Pathology Course  
2020

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Edited by: Michelle Kunc, Jhia Teh, Sally Barker and Yvonne Tsitsiou
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 we have coordinated PACES and Pathology revision courses, 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 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. We would also like to thank the previous MedED guide editors:

- 2016-2017: Daniel Campioni-Norman, Rhys Smith, Helen-Cara Younan and Rebekah Judge
- 2017-2018: Charlie Caird, Stephanie EzeKwe, Mohammad Fallaha, Samyukta Sundar
- 2018-2019: Sophia von Widekind, Lasith Ranasinghe, Daniel Huddart, Alex Huddart

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 students and the Pathology Course lecturers. 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

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Dr Jack Stuart and Dr En Lin Goh

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<td>Bull's-eye appearance in central pallor</td>
<td>Liver disease, hyposplenism, thalassaemia, IDA</td>
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**Anaemia**

**Hb:** Men: $<135 \text{ g/L (13.5 g/dL)}$, Women: $<115 \text{ g/L (11.5 g/dL)}$.

**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) $\rightarrow$ hyperdynamic circulation e.g. tachycardia, flow murmurs (ejection-systolic loudest over apex) $\rightarrow$ heart failure.

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<td>Pregnancy</td>
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<td>Myelodysplastic syndromes</td>
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</tbody>
</table>

**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.

**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 $>50$yrs), Menorrhagia (women $<50$ yrs), Hookworm infestation (developing countries)

**Increased utilisation** | Pregnancy/lactation Infants/children - growth | Loss of Fe each day fetus is not in utero, Suboptimal diet

**Decreased Intake** | Prematurity Infants/children/elderly | Absence in villous surface in duodenum, Rapid transit, ↓ acid which helps Fe absorption

**Decreased absorption** | Coeliac Post-gastric surgery | Chronic loss of Hb in urine $\rightarrow$ Fe deficiency

**Intravascular haemolysis** | Microangiopathic Haemolytic anaemia PNH |
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). With severe symptomatic anaemia: IV iron such as Ferrinject / Monofer (anaphylaxis risk)

### 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 EPO deficiency.

### 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 Pyridoxine (vitamin B6 promotes RBC production).

### Interpretation of Plasma Iron Studies

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<th>Iron</th>
<th>TIBC</th>
<th>Ferritin</th>
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<td>↑</td>
<td>↓</td>
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<tr>
<td>Anaemia of chronic disease</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Chronic haemolysis</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
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<td>Haemochromatosis</td>
<td>↑</td>
<td>↓ (or N)</td>
<td>↑</td>
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<td>Pregnancy</td>
<td>↑</td>
<td>↑</td>
<td>N</td>
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<tr>
<td>Sideroblastic anaemia</td>
<td>↑</td>
<td>N</td>
<td>↑</td>
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</table>

TIBC = total iron binding capacity

**NB:** Ferritin is an acute phase protein and ↑ with inflammation e.g. infection, malignancy Check CRP with every ferritin you send in clinical practice.
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 haemolyis), liver disease, hypothyroidism, and pregnancy.
- **Other haematological disease**: Myelodysplasia, myeloma, myeloproliferative disorders, aplastic anaemia.

**Megaloblastic blood film** = Hypersegmented polymorphs, leucopenia, macrocytosis, anaemia, thrombocytopenia.

**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 paraparesis, 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)

**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. If cause of anaemia is not known then folic acid must not be given, as this will exacerbate the neuropathy of B12 deficiency
# Haemolytic Anaemias

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

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<th>Extravascular</th>
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<td>↑bilirubin (unconjugated)</td>
<td>↑ free plasma Hb</td>
<td>Splenomegaly</td>
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<td>↑urobilinogen</td>
<td>↓ haptoglobin (binds free Hb)</td>
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<td>↑LDH</td>
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<td>Reticulocytosis (↑ MCV and polychromasia)</td>
<td>Methaemalbuminaemia (Haem + albumin in blood)</td>
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<tr>
<td>May have pigmented gallstones</td>
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| 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 Membrane Defect | Hereditary spherocytosis Hereditary elliptocytosis |
| Enzyme Defect | G6PD deficiency Pyruvate kinase deficiency |
| Haemoglobinopathies | Sickle Cell Disease Thalassaemias |

## 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

**Treatment:** Splenectomy, Folic acid

**Hereditary Elliptocytosis**
- Almost all forms are autosomal dominant – spectrin mutations
  - Except for Hereditary Pyropoikilocytosis (erythrocytes are abnormally sensitivity to heat) – autosomal recessive (small print)
- Severity ranges from hydrops foetalis to asymptomatic
- Erythrocytes are elliptical in shape on blood film

**South East Asian Ovalocytosis (lecture small print):**
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• 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 is a good treatment)

**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: Sickle Cell Disease**
- **Umbrella term – states a/w pathological effect of sickling**
- **Autosomal recessive**
- **Single base mutation; GAG → GTG. Glu → Val at codon 6 of β chain → 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
- **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:**

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<th>Vaso-occlusion + infarction (SICKLED)</th>
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<td>Stroke</td>
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<td>Infections (hyposplenism, CKD)</td>
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<td>Folate deficiency</td>
<td>Crises (splenic, sequestration, chest and pain)</td>
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<td>Aplastic crises (Parvovirus B19)</td>
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<td>Dactilitis (impaired growth)</td>
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<td>Mesenteric ischaemia</td>
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<td>Priapism</td>
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**Age of Onset:**

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• Child – strokes, splenomegaly + splenic crises, dactylitis
• Teens – impaired growth, gallstones, psych, priapism
• Adult – hyposplenism, CKD, retinopathy, pulomary hypertension

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
• Exchange transfusion in severe crises
Chronic:
• all should be on:
  o Penicillin V, pneumovax, HIB vaccine
• Some benefit from:
  o Folic acid & Hydroxycarbamide (increases HbF %)
  o Regular exchange transfusions
  o Carotid Doppler monitoring in early childhood with prophylactic exchange transfusion if turbulent carotid flow.

Haemoglobinopathies: Thalassaemia
Unbalanced Hb synthesis→ unmatched globins precipitate→ haemolysis and ineffective erythropoiesis

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.
  o B0 – no expression of the gene
  o B+– some expression of the gene
  o B – normal gene
  o β- thalassaemia minor (e.g. or β/β or β/β ) → Asymptomatic carrier, mild anaemia
  o β- thalassaemia intermedia (e.g. β/β or β/β ) → Moderate anaemia, splenomegaly, bony deformity, gallstones
  o β- thalassaemia major (β/β0) → 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 desferrioxamine to stop iron overload, plus folic acid

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

Autoimmune

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

<table>
<thead>
<tr>
<th>Warm (WAIHA) – most common</th>
<th>Cold Agglutinin Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Features</strong></td>
<td></td>
</tr>
<tr>
<td>37°C</td>
<td>&lt;37°C</td>
</tr>
<tr>
<td>IgG</td>
<td>IgM</td>
</tr>
<tr>
<td>Positive Coombs test</td>
<td>Positive Coombs test</td>
</tr>
<tr>
<td>Blood film - spherocytes</td>
<td>Often with Raynaud's</td>
</tr>
<tr>
<td><strong>Causes</strong></td>
<td></td>
</tr>
<tr>
<td>Mainly primary idiopathic</td>
<td>Primary idiopathic</td>
</tr>
<tr>
<td>Lymphoma, CLL, SLE, methyl dopa</td>
<td>Lymphoma, Infections: EBV, mycoplasma</td>
</tr>
<tr>
<td><strong>Management</strong></td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>Treat underlying condition</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>Avoid the cold</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>Chlorambucil (chemo)</td>
</tr>
</tbody>
</table>

Paroxysmal Cold Haemoglobinuria (PCH):
Haemoglobin 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
- 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.
- MAHA, fever, renal impairment, neuro abnormalities, thrombocytopenia (classic pentad of symps).

HUS: Haemolytic uraemic syndrome
- Caused by E. Coli à toxin damages endothelial cells à fibrin mesh and RBC damage à impaired renal function + microangiopathic haemolytic anaemia.
- Diarrhoea, renal failure, no neuro problems, children and elderly.
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
Includes: Vascular defects (easy bruising), platelet disorders (low or abnormal function), coagulation disorders (factor deficiency) or mixed (DIC).

<table>
<thead>
<tr>
<th>Vascular defects, platelet disorders</th>
<th>Coagulation disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial bleeding into skin, mucosal membranes</td>
<td>Bleeding into deep tissues, muscles, joints</td>
</tr>
<tr>
<td>Bleeding immediate after injury</td>
<td>Delayed, but severe bleeding after injury</td>
</tr>
<tr>
<td>Bleeding often prolonged</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquired</td>
</tr>
<tr>
<td>Aspirin, Cardiopulmonary bypass</td>
</tr>
<tr>
<td>Uraemia</td>
</tr>
<tr>
<td>Storage pool disease</td>
</tr>
<tr>
<td>Thrombocytopenia (glycoprotein deficiency)</td>
</tr>
<tr>
<td>Congenital</td>
</tr>
<tr>
<td>Bone marrow failure</td>
</tr>
<tr>
<td>Thrombocytopenia (norm plt count 150-400x10^9 g/l)</td>
</tr>
<tr>
<td>↓production</td>
</tr>
<tr>
<td>Auto-Immune Thrombocytopenic Purpura (AITP) – formally idiopathic (ITP)</td>
</tr>
<tr>
<td>Drugs e.g. heparin, DIC, HUS, TTP</td>
</tr>
<tr>
<td>↑destruction</td>
</tr>
</tbody>
</table>

Features

<table>
<thead>
<tr>
<th>Features</th>
<th>Acute ITP</th>
<th>Chronic ITP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak age</td>
<td>Children (2-6 yrs)</td>
<td>Adults</td>
</tr>
<tr>
<td>F:M</td>
<td>1:1</td>
<td>3:1</td>
</tr>
<tr>
<td>Preceding infection</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Onset of symptoms</td>
<td>Abrupt</td>
<td>Abrupt - indolent</td>
</tr>
<tr>
<td>Plt count at presentation</td>
<td>&lt;20,000</td>
<td>&lt;50,000</td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>Duration</td>
<td>2 - 6 weeks</td>
<td>Long-term (associated with autoimmune disease, CLL, HIV)</td>
</tr>
<tr>
<td>Spontaneous remission</td>
<td>Common, usually self lim.</td>
<td>Uncommon (Rx: IVIg, steroids, splenectomy)</td>
</tr>
</tbody>
</table>

### 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. sev <1%, mod 1-5%, mild 5-25%
- **Management**: Avoid NSAIDs and IM injections, desmopressin (vWF release which is VIII carrier), factor VIII concentrates as replacement which is life long

#### Haemophilia B (Christmas disease)
- **Factor IX deficiency**
- X-linked recessive affecting 1/50,000 males
- Clinically like haemophilia A.
- **Management**: Factor IX concentrates

#### Von Willebrand’s Disease
- **Several types – quantitative (deficiency) vs. qualitative**
  - Variable phenotype from complete deficiency to asymptomatic mild deficiency
- ↓ platelet function and ↓ factor VIII (vWF carries factor VIII in circulation)
- Mostly autosomal dominant 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**: ↑ APTT, ↑ bleeding time, ↓ Factor VIII, ↓ vWF Ag. Normal INR & plts
- **Management**: Desmopressin, 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
- ↓ absorption of vitamin K
- Abnormalities of platelet function

#### 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
Venous Thrombosis

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

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

<table>
<thead>
<tr>
<th>Disorder</th>
<th>INR</th>
<th>APTT</th>
<th>Thrombin time</th>
<th>Platelet count</th>
<th>Bleeding time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>←↔</td>
<td>←↔</td>
</tr>
<tr>
<td>DIC</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↓</td>
<td>↑↑</td>
</tr>
<tr>
<td>Liver disease</td>
<td>↑</td>
<td>↑</td>
<td>←↔↑</td>
<td>←↔↓</td>
<td>←↑↑</td>
</tr>
<tr>
<td>Platelet defect</td>
<td>←↔</td>
<td>←↔</td>
<td>←↔</td>
<td>←↔↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Vit K def</td>
<td>↑↑</td>
<td>↑↑</td>
<td>←↔</td>
<td>←↔</td>
<td>←↔</td>
</tr>
<tr>
<td>Haemophilia</td>
<td>←↔</td>
<td>↑↑</td>
<td>←↔</td>
<td>←↔</td>
<td>←↔</td>
</tr>
<tr>
<td>Von Willebrand’s</td>
<td>←↔</td>
<td>↑↑</td>
<td>←↔</td>
<td>←↔</td>
<td>↑</td>
</tr>
</tbody>
</table>

### 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) general (with some DOACs LMWH can be stopped immediately)
  o 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
• 1st VTE with known cause – 3 months oral anticoagulant
• Cancer VTE – 3-6months LMWH (sometimes this is continued until cancer considered “in remission”)
• 1st VTE unknown cause – 3-6months anticoagulation, possibly lifelong
• 1st VTE in thrombophilic patient – 3 months anticoagulation, possibly lifelong
• Recurrent VTE – lifelong treatment
• TEDS to prevent postphlebitic syndrome

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)
• Unfractionated heparin (used if renal impairment): given IV, loading dose then infusion, monitor APTT
• 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

<table>
<thead>
<tr>
<th>Target INR</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>1st episode DVT or PE, atrial fibrillation (2-3), cardiomyopathy, symptomatic inherited thrombophilia, mural thrombus, cardioversion</td>
</tr>
<tr>
<td>3.5</td>
<td>Recurrent DVT or PE, mechanical prosthetic valve (2.5-3.5), coronary artery graft thrombosis, antiphospholipid syndrome</td>
</tr>
</tbody>
</table>

In Cases of Raised INR

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

Bleeding and DOACs:
• Dabigatran has an antidote, however it is extremely expensive (idaracizumab)
• Apixaban has an antidote being developed
• **Edoxaban, Rivaroxaban** do not have an "antidote".
• Non life-threatening bleeds, pre-op: Half-lives are approximately 12 hours so withholding one dose may be enough
• Life threatening bleeds, emergency surgery: Prothrombin complex concentrate will reverse the effects.

## 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 à 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 of bone marrow (BM) and blood
“Acute” thus rapidly progressing and fatal
Immature blasts > 20% BM cells

**Clinical features:**
- BM function failure – Anaemia, Thrombocytopenia (bleeding), Neutropenia (infection)
  - Common to many haem 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 myelopoiesis; 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)

---

<table>
<thead>
<tr>
<th></th>
<th>Acute Lymphoblastic Leukaemia</th>
<th>Acute Myeloid Leukaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiology</strong></td>
<td>Childhood (mnemonic – “Children get it ALL”)</td>
<td>Adulthood (risk increases with age) and under-2s (infant peak)</td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
<td>All clinical features listed above, plus:</td>
<td>As listed above, plus: Lymphadenopathy less common</td>
</tr>
<tr>
<td></td>
<td>Lymphadenopathy +++</td>
<td>Quick subtype facts:</td>
</tr>
<tr>
<td></td>
<td>CNS involvement +++</td>
<td>M3: Acute promyelocytic leukaemia – prone to DIC</td>
</tr>
<tr>
<td></td>
<td>Testicular enlargement</td>
<td>M4+5: Monoblasts/monocytes - Skin / gum infiltration + hypokalaemia</td>
</tr>
<tr>
<td></td>
<td>Thymic enlargement (mediastinum)</td>
<td></td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>High WCC (blasts)</td>
<td>High WCC (blasts)</td>
</tr>
<tr>
<td></td>
<td>Lymphocytes (or precursors) +++</td>
<td>Auer rods and granules</td>
</tr>
<tr>
<td></td>
<td><strong>Flow cytometry:</strong> CD34 = precursor/stem cells</td>
<td>Flow cytometry: CD34 = precursor/stem cells</td>
</tr>
<tr>
<td></td>
<td>CD3 = T lymphocytes</td>
<td>CD3 = T lymphocytes</td>
</tr>
<tr>
<td></td>
<td>CD19 = B lymphocytes</td>
<td>CD19 = B lymphocytes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MPO = Myeloid cells</td>
</tr>
</tbody>
</table>
### 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)  
95% remission rate with imatinib  
O/E: splenomegaly - often massive

#### Investigations
- **Ph+ve (Philadelphia chromosome)** in 80% = chromosomal translocation (9;22)  
- PCR for **BCR-ABL** (Philadelphia Ch) fusion gene  
- Monitor disease and therapeutic response  
- **WBC, Neutrophils 50-500**  
- 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.  
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 Ig
- Smear cells (remember SMEAR CLLs) – seen on blood film Ix
- Abnormal BM – lymphocytic replacement

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
- Supportive treatment with transfusions, infection prophylaxis
- 1st line: if p53 deletion = alemtuzumab otherwise = clinical trial or chlorambucil
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, 6-8 cycles in stage 3/
2. Radiotherapy –
   - Often used alongside chemo in bulky areas – high risk of breast cancer in women
3. Intensive chemo and autologous SCT –
   - Relapsed patients

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
**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
- No graft versus 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
- 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
<table>
<thead>
<tr>
<th>B-cell Lymphomas</th>
<th>Comments</th>
<th>Histology</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Burkitt’s</strong></td>
<td>Three types:</td>
<td>All very aggressive, fast growing (t(8;14)) translocation (c)-myc oncogene overexpression Rapidly responsive to Rx</td>
<td>“Starry sky” appearance</td>
</tr>
<tr>
<td></td>
<td>Endemic</td>
<td>Most common malignancy in equatorial Africa EBV-associated Characteristic jaw involvement and abdominal masses</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sporadic</td>
<td>Found outside Africa EBV-associated Jaw less commonly involved</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immuno-deficiency</td>
<td>Non-EBV-associated HIV/post transplant patients</td>
<td></td>
</tr>
<tr>
<td><strong>Diffuse Large B-cell (DLBC)</strong></td>
<td>Middle aged and elderly Aggressive Richter’s transformation Other lymphomas occur secondary to DLBCL</td>
<td>“Sheets of large lymphoid cells”</td>
<td>Rituximab-CHOP Auto-SCT for relapse</td>
</tr>
<tr>
<td><strong>Mantle cell lymphoma</strong></td>
<td>Middle-aged, M&gt;F Aggressive Disseminated at presentation Median survival 3-5 years (t(11;14)) translocation Cyclin D1 deregulation</td>
<td>“Angular nuclei”</td>
<td>Rituximab-CHOP Auto-SCT for relapse</td>
</tr>
<tr>
<td><strong>Follicular</strong></td>
<td>Indolent Mostly incurable Median survival 12-15 yrs (t(14:18)) translocation</td>
<td>“Follicular pattern” “Nodular appearance”</td>
<td>Watch and wait Rituximab CVP</td>
</tr>
<tr>
<td><strong>Mucosal associated lymphoid tissue (MALT)</strong></td>
<td>Marginal zone NHL Middle-aged Chronic antigen stimulation: - (H. pylori) (à) gastric MALT lymphoma - Sjogren’s syndrome (à) parotid lymphoma</td>
<td></td>
<td>Remove antigenic stimulus e.g. (H. pylori) triple therapy, Chemotherapy</td>
</tr>
</tbody>
</table>
### Multiple Myeloma (MM) and Other Paraproteinaemias

#### Multiple Myeloma

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

**Clinical features (CRAB):**  
- Calcium high – thirst, moans, groans, stones, bones  
- Renal failure (plus amyloidosis and nephrotic syndrome)  
- Anaemia (+pancytopenia)  
- Bones: 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)  
- Rouleaux on blood film (RBC stacking)  
- Bence-Jones protein in urine  
- ESR very high  
- >10% plasma cells in BM  

**Staging:** Durie-Salmon staging system

**Treatment:**  
- Supportive for CRAB symptoms inc, bisphosphonates  
- Aim of treatment: induce remission for consideration of autologous stem cell transplant  
- Options:  
  o First line – Bortezomib + / - dexamethasone, cyclophosphamide, lenalidomide  
  o Auto-SCT – curative, best for younger patients  
  o If not suitable for SCT – multiple other new agents e.g. daratumumab

---

<table>
<thead>
<tr>
<th>T-cell Lymphomas (rarer)</th>
<th>Comments – Alemtuzumab (anti CD-52) can be used in Rx</th>
</tr>
</thead>
</table>
| 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** |
### Waldenstrom's Macroglobinaemia (Lymphoplasmacytoid Lymphoma - LPL)

**Elderly men**
Low-grade NHL; lymphoplasmacytoid cells produce monoclonal serum IgM that infiltrates the LNs/BM
Weight loss, fatigue, hyperviscosity syndrome (visual problems, confusion, CCF, muscle weakness)
**Treatment:** plasmapheresis for hyperviscosity; chlorambucil, cyclophosphamide + other chemo

### Systemic Amyloidosis (see other path sections)
Ig light chains = paraprotein -> deposition of abn proteinaceous subst in tissues
Primary or secondary (e.g. due to chronic immune cell stimulation)
Diagnosed via 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** = Velcade (bortezomib) / Chemo / auto-SCT

### 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

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Blood features</th>
<th>Bone marrow features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory anaemia (RA)</td>
<td>Anaemia, no blasts</td>
<td>Erythroid dysplasia with &lt;5% blasts</td>
</tr>
<tr>
<td>Refractory anaemia with ringed sideroblasts (RA + RS)</td>
<td>Anaemia, no blasts</td>
<td>Erythroid dysplasia with &gt;15% ringed sideroblasts</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia (RCMD)</td>
<td>Cytopenia in ≥ 2 cell lines</td>
<td>Dysplasia in &gt;10% cells in ≥ 2 cell lines</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD + RS)</td>
<td>Cytopenia in ≥ 2 cell lines</td>
<td>Dysplasia in &gt;10% cells in ≥ 2 cell lines and &gt;15% ringed sideroblasts</td>
</tr>
<tr>
<td>Refractory anaemia with excess blasts – 1 (RAEB I)</td>
<td>Cytopenias, &lt;5% blasts, no Auer rods</td>
<td>Dysplasias, 5-9% blasts</td>
</tr>
<tr>
<td>Refractory anaemia with excess blasts – 2 (RAEB II)</td>
<td>Cytopenias or 5-19% blasts or Auer rods</td>
<td>Dysplasias, 10-19% blasts or Auer rods</td>
</tr>
<tr>
<td>MDS with 5q deletion</td>
<td>Anaemia, normal or increased platelets</td>
<td>Megakaryocytes with hypolobated nuclei and &lt;5% blasts</td>
</tr>
<tr>
<td>Myelodysplasia Syndrome Unclassified</td>
<td>Complex - cytopenias, no blasts, no Auer rods</td>
<td>Complex - myeloid or megakaryocytic dysplasia, &lt;5% blasts</td>
</tr>
</tbody>
</table>
Aplastic Anaemia

- The inability of BM to produce adequate blood cells
- Haemopoietic 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
  - Inherited (10%) – see below
- Secondary (10-15%) – due to malignant infiltration, radiation, drugs incl. chemo, viruses, Al e.g. SLE

Management:
- Supportive – transfusions, Abx, iron chelation
- Drugs – to promote marrow recovery – growth factors and oxymethalone (androgen)
- Immunosuppressants – idiopathic AA
- SCT

Inherited AA / BM failure syndrome

Fanconi Anaemia (cf Fanconi Syndrome = renal)
- Autosomal recessive. Pancytopenia
- Presents at 5-10yrs
- Skeletal abnormalities (radii, thumbs), renal malformations, microphthalmia, 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.

<table>
<thead>
<tr>
<th>&quot;Philadelphia Chromosome positive&quot;</th>
<th>&quot;Philadelphia Chromosome negative&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Myeloid Leukemia (CML)</td>
<td>Polycythemia vera (PV)</td>
</tr>
<tr>
<td></td>
<td>Myelofibrosis (MF)</td>
</tr>
<tr>
<td></td>
<td>Essential thrombocytosis (ET)</td>
</tr>
</tbody>
</table>

Ph –ive associated with JAK2 mutations, particularly PV (>95%)
Associated with variable increases in reactive polyclonal BM fibrosis and terminal acute leukaemia transformation.

Polycythaemia

Raised red cell mass, Hb, red cell count and packed cell volume
Primary 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)


Clinical Features:
- Hyperviscosity / hypervolaemia / hypermetabolism
- Blurred vision, headache
- Plethoric (“red nose”), gout, thrombosis and stroke, retinal vein engorgement, erythromelalgia
- 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 à 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”

Treatment
- Support with blood products, in some cases - splenectomy
- Hydroxycarbamide, thalidomide, steroids and SCT also used.

Essential Thrombocythaemia (or thrombocytosis)
An MPD where megakaryocytes dominate the BM
50% associated with JAK2

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

Investigations
- Platelet count >600x10⁹
- 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.

FFP
- Use Vit K first
- 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
### Adverse Reactions to Transfusions

#### Immediate

<table>
<thead>
<tr>
<th>Immune</th>
<th>Delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrong blood: ABO</td>
<td>Delayed haemolytic transfusion reaction (DHTR)</td>
</tr>
<tr>
<td>Febrile non-haemolytic</td>
<td>Port-transfusion purpura</td>
</tr>
<tr>
<td>Allergic/anaphylaxis</td>
<td>Transplant-associated GVHD</td>
</tr>
<tr>
<td>Transfusion related acute lung injury (TRALI)</td>
<td></td>
</tr>
</tbody>
</table>

#### Non-immune

<table>
<thead>
<tr>
<th>Bacterial contamination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms occur within minutes to hours</td>
</tr>
<tr>
<td>More commonly occurs with platelet transfusion</td>
</tr>
</tbody>
</table>

#### Delayed (>24 hours)

<table>
<thead>
<tr>
<th>Delayed-haemolytic transfusion reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occurs within 1 week</td>
</tr>
<tr>
<td>Extravascular haemolysis – IgG-mediated</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Graft vs host disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms include diarrhoea, liver failure, skin desquamation and bone marrow failure</td>
</tr>
<tr>
<td>Donor lymphocytes recognise recipient’s HLA as foreign and attack gut, liver, skin and bone marrow</td>
</tr>
<tr>
<td>Prevent by irradiating blood components for immunosuppressed recipients</td>
</tr>
</tbody>
</table>
Symptoms/Signs of an Acute Transfusion Reaction

Stop the transfusion and call a doctor
Observations and documentation check

Transfusion Reaction Flowchart

- Febrile non-haemolytic transfusion reaction
  - Mild fever
  - Urticaria

- ABO incompatibility
  - Bleeding
  - Dark urine

- Bacterial infection of unit
  - High fever
  - Swelling

- TACO fluid overload
  - Raised CVP

- Reaction involves mild fever or urticarial rash only
  - Normal CVP

- Significant change in observations with collapse/shock?
  - No
  - Severe allergic reaction

- Significant fever?
  - And
  - No
  - TRALI

Adapted from Handbook of Transfusion Medicine
Microbiology
### Tuberculosis and other Mycobacteria

- **Gram +ve; aerobic; acid alcohol fast; thick, waxy cell wall (complex, immunogenic)**

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Post-primary (Young adults)</th>
<th>Primary (Children, elderly, HIV)</th>
</tr>
</thead>
</table>
| Cough ± Haemoptysis | ?Re-activation/Re-infection | Multiplicates at pleural surface (Ghon focus). Taken by mΦ to LN (Primary complex). Generalised lympho-haematogenous spread. Granuloma is characteristic lesion (Langhan’s giant cells)
| Fever (with night sweats) | Upper lobes affected | Can be asymptomatic, esp in children
| Weight loss (?>anorexia) | May progress rapidly to cavitation | Rarely:
| Malaise | Classic lesion: caseating granuloma | -Tuberculoma
| Ethnicity | Military spread rare | -‘Progressive primary’; focus or node ulcerates into bronchus → pneumonia, cavity formation, bronchiectasis, consolidation, collapse
|                         | Healing by fibrosis + calcification | -Military TB – progressive, disseminated haematogenous spread. ‘Rich’ foci |

#### TB treatment

**1st line**
- Rifampicin (RIF) – Drug interactions (raised transaminases, induces cytochrome P450), orange secretions hepatotoxicity
- Isoniazid (INN) – peripheral neuropathy (give B6/pyridoxine), hepatotoxicity
- Pyrazinamide – Hyperuricaemia, hepatotoxicity
- Ethambutol – optic neuritis, visual disturbances

- IMA + RIF + PYR + ETH for 2/12 then INN + RIF for 4/12
- TB meningitis – Increase 2nd stage of INN + RIF to 8-10/12
- LATENT TB – 6/12 Isoniazid

DOTS, adherence is key. Vit D supplements.

**2nd line**
- Injectables (capreomycin, kanamycin, amikacin), Quinolones (moxifloxacin), Cycloserine, Ethionamide/Propionamide, PAS, Lineolizid, Clofazamine
- Resistance
  - Mono – one drug only
  - MDRTB – RIF + INN
  - XDRTB – RIF + INN + Injectables (kanamycin/amikacin) + Quinolones

Latent TB – 6-9/12 INN
Prophylaxis – INN alone

#### TB meningitis (2%)

Subacute presentation
- Weight loss, fever, night-sweats
- Headache, neck-stiffness
- Personality change, ↓ GCS
- Focal neurological deficit
  - Diagnosis: CT – tuberculomata, LP – Lymphocytosis
  - Rx – >12/12 anti-TB + steroids

#### Extrapulmonary TB (20%)

- Lymphadenitis
- Pericarditis
- Abdominal (peritonitis, ileitis)
- Genito-urinary, renal, testicular
- Misc: skin, liver etc
- Increased risk in HIV coinfection

#### Epidemiology

Increasing incidence in UK
- RFs: recent migrant, HIV+, homeless, drug users, prison, close contacts, young adults/elderly
- RF for reactivation of latent TB: immunosuppression, malnutrition, ageing, chronic alcohol excess

#### Spinal TB (4%)

- Fever, sweats, wt loss, Back pain
- Haematogenous spread → initial discitis → Vertebral destruction + collapse ± Anterior extension (causing iliac/abdominal abscess)
- Ix – MRI/CT ± Biopsy/Aspirate
- Treatment – 12-12 anti-TB

#### Investigation

Imaging:
- CXR (Upper lobe cavitation – post-primary), CT
- Sputum microscopy – ZN/auramine staining: Gram +ve rods, acid fast, aerobic, intracellular
- Tuberculin skin tests (TST), Mantoux/Heaf using PPD
- IGRA: interferon-γ release assays e.g. Elispot, Quantiferon
- NAAT: PCR-line probe assays, tests for sensitivities
- Other: Liquid culture mediums

#### Vaccination: BCG

Attenuated strain of M. Bovis (BCG=Bacille Calmette-Guerin)
- Efficacy 0-80% – Bad for pulmonary TB. Good for leprosy, TB meningitis, disseminated TB.
- Babies born in or with parents/grandparents from areas with incidence >40/100,000
- Previously unvaccinated new immigrants from high prevalence countries for TB
- Contraindicated in HIV pts
- HIV –ve latent TB → active TB 5-10% lifetime risk
- HIV +ve latent TB → active TB 5-10% yearly risk
- Be aware of immune reconstitution inflammatory syndrome (IRIS) in HIV patients → development of symptoms after HIV tx started

#### Leprosy – Hansen’s disease

M. Lepra + M. Lepromatosis
- Life-long illness. Incubation 2-10yrs
- Poor transmission via nasal secretions
- Most disability 2nd to nerve damage
- Rx – rifampicin, dapsone, clofazimine – if multibacillary

**Key manifestations**
- Skin: Depigmentation, macules, plaques, nodules, trophic ulcers
- Nerves: Thickened nerves, sensory neuropathy
- Eyes: Keratitis, iridocycitis
- Bone: Periostitis aseptic necrosis
- Immunological/Clinical spectrum of leprosy
- Tuberculoid (TT), Paucibacillary. Th1-mediated
- Disfigured lesions
- BT – nerve damage
- Borderline (BB) – multiple plaques
- BL

#### Other mycobacteria (non-tuberculous)

Environmental, no person-person transmission, associated with impaired immunity, poor response to standard anti-TB regimen
- M. Avium-intracellulare complex
- Children – Pharyngitis/cervical adenitis
- Pulmonary – Underlying lung disease (resembles TB)
- Disseminated – Cytotoxics, lymphoma etc
- AIDS – Disseminated multibacillary infection, Mycobacteraemia (consider in HIV pts with franking diarrhoea)
- M. Marinum (fish tank granuloma)
- Single or clusters of papules/plaques
- Swimming pool/aquarium owners
- M. Ulcers (Buruli Ulcer) – insect transmission; tropics/Aus
- Early – painless nodule
- Usually slowly progressive leading to ulceration, scarring + contractures
- Seldom fatal, hideous deformity
Respiratory Tract Infections

**Pneumonia**
- Inflammation of lung alveoli, Pts are sick. Can be lobar/ bronchopneumonia

**Bronchitis**
- Inflammation of medium sized airways. Mainly in smokers. Cough with sputum most days for 3 months, for 2 or more consecutive years.

**Presentation** – Fever, Cough, Pleuritic chest pain, SOB

**Presentation** – Cough, fever, increased sputum production, increased SOB

CXR: normal

**Organisms**: Viruses, *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*

**Rx** – Supportive (O2, fluids etc.) + Abx

**Rx** – Bronchodilation; Physiotherapy +/- Abx

---

<table>
<thead>
<tr>
<th>Classical Causes</th>
<th>Pathogen</th>
<th>Assoc with</th>
<th>Micsoscope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs on Chest Exam + CXR</td>
<td>S. Pneumonia</td>
<td>Rusty-coloured sputum. Usually lobar on CXR. Vaccinate groups at risk</td>
<td>+ve diplococci</td>
</tr>
<tr>
<td>Signs on Chest Exam + CXR</td>
<td>H. influenza</td>
<td>Assoc. w/ smoking, COPD</td>
<td>-ve cocci-bacilli</td>
</tr>
<tr>
<td>Signs on Chest Exam + CXR</td>
<td>M. catarrhalis</td>
<td>Assoc. w/ smoking</td>
<td>-ve coccus</td>
</tr>
<tr>
<td>Signs on Chest Exam + CXR</td>
<td>S. aureus</td>
<td>Assoc. w/ recent viral infection (EMQs: post-INFLUENZA infection) ± cavitation on CXR</td>
<td>+ve cocci “grape-bunch clusters”</td>
</tr>
<tr>
<td>Signs on Chest Exam + CXR</td>
<td>K. pneumonia</td>
<td>Alcoholism, elderly. Haemoptysis</td>
<td>-ve rod, enterobacter</td>
</tr>
</tbody>
</table>

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**Atypical Pneumonia Causes**
- NO signs on chest examination or signs not in keeping with CXR
- Organisms with no cell wall à don’t respond to penicillin Abx. Use Macrolides + Tetracyclines

**Consider**
- Travel, air conditioning, water towers, HEPATITIS, Low Na
- Common – systemic symptoms, joint pain, cold agglutinin test, erythema multiforme. Risk SJS, AIHA
- Hard to diagnose – TWAR agent
- Birds
- Whooping cough in unvaccinated – (often travelling community in EMQs)
- Poor response to Abx

---

**Immunosuppression + Respiratory Tract Infections**

| HIV | P. Jiroveci (PCP), TB, Cryptococcus neoformans |
| Neutropenia | Fungi – Aspergillus spp. |
| Bone Marrow Tx | Aspergillus + CMV |
| Splenectomy | Encapsulated organisms – H. influenza, S. pneumonia, N. Meningitidis |
| Cystic Fibrosis | Pseudomonas aeruginosa, Burkholderia cepacia (high mortality) |
Diagnosis:

- Urine Antigen Tests in severe CAP for *S. pneumoniae, Legionella*
- Antibody tests – Paired serum samples (At presentation + 10-14/7). Rise in Ab level over time. Most useful for difficult-to-culture (*Chlamydia, Legionella*)
- Immunofluorescence – Antibody labelled with fluorescent dye – used in Virology. (*PCP – Also detected by Silver stain in cytology lab. Boat-shaped organisms*)

(Hospital acquired pneumonia – >48hrs into hospital stay without previous infection.)

BAL to differentiate URT + LRT microbes:
- URTI: Sinusitis, Tonsillitis
- LRTI: Bronchitis, Pneumonia, Empyema, Bronchiectasis, Lung abscess

### Abx for Community Acquired Pneumonia

<table>
<thead>
<tr>
<th>Classical</th>
<th>Wilnecillin 1st line (Amoxicillin) or Macrolide (Penn. Allergic) (5-7days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate-Severe</td>
<td>Penicillin + Macrolide (Co-amoxiclav + Clarithromycin) (2-3 weeks)</td>
</tr>
</tbody>
</table>

### Abx for Hospital Acquired Pneumonia

<table>
<thead>
<tr>
<th>1st Line: Ciprofloxacin ± Vancomycin</th>
<th>2nd Line/ITU: Piptazobactam + Vancomycin (ITU pts increased risk of resistant bacteria/MRSA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspiration: Cefuroxime + Metronidazole (need gram +ve, -ve and anaerobic cover for aspiration)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Special therapy – CAP</th>
<th>Special therapy – HAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Legionella</td>
<td>Pseudomonas spp.</td>
</tr>
<tr>
<td>S. aureus</td>
<td>MRSA</td>
</tr>
<tr>
<td>Flucloxacillin</td>
<td>Vancomycin</td>
</tr>
</tbody>
</table>

**A simplistic antibiotic framework**

- **Blue bugs (gram +ve)**: S. Aureus
- **Pink bugs (gram –ve)**: Pseudomonas

- **Amoxycillin**
- **Flucloxacillin**
- **Co-amoxiclav augmentin**
- **Cefuroxime**
- **Cefotaxime**
- **Ceftazidime**
- **Vancomycin**
- **Gentamicin**
- **Meropenem or Piperacillin + Tazobactam**

**Atypical pneumonia**
- Clarithromycin / doxycycline
**Infective Endocarditis**

**Definition:** Infection of innermost layer of heart, usually the valves. Poor vascular supply.

### History
- **Fever** – often presents as PUO
- **Non-specific symptoms** – anorexia, weight loss, malaise, fatigue, rigors and night sweats, weakness
- **Acute symptoms** – SOB, chest tightness, embolic complications
- **Dental history** – important route of infection
- **RF (risk factors)** – RHD, congenital heart disease, cardiac sx, valve replacement, long term lines
  - Bacteraemias (S. aureus, Enterococcus), GI/Bowel issues

### Examination
- **Heart murmurs** that often change
  - **If SUBACUTE:** Clubbing, Splinter haemorrhages, Osler's nodes, Janeway lesions, Roth spots, Splenomegaly, Haematuria

### Investigations
- Urinalysis, FBC (Hb), U&E, CRP (monitor therapy), ESR, 3x blood cultures wo ABE, Serology (if culture -ve), CXR, Echo

### Dukes Criteria: Diagnosis
- 2 major, or 1 major + 3 minor, or 5 minor criteria
  - **Major criteria:**
    - Persistent bacteraemia (>2 +ve blood cult.)
    - Echo findings – vegetations seen
    - +ve serology for bartonella, coxiella, brucella
  - **Minor criteria:**
    - Predisposing RF – murmur, IVDU etc.
    - Fever >38°C or high CRP
    - Evidence of immune complex formation: splinter haemorrhages, haematuria
    - Vascular phenomena – Major arterial emboli – stroke, PE
    - Positive echo that does not meet major criteria

### Infective agents
- **Subacute bacterial endocarditis (SBE)** – Low virulence strep (often S. viridans). Mid-moderate illness progressing over weeks/months.
  - Propensity to haematogenously seed extracardiac sites
- **Acute bacterial endocarditis (ABE)** – Fulminant illness days-weeks. S. aureus (frequently metastatic infection).
  - Coagulase negative staphylococci cause most cases of prosthetic valve endocarditis

### Treatment
- **Streptococcus viridans – Bacitracin +** Gentamicin
- **MSSA endocarditis –** Eloxacin for 4/52
- **MRSA endocarditis –** Vancomycin + Gent/Rifampicin/Eloxacin
- **Enterococcal endocarditis –** Ampicillin + Gent

### Indications for Surgical Intervention
- >1 serious systemic embolus/high risk
- Uncontrolled infection
- Significant valve dysfunction
- Lack of response to antibiotics
- Local suppuration complication eg perivalvular abscess. (Watch for

### Clinical Point: If infective endocarditis is suspected, please make sure that appropriate blood cultures (at least 3 or new guidelines even suggest 6!) are taken from different sites. The reason for this is that knowing the responsible bacterium and appropriate sensitivities is invaluable when treating a patient and may even mean they can be treated as an outpatient and avoid unwanted side effects. Similarly, remember that by making a diagnosis of infective endocarditis you are committing a patient to 6 weeks of intravenous antibiotics (as the valves have such a poor vascular supply) so treat with care.
## GI infections

<table>
<thead>
<tr>
<th>Organism</th>
<th>Subspecies</th>
<th>Clinical Symptoms</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clostridia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Botulinum</td>
<td></td>
<td>Canned/vacuum packed foods: Honey (kids), beans (students). Ingestion of preformed toxin (inactivated by cooking)</td>
<td>Antitoxin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blocks Ach release from peripheral nerves à paralysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Descending paralysis</strong> - differentiates from GBS</td>
<td></td>
</tr>
<tr>
<td>Perfringens</td>
<td></td>
<td>Reheated meats, superantigen enterotoxin (bind directly to TCR + MHC outside peptide binding site à massive cytokine production by CD4 ie systemic toxicity + suppression of adaptive response)</td>
<td>Metronidazole 2nd line = Vancomycin - PO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acts on small bowel, 8-16hrs incubation.</td>
<td>Self limiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Watery diarrhea + cramps, lasts 24hrs. Also causes gas-gangrene</td>
<td></td>
</tr>
<tr>
<td>Difficile</td>
<td></td>
<td>2 exotoxins (A,B) Get <strong>pseudomembranous colitis</strong> (i.e an inflamed bowel) Caused by Abx usually cephalosporins/ fluoroquinolones</td>
<td></td>
</tr>
<tr>
<td>Bacillus cereus</td>
<td>S. aureus</td>
<td>Reheated rice (spores germinate) and sudden vomiting Superantigen — short incubation (4hrs) Increased cAMP— long incubation (18hrs). Watery non-bloody diarrhoea</td>
<td>Don’t treat, self limited</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Main virulence factor: Protein A. Catalase, coagulase +ve.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Appears in tetrads, clusters on gram stain. Beta haemolytic on blood agar</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Produces enterotoxin (exotoxin that acts as superantigen, releasing IL1 and IL2 à prominent vomiting + watery, non bloody diarrhoea)</td>
<td></td>
</tr>
<tr>
<td><strong>Staph</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. aureus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gram -ve Enterobacteriaceae (Facultative anaerobes, oxidase negative)</strong></td>
<td>ETEC</td>
<td><strong>Toxigenic, Travellers diarrhoea</strong>&lt;br&gt;Heat labile LT stimulates adenyl cyclase and cAMP&lt;br&gt;Heat stable ST stimulates guanylate cyclase. Act on the jejunum, ileum not on colon.</td>
<td>Self limiting - can treat with ciprofloxacin (avoid Abx) Source: human faeces-contaminated food/water</td>
</tr>
<tr>
<td></td>
<td>EIEC</td>
<td>Invasive dysentery</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EHEC</td>
<td><strong>Haemorrhagic, Caused by verotoxin</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HUS</td>
<td>Anaemia, thrombocytopenia, renal failure (0157:H7 toxin)</td>
<td></td>
</tr>
<tr>
<td>Salmonella: O, H, Vi Ag’s H2S producers, TSI agar, XLD</td>
<td>EPEC</td>
<td>Infantile diarrhoea (Paeds)</td>
<td>Ceftriaxone or ciprofloxacin</td>
</tr>
<tr>
<td></td>
<td>Typhi + Paratyphi (enteric fever)</td>
<td>Only transmitted by humans Multiplies in Peyers patches, 3% carriers (in gallbladder) Slow onset fever + CONSTITUTION, relative bradycardia Splenomegaly and rose spots, anaemia and leukopaenia</td>
<td></td>
</tr>
<tr>
<td>Organism</td>
<td>Subspecies</td>
<td>Clinical Symptoms</td>
<td>Treatment</td>
</tr>
<tr>
<td>----------</td>
<td>------------</td>
<td>-------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Vibrios</td>
<td>Cholera</td>
<td>Rice water stool. Human faeces (eg in shellfish)</td>
<td>Supportive</td>
</tr>
<tr>
<td>- (comma shaped)</td>
<td></td>
<td>↑cAMP opens Cl⁻ channel at apical membrane of enterocytes -&gt; efflux of Cl⁻ to lumen (loss of H₂O and electrolytes). Massive diarrhoea without inflammation</td>
<td></td>
</tr>
<tr>
<td>Late lactose fermenters</td>
<td>Parahaemolyticus</td>
<td>Ingestion of raw undercooked seafood (common in Japan)</td>
<td>Doxycycline</td>
</tr>
<tr>
<td>Oxidase +ve</td>
<td></td>
<td>3/7 of diarrhoea which is often self limiting</td>
<td></td>
</tr>
<tr>
<td>Campylobacter</td>
<td>Jejuni</td>
<td>Cellulitis in shellfish handlers</td>
<td>Doxycycline</td>
</tr>
<tr>
<td>- (curved, comma or S shaped)</td>
<td></td>
<td>Fatal septicaemia with D+V in HIV pts</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drinking unpasteurised milk, food eg: poultry</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Prodrome of headache and fever, abdo cramps, bloody (foul-smelling) diarrhoea</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Curved, S-shaped, Microaerophilic, Oxidase +ve, motile, sensitive to nalidixic acid (first quinolone).</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Assoc with Guillain-Barre, reactive arthritis (Reiter's)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Erythromycin or Cipro if first 4-5/7</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td></td>
<td>GI watery diarrhoea, cramps, headache, fever, little vomiting.</td>
<td>Ampicillin, Ceftriaxone, Cotrimoxazole</td>
</tr>
<tr>
<td>V or L shaped, β haemolytic, aesculin +ve, tumbling mobility</td>
<td></td>
<td>Perinatal infection, immunocompromised patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Outbreaks of febrile gastroenteritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Refrigerated food (unpasteurised dairy, vegetables)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Motile trophozoite in diarrhoea</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-motile cyst in non-diarrhoeal illness</td>
<td></td>
</tr>
<tr>
<td>Protozoa: Entamoeba Histolytica</td>
<td></td>
<td>4 nuclei and no animal reservoir. Colonize colon</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Makes a flask-shaped ulcer on histology</td>
<td></td>
</tr>
<tr>
<td>EMQ: MSM</td>
<td></td>
<td>Symptoms: dysentery, wind, tenesmus. Chronic weight loss + RUQ pain due to liver abscess</td>
<td></td>
</tr>
<tr>
<td>Also: food, water, soil</td>
<td></td>
<td>Stool microscopy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Metronidazole + Paromomycin if luminal disease</td>
</tr>
</tbody>
</table>
| Giardia lamblia | Pear shaped trophozoite 2 nuclei  
| EMQ: Travellers/hikers/MSM/mental hospitals | Trophozoites/cysts found in stool  
| | Get it by ingesting cysts from faecally contaminated H₂O  
| | Malabsorption of protein + fat - foul smelling non-bloody diarrhoea  
| | Dx = ELISA string test | Metronidazole |
| Cryptosporidium Parvum | Infected the jejunum. Severe diarrhoea in immunocompromised. Oocysts seen in stool by modified Kinyoun acid fast stain | Paromomycin  
| | | Nitazoxanide in kids |
| Mycobacteria – M.Tb, MAI | Always a possibility (especially in HIV +ve pts)  
| Viruses: Secretory Diarrhoea | Rotavirus - <6yrs  
| | Adenovirus – Types 40,41 cause non bloody diarrhoea (<2yrs)  
| | Norovirus – Adult outbreaks, vomiting.  
| | Poliovirus  
| | Enteroviruses (coxsackie, ECHO)  
| | Hepatitis A |
Urinary Tract Infection
Classification: Uncomplicated Vs Complicated (functionally or structurally abnormal tract)

Common organisms, presentation and management of urinary tract infections
UTI is common in women because they have short urethras:
- Ax: Contamination (eg from rectum). Bacterial adhesion eg:proteus fimbriae; klebsiella k antigen
- Bugs: E. coli, Proteus, Klebsiella, Staphylococcus saprophyticus (frequent causes of Lower UTIs)
- Px: Frequency, dysuria, abdo/flank pain (Very young: non-specific; Old: asymptomatic)
- Dx: Clinical, Dipstick (nitrite, leucocytes +ve), Bloods - WBCs, Neutrophils, CRP, MSU MC&S (see organism, pyuria)
- Rx: Nitrofurantoin is 1st line from NICE or Trimethoprim if low risk of resistance, but check EGFR is >45ml/min if giving Nitrofurantoin"

If pyelonephritis – Broad spec IV Abx eg: Co-amoxiclav ± Gent; Cefuroxime ± Gent.

Wound, Bone and Joint Infections
Describe the aetiology, organisms, presentation, diagnosis and management

Surgical site infection
- Ax: Wound contamination
- Bugs: Staphylococcus aureus, E. coli, Pseudomonas, Haemolytic strep. Rx: Flucloxacillin

Septic arthritis
- Ax: Abnormal joint (eg RA) or Immunosuppression & bacteraemia (eg diabetes, IVDU)
- Bugs: Staph aureus(46%), Streptococci (22%), less commonly various gram -ve organisms eg: E-Coli. Bug adheres to synovial membranes and proliferates in fluid.
- Px: Unwell febrile patient with red hot swollen joint (50%: knee, unable to weightbear). Host inflammatory response damages joint.
- Dx: Blood culture before Abx, joint aspirate (>50,000cells/mm³), inflammatory markers. Imaging shows effusion
- Rx: IV antibiotics (cephalosporin or flucloxacillin) MRSA - Vanc. Drain joint.

Osteomyelitis
- Ax: Local or haematogenous spread. Brodie abscess (subacute) à frank osteomyelitis
- Bugs: Staphylococcus aureus
- Px: Pain, fever, local swelling
- Dx: MRI best imaging, bone biopsy for culture/histology
- Rx: Antibiotics treat most cases. Second-line = Debridement. Remove sequestra and infected bone

Prosthetic Joint Infection
- Ax: Local (wound infection); Systemic bacteraemia (eg UTI)
- Bugs: Staphylococcus, Gram negatives eg Enterobacteriaceae
- Px: Pain, failure of joint, sinus, patient complains joint was ‘never right’
- Dx: Radiology – ‘loosening’. Joint aspirate – done with caution as risk of introducing infection if joint is not infected.
- Rx: Remove metalwork and revise joint replacement: single or two stage revision. Use Abx-impregnated cement.
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: clindamycin (often used in penicillin allergic patients with cellulitis), cephalosporins, ciprofloxacin
- 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**
- Acute: often bacterial
- Chronic: headaches for months: more likely to be eg: TB or Cryptococcus
- Aseptic: usually viral

- **Bacterial:** *Neisseria meningitidis* Gram -ve, *Streptococcus pneumoniae* Gram +ve,
  - Neonates: GI flora: Group B *Streptococci*, *Listeria monocytogenes*, *E. coli*
  - Elderly: Group B *Strep*, *Listeria m.*, *Mycobacterium tuberculosis* (subacute)
- **Viral:** Enterovirus eg coxsackie, mumps, HSV2 + echovirus – children <1yr
- **Fungal:** *Cryptococcus neoformans* (chronic)

**Aetiology, presentation, diagnosis and management of bacterial meningitis**

Bacterial meningitis
- Ax: spread systemic (eg from mucosa) or local (eg skull #). Overcrowding.
- Risk factors
  - *N. meningitidis*: Complement deficiency, hyposplenism (susceptible to encapsulated organisms), hypogammaglobulinaemia
  - *S. pneumoniae*: Complement deficiency, hyposplenism, Immune defect (alcoholic), infection (pneumonia),entry #, previous head trauma w/ CSF leak

- Px: Headache, vomiting, photophobia, irritable, fever, focal neuro signs, rash.
- Dx: Clinical + blood cultures, serum-Ag, EDTA-PCR, throat swab
CSF - WCC (polymorphs)↑, protein ↑, glucose ↓
- Rx: **Resuscitate! Ceftriaxone and corticosteroids** (cover *Listeria* with ampicillin)
- If consciousness affected, consider IV acyclovir to cover encephalitis
- Consider Glasgow Meningococcal Septicaemia Prognostic Score.

NB Viral meningitis: no change in consciousness or focal neurology (unlike viral encephalitis)
### CSF Analysis

<table>
<thead>
<tr>
<th></th>
<th>Glucose</th>
<th>White Cells</th>
<th>Cell Type</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td>Low</td>
<td>High</td>
<td>Polymorphs</td>
<td></td>
</tr>
<tr>
<td>Partially treated bacterial</td>
<td>Normal</td>
<td>High</td>
<td>Polymorphs</td>
<td></td>
</tr>
<tr>
<td>Virus</td>
<td>Normal</td>
<td>High</td>
<td>Mononuclear</td>
<td>Protein</td>
</tr>
<tr>
<td>TB/Cryptococcus</td>
<td>Low</td>
<td>High</td>
<td>Mononuclear</td>
<td>Protein</td>
</tr>
</tbody>
</table>

### Sexually Transmitted Infections

#### Common Presentations:

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

<table>
<thead>
<tr>
<th>Discharge</th>
<th>Ulceration</th>
<th>Rashes, Lumps/Growths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonorrhoea</td>
<td>Syphilis</td>
<td>Genital warts - HPV</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>HSV</td>
<td>Molluscum contagiosum</td>
</tr>
<tr>
<td>Trichomonas</td>
<td>LGV</td>
<td>Scabies</td>
</tr>
<tr>
<td>Candida</td>
<td>Chancroid</td>
<td>Pubic lice</td>
</tr>
<tr>
<td>Bacterial Vaginosis</td>
<td>Donovanosis</td>
<td></td>
</tr>
</tbody>
</table>

#### Genital ulcers: If -
- Painful = **herpes** > chancroid
- Painless = **syphilis** > lymphogranuloma venereum (LGV) + granuloma inguinale

#### Gonorrhoea
- *Ophalmia neonatorum* (neonatal conjunctivitis) develops if left untreated when transfer to child from birth canal.
- Pts with complement deficiencies: they get disseminated gonococcal infection -> Septicaemia, rash and/or arthritis

**Diagnosis**: urethral (sensitivity 95%) / rectal (sensitivity 20%) smears – producing a culture from these is Gold Standard.

**Treatment**: Ceftriaxone IM – 250mg single dose OR Cefixime PO – 400mg single dose
- If resistant Spectinomycin IM – 2g single dose

<table>
<thead>
<tr>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated Infection (90%)</td>
<td></td>
</tr>
<tr>
<td><strong>Non-gonococcal Urethritis (NGU)</strong></td>
<td></td>
</tr>
<tr>
<td>- Most common STI in Europe</td>
<td></td>
</tr>
<tr>
<td>- Mucoidal/Mucopurulent discharge</td>
<td></td>
</tr>
<tr>
<td><strong>Post-gonococcal Urethritis (PGU)</strong></td>
<td></td>
</tr>
<tr>
<td>- Following gonorrhoea rx</td>
<td></td>
</tr>
<tr>
<td>- Prevented by concomittant rx with a tetracycline</td>
<td></td>
</tr>
<tr>
<td>1) Mucopurulent cervicitis</td>
<td></td>
</tr>
<tr>
<td>- Erythema and oedema</td>
<td></td>
</tr>
<tr>
<td>2) Urethra (vaginal leakage)</td>
<td></td>
</tr>
</tbody>
</table>
**Chlamydia**

*Chlamydia trachomatis*: Obligate intracellular pathogen. Cannot be cultured on agar. Gram negative.
- Assoc. with younger age. In the UK 10% of <25s are affected.
- Often asymptomatic (in 50% of men and 80% of women)
- Unique growth cycle, existing in two forms:
  - Elementary bodies, stable, extracellular
  - Reticulate particles, intracellular, metabolically active
- Serovars A, B, C – Trachoma – infection of the eyes which can -> blindness
- Serovars D-K – Genital chlamydia infection, ophthalmia neonatorum

**Complications:**
- PID, Tubal factor infertility, ↑risk ectopic, ↑risk endometriosis, Chronic pelvic pain, Epididymitis, Reiters syndrome, Adult conjunctivitis, Ophthalmia neonatorum

**Diagnosis:**
- NAAT (nucleic acid amplification tests). Gold standard. High specificity + sensitivity

**Treatment of uncomplicated Chlamydia:**
- Azithromycin – 1g (4 capsules) stat
- Doxycycline – 100mg BD 7/7
  - S/E – N&V, photosensitivity; C/I pregnancy (disturbance bone growth, tooth discoloration)
- Erythromycin – 500mg QDS 7/7 or 500mg BD 2/52. S/E – GI

**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
- *Early LGV* – 1° stage 3-12/7 – Genital ulcer: painless, non-indurated. Balanitis, proctitis, cervicitis
- *Early LGV* – 2° stage 2-25/52 – Inguinal buboes: painful, 2/3 unilateral. May rupture. Fever, malaise, Rarely (hepatitis, meningoencephalitis, pneumonitis), Proctocolitis, Hyperplasia of lymphoid tissue
- *Late LGV* – Inguinal LNpathy, abscess formation, genital elephantiasis, genital ulcers, frozen pelvis, rectal strictures, perirectal abscesses + fistulae, lymphorroids
- *Current LGV outbreak*: Rectal symptoms – Pain, tenesmus, bleeding, mucous discharge. O/E – Proctitis

**Diagnosis:**
- NAAT (currently unlicensed)
- If positive will be sent to ref lab at central HPA
- Confirmation of *C trachomatis* by real time PCR on 2 platforms
- Genotypic identification of L1, L2 or L3 serovar

**Treatment:**
- Tetracyclines: **Doxycycline 100mg BD for 21/7**
- Erythromycin 500mg QDS for 21/7 / Azithromycin 1g weekly 3/52
**Syphilis**

*Treponema pallidum* – Obligate gram-negative spirochaete. Majority of cases are in those who are HIV +ve. Often co-infected with HCV or another STI. Rising in UK.

- Treponemes seen in 1° lesions by dark-ground microscopy. Can be detected with multiplex real-time PCR
- Detection of antibody is diagnostic method of choice.

1. **Non-Treponemal tests**
   - Detect non-specific antigens
   - VDRL slide test: detects lipoidal antibody on both host and treponemal cells
   - Reagents contain cardiolipin, lecithin and cholesterol – can get biological false +ves
   - RPR is a modified VDRL test
   - Positive is indicative of treponemal infection
   - Usefull in primary syphilis
   - Titre falls in response to treatment therefore 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

---

**Syphilis**

<table>
<thead>
<tr>
<th>1° syphilis</th>
<th>Macule -&gt; papule -&gt; indurated painless genital ulcer appearing 1-12 weeks following transmission. Often solitary. May persist 4-6 weeks (chancre) Clean base with serous exudate. Regional adenopathy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2° syphilis</td>
<td>Systemic bacteraemia. Low grade fever, malaise, Symmetrical, Non-pruritic, Maculo-papular rash on back, trunk, arms, legs, palms, soles, face 1-6/12 following infection. Mucosal lesions, Uveitis, choroidoretinitis, alopecia, ‘snail track’ oral ulcers, condyloma acuminata (genital warts). Neurological involvement (Aseptic meningitis, Cranial nerve palsies, Optic neuritis, Acute nerve deafness)</td>
</tr>
<tr>
<td>Latent</td>
<td>No obvious signs but serological infection (asymptomatic)</td>
</tr>
</tbody>
</table>
| 3° syphilis | Gumma (granuloma) – Rare. 2-40 yrs later. Skin, bone, mucosa. Spirochaetes scanty – DTH reaction  
Cardiovascular – 10-30 yrs later. Uncomplicated + complicated aortitis. +++ spirochaetes, +++ inflammation  
Neurosyphilis (most common in HIV +ve) – 2-30 yrs later. Meningovascular, General paresis of the insane, Tabes dorsalis, Gumma. Spirochaetes in CSF. Small vessel vasculitis. Argyll-Robertson pupil (prostitute’s pupil – accommodates but does not react) |

Treatment: **Single dose IM Benzathine Penicillin (Doxycycline if allergic)**

- Monitor RPR, need to see a four-fold reduction to consider tx successful
- NB: Jarisch-Heimer reaction (fever, headache, myalgia, sometimes exacerbation of syphilitic symptoms) – common, develops within hours of abx administration and clears within 24hrs.

**Congenital syphilis**: may occur during pregnancy or birth. Often 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-negative coccobacillus (like Hib)
- Tropical ulcer disease mainly in Africa. Rare in UK
- Often multiple ulcers, frequently painful
- Diagnosis – Culture (Chocolate agar), PCR

Donovanosis = Granuloma inguinale
- Klebsiella granulomatis. Gram negative bacillus
- Africa, India, PNG, Australian aboriginal communities
- Large, expanding ulcers starting as papule or nodule that breaks down. Beefy red appearance
- 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)

Trichomoniases
- Flagellated protozoan – T. vaginalis
- Diagnosis – Wet prep microscopy, PCR
- Asymptomatic or urethritis in men. Discharge in women. Assoc. ↑ risk of HIV acquisition
- Treatment – Metronidazole

Bacterial vaginosis
- Abnormal vaginal flora, polymicrobial, ↓ lactobacilli. Discharge, odour
- Sexually associated, not transmitted. May be associated with hygiene practices
- Diagnosed on microscopy of gram stain, raised pH, whiff test, clue cells
- Still not fully understood. Often recurrent. Assoc. with preterm delivery

Candidiasis
- Usually Candida albicans, yeast
- If symptomatic, white thick discharge, itching, soreness, redness
- Common presentation in women as vulvovaginitis, men balanitis
- Not sexually transmitted, can be part of normal flora
- Treated with topical or oral antifungals, e.g. clotrimazole or fluconazole
- Recurrence may be associated with immunodeficiency or hygiene practices

Molluscum contagiosum
- Pox virus, dsDNA
- Hands + faces in children, spread skin to skin contact.
- In adults, causes genital lesions + spread via sexual contact.
- Facial molluscum in adult = HIV until proved otherwise. Get giant lesions in the immunocompromised
- Treatment if required, is destructive – cryotherapy.

Genital Warts
- dsDNA Human Papillomavirus. Visible genital warts: HPV 6 or HPV11 (not assoc. with ↑ risk cervical dysplasia)
- Often Asx; warts can recur after Tx. Incubation time 3 weeks à 8 months
- Diagnosis by Examination – 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

<table>
<thead>
<tr>
<th>Target</th>
<th>Class</th>
<th>Example</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhibit cell wall synthesis</strong></td>
<td>β-lactams: Penicillins, cephalosporins, carbapenems</td>
<td>Benzylpenicillin, ceftriaxone, meropenem</td>
<td>Gram positive Gram negative: 3rd gen ceph’s, carbapenems</td>
</tr>
<tr>
<td></td>
<td>Glycopeptides</td>
<td>Vancomycin, Teicoplanin</td>
<td>MRSA, C.Diff</td>
</tr>
<tr>
<td></td>
<td>Aminoglycosides</td>
<td>Gentamicin</td>
<td>Gram negative sepsis</td>
</tr>
<tr>
<td></td>
<td>Tetracyclines</td>
<td>Doxycycline</td>
<td>Intracellular-chlamydia</td>
</tr>
<tr>
<td></td>
<td>Macrolides</td>
<td>Erythromycin</td>
<td>Gram +ve (PCN allergy)</td>
</tr>
<tr>
<td></td>
<td>Chloramphenicol</td>
<td>Eye drops</td>
<td>Bacterial conjunctivitis</td>
</tr>
<tr>
<td></td>
<td>Oxazolidinones</td>
<td>Linezolid</td>
<td>Gram +ve, MRSA + VRE</td>
</tr>
<tr>
<td><strong>Inhibit DNA synthesis</strong></td>
<td>Fluoroquinolones</td>
<td>Ciprofloxacin</td>
<td>Gram negative</td>
</tr>
<tr>
<td></td>
<td>Nitroimidazoles</td>
<td>Metronidazole</td>
<td>Anaerobes + protozoa</td>
</tr>
<tr>
<td><strong>Inhibit RNA synthesis</strong></td>
<td>Rifamycin</td>
<td>Rifampicin</td>
<td>Mycobacteria – used in TB</td>
</tr>
<tr>
<td><strong>Cell membrane toxin</strong></td>
<td>Polymyxin</td>
<td>Colistin</td>
<td>Gram negative</td>
</tr>
<tr>
<td></td>
<td>Cyclic lipopeptide</td>
<td>Daptomycin</td>
<td>Gram +ve, MRSA + VRE</td>
</tr>
<tr>
<td><strong>Inhibit folate metabolism</strong></td>
<td>Sulfonamides</td>
<td>Sulphamethoxazole</td>
<td>PCP (with trimethoprim – co-trimoxazole)</td>
</tr>
<tr>
<td></td>
<td>Diaminopyrimidines</td>
<td>Trimethoprim</td>
<td>UTI</td>
</tr>
</tbody>
</table>

NB: Gram +ves: eg *Staphylococcus* + *Streptococcus*. Gram -ves: eg *E. coli*, *Pseudomonas*

**Broad** spectrum: Co-amoxiclav, Tazocin, Ciprofloxacin, Meropenem

**Narrow** spectrum: Flucloxacillin, Metronidazole, Gentamicin

**The four mechanisms of antibiotic resistance – BEAT drug action**

1. **Bypass** antibiotic-sensitive step in pathway eg: MRSA
2. **Enzyme-mediated** drug inactivation eg: β-lactamases
3. Impairment of **Accumulation** of the drug eg: tetracycline resistance
4. Modification of the drug’s **Target** in the microbe eg: Quinolone resistance
Typical antibiotics used against various focal and systemic infections
(Always use local guidelines!)

<table>
<thead>
<tr>
<th>Site</th>
<th>Organism/severity/circumstance</th>
<th>Antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. aureus</td>
<td></td>
<td>Flucloxacillin (unless allergy)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>β-haemolytic Streptococcus Mild</td>
<td>Benzylpenicillin</td>
</tr>
<tr>
<td>Community-acquired</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pneumonia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital-acquired</td>
<td>Severe</td>
<td>Co-amoxiclav + clarithromycin (covers atypicals)</td>
</tr>
<tr>
<td>pneumonia</td>
<td></td>
<td>Amoxicillin</td>
</tr>
<tr>
<td>Bacterial meningitis</td>
<td>Meningococcus/streptococcus</td>
<td>Ceftriaxone (amox if listeria likely; young/old/IC)</td>
</tr>
<tr>
<td>UTI</td>
<td>Community</td>
<td>Trimethoprim/ nitrofurantoin (3days)</td>
</tr>
<tr>
<td>Nosocomial</td>
<td>Co-amoxiclav or cephalaxin</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>Severe</td>
<td>Tazocin/ceftriaxone, Metronidazole ± Gent</td>
</tr>
<tr>
<td>Neutropenic</td>
<td></td>
<td>Tazocin + gentamicin</td>
</tr>
<tr>
<td>Colitis</td>
<td>Clostridium difficile</td>
<td>Metronidazole PO (stop ceph!)</td>
</tr>
</tbody>
</table>

Microbiology in immunocompromised hosts

Causes of immunocompromise:
1. Transplant
2. AIDS
3. Iatrogenic: chemotherapy (neutropaenia)/ biologics (cause specific immune deficiencies)
4. Rare genetic causes

Pathogens of specific concern

Do not cause disease in immunocompetent/ cause more severe disease in immunocompromised.

Viruses
- **Herpesviridae**: 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.

Fungi
- Candida
- Cryptococci
- Aspergillus
- Dermatophytes
- Mucormycosis
**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.

3 antigenically different flus tend to affect humans each year

1. Influenza A (H1) (peaks beginning of January)
2. Influenza A (H1N1) (peaks end of December)
3. Influenza B (peaks March)

- Trivalent vaccine in targeted pop’s = purified fraction with HA + NA of inactivated virus

Natural reservoir of Influenza A is ducks

Humanàhuman transmission of bird flu (H5N1) difficult as virus does not replicate very well at cold temperatures of upper airways (32°C).

Better in deeper lung tissue (still not ideal – 41.5°C) and from here it is difficult to escape.

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

- **NA – neuraminidase (sialidase) activity**
  - Cleaves sialic acid residues exposing receptors on host cell, disrupts mucin barrier.

- **HA – haemogglutinin 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** = Mutation occur to HA/NA to give new strains of the virus

**Antigenic Shift** = Complete change of HA/NA

- Can only occur with influenza A
- There is trading 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 (Influenza A only) – Targets M2 ion channel. BUT single AA mutation (S31N) in M2 = resistance (now in many ‘flu A strains incl. H1N1)
- Neuraminidase inhibitors: Oseltamivir (Tamiflu), Zanamivir (Relenza), Sialic acid – Effective only if given <48hrs after infection
## Virology Summary Table

<table>
<thead>
<tr>
<th>Virus</th>
<th>Virology</th>
<th>Clinical</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Herpesviridae</strong></td>
<td><strong>Herpes Simplex Virus (HSV)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enveloped, dsDNA genome</td>
<td>1. Herpes labialis (cold sores) (HSV-1)&lt;br&gt;a. Incubation 2-12/7. Severe painful ulceration, tendency to coalesce, erythematous base&lt;br&gt;b. Fever + submandibular lymphadenopathy. Differential – Herpangina (Coxsackie A)&lt;br&gt;2. Genital ulceration (HSV-2)&lt;br&gt;a. Incubation 4-7/7. Fever, dysuria, malaise, Inguinal lymphadenopathy, Pain++, vesicular rash&lt;br&gt;b. Herpes meningitis 1-2/52 later in 4-8% of 1° genital herpes. SACRAL RADICULOMYELTIS – urinary retention (self limiting)&lt;br&gt;In immunocompromised:&lt;br&gt;1. Cutaneous dissemination&lt;br&gt;2. Oesophagitis – <em>pain on swallowing</em>&lt;br&gt;3. Hepatitis&lt;br&gt;4. Viraemia&lt;br&gt;<strong>Congenital infection (85% perinatal):</strong>&lt;br&gt;1. Neurological: Microcephaly, encephalomalacia, hydranencephaly&lt;br&gt;2. Skin: scarring, active lesions, hypo- and hyperpigmentation&lt;br&gt;3. Eyes: microphthalmia, retinal dysplasia, optic atrophy, and/or chorioretinitis</td>
<td><strong>Aciclovir:</strong> guanosine analogue&lt;br&gt;- Competitively inhibits viral DNA polymerase by acting as an analogue to deoxyguanosine triphosphate (dGTP).&lt;br&gt;- Incorporation of aciclovir triphosphate into DNA results in chain termination&lt;br&gt;- Absence of a 3’ hydroxyl group prevents the attachment of additional nucleosides&lt;br&gt;OR <strong>Valaciclovir</strong></td>
</tr>
<tr>
<td>Varicella Zoster Virus (VZV)</td>
<td>Enveloped, dsDNA genome</td>
<td><strong>Chicken pox:</strong> 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</td>
<td><strong>Acyclovir</strong> 800mg PO TDS 7/7 or <strong>ValAciclovir</strong> 1g TDS&lt;br&gt;- <strong>Indications:</strong> All adults with chickenpox (at risk of complications), <strong>Neonates</strong>,</td>
</tr>
</tbody>
</table>
dermatomal distribution when it is reactivated

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) à stress/↓immunity (immunocompromised, >50yrs), Painful rash in specific 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

---

<table>
<thead>
<tr>
<th><strong>Immunocompromised. Eye involvement, All pts presenting with pain</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-exposure prophylaxis: VZIG (Immunocompromised, Pregnant women)</td>
</tr>
<tr>
<td>Live vaccine against varicella – Attenuated Oka strain (Contraindicated in pregnancy)</td>
</tr>
</tbody>
</table>

**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 Famiclovir 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

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<table>
<thead>
<tr>
<th><strong>Human Cytomegalovirus (HCMV)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enveloped, dsDNA genome</strong></td>
</tr>
<tr>
<td>Lies latent in monocytes and dendritic cells</td>
</tr>
</tbody>
</table>

**In immunocompromised** (major issue for transplant patients):
1. Encephalitis
2. Retinitis
3. Pneumonitis
4. Colitis

**1st line Ganciclovir (IV)/valganciclovir (oral):** guanosine analogue chain terminator
**2nd line Foscarnet (IV):** Non-competitive inhibitor of viral DNA polymerase

---
| **CMV cells** – ‘**owls eye inclusions’** | **5. Marrow suppression**<br><br>**Congenital infection:**<br>1. Ears: sensorineural deafness<br>2. Eyes: chorioretinitis<br>3. Heart: myocarditis<br>4. Neurology: microcephaly, encephalitis<br>5. Lung: pneumonitis<br>   - Liver: hepatitis, jaundice, hepatosplenomegaly | **o** Pyrophosphate analogue, inhibits nucleic acid synthesis without requiring activation. Also used as prophylaxis post organ transplant.<br>**o** Nephrotoxic!  <br>- **3rd line Cidofovir (IV):** cytidine analogue chain terminator<br>  - Often used in treatment of non-herpes viral infections in the opportunistic post-transplant setting:<br>  - Eg: BK virus for BK nephropathy/BK cystitis/Adenovirus/PML (JC virus) IVIg (adjunct in pneumonitis) |

| **Epstein-Barr virus (EBV)** | **Enveloped, dsDNA genome**<br><br>Lies latent in B cells<br><br>*EBV not dangerous in pregnancy.* | **1. Glandular fever: Triad of fever, pharyngitis, lymphadenopathy (incubation 4-6/52) + maculopapular rash.*<br>   - a. Diagnosis - blood film, monospot agglutination, EBV antibodies Nb: Paul-Bunnell test<br>2. Predisposes to Burkitt’s lymphoma (African kids with a big jaw)**<br><br>**In immunocompromised:**<br>Post-transplant lymphoproliferative disease (Predisposes to lymphoma. Treatment – reduce immunosuppression + give Rituxumab (anti-CD20 monoclonal Ab))<br>1. Largely supportive care<br>   - Avoid penicillins: can provoke wide-spread maculopapular rash in EBV infection (infectious mononucleosis exanthema) |

<p>| <strong>Human Herpesvirus 6 (HHV 6) also known as Roseola Virus</strong> | <strong>Latent in monocytes/lymphocytes</strong> | <strong>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.</strong>&lt;br&gt;&lt;br&gt;Most common cause of febrile convulsions.&lt;br&gt;Route of transmission: Droplet infection | <strong>Symptomatic treatment – fluids</strong>&lt;br&gt;&lt;br&gt;Dx: Usually clinical diagnosis, blood PCR&lt;br&gt;<strong>In immunocompromised:</strong>&lt;br&gt;• Chemoradiotherapy, surgical |</p>
<table>
<thead>
<tr>
<th><strong>herpesvirus 8 (HHV8)</strong> also known as Kaposi’s sarcoma herpesvirus (KSHV)</th>
<th>genome</th>
</tr>
</thead>
</table>
| Genitally transmitted | • Kaposi’s sarcoma (Pathognomonic for HIV)  
• Primary effusion lymphoma (assoc with EBV coinfection)  
• Castleman’s disease (non-cancerous growth in the LNs). |
| **Polyomaviridae** |
| **JC virus** | Unenveloped, dsDNA genome |
| In immunocompromised (especially AIDS):  
1. Progressive multifocal leukoencephalopathy  
2. Rapidly demyelinating disease + neurological deficits |
| • Anti-retrovirals |
| **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 |
| **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

Dx: ALT↑↑ AST↑
- HBsAg (infection or vaccine)
- HBeAg (infectivity)
- HBcAb (acute IgM)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Interferon alpha</td>
<td></td>
</tr>
<tr>
<td>2. Lamivudine (nucleoside analogue)</td>
<td></td>
</tr>
<tr>
<td>3. Entecavir (nucleoside analogue)</td>
<td></td>
</tr>
<tr>
<td>4. Telbivudine (nucleoside analogue)</td>
<td></td>
</tr>
<tr>
<td>5. Tenofovir (nucleoTide analogue)</td>
<td></td>
</tr>
</tbody>
</table>

**Treatment goal** – Prevent progression to cirrhosis + HCC. Maintain serum HBV DNA level as low as possible à 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 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

2. **Initially interferon therapy (Peg INF α 2b/2a)**

Now highly effective directly acting antivirals à 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
| **Hepatitis D virus** | Deltavirus, enveloped virus, negative sense, single-stranded circular RNA | Always coinfection with HBV  
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) |
| **Congenital infection: (Congenital Rubella Syndrome)** | | | 1. MMR vaccine  
• No antiviral therapy available |
| | | | | 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 |
<table>
<thead>
<tr>
<th>Virus</th>
<th>Genome Characteristics</th>
<th>Symptoms</th>
<th>Congenital Infection</th>
<th>Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Human parvovirus B19</strong></td>
<td>Unenveloped, dsDNA</td>
<td>1. Slapped cheek (fifth disease)</td>
<td>1. <strong>Intrauterine blood transfusion</strong> (congenital infection)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>genome</td>
<td>a. Erythema infectiosum</td>
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<tr>
<td></td>
<td></td>
<td>b. Transient aplastic crisis</td>
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<td></td>
<td></td>
<td>c. Arthralgia</td>
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<td></td>
<td></td>
<td>d. Fever and malaise</td>
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<td></td>
<td></td>
<td>2. Viral myocarditis</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td><strong>Congenital infection:</strong></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>1. Foetal anaemiaà cardiac failureà hydrops foetalis</td>
<td></td>
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</tr>
<tr>
<td><strong>Morbillivirus</strong></td>
<td>Enveloped, negative</td>
<td>1. Measles</td>
<td></td>
<td>MMR vaccine</td>
</tr>
<tr>
<td></td>
<td>sense ssRNA genome</td>
<td>a. Fever, malaise</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>b. Cough, coryzal symptoms, conjunctivitis</td>
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<td></td>
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<td>c. Koplik’s spots (buccal mucosa)</td>
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<tr>
<td></td>
<td></td>
<td>d. Maculopapular rash</td>
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<tr>
<td></td>
<td></td>
<td><strong>Congenital infection:</strong></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>1. No foetal abnormalities</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>2. Foetal loss, preterm delivery</td>
<td></td>
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<tr>
<td><strong>Zika virus</strong></td>
<td>Enveloped flavivirus,</td>
<td><strong>Congenital infection:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>positive sense ssRNA</td>
<td>1. Severe microcephaly + skull deformity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>genome</td>
<td>2. Decreased brain tissue, subcortical calcification</td>
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<tr>
<td></td>
<td></td>
<td>3. Retinopathy, deafness</td>
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<td></td>
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<td>4. Talipes (feet turned in like club foot), contractures</td>
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<td></td>
<td></td>
<td>5. Hypertonia</td>
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<td></td>
</tr>
</tbody>
</table>


## Serology in Hepatitis

<table>
<thead>
<tr>
<th></th>
<th>Acute infection</th>
<th>Chronic Infection</th>
<th>Previous infection</th>
<th>Vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatitis A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HAV IgM</td>
<td>+</td>
<td>N/A</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anti-HAV IgG</td>
<td>-</td>
<td>N/A</td>
<td>+</td>
<td>+</td>
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<tr>
<td><strong>Hepatitis B</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>IgM anti-HBc</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Hepatitis C</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HCV IgG*</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>N/A</td>
</tr>
<tr>
<td>HCV RNA</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Hepatitis E</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HEV IgM</td>
<td>+</td>
<td>N/A</td>
<td>-</td>
<td>**</td>
</tr>
<tr>
<td>Anti-HEV IgG</td>
<td>-</td>
<td>N/A</td>
<td>+</td>
<td>**</td>
</tr>
</tbody>
</table>

* 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 (Toxoplasmosis, Other(HIV, HBV), Rubella, CMV, HSV)
- Ax: Transmission from mother
- Px: Non-specific: (Thrombocytopenia, Other(ears/eyes - cataracts, choroidoretinitis), Rash, Cerebral abnormality eg: microcephaly, Hepatosplenomegaly)
- 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: Septic screen: 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 >10⁵cfu/ml. Microscopy: pyuria (pus cells) + clinical symptoms
PUO + Fever in the Returning Traveller + Malaria

PUO (Pyrexia of Unknown Origin)

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

<table>
<thead>
<tr>
<th>PUO Type</th>
<th>Examples</th>
</tr>
</thead>
</table>
| Classical PUO – as defined above incl. >3/7 in hospital or >3 O/P visits with ambulatory Ix | 1) Infections  
2) Neoplasms  
3) Connective tissue diseases  
4) Misc. Conditions (Abscesses, Endocarditis, Tuberculosis, Complicated UTIs), 5) Undiagnosed conditions |
| Healthcare-associated PUO – develops in a patient following >24hrs in hospital | Surgery, drugs eg: vancomycin; penicillins; serotonergics, medical devices (catheter, IV line bacteraemia), LRTI (incl. ventilator-associated in ITU), C. diff colitis, Immobilisation |
| Neutropaenic PUO – Fever concomitant with neutropaenia (<500/uL) and subsequent lack of cellular response. MEDICAL EMERGENCY. | Chemotherapy, Haematological malignancies. Look for conditions that require neutrophils (eg fungal [aspergillus], bacterial sepsis), Mycobacteria, GVHD, Drug fever |
| HIV-associated PUO – HIV +ve patients frequently have PUO | Seroconversion, TB, Kaposi’s sarcoma, Bacterial, Disseminated MAI, PCP, CMV, Cryptococcus, Toxoplasmosis, Lymphoma Histoplasmosis, Drug fever etc |

PUO Workup – Observe fever! If possible, withhold therapy until diagnosis is reached
- Febrile neutropaenia: Empirical treatment should be started after taking samples for culture UNLESS patient is unstable. Try to identify source as this will tell you the most likely pathogens to treat with antibiotics.

Don't Forget
- 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: Malaria (check if prophylaxis taken), Dengue (rash), Typhoid, Rickettsia, Bacterial diarrhoea, UTI, Pneumonia, HIV Seroconversion, brucella, viral haemorrhagic fevers (ebola/lassa fever etc.) Timing is key!

Typhoid

Salmonella typhi and paratyphi. Anaerobic Gram -ve bacillus
Enteric fever infecting Peyers patches. Transmitted by food + water
Clinically – Fever, Headache, Abdo pain, Diarrhoea or constipation, Rose spots (30%), Relative bradycardia (non-specific & <50%), Hepatosplenomegaly (50%)

Chronic carriage – Gallstones, Immunosuppression

**Diagnosis:** Hx, Blood cultures, Stool

**Management:** IV fluids, Oral or iv antibiotics. Notifiable disease.

### Malaria

Female Anopheles mosquito (bites at night, attracted by heat + CO₂. Needs blood proteins for eggs)

<table>
<thead>
<tr>
<th>Species</th>
<th>Severity + Liver stage</th>
<th>Length of Rhythm</th>
<th>Blood film</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| P. *Falciparum*  
most common esp Africa, Asia | V. severe. >2% parasitaemia | 48hr (tertian) | Young trophozoites (rings) in the absence of mature trophozoites and schizonts. Crescent-shaped gametocytes. | 1. Oral Malarone = atovaquone + proguanil  
2. Oral Artermisinin Combination Therapy (ACT) e.g. Riamet = Artemisinin + Lumefantrine  
3. Quinine w/ Doxycycline or Clindamycin
If seriously ill: ABC approach, correct hypoglycaemia, cautious rehydration, organ support IV artesunate (over IV quinine), followed by artemisinin + lumefantrine |
| P. *Vivax*  
Chronic liver stage (hypnozites) | 48hr | Schüffner's dots, >20 merozites/schizont | Chloroquine then primaquine |
| P. *Ovale*  
Chronic liver stage (hypnozites) | 48hr | Schüffner's dots | Chloroquine then primaquine |
| P. *Malariae*  
Benign | 72hr (Quartan) | Similar morphology to *Plasmodium Knowlesi* | Chloroquine – but if chloroquine resistant then give Quinine, Malarone or Riamet. |
Zoonoses

**WHO definition** – Diseases + infections which are transmitted naturally between vertebrate animals and man

<table>
<thead>
<tr>
<th>Mice</th>
<th>Hantan viruses(fleas), Lyme borreliosis, Ehrlichia, Bartonella, Lymphocytic choriomeningitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rats</td>
<td>Rabies, Leptospirosis, Lassa fever, Hantan viruses, Plague, Pasterueltosis, Haverhill fever (Rat-bite)</td>
</tr>
<tr>
<td>Cats</td>
<td>Bartonellosis (cat scratch), Leptospirosis, Q-Fever, Toxoplasmosis, Rabies, Ringworm, Toxocariasis</td>
</tr>
</tbody>
</table>

**Major Features of Severe or Complicated F. Malaria in Adults**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired Consciousness or seizures</td>
<td></td>
</tr>
<tr>
<td>Renal Impairment</td>
<td></td>
</tr>
<tr>
<td>Acidosis (pH&lt;7.3)</td>
<td></td>
</tr>
<tr>
<td>Hypoglycaemia (&lt;2.2mmol/l)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary Oedema or ARDS</td>
<td></td>
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<tr>
<td>Anaemia (Hb&lt;8g/dl)</td>
<td></td>
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<tr>
<td>Spontaneous bleeding/DIC</td>
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<tr>
<td>Shock (algid Malaria - BP&lt; 90/60mmHg)</td>
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<tr>
<td>Haemoglobinuria (without G6PDD)</td>
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</tr>
<tr>
<td>Other indications for parental therapy: Parasitaemia &gt;2%, Pregnancy, Vomiting</td>
<td></td>
</tr>
</tbody>
</table>

**Common Signs**

Fever, Splenomegaly, **No signs**

**Uncommon signs**

Focal neurology/ Reduced GCS/ coma/Shock/ Hepatomegaly

**P. Falciparum Malaria**

**Common symptoms**

Fever + Rigors (rigors also feature in septicaemia such as pyelonephritis)

- Flu-like illness
- Headache
- Back pain
- Myalgia
- Nausea + Vomiting

**Uncommon symptoms**

- Diarrhoea
- Abdominal cramps
- Cough
- Dark urine
- Confusion

**Investigations**

- Thick film – to find parasitaemia
- Thin film – to distinguish malarial species
- Various antigen tests
- Bloods: WCC rarely raised. 70% ↓platelets 50% deranged LFTs, 30% anaemia
<table>
<thead>
<tr>
<th>Category</th>
<th>Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs</td>
<td>Hydatid disease, Leptospirosis, Brucellosis, Q-Fever, Rabies, (MRSA!!),</td>
</tr>
<tr>
<td></td>
<td>Ringworm, Toxocariasis</td>
</tr>
<tr>
<td>Small ruminants</td>
<td>Anthrax, Brucellosis, Q-Fever, Cryptosporidiosis, Enzootic abortion,</td>
</tr>
<tr>
<td></td>
<td>Louping ill, Orff virus, Rift Valley fever, Toxoplasmosis</td>
</tr>
<tr>
<td>Cattle</td>
<td>Anthrax, Leptospirosis, Brucella, Bovine TB, Anaplasmosis, Toxoplasmosis,</td>
</tr>
<tr>
<td></td>
<td>E. coli 0157, Rift Valley fever, Ringworm</td>
</tr>
<tr>
<td>Swine</td>
<td>Brucellosis, Leptospirosis, Erysipeloid, Cysticercosis, Trichinella, HEV,</td>
</tr>
<tr>
<td></td>
<td>Influ A!, Streptococcal septis</td>
</tr>
<tr>
<td>Birds</td>
<td>Psitticosis, Influenza, Cryptococcus, Influ A!!!, Poultry- salmonella, West-Nile fever</td>
</tr>
<tr>
<td>Water-sports assoc</td>
<td>Leptospirosis, HAV, Giardia, Toxoplasmosis, Mycobacterium marinum/ulcers,</td>
</tr>
<tr>
<td></td>
<td>Burkholderia pseudomallei, E. coli</td>
</tr>
<tr>
<td>Water-borne</td>
<td>Campylobacter, Salmonella, VTEC O157, Cryptosporidium</td>
</tr>
<tr>
<td>Food-associated</td>
<td>Listeria (cow cheese-human), Taenia, Cysticercosis, toxoplasmosis,</td>
</tr>
<tr>
<td></td>
<td>trichinellosis, yersinia, Giardia</td>
</tr>
</tbody>
</table>

**Brucellosis** – Gram-ve, aerobic bacilli (facultative intracellular), endemic worldwide.
- **Mode of transmission** – Inhalation, Skin or mucus membrane contact.
- From consumption of contaminated food (untreated milk/dairy products), animal contact or environmental contamination. Also includes laboratory acquired.
- **Symptoms** – Fever – Classically undulant fever (peaks in eve. normal by morn), malaise, rigors, sweating, myalgia/arthralgia, tiredness (incubation 3-4/52)
- **Complications** – endocarditis, osteomyelitis (occasionally meningoencephalitis)
- **Signs** – arthritis, spinal tenderness, lymphadenopathy, splenomegaly, hepatomegaly, epididymo-orchitis. Rarely – jaundice, CNS abnormalities, cardiac murmur, pneumonia.
- **Ix** – Serology - anti-O-polysaccharide antibody. (Titres >1:160). WCC usually normal. Leucocytosis rare, significant number of pts neutropaenic.
- **Rx** – 4-6/52 Tetracycline or Doxycycline combined with Streptomycin. Or PO doxycycline + rifampicin 8/52

**Rabies** – Rhabdovirus, affects warm-blooded animals; dogs and bats are the most common vectors.
- Migrates to CNS (mths/ysrs) – fatal encephalitis – Negri bodies = pathognomonic
- Prodrome (fever, headache, sore throat) – acute encephalitis (hyperactive state)
- IFA for rabies antigen in brain tissue.
- Serology - neutralisation tests/ELISA for specific IgM.
- Treatment – Rabies IgG post exposure

**Plague** – *Yersinia pestis*, gram-ve lactose fermenter. In rats, transmitted by fleas. Still seen in some American National Parks such as Yosemite. Dx: PCR
- **Bubonic plague** – flea bites human – Swollen LN (Bubo) – dry gangrene
- **Pneumonic plague** – Usually seen during epidemics, person-to-person spread
- **Treatment** – Streptomycin, Doxycycline, Gentamicin, Chloramphenicol (in meningitis)

**Leptospirosis** – Gram -ve, *L. interrogans*, Obligate, aerobic, motile spirochaetes
- Excreted in dog/rat urine. Penetrates broken skin/swimming in contaminated water.
- High spiking temp/headache/conjunctival haemorrhages/jaundice, malaise, myalgia, meningism, carditis, renal failure, haemolytic anaemia (incubation 10-14/7)
- Rx – Amoxicillin, erythromycin, doxycycline or ampicillin

**Anthrax** - Bacillus anthracis (Rx. Cipro/doxy)
- Cutaneous – Painless round black lesions + rim of oedema
- Pulmonary (Woolsorters disease) – Massive lymphadenopathy + mediastinal haemorrhage, pleural effusion and resp. failure.

**Lyme disease** - *Borrelia burgdoferi* (spirochaete). Arthropod-borne (Ixodes = tick)
- Early localized – Cyclical fevers, non-specific flu-like symptoms. Erythema chronicum migrans (ECM) – ‘Bullseye Rash’
- Early disseminated – Malaise, lymphadenopathy, hepatitis, carditis, arthritis
- Late persistent – Arthritis, focal neurology, neuropsychiatric disturbance, ACA (acrodematitis chronic atrophicans)
- Dx: Biopsy edge of ECM + ELISA for Lyme Abs
- Treatment: Doxycycline 2-3/52, (also amoxicillin, cephalosporins). If CNS issues, IV ceftriazone 2-4/52. Post Rx, few pts get ‘ME’ type symptoms.

**Q fever** - *Coxiella burnetii* (Rx.= doxy), looks like atypical pneumonia
- Cattle/sheep infection, 2-5/52 post-infection – fever dry cough + fatigue + pleural effusion and diarrhea – NO RASH!

**Leishmania** – protozoa
- **Cutaneous**, eg: *L. major, L. tropica*
  - Transmitted through bite of the sandfly (south & central America+ middle east)
  - 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, Type IV reaction
- **Diffuse cutaneous**
  - Pts with immunodeficiency. Nodular skin lesions arise but do NOT ulcerate – Lots of nodules, esp nose, Skin test–ve as immunodeficient
- **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 + distension/anorexia/wt. loss
  - Leishmania donovani: invasion of reticuloendothelial system -> hepatosplenomegaly, BM invasion. Later disfiguring dermal disease (PKDL)
Fungal infections and their diagnosis

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. *Trichophyton 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
    - 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 + in dia ink staining
    - Rx: 3/52 amphotericin B +/- flucytosine

Antifungals

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

<table>
<thead>
<tr>
<th>Class</th>
<th>Target</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyene e.g. Amphotericin</td>
<td>Cell membrane integrity</td>
<td>Yeast</td>
</tr>
<tr>
<td>Azole e.g. Fluconazole</td>
<td>Cell membrane synthesis</td>
<td>Yeast</td>
</tr>
<tr>
<td>Terbinafine</td>
<td>Cell membrane</td>
<td>Mould (vs. dermatophytes)</td>
</tr>
<tr>
<td>Flucytosine</td>
<td>DNA synthesis</td>
<td></td>
</tr>
<tr>
<td>Echinocandin e.g. caspofungin</td>
<td>Cell wall</td>
<td>Yeast (less toxic SE)</td>
</tr>
</tbody>
</table>
Prion Disease

Protein-only infectious agent. Rare transmissible 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 à 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

<table>
<thead>
<tr>
<th>Prion</th>
<th>EEG</th>
<th>MRI</th>
<th>CSF Analysis</th>
<th>PNRP analysis</th>
<th>Genetics</th>
<th>Western Blot PrP Sc</th>
<th>Post-mortem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic CJD</td>
<td>Serial EEG shows periodic triphasic changes</td>
<td>Normal/ highlighting basal ganglia</td>
<td>14-3-3 protein +ve</td>
<td>No mutations</td>
<td>Most cases 129 codon MM</td>
<td>Types 1-3</td>
<td>1. Spongiform vacuolation 2. PrP amyloid plaques</td>
</tr>
<tr>
<td>Variant CJD</td>
<td>Non-specific slow waves</td>
<td>Posterior thalamus highlighted on MRI-T2 (pulvinar sign)</td>
<td>14-3-3 can be normal</td>
<td>No mutations</td>
<td>ALL cases 129 codon MM</td>
<td>Type 4t from tonsillar biopsy (100% sens. + spec.)</td>
<td>1. PrP Sc 4t detetable in CNS + lymphoreticular tissue 2. Florid plaques</td>
</tr>
<tr>
<td>Iatrogenic CLD</td>
<td>Non-specific</td>
<td>Sometimes high signal in basal ganglia</td>
<td>No mutations</td>
<td>Most:129 codon homozygous (MM or VV)</td>
<td>Types 1-3</td>
<td>1.</td>
<td></td>
</tr>
<tr>
<td>Inherited Prion Disease</td>
<td>Non specific</td>
<td>Sometimes high signal in basal ganglia</td>
<td>Mutations present + diagnostic</td>
<td>129 codon homozygosity may confer earlier onset</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type</th>
<th>Prion Disease</th>
<th>Aetiology</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic CJD</td>
<td>sCJD</td>
<td>Either somatic PRNP mutation OR spontaneous conversion of PrPc to PrP Sc and subsequent seeding</td>
<td>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</td>
</tr>
<tr>
<td>Acquired CJD</td>
<td>vCJD (variant)</td>
<td>Exposure to bovine spongiform encephalopathy (BSE)</td>
<td>Younger age of onset – typically 30yrs. Mean survival 14/12. Psychiatric symptoms to start (anxiety, paranoia,</td>
</tr>
<tr>
<td>Gram Positive</td>
<td>Gram Negative</td>
<td>rods</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>---------------</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td>Cocci</td>
<td>rods</td>
<td>Cocci</td>
<td>rods</td>
</tr>
<tr>
<td>Streptococcus + enterococcus (diplococci + chains)</td>
<td>Bacillus: cereus, anthracis</td>
<td>Moraxella: catarrhalis</td>
<td></td>
</tr>
<tr>
<td>Clostridium:* difficile, Perfringens, botulinum, tetani</td>
<td>Diphtheria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Listeria</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coccobacilli Spirochaetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. influenza/ducreyi, Bordetella Pertussis, Pseudomonas aeruginosa, Chlamydia trachomatis</td>
</tr>
<tr>
<td>Treponema pallidum e.g. syphilis, Leptospirosis Borrelia e.g. Lyme disease</td>
</tr>
</tbody>
</table>

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

Rx – Metronidazole, cephemycins. 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
Fluid Balance

- Total body water = 60%
- Intracellular: Extracellular fluid is 2:1
- Extracellular fluid:
  - Intravascular
  - Interstitial (between cells – the largest component of the ECF)
  - Transcellular (within epithelial-lined spaces, e.g. CSF, joint fluid, bladder urine, aqueous humour)
- 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

Osmolality and osmolarity 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 (<135mmol/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 sodiums 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),
Define whether it is true hyponatraemia using serum osmolality:

<table>
<thead>
<tr>
<th>Osmolality</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Glucose/mannitol infusion</td>
</tr>
<tr>
<td>Normal</td>
<td>Spurious Drip arm sample Pseudohyponatraemia (hyperlipidaemia/ paraproteinaemia)</td>
</tr>
<tr>
<td>Low</td>
<td>True hyponatraemia</td>
</tr>
</tbody>
</table>

TURP syndrome -> hyponatraemia from water absorbed through damaged prostate
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⁺:

<table>
<thead>
<tr>
<th>Hydration status</th>
<th>Urinary sodium (mmol/l)</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolaemia</td>
<td>&gt; 20 = Renal</td>
<td>Diuretics, Addison’s, Salt-losing nephropathies (kidney is failing to reabsorb sodium so water lost as well)</td>
</tr>
<tr>
<td></td>
<td>&lt; 20 = Non-renal</td>
<td>Vomiting, Diarrhoea, Excess sweating, Third space losses (ascites, burns). Kidney is doing its job and holding onto sodium</td>
</tr>
<tr>
<td>Euvolaemia</td>
<td>&gt; 20</td>
<td>SIADH, Primary polydipsia (will have high urine volume), Severe hypothyroidism, glucocorticoid deficiency</td>
</tr>
<tr>
<td>Hypervolaemic</td>
<td>&gt; 20 = Renal</td>
<td>AKI, CKD (kidneys not retaining sodium)</td>
</tr>
<tr>
<td></td>
<td>&lt; 20 = Non-renal</td>
<td>Cardiac Failure, Cirrhosis, Inappropriate IV fluid.</td>
</tr>
</tbody>
</table>
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, Addisons – 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 advise 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 per 24h.

△△ 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**

**Laboratory criteria:**
- True hyponatraemia (low serum osmolality)
- Clinically **euvolaemic**
- Inappropriately high urine osmolality and increased renal sodium excretion (>20mmol/l)
  - This is because there is a slight increase in circulatory volume which inhibits the release of angiotensin and aldosterone which increases sodium excretin
- Normal 9am cortisol and TFTs (ie. It’s a 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, carbamazepine, proton pump inhibitors

**Treatment:** Fluid restriction and treat the cause, demeclocycline and tolvaptan are able to induce a state of diabetes insipidus that may help to correct the SIADH although the cost is prohibitive.

**Hypernatraemia**
- Less common than hyponatraemia, but usually clinically significant (Plasma Na⁺ > 148mmol/L)
• 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!

<table>
<thead>
<tr>
<th>Hydration status</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolaemia (where water is lost more than</td>
<td>GI loss: Vomiting, Diarrhoea</td>
</tr>
<tr>
<td>sodium, this is the most common form of</td>
<td>Skin loss: Excessive sweating, Burns</td>
</tr>
<tr>
<td>hypernatremia)</td>
<td>Renal loss:</td>
</tr>
<tr>
<td></td>
<td>• Loop diuretics</td>
</tr>
<tr>
<td></td>
<td>• Osmotic diuresis (glucose, mannitol), following initial hyponatraemia</td>
</tr>
<tr>
<td>Euvolaemia</td>
<td>Respiratory (tachypnoea)</td>
</tr>
<tr>
<td></td>
<td>Skin (sweating, fever)</td>
</tr>
<tr>
<td></td>
<td>Renal (diabetes insipidus)</td>
</tr>
<tr>
<td>Hypervolaemia</td>
<td>Mineralocorticoid excess (Conn’s Syndrome)</td>
</tr>
<tr>
<td></td>
<td>Inappropriate saline</td>
</tr>
</tbody>
</table>

**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 euvoalaemic
- Polyuria and polydipsia
- Urine: plasma osmolality is <2. (Urine is dilute despite concentrated plasma)

**Cranial** Diabetes Insipidus:
- Lack of/No ADH
- Causes: surgery, trauma, tumours

**Nephrogenic** Diabetes Insipidus:
- Receptor defect – insensitivity to ADH
- Treatment with thiazide diuretics (bizzare!)
- Causes:
  - Inherited channelopathies
  - Lithium, demeclocycline

**Diagnosis:** 8hr fluid deprivation test
- Normal: Urine concentration ↑ >600mOsmol/kg
- Primary polydipsia: Urine concentrates >400-600mOsmol/kg
- Cranial DI: urine concentrates only after giving desmopressin
- Nephrogenic DI: low concentration urine after desmopressin
Hyperkalaemia

Causes
- 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)
  - K-sparing diuretics (spironolactone)
  - Mineralocorticoid deficiency (Addison's)
  - NSAIDs, ACEi, ARBs

Potassium

Normal range: ~3.5 – 5.5 mmol/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 (<3.5 mmol/L)

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

1. GI loss
2. Renal loss
   - Hyperaldosteronism, 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)
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 hypokalaemia (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)

Treatment involves oral SandoK® and monitoring potassium levels, or if lower than 3.0, consider intravenous potassium chloride (no greater than 10mM/hr or risk arrhythmia)
Typical investigations include an aldosterone-renin ration (high implies Conn’s)

Hyperkalaemia (>5.5 mmol/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.

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 an elevated potassium >5.5 if there are ECG changes and if the potassium is >6.5 regardless of ECG changes.

Treatment involves:
1. 10mls 10% calcium gluconate (This is cardioprotective, it does nothing to lower the serum potassium)
2. 100mls 20% dextrose or 50ml of 50% dextrose (the total difference between them is only 5g of glucose and you should prescribe whichever is more readily available / according to your trust guidelines) and 10 units insulin.
3. Salbutamol is a useful adjunct as well.
4. 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 contransporter. 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

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?

<table>
<thead>
<tr>
<th>Acid - Base</th>
<th>pH</th>
<th>Bicarbonate</th>
<th>CO2</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic Acidosis</td>
<td>↓</td>
<td>↓</td>
<td>N/↓ (If compensated)</td>
<td>Lactate build up DKA Renal tubular acidosis Intestinal fistula</td>
</tr>
<tr>
<td>Metabolic Alkalosis</td>
<td>↑</td>
<td>↑</td>
<td>N/↑ (If compensated)</td>
<td>Pyloric stenosis Hypokalaemia Ingestion of bicarbonate</td>
</tr>
<tr>
<td>Respiratory Acidosis</td>
<td>↓</td>
<td>N/↑ (If compensated)</td>
<td>↑</td>
<td>Lung injury – pneumonia, COPD Decreased ventilation – Morphine OD</td>
</tr>
<tr>
<td>Respiratory Alkalosis</td>
<td>↑</td>
<td>N/↓ (If compensated)</td>
<td>↓</td>
<td>Mechanical Ventilation Anxiety/ panic attack</td>
</tr>
</tbody>
</table>

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

\[ (Na^+ + K^+) - (Cl^- + HCO_3^-) \]

- 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
Osmolar Gap

- 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

Liver Function Tests

- Markers of liver cell damage
  - ALT
  - AST
  - ALK Phos
  - GGT
  - Bilirubin

- Markers of Synthetic Function
  - Clotting (INR)
  - Albumin
  - Glucose

Mnemonic for elevated anion gap metabolic acidosis:

- Ketoacidosis (DKA, alcoholic, starvation)
- Uraemia (renal failure)
- Lactic Acidosis
- Toxins (ethylene glycol, methanol, paraldehyde, salicylate)

Liver Enzymes

<table>
<thead>
<tr>
<th>Aspartate aminotransferase (AST)</th>
<th>Found in the Liver, cardiac and skeletal muscle, and the kidney and brain.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine</td>
<td>AST:ALT = 2 is supportive of alcoholic hepatitis</td>
</tr>
</tbody>
</table>
| **aminotransferase (ALT)** | Found primarily in the liver, more sensitive than AST for hepatocyte damage.
Raised when hepatocytes die. AST:ALT =1 supportive of viral hepatitis |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alkaline Phosphatase (ALP)</strong></td>
<td>Found in the liver, bones, placenta, Raised with cholestasis (either intrahepatic or extrahepatic) and bone disease, ↑++ in pregnancy</td>
</tr>
<tr>
<td><strong>Gamma GT (GGT) Aspartate aminotransferase (AST)</strong></td>
<td>Found in hepatocytes and biliary cells, also found in the kidney and pancreas. Elevated in chronic alcohol use Also bile duct disease and metastases. Used to confirm hepatic source of ↑ALP</td>
</tr>
</tbody>
</table>

**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 thrombophilia, 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:

<table>
<thead>
<tr>
<th>Type of jaundice</th>
<th>Causes</th>
<th>Lab findings</th>
</tr>
</thead>
</table>
| Pre-hepatic      | Haemolysis [See haem section]  
Congestive heart failure | Elevated unconjugated bilirubin  
Reduced haemoglobin  
Reduced haptoglobin  
Raised LDH |
| Hepatic          | Acute or chronic liver failure  
Gilbert syndrome  
Crigler-Najjar syndrome  
Viral Hepatitis  
Alcoholic Hepatitis  
PBC | Elevated Unconjugated bilirubin  
Raised Aminotransferases  
Synthetic dysfunction may be present |
| Post-hepatic     | Obstruction of the biliary tree from any cause (Think intraluminal – Stones, strictures, Luminal – Mass/Neoplasm, Inflammation e.g. PSC/PBC, Extra-luminal – Pancreatic Ca, cholangio Ca | Elevated conjugated bilirubin  
Elevated bilirubin in the urine [Dark urine pale stools] |
Porphyrias
7 disorders caused by deficiency in enzymes, involved in haem biosynthesis, leading to build up of toxic haem precursors.

**Acute Intermittent Porphyria (AIP)**
- Autosomal dominant inheritance
- **HMB** (Hydroxymethylbilane) synthase deficiency
- **Symptoms** (neuro-visceral only) - abdo pain, seizures, psych disturbances, nausea & vomiting, tachycardia, hypertension, sensory loss, muscle weakness, constipation, urinary incontinence. NO cutaneous manifestations due to absence of porphyrinogens
- **Diagnosis** - ALA + PBG in urine (“Port wine urine”)
- **Precipitating factors**
  - ALA synthase inducers (steroids, ethanol, barbiturates)
  - Stress (infection, surgery)
  - Reduced caloric intake and endocrine factors (e.g. premenstrual)
- **Treatment** – avoid precipitating factors, analgesia, IV carbohydrate/ haem arginate

**Acute Porphyrias with Skin Lesions**
- Hereditary coproporphyria (HCP) and Variegate porphyria (VP)
- Autosomal dominant
- HCP -
- **Symptoms** – neurovisceral + skin lesions
- Raised porphyrins in faeces or urine

**Non-Acute Porphyrias**
- **Skin lesions ONLY**
  - Congenital Erythropoietic porphyria (CEP)
  - Erythropoietic protoporphyria (EPP)
  - Porphyria Cutanea Tarda (PCT)

**EPP**
- Photosensitivity, burning, itching oedema following sun exposure

**PCT**
- Inherited/ acquired
- Uroporphyrinogen decarboxylase deficiency
- **Symptoms** (cutaneous) – Vesicles (crusting, pigmented, superficial scarring) on sun exposed sites
- **Diagnosis** - ↑ urinary uroporphyrins + coproporphyrins + ↑ ferritin
- **Treatment** – avoid precipitants (alcohol, hepatic compromise), phlebotomy
### Hypothalamo-Pituitary Axis

<table>
<thead>
<tr>
<th>Hypothalamic Hormones</th>
<th>Action on Pituitary Hormones</th>
</tr>
</thead>
<tbody>
<tr>
<td>GHRH</td>
<td>Stimulates – GH</td>
</tr>
<tr>
<td>GnRH</td>
<td>Stimulates – LH/ FSH</td>
</tr>
<tr>
<td>TRH</td>
<td>Stimulates – TSH</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Inhibits – Prolactin</td>
</tr>
<tr>
<td>CRH</td>
<td>Stimulates – ACTH</td>
</tr>
</tbody>
</table>

### 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.

**Procedure:**
- 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

**Interpretation:** Involves interpreting three aspects
1. **Insulin Tolerance test**
   - Adequate cortisol response = ↑ greater than 170 nmol/l to above 500nmol/l.
   - Adequate GH response = ↑ greater than 6mcg/L
2. **Thyrotrophin Releasing Hormone Test**
   - 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**
   - 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 clomiphen.
- 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**)

### 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

<table>
<thead>
<tr>
<th>TFT</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑TSH ↓T4</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>↑TSH ↔T4</td>
<td>Treated hypothyroidism or subclinical hypothyroidism (look</td>
</tr>
</tbody>
</table>
### 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

---

<table>
<thead>
<tr>
<th>Condition</th>
<th>Types</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hyperthyroidism</strong></td>
<td>High Uptake</td>
<td>Graves disease: 40 - 60%, F&gt;M (9:1), autoantibodies ++, high uptake on isotope scan (with Tc99)</td>
</tr>
<tr>
<td></td>
<td>Low Uptake</td>
<td>Toxic multinodular goitre: 30 - 50%, high uptake</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toxic adenoma: 5%, ‘hot nodule’ on isotope scan (1 area of uptake)</td>
</tr>
<tr>
<td><strong>Hypothyroidism</strong></td>
<td>Autoimmune</td>
<td>Subacute De Quervains thyroiditis: self-limiting post viral painful goiter. Initially hyperthyroid, then hypothyroid</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>Postpartum thyroiditis (like De Quervain’s but postpartum)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primary atrophic hypoT: diffuse lymphocytic infiltration &amp; atrophy. No goiter so small thyroid. No known antibodies detected yet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hashimotos thyroiditis: Plasma cell infiltration &amp; goitre. Elderly females. May be initial ‘Hashitoxicosis’. ++ Autoantibody titres (anti TPO/TG)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Iodine deficiency (common worldwide)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post thyroidectomy/radioiodine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drug induced – antithyroid drugs, lithium, amiodarone</td>
</tr>
</tbody>
</table>
- 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

### Thyroid Neoplasia

**Papillary**
>60% of cases, 30-40y, surgery +/- radioiodine, Thyroxine (to ↓TSH). May see psammoma bodies on histology, these patients have a very good prognosis.

**Follicular**
25%, Middle age, well differentiated but spreads early, Surgery + RI + thyroxine

**Medullary**
5% originates in parafollicular “C” cells – linked to MEN2. Produce calcitonin

**Lymphoma**
5% MALT origin. Risk factor: chronic Hashimotos (as lots of lymphocytes that proliferate), good prognosis

**Anaplastic**
Rare. Elderly. Poor response to any treatment.

### 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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Causes</th>
<th>Symptoms &amp; Signs</th>
<th>Investigations</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cushing’s</strong></td>
<td>Pituitary tumour – “Cushing’s disease” (85%) Adrenal tumour (10%) Ectopic ACTH-producing tumour (5%) Iatrogenic steroid use</td>
<td>Moon face Buffalo hump, striae Acne Hypertension Diabetes Muscle weakness (proximal myopathy) Hirsuitism</td>
<td>Low dose dexamethasone (0.5mg) High dose dexamethasone (2 mg). Low dose dex will fail to suppress cortisol in all of these, but high dose will succeed in pituitary cushings</td>
<td>Treat underlying disease – surgical removal of lesion</td>
</tr>
<tr>
<td><strong>Addison’s</strong></td>
<td>Autoimmune TB Tumour mets Adrenal haemorrhage (meningococcus) Amyloidosis</td>
<td>↑ K⁺ ↓ Na⁺ + ↓ glucose Postural hypotension Skin pigmentation Lethargy Depression</td>
<td>SynACTHen test</td>
<td>Hormone replacement – hydrocortisone/ fludrocortisone if primary adrenal lesion</td>
</tr>
<tr>
<td><strong>Conn’s</strong></td>
<td>Adrenal tumour</td>
<td>Uncontrollable hypertension ↑ Na⁺ ↓ K⁺</td>
<td>Aldosterone : Renin Ratio. Raised aldosterone low renin</td>
<td>Aldosterone antagonists/potassium sparing diuretics – Spironolactone, eplerenone, amiloride</td>
</tr>
<tr>
<td><strong>Phaeo</strong></td>
<td>Adrenal medulla tumour = ↑ Adrenaline</td>
<td>Hypotension Arrhythmias Death if untreated</td>
<td>Plasma and 24h urinary metadrenaline measurement/ catecholamine s &amp; VMA</td>
<td>Alpha blockade, beta blockade then surgery when blood pressure well controlled.</td>
</tr>
</tbody>
</table>
# Therapeutic Drug Monitoring

<table>
<thead>
<tr>
<th>Drug</th>
<th>Signs toxicity</th>
<th>Signs under treatment</th>
<th>Interactions and cautions</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>Ataxia and nystagmus</td>
<td>Seizures</td>
<td>At high levels liver becomes saturated à surge in blood levels</td>
<td>Omit / reduce dose</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Arrhythmias, heart block, confusion, xanthopsia (seeing yellow)</td>
<td>Arrhythmias</td>
<td>Levels increased with Hypokalaemia. Reduce dose in renal failure and in elderly</td>
<td>Digibind aka Digoxin immune Fab</td>
</tr>
<tr>
<td>Lithium</td>
<td>Tremor (early), lethargy, fits, arrhythmia, renal failure</td>
<td>Relapse of mania in bipolar disorder</td>
<td>Excretion impaired by hyponatraemia, ↓ renal func and diuretics</td>
<td>RF may need haemodialysis</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Tinnitus, deafness, nystagmus, renal failure</td>
<td>Uncontrolled infection</td>
<td>Mostly use single daily dosing. Monitor peak and trough level before next dose</td>
<td>Omit / reduce dose</td>
</tr>
<tr>
<td>Theophyline</td>
<td>Arrhythmias, anxiety, tremor, convulsions</td>
<td>Zero effect on bronchial smooth muscle</td>
<td>Variation t1/2; eg 4hrs smokers 8hrs non-smokers, 30hrs liver disease. Level ↑ by erythromycin, cimetidine and phenytoin</td>
<td>Omit / reduce dose</td>
</tr>
</tbody>
</table>

**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

Two main hormones involved in calcium metabolism:

1. **PTH** (Parathyroid Hormone):
   - ↑ tubular 1α hydroxylation of vitamin D (25(OH)D)
   - Mobilises calcium from bone
   - ↑ renal calcium reabsorption
   - ↑ renal phosphate excretion

2. **1,25 (OH)2D** (Calcitriol)
   - ↑ Calcium and phosphate absorption from the gut
   - Bone remodeling
## Disorders of Calcium Balance

<table>
<thead>
<tr>
<th>Condition</th>
<th>Primary defect</th>
<th>Ca</th>
<th>PO4</th>
<th>PTH</th>
<th>Alk phos</th>
<th>Vit D</th>
</tr>
</thead>
<tbody>
<tr>
<td>1° hyperparathyroidism</td>
<td>Increase of PTH. (80% parathyroid adenoma)</td>
<td>↑</td>
<td>↓</td>
<td>↑/N</td>
<td>↑/N</td>
<td>N</td>
</tr>
<tr>
<td>2° hyperparathyroidism</td>
<td>Renal osteodystrophy</td>
<td>↓/N</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>N</td>
</tr>
<tr>
<td>3° hyperparathyroidism</td>
<td>Autonomous PTH secretion post renal transplant</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↑/N</td>
<td>N</td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
<td>Low levels of PTH. 1°: DeGeorge syn 2°: Post thyroid surgery</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓/N</td>
<td>N</td>
</tr>
<tr>
<td>Rickets/ osteomalacia</td>
<td>Vitamin D deficiency</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Paget’s disease</td>
<td>Re-modelling of bone</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>↑</td>
<td>N</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Bone loss</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>
### Hypercalcaemia

#### Symptoms:
- Stones (renal)
- Bones (pain)
- Groans (psych)
- Moans (abdo pain)
- Polyuria
- Muscle weakness

#### Treatment:
- Correct dehydration
- Bisphosphonates
- Correct cause eg chemo for cancer

---

**ALP ↑** (↑ bone turnover)
- Bone metastasis
- Thyrotoxicosis
- Sarcoidosis (↑1αOH)

**ALP ↔**
- Myeloma
- Excess Vit D
- Sarcoid
- Milk alkali syndrome (+ ↑HCO₃⁻)

---

**Urea ↑**
- Dehydration

**Urea ↔**
- Cuffed specimen

**Phosphate ↓**
- 1° or 3° hyperparathyroidism (confirm with ++PTH)

**Phosphate ↑**

---

**Albumin ↑**

**Albumin ↓ / ↔**
Renal stones

- 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 Ca intake, thiazides à hypocalciuric, citrate (alkalinise urine)

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Frequency</th>
<th>X-ray appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium – mixed</td>
<td>~45%</td>
<td>Radioopaque</td>
</tr>
<tr>
<td>Calcium oxalate</td>
<td>~35%</td>
<td>Radioopaque</td>
</tr>
<tr>
<td>Calcium phosphate</td>
<td>~1%</td>
<td>Radioopaque</td>
</tr>
<tr>
<td>Triple phosphate “Struvite”</td>
<td>~10%</td>
<td>Radioopaque/stagho</td>
</tr>
<tr>
<td>Uric acid</td>
<td>~5%</td>
<td>Radioopaque</td>
</tr>
<tr>
<td>Cysteine</td>
<td>~1-2%</td>
<td>Radiolucent</td>
</tr>
<tr>
<td>Others eg xanthine</td>
<td>Rare</td>
<td></td>
</tr>
</tbody>
</table>

- Investigations for recurrent stones:
  - Serum: Cr, bicarb, Ca, phosphate, urate, PTH (if hypercalcaemic)
  - Stone analysis

Symptoms: perioral paraesthesia, carpopedal spasm, neuromuscular excitability (Trousseau’s and Chvostek’s sign)

Treatment:
Mild: give calcium
Chronic Kidney Disease: alfacalcidol
Severe: 10% calcium gluconate IV

Hypocalcaemia

Artefact (e.g. hypoalbuminaemia)

With ↑ Phosphate
Chronic kidney disease
Hypoparathyroidism (inc post thyroid surgery)
Pseudohypoparathyroidism
Hypomagnesaemia

With ↔ / ↓ Phosphate
Osteomalacia
Acute osteoporosis
Overhydration
Respiratory alkalosis (↓ ionised/active Ca^{2+})
- 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)

**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), Statin related myopathy, Rhabdomyolysis

**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 (Pagets, osteomalacia), Liver (Cholestasis, Cirrhosis)
  - <5x ULN = Bone (tumours, fractures, osteomyelitis), Liver (infiltrative disease, hepatitis)

**BNP [Brain natriuretic peptide]**
- A natriuretic 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 is more sensitive than BNP and has greater prognostic value

**Troponin (not an enzyme)**

Troponin I/T = myocardial injury biomarker

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

---

**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 MASS or CONCENTRATION, not activity
Lipoprotein Metabolism

<table>
<thead>
<tr>
<th>Types</th>
<th>Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Hypercholesteraemia</td>
<td>Familial hypercholesteraemia (type II)</td>
</tr>
<tr>
<td></td>
<td>Polygenic hypercholesteraemia</td>
</tr>
<tr>
<td></td>
<td>Familial hyper-α-lipoproteinaemia</td>
</tr>
<tr>
<td></td>
<td>Phytosterolaemia</td>
</tr>
<tr>
<td>Primary Hypertriglyceridaemia</td>
<td>Familial Type I</td>
</tr>
<tr>
<td></td>
<td>Familial Type V</td>
</tr>
<tr>
<td></td>
<td>Familial Type IV</td>
</tr>
<tr>
<td>Primary Mixed Hyperlipidaemia</td>
<td>Familial Combined hyperlipidaemia</td>
</tr>
<tr>
<td></td>
<td>Familial dysβlipoproteinaemia</td>
</tr>
<tr>
<td></td>
<td>Familial hepatic lipase deficiency</td>
</tr>
<tr>
<td>Hypolipidaemia</td>
<td>Aβ-lipoproteinaemia</td>
</tr>
<tr>
<td></td>
<td>Hypoβ-lipoproteinaemia</td>
</tr>
<tr>
<td></td>
<td>Tangier Disease</td>
</tr>
<tr>
<td></td>
<td>Hypoα-lipoproteinaemia</td>
</tr>
</tbody>
</table>

- **Lipoproteins In order of density:** Chylomicron < FFA < VLDL < IDL < LDL < HDL
- **PCSK9**
  - Binds LDLR and promotes its degradation
  - Loss of function mutation of PCSK9 à low 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 gut 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 adverse events in the form of suicide

○ Surgical
  ▪ Bariatric surgery is indicated in patients with a BMI >40 or >35 with a comorbidity associated with obesity
  ▪ Includes gastric band, gastric sleeve and gastric bypass (roux en y or mini)
    • Bypass also has the added improvement of improving diabetic control in type 2 diabetics.
    ▪ To be considered requires extensive screening and must commit to long term follow up usually.

### Nutrition

<table>
<thead>
<tr>
<th>Fat soluble vitamins</th>
<th>Deficiency</th>
<th>Excess</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>A - Retinol</td>
<td>Colour Blindness</td>
<td>Exfoliation Hepatitis</td>
<td>Serum</td>
</tr>
<tr>
<td>D - Chole-calciferol</td>
<td>Osteomalacia/ Rickets</td>
<td>Hyper-calcaemia</td>
<td>Serum</td>
</tr>
<tr>
<td>E - Tocopherol</td>
<td>Anaemia /neuropathy ?malignancy/IHD</td>
<td></td>
<td>Serum</td>
</tr>
<tr>
<td>K - Phyto- menadione</td>
<td>Defective clotting</td>
<td></td>
<td>PTT</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Water soluble vitamins</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>B1 - Thiamine</td>
<td>Beri-Beri Neuropathy Wernicke Syndrome</td>
<td>RBC transketolase</td>
<td></td>
</tr>
<tr>
<td>B2 - Riboflavin</td>
<td>Glossitis</td>
<td>RBC glutathione reductase</td>
<td></td>
</tr>
<tr>
<td>B6 - Pyridoxine</td>
<td>Dermatitis/ anaemia</td>
<td>Neuropathy</td>
<td>RBC AST activation</td>
</tr>
<tr>
<td>B12 - Cobalamin</td>
<td>Pernicious anaemia</td>
<td></td>
<td>Serum B12</td>
</tr>
<tr>
<td>C - ascorbate</td>
<td>Scurvy</td>
<td>Renal stones</td>
<td>Plasma</td>
</tr>
<tr>
<td>Folate</td>
<td>Megaloblastic anaemia Neural tube defect</td>
<td>RBC folate</td>
<td></td>
</tr>
</tbody>
</table>
### B3 - Niacin

- Pellagra – 3Ds
  - Dementia, dermatitis, diarrhoea

### Trace elements

<table>
<thead>
<tr>
<th>Iron</th>
<th>Hypochromic anaemia</th>
<th>Haemochromatosis</th>
<th>FBC</th>
<th>Fe</th>
<th>Ferritin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iodine</td>
<td>Goitre Hypothyroid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zinc</td>
<td>Dermatitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copper</td>
<td>Anaemia</td>
<td>Wilson’s</td>
<td>Cu</td>
<td></td>
<td>Caeroplasmin</td>
</tr>
<tr>
<td>Fluoride</td>
<td>Dental caries</td>
<td>Fluorosis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Specific conditions

- **Crohns**
  - 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**

- 1969 – Phenylketonuria
- 1970 – Congenital hypothyroidism
- 2004 – Cystic Fibrosis
- 2006 – Sickle cell disease
- 2009 – Medium Chain AcylCoA dehydrogenase Deficiency

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Outcomes</th>
<th>Screening Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phenylketonuria</strong></td>
<td>Phenylalanine hydroxylase deficiency</td>
<td>Phenylalanine levels</td>
</tr>
<tr>
<td><strong>Congenital</strong></td>
<td>Dysgenesis/Agenesis of</td>
<td>TSH levels</td>
</tr>
</tbody>
</table>

---

93
Hypothyroidism
thyroid gland

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 (if the 2017 paper is anything to go by). 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:

<table>
<thead>
<tr>
<th>Have cystic fibrosis</th>
<th>Don’t have cystic fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test positive</td>
<td>90 (true positive)</td>
</tr>
<tr>
<td></td>
<td>5 (false positive)</td>
</tr>
<tr>
<td>Test negative</td>
<td>10 (false negative)</td>
</tr>
<tr>
<td></td>
<td>80 (true negative)</td>
</tr>
</tbody>
</table>

- **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!
<table>
<thead>
<tr>
<th>Group</th>
<th>Examples</th>
<th>Key Features</th>
</tr>
</thead>
</table>
| **Group 1 – accumulation of toxins** | Organic adicaemias  
Includes propionic acidaemia etc…  
Urea cycle disorders  
9 in total, includes ornithine transcarbamylase deficiency | High urea, ketones  
Metabolic acidosis  
Treat with low protein diet, acylcarnitine and haemofiltration  
Often have funny smells due to the organic acids  
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  
Galactossaemia  
Fatty acid oxidation disorders  
Includes MCADD | Hypoglycaemia and lactic acidosis  
Hepatomegaly, developmental delay  
Hepatoblastoma risk high  
Treat with regular CHO  
Increased Gal-1-phosphate levels cause cataracts  
Hypoglycaemia, neonatal conjugated jaundice  
Test urine reducing agents  
Treat with low lactose/galactose diet  
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  
Glycosylation disorders | Poor feeds, seizuresa  
Retinopathy  
Hepatomegaly and mixed hyperbiliribinaemia  
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 mucuooligopolysaccharides 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 – Corticotrophic, Somatotrophic (Those with gigantism and acromegaly are at a vastly increased risk of contracting type 2 diabetes), Catecholaminergic or secondary to either increased insulin resistance or absolute deficiency.

Diabetes Mellitus

Approximately 2 million people in Britain suffer from Diabetes mellitus with 90% of these being type 2 diabetics.

Diagnosis – made with either typical symptoms plus one of Fasting glucose >7, Oral glucose tolerance test >11.1 or random glucose >11.1, or made without symptoms via 2 of the above tests.

NICE guidelines also recommend you can also use HbA1C >48 as one of these tests.

With a random or oral glucose tolerance test >7.8 but <11.1 it is classified as Impaired glucose tolerance.

A fasting glucose >6.1 but <7.0 is classified as impaired fasting glucose.

Interestingly both IGT and IFG share the same macrovascular risks as the WHO classified Diabetics but the microvascular side effects are seen more frequently in those with the full diagnosis of Diabetes mellitus.

DKA and hyperosmolar hyperglycemic state (HHS) are more common in type 1 DM and type 2 DM, respectively.

HHS Criteria:
- pH > 7.3, Osmolarity > 320mOsm, Blood Glucose > 30mM
- HHS develops over few days.
- Patients present similarly to DKA, acutely unwell with confusion and clinical dehydration.
- The loss of fluid may be as high as 20% of bodyweight!
- Management:
  - Fluid replacement – Aggressive, can usually use normal saline +/- potassium
    - Aim +3-6L by 12h depending on weight and extent of dehydration
    - Aiming to reduce Glucose no more than 5mM/h and Na+ by 10mM/24h
  - Monitoring
    - Serial U+Es and glucose readings
  - Potassium
    - supplementation only needed if K+ between 3.5-5.5
  - Insulin
    - Can be used if glucose no longer falling with fluids alone
    - Use 0.05u/Kg/hr fixed dose
  - Monitor pressure areas – high risk of ulceration
  - Monitor neuro obs
- Resolution may take up to 72h

DKA Criteria:
- pH < 7.3, Plasma Glucose >11mM, Blood Ketones>3mM (2+ in urine).
- DKA is rapid.
Medical emergency, presenting with collapse/confusion, a dehydrated/shocked patient, may be associated with kussmaul breathing, abdominal pain, nausea, vomiting.

Precipitants include: Infection, surgery, missed insulin doses, trauma.

Driving factor is a state of absolute insulin deficiency

Patients lose up to 10% of bodyweight in water

Management

- Bloods (inc VBG unless concerns over respiratory function where ABG would be more appropriate), ECG, spot ketones + glucose.
  - Fluids
    - These must be started first
    - Replacement of deficit + maintenance over 24h
    - Front load replacement and taper off gradually
    - N. Saline is fluid of choice
    - If potassium low add in 40mM KCl (n.b. you cannot administer >10mM/h K+ outside of ITU)
  - Insulin
    - Started after fluids
    - ensure K+ not <3.5
    - 0.1u/kg/h fixed dose regimen
    - DO NOT STOP background basal insulin – the state of deficiency the patient is in is in the context of this being present.
  - Early senior review +/- ITU involvement
  - Monitoring
    - Aiming to reduce Ketones by 0.5/h and glucose by around 3/h
    - Catheterisation is useful, aiming O/P >0.5ml/kg/hr
  - Resolution is when ketones <0.6 and pH >7.3
**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** – iatrogenic insulin, sulfonylurea excess, insulinoma

**Hypoinsulinaemic hypoglycaemia** – +ve ketones – Alcohol binge 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 receptors
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

**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 hyperbilirubinaemia 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.*

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 byproduct 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))

24hour collection
• Proteinuria quantification (superceded 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 a rise in serum creatining over 26.5 in 48h or to 1.5x baseline in 48h (3x is severe). It can also be defined as a urine output of less than 0.5mls/kg/hr but prostate and bladder pathology can acutely cause this too
Pre-renal – reduced renal perfusion with no structural abnormality of the kidney, 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:**
1. Pulmonary oedema
2. Refractory hyperkalaemia
3. Metabolic acidosis
4. Uraemic encephalopathy
5. Also some drug toxicity (lithium for example)

### Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (ml/min)</th>
<th>Prevalence (% of pop)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal GFR</td>
<td>&gt;90</td>
<td>3.3 %</td>
</tr>
<tr>
<td>2</td>
<td>Mild GFR</td>
<td>60-89</td>
<td>3 %</td>
</tr>
<tr>
<td>3</td>
<td>Moderate GFR</td>
<td>30-59</td>
<td>4.3 %</td>
</tr>
<tr>
<td>4</td>
<td>Severe GFR</td>
<td>15-29</td>
<td>0.2 %</td>
</tr>
<tr>
<td>5</td>
<td>End-stage kidney failure</td>
<td>&lt;15 or dialysis</td>
<td>0.2 %</td>
</tr>
</tbody>
</table>

**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
  - Hemodialysis
    ▪ Done via a tunneled central line (AKA Tessio line) or an arteriovenous fistulae (requires a surgery to create)
    ▪ Usually done around 3x/week depending on the patients 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**
  - Done 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 with own convenience
  - Increased risk of 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)
    - Standardised to the right side for ease of recognition
    - Right mesocolon is not fixed therefore easier to access the iliac vessels to connect the transplant to
Immunology
Primary Immune Deficiencies

<table>
<thead>
<tr>
<th>SCID</th>
<th>CD4 T cell</th>
<th>CD8 T cell</th>
<th>B cell</th>
<th>IgM</th>
<th>IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Di George</td>
<td>↓</td>
<td>↓</td>
<td>+</td>
<td>+</td>
<td>↓</td>
</tr>
<tr>
<td>BLS</td>
<td>↓</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>↓</td>
</tr>
</tbody>
</table>

CVID (Common Variable Immunodeficiency)

- **CD4 T cell**
- **CD8 T cell**
- **B cell**
- **IgM**
- **IgG**
- **IgA**

- **SCID**
- **Brutons**
- **Hyper IgM**
- **Selective IgA Deficiency**
- **CVID**

**Neutrophil count**
- Absent

**Leukocyte adhesion markers**
- Normal

**Nitroblue test of oxidative killing (NBT)**
- Usually absent (because no neutrophils)
- No

**Pus**
- No

**Chronic Granulomatous Disease**

- **Kostmann syndrome (congenital neutropenia)**
  - Absent
  - Normal
  - Usually absent (because no neutrophils)
  - No

- **Leukocyte adhesion deficiency**
  - Increased during infection
  - Absent
  - Normal
  - No

- **Chronic Granulomatous Disease**
  - Normal
  - Normal
  - Abnormal
  - Yes
<table>
<thead>
<tr>
<th>Factors</th>
<th>Features</th>
<th>Disease</th>
<th>Disease characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>External epithelia</td>
<td>Keratinised cells</td>
<td>Burns</td>
<td>High risk infection &gt;70% deaths with 5 days is related to infection</td>
</tr>
<tr>
<td></td>
<td>Sebaceous glands</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Secreted mucous</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cilia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucosal surfaces</td>
<td></td>
<td>IgA deficiency</td>
<td>Complete deficiency of IgA affects 1:600 caucasoid individuals</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Genetic and environmental factors important in development</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Associated with recurrent respiratory and gastrointestinal tract infections in 30%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Commensal bacteria</td>
<td>Competition</td>
<td>Antibiotic use</td>
<td>Organisms rapidly colonise an undefended niche</td>
</tr>
<tr>
<td></td>
<td>Bactericidins and fatty acids</td>
<td></td>
<td>- Candida albicans</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Clostridium difficile</td>
</tr>
<tr>
<td></td>
<td>Production of neutrophils</td>
<td>Reticular dysgenesis</td>
<td>Failure of stem cells to differentiate along myeloid or lymphoid lineage Failure of production of: Neutrophils, Lymphocytes, Monocyte/macrophages, Platelets</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fatal in very early life unless corrected with bone marrow transplantation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Autosomal recessive severe SCID (most severe form) Mutation in mitochondrial energy metabolism enzyme adenylate kinase 2 (AK2)</td>
</tr>
<tr>
<td></td>
<td>Neutrophil maturation</td>
<td>Kostmann syndrome</td>
<td>Specific failure of neutrophil maturation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Autosomal recessive severe congenital neutropenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cyclic neutropenia</td>
<td>Classical form due to mutation in HCLS1-associated protein X-1 (HAX1) Specific failure of neutrophil maturation Autosomal dominant episodic neutropenia every 4-6 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mutation in neutrophil elastase (ELA-2)</td>
</tr>
</tbody>
</table>
### Migration to site of infection

**Leukocyte adhesion deficiency**

- [Deficiency of CD18 (b2 integrin subunit) in LAD1]

**CD11α/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

### Phagocytosis

<table>
<thead>
<tr>
<th>Phagocytosis</th>
<th>Opsonisation</th>
<th>Complement and antibody defects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phagocytosis</strong></td>
<td><strong>Opsonisation</strong></td>
<td><strong>Complement and antibody defects</strong></td>
</tr>
<tr>
<td>Migration to site of infection</td>
<td>Leukocyte adhesion deficiency</td>
<td>CD11α/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.</td>
</tr>
</tbody>
</table>

Leukocyte adhesion deficiency characterised by:
- Very high neutrophil counts in blood
- Absence of pus formation
- Delayed umbilical cord separation

### Killing

<table>
<thead>
<tr>
<th>Killing</th>
<th>Oxidative</th>
<th>Chronic granulomatous disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent respiratory burst</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
- Deficiency of one of components of NADPH oxidase
- Inability to generate oxygen free radicals
- 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)
Negative Nitro-Blue Tetrazolium test (NBT). NBT is a dye that changes colour from yellow to blue following interaction with hydrogen peroxide.
Dihydrorhodamine (DHR) flow cytometry test. DHR is oxidized to rhodamine, which is strongly fluorescent, following interaction with hydrogen peroxide.

<table>
<thead>
<tr>
<th>Recruitment of other cells</th>
<th>Cytokine production</th>
<th>Deficiency of IL-12 and IFNγ and their receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptibility to infection with mycobacteria (TB and atypical), BCG, Salmonella.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection with mycobacteria activates IL12-IFNγ network:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
- Infected macrophages stimulated to produce IL12
- IL12 induces T cells to secrete IFNγ
- IFNγ feeds back to macrophages & neutrophils |
<table>
<thead>
<tr>
<th>Alternative pathway</th>
<th>Classical pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutive ‘tick over’ of complement activation</td>
<td>Constitutive ‘tick over’ of complement activation</td>
</tr>
<tr>
<td>Antibody dependent.</td>
<td>Antibody dependent.</td>
</tr>
<tr>
<td>Necessary against infection and clearance of waste (apoptotic cells and immune complexes).</td>
<td>Necessary against infection and clearance of waste (apoptotic cells and immune complexes).</td>
</tr>
</tbody>
</table>

**Factor B/ Factor I/ Factor P deficiency**

- Deficiency in early classical pathway (C1/2/4)
- Inability to form granulomas
- Inability to mobilise complement rapidly in response to bacterial infections -> Recurrent infections with encapsulated bacteria
- All very rare
- Immune complexes fail to activate complement pathway à increased susceptibility to infection
- Increased load of self-antigens – particularly nuclear components – which may promote auto-immunity (SLE)
- 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

- Stimulates production of TNF
- Activates NADPH oxidase
- Stimulates oxidative pathways

- Increased load of self-antigens – particularly nuclear components – which may promote auto-immunity (SLE)
- 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

- Almost all patients with C2 deficiency have SLE
- Severe skin disease
- Increased no. infections
<table>
<thead>
<tr>
<th>Mannose binding lectin</th>
<th>Not dependent on acquired immune response</th>
<th>MBL deficiency</th>
<th>30% of all individuals are heterozygote for mutant protein</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Involves C2 and C4 but not C1</td>
<td></td>
<td>6-10% have no circulating MBL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Associated with increased infection in patients who have another cause of immune impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Premature infants</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Chemotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• HIV infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Antibody deficiency</td>
</tr>
<tr>
<td>C3</td>
<td>All pathways converge on C3</td>
<td>C3 deficiency</td>
<td>Severe susceptibility to bacterial infections (esp. encapsulated – meningococcus, streptococcus, haemophilis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Increased risk of development of connective tissue disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Secondary C3 deficiency</td>
<td>Nephritic factors: auto-antibodies directed against parts of the complement pathway</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nephritic factors stabilise C3 convertases resulting in C3 activation and consumption</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Often associated with glomerulonephritis (classically membranoproliferative)</td>
</tr>
<tr>
<td>Terminal common pathway</td>
<td>Results in formation of MAC</td>
<td>Any defect</td>
<td>Inability to make membrane attack complex</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inability to use complement to lyse encapsulated bacteria</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Results in specific hole in immune system</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Neisseria meningitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Streptococcus pneumonia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Haemophilus influenza</td>
</tr>
<tr>
<td>Haem stem cells</td>
<td>Bone marrow</td>
<td>Reticular dysgenesis</td>
<td>SEE ABOVE</td>
</tr>
<tr>
<td>Lymphoid progenitors</td>
<td>Bone marrow</td>
<td>SCID (In general)</td>
<td>Unwell by 3 months of age (protected beforehand by IgG from mother across placenta then colostrum) with:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Infections of all types</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Failure to thrive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Persistent diarrhoea</td>
</tr>
</tbody>
</table>
### T cell maturation/selection in thymus

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>X-linked SCID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymus</td>
<td>45% of all severe combined immunodeficiency</td>
</tr>
</tbody>
</table>

- **Unusual skin disease:**
  - Colonisation of infant's empty bone marrow by maternal lymphocytes
  - Graft versus host disease

- **Family history of early infant death**
- **20 possible pathways identified:**
  - Deficiency of cytokine receptors
  - Deficiency of signalling molecules
  - Metabolic defects

- **Effect on different lymphocyte subsets (T, B, NK) depend on exact mutation**

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>DiGeorge syndrome (22q11.2 deletion syndrome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deletion at 22q11.2. TBX1 may be responsible for some features, usually sporadic. Developmental defect of pharyngeal pouch. Remember CATCH-22:</td>
<td></td>
</tr>
<tr>
<td>- Cardiac abnormalities (especially tetralogy of Fallot)</td>
<td></td>
</tr>
<tr>
<td>- Abnormal facies (high forehead, low set ears)</td>
<td></td>
</tr>
<tr>
<td>- Thymic aplasia (T cell lymphopenia)</td>
<td></td>
</tr>
<tr>
<td>- Cleft palate</td>
<td></td>
</tr>
<tr>
<td>- Hypocalcaemia/hypoparathyroidism</td>
<td></td>
</tr>
<tr>
<td>- 22 – chromosome</td>
<td></td>
</tr>
</tbody>
</table>

- **Normal numbers B cells and reduced numbers T cells**

- **Homeostatic proliferation with age álmmune function improves with age**

- **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
<table>
<thead>
<tr>
<th>T cell activation and effector functions</th>
<th>Cytokine release</th>
<th>Deficiency of IL-12, IFNγ and their receptors</th>
<th>SEE ABOVE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Export of mature T cells to periphery</strong></td>
<td><strong>T-B cell communication</strong></td>
<td><strong>Hyper IgM syndrome</strong></td>
<td>Failure to express CD40L on activated T cells. SEE BELOW.</td>
</tr>
<tr>
<td><strong>B lymphocyte maturation</strong></td>
<td><strong>Pro B cells → Pre B cells → Mature B cells</strong></td>
<td><strong>Bruton’s X-linked hypogammaglobulinaemia</strong></td>
<td>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, bacterial, enterovirus</td>
</tr>
<tr>
<td><strong>Class switching</strong></td>
<td><strong>Selective IgA deficiency</strong></td>
<td><strong>Hyper IgM syndrome</strong></td>
<td>Prevalence = 1:600</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2/3(^{rd}) individuals asymptomatic and 1/3(^{rd}) have recurrent respiratory tract infections. Also GI infections. Genetic component but cause unknown. 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)</td>
</tr>
</tbody>
</table>
| | | | • 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 |
| | | | Usually have normal number of CD8+ cells
| | | | Normal number of B cells
| | | | Failure to make IgG or IgA antibody (no class switching)
| | | | Clinically:
| | | | • Unwell by 3 months of age and failure to thrive
| | | | • Infections of all types
| | | | • May be associated with sclerosing cholangitis
| | | | • Family history of early infant death

Export of mature T cells to periphery

**T-B cell communication**

Pro B cells → Pre B cells → Mature B cells
<table>
<thead>
<tr>
<th>Common variable immune deficiency</th>
<th>Heterogenous group of disorders with disease mechanism unknown à Low IgG, IgA and IgE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical features</td>
<td>Recurrent bacterial infections with severe end-organ damage</td>
</tr>
<tr>
<td></td>
<td>1. Bronchiectasis, persistent sinusitis, recurrent GIT infection</td>
</tr>
<tr>
<td></td>
<td>Autoimmune disease</td>
</tr>
<tr>
<td></td>
<td>Granulomatous disease</td>
</tr>
</tbody>
</table>

- Pneumocystis jiroveci infection, autoimmune disease and malignancy

Results in:
- Normal number circulating B cells
- Normal number of T cells and normal in vitro T cell responses
- Elevated serum IgM
- Undetectable IgA, IgE, IgG (failure of class switching)
- No germinal centre development within lymph nodes and spleen
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, antibiotic prophylaxis, BMT is definitive. For chronic granulomatous disease – IFN-gamma is specific tx.

**Complement Deficiencies**

<table>
<thead>
<tr>
<th></th>
<th>C3</th>
<th>C4</th>
<th>CH50</th>
<th>AP50</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1q deficiency</td>
<td>+</td>
<td>+</td>
<td>↓</td>
<td>+</td>
</tr>
<tr>
<td>Factor B deficiency</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>↓</td>
</tr>
<tr>
<td>C9 deficiency</td>
<td>+</td>
<td>+</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>SLE</td>
<td>↓</td>
<td>↓</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

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**

<table>
<thead>
<tr>
<th>T cell deficiency</th>
<th>Antibody deficiency (or CD4 T cell deficiency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral infections (Cytomegalovirus)</td>
<td>Bacterial infections (Staphylococcus, Streptococcus)</td>
</tr>
<tr>
<td>Fungal infection (Pneumocystis, Cryptosporidium)</td>
<td>Toxins (Tetanus, Diptheria)</td>
</tr>
<tr>
<td>Some bacterial infections – esp. intracellular organisms (MTB, Salmonella)</td>
<td>Some viral infections (Enterovirus)</td>
</tr>
<tr>
<td>Early malignancy</td>
<td></td>
</tr>
</tbody>
</table>

**Diagnosis:** WCC, lymphocyte subsets, serum Ig and electrophoresis, functional tests, HIV

**Management of T cell deficiencies:** infection prophylaxis and treatment, Ig replacement, BMT, 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 IgA deficiency (not effective if no IgG)
## 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, rhinoconjunctivitis, 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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Allergen</th>
<th>Pathology</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopic Dermatitis (Infantile eczema)</td>
<td>Irritants, food and environmental</td>
<td>Defects in β defensin predispose to <em>Staph aureus</em> superinfection</td>
<td>Clinical.</td>
<td>Emollients, skin oils, topical steroids, antibiotics, PUVA phototherapy etc</td>
</tr>
<tr>
<td>Food Allergy</td>
<td>Milk, egg, peanut, tree nut, fish, shellfish</td>
<td>IgE (anaphylaxis, OAS); cell mediated (coeliac); IgE/cell mediated (atopic dermatitis)</td>
<td>Food Diary, Skin Prick Tests, RAST, Challenge Test. Most resolve by adulthood.</td>
<td>Dietician, Food Avoidance, Epipen, Control asthma if present</td>
</tr>
<tr>
<td>Oral Allergy Syndrome (OAS)</td>
<td>Birch pollen + rosacea fruit, ragweed + melons, mugwort + Celery (cross-reactivity)</td>
<td>Exposure to allergen induces allergy to food. Symptoms limited to mouth, 2% get anaphylaxis</td>
<td>Clinical Diagnosis, Skin Prick Testing can be useful</td>
<td>Avoid food</td>
</tr>
<tr>
<td>Latex Food Syndrome</td>
<td>Chestnut, avocado, banana, potato, tomato, kiwi, papaya, eggplant, mango, wheat, melon</td>
<td>Some foods have latex like components and hence latex allergy sufferers will also have food allergies</td>
<td>Skin Prick Test</td>
<td>Strict avoidance of causative food</td>
</tr>
<tr>
<td>Allergic Rhinitis</td>
<td>Seasonal (tree and grass pollen, fungal spores); Perennial (pets, house dust mite); Occupational (latex, lab animals)</td>
<td>Nasal itch and obstruction, sneezing, anosmia, eye symptoms</td>
<td>Pale bluish swollen nasal mucosa; Skin Prick Test and RAST</td>
<td>Allergen avoidance, Anti-Histamine, Steroid Nasal Spray, Sodium Cromoglycate Eye Drops, Oral Steroids, Ipratropium Nasal Spray, Grass pollen desensitisation</td>
</tr>
</tbody>
</table>
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.

Management: Elevate Legs, 100% Oxygen, IM Adrenaline 500 mcg, inhaled bronchodilators, Hydrocortisone 100mg IV, Chlorphenamine 10mg IV, IV Fluids, Seek Help.

Investigations in allergy

Skin prick tests
- Useful to confirm clinical history. Negative test excludes IgE-mediated allergy.
- Positive control = histamine, negative control = dilutent.
- A positive test is a wheal \( \geq 2 \) mm 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 anti-histamines, 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:
  1. Ara h 2 – High risk anaphylaxis to peanut and nuts
  2. 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.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Antigen</th>
<th>Pathology</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heamolytic Disease of the Newborn (HDN)</strong></td>
<td>Antigens on neonatal erythrocytes</td>
<td>Maternal IgG mediated reticulocytosis and anaemia</td>
<td>Positive Direct Coombs Test</td>
<td>Maternal Plasma Exchange, Exchange Transfusion</td>
</tr>
<tr>
<td><strong>Autoimmune Haemolytic Anaemia (+ ITP = Evan's Syndrome)</strong></td>
<td>Numerous autoantigens eg: Rh blood group Ag</td>
<td>Destruction of red blood cells by auto antibody + complement + FcR+ phagocytes, anaemia</td>
<td>Positive Direct Coombs Test, Anti Red Cell Ab</td>
<td>Steroids</td>
</tr>
<tr>
<td><strong>Autoimmune Thrombocytopenic Purpura</strong></td>
<td>Glycoprotein Ib/IIia on platelets</td>
<td>Bruising/Bleeding (Purpura)</td>
<td>Anti Platelet Antibody</td>
<td>Steroids, IVIG, Anti-D Antibody, splenectomy</td>
</tr>
<tr>
<td><strong>Goodpasture’s Syndrome</strong></td>
<td>Non-collagenous domain of basement membrane collagen type IV</td>
<td>Glomerulonephritis is, pulmonary haemorrhage</td>
<td>Anti GBM Ab</td>
<td>Corticosteroids and Immunosuppression</td>
</tr>
<tr>
<td><strong>Pemphigus Vulgaris</strong></td>
<td>Epidermal Cadherin</td>
<td>Non-tense blistering of skin and Bullae</td>
<td>Direct Immunofluorescence showing IgG deposition</td>
<td>Corticosteroids and Immunosuppression</td>
</tr>
<tr>
<td><strong>Graves disease</strong></td>
<td>TSH receptor</td>
<td>Hyperthyroidism</td>
<td>Anti TSH-R Ab</td>
<td>Carbimazole and Propylthiouracil</td>
</tr>
<tr>
<td><strong>Myasthenia Gravis</strong></td>
<td>Acetylcholine receptor</td>
<td>Fatiguable muscle weakness, Double Vision</td>
<td>Anti Ach-R Ab Abnormal EMG Tensilon Test</td>
<td>Neostigmine, Pyridostigmine, (If serious use IVIG and Plasmaphoresis)</td>
</tr>
<tr>
<td><strong>Acute Rheumatic Fever</strong></td>
<td>M proteins on Group A strep</td>
<td>Myocarditis, Arthritis, Sydenham’s Chorea</td>
<td>Clinical, based on Jones Criteria</td>
<td>Aspirin, Steroids and Penicillin</td>
</tr>
<tr>
<td><strong>Pernicious Anaemia</strong></td>
<td>Intrinsic Factor and Gastric Parietal Cells</td>
<td>↓Hb ↓B12</td>
<td>Anti Gastric Parietal Cell Ab, Anti-IF Ab, Schilling Test</td>
<td>Dietary B12 or IM B12</td>
</tr>
<tr>
<td><strong>Churg-Strauss Syndrome (eGPA)</strong></td>
<td>Medium and Small Vessel Vasculitis</td>
<td>Allergy →Asthma→ Systemic Disease (Male predominance)</td>
<td>p-ANCA (against myeloperoxidase ), Granulomas, Eosinophil Granulocytes</td>
<td>Prednisolone, Azathioprine, Cyclophosphamide</td>
</tr>
<tr>
<td><strong>Wegener’s Granulomatosis (GPA)</strong></td>
<td>Medium and Small Vessel Vasculitis</td>
<td>Sinus Problems, Lung Cavitations + haemorrhage, Crescent Glomerulonephritis is</td>
<td>c-ANCA (against Proteinase 3) granulomas</td>
<td>Corticosteroids, cyclophosphamid e, co-trimoxazole</td>
</tr>
<tr>
<td><strong>Microscopic Polyangiitis</strong></td>
<td>Pauci-immune necrotizing, small</td>
<td>Purpura, livedo, many different</td>
<td>p-ANCA (against myeloperoxidas)</td>
<td>Prednisolone, Cyclophosphami</td>
</tr>
<tr>
<td>Chronic Urticaria</td>
<td>vessel vasculitis</td>
<td>organs affected</td>
<td>medications</td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------</td>
<td>----------------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Persistent Itchy Wheals Lasting &gt; 6 Weeks. Associated with Angioedema in 50% of cases. IgG against FcεR1 or IgG against IgE (Exclude Urticarial Vasculitis in those who respond poorly to Anti-histamine)</td>
<td>Challenge Test, ESR (Raised in Urticarial Vasculitis), Skin Prick Testing</td>
<td>Avoid precipitants, Check for thyroid disease, Preventative antihistamine, IM adrenaline for pharyngeal angioedema, 1% Menthol in Aqueous Cream for pruritis (Also Doxepin and Cyclosporin)</td>
<td></td>
</tr>
</tbody>
</table>

**MPA**

Medications (NSAIDS) Cold, Food, Pressure, Sun, Exercise, Insect Stings, Bites and Idiopathic

Azathioprine, plasmaphoresis
### Type III Hypersensitivity Disorders

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

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

### Type IV Hypersensitivity Disorders

Delayed hypersensitivity. T-cell mediated.

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Antigen</th>
<th>Pathology</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1 Diabetes Mellitus</strong></td>
<td>Pancreatic Beta Cell proteins. (Glutamate Decarboxylase GAD)</td>
<td>Insulitis, Beta Cell Destruction</td>
<td>Blood Glucose, Ketonuria, Glutamate Decarboxylase Antibodies, Islet Cell Antibodies</td>
<td>Insulin via Injections or continuous infusion</td>
</tr>
</tbody>
</table>
### 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

### HLA Associations

<table>
<thead>
<tr>
<th>Disease</th>
<th>Susceptibility allele</th>
<th>Relative risk (fold)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankylosing spondylitis</td>
<td>HLA B27</td>
<td>87</td>
</tr>
<tr>
<td>Goodpasture's syndrome</td>
<td>HLA DR15/DR2</td>
<td>10</td>
</tr>
<tr>
<td>Graves Disease</td>
<td>HLA- DR3</td>
<td>4</td>
</tr>
<tr>
<td>Systemic Lupus Erythematosis (SLE)</td>
<td>HLA-DR3</td>
<td>6</td>
</tr>
<tr>
<td>Type I diabetes</td>
<td>HLA DR3/DR4</td>
<td>25</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>HLA-DR4</td>
<td>4</td>
</tr>
</tbody>
</table>

Other genetic polymorphisms
- **PTPN22**: tyrosine phosphatase expressed in lymphocytes, associated development of RA, SLE and T1DM.
- **CTLA4**: receptor for CD80/CD86 expressed by T cells, transmits inhibitory signal to control T cell activation. Associated with SLE, T1DM, Autoimmune thyroid disease.

### 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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Autoantibody (IgG unless otherwise stated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiphospholipid Syndrome (Hugh’s Syndrome)</td>
<td>Antibodies against cardiolipin and β2 glycoprotein, lupus anticoagulant,</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>Anti-smooth muscle antibody, Anti Liver Kidney microsomal-1 (anti-LKM-1). Anti Soluble Liver Antigen (anti-SLA)</td>
</tr>
<tr>
<td>Autoimmune haemolytic Anaemia</td>
<td>Anti-Rh Blood Group Antigen</td>
</tr>
<tr>
<td>Autoimmune Thrombocytopenic Purpura</td>
<td>Anti-Glycoprotein llb-Illa or lb-IX Antibody</td>
</tr>
<tr>
<td>Churg-Strauss Syndrome (eGPA)</td>
<td>Perinuclear/protoplasmic-staining antineutrophil cytoplasmic antibodies (p-ANCA)</td>
</tr>
<tr>
<td>Condition</td>
<td>Antibodies</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Coeliac disease</td>
<td>Anti-tissue transglutaminase antibody (IgA), Anti-endomysial antibody (IgA)</td>
</tr>
<tr>
<td>Congenital heart block in infants of mothers with SLE</td>
<td>Anti-Ro antibody</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>Anti-endomysial antibody (IgA)</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>Anti-Jo-1 (t-RNA Synthetase)</td>
</tr>
<tr>
<td>Diffuse Cutaneous Scleroderma</td>
<td>Antibodies to Topoisomerase/Scl70, RNA Pol I,II,III, Fibrillarin (nucleolar pattern)</td>
</tr>
<tr>
<td>Goodpasture's Syndrome</td>
<td>Anti-GBM Antibody</td>
</tr>
<tr>
<td>Graves Disease</td>
<td>Anti-TSH Receptor Antibody (stimulatory antibody)</td>
</tr>
<tr>
<td>Hashimoto's Thyroiditis</td>
<td>Antibodies to Thyroglobulin and Thyroperoxidase</td>
</tr>
<tr>
<td>Limited cutaneous scleroderma (CREST)</td>
<td>Anti-centromere antibody</td>
</tr>
<tr>
<td>Microscopic Polyangitis (MPA)</td>
<td>Perinuclear/protoplasmic-staining antineutrophil cytoplasmic antibodies (p-ANCA)</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>Anti-U1RNP antibody (speckled pattern)</td>
</tr>
<tr>
<td>Myasthenia Gravis</td>
<td>Anti-Ach Receptor Antibody</td>
</tr>
<tr>
<td>Pernicious anaemia</td>
<td>Antibody to gastric parietal cells (90%) and intrinsic factor (50%)</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>Anti-Jo-1 (t-RNA Synthetase)</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>Anti-mitochondrial antibody</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Anti-CCP Antibodies, Rheumatoid Factor (less specific)</td>
</tr>
<tr>
<td>Sjogren's syndrome</td>
<td>Anti-Ro, Anti-La antibody (speckled pattern), 60-70% have positive RF</td>
</tr>
<tr>
<td>Systemic Lupus Erythematosis</td>
<td>Antibodies to dsDNA Histones(Homogenous) and Ro La, Sm, U1RNP (speckled)</td>
</tr>
<tr>
<td>Type 1 Diabetes Mellitus</td>
<td>Antibodies to Glutamate Decarboxylase and pancreatic β Cells</td>
</tr>
<tr>
<td>Wegener’s Granulomatosis (GPA)</td>
<td>Cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA)</td>
</tr>
</tbody>
</table>
# Immune Modulation

<table>
<thead>
<tr>
<th>Boost the immune response</th>
<th>Suppress the immune response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccination</td>
<td>Non-specific immunosuppression</td>
</tr>
<tr>
<td>Replacement of missing components</td>
<td>Targeting specific components of the immune response</td>
</tr>
<tr>
<td>(Bone marrow transplantation, Igs, T cells)</td>
<td></td>
</tr>
<tr>
<td>Cytokine therapy</td>
<td>Antibody removal (plasmapheresis)</td>
</tr>
<tr>
<td>Blocking immune checkpoints</td>
<td></td>
</tr>
</tbody>
</table>

## Boosting the immune response

**Vaccination:** see later

**Human Normal Immunoglobulin (Antibody replacement)**
- From >1000 donors (all screened for HIV, Hep B and Hep C)
- Contains preformed IgG against full range of organisms
- Given every 3-4 weeks, half life is 18 days, IV or sub-cut
- Used for primary antibody deficiencies (CVID, Brutons etc.), secondary deficiencies (CLL and Multiple Myeloma, post-BMT) and passive vaccination.

**Specific Immunoglobulin (passive vaccination) – post-exposure prophylaxis**
- Ig specific to Rabies, Varicella Zoster, Hep B, Tetanus
- Derived from plasma donors with high IgG titres of specific Ab

**Recombinant Cytokines**
- **AIM:** boost immune response to cancer and some pathogens
- **Interferon alpha:** Hepatitis C, Hepatitis B, Kaposi’s sarcoma, Hairy cell leukaemia, chronic myelogenous leukaemia, malignant myeloma
- **Interferon beta:** Relapsing MS (past), Bechets
- **Interferon gamma:** Chronic granulomatous disease

**Blocking immune checkpoints**
- Ipilimumab – antibody specific for CTLA4 – blocks downregulatory immune checkpoint and allows T cell activation; indications: advanced melanoma
- Pembrolizumab/Nivolumab – antibody specific for PD-1 - blocks downregulatory immune checkpoint and allows T cell activation; indications: advanced melanoma
Immunosuppressive therapy

Side Effects of Immunosuppressive Therapies

<table>
<thead>
<tr>
<th>Chronic Infection</th>
<th>Chronic Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB</td>
<td>• Check history/travel/ contacts/CXR/Elispot</td>
</tr>
<tr>
<td></td>
<td>• Give Prophylaxis or treatment if required</td>
</tr>
<tr>
<td>HIV</td>
<td>• Check HIV status prior to Rx</td>
</tr>
<tr>
<td></td>
<td>• Consider risks vs benefits</td>
</tr>
<tr>
<td>Hep B – check core antibody pre treatment</td>
<td></td>
</tr>
<tr>
<td>Hep C – check antibody pre treatment</td>
<td></td>
</tr>
<tr>
<td>Further IX for active disease if positive</td>
<td></td>
</tr>
<tr>
<td>John Cunningham Virus (JCV)</td>
<td>• Polymoma virus that can reactivate</td>
</tr>
<tr>
<td></td>
<td>• Destroys oligodendrocytes</td>
</tr>
<tr>
<td></td>
<td>• Progressive multifocal leukoencephalopathy (PML)</td>
</tr>
</tbody>
</table>

Malignancy

Lymphoma – EBV

Melanoma – particularly anti TNF alpha

Other skin cancers - HPV

Autoimmunity

Dysregulation of immune system -> SLE, vasculitis, AIH etc
<table>
<thead>
<tr>
<th>TYPE</th>
<th>EXAMPLES</th>
<th>MODE OF ACTION</th>
<th>INDICATIONS</th>
<th>SIDE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Prednisolone</td>
<td>Inhibits phospholipase A2 hence blocks arachidonic acid, reduces prostaglandin synthesis inhibits phagocyte trafficking, phagocytosis and release of proteolytic enzymes, lymphopenia, promotes apoptosis, blocks cytokine gene expression, decreased Ab production</td>
<td>Auto-immune disease, auto-inflammatory disease, prevention and treatment of transplant rejection</td>
<td>Transient neutrophilia, diabetes, central obesity, adrenal suppression, cataracts, glaucoma, pancreatitis, osteoporosis, moon face, acne, hirsutism, hypertension, dyslipidaemia, peptic ulceration, avascular necrosis</td>
</tr>
<tr>
<td>Anti-proliferative agents</td>
<td>Cyclophosphamide</td>
<td>Alkylates guanine base of DNA, Damages DNA and prevents cell replication, Affects B cells &gt; T cells, but at high doses affects all cells with high turnover</td>
<td>Connective tissue disease, vasculitis, anti-cancer agent</td>
<td>Bone marrow suppression, infection, malignancy, teratogenic, hair loss, sterility, haemorrhagic cystitis</td>
</tr>
<tr>
<td>cytotoxic agents: inhibit DNA synthesis; cells with rapid turnover most sensitive</td>
<td>Mycophenolate Mofetil</td>
<td>Inhibits IM PDH prevents guanine synthesis Blocks de novo nucleotide synthesis – prevents replication of DNA, Prevents T&gt;B cell proliferation Antimetabolite agent Metabolised by liver to 6 mercaptopurine, blocks de novo purine (eg adenine, guanine) synthesis – prevents replication of DNA, preferentially inhibits T cell activation &amp; proliferation</td>
<td>Transplantation, auto-immune diseases, vasculitis</td>
<td>Bone marrow suppression, infection (herpes virus reactivation, progressive multifocal leukoencephalopathy), malignancy, teratogenic Bone marrow suppression, infection, malignancy, teratogenic, hepatotoxicity, neutropenia Some people have TPMT polymorphism, and are therefore unable to metabolise azathioprine</td>
</tr>
<tr>
<td></td>
<td>Azathioprine</td>
<td></td>
<td>Transplantation, Auto-immune disease, Auto-inflammatory diseases</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Methotrexate</td>
<td>Inhibits dihydrofolate reductase (DHFR) therefore decreases DNA synthesis</td>
<td>RA, Psoriasis, Crohn’s, used in chemotherapy and as an abortifacient</td>
<td>Bone marrow suppression, infection, malignancy, teratogenic, pneumonitis, pulmonary fibrosis, hepatotoxicity, folate deficiency (macrocytic megaloblastic anaemia)</td>
</tr>
<tr>
<td><strong>Plasmapheresis</strong></td>
<td>aim - removal of pathogenic antibody; Plasma treated to remove immunoglobulins and then reinfused (or replaced with albumin in ‘plasma exchange’)</td>
<td>Severe antibody-mediated disease (Goodpastures syndrome, myasthenia gravis, vascular rejection) Antibody mediated rejection</td>
<td>Rebound antibody production limits efficacy, anaphylaxis</td>
<td></td>
</tr>
<tr>
<td>------------------</td>
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<td>-----------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Inhibitors of cell signalling</strong></td>
<td>Tacrolimus inhibits calcineurin which normally activates transcription of IL-2, hence reduces T cell proliferation</td>
<td>Rejection prophylaxis in transplantation</td>
<td>Nephrotoxic, hypertension, neurotoxic, diabetogenic</td>
<td></td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>Blocks clonal proliferation of T cells JAK inhibitor</td>
<td>Rheumatoid arthritis</td>
<td>Nephrotoxic, hypertension, neurotoxic, dysmorphism, gingival (gum) hypertrophy Hypertension, less nephrotoxic</td>
<td></td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Apremilast PDE4 inhibitor</td>
<td>Psoriasis, psoriatic arthritis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Agents directed at cell surface antigens block signalling, cell depletion**

<table>
<thead>
<tr>
<th>Basiliximab</th>
<th>Anti-CD25 (alpha chain of IL-2 receptor), inhibits T cell proliferation</th>
<th>Allograft rejection</th>
<th>Infusion reactions, Infection, Malignancy, GI disturbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abatacept</td>
<td>Anti-CTLA4-Ig, reduces T cell activation</td>
<td>Rheumatoid arthritis</td>
<td>Infusion reactions, infection (TB, HBV, HCV), malignancy, cough</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Anti-CD20, depletes mature B cells (not plasma cells)</td>
<td>Lymphoma, rheumatoid arthritis, SLE</td>
<td>Infusion reactions, infection (PML), exacerbation CV disease</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>Anti-alpha4 integrin (binds to VCAM1 and MadCAM1 to mediate rolling/arrest of leukocytes), inhibits T cell migration</td>
<td>Relapsing-remitting MS, Crohn's disease</td>
<td>Infusion reactions, infection (PML), malignancy, hepatotoxic</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>Anti-IL-6 receptor, Reduces macrophage, T cell, B cell, neutrophil activation</td>
<td>Castleman’s disease, Rheumatoid arthritis</td>
<td>Infusion reactions, Infection, Hepatotoxic, hyperlipidaemia, malignancy</td>
</tr>
<tr>
<td>Muromonab-CD3</td>
<td>Blocks CD3 on T cells, mouse monoclonal antibody (OKT3)</td>
<td>Active allograft transplant rejection</td>
<td>Fever, leucopenia</td>
</tr>
<tr>
<td>Agents directed at cytokines</td>
<td>Block action of cytokines</td>
<td>Action</td>
<td>Adverse Effects</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---------------------------</td>
<td>--------</td>
<td>----------------</td>
</tr>
<tr>
<td>Anti-thymocyte globulin (ATG)</td>
<td>Lymphocyte depletion, Modulation of T cell activation and migration</td>
<td>allograft rejection (renal, heart)</td>
<td>Infusion reactions, Leukopenia, Infection, Malignancy</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>IL-2 receptor antibody, targets CD25</td>
<td>Organ transplant rejection prophylaxis</td>
<td></td>
</tr>
<tr>
<td>Efalizumab</td>
<td>Anti-CDIIa, inhibits migration of T cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alemtuzumab (Campath)</td>
<td>Monoclonal antibody that binds to CD52 found on lymphocytes resulting in depletion</td>
<td>Chronic lymphoid leukaemia, MS</td>
<td>CMV infection</td>
</tr>
<tr>
<td>Infliximab</td>
<td>anti-TNFa</td>
<td>Rheumatoid arthritis, Ankylosing spondylitis, Psoriasis, psoriatic arthritis, Inflammatory bowel disease</td>
<td>Infusion/injection site reactions, Infection (TB, HBV, HCV), Lupus-like conditions, Demyelination, Malignancy (lymphoma)</td>
</tr>
<tr>
<td>Adalimumab (fully human monoclonal antibody)</td>
<td>TNFalpha/TNFbeta receptor p75-IgG fusion protein</td>
<td>Rheumatoid arthritis, Ankylosing spondylitis, Psoriasis and psoriatic arthritis psoriasis, psoriatic arthritis</td>
<td>Injection site reactions, Infection (TB, HBV, HCV), Lupus-like conditions, Demyelination, Malignancy</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>anti-IL-12 and IL-23 (binds to p40 subunit)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Golimumab</td>
<td>anti-IL-17A</td>
<td>Psoriasis, psoriatic arthritis, ankylosing spondylitis</td>
<td>Infection (TB)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>anti-RANK ligand antibody, Inhibits RANK mediated osteoclast differentiation and function</td>
<td>Osteoporosis, multiple myeloma, bone metastases</td>
<td></td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>anti-IL-12 and IL-23 (binds to p40 subunit)</td>
<td>Psoriasis, psoriatic arthritis, ankylosing spondylitis</td>
<td>Infection, avascular necrosis of jaw</td>
</tr>
</tbody>
</table>
**Injection site reactions**

- Peak reaction at ~48 hours
- May also occur at previous injection sites (recall reactions)
- Mixed cellular infiltrates, often with CD8 T cells
- Not generally IgE or immune complexes

**Infusion Reactions**

- Urticaria, hypotension, tachycardia, wheeze – IgE mediated
- Headaches, fevers, myalgias – not classical type I hypersensitivity
- Cytokine storm
Allergen Desensitization
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
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Allograft – from the same species</td>
<td>Deceased donor</td>
</tr>
<tr>
<td>Xenograft – from different species</td>
<td>Solid organs: kidney, heart, pancreas, lungs, liver,</td>
</tr>
<tr>
<td>Split graft – shared by two recipients</td>
<td>Others: cornea, heart valves, bone, skin, composite</td>
</tr>
<tr>
<td></td>
<td>Living donor – bone marrow, kidney, liver</td>
</tr>
</tbody>
</table>

Transplant rejection is the immune system mounting a response to a foreign antigen as it should
3 Stages: Recognition → Activation → Effector Function

Recognition

Reminder – Immune Recognition
T-Cells (TCs) recognise antigen with MHCs on APCs
B-Cells (BCs) can recognise just antigen

HLA classes

HLA Class I (A,B,C) – expressed on all cells
HLA Class II (DR, DQ, DP) – expressed on antigen-presenting cells but also can be upregulated on other cells under stress

Minimising HLA differences between donor and recipient improves transplant outcome

In transplant the following are recognized:
- HLA (most important DR>B>A) - human leukocyte antigens coded on chromosome 6 by Major Histocompatibility complex (MHC); cell surface proteins, Presentation of foreign antigens on HLA molecules to T cells is central to T cell activation
- Minor HLA – other polymorphic self peptides
- ABO Blood Antigens

In transplant there are 2 types of recognition:
127
1. **Direct**
   Donor APC presenting antigen and/or MHC to recipient T-cells. Acute rejection mainly involves direct presentation.

2. **Indirect**
   Recipient APC presenting donor antigen to recipient T-cells – i.e. the immune system working normally, as it would for an infection. Chronic rejection mainly involves indirect presentation.

---

### Activation and Effector Function – Types of Transplant Rejection

<table>
<thead>
<tr>
<th>Rejection components: T-cell mediated; antibody mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immune response to transplant:</strong></td>
</tr>
<tr>
<td>• <strong>Phase 1:</strong> recognition of foreign antigens</td>
</tr>
<tr>
<td>• <strong>Phase 2:</strong> activation of antigen-specific lymphocytes; proliferation and maturation of B cells with Ab production</td>
</tr>
<tr>
<td>• <strong>Phase 3:</strong> effector phase of graft rejection</td>
</tr>
<tr>
<td>1. Graft infiltration by alloreactive CD4+ cells</td>
</tr>
<tr>
<td>2. Cytotoxic T cells – release of toxins to kill target, punch holes in target cells, apoptotic cell death</td>
</tr>
<tr>
<td>3. Macrophages – phagocytosis, release of proteolytic enzymes, production of cytokines, production of oxygen radicals and nitrogen radicals</td>
</tr>
<tr>
<td>4. Abs bind to graft endothelium</td>
</tr>
</tbody>
</table>

---

### Matching

**Important to reduce Ag differences and therefore recognition and rejection:**
- Determine donor and recipient blood group and HLA type (esp. BM, kidney) – PCR.
  Maximise similarity.
• Check recipient’s pre-formed Ab against ABO and HLA – via CDC, FACS and Luminex
• Cross match – via CDC and FACS. Tests if serum from recipient is able to bind/kill donor lymphocytes- positive crossmatch is contraindication for transplantation.
• After transplant check again for new antibodies vs the graft.

1. Pre-transplant induction agent: suppress T cell responses eg: anti-CD52 Alemtuzumab or anti-CD25 Basiliximab or OKT3/ATG

2. Immunosuppressants post-transplant to reduce rejection eg: CNI + MMF/Aza +/- steroids

3. Treat episodes of acute rejection:
   ▪ Cellular – Steroids, 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; cyclophosphamide; other drugs)
• Replace with own (autologous) or HLA-matched donor (allogeneic) bone marrow
• Graft-versus-host disease
  o Allogeneic HSCT leads to reaction of donor lymphocytes against host tissues
  o Related to degree of HLA-incompatibility
  o Also graft-versus-tumour effect
  o GVHD prophylaxis: Methotrexate/Cyclosporine
  o Symptoms: skin (rash), gut (nausea, vomiting, abdominal pain, diarrhoea, bloody stool), liver (jaundice)
  o Treat with corticosteroids

**Post-transplantation complications**

**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

**Note:**
- **CDC** = Complement Dependent Cytotoxicity
- **FACS** = Flow Cytometry
- **Luminex** = like solid phase FACS – can pick up Abs to individual HLAs
Epidemiology

- ~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)

Pathogenesis

- RNA Retrovirus which targets CD4+ T helper cells as hosts (also CD4+ monocytes and dendritic cells)
- Replicates inside cells using an enzyme called Reverse Transcriptase (RT) to convert RNA into DNA which can be integrated into host cell’s genes
- CD4 molecule is receptor for HIV. The virus binds via gp120 (initial binding) and gp41 (conformational change) – on CD4+ T cells
- Most strains use CCR5 and CXCR4 chemokine co-receptors (on macrophages)
- Gag protein – intrastructural support for HIV

The immune response to the virus

The Innate response

- 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-gp120 and anti-gp41
- 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 by 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)
- 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**

- Median time from infection with HIV to development of AIDS is 8 - 10 years (typical progressors)
- Rapid progressors (10%) in 2 - 3 years.
- Long Term Non Progressors (<5%) stable CD4 counts and no symptoms after 10 years
- Initial viral burden (set point) predicts disease progression.

**Diagnosis**

**Screening Test:** Detects anti-HIV Ab via ELISA  
**Confirmation Test:** Detects Ab via Western Blot  
A positive test requires the patient to have SEROCONVERTED (i.e. started to produce Ab)  
This happens after ~10 weeks incubation period

**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 for patients with chronic infection: **Commence immediately once diagnosis confirmed**

**OLD GUIDELINES** for starting treatment (BHIVA Guidelines):
- If CD4 <200, Or patient is symptomatic. Start thinking about it when CD4 <350.

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

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

**Pregnancy – Zidovudine:**
- Antepartum PO; For delivery IV  
- PO to newborn for 6/52 à 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.
Life Cycle & Treatment

1. Attachment/entry
   - Attachment inhibitors
   - 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

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Side Effects</th>
</tr>
</thead>
</table>
| Fusion Inhibitors            | Enfuvirtide               | Local Reactions to injections
|                              |                           | Hypersensitivity (0.1-1%)                         |
| Attachment Inhibitors        | Maraviroc                 | Unknown                                           |
| Nucleoside Reverse Transl   | Zidovudine                | Generally Rare; fever, headache, GI disturbance, BMS (Zidovudine), Peripheral Neuropathy (Zalcitabine, Stavudine), Mitochondrial Toxicity (Stavudine), Hypersensitivity (Abacavir) |
| Transcriptase Inhibitors (NRTI) | Didanosine               | Emtricitabine                                     |
|                              | Stavudine                 | Epzicom                                           |
|                              | Lactuvudine               | 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                 | Hyperlipidemias, Fat Redistribution and Type 2 Diabetes |
|                              | Nelfinavir                |                                                   |
|                              | Ritonavir                |                                                   |
|                              | Amprenavir               |                                                   |
|                              | Saquinavir               |                                                   |
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.

**Memory**

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)

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

**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

## Vaccination

### Childhood vaccination schedule (2018)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Vaccine Schedule</th>
<th>PCV</th>
<th>R</th>
<th>Men B</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 months</td>
<td>DTaP/IPV/HiB/He p B (6 in 1 injection)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>DTaP/IPV/HiB/He p B (6 in 1 injection)</td>
<td>Men C</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>4 months</td>
<td>DTaP/IPV/HiB/He p B (6 in 1 injection)</td>
<td>PCV</td>
<td></td>
<td>Men B</td>
</tr>
<tr>
<td>12-13 months</td>
<td>Hib/Men C</td>
<td>PCV</td>
<td>MM</td>
<td>Men B</td>
</tr>
<tr>
<td>2 yrs - 8 yrs</td>
<td>Flu</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 years 4 months</td>
<td>DTaP/IPV</td>
<td>MMR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Girls 12-13 years</td>
<td>HPV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 yrs</td>
<td>T/D/aP</td>
<td>Men ACWY</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Other Vaccines

- At risk groups (and over 65):
  - Influenza, PCV, BCG
- Travel:
  - Cholera, Hep A, Hep B, Jap Enceph, Tick-Bourne Enceph, Typhoid, Yellow Fever
- Pregnant women weeks gestation:
  - DTaP/IPV:
- Aged 70-79 years:
  - Shingles

### Consequences of vaccination

Vaccination relies on memory:

- The best vaccines activate both B and T cells.
- Persistence of antigen results in a larger response and the generation of more memory cells

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

### Perfect vaccine:

1. Good protection
2. Single injection
3. No adverse effects
4. Easy storage

### Route of administration

- Subcutaneously – good. Uptake, processing and presentation to Langerhans cells in skin
- Intramuscular OK
• Intravenously Ag is taken to spleen
• Orally (gastrointestinal). Good general response and local response within gut tissue
• Intranasal (respiratory) OK, but may get allergic responses

Influenza - CD8 T cells control the virus load; antibody provides a protective response; protection begins within 7 days after immunization
TB – T cell mediated response; protection after BCG lasts about 10-15 years

**Ways to ensure good response to generate effective memory**
1. live vaccine
2. more persistent antigen
3. assisted activation of immune response

**Cancer vaccines/Dendritic Cell Vaccines**
1. Cancer cells are self, most macromolecules are normal self-antigens
2. Need to find antigens that clearly mark the cancer cells as different from host cells
3. Tumour-bearing animals and cancer patients demonstrate acquired defects in dendritic cells (DC) maturation and function
4. DC cancer vaccine trails in progress

**Why doesn’t vaccination work effectively in the elderly?**
Immune senescence: Increased frequency of terminally differentiated effector memory T cells in the elderly; Increased expression of senescence markers; Much reduced production of recent thymic emigrants which drive the naïve T-cell repertoire.
Nutrition: insufficient energy because of poor nutrition; Reduced availability of trace elements and minerals (reduced gut absorption)

**Types of Vaccine**

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live</td>
<td>Lifelong immunity – no booster needed</td>
<td>Careful in immunodeficient patients</td>
<td>Sabin polio (oral - no longer used)</td>
</tr>
<tr>
<td>Vaccines</td>
<td>Protection against cross reactive strains</td>
<td>Reversion to virulence</td>
<td>MMR</td>
</tr>
<tr>
<td>(use live organism to induce immune response)</td>
<td>Activates all phases of immune system</td>
<td>Harder to store (require refrigerator)</td>
<td>Chicken pox (varicella)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yellow fever</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BCG</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Typhoid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Live attenuated:</strong> BCG, MMR, typhoid</td>
</tr>
</tbody>
</table>
## Inactivated Vaccines
- Easy storage
- Cheaper
- Safe in immunodeficient patients
- No mutation or reversion
- Can eliminate wild-type virus from community

## DNA Vaccines
**Plasmid containing gene inserted into muscle cell, expressed and presented at cell surface inducing immune response**
- Resembles a virally infected cell
- Good immunity

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- Resembles a virally infected cell
- Good immunity

### Inactivated: Salk (polio), Anthrax, Cholera, Bubonic plague, Hep A, Rabies, Pertussis, Influenza
### Component/subunit: Hep B (Hbs antigen), HPV (Capsid), Influenza (haemagglutinin, Neuraminidase),
### Conjugate: Tetanus (Exotoxin), Hib, Meningococcus, Pneumococcus
### Toxoids: Diphtheria, Tetanus

**Experimental; against west nile virus, approved for use in horses.**

HIV positive patients may have MMR but not BCG or Yellow fever.

### Adjuvants – ‘increase the immune response without altering its specificity’;

Depot adjuvant acts by slowing the release of antigen. When the mixture of adjuvant and antigen are injected the adjuvant provides a “steady stream” of antigen for the response

- **ALUM:** 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 that helps prime naïve B cells (mainly antibody mediated response). Generally safe and mild
- **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)
- **Interleukin 2:** in individuals with Hep B Sag in order to get them to seroconvert

### Passive Vaccines: Giving Immunoglobulins (last for 3 weeks)
- **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)

**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.
Histopathology
Cellular Types
Table below illustrates the pathological process occurring for each cell type infiltrate.

<table>
<thead>
<tr>
<th>Neutrophils</th>
<th>Acute Inflammation (sterile or non-sterile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrophages</td>
<td>Late acute inflammation</td>
</tr>
<tr>
<td></td>
<td>Chronic inflammation (including granulomas e.g. Sarcoidosis)</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>Chronic inflammation</td>
</tr>
<tr>
<td></td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Plasma Cells</td>
<td>Chronic inflammation</td>
</tr>
<tr>
<td></td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>Allergic reactions</td>
</tr>
<tr>
<td></td>
<td>Parasitic infections</td>
</tr>
<tr>
<td></td>
<td>Tumours e.g. Hodgkin's disease</td>
</tr>
</tbody>
</table>

Tumour Types
There are many tumour types, Carcinomas, Sarcomas, Lymphoma, Melanoma etc. The tables below detail the classic histological appearance for Carcinomas.

<table>
<thead>
<tr>
<th>Carcinomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell type</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>Squamous cell carcinomas</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Adenocarcinomas</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

HistoChemical Stains
Fontana: +ve for melanin
Congo Red: +ve for Amyloid (Apple green birefringence)
Prussian Blue: +ve for iron (haemochromatosis)

ImmunoHisto Stains
CD45: +ve for lymphoid cells
Cytokeratin: Epithelial marker
Cardiac Pathology

Atherosclerosis
Chronic inflammation in intima of large arteries characterized by intimal thickening and lipid accumulation.

Steps of atherogenesis:
1. Endothelial injury
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 results in more macrophages and T cells entering the plaque
7. Vascular smooth muscle cells form the fibrous cap

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 à 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

Myocardial Infarction

Pathogenesis: a dynamic interaction between coronary atherosclerosis, plaque rupture, superimposed platelet activation, thrombosis and vasospasm à occlusive intracoronary thrombus overlying a 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
  o Contractile dysfunction due to loss of muscle à cardiogenic shock
  o Congestive cardiac failure – due to ventricular dysfunction (and arrhythmias)
  o LV infarct – papillary muscle dysfunction/necrosis/rupture à mitral regurgitation
  o Cardiac rupture of; ventricular wall (àhaemopericardium), septum (left to right shunt, VSD), papillary muscle (MR)
  o Ventricular aneurysm – usually develops >4 weeks post-MI (causes persistent ST elevation)
● Arrhythmias**
  o VF – usually occurs in the first 24hrs, common cause of sudden death
  o 90% of patients develop an arrhythmia following MI
● Pericardial
  o Early/peri-infarct associated pericarditis (dusky haemorrhagic tissue)
  o Pericardial effusion (+/- tamponade)
  o Dressler’s syndrome – chest pain, fevers and effusion weeks-months after MI
Fibrinous Pericarditis – occurs if infarct extends to epicardium

- **Mural thrombus** à 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 wks - granulation tissue, new blood vessels, myofibroblasts, collagen synthesis
- Weeks-months - strengthening, decellularising scar tissue.

### Heart Failure

**Common causes of Heart Failure:**

- Ischaemic heart disease
- Valve disease
- Myocarditis
- Hypertension
- Dilated cardiomyopathy
- Arrhythmias

**Complications:**

- Sudden Death
- Systemic emboli
- Arrhythmias
- Deep vein thrombosis and pulmonary embolism

**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. Eventually leading to decreased peripheral blood pressure and flow.

**RV failure:** Often 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.

**Investigations:** BNP, CXR, ECG, Echo
# Cardiomyopathy

<table>
<thead>
<tr>
<th>Pattern of cardiomyopathy</th>
<th>Mechanisms of heart failure</th>
<th>Causes</th>
<th>Indirect myocardial dysfunction (not cardiomyopathy-induced)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilated</td>
<td>Systolic dysfunction</td>
<td>Idiopathic, alcohol, peripartum, genetic, sarcoidosis, haemochromatosis, myocarditis.</td>
<td>IHD, valvular heart disease, hypertension, congenital HD.</td>
</tr>
<tr>
<td>Hypertrophic</td>
<td>Diastolic dysfunction</td>
<td>Genetic, storage diseases</td>
<td>Hypertension, AS</td>
</tr>
<tr>
<td>Restrictive</td>
<td>Diastolic dysfunction</td>
<td>Sarcoidosis, amyloidosis, radiation-induced fibrosis,</td>
<td>Pericardial constriction</td>
</tr>
</tbody>
</table>

## 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 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 DCM 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:
  - **Carditis**
  - **Arthritis**
  - **Sydenham’s chorea**
  - **Erythema marginatum**
  - **Subcutaneous 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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathology</th>
<th>Characteristics of Vegetations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rheumatic heart disease</strong></td>
<td>Antigenic mimicry – cross reaction of anti-streptococcal antibodies with heart tissue.</td>
<td>Small, warty vegetations found along the lines of closure of valve leaflet - 'verrucae'.</td>
</tr>
<tr>
<td><strong>Infective endocarditis</strong></td>
<td>Colonisation or invasion of heart valves or mural endocardium by microbe.</td>
<td>Large, irregular masses on valve cusps, extending into the chordae.</td>
</tr>
<tr>
<td><strong>Non-bacterial thrombotic endocarditis (marantic)</strong></td>
<td>DIC / Hypercoagulable states</td>
<td>Small, bland vegetations attached to lines of closure. Formed of thrombi.</td>
</tr>
<tr>
<td><strong>Libman-Sacks endocarditis</strong></td>
<td>Pathogenesis unknown. Associated with SLE and anti-phospholipid syndrome.</td>
<td>Small (up to 2mm), warty vegetations that are sterile and platelet-rich.</td>
</tr>
</tbody>
</table>

### Infective Endocarditis – colonization of endocardium

**Bacteraemia secondary to:**
- Poor dental hygiene
- IVDU
- Soft tissue infection
- Dental treatments
- Cannulae/lines
- Cardiac surgery/pacemakers

<table>
<thead>
<tr>
<th>Acute</th>
<th>Subacute</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Causative organisms</strong></td>
<td><strong>Staph. aureus, Strep. pyogenes</strong></td>
</tr>
<tr>
<td><strong>Virulence</strong></td>
<td>High</td>
</tr>
<tr>
<td><strong>Vegetation morphology</strong></td>
<td>Larger and more localised</td>
</tr>
<tr>
<td><strong>Spread</strong></td>
<td>Aorta</td>
</tr>
</tbody>
</table>

<sup>*</sup>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

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.
# Valve disease

<table>
<thead>
<tr>
<th>Pathophysiology</th>
<th>Aortic Stenosis</th>
<th>Aortic Regurgitation</th>
<th>Mitral Stenosis</th>
<th>Mitral Regurgitation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Narrowed aortic valve</strong></td>
<td><strong>Incompetent aortic valve blood flows back into LV after systole</strong></td>
<td><strong>Narrowed mitral valve high velocity, high pressure flow. Back pressure in left atrium dilatation</strong></td>
<td><strong>Incompetent mitral valve blood flows back into left atrium during systole</strong></td>
<td></td>
</tr>
<tr>
<td><strong>High velocity, high pressure flow.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Causes | Calcification (old age), congenital bicuspid valve | Infective endocarditis, dissecting aortic aneurysm, LV dilation, connective tissue disease e.g. Marfans, Ank Spond | 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

cliniacally 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

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Chronic bronchitis</th>
<th>Bronchiectasis</th>
<th>Asthma</th>
<th>Emphysema</th>
<th>Small airway disease / Bronchiolitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Site</strong></td>
<td>Bronchus</td>
<td>Bronchus</td>
<td>Bronchus</td>
<td>Acinus</td>
<td>Bronchiole</td>
</tr>
<tr>
<td><strong>Pathology</strong></td>
<td>Dilatation of the airways and excess mucus production</td>
<td>Airway dilatation and scarring</td>
<td>SM cell hyperplasia, excess mucus, inflammation</td>
<td>Airspace enlargement, wall destruction</td>
<td>Inflammator y scarring / obliteration</td>
</tr>
<tr>
<td><strong>Aetiology</strong></td>
<td>Tobacco smoke, air pollution</td>
<td>See below</td>
<td>Immunologic: allergens, drugs cold air, exercise</td>
<td>Tobacco smoke, α1-AT deficiency</td>
<td>Tobacco smoke, air pollutants</td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
<td>Cough &amp; sputum on most days for 3 months over 2 years</td>
<td>Cough, purulent sputum, fever</td>
<td>Episodic cough, wheezing, dyspnoea</td>
<td>Dyspnoea, cough</td>
<td>Dyspnoea, cough</td>
</tr>
<tr>
<td><strong>Histological features</strong></td>
<td>Dilatation of the airways, goblet cell hyperplasia and hypertrophy of mucous glands</td>
<td>Permanent dilatation of the bronchi</td>
<td>Whorls of shed epithelium (Curschmann spirals), eosinophils, Charcot-Leyden crystals</td>
<td>Loss of the alveolar parenchyma distal to the terminal bronchiole</td>
<td></td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td>Recurrent infections, chronic hypoxia, Pulm HTN</td>
<td>Recurrent infections, haemoptysis, pulm HTN, amyloidosis</td>
<td>Chronic asthma, Death</td>
<td>Pneumothorax, Resp failure, Pulm HTN</td>
<td></td>
</tr>
</tbody>
</table>

### Causes of Bronchiectasis:
- **Inflammatory**
  - Post-infectious (especially children)
  - Abnormal host defense 1° (hypogammaglobulinaemia) and 2° (chemotherapy, NG)
  - Obstruction (extrinsic/intrinsic/middle lobe syn.)
  - Post-inflammatory (aspiration)
Interstitial Lung Disease

Group of >200 diseases characterized by inflammation and fibrosis of the pulmonary connective tissue, particularly the most peripheral and delicate interstitium of the alveolar wall.

Account for 15% of respiratory practice

Show features of RESTRICTIVE lung disease on spirometry:
- Decreased CO diffusion capacity
- Decreased lung volume
- Decreased compliance

Usually present with:
- SOB
- End-inspiratory crackles
- Cyanosis, pulmonary HTN and cor pulmonale

Difficult to differentiate initial cause in end-stage as all have honey-comb lung

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 à cyanosis and pulmonary HTN +/- cor pulmonale, and clubbing.
- **Rx**: steroids, cyclophosphamide, azathioprine, but little impact on survival

**Pneumoconiosis**

Typically an occupational lung disease; a non-neoplastic lung reaction to inhalation of mineral dusts or inorganic particles. The majority of pneumoconioses affect the **upper lobe**. e.g. coal worker’s pneumoconiosis, silicosis, asbestosis.

NB: asbestosis can cause benign pleural lesions (plaques, fibrosis) but can also cause malignant lesions (adenocarcinoma, mesothelioma). Asbestosis 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.

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 rectiwigula), **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
- **Lobar pneumonia** – Fibrinosuppurative consolidation. Stages: 1. Consolidation; 2. Red Hepatisation (neutrophilia); 3. Grey Hepatisation (Fibrosis); 4. Resolution
- **Atypical** – interstitial pneumonia. No intra-alveolar inflammation.
Tumours of the Lung

Squamous cell carcinoma (30-50%)
- Risk factors: M>F, closely correlated 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.
- 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.
- 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, cerebellar degeneration.
- Highly malignant, metastasize early, usually by diagnosis commonly to bone, adrenal, liver and brain. It has a poor prognosis due to rapid metastases despite being very 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.

Paraneoplastic syndromes:
ADH → SIADH
ACTH → Cushing’s syndrome
PTH/ PTHrP → primary hyperparathyroidism, hypercalcaemia and bone pain
Calcitonin → hypercalcaemia
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:
- 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 DVTs. Risk factors include female, immobility, cardiac disease, cancer, primary and secondary hypercoagulable states (Virchow's triad = blood stasis + damage to endothelium + 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 associated with left heart disease (systolic/diastolic dysfunction, valve disease)
- Class 3:
  - Pulmonary hypertension due to lung disease
- Class 4:
  - Chronic Thromboembolic Pulmonary Hypertension
- 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


Diffuse alveolar damage: ARDS in adults (e.g. infection, aspiration, trauma etc); HMD (hyaline membrane disease) in neonates (e.g. insufficient surfactant production in prems). Rapid onset respiratory failure. Histo: lung expanded, firm, plum-coloured, airless.
### GI Disease

#### Oesophagus

Squamous epithelium (proximal 2/3) and columnar epithelium (distal 1/3), joined by the squamo-columnar junction/ Z-line

<table>
<thead>
<tr>
<th>Disease</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| **Reflux oesophagitis = GORD** | Commonest cause of oesophagitis  
**Complications:** ulceration, haemorrhage à haematemesis/melaena, Barrett’s oesophagus, stricture, perforation  
Los Angeles Classification  
**Tx:** lifestyle changes (stop smoking, weight loss), PPI/H2 receptor antagonists |
| **Barrett’s oesophagus** | Intestinal metaplasia of squamous mucosa à columnar epithelium (have goblet cells) following chronic GORD à upwards migration of the SCJ  
Seen in 10% of those with symptomatic GORD  
Can lead to adenocarcinoma: metaplasia à dysplasia à Ca |
| **Oesophageal Adenocarcinoma** | Associated with Barrett’s oesophagus so usually seen in distal 1/3  
Other risk factors incl: smoking, obesity, prior radiation therapy  
Most common in Caucasians, M>>F |
| **Squamous cell oesophageal carcinoma** | Associated with ETOH and smoking  
Other risk factors incl: achalasia of cardia, Plummer-Vinson syndrome, nutritional deficiencies, nitrosamines, HPV (in high prevalence areas)  
6x more common in Afro-Carribians, 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) à palliative care |
| **Varices** | Engorged dilated veins, usually due to portal HTN (back pressure)  
Pt vomits units of blood  
Emergency endoscopy à sclerotherapy/banding |

### Stomach

Lined by gastric mucosa, columnar epithelium (mucin secreting) and glands.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| **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, Al e.g. pernicious anaemia, ETOH, smoking  
**Special types** – Chemical (foveolar hyperplasia, chronic inflammation), |

---
Infection (CMV, HSV, strongyloides), Inflammatory Bowel Disease
Complications: Chronic gastritis may lead to gastric ulcer formation
It may also however result in intestinal metaplasia → dysplasia → cancer

| **Gastric ulcer** | Breach through muscularis mucosa into submucosa. 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 lymphoma** | Caused by *H. pylori* – chronic antigen stimulation
Rx: remove cause (*H. pylori* using triple therapy – PPI, Clarithromycin + Amox or Metro |

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### Duodenum

<table>
<thead>
<tr>
<th><strong>Disease</strong></th>
<th><strong>Characteristics</strong></th>
</tr>
</thead>
</table>
| **Duodenal ulcer** | 4 times more common than GU
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)

### 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
  - Associated with Down’s syndrome (2%)
  - Genetics – RET proto-oncogene Cr10+
  - Biopsy – hypertrophied nerve fibres, no ganglia
  - Treatment – resection of affected (constricted) segment

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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.) à 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, obstruction
- Commonly in ‘Watershed areas’ eg: splenic flexure (SMA transition to IMA), rectosigmoid (IMA transition to internal iliac).
<table>
<thead>
<tr>
<th>Disease</th>
<th>Crohn’s Disease</th>
<th>Ulcerative Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiology</strong></td>
<td>− Western populations</td>
<td>− Slightly more common than Crohn’s</td>
</tr>
<tr>
<td></td>
<td>− Peak onset 20’s, F&gt;M</td>
<td>− White &gt; non-whites</td>
</tr>
<tr>
<td></td>
<td>− White 2-5x &gt; non-white</td>
<td>− Peak age is 20-25 yrs</td>
</tr>
<tr>
<td></td>
<td>− Smoking worsens symptoms</td>
<td></td>
</tr>
<tr>
<td><strong>Aetiology</strong></td>
<td>Unknown. MZ twin concordance 50%</td>
<td>Unknown MZ twin concordance 15%</td>
</tr>
<tr>
<td></td>
<td>“hygiene hypothesis” – less food contamination à less enteric infection à inadequate development of processes that regulate mucosal immune response à exaggerated immune response to pathogens that would cause self-limiting disease</td>
<td></td>
</tr>
<tr>
<td><strong>Pathophysiology</strong></td>
<td>− Affects whole GI tract (mouth to anus), most common in terminal ileum and caecum.</td>
<td>− Extends proximally from rectum</td>
</tr>
<tr>
<td></td>
<td>− Patchy distribution à ‘skip lesions’. Areas of healthy mucosa lie above diseased mucosa -&gt; ‘cobblestone appearance’</td>
<td>− Continuous involvement of mucosa</td>
</tr>
<tr>
<td></td>
<td>− First lesion = ‘aphthous ulcer’. These are deep ‘rosethorn ulcers.’ Can join together to form serpentine ulcers.</td>
<td>− Small bowel not affected unless v. severe pancolitis causes ‘backwash ileitis’</td>
</tr>
<tr>
<td></td>
<td>− Non-caseating granulomas seen</td>
<td>− Extensive superficial broad ulcers</td>
</tr>
<tr>
<td></td>
<td>− Transmural inflammation</td>
<td>− Inflammation superficial, confined to mucosa</td>
</tr>
<tr>
<td></td>
<td>− Fistula/fissure formation common</td>
<td>− No granulomas/ fissures/ fistulae / strictures.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>− Islands of regenerating mucosa bulge into lumen à pseudopolyps (can fuse to form mucosal bridges)</td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
<td>Usually presents with intermittent diarrhoea, pain and fever</td>
<td>Associated more with bloody diarrhoea, mucus. Crampy abdo pain relieved by defecation</td>
</tr>
</tbody>
</table>
Infection
See microbiology section and page 380 OHCM 7th ed.

**C. difficile**
- Abx (eg: Cipro, Ceph’s) kill off commensals allowing *C. diff* to flourish. Its exotoxins cause pseudomembranous colitis.
- Ix: stool culture
- Rx: Metronidazole (covers anerobic) or Vancomycin (effective but 2nd line)

**Other 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
Often asymptomatic, sometimes PR bleed
Complications: Diverticulitis: fever and peritonism; gross perforation, fistula, obstruction (due to fibrosis)

Inflammatory Bowel Disease
See tables above under “Inflammatory diseases”.

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

<table>
<thead>
<tr>
<th>Carcinoid syndrome</th>
<th>Carcinoid crisis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchoconstriction</td>
<td>Life threatening vasodilatation, Hypotension, Tachycardia, Bronchoconstriction, Hyperglycaemia</td>
</tr>
<tr>
<td>Flushing</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td></td>
</tr>
</tbody>
</table>

**Investigation:** 24hr urine 5-HIAA (main metabolite of serotonin)
**Treatment:** Octreotide (somatostatin analogue)

Tumours of the Colon and Rectum

<table>
<thead>
<tr>
<th>Neoplastic polyps</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adenomas</strong></td>
<td></td>
</tr>
<tr>
<td>- Benign dysplastic lesions that are the precursor lesion to most adenocarcinomas (although most remain benign)</td>
<td></td>
</tr>
<tr>
<td>- Found in 50% &gt;50yrs in Western world</td>
<td></td>
</tr>
<tr>
<td>- Mostly asymptomatic so need regular surveillance if over 3.4cm 45% malignant change .</td>
<td></td>
</tr>
<tr>
<td>- Classified based on architecture as tubular, tubulovillous or villous.</td>
<td></td>
</tr>
<tr>
<td>- Villous adenoma (rare) à hypoproteinaemic hypokalaemia because they leak large amounts of protein and K.</td>
<td></td>
</tr>
<tr>
<td>- Large size is most important risk factor for malignancy, in addition to degree of dysplasia and increased villous component.</td>
<td></td>
</tr>
<tr>
<td>- Adenoma à carcinoma progression ‘classical chromosomal instability sequence’</td>
<td></td>
</tr>
<tr>
<td>o Normal colon à at risk mucosa after “first hit” mutation in 1st copy of APC gene (those with FAP born with this mutation)</td>
<td></td>
</tr>
<tr>
<td>o At risk às adenoma after “second hit” mutation to remaining APC gene</td>
<td></td>
</tr>
<tr>
<td>o Progression to carcinoma follows activation of KRAS, LOF mutations of p53</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-neoplastic polyps</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hamartomatous polyp</strong></td>
<td>Found sporadically in some genetic/acquired syndromes</td>
</tr>
<tr>
<td>Juvenile polyps are focal malformations of mucosa and lamina propria, vast majority in those &lt;5yrs old, mostly in rectum à bleeding. Usually solitary, but up to 100 found in juvenile polyposis (AD) that may require colectomy to stop haemorrhage.</td>
<td></td>
</tr>
</tbody>
</table>
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 à regular surveillance of GI tract, pelvis and gonads.

<table>
<thead>
<tr>
<th>Hyperplastic polyp</th>
<th>Seen at 50-60yrs, thought to be caused by shedding of epithelium à cell buildup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory</td>
<td>Pseudo-polyps eg: IBD</td>
</tr>
</tbody>
</table>

### Colorectal cancer

| **Epidemiology** | 2\textsuperscript{nd} 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 |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aetiology</strong></td>
<td>Diet (↓fibre, ↑fat), Lack of exercise, Obesity, Familial syndromes, chronic IBD, NSAIDS protective (COX2 over-expressed in 90%)</td>
</tr>
</tbody>
</table>
| **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 |
| **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) à Abdomino-perineal resection  
>1-2cm above anal sphincter à Anterior resection  
Sigmoid cancer à Sigmoid colectomy  
Descending colon and distal transverse à left hemicolecction.  
Caecum, ascending colon and proximal transverse à right hemicolecction.  
Transverse colon à extended right hemicolecction.  
Radiotherapy: post-op to decrease local recurrence  
Chemotherapy in palliation: 5-FU (fluouracil) |
<table>
<thead>
<tr>
<th>Familial syndromes</th>
<th>Familial adenomatous polyposis (FAP)</th>
<th>Hereditary non-polyposis colorectal cancer/Lynch syndrome (HNPCC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>− 70% AD mutation in APC gene (C5q1), 30% AR mutation in DNA mismatch repair genes</td>
<td>− 70% AD mutation in APC gene (C5q1), 30% AR mutation in DNA mismatch repair genes</td>
<td>− AD mutations in DNA mismatch repair genes</td>
</tr>
<tr>
<td>− Present 10-15yrs - &gt;100 adenomatous polyps required for diagnosis, usually 100-1000s seen. ALL will à adenocarcinoma if left untreated by 30yrs therefore most have prophylactic colectomy.</td>
<td>− Present 10-15yrs - &gt;100 adenomatous polyps required for diagnosis, usually 100-1000s seen. ALL will à adenocarcinoma if left untreated by 30yrs therefore most have prophylactic colectomy.</td>
<td>− Carcinomas usually in right colon, few polyps but fast progression to malignancy therefore present usually &lt;50yrs</td>
</tr>
<tr>
<td>− Increased risk of neoplasia elsewhere, eg: ampulla of Vater and stomach</td>
<td>− Increased risk of neoplasia elsewhere, eg: ampulla of Vater and stomach</td>
<td>− Associated with endometrial, ovarian, small bowel, transitional cell and stomach carcinoma.</td>
</tr>
<tr>
<td>− At birth, hypertrophy of retinal pigment epithelium</td>
<td>− At birth, hypertrophy of retinal pigment epithelium</td>
<td>− At birth, hypertrophy of retinal pigment epithelium</td>
</tr>
<tr>
<td>Gardners – like FAP with extra intestinal features eg: osteoma’s, dental caries</td>
<td>Gardners – like FAP with extra intestinal features eg: osteoma’s, dental caries</td>
<td></td>
</tr>
</tbody>
</table>
**Pancreatic Disease**

**Role of the pancreas:** produces 2L a day of enzymic HCO$_3^-$ rich fluid, stimulated by secretin and CCK.

**Secretin:** produced by s-cells of the duodenum, controls gastric acid secretion and buffering with HCO$_3^-$

**CCK:** responsible for stimulating digestion of fat and protein. Made by I-cells in the duodenum. Causes release of digestive enzymes.

---

**Exocrine vs. Endocrine**

<table>
<thead>
<tr>
<th></th>
<th>Exocrine</th>
<th>Endocrine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Function</strong></td>
<td>Digestive – proteases, lipases and amylase</td>
<td>Endocrine</td>
</tr>
<tr>
<td><strong>Secretions</strong></td>
<td>Secretes products into ducts e.g. digestive enzymes</td>
<td>Secretes products into bloodstream e.g. hormones</td>
</tr>
</tbody>
</table>
| **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 H$_2$O into pancreatic system  
PP: pancreatic polypeptide, self regulates secretion activities |

---

**Metabolic syndrome**

- 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

- **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**

<table>
<thead>
<tr>
<th>Macrovascular:</th>
<th>Microvascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac – MI</td>
<td>Ocular – diabetic retinopathy</td>
</tr>
<tr>
<td>Renal – Glomerulonephritis, pyelonephritis</td>
<td>PVS – claudication, change in colour/temp, poor healing ulcer</td>
</tr>
<tr>
<td>Cerebral – CVA</td>
<td></td>
</tr>
</tbody>
</table>
Acute Pancreatitis

Scored using GLASCOW Scale ≥3 à ITU referral

‘I GET SMASHED’: Idiopathic, Gallstones, Ethanol, Trauma, Steroids, Mumps, Autoimmune, Scorpion venom, Hyperlipidaemia, ERCP, Drugs e.g. thiazides

- **Presentation**: severe epigastric (or central) pain radiating to back, relieved by sitting forward, vomiting prominent
  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.**
- **Histology** – Coagulative necrosis

Chronic Pancreatitis

- **Causes**: Alcoholism, Cystic Fibrosis, hereditary, pancreatic duct obstruction e.g. stones/tumour, autoimmune (IgG4 sclerosing)
- **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, 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 polyarthritis 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%

Pancreatic carcinoma

<table>
<thead>
<tr>
<th>Ductal adenocarcinoma of the pancreas</th>
</tr>
</thead>
</table>
| **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, ↑Ca²⁺  
CT/MRI/ERCP |
<table>
<thead>
<tr>
<th>CA19.9 &gt;70IU/mL</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chemotherapy is palliative (5-FU)</td>
</tr>
<tr>
<td></td>
<td>Surgery (15% of cases): Whipple’s procedure – surgical resection</td>
</tr>
<tr>
<td></td>
<td>Prognosis v poor: 5yr survival rate &lt;5%</td>
</tr>
</tbody>
</table>

### 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
  - 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

**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 phaeo), Pituitary adenoma.
- **MEN 2A-** Parathyroid, Thyroid, Phaeo
- **MEN 2B-** Medullary Thyroid, Phaeo, 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

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
- 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

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

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 (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

Histopathology:
1. Portal Inflammation
2. Interface hepatitis (PEICEMEAL 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)

**Cirrhosis**

**Diffuse** abnormality of liver architecture that interferes with blood flow and liver function.

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** results in anastomoses.

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

<table>
<thead>
<tr>
<th></th>
<th>Score of 1</th>
<th>Score of 2</th>
<th>Score of 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>&gt;35</td>
<td>28-35</td>
<td>&lt;28</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>&lt;34</td>
<td>34-50</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Clotting Prothrombin time</td>
<td>&lt;4</td>
<td>4-6</td>
<td>&gt;6</td>
</tr>
</tbody>
</table>
(Distention) Ascites

<table>
<thead>
<tr>
<th>Encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
</tr>
</tbody>
</table>

- 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

<table>
<thead>
<tr>
<th>Liver Disease</th>
<th>Macroscopic Characteristics</th>
<th>Microscopic Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic Steatosis (Fatty Liver)</td>
<td>Large, pale, yellow and greasy liver</td>
<td>Accumulation of fat droplets in hepatocytes (=steatosis) Chronic exposure à fibrosis (late stage)</td>
</tr>
<tr>
<td>Alcoholic hepatitis</td>
<td>Large, fibrotic liver</td>
<td>Hepatocyte ballooning and necrosis due to accumulation of fat, water and proteins</td>
</tr>
<tr>
<td>Alcoholic Cirrhosis</td>
<td>Yellow-tan, fatty, enlarged. Transforms into shrunken, non-fatty, brown organ.</td>
<td>Mallory Denk Bodies Fibrosis See acutely after night of heavy drinking. Ranges from asymptomatic to fulminant liver failure. Each episode has 10-20% mortality.</td>
</tr>
</tbody>
</table>

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 Cirrhosis (PBC)**
- Autoimmune inflammatory destruction of medium sized **intrahepatic bile ducts** à cholestasis à SLOW development of cirrhosis over many years
- **F > M 10:1**
- 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 à remission in 25%

(B) **Primary Sclerosing Cholangitis (PSC)**
- Inflammation and obliterative fibrosis of **extrahepatic and intrahepatic** bile ducts à 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

<table>
<thead>
<tr>
<th>Benign</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatic adenoma</strong></td>
<td>• Associated with OCP</td>
</tr>
<tr>
<td></td>
<td>• Present with abdo pain/ intraperitoneal bleeding</td>
</tr>
<tr>
<td></td>
<td>• Resection if symptomatic, &gt;5cm or if no shrinkage when stopping OCP</td>
</tr>
<tr>
<td><strong>Haemangioma</strong></td>
<td>• Most common benign lesion</td>
</tr>
<tr>
<td></td>
<td>• No rx</td>
</tr>
<tr>
<td><strong>Malignant</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Hepatocellular Carcinoma</strong></td>
<td>• <strong>Causes</strong>: Hepatitis B + C, alcoholic cirrhosis,</td>
</tr>
<tr>
<td></td>
<td>haemochromatosis, NAFLD, Aflatoxin, androgenic steroids.</td>
</tr>
<tr>
<td>---------------------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Ix:</strong> alpha-fetoprotein, USS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>● Adenocarcinomas arising from bile ducts</td>
</tr>
<tr>
<td></td>
<td>● 10% of liver tumours</td>
</tr>
<tr>
<td></td>
<td>● Can be intra or extrahepatic</td>
</tr>
<tr>
<td></td>
<td>● Poor prognosis</td>
</tr>
<tr>
<td><strong>Causes:</strong></td>
<td>primary sclerosing cholangitis, parasitic liver disease</td>
</tr>
<tr>
<td></td>
<td>chronic liver disease</td>
</tr>
<tr>
<td></td>
<td>congenital liver abnormalities, Lynch syndrome type II</td>
</tr>
<tr>
<td><strong>Haemangiosarcoma</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Hepatoblastoma</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Secondary Tumours</strong></td>
<td>● MOST COMMON malignant liver lesion.</td>
</tr>
<tr>
<td></td>
<td>● Usually from GI tract, breast or bronchus.</td>
</tr>
<tr>
<td></td>
<td>● Usually multiple</td>
</tr>
</tbody>
</table>
### Genetic Causes of Cirrhosis

<table>
<thead>
<tr>
<th></th>
<th>Haemochromatosis</th>
<th>Wilson's Disease</th>
<th>Alpha 1 Antitrypsin Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence</strong></td>
<td>Homozygotes 1 in 400 Heterozygotes 1 in 10 (carriers) (Caucasians)</td>
<td>1 in 30,0000 (v. rare)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>40-50yrs</td>
<td>11-14yrs</td>
<td></td>
</tr>
<tr>
<td><strong>Pathophysiology</strong></td>
<td>Autosomal recessive</td>
<td>Autosomal recessive</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td></td>
<td>Mutated HFE gene at 6p21.3 à ↑Fe gut absorption which deposits in liver, heart, pancreas, adrenals, pituitary, joints, skin à fibrosis</td>
<td>Mutated gene ATP7B (Chr 13): Encodes copper transporting ATPase expressed on canalicular membrane therefore à ↓biliary Cu excretion and deposition in liver, CNS, iris.</td>
<td>A1AT accumulates in hepatocytes à intracytoplasmic inclusions à hepatitis Lack of A1AT in lungs à emphysema</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>Fe deposits in liver – stains with Prussian blue stain</td>
<td>Cu stains with Rhodanine stain</td>
<td>Intracytoplasmic inclusions of A1AT which stain with Periodic acid Schiff</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mallory bodies and fibrosis on microscopy</td>
<td></td>
</tr>
<tr>
<td><strong>Signs/symptoms</strong></td>
<td>• Skin bronzing (melanin deposition) • Diabetes • Hepatomegaly with micronodular cirrhosis • Cardiomyopathy • Hypogonadism • Pseudogout</td>
<td>• 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</td>
<td>Kids: neonatal jaundice Adults: emphysema and chronic liver disease</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>• ↑ Fe, ↑ Ferritin • Transferrin saturation &gt; 45% • ↓ TIBC</td>
<td>• ↓ serum caeruloplasmin • ↓ serum copper • ↑ urinary copper</td>
<td>↓A1AT Absent α-globulin band on electrophoresis</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Venesection Desferrioxamine 30% with cirrhosis → HCC</td>
<td>Lifelong penicillamine. Good prognosis with early treatment but any neuro damage is permanent and may require liver transplant</td>
<td></td>
</tr>
</tbody>
</table>
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 alkalinise 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.
- Grading: Gleason system, based on degree of differentiation and glandular patterns.
- Diagnosis: History, examination, PSA (over 4ng/ml is indicative)

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 à 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

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<thead>
<tr>
<th>% of Testicular Tumours</th>
<th>GERM CELL</th>
<th>NON GERM CELL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>95%</td>
<td>5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seminoma, spermatocytic seminoma, embryonal carcinoma, yolk sac tumour, choriocarcinoma, teratoma</td>
</tr>
<tr>
<td>Leydig cell tumour (derived from stroma), Sertoli cell tumour (derived from sex cord)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Predisposing Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptorchidism, testicular dysgenesis, genetic factors e.g. Kleinfelters, testicular feminisation</td>
</tr>
</tbody>
</table>

**Benign Renal Tumours**

<table>
<thead>
<tr>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal <strong>epithelial</strong> tumour with a papillary architecture &lt; 5mm</td>
</tr>
<tr>
<td>Bland epithelial cells growing in a papillary or tubopapillary pattern</td>
</tr>
<tr>
<td>Well circumscribed cortical nodules</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncocytic renal <strong>epithelial</strong> neoplasm</td>
</tr>
<tr>
<td><strong>Macroscopic</strong> – mahogany brown</td>
</tr>
<tr>
<td><strong>Microscopic</strong> – sheets of cells, pink cytoplasm, form a nest of cells</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesenchymal tumour composed of fat, bloods vessels and muscle</td>
</tr>
<tr>
<td>Fat spaces, thick bloods vessels and spindle cell components</td>
</tr>
</tbody>
</table>

**Malignant Renal Tumours**

<table>
<thead>
<tr>
<th>Renal cell carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common – <strong>epithelial tumour</strong> RFS – smoking, HTN, obesity, long-term dialysis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Childhood renal neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd most common childhood malignancy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Epithelial neoplasm arising from the urothelial tract (anywhere from renal pelvis, ureter, bladder, urethra)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most commonly in the bladder</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Renal cell carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common – <strong>epithelial tumour</strong> RFS – smoking, HTN, obesity, long-term dialysis</td>
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</tr>
</thead>
<tbody>
<tr>
<td>Most commonly in the bladder</td>
</tr>
</tbody>
</table>
• Clear Cell (70%)
  Macroscopic – golden yellow with haemorrhagic areas
  Microscopic – nests of epithelium with clear cytoplasm

• Papillary (15%)
  Macroscopic – friable brown tumour
  Microscopic – papillary/tubopapillary growth pattern >5mm

• Chromophobe (5%)
  Macroscopic – 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 – papillary fronds lined by urothelium
  Can either be low grade or high grade

• Invasive 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
  Adenocarcinaoma: 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 – breakdown of selectivity of glomerular filtration barrier.
   - Nephritic syndrome

2. **Tubules & interstitium**
   - Acute tubular necrosis
   - Tubulointerstitial nephritis:
     - Acute pyelonephritis
     - Chronic pyelonephritis & reflux nephropathy
     - Interstitial nephritis

3. **Blood vessels**
   - Thrombotic microangiopathies (haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura)

---

**Nephrotic Syndrome**

Syndrome characterised by:

- Proteinuria (>3g/24h) + hypoalbuminaemia + oedema (+ hyperlipidaemia)

Key words in EMQs:

- “Swelling” (characteristically facial in kids and peripheral in adults)
- “Frothy” urine

**PRIMARY causes of Nephrotic Syndrome**

<table>
<thead>
<tr>
<th></th>
<th>Minimal change disease</th>
<th>Membranous glomerular disease</th>
<th>Focal Segmental Glomerulosclerosis (FSGS)</th>
</tr>
</thead>
</table>
| **Epidemiology**        | Most common in children (75% cases) with second peak in elderly | Common in adults (~30%) | Common in adults (~30%)
<p>|                        |                        |                              | Most common in Afro-Caribbean people |
| <strong>Light microscopy</strong>    | No changes             | Diffuse glomerular basement membrane thickening | Focal and segmental glomerular consolidation and scarring, Hyalinosis |
| <strong>Electron Microscopy</strong> | Loss of podocyte foot processes | Loss of podocyte foot processes, Subepithelial deposits = ‘spikey’ | Loss of podocyte foot processes |
| <strong>Immunofluorescence</strong>  | No immune deposits     | Ig and complement in granular deposits along entire GBM | Ig and complement in scarred areas |
| <strong>Response to steroids</strong>| 90% respond           | Poor                        | 50% respond                         |
| <strong>Prognosis</strong>           | &lt; 5% ESRF             | 40% ESRF after 2-20 yrs     | 50% ESRF in 10 yrs                  |
| <strong>Miscellaneous</strong>       |                        | Can be 1° or 2° to SLE, infection, drugs and malignancy | 1° but can be 2° to obesity and HIV nephropathy |</p>
<table>
<thead>
<tr>
<th></th>
<th>Diabetes</th>
<th>Amyloidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histology</strong></td>
<td>Diffuse glomerular basement membrane thickening Mesangial matrix nodules – aka Kimmelstiel Wilson nodules</td>
<td><strong>Apple green birefringence</strong> with Congo red stain</td>
</tr>
<tr>
<td><strong>Hints in question</strong></td>
<td>Asian</td>
<td>May have chronic inflammation - rheumatoid arthritis, chronic infections (TB) – causes AA protein deposition. May have immunoglobulin light chains deposition – most common from multiple myeloma – AL protein deposition. Clinical clues of amyloidosis - Macroglossia, heart failure, hepatomegaly.</td>
</tr>
</tbody>
</table>

**SECONDARY causes of Nephrotic Syndrome**

**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)
- **Oliguria**
- **Hypertension**

**Causes of Nephritic Syndrome**

1. **ACUTE POSTINFECTIOUS (POST STREPTOCOCCAL) GN**
   - Occurs 1-3 wks after *streptococcal throat infection* or *impetigo* (usually 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**

2. **IgA NEPHROPATHY (BERGER DISEASE)**
   - Commonest GN worldwide
   -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 progress to ESRF
• Biopsy:
  o FM: granular deposition of IgA and complement in mesangium

3. RAPIDLY PROGRESSIVE (CRESCENTIC) GN
• Most aggressive GN – can cause ESRF within weeks.
• Presents as a nephritic syndrome, but oliguria and renal failure are more pronounced
• Classification based on immunological findings:
  o Type 1: Anti-GBM antibody
  o Type 2: Immune complex
  o Type 3: Pauci-immune / ANCA-associated
• Regardless of cause, all are characterised by presence of crescents in glomeruli

<table>
<thead>
<tr>
<th>TYPE 1</th>
<th>TYPE 2</th>
<th>TYPE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenesis</td>
<td>Immune complex mediated</td>
<td>Pauci-immune i.e. lack of anti-GBM or immune complex</td>
</tr>
<tr>
<td>Anti-GBM antibody against COL4-A3 (collagen type IV)</td>
<td>SLE, IgA nephropathy, post infectious GN</td>
<td>c-ANCA: Wegener’s granulomatosis</td>
</tr>
<tr>
<td>Causes</td>
<td>SLE, IgA nephropathy, post infectious GN</td>
<td>p-ANCA: microscopic polyangiitis</td>
</tr>
<tr>
<td>Goodpastures syndrome. HLA-DRB1 association</td>
<td>SLE, IgA nephropathy, post infectious GN</td>
<td>c-ANCA: Wegener’s granulomatosis</td>
</tr>
<tr>
<td>Linear deposition of IgG in GBM</td>
<td>Granular (lumpy bumpy) IgG immune complex deposition on GBM/mesangium</td>
<td>Lack of/scanty significant immune complex deposition</td>
</tr>
<tr>
<td>Lungs – pulmonary haemorrhage</td>
<td>Often limited (except in SLE)</td>
<td>Vasculitis – particularly presenting as skin rashes or pulmonary haemorrhage</td>
</tr>
<tr>
<td>Lungs – pulmonary haemorrhage</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 asymptomatic haematuria
• 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
Asymptomatic Haematuria
If this appears in an EMQ – 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, 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

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

Haemolytic Uraemic Syndrome (HUS) and Thrombotic Thrombocytopenic Purpura (TTP) are characterised by:

- Thrombosis (generally renal in HUS and widespread in TTP)
- Triad of:
  1. Microangiopathic haemolytic anaemia (MAHA)
  2. Thrombocytopenia
  3. Sometimes renal failure (generally in HUS)

**Pathophysiology:** widespread fibrin deposition in vessels associated with ADAMTS3 (platelet surface protein) → formation of platelet-fibrin thrombi which damage passing platelets and RBCs → platelet and RBC destruction (i.e. thrombocytopenia and MAHA)

<table>
<thead>
<tr>
<th></th>
<th>HUS</th>
<th>TTP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiology</strong></td>
<td>Usually affects children</td>
<td>Usually affects adults</td>
</tr>
<tr>
<td><strong>Pathophysiology</strong></td>
<td>Usually associated with diarrhoea caused by <em>E. coli</em> O157:H7 with outbreaks caused by children visiting petting zoos. Can be 'non-diarrhoea associated' due to abnormal proteins in complement pathway/endothelium – can be familial</td>
<td>Thrombi occur throughout circulation, esp. in CNS</td>
</tr>
<tr>
<td><strong>Thrombi confined to kidneys</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Signs/symptoms (both)</strong></td>
<td>↓plt → bleeding (petechiae, haematemesis, melena). MAHA → pallor and jaundice</td>
<td>Usually no renal failure. <strong>Neuro symptoms</strong> (headache, altered consciousness, seizures, coma)</td>
</tr>
<tr>
<td><strong>Diagnosis (both)</strong></td>
<td>Usually involves <strong>renal failure</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓Hb ↓plt</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Signs of haemolysis: ↑bilirubin, ↑reticulocytes, ↑LDH</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fragmented RBCs on blood smear</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Coomb's test negative (as not AIHA)</td>
<td></td>
</tr>
</tbody>
</table>
Acute Renal Failure

A rapid loss of renal function manifesting as increased serum creatinine and urea. Complications include metabolic acidosis, hyperkalaemia, fluid overload, HTN, ↓Ca²⁺ and uraemia.

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.

RENFAL
- Acute Tubular Necrosis (ATN): commonest renal cause of ARF.
- Acute glomerulonephritis.
- Thrombotic microangiopathy.

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 (19.5%)
- Glomerulonephritis (15.3%)
- Hypertension & Vascular disease (15%)
- Reflux nephropathy (chronic pyelonephritis) (9.5%)
- Polycystic kidney disease (9.4%)

Classified into 5 stages by GFR:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal renal function (often proteinuria)</td>
<td>&gt;90</td>
</tr>
<tr>
<td>2</td>
<td>Mildly impaired</td>
<td>60-89</td>
</tr>
<tr>
<td>3</td>
<td>Moderately impaired</td>
<td>30-59</td>
</tr>
<tr>
<td>4</td>
<td>Severely impaired</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>Renal failure (generally requires replacement therapy)</td>
<td>&lt;15 (or if being treated with renal replacement therapy)</td>
</tr>
</tbody>
</table>

Adult Polycystic Kidney Disease (APCKD)

- **Autosomal dominant inheritance.** 85% due to mutations in PKD1 on chromosome 16 (encoding polycystin-1), remainder in PKD2 on chromosome 4 (encoding polycystin-2)
- Accounts for 10% of cases of CKD
- **Pathologic features:** large multicystic kidneys with destroyed renal parenchyma, liver cysts (in PKD1) and berry aneurysms.
- **Clinical features:** haematuria, flank pain, UTI. Clinical features are often due to cyst complications such cyst rupture, cyst infection and cyst haemorrhage.
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.

Categorization:
- **Class I** – minimal mesangial lupus nephritis – immune complexes but no structural alteration
- **Class II** – mesangial proliferative lupus nephritis – immune complexes and mild/mod increase in mesangial matrix and cellularity
- **Class III** – focal lupus nephritis – active swelling and proliferation in less than half the glomeruli
- **Class IV** – Diffuse lupus nephritis – involvement of more than half the glomeruli
- **Class V** – membranous lupus nephritis - subepithelial immune complex deposition
- **Class VI** – advanced sclerosing – complete sclerosis of >90% of the glomeruli.

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

Pelvic Inflammatory Disease (PID / Salpingitis)
Infection ascending from vagina and cervix up to uterus and tubes, leading to inflammation (endometritis, salpingitis) and the formation of adhesions.

*Chlamydia trachomatis* and *Neisseria gonorrhoea* are most common organisms in UK. TB and schistosomiasis are common causes in some parts of the world.

**Clinically:** lower abdo pain, dyspareunia, vaginal bleeding/discharge, fever, adnexal tenderness, and cervical excitation

**Complications:**
- Fitz Hugh Curtis syndrome – RUQ from peri-hepatitis + violin string peri-hepatic adhesions
- Infertility
- ↑Risk of ectopic pregnancy
- Intestinal obstruction → bacteraemia
- Tubo-ovarian abscess
- Chronic pelvic pain
- Peritonitis
- Plical fusion

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: regurgitant/implantation from retrograde menstrual flow of endometrial cells; metaplastic transformation of coelomic epithelial cells; vascular or lymphatic dissemination of endometrial cells

Ectopic tissue is functional, undergoing cyclical bleeding → pain, scarring and infertility

**Clinically:**
- 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 uterus which is retroverted in advanced disease

**Macroscopically:**
- red-blue to brown nodules - “powder burns”
- “chocolate cysts” in ovaries (endometriomas)

**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. 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:

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
10% of women with postmenopausal bleeding will have malignancy.
Staged with FIGO system

Subdivided into:
- ENDOMETRIOID – 80% (i.e. look similar to normal endometrial glands)
  - 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
  - Mainly adenocarcinomas (85%), but may show squamous differentiation
- NON-ENDOMETRIOID – 20%
  - These include papillary, serous and clear cell. More aggressive.
  - Pathophysiology: unrelated to estrogen excess; usually in elderly women with endometrial atrophy

Vulval Intraepithelial Neoplasia (VIN) and Vulval Carcinoma

Normal vulval histology: squamous epithelium

VIN (similar to CIN)
- Dysplasia of epithelium; associated with HPV-16
- Graded as VIN I, II and III
- Progression to invasive disease is lower than for CIN (~ 5%)
- Usual type (warty, basaloid, mixed):
  - women aged 35-55yrs
  - associated with warty/basaloid SCC
- Differentiated type:
  - older women
  - associated with keratinizing SCC
  - higher risk of malignant transformation than usual type

Vulval Carcinoma
Mainly squamous cell carcinoma; can arise from VIN (pre-malignant stage) or from other skin abnormalities (Paget’s of the vulva - adenocarcinoma in situ)

Ovarian Carcinoma
- Leading cause of death from gynaecological malignancy in the UK

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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:

<table>
<thead>
<tr>
<th>Subtypes</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous cystadenoma</td>
<td>Most common type Mimics tubal epithelium i.e. columnar epithelium Psammoma bodies common most common malignancy affects women aged 30-40yrs</td>
</tr>
<tr>
<td>Mucinous cystadenoma</td>
<td>Mucin secreting cells, similar to those of endocervical mucosa. OR intestinal type – metastatic from appendix in some cases → pseudomyxoma peritonei No psammoma bodies most common oestrogen-secreting tumour affects younger women</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>Mimics endometrium – i.e. form tubular glands endometriosis is risk factor Abundant clear cytoplasm – intracellular glycogen Hobnail appearance malignant with poor prognosis</td>
</tr>
<tr>
<td>Clear cell</td>
<td></td>
</tr>
<tr>
<td>Dysgerminoma</td>
<td>Female counterpart of testicular seminoma rare, but the most common ovarian malignancy in young women sensitive to radiotherapy 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</td>
</tr>
<tr>
<td>Teratoma</td>
<td></td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>Secrete hCG malignant</td>
</tr>
</tbody>
</table>
Sex cord/stroma (10%)

- From sex cord or stroma of gonad
- Can differentiate toward female (granulosa and theca cells) or male (Sertoli and Leydig cells) structures

<table>
<thead>
<tr>
<th>Sex cord/stroma (10%)</th>
<th>From sex cord or stroma of gonad</th>
<th>No hormone production 50% associated with Meig’s syndrome (ascites + pleural effusion)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Can differentiate toward female (granulosa and theca cells) or male (Sertoli and Leydig cells) structures</td>
<td>Fibroma (from cells of ovarian stroma)</td>
</tr>
<tr>
<td></td>
<td>Granulosa-Theca cell tumour</td>
<td>Produce E2 Look for oestrogenic effects – irregular menstrual cycles, breast enlargement, endometrial/breast cancer</td>
</tr>
<tr>
<td></td>
<td>Sertoli-Leydig cell tumour</td>
<td>Secrete androgens Look for defeminisation (breast atrophy) and virilisation (hirsutism, deepened voice, enlarged clitoris)</td>
</tr>
</tbody>
</table>

FIGO staging
- Stage I: limited to ovaries (75-90%)
- Stage II: limited to pelvis (45-60%)
- Stage III: limited to abdomen (including regional LN metastases) (30-40%)
- Stage IV: distance metastases outside abdominal cavity (<20%)

Cervical Intraepithelial Neoplasia (CIN) and Cervical Glandular Intraepithelial Neoplasia (CGIN)

Normal cervical histology:
Outer cervix 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

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 lower 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

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
- RFs: Early exposure to HPV (early first sexual experience, multiple partners, non-barrier contraceptive), COCP and high parity, smoking (dose-response effect), immunosuppression
- Usually arises from CIN
- Most commonly squamous cell carcinoma (70-80%), but ~20% are adenocarcinomas, adenosquamous carcinomas and others.
- Invasion through the basement membrane marks the change from CIN to carcinoma
- Clinically: post-coital bleeding, intermenstrual bleeding, postmenopausal bleeding, discharge, pain. Staged using FIGO system
  - Stage 0: CIN
  - Stage I: limited to cervix (80-95%)
  - Stage II: extended beyond uterus but not to pelvic side wall or lower 1/3 vagina (75%)
  - Stage III: extension to pelvic side wall and/or lower 1/3 vagina (50%)
  - Stage IV: extension beyond true pelvis or involvement of bladder/bowel mucosa (20-30%)
Breast Pathology

Majority of the lesions are benign and common presenting symptoms include pain (mastalgia/ mastodynia), palpable masses and/or nipple discharge.

Investigations of breast disease:

1. Clinical Examination
2. Imaging – sonography/mammography
3. Pathology –
   - **Cytopathology** – cells spread across a slide and stained. Coded from C1 (inadequate sample), C2 (benign), C3 (atypia), C4 (suspicious of malignancy) to C5 (malignant)
   - **Histopathology** – intact tissues removed showing architectural and cellular detail. Normal breast histology is a ductal-lobular system lined by inner glandular epithelium

Inflammatory Conditions

**Acute Mastitis**
- Painful, red breast and fever
- **Lactational** secondary to *staphylococcal infection (often polymicrobial)* via cracks in nipple.
- **FNA cytology** shows an abundance of neutrophils
- Tx: continued expression of milk + antibiotics +/- surgical drainage
- Non-lactational – **keratinising squamous metaplasia** block lactiferous ducts leading to peri-ductal infalmation and rupture.
- Tx: antibiotics + treatment of duct ectasia

**Mammary Duct Ectasia**
- Occurs mainly in multiparous, 40-60yr old women. Smoking = biggest risk factor
- Inflammation and dilatation of large breast ducts
- Poorly defined palpable periareolar mass with **thick, white nipple secretions**.
- Dilatation in one or more of the larger lactiferous ducts, which fill with a stagnant brown or green secretion. This may discharge. These fluids then set up an irritant reaction in surrounding tissue leading to periductal mastitis or even abscess and fistula formation.
- In some cases, a chronic indurated mass forms beneath the areola, which mimics a carcinoma. Fibrosis eventually develops, which may cause slit-like nipple retraction.
- Mimics mammographic appearance of cancer
- **Cytology** – proteinaceous material and macrophages

**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 spaces, histiocytes and giant cells
Benign neoplastic conditions

Fibroadenoma (‘breast mouse’)
- Most common benign tumour, from stroma, often multiple and bilateral
- Occurring at any age within the reproductive period, usually at 20-30yrs
- Epithelium responsive to hormones therefore increase in size during pregnancy and calcify after menopause.
- Spherical, freely mobile, variable size and rubbery.
- Overgrowth of collagenous mesenchyme. “Shelling out” is curative
- FNA cytology – branching sheets of epithelium, bare bipolar nuclei and stroma
- Histology – multinodular mass of expanded intralobular stroma

Duct papilloma
- Benign papillary tumour arising within the duct system of the breast.
  - Small terminal ductules - peripheral papillomas)
  - Larger lactiferous ducts - central papillomas
- Causes bloody discharge.
- Not seen on mammogram.
- Cytology of nipple discharge – branching papillary groups of epithelium
- Histology – papillary mass within a dilated duct lined by epithelium

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

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

Proliferative conditions

A diverse group of intraductal epithelial proliferations, associated with varying risks of developing invasive breast carcinoma.

1. Usual epithelial hyperplasia
- Not considered a precursor lesion although slightly increased risk of carcinoma
- Growth of glandular tissue and epithelial cells forming fronds

2. Flat epithelial atypia
- 4x risk of developing carcinoma
- Multiple layers of epithelial cells and lumens are 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:
  o Gender
  o 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%.
  o 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
  o Advancing age
  o Family history
  o Race (Caucasian>Afro-Caribbean>Asian>Hispanic)
  o Obesity, tobacco, alcohol, radiation exposure
• Presentation: hard fixed lump, Paget’s disease (eczema of the nipple first then areola – normal eczema never affects the nipple), peau d’orange, nipple retraction.
• Screening: 47 to 73yr old women invited every 3 years for mammography (looks for abnormal areas of calcification or a mass within the breast)

Carcinoma in situ (30%)

• Neoplastic epithelial proliferation limited to ducts/lobules by basement membrane
  o 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.
  o 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.
  o Invasive ductal = carcinoma that cannot be subclassified into another group. Most common. Big, pleiomorphic cells – invasive cells move intro stroma
  o Invasive lobular = cells aligned in single file chains/strands.
  o Tubular carcinomas = well-formed tubules with low grade nuclei. Rarely palpable as <1cm.
  o Mucinous carcinoma cells produce abundant quantities of extracellular mucin which dissects into surrounding stroma.

Triple Assessment: examination, radiological examination (mammography/USS/MRI), FNA & cytology
Neoplastic lesions undergo core needle biopsy to confirm histological subtype and grading. Assessment of nuclear pleomorphism, tubule formation and mitotic activity. Each gets a score /3, total score /9.

- 3-5/9 = grade 1/well differentiated
- 6-7/9 = grade 2/moderately differentiated
- 8-9/9 = grade 3/poorly differentiated.

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. HER2 positive associated with bad prognosis.

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

**Male Breast Cancer**

Differences between male and female breast cancer:

- Lesions are easier to find in males due to the smaller breast size; however, lack of awareness may postpone seeking medical attention.
- The presence of gynecomastia may mask the condition.
- The diagnosis is made later in males
- Lesions are less contained in males as they do not have to travel far to infiltrate skin, nipple, or muscle tissue.
- Almost half of male breast cancer patients are stage III or IV.

In familial cases, male BRCA2 carriers are at higher risk, rather than BRCA1 carriers.
Cerebral Pathology

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.

<table>
<thead>
<tr>
<th></th>
<th>Stroke</th>
<th>TIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td>100 000 new strokes/yr in UK</td>
<td>0.4/1000 a year</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15% of 1st strokes preceded by TIA</td>
</tr>
<tr>
<td>Aetiology / Risk factors</td>
<td>Same as atheroma: Smoking, DM, HTN, FH, past TIAs, OCP, PVD, ↑ETOH, Hyperviscosity e.g. Sickle cell anaemia, polycythaeamia vera</td>
<td></td>
</tr>
<tr>
<td>Symptoms / Signs</td>
<td>Sudden onset FAST, numbness, loss of vision, dysphagia (depends on territory)</td>
<td>Symptoms last &lt;24hrs, Amaurosis fugax, Carotid bruit</td>
</tr>
<tr>
<td>Vascular territories commonly affected</td>
<td>Anterior vs. Posterior territory Commonest = MCA</td>
<td>Any – characteristically embolic atherogenic debris from the carotid artery travels to the ophthalmic branch of internal carotid</td>
</tr>
<tr>
<td>Investigation</td>
<td>CT/MRI (infarct vs. haemorrhage) Ix for vascular risk: BP, FBC, ESR, U&amp;E, glu, lipids, CXR, ECG, carotid doppler</td>
<td>Carotid US Ix for vascular risk: BP, FBC, ESR, U&amp;E, glu, lipids, CXR, ECG, carotid doppler</td>
</tr>
<tr>
<td>Management</td>
<td>Aspirin +/- dipyridamole Thrombolytics (if &lt;3h from event) +/- carotid endarterectomy Long term: treat HTN, ↓lipids, anticoag</td>
<td>Aspirin + dipyridamole +/- carotid endarterectomy Long term: treat HTN, ↓lipids, anticoag</td>
</tr>
</tbody>
</table>

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. **Basilar artery**
   1. Proximal (usually thrombosis): impaired EOM, vertical nystagmus, reactive miosis, hemi- or quadriplegia, dysarthria, locked-in syndrome, coma
   2. Distal (usually embolic, i.e. top of the basilar syndrome): somnolence, memory and behavior abnormalities, oculomotor deficit

5. **PICA (lateral medullary or Wallenberg syndrome):** ipsilateral ataxia, ipsilateral Horner’s, ipsilateral facial sensory loss, contralateral limb impairment of pain and temperature sensation, nystagmus, vertigo, nausea/vomiting, dysphagia, dysarthria, hiccups

6. **Medial medullary infarct** (anterior spinal artery, which can be associated with anterior cord infarct): contralateral hemiparesis (facial sparing), contralateral impaired proprioception and vibration sensation, ipsilateral tongue weakness

7. **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 PKD, Ehler’s Danlos and Pts with Aortic Coarctation. Also associated with vascular abnormalities incl AV malformations, capillary telangiectasias, venous and cavernous angiomas, Ehlers Danlos.

**Traumatic**

**Extradural haemorrhage:** Skull fracture, ruptured middle meningeal artery → rapid arterial bleed, lucid interval then LoC,

**Subdural haemorrhage:** Prev history of minor trauma → damaged bridging veins with slow venous bleed, often elderly/alcoholic, associated with brain atrophy, fluctuating consciousness

**Traumatic parenchymal injury**

- Concussion: **Transient LoC and paralysis, recovery in hours or days**
- Diffuse axonal injury: Vegetative state, post traumatic dementia
- Contusions: When brain contacts skull +/- fracture.
- Coup= where impact occurs, contracoup= opposite to region of impact
- Traumatic intracerebral haemorrhage

**Increased ICP:** Caused by oedema, space occupying lesion (e.g. tumour, abscess) or both → brain herniation.

Six types: Uncal, Central (transstentorial), Cingulate (subfalcine), Transcalvarial, Upward, Tonsillar.

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Cerebral infection

Meningitis

8. Bacterial
   - **Neonatal to 3 months**: Group B streptococcus (GBS) early (90% day 1–5) or late (10% 6 days–3 months), E. coli, Listeria monocytogenes.
   - **1 month to 6 years**: Neisseria meningitidis (meningococcus), Streptococcus pneumoniae, Haemophilus influenzae type B (Hib).
   - **>6 years**: N. meningitidis (14–25 years), Strep. pneumoniae, mumps (pre-MMR).
   - **Mycobacterium tuberculosis**: Can cause TB meningitis at all ages. Most common in children 6 months–6 years.
   - **Older adults**: Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae type b (Hib), group B Streptococcus, Listeria monocytogenes

9. Viral
   1. Enteroviruses (80%), cytomegalovirus (CMV), arbovirus. Herpes simplex virus (HSV) is more likely to cause encephalitis
   2. Herpes simplex most common in adults. All others most common in children and infants.

10. Associations
   - **Impaired immunity**: Young age, HIV, defects of complement system leading to meningococcal susceptibility (see chapter on primary immune deficiency), asplenia secondary to sickle cell disease (Strep. pneumoniae and Hib susceptibility).
   - **Environmental factors**: Crowding, poverty and close contact with affected individuals (transmission by respiratory secretions).

<table>
<thead>
<tr>
<th>CSF</th>
<th>Pyogenic</th>
<th>TB</th>
<th>Viral (aseptic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Often turbid</td>
<td>Often fibrin web</td>
<td>Usually clear</td>
</tr>
<tr>
<td>Predominant cell</td>
<td>Polymorphs e.g. neutrophils</td>
<td>Mononuclear - lymphocytes</td>
<td>Mononuclear – lymphocytes</td>
</tr>
<tr>
<td>Cell count/mm³</td>
<td>90-1000+</td>
<td>10-1000</td>
<td>50-1000</td>
</tr>
<tr>
<td>Glucose (40-90 mg/dl)</td>
<td>↓(&lt;40)</td>
<td>↓(&lt;40)</td>
<td>Normal (&gt;40)</td>
</tr>
<tr>
<td>Protein (15-45 g/L)</td>
<td>↑ (often &gt;250)</td>
<td>↑ (50-500)</td>
<td>←/↑ (&lt;100)</td>
</tr>
<tr>
<td>Bacteria</td>
<td>In smear and culture</td>
<td>Often none in smear</td>
<td>None seen or cultured</td>
</tr>
</tbody>
</table>

Viral Encephalitis

- May be localised e.g. temporal or frontal lobes or general
- May involve the meninges → meningoencephalitis
- Viruses: Enteroviruses, HSV1, HSV2, VZV, arboviruses, adenoviruses, HIV, mumps (rare now due to immunisation), rubella and rabies.
- Post-measles: Subacute sclerosing panencephalitis (SSPE).
- Symptoms: Drowsiness, seizures, behavioural changes, headache, fever
Brain tumours

Secondary tumours are metastatic lesions (commonest form of adult brain tumours): Most common primaries are: lung, breast, malignant melanoma
Well demarcated, solitary or multiple with surrounding oedema.

Primary tumours originate in the brain, spinal cord or meninges, rarely metastasise outside CNS, commonest group= astrocytomas (range from pilocytic astrocytoma to glioblastoma multiforme)

Buzzwords –
- NF2 (neurofibromatosis type II) – meningioma
- Ventricular tumour, hydrocephalus – Ependymoma
- Indolent, childhood – pilocytic astrocytoma
- Soft, gelatinous, calcified – oligodendroma

Classification of nervous system tumours (* = most common)

- Neuroepithelial
  - Astrocytic tumours: astrocytoma*, glioblastoma
  - Oligodendroglial tumours: oligodendroglioma
  - Oligoastrocytic tumours: oligoastrocytoma
  - Neuronal and mixed neuronal-glial tumours: ganglion cell tumours, cerebral neurocytomas/Neuroblastoma
  - Embryonal tumours: medulloblastoma, primitive neuroectodermal tumours (PNET)
  - Other: pineal, ependymal, and choroid plexus tumours
- Meningeal: meningiomas*, mesenchymal, hemangioblastomas
- Cranial and paraspinal nerves: schwannoma, neurofibroma
- Lymphomas and hematopoietic: primary CNS lymphoma, plasmacytoma
- Germ cell: germinomas, teratomas, choriocarcinomas
- Sellar region: craniopharyngiomas, spindle cell oncocytoma, pituitary adenomas*
- Cysts: epidermoid/dermoid cysts, colloid cysts
- Local extension: chordomas, glomus jugulare tumours
- Metastatic tumours*: lung (small cell),* breast*

Familial syndromes associated with CNS tumours
- Von Hippel-Lindau: hemangioblastoma of cerebellum, brainstem and spinal cord, retina; renal cysts, pheochromocytomas
• Tuberous sclerosis: giant cell astrocytoma; cortical tuber; suprapendymal nodules and calcifications on CT
• Neurofibromatosis type 1: optic glioma, neurofibroma astrocytoma,
• Neurofibromatosis type 2: vestibular schwannoma, menigioma, ependymoma, astrocytoma
• Li-Fraumeni: astrocytoma, PNET; many other tumours too (sarcomas, breast cancer, leukemia)
• Turcot syndrome: glioblastoma multiforme, medulloblastoma, pineoblastoma
• 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. The outcome is dementia.

**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.

<table>
<thead>
<tr>
<th>Diseases causing dementia</th>
<th>Pathological protein (misfolded)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s disease</td>
<td>Tau, beta-amyloid</td>
</tr>
<tr>
<td>Dementia with Lewy bodies</td>
<td>Alpha-synuclein, ubiquitin</td>
</tr>
<tr>
<td>Corticobasal degeneration</td>
<td>Tau</td>
</tr>
<tr>
<td>Frontotemporal dementia linked to Chr 17</td>
<td>Tau</td>
</tr>
<tr>
<td>Pick’s disease</td>
<td>Tau</td>
</tr>
</tbody>
</table>

**Alzheimer’s disease**

Commonest cause of dementia, usually begins >50yrs, generalised atrophy of the brain, widened sulci, narrowed gyri and enlarged ventricles (most marked in temporal and frontal lobes with loss of cholinergic neurons). Clinical diagnosis although PET and MRI may help. Senile plaques of beta-amyloid protein and neurofibrillary tangles of tau protein. Rx is symptomatic: anti-cholinesterases, nAChR agonists, glutamate antagonists.

**Dementia with Lewy bodies**

Psychological disturbances occur early. Day-to-day fluctuations in cognitive performance, visual hallucinations, spontaneous motor signs of Parkinsonism, recurrent falls and syncope, pathologically indistinguishable from PD
Idiopathic Parkinson’s Disease

↓ stimulation of the motor cortex by the basal ganglia (caused by death of dopaminergic neurons in substantia nigra)

‘TRAP’ Tremor, Rigidity, Akinesia, Postural instability, some develop psychiatric features later in disease e.g. Parkinsons Disease Dementia, hallucinations, anxiety

Lewy bodies present in affected neurons (alpha synuclein protein is main component; mutations reported in familial PD)

Parkinson Plus syndromes

11. **Lewy Body dementia** – fluctuating cognition, visual hallucinations and early dementia
12. **Progressive supranuclear palsy**: tauopathy with limited vertical gaze (downgaze more specific), early falls, axial rigidity and akinesia, dysarthria, and dysphagia
13. **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
14. **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)
15. **Vascular parkinsonism**: multi-infarct presentation with gait instability and lower body parkinsonism; less likely associated with tremor

Multiple Sclerosis

Autoimmune demyelinating disease (remember myelin: produced by oligodendrocytes, wraps round axons, important for axon conduction).

20-40 yrs, usually presents with focal sx: optic neuritis, poor coordination.

Classifications:
- Primary progressive (10% - get continually worse),
- Relapsing remitting (better between episodes but progresses over years)

Pathology: MS plaques showing sharp margins of myelin loss

**EMQ giveaway markers**: Myelin Basic Protein and Proteo-lipid protein
# Metabolic Bone Disease

<table>
<thead>
<tr>
<th>Metabolic Bone Disease</th>
<th>Osteoporosis</th>
<th>Osteomalacia / rickets</th>
<th>Hyperparathyroidism (primary)</th>
<th>Paget’s Disease</th>
<th>Renal Osteodystrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aetiology</strong></td>
<td>Age related (post-menopause in females) or secondary to systemic disease/drugs</td>
<td>↓dietary Vit D, ↓sunlight, malabsorption of Vit D (GI causes), and genetic causes</td>
<td>Excess PTH production → ↑Ca reabsorption and ↑PO4 excretion</td>
<td>A disorder of bone turnover</td>
<td>All skeletal changes assoc w CKD: Osteitis fibrosa cystica (2° PTH), Osteomalacia, Osteosclerosis, Adynamic bone disease, Osteoporosis</td>
</tr>
<tr>
<td><strong>Disease features</strong></td>
<td>↓bone mass DEXA scan: T score &gt; 2.5 SD below normal (1-2.5 = osteopaenia)</td>
<td>↓bone mineralization</td>
<td>Bone changes of osteitis fibrosa cystica</td>
<td>Both lytic and sclerotic lesions</td>
<td>Depends on the form of bone disease</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Low impact fractures (#) (hip - NOF, vertebrae; wrists - Colles’) Pain (back)</td>
<td>Adults: Bone pain/tenderness, proximal muscle weakness Children: Bone pain, bowing tibia, rachitic rosyary, frontal bossing, pigeon chest, delayed walking</td>
<td>Hypercalcaemia: ‘Moans, stones, bones, groans’ Depression/confusion, renal stones, bone pain and #, constipation, pancreatitis, Polyuria, polydipsia</td>
<td>Bone pain Microfractures Nerve compression Skull changes ↑ head size Deafness High output cardiac failure</td>
<td>Depends on the form of bone disease</td>
</tr>
<tr>
<td><strong>Risk Factors</strong></td>
<td>+ Age, female, smoking, poor diet, low BMI ... Poor diet, malabsorption, CLD, CKD, lack of sunlight</td>
<td>Secondary hyperPTH → CRF, ↓vit D, malabsorption</td>
<td>&gt;50 years old M=F Caucasian</td>
<td>Mixed lytic and sclerotic SKULL Osteoporosis circumscripta Cotton wool VERTEBRAE: Picture frame Ivory vertebra PELVIS: Sclerosis and lucency</td>
<td>Depends on the form of bone disease</td>
</tr>
<tr>
<td><strong>X ray</strong></td>
<td>Usually none</td>
<td>Looser’s zones (pseudo fractures) Splaying of metaphysis</td>
<td>Brown’s tumours Salt and pepper skull Subperiosteal bone resorption in phalanges</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>Loss of cancellous bone</td>
<td>Excess of unmineralized bone (osteoid)</td>
<td>Osteitis fibrosa cystica (marrow fibrosis + cysts – aka Brown Tumour)</td>
<td>Huge osteoclasts w &gt; 100 nuclei Mosaic pattern of lamellar bone (like jigsaw puzzle)</td>
<td>Depends on the form of bone disease</td>
</tr>
<tr>
<td><strong>Bio Chemistry</strong></td>
<td>↔Ca; ↔PO4; ↔ALP</td>
<td>↔/↑Ca ↓PO4 ↑ALP</td>
<td>↑Ca; ↑↓PO4; ↑↑ALP ↑PTH (or inappropriately normal)</td>
<td>↔Ca; ↔PO4; ↑↑ALP</td>
<td>↓Ca; ↑PO4, 2° hyperPTH, metabolic acidosis</td>
</tr>
</tbody>
</table>
Non-Neoplastic Bone Disease

Gout vs. Pseudogout

<table>
<thead>
<tr>
<th></th>
<th>Gout</th>
<th>Pseudogout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td>Male, middle aged</td>
<td>&gt;50 yrs</td>
</tr>
<tr>
<td>Aetiology</td>
<td>↑dietary purine intake, ETOH, diuretics, inherited metabolic abnormalities</td>
<td>Idiopathic HyperPTH, DM, Hypothyroid, Wilsons</td>
</tr>
<tr>
<td>Joints affected</td>
<td>Great toe- MTP (podagra), lower extremities e.g. knee</td>
<td>Knee and shoulder</td>
</tr>
<tr>
<td>Clinical features</td>
<td>Hot, swollen, red, exquisitely painful joint. Tophus (s/c deposits of urate) is the pathognomonic lesion e.g. on pinna and hands.</td>
<td>Hot swollen joint w/ effusion</td>
</tr>
<tr>
<td>Crystal type</td>
<td>Urate crystals, needle shaped</td>
<td>Calcium pyrophosphate crystals, rhomboid shaped</td>
</tr>
<tr>
<td>Investigations</td>
<td>Negatively birefringent crystals</td>
<td>Positively birefringent</td>
</tr>
<tr>
<td>Management</td>
<td>Acute attack: colchicine. Long term: allopurinol. Conservative: ↓ETOH and purine intake e.g. sardines, liver</td>
<td>NSAIDs or intra-articular steroids</td>
</tr>
</tbody>
</table>

Trauma
- Fractures: e.g. Simple, compound, greenstick, comminuted, impacted
- 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)
- Adults – S. Aureus. Vertebrae, jaw (2º to dental abscess) and toes (2º to diabetic skin ulcer)
- Children – Haemophilus influenza, Group B strep. Long bones
- Presentation: pain, swelling and tenderness. General features of malaise, fever, chills, leukocytosis.
- X-ray changes ~10 days post onset. Lytic destruction of bone.
- Rare causes: TB (immunocompromised patients), syphilis (congenital or acquired)

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.
Characteristic deformities:
- Radial deviation of wrist and ulnar deviation of fingers.
- “swan neck” and “Boutonniere” deformity of fingers.
- “Z” shaped thumb
# Neoplastic Bone Disease

## Benign vs Malignant Bone Disease X Rays

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>No periosteal reaction</td>
<td>Acute periosteal reaction – Codman’s triangle, onion skin, sunburst</td>
</tr>
<tr>
<td>Thick endosteal reaction</td>
<td>Broad border between lesion and normal bone</td>
</tr>
<tr>
<td>Well developed bone formation</td>
<td>Varied bone formation</td>
</tr>
<tr>
<td>Inraosseous and even calcification</td>
<td>Extraosseous and irregular calcification</td>
</tr>
</tbody>
</table>

## Malignant Bone Tumours

<table>
<thead>
<tr>
<th>Name</th>
<th>Age</th>
<th>Bone</th>
<th>Histology</th>
<th>X-ray Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteosarcoma</td>
<td>Adolescence</td>
<td>Knee (60%)</td>
<td>Malignant mesenchymal cells ALP +ve</td>
<td>Elevated periosteum (Codman’s triangle) Sunburst appearance</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>&gt;40 yrs</td>
<td>Axial skeleton Femur/tibia/pelvis</td>
<td>Malignant chondrocytes</td>
<td>Lytic lesion with fluffy calcification, Axial skeleton</td>
</tr>
<tr>
<td>Ewing’s sarcoma</td>
<td>&lt;20 yrs</td>
<td>Long bones, pelvis</td>
<td>Sheets of small round cells CD99 +ve T 11:22 translocation</td>
<td>Onion skinning of periosteum</td>
</tr>
<tr>
<td>Giant cell (borderline malignancy)</td>
<td>20-40 yrs F&gt;M</td>
<td>Knee- epiphysis</td>
<td>Osteoclast-type multinucleate giant cells on background of spindle/ovoid cells</td>
<td>Lytic/lucent lesions right up to articular surface</td>
</tr>
</tbody>
</table>

## Benign Bone Tumours

<table>
<thead>
<tr>
<th>Name &amp; age affected</th>
<th>Bone</th>
<th>Special features</th>
<th>Histology</th>
<th>X-ray</th>
</tr>
</thead>
</table>
| **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 | Radiolucent nidus with sclerotic rim '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%  
**Ends so often in the hands** | Benign tumours of cartilage  
**Ollier’s syndrome** = multiple enchondromas  
**Maffuci’s syndrome** = multiple enchondromas + haemangiomas | Normal cartilage | Lytic lesion  
**Cotton wool calcification**  
Expansile, O ring sign |
| **Osteochondroma**  
(=exostosis)  
(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 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 | A bit of bone is replaced by fibrous tissue  
**Albright syndrome** = polyostotic dysplasia + café au lait spots + precocious puberty | 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

Key terms

- **Hyperkeratosis**: ↑ in S. corneum / ↑keratin
- **Parakeratosis**: nuclei in S. corneum
- **Acanthosis**: ↑ in s. spinosum
- **Acantholysis**: ↓ cohesions between keratinocytes
- **Spongiosis**: intercellular edema
- **Lentiginous**: linear pattern of melanocyte proliferation within epidermal basal cell layer (reactive or neoplastic)

Dermatitis / eczema

**Interchangeable terms** used to describe a group of disorders with the **same histology** and presenting with inflamed, dry **itchy** rashes.

<table>
<thead>
<tr>
<th>Dermatitis / eczema</th>
<th>Histology</th>
<th>Clinical features</th>
</tr>
</thead>
</table>
| **Atopic dermatitis** | **ACUTE:**  
- Spongiosis  
- Inflammatory infiltrate in dermis  
- Dilated dermal capillaries  
**CHRONIC:**  
- Acanthosis  
- Crusting, scaling | **Infants:** face, scalp  
**Older:** flexural areas  
If chronic - lichenification  
Persists into adulthood in those with FHx of atopy | 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) |
| **Contact dermatitis** | | Inflammatory reaction to a yeast - Malassezia  
**Infants:** cradle cap (large yellow scales on scalp)  
**Young adults:** mild erythema, fine scaling, mildly pruritic- affects face, eyebrow, eyelid, anterior chest, external ear |
Psoriasis

Common chronic inflammatory dermatosis with well-demarcated red scaly plaques. Commonest form is **chronic plaque psoriasis** with salmon pink plaques with silver scale affecting extensor aspects of knees, elbows and scalp. Rubbing them causing pin-point bleeding (**Auspitz’ sign**)

**Koebner phenomenon** – lesions form at sites of trauma.

Cells in psoriatic plaque have increased proliferation rate.

**Histo:** Parakeratosis, loss of granular layer, clubbing of rete ridges giving “test tubes in a rack” appearance; Munro’s microabscesses.

**Pathophysiology:** Type IV T-cell hypersensitivity reaction.

Other forms include:

- Flexural psoriasis – seen later in life, usually groin, natal cleft and sub-mammary areas.
- Guttate psoriasis – “rain-drop” plaque distribution, often in children, usually seen 2 weeks post-Strep throat.
- Erythrodermic/pustular psoriasis – severe widespread disease, often systemic symptoms, can be limited to hands and feet = palmo-plantar psoriasis.

Associated with:

- Nail changes:
  - Pitting
  - Onycholysis
  - Subungual Hyperkeratosis
- Arthritis (5-10%)

Lichen Planus

- Lesions are “**pruritic**, **purple**, **polygonal**, **papules** and **plaques**” 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.
- Aetiology unknown.
- **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:
  - Sulphonamides
  - NSAIDs
  - Allopurinol
  - Penicillin
  - Phenytin
## Bullous Disease

<table>
<thead>
<tr>
<th>Dermatitis herpetiformis</th>
<th>Pathophysiology</th>
<th>Clinical features</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Associated with coeliac IgA Abs bind to basement membrane → subepidermal bulla</td>
<td>Itchy vesicles on extensor surfaces of elbows, buttocks</td>
<td>Microabscesses which coalesce to form subepidermal bullae Neutrophil &amp; IgA deposits at tips of dermal papillae</td>
</tr>
</tbody>
</table>

| Pemphigoid | IgG Abs bind to hemidesmosomes of basement membrane → subepidermal bulla | Large tense bullae on erythematous base. Often on forearms, groin and axillae. ELDERLY. Bullae do not rupture as easily as pemphigus | Subepidermal bulla with eosinophils Linear deposition of IgG along basement membrane |

| Pemphigus | IgG Abs bind to desmosomal proteins → intraepidermal bulla | Bullae are easily ruptured. Found on skin AND mucosal membranes | Intraepidermal bulla Netlike pattern of intercellular IgG deposits Acantholysis |

## Cutaneous Neoplasms

<table>
<thead>
<tr>
<th>Epidermal (i.e. from keratinocytes)</th>
<th>Characteristics</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>Seborrhoeic Keratosis</td>
<td>Rough plaques, waxy, “stuck on” appear in middle age / the elderly</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Premalignant</th>
<th>Actinic (Solar/Senile) Keratosis</th>
<th>Rough, sandpaper like, scaly lesions on sun-exposed areas</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratoacanthoma</td>
<td>Rapidly growing dome shaped nodule which may develop a necrotic, crusted centre. Grows over 2-3 weeks and clears spontaneously</td>
<td>Similar histology to SCC – hard to differentiate</td>
<td></td>
</tr>
<tr>
<td>Bowen's Disease</td>
<td>Intra-epidermal squamous cell carcinoma in situ</td>
<td>Full thickness atypia/dysplasia</td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td>Squamous cell carcinoma</td>
<td>When Bowen's has spread to involve dermis</td>
<td>Acantholysis throughout epidermis,</td>
</tr>
</tbody>
</table>
Similar clinical features to Bowen’s but may ulcerate
nuclear crowding and spreading through basement membrane into dermis

<table>
<thead>
<tr>
<th>Basal cell carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aka “rodent” ulcer</td>
</tr>
<tr>
<td>Slow growing tumour; rarely metastatic but locally destructive</td>
</tr>
<tr>
<td>Pearly surface, often with telangiectasia</td>
</tr>
<tr>
<td>Mass of basal cells pushing down into dermis</td>
</tr>
<tr>
<td>Palisading (nuclei align in outermost layer)</td>
</tr>
</tbody>
</table>

**Melanocytic (i.e. from melanocytes)**

- **Benign** – melanocytic nevi (=moles). They can be junctional, compound or intradermal.
- **Malignant** – melanoma
  - **Histo:** 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
  - **Subtypes:**
    - Lentigo maligna melanoma - occurs on sun exposed areas of elderly caucasians, flat, slowly growing black lesion
    - Superficial spreading malignant melanoma – irregular borders with variation in colour
    - Nodular malignant melanoma – can occur on all sites, more common in the younger age group.
    - Acral Lentiginous melanoma - occurs on the palms, soles and subungual areas

**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)

**Pityriasis Rosea**

- **Salmon pink** rash appears first (=herald patch) followed by oval macules in Christmas tree distribution.
- Appears after viral illness.
- Remits spontaneously
## Connective Tissue Diseases

<table>
<thead>
<tr>
<th>Comment</th>
<th>SLE</th>
<th>Limited scleroderma (=CREST)</th>
<th>Diffuse scleroderma</th>
<th>Polymyositis &amp; Dermatomyositis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Autoimmune multi-system disorder</td>
<td>Autoimmune multi-system disorders</td>
<td>Scleroderma literally means “hard skin” - reflecting the main clinical feature of skin fibrosis</td>
<td>Autoimmune inflammatory disorder of muscle +/- skin</td>
</tr>
<tr>
<td></td>
<td>Type III hypersensitivity reaction</td>
<td>Scleroderma</td>
<td>Associated with underlying malignancy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ in classical complement deficiencies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Can be drug-induced</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>↑ in AfroC. F&gt;M</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA association</td>
<td>HLA DR3 (or 2)</td>
<td>HLA DR5 &amp; DRw8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoantibody</td>
<td>ANA (95%)</td>
<td>Anti-centromere</td>
<td>Anti Scl-70 Fibrillarin RNA pol I, II, III PM-Scl</td>
<td>Anti Jo-1 (=tRNA synthetase)</td>
</tr>
<tr>
<td></td>
<td>● Anti dsDNA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>● Anti-Sm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drug-induced Anti-histone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>LE bodies</td>
<td>↑collagen in skin and organs. Onion skin thickening of arterioles</td>
<td>Inflammation within or around muscle fibres</td>
<td>Endo-mysial inflam. infiltrate</td>
</tr>
<tr>
<td></td>
<td>Kidney – see Renal</td>
<td></td>
<td></td>
<td>‘drop out’ of capillaries and myofibre damage</td>
</tr>
<tr>
<td></td>
<td>CNS – small vessel angiopathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spleen – onion skin lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heart – Libman-Sack Endocarditis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Signs &amp; symptoms</td>
<td>4 of 11 ACR criteria (SOAP BRAIN MD)</td>
<td>Skin changes on face and distal to elbows and knees</td>
<td>Skin changes can occur anywhere</td>
<td>Proximal muscle weakness</td>
</tr>
<tr>
<td></td>
<td>Serositis</td>
<td></td>
<td></td>
<td>↑ CK &amp; abnormal EMG</td>
</tr>
<tr>
<td></td>
<td>Oral ulcers</td>
<td>Calcinosi</td>
<td>Widespread organ involvement</td>
<td>DM has cutaneous features:</td>
</tr>
<tr>
<td></td>
<td>Arthritis</td>
<td>Raynaud’s</td>
<td>Associated with pulmonary fibrosis</td>
<td>(1) Heliotrope rash</td>
</tr>
<tr>
<td></td>
<td>Photosensitivity</td>
<td>Esophageal dysmotility</td>
<td></td>
<td>(2) Gottron papules</td>
</tr>
<tr>
<td></td>
<td>Blood disorders (AIHA, ITP, leucopenia)</td>
<td>Sclerodactyly Telangiectasia</td>
<td>Associated with pulmonary fibrosis</td>
<td>Associated w. pulmonary fibrosis</td>
</tr>
<tr>
<td></td>
<td>Renal involvement ANA +ve Immune phenomena (dsDNA, anti-Sm, Antiphospholipid Ab)</td>
<td>Associated with pulmonary hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neuro symptoms Malar rash Discoid rash</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasculitides</td>
<td>Disease</td>
<td>Key words</td>
<td></td>
<td></td>
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<tr>
<td>---</td>
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<td>---</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large Vessel</td>
<td>Takayasu's arteritis</td>
<td>&quot;Pulseless&quot; disease&lt;br&gt;In Japanese women&lt;br&gt;Vascular symptoms: Absent pulse, bruises, claudication&lt;br&gt;Elderly; <em>scalp tenderness, temporal headache</em>, Jaw claudication, blurred vision&lt;br&gt;↑ESR&lt;br&gt;Overlap with polymyalgia rheumatica&lt;br&gt;Histo: Granulomatous transmural inflammation + giant cells + skip lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Temporal arteritis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium Vessel</td>
<td>Polyarteritis nodosa (PAN)</td>
<td>Renal involvement is main feature&lt;br&gt;Can involve other organs but spares lungs&lt;br&gt;30% have underlying Hep B&lt;br&gt;Microaneurysms on angiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kawasaki’s disease</td>
<td>Children &lt; 5yrs&lt;br&gt;<strong>Fever</strong> &gt; 5 days&lt;br&gt;<strong>Rash</strong> – red palms and soles with later desquamation&lt;br&gt;Conjunctivitis&lt;br&gt;Inflammation of lips, mouth or tongue (strawberry tongue)&lt;br&gt;Cervical LNs&lt;br&gt;Coronary arteries may be involved with aneurysm formation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Buerger’s disease (Thrombangitis obliterans)</td>
<td>Heavy smokers, usually men &lt; 35 years&lt;br&gt;Inflammation of arteries of extremities – usually tibial and radial&lt;br&gt;Pain; ulceration of toes, feet, fingers&lt;br&gt;Angiogram: <em>corkscrew appearance</em> from segmental occlusive lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small Vessel</td>
<td>Wegener’s granulomatosis</td>
<td>Triad of:&lt;br&gt;(1) Upper resp tract: sinusitis, epistaxis, <em>saddle nose</em>&lt;br&gt;(2) Lower resp tract: cavitation, <em>pulmonary haemorrhage</em>&lt;br&gt;(3) Kidneys: crescentic <em>glomerulonephritis</em>&lt;br&gt;cANCA (anti-PR3) +ve</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Churg Strauss</td>
<td>Asthma, allergic rhinitis&lt;br&gt;&lt;strong&gt;Eosinophilia&lt;/strong&gt;&lt;br&gt;Later systemic involvement&lt;br&gt;&lt;br&gt;pANCA (anti-MPO) +ve&lt;br&gt;&lt;strong&gt;Pulmonary renal** syndrome:&lt;br&gt;(a) Pulmonary haemorrhage&lt;br&gt;(b) Glomerulonephritis&lt;/br&gt;&lt;br&gt;pANCA (anti-MPO) +ve&lt;br&gt;IgA mediated vasculitis&lt;br&gt;In children &lt; 10 years&lt;br&gt;&lt;strong&gt;Preceding URTI&lt;br&gt;Palpable purpuric rash* (lower libs extensors + buttocks)&lt;br&gt;Colicky abdo pain&lt;br&gt;&lt;strong&gt;Glomerulonephritis&lt;br&gt;Arthritis&lt;br&gt;Orchitis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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.

PRIMARY (AL amyloidosis)
- Most common
- Deposition of amyloid L protein
- Most associated with plasma cell dyscrasias and with paraproteins, e.g. 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 secondary to chronic infections / inflammation
  - E.g. autoimmune diseases: 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

FAMILIAL AMYLOIDOSIS
(b) Several kinds, all rare
(c) Most common = Familial Mediterranean Fever (AR)
  - +++ production of IL-1 → attacks of fever and inflammation of serosal surfaces (pleura, peritoneum, synovium)
  - Associated gene encodes pyrin
  - AA amyloid, predominant renal deposition

Clinical features: caused by amyloid deposits in various organs:
- KIDNEY: nephrotic syndrome = most common presentation
- HEART: 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** (otherwise pink/red) – caused by beta-pleated sheet configuration
Misfolded proteins unstable and self-associated to form the fibrils
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
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, lupus pernio, 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
- **CNS involvement
- **CONSTITUTIONAL SX**: malaise, fever, wt loss, night sweats

**DIAGNOSIS OF EXCLUSION**

**Investigations**: ↑Ca2+, ↑ESR, ↑ACE, transbronchial biopsy, (Kveim test historical – intradermal injection of sarcoid splenic tissue → granuloma formation)