⇒ loose whole nephron

Tubulointerstitial Diseases

- Involve tubules and renal interstitium (not glomerulus)

Acute Tubular Necrosis (ATN)

- Ischaemic:
    - Patchy areas of tubular necrosis (proximal convoluted tubules and straight segements of the loop of Henle) and thinning of epithelial brush border
    - Loss of basement membrane → scarring, loos of architecture → permanent loss
    - Regeneration if not too severe
- Toxin-mediated (e.g. aminoglycosides, radio-contrast agents, heavy metals, arsnic, solvents):
    - Necrosis is continuous not patchy
    - No loss of basement membrane → empithelium can regrow down the nephron → resolution
- Intra-tubular obstruction → ↓GFR
- Reduction in sodium reabsorption & loss of medullary concentration gradient → inability to concentrate urine → isoosmolar urine with Na > 20 mmol/L
- Lasts 1-2 weeks, followed by gradual improvement in serum urea and creatinine, and diuresis (due to accumulated plasma electrolytes)
- Prevent preoperatively by maintaining hydration → maintained renal blood flow

Acute Papillary Necrosis

- Diabetes
- Also in urinary outflow obstruction → ↑pressuve in renal pelvis → ↓perfusion

Acute Interstitial Nephritis (AIN)

- =Intense, often patchy, interstitial inflammatory infiltrate of lymphocytes & monocytes
- Glomeruli normal but may be tubular necrosis
- ↓GFR due to tubular obstruction and altered intra-renal haemodynamics
- Associated with drugs (e.g. penicillins & amoxycillin) – sometimes with infections & systemic diseases. Also NSAIDs – but after months of exposure & severe proteinuria
- Symptoms: fever, maculo-papular rash, eosinophilia, arthralgia, flank pain
- Urine has pyuria, mild haematuria and mild proteinuria
- Treatment: withdraw drug +/- steroids

Acute Pyleonephritis

- Caused by supprative infection: E coli, Proteus, Klebsiella, Enterobacter
- From ascending UTI or haemoatogenous spread of infection (eg scepticaemia)

Chronic Pyleonephritis

- Not a disease, but a description of what happens to the kidney – it becomes dilated and replaced by fat
- Causes:
    - Recurrent infection
    - Obstructive uropathy
    - Vesicoureteric reflux (especially in kids with malformed vesicoureteric valves. Present in puberty with renal failure – subclinical before that)
    - Kidney stones (→ ↑infection)

Renal Tumours

Renal adenoma/Papillary adenoma

- Most people have one or two
- Associated with renal scarring
- < 5 mm diameter
- Papillary architecture
- No clear cells (if there were then malignant)

Other benign renal tumours

- Renal Oncocytoma: Have oncocytes: cells with abundant mitochondria (pink and granular) – tired epithelial cells. Grossly form a stalate scar
- Renal fibroma
- Aniomyolipoma: composed of fat, smooth muscle and thick blood vessels. Associated with Tuberous Sclerosis

Renal Cell Carcinoma

- = Conventional Clear Cell Renal Cell Carcinoma
- 75% of renal epithelial tumours in adults
- Predominantly clear cell tumours
- Annual incidence 3/100,000
- Risk factors: smoking, obesity, hypertension, unopposed oestrogen
- 3% familial, Von Hippel-Lindau disease
- Clinical features: haematuria, back pain, abdominal mass. Often metastasised before diagnosis
- Histology:
  - Clear Cell Renal Cell Carcinoma
    - Metastasise up the renal vein to the heart → emboli → cannon ball metastasis of the heart
    - Sheets of clear cells
    - 3 p25 deletion diagnostic feature
  - Papillary RCC: Better prognosis
  - Chromophobe RCC: Better pronosis, large cells, abundant cytoplasm, small dark nucleus
  - Sarcomatoid RCC: Highly malignant, highly anaplastic

Transitional Papillary Cell Carcinoma

- Present with painless haematuria
- Can cause hydronephrosis, flank pain, and renal colic from clots
- Peak in 6^{th} – 7^{th} decade, M > F
- Derived from epithelium of renal pelvis
- Associated with smoking, analgesic abuse, azo dyes
- Often associated with Transitional Cell carcinoma of the bladder and ureter

Nephroblastoma (Wilms' Tumour)

- Very aggressive, presents with abdominal mass with or without haematuria. Pain and intestinal obstruction can occur
- 50% present < 3 years, 90% < 10 years, rare in adults
- Derived from metanephric blastema
  - Dark with scant cytoplasm
  - Triphasic histology: epithelial cells, stromal cells, blastema
- Now around 80% cure
- Associated with syndromes:
  - WAGR: Wilms, aniridia, genital anomalies and mental retardation
  - Denys Drash Syndrome: Gonadal dysgenesis, nephropathy
  - Beckwith-Wiedemann syndrome

Other Renal Tumours

- Angiomyolipoma: Benign – but grow and haemorrhage. Composed of fat, smooth muscle and dilated blood vessels
- Juxtaglomerular Cell Tumour: Very rare, benign but causes malignant hypertension

Glomerulonephritis

- Diagnosis:
  - Urine biochemistry: urine sodium > 20 mmol/L (if pre-renal failure then < 20, ie frantically trying to reabsord Na)
  - Urine analysis: Blood morphology and casts, protein (usually mild)
  - Ultrasound: exclude obstruction, looking for normal or slightly enlarged kidneys, echogenic (dark on US ⇒ ↑fluid)
  - CXR: look for Goodpastures Syndrome, Wagner's Granulomatosis
  - Bloods: ANA (connective tissue disorders), ANCA (Anti-neutrophil cytoplasmic antigen ⇒ Wagner's Granulomatosis), Anti-dsDNA (⇒ SLE), anti-GBM

- Histology:
  - Glomerula epithelial cells usually have interdigitating foot processes. If they swell, ↓ gaps between them → proteinurea
  - Mesangial cells (supporting framework) are the first to react to injury and the last to return to normal
  - Crescents: protein material in Bowmen's capsule. Leads to scarring and fibrosis of glomeruli

Classification

- Nephritic Syndrome = proliferative Nephritis/GN:
  - Presentation:
    - Presentation: anuria, haematuria, headache
    - ASO titres always raised
    - Histology: Large glomeruli (diffuse changes of predominantly mesangial cells), polymorphs and black deposits on epithelial side of BM, can occasionally lead to crescents (ie lots of cell proliferation compared with Nephrotic Syndrome)
  - Usually delayed reaction to strep infection
  - Mesangial IgA disease. Examine for IgA deposits with immunoflouresence → recurrent haematuria
  - Rapidly Progressive Glomerulo Nephritis ~ crescentic glomerulonephritis (Can be due to IgA or Post-strep, plus other causes below)
- Nephrotic Syndrome = non-proliferative (change in charge on BM → leaks protein)
  - Membranous: middle aged adult, Histology: BM accentuated
  - Minimal change: oedematous kid. Only see changes on electron microscope
  - Focal and segmental glomerulosclerosis,
- Nephrotic/Nephritic: elements of both
- Systemic diseases that may present as GN:
  - Lupus nephritis: deposits of immune complexes everywhere within the glomerulus
  - Arteritis: Microscopic polyarteritis
  - Amyloid: Nephrotic Syndrome or renal failure. Histology with Congo Red Stain
  - Diabetes
  - Hypertension
- Treatment: Loop diuretics

Rapidly Progressive Glomerulo-Nephritis

- ~ crescentic glomerulonephritis = Cellular proliferation in glomeruli, and crescent formation
- A description not a diagnosis
- Presentation:
  - Nephritic presentation
  - →↓GFR but tubular function OK so Na/H20 reabsorbed → oedema
- Due to:
  - Immune complex mediated GN:
    - Post infection: e.g. post-streptococcal (rarely crescents, dialysis rarely needed) also staph
    - Lupus nephritis
    - Others, including vasculitis
  - Anti-glomerular-basement membrane diseases (Goodpasture's syndrome):
    - GN +/- lung involvement (shared antigen)
    - Linear immunoflourescence
    - Can measure serum anti-GBM antibody
    - Treatment: immunosuppression +/- plasma phoresis
  - Pauci-immune:
    - Wegner's Granulmoatosis: Causes GN, URTI, LRTI, non-caseating granuloma, cANCA is highly specific, -ive immunflourescence, typically older patients
    - Microscopic polyarteritis (also joints)
- Differential of crescents:
  - Extrinsic: SLE, Wanger's, Goodpastures
  - Intrinsic → immunoflourescence
    - Linear: IgG → Goodpastures
    - Diffuse: Mesangel
- Prognosis dependent on % of crescents
- Treatment: immunosuppressive +/- dialysis

Hypertension

- Histologic changes: intimal fibrosis, hyaline deposition, downstream infarction → progressive scarring, granular surface
- Need to aggressively treat hypertension in people with other risk factors for kidney disease (eg diabetes)

Ureter

- Congenital abnormalities:
  - Double/bifid ureters
  - Megaureter
  - Hydroureter
  - Usually present with UTIs
  - May have abnormalities elsewhere
- Ureteritis:
  - Associated with generalised UTI
  - May be caused by stones lodging the ureter
  - Rarely caused by Tb
- Transitional Cell Carcinoma:
  - Transitional between squamous and glandular epithelium. Tumours typically papillary/frond like
  - Similar histology to renal and bladder TCC
  - Infiltrates early to retroperitoneum with poor prognosis

Acute Renal Failure

- =Abrupt reduction in glomerular filtration rate → ↑plasma urea & creatinine and (usually) ↓urine volume (<400mL/day)
- Assess severity using Cockcroft-Gault equation. Normal clearance ~ 100 ml/min
- Differentiating causes via urine:
  - Dysmorphic RBC ⇒ glomeruli, not more distal, bleeding
  - Casts:
    - Hyaline: if oligouria
    - Granular: tubular origin
    - RBC cases: glomerulo-nephritis

Pre-renal Acute Renal Failure

- =↓ in glomerular perfusion in absence of structural kidney damage
- Kidney usually autoregulates – but can't cope with extremes
- Leads to very concentrated urine (i.e. ↑urine to plasma ratio of Na)
- Urea is re-absorbed preferentially to creatinine at low urine flows ⇒ plasma urea to creatinine is increased
- Can't interpret results if patient has had recent diuretics
- If prolonged → ischaemic damage → loss of reabsorbing capacity → dilute urine
- Causes:
  - Volume depletion: GI loss, burns, haemorrhage
  - Cardiac failure
  - Reno-vascular disease
  - Vasoconstriction in kidneys, e.g. due to NSAIDs (→ ↓vasodilating PGs), ACE inhibitors (→ ↓efferent arteriolar tone → ↓intraglomerular pressure
  - Systemic vasodilation: sepsis or antihypertensives

Intrinsic Acute Renal Failure

- Due to:
  - Acute Tubular Necrosis
  - Acute Interstitial Nephritis
  - RPGN
    - Urine chemistry midway between pre-renal acute renal failure and acute tubular necrosis - ↑urine to plasma ratios for osmolality and creatinine, and Na between 20 – 40 mmol/L

Post-renal Acute Renal Failure

- Due to obstruction: usually in urethra. If at ureteric level must be bilateral to lead to severe kidney failure
- → ↑tubular pressure → ↓glomerula filtration
- Auria: but partial obstruction may give moderate tubular dysfunction → osmotic diuresis →polyuria
- Usually obvious from history, confirm with ultrasound of kidneys

Investigations

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

Other blood tests

- ↑Ca and ↑urea = malignancy
- ↑creatinine kinase: rhabdomyolysis
- Eosinophils: allergic interstitial nephritis

Renal Imaging

- Catheterisation can rule out urethral obstruction
- Ultrasound useful in diagnosing obstruction, identifying stones and identifying kidney size
- Contrast studies may help establish site of obstruction

Renal Biopsy

- Usually only necessary in rapidly progressive glomerulonephritis
- Only if histology will influence management
- Major contraindication: bleeding tendency (check FBC and clotting first)
- Risk of serious complications < 1% (fistula, haematoma, infection, surgery, etc)

Male Genitourinary

Prostate

Anatomy

- Normally 20 – 30 g. Grossly enlarge can be 500g
- Prostate can become infected, hyperplastic or malignant
- Used to be described in lobes. Now described in zones:
  - Anterior zone
  - Transition and central zone: main site of benign hyperplasia
  - Peripheral zone: main site of malignancy. Next to rectum – can palpate on PR
- PR exam:
  - Even if normal, don't ignore ↑PSA. Cancers can be small or diffuse, or anterior, in an already large prostate → PR isn't sensitive
  - Nodularity can be detected on PR. This is due to desmoplasia (fibrous reaction) – usually to a *slower* infiltrating cancer

Prostatitis

- Acute:
  - Gonorrhoea most common cause: pain, discharge, haematuria, tender on PR
  - May be infarction secondary to hyperplasia compressing blood supply

- Granulomatous:
  - Tb (rare)
  - Fungal (only immunocompromised)
  - Leakage of prostatic secretion into interstitium post surgery
  - Resolving prostates (hard, nobbley prostate, ↑PSA, mistaken for malignancy). Suspect post surgery, but still need biopsy

Benign Prostatic Nodular Hyperplasia

- Not benign if not treated: → hydronephros → kidney failure → death!
- Common: 75% of all men over 75 years of age
- Testosterone ↓ with age → ↑oestrogen → potentiates effect of Dihydrotestosterone (DHT) on the prostate → prostatic hyperplasia
- Morphology: nodular proliferation of ducts, mainly in the central zone
- Histology: epithelial nodules, fibrosis, chronic inflammation, focal infarction
- Management:
  - Transurethral prostatic resection (TURP): always → retrograde ejaculation + risk of impotence and incontinence
  - 5 α reductase inhibitors (blocks Testosterone → DHT). Usually preferred. OK if not acute obstruction

Prostatic Carcinoma

- Occurs in 25% of males over 70 years. (More if include indolent central or transition zone tumours)
- 6% mortality in males
- Predominantly adenocarcinoma occurring in the peripheral zone
- Key histological features: single cell basal layer in duct epithelium, prominent nucleolis, lots of small glands
- Graded according to Gleason score
- Prostate Specific Antigen:
  - PSA – a tumour marker. Screening test only. ↑serum PSA correlates with tumour burden. PSA is a lytic agent that makes seminal fluid runny. If > 4 then do free to bound ratio, and/or follow/refer patient
  - ↑in benign *and* malignant tumours, or inflammation
- Prognosis related to Grade (using Gleason score: 2 is good, 10 is very bad)
- Spreads to pelvic lymph nodes via perineural infiltration
- Management:
  - Transurethral resection
  - Radiotherapy
  - Radical prostatectomy (selected on basis of tumour bulk and grade (not if very high grade – will already have metastatised). 50% have complications (impotence, incontinence)

Workup of Obstruction from Enlarged Prostate

- Investigations:
  - CK: checking renal function
  - K and Na: checking renal failure
  - Blood gases for metabolic acidosis
  - PSA
  - Ultrasound: look for distended bladder and hydronephrosis
  - ECG if ↑K: if ECG changes or if K high then may need anti-arrthymic
- Management:
  - Catheterise: should see K and CR resolve over a day (depending on remaining renal function)
  - If high K, then insulin + glucose
- Complications of obstruction:
  - Enlarged bladder: hyperplasia of detrussor muscle fibres, ↑space between trebeculated fibres
  - ↑Back pressure in ureter → hydronephrosis
    - ↓filtration → ↑Cr
    - ↓function of tubular epithelium due to poor perfusion → ↓active transport of K
    - Acidosis
- Moral: Must act on a distended bladder to protect the kidney

Acute Scrotum

- Must examine the genitalia of every boy who presents with acute lower abdominal pain (may not localise to testis)
- In descending order of frequency, causes of an acute scrotum are:
  - Torsion of the appendix testis
  - Testicular torsion
  - Idiopathic scrotal oedema. Symmetric swelling, no testicular tenderness. May include penis, inguinal and perineal regions. Exclude torsion
  - Rarely, epididymo-orchiditis
- US and nuclear medicine have little role.

Torsion of Appendix Testis

- Most commonly caused by Hydatid of Morgagni (Mullerian duct remnant) at top of testis
- Peak incidence at 10 –12 years. Oestrogen stimulates enlargement of the remnants → predisposes to torsion
- Symptoms range from minimal inflammation to florid, swollen hemi-scrotum indistinguishable from testicular torsion
- Urgent surgical referral

Testicular Torsion

- Testes are covered by tunica vaginalis – has parietal and visceral surface (like lungs in pleura)
- Testis rotates on its chord within parietal tunica vaginalis
- Once torsion has occurred in one, more likely in another
- < 6 hours will probably not cause infarct
- Two peaks for incidence:
  - Neonatal: Testis usually dead by diagnosis. May not operate (will atrophy). May 'pex' contralateral side to prevent torsion
  - Age 13 – 15: History and presentation variable. Surgical emergency. If testis viable, untwist and fix. Fix contra-lateral side
- Need to remove a torted testis, otherwise he will develop autoantibodies for spermatozoa → infertility of other testis

Epididymo-Orchitis

- Very rare in children. Two peaks
  - Newborn, with underlying urinary tract anomaly. Do US and MCU. MSU to rule out infection
  - In 13+ due to reflux up the vas → infection/inflammation
- Mumps orchitis does not occur in pre-pubertal boys

Testis

Undescended testis

- = Cryptorchidism
- Descent complete in 96% at birth, in 99% at 3 months
- Premature will have ↑rate of undescended testis (5% at 1 year)
- Two types:
  - Arrest of descent: at internal or external ring, or at scrotal neck
  - Ectopic: outside of the line of descent
- May present with a hernia
- Surgical correction at about 12 months
- Sequalae of non-descent:
  - 20 times risk of malignancy
  - ?Impact on fertility (due to ?higher temperature impairs spermatogenesis)
  - If don't bring them down they may end up over the pubic ramus → very uncomfortable sex!

No testis

- If bilateral undescended testis and hypospadias → ambiguous genitalia → urgent referral
- Torsion in utero → no testis
- No testis = anorchia. Maybe no kidney on that side ⇒ check

Retractile Testis

- Normally in scrotum but retracts upwards during examination
- Testis normal size
- Follow-up 2 yearly
- Surgery unnecessary. Will drop into scrotum at puberty

Hydrocele

- Fluid collection between the layers of the tunica vaginalis secondary to trauma, infection or idiopathic. Implies a patent process vaginalis
- May be bigger in the evening than in the morning
- Transluminates well, is non-tender and non-reducible
- Herniotomy if not resolved by age 2. 50% disappear in first year. Remove tunica vaginalis → removes potential space
- Predisposes to hernia

Infection

- Epididymo-orchitis:
  - Bacterial infection: E Coli, Klebsiella, Proteus
  - In adults also Gonorrhoea
  - Usually self-limiting → antibiotics
  - Key differential: torsion. If in doubt, emergency referral
- Primary Orchitis:
  - Mumps, Tb, tertiary syphilis
  - Rare

Other

- Spermatocoele: dilation of a chord of epididimis: common benign small lump on testis. Translucent to torch
- Haematocoele: Haemorrhage into tunica vaginalis or tunica albicinia (rugby injury, bleeding disorder)

Tumours

- Incidence 3.5/100,000
- 3% bilateral
- 7% associated with undescended testis
- Germ cell tumours:
  - 95% of testicular tumours
  - Derived from germ cells
  - Peak in 15 – 34 year olds
  - Painless swelling of the testis
  - Seminoma:
    - 40% of testicular tumours
    - Gross: lobulated pale tumour mass
    - Micro: Undifferentiated germ cells + ↑ lymphocytes. Aggressive. Metastasise to inguinal and paraaortic nodes
    - Treatment: Orchidectomy via inguinal region (never via scrotum → different lymphatic drainage. Also never biopsy suspected testicular cancers). Very responsive to radiotherapy
  - Teratoma:
    - 30% of testicular tumours
    - All can recapitulate ectodermal, mesodermal and endodermal tissue
    - Benign teratoma: More common in ovary than testis. 3% chance of malignant change. Mature tissues (usually skin elements – epidermis, hair follicales, etc)
    - Malignant teratoma: metastasise to para-aortic lymph nodes (especially neural cells – very aggressive). Gross appearance – lots of variety. Treatment: chemo +/- radiotherapy. Chemo stimulates cells to mature → still malignant but slower growing → excision of affect lymph nodes
  - Embryonal carcimoma: poorly differentiated, resembles adenocarcinoma. Highly malignant. May express tumour marker alphagetoprotein

    - Choriocarcinoma: Placental tissues (resembles hydatiform mole). Expresses βHCG → positive for pregnancy test. Contains highly malignant syncitiotrophoblast and cytotrophoblast cells. Responds well to chemotherapy
    - Mixed tumours: Teratoma and seminoma
- Sex chord/stromal tumours:
    - Leydig tumours: 90% benign. Small brown mass. Present with overproduction of testosterone: precocious puberty or gynaecomastia in post-puberty. Can produce androgens, oestrogen or corticosteroids
    - Sertoli cell tumours: Rare. 90% benign. Within seminephrous tubules of the testis. Local infiltration
- Lymphoma: Older males, often bilateral, poorly differentiated and poor prognosis
- Testicular tumours present relatively young, lymphoma in older men

Penis

Smegma

- Yellowish coloured secretion-desquamation which occurs normally and keeps the foreskin separate from the glans
- May appear like a dermoid cyst underneath the skin
- Is normal, and will eventually extrude spontaneously

Retraction of the foreskin

- By age 4 most boys foreskins will be able to be retracted
- May have intermittent pain during separation of the adhesions and the foreskin may be red or swollen for a day or two

Phimosis

- Irretractable, scarred foreskin. May balloon on urination
- If mild, application of Betnovate ointment to the tight portion of the foreskin (retract loose bit to access it) is effective
- If ongoing problems → circumcision
- Paraphimosis: foreskin stuck behind glans → swollen. Always put foreskin back after catheterisation

Balanitis

- May be distal or involve whole penile shaft
- Can be secondary to phimosis
- Treat with topical bactrim or oral antibiotics

Hypospadias

- Combination of dorsal hood, proximal urethral opening and chordee (central penile tilt)
- Presentation varies from mild to severe peno-scrotal type with ambiguous genitalia (check for testis)
- Correct at 9 – 12 months
- ↑UTIs
- ↑Infertility as the opening moves closer to the base of the penis

Other

- Epispadias: abnormal opening of urethra on ventral surface
- Fractured Penis: Rupture of corpus cavernosum during errection
- Condyloma: Genital wart. Usually flat. Associated with HPV.
- Erythroplasia of Queyrat (= Bowen's disease): non-invasive cancer of the penis. Premalignant condition. Usually starts in coronal sulcus.
- Squamous cell carcinoma: Very rare, ↑ risk if not circumsized. Early spread to lymph nodes but doesn't deseminate widely

Scrotum

- Steatocystoma: benign sebaceous cysts, hereditary
- Fournier's gangrene: Ischaemic necrosis. Little collateral flow to the scrotum so occlusion → domino effect. Treatment: debridement
- Squamous cell carcinoma

Urinary Tract Infections

- Epidemiology:
  - More common in women, older people, and long term care
  - 20% in women 65 – 75, 3% of men
- Definition: Lots of terms with subtle variations in meaning: UTI, bacteriuria, bladder bacteriuria, asymptomatic, etc, etc
- Presentation:
  - Asymptomatic bacteruria = 2 consecutive positive cultures without symptoms attributable to the urinary tract
  - Acute symptomatic urinary infection = urgency, frequency and dysuria (pain on urination). NB urgency and frequency may be unrelated to infection (eg bladder instability)
  - In elderly may present atypically: delirium, falls, immobility
  - Cloudy urine, dark urine (volume depletion), and smelly urine are all normal!
- Causes of dysuria:
  - Urinary tract infection +/- vaginitis
  - Vaginitis (Candida albicans, trichomonas vaginalis, gardnerella vaginalis)
  - STDs
  - Other: trauma, urethral syndrome
- Investigations:
  - Dipstick: Under-rated
    - Nitrites (produced by an enzyme in *most* infectious bacteria which breaks nitrates down to nitrites) $\Rightarrow$ presumptive diagnosis
    - If no leuckocytes, nitrates, protein or blood then no infection
  - Urine Microscopy:
    - Some RBC and WBCs are normal
    - Look for casts, crystals, bacteria. Absence of bacteria not significant (treat empirically)
    - If RBC > WBC then ?stone
  - Culture:
    - Bacteruria $\Rightarrow$ 10E5 colony forming units (cfu) per ml of urine. However, this was set using morning samples in young women via catheterisation $\Rightarrow$ not much value.
    - In kids, a much smaller number may be significant, especially if:
      - In a boy
      - Obtained by catheter. In a supra-pubic aspirate any growth is important
    - Most UTIs are caused by a single bug. If multiple organisms then contaminated sample. Bugs can grow in transit $\rightarrow$ send to lab straight away or refrigerate
    - Antibiotic sensitivity: if multi-resistent then usually from Asia where antibiotics are freely available
  - Haematuria in 50% - but if asymptomatic $\rightarrow$?bladder carcinoma
  - Intravenous pyleogram or intravenous urogram
- Microbiology:

	GP	Hospital
E Coli	75%	40%
Coag –ive Staph	7%	6%
Proteus	6%	15%
Klebsiella	3%	12%
Enterococcus	3%	15%
Pseudomonas	1%	6%

  - Hospital acquired are more antibiotic resistant
  - Pathogenesis: bacterial adherence
    - Uropathic strains: fimbriae – microbial adhesions. Different types in different bugs, and different densities of receptors in hosts $\rightarrow$ genetic predisposition
    - Catheter: adhering strains.
      - Tightly asherent $\rightarrow$ none grown from urine.
      - Thick layer of 'biofilm' forms in lumen of catheter containing bugs. Antibiotics can't penetrate $\Rightarrow$ Change catheter.
      - Risk factors: $\uparrow$ duration of use (but regular changing makes it worse), female sex, absence of systemic antibiotics, catheter care violations

    - Prevention: avoid catheterisation, lots of fluid, alternative method for bladder drainage (eg condom catheter), closed, sterile bladder drainage, appropriate aseptic technique at insertion
- Complications: Ascending infection → renal scarring → hypertension, etc
- Treatment:
    - Oral trimethoprim in uncomplicated infections. ↑E coli resistance – will need to change this soon
    - Oral quinolones are the main second line agents (eg norfloxacine)
    - *Don't* treat asymptomatic positive urine cultures (ie don't test unless symptoms)
    - Single dose therapy is worse than conventional therapy (7 – 10 days). For adult women, single does therapy has an odds ratio compared to conventional treatment (5 days or more) of 0.7 for TMP/SMZ (trimethoprim/sulfamethoxazole), and 0.4 for amoxycillin
    - Short course possibly as effective as conventional (watch this space)
- Men:
    - If unknown cause - ?referral to urologist for kidney scan (e.g. stone)
    - Always do urine culture in addition to antibiotics
    - Do swab if discharge

Bladder

Interstitial Cystitis

- Usually elderly patients
- Urine sterile
- If severe then intractable pain with decreasing bladder capacity
- Microscopy → ulcerative chronic cystitis
- ?Viral aetiology

Bladder Tumours

Transitional Cell Carcinoma

- Classic association with azo dyes (clothing, plastics, batteries) and smoking
- Present with painless haematuria (ALWAYS investigate painless haematuria)
- Develop as a flat carcinoma-in-situ → papillary tumour → infiltrates
- Management: regular scrapping it out until pathology says its metastatic then cystectomy

Other Bladder Tumours

- Squamous cell carcinoma: common in Egypt due to Schistosoma (parasite). Early infiltration
- Adenocarcinoma: Rare. Resembles large bowel adenocarcinoma. Derived from urachal remnant
- Rhabdomyosarcoma: In childhood. Aggressive but responds to chemo.

Thyroid Nodules

- Are common (occur in 10 – 60% depending on definition) but clinical malignancy is rare (2 – 10/100,000/year)
- Evaluation:
  - Presents with lump in lower neck
  - Age: young with nodules more likely to be cancer
  - Gender: Females have more nodules, male's nodule more likely to be cancer
  - Risk factors: radiation, family history, large solitary nodule bigger risk than many small ones
  - Symptoms:
    - Systemic: ↓weight and appetite, night sweats
    - Local: pain, stridor
  - Tests:
    - Usually normal thyroid function
    - Tumour markers: thyroglobulin, calcitonin
    - Imaging: Not specific: Cold spots – can be cancer but also normal. Hot spots unlikely to be cancer
    - US
    - FNA best
- Benign types:
  - Haemorrhage into a thyroid cyst: painful and instantly palpable
  - Adenoma: always follicular, encapsulated, universally benign. Usually cold on scan, may be hot
- Malignant:
  - **Papillary** Thyroid Cancer:
    - 60% of carcinomas
    - Have papillary (finger like) architecture with fibro vascular core
    - Metastasises to lymph nodes
    - May also have calcified bits ⇒ Psammoma bodies (also found in meningiomas, serous cystadenoma of the ovary)
    - Prognosis: If extrathyroid lesions then 62% survival @ 15 years
  - **Follicular** carcinoma: rarely multifocal, capsular invasion, metastasises via blood vessels. If gross invasion then 50% survival at 6 years. Hard to differentiate from adenoma on FNA
  - Anaplastic (undifferentiated carcinoma): highly malignant, old age, poor prognosis
  - Medullary/C Cell carcinoma: parafollicular cells (↑serum calcitonin). Usually part of Multiple Endocrine Neoplasia Syndrome (MEN)
  - Treatment: near total thyroidectomy. If staging indicates high risk then radioiodine for remnant ablation
  - Also lymphoma
- Multinodular Goitre:
  - With time, all thyroids have:
    - Anatomical heterogeneity: cold/fibrosed regions, hyperplasia, calcification, etc
    - Functional heterogeneity: various degrees of autonomy
  - If pronounced, then multinodular goitre:
    - Can be substantially enlarged with cystic appearance
    - Growth may → haemorrhage → tender
    - Treatment: Cut it out or thyroxine (slows it down)
- In addition to a tumour, a single nodule may be:
  - A hyperplastic nodule (ie physiological)
  - Multinodular goitre with a prominent nodule
  - Thyroglossal duct cysts

Gynaecology

Vulval Lesions

- Non-neoplastic epithelial disorders:
  - *Lichen Sclerosis*:
    - 1/3 of lesions, commonest after menopause
    - Pruritic, affecting any part of the vulva
    - Multiple irregular white patches, shiny wrinkled atrophic skin
    - ↑ risk of SCC
    - Microscopy: subepithelial homogenous collagen + band of lymphocytes
  - Squamous Hyperplasia:
    - Non specific thickening of the epithelium + inflammatory reaction below the BM: acanthosis, hyperkeratosis
    - Non specific diagnosis
  - Other dermatoses: Lichen simplex chronicus, spongiotic dermatitis (contact dermatis eg perfumed toilet paper), Psoriasis, Lichen planus
- *Vulval Intraepithelial Neoplasia* (VIN):
  - Often multi-focal white-pink-red raised lesions which itch/burn/asymptomatic
  - Preinvasive dysplastic squamous lesions
  - Dysplasia is graded VIN1, VIN2, VIN3
  - Untreated 7/8 progress to SCC Unlike CIN)
  - Risk factors similar to cervical carcinoma
  - 60% have lesions in other areas
- *Squamous Cell Carcinoma*:
  - 90% of vulval cancer and 5% of gynae cancer
  - Two types:
    - Elderly women (70+): 65%, related to Lichen Sclerosis & squamous hyperplasia, well differentiated – islands of invading cells
    - Younger women (40+): 35%, related to HPV, Cervical cancer risk factors, poorly differentiated
  - Raised white warty mass
  - Micro: resembles SCC at other sites
  - Often present late
  - Prognosis depends on stage. Factors in order of importance are:
    - Lymph node metastasis
    - Depth of invasion
    - Size
- See also **Error! Reference source not found.**, page **Error! Bookmark not defined.**

Cervical Cancer

- Reference: Cervical Screening, Information for Health Professionals, National Cervical Screening Programme, Health Funding Authority, October 1998

Epidemiology

- In NZ, about 200 new cases per year, 70 – 80 deaths
- One in 97 women can expect to get it before 75
- 75% of cases and 80% deaths are over 35, but CIN lesions can develop young (ie many woman coming for colposcopy after abnormal smears are 25 – 30).

Aetiology

- Human Papilloma Virus (HPV):
  - HPV 6, 11: condyloma acuminatum
  - HPV 16 or 18: Genital dysplasia. Is a necessary but not sufficient condition for cervical cancer
  - Koilocytes: HPV infected keratinocytes with a perinumclear halo. Episomal viral DNA
  - Dysplasia: pleomorphic, hyperchromatic mitotically active, high nuclear/cytoplasmic ratio. Integrated DNA (Kettle fry nuclei)
  - HPV Carcinogenesis:
    - Not typical mechanisms

    - E6 binds to p53 (tumour suppressor and accelerates its degradation)
    - E7 binds to RB displacing transcription factors usually sequestered by RB
- Other risk factors:
    - Early age at first intercourse
    - Muptiple sexual partners
    - High risk male partners
    - Smoking,
    - Herpes
    - Immunosuppression
- Occurs in the transformation zone: junction in the endocervix between squamous cells of the vagina and columnar cells of the uterus. Completes development at age 18 – 20, shifting into the endocervix. Previously in the exocervix and more vulnerable to damage/infection ⇒ significance of age at first intercourse

Classification

- 3 grading systems:

	Histology	Cytology
Mild dysplasia	CIN1	LSIL
Moderate Dysplasia	CIN2	HSIL
Severe Dysplasia	CIN3	HSIL
Carcinoma-in-situ	CIN3	HSIL

- Low grade changes: Low Grade Squamous Intraepithelial Lesion (LSIL) (=CIN1 – Cervical intraepithelial neoplasia. More likely to be HPV types 6 & 11). Nucleus is slightly enlarged and irregular. In bottom third of cells on top of base membrane in transformation zone. If found on screening → more regular smears. 50 – 60% return to normal
- High Grade Changes: HSIL (covers CIN 2 and 3/CIN – carcinoma-in-situ. More likely to be HPV 16 & 18). Nucleus of every cell is very enlarged and irregular in shape. Affected cells right to surface. If found on screening → refer for colposcopy. Treated the same but CIN3 more likely to progress than CIN2
- Invasive cancer: basement membrane has been breached. Can get glandular extension in CIN3 – metaplasia down glands – but still not invasive as the BM is not breached

Progression

- Cervical Dysplasia: grade depends on proportion of the epithelium occupies by malignant cells
- Cervical Carcinoma:
    - Micro: islands of infiltrating neoplastic squamous cells that may show keratinisation
    - Outcome: depends on stage
        - Size and depth of invasion. > 10 mm invasion → poorer outcome
        - Lymph node involvement → poor outcome
        - Stage 1: confined to cervix. 90 – 95% 5 year survival
        - Stage 3: lymph node positive: 30% 5 year survival
- Cervical glandular neoplasia:
    - Also HPV related, but much less common than cervical squamous carcinoma (which has a higher rate of replication)
    - Invasive adenocarcinoma has infiltrating neoplastic glands
    - Comprises 20% of tumours in a screened population vs 5% in unscreened

Cervical Screening

- Pap smears collect exfoliated cells from he cervix
- Currently reported on the Bethesda system which divides dysplasia into LGSIL, HGSIL and ASCUS (Atypical squamous cells of unknown significance – not sure whether they're dysplastic or reactive. Some will be CIN3 so still need followup)
- Procedure:
    - Explain first. Ask about abnormal bleeding, post-coital bleeding, abnormal discharge, if pregnant, and previous smear history and experiences
    - Patient Education: discuss feelings about having a smear, emphasise preventative nature, explain what cervix is, show equipment
    - Ensure screen/curtain for patient and sheet
    - Label slides first
    - Either:

    - Spatula first, one full turn, and if poor endocervical sample follow with brush (only turn one turn otherwise bleeding) and use a second slide for the brush.
    - Broom does both well (sample of choice for all age groups) – turn 5 times and wipe both sides once down slide. Thin prep: cells mixed up and rubbish removed → better reading. Can't use wooden spatula.
  - Putting on slide: wipe spatula once, roll brush. Fix quickly – within one second – as drying causes distortion of cells. Fix either in 95% ethyl alcohol for 20 - 30 minutes or cytofix sprayed from 20 – 30 cms.
  - Data on lab form includes LMP and clinical details.
  - Biggest cause of ↓ sensitivity is poor sampling. Smears can be unsatisfactory if blood, inflammatory cells or lubricant present. Smears taken 4 – 5 days prior to the next period may show cytolysis (cellular degeneration due to ↑ bacilli)
- Relationship between screening results and lesions (From OHCS, p 34):

	Papanicolaou class	Action	Histology
1	Normal	Repeat in 3 years (unless clinical suspicion)	0.1% CIN II – III
2	Inflammatory	Repeat in 6 months (colposcopy after 3 abnormal)	6% CIN II – III
	Mild Atypia	Repeat in 4 months (colposcopy after 2 abnormal)	20 – 37% CIN II – III
3	Mild/Moderate dyskaryosis	Colposcopy	50 – 75% CIN II – III
4	Severe dyskaryosis	Colposcopy	80 – 90% CIN II – III
	Malignant cells		5% invasion
5	Invasion suspected	Urgent Colposcopy	50% invasion
	Abnormal glandular cells	Urgent Colposcopy	?Adenocarcinoma

- Why screen?
  - Success rate for adequate treatment of pre-cancers is 98 – 100%
  - Women most likely to get cervical cancer are those not regularly screened
- Protocol:
  - 3 yearly screening should be offered to all women aged 20 – 69 years who have been sexually active. Can stop if > 5 years with no sex (this bit not in the guideline)
  - Screening should be yearly for 2 years from 20, or earlier if > 2 years since commencing regular sex
  - Normal or benign/reactive changes:

Satisfactory	Previously normal	Smear in 3 years
	First smear, or more than 5 years since last smear	Smear in 1 year
	Previous abnormal smears	See below
Satisfactory but limited	Previously normal	Smear in 1 year
	First smear, or more than 5 years since last smear	Smear in 1 year
	Abnormal smear in last 5 years	Smear in 6 months
Unsatisfactory smear		Smear in 1 – 3 months

  - Abnormal:

CIN1 or HPV	Previous normal smear	Smear in 6 months
	Previous abnormal smear	Smear in 6 months, if normal then 2 * 1 year, if abnormal then colposcopy
CIN 2 or 3 → Colposcopy	If LSIL or less	Smears at 6 months, 1 year, 1 year, 3 yearly, if abnormal then colposcopy
	If HSIL	Smear at 6 months then annual until 70, if abnormal then colposcopy

Effectiveness of Screening

- Maximum prevention: 90% of squamous cancers
- Less than 100% because of:
  - Less than 100% enrolment
  - False negatives in sampling (eg a lesion is more likely to bleed and compromise the sample)
  - False negatives in laboratory diagnosis

    - Interval cancers: minimum time from infection to invasive is ~ 18 months. Normal is ~ 10 years
- Much less effective at glandular lesions: clinical suspicion should overrule a 'normal' smear

Other Cancers

Ovarian cancer

- Risk factors: nulliparity, infertility, early menarche, family history, no past pill use
- Presentation:
    - 75% asymptomatic until advanced
    - Swelling with palpable mass
    - Pressure effects (eg on bladder)
    - Infarction, haemorrhage, peritonism
    - Ascites
    - Torsion
    - Endocrine: virilisation, menstrual irregularity, PMB
- Types:
    - Epithelium: 70%
        - Benign (60%): younger – serous cystadenoma, mucinous cystadenoma. If cysts have smooth internal epithelium likely to be benign
        - Borderline (20%): mucinous tumour of boderline malignancy. 6% recurrence (but still treatable) so need long term followup
        - Malignngnat (20%): serous cystadenocarcinoma
    - Ovum: 20%
        - Dermoid cyst (teratoma)
        - Occur in children and young women, in contrast to epithelial tumours
        - Commonest is benign, but in young children they are often malignant
        - Micro: variety of mature cell types: skin, gut, neural tissue, etc
    - Others: 5%
        - Stroma: lymphoma, fibroma
        - Granulosa cell tumour $\rightarrow \uparrow$oestrogen $\rightarrow$ amenorrhoea and breakthrough bleeding
        - Thecal cell tumour $\rightarrow \uparrow$androgen $\rightarrow$ infertile, hirsutism, amenorrhoea
- Investigations: Ca125, FBC, electrolytes, LFTs, US + CT (for mets or possible primary elsewhere)
- Treatment: Surgery for staging +/- debulking, chemo (usually platinum)
- Other ovarian cysts:
    - Present with mass effects of torsion:
        - Follicular cyst
        - Corpus luteum cyst
    - Polycystic ovaries
    - Endometriosis

Endometrial Neoplasia

- Endometrial hyperplasia:
    - Simple hyperplasia: cystic glands with pseudostratified mitotically active cells. No atypic, minimal risk of carcinoma
    - Complex hyperplasia: More crowded gland with budding and infolding. With atypia, 5% progress to carcinoma
    - Complex hyperplasia with atypia: crowded, folded gland in which the lining cells are pleomorphic with loss of polarity and increased nuclear cytoplasmic ratio. > 25% progress to cacinoma
- Endometrial polyps:
    - Most are hyperplastic polyps
    - Often seen with generalised hyperplasia
    - Due to an area responding to oestrogen but resistant to progesterone
    - Micro: a polypoid collection fo cystic hyperplastic glands in a fibrotic stroma
- Endometrial Cancer:
    - Presentation: irregular PV bleeding, often post menopausal
    - Risk factors: obesity, nulliparity, diabetes, unopposed oestrogen therapy, pelvic irradiation, endogenous unopposed oestrogen (functioning ovarian tumour, anovulatory cycles, fat), family history for breast, ovarian or colon cancer

- Peak age 55 - 60
- Investigate endometrial thickness with trans-cervical ultrasound:
  - Reproductive endometrium: 0.5 – 1.5 cm
  - Menopausal endometrium: < 5 mm. If bleeding, repeat US in 4 – 6 months and look for change
  - If menopausal and 5 – 9mm, do endometrial sample. 90% are normal proliferative endometrium. 5% are atypical (pre-cancerous), 5% are carcinoma
  - If > 9 mm, straight to D&C to get good endometrial sample (high suspicion of cancer). Not hysteroscopy (can force malignant cells into the peritoneum)
- Macro: fungating mass in the fundus
- Micro: adenocarcinoma
- Treatment: hysterectomy and oophorectomy + chemo and radiotherapy
- Prognosis:
  - Stage 1: invade wall, 90% 5 year survival
  - Stage 2: invade cervix, 50% 5 year survival
  - Stage 3: lymph nodes, 20% 5 year survival

Breast

Developmental Problems

- Inverted nipples are common. If a previously normal nipple inverts ⇒ cancer until proven otherwise (although nipple retraction is more likely to be inflammatory than malignant)
- Virginal/ Adolescent Hypertrophy: very large breasts developing around puberty. Problem with stroma. Aetiology unknown
- Hypomastia: almost complete failure of breast development. May be unilateral
- Accessory nipples (don't have lobular tissue underneath)

Breast discharge

- Causes:
  - Duct ectasia (periductal mastitis) – most common cause in pre-menopausal women. Discharge may be serous, greenish or bloody.
  - Carcinoma: usually associated with a palpable mass – cause in 10% over age 55. Cancer unlikely if discharge is coming from both nipples and/or multiple ducts. Cytologic examination has 50% sensitivity.
- Management:
  - History and exam
  - Get mammogram, re-examine in 3 and 12 months, and repeat mammogram in 12 months
  - Sample to discharge to lab
  - Check serum PRL, especially if a pre-menopausal woman has irregular periods
- Pregnancy and discharge:
  - Epithelial hyperplasia may → blood-stained discharge (usually normal)
  - Galactocoele: a milk filled cyst due to plugged duct

Inflammatory Breast Disease

- Acute Mastitis and breast abscess:
  - Usually occurs in early lactation
  - Usually staph aureus (abscess), less often strep (cellulitis)
- Fat Necrosis:
  - A solid mass caused by injury (eg seat belt injury)
  - Necrotic fat cells surrounded by an inflammatory infiltrate, with later calcification and scarring. Can mimic carcinoma
- Duct ectasia
  - Uncommon cause of a breast mass. Usually older woman, tender and nipple retraction
  - Chronic inflammation and fibrosis around ducts loaded with lipid and macrophagic rich material
  - Cause unknown
  - → preductal mastitis (periareolar inflammation, abscess formation, unilateral, single duct, etc
- Plasma cell mastitis: Rare cause of a breast mass. Probably the same as duct ectasia but with ↑plasma cells
- A tumour can block lymphatics causing inflammation ⇒ cancer is always a differential

Fibrocystic Disease

- A 'catch-all' category for gross and micro cysts
- Don't call it mammary dysplasia
- Commonest disease of the breast
- Cause obscure – unopposed oestrogen a known factor. Women on combined pill get less fibrocystic disease
- Classification by size:
  - Gross cysts: very easy to diagnose on US. 40s. Drain with FNA
  - Micro cysts: usually 30's and 40's. May have cyclical pain. Resolves after menopause
  - Galactocoele – milk filled cyst, usually with lactation
- 5 components (either separately or together):
  - Cysts:
    - Dilated ducts containing cloudy serous fluid (sometimes bloody or infected)
    - All breasts contain microcysts during childbearing years. Abnormal when > ~ 2mm
    - Histology: epithelium may be flattened, cuboidal, columnar, piled up or show spocrine metaplasia. Surrounding stroma likely to be fibrous
  - Fibrosis:
    - Dense collagenisation distorting/compressing epithelial structures
    - Most common in upper outer quadrants, patient's in 30s
  - Sclerosing adenosis:
    - Usually a tender lump in the upper outer quadrant, patient around 40
    - Benign proliferation of small ductules in a fibrous stroma, but histologically circumscribed
    - Lining cells proliferate to fill the ducts
    - Increased risk of cancer with florid (2*) and atypical (4*) hyperplasia
    - Mimics cancer both clinically and microscopically
  - **Apocrine Metaplasia**: Benign metaplastic change to tall cells with eosinophillic cytoplasm resembling those of apocrine sweat glands
  - Duct (and sometimes lobular) epithelial hyperplasia

Generally Benign Breast Tumours

Fibroadenoma

- Most common benign breast tumour – *no* malignant potential
- Hypertrophy of a lobule, compressed by stroma ($\rightarrow$ sharply circumscribed), hard and very mobile – up to 2 – 3 cm diameter.
- Common in 16 – 24 years. Rapid growth for 6 months, 1/3 will regress.
- Diagnosis by FNA.
- Histology: $\uparrow$fibrous tissue surrounding normal ducts that are often crushed flat. Risk of subsequent cancer = 2.17

Phyllodes Tumour

- 'Worrisome' mixture of stromal and epithelial cells
- 30 – 50 years
- Shiny skin + vascular markings
- Wide spectrum from benign to frankly malignant. Grow rapidly
- Diagnosis: FNA + core biopsy. Cleft into the tumour on US is characteristic
- Treatment: excision with 1 cm margin
- Recur locally

Papilloma

- < 1 cm epithelial proliferation in a major duct just below the nipple
- Can $\rightarrow$ bloody discharge and/or nipple retraction
- 1 in 100 is a papillary carcinoma

Breast Cancer

Epidemiology

- In NZ, 1600 cases each year, 580 die. Commonest cause of cancer death in women.
- 10% life time incidence (usually over 70)
- Maori rate similar to non-Maori

- 75% diagnosed with breast cancer are over 50. Uncommon under 40. Younger if genetic risk

Risk Factors

- Major risks:
  - Woman (100 * men)
  - Age
  - Previous breast cancer, also previous (or family) history of endometrial, prostate, or ovarian cancer
  - Biopsy showing an at risk condition e.g. atypical hyperplasia
  - Genetic predisposition (eg BRAC1 or 2 account for 5% of breast cancers)
  - Family History:
    - Most with family history don't develop it, most who get it won't have a family history
    - Risk is above population risk for only 1% of female population
    - 4% have a moderate increase in risk if:
      - a mother, sister or father developed breast cancer before 50, or in both breasts
      - More than one close relative on the same side of the family who had breast or ovarian cancer (geneticist said only genetic if 3 or more affected relatives – it is so common have to have a high incidence in family before suspecting a family loading)
- Minor risks:
  - Oestrogen exposure:
    - Slight increase for OC and Depo-Provera (only while taking it – and usually young so less of an issue)
    - Longer duration between menarche and menopause
    - First child beyond 35 or no children
  - Not having lactated → slight ↑risk of premenopausal cancer
  - Obesity
  - HRT for more than 5 years increases risk by about 30%. Risk disappears within 5 years of stopping
  - Radiation, environmental hazards
- Not risk factors:
  - Smoking
  - Small (now disproven?) relationship with low fat, high fibre diet

Symptoms

- Usual presentation is a dominant, painless mass
- New lump or thickening
- Change in breast shape or size
- Puckering or dimpling of the skin
- Change in a nipple
- Lumpiness in one breast soon after period ends
- Pain in the breast that is unusual
- Presenting symptoms:
  - Painless mass: 66%
  - Painful mass: 11%
  - Nipple discharge: 9%

Investigations

- History and clinical exam
- Mammogram:
  - Not sensitive < age 35
  - Calcifications: low risk are coarse or rounded, high risk are clustered or branching
  - Shadows: malignant are less circumscribed
- Ultrasound
- FNA → Cytology
- Core or hook wire biopsy

Pathogenesis

- Most tumours occur in the epithelial component lining the ducts and lobules. Epithelial hyperplasia (1 – 2 times risk) → Atypical hyperplasia – proliferation and atypia of ductal or lobular epithelium. Risk of subsequent cancer = 4 times.

- Tumour cells secrete cytokines → fibrosis → lump. Easier to detect in an older woman (↑fat and ↓intra-lobular fibrosis)
- All breast cancers are different. Tumour growth rates vary considerably. On average takes 9 years to reach 1 cm.
- Death is from metastases which can occur at any time
- Spreads to lymph nodes via lymphatics *and* directly to distant sites via blood stream – not via lymph nodes then to distant sites (although lymph node involved ⇒ ↑risk of blood spread as well)
- Lots of implicated genes. Those in familial breast cancer include:
  - BRAC1:
    - Autosomal dominant (but recessive at the level of the cell): if carrier then 65 – 75% risk (ie high penetrance)
    - A tumour suppressor gene, expressed in breast, ovary, thymus, testis
    - Accounts for 40 – 50% of familial breast cancer
  - BRAC2:
    - Associated with male breast cancer, not ovarian
    - 10% of inherited breast cancer

Differential Diagnosis

- Classification:

	In-situ	Infiltrative (invasive)
Ductal	Intraductal carcinoma	Infiltrating ductal carcinoma: • No special type (NOS) • Medullary carcinoma • Mucinous carcinoma • Tubular carcinoma • Metaplastic
Lobular	Non-infiltrating (in situ) lobular carcinoma	Infiltrating lobular carcinoma

  - Most cancers are intraductal
  - Plus Paget's Disease of the Nipple
- **Non-infiltrating/in-situ breast cancer**: Does not metastasise but recurrence is a problem
  - Intraductal carcinoma (20 – 30%):
    - Comedocarcinoma: solid intraductal proliferation, central necrosis, microcalifications on mmammogram
    - Classified by nuclear grade (low, intermediate and high) and the presence or absence of necrosis.
    - Can eventually become invasive: removal → cure
  - Paget's disease (a type of ductal carcinoma in situ): lesion of the nipple caused by malignant cells arising from ducts and invading the nipple epithelium. Looks inflamed (early on can look like eczema). Most often an underlying duct carcinoma.
  - Lobular carcinoma in situ:
    - Usually an incidental finding on biopsy affecting terminal ductules
    - Proliferation of terminal ductules and acini
    - 1% per year risk of invasive carcinoma in same *or* opposite breast – removal isn't necessarily cure
- **Invasive/infiltrating breast cancer**:
  - Main risk factor: ↑age
  - Infiltrative ductal carcinoma (65 – 80%):
    - No special type: Most common. Grossly stellate or multinodular and very hard. Histologically compressed ductules in a very desmoplastic stroma
    - Medullary: Big, bulky and soft, plentiful lymphocytes, better prognosis than other types
    - Mucinous (colloid, gelatinous) carcinoma: Grossly: gelantinous mass. Histologically: clumps of cells in lakes of mucin. Better prognosis
    - Tubular Carcinoma: well-formed glands, best prognosis
  - Infiltrative lobular carcinoma:
    - Histological: Indian files around ducts, small cells
    - Often bilateral
- Features of invasive cancers:
  - Usually dominant mass
  - Usually painless

    - In time fixed to deep fascia → immobile
    - Orange peel appearance: blocked lymphatics → oedema + suspensory ligaments contract → distorted shape
    - Also nipple retraction, ulceration of overlying skin
    - Majority arise in the outer quadrants – particularly the upper, outer quadrant
- On mammography:
    - Infiltrative edge: not well demarcated
    - ↑density compared with adipose tissue
    - Micro-calcifications: small clustered areas of necrosis

Prognosis

- Stage: axillary metastases most important, also size. Cancers found on mammography or by self-examination are smaller ⇒ better prognosis
- Grade
- Oestrogen receptor sensitivity: if positive then better – more differentiated and Tomoxafen → regression

Treatment

- 5 year survival if treatment before metastasis – 95%
- 5 year survival if treatment after metastasis – 17%
- Two options (similar long-term survival):
    - Removal of the lump + radiation therapy
    - Mastectomy (or radical mastectomy)
- +/- radiotherapy
- +/- Tamoxifen (anti-oestrogen)
- Management:
    - Most common metastasis is in the bone. Bisphosphonates → slow osteolysis
    - If hormone sensitive → irradiate/remove ovaries

Skin

- Structure of skin:
  - Epidermis:
    - Stratum corneum
    - Stratum lucidum
    - Stratum granulosum
    - Stratum spinosum
    - Stratum germanitivum (base of epidermis)
  - Dermis:
    - Papillary dermis
    - Reticular dermis
  - Subcutaneous tissue
- Basic terms: Non-specific reactive changes
  - Hyperkeratosis: thickening of the stratum corneum. Eg due to trauma (eg the lump where you hold a pen)
  - Parakeratosis: Nuclei are seen in the stratum corneum (would normally have died off, eg psoriasis)
  - Acanthosis: thickening of the epidermis, eg due to irritation

Viral Infections

Muluscum

- Viral infection with pox virus
- Small solid papules with umbilication in middle. Stay fairly localised
- If you squeeze them then virus released (ie infective)
- Histology: acanthosis and molluscum bodies
- Disappear in under 9 – 12 months. Treat if severe

Verrucae (Warts)

- Papova virus: **Pa**pillary lesion + **po**lyoma (lots of them) + **va**cuolation of cells containing the virus
- Locations:
  - Verruca vulgaris
  - Verruca plana: flat, eg on face
  - Verruca plantaris: on feet, can be painful
  - Verruca palmaris: on hands, can be painful
  - Condyloma accuminatum: Genital. Rarely premalignant
- Histology:
  - Hyperkeratosis/parakeratosis
  - Acanthosis
  - Nuclear and cytoplasmic inclusions
  - Perinuclear vacuolation

Naevi and Melanoma

- Naevi = hamartoma of the skin. With respect to melanocytes, a benign neoplasm

Melanocytic Naevi

- Normal skin: epidermal cells, plus melanocytes, Langerhans cells (Antigen Presenting Cells – APC), prickle cells and merkel cells (sensory receptors)
- Benign melanocytic naevi:
  - Junctional: epidermis only, early active growth to <0.5 cm. Can be non-pigmented. Overgrowth of melanocytes in nests along the junction of the dermis and epidermis.
  - Compound: epidermis and dermis, older active growth (moles on palms, soles and genitalia stay junctional)
  - Intradermal: stopped growing, loss of tyrosinase → small and pale. Don't become malignant – must have junctional activity to do this
- Dysplastic melanocytic naevi:
  - Uncontrolled proliferation without malignancy, mole > 0.5 cm

    - Mostly benign with possibility of malignancy
- Halo naevi: Fairly common, especially in kids. Depigmented halo around the mole, but the mole is normal (cf depigmented melanoma where pigmented lesion is not normal and not central)
- Pathogenesis: ?Somatic mutation

Melanoma

- Host Risk Factors: Skin colour, Naevi, Atypical naevi, DNA repair, Immune status
- Environment Risk Factors: UV light (geography, season, time), behaviour. Risk from sun determined by age 15. After that sunscreen mainly protects against squamous and basal cell carcinomas
- Epidemiology:
    - 1 – 3% of childhood cancers
    - Females 14/100,000, males 9/100,000. Difference is in the distribution on the legs
- Spotting them:
    - A: asymmetry
    - B: border irregular – e.g. growing a peninsular
    - C: colour – 3 or more, colour not symmetrical, areas of black, varigated
    - D: dimension > 0.5 cm
    - E: elevated $\rightarrow \uparrow$dermal penetration
- Watch out for:
    - Changes: but moles can change for lots of reasons
    - Bleeding, itching and halo (although can get two tone moles – OK if symmetrical)
    - If have > 100 moles, 100 to 200 times normal risk: need regular checks
- Progression:
    - Radial Growth Phase: initially growth is along the dermoepidermal junction and within the epidermis
    - Vertical Growth Phase: Growth into the dermis $\rightarrow$ malignant cells in contact with lymphatics and capillaries $\rightarrow$ metastasis
    - Nodular melanoma: bad news
    - Acral Letigenous Melanoma: on palms and soles
- Pathology:
    - Features of malignant cells: irregular, hyperchromatic, large N:C ratio, mitoses (blackberry nuclei), abnormal number of mitosis
    - Radical/Superficial/Horizontal growth phase: cells in contact with dermis, don't metastasise
    - Vertical growth: mass of atypical melanocytes infiltrating dermis, lymphocytes, not necessarily pigmented, metastasises
- Prognosis:
    - Breslow tumour thickness (> 0.76 cm bad) or Clarkes levels (grade 1- 5, 3 ~ Breslow 0.76, bigger = worse)
    - Ulceration > 3 mm (bad)
    - High mitotic rate (bad)
    - Regression an indication of metastasis (bad)
    - Tumour infiltrating lymphocytes (bad)
- Treatment: surgical excision
- Hutchison's Freckle: freckly melanoma. Malignant change o melanocytes along the epidermis border but no infiltration. Like a 'melanoma in situ'. Takes years to become invasive. On sun damaged skin. On elderly watch for a while. Now showing up on younger people – excise before they get too big

Other Naevi

- Epidermal Naevi:
    - Defined according to their predominant cell type
    - Circumscribed distribution over a part of the body surface, usually dermatomal
    - Any size, never cross the midline, uncommon on face and head
- Sebaceous Naevi: hamartomas of predominantly sebaceous glands. Usually on scalp (lesion is bald). Raised, velvety surface, present at birth, usually small. $\uparrow$Risk of basal-cell carcinoma, but no longer prophylaically excised
- Dermal Melanocytic naevus (Mongolian spot): macular blue-grey pigmentation present at birth, over sacral area in Mongoloid and some other races. Looks like a large bruise. Rarely persist into adulthood.

- Congenital naevocellular naevus: Small is < 1.5 cm, intermediate = 1.5 – 20 cm, large is > 20 cm. If over lower sacrum → ?spinabifida occulta. May arise or darken in puberty. Large ones have ↑risk of melanoma
- Spitz naevus: appears in early childhood as a firm, round red or reddish brown nodule. May bleed and crust. Benign. Local excision.

Other Tumours

Benign

- Epidermal cyst:
  - Collection of epidermal cells within the dermis. Either around the base of a hair follicle or from trauma (eg on a builders hands)
  - If it becomes infective → ulcerates and smells
- Basal cell papilloma (= Seborrhoeic Keratosis)
  - Raised, sharply demarcated, can be brown pigmented papule or plaque, shiny, bleeds easily if scrapped
  - Results from proliferation of squamous basaloid cells which sit on top of and do not invade the dermis (grow up, compared to BCC which grows down)
  - Exposure to sun in older patients
  - Histology: hyperkeratosis
- Keratoacanthoma:
  - Uncommon
  - On lip, up to 1 cm. Develops quickly (eg 4 weeks) then heals with a scar
  - A 'self healing squamous cell carcinoma'. Inflammatory reaction at the base – body is rejecting it
- Dermatofibroma (= sclerosing haemangioma):
  - Slightly elevated and brown
  - Histology: expands into dermis
  - Not malignant – but recurs if not all cut out

Premalignant

- Actinic keratosis (= Solar Keratosis)
  - In situ proliferation of neoplastic squamous epidermal cells caused by UV light. Often on face, white
  - May spread within the epidermis, stop growing, recede or progress to invasive squamous cell carcinoma
  - Histology: large, irregular nuclei, overgrowth of epidermis, hyperkeratosis and parakeratosis

Malignant

- Basal cell carcinoma:
  - Most common malignant tumour
  - Flat and paler than surrounding skin
  - Often on bridge of nose where glasses sit
  - Don't metastasis but does invade
- Squamous cell carcinoma:
  - If neglected will invade (claw-like infiltration)
  - 4% metastasise
  - On sun exposed areas, may have cutaneous horns
  - Histology: hyperkeratosis

Inflammatory skin lesions

Psoriasis

- Chronic characterised by erythematous scaly plaques
- May be inherited (autosomal dominant with mixed penetrance)
- Associated with trauma, infection, childbirth
- Characterised by rapid turnover of epidermis. Normally 28 days, reduced to 4 days → parakeratosis
- Histology: epidermal squamous cell hyperplasia

- Psoriasis vulgaris:
  - Elbows, knees, scalp
  - Histology: parakeratosis, acanthosis, focal thinning, oedema of dermal papillae, micro-abscesses in the stratum corneum
- Pustular psoriasis:
  - Abscess formation within the epidermal layer → widespread sluffing → risk of infection/electrolyte imbalance
  - Generalised or locaised

Bullous Lesions

- Epidermis sloughs off dermis
- Intraepidermal: if any of the epidermis is left attached
  - Burns
  - Herpes
  - Pemphigus:
    - 40 – 60 years, very fragile blisters on oral and nasal mucosa and skin. 40% mortality
    - Histology: BM is intact, acantholysis
    - Pathogenesis: Autoimmune reaction to desmosomes in the epidermis → infection etc. IgG **above** the basement membrane
- Subepidermal:
  - Pemphigoid Bulli:
    - Smaller, localised blisters, generally rest of skin remains in tact. Usually self-limiting, chronic relapsing, > 60 years
    - Histology: Epidermis lifts in total
    - Pathogenesis: IgE **in** the BM

Eye

Glaucoma

- Usually due to outflow obstruction: damage to the trabecular messwork overlying the channel of schlemm → ↑resistance to flow → ↑ steady state introcular pressure → ↓vascular perfusion of the neural tissue → blindness
- Classification:
  - Primary:
    - Open angle (chronic)
    - Closed angle (acute)
  - Secondary: eg iritis, trauma, blood in the eye, etc

Primary Open-angle Glaucoma

- Epidemiology:
  - Leading cause of preventable blindness
  - Risk factors: age, near-sightedness, African/Asian ancestry, family history, past eye injury, a history of severe anaemia or shock, steroid medication
  - Most common sort, gradual impairment of aqueous drainage, insidious loss of sight
  - 2% over 50 years
  - 1 in 7 risk if primary relative has it
- Presentation:
  - Central field defect – arcurate shape with macular sparing
  - Cupping of the disk due to ischaemic atrophy of the nerve fibre layer
  - Bullous keratopathy – oedema of the cornea
- Screen with tonometry (measuring intra-ocular pressure), test visual fields.
- Is diagnosed by cupping of the optic disk: not by ↑intra-ocular pressure. 17% of people with glaucoma have 'normal' IOP.
- Pathology:
  - ↑Resistance to outflow (pathogenesis not clearly understood) → ↑aqueous humour → ↑intra-ocular pressure (normal is < 22 mmHg)
  - Leads to damage to ganglion nerve cell axon (final output) at the optic nerve head. Due to vascular insufficiency as nerves exit the eye
  - Affects peripheral bundles preferentially: spares papillo-macular bundle
- Treatment: Medication, laser treatment to enlarge the drain (trabeculoplasty)

Primary Angle-closure Glaucoma

- Iris is pushed forward and acutely occludes the trabecular messwork → ↓drainage
- Rare but vision threatening
- Unilateral, acute visual loss, pain, nausea and vomiting, dilated, non-reactive pupil
- Precipitating factors: long sited (narrow anterior chamber, narrow iridocorneal angle), and when pupil dilated for a long time (dim light)
- Can be congenital
- Once resolved, put hole through iris (iridotomy): no further obstruction possible

Secondary Glaucoma

- Secondary open angle glaucoma: Outflow system is obstructed mechanically by debris (ie gunge up trabecular messwork). Rare. Eg Haemolytic glaucoma, lens protein glaucoma
- Secondary closed angle glaucoma: Can be due to neovascularisation 'zipping up' the angle, secondary to ischaemic eyes (eg diabetes, central retinal vein occlusion)

Eye Infections

- Viral Infections:
  - Adenovirus types 8 (epidemic) and 3 and 7 (sporadic). Conjunctivitis with pre-auricular lymph node pherplasia. Over about a week get small white spots (WBC accumulations) just below the surface of the cornea
  - HSV:
    - Gives Herpes Simplex Keratitis.
    - Dendritic ulceration with neovascularisation. Chronic inflammation and scarring. May lead to small white vesicles around the eye.

    - Viewed with fluorescein drops under cobalt light (stains where there is no epithelium)
    - Branching pattern ⇒ Herpes Simplex Virus. Never give steroids: → worse infection → permanent damage
- Bacterial: Usually puss. Always bilateral
    - Trachoma: Due to Chlamydia. Commonest cause of blindness in the tropics. Less common than other causes in NZ. Chronic. Suspect if no response to topical antibiotics. Initially the conjunctival epithelium is infected → scarring of the eye lid → abrasion of cornear → over years get panus (fibrovascular layer) over the cornea
    - Gonorrhoea: ↑pre-auricular nodes

Retinal Vascular Disease

- Damage to large vessels in the eye
- Occlusion of the central retinal artery:
    - Due to athermoa, thrombus, embolis, arteritis
    - Retina is white and totally infracted
- Occlusion of the central retinal vein:
    - Haemorrhagic infarction
    - Collateral supply means some vision is recoverable
    - Retina is a mass of red, veins big and tortuous, cotton wool spots

Focal Ischaemic Retinal Disease

- Affects little vessels
- Features:
    - Cotton wool spots:
        - Fluffy and off-white/yellow
        - Due to micro-infarction → superficial area of necrosis and oedema
        - Axons are disrupted and become distended (cytoid bodies)
        - Resolve in 6 weeks
    - Hard exudates:
        - Discrete, brighter white, often around macula
        - Plasma leaks from damaged capillaries (secondary to thickened basement membrane) in the outer plexiform layer (deeper in the retina) and forms proteinaceous lakes
        - Resolves over several months
    - Haemorrhage: usually arises from microemboli/thrombi damaging vessels
        - Flame: a small arteriole bursts into nerve fibre layer and spreads along nerve fibres
        - Dot: capillary bursts into outer plexiform layer
        - Blot: into the subretinal space
        - Roth's spots: central white infarct surrounded by haemorrhage
    - Microaneurysms:
        - Round or oval dilations of capillaries – look like lots of very little red dots
        - Central in diabetes, peripheral in central retinal vein occlusion
        - Due to reduced numbers of pericytes surrounding capillaries
    - Neovascularisation:
        - Response of the eye to vascular insufficiency, secondary to angiogenesis factors from ischaemia: proliferate around the margin of non-perfusion. Detect with fluorescein angiogram
        - Appears as fine lace work of new vessels. They leak and bleed
        - Sites:
            - Iris surface → neovascular glaucoma, ectropion uvea
            - Pupillary membrane → Posterior Synichiae
            - Vitreal Surface → haemorrhage, pre-retinal fibrovascular membranes → scarring → retinal detachment
            - Easy to see if over optic disk (normally should only be large vessels)
- Differentiating between Hypertensive and diabetic retinopathy:

	Hypertensive Retinopathy	Diabetic Retinopathy
Vessel	Arterioles	Capillaries/veins
Site	Superficial nerve fibre layer	Deep (non-proliferative) Superficial (proliferative)
Pathology	Medial hypertrophy	Pericyte loss BM thickening Microaneurysms

Diabetic Retinopathy

- 1/3 diabetes with > 30 years disease will loose some sight. Diabetics 25 times more likely to go blind
- Risk related to duration ⇒ Type 1 (juvenile onset) more likely to cause damage
- Retinal exam essential:
  - At diagnosis for maturity onset (may have had diabetes for 5 – 10 years)
  - After 5 years for juvenile onset and annually thereafter
  - Fluorescein angiography (injected in arm then photograph retina) to test for neovascularisation
- Causes: Thickened basement membrane of retinal microcirculation → leakage, oedema, nonperfusion and micro-aneurysms
- Macular retinopathy: boggy, leaky macula → blurred vision
- **Non-proliferative retinopathy** (= **Background** Retinopathy): Progression: oedema (→ blurred vision) → microaneurysms → hard exudates → cotton wool spots → small haemorrhages → venous bleeding
- **Proliferative retinopathy**:
  - Neovascularisation
  - Retinal detachment due to shrinkage of subsequent scars
  - Vitreous haemorrhage (can also be due to vitreous collapse tearing at retina or retinal venous occlusion – usually due to ↑BP → expanded artery → compresses adjacent vein)
- Treatment:
  - Regular checks
  - Blood sugar control
  - Treatment of vascular disease (eg ↓BP)
  - Laser treatment (photocoagulation): 2 – 3,000 burns (but NEVER on macula). ↓O2 demand → ↓neovascularisation. Complications: ↓peripheral and night vision, macula oedema
  - Vitrectomy: if non-resolving vitreous haemorrhage or fibrovascular contraction of vitreous (which has risk of → retraction of retina → tear)
  - Retinal repair: reattach retina
- Diabetes can also cause: neovascular glaucoma (blocking flow past lens), more susceptible to damage from ↑IOP, cataract, extraocular muscle palsy

Hypertensive Retinopathy

- Rarely causes visual loss. Requires diastolic BP > 120 for many years
- → Arteriolar constriction: very narrow artery
- → Thickened arterioles (due to medial thickening) compressing underlying veins
- → Flame haemorrhages: spread longitudinally along fibres
- Bilateral and symmetric. More cotton wool spots (nerve fibre hypoxia)
- Retinopathy regresses if hypertension controlled (cf diabetes which doesn't)

Tumours

- Can occur on the iris, ciliary body, choroids

Malignant Melanoma of the Choroid

- Presentation: elderly, usually white, visual loss from retinal detachment or incidental
- Retinal appearance: light to darkly pigmented ovid, elevated mass. Many variants
- 2nd most common site of melanoma after the skin
- Prognosis depends on cell type (Spindle A, Spindle B, Epitheloid or Mixed) and Stage. Overall 50% at 15 years

Retinoblastoma

- Life threatening
- 1:20,000 live births. First few years of life
- Types:
  - 60% sporadic
  - 40% familial (90% bilateral and/or multifocal)
- Presentation: strabismus (squint), 'white' patches on papillary/red reflex (leukocoria), red eye
- Pathogenesis:
  - Due to variety of mutations in the tumour supressor gene RB1 at 13q14 – inactivated a protein which down regulates cell growth

    - Need both alleles to be mutated to cause cancer. Hereditary neuroblastoma = inherit one defective gene from parent, with other allele in one cell undergoing spontaneous mutation. If non-hereditary, need to acquire mutations to both alleles in one cell
- Gross appearance: flat, elevated, diffuse, multicentric pale tumour nodules of plaques
- Microscopic appearance: small round cells with hyperchromatic nuclei, rosettes are characteristic, areas of necrosis and calcification
- Treatment: remove eye
- Complications:
    - Metastasis eg in CNS. From occurrence in eye to spreading down the optic track is ~ 6 months
    - Survivors have a 20% chance of developing malignant tumours at 10 years: osteosarcoma or rhabdomyosarcoma
- Prognosis: 90% 5 year survival (less if optic nerve invasion).

Regulation

Medical Error and Misadventure

- Medical mishap = treatment was properly given but suffered a rare (<1% occurrence) and was severe (ACC definition is in hospital for at least 14 days, in capacitated for 28 or died)
- Medical error = Person treating you did not provide treatment of a reasonable standard.
- Medical misadventure = mishap + error
- Negligence:
  - Do you owe a duty of care
  - Did you fail in that duty (according to standard of a reasonable practitioner)
  - In failing, did the person suffer as a consequence
  - Court decides whether error is negligence
- Types of censure:
  - From Health and Disability Commissioner (mediate, refer to professional body, referral to their director of proceedings)
  - From Medical Council (censure, practice restrictions, struck off, fines)
  - Criminal charges – eg Manslaughter – only if 'major departure' from accepted practice (1997 Crimes Act amendment)

Medical Council

- Protects public by determining competence of and registering doctors
- To be registered must have: acceptable degree, competent in English, no convictions with a possible prison term > 3 months, be mentally and physically fit and not subject to disciplinary proceedings
- Types of registration include: probationary, general, vocational
- Council can review or monitor competence or 'fitness to practice'
- Also has disciplinary process
- Council consists of 4 doctors elected by doctors, 4 people appointed by the Minister, 1 Ministry of Health and 1 Med School Dean.

Certification of Death

- Confirm identity of patient
- Signs of death:
  - No circulation: no carotid pulse or heart sounds over 1 – 3 minutes
  - Absent respiration: no movement or fogging of a mirror
  - Unreactive pupils
  - 'railroading of retinal blood vessels – rows of RBCs settling out
  - Absence of pattern on EEC or ECG
- Signs of brain death (ie on respirator)
  - Fixed dilated pupils
  - No corneal reflex
  - No tracheal reflex (ie tug on ET tube)
  - No eye movements on putting cold water in ear
  - No Cranial nerve response to pain (eg supra-orbital pressure)
  - No respiratory response to hypercapnea
- Problems when deeply unconscious: near drowning, hypothermia, epilepsy, drugs (eg barbiturate poisoning)
- Suspicious injuries on a dead person: bruise, abrasion, laceration, incised wounds (suicide look for tentative cuts, assault look for defence injuries), stab wounds (go deeper than the length of the blade, always check), pattern wounds
- Person certifying death should have no conflict of interest
- Death Certificate:
  - If you've attended a patient must issue a certificate or report to the coroner, if you are 'available'
  - Are now able to sign for eg GP partner if you've reviewed notes and seen body
  - Different form for infants over 20 weeks gestation or > 400 gm and < 28 days old. Can be filled in by midwife
- Other forms:
  - Need an addition form before cremation, which is then cleared by the Medical Referee

    - Certificate of Life Extinct: police form to say the person is dead – eg if being referred to the Coroner. Does not include cause of death. Always take your own careful notes
- Changes following death:
    - Rigidity – 'rigor mortis'. Linking of actin and myacin fibres following ATP depletion. Lasts from 6 – 8 hours after death to about 36 hours.
    - Lividity – bloods seeps downwards – red congestion on downside of body
    - Temperature – indicator of time elapsed since death. Depends on temperature at death, BMI, clothing, etc
    - Decomposition
    - Rough guide to time of death:

Warm	Flaccid	< 3 hours
Warm	Stiff	3 – 8 hours
Cold	Stiff	8 – 36 hours
Cold	Flaccid	> 36 hours

- Homicide:
    - = killing another, either directly or indirectly, or by accelerating death
    - murder = intent to kill or cause serious injury or to facilitate another crime
    - infanticide = death of child under 10 by a mother who has given birth or lactating
    - Can be hard to distinguish murder from suicide or accident in MVA, fire, drowning, or cot death

Coroner

- Has the status of a district court judge
- To initiate a coroners case, report the death to the police (who act as the coroner's investigating agents)
- Must refer a death to the coroner if:
    - No known cause, suicide, unnatural or violent
    - No certificate issued
    - Died undergoing medical, surgical or dental procedure
    - Detained under A&D Act, committed or in prison
    - Child in CYPS or foster care
- Coroner can order an autopsy and/or hold an inquest
- Other court settings: District or High court
    - Expert witness can give an opinion, ordinary witness can only recount facts
    - Don't take sides, be fair, stick to what you know, use notes taken on the occasion (with the permission of the judge)

Sexual health

Vaginal Discharge

- Cervical secretions in women not on the pill, and which change during the cycle, are part of normal discharge. Mucus is clear or clear/white. Some inflammatory cells are normal in the latter half of a cycle
- Desquamating vaginal cells with healthy lactobacilli are major part of normal discharge – pH < 4.5

	Bacterial Vaginosis	**Trichomoniasis**	**Candidiasis**
Prominent symptoms	Discharge odour	Discharge, vulval irritation	Pruritis
Classical signs	No vulvitis or vaginitis	Vulvitis, vaginitis, strawberry cervix	Vulvitis, vaginitis – fissured and sore
Classical discharge	Greyish-white, thin, may be frothy	Green/yellow, watery, pools in posterior fornix, may be frothy	White, flocculent, thrush plaques
Risk factors			Pregnancy, antibiotics, steroids, diabetes
Vaginal pH	pH > 4.5 (often 5.0 – 6.0)	pH > 4.5 (often 6.0 – 7.0)	pH < 4.5 (often 3.0)
KOH test (amine/Whiff test)	Positive	Weakly positive	Negative
Wet mount preparation	Clue cells present (vaginal cells covered by anaerobes & Gardnerella vaginalis). Replacement of lactobacilli with small coccobacilli (Gardnerella) or motile curved rods (Mobilunus). Few pus cells	Trichomonads (motile flagellate), pus cells	Yeast cells (blastospores)
Gram stained smear	Clue cells: G-ive curved rods. G variable coccobacilli.	Pus cells: acridine orange stain	
Notes	Also called Gardnerella. Multiplication of anaerobic bacteria and gardnerella. Associated drop in lactobacilli ↑Risk of prem delivery	Possibly commonest STI worldwide – mainly 3rd world. A Protozoa. Doesn't culture well. Can cause PID, prem delivery. Exclude gonorrhoea	Most common cause of discharge Candida albicans often normally present. Poor immunological control → recurrent candidiasis
Treatment	Anti-anaerobe: oral metronidazole	Oral: doxycycline (remember 7 day rule)	Clotrimazole pessary

Neisseria Gonorrhoea

- Description: G –ive diplococci
- Symptoms:
  - Male: 80% symptomatic. Discharge & dysuria (razor blade pain). 30% also have chlamydia
  - Female: only 20% symptomatic – can have vaginal discharge or pelvic pain. Pick up with opportunistic/selective screening if under 25, multiple partners, changed partner in last 6 months, IUCD, etc
  - Rectal and pharyngeal: often asymptomatic
- Diagnosis: gram stain microscopy if symptomatic or contact, or culture on chocolate agar
- Advice: no sex until minimum of 3 days since treatment completed
- Treatment:
  - Amoxycillin 3 gm and Progenicid 1 gm stat, or
  - Ciprofloxacin 500 mgs (a quinolone) stat if penicillin allergy or if resistant (e.g. acquired overseas). Specialist endorsement required. If resistant to that then Ceftriaxone.
  - Azithromycin will cover gonorrhoea if it is being used to treat concurrent chlamydia
  - Resistance possible
- Contact tracing required. Treat partners

- Test for cure at 14 days (legal requirement)
- Complications: PID

Chlamydia Trachomatis

- Description: obligate intracellular bacteria, STIs are types D – K. Highest in 20 – 24 year age group
- Symptoms:
  - Urethritis, unexplained cystitis, mucopurulent cervicitis, pelvic pain, irregular bleeding
  - 80% of females and 50% of males have no symptoms
  - Often asymptomatic: suspect and test if sexual contacts have it, if patients asks for STI tests, patients under 25 with new/multiple partners
  - Up to 30% associated with concurrent N Gonorrhoea infection
- Diagnosis:
  - Female: swab from affected area, including from endocervix. Rotate 6 – 10 times. Urine test alone not sufficient. Most common site of single infection is cervix (ie urine is clear)
  - Male: urine test
  - New PCR test easier sampling
  - Opportunistic infection has been shown to reduce rates of PID and ectopic pregnancy
- Advice:
  - Abstain until treated – if not use condoms
  - Contact trace
- Treatment:
  - Without test results: Doxycycline 100mgs bd for 7 days (remember 7 day rule for patients on OC)
  - Known positive **and** partners: Azithromycin 1 g stat orally – directly observed treatment
  - In pregnancy: erythromycin ethylsuccinate 800mg qid for 7 days – must be treated to prevent amnionitis and premature rupture of membranes
  - In PID: Doxycycline/erythromycin for 14 days and ornidazole 500 mgs bd for 7 days, plus consider gonorrhoea in which case penicillin/ciprofloxacin in addition
  - Test of cure in 3 weeks if non-compliance or re-infection suspected. Urine test is adequate for males and females
  - Test high risk patients only for cure
  - If reinfection, the ?untreated partner
- Complications:
  - Neonatal: conjuncitivitis, pneumonitis 2 – 4 weeks laters
  - See PID

Suspicion of Abuse or Interpersonal Violence

- It is common and victims are high users of health services
- Epidemiology: 20% of women report sexual abuse before 16, full intercourse reported by 4%. Sexual abuse of boys is about 1/3 as common as for girls.
- Adult women: 25% report sexual abuse, 12% rape
- Men: 5% report sexual abuse, 3% rape (?under-reporting)
- 10 – 16 % of rapes reported to police
- Effects:
  - Acute and long term effects are related to age of victim, extent and duration of abuse, relationship with abuser and response of others
  - Acute effects: numbness, shock, disbelief, anxiety
  - Long-term effects: feelings of helplessness, depression, sleep disturbances, nightmares, flashbacks, guilt, self-blame, shame. Measurable long-term psychiatric sequalae in 25%
- What is patient's age:
  - < 14: all suspected cases should be referred to CYPFS, or if older but abuser still has access to young people.
  - 14 – 17 don't make a decision about what to do on your own $\Rightarrow$ need to put caveats on confidentiality
- History questions (but don't introduce it in a crisis situation)
  - Suspect if physical injuries, chronic undiagnosed pelvic pain, heightened anxiety about an examination, STD's without being worried about health risks
  - They will be reluctant to discuss it
  - Physical: 'have you ever been hit, slapped or shoved by a parent or partner. Ever had bruises or had to stay in bed…

    - Sexual: Did anything sexually frightening happen to you as a child or young adult, have you ever been made to participate in sexual activity that made you feel comfortable. Was it your choice, or were you forced or coerced?
    - Psychological: Does your partner ever ignore you , call you names, make fun of you, threaten to leave you, punish the children when he is angry with you, are you fearful of anyone at the moment?
- Most helpful response is: being believed, being supported, not being blamed, being helped not to feel odd or alone

Rape/Non-Consensual Intercourse

- Rape: = sexual contact without consent (including consent under threat) which involves oral, genital or anal penetration, otherwise unlawful sexual contact
- Therapeutic role:
    - Recognise & treat physical injury
    - Attention to emotional trauma
    - Prevention of pregnancy – offer ECP. Legal requirement under the Contraception, Sterilisation and Abortion Act.
    - Check for infection (NB incubation of chlamydia is 21 days) and offer prophylaxis (but may interfere with ECP – do it after)
    - Referral to support services
    - If not sure about making a police complaint, bring in crisis counselling team
    - Victim compensation – inform re ACC entitlement
- Forensic role:
    - When did it happen: If less than 7 days then may be forensic requirements. If very recent then nil-by-mouth and collect all urine and toilet paper until forensic examination. Ring forensic specialist (DSAC = Doctors for Sexual Abuse Care)
    - Keep detailed records at the time of examination
    - Forensic specialist will do genital exam, blood tests, urine (drug screen), colposcopy (for genital injury), finger nail scrapings, etc and appear as expert witness
- Supportive role:
    - Communicate empathy: 'that sounded really unpleasant for you'
    - 'You are safe now' (don't say if not true)
    - Reinforce 'Its not your fault' – victims blame themselves
- Follow-up at 1 week, 1 month and 3 months (pregnancy, HIV test, Hep B and C, Syphilis)