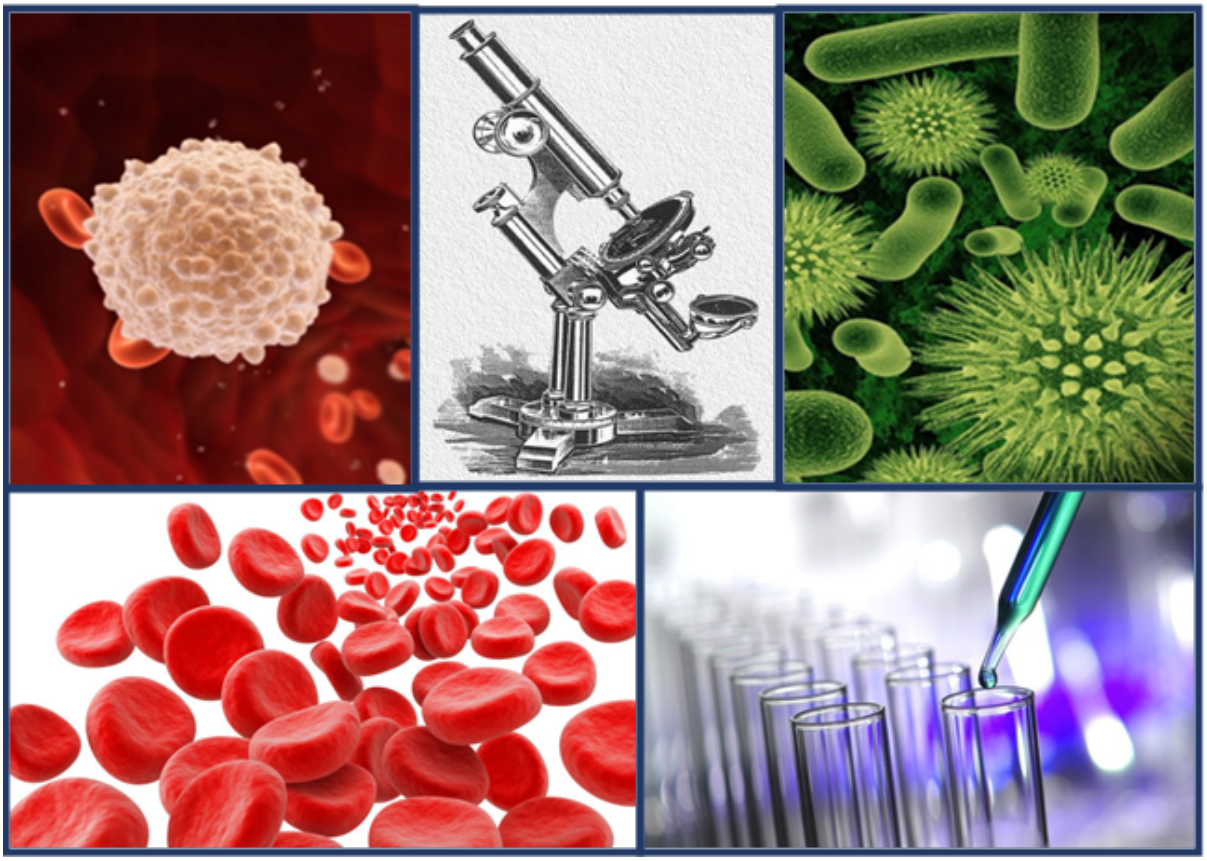
Pathology Course
2022-23



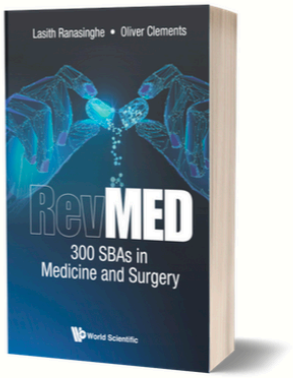
Edited by: **Dr Rishi Banerjee, Dr Jack Stuart, Luke Kostanjek, Dr John Asumang, Dr Nicole James, Dr Jared Bhaskar, Akash Srinavasan, Beccy Thompson, Jonathan Guo, and Tarush Gupta**

Supervised by: **Philip Macanovic, Siddhant Patki and Keir Bhaskar**

FEEDBACK

Pre-exam: https://forms.office.com/e/ahgUwpk2UN
Post-exam: https://forms.office.com/e/vQuUJvHBsM

Get the best out of your revision with our RevMED Series!



RedMED: 300 SBAs in Medicine and Surgery

"Full of classic exam-style SBAs: all you need to get through your exams."

"RevMED was an excellent resource for my revision as I benefit from active learning through SBAs."

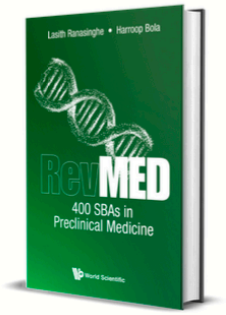
Reviews from previous Year 5 Students

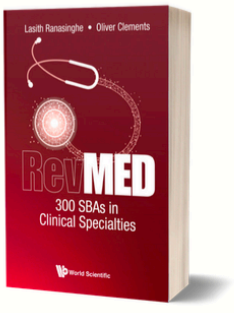
The RevMED series contains questions on a broad variety of topics in general medicine and surgery that covers the basics, but also challenges even the most able students. The explanations include up-to-date guidelines and a thorough exploration of not only the correct answer, but a breakdown of the incorrect options as well. Therefore, each SBA is a form of case-based tutorial that can succinctly communicate a concept in general medicine or surgery.

RevMED is designed by medical students who recently sat clinical written examinations and has been reviewed by doctors/professors thereby assuring clinical accuracy.

Also available:

RevMED: 400 SBAs in Preclinical Medicine
RevMED: 300 SBAs in Clinical Specialties





Scan this QR code to view these titles on amazon:

World Scientific
Connecting Great Minds

Introduction

The Medical Education Society (MedED) was established in 2004 by three students who were keen to develop schemes whereby senior students tutor younger ones - 'peer-to-peer' learning. It was decided that teaching would be outside the formal curriculum and the topics covered would reflect learning needs identified by members of the society and student body.

This year, MedED having been working hard to provide year 5 students with support to cover all aspects of the syllabus. We have coordinated a PACES tutoring scheme, Mock PACES exams, Pathology and Specialties management guides, and a lecture series based the Pathology Specialties modules, which are being delivered by past ICSM students. We hope you enjoy our Year 5 events and find their content useful for your revision.

We would like to thank all the students and doctors involved in the production of this guide for their support and for taking time out of the schedules to come back and teach us.

If you have any questions please contact us at: medical.education@imperial.ac.uk.

Please note: MedED does not represent the ICSM Faculty or Student Union. This guide has been produced by ICSM Students & Alumni, who will also be delivering lectures in the Pathology lecture series. We have made every effort to ensure that the following information is accurate and reliable. However, this guide should not be used to replace formal ICSM teaching and education materials.

With best wishes,

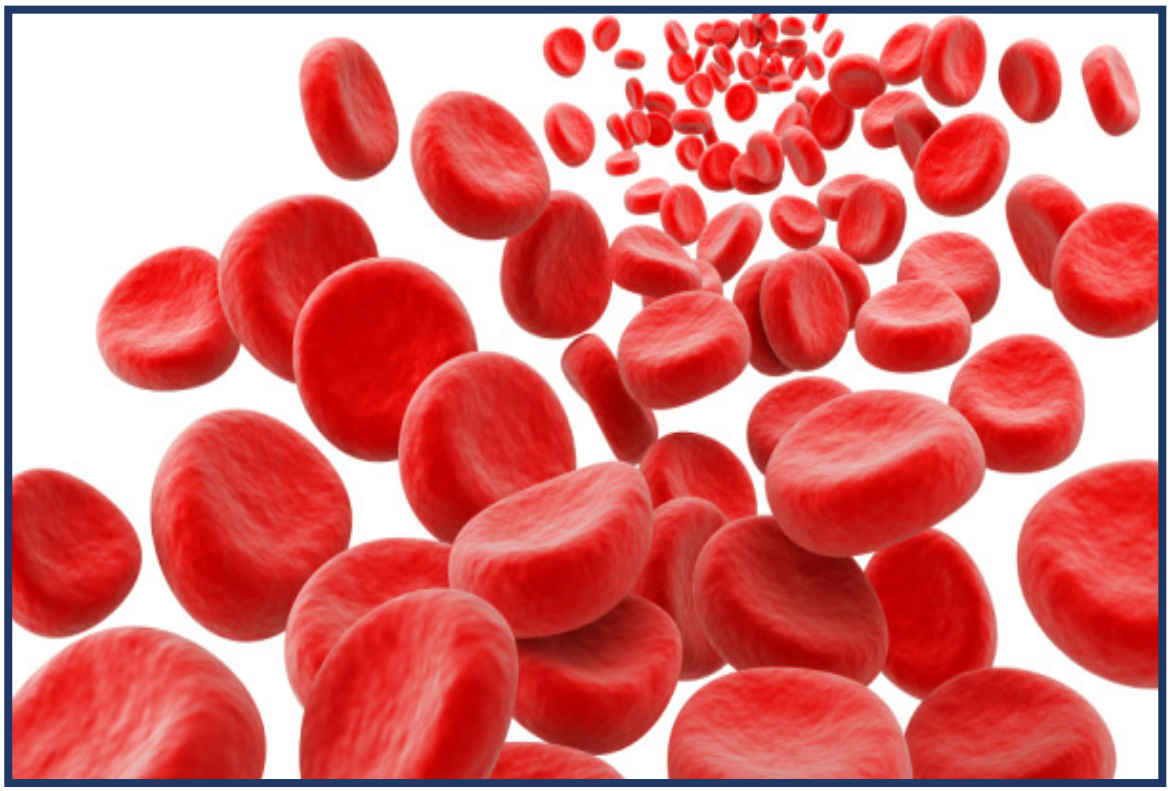
The MedED Team

Contents:

Histopathology Page 163

Jonathan Guo and Tarush Gupta

Haematology



Edited by Dr. Jack Stuart and Dr. Rishi Banerjee

Peripheral Blood Films

Observation	Description	Underlying Condition
Acanthocytes (Spur/spike cells)	RBCs show many spicules	Liver disease, hyposplenism, abetalipoproteinaemia-rare
Basophilic RBC stippling	Accelerated erythropoiesis or defective Hb synthesis, small dots at the periphery are seen (rRNA)	Lead poisoning, megaloblastic anaemia, myelodysplasia, liver disease, haemoglobinopathy e.g. thalassaemia
Burr cells (Echinocyte)	Like a sea urchin with regular spicules	Often artefact if blood has sat in EDTA prior to film being made. Uraemia, renal failure, GI bleeding, stomach carcinoma
Heinz bodies	Inclusions on very edge of RBCs due to denatured Hb	Glucose-6-phosphate dehydrogenase deficiency, chronic liver disease
Howell-Jolly bodies	Basophilic (purple spot) nuclear remnants in RBCs [Note: much bigger purple spots in *nucleated* RBCs)	Post-splenectomy or hyposplenism (e.g. sickle cell disease, coeliac disease, congenital, UC/Crohn's, myeloproliferative disease, amyloid) Megaloblastic anaemia, hereditary spherocytosis
Leucoerythroblastic	A phrase to denote the presence of nucleated red blood cells **and** myeloid precursors in peripheral blood	Marrow infiltration i.e. myelofibrosis, malignancy
Pelger Huet Cells	Hyposegmented neutrophil with 2 lobes like a dumbbell Pseudo-pelger huet cells are also hypogranular	Congenital (lamin B Receptor mutation) Acquired (myelogenous leukaemia and myelodysplastic syndromes [*pseudo-pelger* in MDS])
Polychromasia	Bluish red blood cells due to presence of DNA. Polychromatic cells are usually *reticulocytes* which are immature RBCs	Usually increased naturally in response to shortened RBC life ↑in haemolytic anaemias ↓aplastic anaemia, chemo
Right shift	Hypermature white cells - hypersegmented polymorphs (>5 lobes to nucleus)	Megaloblastic anaemia, uraemia, liver disease
Rouleaux formation	Red cells stacked on each other	Chronic inflammation, paraproteinaemia, myeloma
Schistocytes	Fragmented parts of RBCs – typically irregularly shaped with sharp edges and no central pallor	Microangiopathic anaemia, e.g. DIC, haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura, pre-eclampsia
Spherocytes	Sphere shaped RBC Often a little smaller	Hereditary spherocytosis, Autoimmune Haemolytic Anaemia
Stomatocytes	Central pallor is straight or curved rod-like shape. RBCs appear as 'smiling faces' or 'fish mouth'	Can be artefact during slide preparation. If not: Hereditary stomatocytosis, high alcohol intake, liver disease

Target cells (codocyte)	Bull's-eye appearance in central pallor	Liver disease, hyposplenism, thalassaemia, IDA

Anaemia

Hb: Men: **<135 g/L (13.5g/dL)**, Women: **< 115g/L (11.5g/dL)**

(Note: there is a growing argument that women should be labelled anaemic based on male reference ranges, as a lot of women with Hb 115-135 will actually have iron deficiency)

Causes: *reduced* ***production*** of RBCs or *increased* ***loss*** of RBCs (haemolytic anaemias) or *increased plasma* ***volume*** (pregnancy).

Symptoms: fatigue, dyspnoea, faintness, palpitations, headache, tinnitus, anorexia.

Signs: pallor, in severe anaemia (Hb < 80g/L) → hyperdynamic circulation e.g. tachycardia, flow murmurs (ejection-systolic loudest over apex) → heart failure.

High MCV often means there is decreased production of RBCs – e.g. folate and b12 are needed for cell production.

Low MCV often means there is a normal number of RBCs (but not always) but there is not much to go in them. E.g. iron deficiency, thalassaemia

Low MCV (microcytic anaemia) (FAST)	Normal MCV (normocytic anaemia)	High MCV (macrocytic anaemia) (FATRBC)
Iron-deficiency anaemia	Acute blood loss	Fetus (pregnancy)
Anaemia of chronic disease	Anaemia of chronic disease	Antifolates (e.g. phenytoin)
Sideroblastic anaemia	Bone marrow failure	Thyroid (hypothyroidism)
Thalassaemia (may not be anaemic if mild)	Renal failure	Reticulocytosis (release of larger immature cells e.g. with haemolysis)
	Hypothyroidism	B12 or folate deficiency
	Haemolysis	Cirrhosis (Alcohol excess or liver disease)
	Pregnancy	Myelodysplastic syndromes

Iron-Deficiency Anaemia (IDA)

Signs: Koilonychia, atrophic glossitis, angular cheilosis, post-cricoid webs (Plummer-Vinson syndrome), brittle hair and nails.

Blood film: Microcytic, hypochromic, anisocytosis (varying size), poikilocytosis (shape) pencil cells.

Causes: Bleeding until proven otherwise - Menorrhagia in young women

Classification	Causes	Discussion
Blood Loss	Gastrointestinal loss	Meckel's diverticulum (older children) Peptic ulcers / Gastritis (chronic NSAID use) Polyps/colorectal Ca (most common cause in adults >50yrs) Menorrhagia (women <50 yrs) Hookworm infestation (developing countries)
Increased utilisation	Pregnancy/lactation Infants/children - growth	
Decreased Intake	Prematurity Infants/children/elderly	Loss of Fe each day fetus is not in utero Suboptimal diet
Decreased absorption	Coeliac Post-gastric surgery	Absence in villous surface in duodenum Rapid transit, ↓ acid which helps Fe absorption
Intravascular haemolysis	Microangiopathic Haemolytic anaemia PNH	Chronic loss of Hb in urine → Fe deficiency

2013 NICE guidelines for Iron deficiency anaemia: if no obvious cause then patients should have OGD + colonoscopy, urine dip, coeliac investigations.

Treatment: Treat the cause.
Oral iron (SE: nausea, abdominal discomfort, diarrhea/constipation, black stools).
Giving oral iron on alternate days has been shown to be almost as quick at improving anaemia and has less toxicity
IV iron such as Ferrinject / Monofer (anaphylaxis risk)
Indications: poor oral absorption, failure of oral iron trial, or need for rapid rise (e.g. imminent major surgery)
Note: in sepsis and severe infection, iron will not absorb well and can fuel sepsis. Blood transfusions are better in this scenario.

Anaemia of Chronic Disease

Cytokine driven inhibition of red cell production

Causes:
- Chronic infection (e.g. TB, osteomyelitis)
- Vasculitis
- Rheumatoid arthritis
- Malignancy etc.

Ferritin (intracellular protein, iron store) is high in ACD: Fe sequestered in macrophage to deprive invading bacteria of Fe (unless the patient has co-existing iron deficiency anaemia)

In renal failure: not cytokine driven but due to Erythropoietin (EPO) deficiency (EPO made by kindey).

- Inflammatory markers like IFNs, TNF and IL1 reduce EPO receptor production (and thus EPO synthesis) by kidneys.

- Iron metabolism is dysregulated. IL6 and LPS stimulate the liver to make hepcidin, which decreases iron absorption from gut (by inhibiting transferrin) and also causes iron accumulation in macrophages.

Sideroblastic Anaemia

Ineffective erythropoiesis → iron loading (bone marrow) causing haemosiderosis (endocrine, liver and cardiac damage due to iron deposition)

Diagnosis: Ring sideroblasts seen in the marrow (erythroid precursors with iron deposited in mitochondria in a ring around the nucleus).

Causes: myelodysplastic disorders, following chemotherapy, irradiation, alcohol excess, lead excess, anti-TB drugs or myeloproliferative disease.

Treatment: Remove the cause and consider Pyridoxine (vitamin B6 promotes RBC production). Consider giving EPO.

Interpretation of Plasma Iron Studies

Disease	Iron	TIBC	Ferritin
Iron deficiency	↓	↑	↓
Anaemia of chronic disease	↓	↓	↑
Chronic haemolysis	↑	↓	↑
Haemochromatosis	↑	↓ (or N)	↑
Pregnancy	↑	↑	N
Sideroblastic anaemia	↑	N	↑
			TIBC = total iron binding capacity

NB1: Transferrin saturations are also a good way of measuring iron status. Transferrin saturation = serum iron / TIBC. If <20% then that indicates iron deficiency.

NB2: Ferritin is an acute phase protein and ↑ with inflammation e.g. infection, malignancy Check CRP with every ferritin you send in clinical practice. If there is an inflammatory state, transferrin saturations are more useful

Pancytopenia investigation

Examination for splenomegaly – associated with myelofibrosis and lymphoproliferatives disorders

Suggested investigation of pancytopenia:

- B12/Folate/Iron (note: iron deficiency alone shouldn't cause pancytopenia)
- Abdominal examination to assess for spleen (suggestive of myelofibrosis)
- Reticulocyte count
    - If low, implies bone marrow is not responding appropriately which could imply bone marrow failure such as in **aplastic anaemia** / bone marrow failure syndromes
- Blood film
    - To look for **abnormal cells** (eg. blasts): While acute leukaemia often presents with high white counts it can present with low counts
    - Rare haematological malignancies such as hairy cell leukaemia, LGL leukaemia, can also cause pancytopenia
    - To look for **dysplasia:** dysplastic changes (see MDS section) are suggestive of myelodysplasia which can present with pancytopenia
- **Myeloma screen**: if it has infiltrated the bone marrow this could cause pancytopenia
- Parvovirus can also cause pancytopenia in immunosuppressed patients and can be tested by blood PCR
- Some medications can cause pancytopenia
- Unless there is a clear cause on above tests, patients are likely to require a bone marrow biopsy to diagnose

Macrocytic Anaemia

Causes of macrocytosis:

- Megaloblastic: B_{12} deficiency, folate deficiency, cytotoxic drugs.
- Non-megaloblastic: Alcohol (most common cause of macrocytosis without anaemia), reticulocytosis (e.g. in haemolysis), liver disease, hypothyroidism, and pregnancy.
- Other haematological disease: Myelodysplasia, myeloma, myeloproliferative disorders, aplastic anaemia.

Megaloblastic blood film = Hypersegmented polymorphs, leucopenia, macrocytosis, anaemia, thrombocytopenia with megaloblasts. Megaloblasts are red cell precursors with an immature nucleus and mature cytoplasm. B12 and folate are required for nucleus maturation.

Vitamin B_{12}

Source: Meat and dairy products (we have large body stores)
Causes of deficiency:

- Dietary (e.g. vegans)
- Malabsorption:
    - Stomach (lack of intrinsic factor which is produced by gastric parietal cells) → Pernicious anaemia, post gastrectomy
    - Terminal ileum (absorption) due to ileal resection, Crohn's disease, bacterial overgrowth, tropical sprue and tapeworms.

Clinical Features:

- Mouth: Glossitis, angular cheilosis
- Neuropsychiatric: Irritability, depression, psychosis, dementia.
- Neurological: Paraesthesiae, peripheral neuropathy (loss of vibration and proprioception first, absent ankle reflex, spastic paraperesis, *subacute combined degeneration of spinal cord*)

Pernicious anaemia:

- Autoimmune atrophic gastritis → achlorhydria and lack of gastric intrinsic factor
- Most common cause of a macrocytic anaemia in Western countries (Usually >40yrs)
- Specific tests: Parietal cell antibodies (90%), Intrinsic factor antibodies (50%), Schilling test (outdated)

Treatment: Replenish stores with IM hydroxocobalamin (B12) with 6 injections over 2 weeks.
NICE recommend testing for anti-parietal cell / anti-intrinsic factor antibodies as if there is an autoimmune cause rather than dietary, patients will need 3-monthly IM injections

Folate

Source: DIET - green vegetables, nuts, yeast & liver, synthesized by gut bacteria (low body stores, cannot produce de novo)

Causes of deficiency:

- Poor diet
- Increased demand: pregnancy or ↑ cell turnover (haemolysis, malignancy, inflammatory disease and renal dialysis).
- Malabsorption: coeliac disease, tropical sprue.
- Drugs: alcohol, anti-epileptics (phenytoin), methotrexate, trimethoprim.

Treatment: Give oral folic acid. Ensure B12 is checked and replaced prior to folic acid otherwise folic acid may exacerbate the neuropathy of B12 deficiency

Haemolytic Anaemias

Breakdown of RBCs, before their normal life span of ~120 days.

All Haemolytic Anaemias	Intravascular	Extravascular
↑bilirubin (unconjugated)	↑ free plasma Hb	Splenomegaly
↑urobilinogen	↓haptoglobin (binds free Hb)	
↑LDH	Haemoglobinuria (dark red urine)	
Reticulocytosis (↑ MCV and polychromasia)	Methaemalbuminaemia (Haem + albumin in blood)	
May have pigmented gallstones		

Erythroid hyperplasia states – susceptible to parvovirus B19 (aplastic crisis), iron overload, osteoporosis.

Reticulocyte count: if the patient is acutely anaemic, you would expect a high reticulocyte count as this means the bone marrow is responding and working harder to produce more red cells.

Causes:

Inherited		Acquired	
Membrane Defect	Hereditary spherocytosis	**Immune**	Autoimmune – warm or cold
	Hereditary elliptocytosis		Alloimmune – haemolytic transfusion reactions
Enzyme Defect	G6PD deficiency		
	Pyruvate kinase deficiency	**Non-immune**	Mechanical e.g, metal valves, trauma
Haemoglobinopathies	Sickle Cell Disease		PNH, MAHA
	Thalassaemias		Infections (i.e. Malaria), Drugs

Inherited Haemolytic Anaemias

Membrane Defects

Hereditary Spherocytosis

- Autosomal dominant - FHx to aid diagnosis (25% recessive or de novo!)
- Spectrin or ankyrin deficiency (membrane proteins)
- Susceptibility to effect of parvovirus B19 and often develop gallstones
- Extravascular haemolysis - splenomegaly

Diagnosis: spherocytes, ↑osmotic fragility (lysis in hypotonic solutions), [-ve DAT (Coombs) – not autoimmune Ab mediated], flow cytometry (EMA binding test)
Treatment: Folic acid, some require splenectomy

Hereditary Elliptocytosis

- Almost all forms are autosomal dominant – spectrin mutations
    - Except for Hereditary Pyropoikilocytosis (erythrocytes are abnormally sensitivity to heat) – autosomal recessive (small print)
- Mostly asymptomatic but some forms can be more severe
- Erythrocytes are elliptical in shape on blood film

South East Asian Ovalocytosis (lecture small print):

- Recessive – heterozygous +/- malaria protection

Enzyme Defects

Glucose-6-phosphate dehydrogenase (G6PD) Deficiency

- Commonest RBC enzyme defect – X linked
- Prevalent in areas of malarial endemicity i.e. African, Mediterranean and Middle Eastern populations
- Attacks - rapid anaemia and jaundice, with bite cells and Heinz bodies (blue deposits, oxidized Hb).
- Precipitated by oxidants as G6PD helps RBCs make glutathione which protects them from oxidant damage - drugs (usually 2-3 days after starting) (e.g. primaquine, sulfonamides, aspirin), broad beans (within 1 day of eating)(favism), acute stressors, moth balls, acute infection
- Intravascular haemolysis: dark urine

Diagnosis: Enzyme assay ~2- 3 months after a crisis: young RBCs may have sufficient enzyme so results may appear normal
Treatment: Avoid precipitants; transfuse if severe, genetic screening (rare subtypes give chronic haemolysis for which splenectomy can be needed)

Pyruvate Kinase Deficiency

- Autosomal recessive (but autosomal dominant has been observed with the disorder)
- Clinical features: can be severe neonatal jaundice, splenomegaly, haemolytic anaemia

Treatment: most do not require treatment (can incl blood transfusion or splenectomy)

Haemoglobinopathies

Haemoglobin - physiology

Normal Haemoglobin is comprised of 4 globins and heme
The 4 globins arrange around the heme molecule in 2 pairs

Normally we have 4 alpha globin genes (2 from each parent)
Normally we have 2 beta globin genes (1 from each parent)

The types of globin pairs used determine the type of haemoglobin:

- 2 alpha and 2 beta globins produce HbA (95% of normal haemoglobin)
- 2 alpha and 2 gamma globins produce HbA2 (<3% of normal haemoglobin)
- 2 alpha and 2 delta globins produce HbF (<1% of adult haeoglobin, but more common in babies under 6 months)

The mutations in sickle cell disease and beta thalassaemia affect the beta globin genes
The mutations in alpha thalassaemia / HbH disease are deletions of the alpha globin genes

Haemoglobinopathies: Sickle Cell Disease

- Umbrella term – states associated with pathological effect of sickling
- Autosomal recessive
- Single base mutation; GAG → GTG. Glu → Val at codon 6 of β chain → causes HbS instead of HbA.

Sickle cell anaemia - Hb SS - severe
Sickle cell trait HbAS – usually asymptomatic except under stress (e.g cold, exercise)

Rarer forms:

- *Sickle-haemoglobin C disease* – HbSC: one HbS inherited from one parent, and one HbC (defective b chain) inherited from the other
    - Usually slightly milder than HbSS but not always

- *Sickle* β *thalassaemia* – HbS/β: one HbS from one parent, β thalassaemia trait/ β0 from other. Sickle β0 similar in severity to HbSS

- Sickle cell anaemia manifests at 3-6mths (coincides with decreasing fetal Hb (HbF))
- ↓O2 tension -> HbS polymerisation -> sickling

Important features:

Haemolysis	Vaso-occlusion + infarction (SICKLED)
Anaemia 60-80g/L	Stroke
Splenomegaly	Infections (hyposplenism, CKD)
Folate deficiency	Crises (splenic, sequestration, chest and pain)
Gallstones	Kidney (papillary necrosis, nephrotic
Aplastic crises (Parvovirus B19)	Liver (gallstones)
	Eyes (retinopathy)
	Dactilitis (impaired growth)
	Mesenteric ischaemia
	Priapism

Age of Onset:
- Child – strokes, splenomegaly + splenic crises, dactylitis
- Teens – impaired growth, gallstones, psych, priapism
- Adult – hyposplenism, CKD, retinopathy, pulmonary hypertension, iron overload from transfusions

Diagnosis: sickle cells and target cells on blood film, sickle solubility test, Hb electrophoresis, Guthrie test (birth) to aid prompt pneumococcal prophylaxis (+FHx)

Treatment*:*
Acute:
- Opioid analgesia for painful crises
- Blood transfusion (usually an *exchange* transfusion) in severe crises, particularly in chest crises
    - *Top up* transfusions usually cause more harm than good as they can increase sickling; unless Hb is very low i.e <60

Chronic:
- all should be on:
    - Penicillin V, pneumovax, HIB vaccine, folic acid
- Some benefit from:
    - Hydroxycarbamide (increases HbF %). Shown to reduce crises and prevent organ damage e.g. kidney, heart
    - Regular exchange blood transfusions
        - Used in patients who have had a stroke, recurrent chest crisis, and other indications
    - Carotid Doppler monitoring in early childhood with prophylactic exchange transfusion if turbulent carotid flow.
    - Crizanlizumab – recently approved by NICE for sickle cell. Reduces painful crises.
    - Voxelotor: increases haemoglobin. Currently used infrequently.
    - Allogeneic stem cell transplant (not funded in the UK in adults but done in other countries or considered in children with good sibling donors)

Haemoglobinopathies: Thalassaemia

Unbalanced Hb synthesis→ unmatched globins precipitate→ haemolysis and ineffective erthyropoiesis

β Thalassaemia:

- Point mutations – ↓ β-chain synthesis (spectrum of disease), excess α-chains
- ↑HbA2 and HbF
- Skull bossing, maxillary hypertrophy, hairs on end skull X-ray
- Hepatosplenomegaly
- Phenotypes (genotypes) – there is varying severity.
    - *B_0 – no expression of the gene*
    - *B_+– some expression of the gene*
    - *B – normal gene*
  - *β- thalassaemia minor (e.g. β_+/β_+ or β_0/β_+)* → Asymptomatic carrier, mild anaemia
  - *β- thalassaemia intermedia* (e.g. *or β_+/β or β_0/β*)→ Moderate anaemia, splenomegaly, bony deformity, gallstones
  - *β- thalassaemia major (β_0/β_0)* → 3-6mths severe anaemia, FTT, hepatosplenomegaly (extramedullary erythropoiesis), bony deformity, severe anaemia + heart failure

Diagnosis: Hb electrophoresis (Guthrie test at birth)
Treatment:

- Minor and some intermedia forms may not need regular treatment
- Blood transfusions with iron chelation to stop iron overload, plus folic acid
- Regular screening for iron overload in heart and liver

α- Thalassaemia:

- Deletions - reduced α-chain synthesis, excess β-chains
- 4 α genes, severity depends on number deleted
  - *α- thalassaemia trait (1/2 deleted)* → Asymptomatic, mild anaemia
  - *HbH disease (3 deleted)* → Moderate anaemia, splenomegaly
  - *Hydrops Foetalis (4 deleted)* → Incompatible with life

Acquired Haemolytic Anaemias

Autoimmune

+ve Direct antiglobulin test (DAT) (Coombs positive)

	Warm (WAIHA)– most common	Cold Agglutinin Disease
Features	37°C	<37°C
	Ig**G**	Ig**M**
	Positive Coombs test	Positive Coombs test
	Blood film - spherocytes	Often with Raynaud's
Causes	Mainly primary idiopathic	Primary idiopathic
	Lymphoma, CLL, SLE, methyldopa	Lymphoma, Infections: EBV, mycoplasma
Management	Steroids	Treat underlying condition
	Splenectomy	Avoid the cold
	Immunosuppression	Chemotherapy if lymphoma

Paroxysmal Cold Haemoglobinuria (PCH):
Heamoglobin in the urine usually caused by a viral infection eg: measles, syphilis, VZV

Donath-Landsteiner antibodies → stick to RBCs in cold → complement-mediated haemolysis on rewarming (self-limiting as IgG so dissociate at higher temp than IgM).

Non-Immune (Coombs Negative)

Note: non-immune is a simplified term for classification. Some of these processes involve abnormalities of the immune system!

Paroxysmal Nocturnal Haemoglobinuria (very rare)

- Acquired loss of protective surface GPI markers on RBCs (platelets + neutrophils) → complement-mediated lysis → chronic intravascular haemolysis especially at night.
- Morning haemoglobinuria, thrombosis (+Budd- Chiari syndrome – hepatic v thromb).
- Diagnosis: immunophenotype shows altered GPI or Ham's test (in vitro acid-induced lysis).
- Treatment: iron/folate supplements, prophylactic vaccines/antibiotics. Expensive monoclonal antibodies (eculizumab) that prevents complement from binding RBCs

Microangiopathic Haemolytic Anaemia (MAHA)

Microangiopathic haemolytic anaemia (MAHA) – mechanical RBC destruction (forced through fibrin/plt mesh in damaged vessels) → schistocytes
Causes: HUS, TTP, DIC, pre-eclampsia, eclampsia. Rx – usually plasma exchange

TTP: *Thrombotic thrombocytopenic purpura*

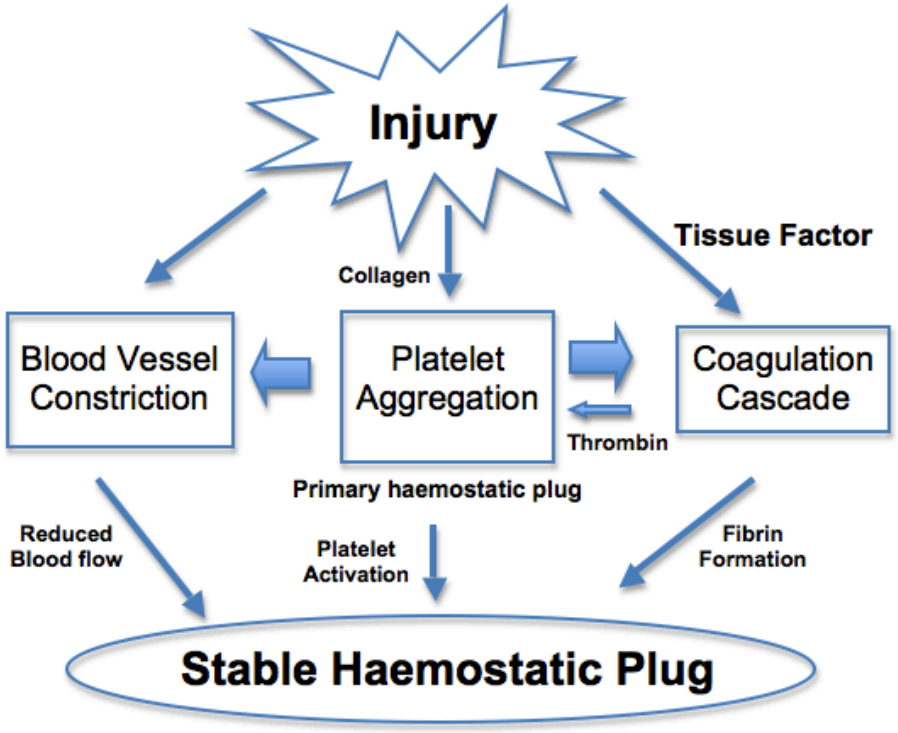
- **Auto Immune –** *antibodies against ADAMTS13 lead to long strands of VWF which act like cheese wire in the blood vessels, cutting up RBCs.*
- ***Pentad of symptoms:*** *MAHA, fever,* renal impairment (less pronounced than HUS), neuro abnormalities, thrombocytopenia
- *TTP is a haematological emergency requiring emergency plasma exchange*

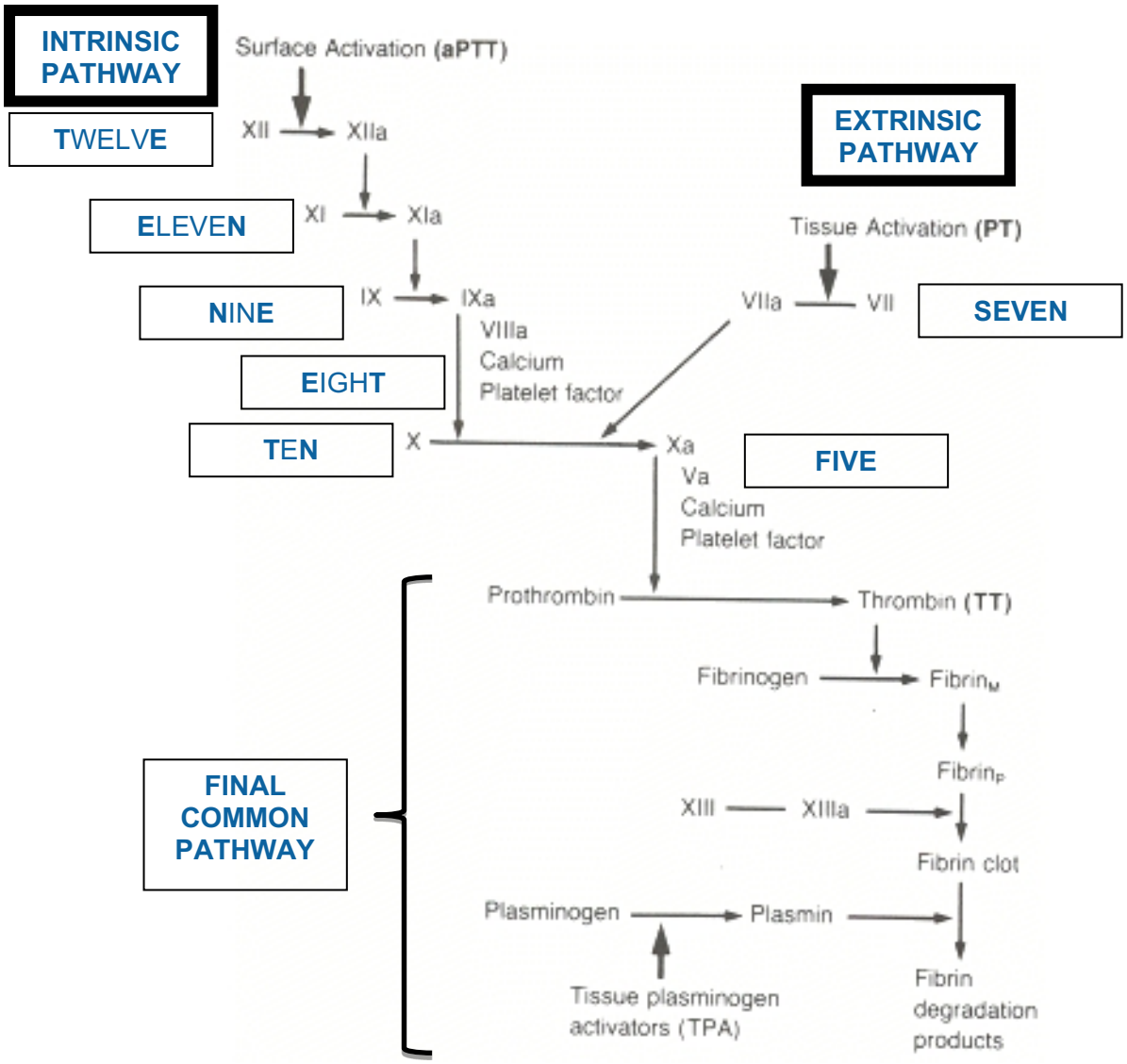
HUS: Haemolytic uraemic syndrome

- Caused by E. Coli: toxin damages endothelial cells, forms fibrin mesh and damages RBCs + impaired renal function + microangiopathic haemolytic anaemia.
- Diarrhoea, renal failure, no neuro problems, children and elderly.

Haemostasis

Coagulation Cascade





Phases: Initiation → Amplification → Propagation and thrombin burst → Stable clot

Other Key Players - Inhibitors: Tissue factor pathway inhibitor (TFPI), Protein C, S, Antithrombin III.

Intrinsic Pathway:
Activated partial thromboplastin time (**APTT**): Monitor heparin therapy.
Starts with factor **TWELVE**.

Remember the next factor starts with the last letter of the previous factor!

Extrinsic Pathway:
Prothrombin time (**PT**) - Monitor warfarin therapy (INR).
Starts with factor **SEVEN.**

Common Pathway:
Thrombin time **(TT**).
Starts with activated factor **FIVE.**

Bleeding Disorders

There are two approaches to bleeding disorders:

1. The bleeding patient:
    a. Many bleeding disorders can have normal initial laboratory tests
    b. If someone has a significant bleeding history on a validated questionnaire this needs careful assessment
2. Abnormal bleeding tests:
    a. Many bleeding test abnormalities have very little clinical significance without a history of bleeding
    b. But if a patient does have a history of bleeding or are due to have a procedure these need appropriate investigation

Includes: Vascular defects (easy bruising), platelet disorders (low or abnormal function), coagulation disorders (factor deficiency) or mixed (DIC).

Vascular defects, platelet disorders	Coagulation disorders
Superficial bleeding into skin, mucosal membranes	Bleeding into deep tissues, muscles, joints
	Delayed, but severe bleeding after injury
Bleeding immediate after injury	Bleeding often prolonged

Vascular Defects

1. **Congenital***:* Osler-Weber-Rendu syndrome, connective tissue disease (e.g. Ehlers-Danlos syndrome)
2. **Acquired***:* Senile purpura, infection (e.g. meningococcal, measles, dengue fever), steroids, scurvy (perifollicular haemorrhages)

Platelet Disorders

Causes		
↓Platelet function	Acquired	Aspirin, Cardiopulmonary bypass
		Uraemia
	Congenital	Storage pool disease
		Thrombasthenia (glycoprotein deficiency)
Thrombocytopenia (norm plt count 150-400x10^9 g/l)	↓production	Bone marrow failure
	↑destruction	Auto-Immume Thrombocytopenic Purpura (AITP) – formally idiopathic (ITP)
		Drugs e.g. heparin, DIC, HUS, TTP

Features	Acute ITP	Chronic ITP
Peak age	Children (2-6 yrs)	Adults
F:M	1:1	3:1
Preceding infection	Common	Rare
Onset of symptoms	Abrupt	Abrupt - indolent
Plt count at presentation	<20,000	<50,000
Duration	2 - 6 weeks	Long-term with acute flares (associated with autoimmune disease, CLL, HIV, hepatitis)
Spontaneous remission	Common, usually self lim.	Uncommon (Rx: IVIg, steroids, immune suppression, TPO agonists, splenectomy)

Coagulation Disorders: Inherited

Haemophilia A
- Factor VIII deficiency
- X-linked recessive affecting 1/10,000 males
- *Presentation:* often early in life or prolonged bleeding after surgery/trauma
- **Diagnosis:** ↑APTT, normal PT and ↓ factor VIII assay.
- **Severity:** related to factor level eg. severe <1%, moderate 1-5%, mild 5-25%
- **Management:** Avoid NSAIDs and IM injections, prophylaxis with factor VIII in more severe cases or treatment only for bleeds in milder cases
- Note: Can also be acquired – rare autoimmune condition treated with immune suppression.

Haemophilia B (Christmas disease)
- Factor IX deficiency
- X-linked recessive affecting 1/50,000 males
- Clinically like haemophilia A.
- **Management:** Factor IX concentrates either as prophylaxis or just for bleeds

Von Willebrand's Disease
- Several types – quantitative (deficiency) vs. qualitative
  - Variable phenotype from complete deficiency to asymptomatic mild deficiency
  - Type 1: low levels of VWF
  - Type 2: deficiency in function of VWF compared to level (mutations causing poor function)
  - Type 3: Absent VWF – can present like haemophilia
- ↓ platelet function and ↓ factor VIII (vWF carries factor VIII in circulation)
- Mostly autosomal affecting 1/10,000
- *Presentation:* often bleeding indicative of platelet disorders (i.e. mucocutaneous bleeding) but can also include bleeding indicative of coagulation disorders
- **Diagnosis:**
  - Note can be complicated to diagnose particularly type 2– would need haematology input!
  - ↑ APTT, normal PT/INR **(but both APTT + INR may be completely normal**)
  - ↓ Factor VIII,
  - ↓ vWF Ag (or normal Antigen level with reduced function in type 2)
  - Normal platelet count
- **Management:**
  - Prophylaxis indicated in some patients
  - Treatment of bleeds: Tranexamic acid, Desmopressin (some patients respond), combined VWF and Factor VIII concentrates

Coagulation Disorders: Acquired

Disseminated intravascular coagulation (DIC)
- Widespread activation of coagulation
- Clotting factors and platelets are consumed → ↑ risk of bleeding
- Causes: Malignancy, sepsis, trauma, obstetric complications, toxins.
- Low plts, low fibrinogen, high FDP/D-Dimer, long PT/INR.
- Treat the cause and give transfusions, FFP, platelets, cryo etc.

Liver Disease
- ↓ synthesis of II, V, VII, IX, X, XI and fibrinogen

- High levels of VIII / VWF
- ↓ absorption of vitamin K
- Abnormalities of platelet function
- Note that chronic liver disease is often a having prolonged INR/APTT

Buses that go down High St Ken! (27, 9 and 10)

prothrombotic state despite

Vitamin K Deficiency

- Vit K needed for synthesis of Factors II, VII, IX and X
- **And** Protein C/S (this is why warfarin may be pro-coagulant initially)
- Causes: Warfarin, vitamin K malabsorption/malnutrition, Abx therapy, biliary obstruction
- **Treatment:** IV vitamin K or FFP for acute haemorrhage

Disorder	INR	APTT	Thrombin time	Platelet count	Bleeding time	
Heparin	-	--	--	«	«	
DIC	--	--	-	-	-	-D-d
Liver disease	-	-	«/-	«/¯	«/-	-AST
Platelet defect	«	«	«	«	-	
Vit K def	-	-	«	«	«	
Haemophilia	«	-	«	«	«	
Von Willebrand's	«	--	«	«	-	

Venous Thrombosis

Risk factors: remember Virchow's triad = vessel wall, blood and flow

"2-level" Wells score:

https://www.mdcalc.com/wells-criteria-dvt

https://www.mdcalc.com/wells-criteria-pe

- High Wells score – Ultrasound affected limb for DVT / CTPA for PE
- Intermediate Wells score – D-DIMER: if high, ultrasound/CTPA; if low, rule out
- Low Wells score – consider other diagnosis

Inherited	Acquired
Antithrombin deficiency	Age, Obesity
Protein C deficiency	Previous DVT or PE
Protein S deficiency	Immobilisation
Factor V Leiden – 5% caucasian pop, resistance to protein C	Major surgery – esp ortho, >30 mins, plaster cast immobilsation
Prothrombin G20210A	Long distance travel
Lupus anticoagulant	Malignancy - esp pancreas.10% idiopathic VTE due to Ca
Coag excess – VIII (10%), II (2%), fibrinogen	Pregnancy, COCP, HRT

	Antiphospholipid syndrome
	Polycythaemia
	Thrombocythaemia

Prevention and Treatment of VTE

DVT prophylaxis:

- Daily subcutaneous LMWH (prophylactic dose), TED stockings
- Note: Some DOACs are now licensed for DVT prophylaxis e.g. in post-op ortho patients

Treatment of DVT/PE:

- LMWH (treatment dose) followed by Warfarin or Apixaban/Rivaroxaban/Edoxaban (DOACs)
  - LMWH stopped once INR in therapeutic range (2-3) (with some DOACs LMWH can be stopped immediately)
    - Reason for continuing LMWH while warfarin started: Warfarin also affects protein C/S and often leads to procoagulant state in the first few days before anticoagulant effect

Duration of treatment:

- 3 months minimum
- For clearly provoked VTE consider stop at this point
- Otherwise, needs a clinical decision to be made: there are risk stratification tools used for this. Young men and patients with high baseline D-Dimer are at greater risk.
- Recurrent VTE usually needs lifelong treatment

Heparin:

- Potentiates antithrombin III which inactivates thrombin, and factors 9, 10, 11
- LMWH: given SC once daily, does not require monitoring (except late pregnancy and renal failure when anti-Xa levels can be monitored)
- Unfractionated heparin (used if renal impairment): given IV, loading dose then infusion, monitor APTT (or anti-Xa/heparin levels in some trusts)
- Antidote: protamine sulphate
- Side effects: **bleeding** and **heparin induced thrombocytopenia (HIT)** □ **osteoporosis** with long-term use (HIT and osteoporosis more common with UFH)

Warfarin:

- Inhibits the reductase enzyme responsible for regenerating the active form of vitamin K and therefore inhibits the synthesis of factors 2, 7, 9, 10 and proteins C, S and Z
- Risk of teratogenicity
- Reversal:
  - IV vitamin K (Takes 6 hours)
  - Prothrombin complex concentrate (Octaplex/Beriplex - takes 30 mins)
- Dose adjusted to maintain INR in therapeutic range

Target INR

Target INR	Indications
2.5	**1st episode DVT or PE, atrial fibrillation (2-3)**, cardiomyopathy, symptomatic inherited thrombophilia, mural thrombus, cardioversion
3.5	**Recurrent DVT or PE, mechanical prosthetic valve (2.5-3.5)**, coronary artery graft thrombosis, antiphospholipid syndrome

In Cases of Raised INR

INR	Protocol
5-8, no bleeding	Withhold few doses, reduce maintenance. Restart when INR <5.
5 – 8, minor bleeding	Stop warfarin. Vit K slow IV. Restart when INR <5.
>8, no bleed/minor bleed	Stop warfarin. Vitamin K (oral/IV) no bleeding/if risk factors for bleeding or minor bleeding. Check INR daily.
Major bleeding, (including intracranial haemorrhage)	Stop warfarin. Give prothrombin complex concentrate. If unavailable, give FFP. Also give vitamin K IV.

Bleeding and DOACs:

- **Life/organ threatening bleeds:**
  - A normal APTT/PT does not exclude anticoagulant effect still present
  - Depends on half life of particular agent as to whether effect likely present
  - **Dabigatran** – ***idracizumab*** can be used to reverse depending on local availability
  - **Rivaroxaban and Apixaban** (?+ **edoxaban**) – ***andexanet alfa*** can be used but most trusts do not have this due to high cost. Prothrombin complex concentrate is often used instead (but doesn't have good evidence)
- Non life-threatening bleeds, pre-op: Half-lives are approximately 12 hours so withholding doses may be enough

Obstetric Haematology

Haematological changes in pregnancy

Plasma volume	↑↑
Red cell mass	↑
Haemoglobin	↓
MCV	↑
Haematocrit	↓
Platelets	↓
WCC	↑
Factors VII, VIII, IX, X, XII	↑
Factor XI	↓
Protein S	↓

HELLP syndrome

- Haemolysis, elevated liver enzymes, low platelets
- Life-threatening complication associated with pregnancy
- Key features – MAHA, ↑↑AST, ↑↑ALT, ↓platelets, normal APTT, PT
- Differentials include DIC (↑APTT, ↑PT, ↓fibrinogen), AFLP (marked transaminitis)
- Management – supportive, delivery of foetus

Haemolytic Disease of the Newborn (HDN)

- A person may form red cell Ab through blood transfusion or if fetal cells enter woman's circulation during pregnancy or delivery
- If maternal Ab level is high, it can destroy fetal red cells if they have corresponding red cell Ag → fetal anaemia + jaundice (HDN)
- Only IgG can cross placenta
- Ab most often responsible is anti-D, therefore always transfuse RhD negative blood to RhD negative women of childbearing age
- Other Ab: anti-c, anti-K, IgG ABO

Preventing Anti-D Formation

- In women who are RhD negative
- Give mother intra-muscular anti-D Ig when she is at high risk of feto-maternal haemorrhage
- Routine antenatal prophylaxis at 28 and 34 weeks
- During pregnancy if sensitising event occurs (abortion, miscarriage, abdo trauma, ECV, amniocentesis etc.)
- At delivery if baby is RhD positive

Leukaemia

Acute Leukaemia (ALL and AML)

Neoplastic process affecting blood precursor cells
"Acute," rapidly progressing and fatal
Immature blasts > 20% of bone marrow (BM) cells

Clinical features:

- BM function failure – Anaemia, Thrombocytopenia (bleeding), Neutropenia (infection)
    - Common to many haematological disease processes
- Organ infiltration – hepatomegaly, splenomegaly, lymphadenopathy, bone pain, CNS, skin, gum hypertrophy

Aetiology:

- **Unknown – most of the time no clear triggers**
- Ionising radiation - radiotherapy
- Cytotoxic drugs - chemotherapy
- Benzene
- Pre-leukaemic disorders, e.g: Myelodysplastic syndromes (MDS)/Myeloproliferative disorders (MPD)
- Down's: significantly increased risk of AML/ALL
- Neonates: often (30%) develop transient abnormal myelopoeisis; resembles AML but resolves spontaneously and completely after few weeks

Diagnosis (haem malignancy in general)**:**

- Morphology +/- cytochemistry (stains)
- Immunophenotyping using flow cytometry (lineage, differentiation)
- Cytogenetics (chromosomal translocations)
  Molecular genetics (PCR, point mutations etc)

AML or ALL ?

- Often can be difficult to tell
- Morphology (microscopic appearance) can be quite similar
- Diagnosis will usually be confirmed with immunophenotyping (looking at what markers the cells express)
- Treatment is similar in that it involves intensive chemotherapy but also quite different !

	Acute Lymphoblastic Leukaemia	Acute Myeloid Leukaemia
Epidemiology	Childhood (mnemonic – "Children get it ALL")	Adulthood (risk increases with age) and under-2s (infant peak)
Clinical features	All clinical features listed above, plus: Lymphadenopathy +++ CNS involvement +++ Testicular enlargement Thymic enlargement (mediastinum) "extra-medullary" disease more common ie solid leukaemia deposits outside the bone marrow	As listed above, plus: Lymphadenopathy less common Quick subtype facts: M3: Acute promyelocytic leukaemia – prone to DIC & bleeding M4+5: Monoblasts/monocytes - Skin / gum infiltration + hypokalaemia
Investigations	High WCC (blasts) Blasts often have tails / blebs of cytoplasm **Flow cytometry:** CD34 = precursor/stem cells CD3, 4, 8 = T lymphocytes CD19, 20, 22 = B lymphocytes	High WCC (blasts) **Auer rods** and granules (Auer rods not always present) **Flow cytometry:** CD34 = precursor/stem cells CD33, CD13, CD117, MPO = Myeloid cells
Treatment	*Chemotherapy:* **Remission induction:** Chemo agents often given with steroids **Consolidation:** High dose multi drug chemotherapy CNS treatment (intrathecal chemo) **Maintenance:** 2 years in girls and adults, 3 years in boys Consider allo-Stem Cell Transplant if high risk of relapse **Targeted treatments:** Nelarabine (T-ALL), CAR-T cells, Inotuzumab Blinatumumab (B-ALL), imatinib if 9;22 translocation *Supportive:* Blood products, ABx, Allopurinol, fluid, electrolytes – to prevent tumour lysis syndrome	*Chemotherapy:* **Remission induction**: Daunorubicin, cytarabine **Consolidation:** Cytarabine Older patients: azacytidine +/- venetoclax No CNS prophylaxis / maintenance therapy needed usually Consider allo-SCT if high risk of relapse **Targeted treatments**: ATRA for acute promyelocytic leukaemia (often don't need conventional chemo) Midostaurin – FLT3 mutations Gemtuzumab – CD33 immunotherapy Enasidenib– IDH mutations *Supportive:* Similar principles to ALL Prognosis worse with age

Common mutations / chromosomal abnormalities ***beyond yr5 path***	t(9;22) BCR-ABL1 (Philadelphia chromosome) t(4;11) KMT2A rearrangement high hyperdiploidy (lots of extra chromosomes) low hypodiploidy (lots of chromosomes missing)	FLT3 mutations NPM1 mutations IDH mutations t(8;21) RUNX1-RUNX1T1 inv(16) inv(3) / MECOM rearrangement -5 / -7 (loss of chromosome 5 or 7) TP53 mutations

Chronic Myeloid Leukaemia

A myeloproliferative disease (others discussed later)
Middle-aged typically (40 to 60).
Often diagnosed on routine bloods (large number of differentiated neutrophils)
Or present with generally feeling unwell / weight loss / infections / bruising
95% remission rate with imatinib
O/E: splenomegaly - often massive

Investigations

- Ph+ve (Philadelphia chromosome) in 80% = chromosomal translocation (9;22)
  - Used to be diagnosed with karyotype, but now FISH is used
- PCR for BCR-ABL (Philadelphia Ch) fusion gene
- Monitor disease and therapeutic response
- High White Blood Cell count with high neutrophils and high basophils (note: very few conditions cause an elevated basophil count!)
- Hypercellular BM with spectrum of immature (e.g. myelocytes) and mature granulocytic cells in the blood

1. **Chronic phase**
   - <5% blasts in BM/blood, WBC increases over years
   - Rx = Imatinib (BCR-ABL tyrosine kinase inhibitor) or dasatinib/nilotinib for resistance; ***extremely*** effective and well tolerated. Treatment usually started immediately after diagnosis confirmation regardless of symptoms

2. **Accelerated Phase**
   - >10% blasts in BM/blood
   - Increasing manifestations, such as splenomegaly, lasting up to a year
   - Less responsive to therapy

3. **Blast Phase**
   - >20% blasts in BM/blood
   - Resembles acute leukaemia; timeframe = months (+/- WL, lethargy, night sweats)
   - Treatment similar to AML, possibly with allogeneic SCT for young pts.

Chronic Lymphocytic Leukaemia

A “lymphoproliferative disease” like lymphoma.

CLL and Small lymphocytic lymphoma (SLL) are essentially the same disease process with slightly different presentations – CLL is primarily seen in the BM, SLL in the LNs.

M>F, elderly (median 65-70)

Clinical features

- May be asymptomatic, often diagnosed on routine bloods (80% cases)
- Symmetrical painless lymphadenopathy
- BM failure - anaemia & thrombocytopenia symptoms, recurrent infections (50% deaths)
- Weight loss, low grade fever, night sweats
- Hepatomegaly & splenomegaly (less prominent)
- Associated with autoimmunity (Evan's Syndrome) – AIHA, ITP
- Can progress to a form of lymphoma (DLBC, see later) – Richter's transformation

Investigations

- High WBC with lymphocytosis >5 (high % of WBC composed of lymphocytes, small mature)
- Low serum immunoglobulin
- Flow cytometry to confirm a monoclonal population
    - Usually CD5+ CD23+
- Smear cells (remember SMEAR CLLs) – seen on blood film Ix
- Abnormal BM – lymphocytic replacement
- Mutation status: TP53 mutation = worse , IGHV rearrangement = better

Prognostic factors

- LDH raised, CD38 +ve, 11q23 deletion **= bad**
- Hypermutated Ig gene, Low ZAP-70 expression, 13q14 deletion **= good**

Binet Staging A, B & C (Rai Staging I-IV could also be used)

Stage A

- High WBC
- <3 groups of enlarged lymph nodes
- Usually no treatment required

Stage B

- >3 groups of enlarged lymph nodes

Stage C

- Anaemia or thrombocytopenia

Treatment

- Many patients benefit from ***watchful waiting*** if they are asymptomatic with slowly progressive disease. 1/3 patients never need any treatment
- Supportive treatment with transfusions, infection prophylaxis
- Options are: anti-CD20 (rituximab or Obinutuzumab) with chemotherapy; oral BTK inhibitors (ibrutinib); BCL2 inhibitor (venetoclax)

Lymphoma

Neoplastic tumour of lymphoid tissue

- Often lymph nodes (+ Bone marrow +/- spill out to blood)
- Sometimes other lymphoid tissues – spleen, MALT (mucosal associated lymphoid tissue)
- Rarely, "anywhere" – skin (often T-cell), CNS, testes, breast

Hodgkin's Lymphoma (20%)

- M>F; bimodal age incidence – 20-29 year olds and >60 year olds
- EBV-associated
- Spreads contiguously to adjacent lymph nodes; often involves single LN group

Clinical presentation

- Asymmetrical painless lymphadenopathy +/- obstructive/mass effect symptoms
- "B-symptoms"
    - Fever >38. Classical *Pel-Ebstein* fever (cyclical 1-2wk) seen in a minority
    - Drenching sweats at night
    - Weight loss >10% in 6 months unintentional
- Pain in affected nodes after alcohol
- Nodes tend to be mediastinal / cervical but not always

Investigations

- CT/PET. Tissue diagnosis: LN or BM biopsy - cells stain with CD15 & CD30
- Reed-Sternberg cell – bi-nucleate/multinucleate ('owl eyed') cell on a background of lymphocytes & reactive cells
- Subtypes: nodular sclerosing (most common), mixed cellularity, lymphocyte rich, lymphocyte depleted, nodular lymphocyte predominant (not classical HL)

Staging (Ann-Arbor)

Stage 1 – one LN region (LN region can include spleen)
Stage 2 – two or more LN regions on the same side of the diaphragm
Stage 3 – two or more LN regions on opposite sides of the diaphragm
Stage 4 – extranodal sites (liver, BM)

A: No constitutional symptoms B: Constitutional symptoms

E.g. Stage 2a – patient with involvement in 3 LN regions above the diaphragm, pain after alcohol and SVC syndrome *but* no weight loss, night sweats etc.

Treatment - prognosis excellent, especially in the young but intensive treatment

1. Combination chemotherapy –
    - Used in most cases
    - ABVD: Adriamycin, bleomycin, vinblastine and dacarbazine
    - 2-4 cycles in stage 1/2, 6 cycles in stage 3/4
    - Usually patients have an interim PET scan to guide treatment
2. Radiotherapy –
    - Often used alongside chemo in bulky areas or limited disease– very high risk of breast cancer in women
3. Relapsed patients
    - Options are second line chemotherapy agents, brentuximab (Anti-CD30), pembrolizumab (PDL1 immunotherapy), nivolumab
    - May need autologous or allogeneic stem cell transplant

Stem cell transplant / bone marrow transplant

- Stem cells are harvested from one of three sources: peripheral blood (following stimulation by G-CSF), BM or umbilical cord blood
- Used in leukaemia, lymphoma, multiple myeloma, aplastic anaemia, MDS, sickle cell anaemia and thalassemia major. Can be used in other conditions too!

- Works best if the patient is in remission as a "consolidation" treatment to reduce relapse risk

Autologous SCT
- Patients own SCs are harvested and frozen
- Enables high dose chemo +/- radiotherapy to eradicate malignant cells at the cost of partial or even complete bone marrow ablation
- Frozen SCs then reintroduced into patient
- Used more in multiple myeloma and lymphoma, particularly with relapse, not used in leukaemia so much
- No "graft vs leukaemia" effect
- No graft vesus host disease (GVHD) risk and lower risk of infection

Allogeneic SCT
- HLA-matched donor SCs are harvested
- Patients own BM completely eradicated by high-dose chemo +/- radiotherapy
- Donor SCs are introduced and colonise "empty" BM
- Used more in leukaemia due to "graft vs leukaemia" effect
- GVHD risk, risk of opportunistic infections, infertility and secondary malignancies

Non-Hodgkin's Lymphoma (80%)

All lymphomas other than Hodgkin's: dozens of different subtypes
May be classified according to:
- Mature or immature
- Histology:
  - High Grade
    Very Aggressive – Burkitt's
    Aggressive – Diffuse Large B-Cell, Mantle Cell
  - Low Grade
    Indolent – Follicular, Marginal Zone, Small Lymphocytic
- Lineage: B or T Cell (see tables below)

Presentation varies significantly from subtype to subtype
- **Similarities**: painless lymphadenopathy, often involving multiple sites, constitutional symptoms, **no pain after alcohol**
- Staging as per Hodgkin's

B-cell Lymphomas		Comments	Histology	Treatment
Burkitt's	**Three types:**	All very aggressive, fast growing t(8;14) translocation c-myc oncogene overexpression Rapidly responsive to Rx	"Starry sky" appearance	Chemotherapy (rituximab (anti CD20 - found on B cells) & secondary CNS prophylaxis
	Endemic	Most common malignancy in equatorial Africa EBV-associated Characteristic jaw involvement and abdominal masses		
	Sporadic	Found outside Africa EBV-associated Jaw less commonly		

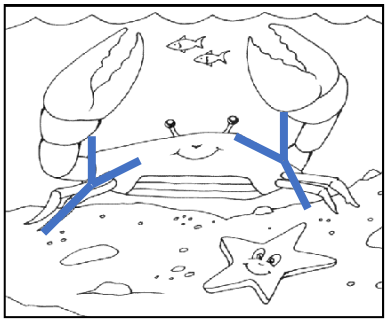
		involved		
	Immuno-deficiency	Non-EBV-associated HIV/post transplant patients		
Diffuse Large B-cell (DLBC)		Middle aged and elderly Aggressive Can be transformed from low grade lymphoma	"Sheets of large lymphoid cells"	Rituximab-CHOP Auto-SCT or CAR-T for relapse
Mantle cell lymphoma		Middle-aged, M>F Aggressive Disseminated at presentation Median survival 3-5 years t(11;14) translocation Cyclin D1 deregulation	"Angular/ clefted nuclei"	Rituximab-CHOP and high dose cytarabine Auto-SCT for relapse Oral options for less fit
Follicular		Indolent Mostly incurable Median survival 12-15 yrs t(14:18) translocation	"Follicular pattern" "Nodular appearance"	Watch and wait Rituximab or obinutuzumab + chemo
Mucosal associated lymphoid tissue (MALT)		Marginal zone NHL Middle-aged Chronic antigen stimulation: • *H. pylori* → gastric MALT lymphoma • Sjogren's syndrome → parotid lymphoma		Remove antigenic stimulus e.g. *H. pylori* triple therapy, Chemotherapy

T-cell Lymphomas (rarer)	**Comments –** Alemtuzumab (anti CD-52) can be used in Rx
Anaplastic large cell lymphoma	Children and young adults Aggressive Large "epithelioid" lymphocytes t(2;5) Alk-1 protein expression
Peripheral T-Cell Lymphoma	Middle-aged and elderly Aggressive Large T-cells
Adult T cell leukaemia/lymphoma	Caribbean and Japanese HTLV-1 infection, aggressive
Enteropathy-associated T cell lymphoma (EATL)	Associated with longstanding coeliac disease
Cutaneous T Cell Lymphoma	Associated with mycosis fungoides

Multiple Myeloma (MM) and Other Paraproteinaemias

Multiple Myeloma

Multiple Myeloma: neoplasia of plasma cells (effector B cells antibodies) of BM
Production of monoclonal immunoglobulin - "paraprotein" -> **IgG** most common
Middle-Aged to Elderly
Increased incidence in Afro-Caribbeans



Clinical features (CRAB):

- **C**alcium high – thirst, moans, groans, stones, bones
- **R**enal failure (plus amyloidosis and nephrotic syndrome)
- **A**naemia (+pancytopenia)
- **B**ones: pain, osteoporosis, osteolytic lesions, fractures e.g. wedge compression, pepper pot skull
- + Hyperviscosity syndrome

Investigations:

- Dense narrow band on serum electrophoresis (compared with broad band in polyclonal)
    - In "gamma region"
    - Will then be identified as IgG/IgM/IgA/IgD/IgE
    - Will be identified as either kappa or lambda light chain
- Rouleaux on blood film (RBC stacking)
- Look for CRAB symptoms:
    - Bone profile to check calcium
    - Urea and electrolytes to assess renal function
    - Full blood count for anaemia
    - Low dose CT body / MRI whole body to look for bony lesions
- Bence-Jones protein in urine
- ESR very high
- >10% plasma cells in BM

Staging: Durie-Salmon staging system / ISS

Treatment:

- Supportive for CRAB symptoms inc, bispohosphonates
- Aim of treatment: induce remission for consideration of autologous stem cell transplant which will prolong remission
- Not *curable*
- Average survival 5-7 yrs but improving with new treatments
- Options:
    - First line – Bortezomib + / - dexamethasone, cyclophosphamide, lenalidomide
    - When in remission => Auto-SCT – best for younger patients as prolongs remission
    - If not suitable for SCT – multiple other new agents e.g. daratumumab (anti-CD38) carfilzomb / ixazomib (protease inhibitors) panobinostat

	MGUS	Smouldering MM	Multiple Myeloma
M-spike	<30g/l	>30g/l	>30g/l Or serum free light chain ratio >100
Bone marrow	<10% clonal plasma cells	>10% clonal plasma cells	Any clonal plasma cell population Automatically diagnostic if >=60% plasma cells
CRAB	None	None	1+

Organ damage	None	None	Hypogammaglobulinaemia Occult bone disease Hyperviscosity Cytopenia
Significance	No treatment needed Small transformation rate	No treatment needed Higher transformation rate	Treatment needed

Waldenstrom's Macroglobinaemia (Lymphoplasmacytoid Lymphoma - LPL)

Elderly men typically
Low-grade NHL; lymphoplasmacytoid cells producing monoclonal serum IgM infiltrate the LNs/BM
Weight loss, fatigue, hyperviscosity syndrome (visual problems, confusion, CCF, muscle weakness)
Treatment: plasmapheresis for hyperviscosity; rituximab / bendamustine or ibrutinib for active disease

Systemic Amyloidosis (see other path sections)

- Different types of amyloidosis
- AL Amyloidosis is due to build of mis-folded light chains
- This can be in the presence or absence of myeloma
- Misfolded light chains deposit in the tissues & cause problems
- Other types of amyloidosis involve different types of misfolded proteins AL Amyloidosis will result in an abnormal kappa:lambda light chain ratio

- Definitively diagnosed via biopsy of affected organ using congo-red stain -> apple green birefringence
- New diagnostic test is the SAP scan at the national amyloidosis centre at the Royal Free
- Presents with macroglossia, carpal tunnel syndrome, peripheral neuropathy, HF, RF

- Treatment = similar to myeloma

Myelodysplastic Syndromes

Heterogeneous group of progressive disorders featuring ineffective proliferation and differentiation of abnormally maturing myeloid stem cells.

- **Characterised by**: peripheral cytopenia; qualitative abnormalities of cell maturation; risk of AML transformation.
- Typically seen in the elderly; symptoms usually develop over weeks/months (incidental)
- By definition all patients have <20% blasts (>20% blasts = acute leukaemia)

Clinical Features

- BM failure and cytopenias – infection, bleeding, fatigue
- Hypercellular BM
- Defective cells:
  - RBCs e.g. ring sideroblasts (abn nucleated blast surrounded by iron granule ring)
  - WBCs – hypogranulation, Pseudo-Pelger-huet anomaly (hyposegmented neutro)
  - Platelets – micromegakaryocytes, hypolobated nuclei

N.B. In the exam – use an 'investigative approach' to pick out clues that lead to classification

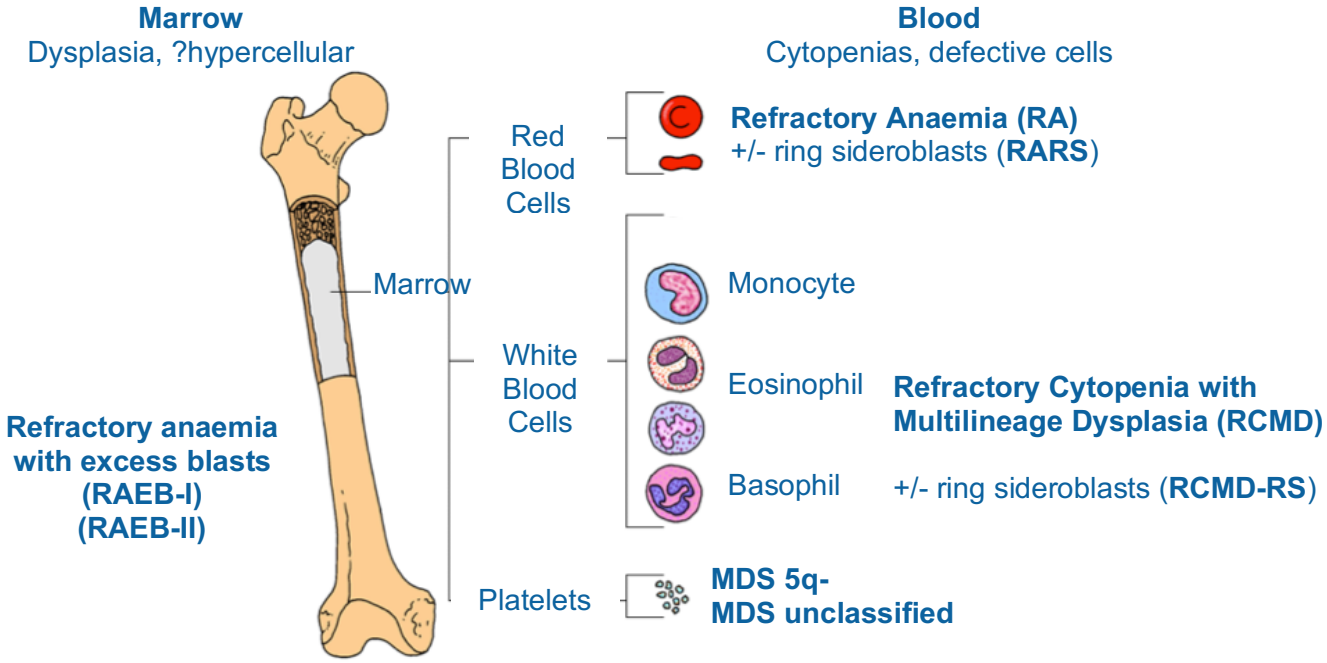
Redundant term sometimes used in old EMQs - Refractory anaemia with excess blasts in transformation (RAEB-T); characterised by 21-30% myeloblasts in the marrow – now considered as AML.

Treatment

- Supportive – transfusions, EPO, G-CSF, ABx
- Biological modifiers – immunosuppressive drugs, lenalidomide, azacytidine
- Chemotherapy – similar to AML
- Allogeneic SCT

Prognosis

Depends on International Prognostic Scoring System (IPSS): BM blast %; karyotype; degree of cytopenia; mortality rule of 1/3: 1/3 die from infection,1/3 bleeding and 1/3 acute leukaemia.



Subtype	Blood features	Bone marrow features
Refractory anaemia (RA)	Anaemia, no blasts	Erythroid dysplasia with <5% blasts
Refractory anaemia with ringed sideroblasts (RA +RS)	Anaemia, no blasts	Erythroid dysplasia with >15% ringed sideroblasts
Refractory cytopenia with multilineage dysplasia	Cytopenia in ≥ 2 cell lines	Dysplasia in >10% cells in ≥ 2 cell lines

(RCMD)		
Refractory cytopaenia with multilineage dysplasia and ringed sideroblasts (RCMD + RS)	Cytopenia in ≥ 2 cell lines	Dysplasia in >10% cells in ≥ 2 cell lines and >15% ringed sideroblasts
Refractory anaemia with excess blasts – 1 (RAEB I)	Cytopenias, <5% blasts, no Auer rods	Dysplasias, 5-9% blasts
Refractory anaemia with excess blasts – 2 (RAEB II)	Cytopenias *or* 5-19% blasts *or* Auer rods	Dysplasias, 10-19% blasts *or* Auer rods
MDS with 5q deletion	Anaemia, normal or increased platelets	Megakaryocytes with hypolobated nuclei and <5% blasts
Myelodysplasia Syndrome Unclassified	Complex - cytopenias, no blasts, no Auer rods	Complex - myeloid or megakaryocytic dysplasia, <5% blasts
Note: These subtypes are not particularly important for yr 5 path.		

Aplastic Anaemia

- The inability of BM to produce adequate blood cells
- Haemopoeitic stem cell numbers are reduced in BM trephines (hypocellular BM)
- AA typically refers to anaemia – i.e. just RBCs – however these patients can have a pancytopenia as well
- Symptoms/signs relate to each cytopaenia
- Patients typically present with bleeding problems
- Can affect any age

AA closely linked to: Leukaemia, Paroxysmal nocturnal haemoglobinuria (PNH)

Classification:

- Primary:
  - Idiopathic (70%) – vast majority unexplained pathology but increasingly finding mutations with NGS
  - Inherited (10%) – see below
- Secondary (10-15%) – due to malignant infiltration, radiation, drugs incl. chemo, viruses, AI e.g. SLE

Management:

- Supportive – transfusions, Abx, iron chelation
- Drugs – to promote marrow recovery – growth factors and oxymethalone (androgen)
- Immunosuppressants – idiopathic AA
- Stem cell transplant

Inherited AA / BM failure syndrome

Fanconi Anaemia (cf Fanconi Syndrome = renal)

- Autosomal recessive. Pancytopenia
- Presents at 5-10yrs
- Skeletal abnormalities (radii, thumbs), renal malformations, microopthalmia, short stature, skin pigmentation
- MDS (~30%), AML risk (10% progress)

Dyskeratosis Congenita

- X-linked. Chromosome instability (telomere shortening)
- Skin pigmentation, nail dystrophy, oral leukoplakia (triad) + BM failure

Schwachman-Diamond Syndrome

- Autosomal recessive. Primarily neutrophilia +/- others
- Skeletal abnormalities, endocrine and pancreatic dysfunction, hepatic impairment, short stature
- AML risk

Diamond-Blackfan Syndrome

- Pure red-cell aplasia; normal WCC and platelets
- Presents at 1yr/neonatal
- Dysmorphology

Myeloproliferative Disorders

A group of conditions characterized by clonal proliferation of one or more haemopoietic component i.e. increased production of mature cells.

"Philadelphia Chromosome positive"	"Philadelphia Chromosome negative"
Chronic Myeloid Leukemia (CML)	Polycythemia vera (PV) Myelofibrosis (MF) Essential thrombocytosis (ET)

Ph –ive associated with JAK2 mutations, particularly PV (>95%)

Associated with variable increases in reactive polyclonal BM fibrosis and terminal acute leukaemia transformation.

All are at risk of transformation to myelofibrosis and acute leukaemias. For many patients this risk is very low.

Polycythaemia

Raised red cell mass, Hb, red cell count and packed cell volumePrimary causes:

- Polycythaemia vera
- Familial polycythaemia

Secondary causes (EPO)*:*

- Disease states (renal Ca), high altitude, chronic hypoxia e.g. COPD

Relative (Pseudo) Polycythaemia

Red cell mass normal but plasma volume reduced

- Dehydration, burns, vomiting, diarrhoea, cigarette smoking

Polycythaemia Rubra Vera (PRV)

An MPD where erythroid precursors dominate the BM. Incidence rises with age.

Point mutations: JAK2 (V617F). Independent of normal mechanisms of regulation.

Clinical Features:

- Hyperviscosity / hypervolaemia / hypermetabolism
- Blurred vision, headache
- Plethoric (“red nose”), gout, thrombosis and stroke, retinal vein engorgement, erythromelagia
- Splenomegaly
- Histamine release > aquagenic pruritis (contact with water) and peptic ulcers
- **Investigations:**
- Raised Hb, HCT; also possibly platelets, WCC (neutrophils & basophils)
- Low serum EPO

Treatment:

- Venesection
- Hydroxycarbamide (maintenance), aspirin

Myelofibrosis

A MPD where myeloproliferation → fibrosis of BM or replacement with collagenous tissue Primary (idiopathic) vs secondary following PRV, ET, leukaemia etc).

Clinical Features:

- Usually elderly

- Pancytopaenia-related symptoms
- Extramedullary haematopoeisis - hepatomegaly, **massive** splenomegaly, WL, fever
- Can present with Budd-Chiari syndrome

Investigations
- Blood film – tear-drop poikilocytes (dacrocyte), leukoerythroblasts (primitive cells)
- BM – fibrosis, "dry tap"
- Molecular tests: JAK2 mutation (60%), MPL mutation

Treatment
- Support with blood products, in some cases – splenectomy
- Stem cell transplant is the only curative option
- Ruloxitinib, hydroxycarbamide, thalidomide, steroids .

Essential Thrombocythaemia (or thrombocytosis)
An MPD where megakaryocytes dominate the BM
50% associated with JAK2
Also associated with MPL mutation and CALR

Clinical features
- Incidental finding in 50%
- Venous and arterial thrombosis (stroke & MI), gangrene and haemorrhage
- Erythromelalgia
- Splenomegaly, dizziness, headaches, visual disturbances

Investigations
- Platelet count >600x10^9
- Blood film – large platelets and megakaryocyte fragments
- Increased BM megakaryocytes (not reactive)

Treatment
- Aspirin
- Anagrelide – reduce formation of plts from megakaryocytes
- Hydroxycarbamide

Blood Transfusions
When to transfuse
Red Cells
- Treat Iron/Folate/B12 deficiency first unless active bleeding
- For transfusion dependent patients use a threshold 70-90g/l (depends on what level patient gets symptomatic)
- Most guidelines suggest a threshold of 70g/l if asymptomatic; 80g/l if symptomatic
- Higher threshold of up to 90-100g/l for patients with coronary heart disease
- Only transfuse one unit at a time unless active bleeding
- Can be transfused "stat" but routinely would be 2-3 hours

Platelets
- Consumptive disorders e.g. TTP, DIC, HIT
  - Do not transfuse unless actively bleeding (plts will be destroyed)
  - Reduced production e.g. leukaemias
- Transfuse when <10bn/litre
  - Higher threshold of 20 in sepsis
- Pre-procedure: Various thresholds depending on procedure.

- Bleeding thresholds vary on site (highest thresholds for eye / brain)

FFP

- Coinsider using Vitamin K first if appropriate
- Do not use unless patient is bleeding or undergoing a procedure e.g. surgery
- Dose depends on patient weight, INR and target INR
- Needs 30 minutes to thaw out first

	Immediate	Delayed
Immune	Wrong blood: ABO Febrile non-haemolytic Allergic/anaphylaxis Transfusion related acute lung injury (TRALI)	Delayed haemolytic transfusion reaction (DHTR) Port-transfusion purpura Transplant-associated GVHD
Non-immune	Bacterial infection Transfusion associated cardiac overload (TACO)	Viral infections Iron overload

Adverse Reactions to Transfusions

Acute (≤24 hours)

Anaphylaxis

- Symptoms occur within minutes
- Risk increases in patients with **IgA deficiency**

ABO incompatibility

- Symptoms occur within minutes to hours
- Intravascular haemolysis – **IgM-mediated**

Bacterial contamination

- Symptoms occur within minutes to hours
- More commonly occurs with **platelet transfusion**

Febrile non-haemolytic transfusion reaction

- Rise in temperature of ≤1ºC without circulatory collapse
- Caused by release of cytokines by leukocytes and prevented by leukodepletion

Transfusion-related circulatory overload

- Symptoms of pulmonary oedema/fluid overload occur within hours
- Look for signs of heart failure: ↑**JVP**, ↑**PCWP**

Transfusion-related acute lung injury

- Symptoms similar to TACO
- Caused by interaction with anti-HLA antibodies in donor blood with recipient
- **Absence of heart failure**

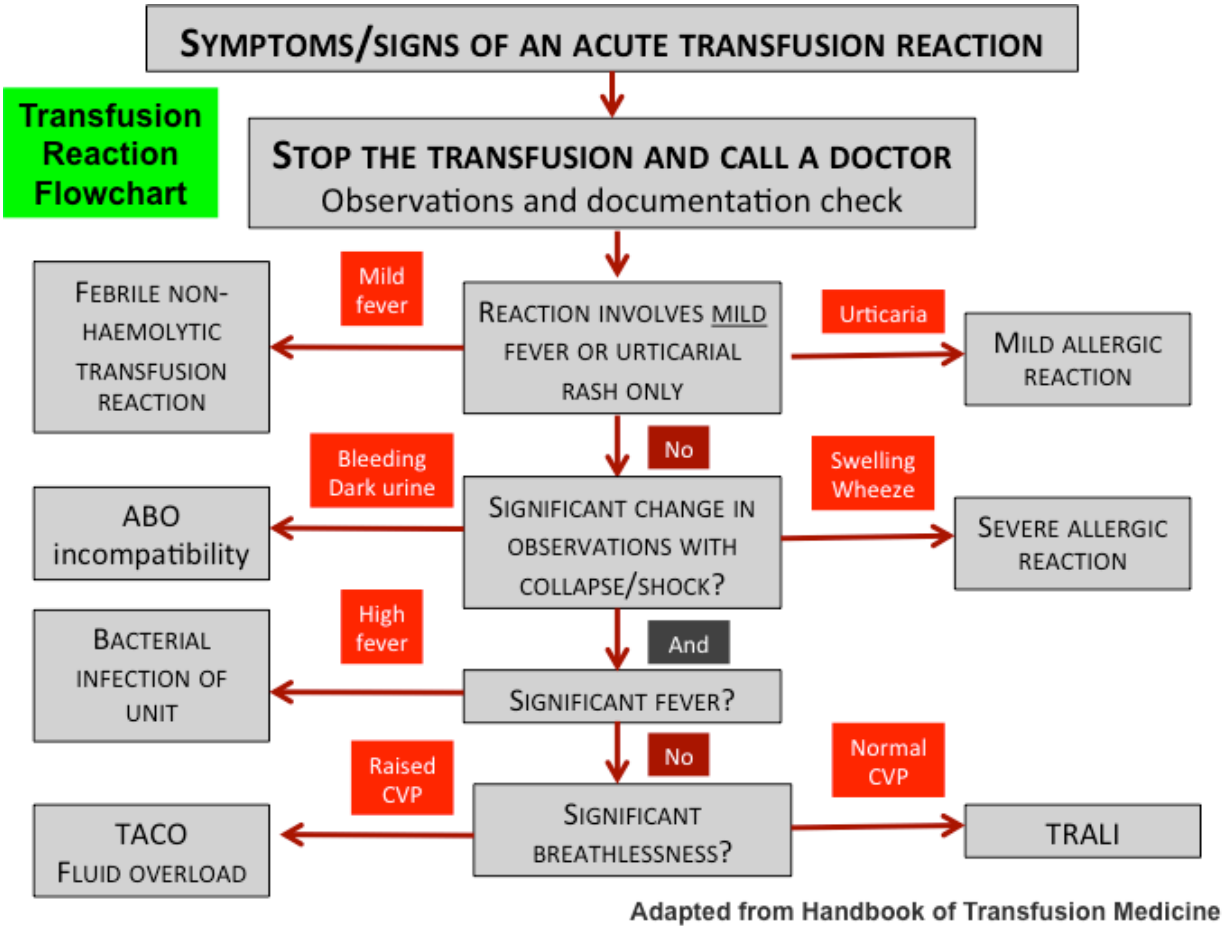
Delayed (>24 hours)

Delayed-haemolytic transfusion reaction

- Occurs within 1 week
- Extravascular haemolysis – **IgG-mediated**

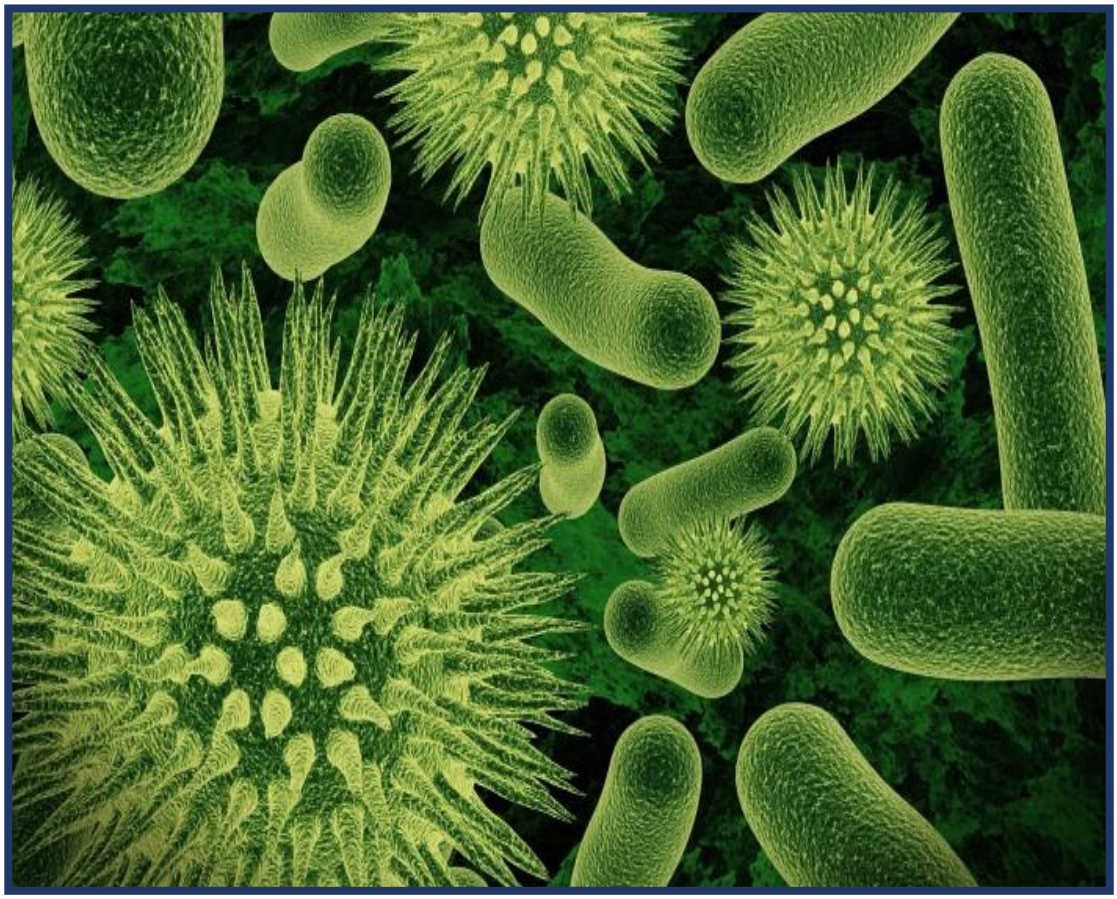
Graft vs host disease

- Symptoms include diarrhoea, liver failure, **skin desquamation** and bone marrow failure
- Donor lymphocytes recognise recipient's HLA as foreign and attack gut, liver, skin and bone marrow
- Prevent by irradiating blood components for immunosuppressed recipients



Adapted from Handbook of Transfusion Medicine

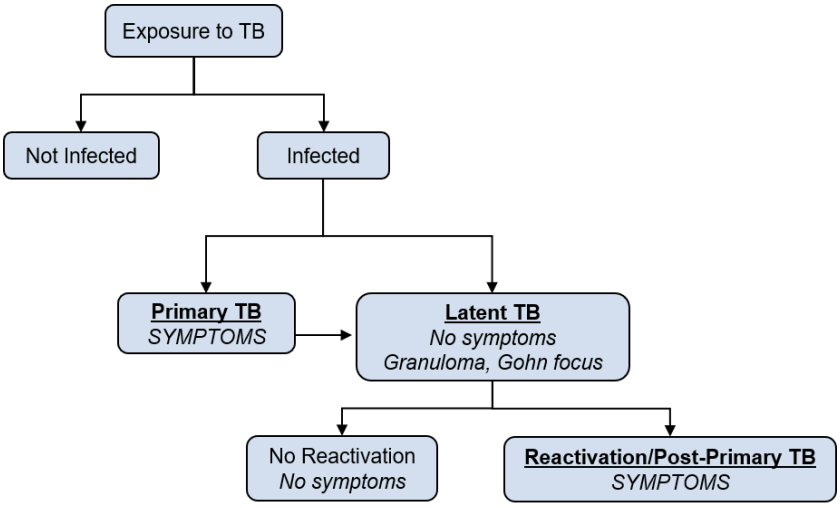
Microbiology



Edited by **Luke Kostanjek and Dr John Asumang**

Tuberculosis and other Mycobacteria

Tuberculosis



- Infection is usually asymptomatic → becomes latent in a Gohn focus / granuloma. Upon reactivation (e.g. due to immunosuppression), it becomes symptomatic.
    - Less commonly, primary TB infection is symptomatic (risk factor = immunosuppressed)
- Classic lesions: **caeseating granulomas**
- Risk factors: travel (South Asia / Eastern Europe), HIV+, homeless, IVDU, contact
- Presentation:
    - General: **fever**, **night sweats**, weight loss
    - Respiratory: cough, **haemoptysis**
    - Less commonly… (seen in **immunosuppression**)
        - Subacute meningitis: headaches, personality change, meningism, confusion. Diagnose with LP (see meningitis section)
        - Spinal (Pott's disease): back pain, discitis, vertebral destruction, iliopsoas abscess
        - Milliary TB: disseminated haematogenous spread (seen on CXR)
        - *Also lymphadenitis, pericarditis, peritonitis, renal, testicular, liver TB*
- Investigations:
    - **CXR**: upper lobe cavitation (in post-primary)
    - **Sputum samples** x3
        - Microscopy on **Ziehl-Neelson** stain; culture on **Lowenstein-Jensen** medium for 6wks (gold standard)→ **acid fast bacilli** seen
        - Bronchoalveolar lavage if unable to produce sputum
    - **Tuberculin skin tests** (Mantoux/Heaf): shows exposure (active/latent/ BCG)
    - **IGRA** (Elispot/Quantiferon): shows exposure (active/latent) – NOT BCG
- Treatment:
    - **RIPE: rifampicin, isoniazid, pyrazinamide, ethambutol**
        - All 4 for 2 months, then continue rifampicin and isoniazid for further 4 months (longer in meningitis / Pott's disease)
        - Side effects: rifampicin – orange secretions; isoniazid – peripheral neuropathy; pyrazinamide – hepatotoxic; ethambutol – optic neuritis
    - 2nd line: injectables (amikacin, kanamycin), quinolones, linezolid
        - Resistance is becoming problematic
    - Prophylaxis: isoniazid monotherapy
- Vaccination: **BCG** (Bacille-Calmette-Guerin)
    - Attenuated strain of M. bovis, given to high-risk pts
    - Contraindicated in immunosuppression (live vaccine)

Other Mycobacterial Diseases:
Leprosy (Hansen's disease): M. Leprae. Skin depigmentation, nodules, trophic ulcers, **nerve thickening**. Lifelong illness, most disability due to nerve damage
Mycobacterium Avium-Intracellulare complex: disseminated infection in **immunocompromised**; resembles TB if underlying lung disease
Mycobacterium Marinarum (fish tank granuloma): aquarium owners, papules/plaques
Mycobacterium ulcerans (Buruli ulcer): tropics / Australia, painless nodules progressing to ulceration, scarring and contractures

Respiratory Tract Infections

Pneumonia (see below): *inflammation of lung alveoli*

- Sx: pts are sick – fever, cough, SOB, pleuritic chest pain
- Ix: CXR (abnormal), calculate CURB-65, sputum cultures, atypical screen
- Rx: supportive (O2, fluids, etc), Abx (guided by CURB-65)

Other respiratory tract infections:
Lower respiratory tract infection (LRTI): broad term for lung infection – includes pneumonia, bronchitis, empyema, abscess. Viral or bacterial. No CXR changes. Supportive Rx +/- Abx
Bronchitis: inflammation of medium sized airways, mostly in smokers. Viral or bacterial. No CXR changes. Rx: bronchodilation, chest physio +/- Abx

Classification of Pneumonia:

- Community-acquired vs Hospital-acquired
  - Hospital-acquired = after >48hrs of hospital admission
    - Common pathogens = S. aureus, Klebsiella, Pseudomonas, Haemophilus
- Typical vs Atypical
  - Typical = classic signs and symptoms, classic CXR changes (i.e. consolidation), respond to penicillin Abx
  - Atypical = no / atypical signs and symptoms, not in-keeping with CXR, don't respond to penicillin Abx (because no cell wall). May have extra-pulmonary features, e.g. hepatitis, hyponatraemia
  - *NB this has nothing to do with how common the pathogen is – some atypical pneumonias are common!*

Typical Pneumonia Causes:

Pathogen	Buzzwords	Micoscope
Streptococcus pneumoniae	Most common. Rusty-coloured sputum. Lobar on CXR. Vaccinate groups at risk	+ve diplococci
Haemophilus influenzae	Assoc. w/ smoking, COPD	-ve cocco-bacilli
Moraxella catarrhalis	Assoc. w/ smoking	-ve cocci
Staphylococcus aureus	Assoc. w/ recent viral infection (post-influenza) ± cavitation on CXR	+ve cocci "grape-bunch clusters"
Klebsiella pneumoniae	Alcoholics, elderly. Haemoptysis	-ve rod, enterobacter

Atypical Pneumonia Causes:

Pathogen	Buzzwords
Legionella pneumophilia	Travel, air conditioning, water towers, hepatitis, hyponatraemia
Mycoplasma pneumoniae	Uni students / boarding schools, dry cough, arthralgia, cold agglutinin test / AIHA, erythema multiforme
Chlamydia pneumoniae	
Chlamydia psittaci	Birds

Immunosuppression + Respiratory Tract Infection:

- HIV: P. jiroveci, TB, Cryptococcus neoformans
- Splenectomy: encapsulated organisms = H. influenzae, S. pneumoniae, N. meningitidis
- Cystic fibrosis: Pseudomonas aeruginosa, Burkholderia cepacia
- Neutropenia: Aspergillus

Diagnosis of Pneumonia:

- CXR: consolidation (if typical)
- Sputum MC&S
    - Consider broncho-alveolar lavage if non-productive
- Atypical screen: Legionella urine antigen, serum antibody tests for organisms difficult to culture (Chlamydia, Legionella)

Treatment of Community-Acquired Pneumonia:

Calculate CURB-65 → 1 point for confusion, urea >7, RR >30, BP <90/60, ≥65yo

Antibiotics – based on CURB score

- Penicillins work well against typical organisms but don't work against atypicals (as no cell wall). Therefore, macrolides are used to provide atypical cover.

CURB 0-1 (mild)	Amoxicillin PO 5d 2nd line (pen allergic) macrolide PO 5d Outpatient treatment
CURB 2 (mod)	Amoxicillin PO 5-7d + Clarithromycin PO 5-7d Consider admission
CURB 3-5 (severe)	Co-amoxiclav IV 7d + Clarithromycin IV 7d Admit +/- consider ITU

Treatment of Hospital-Acquired Pneumonia:

- Varies depending on trust guidelines
- 1st line: ciprofloxacin + vancomycin
- If severe: tazocin + vancomycin
- Aspiration pneumonia: tazocin + metronidazole

Infective Endocarditis

Infection of innermost layer of heart, usually the valves

- Bacteria form vegetations on the valves → parts fly off around the body → various immune and embolic phenomena
- Usually involves mitral and aortic valves. R sided (tricuspid) is most common in IVDU

Risk factors:

- **Bacteraemia:** long-term lines (e.g. ITU), IVDU, poor dentition / dental abscess
- **Abnormal valves:** prosthetic valve, rheumatic heart disease
- Immunosuppression

Classification: Acute Vs Subacute

- Acute: fulminant illness, pt is very unwell
- Subacute: over weeks-months, pt less unwell, more signs O/E (see below)

Pathogens:

- Acute (high-virulence bacteria): **Strep pyogenes** (Group A Strep), **Staph aureus** (*most common in IVDU*), **CoNS** (*most common in prosthetic valve)*
- Subacute (low-virulence bacteria): **Staph epidermidis**, **Strep viridans**, HACEK
    - *HACEK organisms are uncommon causes and do not grow on culture → consider if high suspicion but culture -ve*
        - **H**aemophilus, **A**cinetobacter, **C**ardiobacterium, **E**ikinella, **K**ingella

Signs and symptoms:

- **Fever** (often presents as PUO)
- Non-specific Sx: anorexia, weight loss, malaise, fatigue, night sweats, SOB
- **New heart murmur**, often changes day to day, usually regurgitant
- In subacute:
    - Embolic phenomena: **Janeway lesions**, **splinter haemorrhages**, **splenomegaly**, septic abscesses in lungs/brain/spleen/kidney, microemboli
    - Immune phenomena: **Roth spots**, **Osler's nodes**, **haematuria** (due to glomerulonephritis)

Investigations:

- Blood cultures - >3x from different sites, ideally before starting Abx
- Echo

Duke's Criteria (for diagnosis):

- For diagnosis, you need 2 major, OR 1 major + 3 minor, OR 5 minor criteria
- Major:
    - Positive blood culture growing typical organisms (>2x cultures >12hrs apart)
    - New regurgitant murmur or evidence of vegetation on echo
- Minor:
    - Risk factor (see above)
    - Fever >38°
    - Embolic phenomena (see above)
    - Immune phenomena (see above)
    - Positive blood cultures not meeting major criteria

Treatment:

- IV Abx for ~6wks (use local guidelines)
    - Start empirically as soon as cultures taken, then change according to sensitivities
    - Acute: flucloxacillin
    - Subacute: bezylpenicillin + gentamycin
    - Prosthetic valve: vancomycin + gentamycin + rifampicin

Surgical debridement sometimes considered

GI Infections

There are 3 different clinical syndromes:

- **Secretory diarrhoea**
  - Toxin production → Cl- secreted into lumen → loss of water and electrolytes → D+V
  - **Watery diarrhoea, no fever**
  - *Cholera, ETEC, EPEC, viruses*
- **Inflammatory diarrhoea**
  - Inflammation and bacteraemia
  - **Bloody diarrhoea (dysentery), fever**
  - *Campylobacter jejuni, Shigella, non-typhoidal Salmonella, EIEC*
- **Enteric fever**
  - Unwell with fever, **fewer GI symptoms**
  - *Typohoidal salmonella, Yersinia, Brucella*

Organism		Symptoms / Buzzwords	Treatment
Clostridium	Botulinum	Canned/vacuum packed foods: Honey(kids), beans (students). Ingestion of preformed toxin (inactivated by cooking) Blocks Ach release from peripheral nerves → paralysis **Descending paralysis** - differentiates from GBS	Antitoxin
	Perfringens	Reheated meats, 8-16hrs incubation Watery diarrhoea + cramps, lasts 24hrs. Also causes **gas-gangrene**	
	Difficile	2 exotoxins (A,B) **Pseudomembranous colitis** Caused by Abx - usually cephalosporins/ fluorquinolones *Suspect if severe diarrhoea if recent Hx of Abx*	Metronidazole 2nd line - Vancomycin
Bacillus	Cereus	Reheated rice – *suspect after re-heated takeout* Short incubation ~4hrs Sudden vomiting and non-bloody diarrhoea Reheated rice (spores germinate) and sudden vomiting Superantigen — short incubation (4hrs) Increased cAMP— long incubation (18hrs). Watery non-bloody diarrhoea	Self-limiting
Staph	Aureus	Gram +ve clusters of cocci on gram stain Produces enterotoxin (acts as superantigen → IL1/2 release) Short incubation ~2hrs Prominent vomiting, watery diarrhoea	Self-limiting
Gram -ve Enterobacteriacae E. Coli	ETEC	**T**oxigenic Traveller's diarrhoea	Self-limiting but can treat with cipro *Transmitted in faeces / contaminated water*
	EIEC	**I**nvasive dysentery	
	EHEC	**H**aemorrhagic	
	HUS	Anaemia, thrombocytopenia, renal failure (0157:H7 toxin)	
	EPEC	Infantile diarrhoea (**P**aeds)	

Salmonella	Typhi + Paratyphi	Enteric fever: onstipation, fever, rose spots, splenomegaly *(See fever in the returning traveller)*	IV ceftriaxone then PO azithromycin
	Enteritides	**Poultry**, eggs and meat Non-bloody diarrhoea	Self-limiting Ceftriaxone if required
Shigella		Affects the distal ileum + colon → mucosal inflammation, fever, pain, bloody diarrhoea	Self-limiting Cipro if required
Vibrio	Cholera	**Rice water stool** (massive diarrhoea without inflammation) Comma shaped bacteria (all vibrio)	Self-limiting
	Parahaem -olyticus	Raw seafood (common in Japan)	Self-limiting
	Vulnificus	Cellulitis in shellfish handlers	Self-limiting
Campylobacter	Jejuni	Undercooked **poultry** *(chicken at a BBQ)* Prodrome of fever and headache, then abdo cramps and **bloody diarrhoea** Lasts ~10d Associated with GBS, reactive arthritis	Erythromycin or cipro if in first 5 days
Listeria	Monocyto genes	Refrigerated food, unpasteurised dairy Perinatal infection Severe infection in immunocompromise	Ampicillin
Protozoa			
Entamoeba	Histolytica	**Flask-shaped ulcer** on histology Dysentery, flatulence, tenesmus More common in **MSM**	Metronidazole
Giardia	Lamblia	**Pear-shaped** trophozoite Causes malabsorption of fat → foul-smelling non-bloody diarrhoea	Metronidazole
Cryptosporidium	Parvum	Severe diarrhoea in **immunocompromised**	Paromomycin
Viruses			
Norovirus		Secretory diarrhoea Adult outbreaks	Self-limiting
Adenovirus		Secretory diarrhoea <2yo	Self-limiting
Rotavirus		Secretory diarrhoea <6yo	Self-limiting

Urinary Tract Infection

Classification:

- Uncomplicated Vs Complicated
    - Complicated = functionally / structurally abnormal tract, men, catheters, pregnant
- Lower Vs Upper / Pyelonephritis
    - Lower = only bladder; Upper / Pyelo = kidney infection, systemically unwell

Common organisms, presentation and management of urinary tract infections

UTI is common in women because they have short urethras

- Usually due to contamination (e.g. from rectum). Can be haematogenous (via blood).
- Pathogens:
    - E. coli: most common, adhesion with fimbriae
    - Staphylococcus saphrophyticus: common in young females
    - Proteus, Klebsiella: in abnormal urinary tracts
    - S. aureus: if due to haematogenous spread
- Sx: Frequency, dysuria, abdo pain
    - Elderly: non-specific, delirium, falls
    - Pyelonephritis: systemically unwell, fever + rigors, loin pain
    - Urosepsis: sepsis due to UTI
- Ix:
    - Clinical Dx if typical symptoms
    - Urine dip: +ve nitrites and leukocytes
        - Nitrites are quite specific for UTI – if nitrites -ve, unlikely to be UTI
        - Leukocytes are not specific (seen in any inflammation of urinary tract)
    - Urine MC&S: culture of $>10^4$ colony forming units / ml is diagnostic (10^3 for E. coli / S. saprophyticus)
        - Contamination (i.e. not MSU sample): mixed growth, squamous cells
- Rx: (check trust guidelines, dependent of)
    - Lower UTI: nitrofurantoin / trimethoprim / cephalexin PO, 3d if uncomplicated / 7d if complicated or male
    - Pyelonephritis: admit, IV co-amox + gent

Wound, Bone and Joint Infections

Describe the aetiology, organisms, presentation, diagnosis and management

	Aetiology	Organisms	Presentation	Diagnosis	Management
Surgical site infection	Wound contamination	S. aureus, E. coli, Strep, Pseudomonas	Pain, swelling, failure to heal	Clinical + wound swabs	Abx: fluclox for Staph
Osteomyelitis	Local or haem spread → bone infection	S. aureus	Pain, swelling, unwell + febrile	MRI Blood culture Bone biopsy for culture / histology	IV Abx Debridement is 2nd line

Septic arthritis	Local or haem spread to abnormal joint (e.g. RA) → joint infection	S. aureus, Strep, E. coli	Red, hot, swollen joint, unwell + febrile	Joint aspirate – MC&S Blood culture	IV Abx Drain joint
Prosthetic joint infection	Local or haem spread Prosthetic joint is risk factor for septic arthritis	CoNS, S. aureus, E. coli	Red, hot, swollen joint, failure of joint, pt complains joint was 'never right'	XR/CT/MRI – 'loosening' Joint aspirate (caution – can cause infection if not infected)	IV Abx Remove prosthesis and revise replacement

Hospital Acquired Infections

Onset of infection >48 hours after hospital admission

Common organisms and sites

GI: *Clostridium difficile* diarrhoea.

- Transmission: Spore ingestion.
- Predisposing factor: existing gut flora disturbed by antibiotics, **particularly 3Cs: c**lindamycin (often used in penicillin allergic patients with cellulitis), **c**ephalosporins, **c**iprofloxacin
- Pathology: Toxin. Pseudomembranous colitis.
- Rx: Oral metronidazole.

UTI: *E. coli*. Resistance: Extended spectrum beta-lactamases

- Risk factor: Catheter
- Other organisms*: Klebsiella, Proteus, Pseudomonas*

Bacteraemia: Methicillin-resistant *Staphylococcus aureus,* coag –ve staph, E.Coli
Surgical site infection: MRSA, Coagulase-negative *Staphylococcus*

CNS Infection and Meningitis

Meningitis (see below): inflammation of meninges

- Causes:
  - **Bacterial:** *Neisseria meningitidis* (Gram -ve), *Streptococcus pneumoniae* (Gram +ve)
    - Neonates: Group B *Strep*, *Listeria monocytogenes*, *E. coli*
    - Elderly: Group B *Strep*, *Listeria monocytogenes*
  - **Viral:** Enterovirus (coxsackie, echovirus), mumps, HSV2
    - Viral presents the same as bacterial (but often less severe)
  - **Fungal:** *Cryptococcus neoformans* (chronic)
  - **NB chronic / subacute meningitis** presents with headaches for months, caused by TB or cryptococcus

Encephalitis: inflammation of brain parenchyma

- Sx: confusion, fluctuating consciousness
- Most commonly caused by HSV1
- Rx: IV acyclovir

Brain abscess: localized collection of infection

- Sx: as for SOL, swinging fever
- From local extension (e.g. otitis media) or haematogenous spread (e.g. endocarditis)

Aetiology, presentation, diagnosis and management of bacterial meningitis

Bacterial meningitis

- Systemic spread (i.e. haematogenous) or local (e.g. skull #)
- Risk factors
    - Overcrowding, young adults / very young or old
    - *N. meningitidis*: Complement deficiency, hyposplenism (susceptible to encapsulated organisms), hypogammaglobulinaemia
    - *S. pneumoniae*: Complement deficiency, hyposplenism, immunosuppressed (alcoholic), infection (pneumonia), entry #, previous head trauma w/ CSF leak
- Sx: Headache, vomiting, photophobia, fever, focal neuro signs, rash (meningococcal)
  Dx: Clinical + blood cultures, lumbar puncture for CSF analysis (see below)
  Rx: **Resuscitate! IV ceftriaxone and corticosteroids** (cover Listeria with ampicillin)
    - If consciousness affected, consider IV acyclovir to cover encephalitis

CSF Analysis	Appearance	Glucose	White Cells	Cell Type	Other
Bacteria	**Turbid**	**Low**	High	**Polymorphs**	
Partially treated bacterial	Turbid	Normal	High	Polymorphs	
Virus	Clear	Normal	High	**Mononuclear**	
TB	Clear / turbid	Low	High	Mononuclear	**Protein**

NB normal CSF glucose levels are 2.2-2.3 (~60% blood level)

Sexually Transmitted Infections

Common Presentations:

Men	Women
Asymptomatic	Asymptomatic
Urethral discharge	Vaginal discharge (+/- urethral, rectal)
Dysuria	Ulceration painful/painless
Scrotal pain/swelling	Itching/soreness, “lumps/growths”
Rash/sores	Abnormal bleeding; IMB, PCB
Systemic symptoms	Abdo pain, Dyspareunia, Dysuria
	Systemic symptoms

Discharge	Ulceration	Rashes, Lumps/Growths
Gonorrhoea	Syphilis - painful	Genital warts - HPV
Chlamydia	HSV - painless	Molluscum contagiosum
Trichomonas	LGV	Scabies
Candida	Chancroid	Pubic lice
Bacterial Vaginosis	Donovanosis	

Gonorrhoea

- *Neisseria gonorrhoeae:* obligate intracellular Gram –ve diplococcus.

Men	Women
Uncomplicated Infection (90%)	
Gonococcal Urethritis • Most common STI in Europe • Mucoid/Mucopurulent discharge	1) Mucopurulent cervicitis • Erythema and oedema • Urethra (vaginal leakage)
Post-gonococcal Urethritis (PGU) • Following gonorrhoea Rx • Prevented by concomitant Rx with a tetracycline	
Rectal proctitis • Mainly in MSM	
Complicated Infection (10%)	
• Prostatitis	PID (Salpingitis) • Ascending infection

- ***Opthalmia neonatorum*** (neonatal conjunctivitis) develops if left untreated when transfer to child from birth canal.
- Disseminated gonococcal infection in pts with complelement deficiencies -> sepsis, rash, arthritis
- **Diagnosis**: urethral (sensitivity 95%) / rectal (sensitivity 20%) smears – producing a culture from these is Gold Standard.
- **Treatment:** Ceftriaxone IM – 250mg single dose

Chlamydia

- *Chlamydia trachomatis:* Obligate intracellular gram -ve pathogen. Cannot be cultured on agar
- Common in young adults – in the UK 10% of <25yo are infected
- Often **asymptomatic** (50% men, 80% women)
- **Classification:**
  - Serovars A, B, C: trachoma (infection of the eyes which can cause blindness)
  - Serovars **D-K**: genital chlamydia, ophthalmia neonatorum
- Diagnosis: **NAAT** (nucleic acid amplification tests) from genital swabs
- Treatment: **azithromycin** 1g stat, or **doxycycline** 100mg BD for 7 days
- Complications:
  - **PID** → tubal factor infertility, ectopic pregnancy, chronic pelvic pain
  - Epididymitis
  - Reiter's syndrome
  - Adult conjunctivitis, ophthalmia neonatorum

Lympho-granuloma venereum (LGV)

- Lymphatic infection with Chlamydia trachomatis: serovars **L1, L2 and L3**
- Endemic in parts of developing world. More recently MSM in developed world
- Symptoms:
  - Early LGV (1° stage): 3-12 days, painless genital ulcer, proctitis, balanitis, cervicitis
  - Early LGV (2° stage): 2wks – 6 months, **painful inguinal buboes**, fever, malaise
    - Rarely: hepatitis, meningo-encephalisis, pneumonitis

    - Late LGV: **inguinal lymphadenopathy**, **genital elephantiasis**, genital and perianal ulcers / abscesses, frozen pelvis
    - Current LGV outbreak: rectal symptoms / proctitis (pain, tenesmus, bleeding)
- Diagnosis: NAAT, genotypic identification of L1/2/3 serovar
- Treatment: doxycycline 100mg BD for 3wks

Syphilis

- *Treponema pallidum* – Obligate gram-negative spirochaete

Syphilis
1° syphilis Macule → papule → **painless solitary genital ulcer** appearing 1-12 weeks following transmission. May persist 4-6 weeks (chancre). Regional adenopathy.
2° syphilis Systemic bacteraemia 1-6 months after infection → fever, malaise, lymphadenopathy **Rash on palms and soles** (also back, trunk, limbs) **Condyloma acuminate (**genital warts) Mucosal lesions, uveitis Neurological involvement
Latent – No obvious signs but serological infection (**asymptomatic**)
3° syphilis 2-30yrs later, 3 different syndromes: • **Gummatous** – skin / bone / mucosa granulomas Spirochaetes scanty • **Cardiovascular** – mimics any cardiac disease, especially causes aortic root dilatation / aortitis. +++ spirochaetes, +++ inflammation • **Neurosyphilis** – dementia, tabes dorsalis, Argyll-Robertson pupil. Spirochaetes in CSF.

- Diagnosis:
    - Treponemes seen in 1° lesions by **dark-ground microscopy**. Can be detected with PCR
    - Antibody tests are tests of choice (treponemal and non-treponemal)

1. Non-Treponemal tests
    - Detect antibodies against **non-specific antigens**
    - VDRL slide test: detects lipoidal antibody on host and treponemal cells
    - Can get **false +ves** → need to confirm with treponemal test
    - RPR is a modified VDRL test
    - Useful in primary syphilis
    - Titre falls in response to treatment → can be used to monitor response
2. Treponemal tests
    - Detect Abs against **specific antigens** from T. pallidum
    - Examples: Enzyme Immunoassay (EIA), Fluorescent treponemal antibody (FTA), T. pallidum haemagglutination test (TPHA), T. pallidum particle agglutination test (TP-PA)
    - More specific than non-treponemal test
    - Remains **positive for years** despite effective Tx

- Treatment: **Single dose IM Benzathine Penicillin** (Doxycycline if allergic)
    - Monitor RPR, need to see a four-fold reduction to consider Tx successful
    - NB: **Jarisch-Herxheimer reaction** (flu-like symptoms, sometimes exacerbation of syphilitic symptoms) – common, develops within hours of Abx, clears within 24hrs.

Congenital syphilis: may occur during pregnancy or birth. Develop features over the first couple of years including hepatosplenomegaly, rash, fever, neurosyphilis and pneumonitis. Late congenital syphilis can occur in 40%.

Other bacterial STIs

Chancroid: Haemophilus ducreyi. Gram -ve coccobacillus (like Hib)

- Tropical ulcer disease mainly in Africa, rare in UK
- Multiple painful ulcers
- Diagnosis: culture (**chocolate agar**), PCR

Donovanosis = Granuloma inguinale

- Klebsiella granulomatis. Gram negative bacillus
- Africa, India, PNG, Australian aboriginal communities
- Large, **beefy red ulcers**
- Diagnosis: Giemsa stain of biopsy or tissue crush. **Donovan bodies**
- Treated with azithromycin

Enteric pathogens (Oro-anal contact)

- Shigella, salmonella, Giardia (protozoan), Occasionally others (Strongyloides)

Trichomoniasis

- Flagellated protozoan – T. vaginalis
- Men: usually asymptomatic, sometimes urethritis
- Females: discharge, **strawberry cervix**
- Diagnosis: wet prep microscopy, (flagellated organisms seen), PCR
- Treatment: **metronidazole**
- Associated with increased risk of HIV infection (due to mucosal damage)

Bacterial vaginosis

- Abnormal vaginal flora, polymicrobial, ↓lactobacilli.
- Discharge, odour
- Sexually associated, **not** transmitted. Associated with hygiene practices (soaps)
- Diagnosis: microscopy of gram stain, raised pH, whiff test, **clue cells**
- Treatment: lifestyle - just use water for washing (no soaps). Metronidazole PO/topical

Candidiasis

- Usually Candida albicans, yeast
- Thick white discharge (“cottage cheese”), itching, soreness, redness
- Vulvovaginitis in women, balanitis in men
- **Not** sexually transmitted; can be part of normal flora
- Associated with **immunodeficiency** (incl. pregnancy, DM), **hygiene** practices (soaps)
- Treatment: PO / topical antifungals, e.g. clotrimazole or fluconazole

Molluscum contagiosum

- Pox virus, dsDNA
- Small papules with central punctum
- Children: hands and faces, spread by skin-to-skin contact.
- Adults: genital lesions, spread via sexual contact.
- Widespread lesions in immunosuppressed / HIV
- Usually no treatment necessary; cryotherapy if persistent / extensive

Genital Warts

- dsDNA Human Papillomavirus. Visible genital warts: HPV 6 or HPV11 (not assoc. with ↑ risk cervical dysplasia)
- Clinical diagnosis – papular, planar, pedunculated, carpet, keratinised, pigmented
- Home treatment – Podophyllotoxin solution or cream. Not for pregnant women
- Clinic treatment – Cryotherapy. 2nd line – Imiquimod
- Oncogenic HPV types (16, 18) assoc. with cervical, anal, penile, vulval, head, neck cancers. Vaccine in 2012 changed to quadrivalent to include 6 and 11

Viral STIs

- Hepatitis – HAV (oro-anal sex), HBV, HCV (Mainly HIV+ve MSM, rarely sexually transmitted in heterosexuals)
- Herpes
- HIV

Antimicrobial Agents

Classification of the main groups of agents

Target	Class	Example	Indication
Inhibit cell wall synthesis	β-lactams: - Penicillins - Cephalosporins ($1^{st}/2^{nd}/3^{rd}$ generations) - Carbapenems	 Amoxicillin Ceftriaxone Meropenem	Gram positive Gram negative: 3^{rd} gen cephalosporins, carbapenems
	Glycopeptides	Vancomycin, Teicoplanin	MRSA, C.Diff
Inhibit protein synthesis	Aminoglycosides	Gentamicin	Gram negative sepsis
	Tetracyclines	Doxycycline	Intracellular, e.g. chlamydia
	Macrolides	Erythromycin	Gram +ve (penicillin allergy), atypical pneumonia
	Chloramphenicol	Eye drops	Bacterial conjuctivitis
	Oxazolidinones	Linezolid	Gram +ve, MRSA + VRE
Inhibit DNA synthesis	Fluoroquinolones	Ciprofloxacin	Gram negative
	Nitroimidazoles	Metronidazole	Anaerobes + protozoa
Inhibit RNA synthesis	Rifamycin	Rifampicin	Mycobacteria – used in TB
Cell membrane toxin	Polymyxin	Colistin	Gram negative
	Cyclic lipopeptide	Daptomycin	Gram +ve, MRSA + VRE
Inhibit folate metabolism	Sulfonamides	Sulphamethoxazole	PCP (with trimethoprim = co-trimoxazole)
	Diaminopyrimidines	Trimethoprim	UTI

Broad spectrum: Co-amoxiclav (amoxicillin + clavulanic acid), tazocin (piperacillin + tazobactam), ciprofloxacin, meropenem
Narrow spectrum: flucloxacillin, metronidazole, gentamicin

The four mechanisms of antibiotic resistance – BEAT drug action

1. **B**ypass antibiotic-sensitive step in pathway e.g: MRSA
2. **E**nzyme-mediated drug inactivation e.g: β-lactamases
3. Impairment of **A**ccumulation of the drug e.g: tetracycline resistance
4. Modification of the drug's **T**arget in the microbe e.g: Quinolone resistance

Typical antibiotics used against various focal and systemic infections

(Each trust will have protocols for antibiotic choice/dosing – use local guidelines!)

Site	Organism/severity/circumstance	Antibiotic
Skin	S. aureus	Flucloxacillin (unless allergy)
Pharyngitis	β-haemolytic Streptococcus	Benzylpenicillin
Community-acquired pneumonia	Mild	Amoxicillin
	Severe	Co-amoxiclav + clarithromycin
Hospital-acquired pneumonia		Co-amox + gent or tazocin
Bacterial meningitis	Meningococcus/streptococcus	Ceftriaxone (+ amox if RFs for listeria – young/old)
UTI	Community	Trimethoprim / nitrofurantoin
	Nosocomial	Co-amoxiclav or cephalexin
Sepsis	Severe	Tazocin / ceftriaxone, metronidazole ± Gent
	Neutropenic	Tazocin + gentamicin
Colitis	Clostridium difficile	Metronidazole (stop ceph!) Vancomycin (2nd line)

Microbiology in Immunocompromised hosts

Reasons why someone may be immunosuppressed

- Genetic (rare)
- Acquired
    - Transplant
        - Solid organ transplant
        - Human stem cell transplant (requires short term immunosuppression)
    - Chronic conditions e.g. AIDS
    - Iatrogenic: Chemotherapy (neutropaenia)/Bologics (cause specific immune deficiencies)/corticosteroids

Viral infections in immunocompromise present differently:

- Disseminated
- Different organs
- More severe
- Oncogenic (HHV8 = Kaposi sarcoma)

Pathogens of specific concern

Either:

- Do not cause disease in immunocompetent
- Cause more severe/disseminated disease in immunocompromised

- Require consideration of prophylaxis/treatment in immunocompromised patients (normally antivirals)

Viruses

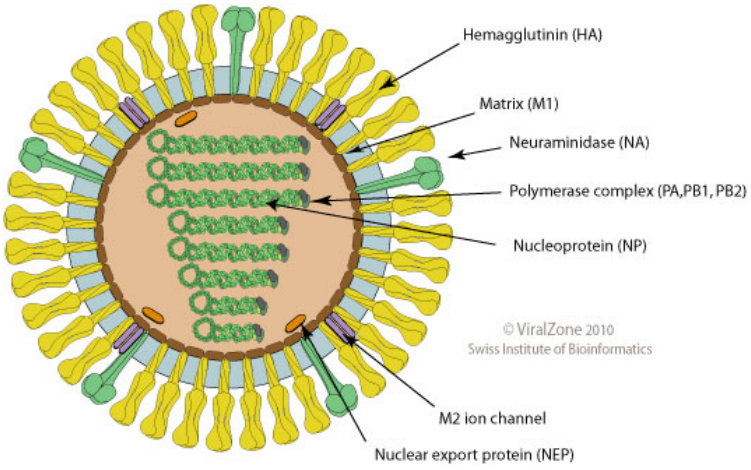
- **Herpesviridae (cause latent infections):** CMV, EBV, HSV, HHV8, VZV
- **Polyomaviridae:** JC virus + BK virus
- **Respiratory viruses:** Influenza A and B, Parainfluenza 1, 2, 3 and 4, Respiratory Syncytial Virus (RSV), Adenovirus, MERS coronavirus
- **Hepatitis viruses:** A (normally vaccinate prior to immunosuppression), B, C, E (increased risk of chronicity)

Fungi

- Candida
- Cryptococci
- Aspergillus
- Dermatophytes
- Mucormycosi

Key Influenza Virus

Family Orthomyxoviridae.
Enveloped virus, wild-type virion has a filamentous morphology, negative sense segmented RNA genome (8 segments).



Pandemic Flu

- A pandemic virus will have novel antigenicity.
- A pandemic virus will replicate efficiently in human airway.
- A pandemic virus will transmit efficiently between people.

Influenza A and B generally cause the seasonal epidemics of disease - different subtypes of these come to prominence each year. Most common subtypes are

1. Influenza A (H1)
2. Influenza A (H3N2)
3. Influenza B

Natural reservoir of Influenza A is ducks
Human → human transmission of bird flu (H5N1) difficult as virus does not replicate very well at cold temperatures of upper airways (32^{O}C).
Better in deeper lung tissue (still not ideal – 41.5^{O}C) and from here it is difficult to escape.

Predominantly a respiratory disease because virus is activated by **human airway tryptase** found in lung tissue

RNA segments = 8 segments of nucleocapsid protein, v. prone to mutation.

- **NA – neuraminidase (sialidase) activity**
  - Cleaves sialic acid residues allowing exit of virions from the host cell, disrupts mucin barrier.
- **HA – haemagglutinin activity: (**Named for causing agglutination of RBCs/URT cells**)**
  - Binds sialic acid receptors, virus entry. Endosomal-viral envelope fusion = release
  - Virus strains named after this structure e.g. H5N1=HA5, NA1

Antigenic Drift = Accumulation of point mutations (Due to error prone RNA polymerases) changes the nature of the antigen over time (drift)
Antigenic Shift = Recombination of genomic segments of two co-infecting flu strains→ leads to rapid potentially whole antigenic change for a viral strain (shift)

- Potentially allows exchange of RNA segments between human and animal strains

Pathogenesis

- Cleavage of influenza HA by clara tryptase in the lung leads to extended tropism/growth for H5 + H7

Causes for severe outcomes of flu

- Secondary bacterial pneumonia/Mutant virus/Co morbidity/Cytokine storm

Antivirals for Influenza

- Amantadine - Targets M2 ion channel
  (Influenza A only - Ineffective against influenza B due to their lack of the M2 protein, influenza B has an alternative ion channel called BM2)

BUT **no longer recommended** treatment as single AA mutation (S31N) in M2 = resistance (now present in >50% of influenza A subtypes)

- Polymerase inhibitors: Baloxavir

- Neuraminidase inhibitors (effective against Influenza A & B):

    - Oral **Oseltamivir (Tamiflu)**,
    - Inhaled Zanamivir (Relenza – used in patients with underlying respiratory disease),
    - IV Peramivir (licensed in the UK but not used widely) – Effective only if given <48hrs after infection

Virology Summary Table

Virus	Virology	Clinical	Treatment
Herpesviridae			
Herpes Simplex Virus (HSV)	Enveloped, dsDNA genome Lies latent in sensory neurons	1. Herpes labialis (cold sores) (HSV-1) a. Incubation 2-12/7. Severe painful ulceration, tendency to coalesce, erythematous base b. Fever + submandibular lymphadenopathy. Differential – Herpangina (Coxsackie A) 2. Genital ulceration (HSV-2) a. Incubation 4-7/7. Fever, dysuria, malaise, Inguinal lymphadenopathy, Pain++, vesicular rash b. Herpes meningitis 1-2/52 later in 4-8% of 1° genital herpes. SACRAL RADICULOMYELTIS – urinary retention (self limiting) **In immunocompromised:** 1. Cutaneous dissemination 2. Oesophagitis – *pain on swallowing* 3. Hepatitis 4. Viraemia **Congenital infection (85% perinatal):** 1. Neurological: Microcephaly, encephalomalacia, hydranencephaly 2. Skin: scarring, active lesions, hypo- and hyperpigmentation 3. Eyes: microphthalmia, retinal dysplasia, optic atrophy, and/or chorioretinitis	**Aciclovir:** guanosine analogue - Competitively inhibits viral DNA polymerase by acting as an analogue to deoxyguanosine triphosphate (dGTP). - Incorporation of aciclovir triphosphate into DNA results in chain termination - Absence of a 3' hydroxyl group prevents the attachment of additional nucleosides OR **Valaciclovir**
Varicella Zoster Virus (VZV)	Enveloped, dsDNA genome Lies latent in sensory neurons; hence dermatomal distribution when it is reactivated	**Chicken pox:** Fever, malaise, headache followed by characteristic crops of rash (dew on a rose petal). Lesions scab after 1/52 (no longer contagious). Complications — scarring/pneumonitis/haemorrhage/Eye involvement/Reye's syndrome/ Neurological – Acute cerebellar ataxia, Guillain Barre, Ramsay Hunt syndrome – facial palsy + vesicles in ear – Geniculate ganglion of CNVII (hearing loss + vertigo), Encephalitis (vasculopathy), Post-herpetic neuralgia **Shingles** (reactivation) → stress/↓immunity (immunocompromised, >50yrs), Painful rash in specific	**Acyclovir** 800mg PO 5x/day 7/7 or ValAciclovir 1g TDS - Indications: All **adults** with chickenpox (at risk of complications), **Neonates**, **Immunocompromised**, **Eye** involvement, All pts presenting with pain Post-exposure prophylaxis: VZIG (Immunocompromised, Pregnant women) Live vaccine against varicella – Attenuated

		dermatome **In immunocompromised:** 1. Rare complications more likely 2. Acute retinal necrosis 3. Progressive outer retinal necrosis (PORN) 4. Multidermatomal shingles **Congenital infection:** 1. Eyes: chorioretinitis, cataracts 2. Neurological: microcephaly, cortical atrophy 3. MSK/skin: limb hypoplasia, cutaneous scarring **Neonate** 1. Purpura fulminans 2. Visceral infection 3. Pneumonitis	Oka strain (Contraindicated in pregnancy) Rx of shingles – Symptomatic children OR (If <24hrs of rash) Healthy Adult smokers, Chronic lung disease, >20/40 gravid - Aciclovir 800mg PO 5x daily OR Famciclovir 250 mg PO TDS OR Valaciclovir 1000mg PO TDS - Topical eye drops plus oral for ophthalmic - PEP 7-9/7 for Immunocompromised Diagnosis • Exam – vesicles (?HSV) • Cytology – scrapings for multinucleated giant cells (Tzanck cells) • Immunofluorescence cytology – cells from vesicles • PCR – especially if rash is old, CNS and ocular disease
Human Cytomegalovirus (HCMV)	Enveloped, dsDNA genome Lies latent in monocytes and dendritic cells CMV cells –'owls eye inclusions'	In **immunocompromised** (major issue for **transplant patients**): 1. Encephalitis 2. Retinitis 3. Pneumonitis 4. Colitis 5. Marrow suppression **Congenital infection:** 1. Ears: sensorineural deafness 2. Eyes: chorioretinitis 3. Heart: myocarditis 4. Neurology: microcephaly, encephalitis 5. Lung: pneumonitis • Liver: hepatitis, jaundice, hepatosplenomegaly	- **1st line Ganciclovir (IV)/valganciclovir (oral):** guanosine analogue chain terminator - **2nd line Foscarnet (IV):** Non-competitive inhibitor of viral DNA polymerase o Pyrophosphate analogue, inhibits nucleic acid synthesis without requiring activation. Also used as prophylaxis post organ transplant. o Nephrotoxic! - **3rd line Cidofovir (IV):** cytidine analogue chain terminator o Often used in treatment of non-herpes viral infections in the opportunistic post-transplant setting: o Eg: BK virus for BK nephropathy/BK cystitis/Adenovirus/PML (JC virus) IVIg (adjunct in pneumonitis)

Epstein-Barr virus (EBV)	Enveloped, dsDNA genome Lies latent in B cells *EBV not dangerous in pregnancy.	1. Glandular fever: Triad of fever, pharyngitis, lymphadenopathy (incubation 4-6/52) + maculopapular rash. a. Diagnosis - blood film, monospot agglutination, EBV antibodies Nb: Paul-Bunnell test 2. Predisposes to Burkitt's lymphoma **In immunocompromised:** Post-transplant lymphoproliferative disease (Predisposes to lymphoma. Treatment – reduce immunosuppression + give Rituximab (anti-CD20 monoclonal Ab))	1. Largely supportive care • Avoid penicillins: can provoke wide-spread maculopapular rash in EBV infection (infectious mononucleosis exanthema)
Human Herpesvirus 6 (HHV 6) also known as **Roseola Virus**	Latent in monocytes/lymphocytes	1. Roseola infantum (=exanthum subitum, Sixth disease). 3/7 fever, then sudden appearance of a maculopapular rash – mainly on trunk, but sometimes spreads to face and extremities. Most common cause of febrile convulsions. Route of transmission: Droplet infection	Symptomatic treatment – fluids Dx: Usually clinical diagnosis, blood PCR
Human herpesvirus 8 (HHV8) also known as Kaposi's sarcoma herpesvirus (KSHV)	Enveloped, dsDNA genome Genitally transmitted	**In immunocompromised:** • Kaposi's sarcoma (Pathognomonic for HIV) • Primary effusion lymphoma (assoc with EBV coinfection) • Castleman's disease (non-cancerous growth in the LNs).	• Chemoradiotherapy, surgical excision, initiation of HAART (highly active antiretroviral therapy) for causative HIV infection
Polyomaviridae			
JC virus	Unenveloped, dsDNA genome	**In immunocompromised** (especially AIDS): 1. Progressive multifocal leukoencephalopathy 2. Rapidly demyelinating disease + neurological deficits	• Anti-retroviral therapy for HIV
BK virus	Unenveloped, dsDNA genome	**In immunocompromised** (especially transplant): 1. BK haemorrhagic cystitis 2. BK nephropathy	1. **Cidofovir** (cytidine analogue chain terminator)
Respiratory viruses			
Influenza virus	Enveloped, negative sense segmented genome (8 segments)	URTI; systemic features include muscle aches	1. **Oseltamivir (Tamiflu)-** inhibits NA, blocks virion release • Amantadine (not really used clinically)- inhibits M2 ion channel; blocks

			uncoating
Adenovirus	Unenveloped, dsDNA genome	**In immunocompromised** (especially transplant): 1. Encephalitis 2. Pneumonitis 3. Colitis	Usually self-limiting, so supportive care in ITU or HDU setting In multi-organ involvement: **Cidofovir; IVIG**
Coronaviruses	Positive sense ssRNA genomes Causative organisms for SARS and MERS pandemics	URTIs, sometimes with systemic symptoms e.g. myalgia Severe infections can cause ARDS, respiratory failure, shock, multiple organ dysfunction	Usually self-limiting Dexamethasone + remdesivir if severe/requiring hospital admission
Hepatitis viruses			
Hepatitis A virus	Unenveloped picornavirus, positive sense ssRNA genome	1. Acute hepatitis – 2-6 weeks incubation, severe in elderly Faeco-oral transmission Dx: Acute - Anti-HAV IgM (IgM persists up to 14w)	1. Largely supportive care Vaccine Live attenuated and inactivated preparations
Hepatitis B virus	Enveloped hepadnavirus (reversivirus); hybrid genome, mostly DNA with an associated RNA species	1. Acute and chronic disease 2. Transmission via bodily fluids: sexual, vertical, blood products 3. **Virus is cleared in the majority of individuals:** 90% clearance > 5 y.o.; 10% clearance in neonates **In immunocompromised** (especially B-cell depleting therapies i.e. rituximab): • Risk of reactivation **HBV serology** *HBs (surface) Ag* If present is an indication of active infection. Persists in chronic infection *HBeAg* Marker of infectiousness (not always present in active infection, but if +ve shows patient is actively infectious Anti-HBc* (core) Ab IgM – antibodies to acute infection Anti-HBc* (core) Ab IgG – antibodies to past infection (i.e. positive	1. **Interferon alpha** 2. **Lamivudine (nucleoside analogue)** 3. **Entecavir (nucleoside analogue)** 4. **Telbivudine (nucleoside analogue)** 5. **Tenofovir (nucleoTide analogue)** Treatment goal – Prevent progression to cirrhosis + HCC. Maintain serum HBV DNA level as low as possible → attain histology improvement, ALT normalization. Loss of HBVeAg and seroconversion to HBVeAb Pegylated Interferon (INF) Alpha 2a (subcut) – Direct antiviral effect + upregulates expression of MHC on cell surfaces 1. **Vaccine:** Recombinant vaccine, purified

		in cleared prev. infection AND in chronic infection) *not present if immunity is from the vaccine – vaccine contains **Surface Ag only**	HbSAg
Hepatitis C virus	Enveloped flavivirus, positive sense ssRNA genome	1. Acute and chronic disease 2. Mainly blood product spread ▪ **60-80% chronicity** Complications: Cirrhosis, Cryoglobulin Ax disease + glomerulonephritis. - Genotypes 1 (40-50% of HCV UK burden), 4, 5, and 6 – Treatment less successful - Genotypes 2 and 3 – (40-50% of HCV UK burden) Treatment more successful Measure HCV RNA to confirm infection and assess treatment response (anti-HCV Ab develops after acute infection)	2. Initially interferon therapy (Peg INF α 2b/2a) Now highly effective directly acting antivirals → **curative** 3. **NS3/4 protease inhibitors (-previrs, block translation):** *telaprevir, boceprevir, simeprevir, asunaprevir* (learn one or two) 4. **NS5A inhibitors (-asvirs, block release):** *ledipasvir, daclatasvir* 5. **Direct polymerase inhibitors** (-buvirs, block replication): *Sofosbuvir, dasabuvir*
Hepatitis D virus	Deltavirus, enveloped virus, negative sense, single-stranded circular RNA	1. Coinfection (simultaneously) with Hep B 2. Superinfection (on top of chronic) Hep B (more severe – often leads to cirrhosis within 2-3yrs) Transmission: Sexual, parental, perinatal (only possible in combination with HBV)	Peginterferon-α
Hepatitis E virus	Unenveloped positive sense ssRNA genome	1. Acute hepatitis – India 2. Faeco-oral transmission Rare complications: CNS disease – Bell's palsy, Guillain Barre, other neuropathy; Chronic infection	Largely supportive care Vaccine - Effective in trials- recombinant HEVg1
Paediatric infections			
Rubella virus	Enveloped virus, positive sense ssRNA genome	1. German measles a. Maculopapular rash b. Lymphadenopathy c. Fever d. Lesions on soft palate (Forchheimer sign)	1. **MMR vaccine** • No antiviral therapy available

		Congenital infection: (Congenital Rubella Syndrome) 1. Ears: sensorineural deafness 2. Eyes: Cataracts, glaucoma, retinopathy, microphthalmia 3. Heart: PDA, VSD 4. Neurology: microcepahly, psychomotor retardation 5. Pancreas: insulin dependent DM (late) 20% incidence of spontaneous abortion if infected before 8 wks. If infected between 13-18wks may have hearing defects and occasionally retinopathy. However, if >20 weeks at infection there is no documented risk.	
Human parvovirus B19	Unenveloped, dsDNA genome	1. Slapped cheek (fifth disease) a. Erythema infectiosum b. Transient aplastic crisis c. Arthralgia d. Fever and malaise 2. Viral myocarditis **Congenital infection:** 1. Foetal anaemia → cardiac failure → hydrops foetalis	1. **Intrauterine blood transfusion** (congenital infection)
Morbillivirus	Enveloped, negative sense ssRNA genome	1. Measles a. Fever, malaise b. Cough, coryzal symptoms, conjunctivitis c. Koplik's spots (buccal mucosa) d. Maculopapular rash **Congenital infection:** 1. No foetal abnormalities 2. Foetal loss, preterm delivery	MMR vaccine
Zika virus	Enveloped falvivirus, positive sense ssRNA genome	**Congenital infection:** 1. Severe microcephaly + skull deformity 2. Decreased brain tissue, subcortical calcification 3. Retinopathy, deafness 4. Talipes (feet turned in like club foot), contractures 5. Hypertonia	

Serology in Hepatitis

	Acute infection	Chronic Infection	Previous infection	Vaccinated
Hepatitis A				
Anti-HAV IgM	+	N/A	-	-
Anti-HAV IgG	-	N/A	+	+
Hepatitis B				
HBsAg	+	+	-	-
Anti-HBc	+	+	+	-
IgM anti-HBc	+	-	-	-
Anti-HBs	-	-	+	+
Hepatitis C				
Anti-HCV IgG*	-	+	+	N/A
HCV RNA	+	+	-	N/A
Hepatitis E				
Anti-HEV IgM	+	N/A	-	**
Anti-HEV IgG	-	N/A	+	**

* Although the use of Anti-HCV IgM and IgG serology is theoretically possible to differentiate between acute and chronic HCV infection this is a controversial topic. In clinical practice HCV IgM is rarely available and its utility still contested.
** Not yet widely available

Neonatal and Childhood Infections

Important infections: aetiology, presentation, diagnosis and management

Congenital infection: TORCH (**T**oxoplasmosis, **O**ther(HIV,HBV), **R**ubella, **C**MV, **H**SV)

- Ax: **Transmission from mother**
- Px: Non-specific: (**T**hrombocytopenia, **O**ther(ears/eyes - cataracts, choroidoretinitis), **R**ash, **C**erebral abnormality eg: microcephaly, **H**epatosplenomegaly)
- Dx: Serology
- Rx: **Prevention**! TORCH screen.

Neonatal (<6 weeks old) infection:

Early onset sepsis (<48 hrs after birth): **Group B *streptococci***, *E. coli*, *Listeria*

- Ax: Maternal: PROM, fever, foetal distress. Foetal: resp distress, acidosis, asphyxia
- Px: Fever, unwell - meningitis
- Dx: Septic screen: FBC, CRP, blood culture, deep ear swab, CSF, surface swab, CXR
- Rx: ABC, supportive, nutrition, Abx: BenPen + Gentamicin. Amox/Ampicillin if Listeria

Late-onset sepsis (>48 hrs after birth): Coagulase negative staph + GBS, *E. coli*, *Listeria*

- Px: Bradycardia, apnoea, poor feeding, irritability, convulsions, jaundice, resp distress, focal inflammation – examine umbilicus
- Dx: Septic screen + urine
- Rx: Antibiotics: 1st line = Benzylpenicillin + Gent, 2nd line (if v. ill) = Tazoxin + Vanc. Late-onset from community: Amox + Cefotaxime - Listeria & community meningitis (BenPen given in GP).

Childhood infection

- Bugs: VZV, HSV, Secondary bacterial infection
- Px: Non-specific: Fever, abdominal pain
- Dx: FBC, CRP, blood/urine/sputum culture

Bacterial meningitis: (more next section)

Neisseria meningitidis (non-blanching petechial rash) Commonest >3months of age.
Streptococcus pneumoniae <2yr old
Haemophilus influenzae in <3 month olds and unvaccinated children
GBS, E.Coli, Listeria common 1-3months so empirical Abx at this age incl Amox

Respiratory tract infections are common

- Bugs: Viruses (esp. in young). Then *S. pneumoniae, mycoplasma* possible if >4yr

Urinary tract infections

- Bugs: *E. coli,* then *proteus, klebsiella, enterococcus*
- Dx: Culture >10^5cfu/ml. Microscopy: pyuria (pus cells) + clinical symptoms

PUO + Fever in the Returning Traveller + Malaria

PUO (Pyrexia of Unknown Origin)

>38.3ºC fever on several occasions persisting >3/52 without diagnosis despite >1/52 of intensive Ix

PUO Type	Examples
Classical PUO *As defined above incl. >3/7 in hospital or >3 O/P visits with ambulatory Ix*	- Infections (incl. abscesses, endocarditis, TB) - Malignancy - Connective tissue disease
Healthcare-associated PUO *Develops in a patient following >24hrs in hospital*	- Hospital-acquired infections (LRTI, C. diff, UTI) - Medical devices (catheter, IV line bacteraemia) - Surgery - Drugs (vancomycin, penicillins, serotonergics) - Immobilisation
Neutropenic PUO *Fever concomitant with neutropenia (<500/uL) and subsequent lack of cellular response.* *MEDICAL EMERGENCY*	- Chemotherapy - Haematological malignancies - Drugs (clozapine, carbimazole)
HIV-associated PUO *HIV +ve patients frequently have PUO*	- Seroconversion - Infection (TB, bacteria, PCP, MCV, etc.) - Malignancy (Kaposi's sarcoma, lymphoma) - Drugs

PUO Workup – Observe fever! If possible, withhold therapy until diagnosis is reached

- Febrile neutropaenia: Take blood cultures, then immediately start empirical Abx. Try to identify source as this will guide antibiotic choice.

Consider other causes…

- Vasculitis screen: pANCA, cANCA, Rho, La etc… (Rheumatology r/v if arthritis)
- Bence Jones/protein electrophoresis (myeloma etc.)
- Dip urine/casts
- Familial diseases eg: FMF, Fabry's disease, cyclic neutropenia
- Fever in returning traveler

Fever in a Returning Traveller

Causes: tropical diseases (especially malaria, typhoid, dengue, viral haemorrhagic fevers), bacterial diarrhoea (E. coli, cholera)

- Don't forget about common UK causes too, e.g. UTI, pneumonia, influenza
- Beware of questions pointing you towards STIs (e.g. HIV seroconversion)

Typhoid

- Salmonella typhi and paratyphi (anaerobic gram -ve bacilli)
- Travel to India, transmitted in food and water, incubation 1-2wks
- Causes **enteric fever** by infecting Peyers patches in intestines

    - **Fever**, headache, **constipation** (not diarrhoea!)
    - **Rose spots**, relative bradycardia, hepatosplenomegaly
- Ix: blood and stool cultures
- Rx: IV ceftriaxone then PO azithromycin
- Complications: GI perforation
- Vaccinate against S. typhi

Dengue:

- Flavivirus spread by the **Ades mosquito**
- South-East Asia, urban environments, short incubation (days)
- Sx: myalgia, fever, rash. Reasonably mild + self-limiting
- If re-infected with a different serotype…
    - **Dengue haemorrhagic fever / dengue shock syndrome**
    - Rare in travellers (as uncommon to be re-infected)
    - Supportive management

Malaria

- Protozoal infection (Plasmodium spp.) spread by **female Anopheles mosquito** (bites at night, attracted by heat + CO_2)
- Life cycle involves mosquitoes and humans (RBCs and liver)
- Returning traveller from endemic areas (Asia / Africa / South America) – ask about whether they took malaria prophylaxis while away
- Classified by species: **Falciparum Vs Non-Falciparum**
    - P. falciparum: most common and most severe (see below)
    - Non-falciparum: P. vivax, P. ovale, P. malariae, P. knowlesi
        - Symptoms as for falciparum but less severe
        - 48hr (tertian) fever (apart from P. malariae – 72hrs)
        - Schüffner's dots on blood film
        - Rx: chloroquine then primaquine

- Falciparum malaria:
    - Sx: 48hrly (tertian) fever, generally unwell, hepatosplenomegaly, anaemia
    - Ix: thick and thin blood films
        - Thick demonstrates malaria; thin demonstrates species
    - Rx:
        - Mild: artemesin combination therapy (Riamet – artemether + lumefantrine)
        - Severe: IV artesunate

Features of Severe Falciparum Malaria
Impaired Consciousness or seizures
Renal Impairment
Acidosis (pH<7.3)
Hypoglycaemia (<2.2mmol/l)
Pulmonary Oedema or ARDS
Anaemia (Hb<8g/dl)
Spontaneous bleeding/DIC
Shock (BP< 90/60mmHg)
Haemoglobinuria (without G6PDD)
Other indications for IV therapy: Parasitaemia >2%, Pregnancy, Vomiting

Zoonoses

Diseases + infections which are transmitted naturally between vertebrate animals and man

Mice	Hantan viruses(fleas), Lyme borreliosis, Ehrlichia, Bartonella, Lymphocytic choriomeningitis
Rats	Rabies, Leptospirosis, Lassa fever, Hantan viruses, Plague, Pasteruellosis, Haverhill fever (Rat-bite)
Cats	Bartonellosis (cat scratch), Leptospirosis, Q-Fever, Toxoplasmosis, Rabies, Ringworm, Toxocariasis
Dogs	Hydatid disease, Leptospirosis, Brucellosis, Q-Fever, Rabies, (MRSA!!), Ringworm, Toxocariasis
Small ruminants	Anthrax, Brucellosis, Q-Fever, Cryptosporidiosis, Enzootic abortion, Louping ill, Orff virus, Rift Valley fever, Toxoplasmosis
Cattle	Anthrax, Leptospirosis, Brucella, Bovine TB, Anaplasmosis, Toxoplasmosis, E. coli 0157, Rift Valley fever, Ringworm
Swine	Brucellosis, Leptospirosis, Erysipeloid, Cysticercosis, Trichinella, HEV, Influ A!, Streptococcal sepsis
Birds	Psitticosis, Influenza, Cryptococcus, Influ A!!!, Poultry- salmonella, West-Nile fever
Water-sports assoc	Leptospirosis, HAV, Giardia, Toxoplasmosis, Mycobacterium marinum/ulcerans, Burkholderia pseudomallei, E. coli
Water-borne	Campylobacter, Salmonella, VTEC O157, Cryptosporidium
Food-associated	Listeria (cow cheese-human), Taenia, Cysticercosis, toxoplasmosis, trichinellosis, yersiniosis, Giardia

Brucellosis – Gram-ve, aerobic bacilli (facultative intracellular)

- **Transmission:** contaminated food (untreated milk / dairy products), direct animal contact (cows, goats, sheep, pigs)
- **Presentation:** undulant fever (peaks in evening), myalgia, arthritis, spinal tenderness, hepatosplenomegaly, epididymo-orchitis
- **Ix:** Serology - anti-O-polysaccharide antibody. WCC usually normal / neutropenia
- **Rx –** 4-6wks doxycycline + streptomycin
- **Complications**: endocarditis, osteomyelitis, meningoencephalitis

Rabies – Rhabdovirus, dogs and bats are the most common vectors.

- **Transmission:** dogs, bats
- **Presentation:**

    a. Prodrome – fever, headache, sore throat
    b. Acute encephalitis (hyperactive state)
    c. Migration to CNS (after months – yrs) → fatal encephalitis, hypersalivation, hydrophobia
- **Ix:** Serology for IgM, Negri bodies (pathognomonic)
- **Rx:** rabies IgG post-exposure (before symptoms) + Full rabies vaccination course

Plague – *Yersinia pestis,* gram-ve lactose fermenter
- **Transmission:** reservoir in rats, transmitted by fleas
    - Still seen in some American National Parks, e.g. Yosemite
- **Presentation:**
    - **Bubonic plague** – flea bites human – Swollen LN (Bubo) – dry gangrene
    - **Pneumonic plague** – Usually seen during epidemics, person-person spread
- **Ix:** PCR
- **Rx**: Streptomycin, Doxycycline, Gentamicin, Chloramphenicol (in meningitis)

Leptospirosis – Gram –ve, *L interrogans,* obligate, aerobic, motile spirochaetes
- **Transmission:** excreted in dog/rat urine, penetrates broken skin / swimming in contaminated water
- **Presentation:** high fever, conjunctival haemorrhages, jaundice, meningism, renal failure, haemolytic anaemia
- **Rx**: amoxicillin, erythromycin, doxycycline or ampicillin

Anthrax - Bacillus anthracis
- Cutaneous: Painless round black lesions + rim of oedema
- Pulmonary: Massive lymphadenopathy + mediastinal haemorrhage
- **Rx:** doxycycline / ciprofloxacin

Lyme disease - Borrelia burgdoferi (spirochaete). Arthropod-borne (Ixodes = tick)
- **Transmission:** Ixodes tick on deer (hiking)
- **Presentation:**
    - Early: erythema chronicum migrans (bullseye rash), flu-like
    - Late persistent: focal neurology, neuropsychiatric, arthritis
- **Ix:** Biopsy edge of rash, + ELISA for Lyme Abs
- **Rx**: Doxycycline 2-3wks, (also amoxicillin, cephalosporins)
    - If CNS issues, IV ceftriaxone 2-4wks

Q fever - Coxiella burnetii
- **Transmission:** cattle / sheep
- **Presentation:** atypical pneumonia (dry cough, fever), no rash
- **Rx:** doxycycline

Leishmania – protozoa

- **Cutaneous,** eg: *L. major, L. tropica*
  - **Transmission:** sandfly bite (South America, Middle East)
  - **Presentation:** Skin ulcer at site of bite → multiply in dermal macrophages → heals after 1yr leaving depigmented scar
    - May be single or multiple painless nodules which grow + ulcerate
- **Diffuse cutaneous**
  - Pts with immunodeficiency → nodular skin lesions but do NOT ulcerate
- **Muco-cutaneous,** eg: *L. braziliensis*
  - Dermal ulcer (same as cutaneous leishmaniasis)
  - Months to yrs later → ulcers in mucous membranes of nose and mouth
- **Visceral = Kala Azar,** eg: *L. donovani, L. infantum (L. chagasi* in S. America*)*
  - Usually young malnourished child
  - Abdo discomfort and distension, anorexia, weight loss
  - Leishmania donovani: invasion of reticuloendothelial system → hepato-splenomegaly, BM invasion. Later, disfiguring dermal disease (PKDL)

Fungal Infections

Fungal infections are rarely serious. However rarely than can be fatal; in immunocompromised patients, if infection enters the systemic circulation.

Fungal infections can be difficult to Dx – slow growing, masked by bacteria.

Classify fungal infections

1. Yeasts Vs Moulds: dimorphism – yeast during infection, mould in nature.
2. Superficial (skin, hair, nails) Vs Deep seated (systemic)

Know the key organisms and how to diagnose them

- Superficial – Use Woods Lamp for diagnosis
  - **Tinea**: Dermatophyte e.g. *Tricophyton rubrum*: Ringworm, Athlete's foot
  - **Pityriasis**: *Malassezia globosa/furfur* : seborrhoeic dermatitis, T. versicolor (depigmentation in those with darker skin. Often a spot diagnosis in finals)
- Deep seated – Use clinical details, lab results and imaging for diagnosis
  - **Candida**: Can be deep seated in the immunocompromised
    - Dx: Culture, Mannan, Antibodies
    - Rx: fluconazole for C. albicans, amphotericin-B for invasive disease
  - **Aspergillus**: A spectrum from allergy to invasion (ABPA, Invasive Aspergillosis, Aspergilloma)
    - Presents as pneumonia, esp. in immunocompromised. High mortality.
    - Dx: ELISA, PCR, β-Glucan test, grows on Czapek dox agar
    - Rx: voriconazole
  - **Cryptococcus**: In immunocompromised (particularly HIV)
    - Presents as meningitis with insidious onset in HIV
    - Associated with birds and in particular pigeons!
    - Dx: Cryptococcal Antigen in serum/CSF + india ink staining
    - Rx: 3/52 amphotericin B +/- flucytosine

Antifungals

Class	Target	Indication
Polyene e.g. Amphotericin	Cell membrane integrity	Yeast
Azole e.g. Fluconazole	Cell membrane synthesis	Yeast
Terbinafine	Cell membrane	Mould (vs. dermatophytes)
Flucytosine	DNA synthesis	
Echinocandin e.g. caspofungin	Cell wall	Yeast (less toxic SE)

Amphotericin B is used in the treatment of cryptococcal meningitis + invasive fungal infection

Prion Disease

Protein-only infectious agent. Rare transmissable spongiform encephalopathies in humans and animals resulting in rapid neuro-degeneration and death in months. Currently **untreatable**. If suspected be very careful handling lab samples!
Prion protein gene on Chr20, predominantly expressed in CNS.

Normal protein structure PrP. However abnormal PrP^{SC} abnormally folds → Beta-sheet configuration + protease/radiation resistant. Seed of PrP^{Sc} acts as a template which promotes irreversible conversion of PrP to insoluble PrP^{Sc}

Genetics: codon 129 polymorphism and specific PRNP mutations
Differential: Other neuro-genetic conditions eg. Huntington's, Spinocerebellar ataxia
CJD Treatment:

- Symptomatic: clonazepam – mycolonus: (Valproate, Levetiracetam, Piracetam)
- Delaying prion 'conversion': Quinacrine, Pentosan, Tetracycline

Prion	EEG	MRI	CSF Analysis	PNRP analysis	Genetics	Western Blot PrP^{SC}	Post-mortem
Sporadic CJD	Serial EEG shows periodic triphasic changes	Normal/ highlighting basal ganglia	14-3-3 protein +ve	No mutations	Most cases 129 codon **MM**	Types 1-3	1. Spongiform vacuolation 2. PrP amyloid plaques
Variant CJD	Non-specific slow waves	Posterior thalamus highlighted on MRI-T2 (pulvinar sign)	14-3-3 can be normal	No mutations	**ALL** cases 129 codon **MM**	Type 4t from tonsillar biopsy (100% sens. + spec.)	1. PrP^{SC} 4t detedtable in CNS + lymphoreticular tissue 2. Florid plaques
Iatrogenic CLD				No mutations	Most:129 codon homozygous (**MM or VV**)	Types 1-3	

Inherited Prion Disease	Non specific	Sometimes high signal in basal ganglia		Mutations present + diagnostic	129 codon homozygousity may confer earlier onset		

Type	Prion Disease	Aetiology		Course
Sporadic CJD **80%**	sCJD	Either somatic PRNP mutation OR spontaneous conversion of PrPc to PRP^{SC} and subsequent seeding		Rapid, progressive dementia with myoclonus, cortical blindness, akinetic mutism and lower motor neuron signs Mean onset is 45-75yrs and mean survival time = within 6/12 of symptoms starting
Acquired CJD **<5%**	vCJD (variant)	Exposure to bovine spongiform encephalopathy (BSE)		Younger age of onset – typically 30yrs. Mean survival 14/12. Psychiatric symptoms to start (anxiety, paranoia, hallucinations) followed by the development of neurological symptoms (peripheral sensory symptoms, ataxia and myoclonus). Later symptoms include chorea, ataxia, dementia
	Iatrogenic	Inoculation with human prions most commonly from surgery		Progressive ataxia initially. Dementia and myoclonus later stages. Speed of progression depends on route of inoculation (CNS inoculation fastest)
	Kuru	Exposure to human prions from cannibalistic feasts		Progressive cerebellar syndrome (death within 2yrs) following 45yr incubation Dementia is late or absent. Epidemic was in the 1950/60s
Inherited **15%**	Familial CJD, GSS, FFI, various atypical dementias PRNP mutations	Gerstmann-Straussler-Scheinker syndrome	Autosomal dominant	Develops between 20-60yrs, mean survival = 5yrs with dysarthria progressing to cerebellar ataxia ending in dementia
		Fatal Familial Insomnia	Autosomal dominant (50 families in world)	Insomnia and paranoia progressing to hallucinations and weight loss. Then a mute period. Death 1-18/12 after start of symptoms

Reference Table of Common Bugs			
Gram Positive		**Gram Negative**	
Cocci	**Rods**	**Cocci**	**Rods**
Staphylococcus (clusters). Coag +ve: aureus. Coag –ve: epidermis Streptococcus + enterococcus (diplococci + chains)	**A**ctinomyces:* dental/oral infections **B**acillus: cereus, anthracis **C**lostridium:* difficile, Perfringens, botulinum, tetani **D**iphtheria **L**isteria	Neisseria: meningitidis, gonorrhoeae Moraxella: catarrhalis	Enterobacteriaceae: E. Coli, Salmonella, Shigella, Klebsiella, Yersinia.
		Coccobacilli	**Spirochaetes**
		H. Influenza/ ducreyi, Bordetella Pertussis, Pseudomonas aeruginosa, Chlamydia trachomatis	Treponema pallidum e.g. syphilis, Leptospirosis Borrelia e.g. Lyme disease.

* Obligate anaerobes (also includes Gram –ve's such as *Bacteroides*). Found in GIT.

Rx – Metronidazole, cephamycins. NB. Aminoglycosides (e.g. Gentamycin) are useless.

Obligate Intracellular microbes:

- Bacteria: Chlamydia trachomatis, Rickettsia, Coxiella (Q fever), Mycobacteria leprae,
- Protozoa: Toxoplasma, cryptosporidium, Leishmania spp,
- Fungi including: pneumocystis jirovecii (PCP)

Chemical Pathology

Edited by Dr. Nicole James and Dr. Jared Bhaskar

Fluid Balance

Body fluid volumes - figures based on 70kg male

The **60-40-20 rule:**

- 60% total body weight = water
- 40% of body weight = intracellular
- 20% of body weight = extracellular

Compartment	Volume in litres	Percentage of total volume
Intracellular	28 L	60-65%
Extracellular • Interstitial (between cells) • Intravascular • Transcellular (within epithelial-lined spaces e.g. CSF, joint fluid, bladder urine, aqueous humour	14 L • 10L • 3L • 1L	35-40% • 24% • 5% (4-6%) • 3%

Figures are approximate

Note: Males have more water per unit weight than females (higher fat content in the latter)

Think of the cells as primitive organisms that used to live in the sea, they require salty water to survive, therefore the extracellular fluid is higher in sodium and chloride, and lower in potassium than the intracellular fluid.

Osmolality vs. Osmolarity

Osmolality = total number of particles in solution - measured with an osmometer, units = mmol/kg.
Osmolarity = calculated, units = mmol/l

Determinants in serum/plasma:

- Physiological = Na^+ + K^++ Cl^- + $HCO3^-$ + urea + glucose
- Pathological = Endogenous (i.e. glucose), Exogenous (ethanol, mannitol)

Osmolarity = $2(Na^+ + K^+)$ + urea + glucose

We don't need to know the concentration of negative ions, as it will equal the concentration of total positive ions (so just double that and add the uncharged solutes in)

- Osmola**lity** and osmola**rity** should roughly equate
- The difference is termed the **osmolar gap** and can be useful in metabolic acidosis cases (see section below). This is because if the osmolarity is lower than the osmolality, we can assume there are extra (unmeasured) solutes that are dissolved in the serum
- Osmolality is one of the diagnostic criteria for SIADH: the normal range for serum osmolality is **275 – 295 mmol/kg**

Sodium

Normal range: **135 - 145 mmol/L**

- 70% freely exchangeable, the rest complexed in bone
- Predominantly an **extracellular** cation, largely maintained by active pumping from ICF > ECF by Na^+/K^+ ATPase
- ECF volume is directly dependent on Na^+

Hyponatraemia

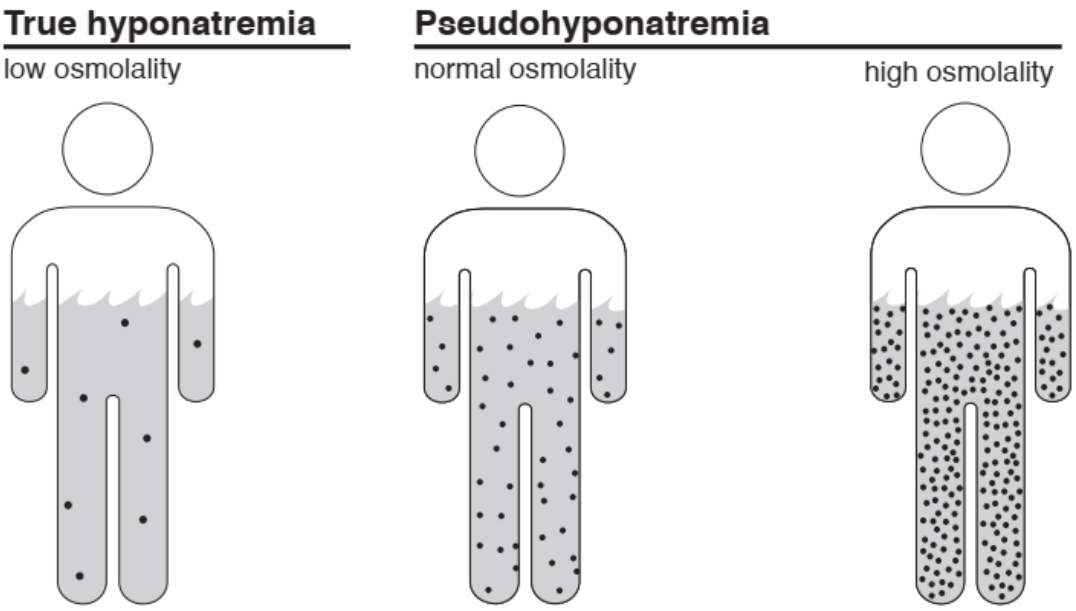
- Mild hyponatraemia (130-135 mmol/L) is relatively common in hospital
- Treat underlying cause, not the hyponatraemia, unless severe (<125mmol/L) and symptomatic
- Hyponatraemia that is compensated (usually chronic) is rarely an emergency to treat: even with sodium in the 110-120 range that are asymptomatic, it is more dangerous to correct them too fast than to leave the patient at that level.
- **Symptomatic hyponatraemia is a medical emergency**
    - Nausea and vomiting (<134 mmol/L)
    - Confusion (<131 mmol/L)
    - Seizures, non-cardiogenic pulmonary oedema (<125 mmol/L)
    - Coma (<117 mmol/L) and eventual death

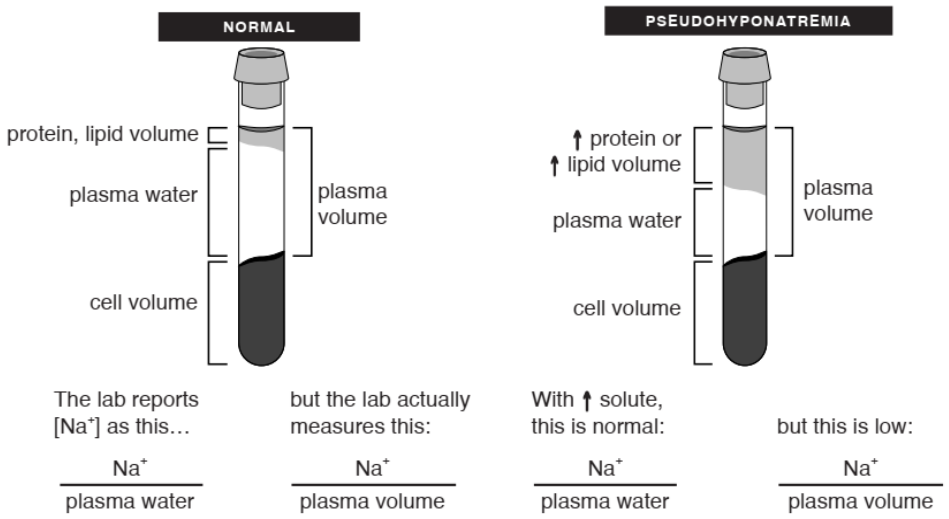
Define whether it is **true** hyponatraemia using serum osmolality:

Osmolality	Causes
High	Glucose/mannitol infusion
Normal	Spurious Drip arm sample Pseudohyponatraemia (hyperlipidaemia/ paraproteinaemia)
Low	True hyponatraemia

TURP syndrome → hyponatraemia from irrigation absorbed through damaged prostate

- Glycine 1.5% used to irrigate during TURP
- Clinical presentation due to metabolism of glycine and hyponatraemia caused by dilution



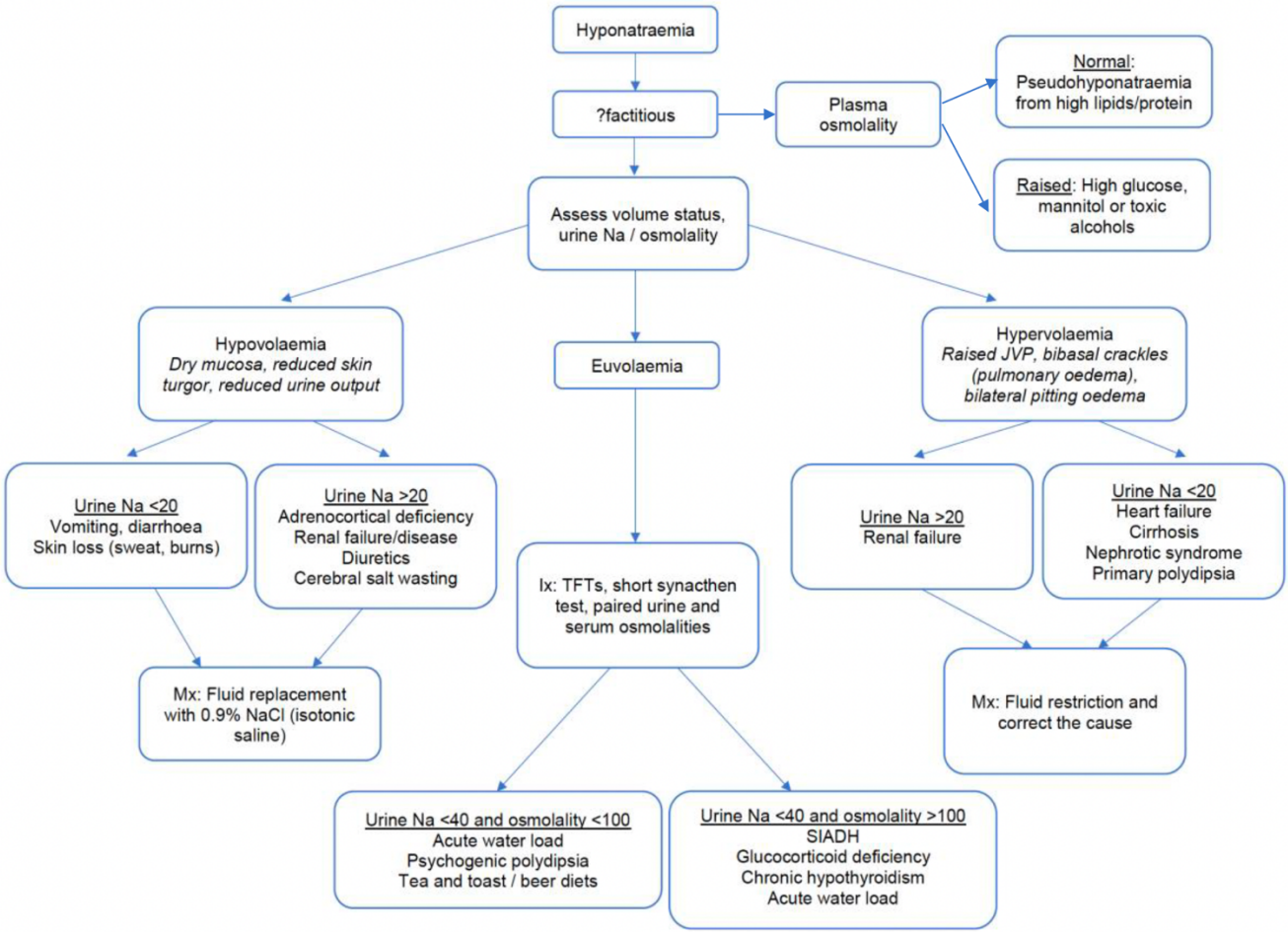


In pseudo-hyponatraemia, the increase in protein or lipid volume is “sensed” by the analyser in the lab to be water. Hence the sodium appears diluted and osmolality will be normal.

Hyponatraemia with elevated plasma osmolality is due to an excess of osmotically active solutes in the plasma. Often this is glucose (in HHS) but can also be mannitol. This draws water from cells into the plasma, which dilutes down the sodium. This is technically a true hyponatraemia however it is due to another chemical in the blood.

Diagrams from the Fluid, Electrolyte and Acid-Base Handbook by Joel Topf MD

Treating the hyponatraemic patient – adapted from the lecture by Dr Amir Sam



True Hyponatraemia (Osmolality is LOW)

This can be distinguished using hydration status and urinary Na^+:

Hypovolaemia	**> 20 = Renal**	**Diuretics, Addison's, Salt-losing nephropathies (kidney is failing to reabsorb sodium so water lost as well)**
	< 20 = Non-renal	Vomiting, Diarrhoea, Excess sweating, third space losses (ascites, burns). Kidney is doing its job and holding onto sodium
Euvolaemia	> 20	SIADH, severe hypothyroidism, glucocorticoid deficiency
Hypervolaemic	> 20 = Renal	AKI, CKD (kidneys not retaining sodium)
	< 20 = Non-renal	Cardiac Failure, Cirrhosis, Inappropriate IV fluid.

Because diuretics can affect the urinary sodium, it is important to stop diuretics before measuring urinary sodium to aid diagnosis.

Cirrhosis causes hyponatraemia because in liver failure there is poor breakdown of vasodilators like nitric oxide, these cause a low blood pressure and the subsequent ADH release causes water retention, which dilutes down the sodium. A similar phenomenon happens in heart failure (low cardiac output causes ADH release), but BNP/ANP are natriuretic and thought to worsen hyponatraemia as well.

Management

- Hypovolaemia
  - Treat the cause – e.g. antiemetics
  - Supportive – Replace deplete fluid slowly with regular checking of sodium to ensure not rising too fast
- Euvolaemic
  - See SIADH below
  - Hypothyroid – Levothyroxine, Addison's – Hydrocortisone +/- Fludrocortisone
- Hypervolaemic
  - Fluid restrict +/- diuresis
  - Cirrhosis usually will require specialist input

In exceptional circumstances hypertonic (3%) saline may be used, for example in a patient who is in status epilepticus secondary to hyponatraemia, however this should be on advice of a specialist and will not usually be done outside of ITU.

Rapid correction can lead to **central pontine myelinolysis** (pseudobulbar palsy, paraparesis, locked-in syndrome) therefore aim to increase Na^+ by **no more than 8-10 mmol/L per 24 hours**.
ΔΔ CPM = malnourished alcoholics

NB: Be aware of hyponatraemia post-surgery due to:

- Over hydration with hypotonic IV fluids
- Transient ↑ in ADH due to stress of the surgery.

SIADH

Diagnostic criteria:

- **True hyponatraemia (<135) + low plasma/serum osmolality (<270) + high urine sodium (>20) + high urine osmolality (>100) + no adrenal/thyroid/renal dysfunction**
- Clinically **euvolaemic**
- SIADH is characterised by **inappropriate** ADH secretion (not in response to a stimulus)
- Increased ADH → increased water reabsorption → low plasma Osm (secondary to dilution) → less water is excreted in the urine → urine Osm is high
- Confirming the diagnosis requires a normal 9am cortisol and normal TFTs (i.e. diagnosis of exclusion)

Causes include:

- **Malignancy** – small cell lung cancer (most common), pancreas, prostate, lymphoma (ectopic secretion)
- **CNS disorders** – meningoencephalitis, haemorrhage, abscess (pretty much any CNS pathology
- **Chest disease** – TB, pneumonia, abscess
- **Drugs** – opiates, SSRIs, TCAs, carbamazepine, PPIs

Treatment: **Fluid restriction** and treat the cause, demeclocycline (increases ADH resistance) and tolvaptan can induce a state of diabetes insipidus that may help to correct the SIADH although the cost is prohibitive. If severe, can consider giving **slow IV hypertonic 3% saline**.

Hypernatraemia

- Less common than hyponatraemia, but usually clinically significant (Plasma Na^+ > 148mmol/L)
- Investigation: **Raised urea, albumin, and PCV**
- In hospital often iatrogenic, common problem in ITU patients
- The only question to ask is why the patient is unable to drink water, the sensation of thirst is heavily driven by hypernatremia, most people should be able to self-correct their sodium unless they become unwell therefore this is usually unmasked in hospital when patients are acutely unwell.
- Symptoms = thirst--> confusion--> seizures + ataxia--> coma
- Can be classified based on hydration status

Rapid correction can lead to cerebral oedema!

Hydration status	Cause
Hypovolaemia (where water is lost more than sodium, this is the most common form of hypernatraemia)	**Low urinary sodium:** • GI loss: Vomiting, diarrhoea • Skin loss: Excessive sweating, burns **High urinary sodium >20** – renal losses: • Loop diuretics • Osmotic diuresis (uncontrolled DM, glucose, mannitol), *following initial hyponatraemia* • Diabetes insipidus • Renal disease (impaired concentrating ability)
Euvolaemia	Respiratory (tachypnoea) Skin (sweating, fever) Diabetes insipidus

Hypervolaemia	Mineralocorticoid excess (Conn's Syndrome) Inappropriate saline

Management

- Generally slow fluids are recommended for most forms of hypernatremia as it is commonly hypovolaemic
    - Fluid choice is not critical, speed is – even normal saline will work (albeit slower than dextrose or Hartmann's, and will cause some panic as there will be an initial rise in sodium before it falls)
    - Slow and steady, like with hyponatraemia do not correct too quickly
    - Encouraging PO fluids is the best way – the body will regulate its own sodium safely!

Diabetes Insipidus

Clinical Features:

- Hypernatraemia (lethargy, thirst, irritability, confusion, coma, fits)
- Clinically euvolaemic
- Polyuria and polydipsia
- Urine: plasma osmolality is <2
  (Urine is dilute despite concentrated plasma)

Cranial Diabetes Insipidus (>50% increase in osmolality after ADH analogue administered):

- **Lack of/No ADH production**
- Causes: surgery, trauma, tumours (craniopharyngioma), autoimmune hypophysitis (from CTLA-4 ipilimumab)
- Mx: **desmopressin**

Nephrogenic Diabetes Insipidus:

- *Receptor defect* – **insensitivity to ADH**
- Causes:
    - Inherited channelopathies
    - Drugs: Lithium, demeclocycline
    - Electrolyte disturbances: hypokalaemia, hypercalcaemia
- Treatment with thiazide diuretics (bizarre!)

Investigations for suspected diabetes insipidus
Step 1: Serum glucose (to exclude diabetes mellitus)
Step 2: Serum K+ (exclude hypokalaemia)
Step 3: Serum Ca (exclude hypercalcaemia)
Step 4: Plasma and urine osmolality
Step 5 (diagnostic): 8-hour water deprivation test (interpretation of results below)

Note: Significant DI is **excluded** if urine to plasma (U:P) osmolality ratio is >2:1, provided plasma osmolality is no greater than 295mOsmol/kg.
In DI, **despite raised plasma osmolality, urine is dilute with a U:P ratio <2.**

Diagnosis	Urine osmolality
Normal	Urine osmolality >600mOsmol/kg U:P ratio >2 (normal concentrating ability)
Primary polydipsia	Urine concentrates, but less than normal, e.g. >400–600mOsmol/kg
Cranial DI	**Urine osmolality increases to >600mOsmol/kg only after desmopressin** (if equivocal an extended water deprivation test may be tried (no drinking from 18:00 the night before)
Nephrogenic DI	No increase in urine osmolality even after desmopressin

Potassium

Normal range: **~3.5 – 5.5mmol/L**

- The *predominant* intracellular cation (only 2% extracellular), maintained by active pumping from ECF → ICF by Na^+/K^+ ATPase
- 90% freely exchangeable, the rest bound in RBCs, bone, and brain tissue

Hypokalaemia (<3.5mmol/L)

Either depletion or shift into cells (very rarely decreased intake):

1. **GI loss:** vomiting, diarrhoea
2. **Renal loss**
   - Hyperaldosterism *(consider in a patient with **high BP and low K+**), iatrogenic* excess cortisol
   - Increased sodium delivery to distal nephron (thiazide and loop diuretics)
   - Osmotic diuresis
3. **Redistribution into the cells**
   Insulin, beta-agonists, metabolic alkalosis (see box below), refeeding syndrome
4. **Rare causes**
   Rare tubular acidosis type 1 & 2, hypomagnesaemia

Renal tubular acidosis (3 types, 1,2 and 4. Type 3 is rarely relevant)
***Type 1:** most severe, distal failure of H+ excretion and subsequent acidosis and hypokalemia (failed hydrogen potassium pumping)*
***Type 2:** milder, proximal failure to reabsorb bicarbonate, leads to acidosis and hypokalaemia*
***Type 4:** aldosterone deficiency or resistance (acidosis and hyperkalaemia)*

Clinical features of hypokalaemia:

- Muscle weakness, cardiac arrhythmias, polyuria and polydipsia (nephrogenic DI)

Treatment:

1. *Serum K+ **3.0-3.5mmol/L = Oral KCl** (2 SandoK tablets TDS for 48h), recheck serum K+*
2. *Serum K+ **<3.0mmol/L** (risk of cardiac arrest) = **IV KCl** (**max rate 10mmol/h** otherwise risk of arrhythmia; insert central line if higher)*

Typical investigations include an aldosterone-renin ration (high implies Conn's as high aldosterone e.g. produced from a tumour, will cause negative feedback and switch off renin production)

Hyperkalaemia (>5.5mmol/L)

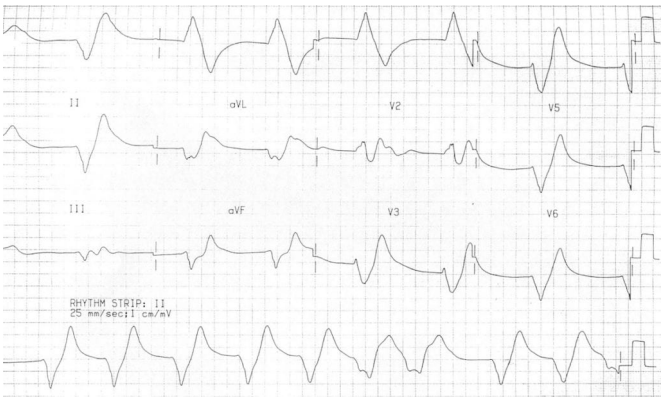
Less common than hypokalaemia, but more dangerous.
Caused by excessive intake (almost always iatrogenic), movement out of cells or ↓ excretion:
*Assessment of a patient with hyperkalaemia should involve an ECG as well as **repeat sampling**; it is not uncommon for a spurious result to appear due to a haemolysed blood sample.*

Artefact	Haemolysis EDTA contamination from FBC bottle
Excessive Intake	Oral (fasting)
	Parenteral
	Stored blood transfusion
Transcellular Movement (ICF>ECF)	Acidosis
	Insulin shortage (DKA)
	Tissue damage/catabolic state (rhabdomyolysis)
Decreased excretion	Acute Renal Failure (oliguric phase)
	CRF (late)
	Drugs: K sparing diuretics (spironolactone), NSAIDs, ACEi, ARBs
	Mineralocorticoid deficiency (Addison's)
	Type 4 renal tubular acidosis

*ECG changes associated with **hyperkalaemia**:*

1. *Loss of P waves*
2. *Tall, tented T waves*
3. *Widened QRS*

*The ECG is "pulled apart" to eventually create a **'sine wave'** if severe hyperkalaemia is left untreated.*



Treatment protocols vary depending on trusts however most would advocate intervention in anyone with:

1. *Potassium >5.5 with ECG changes or*
2. *Potassium is >6.5 regardless of ECG changes.*

Treatment involves:
Repeat bloods if K+ >6.5 (possible haemolysis)

1. 10mls 10% calcium gluconate (this is cardioprotective, it does nothing to lower the serum potassium)
2. 100mls 20% dextrose and 10 units of short-acting insulin such as Actrapid (insulin will drive the potassium back into the cells, and the dextrose is to prevent hypoglycaemia).
3. Nebulised salbutamol is a useful adjunct as well.
4. In some cases: consider calcium resonium 15g PO or 30g PR (binds potassium in gut)
5. Always treat the cause.

NB: In patients who are on **Digoxin** care should be taken when administering calcium intravenously as it can precipitate arrhythmias, **cardiac monitoring** should be performed.

Remember that a high (or upper end of normal) sodium and low (or lower end of normal) potassium can imply Conn's syndrome, whereas a low (or lower end of normal) sodium and a high (or upper end of normal) potassium can imply Addison's disease.

NB: H+ and Potassium are intimately linked as one moves into cells one moves out.
This is because of the hydrogen-potassium co-transporter. A rise is potassium means the body compensates by pumping potassium into cells, along with hydrogen ions too (and vice-versa)
For every drop in pH of 0.1 there is an increase in K+ of 0.7

Acid - Base

Parameter	Normal Range
pH	7.35 – 7.45
CO2	4.7 – 6kPa
Bicarbonate	22 – 30 mmol/l
O2	10 – 13kPa

Steps to solve simple problems:
Look at the case (if there is one)

- pH – **acidic/ alkali?**
- CO2 – **does it fit with the pH?**
- Bicarbonate – **does it fit with the pH?**
- Compensation – **is there any? Partial/ Complete?**

H^+ = Equivalent to pH
180 = Constant (*K*)

Compensatory response	pH	PCO_2	[$HCO3^-$]	Cause
Metabolic acidosis Hyperventilation (immediate)	↓	↓	↓	Anion gap = Na+K-Cl-HCO_3 (**14-18 range**) **High AG**: Ketones, lactate (shock, ischaemia, sepsis), EtOH, aspirin, biguanides (metformin), ethylene glycol, uraemia **Normal AG**: Diarrhoea (small bowel GI loss of HCO_3), Acetazolamide (CA inhibitor), high output stoma, pancreatic fistula (loss of bicarb), Addison's, renal tubular acidosis, ammonium chloride ingestion
Metabolic alkalosis Hypoventilation (immediate)	↑	↑	↑	Vomiting (H+ loss)(bulimia), Loop diuretics (**K+ depletion**), hypokalaemia, Conn's (hyperaldosteronism, **K+ loss**), antacid use, burns
Respiratory acidosis ↑ renal [$HCO3^-$] reabsorption (delayed)	↓	↑	↑	**Hypoventilation** (T2 resp failure): Acute/chronic lung disease (commonest = COPD), opioids, sedatives, neuromuscular weakness Normal/high PaCO2 worrying - ITU RV/vent support (exhaustion
Respiratory alkalosis ↓renal [$HCO3^-$] reabsorption (delayed)	↑	↓	↓	**Hyperventilation**: Stroke; SAH, meningitis, asthma, anxiety, PE, pregnancy, altitude (hypoxaemia), salicylates (early – brainstem stimulation)

Compensation Return of pH towards normal at the expense of other values
Extra information (metabolic acidosis) – Anion and Osmolar gap: Used to screen for organic poisoning, DKA and to provide more information about a metabolic acidosis

Anion Gap

- Difference between total concentration of principal cations and principal anions = Concentration of *unmeasured* anions in the plasma
- Almost entirely contributed by albumin (beware in hypoalbuminaemia)
- Normal range = **14 - 18mmol/l**

$$(Na^+ + K^+) - (Cl^- + HCO3)$$

Mnemonic for elevated anion gap metabolic acidosis:

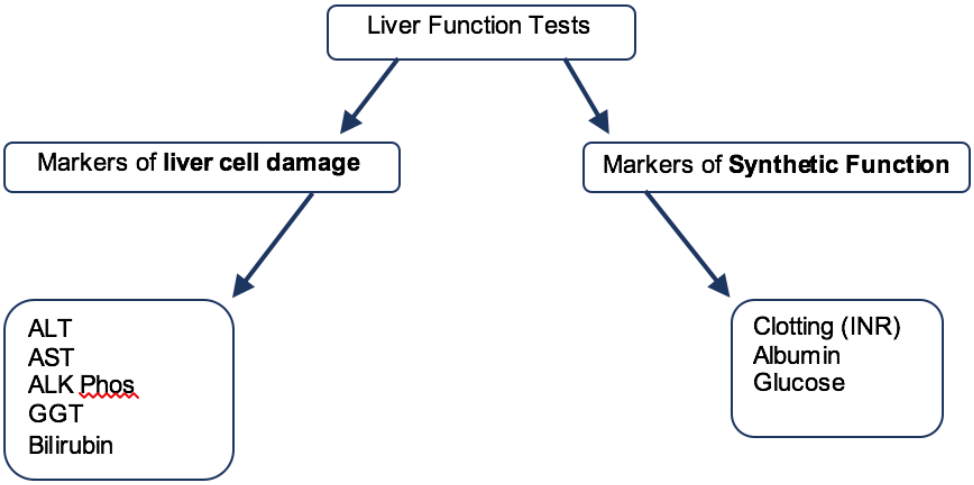
- **K**etoacidosis (DKA, alcoholic, starvation)
- **U**raemia (renal failure)
- **L**actic Acidosis
- **T**oxins (ethylene glycol, methanol, paraldehyde, salicylate)

Osmolar Gap

Osmolality (**measured**) – Osmolarity (**calculated**)

- Normal osmolar gap = **< 10**
- An elevated osmolar gap provides indirect evidence for the presence of an abnormal solute
- The osmolar gap is increased by extra solutes in the plasma (e.g. alcohols, mannitol, ketones, lactate)
- Can be raised in advanced CKD due to retained small solutes
- Helpful in differentiating the cause of an elevated anion gap metabolic acidosis

Liver Function Tests



Best marker of liver function in acute liver injury = Prothrombin time

Transaminitis in the **1000s**	**Acute viral** hepatitis, toxins (e.g. paracetamol), ischaemic hit
AST and ALT raised Found in the Liver, cardiac and skeletal muscle, and the kidney and brain	(Hepatic) Hepatitis/transaminitis **ALT > AST = chronic liver disease** (incl. NASH), chronic Hep C, hepatic obstruction, advanced fibrosis/cirrhosis (AST: ALT ratio >0.8 in absence of EtOH) **AST:ALT 2:1** supportive of **EtOH** liver disease **AST:ALT 1:1** supportive of **viral** hepatitis
Raised **GGT and ALP** GGT found in hepatocytes and biliary cells, kidney and pancreas	Cholestatic/obstructive picture **GGT raised** in **chronic EtOH** use, bile duct disease and metastases – used to confirm hepatic source of raised ALP
Isolated raised ALP ALP present in high conc in liver, bone (osteoblastic activity), intestine and placenta	1) Physiological: Pregnancy (3T), childhood (growth spurt) 2) Pathological: • >5x ULN = Bone (Paget's disease - osteoblasts), osteomalacia, liver (cholestasis, cirrhosis) • <5x ULN = Bone (primary tumours e.g. sarcoma, fractures, osteomyelitis), liver (infiltrative disease, hepatitis), renal osteodystrophy Caveat: Plasma cells suppress osteoblasts, hence ALP is normal in myeloma
Low albumin (liver synthetic function)	Chronic liver disease, malnutrition, protein-losing enteropathy, nephrotic syndrome, sepsis (3rd spacing)
Low urea	Severe liver disease, (synthesised in liver), malnutrition, pregnancy
Raised **urea (x10 ULN)**	1) Upper GI bleed (or large protein meal) 2) Dehydration/AKI (urea excreted renally)

Synthetic hepatocellular dysfunction

- Albumin
  - Average adult synthesises 200mg/kg of albumin per day
  - Important serum protein which binds many hormones, calcium and other metabolites.
  - Hypoalbuminaemia is common in hospital patients as acute illness/systemic inflammation and malnutrition can contribute to a reduced albumin
  - Hypoalbuminaemia in critically ill patients is a poor prognostic factor
- Clotting factors
  - The liver synthesises Factor V, VII, IX, X, XII, XIII and fibrinogen and prothrombin
  - In practical terms INR (International normalised ratio) is measured, this is the prothrombin time standardised for age and population expressed as a ratio of 'normal'.
  - Deranged clotting is not diagnostic of hepatocellular dysfunction on its own as it could be due to multiple other aetiologies – for example iatrogenic (therapeutic warfarinisation), hereditary thrombophillia, acquired consumption (DIC).
- Synthetic markers of liver function can be deranged without there being any actual damage to the liver – the context of the signs and symptoms, as well as the non-synthetic markers are needed to make an accurate assessment of any patient.

Jaundice

- Elevated serum bilirubin manifesting as yellowing of the skin or sclera (icterus)
- Bilirubin is a breakdown product of heme, and the majority is produced by breakdown of haemoglobin.
  - Normal metabolism of bilirubin involves conjugation in hepatocytes, and subsequent secretion into the bile ducts and then the GI tract
  - Conjugated bilirubin is metabolised further in the GI tract into urobilinogen
  - Urobilinogen is then partially reabsorbed and excreted in the kidneys as Urobilin
  - The rest of the urobilinogen is converted to stercobilin which is the brown pigment in faeces.
- Disorder of bilirubin metabolism can therefore be **pre-hepatic** [raised bilirubin production], **hepatic** [decreased ability to conjugate bilirubin] or **post-hepatic** [decreased ability to excrete conjugated bilirubin].
- Bilirubin can be measured as **total or as split conjugated/unconjugated** which will be useful for below:

	Prehepatic 1) Haemolytic anaemia 2) Ineffective erythropoiesis e.g. thalassemia 3) Congestive cardiac failure	**Hepatic** 1) Hepatocellular dysfunction (viral, alcoholic hepatitis) 2) Impaired conjugation/BR excretion, BR uptake (Gilbert syndrome, Crigler Najjar syndrome)	**Post-hepatic** Obstruction of biliary tree: 1) Intraluminal (stones, strictures) 2) luminal (mass/neoplasm, inflammation e.g. PBC, PSC) 3) extra-luminal (Ca pancreas, cholangio Ca_)
Conjugated BR	**Absent**	↑↑	↑↑
Unconjugated BR	Normal/Increased	↑↑	Normal
Urobilinogen	Normal/**increased**	↑↑	**Decreased/absent**
Urine bilirubin	**Absent**	Present	Present

Conjugated BR in urine	**Absent**	Present	Present
Urine colour	Normal	Dark (urobilinogen + conjugated BR)	Dark (conjugated BR leaks out of hepatocytes)
Stool colour	Normal	Normal/Pale	**Pale**
AST/ALT	Normal	↑↑	↑
ALP	Normal	Normal/↑	↑↑
Splenomegaly	Present	Present	Absent

Explanation for table above:

- **Prehepatic:** No urine bilirubin because unconjugated BR (from haem break down by macrophages in spleen) is tightly bound to albumin, unable to pass through glomerulus; would expect **raised LDH and reduced haptoglobin** in increased haemolysis
- **Post-hepatic**: Dark urine seen due to increase urobilinogen/conjugated BR (lots of them absorbed by blood), pale stool = low levels of stercobilinogen + dark urine
- Hepatomegaly with **smooth** margin: Viral hepatitis, biliary tract obstruction, hepatic congestion 2° to (HF; Budd Chiari)
- Hepatomegaly with a **craggy** border: Hepatic metastatic disease, polycystic disease, cirrhosis (will shrink)

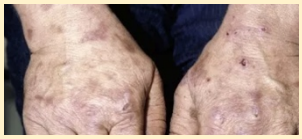
Porphyrias

7 disorders caused by deficiency in enzymes, involved in haem biosynthesis, leading to build up of toxic haem precursors.

Differentiating the acute porphyrias

- Skin lesions – present in HCP and VP but not in AIP
- Urine and faeces for porphyrins – raised in HCP and VP but not AIP
- Urine PBG – raised in all three (send urine sample protected from light)

Acute porphyria (Think the **Ps**) **Autosomal dominant** HMB (Hydroxymethylbilane) synthase deficiency Neurovisceral only i.e. **p**ainful abdomen, seizures, **p**eripheral neuropathy, **p**sychosis, **Port urine,** muscle weakness, constipation, urinary incontinence. NO cutaneous manifestations due to absence of porphyrinogens Hyponatraemia + AIP = think SIADH Urine colour change + abdo pain = think AIP!	**Acute intermittent porphyria** (2nd commonest) **Dx: ↑ urinary porphobilinogen and aminolevulinic acid** **Precipitating factors** • *ALA synthase inducers (steroids, ethanol, barbiturates)* • *Stress (infection, surgery)* • *Reduced caloric intake and endocrine factors (e.g. premenstrual)* Mx: avoid precipitating factors, adequate nutrition and analgesia, Mx of underlying infection/illness, IV carbohydrate, IV haem arginate
Acute porphyria with skin symptoms (i.e. **neurovisceral + skin**) Skin lesion fragility	**HCP + VP** Both **autosomal dominant**

	Skin lesions on back of hands -> blistering under sun **Ix:** Stool sample for **coproporphyrinogen III**
Cutaneous (skin) porphyrias (non-acute) **Skin lesions only**  Blistering skin lesions + pigmentation	**1) Porphyria Cutanea Tarda (PCT) commonest** Uroporphyrinogen decarboxylase deficiency Photosensitivity, facial hyperpigmentation, hypertrichosis, blistering, milia, scarring, exacerbated by ETOH ↑ **urinary uroporphyrins and coproporphyrins** (pink red fluorescence with Wood's lamp), often ↑ **ferritin, abnormal LFTs** Mx: Avoid sun, precipitants (EtOH, hep C, HIV), chloroquine 2) **EPP** found in children, cutaneous erythema without blisters/bullae (blistering found in CEP), cannot use urine as protoporphyrin is lipophilic **Ix: RBC protoporphyrin levels** 3) Congenital erythropoietic porphyria (**CEP**)

Pituitary

Hypothalamo-Pituitary Axis

Hypothalamic Hormones	Action on Pituitary Hormones
GHRH	Stimulates – GH
GnRH	Stimulates – LH/ FSH
TRH	Stimulates – TSH Stimulates – Prolactin
Dopamine	Inhibits – Prolactin
CRH	Stimulates – ACTH

Combined Pituitary Function Test (CPFT)

Indications:

- Assessment of all components of anterior pituitary function used particularly in pituitary tumours or following tumour treatment.

Contraindications:

- Ischaemic heart disease
- Epilepsy
- Untreated hypothyroidism (impairs the GH and cortisol response)

Side-effects:

- Sweating, palpitations, loss of consciousness (all the adrenergic effects of hypoglycaemia)
- Rarely - convulsions with hypoglycaemia.
- Patients should be warned that with the TRH injection they may experience transient symptoms of a metallic taste in the mouth, flushing and nausea.

Summary of process

- Administration of LHRH (GnRH), TRH and insulin
- Then measure the 0 minute, 30 minute, 60 minute, 90 minute and 120 minute levels of the pituitary hormones

Procedure:

1. Fast patient overnight, ensure good IV access, weigh patient
2. Mix into 5ml syringe: **insulin** dose (**0.15 units/kg)**, **TRH** 200mcg, **LHRH** 100mcg → give IV
3. Bloods: basal thyroxine plus glucose, cortisol, GH, LH, FSH, TSH, prolactin every 30min for 1 hour
    - Glucose, cortisol, GH up to 2 hours
4. Replacements: **urgent** hydrocortisone, T4, oestrogen, GH

Interpretation: Involves interpreting three aspects

1. **Insulin** Tolerance test (hypoglycaemia **<2.2mmol/L**) → ↑ACTH + ↑GH (metabolic stress)
    - Adequate cortisol response = ↑ greater than 170 nmol/l to above 500nmol/l.
    - Adequate GH response = ↑ greater than 6mcg/L

2. **Thyrotrophin Releasing Hormone** Test → ↑TSH + ↑Prolactin (dopamine suppress prolactin production, high prolactin → hypothyroidism)
    - The normal result is a TSH rise to >5 mU/l (30 min value > 60 min value)
    - Hyperthyroidism = TSH remains suppressed
    - Hypothyroidism = exaggerated response.
    - With the current sensitive TSH assays basal levels are now adequate and dynamic testing is not usually needed to diagnose hyperthyroidism.

3. **Gonadotrophin Releasing Hormone** Test → ↑LH/FSH
    - Normal peaks can occur at either 30 or 60 minutes
        - LH should > 10 U/l and FSH should > 2 U/l.
    - An inadequate response = possible early indication of hypopituitarism.
    - Gonadotrophin deficiency is diagnosed on the basal levels rather than the dynamic response.
        - **Males** = low testosterone in the absence of raised basal gonadotrophins
        - **Females** = low oestradiol without elevated basal gonadotrophins and no response to clomiphene.
        - Pre-pubertal children should have no response of LH or FSH to LHRH.
    - If sex steroids are present (i.e. precocious puberty), the pituitary will be "primed" and will therefore respond to LHRH. Priming with steroids MUST NOT occur before this test.

Tumours

- Can produce any combination of pituitary hormones, or be non-secreting
- **Microadenoma < 10mm**, usually **benign**
- **Macroadenoma > 10mm**, **aggressive**
- Can compress **optic chiasm = bitemporal hemianopia**
- **A non-functioning** adenoma may crush the stalk, leading to increase prolactin levels (lower dopamine inhibition as reduced blood flow). However, the increased prolactin will be relatively small (but will be **massively raised in prolactinoma**)

Prolactinaemia

Mild elevation (<1000 miu/l)	Moderate elevation (>1000 miu/l, <5000 miu/l)	Extreme elevation (**>5000** miu/l)
• Stress • Recent breast examination • Vaginal examination • Hypothyroidism • PCOS	• Hypothalamic tumour • Non-functioning pituitary tumour compressing the hypothalamus • Microprolactinoma • PCOS • Drugs, e.g. domperidone, phenothiazines	• **Macroprolactinoma**

Prolactinoma	Findings: ↑↑↑ **prolactin (>6000),** no in ↑ **in** GH **(>10)** and cortisol **(>550nM)** 1st line Mx: Replacements (hydrocortisone, T4, oestrogen, GH), DA antagonists (cabergoline, bromocriptine) 2nd line Mx: T**ransphenoidal** excision (if visual/pressure Sx not responding to medical Tx)
Non-functioning pituitary adenoma	Findings: ↑↑ **prolactin (1000-5000)** Mx: Cabergoline/bromocriptine; watch and wait if asymptomatic**Can do nothing if not causing patients any Sx**
Acromegaly Ix: **OGTT (gold standard)**, IGF-1	Findings: ↑↑**GH** (even before baseline), ↑ **Prolactin**, no ↑ in cortisol Mx:

(only good for f/u after Dx) Signs: High glucose, Ca, Phosphate	1. **Transsphenoidal surgery (best)** 2. Pituitary radiotherapy (if surgery fails) 3. Cabergoline 4. Octreotide (expensive) - somatostatin analogue (cannot stop once started) 5. GH antagonist - pegvisomant F/U: yearly GH, IGF-1 ± OGTT, visual fields, vascular assessment, BMI, photos

Neurohypophysopathies

Anterior Hormones

- ADH
- Oxytocin

Excess ADH

Lung - lung paraneoplasias – usually small cell lung cancer, pneumonia
Brain - Traumatic brain injury, meningitis, primary or secondary tumours
Iatrogenic – SSRIs, Amitryptiline, carbamazepine, PPIs
Effect – SIADH – Euvolaemic Hyponatraemia

ADH failure

Diabetes insipidus –increased diuresis due to either failure of production or insensitivity to ADH, leads to decreased urine osmolality and increased serum osmolality
Neurogenic – Failure of production – 50% idiopathic
Nephrogenic – commonly iatrogenic – lithium, also hypercalcaemia, renal failure
Dipsogenic – Failure/damage to hypothalamus and thirst drive, hypernatraemia without increased thirst response.

Thyroid

Reference ranges
TSH: 0.33-4.5 mu/L
Free T4: 10.2-22.0 pmol/L
Free T3: 3.2- 6.5 pmol/L

Thyroid Function Tests

↑TSH ↓T4	Hypothyroidism: atrophic, Hashimoto's, subacute (De Quervain's), postpartum, Riedel thyroiditis
↑TSH ↔T4	Treated hypothyroidism or subclinical hypothyroidism (look for assoc hypercholesterolaemia)
↑TSH ↑T4	TSH secreting tumour or thyroid hormone resistance
↓TSH ↑T4 or ↑T3	Hyperthyroidism: Grave's disease, toxic multinodular goitre (Plummer's), toxic adenoma, drugs (thyroxine, amiodarone), ectopic (trophoblastic tumour, struma ovarii)
↓TSH ↔T3 and T4	Subclinical hyperthyroidism. This may progress to primary hypothyroidism, especially if the patient is anti-TPO antibody positive
↓TSH ↓T4	Secondary hypothyroidism (hypothalamic/pituitary disorder)
↑(later ↓)TSH ↓T3 and ↓ T4	Sick euthyroidism (with any severe illness). The body tries to shut down metabolism as the thyroid gland has reduced output
↔TSH, abnormal T4	? assay interference, changes in TBG, amiodarone

Treatment
Hyperthyroid

- Medical
  - Symptom relief – Beta blockers, topical steroids for dermopathy, eye drops for patients with symptomatic eye disease in graves. –.
  - Antithyroid medications
    - **Carbimazole** most commonly used
      - Two approaches – **Titration** to normal T3 or **block and replace** [cause hypothyroidism then give levothyroxine – uncommon as high risk of side effects]
      - Side effects – Agranulocytosis (rare), rashes (common)
- **Radio-iodine**
  - Good efficacy for primary treatment, sometimes used after medical therapy has failed
  - Risk of permanent hypothyroidism
  - Contraindicated in pregnancy and lactating women
- **Surgical Hemi/total thyroidectomy**
  - Seven indications for surgical thyroidectomy (/hemi)
    - Women intending to become pregnant in the next 6/12
    - Local compression secondary to thyroid goitre (oesophageal/tracheal)
    - Cosmetic
    - Suspected cancer
    - Co-existing hyperparathyroidism
    - Refractory to medical therapy

- N.b. Prior to surgery patients MUST be euthyroid prior to surgery
- Total thyroidectomy patients will require thyroid replacement

- Thyroid storm
  - An acute state that presents as shock, with pyrexia, confusion, vomiting.
  - Must be treated with HDU/ITU support, usually require cooling, high dose anti-thyroid medications, corticosteroids and circulatory and respiratory support.

Hypothyroid – Thyroid replacement therapy

Hyperthyroidism	High Uptake	**Graves disease**: 40 - 60%, F>M (9:1), **painless** goitre, anti-TSH receptor Abs, high diffuseuptake on isotope scan (with Tc99)
		Toxic multinodular goitre (Plummer's)**:** 30 - 50%, high uptake hot nodules, **painless**, enlarged follicular cells distended with colloid + flattened epithelium
		Toxic adenoma: 5%, **solitary** 'hot nodule' on isotope scan (1 area of uptake)
	Low Uptake	**Subacute De Quervains thyroiditis**: self-limiting post viral painful goiter. Initially hyperthyroid, then hypothyroid
		Postpartum thyroiditis (like De Quervain's but postpartum)
		Ectopic: trophoblastic tumour, struma ovarii (excessive hCG)
Hypothyroidism	Autoimmune	**Primary atrophic hypoT** (commonest cause in UK): diffuse lymphocytic infiltration causing atrophy**. No goitre** so small thyroid. No **known** antibodies detected yet, associated with pernicious anaemia/vitiligo/endocrinopathies
		Hashimotos thyroiditis: Plasma cell infiltration & goitre. Elderly females. May be initial 'Hashitoxicosis'. ++ Autoantibody titres (**anti TPO/TG**), **Hurthle cells**, painless
	Other	**Iodine deficiency** (common worldwide)
		Post thyroidectomy/radioiodine
		Drug induced – antithyroid drugs, lithium, amiodarone
		Riedel's thyroiditis: dense fibrosis replacing normal parenchyma, painless, **stony hard**

Thyroid Neoplasia

Higher risk of neoplasm: Solitary, solid, young, male, cold nodules

Papillary (75-85%) 20-40 years, female Associated with irradiation Very good prognosis	Painless cervical lymphadenopathy, no obvious clinical abnormality of thyroid Tumour marker: Thyroglobulin Spread: **Lymph nodes** and lung **Histology: Psammoma bodies** (foci of calcification), empty-appearing nuclei with central clearing (**Orphan Annie eyes**) Mx: Surgery +/- radioiodine, thyroxine (to ↓TSH)
Follicular (10-20%) 40-60 years	Well-differentiated but spreads early Tumour marker: Thyroglobulin Spread: **Blood** >> lungs, bone, liver, breast, adrenals Histology: Fairly uniform cells forming small follicles, reminiscent of normal thyroid Mx: Surgery + radioiodine + thyroxine
Medullary (5%) 50-60 years 80% sporadic 20% familial **MEN2**	Neuroendocrine neoplasm derived from **parafollicular C cells** secreting **calcitonin** Tumour marker: CEA, calcitonin Histology: Sheets of dark cells, amyloid deposition within tumour (calcitonin broken down to amyloid) Mx: Screen for phaeochromocytoma pre-op + surgery + node clearance
Anaplastic Elderly Rare, most die within 1 yr	Early and wide metastases common Spread: very aggressive → local, lymph nodes, blood Histology: Undifferentiated follicular, large pleomorphic giant cells, spindle cells with sarcomatous appearance
Lymphoma	**MALToma** Risk factor: Chronic Hashimoto's (lymphocyte proliferation) Good prognosis

Multiple Endocrine Neoplasia

These are a group of 3 inherited disorders (autosomal dominant), whereby there is a predisposition to develop cancers of the endocrine system. There are 3 forms outlined below.

MEN1 (3Ps): Pituitary, Pancreatic (e.g. insulinoma), Parathyroid (hyperparathyroidism)

MEN2a (2Ps, 1M): Parathyroid, Phaeochromocytoma, Medullary thyroid

MEN2b (1P, 2Ms): Phaeochromocytoma, Medullary thyroid, Mucocutaneous neuromas (& Marfanoid)

Adrenals

Condition	Causes	Symptoms & Signs	Investigations	Treatment
Addison's Disease	Autoimmune (1° Europe) TB (1° worldwide) Tumour mets Adrenal haemorrhage (meningococcus) Amyloidosis	↑ K^+ ↓ Na^+ ↓glucose Postural hypotension Skin pigmentation Lethargy Depression Can progress to Addisonian crisis	SynACTHen test	Hormone replacement – hydrocortisone/ fludrocortisone if primary adrenal lesion
Cushing's Syndrome	**ACTH dependent:** (↑ACTH) • Pituitary tumour – "Cushing's disease" (85%) • Ectopic ACTH-producing tumour (5%) (small cell lung cancer, carcinoid tumour) **ACTH independent:** • Adrenal adenoma/cancer (10%), adrenal nodular hyperplasia, iatrogenic steroid use	Moon face Buffalo hump Central obesity Striae Acne Hypertension Diabetes Muscle weakness (proximal myopathy) Hirsutism Bruising	1st line: Overnight dexamethasone suppression test or 24h urinary free cortisol. +ve suggests true Cushing's syndrome 2nd line: **Low-dose 0.5mg** or **High-dose 2mg** dexamethasone suppression test (Note: Meeran no longer recommends, use inferior pituitary petrosal sinus sampling instead due to FP rate 20% i.e. Ectopic ACTH can be suppressed by high-dose dex) Low dose dex will fail to suppress cortisol in all of these, but high dose will succeed in pituitary cushings 3rd line: CT/PET	Treat underlying disease – surgical removal of lesion

			scan to identify source of ectopic ACTH	
Conn's Syndrome	Adrenal adenoma	Uncontrollable hypertension ↑ Na^+ ↓ K+	Raised Aldosterone:Renin Ratio	Aldosterone antagonists/potassium sparing diuretics – Spironolactone, eplerenone, amiloride. If >4cm consider surgical excision
Phaeo	Adrenal medulla tumour = ↑ Adrenaline	Triad: Headaches, Hypertension & Hyperhidrosis Arrhythmias Death if untreated	Plasma and 24h urinary metadrenaline measurement/ catecholamines & VMA	Alpha blockade (first), beta blockade then surgery when blood pressure well controlled.

Therapeutic Drug Monitoring

Drug	Signs toxicity	Signs under treatment	Interactions and cautions	Treatment
Phenytoin	Ataxia and nystagmus	Seizures	At high levels liver becomes saturated → surge in blood levels	Treatment mainly supportive. No specific antidote.
Digoxin	Arrythmias, heart block, confusion, xanthopsia (seeing yellow-green)	Arrythmias	Levels increased with Hypokalaemia. Reduce dose in renal failure and in elderly	Digibind (Digoxin immune Fab)
Lithium	Tremor (early), lethargy, fits, arrhythmia, renal failure	Relapse of mania in bipolar disorder	Excretion impaired by hyponatraemia, ↓renal func and diuretics	Treatment mainly supportive. Osmotic or forced alkaline diuresis. If Li >3mmol/L haemodialysis may be used
Aminoglycosides incl. Gentamicin and Vancomycin	Tinnitus, deafness, nystagmus, renal failure	Uncontrolled infection	Mostly use single daily dosing. Monitor peak and trough level before next dose	Omit / reduce dose
Theophylline and aminophylline (which contains theophylline)	Arrythmias, convulsions, anxiety, tremor	Bronchial smooth muscle does not relax – asthma/ COPD worsens/ does not improve	Variation t1/2; e.g. 4hrs smokers 8hrs non-smokers, 30hrs liver disease. Level ↑ by erythromycin, cimetidine and phenytoin	Omit / reduce dose

Calcium

Normal plasma range: **2.2 - 2.6mmol/l**

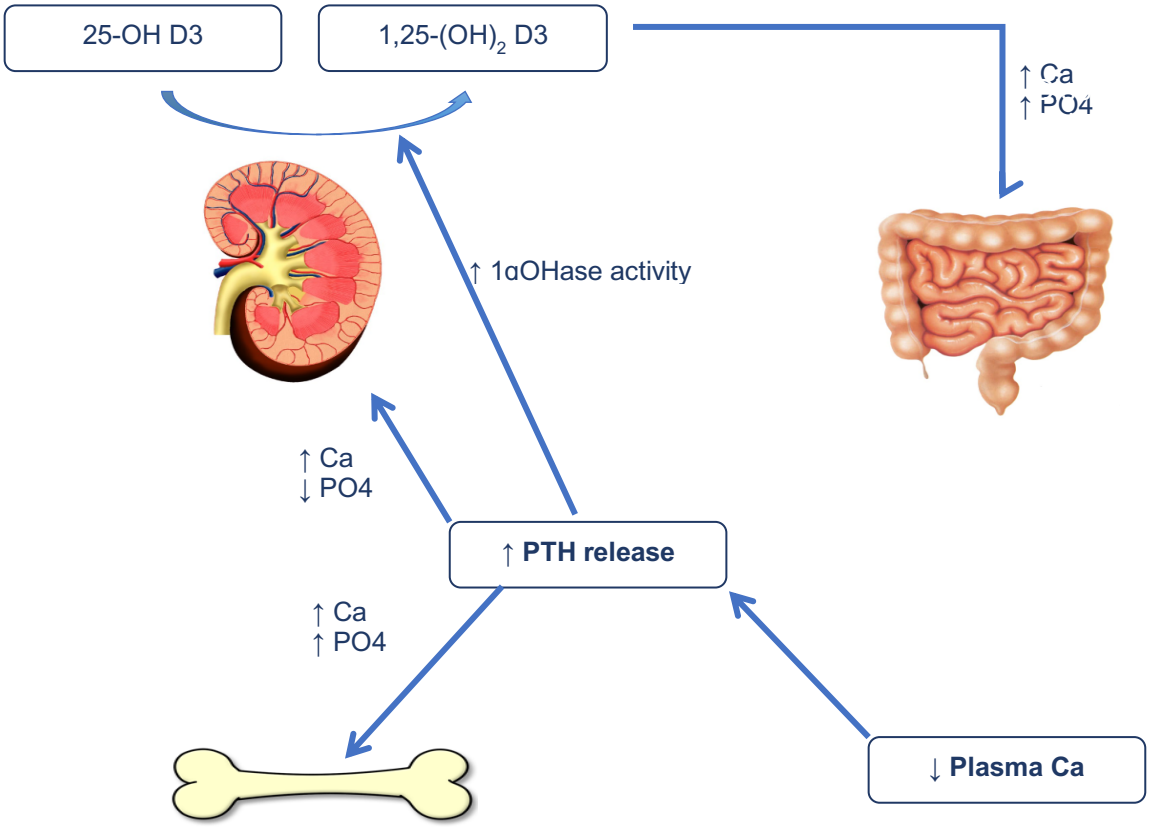
- 45% ionised (free – biologically active form)
- **50% bound to albumin**, therefore *affected by albumin level* – use corrected calcium
- Remaining 5% bound to globulins and other ions including citrate and bicarbonate

Two main hormones involved in calcium metabolism:

1. **PTH** (Parathyroid Hormone):
   - ↑tubular 1α hydroxylation of vitamin D (25(OH)D)
   - Mobilises calcium from bone through osteoclast acitvation

- ↑ renal calcium reabsorption
- ↑ renal phosphate excretion

2. 1,25 (OH)2D (**Calcitriol**)
   - ↑ Calcium and phosphate absorption from the gut
   - Bone remodelling



Condition	Primary defect	Ca	PO4	PTH	Alk phos	Vit D
1° hyperparathyroidism	Intrinsic problem with parathyroid gland causing ↑ PTH	↑	↓	↑/N	↑/N	N
2° hyperparathyroidism	Pathology outside parathyroid gland (eg CKD): stimulation of parathyroid gland to produce more PTH	↓	↑	↑	↑	↓/N
3° hyperparathyroidism	Autonomous PTH secretion	↑/N	↓/↑	↑	↑/N	↓/N
Hypoparathyroidism	Low levels of PTH	↓	↑	↓	↓ / N	N
Rickets/ osteomalacia	Vitamin D deficiency	↓	↓	↑	↑	↓
Paget's disease	Re-modelling of bone	N	N	N	↑	N
Osteoporosis	Bone loss	N	N	N	N	N

1° hyperparathyroidism causes:

- **80% single parathyroid adenoma**
- 15% hyperplasia and multiple adenomas
- 0.5% carcinomas (most carcinomas non-functional)
- Men1 (adenoma) and 2 (hyperplasia)

2° hyperparathyroidism causes:

- **CKD**
- **Vitamin D deficiency**
- **Malabsorption syndromes**

3° hyperparathyroidism causes:

- Prolonged 2° hyperparathyroidism causing unregulated secretion of PTH
- Kidney transplant

Hypoparathyroidism causes:

- **Postsurgical** (most common)
- **Postradiation**
- Autoimmune
- Iron deposition in people with thalassaemia
- Hypo/hypermagnasaemia
- Pseudohypoparathyroidism (resistance to parathyroid hormone)
- DiGeorge syndrome

Disorders of calcium balance

Hypercalcaemia

Ca ≥ 2.6mmol/L.

The commonest cause of hypercalcaemia in the community is **primary hyperparathyroidism.**

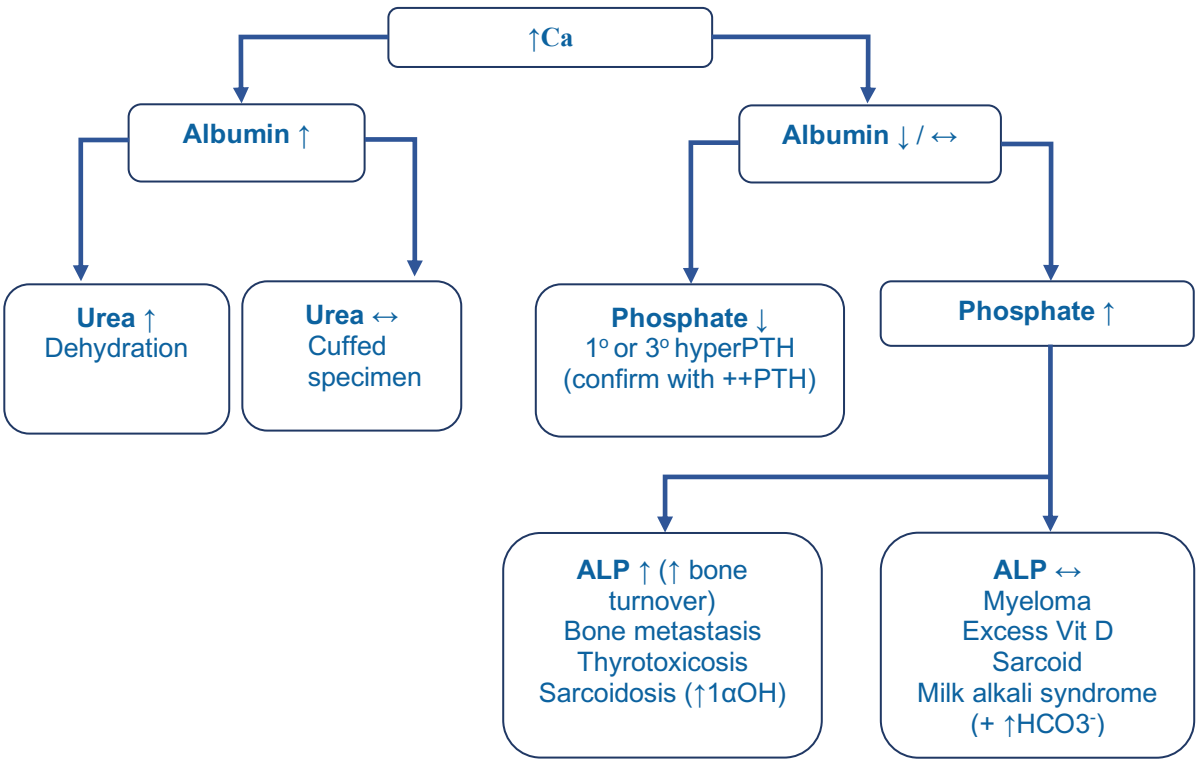
The commonest cause of hypercalcaemia in hospitalized inpatients is **malignancy.**

Symptoms:

- Stones (renal)
- Bones (pain)
- Groans (psych)
- Moans (abdo pain)
- Thrones (polyuria)
- Muscle weakness

Treatment:

- Treat the cause
  - Dehydration
  - Hyperparathyroidism
  - Cancer
  - Sarcoidosis
  - Milk alkali syndrome
  - Thyrotoxicosis
  - Hypervitaminosis D



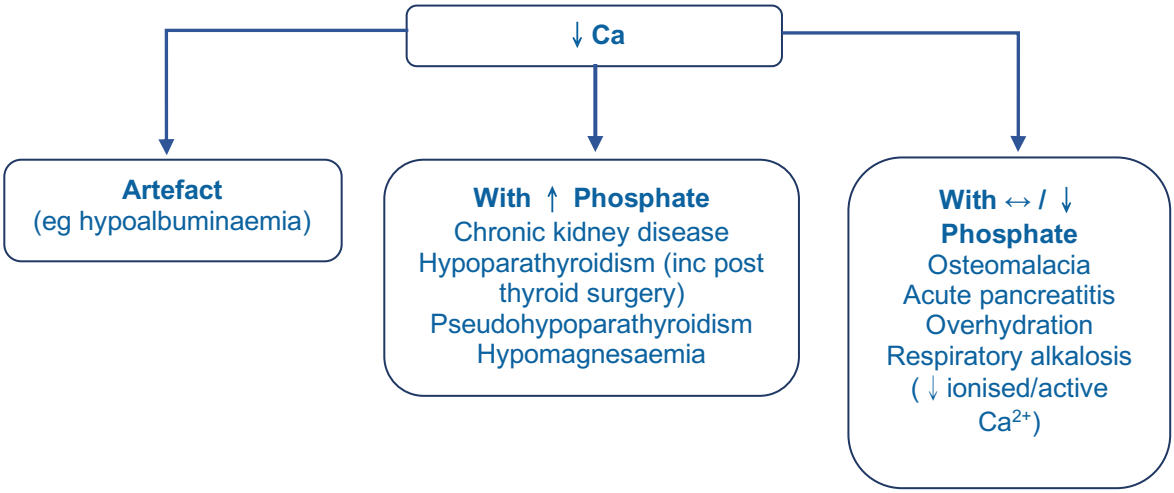
Hypocalcaemia

Symptoms:

- Perioral paraesthesia
- Carpopedal spasm
- Anxious/irritable
- Orientation impairment
- Increased smooth muscle tone
- Neuromuscular excitability (Trousseau's and Chvostek's sign)
- Dermatitis/Impetigo herpetiformis
- Long QT

Treatment:

- If symptomatic or calcium <1.875mmol/L
    - Parenteral calcium
        - 10% calcium gluconate IV
- Asymptomatic/ chronic/ mild hypocalcaemia
    - Oral calcium supplementation e.g. SandoCal (taken not at meal times)
        - If low PTH or vitamin D:
            - Vitamin D supplementation
                - Chronic kidney disease: alfacalcidol
                - Other patients including those with liver disease: vitamin D2 (ergocalciferol) or vitamin D3 (cholecalciferol)



Renal stones (nephrolithiasis)

- Risk factors: dehydration, abnormal urine pH (e.g. meat intake, renal tubular acidosis), increased excretion of stone constituents, urine infection (treat infection), anatomical abnormalities
- Calcium stones:
    - Most patients are NORMOcalcaemic
    - Results from:
        - Hyperoxaluria (increased intake, absorption etc)
        - Hypercalciuria (increased intake, renal leak)
    - Preventative management: avoid dehydration, reduce oxalate intake, maintain normal Ca intake, thiazides → hypocalciuric, citrate (alkalinise urine)

Constituent	Frequency	X-ray appearance
Calcium – mixed	~45%	Radio-opaque
Calcium oxalate	~35%	Radio-opaque
Calcium phosphate	~1%	Radio-opaque
Triple phosphate"Struvite"	~10%	Radio-opaque"staghorn"
Uric acid	~5%	**Radiolucent**
Cysteine	~1-2%	Radio-opaque (light)
Others eg xanthine	Rare	Xanthine lucent, others opaque

- First line investigation: urgent (within 24 hours of presentation) imaging should be offered (low-dose non-contrast CT for most adults; ultrasound for pregnant women, children, and young people)
- Management:
    - IM Diclofenac (analgesia)
    - Stones ≤5mm in diameter: Conservative management
    - Stones 6-20mm: Lithotripsy/Ureteroscopy
    - Stones >20mm: Percutaneous Nephrolithotomy
- Investigations for recurrent stones:
    - Serum: Cr, bicarb, Ca, phosphate, urate, PTH (if hypercalcaemic)
    - Stone analysis
    - Spot urine: pH, MCS, amino acids, albumin
    - 24 hour urine**:** Volume (>2.5L), Ca, oxalate, urate, citrate

Enzymes and Cardiac Markers

Amylase: high serum levels in **acute pancreatitis** (usually >10x upper limit of normal, >3x upper limit of normal required for diagnosis)

- Non-specific – raised in the following (not an exhaustive list):
    - Renal insufficiency
    - Intestinal infarct/ peritonitis
    - Cholecystitis
    - Salpingitis
    - Ectopic pregnancy
    - Abdominal cancers

Lipase: if >3 the upper reference range than highly indicative of **acute pancreatitis**

- More specific than amylase but can be raised in:
    - Renal insufficiency
    - Small intestinal ischaemia/ obstruction
    - Sepsis
    - DKA
    - Cholecystitis

Creatine Kinase: Most widely used as a marker of muscle damage (CK-MM = skeletal muscle, CK-MB (1&2) = cardiac muscles.)

Raised levels due to:

- Physiological: Afro-Caribbean (<5x upper limit of normal)
- Pathological: **Duchenne Muscular Dystrophy** (>10xULN), **MI** (>10xULN), Rhabdomyolysis, Statin related myopathy (spectrum of myalgia to rhabdomyolysis occurring secondary to taking

statins. RF: high dose, genetic predisposition, previous history of myopathy with another statin. Causes rise in CK. Reversible with cessation of statin).

Alkaline Phosphatase: present in high concentrations in liver, bone, intestine and placenta.
We can differentiate liver from bone ALP either by seeing if there is a rise in gamma-GT (liver ALP rises with this), by performing electrophoresis, or by ordering a bone-specific assay of ALP.
Causes of raised ALP:

- Physiological: Pregnancy (3rd trimester), Childhood (during growth spurt)
- Pathological:
    - >5x ULN
        - Bone (**Paget's**, osteomalacia)
        - Liver (**cholestasis**, cirrhosis)
    - <5x ULN
        - Bone (**tumours**, fractures, osteomyelitis)
        - Liver (infiltrative disease, hepatitis)

BNP

- Brain natriuretic peptide - hormone that is primarily released from the ventricles in the heart
- Released in response to ventricular stretch, has roles in reducing systemic vasoconstriction, sodium retention and renal sympathetic activity
- Levels of <100 are highly specific for excluding **heart failure**, >400 is highly sensitive for heart failure
    - Confounding factors to interpretation include CKD

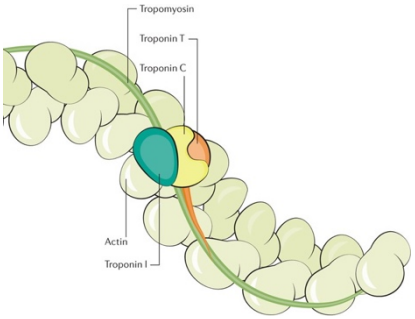
NT-proBNP

- More sensitive than BNP and has greater prognostic value

Troponin (not an enzyme)

Troponin I/T = myocardial injury biomarker

- Not an enzyme but a protein which forms part of the contractile apparatus in cardiomyocytes, released during **MI**
- Measure at 6 hours and then at 12 hours post onset of chest pain (100% Se and 98% Sp at 12-24 hours)
- Remains elevated for 3 – 10 days
- Also raised in: coronary spasm, coronary dissection, PCI, myocarditis, PE, HF, cardiomyopathies, sepsis, cardiac surgery, chest trauma, defibrillation post



What is an "international unit"
In chemical pathology, the term "international unit" or IU is used to show the concentration of an enzyme e.g. the upper limit of normal for ALT is 40IU/litre.

Put simply: *1 international unit is the quantity of enzyme that catalyses 1uMol of substrate in a minute* (at a given temp and pH)

It is a measure of **enzyme activity** not mass or concentration

Lipoprotein Metabolism

Types	Diseases	
Primary Hypercholesteraemia	Familial hypercholesteraemia (type II)	AD: LDLR, apoB, PCSK9 AR: LDLRAP1
	Polygenic hypercholesteraemia	Several polymorphisms
	Familial hyperα-lipoproteinaemia	CETP deficiency
	Phytosterolaemia	ABC G5 & G8
Primary Hypertriglyceridaemia	Familial Type I	Lipoprotein lipase or apoC II def
	Familial Type V	apoA V def (sometimes)
	Familial Type IV	↑synthesis of TG
Primary Mixed Hyperlipidaemia	Familial Combined hyperlipidaemia	
	Familial dysβlipoproteinaemia	
	Familial hepatic lipase deficiency	
Hypolipidaemia	Aβ-lipoproteinaemia	MTP def
	Hypoβ-lipoproteinaemia	Truncated apoB protein
	Tangier Disease	HDL def
	Hypoα-lipoproteinaemia	apoA-I mutations (sometimes)

- Lipoproteins In order of density:
  Chylomicron < FFA < VLDL < LDL < IDL < HDL
- PCSK9
  - Binds LDLR and promotes its degradation
  - Loss of function mutation of PCSK9 → lower LDL levels
  - Novel form of LDL-lowering therapy is Anti-PCSK9 MAb
- Lipoprotein(a) is a CVD RF, Tx: Nicotinic acid
- Management of hyperlipidaemia
  - First line is always conservative – dietary modification and exercise (although dietary intake of cholesterol correlates poorly with actual triglyceride levels)
  - Statin therapy
    - HMG-CoA reductase inhibitor
    - Reduces intrinsic synthesis of cholesterol in the liver
    - Side effects – myopathy/rhabdomyolysis, fatigue
  - Other agents more rarely used include Ezetimibe
- Management of Obesity
  - Conservative measures
  - Medical
    - No medication has been safely proven to provide sustained weight loss

- Orlistat (A pancreatic lipase inhibitor) is used however side effects of profound flatus and diarrhoea are often too cumbersome for patients to tolerate
- Rimonabant (a cannabinoid antagonist) was trialled and discontinued from use as there was an increased risk of suicide

- Surgical
  - Bariatric surgery is indicated in patients with a BMI >40 or >35 with a comorbidity associated with obesity
  - To be considered requires extensive screening and must commit to long term follow up usually.

Nutrition

	Deficiency	Excess	Test
Fat soluble vitamins			
A - Retinol	Colour Blindness	Exfoliation Hepatitis	Serum
D - Chole-calciferol	Osteomalacia/ Rickets	Hyper- calcaemia	Serum
E - Tocopherol	Anaemia /neuropathy/IHD		Serum
K - Phyto- menadione	Defective clotting		PT
Water soluble vitamins			
B_1 - Thiamine	Beri-Beri Neuropathy Wernicke Syndrome		RBC transketolase
B_2 - Riboflavin	Glossitis		RBC glutathione reductase
B_3 - Niacin	Pellagra – 3Ds Dementia, dermatitis, diarrhoea		
B_6 - Pyridoxine	Dermatitis/ anaemia	Neuropathy	RBC AST activation
B_{12} - Cobalamin	Pernicious Anaemia, sub-acute cord degeneration		Serum B_{12}
C - ascorbate	Scurvy	Renal stones	Plasma
Folate	Megaloblastic anaemia Neural tube defect		RBC folate
Trace elements			
Iron	Hypochromic	Haemochromatosis	FBC

	anaemia		Fe and binding studies Ferritin
Iodine	Goitre Hypothyroid	Hypo/Hyperthyroid (Jod-Basedow/Wolf-Chaicoff effects)	TFT
Zinc	Dermatitis		
Copper	Anaemia	Wilson's	Cu Caeroplasmin
Fluoride	Dental caries	Flourosis	

Specific Conditions

- Crohn's
  - Terminal ileal disease can lead to B12 deficiency and fat-soluble vitamins (ADEK) deficiency
  - Folate deficiency can be present in patients on methotrexate therapy
  - Calcium, phosphate, magnesium and zinc can be deranged if there is high output/chronic diarrhoea
- Coeliac
  - Iron deficiency
  - Vitamins ADEK, thiamine, Vitamin B6
- Chronic liver disease
  - Vitamins ADEK, B12, Selenium, Magnesium, Zinc, folate
- Chronic kidney disease
  - Protein energy wasting syndrome
- Pancreatic insufficiency
  - Vitamins ADEK

Metabolic Disorders

UK screening via the Guthrie blood spot test at 6 days age

- Phenylketonuria, congenital hypothyroidism, cystic fibrosis, sickle cell disease, MCAD (medium chain acylCoA dehydrogenase) deficiency

Diseases	Outcomes	Screening Tests
Phenylketonuria	Phenylanine hydroxylase deficiency	Phenylalanine levels
Congenital Hypothyroidism	Dysgenesis/Agenesis of thyroid gland	TSH levels
Cystic Fibrosis	Mutation in CFTR - viscous secretions → ductal blockages	Immune reactive trypsin. If positive → DNA mutation detection
Medium Chain AcylCoA dehydrogenase Deficiency	Fatty acid oxidation disorder	Acylcarnitine levels by tandem Mass Spectrometry
The newborn screening programme measures chemicals in the blood spot, it doesn't involve		

any genetics. An abnormal chemical level doesn't always mean that there is a genetic disorder!

Basic Statistics

It is more likely you will be examined on the stats surrounding screening tests than the actual disorders. Just remember there are 4 definitions to know about:

- Specificity and Sensitivity both refer to the **population**
- Positive and Negative predictive values (PPV/NPV) refer to the **test itself**

For example:

	Have cystic fibrosis	Don't have cystic fibrosis
Test positive	90 (true positive)	5 (false positive)
Test negative	10 (false negative)	80 (true negative)

- *Specificity* is the probability (in %) that someone without the disease will correctly test negative
  - TN/(FP+TN)
  - 85 people without CF in total, and 80 actually test negative. Specificity is 80/85=94% (much easier to think like this than memorise formulae!)
- *Sensitivity* is the probability that someone with the disease will correctly test positive
  - TP/(TP+FN)
  - 100 people with CF in total, and 90 actually test positive. Sensitivity is 90/100=90%
- *PPV* is the probability that someone who tests positive actually has the disease
  - TP/(TP+FP)
  - 95 people tested positive, of which 90 had the disease. PPV=90/95=95%
- *NPV* is the probability that someone who tests negative actually doesn't have the disease
  - TN/(TN+FN)
  - 90 people tested negative, of which 80 didn't have the disease, NPV=80/90=89%

The actual metabolic conditions!

The lecture basically provides a clinical scenario then just lists loads of diseases. In this table I have summarised the major inherited metabolic disorders in a more logical format than the lecture. I have tried where possible to highlight the key buzzwords. Don't worry about this in a huge amount of detail though!

Group	Examples	Key Features
Group 1 – accumulation of toxins	Organic adicaemias Includes propionic acidaemia etc…	High urea, ketones Metabolic acidosis Treat with low protein diet, acylcarnitine and haemofiltration Often have funny smells due to the organic acids

	Urea cycle disorders 9 in total, includes ornithine transcarbamylase deficiency	High ammonia (>200uM) leading to encephalopathy and developmental delay Respiratory alkalosis Vomiting?diarrhoea Treat with low protein diet (stops urea formation)
	Aminoacidopathies Includes PKU and maple-syrup urine disease	High phenylalanine, blue eyes and fair hair/skin Retardation MSUD apparently causes sweaty feet…
Group 2- reduced energy stores	Glycogen storage disorders Includes Von Gierke's	Hypoglycaemia and lactic acidosis Hepatomegaly, developmental delay Hepatoblastoma risk high Treat with regular CHO
	Galactossaemia	Increased Gal-1-phosphate levels cause cataracts Hypoglycaemia, neonatal conjugated jaundice Test urine reducing agents Treat with low lactose/galactose diet
	Fatty acid oxidation disorders Includes MCADD	Hypoglycaemia, cardiomyopathy, rhabdomyolysis Low ketones! Screened with blood acylcarnitine Test urine organic acids Treat with regular carbohydrate
Group 3- large molecule synthesis (all dysmorphic)	Peroxisomal disorders Cannot catabolise very long fatty acids or make bile acids	Poor feeds, seixuresa Retinopathy Hepatomegaly and mixed hyperbiliribinaemia
	Glycosylation disorders	Measure serum transferrins Lead to retardation and nipple inversion
Group 4 – defects in large molecule metabolism	Lysosomal disorders Include Tay Sachs disease	Very slow progressing Neuroregression, hepatosplenomegaly Cardiomyopathy Test urine mucooligopolysaccharides and WBC enzyme levels
Group 5 - mitochondrial	Various: MELAS, Kearn's Sayre, POEMS	Involve the CNS, muscle and heart High lactate and CK Muscle biopsy diagnostic

Hyperglycaemia

Can be induced by myriad causes T1DM/ T2DM/ gestational diabetes/ Cushing's/ acromegaly/ steroids/ pancreatitis/ post stroke/ post MI

Diabetes Mellitus

Diagnosis

- If symptomatic (polydipsia/ polyuria/ blurred vision/ unexplained weight loss/ recurrent infections/ tiredness) then one of the below is adequate to diagnose:
    - HbA1C >48
    - Fasting glucose >7
    - Random glucose >11.1
    - IGTT >11.1
- If asymptomatic then need to arrange repeat testing, preferably with the same test

IGTT of >7.8 but <11.1 = impaired glucose tolerance
Fasting glucose >6.1 but <7.0 is classified as impaired fasting glucose

DKA = more common in T1DM
HHS = more common in T2DM
DKA Criteria:

- pH < 7.3, Plasma Glucose >11mM, Blood Ketones>3mM (2+ in urine).
- Rapid onset
- Medical emergency
- Symptoms: confusion, Kussmaul breathing, abdominal pain, nausea, vomiting
- Precipitants include infection, surgery, missed insulin doses, trauma
- Management
    - **A to E** approach (call for senior help early)
    - Fluids
        - **0.9% saline**
            - SBP <90 give 500ml in 15 mins
            - SBP >90 give 1 litre over 1 hour
    - Insulin
        - Only started <u>after</u> fluids
        - ensure K^+ not <3.5
        - **<u>0.1u/kg/h</u>** fixed rate regimen
    - Early senior review +/- ITU involvement
    - Monitoring
        - Monitor glucose and potassium hourly
            - If K low then KCl (n.b. you cannot administer >10mM/h K^+ outside of ITU)
        - Catheterisation aiming for urine output >0.5ml/kg/hr
    - Resolution is when ketones <0.6 and pH >7.3

HHS Criteria:

- pH > 7.3, Osmolarity > 320mOsm, Blood Glucose > 30mM
- HHS develops over few days
- Patients present acutely unwell with confusion and clinical dehydration
- Management:
    - A to E approach
    - Fluid replacement
        - **0.9% saline over 1 hr**
    - IV insulin
        - Only if >1 mmol/L ketones
        - **0.05u/Kg/hr** fixed rate
    - Monitoring
        - Serial U+Es and glucose readings

Hypoglycaemia

Causes of hypoglycaemia typically classified according to their aetiology – either in the setting of hyper or hypoinsulinaemia, and within hypoinsulinaemia the presence or absence of ketones.

Hyperinsulinaemic hypoglycaemia

- Insulin overdose
- Sulfonylurea excess
- Insulinoma

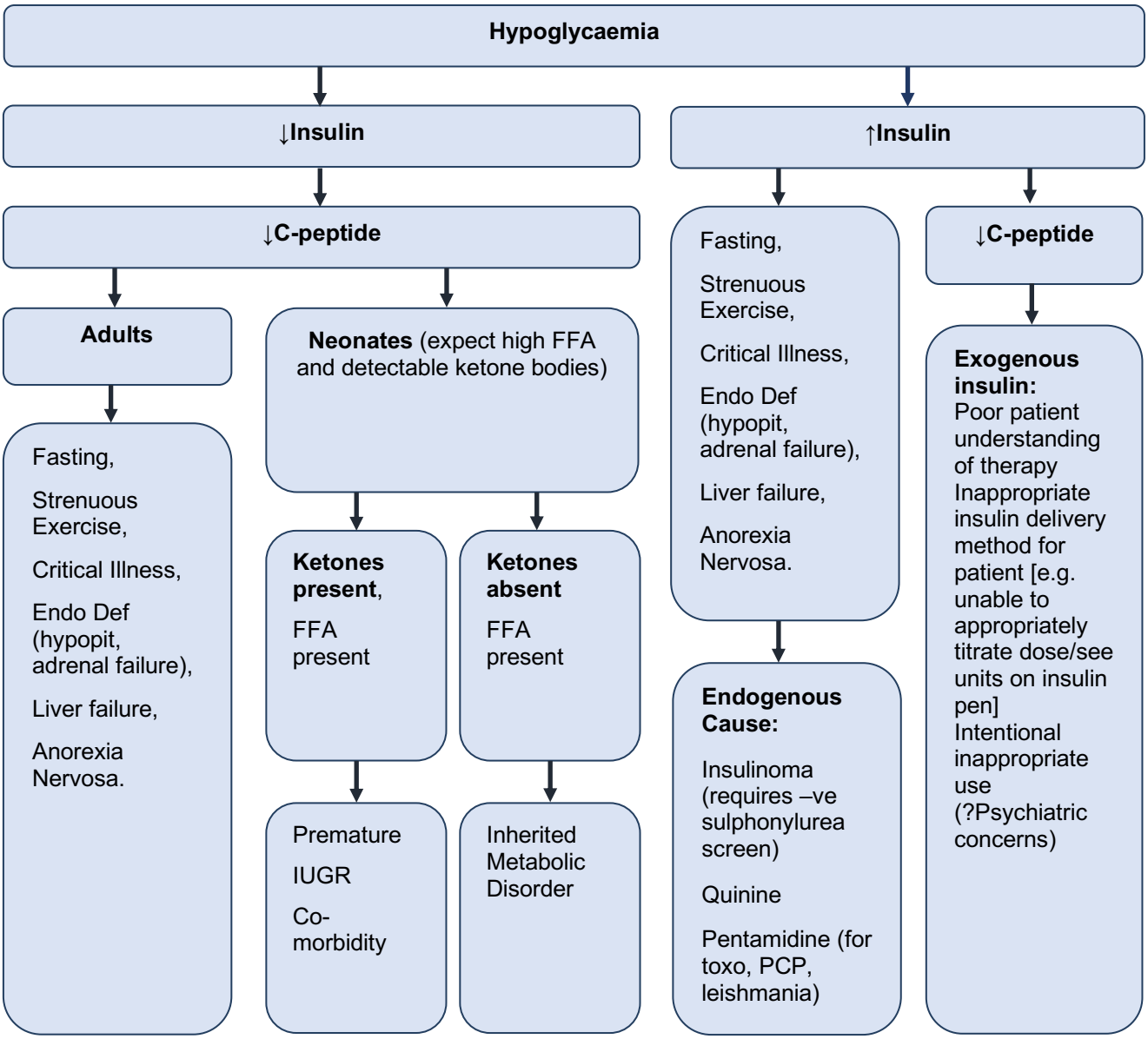
Hypoinsulinaemic hypoglycaemia

- +ve ketones
  - Alcohol binge with no food
  - Pituitary insufficiency
  - Addison's
  - Liver failure
- -ve ketones
  - Non pancreatic neoplasms
    - Fibrosarcomata
    - Fibromata

Non-islet tumour hypoglycaemia

↓ Glucose, ↓ Insulin, ↓ C-peptide, ↓FFA and ↓ Ketones

Tumours that cause a paraneoplastic syndrome, secreting 'big IGF-2', which binds to IGF-1 and Insulin receptor



Paediatric Chemistry (cross-reference with paeds)

Common Problems in Low Birth Weight

- Respiratory distress syndrome
- Retinopathy of prematurity
- Intraventricular haemorrhage
- Patent ductus arteriosus
- Necrotizing enterocolitis – inflammation of bowel wall – necrosis and perforation

Renal Function (basically all parts of the kidney function less well than in adults)

- Functional maturity of glomerular filtration rate only by two years old
- Low GFR for surface area
- Less reabsorption than adult due to short proximal tubule
    - Although usually adequate for small filtered load

- Reduced concentrating ability due to short loops of Henle and distal collecting ducts
- Persistent sodium loss due to distal tubule being relatively aldosterone-insensitive

Electrolyte Disturbances

- High insensible (uncontrollable) water loss due to:
  - High surface area to body weight ratio
  - Skin blood flow is increased
  - Metabolic/respiratory rate is higher than adults
  - Transepidermal fluid loss (skin less of a good barrier as it's immature)
- Hypernatraemia is common in the first 2 weeks of life, although can be a marker of dehydration or an overly concentrated milk formula
- Hyponatraemia
  - First 4-5 days of life
    - Excess total body water usually due to excessive intake.
    - Rarely may be SIADH secondary to infection (pneumonia/meningitis) or intraventricular haemorrhage
  - After first 4-5 days
    - Usually loss of sodium loss due to immature tubular function in patients on diuresis
  - Factitious (i.e. Na^+ normal but appears low) e.g. hyperglycaemia
  - Congenital adrenal hyperplasia
    - Addisonian presentation
    - Usually identified on Guthrie spot

Neonatal Jaundice

This is covered in detail in paediatrics, but in a nutshell learn the below markers of **pathological** jaundice

- Jaundice within the 1st 24 hours of life (acute haemolysis or sepsis)
- Jaundice after 2 weeks of life (hepatobiliary failure)
- Conjugated hyperbilrubinaemia at any stage of infancy

Renal Physiology

Assessing renal function

Normal glomerular filtration rate (GFR) = 120ml/hr.
Age-related decline of approx 1ml/hr/yr.

Clearance = the volume of plasma that can be completed cleared of a marker substance in a unit of time.
If marker is not bound to serum proteins, freely filtered by the glomerulus, and not secreted/reabsorbed by tubular cells, then clearance = GFR.

Insensible Water Loss	High Surface Area High skin blood flow High metabolic/resp rate High transdermal fluid loss
Fluid Overload	Bronchopulmonary Dysplasia Necrotising enterocolitis
Hypernatraemia	Intraventricular haemorrhage Sodium bicarbonate when treating acidosis
Hyponatraemia	Congenital adrenal Hyperplasia Caffeine/theophylline when treating apnoea

Gold standard measure of GFR = inulin. But requires steady state infusion and difficult

to assay so it is reserved for research purposes only.

Creatinine is endogenous marker. This is used in clinical practice to measure renal function. Very variable between individuals and therefore it is best to monitor the trend and use it to look for *change over time*. Creatinine is a by-product of muscle turnover, so muscular individuals will have a higher creatinine than others.

Different equations use the serum creatinine with variable combinations of age, weight, sex and ethnicity to estimate GFR e.g. Cockcroft-Gault and MDRD *(modification of diet in renal disease study)*.

Urine Examination:

Single sample
- Dipstick testing
- Microscopic examination
- Proteinuria quantification (protein:creatinine ratio (PCR))

24-hour collection
- Proteinuria quantification (superseded by PCR above)
- Creatinine clearance estimation
- Electrolyte estimation
- Stone forming elements

Urine microscopy:
- Crystals (stones)
- Red blood cells (stones, UTI)
- White blood cells (UTI, glomerulonephritis)
- Casts (glomerulonephritis)
- Bacteria (UTI)

Acute Kidney Injury

AKI is defined as:
- Rise in serum creatinine over 26 within 48h
- A 50% or greater rise in serum creatinine known or presumed to have occurred within the past 7 days
- A fall in urine output to less than 0.5mL/kg/hour for more than 6 hours.
    - Be wary that prostate and bladder pathology can cause this too

Pre-renal – hallmark is reduced renal perfusion with no structural abnormality of the kidney; however it can become renal if the ischaemia leads to necrosis. Responds to volume replacement
Renal – vascular, glomerular, tubular or interstitial
Post-renal – characterised by obstruction to urinary flow, glomerular filtration requires a pressure gradient, reversal can lead to scarring and permanent renal impairment

Indications for dialysis as an emergency (remember it as the vowels A, E, I, O, U):
1. Acidosis (metabolic)
2. Electrolyte disturbance e.g. refractory hyperkalaemia
3. Intoxication e.g. lithium, aspirin
4. Overload (fluid) e.g. pulmonary oedema
5. Uraemic encephalopathy

Chronic Kidney Disease

Stage	Description	GFR (ml/min)
1	Kidney damage with normal GFR	>90
2	Mild GFR	60-89
3	Moderate GFR	30-59
4	Severe GFR	15-29
5	End-stage kidney failure	<15 or dialysis

Commonest causes:

- Diabetes
- Atherosclerotic renal disease
- Hypertension
- Chronic Glomerulonephritis
- Infective or obstructive uropathy
- Polycystic kidney disease

Consequences:

1] Progressive failure of homeostatic function
- Acidosis
- Hyperkalaemia

2] Progressive failure of hormonal function
- Anaemia (loss of EPO synthesis)
- Renal Bone Disease (secondary hyperparathyroidism due to low Vit D)

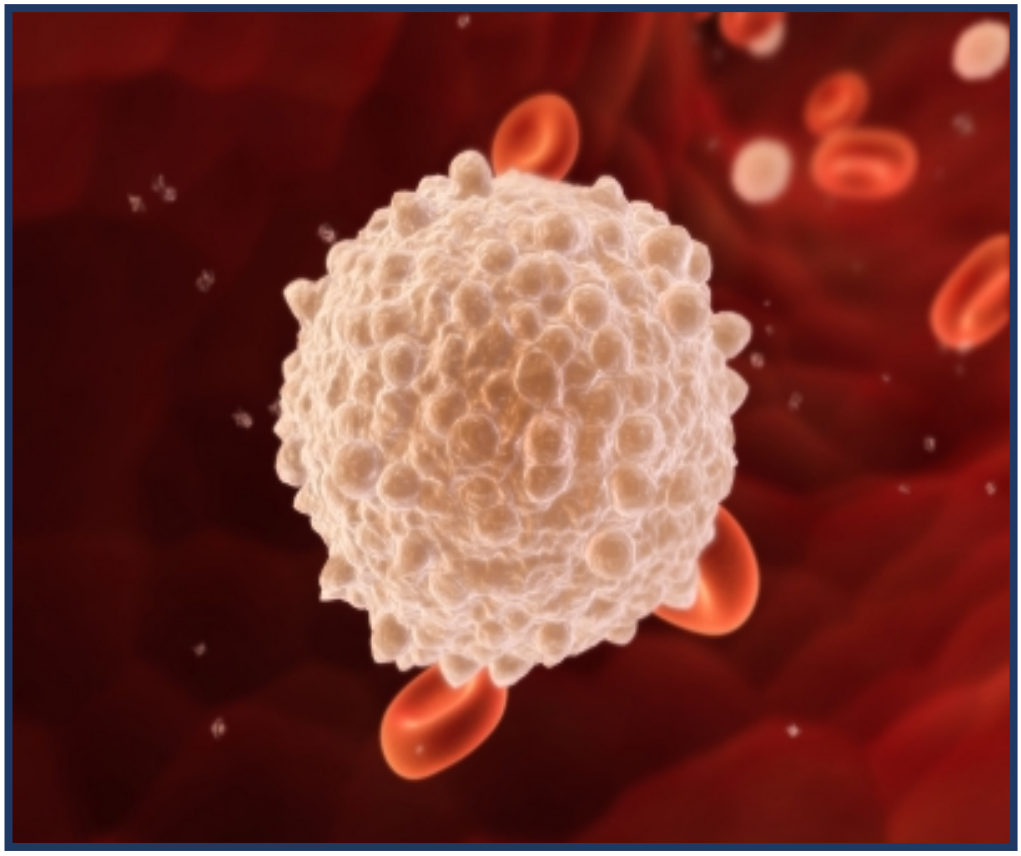
3] Cardiovascular disease
-Vascular calcification and subsequent atherosclerosis (biggest mortality in CKD)
-Uraemic cardiomyopathy

4] Uraemia and Death

Renal replacement therapy

- Dialysis
  - Haemodialysis
    - Done via a tunneled central line (**Tessio line**) or an **arteriovenous fistula**
    - Usually done around 3x/week depending on the patient's individual circumstances
    - Not ideal for those who are still at work as requires several hours hooked up to a machine at the hospital!
  - Peritoneal dialysis
    - Undertaken via a **Tenckoff catheter**
    - Uses the peritoneum as the dialysis membrane, insert dialysate through the catheter, leave for a few hours then drain
    - Can be done at home
    - Increased risk of peritoneal infections
  - Both have pros/cons, depend on patient preference
- Transplant
  - Kidney transplant is the only definitive cure
  - Requires lifelong immunosuppression with agents like tacrolimus or ciclosporin
  - Transplanted kidney is usually in the right iliac fossa
    - Rutherford Morrison (hockey stick scar)
    - Right mesocolon is not fixed therefore easier to access the iliac vessels to connect the transplant

Immunology



Edited by Akash Srinavasan and Beccy Thompson

Immune Response / Physiology

1. Constitutive Barriers to Infection

Skin

- Tightly packed keratinised cells → Physically limits colonisation by microorganisms.
- Physiological factors → Low pH, Low oxygen tension
- Sebaceous glands
    - Hydrophobic oils repel water and microorganisms
    - Lysozyme destroys structural integrity of bacterial cell wall
    - Ammonia and defensins have anti-bacterial properties

Mucosal Surfaces

- Secreted mucous - Physical barrier to trap invading pathogens
    - Secretory IgA prevents bacteria and viruses attaching / penetrating epithelial cells.
    - Lysozyme directly kill invading pathogens
    - Lactoferrin acts to starve invading bacteria of iron.
- Cilia → directly trap pathogens and contribute to removal of mucous, assisted by physical manoeuvres such as sneezing and coughing.

Commensal Bacteria

- Compete with pathogenic microorganisms for scarce resources
- Produce fatty acids that inhibit the growth of many pathogens

2. Innate Immune System

Cells - Polymorphonuclear cells – neutrophils, eosinophils, basophils; Monocytes and macrophages; Natural killer cells; Dendritic cells

- Express receptors for cytokines/chemokines - to detect inflammation
- Express pattern recognition receptors - to detect pathogens
- Capable of phagocytosis / oxidative and non-oxidative killing
- Secrete cytokines and chemokines to regulate inflammation

Soluble components – Complement, Acute phase proteins, Cytokines and chemokines

Polymorphonuclear cells / granulocytes

- Produced in bone marrow & migrate rapidly to site of injury
- Express Fc receptors for Ig - to detect immune complexes
- Release enzymes, histamine, lipid mediators of inflammation from granules

Monocytes & Macrophages

- Monocytes are produced in bone marrow, circulate in blood and migrate to tissues where they differentiate to macrophages
- Capable of presenting processed antigen to T cells
- Different names based on tissue e.g. Liver – Kupffer cell, Kidney – Mesangial cell, Spleen – Sinusoidal lining cells, Bone – Osteoclast, Lung – Alveolar macrophage, Neural tissue – Microglia, Connective tissue – Histiocyte, Skin – Langerhans cell

Pathway

Phagocyte Recruitment - Macrophages, Granulocytes (Neutrophils) & Dendritic cells

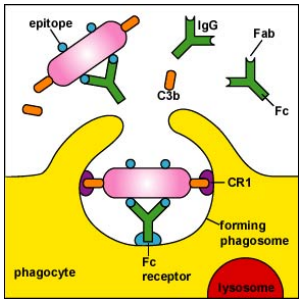
- Cellular damage and bacterial products trigger the local production of inflammatory cytokines and chemokines
- Cytokines activate vascular endothelium enhancing its permeability
- Chemokines attract phagocytes

Recognition of a Microorganism

- Pattern recognition receptors - **toll-like receptors (TLR)** and **mannose receptors** which recognise generic motifs known as pathogen associated molecular patterns (PAMPs) e.g. Bacterial sugars, DNA & RNA
- Fc receptors for Fc portion of immunoglobulin to allow recognition of immune complexes

Endocytosis is facilitated by opsonisation

- Opsonins act as a bridge between the pathogen and the phagocyte receptors. E.g.
    - Antibodies binding to Fc receptors
    - Complement components binding to complement receptors (CR1)
    - Acute phase proteins e.g. c-reactive protein (CRP)



Formation of phagolysosome: The pathogen is then taken up into a phagosome which fuses with lysosome → Protected compartment in which killing of the organism occurs

Microbial Killing Mechanisms

Oxidative Killing

- NADPH oxidase complex converts oxygen to reactive oxygen species e.g. superoxide and hydrogen peroxide
- Myeloperoxidase catalyses production of hydrochlorous acid from hydrogen peroxide and chloride
- Hydrochlorous acid is a highly effective oxidant and anti-microbial

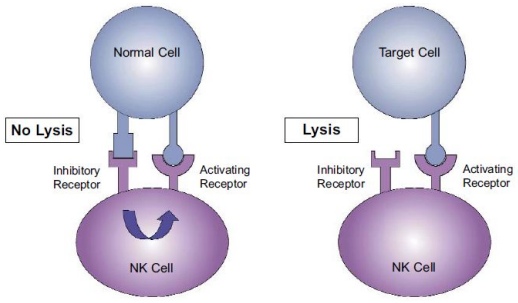
Non-oxidative killing

- Release of bactericidal enzymes such as lysozyme and lactoferrin into phagolysosome
- Enzymes are present in granules, each has a unique antimicrobial spectrum
- Results in broad coverage against bacteria and fungi

Death of a Phagocyte: The Role of Neutrophils

- Process of phagocytosis depletes neutrophil glycogen reserves → followed by cell death
- As the cells die, residual enzymes are released causing **liquefaction** of closely adjacent tissue
- Accumulation of dead/dying neutrophils within the infected tissue results in formation of pus
- Extensive localised formation of pus causes abscess formation

Natural Killer Cells



- Present within blood and may migrate to inflamed tissue
- Express inhibitory receptors for self-HLA molecules - prevent inappropriate activation by normal self
- Express a range of activating receptors, including natural cytotoxicity receptors, that recognise heparan sulphate proteoglycans
- Cytotoxic - kill 'altered self' as in malignant or virus infected cells which lack inhibitory signals

Dendritic Cells

- Reside in peripheral tissues
- Express Fc receptors for Ig - to detect immune complexes
- Following phagocytosis dendritic cells mature:
    - Upregulate expression of HLA molecules
    - Express costimulatory molecules
    - Migrate via lymphatics to lymph nodes – mediated by CCR7
- Present processed antigen to T cells in lymph nodes → prime the adaptive immune response
- Express cytokines to regulate the immune response

3. Adaptive Immune System

Components

- 'Humoral' immunity → B lymphocytes and antibody
- 'Cellular' immunity → T lymphocytes - CD4 T & CD8 T cells
- Soluble components → Cytokines and chemokines

Anatomy of the acquired immune system:

Primary lymphoid organs: Organs involved in lymphocyte development

- Bone marrow: Both T and B lymphocytes are derived from haematopoietic stem cells
    - Site of B cell maturation
- Thymus: Site of T cell maturation.
    - Most active in the foetal and neonatal **period, involutes after puberty**

Secondary lymphoid organs: Anatomical sites of interaction between naïve lymphocytes and microorganisms

- Spleen
- Lymph nodes
- Mucosal associated lymphoid tissue

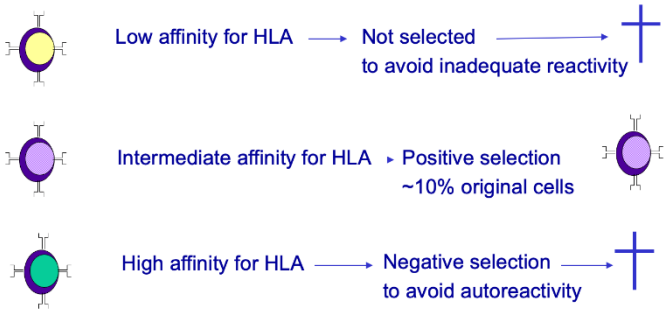
T Cell Maturation: T Cells Arise from haematopoietic stem cells → Exported as immature cells to the thymus where undergo positive and negative selection → Mature T lymphocytes enter the circulation and reside in secondary lymphoid organs

All T Cells express CD3+ and either: (Mnemonic: 8x1 = 8; 4x2 = 8)

- CD8+ T cells recognise peptide presented by HLA class I molecules
- CD4+ T cells recognise peptide presented by HLA class II molecules

Thymus: Site of T cell maturation.

- Most active in the foetal and neonatal **period, involutes after puberty**



Secondary lymphoid organs: Anatomical sites of interaction between naïve lymphocytes and microorganisms

- Spleen
- Lymph nodes
- Mucosal associated lymphoid tissue

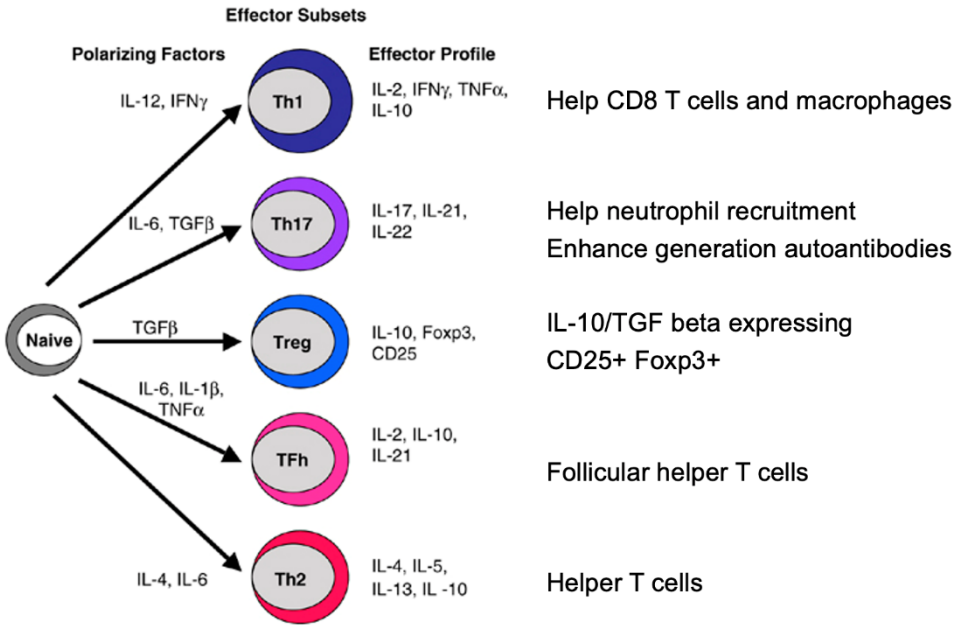
T Cell Maturation: T Cells Arise from haematopoietic stem cells → Exported as immature cells to the thymus where undergo positive and negative selection → Mature T lymphocytes enter the circulation and reside in secondary lymphoid organs

All T Cells express CD3+ and either: (Mnemonic: 8x1 = 8; 4x2 = 8)

- CD8+ T cells recognise peptide presented by HLA class I molecules
- CD4+ T cells recognise peptide presented by HLA class II molecules

CD4+ T Cells (Helper lymphocytes)

- Recognise peptides derived from extracellular proteins presented on HLA Class II molecules (HLA-DR, HLA-DP and HLA-DQ) - Mnemonic: 2 letters for Class II
- Immunoregulatory functions via cell: cell interactions and expression of cytokines
    - Provide help for development of full B cell response and of some CD8+ T cell responses



CD8+ T Cells (Specialised cytotoxic cells)

- Recognise peptides derived from intracellular proteins in association with HLA class I (HLA-A, HLA-B, HLA-C) - Mnemonic: 1 letter for Class I
- Kill cells directly → Perforin (pore forming) and granzymes & Expression of Fas ligand
- Secrete cytokines e.g. IFNg, TNFa → important in defence against viral infections & tumours

T Cell Memory

- Response to successive exposures to antigen is qualitatively and quantitatively different from that of first exposure
- Pool of 'memory' T cells ready to respond to antigen→ More easily activated than naïve cells

B Cell Maturation

- Stem cells in bone marrow become lymphoid progenitors → pro B cells → pre B cells
- Peripherally → IgM expressing B cells
    - with antigen engagement they develop into plasma cells that secrete IgM
    - Or they can undergo germinal centre reaction and develop into plasma cells expressing IgG, IgE and IgA

Central Tolerance of B Cells

- No recognition of self-antigens → survive
- Recognition of self-antigens in bone marrow → negative selection to avoid autoreactivity

Activation of B lymphocytes

- B cell receptor (surface expressed Ig) binds to **antigen**
- Some B cells mature to plasma cells secreting IgM
- If provided with appropriate signals from CD4+ T cells in secondary lymphoid tissue, a germinal centre reaction occurs which results in rapid B cell proliferation.
    - Dendritic cells prime the CD4+ T cells
    - CD4+ T cells help B cell differentiation – requires CD40L:CD40 interaction
- B Cells also undergo highly complex genetic rearrangements
    - Isotype switching to IgG, IgA or IgE
    - Somatic hypermutation to generate high affinity receptors
- Further differentiation
    - plasma cells which produce IgG, IgA or IgE antibody
    - long-lived memory cells

Immunoglobulins

- Soluble proteins made up of two heavy and two light chains
    - Heavy chain determines the antibody class
        - IgM, IgG, IgA, IgE, IgD,
        - subclasses of IgG and IgA also occur.
    - Antigen is recognised by antigen binding regions (Fab) of both heavy & light chains
    - Effector function is determined by the constant region of the heavy chain (Fc)

Antibody function

- Identification of pathogens and toxins (Fab mediated)
- Interact with other components of immune response to remove pathogens (Fc mediated)
    - Complement
    - Phagocytes
    - Natural killer cells
- Particularly important in defence against bacteria of all kinds

B Cell Memory

- Response to successive exposures to antigen is qualitatively and quantitatively different from that of first exposure
    - the lag time between antigen exposure and the production of antibody is decreased (to 2-3 days)
    - the titre of antibodies produced is greatly increased
    - the response is dominated by IgG antibodies of high affinity
    - the response may be independent of help from CD4+ T lymphocytes

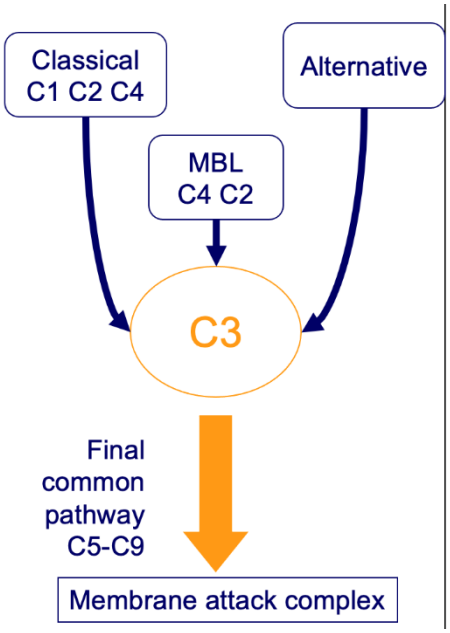
4. Complement

- 20 tightly regulated, linked proteins
  - Produced by liver
  - Present in circulation as inactive molecules
- When triggered, enzymatically activate other proteins in a biological cascade
  - Results in rapid, highly amplified response

Classical	Mannose Binding	Alternate
• Formation of antibody-antigen immune complexes • **Results in change in antibody shape – exposes binding site for C1** • **Binding of C1 to the binding site on antibody results in activation of the cascade** • **Dependent upon activation of acquired immune response (antibody)**	• Activated by the direct binding of MBL to microbial cell surface carbohydrates • Directly stimulates the classical pathway, involving C4 and C2 but not C1 • Not dependent on acquired immune response	• Directly triggered by binding of C3 to bacterial cell wall components • e.g. lipopolysaccharide of gram negative bacteria • teichoic acid of gram-positive bacteria • Not dependent on acquired immune response • Involves factors B, I and P

Activation of C3 convertase

- Activation of C3 is the major amplification step in the complement cascade
  - Triggers the formation of the membrane attack complex via C5-C9 → Punches holes in bacterial membranes



5. Cytokines and Chemokines

Cytokines

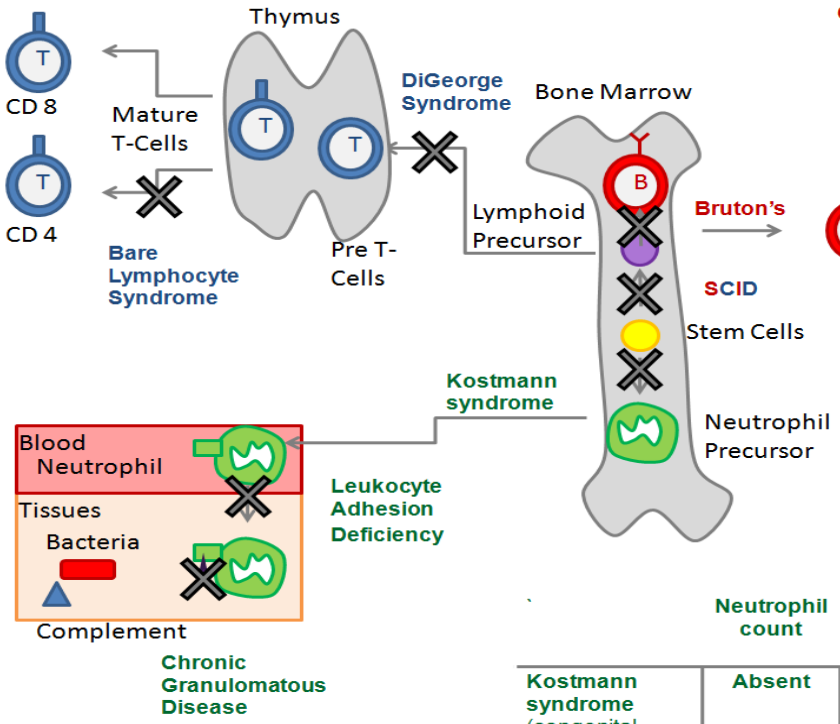
- Small protein messengers
- Immunomodulatory function
- Autocrine or paracrine dependent action
- Examples include IL-2, IL-6, IL-10, IL-12, TNF-alpha, TGF-beta.

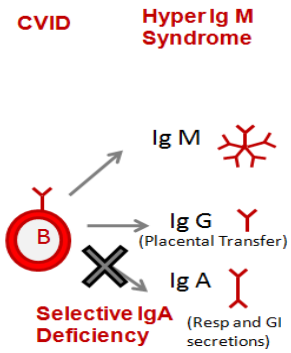
Chemokines

- Chemotactic cytokines – i.e. chemoattractants
- Direct recruitment / homing of leukocytes in an inflammatory response
- CCL19 and CCL21 are ligands for CCR7 and important in directing dendritic cell trafficking to lymph nodes
- Other examples of chemokines include IL-8, RANTES, MIP-1 alpha and beta.

Primary Immune Deficiencies

	CD4 T cell	CD8 T cell	B cell	IgM	IgG
SCID	↓	↓	+↓	+↓	↓
Di George	↓	↓	+	+	↓
BLS	↓	+	+	+	↓





	CD4 T cell	CD8 T cell	B cell	IgM	IgG	IgA
SCID	↓	↓	+↓	+↓	↓	↓
Brutons	+	+	↓	↓	↓	↓
Hyper IgM	+	+	+	++	↓	↓
Selective IgA Def	+	+	+	+	+	↓
CVID	+	+	+	+↓	↓	↓

	Neutrophil count	Leukocyte adhesion markers	Nitroblue test of oxidative killing (NBT)	Pus
Kostmann syndrome (congenital neutropaenia)	Absent	Normal	Usually absent (because no neutrophils)	No
Leukocyte adhesion deficiency	Increased during infection	Absent	Normal	No
Chronic Granulomatous Disease	Normal	Normal	Abnormal	Yes

Factors	Features	Disease	Disease characteristics
External epithelia	Keratinised cells Sebaceous glands	Burns	High risk infection >70% deaths with 5 days is related to infection
Mucosal surfaces	Secreted mucous Cilia	IgA deficiency	- Complete deficiency of IgA affects 1:600 Caucasoid individuals - Genetic and environmental factors important in development - Associated with recurrent respiratory and gastrointestinal tract infections in 30%
Commensal bacteria	Competition Bactericidins and fatty acids	Antibiotic use	Organisms rapidly colonise an undefended niche • Candida albicans • Clostridium difficile
Phagocyte deficiency	Production of neutrophils	Reticular dysgenesis	Failure of stem cells to differentiate along myeloid or lymphoid lineage Failure of production of: Neutrophils, Lymphocytes, Monocyte/macrophages, Platelets Fatal in very early life unless corrected with bone marrow transplantation Autosomal recessive severe SCID (most severe form) Mutation in mitochondrial energy metabolism enzyme adenylate kinase 2 (AK2)
	Specific Failure of Neutrophil maturation	Kostmann syndrome	Autosomal recessive severe congenital neutropenia Classical form due to mutation in HCLS1-associated protein X-1 (HAX1)
		Cyclic neutropenia	Autosomal dominant episodic neutropenia every 4-6 weeks Mutation in neutrophil elastase *(ELA-2)*
	Migration to site of infection	Leukocyte adhesion deficiency - Deficiency of CD18 (b2 integrin subunit) in LAD1	CD11a/CD18 and CD11b/CD18 are usually expressed on neutrophils, bind to ligands on endothelial cells and so regulate neutrophil adhesion/transmigration Here neutrophils lack these adhesion molecules and fail to exit from the bloodstream Leukocyte adhesion deficiency characterised by: • Very high neutrophil counts in blood • Absence of pus formation • Delayed umbilical cord separation

	Oxidative killing	Chronic granulomatous disease	Absent respiratory burst • Deficient NADPH oxidase so oxygen is not converted to **superoxide** that is needed to form HOCl (oxygen free radical) • Impaired killing of intracellular micro-organisms Excessive inflammation • Persistent neutrophil/ macrophage accumulation • Failure to degrade antigens - Granuloma formation - Lymphadenopathy and hepatosplenomegaly - Susceptibility to bacteria esp. catalase positive bacteria i.e. PLACESS (Pseduomonas, Listeria, Aspergillus, Candida, E.Coli, Staph Aureus, Serratia) **Investigations:** - Negative Nitro-Blue Tetrazolium test (NBT). NBT is a dye that changes colour from yellow to blue following interaction with hydrogen peroxide (free radical) - Dihydrorhodamine (DHR) flow cytometry test. DHR is oxidized to rhodamine, which is strongly fluorescent, following interaction with hydrogen peroxide. **Treatment:** Interferon gamma
Phagocytosis	Opsonisation	Complement and antibody defects	Indirectly affects phagocyte function. Prevents endocytosis and phagolysosome formation
Recruitment of other cells	Cytokine production	Deficiency of IL-12 and IFNγ and their receptors	Susceptibility to infection with mycobacteria (TB and atypical), BCG, Salmonella. Infection with mycobacteria activates IL12- IFN γ network: • Infected macrophages stimulated to produce IL12 • IL12 induces T cells to secrete IFN γ • IFN γ feeds back to macrophages & neutrophils • Stimulates production of TNF • Activates NADPH oxidase • Stimulates oxidative pathways Inability to form granulomas

Alternative pathway	Constitutive 'tick over' of complement activation	Factor B/ Factor D/ Factor P (properdin) deficiency - rare	Inability to mobilise complement rapidly in response to bacterial infections → Recurrent infections with encapsulated bacteria Normally properdin stabilizes C3 convertase → triggers MAC complex
Classical pathway	Antibody dependent. Necessary against infection and phagocyte mediated clearance of apoptotic cells and immune complexes.	Deficiency in early classical pathway (C1/2/4)	Immune complexes fail to activate complement pathway → increased susceptibility to infection Increased load of self-antigens – particularly nuclear components – which may promote auto-immunity (SLE) and immune complexes Deposition of immune complexes which stimulates local inflammation in skin, joints and kidneys (SLE) C1q, C1r, C1s, C2, C4 deficiency are all described in SLE - All are rare → C2 deficiency most common Clinical phenotype • Almost all patients with C2 deficiency have SLE • Severe skin disease • Increased no. infections
		Secondary deficiency	Caused by active lupus, due to the persistent production of immune complexes and consequent depletion of complement
Mannose binding lectin	Not dependent on acquired immune response Involves C2 and C4 but not C1	MBL deficiency (MBL2 are common but not associated with immunodeficiency)	Associated with increased infection in patients who have another cause of immune impairment • Premature infants • Chemotherapy • HIV infection • Antibody deficiency
C3	All pathways converge on C3	C3 deficiency	Severe susceptibility to **bacterial infections** (esp. encapsulated – meningococcus, streptococcus, haemophiles) Increased risk of development of connective tissue disease
		Secondary C3 deficiency	Nephritic factors: auto-antibodies directed against parts of the complement pathway Nephritic factors stabilise C3 convertases resulting in C3 activation and consumption Often associated with glomerulonephritis (classically membranoproliferative) and partial lipodystrophy

Terminal common pathway	Results in formation of MAC	Any defect	Inability to make membrane attack complex → Inability to use complement to lyse encapsulated bacteria Results in specific hole in immune system • Neisseria meningitis • Streptococcus pneumonia • Haemophilus influenza
Haem stem cells	Bone marrow	Reticular dysgenesis	SEE ABOVE
Lymphoid progenitors	Bone marrow	SCID (In general) 20 possible pathways identified	Unwell by 3 months of age (before- protected by IgG from mother across placenta and then colostrum) with: • Infections of all types • Failure to thrive • Persistent diarrhoea Poorly developed lymphoid tissue (germinal centres) and thymus Family history of early infant death Effect on different lymphocyte subsets (T, B, NK) depend on exact mutation
		X-linked SCID	45% of all severe combined immunodeficiency Mutation of **gamma chain of IL2 receptor** on chromosome Xq13.1 • Shared by receptor for IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 • Inability to respond to cytokines causes early arrest of T cell and NK cell development and production of immature B cells Phenotype • Very low or absent T cell and NK cell numbers • Normal or increased B cell numbers
		ADA deficiency	16.5% of all severe combined immunodeficiency Adenosine Deaminase Deficiency - Enzyme lymphocytes required for cell metabolism Inability to respond to cytokines causes early arrest of T cell and NK cell development and production of immature B cells Phenotype • Very low or absent T cell and NK cell numbers • Very low or absent B cell numbers

T cell maturation/ selection in thymus	Thymus	DiGeorge syndrome (22q11.2 deletion syndrome)	Deletion at 22q11.2. TBX1 may be responsible for some features, usually sporadic. Developmental defect of pharyngeal pouch. Remember CATCH-22: • Cardiac abnormalities (especially tetralogy of Fallot) • Abnormal facies (high forehead, low set ears) • Thymic aplasia (T cell lymphopenia) • Cleft palate • Hypocalcaemia/hypoparathyroidism • 22 – chromosome Normal numbers of B cells and reduced numbers of T cells Homeostatic proliferation with age so Immune function improves with age
	Positive and negative selection	Bare lymphocyte syndrome type II (BLS type 1 also exists due to failure of expression of HLA class I)	Defect in one of the regulatory proteins involved in Class II gene expression • Regulatory factor X or Class II transactivator → Absent expression of MHC Class II molecules → Profound deficiency of CD4+ cells • Usually have normal number of CD8+ cells • Normal number of B cells • Failure to make IgG or IgA antibody (no class switching)
T cell activation and effector functions	Cytokine release	Deficiency of IL-12, IFNγ and their receptors	SEE ABOVE
	T-B cell communication	Hyper IgM syndrome	Failure to express CD40L on activated T cells. SEE BELOW.
	T cell-APC interaction	Wiskott-Aldrich Syndrome (WAS)	X-linked recessive, Mutation in WAS gene (actin cytoskeleton arrangement), needed to stabilise T cell-APC interaction Thrombocytopenia, eczema (raised IgE), lymphopenia ↓ IgM, ↑ IgA and IgE levels, IgG may be normal, reduced or elevated ↑ risk of malignant lymphoma
B lymphocyte maturation	Pro B cells → Pre B cells → Mature B cells	Bruton's X-linked hypogamma globulinaemia (only **b**oys)	Defective **B** cell tyrosine kinase gene (BTK) → Pre **B** cells cannot develop to mature B cells causing absence of mature B cells and no circulating Ig after ~ 3 months - Recurrent infections during childhood - Absent/scanty lymph nodes and tonsils (1° follicles and germinal centers absent)

	Class switching	Selective IgA deficiency	Prevalence = 1:600 2/3rd individuals asymptomatic and 1/3rd have recurrent respiratory tract infections. Also GI infections. Genetic component but cause unknown
		Hyper IgM syndrome (X-linked recessive)	Inability of B cells to class switch causing production of only IgM due to a T cell defect Most cases caused by mutation in CD40 ligand gene (CD40L, CD154) • Member of TNF Receptor family encoded on Xq26 • Involved in T-B cell communication • Expressed by activated T cells – B cells and other APCs express CD40 Boys present with failure to thrive in first few years of life with: • Recurrent infections - bacterial • Pneumocystis jiroveci infection, autoimmune disease and malignancy Results in: • Normal number circulating B cells • Normal number of T cells but activated cells do not express CD40 Ligand • Elevated serum IgM • Undetectable IgA, IgE, IgG (failure of class switching) • No germinal centre development within lymph nodes and spleen
		Common variable immune deficiency	Heterogenous group of disorders with disease mechanism unknown Failure of differentiation/function of B lymphocytes Defined by • Marked reduction in IgG, with low IgA or IgM • Poor/absent response to immunisation • Absence of other defined immunodeficiency Clinical features • Recurrent bacterial infections with severe end-organ damage 1. Pneumonia, persistent sinusitis, gastroenteritis • Pulmonary - Bronchiectasis, ILD • GI – IBD-like disease, sprue-like illness, bacterial overgrowth • Autoimmune disease – AIHA, RA, pernicious anaemia, thyroiditis, vitiligo • Malignancy – Non-Hodgkin Lymphoma

Diagnosis and Management of Immunodeficiencies

Phagocyte Deficiencies

Consequences: recurrent deep bacterial infections, recurrent fungal infections

Diagnosis: NBT or DHR flow cytometry test

- NBT is a dye that changes colour from yellow to blue, following interaction with hydrogen peroxide
- DHR is oxidised to rhodamine, which is strongly fluorescent, following interaction with hydrogen peroxide

- **Treatment:**
  - **Aggressive management of infection**
  - Infection prophylaxis
    - Antibiotics – e.g. Septrin (= co-trimoxazole) (oral/IV as needed)
    - Anti-fungals – e.g. Itraconazole
- Definitive therapy
  - Haematopoietic stem cell transplantation
    - 'Replaces' defective population

Complement Deficiencies

	C3	C4	CH50	AP50
C1q deficiency	+	+	↓	+
Factor B deficiency	+	+	+	↓
C9 deficiency	+	+	↓	↓
SLE	+↓	↓	+↓	+

Consequences: increased susceptibility to encapsulated bacterial infections, common in EMQs.

Diagnosis: CH50 and AP50 tests

Treatment of complement deficiencies: vaccination, prophylactic Abx, high levels of suspicion + early treatment, screen family members.

Lymphocyte Deficiencies

T cell deficiency	Antibody deficiency (or CD4 T cell deficiency)
Viral infections (Cytomegalovirus)	Bacterial infections (Staphylococcus, Streptococcus)
Fungal infection (Pneumocystis, Cryptosporidium)	Toxins (Tetanus, Diphtheria)
Some bacterial infections – esp. intracellular organisms (MTB, Salmonella)	Some viral infections (Enterovirus)
Early malignancy	

Diagnosis: 1. WCC, 2. Lymphocyte subsets, 3. Serum immunoglobulins (if CD4 deficient as IgG is a surrogate marker for function) and protein electrophoresis, 4. Functional tests, 5. HIV

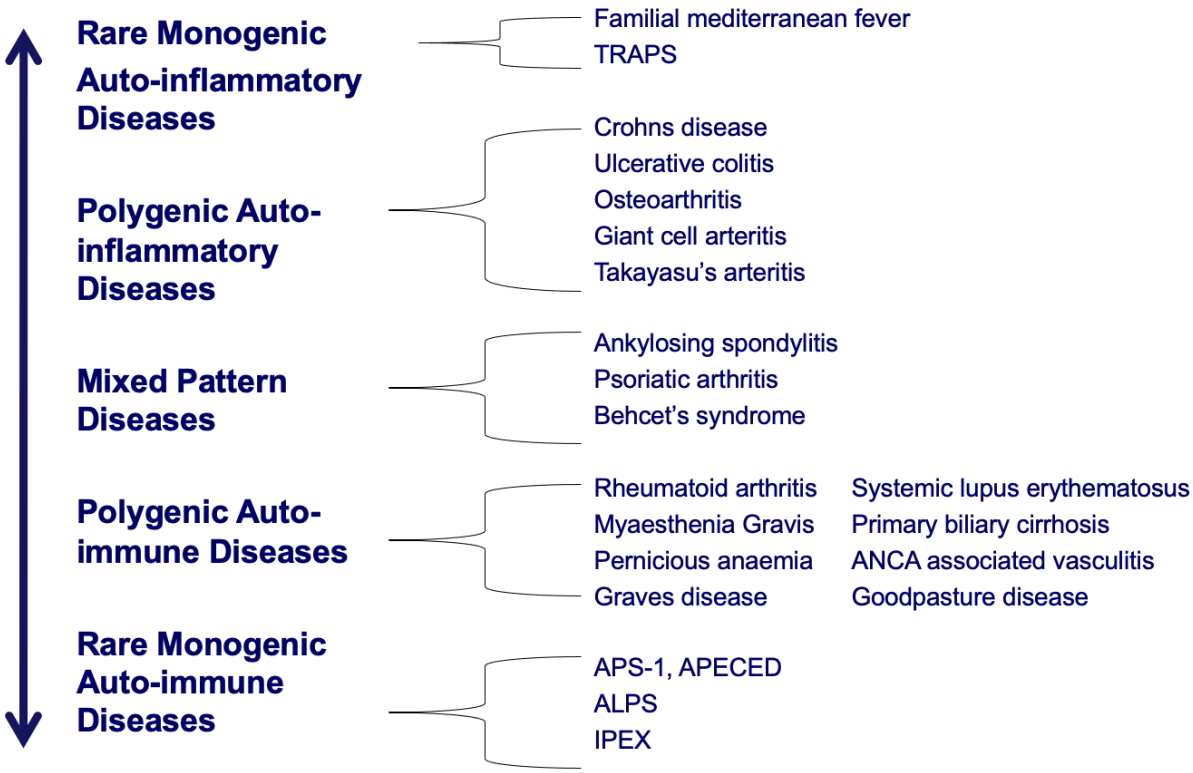
Management of T cell deficiencies: Infection prophylaxis and treatment, Ig replacement, Haematopoietic stem cell transplantation, gene therapy (experimental), Thymic transplantation in DiGeorge syndrome (donor thymic tissue into quadriceps muscle – experimental)

Management of B cell deficiencies: Aggressive treatment of infection, Ig replacement every 3 weeks (pooled plasma containing diverse IgG), BMT, Immunisation in Selective IgA deficiency (not effective if no IgG)

Autoinflammatory and Autoimmune

Immunopathology in absence of infection

- Innate immune response → autoinflammatory
- Mixed Innate/Adaptive → mixed
- Adaptive immune response → autoimmunity



Monogenic Auto-inflammatory Diseases

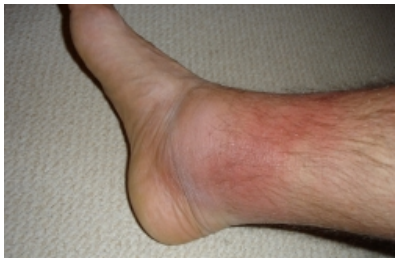
- Mutations in a gene encoding a protein involved in a pathway associated with **innate immune cell function**
- Abnormal signalling via key cytokine pathways involving TNF and/or IL-1 is common

Familial Mediterranean fever

- **Pathogenesis**
- Autosomal recessive condition
- Mutation in *MEFV* gene
- Gene encodes pyrin-marenostrin
- Pyrin-marenostrin expressed mainly in neutrophils
- Failure to regulate cryopyrin driven activation of neutrophils

Clinical presentation

- Periodic fevers lasting 48-96 hours associated with:
  - Abdominal pain due to peritonitis
  - Chest pain due to pleurisy and pericarditis
  - Arthritis
  - Rash



Long term risk of AA amyloidosis

Liver produces serum amyloid A as acute phase protein

Serum amyloid A deposits in kidneys, liver, spleen

- Deposition in kidney often most clinically important
- Proteinuria - nephrotic syndrome
- Renal failure

Treatment

- Colchicine 500ug bd - binds to tubulin in neutrophils and disrupts neutrophil functions including migration and chemokine secretion
- Anakinra (Interleukin 1 receptor antagonist)
- Etanercept (TNF alpha inhibitor)

Monogenic Autoimmune Diseases Mutation of a protein involved in a pathway associated with adaptive immune cell function		
Autoimmune polyendocrine syndrome type 1 (APS1) Auto-immune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (**APECED)**	**Immune dysregulation, polyendocrinopathy, enteropathy (IPEX)**	**Auto-immune lymphoproliferative syndrome (ALPS)**
Abnormality in tolerance	Abnormality of regulatory T cells	Abnormality of lymphocyte apoptosis
Autosomal Recessive	X-linked	Autosomal Dominant (incomplete penetrance)
- Defect in 'auto-immune regulator' – AIRE = Transcription factor involved in development of T cell tolerance in the thymus → Upregulates expression of self-antigens by thymic cells & Promotes T cell apoptosis - Defect in AIRE leads to failure of central tolerance → Autoreactive T & B cells	- Mutations in Foxp3 - required for development of Treg cells - Failure to negatively regulate T cell responses - Autoreactive B cells	- Mutations within FAS pathway (E.g. TNFRSF6 -encodes FAS) → Disease is heterogeneous depending on the mutation - Defect in apoptosis of lymphocytes → Failure of tolerance & lymphocyte 'homeostasis'
Clinical Features		
- Multiple auto-immune diseases: **Hypoparathyroidism, Addison's**, Hypothyroidism, Diabetes, **Vitiligo**, Enteropathy - Antibodies vs IL17 and IL22 → Candidiasis	- Autoimmune diseases: Diabetes Mellitus, Hypothyroidism, Enteropathy - 'Diarrhoea, diabetes and dermatitis'	- High lymphocyte numbers with large spleen and lymph nodes → CD4-CD8- T cells - Auto-immune disease → commonly auto-immune cytopenias - Lymphoma

Polygenic Auto-inflammatory Diseases

- Mutations in genes encoding proteins involved in innate immune cell function
- Local factors at sites predisposed to disease lead to activation of innate immune cells such as macrophages and neutrophils, with resulting tissue damage
- HLA associations are usually less strong

- Not characterised by presence of autoantibodies
- **Examples:** IBD1 gene on chromosome 16 identified as *NOD2* (*CARD-15*) – *mutations* associated with Crohn's disease.
- NOD2 expressed in cytoplasm of myeloid cells = Intracellular receptor for bacterial products - recognises muramyl dipeptide – and stimulates NFKb → Activation induces autophagy in dendritic cells

Mixed Pattern Disease

- Mutations in genes encoding proteins involved in pathways associated with innate immune cell function **AND** adaptive immune cell function
- HLA associations may be present
- Auto-antibodies are not usually a feature

Polygenic Auto-immune Disease

- Mutations in genes encoding proteins involved in adaptive immune cell function
- HLA associations are common
- Aberrant B cell and T cell responses in primary and secondary lymphoid organs lead to breaking of tolerance with development of immune reactivity towards self-antigens
- Auto-antibodies are found

Genetic polymorphisms

- **PTPN22**: Lymphocyte specific tyrosine phosphatase which suppresses T cell activation → Associated development of RA, SLE and T1DM.
- **CTLA4**: receptor for CD80/CD86 expressed by T cells which transmits inhibitory signal to control T cell activation. → Associated with SLE, T1DM, Autoimmune thyroid disease.

HLA Associations

Disease	Susceptibility alelle	Relative risk (fold)
Ankylosing spondylitis	HLA B27	87
Goodpasture's syndrome	HLA DR15/DR2	10
Graves' Disease	HLA- DR3	4
Systemic Lupus Erythematosis (SLE)	HLA-DR3	6
Type I diabetes	HLA DR3/DR4	25
Rheumatoid arthritis	HLA-DR4	4

HLA subtypes associated with diseases

A3	Hemochromatosis	
B8	Addison disease, myasthenia gravis, Graves disease	
B27	Psoriatic arthritis, Ankylosing spondylitis, IBD-associated arthritis, Reactive arthritis	PAIR. Also known as seronegative arthropathies.
DQ2/DQ8	Celiac disease	I ate (8) too (2) much gluten at Dairy Queen.
DR2	Multiple sclerosis, hay fever, SLE, Goodpasture syndrome	Multiple hay pastures have dirt.
DR3	Diabetes mellitus type 1, SLE, Graves disease, Hashimoto thyroiditis, Addison disease	2-3, S-L-E
DR4	Rheumatoid arthritis, diabetes mellitus type 1, Addison disease	There are 4 walls in a "rheum" (room).
DR5	Pernicious anemia → vitamin B_{12} deficiency, Hashimoto thyroiditis	

CC: FirstAid

Hypersensitivity Disorders

Type I Hypersensitivity Disorders

Immediate reaction provoked by re-exposure to an allergen. **IgE mediated**: mast cells release mediators resulting in vasodilation, increased permeability, smooth muscle spasm.

Typical Sx: Angioedema, urticaria, rhino conjunctivitis, wheeze, D&V, ANAPHYLAXIS

4% of children with asthma also had concurrent clinical food allergy
Remember atopic triad (eczema, asthma and hay fever), ? hygiene hypothesis

Disease	Allergen	Pathology	Diagnosis	Treatment
Atopic Dermatitis (Infantile eczema)	Irritants, food and environmental	Defects in β defensin predispose to *Staph aureus* superinfection	Clinical. 80% present in first year of life.	Emollients, skin oils, topical steroids, antibiotics, PUVA phototherapy etc.
Food Allergy	Milk, egg, peanut, tree nut, fish, shellfish	IgE (anaphylaxis, OAS); cell mediated (coeliac); IgE/cell mediated (atopic dermatitis)	Food Diary, Skin Prick Tests, RAST, Challenge Test → Most resolve by adulthood.	Dietician, Food Avoidance, EpiPen, Control asthma if present
Oral Allergy Syndrome (OAS)	Birch pollen + rosacea fruit, ragweed + melons, mugwort + Celery (cross- reactivity)	Exposure to allergen induces allergy to food. Symptoms limited to mouth, 2% get anaphylaxis	Clinical Diagnosis, Skin Prick Testing can be useful	Avoid food. If ingested wash mouth, take antihistamine
Latex Food Syndrome	Chestnut, avocado, banana, potato, tomato, kiwi, papaya, eggplant, mango, wheat, melon	Some foods have latex-like components → latex allergy sufferers also have food allergies	Skin Prick Test	Strict avoidance of causative food
Allergic Rhinitis	Seasonal (tree and grass pollen, fungal spores); Perennial (pets, house dust mite); Occupational (latex, lab animals)	Nasal itch and obstruction, sneezing, anosmia, eye symptoms	Pale bluish swollen nasal mucosa Skin Prick Test and RAST	Allergen avoidance, Antihistamine, Steroid Nasal Spray, Sodium Cromoglycate Eye Drops, Oral Steroids, Ipratropium Nasal Spray
Acute Urticaria	50% Idiopathic 50% caused by food, drugs, latex,	IgE mediated reaction. Wheals which completely	Mainly clinical. (Sometimes skin prick test)	Allergen avoidance, Antihistamines

	viral infections and febrile illnesses	resolve within six weeks		

Anaphylaxis

A severe systemic allergic reaction: respiratory difficulty & hypotension.

IgE-mediated mast cell degranulation - peanut, penicillin, stings, latex
Non-IgE-mediated mast cell degranulation: NSAIDs, IV contrast, opioids, exercise.

DDx of anaphylaxis
- C1 inhibitor deficiency - hereditary angioedema
- ACEi induced angioedema
- Acute anxiety
- Urticaria

Management: Elevate Legs, 100% Oxygen, IM Adrenaline 500 mcg, inhaled bronchodilators, IV Fluids, Seek Help. (Steroids and antihistamines are no longer routinely used in acute management).

Investigations in allergy

Skin prick tests
- Useful to confirm clinical history. Negative test excludes IgE-mediated allergy.
- Positive control = histamine, negative control = dilutant
- A positive test is a wheal ≥ 2mm greater than the negative control
- Discontinue antihistamines 48 hrs before test (corticosteroids are ok)

Quantitative specific IgE to putative allergen (RAST)
- Measure levels of IgE in serum against a particular allergen (e.g. peanut)
- Confirms dx of allergy and monitors response to anti-IgE treatment
- Less sensitive/specific than skin prick testing
- Indications: Can't stop antihistamines, anaphylaxis Hx, extensive eczema etc

Component-resolved diagnostics
- This test measures the IgE response to a specific allergen protein (whilst conventional tests measure response to range of allergen proteins)
- E.g. peanuts contain at least 5 major allergens:
  2. Ara h 2 – High risk anaphylaxis to peanut and nuts
  3. Ara h 8 – Localised oral reactions to peanut and stone fruit only

Challenge Test
- Double-blind oral food challenge is gold standard for food allergy BUT risk of severe reaction when testing.
- Increasing volumes of offending food/drug are ingested under close supervision.

During an acute episode – measure mast cell tryptase (peak at 1-2 hrs, baseline by 6hrs)

Type II Hypersensitivity Disorders

IgG or IgM antibody reacts with cell or matrix associated self-antigen. Results in tissue damage, receptor blockade/ activation.

Disease	Antigen	Pathology	Diagnosis	Treatment
Haemolytic Disease of the	Antigens on neonatal	Maternal IgG mediated	Positive Direct Coombs Test	Maternal Plasma Exchange,

Newborn (HDN)	erythrocytes	reticulocytosis and anaemia		Exchange Transfusion
Autoimmune Haemolytic Anaemia (+ ITP = Evan's Syndrome)	Numerous autoantigens e.g. Rh blood group Ag	Destruction of red blood cells by auto antibody + complement + FcR+ phagocytes, anaemia	Positive Direct Coombs Test, Anti Red Cell Ab	Steroids
Autoimmune Thrombocytopenic Purpura	Glycoprotein IIb/IIIa on platelets	Bruising/ Bleeding (Purpura)	Anti-Platelet Antibody	Steroids, IVIG, Anti-D Antibody, splenectomy
Goodpasture's Syndrome	Non-collagenous domain of basement membrane collagen type IV	Glomerulonephritis, pulmonary haemorrhage	Anti GBM Ab Linear Smooth IF staining of IgG deposits on BM	Corticosteroids and Immunosuppression
Pemphigus Vulgaris	Epidermal Cadherin	Non-tense blistering of skin and Bullae	Direct Immuno-fluorescence showing IgG deposition	Corticosteroids and Immunosuppression
Graves' disease	TSH receptor	Hyperthyroidism	Anti TSH-R Ab	Carbimazole and Propylthiouracil
Myasthenia Gravis	Acetylcholine receptor	Fatigable muscle weakness, Double Vision	Anti Ach-R Ab Abnormal EMG Tensilon Test	Neostigmine, Pyridostigmine, (If serious use IVIG and Plasmapheresis)
Acute Rheumatic Fever	M proteins on Group A strep	Myocarditis, Arthritis, Sydenham's Chorea	Clinical, based on Jones Criteria	Aspirin, Steroids and Penicillin
Pernicious Anaemia	Intrinsic Factor and Gastric Parietal Cells	↓Hb ↓B12	Anti-Gastric Parietal Cell Ab, Anti-IF Ab, Schilling Test	Dietary B12 or IM B12
Churg-Strauss Syndrome (eGPA)	Medium and Small Vessel Vasculitis	Allergy →Asthma→ Systemic Disease (Male predominance)	p-ANCA (against myeloperoxidase), Granulomas, Eosinophil Granulocytes	Prednisolone, Azathioprine, Cyclophosphamide
Wegener's Granulomatosis (GPA)	Medium and Small Vessel Vasculitis	Sinus Problems, Lung Cavitations + haemorrhage, Crescentic Glomerulonephritis	c-ANCA (against Proteinase 3) granulomas	Corticosteroids, cyclophosphamide, co-trimoxazole
Microscopic Polyangiitis (MPA)	Pauci-immune necrotizing, small vessel vasculitis	Purpura, livedo, many different organs affected	p-ANCA (against myeloperoxidas)	Prednisolone, Cyclophosphamide or Azathioprine, plasmapheresis
Chronic Urticaria	Medications (NSAIDS) Cold, Food, Pressure, Sun, Exercise, Insect Stings,	Persistent Itchy Wheals Lasting > 6 Weeks. Associated with Angioedema in	Challenge Test, ESR (Raised in Urticarial Vasculitis), Skin Prick Testing	Avoid precipitants, Check for thyroid disease, Preventative

	Bites and Idiopathic	50% of cases. IgG against FceR1 or IgG against IgE (Exclude Urticarial Vasculitis in those who respond poorly to Antihistamine)		antihistamine, IM adrenaline for pharyngeal angioedema, 1% Menthol in Aqueous Cream for pruritis (Also Doxepin and Cyclosporin)

Type III Hypersensitivity Disorders

IgG or IgM immune complex (Ab vs soluble Ag) mediated tissue damage.

Syndrome	Antigen	Pathology	Diagnosis	Treatment
Mixed Essential Cryoglobulinaemia	IgM against IgG +/- hepatitis C antigens	Joint pain, splenomegaly, skin, nerve and kidney involvement. Associated with Hep C.	A mixture of clinical and biopsies	NSAIDs, Corticosteroids and plasmapheresis
Serum Sickness	Reaction to Proteins in Antiserum (Penicillin)	Rashes, Itching, arthralgia, lymphadenopathy, fever and malaise. Symptoms take 7-12 days to develop	↓C3 Blood shows immune complexes or signs of blood vessel inflammation.	Discontinuation of precipitant, steroids, antihistamines (+/-analgesia)
Polyarteritis Nodosa (PAN)	Hep B, Hep C virus Antigens	Fever, fatigue, weakness, arthralgia, skin, nerve and kidney involvement, pericarditis and MI. Associated with Hep B	Diagnosed by clinical criteria and Biopsy (↑ESR, ↑WCC, ↑CRP) 'Rosary sign'	Prednisolone and Cyclophosphamide
Systemic Lupus Erythematosis (SLE)	Mainly intracellular components: DNA, histones, RNP	M:F=1:9 <u>4 of these 11:</u> serositis, seizures, aphthous ulcers, arthritis, photosensitivity, discoid rash, malar rash, haematology, kidney findings, Antinuclear antibody (ANA +ve), immunological findings (anti-dsDNA, anti-sm)	↓C4 (↓C3 only in SEVERE disease) Ab's to dsDNA, Histones (Drug Induced), Ro, La, Sm, U1RNP ↑ESR, normal CRP (N.B. Hydralyzine, Procainamide and Isoniazid can cause Drug induced SLE)	Mainly; Analgesia Steroids and cyclophosphamide

Type IV Hypersensitivity Disorders

Delayed hypersensitivity. T-cell mediated.

Syndrome	Antigen	Pathology	Diagnosis	Treatment
Type 1 Diabetes Mellitus	Pancreatic Beta Cell proteins. (Glutamate Decarboxylase GAD)	Insulitis, Beta Cell Destruction	Blood Glucose, Ketonuria, Glutamate Decarboxylase Antibodies, Islet Cell Antibodies	Insulin via Injections or continuous infusion
Multiple Sclerosis	Oligodendrocyte Proteins (Myelin Basic Protein, Proteolipid Protein)	Demyelinating Disease, Perivascular Inflammation, Paralysis, Ocular Lesions	CSF shows Oligoclonal Bands of IgG on Electrophoresis.	Corticosteroids, Interferon-β
Rheumatoid Arthritis (Also type III: IgM Ab vs Fc region of IgG)	Antigen in Synovial Membrane	Chronic Arthritis, Rheumatoid Nodules, Lung Fibrosis	X-Ray, Rheumatoid Factor (85% Sensitive), Anti-CCP (95% Specific), ↑ESR, ↑CPR	Analgesia, steroids, DMARDs
Contact Dermatitis	Environmental Chemicals, Poison Ivy, Nickel	Dermatitis with usually short-lived itching, blisters, and wheals	Clinical or use Patch Test	If no resolution use corticosteroids or antihistamines
Mantoux Test	Tuberculin	Skin Induration indicates TB exposure	-	-
Crohn's Disease	-	TH1 mediated. Chronic inflammation in skip lesions in GIT. NOD2 gene mutation in 30%.	Biopsy of lesion (can affect any part of GIT from mouth to anus)	Antibiotics, anti-inflammatory drugs e.g. Mesalazine, TNF alpha antagonists e.g. infliximab, steroids

Other Important Diseases

Limited Cutaneous Scleroderma (CREST syndrome)

- Calcinosis, Raynaud's, Oesophageal dysmotility, Sclerodactyly, Telangiectasia
- + primary pulmonary hypertension
- (Skin involvement up to forearms only + perioral)
- Anti-Centromere Antibodies for diagnosis
- High risk of Lung Fibrosis and Renal Crisis

Diffuse Cutaneous Scleroderma

- CREST + GIT + interstitial pulmonary disease + renal problems
- Anti-topoisomerase/Scl70, RNA Pol I, II, III, Fibrillarin Antibodies
- Females are affected more than men in the ratio 4:1

Sjogren's Syndrome

- M:F=1:9 Onset in late 40s
- Dry mouth (xerostomia), eyes (keratoconjunctivitis sicca), nose and skin
- May affect kidneys, blood vessels, lungs, liver, pancreas and PNS
- Anti-Ro and anti-La antibodies present
- Use Schirmer test to measure production of tears-assessing for dry eye
- May get parotid or salivary gland enlargement

IPEX syndrome

- Immune dysregulation, Polyendocrinopathy, Enteropathy and X-linked inheritance syndrome + autoimmune diseases
- Eczematous dermatitis, nail dystrophy and autoimmune skin conditions such as alopecia universalis and bullous pemphigoid
- Most affected children die within the first 2 years of life.
- IPEX syndrome is an X-linked recessive disorder with exclusive expression in males.
- Bone marrow transplant is only cure. Can use immunomodulators to help.

Coeliac Disease

- Failure of tolerance to gluten. Villous atrophy and enteropathy.
- GIT discomfort, constipation, diarrhoea, bloating, fatigue.
- Iron, B12, folate, fat, vitamins A,D,E & K and calcium deficiencies
- IgA **EMA** (anti-endomysial antibody) disappears with exclusion diet (~95% specific, 85% sensitive)
- IgA **TGT** (anti-transglutaminase antibody) (~95% specific, 90-94% sensitive)
- IgG anti-gliadin antibody – most persistent (30-50% specific, 57-80% sensitive)
- **Dermatitis herpetiformis**
- Link with Down's syndrome
- Beer and pasta aren't gluten-free, rice, eggs, chips and wine are gluten free
- Ireland (memo **EMA**) – 3-10/1000. North Africa (memo **TGT**) – 20/1000
- 95% have **DQ2 or DQ8 – Remember: Two eight or not to eat?**
- Gold standard test is to do a duodenal biopsy, but it is not first line

List of Autoantibodies

4 extractable nuclear antibodies (ENA's) are: Ro, La, Sm and U1RNP

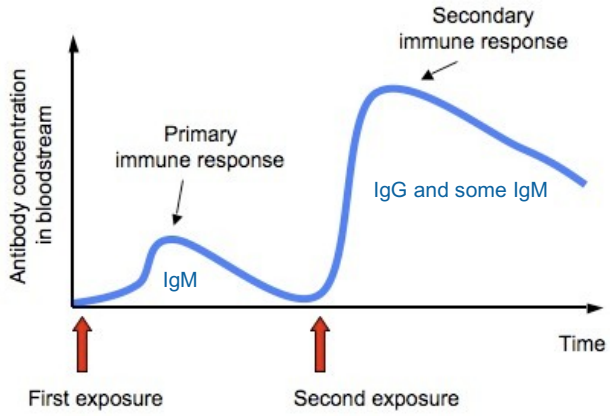
Disease	Autoantibody (IgG unless otherwise stated)
Antiphospholipid Syndrome (Hugh's Syndrome)	Antibodies against cardiolipin and β_2 glycoprotein, lupus anticoagulant,
Autoimmune hepatitis	Anti-smooth muscle antibody, Anti Liver Kidney microsomal-1 (anti-LKM-1). Anti-Soluble Liver Antigen (anti-SLA)
Autoimmune haemolytic Anaemia	Anti-Rh Blood Group Antigen
Autoimmune Thrombocytopenic Purpura	Anti-Glycoprotein IIb-IIIa or Ib-IX Antibody
Churg-Strauss Syndrome (eGPA)	Perinuclear/protoplasmic-staining antineutrophil cytoplasmic antibodies (p-ANCA)
Coeliac disease	Anti-tissue transglutaminase antibody (IgA), Anti-endomysial antibody (IgA)

Congenital heart block in infants of mothers with SLE	Anti-Ro antibody
Dermatitis herpetiformis	Anti-endomysial antibody (IgA)
Dermatomyositis	Anti-Jo-1 (t-RNA Synthetase)
Diffuse Cutaneous Scleroderma	Antibodies to Topoisomerase/Scl70, RNA Pol I,II,III, Fibrillarin (nucleolar pattern)
Goodpasture's Syndrome	Anti-GBM Antibody
Graves' Disease	Anti-TSH Receptor Antibody (stimulatory antibody)
Hashimoto's Thyroiditis	Antibodies to Thyroglobulin and Thyroperoxidase
Limited cutaneous scleroderma (CREST)	Anti-centromere antibody
Microscopic Polyangiitis (MPA)	Perinuclear/protoplasmic-staining antineutrophil cytoplasmic antibodies (p-ANCA)
Mixed connective tissue disease	Anti-U1RNP antibody (speckled pattern)
Myasthenia Gravis	Anti-Ach Receptor Antibody
Pernicious anaemia	Antibody to gastric parietal cells (90%) and intrinsic factor (50%)
Polymyositis	Anti-Jo-1 (t-RNA Synthetase)
Primary biliary cirrhosis	Anti-mitochondrial antibody
Rheumatoid Arthritis	Anti-CCP Antibodies, Rheumatoid Factor (less specific)
Sjogren's syndrome	Anti-Ro, Anti-La antibody (speckled pattern), 60-70% have positive RF
Systemic Lupus Erythematosus	Antibodies to dsDNA+ Histones (Homogenous) and Ro La, Sm, U1RNP (speckled)
Type 1 Diabetes Mellitus	Antibodies to Glutamate Decarboxylase and pancreatic β Cells
Wegener's Granulomatosis (GPA)	Cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA)

Memory

Immune memory = Feature of adaptive immune system - pool of antigen specific cells following infection with enhanced ability to respond to a second infection.

Antigen presenting cells (APCs - macrophages, B lymphocytes, langerhans cells, dendritic cells) present peptides to T lymphocytes to initiate an acquired immune response.



Exposure to pathogen Antigen (s) → Stimulation of specific T and B lymphocytes leads to expansion → Some lymphocytes become Effector cells And some Memory cells → Immunologic memory develops (long lived – up to 65 years)

T Cell Memory (CD4 and CD8): (CD45 RO = memory T cells, CD45 RA = naïve T cells)

- Memory cells remain for a long time following infection
- They continue to proliferate at a low rate
- Subsequent exposure to antigen = rapid and robust response, easier to activate than naïve cells
- Have different cell surface markers
  - Influences migration and adhesion
  - Can access non-lymphoid tissue (the sites of microbe entry)

Central Memory Cells	Effector Memory Cells
Found in lymph nodes & tonsils- roll along and extravasate in High Endothelial Venules (HEVs)	Found in liver and lungs & gut
CCR7+ and CD62L high (allow entry/migrate via HEVs to peripheral lymph nodes)	CCR7-ve and CD62L low (therefore not found in lymph nodes)
Produce IL-2 (to support other cells)	Effector so produce – perforin and IFN-γ
More central memory in CD4 population	More effector memory in CD8 population

B Cell Memory

- B cells stimulated by antigen -> expansion/isotope switching (due to cytokines provided by T helper cells) -> plasma cells producing antibody/memory cells
- Memory cells that can differentiate into plasma cells (long lived)
- These cells produce: Quicker response, more antibodies, higher affinity antibodies, more IgG and generally better antibodies.

CD4+ T cells

- **Th1** Cell mediated, help CD8 and macrophages, produce: IL-2, IFN-Y, TNF
- **Th2** Humoral Response, Helper T cells, produce: IL-4, IL-5, IL-6

- **Th17** Help neutrophil recruitment, produce Il-17 IL-21 IL-22

Mantoux Test

- Inject 0.1 ml of 5 tuberculin (=purified protein derivative) units intradermally, examine arm 48-72 hrs after
- A positive result is indicated by induration (swelling that can be felt) of at least 10 mm in diameter (erythema around not measured). This implies previous exposure to tuberculin protein - thus it could represent previous BCG exposure.

Immune Modulation

Boost the immune response	Suppress the immune response
1. Vaccination 2. Replacement of missing components 3. Cytokine therapy 4. Blocking immune checkpoints - for advanced melanoma	1. Steroids 2. Anti-proliferative agents 3. Plasmapheresis 4. Inhibitors of cell signaling 5. Agents directed at cell surface antigens 6. Agents directed at cytokines

Vaccination

Mechanism of vaccination

- APCs (DC, macrophages, B lymphocytes) present peptides to T cells (both CD4/8)
- Clonal expansion: T cells with appropriate specificity proliferate + differentiate
    - CD4 cells - release cytokines and activate other cells B cells B cells
    - CD8 cells - kill infected cells
- Effector T cells then die by apoptosis OR survive as memory cells
- B cells differentiate to T-cell independent (IgM) memory cells OR undergo germinal centre reaction → T-cell dependent plasma cells (IgG/A/E)
- **End result = immune memory**; after resolution, infection 'remembered' and individuals remain protected. Achieved via:
    - Residual specific T & B memory cells with enhanced capacity to respond to re-infection
    - Pre-formed pool of high affinity Abs
- NOTE: Persistence of antigen results in a larger response and the generation of more memory cells

'Ideal' Vaccine Requirements:
1. Generates immunological memory
2. Practical - single injection, easy storage, inexpensive
3. No adverse effects

Passive vaccination = directly administering pre-formed antibodies/immunoglobulins

- Last for ~3 weeks.
- Examples:
    - HNIG (Human Normal Ig) – Hep A and Measles
    - HBIG (Hep B Immunoglobulin) – Hep B
    - HRIG (Human Rabies Immunoglobulin) – Rabies
    - VZIG (Varicella Zoster Immunoglobulin) – Varicella
    - Paviluzimab – monoclonal antibody for RSV (Respiratory Syncytial Virus)

Other Principles of Vaccination…
Herd immunity – if enough people in a community are immunised against a disease, it is more difficult for the disease to get passed between those who aren't immunised

Vaccination less effective in the elderly due to:

1. **Immune senescence**
    1. Increased frequency of terminally differentiated effector memory T cells
    2. Increased expression of senescence markers
    3. Much reduced production of recent thymic emigrants which drive the naïve T-cell repertoire.
2. **Nutrition**: insufficient energy because of poor nutrition; Reduced availability of trace elements and minerals (reduced gut absorption)

Dendritic Cell / 'Cancer' Vaccines
Initial evidence = Acquired defects in DC maturation/function seen in some malignancies allows cancer to evade immune recognition..

Concept: Patient WBCs harvested and cultured with target 'tumour' antigen → re-infused back into patient to stimulate immune response

1. Novel **tumour specific** antigens (created by mutations) = better target cf. **tumour associated** antigens (normal self-proteins but upregulated)

E.g., Sipuleucel-T (Provenge) – prostate ca.

UK Vaccine Programme

Latest data according to: https://www.nhs.uk/conditions/vaccinations/nhs-vaccinations-and-when-to-have-them/

Childhood vaccination schedule (2022)					
2 months	DTaP/IPV/HiB/Hep B (6 in 1 injection)	R	Men B		
3 months	DTaP/IPV/HiB/Hep B (6 in 1 injection)	R		PCV	
4 months	DTaP/IPV/HiB/Hep B (6 in 1 injection)		Men B		
1 yr	Hib/Men C		Men B	PCV	MMR
2-10 yrs					Flu – annually, Sept/Oct
3 yrs 4 months	DTaP/IPV (4 in 1 booster)				MMR
12-13 yrs					HPV
14 yrs	T/D/aP (3 in 1 booster)		Men ACWY		

Adult Vaccinations

- 50yrs onwards: flu annually
- 65 yrs: Pneumococcal (PPV)
- 70 yrs: Shingles
- Pregnancy (any age): Flu during appropriate season, DTaP/IPV from 16/40 gestation

COVID-19 Vaccinations

- Everyone 5yrs +: 1st and 2nd dose

- 16yrs + OR 12-15yrs at high risk/living with someone immunocompromised: As above + booster dose
- Severely weakened immune system at time of initial vaccine: As above + additional primary dose
- 50yrs+, high risk, pregnant, frontline HCP: As above + seasonal booster

Vaccine Key

D = Diphtheria
T = Tetanus
aP = acellular Pertussis (whooping cough)
IPV = Inactivated Polio
HiB = Haemophilus influenza type b
HepB = Hepatitis b

Men B = Meningitis b
Men C = Meningitis C
Men ACWY = Meningitis ACWY
MMR = Measles, mumps, rubella
PCV = Pneumococcal
R = rotavirus gastroenteritis (oral)
HPV = Human papilloma virus type 16,18 (2 injections, 6 months apart)

Additional vaccines given as per risk:

- Travel: Cholera, Hep A, Hep B, Jap Enceph, Tick-Bourne Enceph, Typhoid, Yellow Fever
- Influenza
  - CD8 T cells control the virus load but response relied on anti-haemagglutinin antibody
  - Protection begins within 7 days after immunization and lasts 6 months
- TB
  - BCG (Bacilli Calmette-Guerin) is an attenuated strain of bovine TB
  - Relies on T cell response
  - Protects against primary infection (19-27%) and progression to active TB (71%)
  - Protection lasts about 10-15 years

Types of Vaccine

	Advantages	Disadvantages	Examples
Live attenuated ***Live pathogen Modified to limit pathogenesis***	• Lifelong immunity possible – no boosters • Protection against different strains likely • Activates all phases of immune system	• Reversion to virulence – e.g., VAPP (Polio vaccine) • Risk for immunosuppressed / deficient* • Storage issues (require refridgeration)	'MMR-VBOY' • MMR • VZV • BCG • Oral – polio (Sabin), typhoid • Yellow fever • Influenza (Fluenz tetra) – 2-17yo
Inactivated/ Component ***Destroyed pathogen OR*** *isolated* ***antigenic proteins***	• No reversion • Safe in immunodeficiency • Easier storage • Low cost • Can eliminate wild-type virus from community?	• Poor response 'immunogenicity' • Repeated boosters or modifications needed • Do not follow natural route	• **Inactivated**: Influenza (quadrivalent), Polio (Salk), Cholera, Bubonic plague, Hep A, Rabies, Pertussis, Anthrax?, • **Component/subunit**: Hep B [HbS antigen], HPV [Capsid], Influenza recombinant quadrivalent)

		of infection i.e. SC injection for Flu	[haemagglutinin, neuraminidase], • **Toxoids**: Diphtheria, Tetanus
Conjugate ***Polysaccharide*** **+** *antigenic* ***protein carrier*** *to enhance response*	• Effective against encapsulated bacteria • Used for children	• Similar to inactivated/ components	'NHS' • **N** meningitidis • **H** influenzae • **S**trep pneumonia (Prevenar) • Tetanus
DNA/RNA vaccines ***Pathogen's genetic material (DNA/RNA) delivered to host cells via viral vector/ lipid complex.*** ***Host cells*** *produce +* ***express protein → immune response***	• mRNA/lipid complex noninfectious & non integrating	• Relatively new technology • DNA may theoretically integrate to host's DNA • Possible autoimmunity responses e.g., SLE • Need target that invokes good immune response	• mRNA: SARS-CoV-2 • Adenoviral vector: AstraZeneca (ChAdOx1-S), Sputnik (Adenovirus types 26, 5) • Ongoing research into other uses

* NOTE: HIV positive patients can receive MMR but not BCG or Yellow fever.

Adjuvants – 'increase the immune response without altering its specificity';

Ways to ensure good response + effective immune memory from vaccine

1. live vaccine
2. more persistent antigen – depot adjuvant
3. assisted activation of immune response – stimulatory adjuvant

Depot adjuvant acts by slowing the release of antigen. Injection of adjuvant + antigen mixture ensures **steady stream** of antigen → prolonged immune response.

- **ALUM:** Most common. Primary adjuvant utilized in humans. Antigens are adsorbed to alum so acts as means of slowly releasing antigen. Activates Gr1+ cells to produce IL-4 -> helps prime naïve B cells (mainly antibody mediated response). Generally safe and mild.

Stimulatory adjuvants mimic action of PAMPS on TLR/other PRRs → boosted immune response

- **CpG**: Immunostimulatory adjuvant activity is linked to unmethylated DNA motif rich in CpG (DNA where a cytosine nucleotide is situated next to a guanine nucleotide) Activates TLRs on APCs stimulating expression of costimulatory molecules.
- **Complete Freund's adjuvant**: water-in-oil emulsion containing mycobacterial cell wall components. Mainly for animals, painful in humans (not used clinically)

- **ISCOMS (Immune Stimulating Complex)**: Experimental – multimeric antigen with adjuvant built in. Cell-mediated immune response and humoral response. With saponin results in strong serum antibody response.
- **Interleukin 2**: to achieve seroconversion in Hep B s Ag+ individuals

Replacement of missing components

Therapy type	Indications
Haematopoietic SCT - ***potential for complete cure***	Life-threatening primary immunodeficiency- **SCID**, Leukocyte adhesion defect Haem malignancy
Ab replacement* – ***preformed IgG to wide range of unspecified organisms***	**Primary Ab def:** • Bruton's X linked agammaglobulinemia • X linked hyper IgM syndrome (pt can't make other classes of Ig) • Common variable immune deficiency **Secondary (acquired) Ab def**: • Haem malignancy – CLL, MM • Post BM transplant Other: • ITP, Kawasaki, GBS, measles, severe myasthenia gravis • toxic epidermal necrolysis • CMV pneumonitis (transplant pts) • dermatomyositis • chronic inflammatory demyelinating polyradiculopathy
Ab replacement – ***High titres IgG to specific pathogens***	Passive immunisation post-exposure - **Hep B** (needle stick, sexual contact with Hep B sAG+) - rabies (injected around bite site) - **VZV** (pregnant <20 weeks OR immunosuppressed + acyclovir/valacyclovir contraindicated) NOTE: no specific tetanus preparation in UK – use generic IVIg
Adoptive T cell transfer	Virus specific T cells EBV-related B cell lymphoproliferative disease, severe viral infections in immunocomp. pts • Allogeneic (donor) or autologous (pt) cells harvested • Grown with viral antigen stimulus → specific T cells • Effector cells (re)infused into pt Tumour infiltrating lymphocyte (TIL) T cell therapy • TILs collected from tumour & expanded with IL-2 • TIL infusion into lymphoid depleted patient → destroy cancer cells • Head & neck SCC, melanoma, lung and gynae ca. TCR • T cells engineered to express receptors specific to tumour antigens CAR-T cell therapy • Similar to TCR • BUT chimeric receptor also targets CD19 → greater immune response to tumour • ALL, Non-Hodgkin lymphoma (less effective in solid ca.)

*** Ab replacement - Human Normal Immunoglobulin (IVIG)**

- From >1000 donors (all screened for HIV, Hep B and Hep C)

- Given every 3-4 weeks, half-life is 18 days, IV or sub-cut

Cytokine Therapy

Recombinant Cytokines

- **AIM**: boost immune response to cancer and some pathogens
- **Examples:**
  1. **IL-2 – ↑ T cell response, renal ca.**
  2. **Interferon alpha** - antiviral effect, Hep B & C (+ ribavirin); anti-cancer, Kaposi sarcoma, hairy cell leukaemia, CML, melanoma, Bechets
     'ABC': Interferon **A**lpha for Hep **B** and **C** + **C**ML
  3. **Interferon beta:** Relapsing-remitting MS,
  4. **Interferon gamma:** ↑ macrophage function, Chronic **g**ranulomatous disease

Immune Checkpoint Blockade – for advanced melanoma

Indications: advanced melanoma, metastatic renal ca., other malignancies?
Risks: autoimmunity

Ipilimumab

- Monoclonal antibody specific for CTLA4
- CTLA4 = inhibitory checkpoint found on T cells – competes with **CD28** to bind **CD86/B7 on APCs** → blocks T cell activation
- CTLA4 blockade → ↑ APC presentation to T cells, **↑ T cell activation**

Pembrolizumab/Nivolumab

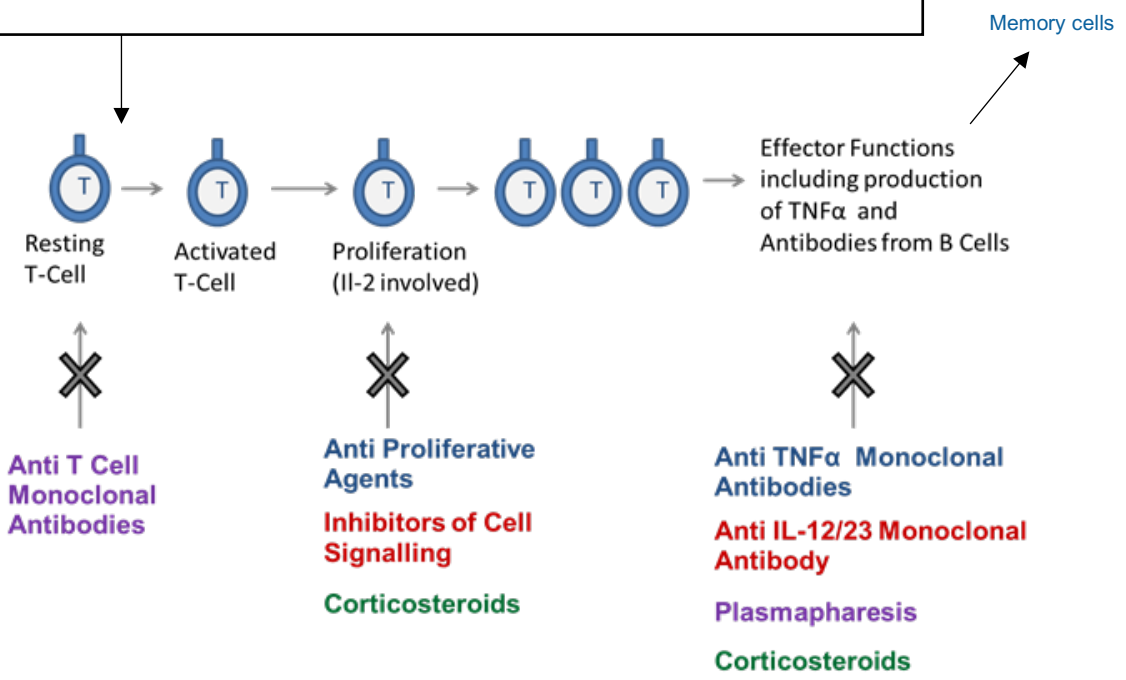
- Monoclonal antibody specific for PD-1
- PD-1 = programmed death receptor, found on regulatory T cells. Binds **PD-L1/2** on APCs/tumour cells → T cell inactivation, death
- PD-1 blockade → T cells remain active, **kill tumour cells**

Immunosuppressive therapy

Mechanisms of Action – Summary

3 signals in naïve T cell priming:

1. Activation – antigen presentation via MHC Class I/II on APC and TCR (+ CD4/8 co-receptor)
2. Survival – co-stimulation via CD86/B7 on APC and CD28 on T cell
3. Differentiation – cytokines determine T cell lineage + effector function



Adverse Effects of Immunosuppressive Therapies	
Infusion reaction	IgE mediated: Urticaria, hypotension, tachycardia, wheeze Not classical Type I hypersensitivity: headache, fevers, myalgia Cytokine storm
Injection site reactions	Peak reaction at ~48 hours May also occur at previous injection sites (recall reactions) Mixed cellular infiltrates, often CD8 T cells Not generally IgE or immune complex-mediated
Acute infection	Risk ~2x background • Prevention: Vaccination (not live), avoid contact • Rx: Stop immunosuppression (temp), Abx – cover for atypicals
Chronic Infection	TB • Check history/travel/ contacts + CXR/Elispot • Give Prophylaxis or Tx as needed
	HIV • Check HIV status prior to Rx • Consider risks vs benefits
	Hep B – check core antibody pre treatment Hep C – check antibody pre treatment Further Ix for active disease if positive serology
	John Cunningham Virus (JCV) • Polyoma virus that can reactivate • Infects + destroys oligodendrocytes • Causes progressive multifocal leukoencephalopathy (PML) • Seen with +++ immunosuppressive agents
Malignancy	Lymphoma – EBV Non melanoma skin ca. - HPV ?Melanoma – particularly anti TNF alpha

	Targeted immunosuppression lower risk cf. transplant regimes
Autoimmunity	Dysregulation of immune system → SLE & lupus-like syndromes, anti-phopsolipid syndromes, vasculitis, interstitial lung disease, sarcoidosis, uveitis, AI hepatitis, demyelination.

TYPE	EXAMPLES	MODE OF ACTION	INDICATIONS	SIDE EFFECTS
(Cortico) Steroids	Prednisolone	Prostaglandins: **Inhibits phospholipase A2** → no breakdown of phospholipids to arachidonic acid → prostaglandin synthesis blocked = reduced inflammation Phagocytes: inhibits phagocyte trafficking, phagocytosis & release of proteolytic enzymes. NOTE: causes transient ↑ neutrophil count Lymphocytes: lymphopenia (sequestered in lymphoid tissue), blocks cytokine gene expression, ↓Ab production, promotes apoptosis.	Allergic disorders Auto-immune & auto-inflammatory disease, prevention & Tx transplant rejection, Malignancy	Metabolic: Diabetes, central obesity, moon face, lipid abnormalities, osteoporosis, hirsutism, adrenal suppression, HTN Immunosuppression → infection Others: Cataracts, glaucoma, peptic ulceration, pancreatitis, avascular necrosis
Anti-proliferative agents inhibit DNA synthesis, cells with rapid turnover most sensitive	Cyclophosphamide	**Alkylates** guanine base of DNA, Damages DNA and prevents cell replication, **Affects B cells > T cells**, but at high doses affects all cells with high turnover	Connective tissue disease, vasculitis, anti-cancer agent	Bone marrow suppression, hair loss, sterility (M>F). **Haemorrhagic cystitis (**toxic drug metabolite acrolein in urine). Malignancy: bladder, haem, non-melanoma skin ca. Infection: *Pneumocystis jiroveci*
	Mycophenolate Mofetil	**Anti-metabolite**, inhibits IM PDH prevents guanine synthesis Blocks de novo nucleotide synthesis – prevents replication of DNA, **Prevents T>B cell proliferation**	Transplantation, auto-immune diseases, vasculitis	Bone marrow suppression Infection: herpes virus reactivation, **progressive multifocal leukoencephalopathy (JC virus)**
	Azathioprine	**Anti-metabolite**, metabolised by liver to 6 mercaptopurine, blocks de novo purine (eg adenine, guanine) synthesis – prevents replication of DNA, preferentially inhibits **T**	Transplantation, Auto-immune disease, Auto-inflammatory diseases	Bone marrow suppression – **TPMT polymorphism** cannot metabolise drug = very susceptible. Check before starting Tx! Infection (less cf. cyclophosphamide). Hepatotoxicity

		cell activation & proliferation > B cell		(uncommon)
	Methotrexate	**Anti-folate**, inhibits dihydrofolate reductase (DHFR) therefore decreases DNA synthesis	RA, Psoriasis, Crohn's, used in chemotherapy and as an abortifacient	Bone marrow supression, infection, malignancy, teratogenic, pneumonitis, pulmonary fibrosis, hepatotoxicity, folate deficiency (macrocytic megaloblastic anaemia)
Plasmapheresis		Removal of pathogenic antibody. Patient blood passes via separator; plasma treated to remove immunoglobulins and reinfused (or replaced with albumin in 'plasma exchange')	Severe **Ab-mediated (Type II) disease**: Goodpasture syndrome, myasthenia gravis, Ab mediated transplant rejection / ABO incompatibility.	Rebound antibody production limits efficacy, – given with anti-proliferative agent to reduce risk. Anaphylaxis
Inhibitors of cell signaling	Tacrolimus	Inhibits **calcineurin** → prevents T cell proliferation/function via reduced IL-2 expression	Rejection prophylaxis (transplantation), SLE, psoriatic arthritis. Can be used in pregnancy.	Nephrotoxic, hypertension, neurotoxic, diabetogenic
	Cyclosporin			Nephrotoxic, hypertension, neurotoxic, dysmorphism, **gingival (gum) hypertrophy**
	Sirolimus, Rapamycin	mTor inhibitor, inhibits T cell proliferation via **IL-2** pathway	Transplantation	Hypertension, less nephrotoxic
	Tofacitinib	JAK1/3 inhibitor. Influences gene transcription via JAK-STAT signalling pathway → inhibits production of inflammatory molecules	Rheumatoid arthritis, psoriatic arthritis, axial spondyloarthriti.	
	Apremilast	PDE4 inhibitor, increases cAMP → influences gene transcription via protein kinase A pathway.	Psoriasis, psoriatic arthritis	

Agents directed against cell surface antigens block signaling, cell depletion	Basiliximab	Anti-CD25 (alpha chain of IL-2 receptor), inhibits T cell proliferation	Allograft rejection (prophylaxis)	Infusion reactions, Infection, Malignancy, GI disturbance
	Abatacept	Anti-CTLA4-Ig fusion protein, reduces co-stimulation of T cells via CD28	Rheumatoid arthritis	Infusion reactions, infection (TB, HBV, HCV), malignancy, cough
	Rituximab	**Anti-CD20**, depletes mature B cells (not plasma cells)	Lymphoma, rheumatoid arthritis, SLE	Infusion reactions, infection (PML), exacerbation CV disease
	Vedolizumab	Anti-alpha-4-beta-7 integrin, inhibits cell migration (blocks integrin binding to MadCAM1)	IBD	Infusion reactions, hepatotoxicity, infection (?PML), malignancy.
	Natalizumab	Anti-alpha-4-beta-1 integrin (binds to VCAM1 and MadCAM1 to mediate rolling/arrest of leukocytes), inhibits T cell migration	Relapsing-remitting MS, Crohn's disease	Infusion reactions, infection (PML), malignancy, hepatotoxic
	Tocilizumab	Anti-IL-6 receptor, Reduces macrophage, T cell, B cell, neutrophil activation	Castleman's disease, Rheumatoid arthritis	Infusion reactions, Infection, Hepatotoxic, hyperlipidaemia, malignancy
	Muromonab-CD3	Blocks CD3 on T cells, mouse monoclonal antibody (OKT3)	Active allograft transplant rejection	Fever, leucopenia
	Anti-thymocyte globulin (ATG)	Lymphocyte depletion, Modulation of T cell activation and migration	allograft rejection (renal, heart)	Infusion reactions, Leukopenia, Infection, Malignancy
	Daclizumab	IL-2 receptor antibody, targets CD25	Organ transplant rejection prophylaxis	
	Efalizumab	Anti-CDIIa, inhibits migration of T cells		
	Alemtuzumab (Campath)	Monoclonal antibody that binds to CD52 found on lymphocytes resulting in depletion	Chronic lymphoid leukaemia, MS, T cell rejection (transplant)	CMV infection
Agents directed at cytokines/receptors	Infliximab	anti-TNFa	Rheumatoid arthritis, Ankylosing spondylitis, Psoriasis, psoriatic arthritis, Inflammatory	Infusion/injection site reactions, Infection (TB, HBV, HCV), Lupus-like conditions, Demyelination, Malignancy (lymphoma)
	Adalimumab (fully human monoclonal Ab)			

	Certolizumab Golimumab		bowel disease, Familial Mediterranean fever.	
	Etanercept	TNFalpha/TNFbeta receptor p75-IgG fusion protein, inhibits both cytokines.	Rheumatoid arthritis, Ankylosing spondylitis, Psoriasis and psoriatic arthritis	Same as TNF-alpha Abs
	Ustekinumab	anti-IL-12 and IL-23 (binds to p40 subunit)	psoriasis, psoriatic arthritis	injection site reactions, infection (TB), malignancy, cough
	Guselkumab	Anti-IL-23 (p19 alpha subunit)	Psoriasis, psoriatic arthritis	Injection site reactions, infection (TB), malignancy.
	Secukinumab	anti-IL-17A	psoriasis, psoriatic arthritis, ankylosing spondylitis	infection (TB)
	Denosumab	anti-RANK ligand, Inhibits RANK mediated osteoclast differentiation and function	**Osteoporosis,** multiple myeloma, bone metastases	Injection site reactions, infection, avascular necrosis of jaw
	Tocilizumab Sarilumab	Anti-IL-6, reduce macrophage, T and B cell, neutrophil activation.	Rheumatoid arthritis, Castleman's disease.	Infusion reactions, infection, hepatotoxicity, liid abnormalities, malignancy.
	IL-1 blockade	Anti-IL-1	Familial Mediterrannean fever, gout, adult onset Still's disease.	
	IL-4 / 5/ 13 blockade	IL-4R alpha subunit antibody, Anti IL-13 Ab, anti IL-5 Ab.	Eczema, asthma, eosinophilic asthma	

Allergen Desensitization

Allergic disorder = immunological process resulting in **immediate** + **reproducible** symptoms after allergen exposure.

- Ususally IgE medaiated Type I
- Allergen normally an otherwise harmless substance

Sensitisation = detection of specific IgE (skin prick. blood test) to allergen – not *necessarily* allergy

Desensitisation = Supervised administration of an allergen

1. Start with tiny dose and escalate every week until maximal dose reached
2. Maintenance dose given monthly for 3-5 years

- Reduces clinical symptoms of monoallergic disorders
- Good for: Bee and wasp venom, grass pollen, house dust mite. NOT food, latex
- Costly, laborious and risk of severe adverse reaction
- However, only Tx that alters natural course of disease.

Transplantation

Terminology

Isograft – transplant from a twin

Allograft – from the same species

Xenograft – from different species

Split graft – shared by two recipients e.g., liver

Allograft Types	
Deceased donor **Solid organs: kidney (most commonly transplanted organ), heart, pancreas, lungs, liver.** **Other: Small bowel, free cells (BM, Pancreas islets), Temporary (blood,skin – burns), cornea, framework (bone, cartilage tendons, nerves), Composite (hand, face).**	**Living donor** Bone marrow, kidney, liver

Transplant rejection is the immune system mounting a response to 'foreign' (non-self) antigens
3 Stages: Recognition → Activation → Effector Function

Recognition

Reminder – Immune Recognition

T-Cells (TCs) recognise antigen **presented via MHC** (I or II) on APCs

B-Cells (BCs) recognise **just antigen**

HLA classes

HLA Class I (A,B,C) – expressed on **all** cells

HLA Class II (DR, DQ, DP) – expressed on **APC**, can be upregulated on other cells under stress

In transplant the following are recognized:

- Human leucocyte antigens (HLA) - most important **DR>B>A**, coded by MHC complex on Chr 6, cell surface proteins, present foreign antigens to T cells → activation
- Minor HLA – other polymorphic self peptides
- ABO Blood Antigens

Foreign antigens can be recognized in 2 ways:

1. **Direct.**
    1. Donor APC presents foreign antigen and/or MHC to recipient T cells. Seen in **Acute rejection.**
2. **Indirect**
    1. Recipient APC presents donor antigen to recipient T-cells – i.e. the immune system working **normally**, as it would for an infection. Seen in **Chronic rejection**.

Activation and Effector Function – Types of Transplant Rejection

Rejection components: T-cell mediated; antibody mediated

T-cell mediated response

- Phase 1: recognition of foreign antigens
- Phase 2: activation of antigen-specific T lymphocytes
- Phase 3: effector phase of graft rejection
    1. Graft infiltration by alloreactive CD4+ cells
    2. Cytotoxic T cells – release of toxins (granzyme B), punch holes in target cells (perforin), apoptotic cell death (Fas ligand)
    3. Macrophages – phagocytosis, release of proteolytic enzymes, production of cytokines, production of oxygen + nitrogen radicals
    4. Abs bind to graft endothelium

T cell activation events

- Proliferate
- Produce cytokines
- Provide help to activate CD8+ cells
- Help antibody production
- Recruit phagocytic cells

Antibody-mediated response

- Phase 1: recognition of foreign antigens
- Phase 2: proliferation and maturation of B cells with Ab production
    - Anti-HLA Ab NOT naturally occurring; Pre-formed d/t prior transplant, pregnancy, transfusion OR post-formed (arise after transplant)
    - Anti A or B Abs naturally occur as per blood group
- Phase 3: Abs bind graft endothelium → intra-vascular disease

	Time	Mechanism	Pathology	Treatment
Hyperacute	Mins - Hrs	Preformed Ab which activates complement	Thrombosis and Necrosis	Prevention: Crossmatch (ABO groups) HLA-matching
Acute – Cellular	<6mo	CD4 activating a Type IV reaction	Cellular Infiltrate	T-Cell Immunosuppression
Acute – Antibody Mediated	<6mo	B-Cell activation - antibody attacks vessels	Vasculitis, C4d	Ab Removal and B-Cell Immunosuppression
Chronic	>6mo	Immune and non-immune mechanism Risk factors: 1. multiple acute rejections 2. HTN	Fibrosis Glomerulopathy Vasculopathy (ischaemia) Bronchiolitis obliterans (lung)	Minimise Organ Damage

		3. hyperlipidaemia		
GvHD	Days - Weeks	**Donor** cells attacking host	Skin (rash), gut (D+V, bloody stool) and liver (jaundice) involvement	Prevention/ Immunosuppression- corticosteroids

Acute vascular rejection – after xenograft, similar to hyperacute but 4-6 days after transplant

Matching

Minimising HLA (+ other Ag) 'mismatch' between donor and recipient improves transplant outcome

- Max possible HLA mismatches = 6
- Parent-child 3/6, sibling-sibling 25% 0/6, 50% 3/6, 25% 6/6

Pre-transplant

- Determine donor & recipient blood group and HLA (esp important for BM, kidney) - Tissue typing (PCR analysis of DNA)
- Check recipient's pre-formed Ab against ABO and HLA – 3 assay types
- Cross match – via CDC and FACS. Tests if serum from recipient is able to bind/kill donor lymphocytes- positive crossmatch is contraindication for transplantation.
- NOTE: screening is done twice pre-transplant – once before transplant & again once once specific organ assigned to pt.

After transplant

- Repeat assays to check for new Abs against graft
- Weekly → monthly checks for rejection
    - E.g., repeat U&E to detect creatinine rise +/- biopsy (kidney transplant)

Assays

Cytotoxicity / Complement Dependent Cytotoxicity – does recipient serum kill donor lymphocytes?

FACS / Flow Cytometry – does recipient serum bind donor lymphocytes?

Solid phase / Luminex =- does recipient serum contain Abs to individual HLA molecules?

Immunosuppressive regimes

- Induction (pre-transplant): suppress T cell response: e.g., anti-CD52 Alemtuzumab or anti-CD25 Basiliximab or OKT3/ATG
- Baseline immunosuppression e.g., CNI + MMF/Azathioprine +/- steroids
- Tx Acute rejection as needed:
    - Cellular – **Steroids** (3x methylpred pulses + oral taper), OKT3/ATG
    - Ab-mediated – IVIG, plasma exchange, anti-C5, anti-CD20

Haematopoietic stem-cell transplantation (HSCT) – graft-versus-host disease

- Eliminate hosts immune system (total body irradiation; cyclophophamide; other drugs)
- Replace with own (autologous) or HLA-matched donor (allogeneic) bone marrow – *details in Haem section*
- Indications: life threatening primary immunodef (SCID, leucocyte adhesion defect), haem ca.
- Graft-versus-host disease
    - Occurs in Allogeneic HSCT - **donor lymphocytes** recognise + attack host HLA
    - Related to degree of HLA-incompatibility
    - Symptoms: skin desquamation, rash, GI disturbance (nausea, vomiting, abdominal pain, diarrhoea, bloody stool), liver failure (jaundice), BM failure

- GVHD prophylaxis: Methotrexate/Cyclosporine, irradiate blood components for immunosuppressed pts
- GVHD Tx: corticosteroids

Post-transplantation complications

Specific risk depends on immunosuppressive agents used.

Infection

- Increased risk of conventional infections: Bacterial, viral, fungal
- Opportunistic infections: CMV, BK virus, *Pneumocystis carinii*

Malignancy

- Viral associated (x100) - Kaposi's sarcoma (HHV8), Lymphoproliferative disease (EBV)
- Skin cancer (x20)
- Other cancers e.g. lung, colon (x2-3)

Atherosclerosis

- Hypertension, hyperlipidaemia
- X20 increase risk in death from MI compared to age-matched general population

HIV

Epidemiology

- >37 M people living with HIV-1/AIDS worldwide (2018 Report)
- 21 million receiving ART
- 101,200 affected UK individuals
- ~70% those on ART have undetectable viral load (UK)
- Previous stats:
  - ~ 39 M people have died of AIDS.
  - >5000 persons infected per day - >10% (600) of these are children
  - Most will die within 20 years if no access to treatment
- Transmission = sexual, infected blood, mother-to-child (vertical – breastfeeding, in utero, intra partum)

HIV-1 Replication cycle

- RNA Retrovirus
- Binds CD4 via gp120 (initial binding) and gp41 (conformational change) on T helper cells, also CD4+ monocytes, DCs
- Binds CCR5 or CXCR4 chemokine co-receptor
- Replicates inside cells using Reverse Transcriptase (RT) enzyme to convert RNA into DNA which can be integrated into host genome
- Hijacks host cell machinery to transcribe DNA & translate mRNA to viral proteins
- Viral proteins packaged and released as mature virions
- Gag protein – intrastructural support for HIV

The immune response to the virus

<u>The Innate response</u>

- Non-specific activation of Macrophages, NK cells and complement

- Stimulation of dendritic cells via TLR
- Release of cytokines and chemokines

Adaptive response

- Neutralising antibodies: anti-gp41 IgM (first weeks), anti-gp120 (later)
- Non-neutralising antibodies: anti-p24 gag IgG
- CD8+ T Cells can prevent HIV entry by producing chemokines MIP-1a, MIP-1b, and RANTES which block co-receptors.

HIV damages the immune response

- HIV remains infectious even when Ab coated
- Activated infected $CD4^+$ helper T cells are killed CD8+ T cells
- Activated infected $CD4^+$ helper T cells are anergised (disabled)
- CD4 T-cell memory lost & failure to activate memory CTL
- Monocytes and dendritic cells are therefore not activated by the $CD4^+$ T cells and cannot prime naïve $CD8^+$ CTL (due to impaired antigen presenting functions)

Key features of HIV-1 infection

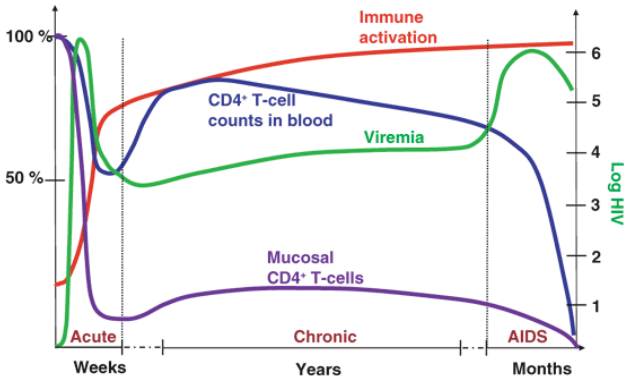
- CD4+ T cell depletion
- Chronic immune activation
- CD4 and CD8 T cell exhaustion
- Disruption of lymph node architecture
- Loss of Ag-specific humoral response

by

- Infected monocytes and dendritic cells are killed by virus or CTL
- Quasispecies are produced due to error-prone reverse transcriptase = these escape from immune response
- Effective immunity requires antibodies to prevent infection and neutralize virus, and sufficient CTL to eliminate latently infected cells

Natural History

3 stages: Acute → Asymptomatic (but progressive) → AIDS



- Transmission high during first 6m, Flu like Sx in ~70%
- Median time from infection to development of AIDS is 8 - 10 years (typical progressors)
- Rapid progressors (10%) in 2 - 3 years.
- Long Term Non Progressors (<5%) show stable CD4 counts and no symptoms after 10 years
- Initial viral burden (set point) predicts disease progression.
- **Important CD4 counts**: 75 Mycobacterium avium complex (MAC) disease; Pneumocystis jirovecii; 300-350 Pulmonary TB; 400 Kaposi's sarcoma

Diagnosis

Screening Test: Detects anti-HIV Ab via **ELISA**
Confirmation Test: Detects Ab via **Western Blot**

- A positive test requires patient to have SEROCONVERTED (i.e. started to produce Ab)
- This happens after ~10 weeks incubation period

HIV-1 RNA tests used when negative serology, high clinical suspicion
HIV-1 RNA and/or DNA in children <18m – serology not useful bc. passive transfer Abs from Mum

After Diagnosis:
Viral Load – PCR is used to detect viral RNA (very sensitive)
CD4 Count – via FACS (flow cytometry), used to assess course of disease, onset of AIDS correlates with diminution in number of CD4+ T cells. **AIDS <200cells/μL blood**.
Resistance Testing – resistance to antiretrovirals:

- Phenotypic: Viral replication is measured in cell cultures under selective pressure of increasing concentrations of antiretroviral drugs – compared to wild-type
- Genotypic: Mutations determined by direct sequencing of the amplified HIV genome

Treatment

BHIVA guidelines: all HIV-1 positive people should commence treatment **immediately** once diagnosis confirmed

- previously only when CD4 <200 or symptomatic)

HAART (Highly Active Anti-Retroviral Therapy) = 2NRTIs + PI (or NNRTI)
Aims:

- Substantial control of viral replication
- Increase in CD4 T cell counts
- Improvement in their host defences - dramatic decline in opportunistic infections (AIDS-related disease) & deaths (mortality)

If started before too much immune damage, similar life expectancy to age & sex-matched controls.
If STOPPED, HIV detectable in blood 2-3w later.

Example regimen: Emtricitabine + Tenofovir + Efavirenz (Available as 1 pill: Atripla)

Pregnancy – Zidovudine: Antepartum PO; For delivery IV
PO to newborn for 6/52 → reduces transmission from 26% to 8%

Limitations of HAART: doesn't eradicate latent HIV-1; fails to restore HIV-specific T-cell responses; toxicities; high pill burden; adherence; threat of drug resistance; QoL; cost; does not usually reverse chronic immune inflammation – RF for CVS, liver, bone & CNS disease.

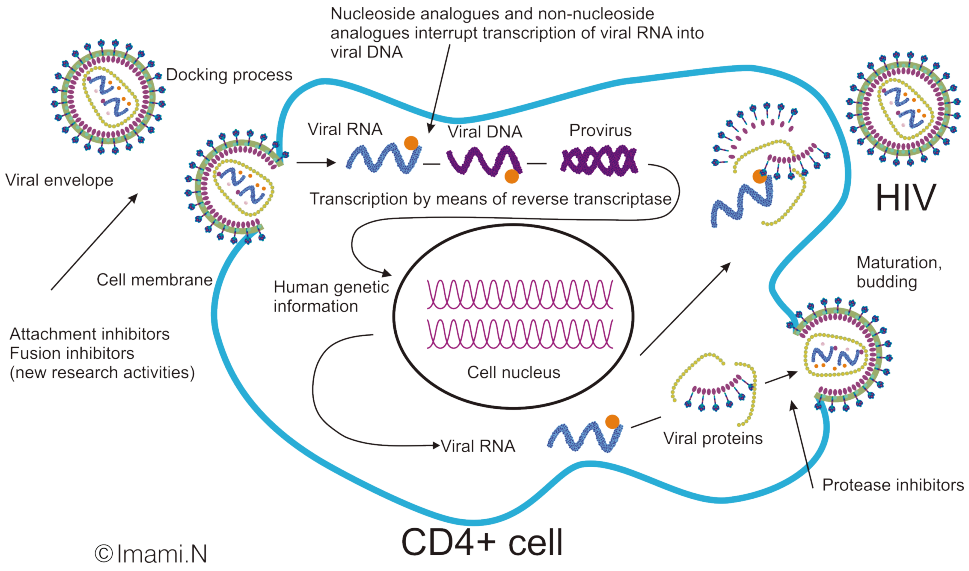
Monitoring

- Regular HIV-1 viral load
- CD4 monitoring not needed if >350 cells/uL
- Assess CVS, osteoporosis risk; monitor liver/renal/bone/lipid toxicity

Life Cycle & Treatment

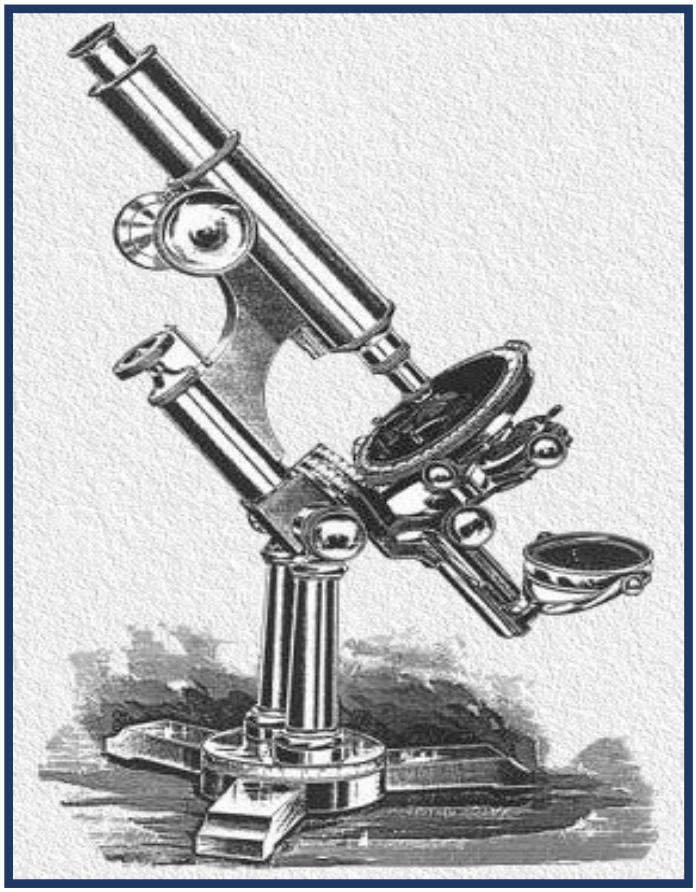
1. Attachment/entry
    - Attachment inhibitiors
    - Fusion inhibitors
2. Reverse transcription & DNA synthesis
    - Reverse transcriptase inhibitors
    - NRTI, NNRTI, NtRTI
3. Integration to host DNA
    - Integrase inhibitors

4. Viral transcription
5. Viral protein synthesis
6. Assembly & Budding
    - Protease Inhibitors



Class	Examples		Side Effects
Fusion Inhibitors	Enfuvirtide		Local Reactions to injections Hypersensitivity (0.1-1%)
Attachment Inhibitors	Maraviroc		Unknown
Nucleoside Reverse Transcriptase Inhibitors (NRTI)	Zidovudine	Abacavir	Generally Rare; fever, headache, GI disturbance, BMS (Zidovudine), Peripheral Neuropathy (Zalcitabine, Stavudine), Mitochondrial Toxicity (Stavudine), Hypersensitivity (Abacavir)
	Didanosine	Emtricitabine	
	Stavudine	Epzicom	
	Lamivudine	Combivir	
	Zalcitabine	Trizivir	
Nucleotide RTI	Tenofovir		Bone and renal toxicity
Non-NRTI	Nevirapine		Hepatitis and Rash
	Delavirdine		Rash
	Efavirenz		CNS Effects
Integration Inhibitors	Raltegravir	Elvitegravir	Unknown
Protease Inhibitors	Indinavir	Fosamprenavir	Hyperlipidemias, Fat Redistribution and Type 2 Diabetes
	Nelfinavir	Lopinavir	
	Ritonavir	Atazanavir	
	Amprenavir	Saquinavir	

Histopathology



Edited by Jonathan Guo and Tarush Gupta

Fundamentals of Histology (RG)

N.B High yield lectures will be annotated * or **
Rob Goldin Lectures will be marked (RG)

Cellular Types **

Table below illustrates the pathological process occurring for each cell type infiltrate.

Neutrophils	Acute inflammation (sterile or non-sterile)
Macrophages	Late acute inflammation Chronic inflammation (including granulomas e.g. Sarcoidosis)
Lymphocytes	Chronic inflammation Lymphoma (sheets of clonal cells ie. Identical)
Plasma Cells	Chronic inflammation Myeloma
Eosinophils	Allergic reactions Parasitic infections Tumours e.g. Hodgkin's disease
Mast Cells	Allergic reactions

Tumour Types **

There are many tumour types, Carcinomas, Sarcomas, Lymphoma, Melanoma etc. The tables below detail the classic histological appearance for Carcinomas (malignancy of epithelial cells)

Carcinomas		
Cell type	**Histological features**	**Site**
Squamous Cell Carcinoma	Keratin production Intracellular bridges (appears as little prickles on edge of cells) Do NOT form glands	Skin Head and neck Oesophagus (upper and middle 1/3) Anus Cervix Vagina
Adenocarcinomas	From glandular epithelium Forms glands that can secrete substances (e.g. mucin)	Lung Breast Stomach Colon Pancreas
Transitional Cell		Urinary tract Kidney Ureters Bladder

Histochemical Stains

Definition: based on a chemical reaction between the stain and the tissue

Fontana: +ve for melanin

Congo Red: +ve for Amyloid (Apple green birefringence)

Prussian Blue: +ve for iron (haemochromatosis)

Go-to stain for most histological samples is Hemotoxylin and Eosin (H&E)

Immunohistochemical Stains

Definition: Involves antibodies directed against a specific antigen. You can then use either immunofluorescence (fluorescently tagged antibody) or immunoperoxidase (visualisation due to chemical reaction) to detect resulting complexes.

- CD45: Lymphoid cell marker
- Cytokeratin: Epithelial marker
- Chromogranin: Neuroendocrine marker (e.g. Insulinomas or phaeochromocytoma)

NB A granuloma is an organised collection of activated epithelioid macrophages.

Cardiac Pathology

Atherosclerosis

Chronic inflammation in tunica intima (innermost layer) of large arteries characterized by intimal thickening and lipid accumulation

Steps of atherogenesis:
1. Endothelial injury causes accumulation of LDL
2. LDL enters intima and is trapped in sub-intimal space
3. LDL is converted into modified and oxidized LDL causing inflammation
4. Macrophages take up ox/modLDL via scavenger receptors and become foam cells
5. Apoptosis of foam cells causes inflammation and cholesterol core of plaque
6. Increase in adhesion molecules on endothelium due to inflammation results in more macrophages and T cells entering the plaque
7. Vascular smooth muscle cells form the fibrous cap, segregating thrombogenic core from lumen

Atherosclerotic plaques have 3 principal components:
1. Cells - including SMC, macrophages and other leukocytes;
2. ECM including collagen;
3. Intracellular and extracellular lipid

Abdominal aorta affected more than thoracic aorta.
More prominent around origins (ostia) of major branches → turbulent blood flow has **low/oscillatory shear stress,** which is **atherogenic**. High laminar flow is protective.

Risk Factors:
Modifiable: Type 2 Diabetes Mellitus, Hypertension, Hypercholesterolaemia, Smoking
Non-modifiable: Gender (Males>Females), increasing age, Family History

Ischaemic heart disease and Myocardial Infarction

Ischaemic heart disease

IHD
Group of conditions that occur when oxygen supply < demands of the myocardium due to narrowed coronary vessels. Includes stable/unstable angina, MI.
Stable angina: ~70% vessel occlusion – pain on exertion.
Unstable angina: ~>90% vessel occlusion – pain at rest also. **High likelihood of impending infarction.**
Prinzmetal angina: Rare, due to coronary artery spasm rather than atherosclerosis.

NB No muscle death in angina.

Myocardial infarction

Pathogenesis: Coronary atherosclerosis → plaque rupture → superimposed platelet activation → thrombosis and vasospasm → occlusive intracoronary thrombus overlying disrupted plaque. This results in myocardial necrosis secondary to ischaemia. Severe ischaemia lasting >20-40mins results in irreversible injury and myocyte death.

Complications of MI:

Mechanical

- Contractile dysfunction due to loss of muscle → cardiogenic shock
- Congestive cardiac failure – due to ventricular dysfunction (and arrhythmias)
- LV infarct – papillary muscle dysfunction/necrosis/rupture → mitral regurgitation
- Cardiac rupture of ventricular wall (haemopericardium), septum (left to right shunt, VSD), papillary muscle (MR)
- Ventricular aneurysm – usually develops >4 weeks post-MI (causes persistent ST elevation)

Arrhythmias*

- VF – usually occurs in the first 24hrs, common cause of sudden death
- 90% of patients develop an arrhythmia following MI

Pericardial

- Early/peri-infarct associated pericarditis (dusky haemorrhagic tissue)
- Pericardial effusion (+/- tamponade)
- Dressler's syndrome – chest pain, fevers and effusion weeks-months after MI
- Fibrinous Pericarditis – occurs if infarct extends to epicardium

Mural thrombus → embolization (often develop in ventricular aneurysms)

Evolution of MI – Histological findings**:

Under 6 hours - **normal** by histology (CK-MB also normal)
6–24 hrs - loss of nuclei, homogenous cytoplasm, necrotic cell death
1-4 days - infiltration of polymorphs then macrophages (clear up debris)
5-10 days - removal of debris
1-2 weeks - granulation tissue, new blood vessels, myofibroblasts, collagen synthesis
Weeks-months - strengthening, decellularising **scar tissue**.

Heart Failure

Primarily, the heart is unable to pump sufficient blood to supply the demand of the body.

Preload: Initial stretch of cardiomyocytes before contraction due to ventricular filling → increase will increase stroke volume.

Afterload: Pressure of vessels against which heart must contract to eject blood → increase will decrease stroke volume.

Common causes of Heart Failure:

- **I**schaemic heart disease
- **M**yocarditis
- **H**ypertension
- **C**ardiomyopathy (dilated)

- Valve disease
- Arrhythmias

Complications:

- Sudden Death (largely arrythmia)
- Systemic emboli
- Arrhythmias

Pathophysiology:

- Pulmonary oedema with superimposed infection
- Hepatic cirrhosis (nutmeg liver)

Cardiac damage → decreased cardiac output → activation of RAS(renin-angiotensin system) → salt and water retention = compensatory mechanism to maintain perfusion. Eventually → fluid overload.
Cardiac damage → decreased stroke volume → activation of sympathetic nervous system via baroreceptors (detect low BP) → maintains perfusion. Eventually → increased total peripheral resistance → increased afterload → LVH and increased EDV → dilatation and poor contractility

LV Failure: pooling of blood within pulmonary circulation due to high pressures in left side of heart → dyspnoea, orthopnoea, PND, wheeze, fatigue, pulmonary oedema. Eventually leading to decreased peripheral blood pressure and flow.
RV failure: Most common cause is secondary to LVF but can be primarily caused by chronic severe pulmonary hypertension. There is minimal pulmonary congestion but engorgement of systemic and portal venous systems, clinically seen as peripheral oedema, ascites, facial engorgement. Congestion and stasis of venous blood in the liver causes *nutmeg liver*

Investigations: BNP/ NT-proBNP, CXR, ECG, Echo

Cardiomyopathy

Pattern of cardiomyopathy	Mechanisms of heart failure	Causes	Indirect myocardial dysfunction (not cardiomyopathy-induced)
Dilated (too thin)	Systolic dysfunction	Idiopathic, alcohol, thyroid disease, haemochromatosis, viral myocarditis.	IHD, valvular heart disease, hypertension, congenital HD.
Hypertrophic (too thick)	Diastolic dysfunction	Genetic, storage diseases	Hypertension, AS
Restrictive (too stiff)	Diastolic dysfunction	Sarcoidosis, amyloidosis, radiation-induced fibrosis,	Pericardial constriction

HCM:

- The heart is typically **thick-walled, heavy and hyper-contracting**.
- Common phenotype: myocardial hypertrophy (especially within the septum and left ventricle) without ventricular dilation.
- Histologically – myocyte disarray. Myocyte disarray is arrhythmogenic.
- **Autosomal dominance** inheritance. Mutation in genes encoding sarcomeric proteins.
- Mutations in the **βMHC (β-myosin) gene** most common. (βMHC mutation is 403 Arg – Gln)
- MYBP-C and Trop-T gene mutations also common. Together with βMHC account for 70-80% of cases.
- Different mutations result in a different amount of hypertrophy and affects the incidence of arrhythmias
- May cause sudden cardiac death in young people. Troponin T mutations have a high risk of sudden cardiac death
- **Hypertrophic obstructive cardiomyopathy (HOCM)** – septal hypertrophy resulting in an outflow tract obstruction
- 15-20% go on to develop a Dilated cardiomyopathy phenotype

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) – myocyte loss with fibrofatty replacement typically affecting the right ventricle.

Acute Rheumatic Fever*

Occurs at a peak age of 5-15years. It is a multisystem illness affecting:

- Heart: pancarditis i.e. endocarditis, myocarditis, pericarditis;
- Joints: arthritis and synovitis;
- Skin: Erythema marginatum, subcutaneous nodules
- CNS: Encephalopathy, Sydenham's chorea

Clinical features:

- Develop 2-4 weeks after strep throat infection.
- Diagnosis: group A strep infection + 2 major criteria or 1 major + 2 minor criteria
- Jones' Major criteria:
    - **C**arditis
    - **A**rthritis
    - **S**ydenham's chorea
    - **E**rythema marginatum
    - **S**ubcutaneous nodules

- Minor criteria:
  - Fever
  - Raised ESR or CRP
  - Migratory arthralgia
  - Prolonged PR interval
  - Previous rheumatic fever
  - Malaise
  - Tachycardia

Commonly affects mitral valve only (70%) but can affect both mitral and aortic (25%).

Lancefield group A strep is the main pathogen.
Antigenic mimicry: cell-mediated immunity and antibodies to streptococcal antigen cross-react with myocardial antigens.
Histology: Beady fibrous **vegetations** (verrucae), **Aschoff bodies** (small giant-cell granulomas) and **Anitschkov myocytes** (regenerating myocytes).

Treatment: Benzylpenicillin. Erythromycin if penicillin-allergic

Vegetative Endocarditis

Disease	Pathology	Characteristics of Vegetations
Rheumatic heart disease	Antigenic mimicry – cross reaction of anti-streptococcal antibodies with heart tissue.	Small, warty vegetations found along the lines of closure of valve leaflet - 'verrucae'.
Infective endocarditis	Colonisation or invasion of heart valves or mural endocardium by microbe.	Large, irregular masses on valve cusps, extending into the chordae.
Non-bacterial thrombotic endocarditis (marantic)	DIC / Hypercoagulable states	Small, bland vegetations attached to lines of closure. Formed of thrombi.
Libman-Sacks endocarditis	Pathogenesis unknown. Associated with SLE and anti-phospholipid syndrome.	Small (up to 2mm), warty vegetations that are sterile and platelet-rich.

Infective Endocarditis – colonisation of endocardium*

Bacteraemia secondary to:
- Poor dental hygiene
- IVDU
- Soft tissue infection
- Dental treatments
- Cannulae/lines
- Cardiac surgery/pacemakers

	Acute	Subacute
Causative organisms	*Staph. aureus, Strep. pyogenes*	*Strep. viridans, Staph. epidermis*, HACEK* (culture -ve), *Coxiella, Mycoplasma,candida*
Virulence	High	Low
Vegetation morphology	Larger and more localised	Friable, soft thrombi. A few mm in size.
Spread	Aorta	Chordae

*N.B: HACEK are group of unusual bacterial causes of infective endocarditis. *Haemophilus, Aggregatibacter, Cardiobacterum, Eikenella, Kingella*

Clinical features:

- **Constitutional:**
  - Fever
  - Malaise
  - Rigors
  - Anaemia
- **Cardiac:**
  - New murmur (MR/AR usually)
- **Immune phenomena:**
  - Roth spots
  - Osler's nodes
  - Haematuria due to glomerulonephritis
- **Thromboembolic phenomena:**
  - Janeway lesions
  - Septic abscesses in lungs/brain/spleen/kidney
  - Microemboli
  - Splinter haemorrhages
  - Splenomegaly

Stereotypical patient: Non-specific systemic symptoms such as fevers, weight loss, night sweats and malaise ongoing for several months. Haematuria (either macroscopic or likely microscopic – very common). Often treated as bacterial infections and may improve with antibiotics only to worsen again when stopped.

Usually mitral/aortic valve unless IVDU when right-sided valves involved

Duke Criteria:

- **Major:**
  - Positive blood culture growing typical IE organisms or 2 positive cultures >12hrs apart
  - Evidence of vegetation/abscess on echo or new regurgitant murmur
- **Minor:**
  - Risk factor (e.g. prosthetic valve, IVDU, congenital valve abnormalities)
  - Fever >38
  - Thromboembolic phenomena
  - Immune phenomena
  - Positive blood cultures not meeting major criteria

Diagnosis:

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

Treatment: Start with broad spectrum Abx once cultures taken. Then treat according to sensitivities.

Subacute: Benzylpenicillin + gentamicin; or vancomycin for 4 weeks.
Acute: **Flucloxacillin** for MSSA, rifampicin + vancomycin + gentamicin for MRSA. (S. aureus IE is very nasty so make sure there is cover for this).

Valve Disease

	Aortic Stenosis	Aortic Regurgitation	Mitral Stenosis	Mitral Regurgitation
Pathophysiology	Narrowed aortic valve high velocity, high pressure flow	Incompetent aortic valve blood flows back into LV after systole	Narrowed mitral valve high velocity, high pressure flow. Back pressure in left atrium dilatation	Incompetent mitral valve blood flows back into left atrium during systole
Causes	Calcification (old age), congenital bicuspid valve	Infective endocarditis, dissecting aortic aneurysm, LV dilation, connective tissue disease e.g. Marfans, Ank Spon	Rheumatic fever	Infective endocarditis, connective tissue disease, post-MI, rheumatic fever, left ventricular dilation (functional MR)

Chronic rheumatic valve disease is predominantly left-sided and most commonly mitral. Mitral > Aortic > Tricuspid > Pulmonic. There is thickening of valve leaflet, especially along lines of closure and fusion of commissures. There is also thickening, shortening and fusion of chordae tendineae.

Mitral valve prolapse clinically appears in middle-aged woman, short of breath with chest pains. Clinical signs often described as mid systolic click + late systolic murmur.

Pericarditis

Inflammation of the pericardium. Types (causes):

- Fibrinous (MI, uraemia)
- Purulent (Staphylococcus)
- Granulomatous (TB)
- Hemorrhagic (tumour, TB, uraemia)
- Fibrous (a.k.a. Constrictive) (arises from any of above**)**

Pericardial effusion - Serous fluid in pericardial sac. Usual cause: Chronic heart failure. Exudative fluids occur secondary to inflammatory, infectious, malignant, or autoimmune processes within the pericardium.
Haemopericardium - myocardial rupture from myocardial infarction or trauma.

Lung Pathology

Obstructive Lung Diseases

Diagnosis	Chronic bronchitis	Bronchiectasis	Asthma	Emphysema	Small airway disease / Bronchiolitis
Site	Bronchus	Bronchus	Bronchus	Acinus	Bronchiole
Pathology	Dilatation of the airways and excess mucus production	Airway dilatation and scarring	Airway constriction due to mast cell degranulation	Airspace enlargement, wall destruction	Inflammatory scarring / obliteration
Aetiology	Tobacco smoke, air pollution	Recurrent infections (CF major RF)	Immunologic: allergens, drugs cold air, exercise	Tobacco smoke, α1-AT deficiency	Tobacco smoke, air pollutants
Clinical features	Cough & sputum on most days for 3 months over 2 years	Cough, purulent sputum, fever	Episodic cough, wheezing, acute dyspnoea	Dyspnoea, cough	Dyspnoea, cough
Histological features	Dilatation of the airways, goblet cell hyperplasia and hypertrophy of mucous glands	Permanent fibrotic dilatation of the bronchi	SM cell hyperplasia, excess mucus (goblet cell hypertrophy), inflammation Whorls of shed epithelium (Curschmann spirals), eosinophils, Charcot-Leyden crystals	Loss of the alveolar parenchyma distal to the terminal bronchiole	
Complications	Recurrent infections, chronic hypoxia. Pulm HTN	Recurrent infections, haemoptysis, pulm HTN, amyloidosis	Chronic asthma, Death	Pneumothorax, Resp failure, Pulm HTN	

Causes of Bronchiectasis:

- Inflammatory
  - Post-infectious (e.g. pertussis)
  - Abnormal host defense 1º (hypogammaglobulinaemia) and 2º (chemotherapy, NG)
  - Obstruction (extrinsic/intrinsic/middle lobe syn.)
  - Post-inflammatory (aspiration)
  - Secondary to bronchiolar disease (OB) and interstitial fibrosis (CFA, sarcoidosis)

    - Systemic disease (connective tissue disorders)
    - Asthma
- Congenital
    - **Cystic fibrosis**
    - **Primary ciliary dyskinesia**
    - Hypogammaglobulinema
    - Young's syndrome = rhinosinusitis, azoospermia and bronchiectasis

Cystic Fibrosis
Caused by AR mutation in CFTR gene (mostly F508del), which affects Cl ion transport → abnormally thick secretions. This allows growth of bacteria and causes frequent lung infections (often with **Pseudomonas Aeruginosa**) → bronchiectasis. Multisystem disease as secretions affect other organ systems e.g. pancreatic insufficiency → malabsorption.

Interstitial Lung Disease

Group of >200 diseases characterized by inflammation and fibrosis of the pulmonary connective tissue, accounting for 15% of respiratory disease burden.

Show features of **RESTRICTIVE** lung disease on spirometry (reduced FEV1 and FVR but normal FEV1/FVC ratio i.e. >70%)::
- Decreased CO diffusion capacity
- Decreased lung volume
- Decreased compliance

Typical presentation
- Chronic shortness of breath
- **Fine end-inspiratory crackles**
- Cyanosis, pulmonary HTN and cor pulmonale

In advanced disease, interstitial lung disease will have a **ground glass/ honeycomb** appearance on CT CAP.

Categorized into:
1. Fibrosing
    a. Cryptogenic Fibrosing Alveolitis/ Idiopathic pulmonary fibrosis
    b. Pneumoconiosis
    c. Cryptogenic organizing pneumonia
    d. Associated with connective tissue disease
    e. Drug-induced
    f. Radiation pneumonitis
2. Granulomatous
    a. Sarcoid
    b. Extrinsic allergic alveolitis
    c. Associated with vasculitides e.g. Wegener's, Churg-Strauss, microscopic polyangiitis
3. Eosinophilic
4. Smoking related

1. Fibrosing Lung Disease
Cryptogenic Fibrosing Alveolitis / Idiopathic Pulmonary Fibrosis
- M>F
- Causative agents unknown

- Histological pattern of fibrosis = **Usual Interstitial Pneumonia**, required for diagnosis (also seen in connective tissue disease, asbestosis and EAA)
    - Progressive patchy interstitial fibrosis with loss of normal lung architecture and **honeycomb change**, beginning at **periphery** of the lobule, usually **sub-pleural**
    - Hyperplasia of type II pneumocytes causing cyst formation – honeycomb fibrosis.
  - Can have inflammatory cause e.g. RA, SLE, systemic sclerosis
- **Clinical presentation**: increasing exertional dyspnoea and non-productive cough. 40-70y at presentation, with hypoxaemia → cyanosis and pulmonary HTN +/- cor pulmonale, and clubbing. Diagnosed by high-resolution CT
- **Rx:** steroids, cyclophosphamide, azathioprine, pirfenidone (not especially effective)

Pneumoconiosis

Occupational lung disease caused by inhlation of mineral dusts or inorganic particles. Classically seen in coal miners. The disease has a predilection for the upper lobes.
NB: Asbestosis can cause benign pleural lesions (plaques, **fibrosis**) but can also cause malignant lesions (adenocarcinoma, mesothelioma). Asbestosis (fibrosis resulting from asbestos exposure) tends to affect the **lower lobe.**

2. Granulomatous Lung Diseases

Granuloma = collection of histiocytes, macrophages +/- multi-nucleate giant cells.
Granulomatous infections include TB, fungal (histoplasma, Cryptococcus, coccidioides, aspergillus, mucor) and others (pneumocystis, parasites). Non-infectious granulomatous conditions include sarcoid, foreign body (aspiration or IVDU), drugs or occupational lung disease.

Extrinsic Allergic alveolitis / Hypersensitivity Pneumonitis/ Cryptogenic Organising Pneumonia / Bronchiolitis Obliterans Organising Pneumonia (BOOP)

Group of **immune-mediated** lung disorders caused by intense/prolonged exposure to inhaled **ORGANIC** antigens → widespread **ALVEOLAR** inflammation (cf asthma = airway inflammation). Extrinsic allergic alveolitis is typically an occupational lung disease and can be acute or chronic.

Histologically there is the presence of polypoid plugs of loose connective tissue within alveoli/bronchioles – granuloma formation and organising pneumonia.

Acute presentation: inhalation of antigenic dust in SENSITISED individual -→ systemic symptoms (fever, chills, chest pain, SOB, cough) within hours of exposure, usually settle by following day. Progresses to chronic EAA.

Chronic presentation: Progressive persistent **productive** cough and SOB, **finger clubbing** and severe weight loss

e.g. **Farmers lung** (mouldy hay/grain/silage – Saccharopolyspora rectivirgula), **Pigeon fancier's lung** (proteins in excreta/feathers), **Humidifier's lung** (heated water reservoirs – thermactinomyces spp.), **Malt-workers lung** (germinating barley – Aspergillus clavatus/fumigatus), **Cheese washer's lung** (mouldy cheese – Aspergillus clavatus/penicillium casei).

Recognise early as progression to fibrosis can be prevented by early removal of antigen.

Pneumonia

- **Bronchopneumonia** – patchy bronchial/peri-bronchial distribution. Low virulence organisms. Typically seen in the elderly and frail.
- **Lobar pneumonia*** – Fibrinosuppurative consolidation. Stages: 1.Consolidation; 2. Red Hepatisation (neutrophilia); 3. Grey Hepatisation (Fibrosis); 4. Resolution
  Typically high virulence organisms (Strep. Pneumoniae – rust coloured sputum).
- **Atypical** – interstitial pneumonitis. No intra-alveolar inflammation.

Tumours of the Lung**

Squamous cell carcinoma (30-50%)

- Risk factors: M>F, strongest correlation with **smoking**
- Highest rate of p53/c-myc mutations.
- Usually proximal bronchi, local spread with late metastasis. Less responsive to chemo.
- **Histology**: Keratinisation, intercellular prickles (desmosomes).
- **Cytology**: Squamous cells.
- There are a variety of subtypes e.g. papillary, basaloid. It is associated with cavitation and hypercalcaemia due to **paraneoplastic syndrome (PTHrp secretion)**..
- **Progression**: Epithelium → hyperplasia →squamous metaplasia→angiosquamous dysplasia→carcinoma in situ→invasive carcinoma

Adenocarcinoma (20-30%)

- Most common in **women** and **non-smokers**.
- Malignant epithelial tumour with glandular differentiation or mucin production.
- Tumour occurs peripherally and metastasizes early.
- **Histology**: Glandular differentiation (gland formation and mucin production).
- **Cytology** – cells containing mucin vacuoles. Molecular – EGFR mutations.
- **Progression**; Atypical adenomatous hyperplasia→non-mucinous BAC→mixed pattern adenocarcinoma

Small cell carcinoma (20% - 25%)

- Usually occurs centrally, proximal bronchi.
- Arising from neuroendocrine cells. Associated with ectopic ACTH secretion, Lambert-Eaton, SIADH.
- **Histology**: Small, poorly differentiated **"oat cells"**
- Highly malignant, metastasize early, usually by diagnosis commonly to bone, adrenal, liver and brain.
- Poor prognosis due to rapid metastases and late presentation – despite being chemosensitive.
- It has a strong relationship to **smoking**. p53 and RB1 mutations are common.

Large cell carcinoma (10% - 15%)

- Poorly differentiated malignant epithelial tumour – large cells, large nuclei, prominent nucleoli. Histology – no evidence of glandular or squamous differentiation. Poor prognosis.
- **Histology**: No evidence of glandular or squamous differentiation. Poor prognosis.

Paraneoplastic syndromes:
ADH → SIADH (Small cell)
ACTH → Cushing's syndrome (Small cell)
PTH/ PTHrP → primary hyperparathyroidism, hypercalcaemia and bone pain (Squamous cell)
Calcitonin → hypocalcaemia
Serotonin → carcinoid syndrome (flushing + diarrhoea + bronchoconstriction)
Bradykinin → cough

Molecular:

- ERCC1 – NSCLC = poorer response to cisplatin
- EGFR – adeno (usually) = target for Anti-EGFR (usually tyrosine kinase inhibitor (TKI)) therapy
- Kras – adeno/squamous = poor prognosis, non-response to TKI
- EML4-ALK – adeno (usually) = no benefit from TKI

Staging – most important prognostic factor:

- Tumour (T1-4) – based on size and invasion of pleura, pericardium
- Lymph node metastasis (N0-2) - N0 – lymph node not involved by tumour, N1 or N2 - lymph nodes involved. 1 vs 2 depends on extent of involvement

- Distant metastasis (M0 or 1) - M1 – tumour has spread to distant sites.

Mesothelioma: Arise from either parietal or visceral pleura. It spreads widely within the pleural space and usually associated with extensive pleural effusion, chest pain and dyspnoea. There is a long latent period of 25-45 years for development of asbestos-related mesothelioma.

Diseases of the Pulmonary Vasculature

Pulmonary embolus (PE)

95% originate from **DVT**s. Risk factors include female, immobility, cardiac disease, cancer, primary and secondary hypercoagulable states (**Virchow's triad** = stasis + vessel wall injury + hypercoagulability).

- Large emboli impact in the main pulmonary arteries leading to acute cor pulmonale, cardiogenic shock and death if >60% of pulmonary bed occluded. (N.B. occluding pulmonary trunk = saddle embolus).
- Small emboli may can be silent or cause peripheral wedge infarctions. Repeated infarctions can result in pulmonary HTN.
- Non-thrombotic emboli – bone marrow, amniotic fluid, tumour, air, foreign body.

Pulmonary Hypertension

Mean pulmonary arterial pressure of **>25mmHg at rest**.

Classified according to aetiology

- **Class 1:**
  - Pulmonary arterial hypertension (idiopathic, hereditary, drug/toxins, associated with congenital heart disease) - primary PAH most common in women aged 20-40yrs
- **Class 2:**
  - Pulmonary hypertension due to left heart disease (systolic/diastolic dysfunction, valve disease)
- **Class 3:**
  - Pulmonary hypertension due to lung disease (eg. ILD)
- **Class 4:**
  - Chronic Thromboembolic Pulmonary Hypertension ie. due to many clots over time which cause fibrosis
- **Class 5:**
  - Pulmonary Hypertension with unclear multifactorial mechanisms (metabolic disorders, systemic disorders, haematological disorders)

Pathophysiology:

- Pre-capillary (chronic hypoxia/embolus)
- Capillary (Pulmonary Fibrosis)
- Post-capillary (left heart disease/ veno-occlusive disease)
- Pulmonary vasoconstriction of arterioles – intimal fibrosis, thickened walls

Complications: RHF – venous congestion of organs (nutmeg liver), peripheral oedema.

Pulmonary Oedema and Diffuse Alveolar Damage

Pulmonary oedema: Intra alveolar fluid accumulation leads to poor gas exchange. Main aetiology: left heart failure. Histology: intra-alveolar fluid, iron laden macrophages ("heart failure cells").
Histology: acute – intra-alveolar fluid, chronic - **iron laden macrophages** ("heart failure cells").

Diffuse alveolar damage: Acute damage to alveoli leading to exudative inflammatory reaction, rapid onset of respiratory failure and often requiring ventilation in ITU:

- ARDS in adults (e.g. infection, drowning, burns, aspiration, trauma etc)

- HMD (hyaline membrane disease) in neonates (e.g. insufficient surfactant production in prems)

Histo: lung expanded, firm, plum-coloured, airless.

CXR: White out of all lung fields

GI Disease (RG)

Oesophagus*

Squamous stratified epithelium **(NO GOBLET CELLS)**, separated from columnar epithelium of the stomach via squamo-columnar junction/ Z-line.

Disease	Characteristics
Reflux oesophagitis = GORD	Commonest cause of oesophagitis **Complications:** ulceration, haemorrhage → haematemesis/melaena, Barrett's oesophagus, stricture, perforation Los Angeles Classification of severity **Tx:** lifestyle changes (stop smoking, weight loss), PPI/H2 receptor antagonists
Barrett's oesophagus	Intestinal metaplasia of squamous mucosa → columnar epithelium (have goblet cells) following chronic GORD → upwards migration of the SCJ Seen in 10% of those with **symptomatic** GORD Can lead to adenocarcinoma: metaplasia → dysplasia → Ca NB Presence of goblet cells is **intestinal metaplasia** – confers even higher risk of development into Ca .
Oesophageal Adenocarcinoma	Associated with Barrett's oesophagus so usually seen in distal 1/3 Other risk factors including: Smoking, obesity, prior radiation therapy Most common in Caucasians, M>>F
Squamous cell oesophageal carcinoma	Associated with ETOH and smoking Other risk factors including: Achalasia of cardia, Plummer-Vinson syndrome, nutritional deficiencies, nitrosamines, HPV (in high prevalence areas) 6x more common in Afro-Caribbeans, M>F Usually found in middle 1/3 (50%). Upper 1/3 – 20%, Lower 1/3 – 30% **Presentation:** Progressive dysphagia (solids then fluids), odynophagia (pain), anorexia, severe weight loss Rapid growth and early spread (to LNs, liver and directly to proximal structures) → palliative care
Varices	Engorged dilated veins, usually due to portal HTN (back pressure) Pt vomits large volumes of blood Emergency endoscopy → sclerotherapy/banding

Stomach

Lined by gastric mucosa (NO GOBLET CELLS), columnar epithelium (mucin secreting) and glands.

Disease	Characteristics
Gastritis	**Acute (neutrophils):** Insult e.g. aspirin, NSAIDs, corrosives (bleach), acute

	H. pylori, severe stress (burns). **Chronic (lymphocytes and plasma cells):** Insult e.g. H-pylori tends to be Antral, AI e.g. pernicious anaemia, ETOH, smoking. **Complications:** Chronic gastritis may lead to gastric ulcer formation. Chronic gastritis due to *H. pylori* may induce lymphoid tissue in stomach and increase future risk of **Mucosa Associated Lymphoid Tissue (MALT) lymphoma**. It may also however result in intestinal metaplasia → dysplasia → cancer.
Gastric ulcer	Breach through muscularis mucosa into submucosa (otherwise an erosion, not an ulcer). Epigastric pain +/- weight loss. **Worse with food** (contrast with duodenal ulcer), relieved by antacids. **RFs:** *H. pylori*, smoking, NSAIDs, stress, delayed gastric emptying. Occurs mainly in elderly. **Ix:** Biopsy for *H. pylori* histology status. Punched out lesion with rolled margins. **Complications:** Anaemia (IDA) and perforation (erect CXR), malignancy.
Gastric Cancer	Higher incidence in Japan, China where more fermented/pickled food eaten. >95% of tumours in stomach will be **adenocarcinomas**. Can be intestinal (well differentiated, goblet cells present following intestinal metaplasia). Diffuse (poorly differentiated, no gland formation – includes **signet ring cell carcinoma**).
Gastric (MALT) lymphoma	Caused by *H. pylori* – chronic antigen stimulation. **Rx:** Remove cause (*H. pylori* using triple therapy – PPI, Clarithromycin + Amoxicillin).

Duodenum

Disease	Characteristics
Duodenal ulcer	4 times more common than gastric ulcer Epigastric pain, worse at night **Relieved by food** and milk Occurs in younger adults RFs: *H. pylori*, drugs, aspirin, NSAIDs, steroids, smoking, ↑ drugs, acid secretion Complications: Anaemia (IDA) and perforation (erect CXR)
Coeliac disease (X-ref with Immuno section)	T cell mediated autoimmune disease (DQ2, DQ8 HLA status). **Presentation**: Young children (paeds) and Irish women (EMQs). **Symptoms (of malabsorption):** Steatorrhoea, abdo pain, bloating, n&v, ↓wt, fatigue, IDA, failure to thrive, rash (dermatitis herpetiformis). Also associated with hyposplenism so may need extra vaccines.

	Ddx: Tropical sprue **Serological tests:** Anti-endomysial Ab (best sen and spec), anti-tissue transglutaminase (IgA), anti-gliadin (poor marker of disease control). **Gold standard Ix:** Upper GI endoscopy and duodenal biopsy (villous atrophy, crypt hyperplasia, increased intraepithelial lymphocytes) **while eating gluten**. NB normal villous:crypt ratio is ~ 2:1. **Rx:** Gluten free diet. Around 10% progress to Duodenal T-cell lymphoma (**EATL**) if not treated adequately.

Congenital Diseases – *paeds*

- Atresia
- Stenosis
- Duplication
- Imperforate anus

Hirschsprung's disease – Absence of ganglion cells in myenteric plexus (80% males).
- Presents with symptoms and signs of obstruction in young babies, mostly males
  - Failure to pass meconium within first 48hrs
- Associated with Down's syndrome (2%)
- Genetics – RET proto-oncogene Cr10+
- **Gold standard Ix:** Full thickness biopsy – hypertrophied nerve fibres, no ganglia
- **Treatment**: Resection of affected (constricted) segment and pull-through of normal functioning bowel

Acquired Diseases

Mechanical

- Obstruction – caused by:
  - Constipation!
  - **Diverticular disease** = v. common
  - Adhesions
  - Herniation
  - External mass (e.g. fetus, aneurysm, foreign body)
  - Volvulus – complete twisting of bowel loop at mesenteric base around vascular pedicle, small bowel (infants), sigmoid > caecal (elderly)
  - Intussusception

Inflammatory (Table Below)

- Acute colitis – caused by:
  - **Infection** (bacterial, viral, protozoal etc.) → diarrhoea v. common.
  - Drug/toxin (esp. abx)
  - Chemo/radiotherapy
- Chronic colitis – caused by:
  - **IBD:** Crohn's disease and ulcerative colitis
  - TB

Ischaemia

- Ischaemic colitis – arterial or venous occlusion, small vessel disease, low flow states (e.g. due to hypovolaemic shock), obstruction.

Commonly in 'Watershed areas' e.g.: splenic flexure (SMA transition to IMA), rectosigmoid (IMA transition to internal iliac).

Inflammatory Bowel Disease**

Disease	Crohn's Disease	Ulcerative Colitis
Epidemiology	− Western populations − Peak onset 20's, F>M − White 2-5x >non-white − Smoking worsens symptoms	− Slightly more common than Crohn's − White > non-whites − Peak age is 20-25 yrs − Smoking **improves** symptoms/protective
Aetiology	Unknown. MZ twin concordance 50% "hygiene hypothesis" – less food contamination → less enteric infection → inadequate development of processes that regulate mucosal immune response → exaggerated immune response to pathogens that would cause self-limiting disease	Unknown MZ twin concordance 15%
Pathophysiology	**Distribution:** Affects **whole GI tract** (mouth to anus), most common in **terminal ileum** and caecum. Patchy distribution → **'skip lesions'**. Areas of healthy mucosa lie above diseased mucosa -> **'cobblestone appearance'**. **Nature of lesions: Transmural** inflammation. **Non-caseating granulomas** seen and fistula/fissure formation common. First lesion = **'aphthous ulcer'**. These are deep **'rosethorn ulcers.'** Can join to form serpentine ulcers.	**Distribution:** Extends proximally from rectum. Continuous involvement of mucosa. Small bowel not affected unless v. severe pancolitis causes **'backwash ileitis'**. **Nature of lesions:** Inflammation **superficial**, confined to mucosa. No granulomas/ fissures/ fistulae /strictures. − Islands of regenerating mucosa bulge into lumen → **pseudopolyps** (can fuse to form mucosal bridges).

Clinical features	Usually presents with intermittent diarrhoea, pain and fever	Associated more with **bloody** diarrhoea, mucus. Crampy abdo pain relieved by defecation
Extra-GI manifestations	− Malabsorption & Fe def. Anaemia → angular stomatitis − **Eyes:** Anterior uveitis (iris & ciliary body), conjunctivitis − **Skin:** Erythema nodosum (tender bruise-like swellings on shins), pyoderma gangrenosum, erythema multiforme, Digitial clubbing − **Joints:** Migratory asymmetrical polyarthropathy of large joints (15%), sacroiliitis, myositis, ankylosing spondylitis − **Liver:** Pericholangitis, primary sclerosing cholangitis (UC>CD), steatosis	
Complications	− Strictures (requiring bowel resection, often recurrent − Fistulae − Abscess formation − Perforation	− Severe haemorrhage − **Toxic megacolon** → perforation (damage to muscularis propria w/disruption of neuromuscular function → colonic dilatation) − 30% require colectomy within 3yrs for uncontrollable symptoms − Adenocarcinoma (20-30x risk)
Investigations	Systemic markers of inflammation e.g. ESR, CRP, Barium contrast, Endoscopy	Rectal biopsy, flexible sig/colonoscopy, AXR, stool culture
Management	*Mild attack:* Prednisolone *Severe attacks:* IV hydrocortisone, metronidazole *Additional therapies:* Azathioprine, methotrexate, infliximab	*Mild:* Prednisolone + mesalazine (5 ASA) *Moderate:* Prednisolone + 5-ASA + steroid enema bd *Severe:* Admit, NBM IV fluids and IV hydrocortisone, rectal steroids *For remission:* All 5-ASA (1st line), azathioprine (2nd line)

Infection**

See microbiology section and page 380 OHCM 7th ed.

Clostridium difficile

Antibiotics (4 Cs of *C. diff*: Ciprofloxacin, Cephalosporins, Co-amoxiclav and Clindamycin) kill off commensals allowing *C. diff* to flourish. Its exotoxins cause pseudomembranous colitis.

Ix: Stool culture/toxin assay

Rx: Vancomycin PO (not absorbed well so accumulates in gut)

- Also put into side room, can use Metronidazole

Other common bacteria: *Campylobacter, Salmonella, Shigella spp.*

Diverticular Disease

High incidence in West probably due to low fibre diet. High intraluminal pressure results in outpouchings at 'weak points' in wall of bowel (seen on barium enema CT or endoscopy). 90% occur in left colon. . **Prescence of diverticulae is diverticulosis (i.e. not diverticulitis)**. Often asymptomatic, sometimes PR bleed

Complications: Diverticulitis: fever and peritonism; gross perforation, fistula, obstruction (due to fibrosis).

Carcinoid Syndrome

- Diverse group of tumours of enterochromaffin cell origin, **Produce 5-HT** (serotonin)
- Commonly found in the bowel (but also lung, ovaries, testes)
- Usually slow growing

Carcinoid syndrome	Carcinoid crisis
• Bronchoconstriction • Flushing • Diarrhoea	Life threatening vasodilatation, Hypotension, Tachycardia, Bronchoconstriction, Hyperglycaemia

Investigation: 24hr urine 5-HIAA (main metabolite of serotonin)
Treatment: Octreotide (somatostatin analogue)

Tumours of the Colon and Rectum*

Neoplastic polyps	
Adenomas	− Benign dysplastic lesions that are the precursor lesion to most adenocarcinomas (although most remain benign). − Found in 50% >50yrs in Western world (very common). − Mostly asymptomatic so need regular surveillance if over 3.4cm 45% malignant change. − Classified based on architecture as tubular, tubulovillous or villous. − Villous adenoma (rare) → hypoproteinaemic hypokalaemia because they leak large amounts of protein and K. − **Large size is most important risk factor** for malignancy, in addition to degree of dysplasia and increased villous component. − Adenoma → carcinoma progression 'classical chromosomal instability sequence': o Normal colon → at risk mucosa after "first hit" mutation in 1st copy of APC gene (those with FAP born with this mutation). o At risk → adenoma after "second hit" mutation to remaining APC gene. o Progression to carcinoma follows activation of KRAS, LOF mutations of p53.

Non-neoplastic polyps	Clinical features
Hamartomatous polyp	Found sporadically in some genetic/acquired syndromes. Juvenile polyps are focal malformations of mucosa and lamina propria, vast

	majority in those <5yrs old, mostly in rectum → bleeding. Usually solitary, but up to 100 found in **juvenile polyposis** (AD) that may require colectomy to stop haemorrhage. Also seen in **Peutz-Jeghers syndrome** (AD - **LKB1**) = multiple polyps, mucocutaneous hyperpigmentation, freckles around mouth, palms and soles. Have increased risk of intussusception and of malignancy → regular surveillance of GI tract, pelvis and gonads.
Hyperplastic polyp	Seen at 50-60yrs, thought to be caused by shedding of epithelium → cell build-up
Inflammatory	Pseudo-polyps eg. IBD

Colorectal cancer	
Epidemiology	2nd commonest cause of cancer deaths in UK. Age 60-79 yrs If found <50yrs consider familial syndrome. Commoner in western population **98% are adenocarcinoma**, 45% in rectum
Aetiology	Diet (↓fibre, ↑fat), Lack of exercise, Obesity, Familial syndromes, chronic IBD, NSAIDS protective (COX2 over-expressed in 90%)
Clinical features	Right sided tumours: Fe def. anaemia, weight loss Left sided tumours: Change in bowel habit, crampy LLQ pain
Investigations	Proctoscopy, sigmoidoscopy, colonoscopy, barium enema, bloods e.g. FBC, CT/MRI Carcinoembryonic antigen (CEA) – monitor disease and response to therapy
Classification	Duke's Staging- helps determine Rx: **(TNM staging also used).** A: Confined to mucosa (5yr survival >95%) B1: Extending into muscularis propria (5yr survival 67%) B2: Transmural invasion, no lymph nodes involved (5yr survival 54%) C1: Extending to muscularis propria, with LN metastases (5yr survival 43%) C2: Transmural invasion, with lymph node metastases (5yr survival 23%) D: Distant metastases (5yr survival <10%)
Management	**Surgery** Rectal cancer/low sigmoid cancer: <1-2 cm above anal sphincter (lower third of rectum) → Abdomino-perineal resection. >1-2cm above anal sphincter → Anterior resection. Sigmoid cancer → Sigmoid colectomy. Descending colon and distal transverse → Left hemicolectomy. Caecum, ascending colon and proximal transverse → Right hemicolectomy. Transverse colon → Extended right hemicolectomy. **Radiotherapy:** post-op to decrease local recurrence. **Chemotherapy in palliation:** 5-FU (fluorouracil)*.

Familial syndromes	**Familial adenomatous polyposis (FAP)** − 70% **AD** mutation in APC tumour suppressor gene (C5q1), 30% AR mutation in DNA mismatch repair genes. − Present 10-15yrs - >100 adenomatous polyps required for diagnosis, usually 100-1000s seen. ALL will → adenocarcinoma if left untreated by 30yrs therefore most have prophylactic colectomy. − Increased risk of neoplasia elsewhere, e.g.: ampulla of Vater and stomach. **Gardners syndrome** – Subtype of FAP with extra intestinal features e.g.: osteomas of the skull, dental caries. **Hereditary non-polyposis colorectal cancer/Lynch syndrome (HNPCC)** − **AD** mutations in DNA mismatch repair genes. − Carcinomas usually in right colon, few polyps but fast progression to malignancy therefore present usually <50yrs. − Associated with extra-colonic cancers also: endometrial, ovarian, small bowel, transitional cell and stomach carcinoma. These patients will need regular monitoring and likely a total colectomy eventually.

Pancreatic Disease (RG)

Role of the pancreas: Produces 2L a day of enzymic $HCO3^-$ rich fluid, stimulated by secretin and CCK. Exocrine pancreas is composed of ducts and acinar cells

Secretin: produced by s-cells of the duodenum, controls gastric acid secretion and buffering with $HCO3^-$
CCK: responsible for stimulating digestion of fat and protein. Made by I-cells in the duodenum. Causes release of digestive enzymes.

Exocrine vs. Endocrine

	Exocrine	Endocrine
Function	Digestive – proteases, lipases and amylase	Endocrine
Secretions	Secretes products into ducts e.g. digestive enzymes	Secretes products into bloodstream e.g. hormones
Islets of Langerhans	N/A	Alpha cells: glucagon increases blood glucose Beta cells: insulin decreases blood glucose Delta cells: somatostatin regulates the above cells D1: a vasoactive peptide, stimulates the secretion of H20 into pancreatic system PP: pancreatic polypeptide, self regulates secretion activities

Metabolic syndrome

Collection of conditions that increase risk of IHD

- Fasting hyperglycaemia >6 mmol/l.
- BP >140/90
- Central obesity (>94cm in M, >80cm F)
- Dyslipidemia: Decreased HDL cholesterol <1mmol/l & Increased TGs >2mmol/l
- Microalbuminaemia

Diabetes Mellitus

Diagnosis: Fasting plasma glucose >7 mmol/L OR random plasma glucose >11.1 mmol/L, OR HBA1c >48 mmol/L.

- **T1DM** – autoimmune destruction of beta cells by CD4+ and CD8+ T-lymphocytes. May present with DKA. Insulin dependent.
- **T2DM** – strongly linked to obesity and insulin resistance.

Both give polyuria (osmotic diuresis), polydipsia (raised plasma osmolality) and hyperglycaemia (predisposes to recurrent infections).

Complications of Diabetes	
Macrovascular	**Microvascular**
Cardiac – IHD	Glomerulonephritis - Renal
PVD – Claudication, change in colour/temp, poor healing ulcers	Ulcers - Peripheral neuropathy
Cerebral – CVA	Ocular – Diabetic retinopathy

Acute Pancreatitis

Scored using GLASCOW Scale ≥3 → Severe Pancreatitis

'I GET SMASHED': Idiopathic, **G**allstones, **E**thanol, **T**rauma, **S**teroids, **M**umps, **A**utoimmune, **S**corpion venom, **H**yperlipidaemia, **E**RCP, **D**rugs e.g. thiazides
Gallstones and ethanol are most common causes

- **Presentation**: severe epigastric (or central) pain radiating to back, relieved by sitting forward, vomiting prominent
  Due to either obstruction or direct acinar injury
  NB: Amylase only transiently increased. Serum lipase is more sensitive.
- Can result in formation of pseudocyst (a pathological collection of fluid), associated with alcoholic pancreatitis or abscess.
- **Histology** – Coagulative necrosis

Patterns of damage: Periductal → necrosis of acinar cells near ducts → obstructive causes.
Perilobular → necrosis at edge of lobules → ischaemic causes.
Panlobular → combination of both.

Other complications can include shock, hypoglycaemia and hypocalcaemia as digestive enzymes react with visceral fat causing precipitation of calcium soaps **(fat necrosis)**.

Chronic Pancreatitis

- **Causes**: Alcoholism (most common), Cystic Fibrosis, hereditary, pancreatic duct obstruction e.g. stones/tumour, autoimmune (IgG4 produced by plasma cells)
- **Presentation**: epigastric pain radiating to back, malabsorption (weight loss and steatorrhoea) and secondary DM (malabsorption due to lack of enzymes to digest food)
- **Histology** – very similar to Ca pancreas – fibrosis and loss of exocrine tissue parenchyma, duct dilatation with thick secretions, calcification
- **Complications** – Pseudocysts, diabetes, pancreatic cancer

Acinar Cell Carcinoma

- Rare, older adults, see enzyme production by neoplastic cells
- **Presentation**: non-specific Sx, abdo pain, wt loss, nausea & diarrhoea. About
- 10% get multifocal fat necrosis and polyarthralgia due to lipase secretion.
- **Histopathology**: neoplastic epithelial cells with eosinophilic granular cytoplasm. Positive immunoreactivity for lipase, trypsin and chymotrypsin.
- **Prognosis**: median survival is 18 months from diagnosis. 5yr survival <10%

Gall Bladder

Gall bladder pathology mostly centred around **gallstones**.

- RFs for gallstones: Increasing age, F>M, OCP, disorders of bile metabolism.
- Most often formed of cholesterol (radiolucent) but can be formed of calcium salts (radio-opaque).

Cholelithiasis: Presence of gallstones in gall bladder (20% of adults in West).
Acute cholecystitis: Acute inflammation (90% associated with gallstones).

Chronic cholecystitis: Chronic inflammation → Fibrosis (90% associated with gallstones).
Cholangiocarcinoma: Adenocarcinomas (90% associated with gallstones).

Pancreatic Carcinoma

	Ductal adenocarcinoma of the pancreas
Epidemiology	85% of all pancreatic malignancies Average age 60yrs M>F
Site	Normally head of the pancreas
Risk Factors	Smoking, Diet Genetic e.g FAP, HNPCC
Clinical features	Weight loss (cachexia) and anorexia Upper abdominal and back pain (chronic, persistent and severe) Jaundice (painless), pruritis, steatorrhoea DM Trousseau's syndrome (25%)- recurrent superficial thrombophlebitis Ascites Abdominal mass Virchow's node Courvoisier's sign
Investigations	Bloods: ↓Hb, ↑Bili, ↑Ca^{2+} CT/MRI/ERCP CA19.9 >70IU/mL
Management	Chemotherapy is palliative (5-FU) Surgery (15% of cases): Whipple's procedure – surgical resection Prognosis v poor: 5yr survival rate <5%

Neuroendocrine Tumours (islet cell tumours)

Normally body or tail of the pancreas.
Circumscribed 1-5cm. Cells arranged in nests or trabeculae with granular cytoplasm.
May be in **MEN 1** patients (~15%). May be multiple lesions.
Unpredictable behaviour
The tumours lie on a spectrum (benign → malignant)
Functional vs. non-functional tumours:

- *Functional – present with Sx related to hormone excess*
    - Insulinoma – hypoglycaemic attacks (most common)
    - Gastrinoma – Zollinger-Ellison syndrome (high acid output): recurrent ulceration
    - Others e.g. VIPoma – diarrhoea
    - Glucagonoma – necrolytic migrating erythema
- *Non-functional* – picked up incidentally on imaging or when grow large enough to produce symptoms of local disease or metastasis

Investigations: CT/MRI - chromogranin can act as a marker

Management: Surgery

Multiple Endocrine Neoplasia (MEN)**

A group of genetic syndromes where there are functioning hormone-producing tumours in multiple organs e.g;

- MEN 1= 'PPP' - Parathyroid hyperplasia/adenoma, Pancreatic endocrine tumour (often phaeochromocytoma), Pituitary adenoma.
- MEN 2A- Parathyroid, Thyroid, Phaeochromocytoma
- MEN 2B- Medullary Thyroid, Phaeochromocytoma, Acoustic Neuroma. **Marfanoid phenotype**

Pancreatic Malformations

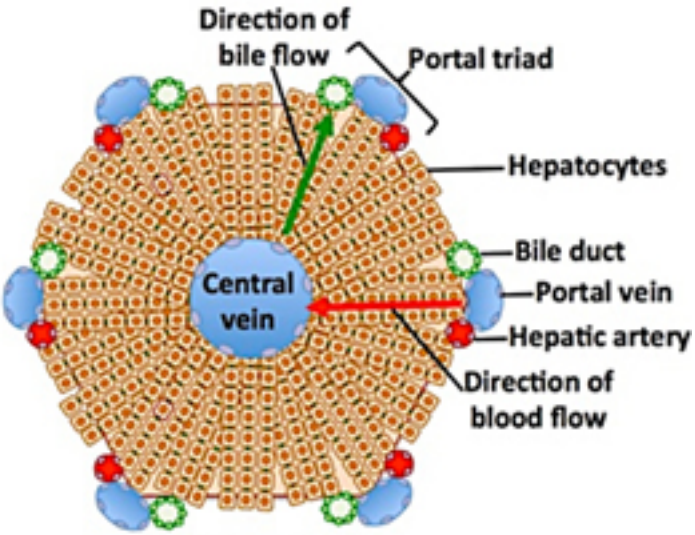
- *Ectopic Pancreas* – esp. stomach, small intestine.
- *Pancreas Divisum* – failure of fusion of dorsal and ventral buds, increased risk of pancreatitis.
- *Annular pancreas* – can present with duodenal obstruction approx. 1yo

Liver Pathology ** (RG)

Basic structural unit is the **hepatic lobule –** thought of as a hexagon. At the centre are the terminal branches of the **hepatic vein** (= **centrilobular vein**). The points of the hexagon are formed by the portal tracts, which contain 3 structures (**portal triad**): branches of the bile ducts, hepatic artery and portal vein.

The liver cells can be split into three zones:

- Zone 1 (closest to the portal triad) – **periportal hepatocytes** receive more oxygen and **affected first in viral hepatitis**
- Zone 2 – mid zone
- Zone 3 (close to terminal hepatic vein) – **perivenular hepatocytes** are the most mature and metabolically active. Zone 3 has most liver enzymes and so **most sensitive to metabolic toxins**



Classic liver lobule

Functions of the Liver:

1. **Metabolism** – involved in glycolysis, glycogen storage, glucose synthesis, amino acid synthesis, fatty acid synthesis and lipoprotein metabolism. **Drug metabolism.**
2. **Protein synthesis** – makes all circulating proteins (except gamma globulins) including albumin, fibrinogen, and coagulation factors.
3. **Storage** – glycogen, vitamins A, D and B12 in large amounts, small amounts of vitamin K, folate, iron and copper.
4. **Hormone metabolism –** Activates vitamin D. Conjugation and excretion of steroid hormones (oestrogen/glucocorticoids). Peptide hormone metabolism (insulin, GH, PTH).
5. **Bile synthesis –** 600-1000ml daily.
6. **Immune function –** antigens from gut reach liver via portal circulation. Phagocytosed by Kupffer cells.

Liver Injury

- A normal liver has hepatocytes with microvilli and stellate cells which lie quiescent in the space of Disse (space between hepatocytes and sinusoid)
- Chronic inflammation causes the loss of microvilli and activation of stellate cells, which produce collagen.
- They become myofibroblasts that initiate fibrosis by deposition of collagen in the space of Disse.
- Myofibroblasts contract constricting sinusoids and increasing vascular resistance.
- Undamaged hepatocytes regenerate in nodules between fibrous septa

Acute Hepatitis

Can either be caused by viruses (Hepatitis A to E) or by drugs.
Histopathology **- SPOTTY NECROSIS** (small foci of inflammation and infiltrates)

Chronic Hepatitis

The severity of inflammation = grade
The severity of fibrosis = stage

Can also be due to viruses (more often Hepatitis B/C) or drugs – also chronic inflammation due to e.g. PBC/PSC, Wilson's or Haemochromatosis.

Histopathology:

1. Portal Inflammation

2. Interface hepatitis (PIECEMEAL NECROSIS) – cannot see the border between the portal tract and parenchyma

3. Lobular inflammation

4. Bridging from the portal vein to central vein (critical stage in the evolution of hepatitis to cirrhosis). **This causes blood to bypass hepatocytes and reduces function of liver (intrahepatic shunting)**

Cirrhosis

Diffuse abnormality of liver architecture that interferes with blood flow and liver function.

Histopathology of a cirrhotic liver

Hepatocyte necrosis
Fibrosis
Nodules of regenerating hepatocytes
Disturbance of vascular architecture

There is a disruption of liver architecture - ↑resistance to blood flow through liver → portal hypertension. **Fibrotic bridges** form between the portal triad and central vein. **Extra hepatic shunting** occurs due to portal hypertension - results in porto-systemic (high pressure causes congestion of blood) e.g. oesophageal varices, anorectal varices and caput medusae.

The major causes of cirrhosis include:

1. **Alcoholic liver disease**
2. **Non-alcoholic fatty liver disease**
3. **Chronic viral hepatitis (hep B+/-D and C)**
4. Autoimmune hepatitis
5. Biliary causes: Primary biliary cirrhosis & Primary sclerosing cholangitis
6. Genetic causes:
    a) Haemochromatosis- HFE gene Chr 6
    b) Wilson's disease- ATP7B gene Chr 13
    c) Alpha 1 antitrypsin deficiency (A1AT)
    d) Galactosaemia
    e) Glycogen storage disease
7. Drugs e.g. methotrexate

It can also be classified according to the size of the regenerating nodules into:

MICRONODULAR (nodules < 3mm). Uniform liver involvement.

- Caused by: **alcoholic hepatitis**, biliary tract disease

MACRONODULAR (nodules > 3mm). Variable nodule size.

- Caused by: viral hepatitis, Wilson's disease, alpha1 antitrypsin deficiency

Modified Child's Pugh Score (ABCDE) - indicates prognosis in liver cirrhosis and takes into account albumin, bilirubin, prothrombin times, presence of ascites and encephalopathy.

	Score of 1	Score of 2	Score of 3
Albumin	>35	28-35	<28
Bilirubin	<34	34-50	>50
Clotting Prothrombin time	<4	4-6	>6
(Distention) Ascites	None	Mild	Moderate/severe
Encephalopathy	None	Mild	Marked

- Total Score <7 = Child's Pugh A (45% 5yr survival)
- Total Score 7-9 = Child's Pugh B (20% 5yr survival)
- Total Score 10+ = Child's Pugh C (<20% 5yr survival)

1. Alcoholic Liver Disease

Liver Disease	Macroscopic Characteristics	Microscopic Characteristics
Hepatic Steatosis (Fatty Liver)	Large, pale, yellow and greasy liver	Accumulation of fat droplets in hepatocytes (=**steatosis**) Chronic exposure → fibrosis (late stage) Fully reversible if alcohol avoided
Alcoholic hepatitis	Large, fibrotic liver	Hepatocyte **ballooning** and necrosis due to accumulation of fat, water and proteins **Mallory Denk Bodies** Fibrosis Seen acutely after night of heavy drinking. Ranges from asymptomatic to fulminant liver failure. Each episode has 10-20% mortality.
Alcoholic Cirrhosis	Yellow-tan, fatty, enlarged. Transforms into shrunken, non-fatty, brown organ.	**Micronodular cirrhosis** – i.e. small nodules + bands of fibrous tissue

2. Non-Alcoholic Fatty Liver Disease (NAFLD)

- = hepatic steatosis in non-alcoholics – histologically looks very similar to alcoholic hepatitis
- Most common cause of chronic liver disease in West

- Mainly in obese individuals with hyperlipidaemia/metabolic syndrome. Diabetes is also a risk factor.
- NAFLD includes:
    - **Simple steatosis:** fatty infiltration, relatively benign
    - **Non-alcoholic steatohepatitis (NASH)**
        - Steatosis + hepatitis (fatty infiltration + inflammation)
        - Can progress to cirrhosis

3. Viral Hepatitis: see micro section

4. Autoimmune Hepatitis

- Common with other autoimmune diseases e.g. coeliac, SLE, RA, thyroiditis, Sjögren's, UC
- 78% female– young and postmenopausal.
- Associated with HLA-DR3
- **Type 1:** ANA (antinuclear Ig), anti-SMA (anti-smooth muscle Ig), anti-actin Ig, anti- soluble liver antigen Ig
- **Type 2**: Anti-LKM Ig (anti liver-kidney-microsomal Ig)
- **Treatment**: Immune suppression until transplant, BUT disease returns in up to 40%

5. Biliary Causes of Cirrhosis

(A) Primary Biliary Cholangitis (PBC)

- Autoimmune inflammatory destruction of small/medium sized **intrahepatic bile ducts** → cholestasis → SLOW development of cirrhosis over many years
- **F > M 10:1** (associated with other AI conditions)
- Peak incidence at 40-50yrs
- ↑**serum ALP,** ↑**cholesterol**, ↑IgM, hyperbilirubinaemia (late)
- **Anti-mitochondrial antibodies** in > 90%
- US scan shows **no bile duct dilatation**
- Histology: **bile duct loss with granulomas**
- Presents with fatigue, pruritus and abdominal discomfort
- Secondary symptoms incl: skin pigmentation, xanthelasma (part. eyelid), steatorrhoea, vitamin D malabsorption, inflammatory arthropathy
- Can treat with ursodeoxycholic acid in early phase → remission in 25%

(B) Primary Sclerosing Cholangitis (PSC)

- Inflammation and obliterative **fibrosis** of **extrahepatic and intrahepatic** bile ducts → multi-focal **stricture formation** with dilation of preserved segments
- **M > F**
- Peak incidence at 40-50yrs
- **Associated with IBD** (especially UC)
- ↑ serum ALP, several associated auto-Ig, particularly **p-ANCA**
- US scan: **bile duct dilatation**
- ERCP: shows **beading of bile ducts** (due to multifocal strictures)
- Histology: **onion skinning fibrosis** – concentric fibrosis
- ↑ incidence of **cholangiocarcinoma**

Liver Tumours

Benign	Clinical Features
Hepatic adenoma	Associated with **OCP**. Present with abdo pain/ intraperitoneal bleeding. Resection if symptomatic, >5cm or if no shrinkage when stopping OCP.
Haemangioma	Most common benign lesion. No Rx.
Malignant	**Clinical Features**
Hepatocellular Carcinoma	**Causes**: Most commonly occurs in patients with chronic liver disease – closely linked with viral hepatitis, alcoholic cirrhosis, haemochromatosis, NAFLD, Aflatoxin, androgenic steroids. Screening in cirrhotic patients with 6 monthly USS. **Ix: Alpha-fetoprotein**, USS.
Cholangiocarcinoma	• **Adenocarcinomas** arising from bile ducts • 10% of liver tumours • Can be intra or extrahepatic • Poor prognosis • 90% Associated with gallstones **Causes**: Primary sclerosing cholangitis, parasitic liver disease chronic liver disease, congenital liver abnormalities, Lynch syndrome type II.
Haemangiosarcoma	Cancer of the vascular epithelium – highly invasive.
Hepatoblastoma	Occurs in children/infants – presents with abdominal mass. Originates from immature liver precursor cells.
Secondary Tumours	• **MOST COMMON** malignant liver lesion • Usually from GI tract, breast or bronchus • Usually multiple

6. GENETIC CAUSES OF CIRRHOSIS

	HAEMOCHROMATOSIS	WILSON'S DISEASE	ALPHA 1 ANTITRYPSIN DEFICIENCY
Incidence	Homozygotes 1 in 400 Heterozygotes 1 in 10 (carriers) (Caucasians)	1 in 30,0000 (v. rare)	
Age	40-50yrs	11-14yrs	
Pathophysiology	**Autosomal recessive** Mutated HFE gene at 6p21.3 → ↑Fe gut absorption which deposits in liver, heart, pancreas, adrenals, pituitary, joints, skin → fibrosis.	**Autosomal recessive** Mutated gene ATP7B (Chr 13): Encodes copper transporting ATPase expressed on canalicular membrane therefore → ↓biliary Cu excretion and deposition in liver, CNS, iris.	**Autosomal dominant** Failure to secrete A1AT in blood → A1AT accumulates in hepatocytes → intracytoplasmic inclusions → hepatitis. Lack of A1AT in lungs → emphysema.
Histology	Fe deposits in liver – stains with **Prussian blue stain**	Cu stains with **Rhodanine stain** Mallory bodies and fibrosis on microscopy	**Intracytoplasmic globules of A1AT which stain with Periodic acid Schiff**
Signs/symptoms	• **Skin bronzing** (melanin deposition) • **Diabetes** • **Hepatomegaly** with micronodular cirrhosis • Cardiomyopathy • Hypogonadism • Pseudogout	• **Liver disease**: acute hepatitis, fulminant liver failure or cirrhosis • **Neuro disease**: parkinsonism, psychosis, dementia (basal ganglia involvement) • **Kayser Fleischer rings:** copper deposits in Descemet's membrane in cornea	Kids: neonatal jaundice Adults: emphysema and chronic liver disease
Investigations	• ↑ Fe, ↑ Ferritin • Transferrin saturation > 45% • ↓ TIBC	• ↓ serum caeruloplasmin • ↓ serum copper • ↑ urinary copper	↓serum A1AT. Absent α-globulin band on electrophoresis.
Treatment	**Venesection** **Desferrioxamine** 30% with cirrhosis → HCC	Lifelong **penicillamine**. Good prognosis with early treatment but any neuro damage is permanent and may require liver transplant.	

Urological Pathology

Stones

- Form in the renal collecting ducts and can be deposited anywhere in tract
- M:F 3:1 incidence
- 3 main types
    - **Calcium Oxalate 75%***
        - Too much calcium absorption from the gut
        - Intrinsic renal problems – impaired calcium absorption from proximal tubule
    - Magnesium Ammonium Phosphate 15%
        - Triple stones
        - Commonly due to urease producing organisms which alkanise urine promoting precipitation of magnesium ammonium phosphate salts
        - Often form "**staghorn calculi**" – very large and painful
    - Uric Acid – 5%
        - In patients with hyperuricaemia (gout/rapid cell turnover)
- Common points of impaction are pelvi-ureteric junction, pelvic brim, vesico-ureteric junction

Management

- Small stones may pass spontaneously

Large stones may be removed by endoscopic or percutaneous methods or using lithotripsy

Benign Prostatic Hyperplasia (BPH)

- Dihydrotestosterone-mediated hyperplasia of prostatic stromal and epithelial cells, resulting in the formation of large nodules.
- Nodule formation compresses prostatic urethra leading to outflow tract obstruction
- **Symptoms**: difficulty urinating, retention, frequency, nocturia, overflow dribbling.
- **Histology** – nodule formation, prostatic epithelial ducts with duct spaces
- **Treatment:** TURP, 5α reductase inhibitors.

Prostate Cancer

- **Adenocarcinoma** is the commonest form in men over 50y.
- Arises from precursor lesion **PIN** (prostatic intraepithelial neoplasia).
- **Risk factors**: age, race, family history, and hormonal and environmental influences.
- Classically arises in peripheral zone of gland, and neoplastic tissue is firm.
- Local spread to the bladder and haematogenous spread to bone (pathological fractures).
- **Grading**: **Gleason system**, based on degree of differentiation and glandular patterns.
- **Diagnosis**: History, examination, PSA (over 4ng/ml is indicative).

Gleason scoring

- 1-5 based on differentiation (5 is worst – least differentiated and most aggressive)
- Take a biopsy and classify the most common pattern seen and the worst pattern seen
- Add these two numbers together to get a result out of 10
- Expressed as X+Y=Z

Testicular Tumours

Most testicular tumours are **germ cell tumours** – arising from germ cells in the testes. Commonly seen in men aged 20-45.
Maldescent of testis- In 1% of males, 90-95% in inguinal canal → 10x increase in Testicular Ca

- Most arise from a precursor lesion - **intratubular germ cell neoplasia**
- **Seminoma**: most common type of germinal tumour. Peak age: 30s. Radiosensitive.
- **Teratoma**: occur at any age from infancy to adult life. Regarded as malignant when occurs in the post-pubertal male. Chemosensitive. Biologic markers for germ cell tumours: AFP, HCG, and LDH
- **Embryonal carcinoma** – resembles embryonic tissue
- **Yolk sac tumour**
- **Choriocarcinoma**

Clinical features: painless enlargement (lump)

	GERM CELL (better prognosis)	NON GERM CELL
% of Testicular Tumours	95%	5%
Types	Seminoma, spermatocytic seminoma, embryonal carcinoma, yolk sac tumour, choriocarcinoma, teratoma	Leydig cell tumour (derived from stroma), Sertoli cell tumour (derived from sex cord)
Predisposing Factors	Cryptorchidism, testicular dysgenesis, genetic factors e.g. Kleinfelder's, testicular feminisation	

Benign Renal Tumours

	PAPILLIARY ADENOMA	ONCOCYTOMA	ANGIOMYOLIPOMA
	Renal **epithelial** tumour with a **papillary** architecture Often incidental < 15mm	Oncocytic renal **epithelial** neoplasm Often Incidental	**Mesenchymal** tumour composed of fat, bloods vessels and muscle
Histology	Bland epithelial cells growing in a papilliary or tubopapilliary pattern Well circumscribed cortical nodules	**Macroscopic** – mahogany brown **Microscopic** – sheets of oncolytic cells, pink cytoplasm, form **nests of cells**	Fat spaces, thick bloods vessels and spindle cell components

Malignant Renal Tumours

RENAL CELL CARCINOMA	NEPHROBLASTOMA /WILM'S TUMOUR	TRANSITIONAL CELL CARCINOMA

Most common – **epithelial tumour** RFs – smoking, HTN, obesity, long-term dialysis, genetics (Von Hippel Lindau syndrome) Presents with **painless haematuria**	Childhood renal neoplasm, presenting as abdominal mass 2nd most common childhood malignancy	Epithelial neoplasm arising from the urothelial tract (anywhere from renal pelvis, ureter, bladder, urethra) Most commonly in the bladder and associated with smoking. Most present with **painless haematuria**.
• **Clear Cell (70%)*** Macroscopic – golden yellow with haemorrhagic areas Microscopic – nests of epithelium with clear cytoplasm • **Papillary (15%)** Macroscopic – fragile, friable brown tumour Microscopic – papilliary/ tubopapilliary growth pattern **>15mm** • **Chromophobe (5%)** Macroscopic – well circumscribed, solid brown tumour Microscopic – sheets of large cells, distinct cell borders	**Microscopic** – 1. Small round blue cells (very undifferentiated) 2. Epithelial component – cells trying to differentiate and form primitive renal tubules	• **Non-invasive papillary** urothelial carcinoma **Frond like growths** projecting from bladder wall, often multifocal Microscopic – papilliary fronds lined by urothelium Can either be **low grade** or **high grade** (higher risk of progression to invasive) • I**nvasive urothelial carcinoma** Tumour with invasive behaviour. Usually grow as solid masses, fixed to tissue

Bladder Tumours

Transitional Cell (Urothelial) Tumours: 90% of all bladder tumours. Male: female = 3:1, and 80% occur between 50-80 years.

Squamous Cell Carcinoma: More frequent in countries with endemic urinary **schistosomiasis**.

Adenocarcinoma: Rare, arising from extensive intestinal metaplasia or from urachal remnant.

Renal Pathology

Disease of the kidney can be classified according to the part of the nephron it affects:

(1) Glomerulus

- Nephrotic syndrome:
  - Primary
    - Minimal change disease
    - Membranous glomerular disease
    - Focal segmental glomerulosclerosis
  - Secondary – e.g. **Diabetes**, amyloidosis, SLE
- Nephritic syndrome:
  - Acute post-infectious (aka Post-streptococcal)
  - IgA nephropathy (aka Berger Disease)
  - Rapidly progressive glomerulonephritis
  - Alport's syndrome (aka Hereditary nephritis)
  - Thin basement membrane disease (aka Benign familial haematuria)

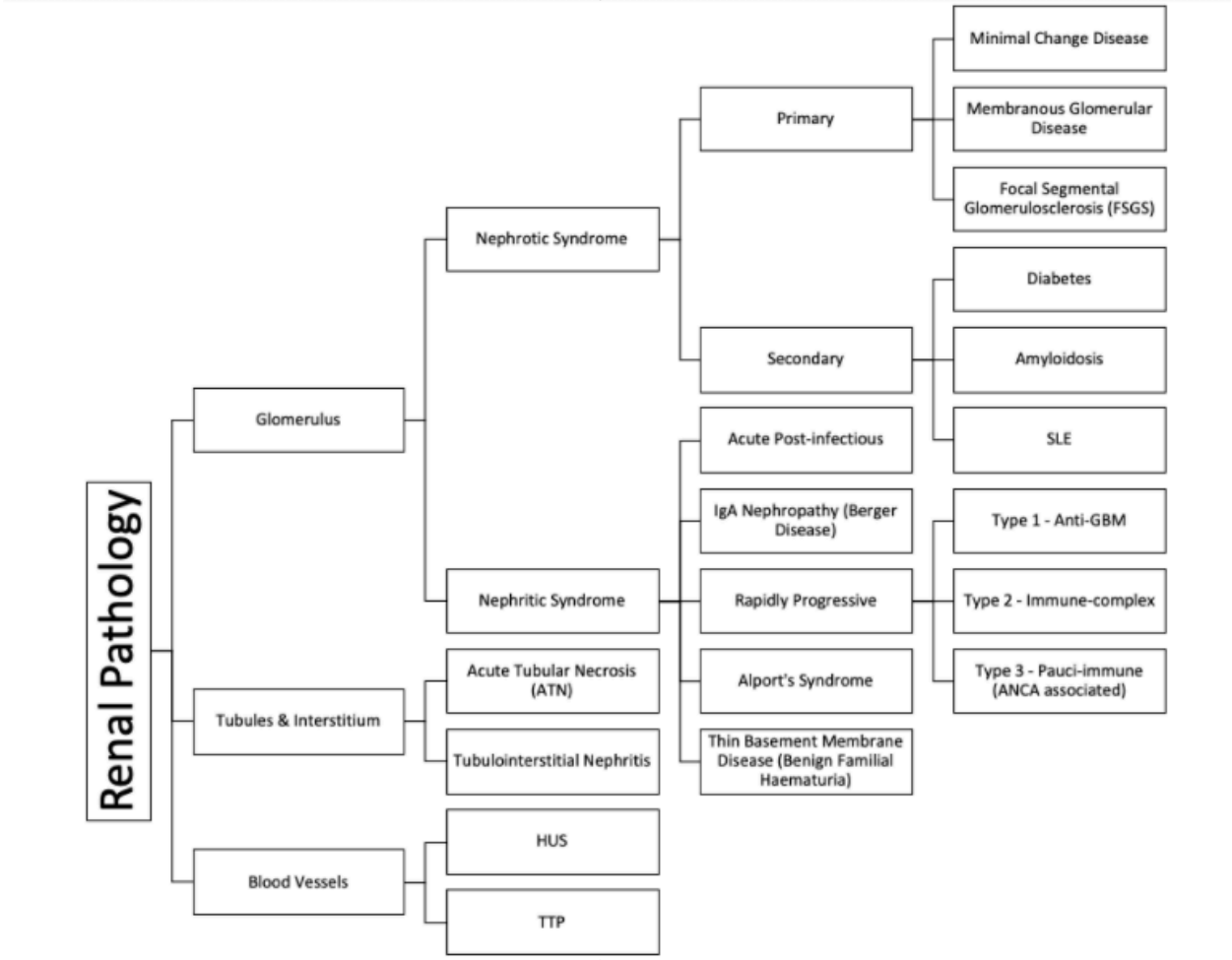
As a general rule, the glomerular vessels are very delicate and so deposition of immune complexes (which may release inflammatory substances and cause further damage) will reduce their function.

(2) Tubules & interstitium

- Acute tubular necrosis
- Tubulointerstitial nephritis

(3) Blood vessels

- Thrombotic microangiopathies (haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP))



Nephrotic Syndrome

Nephrotic syndrome is not a single disease but a constellation of features that can be caused by several renal diseases. It is characterised by the following triad:

1. Proteinuria (>3g/24h / protein:creatinine ratio >300mg/mmol)
2. Hypoalbuminaemia (<30 g/L)
3. Oedema

Other features: hyperlipidaemia, thrombotic disease

Key words in SBAs:

- Swelling (classically periorbital in children)
- Frothy urine (occurs due to proteinuria)

PRIMARY causes of Nephrotic Syndrome

	Minimal change disease	Membranous glomerular disease	Focal Segmental Glomerulosclerosis (FSGS)
Epidemiology	Most common in children (75% cases) with second peak in elderly	Common in adults (~30%)	Common in adults (~30%) Most common in Afro-Caribbean people
Light microscopy	**No changes**	Diffuse glomerular basement membrane thickening	**Focal** and **segmental** glomerular consolidation and scarring, Hyalinosis
Electron Microscopy	Loss of podocyte foot processes	Loss of podocyte foot processes, Subepithelial deposits = 'spikey'	Loss of podocyte foot processes
Immunofluorescence	No immune deposits	Immune complex deposits along **entire GBM**	No immune deposits
Response to steroids	90% respond	Poor	50% respond
Prognosis	< 5% ESRF	40% ESRF after 2-20 yrs	50% ESRF in 10 yrs
Miscellaneous	Possible trigger – recent allergic reaction Associations: eczema, asthma	Can be 1° or 2° to **SLE**, infection, drugs and malignancy. Antibodies against Phospholipase A2 are present in 75%.	**1°** but can be 2° to **obesity**, HIV, drugs (lithium, heroin), lymphoma
Management	Steroids = 1st line Cyclosporin = 2nd line	Steroids ACEi/ARB to control BP	Steroids ACEi/ARB to control BP Calcineurinin inhibitors = 2nd line

SECONDARY causes of Nephrotic Syndrome

	Diabetes	Amyloidosis
Histology	Diffuse glomerular basement membrane thickening Mesangial matrix nodules – aka **Kimmelstiel Wilson nodules**	**Apple green birefringence** with Congo red stain
Other key points	• Classically found in Asians • First presents with microalbuminuria	• **AA (acute phase protein) amyloidosis**: associated with chronic inflammation e.g. rheumatoid arthritis, chronic infections (TB) • **AL (light chain) amyloidosis:** most common from multiple myeloma • Clinical clues of amyloidosis - Macroglossia, heart failure, hepatomegaly

Diagnosis of Nephrotic Syndrome:

- Urine dip – proteinuria, NO haematuria
- Urine PCR - >300mg/mmol
- Serum albumin – low
- Total cholesterol – high
- Immunoglobulins – low
- Renal biopsy – diagnostic investigation of choice in adults (avoided in children)

Nephritic Syndrome

A manifestation of glomerular inflammation (i.e. glomerulonephritis (GN))

Syndrome characterised by: PHAROH

- **Proteinuria** (less than nephrotic syndrome)
- **Haematuria** (coke-coloured urine)
- **Azootemia** – (high urea and creatinine)
- **Red Cell Casts** (in urine – these are red cells that have clumped together & have leaked out into the tubules)
- **Oliguria**
- **Hypertension**

Causes of Nephritic Syndrome

1. . ACUTE POSTINFECTIOUS (POST STREPTOCOCCAL) GLOMERULONEPHRITIS

- Occurs 1-3 weeks after **streptococcal throat infection** or **impetigo** (usually Lancefield Group A α-haemolytic strep = *Strep. pyogenes*).
- Glomerular damage thought to be due to **immune complex deposition**
- Haematuria (red cells casts), proteinuria, oedema, HTN
- **Bloods:** ASOT titre ↑, C3 ↓*
- **Biopsy:**
  - Light microscope (LM): ↑cellularity of glomeruli
  - Fluorescence Microscope (FM): **granular deposits of IgG** and C3 in GBM
  - Electron Microscope (EM): **Subendothelial humps**
- **Management:** Supportive

2. IgA NEPHROPATHY (BERGER DISEASE)

- Commonest GN worldwide

- More common in patients of East / South Asian descent
- Deposition of IgA immune complexes in glomeruli
- Presents **1-2 days** (earlier than Acute postinfectious GN!) after an **URTI** with **frank haematuria***
- Main symptoms are persistent or recurrent frank haematuria, or asymptomatic microscopic haematuria. Other symptoms of nephritic syndrome are not prominent.
- Can present with an associated vasculitic rash
- Can progress to ESRF
- Bloods: ↑IgA
- Biopsy: immunofluorescence shows granular deposition of IgA and C3 in mesangium
- Rule of thirds: 1/3rd are asymptomatic, 1/3rd develop CKD, 1/3rd develop progressive CKD requiring dialysis / transplantation

3. RAPIDLY PROGRESSIVE (CRESCENTIC) GN – More severe

- **Most aggressive form of GN** – can cause ESRF within weeks.
- Presents as a nephritic syndrome, but **oliguria and renal failure are more pronounced**
- Classification based on immunological findings:
  - **Type 1**: Anti-GBM antibody (aka Goodpasture's disease)
  - **Type 2**: Immune complex mediated
  - **Type 3**: Pauci-immune / ANCA-associated
- Regardless of cause, all are **characterised by presence of crescents** in glomeruli
- NOTE: crescents = proliferation of macrophages & parietal cells in Bowman's space which pushes glomerulus to one side

	TYPE 1	TYPE 2	TYPE 3
Pathogenesis	**Anti-GBM antibody** against COL4-A3 (collagen type IV)	**Immune complex** mediated	Pauci-immune **i.e. lack of anti-GBM or immune complex**
Causes	**Goodpasture's syndrome**. HLA-DRB1 association	**SLE, IgA nephropathy, post infectious GN, HSP, Alport's syndrome**	c-ANCA: **Wegener's granulomatosis** p-ANCA: **Microscopic polyangiitis**
Light microscopy	**Crescents**	**Crescents**	**Crescents**
Fluorescence microscopy	**Linear** deposition of IgG in GBM	**Granular** (lumpy bumpy) IgG immune complex deposition on GBM/mesangium	**Lack** of/scanty immune complex deposition
Additional organ involvement	**Lungs** – pulmonary haemorrhage	Often limited (except in SLE)	**Vasculitis –** particularly presenting as skin rashes or pulmonary haemorrhage

4. HEREDITARY NEPHRITIS (ALPORT'S SYNDROME)

- Hereditary glomerular disease caused by mutation in **type IV collagen alpha 5 chain**
- **X linked**
- Nephritic syndrome + **sensorineural deafness** + **eye disorders** (lens dislocation, cataracts)
- Presents at 5-20yrs with nephritic syndrome progressing to ESRF

5. THIN BASEMENT MEMBRANE DISEASE (BENIGN FAMILIAL HAEMATURIA)

- VERY RARELY A CAUSE OF NEPHRITIC SYNDROME – normally exclusively causes an asymptomatic haematuria rather than nephritic syndrome
- Diffuse thinning of GBM caused by mutation in **type IV collagen alpha 4 chain**
- **Autosomal dominant**
- Quite common – prevalence is ~5%
- Usually asymptomatic – incidentally diagnosed with microscopic haematuria
- Renal function usually normal
- Excellent prognosis

Asymptomatic Haematuria

If this appears in an SBA – the differentials include:

1. THIN BASEMENT MEMBRANE DISEASE (Benign familial haematuria)
2. IgA NEPHROPATHY (Berger disease)
3. ALPORT SYNDROME

IgA and Thin basement membrane are more common causes of asymptomatic haematuria than of nephritic syndrome. Differentiation between thin basement membrane and IgA is clinically difficult. If there are no histological findings included in the questions clinical differences include IgA being more likely to cause frank haematuria, more likely to cause a change in renal function Cr raised) and slightly more common in the Asian population.

Acute Tubular Injury (ATI) aka Acute Tubular Necrosis (ATN)

Damage to tubular epithelial cells → cells shed and block of tubules as casts → reduced flow and increased haemodynamic pressure in nephron → reduced pressure gradient across BM → acute renal failure → tubular glomerular feedback reduces blood supply to kidneys further.

Most common cause of acute renal failure.

Causes include:

- Hypovolaemia → Pre-renal ARF → Ischaemia of nephrons (EMQ: cured hypovolaemia but persistent ARF).
- Nephrotoxins – drugs (aminoglycosides, NSAIDs), radiographic contrast agents, myoglobin (e.g. secondary to rhabdomyolysis), heavy metals.

Histopathology: Necrosis of short segments of tubules.

Tubulointerstitial Nephritis

A group of renal inflammatory disorders that involve the tubules and interstitium

Acute pyelonephritis:

- Bacterial infection of the kidney, usually a result of ascending infection, most commonly caused by *E. coli*
- Presents with fever, chills, sweats, flank pain, renal angle tenderness and leukocytosis +/- frequency, dysuria and haematuria
- Leukocytic casts are seen in the urine

Chronic pyelonephritis and reflux nephropathy:

- Chronic inflammation and scarring of the parenchyma caused by recurrent and persistent bacterial infection
- Can be due to:
    - Chronic obstruction – posterior urethral valves, renal calculi
    - Urine reflux (= reflux nephropathy)

Acute interstitial nephritis:

- A hypersensitivity reaction, usually to a drug (abx, NSAIDs, diuretics)
- Usually begins days after drug exposure
- Presents with: fever, skin rash, haematuria, proteinuria, eosinophilia
- Histology: inflammatory infiltrate with tubular injury, eosinophils & granulomas

Chronic interstitial nephritis / Analgesic nephropathy:

- Seen in elderly with long-term analgesic consumption (NSAIDs/paracetamol)
- Symptoms only occur late in disease: HTN, anaemia, proteinuria and haematuria

Thrombotic Microangiopathies

	HUS	TTP
Epidemiology	Usually affects children	Usually affects adults
Characterised by	TRIAD: • MAHA • Thrombocytopenia • Renal failure	PENTAD: • MAHA • Thrombocytopenia • Renal failure • Fever • **Neurological Sx** e.g. confusion, seizures
Pathophysiology	Usually associated with diarrhoea caused by *E.coli* O157:H7 with outbreaks caused by children visiting petting zoos/eating undercooked meat. Can be 'non-diarrhoea associated' due to abnormal proteins in complement pathway/endothelium – can be familial. **Thrombi confined to kidneys.**	A genetic / acquired deficiency of **ADAMTS13** (ADAMTS13 usually cleaves vWF; deficiency → formation of giant vWF multimers → platelet aggregation & fibrin deposition) . **Thrombi occur throughout circulatio**n, esp. in CNS.
Signs/symptoms (both)	↓plt → bleeding (petechiae, haematemesis, melena). MAHA → pallor and jaundice.	
	Usually involves **renal failure**	Usually no renal failure. **Neuro symptoms** (headache, altered

		consciousness, seizures, coma)
Diagnosis (both)	● ↓Hb ↓plt ● Signs of haemolysis: ↑bilirubin, ↑reticulocytes, ↑LDH ● Fragmented RBCs (**schistocytes**) on blood smear as RBCs sheared as they pass through clots ● Coomb's test negative (as not AIHA)	

Acute Renal Failure

A rapid loss of renal function manifesting as **increased serum creatinine and urea**. Complications include metabolic acidosis, hyperkalaemia, fluid overload, HTN, ↓Ca^{2+} and uraemia

1. PRE-RENAL

- Most common cause of acute renal failure
- Caused by renal hypo-perfusion e.g. hypovolaemia, sepsis, burns, acute pancreatitis, and renal artery stenosis.

2. RENAL

- Acute Tubular Necrosis (ATN): commonest renal cause of ARF.
- Acute glomerulonephritis.
- Thrombotic microangiopathy.

3. POST-RENAL

- Obstruction to urine flow as a result of stones, tumours (primary & secondary), prostatic hypertrophy and retroperitoneal fibrosis

Chronic Renal Failure

Progressive, irreversible loss of renal function characterized by prolonged symptoms and signs of uraemia (fatigue, itching, anorexia and if severe eventually confusion).

Commonest causes in the UK;

- Diabetes (20%)
- Glomerulonephritis (15%)
- Hypertension & Vascular disease (15%)
- Reflux nephropathy (chronic pyelonephritis) (10%)
- Polycystic kidney disease (9%)

Classified into 5 stages by GFR*:

Stage	Description	GFR
1	Kidney damage with normal renal function (often proteinuria)	>90
2	Mildly impaired	60-89
3	Moderately impaired	30-59
4	Severely impaired	15-29
5	Renal failure (generally requires replacement therapy)	<15 (or if being treated with renal replacement therapy)

Adult Polycystic Kidney Disease (APCKD)

- PKD is a part of a heterogenous group of disorders characterised by renal cysts and numerous systemic extra-renal manifestations
- **Autosomal dominant inheritance**. 85% due to mutations in **PKD1** on chromosome 16 (encoding polycystin-1), 15% due to mutations in **PKD2** on chromosome 4 (encoding polycystin-2)
- Accounts for 10% of cases of CKD; 2/3rds require renal replacement therapy
- **Pathologic features**: large multicystic kidneys with destroyed renal parenchyma, liver cysts (in PKD1) and **berry aneurysms** (berry aneurysms → SAH + hypertension)
- **Clinical features**: MISHAPES
    - Abdominal **M**ass
    - **I**nfected cysts & increased BP

    - **S**tones
    - **H**aematuria
    - **A**neurysms (Berry)
    - **P**olyuria & nocturia
    - **E**xtra-renal cysts e.g. liver, ovaries, pancreas, seminal vesicles
    - **S**ystolic murmur – due to mitral valve prolapse
- Diagnostic criteria via USS of kidneys is age-specific:
    - 15-39 – 3 or more cysts
    - 40-59 - >2 cysts in each kidney
    - >60 – 4 cysts in each kidney
- RRT is the mainstay of treatment

Lupus Nephritis

Depending on site and intensity of immune complex deposition clinical presentation may be: isolated urinary abnormalities, acute renal failure, nephrotic syndrome or progressive chronic renal failure.

Renal Histology: Immune complex deposition in capillaries → **'wire loop capillaries'**, deposition of immune complexes & complement in the GBM in a **lumpy-bumpy granular fashion**.

Class 1: Minimal mesangial disease, looks near normal on light microscopy
Class 2: Mesangial proliferative disease
Class 3: Focal subendothelial deposits
Class 4: Diffuse subendothelial deposits
Class 5: Subepithelial immune deposits (membranous disease)
Class 6: Advanced sclerosis **(>90%)***

Renal Cell Carcinoma

Types:
- Clear cell carcinoma – well differentiated
- Papillary carcinoma – commonest in dialysis-associated cystic disease
- Chromophobe renal carcinoma – pale, eosinophilic cells

Risk factors: Smoking, obesity, HTN, unopposed oestrogen, heavy metals, CKD

Clinical features: Costovertebral pain, palpable mass, haematuria
Paraneoplastic syndrome: Polycythaemia, hypercalcaemia, HTN, Cushing's syndrome, amyloidosis

Gynaecological Pathology

Massive cross-over with O&G. Pathology exam focussed more on diagnosis. Speciality paper focussed more on investigations and management.

Pelvic Inflammatory Disease (PID / Salpingitis)

Infection ascending from vagina and cervix up to uterus and Fallopian tubes, leading to inflammation (endometritis, salpingitis) and the formation of adhesions.

1. Ascending bacteria from lower genital tract - ***Neisseria gonorrhoea, Chlamydia trachomatis, enteric bacteria***
2. Secondary to abortion/termination of pregnancy – ***S. aureus, Streptococcus, C. perfringens, Coliforms***

C. trachomatis and ***N. gonorrhoea*** are most common organisms in UK.

TB and ***schistosomiasis*** are common causes in other parts of the world.

Clinically: bilateral lower abdo pain, deep dyspareunia, vaginal bleeding/discharge, fever, adnexal tenderness, and cervical excitation

Complications:

- 10% have Fitz Hugh Curtis syndrome – RUQ pain from peri-hepatitis + "violin-string" peri-hepatic adhesions **[BUZZWORD]**
- Infertility
- ↑Risk of ectopic pregnancy
- Bacteraemia → SEPSIS
- Tubo-ovarian abscess
- Chronic PID
- Peritonitis
- Plical fusion – fimbrial ends of fallopian tubes adhere together

Endometriosis

Presence of endometrial glands or stroma in abnormal locations **outside the uterus** e.g. ovaries, uterine ligaments, rectovaginal septum, Pouch of Douglas, pelvic peritoneum

3 theories of aetiology:

1. Regurgitant/implantation from retrograde menstrual flow of endometrial cells;
2. Metaplastic transformation of coelomic epithelial cells;
3. Vascular or lymphatic dissemination of endometrial cells

Clinically:

- Cyclical pelvic pain, dysmenorrhoea, deep dyspareunia, ↓fertility
- Cyclical PR bleeding, haematuria, bleeding from umbilicus (depending on site of endometrial deposits)
- Nodules/tenderness in vagina, posterior fornix or uterus; immobile and retroverted uterus in advanced disease

Macroscopically:

- Red-blue to brown vesicles - "powder burns" **[BUZZWORD]**
- Endometriomas = blood-filled "chocolate cysts" on ovaries **[BUZZWORD]**

Microscopically: endometrial glands and stroma

Adenomyosis

Similar to endometriosis; presence of ectopic endometrial tissue deep within the **myometrium**

Clinically: heavy menstrual bleeding, dysmenorrhoea, and deep dyspareunia.

BUZZWORDS: "Bulky uterus", "Subendothelial linear striations", "Globular uterus".

Leiomyoma (fibroid)

A benign tumour of **smooth muscle origin**
Most common tumour of female genital tract – occurring in 20% of women >35
Can occur **intramural**, **submucosal** or **subserosal**.
Oestrogen stimulation important: enlarge during pregnancy, regress post-menopause

Macroscopically:

- Sharply circumscribed, discrete, round, firm, gray-white tumours. Size variable.

Microscopically:

- Bundles of smooth muscle cells

Clinically:

- Heavy menstrual bleeding, dysmenorrhoea, pressure effects (urinary frequency, tenesmus)
- Subfertility
- In pregnancy: red degeneration of fibroids (haemorrhagic infarction → severe abdo pain), post-partum torsion

Benign to malignant transformation is rare (leiomyosarcoma)
Leiomyosarcomas likely arise de novo, usually occurring in post-menopausal women.

Endometrial Carcinoma

Postmenopausal bleeding is endometrial cancer until proven otherwise
Adenocarcinomas (85%), squamous cell carcinoma (15%)

Subdivided into:

- ENDOMETRIOID – 80% (i.e. look similar to normal endometrial glands)
  - Types: Secretory, endometriod (PTEN mutation in > 50%), mucinous
  - Pathophysiology: **related to oestrogen excess** – usually in peri-menopausal women
  - Risk factors:
    - E2 excess: obesity, anovulatory amenorrhoea (e.g. PCOS), nulliparity, early menarche, late menopause, tamoxifen
    - DM, HTN
- NON-ENDOMETRIOID – 20%
  - Types: Papillary, serous (P53 mut. in 90%) and clear cell (PTEN mut., P53 mut., HER-2 amplifications).
  - Pathophysiology: **unrelated to estrogen excess** – usually in elderly women with endometrial atrophy

Staged with **FIGO** system:

1. Stage 1 – Cancer ONLY in uterus
2. Stage 2 – spread to CERVIX
3. Stage 3 – spread to PELVIC AREA
4. Stage 4 – METASTASIS to rectum/bladder/distal organs

Vulval Intraepithelial Neoplasia (VIN) and Vulval Carcinoma

Normal vulval histology: squamous epithelium (95%)

VIN (similar to CIN) – dysplasia of epithelium

Graded as VIN 1, II and III

Usual type – associated with HPV16/18, smoking and immunosuppression
- Warty, basaloid, mixed
- Women aged 35-55

Differentiated type – associated with lichen sclerosis and more common progression to cancer:
- Keratinised squamous cells
- Older women

Vulval Carcinoma

Mainly squamous cell carcinoma;
Clear cell adenocarcinoma – teenagers, rare, associated with Diethyltilbestrol
Primary vaginal carcinoma – older women usual squamous cell carcinoma

Ovarian Cysts

Follicular cyst – most common
- Due to non-rupture of the dominant follicle/failure of atresia in a non-dominant follicle
- Commonly regress after several menstrual cycles

Corpus luteal – common in early pregnancy
- During the menstrual cycle if fertilisation doesn't occur the corpus luteum breaks down and disappears. If this doesn't happen the corpus luteum may become filled with blood or fluid and become a corpus luteal cyst
- May present with intraperitoneal bleeds

Ovarian Carcinoma**

- Leading cause of death from gynaecological malignancy in the UK
- Ovary is a collection of several different cell types each of which can have neoplastic development – 90% are epithelial ovarian cancers
- Peak incidence is in women aged 75-84 years

Subdivided according to the cell type from which they arise:

		Subtypes	Characteristics
Epithelial (70%)	Benign	Serous cystadenoma	**Most common** benign epithelial tumour Mimics tubal epithelium i.e. columnar epithelium **Histology: columnar epithelium, Psammoma bodies** [BUZZWORDS] Affects women aged 30-40yrs
		Mucinous cystadenoma	**2nd most common** benign epithelial tumour Mucin secreting cells, similar to those of endocervical mucosa. **Histology: mucin secreting cells [BUZZWORD]** Most common oestrogen-secreting tumour Affects younger women

			K-ras mutation in 75% Appendix tumour → metastasis to abdomen, peritoneum and ovaries → **pseudomyxoma peritonei** (very rare complication)
	Malignant	Endometrioid	Mimics endometrium – i.e. form tubular glands (therefore endometriosis is a risk factor) **Histology: tubular glands [BUZZWORD]** Ca125 often raised
		Clear cell	**Histology: clear cells, clear cytoplasm, Hobnail appearance** Strong association with endometriosis
Germ cell (20%)	Usually benign in adults (95%) and malignant in children	Dysgerminoma	Female counterpart of **testicular seminoma** Rare, but the most common ovarian malignancy in young women Sensitive to radiotherapy
	Most common ovarian tumours in younger women (15-21 yo)	Teratoma	Shows differentiation toward somatic structures **Mature teratomas (dermoid cyst) 95% of teratomas**: **Benign**; usually **cystic**; Differentiation of germ cells into **mature tissues** (e.g. skin, hair, teeth, bone, cartilage); usually bilateral and asymptomatic. **Immature teratomas:** **Malignant**, usually **solid**; Contains **immature, embryonal** tissues Secrete AFP
		Choriocarcinoma	Secrete **hCG** **malignant**
Sex cord/ stroma (10%)	Can differentiate toward female (granulosa and theca cells) or male (Sertoli and Leydig cells) structures	Fibroma (from cells of ovarian stroma)	**No hormone production** 50% associated with **Meig's** syndrome (triad of fibroma, ascites + right-sided pleural effusion)
		Granulosa-Theca cell tumour	**Produce E2** Look for oestrogenic effects – irregular menstrual cycles, breast enlargement, endometrial/breast cancer **Histology: Call-Exner bodies [BUZZWORD]**
		Sertoli-Leydig	**Secrete androgens**

		cell tumour	Look for defeminisation (breast atrophy) and virilisation (hirsutism, deepened voice, enlarged clitoris)
Metastatic		Krukenberg tumour	Malignancy of the ovary that has metastasised from usually gastric / colonic cancer **Histology: Mucin producing signet ring cells [BUZZWORD]**

FIGO staging

- Stage I: ONLY in ovaries
- Stage II: spread to PELVIS
- Stage III: spread to ABDOMEN (including regional LN metastases)
- Stage IV: METASTASIS outside abdominal cavity

Cervical Intraepithelial Neoplasia (CIN) and Cervical Glandular Intraepithelial Neoplasia (CGIN)

Normal cervical histology:

Outer cervix (continuous with vagina) covered by squamous epithelium; endocervical canal lined by columnar glandular epithelium. **The squamocolumnar junction (SCJ)** separates them.

Transformation zone (TZ): the area where columnar epithelium transforms into squamous cells (=squamous metaplasia). This is a normal physiological process. This area is susceptible to malignant change due to high rates of cell turnover

CIN: Dysplasia at the TZ as a result of infection by *HPV 16 & 18*.

Graded mild, moderate or severe dyskaryosis on **cytology**, but graded CIN 1-3 on **histology** (from biopsy**)**.

- CIN 1 = dysplasia confined to deepest 1/3 of epithelium
- CIN 2 = lower 2/3
- CIN 3 = full thickness, but basement membrane intact

60-90% of CIN 1 reverts to normal over 10-23 months
30% of CIN 3 progress to cervical cancer over 10 years if left untreated

Risk Factors:

Early age at first intercourse, multiple partners, multiparity, smoking, HIV or immunosuppression

CGIN (cervical glandular intraepithelial neoplasia): less common and more difficult to diagnose on cytology. Treatment requires excision of entire endocervix which can compromise fertility.

Cervical Carcinoma

2nd most common cancer in women worldwide; 2 peaks in incidence: 30-39 years and >70 years
80% Adenocarcinomas, 20% Squamous cell carcinomas
Arises from CIN – invasion through the basement membrane marks the change from CIN 3 to carcinoma

RFs:

- Early exposure to HPV
  - Early first sexual experience
  - Multiple partners
  - Non-barrier contraceptive

- COCP
- High parity
- Smoking (dose-response effect)
- Immunosuppression

There are 2 biological states of HPV infection:

I. Non-productive/latent
II. Productive → cytological and histological changes

Pathophysiology of HPV causing cervical carcinoma:

- HPV virus encodes E6 and E7 proteins which inactivate 2 tumour suppressor genes (TSGs):
- E6 inactivates P53 → proliferation
- E7 inactivates Retinoblastoma (Rb) gene → proliferation

Clinically: post-coital bleeding, intermenstrual bleeding, postmenopausal bleeding, discharge, pain.

Staged using **FIGO system**

- Stage 0: CIN
- Stage I: ONLY
- Stage II: spread into UPPER 1/3 VAGINA
- Stage III: spread into PELVIC SIDE WALL and/or LOWER 1/3 VAGINA Stage IV: METASTASIS beyond pelvis to bladder/bowel

Breast Pathology

Majority of the lesions are benign and common presenting symptoms include pain (mastalgia/ mastodynia), palpable masses and/or nipple discharge.

Triple assessment comprises:

1. Clinical Examination
2. Imaging – USS/mammography
3. Cytology and histology –

- **Cytopathology (obtained via fine needle aspiration (FNA))** – cells spread across a slide, stained and Coded from C1 (inadequate sample), C2 (benign), C3 (atypia), C4 (suspicious of malignancy) to C5 (malignant)

- **Histopathology (obtained via core biopsy)** – intact tissues removed showing architectural and cellular detail and coded B1 (normal), B2 (benign), B3 (uncertain), B4 (suspicious) to B5 (malignant). B5a = DCIS, B5b = invasive carcinoma

    - NOTE: histopathology = gold-standard for diagnosis of breast cancer. Normal breast histology is a **ductal-lobular system** lined by inner **glandular epithelium**

Inflammatory Conditions

1. **Acute Mastitis****

- Presentation: painful, red breast, hot to touch and fever
- Either lactational (more common) or non-lactational
- **Lactational** is usually secondary to ***S. aureus*** **infection (often polymicrobial)** via cracks in the nipple & due to stasis of milk

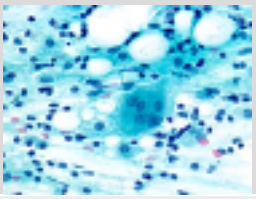
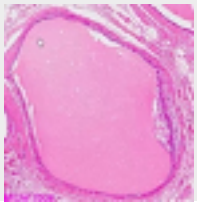
- **FNA cytology** shows an abundance of neutrophils **[BUZZWORD]**
- Tx: continued expression of milk + antibiotics +/- surgical drainage
- Non-lactational – **keratinising squamous metaplasia** block lactiferous ducts leading to peri-ductal inflammation and rupture.

2. Fat Necrosis

- Inflammatory reaction to damaged adipose tissue (typically obese, middle-aged women).
- Presents as **painless** breast mass/skin thickening/mammographic lesion (may mimic carcinoma displaying skin tethering/nipple retraction)
- Causes – trauma, radiotherapy, surgery, nodular panniculitis
- **Cytology** – empty fat spaces , histiocytes and giant cells **[BUZZWORDS]**

Benign Neoplastic Conditions**

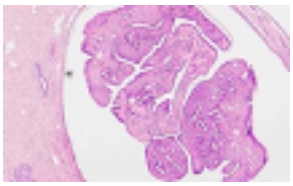
	Fibroadenoma	Breast cyst	Duct ectasia
Definition	Benign neoplasm of a lobule; arising from fibro (stromal) and glandular (adenomal) epithelium	Fluid filled sacs in the breast	Dilatation of milk ducts due to blockage
Epidemiology	**MOST COMMON LUMP IN WOMEN** 20-40yrs	Peri-menopausal (50yrs)	Peri/post-menopausal Risk factors: SMOKING, multiparity
Site-size	Single unilateral 1-5cm May be bilateral and multiple (RARE) Vary in size during pregnancy & menstrual cycles as they are oestrogen driven	Single or multiple Unilateral or bilateral Pain correlates with menstrual cycle	Sub-areolar mass Nipple inversion
Colour-consistency	Well demarcated, spherical, firm, smooth, rubbery	Well demarcated, clear nipple discharge	Firm, thick yellow-green-white nipple discharge. May lead to local infection if ducts get infected → **inflammatory symptoms and abscess formation**
Tender-transilluminable	Painless	Painless Transilluminable	Tender
Fluctuance-fixed	Mobile "Breast mouse" **[BUZZWORD]**	Fluctuant/mobile	Fixed
Cytology	FNA cytology – branching sheets of epithelium, bare bipolar nuclei and stroma		Nipple discharge – proteinaceous material and macrophages **[BUZZWORDS]**

			
Histology	Multinodular mass of expanded intralobular stroma		Duct dilatation, periductal inflammation, proteinaceous material in side the duct 

Others:

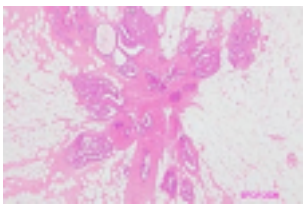
1. **Intraductal Papilloma**

- Benign papillary tumour arising within the duct system of the breast.
  - Small terminal ductules → peripheral papillomas → clinically silent
  - Larger lactiferous ducts → central papillomas → nipple discharge
- Clinically presents with a sub-areolar mass +/- bloody nipple discharge
- Not seen on mammogram.
- **Cytology of nipple discharge** – branching papillary groups of epithelium
- **Histology** – papillary mass within a dilated duct lined by epithelium **[BUZZWORDS]**



2. **Radial Scar**

- Benign sclerosing lesion – central scarring surrounded by proliferating glandular tissue in stellate pattern.
- Usually presents as a **stellate mass** on mammography, closely mimicking carcinoma
  - Lesions >1 cm are sometimes called "complex sclerosing lesions".
- **Histology** – central, fibrous, stellate area **[BUZZWORDS]**

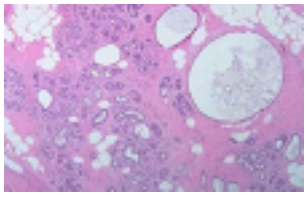


3. **Phyllodes Tumour**

- Arise from interlobular **stroma** (like fibroadenomas – can arise within existing fibroadenomas) with increased cellularity and mitoses.
- Present >50yrs as palpable mass
- Low grade or high grade lesions. Mostly relatively benign, but can be aggressive therefore excised with wide local excision/mastectomy to limit local recurrence.
- Mets very rare
- **Histology:** "branching"/"leaf-like fronds"/"artichoke appearance" [**BUZZWORDS]**

4. **Fibrocystic Disease**

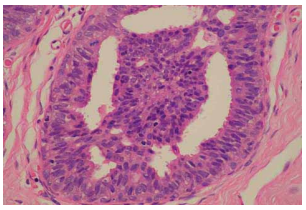
- Presentation: changes according to menstrual cycle (hormone responsive), lumpiness in breasts
- Occurs in 1/3rd of pre-menopausal women
- **Histology** – dilated large ducts which may become calcified **[BUZZWORDS]**



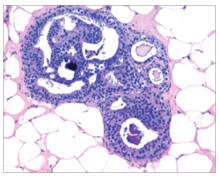
Proliferative Conditions

A diverse group of intraductal epithelial proliferations, associated with varying risks of developing invasive breast carcinoma.

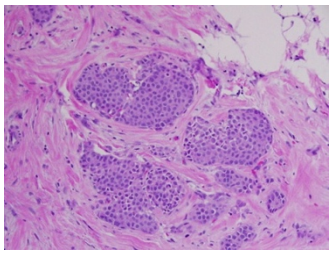
1. **Usual epithelial hyperplasia**
   - Not formally considered a precursor lesion to invasive breast carcinoma although slightly 1-2% increased risk of carcinoma
   - **Histology:** Growth of glandular tissue and epithelial cells forming **fronds**



2. **Flat epithelial atypia a.k.a. atypical ductal carcinoma**
   - 4x risk of developing carcinoma
   - **Histology:** Multiple layers of epithelial cells and lumens more regular and round with punched out areas



3. **In situ lobular neoplasia**
   - 7-12x risk for developing breast carcinoma
   - **Histology:** solid proliferation of aplastic cells with little space with small residue areas where you can still see lumen



Malignant Neoplastic Conditions**

Breast Carcinoma

- Incidence: most common cancer in women, lifetime risk 1 in 8
- Age: 75-80yrs, (younger in Afro-Caribbean's). Sex: 99% in women.
- Risk factors:
  - **Gender**
  - **Susceptibility genes** (12%) – BRCA1/BRCA2, also increased risk of ovarian, prostate and pancreatic malignancy. BRCA mutations cause a lifetime risk of invasive breast carcinoma of up to 85%.
  - **Hormone exposure** – early menarche, late menopause, late 1st live birth (pregnancy → terminal differentiation of milk-producing luminal cells, removing these from pool of potential cancer precursors), OCP/HRT
  - **Advancing age**
  - **Family history**
  - **Race** (Caucasian>Afro-Caribbean>Asian>Hispanic)
  - **Obesity, tobacco, alcohol, radiation exposure**
- Screening: 47 to 73yr old women invited every 3 years for mammography (looks for abnormal areas of calcification or a mass within the breast)
- **Non-invasive** – Ductal carcinoma in situ (DCIS)
- **Invasive** – invasive ductal carcinoma, invasive lobular carcinoma, Paget's disease of the breast

Carcinoma in situ (20%)

- Neoplastic epithelial proliferation limited to ducts/lobules by basement membrane
- **Lobular (LCIS)** – ALWAYS incidental finding on biopsy as no microcalcifications or stromal reactions. 20-40% bilateral. Cells lack adhesion protein E-cadherin. RF for subsequent invasive breast carcinoma.
- **Ductal (DCIS)** – incidence increased dramatically since development of mammography. Appear as areas of microcalcification. 10% present with clinical symptoms. Much increased risk of progressing to invasive breast Ca. High, intermediate and low grade
- Histology **– ducts filled with atypical epithelial cells**
- Inherent but not inevitable risk of progression to invasive breast carcinoma

Invasive breast carcinoma (80%) – malignant epithelial tumours which infiltrate within breast, capacity to spread to distant sites.

- They can be histologically subcategorised into ductal, lobular, tubular and mucinous.
- **Invasive ductal** = carcinoma that cannot be subclassified into another group. Most common. Big, pleiomorphic cells **[BUZZWORD]** – invasive cells move intro stroma
- **Invasive lobular** = cells aligned in single file chains/strands.
- **Tubular carcinomas** = well-formed tubules **[BUZZWORD]** with low grade nuclei. Rarely palpable as <1cm.
- **Mucinous carcinoma** = cells produce abundant quantities of extracellular mucin **[BUZZWORD]** which dissects into surrounding stroma.

Neoplastic lesions undergo core needle biopsy to confirm histological subtype and grading. All breast carcinomas are graded /3 (total score /9) according to 3 criteria:

- Nuclear pleomorphism
- Tubule formation
- Mitotic activity

Grade 1 = well differentiated <5/9
Grade 2 = moderately differentiated 6-7/9
Grade 3 = poorly differentiated 8-9/9

All neoplastic lesions also assessed for oestrogen receptor, progesterone receptor and HER2 receptor status. **ER/PR receptor** positive associated with good prognosis because it predicts response to **Tamoxifen**. HER 2 positive associated with bad prognosis.

The most important prognostic factor of breast cancer = **status of the axillary lymph nodes**

Low grade tumours are often ER/PR +ve and HER2 -ve → responds to Tamoxifen
High grade tumours are often ER/PR -ve and HER2 +ve → responds to Herceptin
Basal cell carcinomas are ER/PR/HER2 -ve (triple negative)

Tamoxifen = mixed agonist/antagonists of oestrogen at its receptor.
Herceptin/trastuzumab = monoclonal Ig to Her2 (direct toxic effect on myocardium, must monitor LVEF)

Basal-Like Carcinoma

- Histologically - sheets of markedly atypical cells with lymphocytic infiltrate
  Stain positive for CK5/6/14
- Often associated with BRCA
- Commonly have vascular invasion and distant metastatic spread

.

Cerebral Pathology

Strokes

Clinical syndrome characterised by rapidly developing focal/global neurological deficit lasting > 24hrs.
A TIA lasts < 24 hrs with complete resolution of symptoms (most TIAs last 1-5 minutes and 1/3 TIAs lead to strokes after 5 years if left untreated)

Infarction

'An area of tissue death due to lack of oxygen'. Accounts for 70-80% of strokes. Cerebral atherosclerosis is the most common cause. Other aetiology includes embolism from intra/extra cranial plaques. TIAs are an important future predictor of a stroke.

	Stroke	TIA
Epidemiology	100 000 new strokes/yr in UK	0.4/1000 a year 15% of 1st strokes preceded by TIA
Aetiology / Risk factors	Same as atheroma: Smoking, DM, HTN, FH, past TIAs, OCP, PVD, ↑ETOH, Hyperviscosity e.g. Sickle cell anaemia, polycythaemia vera	
Symptoms / Signs	Sudden onset FAST, numbness, loss of vision, dysphagia (depends on territory)	Symptoms last <24hrs, Amaurosis fugax, Carotid bruit
Vascular territories commonly affected	Anterior vs. Posterior territory Commonest = MCA	Any – characteristically embolic atherogenic debris from the carotid artery travels to the ophthalmic branch of internal carotid
Investigation	CT/MRI (infarct vs. haemorrhage) Ix for vascular risk: BP, FBC, ESR, U&E, glu, lipids, CXR, ECG, carotid doppler	Carotid US Ix for vascular risk: BP, FBC, ESR, U&E, glu, lipids, CXR, ECG, carotid doppler
Management	Aspirin +/- dipyridamole Thrombolytics (if <3h from event) +/- carotid endarterectomy Long term: treat HTN, ↓lipids, anticoag	Aspirin + dipyridamole +/- carotid endarterectomy Long term: treat HTN, ↓lipids, anticoag

Stroke Syndromes According to Vascular Territory

1. **ACA:** contralateral leg paresis, sensory loss, cognitive deficits (e.g. apathy, confusion, and poor judgment)

2. **MCA:** proximal occlusion involves:

- contralateral weakness and sensory loss of face and arm
- cortical sensory loss
- may have contralateral homonymous hemianopia or quadrantanopia
- if dominant (usually left) hemisphere: aphasia
- if non-dominant (usually right) hemisphere: neglect
- eye deviation towards the side of the lesion and away from the weak side

3. **PCA**
   - contralateral hemianopia or quadrantanopia
   - midbrain findings: CN III and IV palsy/pupillary changes, hemiparesis
   - thalamic findings: sensory loss, amnesia, decreased level of consciousness
   - if bilateral: cortical blindness or prosopagnosia
   - hemiballismus

4. **Lacunar infarcts** (deep hemispheric white matter; involving deep penetrating arteries of MCA, circle of Willis, basilar, and vertebral arteries)
   1. Pure motor hemiparesis (posterior limb of internal capsule): contralateral arm, leg, and face
   2. Pure sensory loss (ventral thalamic): hemisensory loss
   3. Ataxic hemiparesis (ventral pons or internal capsule): ipsilateral ataxia and leg paresis
   4. Dysarthria-clumsy hand syndrome (ventral pons or genu of internal capsule): dysarthria, facial weakness, dysphagia, mild hand weakness and clumsiness

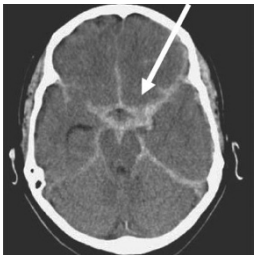
Haemorrhage**

Non Traumatic

Intraparenchymal haemorrhage:

- 50% due to HTN
- Onset is abrupt
- Can cause Charcot-bouchard microaneurysms (likely to rupture)
- **Common site= basal ganglia**

Subarachnoid haemorrhage:



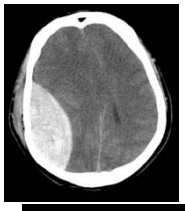
- 85% from ruptured berry aneurysms
- Most at internal carotid bifurcation
- F>M, usually <50yrs
- Thunderclap headache, vomiting and LoC,
- ↑in APKD, Ehler's Danlos and Aortic Coarctation.
- BUZZWORD – hyperattenuation around Circle of Willis

Rare causes

- AV malformations (young people < 50yrs), cavernous angiomas (recurrent low pressure bleeds) capillary telangiectasias, connective tissue disorders like Ehlers-Danlos

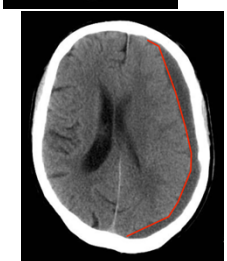
<u>Traumatic</u>

Extradural haemorrhage:



- Skull fracture from TRAUMA
- Most common site - ruptured **middle meningeal artery**
- Rapid arterial bleed, lucid interval then LoC
- BUZZWORD – "lemon" shape

Subdural haemorrhage:



- Prev history of minor head trauma
- Damaged bridging veins with slow venous bleed
- Often elderly/alcoholic/on anti-coagulation,
- Associated with gradual headache, fluctuating consciousness and behaviour changes
- BUZZWORD – “banana” shape

Traumatic parenchymal injury:

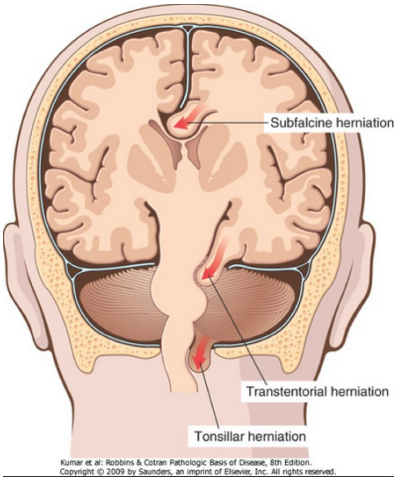
- **Traumatic brain injury** is the single largest cause of death in uder 45s
- IN **skull fractures** look out for otorrhea or rhinorrhea – BUZZWORD “straw-coloured fluid” is CSF + Battle’s sign (haemorrhage on mastoid process)
- **Concussion:** Transient LoC and paralysis, recovery in hours or days
- **Diffuse axonal injury** (occurs at moment of injury due to shear tensile forces breaking axons apart) → commonest cause of Coma, midline structures like Corpus Callosum, rostral brainstem and septum pellucidum affected → Vegetative state, post traumatic dementia
- **Contusions** are collisions between the brain and skull: **Coup**= where impact occurs, **contracoup**= opposite to region of impact

Increased ICP

Caused by oedema, space occupying lesion (e.g. tumour, abscess) or both → brain herniation.

3 main types of **herniation**:

- Subfalcine – herniation of singular cortex beneath the falx (midline fold of the dura)
- Transtentorial/uncal – hernation of medial temporal lobe under tentorium (horizonal dura mater between parietal lobes and cerebellum)
- Tonsillar herniation – herniation of cerebellum through foramen magnum. This compresses the brainstem leading to cardiorespiratory arrest and death (risk if doing a LP if ↑ ICP)



Oedema is excess accumulation of fluid in the brain parenchyma

1. Vasogenic – disruption of the blood-brain-barrier permeability
2. Cytotoxin – secondary to cellular injury (e.g. ischaemic of hypoxic)

Hydrocephalus

An increase in CSF and enlargement of the ventricular system:

1. Communicating – obstruction in outflow of CSF
    a. e.g. in neonates, the lateral ventricles obstruct the cerebral aqueduct causing build-up of CSF in the lateral ventricles → enlarging brain and ventricles
2. Non-communicating – reduced absorption of CSF into sinus veins
    a. E.g. in meningitis the meninges can become fibrous and this reduces absorption

Normal CSF flow: Produced by the choroid plexus → flows through interventricular foramen into 3rd ventricle → flows via cerebral aqueduct into 4th ventricle → sub-arachnoid space → spinal chord and brain → reabsorption via superior sagittal sinus into venous system

Brain Tumours**

Primary tumours originate within the CNS

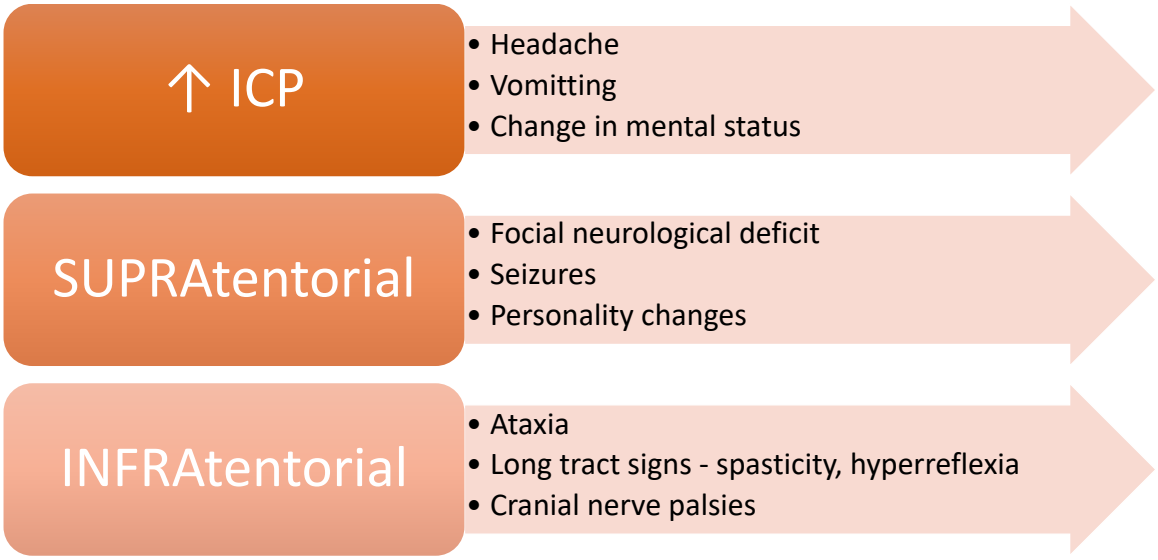
- Extra-axial – cranium, soft tissue, meninges, nerves [BENIGN]
- Intra-axial – glial, neurons, neuroendocrine cells [MALIGNANT]
- **Rarely metastasise** outside the CNS

Secondary tumours are metastatic lesions from other parts of the body:

- **Commonest form of adult brain tumours** (10x more common than primary tumours)
- Most common sources are: lung, breast, malignant melanoma
- Located at grey-white matter junction
- Well demarcated, solitary or multiple with surrounding oedema
- **VERY POOR PROGNOSIS**

Risk factors for brain tumours: previous tumours, radiotherapy to head/neck, neurofibromatosis 1&2, tuberous sclerosis

Signs and symptoms:



Neuroimaging = **MRI**, CT, functional MRI, MR-Spectroscopy, PET-SCAN
Management = surgical resection + radiotherapy +/- chemotherapy

WHO Classification of CNS tumours:

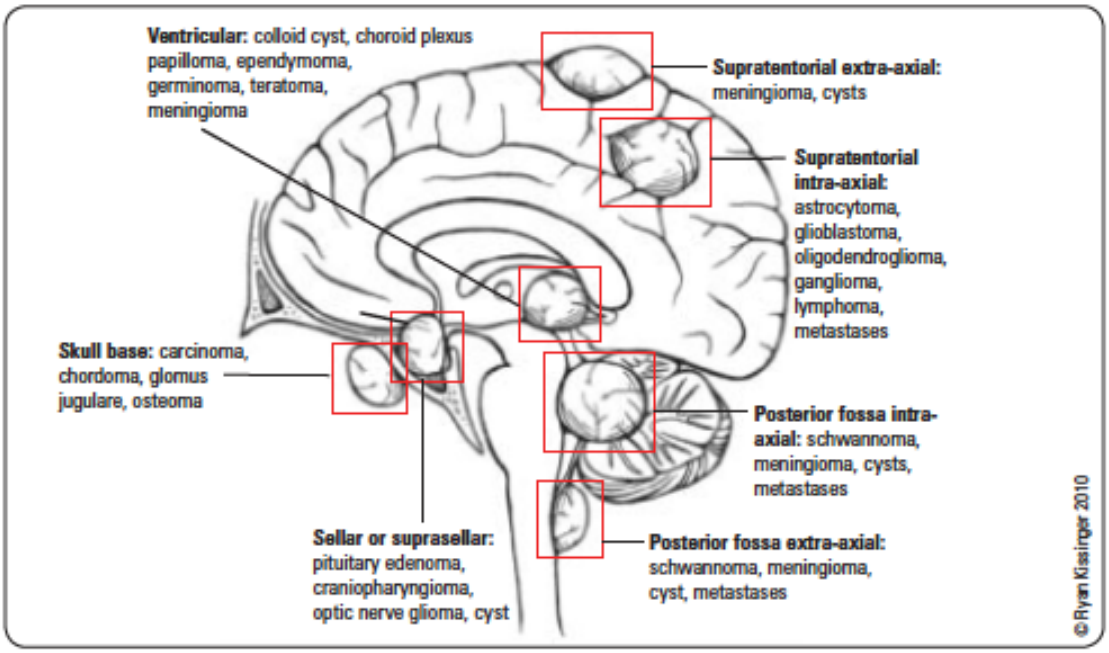
- Tumour type – cell of origin or lineation of differentiation
  - Astrocytes → astrocytoma
  - Oligodendrocytes → oligodendrocytoma [**BUZZWORD** “fried-egg” appearance]
  - Ependyma → ependyoma [**BUZZWORD** “ventricular tumour, hydrocephalus”]
  - Meningothelial cells → meningioma
- Tumour grade – predicted natural clinical behaviour a.k.a. patient survival time
  - Grade 1 – benign
  - Grade 2 – more than 5 years survival
  - Grade 3 – 1-5 years survival
  - Grade 4 – less than 1 year survival
- Molecular profiling – genetics, molecular markers

NOTE: There is no TNM staging for primary brain tumours as they usually do not metastasise outside the CNS

Most common types of brain tumours:

	Astrocytic			Meningeal	Embryonal
Type/ Subtype	Pilocytic astrocytoma (G1)	Diffuse Glioma (G2-3)	Glioblastoma multiforme (G4) - **BAD**	Meningioma	Medulloblastoma
Age group	0–20 years	20-40 years	50+ years Median survival = 8 months **Most common, aggressive primary tumour in adults**	↑ Incidence with age	**2nd most common brain tumour in children** after Astrocytomas
Histology	Piloid "hairy" cells Rosenthal fibres Slow mitotic divisions	Low-moderate cellularity Low mitotic activity No vascular proliferation	High cellularity High mitotic activity Microvascular proliferation Necrosis	Psammoma bodies (calcifications) Mitotic activity determines grading	
Mutation	BRAF mut. in 70%	IDH mut. is associated with longer survival and better response to chemo and radiotherapy	IDH wildtype		
BUZZ-WORDS	Indolent, childhood		Aggressive, poor prognosis	NF 2	

Other 'common' tumours (they're still very rare…): pituitary adenomas, schwannomas, neurofibromas, ependyomas, oligodendrogliomas



Familial syndromes associated with CNS tumours

- Von Hippel-Lindau → hemangioblastomas of cerebellum, brainstem and spinal cord, retina; renal cysts, pheochromocytomas
- Tuberous sclerosis → giant cell astrocytoma; cortical tuber; supependymal nodules and calcifications on CT
- NF 1 → optic glioma, neurofibroma astrocytoma,
- NF 2 → vestibular schwannoma, meningioma, ependymoma, astrocytoma
- Multiple endocrine neoplasia type 1 (MEN-1): pituitary adenoma

Neurodegenerative Diseases

Progressive, irreversible conditions leading to neuronal loss. Common pathogenic mechanism is accumulation of misfolded proteins which may be intra- or extracellular.

Dementia**

"A global impairment of cognitive function and personality without impairment of consciousness. This impairment goes beyond what might be expected from normal ageing. Includes memory impairment and at least one of the following cognitive disturbances: aphasia, apraxia, agnosia or a disturbance in executive functioning".

- Aphasia= language disorder (may be expressive or receptive)
- Apraxia= loss of ability to carry out learned purposeful tasks
- Agnosia= loss of ability to recognise object, people etc.

Incidence: Alzheimer's > vascular > Lewy body > frontotemporal

Alzheimer's Disease

Commonest cause of dementia, usually begins >50yrs
Clinical diagnosis although PET and MRI may help.

Pathophysiology:

5. Accumulation of **beta-amyloid** deposits outside neurons → **senile plaques** that interfere with neuronal communication
6. Hyperphosphorylation of **Tau protein** → dissociation from neuron microfilaments → accumulate into **neurofibrillary tangles** → cerebral atrophy

Radiology: general brain atrophy, widened sulci, narrowed gyri and enlarged ventricles (most →marked in temporal and frontal lobes with loss of cholinergic neurons).
Histology: Senile plaques of **beta-amyloid protein**, **neurofibrillary tangles of tau protein**, cerebral amyloid angiopathy
Rx is symptomatic: anti-cholinesterases, nAChR agonists, glutamate antagonists.

Vascular dementia

2nd most common dementia
Pathophysiology: neuronal death due to infarcts of small and medium sized vessels
Symptoms: step-wise deterioration (BUZZWORD), symptoms reflect area of the brain affected
RFs: atherosclerosis, obesity, smoking, alcohol, diabetes, unhealthy diet, sedentary lifestyle

Lewy body dementia

Psychological disturbances occur early. Day-to-day fluctuations in cognitive performance and alertness, visual hallucinations (**BUZZWORD** – little people/animals running around), spontaneous motor signs of Parkinsonism, recurrent falls and syncope, aggression

Pathologically indistinguishable from PD

Frontotemporal dementia a.k.a. Pick's disease

This only affects the frontal and temporal lobes → atrophy
Histology: Pick bodies = hyperphosphorylated tau
Mutations: progranulin gene
There is a strong FHx and often affects younger people (40-60yrs)
Classical symptoms include personality change, disinhibition, overeating, emotional blunting

Parkinson's Disease

Progressive depletion of dopaminergic neurons in the nigrostriatal pathway from substantia nigra in basal ganglia to striatum. This leads to widespread motor deficits

Lewy bodies present in affected neurons. Alpha-synuclein is main component of Lewy bodies and mutations in this protein are responsible for PD. Alpha-synuclein deposits also found in peripheral ganglia (causing motor retardation) and olfactory bulb (early loss of smell)

Cardinal signs = 'TRAP'

- **T**remor
- **R**igidity
- **A**kinesia
- **P**ostural instability

Some develop psychiatric features later in disease e.g. Parkinsons Disease Dementia, hallucinations, anxiety

Parkinson Plus syndromes

- **Lewy Body dementia** – fluctuating cognition, visual hallucinations and early dementia
- **Progressive supranuclear palsy**: tauopathy with limited vertical gaze (downgaze more specific), early falls, axial rigidity and akinesia, dysarthia, and dysphagia
- **Corticobasal syndrome:** tauopathy with varied presentations but classically presents with unilateral parkinsonism, dystonia/myoclonus, apraxia ± "alien limbs" phenomenon; may also present as progressive non-fluent aphasia
- **Multiple system atrophy**: synucleinopathy presenting as either cerebellar predominant (MSA-C, previously olivopontocerebellar atrophy) or parkinsonism predominant (MSA-P, previously nigrostriatal degeneration); both are associated with early autonomic dysfunction (previously Shy-Drager syndrome)
- **Vascular parkinsonism**: multi-infarct presentation with gait instability and lower body parkinsonism; less likely associated with tremor

Diseases causing dementia	Pathological protein (misfolded)
Alzheimer's disease	Tau, beta-amyloid
Dementia with Lewy bodies	Alpha-synuclein, ubiquitin
Corticobasal degeneration	Tau
Frontotemporal dementia linked to Chr 17	Tau
Pick's disease	Tau

Prion disease

A series of diseases with common molecular pathology often caused by infection and transfer of proteins from organism to host (rather than RNA/DNA)

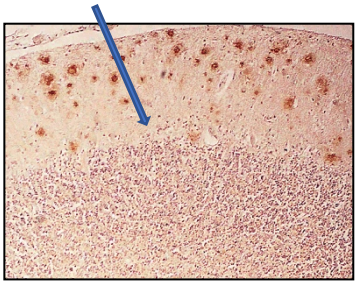
Sporadic (80%): Creutzfeld-Jakob disease [**BUZZWORDs** = rapid <1yr decline]
Acquired (<5%):

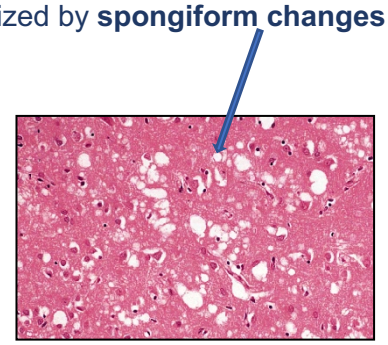
- Kuru [**BUZZWORD** = cannibalism]
- Variant CJD (linked to bovine spongiform encephalopathy a.k.a. mad cow disease)
- Iatrogenic CJD (following flood transfusions of surgical procedures)

Genetic (15%):

- Gerstmann-Straussler-Scheinkler syndrome (GSS)
- Fatal familial insomnia

All prion diseases are **histologically** characterized by **spongiform changes** to brain and **prion protein deposits**





Metabolic Bone Disease**

Metabolic Bone Disease	Osteoporosis	Osteomalacia / rickets	Hyperparathyroidism (primary)	Paget's Disease	Renal Osteodystrophy
Aetiology	Age related (post-menopause in females) or secondary to systemic disease/drugs	↓dietary Vit D, ↓ sunlight, malabsorption of Vit D (GI causes), and genetic causes	Excess PTH production→ ↑ Ca reabsorption and ↑PO4 excretion Causes: parathyroid adenoma, hyperplasia, carcinoma, MEN	A disorder of bone turnover	All skeletal changes assoc w CKD: Osteitis fibrosa cystica (2º↑PTH), Osteomalacia, Osteosclerosis, Adynamic bone disease, Osteoporosis
Disease features	**↓bone mass** DEXA scan: T score > 2.5 SD below normal (1-2.5 = osteopaenia)	**↓bone mineralization**	Bone changes of osteitis fibrosa cystica	Both lytic and sclerotic lesions. 3 stages = osteolytic, mixed, osteosclerotic.	Depends on the form of bone disease
Symptoms	Low impact fractures (#) (hip - NOF, vertebrae; wrists - Colles') Pain (back)	**Adults:** Bone pain/tenderness, proximal muscle weakness **Children:** Bone pain, bowing tibia, rachitic rosary, frontal bossing, pigeon chest, delayed walking	Hypercalcaemia: 'Moans, stones, bones, groans, thrones' Depression/confusion, renal stones, bone pain and #, constipation, pancreatitis, Polyuria, polydipsia	Bone pain Microfractures Nerve compression (→ sensorineural deafness, sciatica) Skull changes ↑ head size Deafness High output cardiac failure	Depends on the form of bone disease
Risk Factors	+Age, female, smoking, poor diet, low BMI ...	Poor diet, malabsorption, CLD, CKD, lack of sunlight	Secondary hyperPTH → CRF, ↓vit D, malabsorption	>50 years old M=F Caucasian	
X ray	Usually none	**Looser's zones** (pseudo fractures) Splaying of metaphysis Bowing of legs in rickets	**Brown's tumours** (collection of multinucleate giant cells) **Salt and pepper skull** Subperiosteal **bone resorption** in **phalanges**	Mixed lytic and sclerotic **SKULL** Osteoporosis circumscripta Cotton wool **VERTEBRAE:** Picture frame Ivory vertebra **PELVIS:** Sclerosis and lucency	Depends on the form of bone disease
Histology	Loss of cancellous bone	Excess of unmineralized bone (osteoid)	**Osteitis fibrosa cystica** (marrow fibrosis + cysts – aka **Brown Tumour**)	**Huge osteoclasts** w > 100 nuclei **Mosaic pattern** of lamellar bone (like jigsaw puzzle)	Depends on the form of bone disease
Bio Chemistry	↔ Ca; ↔ PO4; ↔ ALP	↔/↓Ca ↓ PO4 ↑ALP	↑Ca; ↓/↔ PO4; ↑/↔ ALP ↑ PTH (or inappropriately normal)	↔Ca; ↔PO4; ↑↑↑ALP	↓Ca; ↑PO4, 2º hyperPTH, metabolic acidosis

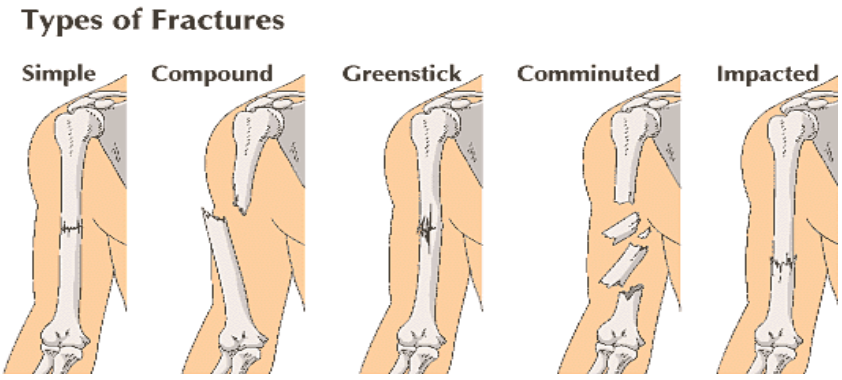
Non-Neoplastic Bone Disease

Gout vs. Pseudogout**

	Gout	Pseudogout
Epidemiology	Obese, middle aged man	>50 yrs women
Aetiology	HYPERURICAEMIA ↑ Intake - ↑dietary purine intake, alcohol excess ↑ Production – tumour lysis syndrome, inherited metabolic abnormalities ↓ Excretion - diuretics,	Idiopathic Electrolytes - HyperPTH, hypoPO4, hypoMg Metabolic - DM, Hypothyroid, Wilsons, haemochromatosis
Joints affected	Acute monoarthritis • Classically 1st MTP (big toe) • Precipitated by trauma/infection Chronic tophaceous gout • Polyarticular arthritis • Tophi deposits in ear lobes, fingers and elbows • Urate kidney stones	Acute monoarthritis: • Knee and shoulder • Precipitated by trauma/infection Chronic: • Polyarticular arthritis
Clinical features	Hot, swollen, red, exquisitely painful joint. Tophus (s/c deposits of urate) is the pathognomonic lesion e.g. on pinna and hands.	Hot swollen joint w/ effusion Chondrocalcinosis on X-ray
Crystal type	Urate crystals, **needle shaped**	Calcium pyrophosphate crystals, **rhomboid shaped**
Investigations	Polarised light → **Negatively** birefringent crystals X-ray → "rat-bite erosions" **[BUZZWORD]**	Polarised light → **Positively** birefringent X-ray → "white lines of chondrocalcinosis" **[BUZZWORD]**
Management	Acute attack: colchicine. Long term: allopurinol. Conservative: ↓ETOH and purine intake e.g. sardines, liver	NSAIDs or intra-articular steroids

Trauma

- Fractures: e.g. Simple, compound, greenstick, comminuted, impacted



- Fracture repair: A) organization of haematoma (pro-callus). B) Formation of fibrocartilaginous callus. C) Mineralisation of fibrocartilaginous callus. D) Remodeling of bone along weight bearing lines.

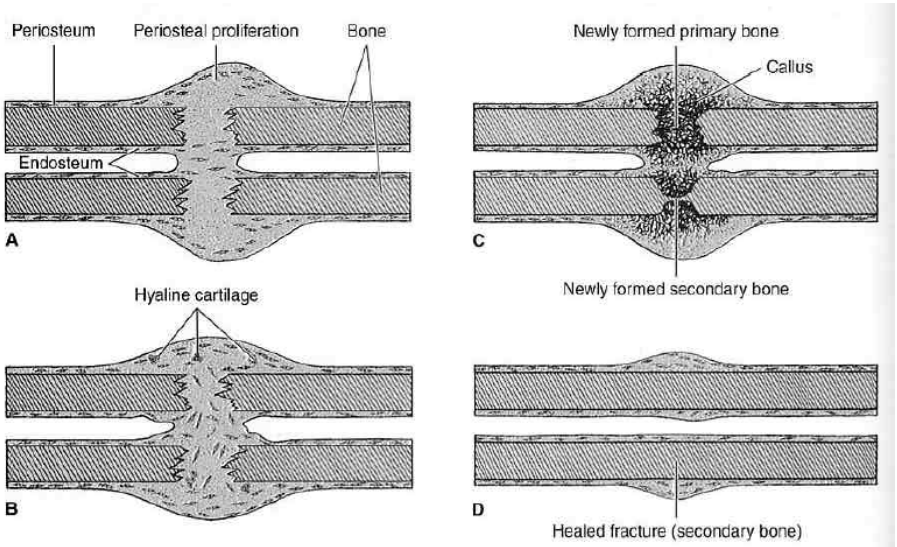


Figure 8–17. Repair of a fractured bone by formation of new bone tissue through periosteal and endosteal cell proliferation.

- Fracture type, neoplasm, metabolic disorder, drugs, vitamin deficiency and infection – influence how the fracture heals

Osteomyelitis

- Haematogenous spread or local infection e.g. post trauma. Bacterial (v occasionally fungal)
- Presentation: pain, swelling and tenderness. General features of malaise, fever, chills, leukocytosis.
- X-ray changes:
    - Early changes include sub-periosteal new bone formation.
    - ~10 days post onset - lytic destruction of bone.

Adults	Children	Sickle cell patients	Immunocompromised	Congenital
S. aureus Vertebrae, jaw (2^o to dental abscess) and toes (2^o to diabetic skin ulcer)	***Haemophilus influenza,*** ***Group B strep.*** Long bones	***Salmonella***	**TB**	**Syphilis**

Osteoarthritis

Degenerative joint disease mainly affecting vertebrae, hips and knees. May see Heberden's nodes (DIPJ) and Bouchard's nodes (PIPJ)

X-Ray features = LOSS

- Loss of joint space
- Osteophytes
- Subchondral sclerosis

- Subchondral cysts

Rheumatoid arthritis (see immunology section)
Clinical presentation: usually slowly progressing course. Symmetrical, small joints of hands and feet (**sparing** DIPJ), wrists, elbows, ankles and knees.
Serology – RF +ve in 60-70%, anti-CCP is more sensitive & specific than RF
Characteristic deformities:

- Radial deviation of wrist and ulnar deviation of fingers.
- “swan neck” and “Boutonniere” deformity of fingers
    - Swan neck = hyperextension of PIPJ & flexion of DIPJ
    - Boutonniere = flexion of PIPJ & hyperextension of DIPJ
- “Z” shaped thumb
- Synovial swelling

Extra-articular features: Pulmonary fibrosis, vasculitis, amyloidosis, pericarditis, subcutaneous nodules, DVT
Histopathology – thickening of synovial membrane, hyperplasia of surface synoviocytes, intense inflammatory cell infiltrate & fibrin deposition & necrosis

Neoplastic Bone Disease

Benign vs Malignant Bone Disease XRays

Benign	Malignant
No periosteal reaction	Acute periosteal reaction – Codman's triangle, onion skin, sunburst **[BUZZWORDS]**
Thick endosteal reaction Regular bone formation Intraosseous and regular calcification	Broad border between lesion and normal bone Varied bone formation Extraosseous and irregular calcification

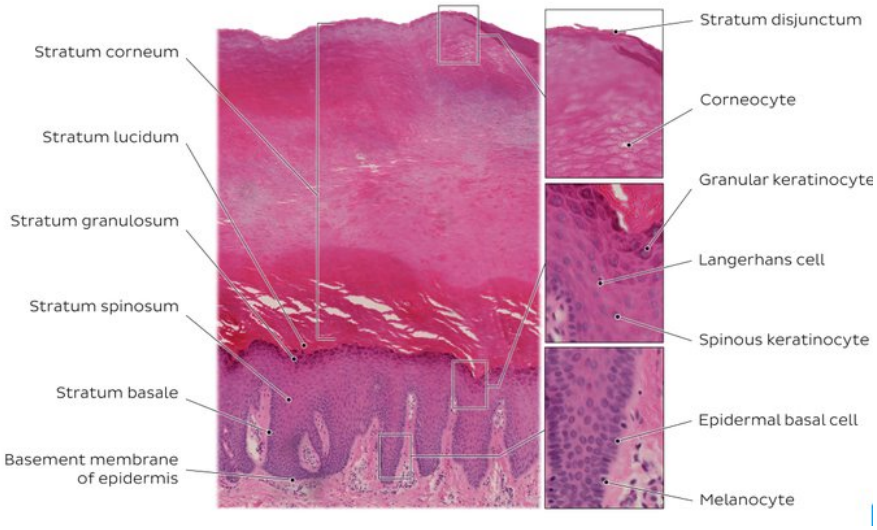
Malignant Bone Tumours**

Name	Epidemiology	Bone	Histology [BUZZWORDS]	X-ray Appearance
Osteosarcoma	Adolescence Very rare – 60% less rare than lung cancer	Knee (60%)	Malignant mesenchymal cells **ALP +ve** Replacement of bone marrow with trabecular bone	Elevated periosteum (**Codman's triangle**) **Sunburst appearance**
Chondrosarcoma	>40 yrs	Axial skeleton Femur/tibia/ pelvis	Malignant **chondrocytes** (proliferation of cartilage)	Lytic lesion with **fluffy calcification,**
Ewing's sarcoma	<20yrs HIGHLY MALIGNANT	Long bones, pelvis	Sheets of **small round cells** CD99 +ve T 11:22 translocation	**Onion skinning** of periosteum
Giant cell *(borderline malignancy)*	20-40yrs F>M	Knee- epiphysis	Osteoclasts and stromal cells "Soap bubble appearance" "Giant multi-nucleate osteoclasts"	Lytic/lucent lesions right up to articular surface

Benign Bone Tumours

Name & age affected	Bone	Special features	Histology	X-ray
Osteoid Osteoma (Adolescent) M:F = 2:1	Tibia diaphysis/ Proximal Femur	Small benign bone forming lesion, night pain relieved by aspirin	Normal bone, arises from osteoblasts	**Central nidus** (luscent) with **sclerotic rim** (opaque) '**Bull's-eye**'
Osteoma **(Middle age)**	Head + neck	Bony outgrowths attached to normal bone *Gardner syndrome:* GI polyps + multiple osteomas + epidermoid cysts	Normal bone	
Enchondroma (Middle age)	Hands 43% **Ie Ends so often in the hands**	Benign tumours of cartilage *Ollier's syndrome =* multiple enchondromas *Maffuci's syndrome =* multiple enchondromas + haemangiomas	Normal cartilage Calcified matrix	Lytic lesion **Cotton wool calcification** Expansile, O ring sign
Osteochondroma (Adolescent) Most common benign tumour	Metaphysis of long bones near tendon attachment sites	Cartilage capped bony outgrowth *Diaphyseal aclasis/ hereditary multiple exostoses =* multiple exostoses + short stature + bone deformities	Cartilage capped **"mushroom"** bony outgrowth	Well defined bony protuberance from bone Cartilage capped bony spur on surface of bone **"mushroom"** on xray
Fibrous dysplasia** **(F>M Middle age)**	Femur & ribs	A bit of bone is replaced by fibrous tissue *McCune-Albright syndrome* = polyostotic dysplasia + café au lait spots + precocious puberty (*See paeds*)	Chinese letters (misshapen bone trabeculae)	**Soap bubble osteolysis** **Shepherd's crook deformity**
Simple Bone cyst	Humerus or femur	Fluid filled unilocular		**Lytic well defined**
Osteoblastoma		Similar to osteoid osteoma		**Speckled mineralisation**

Skin Pathology



From superficial → deep: corneum → lucidem → granulosam → spinosum → basale

Pathological definitions

- **Hyperkeratosis:** ↑ in S. corneum / ↑keratin
- **Parakeratosis:** nuclei in S. corneum
- **Acanthosis:** ↑ in s. spinosum
- **Acantholysis:** ↓ cohesions between keratinocytes
- **Spongiosis: inter**cellular oedema
- **Lentiginous** – linear pattern of melanocyte proliferation within epidermal basal cell layer (reactive or neoplastic)
- **Lichenoid** – sheeny plaque appearance on surface of skin
- **Psoriaform** – thickened skin

Dermatitis / Eczema**

Interchangeable terms used to describe a group of disorders with the **same histology** and presenting with inflamed, dry **itchy** rashes. There is often a **history of atopy** (food allergy, asthma or allergic rhinitis).

Aetiology:

- Inside-out theory – immune system → IgE sensitisation → skin barrier dysfunction
- Outside-in theory – defective skin barrier → allergen exposure → IgE sensitisation

	Histology	Clinical features
Atopic dermatitis	**ACUTE:** ● Fluid collection in dermis (spongiosis) ● Eosinophil infiltrate in	**Infants**: face, scalp, extensor surfaces **Older:** flexural areas **If chronic** - lichenification **IgE mediated**

	dermis ● Dilated dermal capillaries **CHRONIC:** ● Acanthosis ● Crusting, scaling	Persists into adulthood in those with FHx of atopy
Contact dermatitis		**Type IV** hypersensitivity – e.g. to nickel, rubber Erythema, swelling, pruritis Commonly affects ear lobes and neck (from jewellery), wrist (leather watch straps), feet (from shoes)
Seborrhoeic dermatitis		Inflammatory reaction to a yeast – ***Malassezia furfur*** **Infants**: cradle cap (large yellow scales on scalp) and nappy sites **Young adults**: mild erythema, fine scaling, mildly pruritic- affects face, eyebrow, eyelid, anterior chest, external ear

Psoriasis**

Chronic inflammatory dermatosis with erythematous, well-demarcated scaly plaques
Often has early (15-25yrs) and late (50-60yrs) bi-modal distribution

Pathophysiology – Type IV T-cell hypersensitivity reaction within the epidermis → further T cell recruitment → release of pro-inflammatory cytokines (TNF-alpha, IFN-gamma) → keratinocyte hyperproliferation → epidermal thickening

Histology: Parakeratosis [BUZZWORD], neutrophilia, loss of granular layer, clubbing of rete ridges giving "**test tubes in a rack**" appearance; **Munro's microabscesses**

Types of psoriasis:

- **Chronic plaque psoriasis (MOST COMMON)** – with salmon pink plaques and silver scales affecting extensor aspects of knees, elbows and scalp.
- **Flexural** psoriasis – seen later in life, usually groin, natal cleft and sub-mammary areas
- **Guttate** psoriasis – "rain-drop" plaque distribution, often in children on trunk, usually seen 2 weeks post *Group A Beta-haemolytic Strep* infection (GABHS)
- **Erythrodermic/pustular psoriasis (EMERGENCY)** – severe widespread disease, often systemic symptoms, can be limited to hands and feet = palmo-plantar psoriasis
- **Koebner phenomenon –** plaques form at/along sites of trauma

Rubbing them causing pin-point bleeding **(Auspitz' sign)**

Associated with:

- Nail changes:
  - **P**itting
  - **O**nycholysis
  - **S**ubungual **H**yperkeratosis
- Arthritis (5-10%)
  - **D**IP disease
  - **A**rthritis multilans 'telescoping' **[BUZZWORD]**

- **S**pondylopathy
- **S**ymmetrical polyarthritis

Lichen Planus

- Lesions are "**p**ruritic, **p**urple, **p**olygonal, **p**apules and **p**laques" with a mother-of-pearl sheen, and fine white network on their surface called **Wickam's striae**
- Usually on **inner surfaces of wrists**; can also affect oral mucous membrane where the lesions have lacy appearance
- Accumulation of T cells attacking the basement membrane
- **Histo:** hyperkeratosis with **saw-toothing of rete ridges** and basal cell degeneration

Erythema Multiforme

Classically causes **annular target lesions**, most commonly on extensor surfaces of **hands and feet**. It causes pleomorphic lesions and there can be a combination of macules, papules, urticarial weals, vesicles, bullae and petechiae.

Causes:

- Infections:
  - HSV
  - mycoplasma

- Drugs:
  - **S**ulphonamides
  - **N**SAIDs
  - **A**llopurinol
  - **P**enicillin
  - **P**henytoin

Erythema multiforme → Steven Johnson's syndrome (SJS) → Toxic epidermal necrolysis [Spectrum of disease severity]

Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

- Dermatological **emergency**; **sheets of skin detachment** (<10% body surface area in SJS and > 30% in TEN)
- **Nikolsky sign positive**; mucosal involvement prominent
- Commonly caused by drugs (e.g. sulfonamide antibiotics, anticonvulsants)

Bullous Disease

	Pathophysiology	Clinical features	Histology

Dermatitis herpetiformis	Associated with **coeliac** **IgA** Abs bind to basement membrane → subepidermal bulla	Itchy vesicles on **extensor surfaces of elbows**, buttocks	Microabscesses which coalesce to form **subepidermal bullae** Neutrophil & **IgA** deposits at **tips of dermal papillae**
Bullous pemphigoid**	**IgG** Abs and **C3** (complement) bind to **hemidesmosomes** (adhesion molecules) of basement membrane → epidermis lifts off and fluid accumulates in the space SUBepidermal bulla	Large tense bullae on erythematous base. Often on flexural surfaces (forearms, groin and axillae). ELDERLY. Bullae do not rupture as easily as pemphigus.	EOSINOPHILIA **Linear deposition of IgG** along basement membrane
Pemphigus vulgaris**	IgG Abs bind to desmoglein 1 & 3 (adhesion molecules) between keratinocytes in stratum spinosum → acantholysis INTRAepidermal bulla	Bullae are easily ruptured → raw red surface. Found on skin AND mucosal membranes. Nikolsky's sign +ve. Mucosal involvement.	**Intraepidermal bulla** Netlike pattern of **intercellular IgG deposits** Acantholysis
Pemphigus foliaceus	IgG against desmoglein in epidermis → detachment of superficial keratinocytes		

Cutaneous Neoplasms

Epidermal (i.e. from keratinocytes)		Characteristics	Histology
Benign	**Seborrhoeic Keratosis**	Rough plaques, **waxy, "stuck on"** appear in middle age / the elderly	Keratin horns in epidermis, orderly proliferation
Premalignant	**Actinic (Solar/Senile) Keratosis (1st)**	Rough, **sandpaper like texture**, scaly lesions on sun-exposed areas	**SPAIN** **S**olar elastosis **P**arakeratosis **A**typical cells **I**nflammation **N**ot full thickness
	Keratoacanthoma	Rapidly growing dome shaped nodule which may develop a necrotic, crusted	Similar histology to SCC – hard to differentiate

		centre. Grows over 2-3 weeks and clears spontaneously	
	Bowen's Disease (SCC in situ)	Intra-epidermal squamous cell carcinoma in situ Flat, red, **scaly patches on sun-exposed areas**	Full thickness atypia/dysplasia **Basement membrane intact** – i.e. not invading the dermis
Malignant	**Squamous cell carcinoma****	When Bowen's has spread to involve dermis, **ulcerative,** crusting, hyperkeratotic +/- rolled edges Moderately growing; can metastasise and locally destructive	Atypia/dysplasia throughout epidermis, nuclear crowding and **spreading through basement membrane** into dermis
	Basal cell carcinoma**	Aka **"rodent" ulcer** Slow growing tumour; **rarely metastatic** but **locally destructive** Well defined, rolled edges, **pearly surface**, often with **telangiectasia**	Mass of basal cells pushing down into dermis Palisading (nuclei align in outermost layer)

Melanocytic (i.e. from melanocytes)**

- Benign – melanocytic nevi (=moles). They can be junctional, compound or intradermal.
- Malignant – melanoma
  - **Histology:** atypical melanocytes; initially grow horizontally in epidermis (**radial growth phase**); then grow vertically into dermis **(vertical growth phase)**; vertical growth produces "**buckshot appearance**" (=Pagetoid cells)
  - **Breslow thickness** = most important prognostic factor based off depth (every mm worsens prognosis…)
  - **Subtypes;**
    - Superficial spreading (MOST COMMON) – irregular borders with variation in colour
    - Nodular (2nd COMMONEST) – can occur on all sites, more common in the younger age group.
    - Lentigo maligna - occurs on sun exposed areas of elderly caucasians, flat, slowly growing black lesion
    - Acral Lentiginous (RARE) - occurs on the palms, soles and subungual areas

Pityriasis Rosea

- **Salmon pink** rash appears first (=**herald patch**) followed by oval macules in **Christmas tree** distribution.
- Appears after HHV-6 and HHV-7 infections.
- Remits spontaneously

Connective Tissue Diseases

	SLE**	Limited scleroderma (=CREST)	Diffuse scleroderma	Polymyositis & Dermatomyositis	
Background	Autoimmune multi-system disorder Type III hypersensitivity reaction ↑ in classical complement deficiencies Can be drug-induced ↑in AfroC. F>M	Autoimmune multi-system disorders characterised by widespread vasculopathy and fibrosis of skin and internal organs due to excess collagen deposition Scleroderma literally means "hard skin" - reflecting the main clinical feature of skin fibrosis		Skeletal muscle disorders characterised by progressive muscle weakness and inflammation on muscle biopsy **[DEFINITIVE]** Associated with underlying malignancy • DM → ovarian, pancreatic, NHL • PM → lung, bladder, NHL	
HLA association	HLA DR3 (or 2)	HLA DR5 & DRw8			
Auto-antibody	ANA (95%) • Anti dsDNA • Anti-Sm Anti-Smith (most specific) Anti-histone (+ve if drug induced SLE)	Anti-centromere	Anti-topoisomerase II (Scl-70)	Anti Jo-1 (=tRNA synthetase) ↑**CK**/LDH/Myoglobin & abnormal EMG	
Histology	LE bodies Kidney – "wire-loop" appearance of glomeruli **[BUZZWORD]** CNS – small vessel angiopathy Spleen – "onion skin" lesions Heart – Libman-Sack Endocarditis	↑collagen in skin and organs. "Onion skin" thickening of arterioles **[BUZZWORD]**	Inflammation within or around muscle fibres	Endo-mysial inflamm. infiltrate	"drop out" of capillaries and myofibre damage
Signs & symptoms	4 of 11 ACR criteria (**SOAP BRAIN MD**) **S**erositis **O**ral ulcers **A**rthritis	**Distal skin** involvement ONLY **C**alcinosis **R**aynaud's	Skin changes can occur anywhere **(Distal and proximal)**	Proximal muscle weakness → difficulty performing gross motor tasks (e.g. getting up from a chair, climbing steps, combing hair etc)	

	Photosensitivity **B**lood disorders (AIHA, ITP, leucopenia) **R**enal involvement **A**NA +ve **I**mmune phenomena (dsDNA, anti-Sm, Antiphospholipid Ab) **N**euro symptoms **M**alar rash **D**iscoid rash	**E**sophageal dysmotility **S**clerodactyly **T**elangiectasia RARE renal and heart disease Associated with pulmonary hypertension at very old age	**T**endon friction **R**eynauld's phenomenon Widespread organ involvement, early heart, GI and renal disease Associated with pulmonary fibrosis	DM has cutaneous features: (1) Heliotrope rash with eyelid oedema (2) Gottron papules (erythema of knuckles w/ raised scaly eruption) (3) Systemic V-shaped rash (4) Facial rash Associated w. pulmonary fibrosis

Vasculitides

	Disease	Key words
Large Vessel	Takayasu's arteritis	Affects branches of the aortic arch Inflammatory phase → FLAWS Pulseless phase → "**Pulseless**", claudication, cold hands ↑ in Japanese women
	Temporal arteritis (GCA)**	Elderly; **scalp tenderness, temporal headache**, jaw claudication, blurred vision, non-palpable temporal pulse ↑**ESR, age >50** Overlap with polymyalgia rheumatica (PMR) **Ix:** ESR (1st) temporal artery biopsy (definitive) **Histo**: Granulomatous transmural inflammation + giant cells + skip lesions **Mx:** oral Pred IMMEDIATELY
Medium Vessel	Polyarteritis nodosa (PAN)	Renal involvement is main feature Can involve other organs but spares lungs 30% have underlying Hep B **Microaneurysms on angiography ("string of pearls / rosary bead appearance")** **Histo:** fibrinoid necrosis & neutrophil infiltration
	Buerger's disease	**Heavy smokers**, usually men < 35 years Inflammation of arteries of extremities – usually tibial and radial Pain; ulceration of toes, feet, fingers Angiogram: **corkscrew appearance** from segmental occlusive lesions
Small Vessel	Granulomatosis with polyangiitis**	Triad of: (1) Upper resp tract: sinusitis, epistaxis, **saddle nose** (2) Lower resp tract: cavitation, **pulmonary haemorrhage** (3) Kidneys: crescentic **glomerulonephritis** → haematuria & proteinuria

		cANCA +ve
	Eosinophilic granulomatosis with polyangiitis **	**Asthma**, allergic rhinitis **Eosinophilia** Later systemic involvement **pANCA +ve**
	Microscopic polyangiitis	**Pulmonary renal** syndrome: (a) Pulmonary haemorrhage (b) Rapidly progressive glomerulonephritis **pANCA +ve**
	Henoch Schonlein Purpura**	IgA mediated vasculitis In children 3-15 yrs **Preceding URTI → glomerulonephritis** Triad of: ● Purpuric rash on lower limb extensors + buttocks ● Abdo pain ● Arthralgia

Amyloidosis

Multisystem disorder caused by abnormal folding of proteins that are deposited as amyloid fibrils in tissues, disrupting their normal function. There are at least 20 forms but just 2 needed for path.

- Beta-pleated sheet structure
- Resistant to enzyme degradation

PRIMARY (**AL** amyloidosis)

- Most common
- Deposition of Ig light chains
- Most associated with **multiple myeloma** (although most don't have multiple myeloma)
- Most have monoclonal Ig, free light chains in serum and urine (Bence Jones) and increased bone marrow plasma cells

SECONDARY (**AA** amyloidosis)

- Amyloid formed from serum amyloid A = acute phase protein, therefore build up occurs **secondary to chronic infections / inflammation**
    - E.g. autoimmune diseases (60%): **RA**, ank spond, IBD
    - E.g. chronic infections: TB osteomyelitis, IVDU (skin infections)
    - Non-immune: renal cell carcinoma, Hodgkin's

HAEMODIALYSIS ASSOCIATED

(a) Deposition of beta2-microglobulin

- Usually occurs in someone with longstanding chronic renal failure esp. if they are on peritoneal dialysis
- Associated with carpal tunnel syndrome

FAMILIAL AMYLOIDOSIS

(b) Most common = Familial Mediterranean Fever (AR)

- AA amyloid, predominant renal deposition

Clinical features: caused by amyloid deposits in various organs:

- KIDNEY: **nephrotic syndrome** = most common presentation
- HEART: **restrictive cardiomyopathy**, conduction defects, **heart failure**, cardiomegaly
- LIVER/SPLEEN: hepatosplenomegaly
- TONGUE: **macroglossia** in 10%
- NEUROPATHIES: incl carpal tunnel

Pathology:
Apple green birefringence with Congo red stain **under polarized light**

Sarcoidosis

A **multisystem disease** of unknown cause, commonly affecting **young adults**, characterized by **non-caseating granulomas** in many tissues

Histo: **non-caseating granulomas;** also get **Schaumann** and **asteroid** bodies (inclusions of protein and calcium)

1. More severe disease in Afro-Caribbeans
2. F>M, 40-60yrs
3. **Lungs most commonly involved**
4. Often detected at routine CXR → **bilateral hilar lymphadenopathy** (ddx TB, lymphoma, bronchial ca)
5. Also see pulmonary infiltrates → fine nodular shadowing in mid zones
6. Most seek help with insidious shortness of breath, cough, chest pain and night sweats

Extrapulmonary manifestations:

- **SKIN**: erythema nodosum (tender red nodules on shins), lupus pernio (red/purple lesions around nose), skin nodules
- **LNs**: lymphadenopathy, painless and rubbery
- **JOINTS**: arthritis, bone cysts
- **EYES**: **anterior uveitis** → misting of vision and painful red eye; **posterior uveitis** → progressive visual loss; **uveoparotid fever =** bilateral uveitis, parotid enlargement +/- facial nerve palsy (Heerfordt's Syndrome); **keratoconjunctivitis**, **lacrimal gland enlargement**
- **LIVER/SPLEEN: Hepatosplenomegaly**
- **BLOOD: Leukopaenia/ anaemia**
- **Hypercalcaemia/hypercalciuria** → renal calculi + nephrocalcinosis
- **HEART**→ dysrhythmias, cardiomyopathy, conduction defects, pericarditis, valvular lesions
- **CNS involvement**
- **CONSTITUTIONAL SX:** malaise, fever, wt loss, night sweats

DIAGNOSIS OF EXCLUSION

Investigations:

- ↑**Ca2+** (ectopic 1-alpha hydroxylase release by activated macrophages)**,**
- ↑ESR,
- ↑**ACE**
- Transbronchial biopsy → non caseating granuloma

- Spirometry → restrictive,

Histological Stains

Stain	Associated Pathology
Fontana stain	+ve for melanin – Melanoma
Congo red + apple green birefringence	+ve for amyloid – Amyloidosis
Rhodanine stain	Golden brown against blue counterstain +ve for copper – Wilson's disease
Prussian blue	+ve for iron – Haemachromatosis
Perl's stain	+ve for iron – Haemachromatosis
Cytokeratin	+ve for epithelial cells – Carcinoma
CD45	+ve for lymphoid cells – lymphocytes
Ziehl-Neelson	Red against a blue background +ve for acid-fast bacilli – TB
Rhodamine-Auramine stain	Bright yellow – TB
Gomori's methanamine silver stain	Flying saucer shaped cysts – Pneumocystic jirovecii
Modified Kinyoung acid fast stain	+ve for Cryptosporidium parvum
India ink stain	Yeast cells surrounded by halos – Cryptococcus neoformans
Giemsa stain	Cystoplasmic inclusions – Chlamydisa psittaci
Fite stain	+ve for Mycobacterium leprae