

**Third edition**

# **Notes & Notes**

For MRCP part 1 & 2

*By*

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# **Haematology**

**&**

# **Oncology**

**Updated**

**2022**

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## Haematological changes during pregnancy

- Platelet
  - **Isolated thrombocytopenia**
    - occur in 8%
    - Usually mild with platelet above 70
    - Occur due to presence **IgG antibodies**, which are reactive to platelet
    - **No intervention** - recover after delivery
- Hypercoagulable state
  - ↑ clotting factors
  - result of venous stasis secondary to uterine pressure on great veins of lower extremity
- Anemia
  - ↑ plasma volume by 50%
  - RBC mass only ↑ by 30%
  - Result is a dilutional gap of 15-20%
- Leukocytosis
  - result of granulocyte demargination
    - no absolute increase in WBC number

## Hyposplenism

### Causes

- splenectomy
- sickle-cell
- coeliac disease, dermatitis herpetiformis
- Graves' disease
- systemic lupus erythematosus
- amyloid

### Features

- Howell-Jolly bodies
- siderocytes

## Eosinophilia

### Causes

- **Pulmonary causes**
  - asthma
  - allergic bronchopulmonary aspergillosis
  - Churg-Strauss syndrome
  - Loffler's syndrome
  - tropical pulmonary eosinophilia
  - eosinophilic pneumonia
  - hypereosinophilic syndrome
- **Infective causes**
  - schistosomiasis
  - nematodes: Toxocara, Ascaris, Strongyloides
  - cestodes: Echinococcus
- **Other causes**
  - **drugs: sulfasalazine, nitrofurantoin**
  - psoriasis/eczema
  - eosinophilic leukaemia (very rare)

## Eosinopenia (Decrease eosinophils)

### Causes

- Cushing syndrome would result in a decrease in eosinophils.
- Corticosteroids can cause eosinopenia through sequestration of eosinophils in lymph nodes.

## Hyper-eosinophilic syndrome (HES)

### Definition

- peripheral blood eosinophil count of  $>1.5$  for more than 6 months.
- In hypereosinophilic syndrome, the eosinophils represent more than 20 percent of the cell population in the bone marrow.
- HES are defined as the association of Hypereosinophilia (as defined above), with eosinophil-mediated organ damage, in which other causes for the damage have been excluded.

### Features

- Hypereosinophilic syndrome most commonly causes manifestations involving the skin.
- pruritus.
- fatigue, myalgia,
- fever, night sweats,
- diarrhoea
- The most common neurological manifestation of hypereosinophilic syndrome is stroke.
- Other symptoms depend on the organ involved:
  - cardiac disease causes chest pain and dyspnoea,
  - respiratory disease presents with a dry cough.

### Treatment

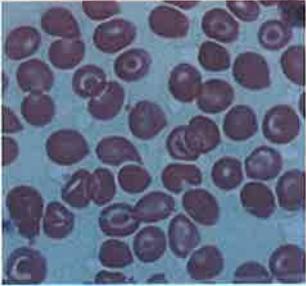
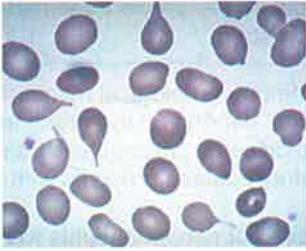
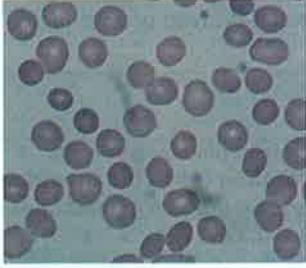
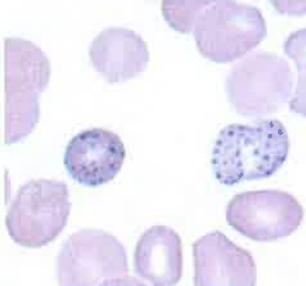
- The first line of treatment of patients with non-myeloid hypereosinophilic syndrome is glucocorticoids.
- The best initial therapy for patients with hypereosinophilic syndrome associated with Fip1-like1-platelet-derived growth factor receptor alpha mutation is imatinib.

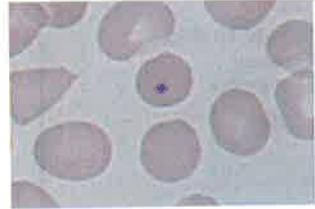
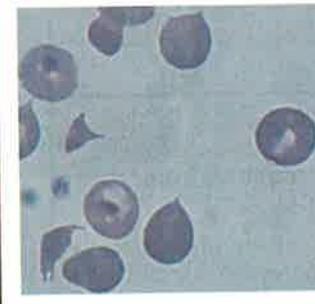
## Lymphopenia

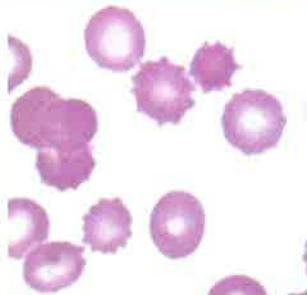
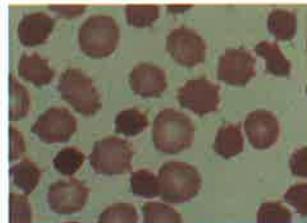
### Causes

- **common finding in elderly patients.**
  - If greater than  $0.5 \times 10^9/l$  no action is normally needed
- immunosuppressive drugs e.g. methotrexate
- viral infections e.g. HIV
- non-viral infections e.g. tuberculosis, malaria
- autoimmune disorders e.g. rheumatoid
- lymphoproliferative disorders

**Blood films: pathological cell forms****Pathological red cell forms**

Abnormality	Associated condition(s)	Appearance
Target cells	Sickle-cell/thalassaemia Iron-deficiency anaemia <b>Hyposplenism</b> Liver disease	
'Tear-drop' (Dacrocyte) poikilocytes	<b>Myelofibrosis</b> (The morphology results because RBCs are <b>mechanically</b> squeezed out of the bone marrow.)	
Spherocytes	Hereditary spherocytosis Autoimmune hemolytic anaemia	
Basophilic stippling	<b>Lead poisoning</b> Thalassaemia Sideroblastic anemia Myelodysplasia	

Abnormality	Associated condition(s)	Appearance
Howell-Jolly bodies	Hyposplenism  (Howell-Jolly bodies are the <b>basophilic remnants of the RBC nucleus</b> .)	
Heinz bodies	G6PD deficiency Alpha-thalassaemia	
Schistocytes ('helmet cells')	Intravascular haemolysis Mechanical heart valve Disseminated intravascular coagulation	
'Pencil' poikilocytes	Iron deficiency anaemia	

Abnormality	Associated condition(s)	Appearance
Burr cells (echinocytes)	<b>Uraemia</b> Pyruvate kinase deficiency liver disease	
Acanthocytes	<b>Abetalipoproteinemia</b>	 (irregularly distributed spicule in red blood cells).
Bite cell (Degmacyte)	G6PD <b>(when spleen removes heinz bodies from RBCs)</b>	

### Blood films: typical pictures

Hyposplenism e.g. post-splenectomy

- target cells
- **Howell-Jolly bodies**
  - These are spherical bluish inclusions within erythrocytes
  - They are nuclear fragments of condensed DNA which are normally removed by the spleen.
  - They are seen in severe haemolytic anaemias or in hypoplastic/asplenic patients.
- Pappenheimer bodies
- siderotic granules
- acanthocytes

**Iron-deficiency anaemia**

- target cells
- 'pencil' poikilocytes

- if combined with B12/folate deficiency a 'dimorphic' film occurs with mixed microcytic and macrocytic cells

### **Myelofibrosis**

- 'tear-drop' poikilocytes

### **Intravascular haemolysis**

- schistocytes

### **Megaloblastic anaemia**

- hypersegmented neutrophils

### **Congenital Pelger–Huet anomaly**

- is a laminopathy associated with mutations in the lamin B receptor.
- This leads to **bilobed nuclei in neutrophils** and in homozygotes,
- can also be associated with:
  - skeletal abnormalities which include shortened limbs.
  - Like this patient, heterozygotes usually suffer no symptoms and the neutrophil anomaly is picked up as an incidental finding.

### **MRCP part-1 – jan 2017**

A 23-year-old man with tiredness and was noted to have a **neutrophil abnormality** on his blood film with **bilobed nuclei**. His father has a skeletal anomaly with a short right arm. Examination reveals no lymphadenopathy, and abdominal examination is entirely normal. What is the most likely diagnosis?

→ Congenital Pelger–Huet anomaly

### **Leucocyte alkaline phosphatase**

Raised in	Low in
<ul style="list-style-type: none"> <li>• myelofibrosis</li> <li>• leukaemoid reactions</li> <li>• polycythaemia rubra vera</li> <li>• infections</li> <li>• steroids, Cushing's syndrome</li> <li>• pregnancy, oral contraceptive pill</li> </ul>	<ul style="list-style-type: none"> <li>• chronic myeloid leukaemia</li> <li>• pernicious anaemia</li> <li>• paroxysmal nocturnal haemoglobinuria</li> <li>• infectious mononucleosis</li> </ul>

### **Leukaemoid reaction**

#### **Definition**

- Presence of immature cells such as myeloblasts, promyelocytes and nucleated red cells in the peripheral blood.

#### **Mechanism**

- This may be due to:
  - infiltration of the bone marrow causing the immature cells to be 'pushed out' or
  - sudden demand for new cells

#### **Causes**

- severe infection
- severe haemolysis
- massive haemorrhage
- metastatic cancer with bone marrow infiltration

**Differentiating chronic myeloid leukaemia from a leukaemoid reaction:**

Chronic myeloid leukaemia	Leukaemoid reaction
low leucocyte alkaline phosphatase score	<ul style="list-style-type: none"> <li>• high leucocyte alkaline phosphatase score</li> <li>• toxic granulation (Dohle bodies) in the white cells</li> <li>• 'left shift' of neutrophils i.e. three or less segments of the nucleus</li> </ul>

**Coagulation study****Prothrombin time (PT)**

- Prothrombin time (PT) is a measure of the time it takes for the extrinsic pathway to create a fibrin clot.
- tests function of factors (I, II, V, **VII**, X)
  - defect in any of these → ↑ PT
  - e.g. vitamin K deficiency
- **best test to follow warfarin therapy**
  - normalized as an INR (international normalized ratio)
  - note also increases PTT time
- also used to measure hepatic function as most of the factors are synthesized in the liver  
Used to monitor the extrinsic pathway
- Factors make up the extrinsic pathway:
  - Damaged endothelium → tissue factor release → Factor VII activation → common pathway activation
- **In patients with vitamin K deficiency, the PT is typically prolonged while the partial thromboplastin time (PTT) is usually normal.**
- **Long-term use of antibiotics → changes in the gut flora → vitamin K deficiency → ↑PT**
  - Long-term use of antibiotics (particularly cephalosporins like cefepime) would cause changes in the gut flora that result in vitamin K deficiency (due to decreased populations of the bacteria that synthesize it).
  - vitamin K deficiency would impair the gamma-carboxylation of factors II, VII, IX, and proteins C and S.
  - As a result, the **PT**, which **measures the clotting time of the extrinsic pathway** (starting with tissue factor and factor VII), would **increase**, just as it would in a patient on warfarin.

**Partial Thromboplastin Time (PTT) (sometimes also called Activated Partial Thromboplastin Time)**

- tests function of all factors EXCEPT (VII, XIII)
  - defect in any of these → ↑ PTT
- when prolonged indicating hemophilia or (sometimes) von Willebrand's Disease.
- **best test to follow heparin therapy**
  - note also increases PT time
- Used to monitor the **intrinsic pathway**
- Factors make up the intrinsic pathway:
  - Factors XII, XI, IX, VIII.
- **elevated APTT could be due to:**
  - treatment with heparin
  - haemophilia
  - von Willebrand's disease, or
  - antiphospholipid syndrome.

The commonest cause of reduced APTT is → **in-vitro clotting cascade activation**, but tests should be repeated to exclude pathological causes of hypercoagulability.

#### DIC vs TTP

- DIC is distinguished from thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) based on coagulation studies.
- Although TTP and HUS are also microangiopathic hemolytic anemias, patients with these conditions do not have derangement or consumption of clotting factors.
  - **DIC → Increased PT, PTT, decreased platelets**
  - **TTP & HUS → normal PT, normal PTT, and decreased platelets.**

#### Isolated factor deficiency

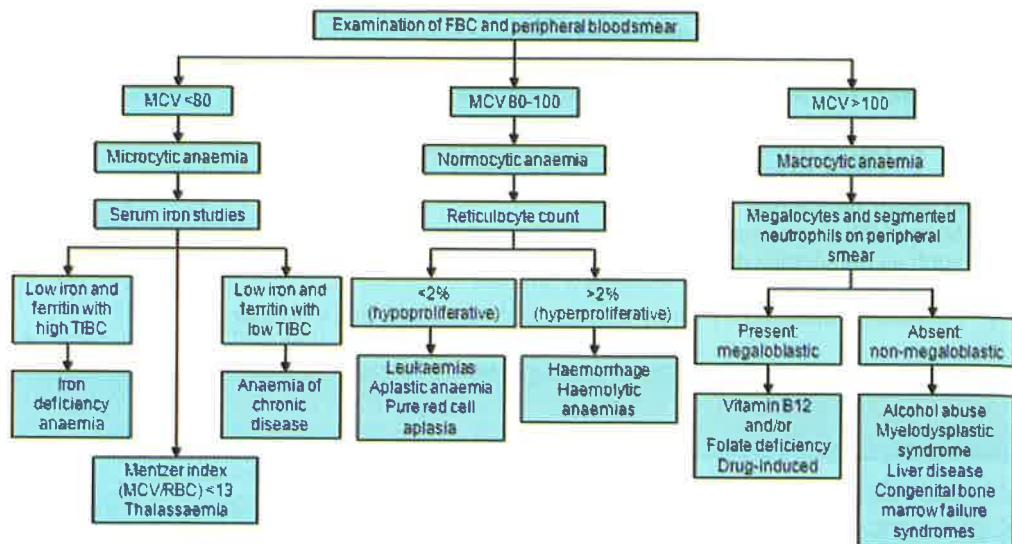
- Normal PT, **increased PTT**, and normal platelets suggests an isolated factor deficiency such as hemophilia A and B, in which there is a deficiency of factors VIII and IX, respectively.
- An isolated elevated PTT may also suggest von Willebrand's disease.

Disease	PT	PTT	Platelet count	Bleeding time
Warfarin (or vitamin K deficiency)	Raised	Raised (in severe or prolonged cases)/nl	Raised	nl
DIC	Raised	Raised	Decreased	Raised
Thrombocytopenia	nl	nl	Decreased	Raised
Bernard-Soulier	nl	nl	Decreased	Raised
Hemophilia (A or B)	nl	Raised	nl	nl
von Willebrand	nl	nl/raised	nl	Raised
Glanzmann's	nl	nl	nl	Raised

#### Giant platelet syndrome (Bernard-Soulier syndrome; BSS)

- is a defect in platelet adhesion.
- The genetic defect is in glycoprotein 1b (GP1b).
- characterized by increased megakaryocytes and abnormally large platelets on peripheral smear, hence its name.
- **thrombocytopenia and an elevated bleeding time but a normal prothrombin time (PT) and partial thromboplastin time (PTT).**
- BSS can be distinguished from a deficiency in von Willebrand factor (vWF) by a **ristocetin test**.
  - Ristocetin is an antibiotic that causes vWF to bind to GP1b, causing agglutination in normal blood.
  - In patients with either defective vWF or GP1b (BSS), platelets do not aggregate in the presence of ristocetin.
  - The addition of normal plasma corrects this defect in von Willebrand's disease, but not in BSS (because the platelet receptor remains defective).

## Assessment of anaemia



From BMJ best practice

### Causes of normocytic anaemia:

- anaemia of chronic disease
- chronic kidney disease
- **aplastic anaemia**
- haemolytic anaemia

### Causes of macrocytic anaemia:

- can be divided into causes associated with a megaloblastic bone marrow and those with a normoblastic bone marrow

Megaloblastic causes	Normoblastic causes
<ul style="list-style-type: none"> <li>• vitamin B12 deficiency</li> <li>• folate deficiency</li> </ul>	<ul style="list-style-type: none"> <li>• alcohol</li> <li>• liver disease</li> <li>• hypothyroidism</li> <li>• pregnancy</li> <li>• reticulocytosis</li> <li>• myelodysplasia</li> <li>• drugs: cytotoxics</li> </ul>

### Causes of microcytic anaemia:

- iron-deficiency anaemia
- thalassaemia\*
  - \*in beta-thalassaemia minor the microcytosis is often disproportionate to the anaemia

- A question sometimes seen in exams gives a history of a normal haemoglobin level associated with a microcytosis. In patients not at risk of thalassaemia, this should raise the possibility of polycythaemia rubra vera which may cause an iron-deficiency secondary to bleeding.
- congenital sideroblastic anaemia
- anaemia of chronic disease (more commonly a normocytic, normochromic picture)
- lead poisoning

## Iron metabolism

### Absorption:

- **Upper small intestine.**
- About 10% of dietary iron absorbed.
- Fe<sup>2+</sup> (ferrous iron) much better absorbed than Fe<sup>3+</sup> (ferric iron).
- Absorption is regulated according to body's need.
- **Increased by vitamin C (ascorbic acid)** and gastric acid.
  - **vitamin C aids iron absorption** by reducing iron from the ferric to the ferrous form, and by chelating it into a complex which enhances absorption.
- Decreased by PPIs, tetracycline, gastric achlorhydria, tannin (in tea).
- From an intake of approximately 6 mg/1000 kcal of dietary iron **only 15% is bioavailable.**

### Oral iron absorption.

#### A. Effectors of iron absorption.

Inhibiting iron absorption	Facilitating iron absorption
<ul style="list-style-type: none"> <li>• Coffee, tea, milk, cereals, dietary fiber, phosphate-containing carbonated beverages</li> <li>• Multivitamin or dietary supplements containing calcium, zinc, manganese or copper</li> <li>• Antacids, H<sub>2</sub> blockers and proton pump inhibitors.</li> <li>• Quinolones and tetracycline antibiotics</li> </ul>	<ul style="list-style-type: none"> <li>• Vitamin C</li> <li>• Acidic foods e.g. tomato sauce</li> <li>• Non enteric coated iron tablets</li> <li>• Fasting ingestion of iron supplements</li> </ul>

#### B. Oral iron absorption test.

Step 1: Measure morning serum iron level (fasting).

Step 2: Ingest approximately 60mg elemental iron (324 mg ferrous sulphate) with water.

Step 3: After 1-2 hours, measure the serum iron level.

Step 4: Compare the serum iron levels.

**Interpretation:** An increase in serum iron of >100 µg/dL suggests gut absorption is generally adequate.

### Distribution in body

- Total body iron = 4g (2500 mg in the RBCs, 500 mg in liver, 500 mg in macrophages and about 500 mg in muscle).
- **Haemoglobin = 70%**
- Ferritin and hemosiderin = 25%
- Myoglobin = 4%
- Plasma iron = 0.1%

- Approximately 4 mg of iron circulate within the plasma. So approximately 0.1% of body iron circulates in the plasma.

### Transport

- Carried in plasma as Fe<sup>3+</sup> bound to transferrin.

### Storage

- Stored as ferritin in tissues.
  - It is the plasma protein responsible for binding iron,
  - is an acute phase reactant protein which is increased in inflammatory conditions.

### Excretion

- The majority of iron contained within the RBCs is metabolised and re-utilised but 1 mg per day is lost through the gut.

## Transferrin

- serum transferrin is the bus that carry absorbed iron to storage places & stored as ferritin.
- transferrin saturation is the % of people [iron] carried by that bus [transferrin].
- TIBC is the no. of empty chairs in that bus.

- Transferrin is a glycoprotein responsible for internal iron exchange
  - Iron (Fe 3+) is carried in the blood bound to transferrin.
  - Fe<sup>2+</sup> (ferrous iron) is oxidised to Fe<sup>3+</sup> (ferric iron) by caeruloplasmin to bind to transferrin
- Transferrin is the binding protein of iron. So when the levels of ferritin are low, the body signals the liver to synthesize more of Transferrin to maintain the levels of iron
- **Pregnancy and oral contraceptive pill (OCP) both increase transferrin.**
- **Transferrin saturation %**
  - The transferrin saturation % (plasma iron /TIBC x 100) is used as a measure of iron stores.
  - In absence of anaemia, transferrin is about 33% saturated with iron (about one third saturated with iron).
  - A value below 16% is indicative of iron deficiency.
- iron deficiency → low serum Fe, rise TIBC, rise the transferrin level.
- iron overload → fall in both TIBC and transferrin
- haemochromatosis → increased in Transferrin saturation%
  - the content within mucosal cells is naturally high in haemochromatosis with high iron store saturation.
  - in haemochromatosis TIBC is low because transferrin is FULL of iron and no more empty space, hence LOW TIBC and for the same reason transferrin saturation is high [FULL]

## Iron studies

- Serum iron
- Total iron binding capacity (TIBC)
- Transferrin
  - raised in iron deficiency anaemia (IDA)
  - raised in pregnancy and by oestrogen
- Transferrin saturation
  - calculated by serum iron / TIBC
- Ferritin
  - raised in inflammatory disorders
  - low in IDA
- Rarer tests
  - transferrin receptors → increased in IDA
- Anaemia of chronic disease

- normochromic/hypochromic, normocytic anaemia
- reduced serum and TIBC
- normal or raised ferritin

## Iron deficiency anaemia (IDA)

- iron deficiency is the most common cause of anemia worldwide.

### Causes

- the commonest cause of iron-deficiency anaemia worldwide being hookworm infection (*Necator americanus* and *Ancylostoma duodenale*), which affects 25% of the global population.
- microcytic anaemia in a female should raise the possibility of either gastrointestinal blood loss or menorrhagia.

### Features

- Koilonychia (spoon-shaped nails)
- atrophic glossitis
- post-cricoid webs
  - Plummer-Vinson syndrome (dysphagia, esophageal webs and iron deficiency)
- other cutaneous manifestations of iron deficiency include:
  - pruritus,
  - dry and brittle hair
    - the hair, skin, nail and mucous membrane changes are often visible before the patient is clinically anemic.
- angular stomatitis

### Investigations

- **Blood film**
  - target cells
  - 'pencil' poikilocytes
  - if combined with B12/folate deficiency a 'dimorphic' film occurs with mixed microcytic and macrocytic cells
- Serum ferritin
  - Hypoferritinæmia confirms IDA and is **the preferred screening test**.
  - **the most sensitive marker for iron deficiency**
    - Ferritin is an acute phase reactant and may be grossly elevated in the context of acute inflammation (when it does not accurately reflect iron stores) and to a lesser degree in chronic inflammation.
      - ❖ British Society Guidelines on the diagnosis and management of iron deficiency anaemia suggest that:
        - ➡ a cut-off of 12-15 mg/L reflects iron deficiency in the absence of inflammation.
        - ➡ Where inflammation is present a ferritin of 50 mg/L or more may still be compatible with iron deficiency.

## Treatment of IDA

### Iron tablet preparations

- Among the tablet preparations, there are:
  1. non-enteric coated pills
    - most commonly used as initial treatment due to their lower cost.
  2. enteric-coated
  3. prolonged-release formulations.
    - Delayed release and enteric-coated iron are better tolerated than the non-enteric coated tablets.
    - less effective since they may contain less iron and their iron may not be released in the duodenum, where iron is absorbed.

- patients who have been treated unsuccessfully with enteric-coated and prolonged-release iron preparations may respond well to the administration of nonenteric-coated ferrous salts
- **Ferrous sulphate** has more elemental iron by mass than the same dose of ferrous gluconate
- **Sustained release preparations** may improve tolerance of oral iron but do not aid absorption.

### Iron prescription

- Ideally, patients should not take iron supplements within 1-2 hours of **antacids** → alkaline environment reduces absorption (acidity required for iron solubility)
- Iron tablets are recommended **between meals or at bedtime** to avoid the alkalinizing effect of food and to take advantage of the peak gastric acid production late at night.
- calcium, phosphorus and magnesium salts contained in iron-containing multivitamin pills impair absorption of elemental iron. For this reason, **multivitamin preparations should never be recommended as a sole therapy for iron deficient anemia.**
- Iron absorption is also delayed with tetracyclines, milk, and phosphate-containing, carbonated beverages such as soft drinks.
- **Iron replacement in chronic renal failure**
  - In chronic renal failure, Erythropoietin (EPO) therapy is only considered in patients where the ferritin is  $>100 \text{ mg/l}$ .
  - If ferritin  $< 100 \rightarrow$  iron replacement is the initial intervention of choice.
- **IV iron**
  - Parenteral iron acts no faster than oral iron. It is indicated when oral iron cannot be tolerated or is not absorbed.
  - **Indications for IV iron include:**
    - unable to tolerate orally,
    - Patients who fail to comply with prescriptions for oral iron supplementation.
    - **A history of exertional angina with anaemia → strongest indication for transfusion**
    - GIT disorders, such as IBD (ulcerative colitis and Crohn's disease), in which symptoms may be aggravated by oral iron therapy
    - **Iron is poorly absorbed from the GI tract in patients with renal failure, as such IV replacement is the modality of choice.**
  - It is considered best practice to administer 1000 mg of low molecular weight iron dextran in 250 mL of normal saline in 1 hour without premedication;
  - a test dose of 10 to 25 mg is infused over 3 to 5 minutes prior to the first infusion.
  - If no acute reaction is observed, the remaining solution is infused over the balance of 1 hour.
  - For those with a history of drug allergies or hypersensitivity, 125 mg of methylprednisolone is infused prior to the test dose.

### British society of gastroenterology (BSG) guidelines 2011:

- correct anaemia and replenish body stores achieved most simply and cheaply with ferrous sulphate 200 mg twice daily.
- Lower doses may be as effective and better tolerated and should be considered in patients not tolerating traditional doses.
- Other iron compounds (eg, ferrous fumarate, ferrous gluconate) or formulations (iron suspensions) may also be tolerated better than ferrous sulphate.
- Oral iron should be continued for 3 months after the iron deficiency has been corrected so that stores are replenished.
- Ascorbic acid (250e500 mg twice daily with the iron preparation) may enhance iron absorption
- Iron treatment should follow transfusion to replenish stores.

## Anemia of Chronic Disease

### Definition

- decreased RBC production due to any longstanding inflammatory, infectious, or malignant disease (includes rheumatoid arthritis, severe trauma, heart disease, diabetes mellitus, and inflammatory bowel disease)

### Mechanism of Anemia of Chronic Disease

- there is primarily a decreased availability of iron, relatively decreased levels of erythropoietin, and a mild decrease in the lifespan of RBCs to 70-80 days (normally 120 days)
  - in anemia of chronic kidney disease, ↓ erythropoietin production by the interstitial fibroblasts, (also known as type I interstitial cells), → anemia.
    - The kidneys are responsible for approximately 90% of erythropoietin production.
- Increase in **hepcidin** level in the course of inflammatory disease → ↓ release of iron from macrophages + ↓ dietary iron absorption.
  - hepcidin is an acute-phase reactant that is increased in states of inflammation
- cytokines, such as interleukins (IL-1 and IL-6), and tumor necrosis factor (TNF-alpha), → destruction of RBC precursors and decrease the number of erythropoietin receptors on progenitor cells.

### Investigations

- RBCs morphology
  - normochromic, normocytic anemia.
- Reticulocyte count
  - ↓ reticulocyte count points to ↓ RBC production as the primary mechanism responsible for anemia,
- ↑ ferritin
- ↓ serum iron
- ↓ TIBC, transferrin saturation, and MCV

### Treatment

- treatment of the underlying disease.
- If underlying disease is unknown or treatment of underlying disease does not improve symptomatic anemia
  - measure EPO
    - if low, administer EPO or erythropoiesis-stimulating agents (ESAs)
      - make sure iron stores are sufficient
      - if insufficient, patients may be resistant to EPO
  - if normal, give packed RBCs

## Hepcidin

- Hepcidin, a peptide hormone synthesized in the liver.
- reduces extracellular iron in the body by several mechanisms:
  - lowers dietary iron absorption by reducing iron transport across gut mucosal cells (enterocytes);
  - reduces iron exit from macrophages, the main site of iron storage;
  - reduces iron exit from the liver. In all three instances this is accomplished by reducing the transmembrane iron transporter ferroportin.
- inflammation → ↑ hepcidin → ↓ serum iron due to:
  - iron trapping within macrophages and liver cells

- decreased gut iron absorption.
- inadequate amount of serum iron being available for developing red cells → anemia
- hemochromatosis → ↓ hepcidin level → iron overload due to:
  - increased **ferroportin** mediated iron efflux from storage and increased gut iron absorption.
- Hepcidin inhibits iron transport by binding to the iron export channel **ferroportin** which is located on the basolateral surface of gut enterocytes and the plasma membrane of macrophages.
  - Inhibiting ferroportin leads to:
    - ↓ iron release from macrophages
    - ↓ dietary iron absorption.

## Thalassaemias

Alpha is located on 16, beta on 11 chromosome .

### Definition

- The thalassaemias are a group of genetic disorders characterised by a reduced production rate of either alpha or beta chains.
- It is a haemoglobinopathy resulting from defective synthesis of globin chains required for Hb synthesis.
- Each copy of **chromosome 16** has two genes for the **alpha globin** subunit (**four in total**).
- And each copy of **chromosome 11** has one genes for the **beta globin** subunit (**two in total**).

### Types of haemoglobin

Haemoglobin	Chains	% Hb in normal adult
Hb A	$\alpha_2\beta_2$ ( two alpha and two beta chains)	97%
Hb A <sub>2</sub>	$\alpha_2\delta_2$ (two alpha and two delta chains)	<3.5%
Hb F.	$\alpha_2\gamma_2$ (two alpha and two gamma chains)	<1%

## Alpha-thalassaemia

- Alpha-thalassaemia is due to a deficiency of alpha chains in haemoglobin
- Alpha-thalassaemia is found in malarial regions of the world (Mediterranean, South-east Asia, Indian sub-continent, Middle East, Sub-Saharan Africa) and should be suspected in patients with these ethnic backgrounds and with microcytosis and/or anaemia.
- Acquired Hb H disease is rare and occurs most commonly in male patients with myelodysplastic syndrome.

### Overview

- 2 separate alpha-globulin genes (four in total) are located on each **chromosome 16**
- There are 4 different alpha-thalassaemias:
  1. **silent carrier** (1 affected alpha-globin gene),
  2. **alpha-thalassaemia trait** (2 affected alpha-globin genes),
  3. **Hb H disease** (typically 3 affected alpha-globin genes)
  4. **Hb Bart hydrops fetalis syndrome** (typically deletion of all 4 alpha-globin genes).
- Clinical severity depends on the number of alpha chains present
  - If 1 or 2 alpha chains are absent then the blood picture would be **hypochromic** and **microcytic**, but the Hb level would be typically **normal**
  - Loss of 3 alpha chains results in a **hypochromic microcytic anaemia** with **splenomegaly** and **HbH in red cells**. This is known as **Hb H disease**

- If all 4 alpha chains absent (i.e. homozygote) then death in utero (hydrops fetalis, Bart's hydrops)
- **Persistence of HbF has survival advantages in severely affected subjects.**
- Co-inheritance of alpha-gene mutations, and persistence of fetal haemoglobin production, may restore the globin balance and result in a milder syndrome.
- **Features**
  - most are asymptomatic.
  - Many patients with Hb H are also clinically well, but are at risk for:
    - acute haemolytic episodes
    - aplastic crises
    - iron overload, even in the absence of chronic transfusions
    - hypersplenism; and
    - endocrine disease.
  - Hemoglobin gel-electrophoresis
    - α-thalassemia trait → normal
    - 3 gene deletion α-thalassemia → HbH ( $\beta,\beta,\beta,\beta$ )
    - 4 gene deletion α-thalassemia → Hb Barts ( $\gamma,\gamma,\gamma,\gamma$ )

## Beta-thalassaemia

Disproportionate microcytic anaemia - think beta-thalassaemia trait

If a person has **MCV > 80** and **MCH > 27**, in the **absence of symptoms**, thalassaemia can be reasonably excluded.

### Overview

- The most common cause of β- Thalassemia is the defect in **mRNA splicing** of the beta globin gene on chromosome 11.
- **autosomal recessive**
- common in Mediterranean populations
- **β thalassaemia minor / trait → protects against malaria**
  - ↑(Hb F) → inhibits the development of the malarial parasite.

### Types

- **β thalassaemia major ( $\beta 0$ ):**
  - prevent any formation of β chains,
  - the most severe form of β thalassemia,
  - 2 gene depletion ( $\beta 0\beta 0$ ) ( $\alpha,\alpha,\alpha,\alpha$  hemoglobin present)
    - ❖ aggregation of alpha-globin tetramers → damage erythrocytes → extravascular hemolysis.
  - HbF tries to convert to HbA during first year of life,
    - ❖ Fetal hemoglobin is protective in an infant with beta-thalassemia major, hence the disease will only present after six months of age, as its levels decrease.
  - extramedullary haemopoiesis with hepatosplenomegaly and bone marrow expansion, "hair on end" appearance of bone.
  - **Diagnosis**
    - **Hemoglobin electrophoresis is the best test for diagnosis**
  - **Features**
    - anaemia
    - splenomegaly
      - ❖ occurs secondary to extramedullary hematopoiesis.
    - bone deformities

- ❖ bone marrow expansion can cause "chipmunk facies" or "crew cut sign" on a skull X-ray.
- Target cells on a peripheral blood smear
- early death if not treated appropriately.
- **Treatment:**
  - lifelong regular blood transfusions, (usually **every two to five weeks**, to maintain the pretransfusion haemoglobin level **above 9–10.5 g/dL**).
  - ❖ **transfusion programme with iron chelation is the best initial approach.**
  - Indications for transfusion:
    - ❖ Hb < 7 g/dL on 2 occasions, > 2 weeks apart (excluding all other contributory causes such as infections) **or**
    - ❖ Hb > 7 g/dL **with:** Facial changes, Poor growth, Fractures, and Extramedullary haematopoiesis
  - en** The transfusional iron overload can be managed with iron chelation, both **DFO** (desferrioxamine) and/or oral (deferasirox).  
**on 16** Desferrioxamine binds iron but needs to be given for 8–12 hours a day for 5–7 days per week, so is a major undertaking for the patient.  
SE: high frequency deafness, retinopathy and Yersinia infection.
  - Stem cell transplantation options offer cure.
  - **parents and other siblings should be screened by genetic testing.**

- **β thalassaemia intermedia (β+):**
  - caused by a mutation in the Kozak consensus sequence of the Beta globin gene on chromosome 11.
  - they allow some β chain formation to occur.
  - In either case there is relative excess of α chains, but these don't form tetramers.
- **β thalassaemia minor / trait:**
  - 1 gene deletion
  - **Features**
    - usually asymptomatic
    - **mild hypochromic, microcytic anaemia - microcytosis is characteristically disproportionate to the anaemia** (marked microcytosis (very low MCV) (i.e. the Microcytosis is disproportionately with very low MCV for the near normal Hb level >9).
    - **HbA2 ( $\alpha_2\delta_2$ ) raised (> 3.5%)** on gel electrophoresis.
      - ❖ **HbA2 levels above 3.5% are screening criteria for the β-thalassemia carrier state.**
      - ❖ Note that in cases of severe iron deficiency anaemia the HbA2 may be normal in thalassemia minor.

- Thalassemia can co-exist with other haemoglobinopathies. The most common of these are:
  - **HbE/thalassaemia:**
    - common in Cambodia, Thailand, and parts of India
    - clinically similar to β thalassaemia major or thalassaemia intermedia.
  - **HbS/thalassaemia:**
    - common in African and Mediterranean populations
    - clinically similar to sickle cell anaemia with additional feature of splenomegaly.
  - **HbC/thalassaemia:** common in African and Mediterranean populations:
    - **HbC/β0 thalassaemia:** causes moderate to severe haemolytic anaemia with splenomegaly.
    - **HbC/β+ thalassaemia:** produce a milder disease.

## Beta thalassaemias (reduction in beta globin chains)

Type	Genotype	Typical findings on CBC	Haemoglobin analysis (HPLC or electrophoresis)
<b>Major</b> (transfusion-dependent)	$\beta^0 / \beta^0$ or $\beta^0 / \beta^+$	<b>Severe</b> microcytic anaemia with target cells (typical Hb 3 to 4 g/dL)	HbA <sub>2</sub> (5% or more). HbF (up to 95%). No HbA
<b>Intermedia</b> (non-transfusion-dependent)	$\beta^+ / \beta^+$	<b>Moderate</b> microcytic anaemia	HbA <sub>2</sub> (4% or more). HbF (up to 50%)
<b>Minor</b> (also called trait or carrier)	$\beta / \beta^0$ or $\beta / \beta^+$	<b>Mild</b> microcytic anaemia	HbA <sub>2</sub> (4% or more). HbF (up to 5%)

$\beta^0$  refers to no beta globin production.

$\beta^+$  refers to decreased beta globin production.

## Delta thalassaemia

- about 3% of adult Hb is made of alpha and delta chains.
- mutations can occur which affect the ability of this gene to produce delta chains.

## Aplastic anaemia

- Characterised by pancytopenia and a hypoplastic bone marrow
- Peak incidence of acquired = 30 years old

### Features

- Assessment of bone marrow cellularity is best made on **trepentine biopsy**, which often shows replacement of the normal cellular marrow by **fatty marrow**.
- normochromic, normocytic anaemia
- leukopenia, with lymphocytes relatively spared
- thrombocytopenia
- may be the presenting feature acute lymphoblastic or myeloid leukaemia
- a minority of patients later develop paroxysmal nocturnal haemoglobinuria or myelodysplasia
- In patients with aplastic anaemia, the bone marrow is markedly **hypocellular**.

### Causes

- idiopathic
- congenital: Fanconi anaemia, dyskeratosis congenita
- drugs: cytotoxics, chloramphenicol, sulphonamides, phenytoin, gold
- toxins: **benzene**
- infections: parvovirus, hepatitis
- radiation

### management

#### Supportive

- blood products
- prevention and treatment of infection

#### Anti-thymocyte globulin (ATG) and anti-lymphocyte globulin (ALG)

- prepared in animals (e.g. rabbits or horses) by injecting human lymphocytes

- is highly allergenic and may cause serum sickness (fever, rash, arthralgia), therefore steroid cover usually given
- immunosuppression using agents such as ciclosporin may also be given

#### **Stem cell transplantation**

- allogeneic transplants have a success rate of up to 80%

## **Pure Red Cell Aplasia (PRCA)**

#### **Overview**

- uncommon disorder
- maturation arrest occurs in the formation of erythrocytes. Erythroblasts are virtually absent in bone marrow; however, white blood cell and platelet production are normal.
- The anemia due to PRCA is usually normocytic but can be macrocytic.

#### **Diagnosis**

- characteristics of PRCA include
  1. Severe unexplained anemia
  2. ↓ Reticulocyte count <1%
  3. The presence of less than 0.5% mature erythroblasts in the bone marrow
  4. Normocellular bone marrow in most cases

#### **Causes**

- most cases of chronic PRCA are idiopathic (acquired primary).
- Secondary PRCA associated with:
  - Autoimmune disorders (eg, type 1 diabetes, thyroiditis, rheumatoid arthritis, Sjögren syndrome)
  - Thymomas
  - Systemic lupus erythematosus
  - Hematologic malignancies
  - Solid tumors
  - **Erythropoietin-induced pure red cell aplasia in treatment of CKD anaemia**

#### **Treatment**

- can be transient and reversible (PRCA due to medications and infections are often reversible.)
- symptomatic anaemia → transfusion
- Treatment of underlying conditions
  - parvovirus B19 infections → High-dose intravenous immunoglobulin
  - PRCA due to drugs → disappear when the drug is stopped.
  - thymoma → thymectomy or gamma irradiation of the thymus
- Immunosuppressive:
  - Corticosteroids are the mainstay of therapy (45% respond) → the first choice
  - cyclosporine, azathioprine, Cyclophosphamide and rituximab are used

## **Fanconi's Anaemia**

- Autosomal recessive
- Aplastic anaemia
- ↑ risk of AML
- Neurological manifestation
- Skeletal abnormalities
- Skin pigmentation (café au lait spots)

## Macrocytic anaemia

Macrocytic anaemia can be divided into causes associated with a megaloblastic bone marrow and those with a normoblastic bone marrow

Megaloblastic causes	Non-megaloblastic causes
<ul style="list-style-type: none"> <li>vitamin B12 deficiency</li> <li>folate deficiency</li> </ul>	<ul style="list-style-type: none"> <li>alcohol</li> <li>liver disease</li> <li>hypothyroidism</li> <li>pregnancy</li> <li>reticulocytosis</li> <li>myelodysplasia</li> <li>drugs: cytotoxics</li> </ul>

- If serum folate levels are low, serum vitamin B12 and methylmalonic acid levels should be measured to exclude concurrent vitamin B12 deficiency before folate levels are corrected.
- Normal serum homocysteine levels make folate deficiency unlikely.
- RBC folate is a more accurate indicator of folate deficiency than serum folate level.

## Vitamin B12 (cobalamin) deficiency

### Function of vitamin B12 deficiency

- Red blood cell development
- Maintenance of the nervous system.
- B12 is necessary for normal folate metabolism, and therefore when there is a primary B12 deficiency, one can see a low red cell folate as a consequence.

### Sources

- Vit B12 is only found in foods of animal origin e.g. meat, fish and eggs.

### Metabolism

- It is absorbed after binding to intrinsic factor (IF) (secreted from parietal cells in the stomach) and is actively absorbed in the **terminal ileum**.
- A small amount of Vit. B12 is passively absorbed without being bound to IF.
- Hepatic stores of vitamin B12 can last for up to 5 years**, so it is not uncommon for vegans to display vitamin B12 deficiency years after starting their diet

### Causes

- Dietary deficiency of Vit B12: like vegetarians
  - An MCV of >115 fL is typically seen in nutritional deficiency.
  - very rare
    - Folate deficiency due to dietary problems is common, particularly in the elderly, but **it does take many years to become B12 deficient** as a result of dietary deficiency.
- Pernicious anaemia
- Post gastrectomy
  - A patient with combined iron deficiency and B<sub>12</sub> deficiency, Which operation is he most likely to have had? → Partial gastrectomy**
- Disorders of terminal ileum (site of absorption): Crohn's, blind-loop, Malabsorption of vitamin B-12 secondary to small bowel bacterial overgrowth, tapeworm, etc.
- Bacterial overgrowth syndrome**
  - characterized by diarrhea, steatorrhea, and macrocytic anemia.
  - The common feature is proliferation of colonic bacteria in the small bowel. In normal individuals, the small bowel is relatively sterile.
  - Common bacteria involved are E.coli or bacteroides.
  - Macrocytic anemia results from increased utilization of vitamin B12 by the colonized bacteria.

- Steatorrhea is caused by reduced concentration of conjugated bile acids.  
Bacteroides can convert conjugated bile acids to unconjugated bile acids, which result in impaired micelle formation.
- Diarrhea is due to steatorrhea.

#### Features of vitamin B12 deficiency

- Macrocytic anaemia
- **mild jaundice** is typical of megaloblastic anaemia (vitamin B<sub>12</sub> or folate deficiency) because of increased destruction of red cell precursors in the bone marrow.
- Sore tongue and mouth
- Neuropsychiatric symptoms: e.g. Ataxia, Mood disturbances
  - Neurological involvement can be present in B12 deficiency even in the absence of anaemia, especially in patients over the age of 60.
  - The peripheral nerves are most commonly involved, followed by subacute degeneration of the spinal cord.
  - **Early signs are loss of peripheral vibration and joint position sense**, which is usually followed by loss of reflexes and weakness.
  - The legs and feet are usually more involved than the hands.
  - In the late stages there may be spasticity, upgoing plantars and ataxia but thankfully this is rare in the UK.
- Serum **methylmalonic acid** levels are **elevated** in vitamin B12 deficiency.
  - more sensitive Serum vitamin B12 levels, and should be used to definitively exclude vitamin B12 deficiency.
  - elevated **homocysteine** and **methylmalonic** acid levels.
- Blood smear will show hypersegmented neutrophils.

#### Treatment

- **even in case of profound anaemia, if the patient is not haemodynamically compromised → no need for blood transfusion.**
- **intramuscular vitamin B<sub>12</sub> and oral folic acid.**
- Patient need to continue on treatment with ferrous sulphate as iron stores are likely to be depleted rapidly once the marrow starts functioning.
- Giving oral folic acid without vitamin B<sub>12</sub> would be hazardous and could precipitate subacute combined degeneration of the spinal cord.

## Pernicious anaemia

#### Epidemiology

- more common in females (F:M = 1.6:1)
- typically develops in middle to old age
- more common if blood group A

#### Pathophysiology

- autoimmune disease caused by antibodies to gastric parietal cells or intrinsic factor
- results in vitamin B12 deficiency
- associated with thyroid disease,
  - diabetes
  - Addison's
  - rheumatoid
  - vitiligo
- predisposes to gastric carcinoma

#### Features

- lethargy, weakness
- dyspnoea
- paraesthesia
- mild jaundice
- diarrhoea
- sore tongue

- possible signs:
  - retinal haemorrhages,
  - mild splenomegaly,
  - retrobulbar neuritis

### Investigation

**Normal serum gastrin excludes pernicious anaemia**

- anti-gastric parietal cell antibodies in 90% (**most common**, but low specificity)
- anti-intrinsic factor antibodies in 50% (**specific** for pernicious anaemia)
- macrocytic anaemia
- pancytopenia** (with low WCC and platelets)
- LDH may be raised due to ineffective erythropoiesis
- also low serum B12,
- hypersegmented polymorphs on film, megaloblasts in marrow
- Schilling test**
  - radiolabelled B12 given on two occasions
    - first on its own
    - second with oral IF
  - urine B12 levels measured

**macrocytic anaemia and isolated B12 deficiency (folate is normal) suggest an isolated problem with B12 absorption → pernicious anaemia**

### Management

- If no neurological involvement: **1 mg of IM Hydroxocobalamin 3 times each week for 2 weeks, then once every 3 months.**
- If a patient has deficient in both vitamin B12 and folic acid then it is important to **treat the B12 deficiency first** to avoid precipitating subacute combined degeneration (SCD) of the cord.

## Sickle cell disease (SCD)

### Overview

- autosomal recessive
- Sickle cell disease is a haemoglobinopathy **caused by the substitution of glutamic acid by valine at position 6** (from the N-terminal) of the beta chain. (In sickle cell anaemia, valine replaces glutamic acid at the sixth amino acid of the beta globin)
- HbS is caused by a single base mutation on the beta-chain**
- The β globin gene is found on the short arm of chromosome 11.

### HbS has the following properties:

- contains two α-like globins and two β-like globins and four haem molecules.
- less negatively charged, due to the loss of glutamate for valine.
- has a life span of only 30 days compared to the normal 120 days.
- less soluble than HbA.
- has lower affinity for oxygen than HbA (right-shift of the oxygendissociation curve), which increases the risk of desaturation, but improves the yield of oxygen to the tissues.

### Types

- Sickle cell trait: heterozygous (HbAS)
  - occurs when a child inherits a sickle gene from one parent and a normal gene from the other parent.
- Sickle cell disease: homozygous (HbSS)
  - occurs when a child inherits a sickle gene from each parent.
- Other, rarer forms of sickle cell disease in which the person has only one copy of the mutation that causes Hb S and one copy of another abnormal Hb allele. Examples:
  - "HbSC": (sickle -haemoglobin C disease).
  - "HbS/β+": (sickle-beta-plus-thalassemia).
  - "HbS/β0" : (sickle-beta-zero-thalassemia)

### Sickling of the erythrocyte

- A low partial pressure of oxygen ( $\text{PO}_2$ ) causes HbS to polymerise and precipitate resulting in sickling of the erythrocyte.
  - **HbSS patients sickle at  $\text{PO}_2$  of 5-6 kPa**
  - **HbAS patients sickle at  $\text{PO}_2$  of 2.5-4 kPa.**
  - **HbSC Sickling occurs at around 4 kPa.**

### Sickle cell disease and malaria

- Sickle cell trait (HbAS) is known to protect against falciparum malaria. As a result, the frequencies of sickle cell carriers are high in malaria-endemic areas.
- Patients with HbSS are at higher risk of severe malaria with complications and have a higher mortality rate.

### Feature

- **Black pigment gallstones occur in 50 % of patients with sickle cell disease**
  - due to an increase in bilirubin excretion.
  - Their small size allows migration into the common bile duct causing low-grade obstruction.
  - Typically leading to hyperbilirubinaemia rather than bile duct dilatation.
  - cholecystectomy is suggested for patients with sickle cell disease if abdominal surgery is being performed for other reasons.
  - Due to decreased life span of the erythrocyte, average 17 days (normal 120 days), there is also a **chronic circulating unconjugated hyperbilirubinaemia**.
- **There is often an inability to concentrate urine**
  - The inner medulla is hypoxic, hypertonic and acidotic and therefore predisposes to sickling of red blood cells, which results in vasoocclusion and reduction in renal medullary blood flow.
  - proximal tubule dysfunction → impairs urinary concentration
  - distal tubular dysfunction → impairs potassium excretion.
- Functional hyposplenism in SCD also renders sufferers susceptible to infection with encapsulated bacteria (pneumococci, meningococci).
  - Patients with sickle cell disease have a predisposition to develop osteomyelitis due to *Salmonella* species.

**Sickle-cell crises:** Four main types of crises are recognised:

- **thrombotic crises**, also known as painful crises or **vaso-occlusive crises**
  - precipitated by infection, dehydration, deoxygenation, acidosis, cold temperatures, extreme exercise and stress.
  - infarcts occur in various organs including the bones (e.g. avascular necrosis of hip, hand-foot syndrome in children, lungs, spleen and brain)
- **sequestration crises**
  - sickling within organs such as the spleen or lungs causes pooling of blood with worsening of the anaemia
  - acute chest syndrome: dyspnoea, chest pain, pulmonary infiltrates, low pO<sub>2</sub> - the most common cause of death after childhood
  - stroke
    - 5-10% of sickle cell patients will suffer a stroke, usually during childhood.
    - The risk can be predicted by transcranial Doppler measurement of middle cerebral artery (MCA) flow rate,
    - prompt institution of a prophylactic transfusion program to reduce the HbS % can prevent further strokes.
    - treatment once occurred → **Exchange transfusion programme**
- **aplastic crises**
  - caused by infection with parvovirus
  - sudden fall in haemoglobin without an appropriate ↑ reticulocytosis.
  - The condition is self-limited, with bone marrow recovery occurring in 7-10 days, followed by brisk reticulocytosis.
- **haemolytic crises**
  - rare
  - The anaemia associated with sickle cell disease is usually only symptomatic below 70 g/L, as oxygen is released more readily from erythrocytes.
    - remember, patients with sickle cell tend to run with a Hb between 70-90 g/L normally
  - The anemia of SC is usually a chronic, reasonably well-compensated hemolytic anemia with an appropriate reticulocytosis. For example, the mean hemoglobin and hematocrit concentrations on average may be 79 g/L and 22.9% respectively, with a **reticulocyte count of between 3-15%**.

**Diagnosis** of sickle cell disease requires the detection of HbS.

- **Sickledex test:** addition of reagent to blood → turbidity confirming the presence of HbS, but it gives no information on other haemoglobins.
- **Haemoglobin electrophoresis** is the only investigation that determines the nature of the haemoglobinopathy
  - predominance of HbS.
  - Absent HbA.
  - HbF 2-20%

### Treatment

- General management
  - analgesia e.g. **opiates**
    - NSAIDs do not usually provide effective analgesia on their own in sickle cell painful crises.
  - rehydrate
  - oxygen

- consider antibiotics if evidence of infection
- blood transfusion
- exchange transfusion: e.g. if neurological complications
- Avoid
  - iron therapy: There is a tendency to iron overload and therefore iron therapy is not usually indicated.
  - Intra-articular steroids have been associated with a sickle cell crisis, the mechanism of which is not fully understood, but they should be avoided.
- **pharmaceutical interventions to prevent sickle cell crisis and other acute complications**
  - Hydroxyurea
    - acts by **inhibiting ribonucleotide reductase**, which inhibits both purine and pyrimidine synthesis.
    - Action: ↑fetal haemoglobin (Hb F) which protects against sickling.
    - reduces the incidence of acute chest syndrome and the need for blood transfusion
    - The major side effect is severe myelosuppression.
  - Malaria chemoprophylaxis in endemic area
- **Acute chest syndrome**
  - defines as 'an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on chest X-ray'.
  - management:
    - Oxygen therapy to maintain saturations > 95%
    - Intravenous fluids to ensure euvoalaemia
    - Adequate pain relief
    - Incentive spirometry in all patients presenting with rib or chest pain
    - Antibiotics with cover for atypical organisms
    - Early consultation with the critical care team and haematology
    - Blood transfusion:
      - ❖ A senior haematologist will make a decision as to whether a simple or exchange transfusion is necessary.
      - ❖ guidelines suggest Hb target of 100-110g/L in either instance.
- All adults who have hyposplenism, including patients with SCD, need:
  - Yearly influenza vaccine.
  - Pneumococcal C vaccine, (adults and children over 2 years) repeated every five years.
  - Haemophilus influenzae type b; if not already given as part of childhood immunisation.
  - Conjugated meningococcal C vaccine; if not already given as part of childhood immunisation.
  - Meningococcal ACWY vaccine; if travelling to areas with high risk of meningitis.
- Patients with sickle cell disease are prone to infections within **encapsulated organisms** because of their asplenic state.
  - These include:
    - *Streptococcus pneumoniae*,
    - *Haemophilus influenzae* and
    - *Neisseria meningitidis*.
  - To combat these infections, patients with homozygous sickle cell disease should be on **lifelong penicillin** and be **vaccinated against these organisms**.

**Salmonella osteomyelitis is seen in patients with sickle cell anaemia**

### screening for sickle cell disease in a pregnant women:

- She will first be screened for sickle cell carrier status.
- If that test is positive, her partner will be screened,
- If both are found to be carriers this is confirmed by genetic testing before offering chorionic villus sampling (CVS) (8-10 weeks) or amniocentesis (14-16 weeks).

### Priapism

- Priapism is most often due to idiopathic thrombosis of the prostatic venous plexus.
- Other causes include:
  - leukaemia,
  - **sickle-cell anaemia** and
  - carcinomatosis.
- Priapism occurs fairly frequently which may lead to permanent impotence if it is not relieved.

## Sideroblastic anaemia

### Definition

- Sideroblastic anaemia is a condition where red cells fail to completely form haem, whose biosynthesis takes place partly in the mitochondrion. This leads to **deposits of iron in the mitochondria** that form a ring around the nucleus called a ring sideroblast.

### Causes:

- It may be congenital or acquired
- Congenital cause: delta-aminolevulinate synthase-2 deficiency
    - The enzyme delta aminolevulinic acid (ALA) is essential in the biosynthesis of heme.
      - Delta ALA requires pyridoxine (vitamin B6) and copper as cofactors.
    - Hereditary sideroblastic anemia follows a **X-linked** genetic inheritance pattern.
  - **Acquired causes**
    - myelodysplasia (seen in older age groups)
    - alcohol
      - the most common reversible cause
    - lead
    - drugs: anti-TB medications, chloramphenicol.
      - Pyridoxine (vitamin B6) deficiency, caused by isoniazid and oral contraceptives, is a reversible cause of sideroblastic anemia.

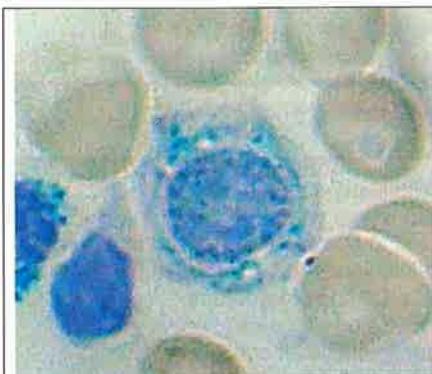
### Investigations

- hypochromic microcytic anaemia (more so in congenital)
- Basophilic stippling:
  - visualization of ribosomes on the surface of red blood cells
  - can be seen on a peripheral blood smear of patients with sideroblastic anemia.
- Ferritin levels are increased
- bone marrow:
  - sideroblasts and increased iron stores
  - Sideroblasts are red cell precursors with iron-laden mitochondria and are detected via **Prussian blue** staining.
  - Ringed sideroblasts are **pathognomonic** for sideroblastic anemia.

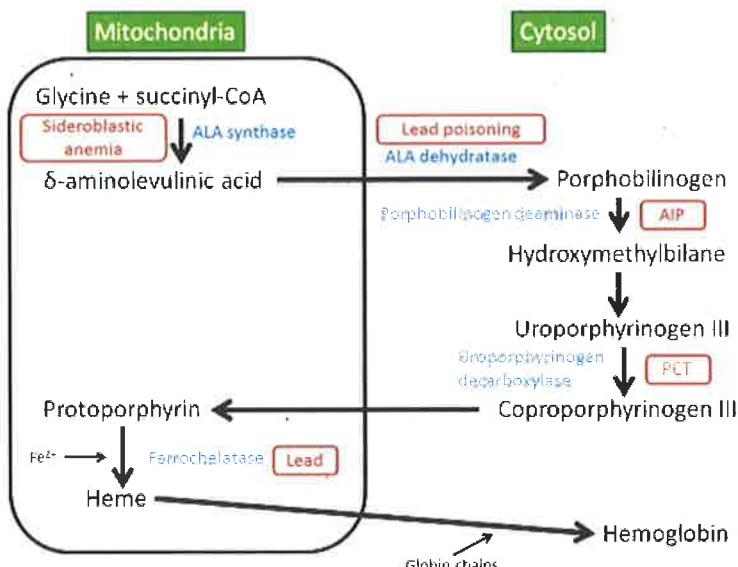
### Management

- supportive
- treat any underlying cause

- removal of toxic agents such as zinc and lead, and drugs such as penicillamine and isoniazid.
- **pyridoxine** may help
- **Deposition of iron in secondary haemochromatosis (haemosiderosis):**
  - Oral iron chelators
    - **First-line : → oral deferasirox**
    - Second-line: → Deferiprone
      - ❖ side effect: bloody dyscrasias and liver dysfunction.
      - ❖ Liver function tests are imperative whilst the patient is being administered both deferiprone and deferasirox.
    - Desferrioxamine results in compliance issues due to the subcutaneous route and long infusion time.
  - Whereas phlebotomy is effective at decreasing iron overload, in a patient who is anaemic this is not a viable option.



The figure illustrates sideroblasts, which are nucleated (immature) erythrocytes with granules of iron in their cytoplasm.



## Haemolytic anaemias: by site

The combination of anaemia and jaundice should always suggest haemolytic anaemia until proved otherwise

- In intravascular haemolysis free haemoglobin is released which binds to haptoglobin.
  - The benefit of this process (**Haptoglobin binds with free plasma hemoglobin**):
    - permits degradative enzymes access to the hemoglobin,
    - preventing the loss of iron via the kidneys,
    - shielding the kidneys from damage by hemoglobin.
- As haptoglobin becomes saturated haemoglobin binds to albumin forming methaemalbumin (detected by Schumm's test).
- Free haemoglobin is excreted in the urine as haemoglobinuria, haemosiderinuria

Intravascular haemolysis	Extravascular haemolysis
<ul style="list-style-type: none"> <li>• mismatched blood transfusion</li> <li>• G6PD deficiency*</li> <li>• red cell fragmentation: heart valves, TTP, DIC, HUS</li> <li>• paroxysmal nocturnal haemoglobinuria</li> <li>• cold autoimmune haemolytic anaemia</li> </ul>	<ul style="list-style-type: none"> <li>• haemoglobinopathies: sickle cell, thalassaemia</li> <li>• hereditary spherocytosis</li> <li>• haemolytic disease of newborn</li> <li>• warm autoimmune haemolytic anaemia</li> </ul>

\*strictly speaking there is an element of extravascular haemolysis in G6PD as well, although it is usually classified as a intravascular cause

## Haemolytic anaemias: by cause

### Heredity causes

- can be subdivided into membrane, metabolism or haemoglobin defects
  - membrane: hereditary spherocytosis/elliptocytosis
  - metabolism: G6PD deficiency
  - haemoglobinopathies: sickle cell, thalassaemia

### Acquired causes

- can be subdivided into immune and non-immune causes
  - Acquired: immune causes
    - autoimmune: warm/cold antibody type
    - alloimmune: transfusion reaction, haemolytic disease newborn
    - drug: methyldopa, **penicillin**
      - ❖ methyldopa → Anti-RBC antibodies
      - ❖ penicillin → reaction between penicillin-like drugs and their antibodies
  - Acquired: non-immune causes
    - microangiopathic haemolytic anaemia (MAHA): TTP/HUS, DIC, malignancy, pre-eclampsia
    - prosthetic cardiac valves
    - paroxysmal nocturnal haemoglobinuria
    - infections: malaria
    - Direct (non-immune) red cell toxicity may occur after lead exposure.

### Laboratory tests

- Hemoglobin: decreased
- MCV: normocytic
- Reticulocyte count and reticulocyte production index: increased
- Unconjugated bilirubin: increased
- LDH: increased (esp. in intravascular hemolysis)
- **Haptoglobin: reduced**

### Microangiopathic anemia

- The patient's newly diagnosed heart murmur along with new anemia and schistocytes indicate aortic stenosis as the underlying cause.
- Aortic stenosis** → mechanical destruction of RBCs (as they travel through the narrowed aortic opening) → microangiopathic anemia
- Schistocytes** are fragmented RBCs. Also called helmet cells, they are pathognomonic of microangiopathic hemolytic anemias.

### Zieve syndrome

- triad of jaundice, hemolytic anemia, and hyperlipidemia.**
- Hepatic dysfunction is usually evident in all cases.
- Hemolytic anemia is reversible.
- Hyperlipidemia due to excess alcohol intake causes metabolic and osmotic abnormalities in (RBCs), making them very susceptible to hemolysis.
- Peripheral blood smear reveals:
  - normocytic normochromic anemia
  - acanthocytes**
    - Acanthocytes are also called spur cells.
    - They have multiple projections on their surface caused by hyperlipidemia.
- Definitive treatment → alcohol cessation.

Zieve's syndrome should be suspected whenever there is anemia and elevation of unconjugated bilirubin in the setting of acute alcohol intake with no obvious sign of gastrointestinal bleeding.

### Autoimmune haemolytic anaemia (AIHA)

- Autoimmune haemolytic anaemia (AIHA) may be divided into 'warm' and 'cold' types, according to at what temperature the antibodies best cause haemolysis.
- It is most commonly idiopathic but may be secondary to a lymphoproliferative disorder, infection or drugs.
- AIHA is characterised by a positive direct antiglobulin test (Coombs' test)**

#### Warm AIHA

- In warm AIHA the antibody (usually IgG) causes haemolysis best at body temperature and haemolysis tends to occur in **extravascular** sites, for example the spleen. Management options include steroids, immunosuppression and splenectomy.
- Causes of warm AIHA**
  - autoimmune disease:** e.g. systemic lupus erythematosus\*
    - SLE can rarely be associated with a mixed-type AIHA
  - neoplasia: e.g. lymphoma, CLL
  - drugs: e.g. methyldopa, Penicillins, Cephalosporins, levodopa, NSAIDs and Quinidine
    - treated by → stopping the drug ± short course of oral prednisolone.
- The bone marrow responds by increasing RBCs production, which will be evident in peripheral blood by increase in the reticulocytes, immature RBCs, which will have high MCV.
- Management** options include steroids, immunosuppression and splenectomy.

- Blood transfusion can be life-saving until immunosuppression can take effect.
- All patients with active haemolysis are at risk of acquiring folate deficiency due to increased metabolic demands and all should receive **folic acid** replacement therapy.

### Cold AIHA

- The antibody in cold AIHA is usually **IgM** and causes haemolysis best at 4 deg C.
- Haemolysis is mediated by complement and is more commonly **intravascular**.
- **Causes of cold AIHA**
  - neoplasia: e.g. lymphoma
  - **infections:** e.g. mycoplasma, EBV
  - **Secondary cold agglutinin disease typically presents with anaemia and haemoglobinuria due to intravascular haemolysis two to three weeks following infection** such as with:
    - *Mycoplasma pneumoniae*
    - Viruses (EBV, CMV, etc)
    - Legionnaires' disease
    - Malaria → **The best diagnostic test → Cold agglutinin titre**
  - Cold agglutinins occur normally but at very low titres.
- Features may include symptoms of Raynaud's and acrocyanoasis
- Patients respond less well to steroids

	<b>Warm AIHA</b>	<b>Cold AIHA</b>
Definition	haemolysis best at body temperature	haemolysis best at 4 deg C
Antibody	<b>IgG</b>	<b>IgM</b>
Site of haemolysis	<b>extravascular</b> (e.g.: spleen)	<b>intravascular</b>
Causes	<ul style="list-style-type: none"> <li>• <b>autoimmune disease:</b> e.g. systemic lupus erythematosus</li> <li>• neoplasia: e.g. lymphoma, CLL</li> <li>• drugs: e.g. methyldopa</li> </ul>	<ul style="list-style-type: none"> <li>• neoplasia: e.g. lymphoma</li> <li>• <b>infections:</b> e.g. mycoplasma, EBV</li> </ul>
Treatment	steroids, immunosuppression and splenectomy.	respond less well to steroids

### Paroxysmal cold haemoglobinuria (PCH)

- a rare type of autoimmune haemolytic anaemia (AIHA) occurring primarily in children/adolescent.
- The classic symptom is a sudden onset of haemoglobinuria following exposure to cold, even for a few minutes.
- Symptoms may occur minutes to hours following exposure to cold.
- Haemoglobinuria is not always present because in some persons with PCH the autoantibody level is not high enough to cause intravascular haemolysis.
- **The direct agglutination test (DAT) (Coomb's test) is usually negative.**

**Cold agglutinin disease**

- caused by autoantibodies that react at temperatures < 37 °C,
- typical causes are:
  - lymphoproliferative disorders,
  - infections such as mycoplasma or Epstein–Barr virus.
  - Around 50% of cases are idiopathic.
  - **Non-Hodgkin's lymphoma is more typically associated with cold agglutinins than Hodgkin's.**

**Hook effect**

- Also called or the **prozone effect**
- In agglutination test, a person's serum (which contains antibodies) is added to a test tube, which contains a particular antigen.
- If the antibodies agglutinate with the antigen to form immune complexes, then the test is interpreted as positive.
- However, if too many antibodies are present that can bind to the antigen, then the antigenic sites are coated by antibodies, and few or no antibodies directed toward the pathogen are able to bind more than one antigenic particle. Since the antibodies do not bridge between antigens, no agglutination occurs. Because no agglutination occurs, the test is interpreted as negative. In this case, the result is a false negative.
- The range of relatively high antibody concentrations within which no reaction occurs is called the prozone.
- The effect can also occur because of antigen excess, when both the capture and detection antibodies become saturated by the high analyte concentration. In this case, no sandwich can be formed by the capturing antibody, the antigen and the detection antibody. In this case, free antigen is in competition with captured antigen for detection antibody binding.
- Examples include:
- high levels of syphilis antibodies in HIV patients or high levels of cryptococcal antigen leading to false negative tests in undiluted samples.
- This phenomenon is also seen in serological tests for Brucellosis.
- when the serum is diluted, the blocking antibody is as well and its concentration decreases enough for the proper precipitation reaction to occur.

**Hereditary spherocytosis****Epidemiology**

- most common hereditary haemolytic anaemia in people of northern European descent

**Aetiology**

- **autosomal dominant** defect of red blood cell cytoskeleton
- the most frequent cause is a mutation in the spectrin gene;
  - spectrin is a component of the red cell membrane.
- **The most common mutation in a Northern European population is a combined spectrin and ankyrin mutation**, which is found in 40–65% of patients.
- the normal biconcave disc shape is replaced by a sphere-shaped red blood cell
- red blood cell survival reduced as destroyed by the spleen

**Pathophysiology**

- Genetic mutation → Defects in RBC membrane proteins (especially spectrin and/or ankyrin) responsible for tying the inner membrane skeleton with the outer lipid bilayer → Continuous loss of lipid bilayer components → Decreased surface area of RBCs in relation to volume → Sphere-shaped RBCs with decreased membrane stability → Inability to change form while going through narrowed vessels:

- Entrapment within splenic vasculature → Splenomegaly
- Destruction via splenic macrophages → Extravascular hemolysis

### Features

Patient with hereditary spherocytosis + acute abdomen → think of: Biliary colic or rupture spleen.

normocytic anaemia, gallstones and family history → hereditary spherocytosis

- failure to thrive
- Congenital skeletal abnormalities (eg, tower-shaped skull, polydactylism) occasionally occur.
- Anemia and pallor
- jaundice ( $\uparrow$ unconjugated bilirubin)
- gallstones (pigment stones)
  - common and may be the presenting symptom
  - (made of calcium bilirubinate)
  - may lead to cholecystitis
- Splenomegaly with left upper quadrant pain
- aplastic crisis precipitated by parvovirus infection

### Complications

- Aplastic crisis
  - can be triggered by parvovirus B19 infection.

### Investigations

- Normocytic anemia (normal MCV)
- increase in both RDW and **MCHC** (the high MCHC, indicating hyperdense cells)
- Findings of hemolytic anemia
  - $\uparrow$  Unconjugated bilirubin
  - $\uparrow$  LDH
  - $\downarrow$  Haptoglobin
  - Reticulocytosis
- Direct antiglobulin (direct Coombs) test
  - to exclude autoimmune hemolytic anemia (positive Coombs test), since spherocytosis is seen in both clinical presentations
  - Direct Coombs' test is negative in Hereditary spherocytosis, as it is not an immune haemolysis
- Eosin-5-maleimide binding test (**EMA**): **test of choice**, as results are readily available (within two hours)
- Osmotic fragility test (Rupture of Spherocytes in mildly hypotonic solution),
  - unreliable and is no longer recommended in routine clinical practice.
  - this has now been replaced by the **eosin-5-maleimide binding to red cells** and then being detected by **flow cytometry**.
- Osmotic gradient elktacytometry
  - used to differentiate hereditary spherocytosis from hereditary stomatocytosis, but is only available in specialised laboratories.
- If the diagnosis is equivocal, the cryohaemolysis test and EMA binding can be used.
- In atypical cases, gel electrophoresis analysis of erythrocyte membranes is the test of choice.
- Blood smear
  - Characteristic spherocytes (absent central pallor)
  - Potentially anisocytosis
- Ultrasound:
  - to evaluate gallbladder complications

**Diagnosis**

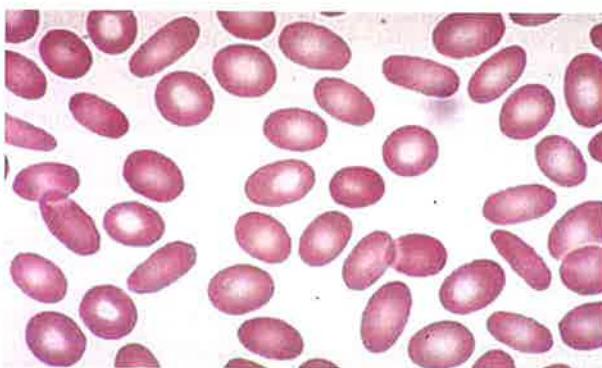
1. The first step in analysis of a spherocytic hemolytic anaemia is → direct antiglobulin test (to determine whether the process is hemolytic or not).
2. If negative → confirm HS with other tests.
3. The osmotic fragility test is unreliable and is no longer recommended in routine clinical practice.
4. Osmotic gradient ektacytometry is used to differentiate hereditary spherocytosis from hereditary stomatocytosis

**Management**

- supportive for most patients: folate replacement
- splenectomy
  - best avoided until at least 6 years of age to reduce the risk of post-splenectomy sepsis.
  - It is important to rule out stomatocytosis where splenectomy is contraindicated because of the thrombotic risk.

**Hereditary elliptocytosis (HE)**

- autosomal dominant condition.
- Elliptocytosis is usually caused by spectrin and spectrin-protein 4.1 defects.
- **Horizontal** membrane protein defects (for example, spectrin ankyrin interaction defect) results in **HE** whereas vertical defects result in hereditary **spherocytosis**.
- **Features**
  - Clinical manifestations range from an asymptomatic carriage to severe haemolytic anaemia.
  - Most patients with HE or its variants lead healthy lives.
  - The degree of haemolysis does not correlate with the percentage of elliptocytes seen in the blood.
  - presence of cigar-shaped elliptocytes on the peripheral blood smear (The hallmark of HE)
  - Elliptocytes are **normochromic and normocytic** and range from few to 100% of erythrocytes.
- Complication
  - Aplastic crisis
- Treatment
  - **Heterozygotes are asymptomatic but show elliptocytes on blood film; they do not have haemolysis and do not require any particular treatment**
  - The treatment for symptomatic hereditary elliptocytosis is splenectomy.



Hereditary elliptocytosis

## Glucose-6-phosphate dehydrogenase (G6PD) deficiency

### Basics

- (G6PD) plays a vital role in the hexose monophosphate pathway
- It is involved in the oxidation of glucose 6-phosphate to 6-phosphoglycerate. This oxidation reaction is needed in RBCs as it provides the only source of **NADPH**
- NADPH → maintains the level of glutathione → protect the RBCs against oxidative damage from compounds like hydrogen peroxide

### Prevalence

- G6PD deficiency is the commonest red blood cell enzyme defect.
- It is more common in people from the Mediterranean, Africa and Chinese

### Aetiology

- inherited in a **X-linked recessive** fashion.
- Homozygotes and heterozygotes can be symptomatic, although the disease typically is more severe in persons who are homozygous for the deficiency.

### Factors which Precipitates crisis:

- infections (the most common cause)
- drugs
- broad (fava) beans
  - Favism is most common in persons with G6PD class II variants, but rarely it can occur in patients with the G6PD A-variant (Class III → African descent).
- henna

### Pathophysiology

- ↓ G6PD → ↓ glutathione → increased red cell susceptibility to oxidative stress
- The haemolytic anaemia is non-immune (direct antiglobulin test [DAT] negative).

### Features

- usually asymptomatic
- neonatal jaundice is often seen
- intravascular haemolysis
  - **Decreased haptoglobin levels**, hematuria, and presence of urinary hemosiderin indicate severe intravascular hemolysis.
- acute hemolysis can cause back or abdominal pain and jaundice secondary to a rise in unconjugated bilirubin
  - Jaundice, in the setting of normal liver function, typically does not occur until > 50% of the erythrocytes have been hemolyzed.
- gallstones are common
- splenomegaly may be present
- **Heinz bodies** (denatured hemoglobin) on blood films

### Diagnosis:

- made by using a G6PD enzyme assay
- usually done by **fluorescent spot test** detecting the generation of NADPH from NADP.
  - The test is positive if the blood spot fails to fluoresce under ultraviolet light.
- In patients with acute hemolysis, testing for G6PD deficiency may be falsely negative because older erythrocytes with a higher enzyme deficiency have been hemolyzed. Young erythrocytes and reticulocytes have normal or near-normal enzyme activity.
- Female heterozygotes may be hard to diagnose because of X-chromosome mosaicism leading to a partial deficiency that will not be detected reliably with screening tests.
- **Acute haemolytic reaction**
  - Blood count is normal between attacks of haemolysis
  - During an attack the blood film may show:
    - irregularly contracted cells
    - bite cells

- blister cells
- Heinz bodies
- Reticulocytosis
- Peripheral blood smear → **Heinz bodies** (rarely seen in clinical practice)
- Reticulocyte count: Increases four to seven days after hemolysis
- Haptoglobin → Decreased

### Treatment

- avoidance exposure to an oxidative stressor in the form of an infection, oxidative drug, or fava beans
- Acute hemolysis is self-limited, but in rare instances it can be severe enough to warrant a blood transfusion
  - Hemolysis typically occurs 24 to 72 hours after ingestion, with resolution within 4 to 7 days.
- **Methaemoglobinemia in G6PD-deficient patients is best treated with exchange transfusion.**

### Some drugs causing haemolysis

- anti-malarials: primaquine
- Quinine/quinidine.
- Ciprofloxacin
- Nitrofurantoin
- chloramphenicol
- **sulph-** group drugs: **sulphonamides, sulphasalazine, sulfonylureas**
- vitamin K, probenecid
- aspirin and (NSAIDs)

### Some drugs thought to be safe

- penicillins
- cephalosporins
- macrolides
- tetracyclines
- trimethoprim
  - In "Co-trimoxazole": the **sulfamethoxazole** causes haemolysis in G6PD, not the trimethoprim.

### Comparing G6PD deficiency to hereditary spherocytosis:

	G6PD deficiency	Hereditary spherocytosis
Gender	Male (X-linked recessive)	Male + female (autosomal dominant)
Ethnicity	African + Mediterranean descent	Northern European descent
Typical history	<ul style="list-style-type: none"> <li>• Neonatal jaundice</li> <li>• Infection/drugs precipitate haemolysis</li> <li>• Gallstones</li> </ul>	<ul style="list-style-type: none"> <li>• Neonatal jaundice</li> <li>• Chronic symptoms although haemolytic crises may be precipitated by infection</li> <li>• Gallstones</li> <li>• Splenomegaly is common</li> </ul>
Blood film	Heinz bodies	Spherocytes (round, lack of central pallor)
Diagnostic test	Measure enzyme activity of G6PD	Osmotic fragility test

### Other notes

- G6PD deficiency confers partial protection against malaria
- Hemolysis begins 24 to 72 hours after exposure to oxidant stress.
- Hemolysis due to oxidant stresses are usually self-limiting within 8 to 14 days due to the compensatory production of young red blood cells with high levels of G6PD.
- Young RBCs are not vulnerable to oxidative damage and hence limit the duration of hemolysis.
- G6PD deficiency is an X-linked inherited disease that primarily affects men.
- Women may be affected if:
  - they are **homozygous**, which occurs in populations in which the frequency of G6PD deficiency is quite high.
  - Heterozygous women (carriers) can experience clinical disease as a result of:
    1. X chromosome inactivation,
    2. gene mosaicism, or
    3. hemizygosity
- Severe hemolysis due to G6PD deficiency may manifest as **methemoglobinemia**

### **Paroxysmal nocturnal haemoglobinuria (PNH)**

The triad of hemolytic anemia, pancytopenia, and thrombosis → PNH

- (PNH) is an acquired disorder leading to haemolysis (mainly intravascular) of hematological cells.
- Caused by increased sensitivity of cell membranes to complement **due to a lack of glycoprotein glycosyl-phosphatidyl-inositol (GPI)**.
- Patients are more prone to venous thrombosis
- **50% of PNH affected individuals are died due to thrombotic complications**

### Pathophysiology

- GPI can be thought of as an anchor which attaches surface proteins to the cell membrane
- complement-regulating surface proteins, e.g. decay-accelerating factor CD 55 (DAF) and Membrane Inhibitor of Reactive Lysis CD 59 (MIRL), are not properly bound to the cell membrane due a lack of GPI
- Hemolysis occurs when patients develop a mild acidosis at night, due to a relative hypoventilation, resulting in the passage of dark urine in the early morning.
- **thrombosis is thought to be caused by a lack of CD59 on platelet membranes** predisposing to platelet aggregation
- Intrinsic hemolytic anemia with intravascular hemolysis

### Features

- symptoms of anemia (Pallor, fatigue, weakness)
- Intermittent jaundice
- haemoglobinuria
  - classically dark-coloured urine in the morning (although has been shown to occur throughout the day)
- Abdominal pain
  - may be due to small mesenteric vein thrombi.

### Complications

- thrombosis e.g. Budd-Chiari syndrome
- Vasoconstriction: headache, pulmonary hypertension
- aplastic anaemia may develop in some patients
- ↑ Risk of acute leukemias

### Investigations

- CBC
  - haemolytic anaemia
  - pancytopenia
- Dipstick analysis of the urine:

- will be positive for 'blood', but the microscopy will show no red blood cells.
  - This because there is intravascular haemolysis, with intravascular release of haemoglobin. This then passes through the renal tubules, ending up in the urine, and turning the dipstick analysis positive. However, because there are no actual red blood cells in the urine, the microscopy will be negative.
- **Flow cytometry (immunophenotyping) of blood**
  - absence of CD55 and CD59 on the surface of RBCs
  - now replaced Ham's test as the gold standard investigation in PNH
- Ham's test:
  - acid-induced haemolysis (normal red cells would not)
  - acidified serum (pH 6.2) is added to blood: PNH cells, but not normal cells, will be lysed.
- Coombs test: negative

#### **Management**

- blood product replacement
- anticoagulation
- **eculizumab**, a monoclonal antibody directed against terminal protein C5 (C5 inhibitor), is reducing intravascular haemolysis
- stem cell transplantation
  - The gold standard curative treatment

#### **Splenectomy**

- Following a splenectomy patients are particularly at risk of infections from:
  - pneumococcus,
  - Haemophilus,
  - meningococcus and
  - Capnocytophaga canimorsus\* (\*usually from dog bites)
- Vaccination
  - if elective, should be done 2 weeks prior to operation
  - Hib, meningitis A & C
  - annual influenza vaccination
  - pneumococcal vaccine every 5 years
- Antibiotic prophylaxis
  - penicillin V: unfortunately clear guidelines do not exist of how long antibiotic prophylaxis should be continued. It is generally accepted though that penicillin should be continued for at least 2 years and at least until the patient is 16 years of age, although the majority of patients are usually put on antibiotic prophylaxis for life

## Blood products

### Whole blood fractions

Fraction	Key points
Packed red cells	<ul style="list-style-type: none"> <li>Used for transfusion in chronic anaemia and cases where infusion of large volumes of fluid may result in cardiovascular compromise.</li> <li>Product obtained by centrifugation of whole blood.</li> <li><b>In a stable patient, red cell packs may be transfused over 90-120 minutes</b> <ul style="list-style-type: none"> <li>➢ Rapid infusion of red cells or fresh frozen plasma may be required in an acutely bleeding patient but not in patient who is stable.</li> </ul> </li> </ul>
Platelet rich plasma	<ul style="list-style-type: none"> <li>Usually administered to patients who are thrombocytopenic and are bleeding or require surgery.</li> <li>It is obtained by <u>low speed</u> centrifugation.</li> </ul>
Platelet concentrate	<ul style="list-style-type: none"> <li>Prepared by <u>high speed</u> centrifugation</li> <li>administered to patients with thrombocytopenia.</li> <li><b>the life span of transfused platelets is only 3-7 days.</b></li> <li><b>platelet transfusion should not take more than 20-30 minutes.</b></li> <li><b>Patients who are refractory to platelet transfusions:</b> <ul style="list-style-type: none"> <li>➢ <b>should be first investigated to check for adequate platelet rises. This is best done on a one or two-hour post platelet transfusion sample.</b></li> <li>➢ Further test would include checking for HLA antibodies</li> </ul> </li> </ul>
Fresh frozen plasma	<ul style="list-style-type: none"> <li>Prepared from single units of blood.</li> <li>Contains clotting factors, albumin and immunoglobulin.</li> <li>Unit is usually 200 to 250ml.</li> <li>Usually used in correcting clotting deficiencies in patients with hepatic synthetic failure who are due to undergo surgery.</li> <li>Usual dose is 12-15ml/Kg<sup>-1</sup>.</li> <li>It should not be used as first line therapy for hypovolaemia.</li> </ul>
Cryoprecipitate	<ul style="list-style-type: none"> <li>Formed from supernatant of FFP.</li> <li>Rich source of Factor VIII and fibrinogen.</li> <li>Allows large concentration of factor VIII to be administered in small volume.</li> </ul>
SAG-Mannitol Blood	<p>Removal of all plasma from a blood unit and substitution with:</p> <ul style="list-style-type: none"> <li>Sodium chloride</li> <li>Adenine</li> <li>Anhydrous glucose</li> <li>Mannitol</li> </ul> <p>Up to 4 units of SAG M Blood may be administered. Thereafter whole blood is preferred. After 8 units, clotting factors and platelets should be considered.</p>

### Plasma derivatives

- plasma derivatives (such as factor VIII) are prepared from several thousand plasma donations, typically 20,000, or 5,000 kg of plasma at a time.
- Pooled plasma** has been sourced from outside the UK since 1999 to avoid vCJD risks.

- The process involves several chemical steps including:
  - ethanol extraction,
  - chromatography, and
  - **viral inactivation steps which results in a freeze-dried product.**
- These products have a long shelf life of several months to years.

### Cell saver devices

These collect patients own blood lost during surgery and then re-infuse it. There are two main types:

- Those which wash the blood cells prior to re-infusion. These are more expensive to purchase and more complicated to operate. However, they reduce the risk of re-infusing contaminated blood back into the patient.
- Those which do not wash the blood prior to re-infusion.

Their main advantage is that they avoid the use of infusion of blood from donors into patients and this may reduce risk of blood borne infection. It may be acceptable to Jehovah's witnesses. It is contraindicated in malignant disease for risk of facilitating disease dissemination.

### Blood products used in warfarin reversal

Immediate or urgent surgery in patients taking warfarin:

1. Stop warfarin
2. Vitamin K (reversal within 4-24 hours)
  - IV takes 4-6h to work (at least 5mg)
  - Oral can take 24 hours to be clinically effective
3. Fresh frozen plasma
  - Used less commonly now as 1st line warfarin reversal
  - 30ml/kg<sup>-1</sup>
  - Need to give at least 1L fluid in 70kg person (therefore not appropriate in fluid overload)
  - Need blood group
  - Only use if human prothrombin complex is not available
4. Human Prothrombin Complex (reversal within 1 hour)
  - Bereplex 50 u/kg
  - Rapid action but factor 6 short half life, therefore give with vitamin K

### Neonatal exchange transfusion

- An exchange transfusion requires blood which is plasma reduced whole blood in CPD (citrate phosphate dextrose/anticoagulant), irradiated and less than five days old.
- The Rh group should either be Rh negative or identical to the neonate, to avoid haemolytic transfusion reaction in the neonate.

#### Blood Transfusion Thresholds

- Sepsis: 7 g/dL
- Upper or lower GI bleeds: 7 g/dL
- Acute neurologic injury or TBI : 7 g/dL
- Stable CV disease: 8 g/dL
- ACS: 10 g/dL

## Blood product transfusion complications

### Complications

- haemolytic: immediate or delayed
- febrile reactions
- transmission of viruses, bacteria, parasites, **vCJD**
- hyperkalaemia
- iron overload
- ARDS
- clotting abnormalities

### Immediate haemolytic reaction

- occur during the transfusion.
- e.g. ABO mismatch
- massive intravascular haemolysis

### Delayed haemolytic transfusion reaction

- occurs 24 hours after the transfusion.
- This happens in a patient who has been previously immunised by transfusions or pregnancy. The antibodies are not detectable initially but become obvious as a secondary immune response to the antigen exposure during the transfusion occurs.

### Febrile reactions

- due to anti HLA antibodies in recipient serum or granulocyte specific antibodies (for example, sensitisation during previous pregnancy or previous blood transfusion).
- Febrile non-haemolytic reactions are very common and are **due to the presence of pyrogenic cytokines released from leucocytes during storage** of the blood units.
  - apart from a mild fever, the patient is very well.
  - ❖ rapid rise in temperature may be due to ABO incompatibility, but With ABO incompatibility patients become shocked very quickly.

### Rhesus D mismatch

- It is very often necessary to give D positive platelets to D negative people due to platelet shortage.
- If the recipient of this mismatch is a female of child bearing age, then prophylactic anti- D should be administered with the platelets to prevent production of immune anti- D.
- If anti-D does not administered, the immune anti-D she has made can cross the placenta when she become pregnant in the future and cause haemolytic disease of the fetus/newborn, if the baby is D positive, and this can be life threatening to the baby.
  - **Advise patient that this is only likely to be of consequence should she become pregnant in the future.**

### Causes a degree of immunosuppression

- e.g. patients with colorectal cancer who have blood transfusions have a worse outcome than those who do not

### The risk of viral transmission

- A broad knowledge of the risks may be required while consenting a patient for blood transfusion.
- in the United Kingdom, the risks;
  - **For hepatitis B are 1 per 1.3 million donations**
  - For HIV are 1 in 6.5 million and
  - For hepatitis C 1 in 28 million donations.

### Transmission of vCJD

- although the absolute risk is very small, **vCJD may be transmitted via blood transfusion**
- a number of steps have been taken to minimise this risk, including:
- → from late 1999 onward, all donations have undergone removal of white cells (leucodepletion) in order to reduce any vCJD infectivity present

- from 1999, plasma derivatives have been fractionated from imported plasma rather than being sourced from UK donors. Fresh Frozen Plasma (FFP) used for children and certain groups of adults needing frequent transfusions is also imported
- from 2004 onward, recipients of blood components have been excluded from donating blood

### iron overload

- secondary to chronic blood transfusion (eg : in myelodysplastic syndrome)
- early signs:
  - grey skin
  - early heart failure
  - diabetes
- treatment:
  - **iron chelation with desferrioxamine subcutaneously**
  - ❖ bind iron
  - ❖ needs to be given for 8 – 12 hours a day for 5 – 7 days per week
  - common side effects of desferrioxamine:
    - ❖ high frequency deafness
    - ❖ retinopathy
    - ❖ Yersinia infection

### irradiated blood products

- the advantage of irradiated red cells**
  - **Inactivates donor lymphocytes**
- Indications for irradiated blood products**
  - Those at risk of transfusion associated with graft versus host disease such as neonates
  - **Those receiving purine analogues-based chemotherapy**
  - **Hodgkin's lymphoma**
  - Immunodeficiency states
  - Post bone marrow transplants

### Pre-operative request for the blood bank for elective surgeries

- Group and save only**
  - A 'group and save' is adequate for elective surgeries and is standard practice in most modern blood banks. This will involve blood grouping and its confirmation as well as an antibody screen.
  - Other options include cross match and a direct Coombs' test are not routinely done for elective surgery

### Transfusion errors

- Mislabelling of samples, requests, or wrongly identifying recipients are the commonest transfusion errors.

**January 2016 exam: What is the risk of variant Creutzfeldt-Jakob Disease (vCJD) transmission via blood transfusion?**

➔ Measures are taken to reduce the risk of vCJD transmission but there remains a very small risk of transmission

## **Transfusion Related Acute Lung Injury (TRALI)**

### **Definition**

- (TRALI) is a rare but serious syndrome characterized by sudden acute respiratory distress within six hours after blood product administration

### **Risk factors**

- Caused by anti-HLA, Human Neutrophil Antigens (HNA) or anti-granulocytes antibody in donor blood.
- Donor's blood sensitization occurs in:
  - Multiparous ♀ develop these antibodies through exposure to fetal blood
  - Previous transfusion
  - Transplantation patient
- When blood is obtained from above mentioned donors, it carries higher risk for recipient to develop TRALI; those who have lung pathology are more susceptible. TRALI symptoms resemble ARDS.

### **Pathophysiology**

- transfused human leukocyte or neutrophil antigen (HLA or HNA) antibodies → activation of donor neutrophils → Neutrophils adhere to pulmonary endothelium to increase permeability and cause pulmonary edema.
- Patients with certain clinical conditions (eg, infection, inflammation, surgery) have primed neutrophils that are susceptible to activation by transfused bioactive substances.
- TRALI has two proposed pathophysiologic mechanisms:
  1. the antibody hypothesis. (antigen-antibody interactions)
    - The human leukocyte antigen (HLA class I, HLA class II) or human neutrophil antigen (HNA) antibody in the transfused component reacts with neutrophil antigens in the recipient. The recipient's neutrophils lodge in the pulmonary capillaries and release mediators that cause pulmonary capillary leakage.
    - As a consequence, many patients with TRALI will develop transient leukopenia.
    - However, transfusions of blood components containing neutrophil antibodies may cause leukopenia, that do not meet the definition of TRALI.
  2. The neutrophil priming hypothesis:
    - does not require antigen-antibody interactions
    - occurs in patients with clinical conditions that predispose to neutrophil priming and endothelial activation such as infection, surgery, or inflammation.
    - Bioactive substances in the transfused component activate the primed, sequestered neutrophils, and pulmonary endothelial damage occurs.
- Both mechanisms lead to pulmonary edema in the absence of circulatory overload.

### **Feature**

- Occurring within 1 to 6 hours of transfusion of plasma-containing blood components.
- Patients present with the rapid onset of dyspnea and tachypnea.
- There may be associated fever, cyanosis, and hypotension.
- Clinical examination reveals hypoxic respiratory distress, and pulmonary crackles may be present without signs of congestive heart failure or volume overload.
- Chest x-ray (CXR) shows evidence of bilateral pulmonary edema unassociated with heart failure (non-cardiogenic pulmonary edema), with bilateral patchy infiltrates, which may rapidly progress to complete "white out" indistinguishable from acute respiratory distress syndrome (ARDS).
- Physiologic findings include acute hypoxemia with  $\text{PaO}_2/\text{FiO}_2$  less than 300 mmHg and normal cardiac function on echocardiogram.

**Diagnosis:**

- confirmed by finding of anti-HLA or anti-Neutrophil antibody in donors' or recipient blood.

**Treatment**

- Early and intensive pulmonary support reduces the risk of a fatal outcome.
- Since the pulmonary edema in TRALI is not related to fluid overload or cardiac dysfunction, but to altered vascular permeability in the lungs with exudation of fluid and protein into the alveoli, it is logical that:
  - maintenance of adequate circulating volume is the most beneficial and appropriate therapy.
  - Corticosteroids,
  - epinephrine
  - and also ventilatory support are treatment options.

**How to distinguish TRALI and ARDS from Pulmonary oedema?**

- In the exam take into account the clinical findings and scenario to distinguish.
- The hallmark of ARDS is refractory hypoxia with non-cardiogenic pulmonary edema
- Normal **pulmonary capillary wedge pressure** is between 5 - 15 mmHg. A PCWP exceeding 15 mmHg suggests mitral stenosis, mitral insufficiency, severe aortic stenosis, aortic regurgitation, ventricular failure, or other cardiac defects or pathologies.
- When the PCWP exceeds 20 mmHg, the transmission of this pressure back into the pulmonary vasculature increases pulmonary capillary hydrostatic pressure which can lead to pulmonary oedema.

**Graft versus host disease (GVHD)** See transplant topic in renal system

**Plasma exchange****Indications for plasma exchange (also known as plasmapheresis)**

- Guillain-Barre syndrome
- myasthenia gravis
- Goodpasture's syndrome
- ANCA positive vasculitis e.g. Wegener's, Churg-Strauss
- TTP/HUS
- cryoglobulinaemia
- hyperviscosity syndrome e.g. secondary to myeloma

**Deep vein thrombosis (DVT)**

Cancer patients with VTE - 6 months of LMWH

Venous thromboembolism - length of warfarin treatment

- provoked (e.g. recent surgery): 3 months
- unprovoked: 6 months

**DVT Risk Factors:**

- Hematological**
  - Thrombophilia: e.g. Activated protein C resistance, protein C and S deficiency
  - Polycythemia
  - Paroxysmal nocturnal hemoglobinuria
  - Hyperviscosity syndrome
- Autoimmune**
  - Antiphospholipid syndrome
  - Behcet's

- **Drugs**
  - Combined oral contraceptive pill: 3rd generation more than 2nd generation
  - Antipsychotics (especially olanzapine) have recently been shown to be a risk factor
  
- **Other conditions**
  - Homocystinuria

### Diagnosis

If a patient is suspected of having a DVT a two-level DVT Wells score should be performed:

#### Two-level DVT Wells score

Clinical feature	Points
Active cancer (treatment ongoing, within 6 months, or palliative)	1
Paralysis, paresis or recent plaster immobilisation of the lower extremities	1
Recently bedridden for 3 days or more or major surgery within 12 weeks requiring general or regional anaesthesia	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than asymptomatic side	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
An alternative diagnosis is at least as likely as DVT	-2

#### Clinical probability simplified score

- DVT likely: 2 points or more
- DVT unlikely: 1 point or less

#### If a DVT is 'likely' (2 points or more)

- a proximal leg vein ultrasound scan should be carried out within 4 hours and, if the result is negative, a D-dimer test
- if a proximal leg vein ultrasound scan cannot be carried out within 4 hours a D-dimer test should be performed and low-molecular weight heparin administered whilst waiting for the proximal leg vein ultrasound scan (which should be performed within 24 hours)

#### If a DVT is 'unlikely' (1 point or less)

- perform a D-dimer test and if it is positive arrange:
  - a proximal leg vein ultrasound scan within 4 hours
  - if a proximal leg vein ultrasound scan cannot be carried out within 4 hours low-molecular weight heparin should be administered whilst waiting for the proximal leg vein ultrasound scan (which should be performed within 24 hours)

#### Management

Low molecular weight heparin (LMWH) or fondaparinux should be given initially after a DVT is diagnosed.

- a vitamin K antagonist (i.e. warfarin) should be given within 24 hours of the diagnosis

- the LMWH or fondaparinux should be continued for at least 5 days or until the international normalised ratio (INR) is 2.0 or above for at least 24 hours, whichever is longer, i.e. LMWH or fondaparinux is given at the same time as warfarin until the INR is in the therapeutic range
- warfarin should be continued for at least 3 months. At 3 months, NICE advise that clinicians should 'assess the risks and benefits of extending treatment'
- NICE add 'consider extending warfarin beyond 3 months for patients with *unprovoked* proximal DVT if their risk of VTE recurrence is high and there is no additional risk of major bleeding'. This essentially means that if there was no obvious cause or provoking factor (surgery, trauma, significant immobility) it may imply the patient has a tendency to thrombosis and should be given treatment longer than the norm of 3 months. In practice most clinicians give 6 months of warfarin for patients with an unprovoked DVT/PE
- for patients with active cancer NICE recommend using LMWH for 6 months
- for patients with active ulcerative colitis who developed DVT :**
  - may require Emergency colectomy, as such warfarinisation would be inappropriate.
  - should be heparinised** as this would be easily reversible if it needs to be discontinued prior to surgery or if severe worsening of bleeding occurs.

#### Time of starting prophylaxis in elective knee replacement surgery:

- LMWH or fondaparinux (s/c factor X inhibitor) → should be started 6 – 12 hours after surgery
- Dabigatran (oral factor X inhibitor) → 1 – 4 hours after surgery

#### Unprovoked VTE

##### → (Malignancy investigations and thrombophilia screening)

- As both malignancy and thrombophilia are obvious risk factors for deep vein thrombosis NICE make recommendations on how to investigate patients with unprovoked clots.

#### Malignancy investigations

- Offer all patients diagnosed with unprovoked DVT or PE who are not already known to have cancer the following investigations for cancer:
  - a physical examination (guided by the patient's full history) and
  - a **chest X-ray** and
  - blood tests (full blood count, serum calcium and liver function tests) and **urinalysis**.
- Consider further investigations for cancer with an abdomino-pelvic CT scan (and a mammogram for women) in all patients aged over 40 years with a first unprovoked DVT or PE

#### Thrombophilia screening

- not offered if patients will be on lifelong warfarin (i.e. won't alter management)
- consider testing for antiphospholipid antibodies if unprovoked DVT or PE
- consider testing for hereditary thrombophilia in patients who have had unprovoked DVT or PE and who have a first-degree relative who has had DVT or PE

#### The next most important investigation:

- Unprovoked VTE → chest X-ray, blood tests and urinalysis
- Unprovoked VTE + family history of VTE → Thrombophilia screening

## Pregnancy: DVT/PE

### Coagulation elements in pregnancy:

- Increased → factors VII, VIII, IX, X, and XII, fibrinogen, plasminogen, and D-dimer.
- **Decreased → factor XI and protein S.**
- Not changed → Factor II, protein C, and anti-thrombin III.

### Overview

- pregnancy is a hypercoagulable state
- majority occur in last trimester

### Pathophysiology

- increase in factors VII, VIII, X and fibrinogen
- **decrease in protein S**
- uterus presses on IVC causing venous stasis in legs

### Management

- warfarin contraindicated
- S/C low-molecular weight heparin preferred to IV heparin (less bleeding and thrombocytopenia)

## Post-thrombotic syndrome

- It is increasingly recognised that patients may develop complications following a DVT.
- Venous outflow obstruction and venous insufficiency result in chronic venous hypertension.
- The resulting clinical syndrome is known as post thrombotic syndrome.

### Features

- painful, heavy calves
- pruritus
- swelling
- varicose veins
- venous ulceration

### Management

- **Compression stockings** should be offered to all patients with deep vein thrombosis to help reduce the risk of post-thrombotic syndrome.
- NICE state the following:
  - Offer below-knee graduated compression stockings with an ankle pressure greater than 23 mmHg to patients with proximal DVT a week after diagnosis or when swelling is reduced sufficiently and if there are no contraindications, and:
    - advise patients to continue wearing the stockings for at least 2 years
    - ensure that the stockings are replaced two or three times per year or according to the manufacturer's instructions
    - advise patients that the stockings need to be worn only on the affected leg or legs.

## Venous thromboembolism: prophylaxis in patients admitted to hospital

Venous thromboembolism (VTE) still accounts for a significant proportion of avoidable hospital deaths. In an effort to tackle this problem NICE produced guidelines in 2010.

### Before admission

- advise women to consider stopping oestrogen-containing oral contraception or HRT 4 weeks before surgery.

- assess the risks and benefits of stopping antiplatelet therapy 1 week before surgery.

### The following patients are deemed at risk of VTE

#### Medical patients

- if mobility significantly reduced for  $\geq 3$  days **or**
- if expected to have ongoing reduced mobility relative to normal state plus any VTE risk factor (see below)

#### Surgical patients and patients with trauma

- if total anaesthetic + surgical time  $> 90$  minutes **or**
- if surgery involves pelvis or lower limb and total anaesthetic + surgical time  $> 60$  minutes **or**
- if acute surgical admission with inflammatory or intra-abdominal condition **or**
- if expected to have significant reduction in mobility **or**
- if any VTE risk factor present (see below)

#### VTE risk factors

- active cancer or cancer treatment
- age  $> 60$  years
- critical care admission
- dehydration
- known thrombophilias
- obesity ( $BMI > 30 \text{ kg/m}^2$ )
- one or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)
- personal history or first-degree relative with a history of VTE
- use of HRT
- use of oestrogen-containing contraceptive therapy
- varicose veins with phlebitis

#### In-patient VTE prophylaxis

As a general rule pharmacological VTE prophylaxis is used for medical patients unless there is a contraindication.

For surgical patients mechanical VTE prophylaxis is offered for patients at risk. Pharmacological VTE prophylaxis is also given for if the risk of major bleeding is low.

#### Pharmacological VTE prophylaxis options:

- fondaparinux sodium
- low molecular weight heparin (LMWH)
- unfractionated heparin (UFH) (for patients with renal failure)

#### Mechanical VTE prophylaxis options:

- anti-embolism stockings (thigh or knee length)
- foot impulse devices
- intermittent pneumatic compression devices (thigh or knee length)

#### Post-procedure VTE prophylaxis

For certain procedures pharmacological VTE prophylaxis is recommended for all patients, using one of the following:

- dabigatran, started 14 hours after surgery
- fondaparinux, started 6 hours after surgery
- LMWH, started 6-12 hours after surgery
- rivaroxaban, started 6-10 hours after surgery.
- Apixaban

Procedure	Length of prophylaxis
Elective hip	28-35 days
Elective knee	10-14 days
Hip fracture	28-35 days

## Superficial thrombophlebitis

- Superficial thrombophlebitis, as the name suggests describes the inflammation associated with thrombosis of one of the superficial veins, usually the long saphenous vein of the leg.
- This process is usually non-infective in nature but secondary bacterial infection may rarely occur resulting in septic thrombophlebitis.
- Around 20% with superficial thrombophlebitis will have an underlying deep vein thrombosis (DVT) at presentation and 3-4% of patients will progress to a DVT if untreated.
- The risk of DVT is partly linked to the length of vein affected - an inflamed vein > 5 cm is more likely to have an associated DVT.

### **Management**

- Traditionally NSAIDs have been used, with topical NSAIDs for limited and mild disease and oral NSAIDs for more severe disease.
- Topical heparinoids have also been used in the management of superficial thrombophlebitis.
- A Cochrane review however found topical NSAIDs and heparinoids have no significant benefit in terms of reducing extension or progression to DVT.
- Oral NSAIDs were however shown to reduce the risk of extension by 67%.
- Compression stockings are also used.
- Remember that the ankle-brachial pressure index (ABPI) should be measured before prescribing compression stockings, particularly if using class 2 or above stockings.
- One of the major changes to the management of superficial thrombophlebitis is the increased use of low-molecular weight heparin. This has been shown to reduce extension and transformation to DVT.
- **SIGN produced guidelines in 2010:**
  - Patients with clinical signs of superficial thrombophlebitis affecting the proximal long saphenous vein should have an ultrasound scan to exclude concurrent DVT.
  - Patients with superficial thrombophlebitis should have anti-embolism stockings and can be considered for treatment with prophylactic doses of LMWH for up to 30 days or fondaparinux for 45 days.
  - If LMWH is contraindicated, 8-12 days of oral NSAIDS should be offered.
  - Patients with superficial thrombophlebitis at, or extending towards, the sapheno-femoral junction can be considered for therapeutic anticoagulation for 6-12 weeks.
- This may be a significant departure from our current practice - the majority of patients with superficial thrombophlebitis (i.e. those affecting the long saphenous vein) should be referred for an ultrasound scan.

## Thrombophilia: causes

### **inherited thrombophilias:**

- the most common → Factor V Leiden
- the higher risk of VTE → Anti-thrombin III deficiency

### **Inherited thrombophilias**

- Gain of function polymorphisms
  - factor V Leiden (activated protein C resistance): most common cause of thrombophilia
  - prothrombin gene mutation: second most common cause
- Deficiencies of naturally occurring anticoagulants
  - antithrombin III deficiency
  - protein C deficiency → **Reduced degradation of factors Va and VIIIa**

- protein S deficiency

The table below shows the prevalence and relative risk of venous thromboembolism (VTE) of the different inherited thrombophilias:

Condition	Prevalence	Relative risk of VTE
Factor V Leiden (heterozygous)	5%	4
Prothrombin gene mutation (heterozygous)	1.5%	3
Protein C deficiency	0.3%	10
Protein S deficiency	0.1%	5-10
Antithrombin III deficiency	0.02	10-20

#### Acquired thrombophilias:

- Antiphospholipid syndrome
- Drugs
  - the combined oral contraceptive pill

**NICE recommend testing for thrombophilia in case of unprovoked venous thromboembolism and family history.**

**Indications of thrombophilia testing:** Thrombophilia testing is considered useful in patients presenting with:

- A first episode of venous thromboembolism (VTE) at a young age (usually considered less than 45 years of age)
- Idiopathic venous thrombosis
- A family history of thrombosis, particularly in a first degree relative
- **VTE in an unusual vascular territory**
- Neonatal purpura fulminans
- Warfarin induced skin necrosis

## Factor V Leiden

Activated protein C resistance (Factor V Leiden) is the most common inherited thrombophilia

Factor V Leiden mutation results in activated protein C resistance

#### Epidemiology

- Factor V Leiden (activated protein C resistance) is **the most common inherited thrombophilia**, being present in around 5% of the UK population.
- present in 5-9% of the European population but is rare in people of Asian and African descent.

#### Aetiology

- It is due to a mutation in the Factor V Leiden mutation.
- mostly inherited in an autosomal dominant fashion

- caused by an amino acid substitution results in replacement of arginine with **glutamine** in the amino acid chain, that impairs the ability of activated protein C and S to **inactivate** factor Va.

#### **Pathophysiology**

- Normally, activated protein C inactivates factor V in the clotting cascade → decreases the activation of thrombin.
- However, in patients with these defects, factor V remains active → activates prothrombin → increases thrombotic events.

#### **Features**

- results in a 30% lifetime risk of VTE for homozygotes and 5-10% for heterozygotes.
- Heterozygotes have a 4-5 fold risk of venous thrombosis.

#### **Diagnosis**

- The gold standard for the diagnosis of factor V Leiden is **genetic testing** for the mutation.

#### **Management**

- **prophylaxis against thromboembolism**.
- Contraceptive medications and devices that contain the hormone estrogen should not be used
  - Non-hormonal and progesterone-only methods are safe for use in these patients
- patients with no history of VTE are **not indicated** for prolonged anticoagulation prophylaxis.

## **Protein C deficiency**

- Protein C deficiency is an **autosomal codominant** condition which causes an increased risk of thrombosis
- Protein C is synthesized in the **liver**.
- It is a relatively common thrombophilia disorder, affecting 1 in 500 individuals.

#### **Function of protein C**

- **inactivation of factors Va and VIIIa.**

#### **Features**

- venous thromboembolism
- skin necrosis following the commencement of warfarin:
  - when warfarin is first started biosynthesis of protein C is reduced. This results in a temporary procoagulant state after initially starting warfarin, normally avoided by concurrent heparin administration. Thrombosis may occur in venules leading to skin necrosis
  - The best initial step for the management of warfarin-induced skin necrosis is stopping warfarin.

#### **Diagnosis**

- **Copperhead snake venom assay**
  - the best test to detect protein-C deficiency

#### **Management**

- Patients with a history of a thrombotic event should receive prophylactic anticoagulation for **life**.

**What pathological process is most likely to be responsible for increased propensity to clot in a patient diagnosed with protein C deficiency?**

➤ **Reduced degradation of factors Va and VIIIa**

## Antithrombin III deficiency

- Antithrombin III deficiency is an inherited cause of thrombophilia occurring in approximately 1:3,000 of the population.
- Inheritance is **autosomal dominant**

### Function of Antithrombin III

- Antithrombin III inhibits several clotting factors, primarily thrombin, factors **II, IX, and X**.
  - the affinity of Antithrombin III for **Factor II and X is much greater**, and it thus has a much stronger inactivation effect on these factors.
- It mediates the effects of heparin

### Features

- recurrent venous thromboses
- arterial thromboses do occur but are uncommon

### Diagnosis

- The best initial test for diagnosing antithrombin III deficiency is **thrombin-heparin cofactor level**.

### Management

- thromboembolic events are treated with lifelong warfarinisation
- heparinisation during pregnancy\*
  - \*as patients with antithrombin III deficiency have a **degree of resistance to heparin, anti-Xa levels should be monitored** carefully to ensure adequate anticoagulation
- antithrombin III concentrates (often used during surgery or childbirth)

## Heredity haemorrhagic telangiectasia (HHT)

Heredity haemorrhagic telangiectasia - autosomal dominant

- Also known as **Osler-Weber-Rendu syndrome**
- characterised by (as the name suggests) multiple telangiectasia over the skin and mucous membranes.

### Genetic

- autosomal dominant
- Two genes: **ENG** (endoglin) and **ALK-1** (activin receptor like kinase-1) encode proteins expressed on vascular endothelial cells. Mutations in these genes cause an imbalance in angiogenesis.

### Epidemiology

- occurs in approximately 1 in 5000 of the population.
- 20 % of cases occur spontaneously without prior family history.
- commonly presents in teenagers. 62% are diagnosed by age 16.

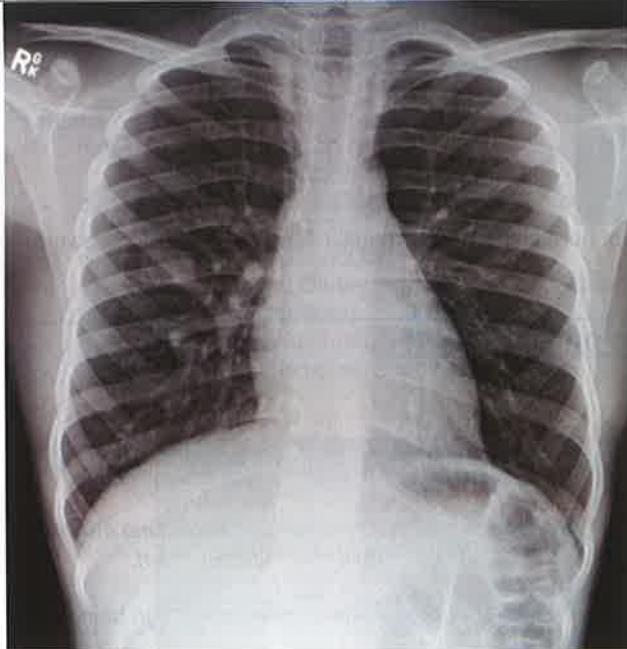
### Features and complications

- **over 90% present with nosebleeds** (**the most common initial mode of presentation**)
- GI telangiectasias and arteriovenous malformations (AVMS) may cause chronic slow bleeding leading to iron deficiency **anemia**
- AVMS in the respiratory system may cause **dyspnoea and cyanosis and paradoxical cerebral emboli**.
- GI telangiectasias and arteriovenous malformations may cause **acute haemorrhage**
- In the brain AVMS, angiomas and aneurysms may lead to **stroke**

### Diagnosis

- There are 4 main **diagnostic criteria** (Curacao criteria).

1. epistaxis: spontaneous, recurrent nosebleeds
  2. telangiectases: multiple at characteristic sites (lips, oral cavity, fingers, nose)
  3. visceral lesions: for example, gastrointestinal telangiectasia (with or without bleeding), pulmonary arteriovenous malformations (AVM), hepatic AVM, cerebral AVM, spinal AVM
  4. family history: a first-degree relative with HHT
- The diagnosis is **definite** if 3 criteria are present, **suspected** with 2 criteria and **unlikely** if fewer than 2 criteria are present.



The chest x-ray shows **multiple pulmonary nodules** representing arteriovenous malformations, the largest in the right mid-zone.



The CT scan shows multiple hepatic arteriovenous malformations



Mucocutaneous telangiectasias involve the lips (**HHT**)



The slide shows the typical appearance of hereditary haemorrhagic telangiectasia (also known as Osler-Weber-Rendu disease)

## Idiopathic thrombocytopenic purpura (ITP)

ITP - give oral prednisolone

- ITP is an immune mediated reduction in the platelet count.
- Antibodies are directed against the glycoprotein IIb/IIIa or Ib-V-IX complex.
- Most often the stimulus is unknown, but it can be secondary to other autoimmune disorders (e.g. SLE), viral infections (e.g. CMV, VZV, hepatitis C, HIV), *Helicobacter pylori*, medication and lymphoproliferative disorders.
- It results in **isolated thrombocytopenia**, with the most common presenting sign being a purpuric rash.
- ITP can be divided into acute and chronic forms:

### **Acute ITP**

- more commonly seen in children
- equal sex incidence
- may follow an infection or vaccination
- usually runs a self-limiting course over 1-2 weeks

### **Chronic ITP**

- more common in young/middle-aged women
- tends to run a relapsing-remitting course

### **Evan's syndrome**

- **ITP in association with autoimmune haemolytic anaemia (AIHA)**

### **Investigations**

- antiplatelet autoantibodies (usually IgG)
- bone marrow aspiration shows megakaryocytes in the marrow. This should be carried out prior to the commencement of steroids in order to rule out leukaemia

### **Management**

- No treatment is an option if asymptomatic.
- **oral prednisolone (80% of patients respond)**
- splenectomy if platelets < 30 after 3 months of steroid therapy
- IV immunoglobulins
- immunosuppressive drugs e.g. cyclophosphamide

### **Prognosis**

- The principal cause of death in patients with ITP is intracranial haemorrhage

## Langerhans cell histiocytosis

.Also called (Eosinophilic granuloma, Histiocytosis X)

### Definition

- Abnormal proliferation of pathogenic Langerhans cells (dendritic cells found in the skin) in single or multiple organs. This leads to inflammation and tissue destruction in different organs of the body
- It is the most common type of histiocytosis (i.e., syndrome characterised by the abnormal proliferation of histiocytes).

### Pathophysiology

- Exact aetiology and pathogenesis is unknown;
- thought to be either a malignant process or due to immune dysregulation

### Features

- more frequent in children (< 15 year )
  - typically presents in childhood with bony lesions
- bone pain, (present in 80% of patients, and are commonly seen on scalp) typically in the skull or proximal femur
- skin rash , cutaneous nodules
- Cranial involvement: Diabetes insipidus → polyurea and polydipsia (common in patients with multi-system disease)
- **recurrent otitis media/mastoiditis**
- GIT involvement : hepatosplenomegaly



Young girl with multiple well defined 'punched out' osteolytic lesions with scalloped edges (geographic skull) are seen in the bilateral parietal regions. The lesions have a characteristic bevelled edge.

### Diagnostics

- X-ray: osteolytic lesions
- Tissue biopsy of lesion (confirmatory test):
  - on electromicroscopy → tennis racket-shaped **Birbeck granules**
  - proliferation of Langerhans cells; polygonal cells with coffee-bean shaped nuclei, eosinophilic cytoplasm, and **Birbeck granules**
  - presence of **CD1a** and langerin (**CD207**) or **Birbeck granules** is definitive for diagnosis.

### Treatment

- Multi-system disease is treated with systemic, multi-agent chemotherapy.

## Myelofibrosis

Myelofibrosis - most common presenting symptom - lethargy

Tear-drop poikilocytes = myelofibrosis

### Overview

- a myeloproliferative disorder
- thought to be caused by hyperplasia of abnormal megakaryocytes
- the resultant release of platelet derived growth factor is thought to stimulate fibroblasts
- haematopoiesis develops in the liver and spleen
- commonly **associated with the JAK2 kinase mutation.**

### Features

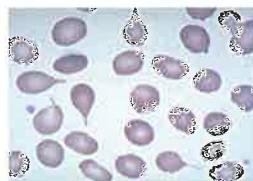
- e.g. elderly person with symptoms of anaemia e.g. **fatigue (the most common presenting symptom)**
- massive splenomegaly
  - (due to extramedullary hematopoiesis)
- hypermetabolic symptoms: weight loss, night sweats etc

### Complications

- Myelofibrosis can change to acute myeloid leukaemia.

### Laboratory findings

- anaemia
- high WBC and platelet count early in the disease
- 'tear-drop' poikilocytes on blood film
- unobtainable bone marrow biopsy - 'dry tap' therefore trephine biopsy needed
  - bone marrow biopsy is characterized by excessive proliferation of megakaryocytes.
- high urate and LDH (reflect increased cell turnover)



Blood film showing the typical 'tear-drop' poikilocytes of myelofibrosis

### Treatment

- Bone marrow transplant is the only curative treatment

## Myelodysplastic syndrome (MDS)

### Overview

- premalignant condition.
- primarily affects elderly people (> 60 ).
- more common in males than in females

### Pathophysiology

- clonal mutation predominates in the bone marrow, suppressing healthy stem cells.
- **the main cause of cytopenias**
  - **In the early stages of MDS → increased apoptosis (programmed cell death).**
  - As the disease progresses and converts into leukemia, → proliferation of leukemic cells overwhelms the healthy marrow.

## Causes

- primary or idiopathic MDS (80%)
- genetic predisposition
- hematopoietic stem cell injury caused by exposure to any of the following:
  - Cytotoxic chemotherapy
  - Radiation
  - Viral infection
  - Genotoxic chemicals (eg, benzene)

## Features

**macrocytic anaemia, thrombocytopenia and neutropenia with a small number of circulating blasts → suggests a diagnosis of myelodysplastic syndrome**

- 80% of patients present because of symptoms of anaemia (fatigue and malaise)
- Petechiae, ecchymoses, and nose and gum bleeding are common manifestations of a low platelet count.
- neutropenia may lead to fever and infections
- **blood film:**
  - dimorphic picture (some red cells are hypochromic and microcytic, while others appear macrocytic)
  - neutrophils are hypogranular and hyposegmented (Pelger-Huet cells).
  - The peripheral blood count may show:
    - single cytopenia (anemia, thrombocytopenia, or neutropenia) in the early phase or
    - bycytopenia (2 deficient cell lines) or
    - pancytopenia (3 deficient cell lines) in later stages.
  - unexplained macrocytic anemia with no evidence of megaloblastic anemia
- **Bone marrow aspirate** stained with **Perls' stain** showed **ring sideroblasts**
  - Ring sideroblasts contain an abnormally high concentration of iron, usually stored in perinuclear mitochondria.
  - Perls' stain (which stains for iron) shows this iron deposition as a dark ring around the margin of the nucleus.
  - Cytogenetic studies of the bone marrow cells:
    - Chromosomal abnormalities are clonal and include 5q-, monosomy 7 (-7) or 7q-, trisomy 8 (+8),
      - ❖ Multiple combinations indicate a very poor prognosis.
      - ❖ A single abnormality, except those involving chromosome 7, indicates good prognosis.

## Classification

- The (French-American-British (FAB) system classifies MDS into the following five subgroups :
  - Refractory anemia (RA)
  - RA with ringed sideroblasts (RARS)
    - RA and RARS are characterized by  $\leq 5\%$  myeloblasts in bone marrow.
    - RARS is defined morphologically as having 15% erythroid cells with abnormal ringed sideroblasts.
    - Both RA and RARS have a prolonged clinical course and a low prevalence of progression to acute leukemia.
      - ❖ progression to acute leukemia occurred in 5% of RARS cases, compared with 25% of RAEB cases
  - RA with excess blasts (RAEB; 6-20% myeloblasts)
  - RAEB in transition to AML (RAEB-T; 21-30% myeloblasts)

- acute myeloid leukemia (AML; >30%).
- Chronic myelomonocytic leukemia (CMML)
  - manifests as
    - ❖ monocytosis of  $\geq 1000/\mu\text{L}$ ,
    - ❖ total white blood cell (WBC) count of  $< 13,000/\mu\text{L}$ , and
    - ❖ trilineage dysplasia.
  - CMML must be differentiated from classic chronic myelocytic leukemia, which is characterized by a negative Ph chromosome.
- WHO classification 2008:
  - Refractory anaemia with unilineage dysplasia- ie anaemia, neutropaenia or thrombocytopaenia (<5% blasts)
  - Refractory anaemia with ring sideroblasts (<5% blasts; >15% sideroblasts)
  - Refractory anaemia with multilineage dysplasia ( based on bone marrow dysplasia in 2 or more myeloid lineages)
  - Refractory anaemia with excess blasts-1(5-9% blasts) and refractory anaemia with excess blasts -2 (10-19%)
    - **Blasts > 20% is now classified as acute myeloid leukaemia.**
  - Myelodysplasia unclassified
  - Myelodysplasia with isolated 5qdel( cytogenetic abnormality with prognostic significance)

### Prognosis

- Median survival is two years.
- **Patients are more likely to have serious infections or life-threatening bleeds than blastic transformation.**
- MDS who progress to acute leukemia have a poor prognosis than that of de novo acute myeloid leukemia (response to chemotherapy is worse)
- International Prognostic Scoring System (IPPS)
  - The revised I (IPSS-R) score is calculated on the basis of five variables:
    1. Hemoglobin level
    2. Absolute neutrophil count
    3. Platelet count
    4. Percentage of bone marrow blasts
    5. Cytogenetic category

### Management

- Supportive therapy,
  - including transfusions of the cells that are deficient (ie, red blood cells [RBCs], platelets), and treatment of infections are the main components of care.
  - As the vast majority are elderly patients with other medical conditions, excessive intervention is unwarranted (لا مبرر له).
  - Granulocyte-colony stimulating factor (G-CSF) and recombinant erythropoietin (r-Epo) can improve blood counts.
    - National Comprehensive Cancer Network (NCCN) guidelines recommend the use of erythropoiesis-stimulating agents (ESAs) for treatment of symptomatic anemia in patients in the R-IPSS very low risk, low risk, or intermediate risk category whose tumor lacks the 5q31 deletion and whose level of endogenous EPO is  $\leq 500 \text{ mU/mL}$ .
    - In cases of the presence of ringed sideroblasts or an **absence of response**, the addition of **granulocyte colony-stimulating factor (G-CSF; filgrastim)**, 1–2  $\mu\text{g}/\text{kg}$  1–3 times per week should be considered.
- hypomethylating agent azacytidine, which has been shown to improve survival compared with either supportive or aggressive therapy and is approved for use in MDS by (FDA).
- Aggressive cytotoxic chemotherapy is generally reserved for treatment of transformation to acute myelogenous leukaemia (AML) in younger patients.

## Leuco-erythroblastic anaemia

- **leuco-erythroblastic anaemia (left-shifted granulocytic series and nucleated red blood cells)**
- This can be seen with:
  - high bone marrow turnover, e.g. in severe haemolytic anaemia
    - (the reticulocyte count will be high),
  - myelofibrosis and chronic myeloid leukaemia
    - (where there will be splenomegaly and the white cell and platelet count will usually be raised)
  - bone marrow invasion.
    - **Often in bone marrow invasion the invading malignancy will already have been diagnosed previously.**
    - The diagnosis requires a bone marrow trephine, which will usually show replacement of haematopoietic tissue with malignant cells.

## Polycythaemia

Polycythaemia may be relative, primary (polycythaemia rubra vera) or secondary

### **Types and causes**

- **Relative causes**
  - dehydration
  - stress: Gaisbock syndrome
- **Primary causes**
  - polycythaemia rubra vera
- **Secondary causes**
  - Erythropoietin-secreting tumours:
    - Renal cell carcinoma
    - Hepatocellular carcinoma
    - Haemangioblastoma
    - Uterine fibroids.
  - Chronic hypoxia:
    - COPD
    - Right-to-left cardiac shunts
    - Sleep apnoea
    - High altitude
    - Chronic carbon monoxide poisoning (including heavy smoking).

### **Features**

- Symptoms of hyperviscosity syndrome, including:
  - dizziness
  - tinnitus
  - headaches
  - blurred vision, and
  - pruritus.
- Signs include:
  - Various ophthalmological changes (for example, dilated retinal veins)
  - Neurological findings,
  - Facial plethora ('ruddy' appearance).

### Differential diagnosis

#### Secondary erythrocytosis

	EPO	Expected plasma volume	Oxygen saturation	Underlying conditions
<b>Relative (apparent) polycythaemia</b> ( $\uparrow$ RBC mass due to $\downarrow$ in plasma volume)	$\leftrightarrow$	$\downarrow$	$\leftrightarrow$	<ul style="list-style-type: none"> <li>• Severe dehydration</li> <li>• Stress erythrocytosis</li> </ul>
<b>Appropriate absolute polycythaemia</b> (physiological $\uparrow$ in RBC mass, secondary to conditions associated with increased stimulation of erythropoiesis due to reduced oxygen saturation)	$\uparrow$	$\leftrightarrow$	$\downarrow$	<ul style="list-style-type: none"> <li>• High-altitude exposure</li> <li>• Hypoxia: chronic pulmonary and cardiac disease</li> </ul>
<b>Inappropriate absolute polycythaemia</b> (non-physiological $\uparrow$ in RBC mass, secondary to conditions associated with autonomous production of EPO, renal diseases that affect the EPO secreting cells, and neoplasms).	$\uparrow\uparrow$	$\leftrightarrow$	$\leftrightarrow$	<ul style="list-style-type: none"> <li>• Paraneoplastic syndrome, especially with:           <ul style="list-style-type: none"> <li>➢ Renal cell carcinoma (RCC)</li> <li>➢ Hepatocellular carcinoma (HCC)</li> </ul> </li> <li>• Polycystic kidney disease (PKD)</li> </ul>

- Absolute erythrocytosis, as opposed to apparent, is defined as an HCT greater than 0.60 in males and HCT greater than 0.56 in females.
- **To differentiate between true (primary or secondary) polycythaemia and relative polycythaemia:**
  - JAK2 mutation
    - JAK2 is a crucial tyrosine kinase which transmits the EPO signal to increase red cells production.
  - Red cell mass studies
    - The discovery of the JAK2 mutation has made red cell mass a second-line investigation for patients with suspected JAK2-negative PRV.
    - In true polycythaemia the total red cell mass in males  $> 35 \text{ ml/kg}$  and in women  $> 32 \text{ ml/kg}$

### Management

- **Venesection of patients who are symptomatic is the first line management of polycythaemia.**
- The diagnostic workup and exclusion of secondary causes usually follows after initial treatment
  - patient with symptoms of hyperviscosity needs to be venesected urgently and an agreed work-up can be performed later.

## Polycythaemia rubra vera (PRV)

Polycythaemia rubra vera is associated with a low ESR

Polycythaemia rubra vera - around 5-15% progress to myelofibrosis or AML

Polycythaemia rubra vera - JAK2 mutation

### **Definition**

- Polycythaemia rubra vera (PRV) is a myeloproliferative disorder caused by clonal proliferation of a marrow stem cell leading to an increase in red cell volume, often accompanied by overproduction of neutrophils and platelets.

### **Aetiology**

- a mutation in JAK2 is present in approximately 95% of patients with PRV and this has resulted in significant changes to the diagnostic criteria.
- occurs due to abnormal negative feedback of hematopoietic growth factor signaling.

### **Epidemiology**

- peak incidence in the sixth decade

### **Pathophysiology**

- mutation in the JAK2 gene → ↑ **tyrosine kinase activity** → uncontrolled, EPO-independent proliferation of the myeloid cell lines → ↑ blood cell mass (erythrocytosis, thrombocytosis, and granulocytosis) → hyperviscosity + slow blood flow → ↑ risk of thrombosis and poor oxygenation.

### **Features**

- **hyperviscosity**
- **pruritus, typically after a hot bath**
- **splenomegaly**
- haemorrhage (secondary to abnormal platelet **function** NOT NUMBER)
- plethoric appearance
- hypertension in a third of patients
- low ESR
- **Low EPO levels**
  - **the strongest pointer towards primary polycythaemia**
  - myeloproliferative → increased red blood cell production by the marrow → turns off endogenous EPO production → low EPO level.
- raised leukocyte alkaline phosphatase (ALP)
- **Mild prolonged PT & PTT:** this is related to the ratio of plasma and citrate. In the blue tubes that are used for coagulation tests the ratio is normally 1 citrate to 9 of whole blood. If there is less plasma due to the polycythaemia there will be excess citrate and this will prolong coagulation tests such as the APTT and prothrombin time.
- Others: hyperuricaemia, peptic ulceration.

### **Investigations**

- full blood count/film (raised haematocrit; neutrophils, basophils, platelets raised in half of patients)
- JAK2 mutation
- serum ferritin
- renal and liver function tests
- **If the JAK2 mutation is negative** and there is no obvious secondary causes the BCSH suggest the following tests:

- red cell mass
- arterial oxygen saturation
- abdominal ultrasound
- serum erythropoietin level
- bone marrow aspirate and trephine
- cytogenetic analysis
- erythroid burst-forming unit (BFU-E) culture

#### Diagnostic criteria

**JAK2-positive PRV** - diagnosis requires both criteria to be present

Criteria	Notes
A1	High haematocrit (>0.52 in men, >0.48 in women) OR raised red cell mass (>25% above predicted)
A2	Mutation in JAK2

**JAK2-negative PRV** - diagnosis requires A1 + A2 + A3 + either another A or two B criteria

Criteria	Notes
A1	Raised red cell mass (>25% above predicted) OR <b>haematocrit &gt;0.60 in men, &gt;0.56 in women</b>
A2	Absence of mutation in JAK2
A3	No cause of secondary erythrocytosis
A4	Palpable splenomegaly
A5	Presence of an acquired genetic abnormality (excluding BCR-ABL) in the haematopoietic cells
B1	Thrombocytosis (platelet count $>450 \times 10^9/l$ )
B2	Neutrophil leucocytosis (neutrophil count $>10 \times 10^9/l$ in non-smokers; $> 12.5 \times 10^9/l$ in smokers)
B3	Radiological evidence of splenomegaly
B4	Endogenous erythroid colonies or low serum erythropoietin

#### Management

- aspirin
- venesection:
  - first line treatment
  - the target hematocrit value after performing phlebotomy is less than 45 %.
- Hydroxyurea:
  - the preferred cytoreductive agent used in high-risk patients.
  - slight increased risk of secondary leukaemia
- phosphorus-32 therapy

- H2-receptor antagonists may be useful in relieving itching

- this is somewhat surprising. Conventionally it is the H1 antagonists that tend to be used for pruritus in other settings.

### Prognosis

- thrombotic events are a significant cause of morbidity and mortality
- 5-15% of patients progress to myelofibrosis
  - **Pastest note → Transition from primary polycythaemia to myelofibrosis occurs in about 30% of patients**, therefore, **the probability of developing myelofibrosis is higher and thus more likely than acute leukaemia**
- 5-15% of patients progress to acute leukaemia (risk increased with chemotherapy treatment)
  - particularly if patients have been exposed to radioactive phosphorous treatment or busulfan therapy.
  - Progression to acute myeloid leukaemia is seen in around 5% of patients.

## Myelofibrosis

- Primary myelofibrosis is a disorder in which normal bone marrow tissue is gradually replaced with a fibrous scar-like material.
- Over time this leads to progressive bone marrow failure.
- Most commonly seen in older adults (5th/6th decade)
- It is almost always accompanied by significant splenomegaly and is JAK2 mutation-positive in about 50% of cases.
- fatigue, splenomegaly and teardrop cells

### Complications

- Portal hypertension
  - occurs in 7% of patients with primary myelofibrosis
  - may be related to increased portal flow resulting from marked splenomegaly and to intrahepatic obstruction resulting from thrombotic obliteration of small portal veins.
  - This may result in variceal bleeding or ascites.
  - Hepatic or portal vein thrombosis may occur.
  - Symptomatic portal hypertension is managed by splenectomy, with or without the creation of a portosystemic shunt.
- Peripheral blood smear
  - **tear-drop** RBC
  - membrane is disrupted when RBC passed through fibrosis to leave bone marrow
  - nucleated RBCs
  - band granulocytes

### Treatment

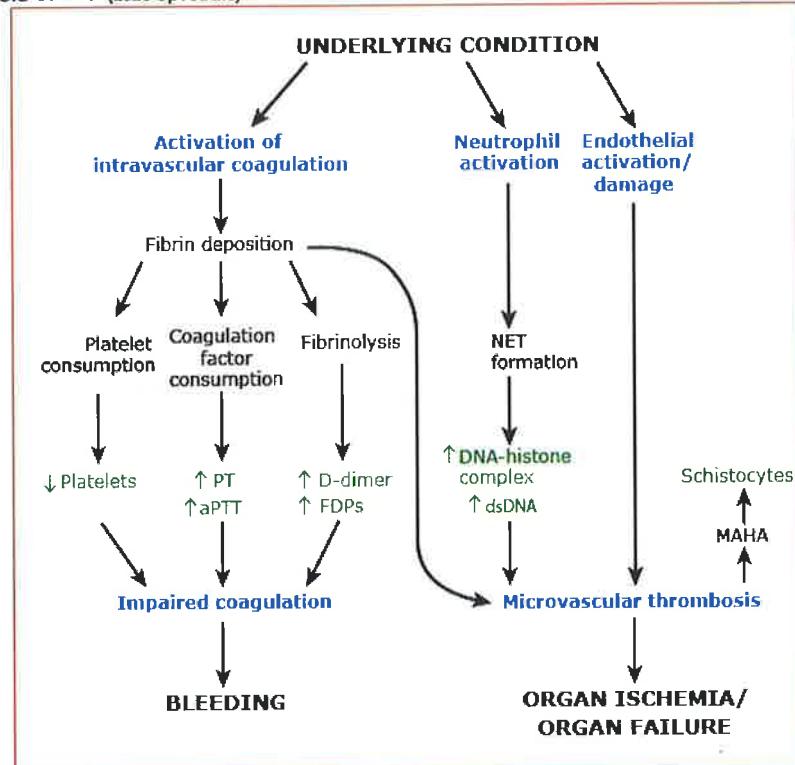
- It is generally incurable,
- although bone marrow transplantation and JAK2 inhibitors have a role in younger patients.

## Disseminated intravascular coagulation (DIC)

### Pathophysiology

- (DIC) is characterized by:
  - systemic activation of blood coagulation → deposition of fibrin → **microvascular thrombi** in various organs → multiple organ dysfunction syndrome (MODS).
  - ongoing activation of coagulation → consumption of coagulation proteins and platelets → may induce severe **bleeding**

## Pathogenesis of DIC (2020 UpToDate)



**NET:** neutrophil extracellular trap; **PT:** prothrombin time; **aPTT:** activated partial thromboplastin time; **FDPs:** fibrin degradation products; **dsDNA:** double-stranded DNA; **MAHA:** microangiopathic hemolytic anemia.

### Epidemiology

- present in 1% of hospitalized patients.

### Common Causes

- Sepsis and severe infection (most commonly)
- Trauma (neurotrauma)
- Organ destruction (eg, pancreatitis)
- Malignancy (solid and lymphoproliferative/myeloproliferative malignancies)
- acute hemolytic transfusion reaction.
- Obstetric complications:
  - Amniotic fluid embolism
  - abruptio placentae
  - (HELLP) syndrome : triad of:
    - Hemolysis,
    - Elevated Liver enzymes,
    - Low Platelets
  - eclampsia

## Diagnosis

- CBC
  - Thrombocytopenia (low Platelet count)
- Coagulation profile
  - prolonged PT and aPTT
  - low plasma fibrinogen
- D-dimers
  - produced by the action of plasmin on cross-linked fibrin
  - These tests reflect the microangiopathy of DIC
  - sensitive, specific, and efficient in the diagnosis of DIC
- Fibrin degradation products (FDP)
  - Increased levels of FDP occur in a variety of conditions in which clot formation and lysis occur.
  - sensitive, specific, and efficient in the diagnosis of DIC

**the combination of the D-dimer and the FDP assay provides the most rapid and specific diagnosis of DIC.**

- Peripheral smear
  - microangiopathic changes on peripheral blood smear
    - The presence of schistocytes, or red cell fragments, is a frequent but non-specific



Peripheral smear in microangiopathic hemolytic anemia showing presence of *schistocytes*

## Treatment

- **Fibrinogen replacement infusion (cryoprecipitate) is the appropriate first choice**
- **Platelet transfusion is recommended if the count is less than  $50 \times 10^9/L$ .**
- When bleeding is the major problem, the aim is to:
  - maintain the prothrombin and activated thromboplastin time at a ratio of 1.5 times of the control
  - maintain the fibrinogen level above 1 g/L.

## Thrombocytopenia

### Causes of thrombocytopenia:

- ❖ ↓ production (bone marrow infiltration, suppression, or fibrosis),
- ❖ ↑ destruction (DIC, ITP, and TTP/HUS),
- ❖ dilution
- ❖ sequestration due to splenomegaly.

### Causes of severe thrombocytopenia

- ITP
- DIC
- TTP
- haematological malignancy

### Causes of moderate thrombocytopenia

- heparin induced thrombocytopenia (HIT)
- drug-induced (e.g. quinine, diuretics, sulphonamides, aspirin, thiazides)
- alcohol
- liver disease
- hypersplenism
- viral infection (EBV, HIV, hepatitis)
- **pregnancy**
- SLE/antiphospholipid syndrome
- vitamin B12 deficiency

### Gestational thrombocytopenia

- very common.
- Most importantly, the patient should be closely monitored from the present time until she delivers
- The platelet count is very mildly reduced
- **no specific intervention**
- Steroids may only need to be considered if the platelet count is persistently less than 30 within the last 2 weeks of pregnancy.
- Steroids may be considered in the last couple of weeks of pregnancy to raise the platelet count temporarily so that a caesarean section or epidural anaesthesia may be undertaken safely. This may well be combined with intravenous immunoglobulin

### immune thrombocytopenia

- the patient is well.
- There is post viral illness with quite marked thrombocytopenia but other full blood count (FBC) parameters are normal.
- The diagnosis is one of exclusion,
- **The most important investigation is a blood film.** Although not diagnostic, this will confirm the FBC findings and also **exclude more sinister pathology such as leukaemia.**
- in the absence of major bleeding, management would be observation, as it can resolve spontaneously.

### Safety for different procedures when thrombocytopenic:

- In general, a platelet count of  $10-20 \times 10^9 /L$  is safe for most procedures. The exceptions to this are major surgery and procedures involving the CNS and eyes. In the latter cases, the platelet count should be above  $50 \times 10^9 /L$ .

## **Thrombocytosis**

### **Definition**

- Thrombocytosis is an abnormally high platelet count, usually  $\geq 450 \times 10^9/L$
- Thrombopoietin is the key hormone in the regulation of megakaryocyte differentiation.

### **Causes**

- reactive: platelets are an acute phase reactant - platelet count can increase in response to stress such as a severe infection or surgery
  - The most common cause of thrombocytosis is a reactive thrombocytosis.
  - May occur as a response to exercise
  - Secondary thrombocytosis does not place the patient at risk for haemostatic or cardiovascular events.
- iron deficiency
- Malignancy
  - secondary cause for thrombocytosis is crucial to exclude before considering a diagnosis of a myeloproliferative disorder.
- essential thrombocytosis (see below), or as part of another myeloproliferative disorder such as chronic myeloid leukaemia or polycythaemia rubra vera
  - adequate iron stores are requisite diagnostic criteria (WHO) for essential thrombocytosis.
- hypsplenism

## **Essential thrombocytosis (ET):**

### **Definition**

- Essential thrombocytosis is one of the myeloproliferative disorders which overlaps with chronic myeloid leukaemia, polycythaemia rubra vera and myelofibrosis.
- Megakaryocyte proliferation results in an overproduction of platelets, in the absence of any identifiable cause.

### **Epidemiology**

- usually affects older people between the ages of 50 and 70 years
- occurs equally in both males and females.

### **Features**

- asymptomatic (25-33%)
- tingling or burning in the hands and feet, headache, visual problems, weakness and dizziness.
  - burning sensation in the hands is a characteristic symptom
  - Erythromelalgia
    - burning pain, warmth, and redness of the extremities
    - The pain increases with exposure to heat and improves with cold
    - These symptoms result from excessive numbers of platelets causing blockages in small or large blood vessels in different parts of the body.
- Other symptoms include sweating, low-grade fever, and pruritus.
- Splenomegaly (40-50%)
- Hepatomegaly (20%)
- both thrombosis and haemorrhage can be seen

### **Investigations**

- Complete blood cell count (CBC)
  - platelet count  $> 600 \times 10^9/l$
  - Around 30% will also have a mildly raised RBC and / or WBC.
    - A red blood cell (RBC) mass study helps to exclude polycythaemia vera. The RBC mass is elevated in polycythaemia vera, but is normal in essential thrombocytosis.

- Genetic studies
  - The majority of patients have mutations in one of three genes:
    1. Janus kinase 2 (**JAK2**),
      - ❖ 50-60% of patients.
    2. calreticulin (**CALR**),
      - ❖ found in 25%
    3. myeloproliferative leukemia virus oncogene (**MPL**).
      - ❖ about 3-5% of cases.
      - ❖ *MPL* codes for the thrombopoietin receptor protein, which promotes the growth and proliferation of megakaryocytes.
      - ❖ The mutations result in constitutive activation of the thrombopoietin receptor protein.
  - Rare cases involve mutations in the thrombopoietin gene (**THPO**),
    - ❖ associated with autosomal dominant hereditary thrombocytosis
- Bone marrow examination
  - ↑ bone marrow cellularity (found in 90% )
  - Megakaryocytic hyperplasia is common
  - Bone marrow reticulin is usually increased, but collagen fibrosis is uncommon
- Elevation of C-reactive protein (CRP), fibrinogen, and interleukin 6 levels suggests secondary thrombocytosis, because those are acute-phase reactants
- Vitamin B-12 levels are increased in 25% of patients
- Uric acid levels are elevated in 25% of patients

### Diagnosis

- British guidelines propose the following five criteria for diagnosis of essential thrombocytosis :
  1. Sustained platelet count  $\geq 450 \times 10^9/L$
  2. Presence of an acquired pathogenetic mutation (eg, in the **JAK2**, **CALR** or **MPL** genes)
  3. No other myeloid malignancy, especially polycythemia vera, primary myelofibrosis, chronic myeloid leukemia, or myelodysplastic syndrome
  4. No reactive cause for thrombocytosis and normal iron stores
  5. Bone marrow aspirate and trephine biopsy showing increased megakaryocyte numbers displaying a spectrum of morphology with predominant large megakaryocytes with hyperlobated nuclei and abundant cytoplasm; reticulin is generally not increased (grades 0-2/4 or grade 0/3)
- Diagnosis requires the presence of criteria 1-3 or criterion 1 plus criteria 3-5.

### Adverse prognostic markers for essential thrombocythaemia (ET):

- Age above 60
- Symptomatology - particularly thrombosis and
- Platelet count above 1500.
- Previous thrombosis
- Obesity
- Cardiovascular risk factors such as smoking, hypertension, and hypercholesterolemia
- Markers of hypercoagulability such as factor V Leiden and antiphospholipid antibodies [4]
- JAK2 mutation

### Management

**Essential thrombocythaemia + high-risk of thrombosis → Aspirin + hydroxycarbamide**

- **low risk → observation only**
- high-risk of thrombosis (eg, age >60, history of thrombosis, or platelet counts >1500).
  - hydroxyurea (**hydroxycarbamide**) is widely used to reduce the platelet count
    - first-line treatment
  - interferon- $\alpha$  is also used in younger patients
    - Interferon alfa is a biologic response modifier.
    - used as second line in older patient
    - Interferon alfa is not known to be teratogenic and does not cross the placenta, perhaps making it safe for use during pregnancy.
    - Italian guidelines recommend interferon alfa as a first-line platelet-lowering therapy for patients younger than 40 years
  - **low-dose aspirin** may be used to reduce the thrombotic risk
    - low-dose aspirin may be useful in treating patients with symptoms of microvascular occlusion (eg, erythromelalgia).
    - Patients with the JAK2 mutation or cardiovascular risk factors can be treated with daily low-dose aspirin
    - Extreme thrombocytosis may promote the abnormal adsorption of large von Willebrand factor (VWF) multimers.
      - ❖ These patients should be screened for the presence of acquired von Willebrand disease (VWD).
        - ➡ if **ristocetin cofactor level** (Functional von Willebrand Factor) is at least 30% in absence of other high-risk factors; Low-dose aspirin therapy (eg, ≤100 mg/day) is acceptable
        - ➡ if it is less than 30%, all aspirin should be avoided.
- **Plateletpheresis**
  - If platelet is very high with symptoms of clotting or bleeding

### Prognosis

- extremely good in ET with survival of over two decades expected.
- The risk of transforming to acute myeloid leukaemia is relatively low (<1%).

## **Thrombotic thrombocytopenic purpura (TTP)**

(TTP) is classically characterised as a **pentad of**: thrombocytopenia, microvascular haemolysis, fluctuating neurological signs, renal impairment and fever.

HUS or TTP? Neuro signs and purpura point towards TTP

TTP - plasma exchange is first-line

### Pathogenesis of thrombotic thrombocytopenic purpura (TTP)

- abnormally large and sticky multimers of von Willebrand's factor cause platelets to clump within vessels
- in TTP there is a deficiency of ADAMTS13 (a metalloprotease enzyme) which breakdowns large multimers of von Willebrand's factor
- The primary event that occurs appears to be endothelial damage, which then leads to → thrombus formation, → end organ damage (eg brain and kidneys) and platelet consumption
- overlaps with haemolytic uraemic syndrome (HUS)

### Causes

- post-infection e.g. urinary, gastrointestinal (Escherichia coli 0157 subtype)
- pregnancy

- drugs:
  - ciclosporin,
  - oral contraceptive pill,
  - penicillin, metronidazole
  - antiplatelets: **clopidogrel** or ticlodipine (< 1%),
  - acyclovir,
  - FK506,
  - Penicillamine
  - sulphonamides
- tumours
- SLE
- HIV

### Features

- rare, typically adult females
- fever
- fluctuating neuro signs (microemboli)
- microangiopathic haemolytic anaemia
- renal failure
- thrombocytopenia
- **Which investigation will be most useful to establish the diagnosis?**
  - **Peripheral blood film**
    - The peripheral blood film reveals fragmented RBCs (schistocytes, eg, spherocytes, segmented RBCs, burr cells, or helmet cells).

### Management

- no antibiotics - may worsen outcome
- **plasma exchange is the treatment of choice**
  - **TTP has an untreated mortality of up to 90% and therefore rapid plasma exchange (PEX) may be a life saving intervention.**
- steroids, immunosuppressants
  - Intravenous methylprednisolone is indicated after treatment with PEX has been completed.
- Vincristine
- Platelet transfusion in TTP is only indicated if there is an on-going life-threatening bleed.
- There is no current role for intravenous immunoglobulin in the routine management of TTP, however there have been reports of its successful use in PEX- and steroid-refractory cases.

### Prognosis

- In adults, the mortality rate 20-50%

**January 2013 exam: H/O confusion + fever + ↓Platelets 65 , ↑Urea 23, ↑Creatinine 366.What is the most likely diagnosis?**

➔ **Thrombotic thrombocytopenic purpura**

## Von Willebrand's disease

The combination of a petechial skin rash combined with a slightly elevated APTT and reduced factor VIII activity make Von Willebrand's disease the most likely diagnosis

Desmopressin - induces release of von Willebrand's factor from endothelial cells

### Overview

- Von Willebrand's disease is the most common inherited bleeding disorder.
- The majority of cases are inherited in an **autosomal dominant** fashion
  - if both parents have the disease, then three-quarters of their offspring will have the disease, assuming they are both heterozygotes.
  - In an autosomal dominant condition, there is no carrier state.
- characteristically behaves like a platelet disorder i.e. epistaxis and menorrhagia are common whilst haemoarthroses and muscle haematomas are rare
- Symptoms are exacerbated by medications that inhibit platelet function, such as aspirin and other NSAIDs.

### Role of von Willebrand factor

- large glycoprotein which forms massive multimers
- Von Willebrand factor is a coagulation protein that **binds to collagen and to the Gpib platelet receptor during platelet adhesion.**
  - promotes platelet adhesion to damaged endothelium
- carrier molecule for factor VIII
- Factor VIII circulates bound to von Willebrand factor (vWF), which **protects factor VIII from degradation.**
  - Decreased vWF (in part) prolongs the PTT by leading to decreased factor VIII.
  - In people with hemophilia, strategies to increase circulating levels of factor VIII include maximizing vWF levels.
  - increases vWF secretion (leading to increased functional levels of factor VIII).
  - Even in hemophilia A, there is still a small amount of normal factor VIII (<5%).
- The intrinsic coagulation pathway is defective in von Willebrand disease.

### Types

- **type 1:** partial reduction in vWF (80% of patients)
  - the most common form
  - patients have up to a 50% reduction in von Willebrand factor (vWF).
  - **Autosomal dominant with variable penetrance**
  - Many are asymptomatic and are only diagnosed following an episode of bleeding associated with a dental extraction or minor surgery.
- **type 2:** abnormal form of vWF
- **type 3:** total lack of vWF (autosomal recessive) (most severe form)

### Investigation

- prolonged bleeding time (due to impaired platelet adhesion and aggregation)
  - The bleeding time would be a good screening test but it will not give a quantitative measurement of bleeding tendency in type I vWBD
  - neither sensitive nor specific
  - **platelet function analyser (PFA100), have better testing characteristics than the bleeding time**
- **APTT may be prolonged** (due to reduced circulating factor VIII).
- factor VIII levels may be moderately reduced

- the most useful test to assess bleeding tendency in Von Willebrand's disease  
? → Plasma factor VIII activity
- vWB antigen and activity (Ristocetin cofactor assay) (RICOF)
  - The most useful test in practice is to do the vWB antigen and activity (RICOF), but you would also do FVIIIc as this is also low in vWD.
- In type I vWD the prothrombin time (PT) and Platelet count will be normal.
- defective platelet aggregation with ristocetin

### Management

- **tranexamic acid for mild bleeding**
- desmopressin (DDAVP):
  - raises levels of vWF by inducing release of vWF from Weibel-Palade bodies in endothelial cells
    - DDAVP is the initial treatment of choice for patients with VWD type 1.
    - ❖ Other therapies such as factor VIII concentrates containing VWF are not usually required.
- factor VIII concentrate
- In **minor trauma**,
  - desmopressin (DDAVP) can be used to increase the concentration of VWF.
  - The choice of treatment for a mild vWB facing a more invasive procedure would be DDAVP, providing there is no contraindication.
  - vWB factor concentrate would be reserved as second line treatment to DDAVP.
- for **major surgery**,
  - factor VIII concentrate is used to increase the concentration of vWF.
    - The most commonly used is Humate-P.
    - Purified or recombinant preparations are avoided since they contain only small concentrations of vWF.
    - In cases of severe vWD or prior to major surgery, **the product of choice is intermediate purity (vWF rich) factor VIII**, which contains the highest concentration of von Willebrand factor.
- for Women with menorrhagia:
  - Oral contraceptives (the Pill) raise the level of von Willebrand factor in the blood for women with Type 1 VWD.

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## Haemophilia

### Definitions

- Haemophilia A is due to a deficiency of factor VIII whilst in haemophilia B (Christmas disease) there is a lack of factor IX
  - Hemophilia A (factor VIII): ~ 80% of cases
  - Hemophilia B (factor IX): ~ 20% of cases

### Etiology

- X-linked recessive disorder
  - Occurs almost exclusively in males due to an X-linked pattern of inheritance.
  - typically skips generations
  - A carrier mother has a 50% chance of passing down the disease to her sons and a 50% chance of passing down the carrier gene to her daughters.
- Up to 30% of patients have no family history of the condition.

### Pathophysiology

- The pathological problem in both haemophilia A and haemophilia B is the inability to form a functional tenase complex to activate factor X to factor Xa
- The intrinsic coagulation pathway is defective in hemophilia.

### Features

- typically present initially with easy bruising secondary to minimal trauma,
- haemoarthroses, haematomas

- Musculoskeletal bleeding is the most common type of haemorrhage.
- prolonged bleeding after surgery or trauma,

Severity	Clinical signs	Factor VIII or IX activity
<b>Physiologic condition</b>	None	≥ 50%
<b>Mild hemophilia</b>	Hematomas following severe trauma	> 5% to < 50%
<b>Moderate hemophilia</b>	Hematomas following mild trauma	≥ 1% to 5%
<b>Severe hemophilia</b>	Spontaneous hematomas	< 1%

**Petechial bleeding is a common sign of platelet disorders, NOT coagulation disorders such as hemophilia**

### Blood tests

- prolonged APTT
- mixing study
  - requested if the aPTT is prolonged.
  - The patient's plasma is mixed with normal plasma and the aPTT repeated.
  - Correction of aPTT with mixing study suggests coagulation factor deficiency.
- **plasma factor VIII and IX assay**
- bleeding time, thrombin time, prothrombin time normal

**Although female carriers of the haemophilia gene do not normally suffer from increased bleeding risk, APTT may be prolonged.**

### Treatment

- factor VIII or IX replacement.
- Side effects:
  - Up to 10-15% of patients with haemophilia A develop antibodies to factor VIII treatment

## Methemoglobinemia

### Methemoglobin

- hemoglobin is oxidized to the ferric ( $\text{Fe}^{3+}$ )
- ↓ affinity for  $\text{O}_2$
- ↑ affinity for cyanide ( $\text{CN}^-$ )
  - $\text{CN}^-$  poisoning treated with methemoglobin

- Methemoglobin (met-Hb) results from the presence of iron in the ferric form ( $\text{Fe}^{3+}$ ) instead of the usual ferrous form ( $\text{Fe}^{2+}$ ).
- met-Hb cannot carry oxygen
- met-Hb is a naturally occurring oxidized metabolite of hemoglobin, and physiologic levels (< 1%) are normal.
- Methemoglobinemia (congenital or acquired) occurs when (RBCs) contain methemoglobin at levels higher than 1%.
- Acquired methemoglobinemia is considerably more common than congenital forms.
- The low level of methemoglobin is maintained through 2 important mechanisms.

1. the hexose-monophosphate shunt pathway within the erythrocyte. Through this pathway, oxidizing agents are reduced by glutathione.
2. The second and more important mechanism involves two enzyme systems:
  - ❖ **diaphorase I:** requires nicotinamide adenine dinucleotide (NADH)
    - the major enzymatic system (This enzyme system is responsible for the removal of 95-99% of the methemoglobin that is produced under normal circumstances.)
    - Cytochrome b5 reductase plays a major role in this process by transferring electrons from NADH to methemoglobin, an action that results in the reduction of methemoglobin to hemoglobin.
  - ❖ **diaphorase II:** requires nicotinamide adenine dinucleotide phosphate (NADPH).
    - plays only a minor role in the removal of methemoglobin.
    - This enzyme system utilizes glutathione production and glucose-6-phosphate dehydrogenase (G6PD) to reduce methemoglobin to hemoglobin.
    - Play a more important role in methemoglobin regulation in patients with cytochrome b5 reductase deficiencies.
    - can be accelerated by exogenous cofactors such as methylene blue

#### **Effect of Methemoglobin:**

- does not bind oxygen, thus leading to a functional **anemia**.
- causes a **left shift of the oxygen-hemoglobin dissociation curve**, resulting in decreased release of oxygen to the tissues.
  - Normal people generate met-Hb but in very low levels in the range of 0.5% to 3%.
  - should be suspected when the oxygen saturation as measured by pulse oximetry is significantly different (lower) from the oxygen saturation calculated from arterial blood gas analysis (saturation gap). (**low SpO<sub>2</sub> with normal PaO<sub>2</sub> and SaO<sub>2</sub>(on ABG)**)
- presence of **anemia and cyanosis** despite oxygen treatment results from both of these effects.

#### **Causes**

- congenital (secondary to a deficiency in methemoglobin reductase)
- acquired
  - **Dapsone**
  - local anesthetics (topical and injectable)
  - nitrates
  - **amyl nitrite**
  - **aniline dyes**
  - The presence of methemoglobin may also be a marker and predictor of sepsis, resulting from release of excessive amounts of nitrous oxide (NO)
  - patients with low catalase activity (inherited or acquired) treated with rasburicase for tumor lysis syndrome → formation of hydrogen peroxide → methemoglobinemia
    - Some authors have suggested that catalase activity be measured before rasburicase therapy is initiated in this setting.

**Drugs that cause methaemoglobinaemia include:**

- Phenacetin
- Sulphonamides
- **Dapsone**
- **Primaquine**
- **Lidocaine**
- **Procaine**
- **Benzocaine**.

### Congenital (hereditary) Methemoglobinemia

- autosomal recessive
- two forms of congenital **cytochrome b5 reductase (b5R) deficiency** exist:

<b>type Ib5R deficiency</b>	<b>type IIb5R</b>
<p>more common</p> <p>cytochrome b5 reductase is absent only in RBCs</p> <p>Homozygotes appear cyanotic but usually are otherwise asymptomatic.</p> <p>Heterozygotes may develop acute, symptomatic methemoglobinemia after exposure to certain drugs or toxins.</p> <p>Methemoglobin levels typically range from 10% to 35%.</p> <p>Life expectancy is not influenced</p>	<p>less common</p> <p>cytochrome b5 reductase is deficient in all cells, not just RBCs.</p> <p>associated with several other medical problems, including mental retardation, microcephaly, and other neurologic complications.</p> <p>Life expectancy is severely compromised, and patients usually die at a very young age.</p>

### presence of abnormal hemoglobins (hemoglobin M [Hb M])

- autosomal dominant
- in most of these hemoglobins, tyrosine replaces the histidine residue, which binds heme to globin.
- This replacement displaces the heme moiety and permits oxidation of the iron to the ferric state.
- Hb M is more resistant to reduction by the methemoglobin reduction enzymes
- Patients with Hb M appear cyanotic but are otherwise generally asymptomatic.

### Feature (are proportional to the methemoglobin level) :

Classical presentation includes cyanosis with chocolate-colored blood

- 3-15% - Slight discoloration (eg, pale, gray, blue) of the skin and blood color changes (brown or chocolate color).
  - Discoloration of the skin and blood is the most striking physical finding.
  - Fatigue, flu-like symptoms, and headaches may be the only manifestations in the initial phase.
- 15-20% - Cyanosis, though patients may be relatively asymptomatic
  - cyanosis is usually the first presenting symptom.
- 25-50% - Headache, dyspnea, lightheadedness (even syncope), weakness, confusion, palpitations, chest pain
- 50-70% - Abnormal cardiac rhythms; altered mental status, delirium, seizures, coma; profound **acidosis**
- >70% - Usually, death

### Treatment:

- Methylene blue :**
  - the first line treatment**
  - contraindicated in G6PD deficiency and ineffective with hemoglobin M.
    - reduction of met-Hb by methylene blue is dependent upon NADPH generated by G6PD.
    - methylene blue has an oxidant potential → hemolysis in G6PD deficient.
- Second line treatment: when methylene blue therapy is ineffective or contraindicated
  - Exchange transfusion:** for patients who do not respond to methylene blue or G6PD-deficient individuals who are severely symptomatic
    - Hyperbaric oxygen treatment: another option
- IV hydration and bicarbonate (for metabolic acidosis)

## Cyanosis without hypoxia

- Persistent cyanosis without hypoxia (a normal  $\text{PaO}_2$ ) suggests a diagnosis of methaemoglobinemia or sulfhaemoglobinemia.
- In a cyanosed patient the amount of reduced haemoglobin in the blood is at least 5 g/dl
- The blue colour of the skin and mucous membranes is due to hypoxia and not hypercapnia. Hypoxia should be corrected by oxygen therapy
- What is the possible cause of Desaturation on  $\text{SaO}_2$  (using an oximeter) in spite of normal  $\text{PaO}_2$ ?
  - Methaemoglobinemia
    - accumulation of reversibly oxidised methaemoglobin causing reduced oxygen affinity of the Hb molecule with consequent cyanosis.
    - It can occur due to:
      - an inherited condition or
      - as a consequence of drugs such as **nitrates**.

## Heparin

- can be given as either:
  - unfractionated, intravenous heparin, or
  - low molecular weight heparin (LMWH), given subcutaneously.
- Heparins generally act by **activating antithrombin III**.
- Unfractionated heparin** forms a complex which inhibits thrombin, **factors Xa, IXa, XIa and XIIa**.
- LMWH however only ↑ the action of antithrombin III on factor Xa**

The table below shows the differences between standard heparin and LMWH:

	Standard Heparin	(LMWH)
administration	Intravenous	Subcutaneous
Action duration	short	long
Mechanism of action	Activates antithrombin III. Forms a complex that inhibits thrombin, factors Xa, IXa, XIa and XIIa	Activates antithrombin III. Forms a complex that inhibits factor Xa
Side-effects	Bleeding  HIT  <b>Osteoporosis</b>	Bleeding  Lower risk of HIT and <b>osteoporosis</b>
Monitoring	Activated partial thromboplastin time (APTT)	Anti-Factor Xa (although routine monitoring is not required)
Notes	Useful in situations where there is a↑ risk of bleeding as anticoagulation can be terminated rapidly	Now standard in the management of venous thromboembolism treatment and prophylaxis and acute coronary syndromes

## Heparin-induced thrombocytopenia (HIT)

- Types

1. Type 1 HIT

- non-immune mediated reaction
- due to a direct effect of the drug on platelets.
- occur soon after the initial administration of heparin (within two days)
- self-limiting condition and the platelet count will normalise with continued heparin administration.

2. Type 2 HIT

- immune mediated condition

- **mechanism:**

- ❖ IgG antibodies against heparin bound to platelet factor 4 (PF4).
- ❖ Antibody-heparin-PF4 complex will be eliminated by the immune system  
(→ thrombocytopenia), and activates platelets → thrombosis
- It is a prothrombotic condition despite being associated with low platelets.
- **typically arises 4 to 10 days after starting heparin therapy.**
- Patients may develop both venous and arterial thromboses,
- low platelet counts and mild abnormalities of coagulation.
- The D-dimer level is raised due to widespread thrombus formation.

- **Features** include a greater than 50% reduction in platelets, thrombosis and skin allergy
- Patients with (HIT), particularly those with associated thrombosis, often have evidence of **increased thrombin generation** that can **lead to consumption of protein C**.

- If these patients are given warfarin without a concomitant parenteral anticoagulant to inhibit thrombin or thrombin generation, the further decrease in protein C levels induced by the vitamin K antagonist can trigger skin necrosis.
- To avoid this problem, patients with HIT should be treated with a direct thrombin inhibitor, or fondaparinux, until the platelet count returns to normal levels.

- **Diagnosis:** HIT is confirmed by:

- HIT antibody
- serotonin-release assay (SRA).

- **Treatment**

- options include alternative anticoagulants such as lepirudin and danaparoid
- Argatroban is not cleared via the kidneys; therefore, this drug is safer than lepirudin/fondaparinux for HIT patients with renal insufficiency.
- Lepirudin is a direct thrombin inhibitor, which is cleared by kidneys exclusively, and is contraindicated in renal insufficiency.
- Fondaparinux can be used in HIT as it does not bind to platelets, but it is contraindicated in renal insufficiency.

## Heparin-induced hyperkalaemia

- Both unfractionated and low-molecular weight heparin can cause hyperkalaemia. This is thought to be caused by inhibition of aldosterone secretion.

## Heparin overdose

- Heparin overdose may be reversed by protamine sulphate, although this only partially reverses the effect of LMWH.
- The dose of protamine sulphate given is dependent upon the dose of LMWH administered and the time of administration.
- If protamine is given **within eight hours** of the LMWH then a maximum neutralising

- dose is **1 mg protamine/100 units (or 1 mg) of LMWH given in the last dose.**
- If more **than eight hours** have passed since the dose of LMWH was given, administer **0.5 mg** protamine per 100 units (or 1 mg) of LMWH given.
  - Protamine is administered by slow IV infusion (over 10 minutes) to avoid a **hypotensive reaction**.
  - Protamine requires a high level of caution when being prescribed and administered.

### **Heparin resistance**

- Heparin resistance is seen in up to 22% of patients undergoing cardiopulmonary bypass surgery.
- Several mechanisms resulting in heparin resistance have been identified, including:
  - **antithrombin deficiency,**
  - increased heparin clearance,
  - elevated heparin-binding proteins,
  - and elevated factor VIII and fibrinogen levels.
- For cardiopulmonary bypass in particular, rapid neutralisation of thrombin is required. In order for heparin to be successful in this, it requires antithrombin III which is an alpha2-globulin. It is therefore thought that **antithrombin III deficiency** is the underlying problem which is seen in patients resistant to heparin during cardiopulmonary bypass.

- **Heparin and thyroid function test**

- Heparin is having an "in vitro" effect on thyroxine (T4) levels.
- IV heparin interferes with the thyroid function tests assay on occasions displacing bound thyroid hormone.
- Normal TSH + high T3 and T4

### **Heparin and delivery**

- Women who are anticoagulated with heparin until the onset of labor generally experience **vaginal delivery with no greater blood loss than non-anticoagulated gravidas.**
- However, Cesarean delivery in heparinized patients is **accompanied by a significantly greater blood loss** than would otherwise be anticipated.
- **If preterm labor develops in a patient receiving heparin, only the mother is anticoagulated, and protamine sulfate can be used** to reverse maternal heparinization.

**What is the best way to monitor rivaroxaban compliance?**

➔ **Prothrombin time (PT)**

## Novel oral anticoagulants (NOACs)

The table below summaries the three NOACs: dabigatran, rivaroxaban and apixaban.

	Dabigatran	Rivaroxaban	Apixaban
<b>UK brand name</b>	Pradaxa	Xarelto	Eliquis
<b>Mechanism of action</b>	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
<b>Route</b>	Oral	Oral	Oral
<b>Excretion</b>	Majority renal	Majority liver	Majority faecal
<b>NICE indications</b>	Prevention of VTE following hip/knee surgery Treatment of DVT and PE Prevention of stroke in non-valvular AF*	Prevention of VTE following hip/knee surgery Treatment of DVT and PE Prevention of stroke in non-valvular AF*	Prevention of VTE following hip/knee surgery Treatment of DVT and PE Prevention of stroke in non-valvular AF*

\*NICE stipulate that certain other risk factors should be present. These are complicated and differ between the NOACs but generally require one of the following to be present:

- prior stroke or transient ischaemic attack
- age 75 years or older
- hypertension
- diabetes mellitus
- heart failure

	Dabigatran	Rivaroxaban	Apixaban
<b>Mechanism of action</b>	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
<b>Route</b>	Oral	Oral	Oral
<b>Excretion</b>	Majority renal	Majority liver	Majority faecal

## Dabigatran

**Stop dabigatran two days before polypectomy**

- **Mode of action:** Dabigatran is a **direct thrombin inhibitor** with a rapid onset of action.
- **It is administered as a prodrug**
  - The prodrug dabigatran etexilate is rapidly converted by tissue esterases to dabigatran.
- it is predominately (80%) excreted by the kidneys.
- The anticoagulant effect starts within minutes of oral ingestion and peaks after 2-3 hours.
- **Advantage of dabigatran:**
  - due to its short half-life, a patient's coagulation status will normalize more rapidly than that of a patient treated with warfarin in almost all cases.
  - No need for routine monitoring
- **Disadvantage of dabigatran**
  - **Dabigatran is not recommended in patients with prosthetic heart valves** because their safety and efficacy have not established.
    - The rates of thromboembolism are higher for valves in the mitral compared with those in the aortic position.
    - **caged-ball valves are the most thrombogenic** followed by tilting-disk and bi-leaflet valves.
  - more thromboembolic events (e.g., valve thrombosis, stroke, TIA, and myocardial infarction) were observed with dabigatran than with warfarin;
  - excessive major bleeding (predominantly postoperative pericardial effusions requiring intervention for hemodynamic compromise) was observed with dabigatran, compared with warfarin.
- **Monitoring of the anticoagulant effects of dabigatran**
  - In general, "routine" monitoring is not required in most cases.
  - However, in some clinical situations a clinician may wish to determine the degree to which dabigatran is reducing the coagulant potential of the blood; e.g., if a patient taking dabigatran requires emergency surgery, has an intracranial or major systemic bleed, or is being considered for thrombolysis due to an ischemic stroke.
  - **The thrombin time (TT) and ecarin clotting time are considered the most accurate measures of dabigatran's anticoagulant effect.**
    - The aPTT and, if available, the thrombin time (TT) should be used to measure the anticoagulant effect of dabigatran,
    - INR and PT tests are unreliable
- **Effect of dabigatran on procedural bleeding risk**
  - **Dabigatran should be discontinued 1 to 2 days (creatinine clearance  $\geq 50$  mL/min)** or 3 to 5 days (creatinine clearance  $<50$  mL/min) before invasive or surgical procedures.
  - Clinicians may want to consider "longer" periods of discontinuation for patients undergoing major surgery in which bleeding could have serious consequences (e.g.,

- cardiac, neurosurgery, major abdominal or pelvic, spinal puncture, or placement of a spinal or epidural catheter or port).
- If surgery is urgent and cannot be delayed, there is an increased risk of bleeding; patients with a normal aPTT appear to have a low risk of serious bleeding.
- conversion from warfarin to dabigatran (eg : patient had difficulty attending for regular INR)
  - if a patient is taking warfarin with a therapeutic INR, it is recommended to : Stop warfarin, perform daily INR, start dabigatran when INR falls below 2.0
  - The anticoagulant effect of dabigatran starts minutes after its oral administration and peaks after 2-3 hours.
- Contraindications
  - Dabigatran is contraindicated if eGFR <30ml/min.
  - Rivaroxaban, a direct inhibitor of activated factor X, is contraindicated if eGFR <15 and needs dose adjustment if eGFR 15–29 mL/minute.

**Ecarin clotting time is prolonged by direct thrombin inhibitors such as dabigatran.**

Treatment with aspirin, warfarin or heparins does not affect Ecarin clotting time.

**Idarucizumab reverses dabigatran**

## Warfarin

Warfarin - clotting factors affected mnemonic - 1972 (10, 9, 7, 2)

P450 inhibitors ↑ INR      INR also ↑ by ABX that kill intestinal flora by ↓ Vit K absorption

Dentistry in warfarinised patients - check INR 72 hours before procedure, proceed if INR < 4.0

### Warfarin action → inhibition of vitamin K epoxide reductase

- Warfarin is an oral anticoagulant which inhibits the reduction of vitamin K to its active hydroquinone form, which in turn acts as a cofactor in the carboxylation of clotting factor II, VII, IX and X (mnemonic = 1972) **and protein C. ( warfarin → reduces protein C levels in the blood)**
- Warfarin inhibits epoxide reductase (specifically the VKORC1 subunit), thereby diminishing available vitamin K and vitamin K hydroquinone in the tissues which inhibits the carboxylation activity of the glutamyl carboxylase.
- The half-life of warfarin is approximately 44 h

### Indications

- venous thromboembolism: target INR = 2.5, if recurrent 3.5
- atrial fibrillation, target INR = 2.5

- mechanical heart valves, target INR depends on the valve type and location. Mitral valves generally require a higher INR than aortic valves.

### Side-effects

- haemorrhage
- teratogenic, although can be used in breast-feeding mothers
  - **the most common teratogenic effect is →Nasal hypoplasia**
- skin necrosis: when warfarin is first started biosynthesis of protein C is reduced. This results in a temporary procoagulant state after initially starting warfarin, normally avoided by concurrent heparin administration. Thrombosis may occur in venules leading to skin necrosis
- purple toes

### Contraindications

- Warfarin is generally avoided in pregnancy.**
  - In the first trimester it is associated with an increased risk of miscarriage, and teratogenic side effects which include chondrodysplasia patellae, asplenia and diaphragmatic herniae.
  - In the second and third trimester it is associated with retroplacental and intracerebral foetal haemorrhage, as well as foetal microcephaly, optic atrophy and developmental delay.

### Monitoring

- Patients on warfarin are monitored using the INR (international normalised ration), the ratio of the prothrombin time for the patient over the normal prothrombin time.
- Warfarin has a long half-life and achieving a stable INR may take several days.

### Factors that may potentiate warfarin

- liver disease
- P450 enzyme inhibitors, e.g.: amiodarone, Clarithromycin, ciprofloxacin
  - **Clarithromycin increase INR more than ciprofloxacin**
    - Clarithromycin is metabolised by CYP3A4 and is an inhibitor, meaning that it does affect INR to a limited extent, leading to an increase.
    - Ciprofloxacin is a moderate inhibitor of CYP1A2; some effect is expected on INR, but not as great as that for clarithromycin.
- cranberry juice
- drugs which displace warfarin from plasma albumin, e.g. NSAIDs
- inhibit platelet function: NSAIDs

### Interaction

- Lipid-lowering agents
  - Simvastatin, rosuvastatin and fibrate → potentiate the anticoagulant effects of warfarin
  - **Atorvastatin and pravastatin are least likely to interfere with warfarin**
  - **Cholestyramine** (a cholesterol-binding resin) is known to **reduce the anticoagulant action of warfarin**
    - Cholestyramine reduces absorption of a number of drugs including warfarin.
- cranberry juice** → ( $\uparrow$ warfarin effect →  $\uparrow\downarrow$  INR). The cause is thought to be bioflavonoids contained in the cranberry juice, which block cytochrome-P450-related warfarin metabolism (CYP2C9)
- Paracetamol given in repeated doses may lead to an enhanced response to warfarin and therefore an increased INR**
- Commonly used drugs that may lead to an increased INR include cephalosporins, azathioprine, cimetidine, metronidazole and testosterone derivatives
- Diazepam** is a p450 enzyme **inducer** and is therefore likely to reduce INR

- the concurrent use of clopidogrel with warfarin increases the bleeding risk.
- Co-enzyme Q10 is similar to vitamin K and reduces warfarin's anticoagulant effect** (warfarin exerts its anticoagulant effect through inhibition of the synthesis of vitamin K dependent clotting factors).

## Warfarin: management of high INR

A 2005 update of the BCSH guidelines emphasised the preference of prothrombin complex concentrate over FFP in major bleeding.

Situation	Management
Major bleeding	<ul style="list-style-type: none"> <li>Stop warfarin</li> <li>Give intravenous vitamin K 5mg</li> <li>Prothrombin complex concentrate - if not available then FFP</li> </ul>
INR > 8.0 Minor bleeding	<ul style="list-style-type: none"> <li>Stop warfarin</li> <li>Give intravenous vitamin K 1-3mg</li> <li>Repeat dose of vitamin K if INR still too high after 24 hours</li> <li>Restart warfarin when INR &lt; 5.0</li> </ul>
INR > 8.0 No bleeding	<ul style="list-style-type: none"> <li>Stop warfarin</li> <li>Give vitamin K 1-5mg by mouth, using the intravenous preparation orally</li> <li>Repeat dose of vitamin K if INR still too high after 24 hours</li> <li>Restart when INR &lt; 5.0</li> </ul>
INR 5.0-8.0 Minor bleeding	<ul style="list-style-type: none"> <li>Stop warfarin</li> <li>Give intravenous vitamin K 1-3mg</li> <li>Restart when INR &lt; 5.0</li> </ul>
INR 5.0-8.0 No bleeding	<ul style="list-style-type: none"> <li>Withhold 1 or 2 doses of warfarin</li> <li>Reduce subsequent maintenance dose</li> </ul>

\*as FFP can take time to defrost prothrombin complex concentrate should be considered in cases of intracranial haemorrhage

**Prothrombin concentrates are products of choice for warfarin reversal in the setting of active bleeding and a markedly raised INR.**

### management of mother and neonate if preterm labor develops in a patient on warfarin

- The management is difficult if preterm labor develops in a patient on warfarin, because both the mother and the fetus are anticoagulated.
- the best management to prevent fetal/neonatal hemorrhage → Give fresh frozen plasma to the neonate immediately after delivery**
- Vitamin K administration does not achieve immediate reversal** of maternal anticoagulation (which may persist for 24 hours); more rapid reversal requires the transfusion of fresh frozen plasma.
- Fetal levels of coagulation factors do not correlate with maternal levels, and infusion of fresh frozen plasma into the mother does not reliably reverse fetal anticoagulation.
- A cesarean delivery may prevent hemorrhagic fetal death, and fresh frozen plasma should be administered to the neonate.

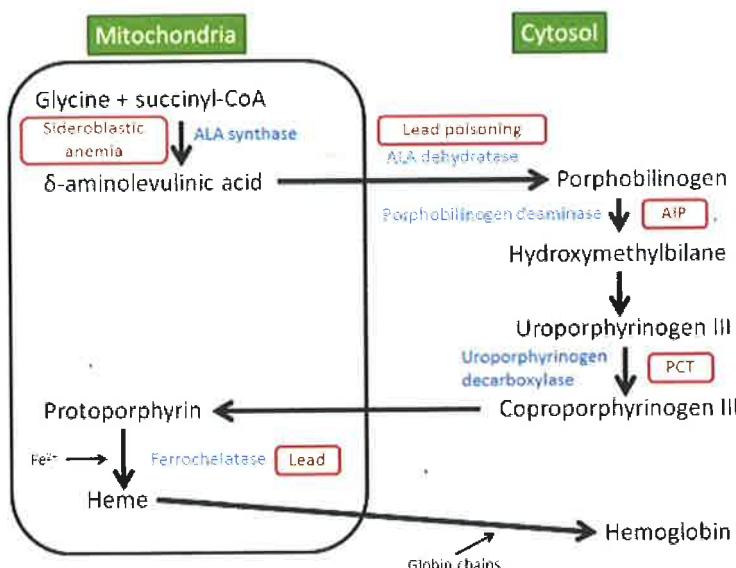
## Porphyrias

AIP - porphobilinogen deAminase; PCT - uroporphyrinogen deCarboxylase

### Overview

#### Acute intermittent porphyria: 6 P's

- **Porphobilinogen deaminase deficiency**
- **Pain in abdomen** (most common, 95% of patients experience)
- **Psychological symptoms** (Anxiety, agitation, hallucination, hysteria, delirium, depression)
- **Peripheral neuropathy** (Patchy numbness and paresthesias)
- **Pee abnormality** (Dysuria, urinary retention/incontinence or dark urine)
- **Precipitated by drugs** (e.g. barbiturates, oral contraceptives, Sulfa drugs)



#### Acute intermittent porphyria (AIP)

AIP can present with **features of an acute abdomen**, hypertension, psychiatric disturbance and hyponatraemia,

#### Aetiology

- **autosomal dominant**
- **caused by a defect in porphobilinogen deaminase, an enzyme involved in the biosynthesis of haem.**

## Epidemiology

- The most common acute porphyria is **acute intermittent porphyria**.
- 20-40-year olds more likely to be affected (only rarely presents before puberty)
- AIP is more common in females (5:1)

## Features

- **90% of affected individuals remain asymptomatic throughout their lives.**
- typically present with **abdominal symptoms**,
- **neuropsychiatric symptoms**
  - Seizures occur in 10-20% of patients with acute intermittent porphyria (AIP).
  - A range of psychiatric symptoms, including hypomania and delirium may be seen.
- **hypertension and tachycardia**
- urine turns deep red on standing
- **Photosensitivity is unusual in AIP**

## Investigations

- Patients excrete urinary porphobilinogen (PBG) between and during acute attacks.
- Faecal porphyrin excretion is usually normal or slightly increased.
- All attacks of porphyria increase the activity of hepatic 5-aminolevulinate (ALA) synthase.
- Lab features
  - hyponatraemia,
  - mild leukocytosis.

## Diagnosis

- **Urinary porphobilinogen assay is the optimal way to establish the diagnosis.**
  - The best initial test
- diagnosis is **confirmed by measuring erythrocyte porphobilinogen deaminase activity.**

## Factors precipitate an acute attack:

- Stress,
- Infection
- Pregnancy
- Menstruation
- starvation
- Drugs
  - sulphonamides,
  - barbiturates
  - phenytoin.
    - Most anti-epileptics should not be given, but gabapentin is safe and the most appropriate choice for seizures occur in (AIP).
  - ACE inhibitors and calcium channel blockers
  - Ibuprofen is safe for use in acute intermittent porphyria, but diclofenac should be avoided.

## Acute intermittent porphyria: drugs

Drugs which may precipitate attack	Safe Drugs
<ul style="list-style-type: none"> <li>• Alcohol</li> <li>• Barbiturates</li> <li>• Benzodiazepines</li> <li>• Tricyclic antidepressants</li> <li>• Halothane</li> <li>• Oral contraceptive pill</li> <li>• Sulphonamides</li> <li>• Cephalosporins</li> <li>• Erythromycin</li> <li>• Isoniazid</li> <li>• flucloxacillin</li> <li>• Anabolic steroids</li> </ul>	<ul style="list-style-type: none"> <li>• Sulphonylureas</li> <li>• Theophylline</li> <li>• Antihistamines</li> <li>• MAOIs</li> <li>• Amiodarone</li> <li>• Simvastatin.</li> <li>• <b>Diuretics</b></li> <li>• <b>calcium channel blockers</b></li> <li>• <b>ACE inhibitors</b></li> </ul>

Treatment of seizures in AIP → Gabapentin

### Treatment:

- decrease the activity of **delta-aminolevulinic acid synthase (ALA)**
  - glucose (carbohydrate loading)
    - high-glucose diets or infusions have been used for mild attacks of pain without neurological symptoms
  - intravenous haem arginate
    - thereby decreasing heme precursor synthesis.
    - The treatment of choice
- opiate analgesia.

### Distinguishing between lead poisoning and acute intermittent porphyria

- Which one of the following features in an adult patient presenting with porphyrinuria would most suggest lead poisoning rather than acute intermittent porphyria as a cause?
  - Anaemia
    - Anaemia occurs only in lead poisoning and is due to:
      - ❖ inhibition of ferrochelatase (the activity of this enzyme is normal in acute intermittent porphyria)
      - ❖ a decrease in red cell lifespan
      - ❖ enzyme inhibition (pyrimidine 5'-nucleotidase) leading to the accumulation of pyrimidine nucleotides in red cells, which in turn reduces the stability of the cell membrane (and is seen on a blood film as basophilic stippling)

## **Porphyrria cutanea tarda (PCT)**

- most common hepatic porphyria
- mechanism
  - defect in uro-porphyrinogen decarboxylase

### **Aetiology**

- **inherited**
  - most cases are sporadic
  - may be inherited (autosomal dominant),
- **acquired**
  - may be caused by hepatocyte damage e.g.
    - alcohol, (the commonest cause),
    - oestrogens (oral contraceptive pill)
    - excess iron (haemochromatosis)
    - hepatitis C

### **Features**

- The most common presenting sign of PCT is **fragility of sun exposed skin after mechanical trauma**, leading to erosions and bullae, worst on dorsal hands, forearms, and face.
- **classically photosensitive rash with bullae,**
  - Bullae develop on sun-exposed areas
  - When exposed to light, uroporphyrinogen generates free radicals that cause blistering of the skin.
  - lesions heal slowly, leaving scars.
- skin fragility on face and dorsal aspect of hands

### **Investigations**

- **plasma total porphyrins**
  - The best initial test
  - Porphyrins are increased in liver, plasma, urine and stool.
- Urine: elevated uroporphyrinogen (Urinary porphyrins) and pink fluorescence of urine under Wood's lamp
- Porphobilinogen (PBG) is normal.
- Assay of red blood cells for uroporphyrinogen decarboxylase (UROD) activity is now available
- **Antinuclear antibodies are frequently seen**

### **Management**

- withdrawal of the precipitant
- phlebotomy to deplete the excess iron stores that exacerbate the porphyria.
  - Venesection is effective (450 ml/week) until haemoglobin is 120 g/L.
- Chloroquine may also be effective because it promotes porphyrin excretion.

## **Variegate porphyria**

- autosomal dominant
- defect in protoporphyrinogen oxidase
- photosensitive blistering rash
- abdominal and neurological symptoms
- more common in South Africans

## Hodgkin's lymphoma (HL)

present at a younger age. Chest discomfort, including cough and shortness of breath, is common.

Hodgkin's lymphoma - most common type = nodular sclerosing

Hodgkin's lymphoma - best prognosis = lymphocyte predominant

### Overview

- Hodgkin's lymphoma is a malignant proliferation of lymphocytes characterised by the presence of the Reed-Sternberg cell.
- haematological malignancy arising from mature B cells.
- Lymphadenopathy, typically painless and most commonly involving the cervical and/or supraclavicular nodal chain, is the most common presenting symptom of HL.

### Epidemiology

- It has a bimodal age distributions being most common in the third and seventh decades

### Risk factors

- history of EBV infection
- family history of Hodgkin's lymphoma
- young adults from higher socio-economic class
- Immunodeficiency: e.g., organ or cell transplantation, immunosuppressants, HIV infection , chemotherapy
- Autoimmune diseases (e.g., rheumatoid arthritis, sarcoidosis)

### Features

- Painless lymphadenopathy
  - Most common is cervical lymph nodes (in ~ 60–70% of patients)
- Mediastinal mass → chest pain, dry cough, and shortness of breath
- Splenomegaly or hepatomegaly may occur if the spleen or liver are involved.
- B symptoms
  - Night sweats,
  - weight loss > 10% in the past 6 months,
  - fever > 38°C (100.4°F)
- Can occur in a variety of diseases, such as non-Hodgkin lymphoma, other malignancies, tuberculosis, and various inflammatory diseases
- Pel-Ebstein fever
  - Intermittent fever with periods of high temperature for 1–2 weeks, followed by afebrile periods for 1–2 weeks. Relatively rare but very specific for HL.
- Alcohol-induced pain
- Pruritus (focal or generalized)

### Histological classification

Type	Frequency	Prognosis	Notes
<b>Nodular sclerosing</b>	<b>Most common</b> (around 70%)	Good prognosis	More common in women. <b>Associated with lacunar cells</b>
Mixed cellularity	Around 20%	Good prognosis	Associated with a large number of Reed-Sternberg cells
<b>Lymphocyte predominant</b>	Around 5%	<b>Best prognosis</b>	
<b>Lymphocyte depleted</b>	Rare	<b>Worst prognosis</b>	

#### Poor prognosis

- weight loss > 10% in last 6 months
- fever > 38 C
- night sweats
- **Other factors associated with a poor prognosis** identified in a 1998 NEJM paper included:
  - age > 45 years
  - stage IV disease
  - haemoglobin < 10.5 g/dl
  - lymphocyte count < 600/l or < 8%
  - male
  - albumin < 40 g/l
  - white blood count > 15,000/l
  - A mass of >10 cm in size

Fatigue, pruritus, EBV infection although they are common, BUT they have no prognostic significance.

### Staging

#### Ann-Arbor staging of Hodgkin's lymphoma

- I: single lymph node
- II: 2 or more lymph nodes/regions on same side of diaphragm
- III: nodes on both sides of diaphragm
  - Spleen is regarded as a Lymph Node region, So **lymphoma with splenomegaly → Stage III**
- IV: spread beyond lymph nodes

Each stage may be subdivided into A or B

- A = no systemic symptoms other than pruritus
- B = weight loss > 10% in last 6 months, fever > 38c, night sweats (**poor prognosis**)

### Diagnosis

- **Lymph node biopsy** would be **more likely to be positive**, RSC is evident on microscopy.
- Bone marrow
  - Hodgkin results in **patchy** bone marrow infiltration, an isolated bone marrow biopsy may yield non-specific results.
  - Bone marrow biopsy is more useful for staging of advanced disease

### Management:

- Early stage (IA or IIA): Radiotherapy and chemotherapy.

- **Secondary malignancy** is the long-term complication of the radiotherapy (**need long term monitoring**)
- Later stage (III, IVA or IVB): Chemotherapy alone.
- Large mass in chest regardless of stage: Radiotherapy and chemotherapy.
- Chemotherapy includes **ABVD**: Adriamycin (also known as Doxorubicin), Bleomycin, Vincristine, Doxorubicin, cyclophosphamide, prednisolone, Rituximab & others
  - **Bleomycin related pulmonary fibrosis is a major toxicity of the ABVD regimen**
    - A high-resolution CT scan and pulmonary function tests are required to diagnose this condition.
    - Oxygen therapy should be used with caution in these patients as there is concern about further lung damage secondary to oxygen free radicals.
  - Although doxorubicin (also known as adriamycin) can cause cardiotoxicity, this is unusual at the doses used in this regimen and one would expect abnormalities on the ECG.
- **Relapsed Hodgkin lymphoma → salvage chemotherapy followed by BEAM conditioned autologous stem cell transplantation as the established gold standard.**

**Prognosis** is good overall, but it depends on classification and staging.

Hodgkin's lymphoma (HL)	Non-Hodgkin's lymphoma (NHL)
Younger age	Older age
more often restricted to lymph nodes in the neck.	Peripheral lymphadenopathy is common
Reed-Sternberg cells are present.	Reed-Sternberg cells are NOT present.
Extra-nodal involvement un common	Extra-nodal involvement is common

### Non-Hodgkin's lymphoma (NHL) (NICE guideline 2016)

- include any kind of lymphoma except Hodgkin's lymphomas.
- Most of NHL are of B cell phenotype, although T cell tumours are increasingly being recognized.
- subtypes of non-Hodgkin's lymphoma (NHL):
  - diffuse large B-cell lymphoma
  - Burkitt lymphoma.

#### **Diagnosis**

- Type of biopsy:
  - first line → excision biopsy
  - if not surgically feasible → needle core biopsy procedure
- in patient with histologically high-grade B-cell lymphoma:
  - use **FISH** (fluorescence in situ hybridisation) to identify a **MYC** rearrangement
  - If a **MYC** rearrangement is found, → use **FISH** to identify the immunoglobulin partner and the presence of **BCL2** and **BCL6** rearrangements.
- Indications of using FDG-PET-CT imaging (fluorodeoxyglucose-positron emission tomography-CT)
  - Staging
  - **to assess response** at completion of planned treatment for:
    - diffuse large B-cell lymphoma
    - Burkitt lymphoma.
  - **to assess response to treatment before autologous stem cell transplantation for high-grade (NHL).**

## Management

- **follicular lymphoma**

- **Asymptomatic** patients with low grade lymphoma such as follicular lymphoma (grade 1 and 2) can be observed closely (**Wait and watch approach**)
  - **The value of intensive chemotherapy is questionable in asymptomatic patients.** No long-term survival benefit has been demonstrated with this approach.
- stage IIA → local radiotherapy as first-line
- stage IIA + asymptomatic + single radiotherapy volume is not suitable → 'watch and wait' (observation without therapy)
- stage IIA + symptomatic + single radiotherapy volume is not suitable → treat as advanced-stage (stages III and IV) symptomatic
- advanced-stage (stages III and IV) asymptomatic → rituximab
- advanced-stage (stages III and IV) symptomatic → rituximab + combination with:
  - cyclophosphamide, vincristine and prednisolone (CVP)
  - cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)
  - mitoxantrone, chlorambucil and prednisolone (MCP)
  - cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon- $\alpha$  (CHVPI) or
  - chlorambucil
- **Relapsed or refractory** advanced-stage (stages III and IV) :
  - induction of remission → Rituximab + combination with chemotherapy
  - maintenance therapy → Rituximab monotherapy
  - **in second or subsequent remission → stem cell transplantation**

- **MALT lymphoma**

- *H. pylori*-positive gastric MALT lymphoma → *Helicobacter pylori* eradication therapy
- *H. pylori*-negative gastric MALT lymphoma → *Helicobacter pylori* eradication therapy
- gastric MALT lymphoma that responds clinically and endoscopically to *H. pylori* eradication therapy but who have residual disease shown by surveillance biopsies of the stomach, + no high-risk features. → 'watch and wait' (observation without therapy)
- residual MALT lymphoma after *H. pylori* eradication therapy + high risk of progression [*H. pylori*- negative at initial presentation or t(11;18) translocation], →
  - chemotherapy (for example, chlorambucil or CVP) + rituximab **OR**
  - gastric radiotherapy.
- Non-gastric MALT lymphoma
  - localised disease sites → radiotherapy
  - if radiotherapy is not suitable **or** disseminated disease → chemotherapy (for example, chlorambucil or CVP) + rituximab
  - localised + asymptomatic + radiotherapy is not suitable → 'watch and wait' (observation without therapy)

- **Mantle cell lymphoma**

- advanced-stage , symptomatic → chemotherapy + rituximab
- localised stage I or II → radiotherapy
- non-progressive + asymptomatic + radiotherapy is not suitable → 'watch and wait' (observation without therapy)
- chemosensitive mantle cell lymphoma → autologous stem cell transplantation
- previously untreated + stem cell transplantation is unsuitable → Bortezomib

## **Haematological malignancies: genetics**

Below is a brief summary of the common translocations associated with haematological malignancies

### **t(9;22) - Philadelphia chromosome**

- present in > 95% of patients with CML
- this results in part of the Abelson proto-oncogene being moved to the BCR gene on chromosome 22
- the resulting BCR-ABL gene codes for a fusion protein which has tyrosine kinase activity in excess of normal
- **poor prognostic indicator in ALL**

### **t(15;17)**

- seen in acute promyelocytic leukaemia (M3)
- fusion of PML and RAR-alpha genes

### **t(1;14)**

- This translocation is associated with MALT (mucosa-associated lymphoid tissue) lymphoma and deregulates BCL10

### **t(8;14)**

- seen in **Burkitt's** lymphoma
- MYC oncogene is translocated to an immunoglobulin gene

### **t(11;14)**

- **Mantle cell lymphoma**
- deregulation of the cyclin D1 (BCL-1) gene

### **t(11; 18)**

- This translocation is associated with MALT (mucosa-associated lymphoid tissue) lymphoma and deregulates MALT1

### **t(14;18)**

- This translocation is associated with follicular lymphoma
- results in a chimeric heavy-chain Ig (chromosome 14) and BCL2 (chromosome 18) gene.
- This disease presents with painless "waxing and waning" lymphadenopathy in addition to constitutional symptoms.

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## **Haematological malignancies: infections**

### **Viruses**

- EBV: Hodgkin's and Burkitt's lymphoma, nasopharyngeal carcinoma
- **HTLV-1: Adult T-cell leukaemia/lymphoma**
- HIV-1: High-grade B-cell lymphoma

### **Bacteria**

- *Helicobacter pylori*: gastric lymphoma (MALT)

### **Protozoa**

- malaria: Burkitt's lymphoma

## Burkitt's lymphoma

Burkitt's lymphoma - c-myc gene translocation

Burkitt's lymphoma is a common cause of tumour lysis syndrome

- Burkitt's lymphoma is a monoclonal proliferation of B lymphocytes, which results (in approximately 90% of the cases) from **chromosome translocations** that involve the Myc gene.
  - chromosome translocation means that a chromosome is broken, which allows it to associate with parts of other chromosomes.
- It is a high-grade B-cell neoplasm.
- There are two major forms:
  1. **endemic** (African) form: typically involves maxilla or mandible
  2. **sporadic** form:
    - abdominal (e.g. ileo-caecal) tumours are the most common form.
    - More common in patients with HIV
- Burkitt's lymphoma is **associated with the c-myc gene translocation, usually t(8;14)**.
  - The classic chromosome translocation in Burkitt's lymphoma involves chromosome 8, the site of the MYC gene.
- The **Epstein-Barr virus (EBV)** is strongly implicated in the development of the African form of Burkitt's lymphoma and to a lesser extent the sporadic form.

### **Microscopy findings**

- 'starry sky' appearance: lymphocyte sheets interspersed with macrophages containing dead apoptotic tumour cells

### **Management**

- Management is with chemotherapy.
  - This tends to produce a rapid response which may cause '**tumour lysis syndrome**'.
    - Rasburicase (a recombinant version of urate oxidase, an enzyme which catalyses the conversion of uric acid to allantoin\*) is often given before the chemotherapy to reduce the risk of this occurring.
      - ❖ \*allantoin is 5-10 times more soluble than uric acid, so renal excretion is more effective
    - **Complications** of tumour lysis syndrome include:
      - ❖ Hyperkalaemia
      - ❖ Hyperphosphataemia
      - ❖ Hypocalcaemia
      - ❖ Hyperuricaemia
      - ❖ acute renal failure

### **Prognosis**

- Localised Burkitt's is associated with around a 90% survival rate,
- although the prognosis is less good in adults.

## Cancer in the UK

The most common causes of cancer in the UK are as follows\*

- |  |   |
|--|---|
| <ul style="list-style-type: none"> <li>• 1. Breast</li> <li>• 2. Lung</li> <li>• 3. Colorectal</li> <li>• 4. Prostate</li> <li>• 5. Bladder</li> </ul> | <ul style="list-style-type: none"> <li>• 6. Non-Hodgkin's lymphoma</li> <li>• 7. Melanoma</li> <li>• 8. Stomach</li> <li>• 9. Oesophagus</li> <li>• 10. Pancreas</li> </ul> |
|--|---|

The most common causes of death from cancer in the UK are as follows:

- |   |   |
|---|---|
| <ul style="list-style-type: none"> <li>• 1. Lung</li> <li>• 2. Colorectal</li> <li>• 3. Breast</li> <li>• 4. Prostate</li> <li>• 5. Pancreas</li> </ul> | <ul style="list-style-type: none"> <li>• 6. Oesophagus</li> <li>• 7. Stomach</li> <li>• 8. Bladder</li> <li>• 9. Non-Hodgkin's lymphoma</li> <li>• 10. Ovarian</li> </ul> |
|---|---|
- Cancer is the cause of 26% of deaths in the UK, and is a more common cause of death than cardiovascular disease.
  - **Lung cancer is the biggest cancer killer in the UK (in both male and female)**, although breast cancer has the highest incidence

\*excludes non-melanoma skin cancer

## Acute lymphoblastic leukaemia (ALL)

### Epidemiology

- ALL is a disease of children.
- Most common malignant disease in children
- Peak incidence: 2–5 years

### Classification (The WHO classification)

- B-cell ALL (around 80–85% of cases)
- T-cell ALL (around 15–20% of cases)

### Risk factors

- Children with certain genetic and immunodeficiency syndromes are at **increased risk**.  
These include:
  - Down syndrome,
  - Neurofibromatosis type 1,
  - Bloom syndrome, and
  - ataxia telangiectasia.

### Features

- The most common presenting symptoms of ALL are nonspecific: **fever**, infection, bleeding, bone pain, or painless **lymphadenopathy**.
  - Fever and lymphadenopathy are rare in AML, but can be common first signs in ALL
- Testicular enlargement (rare finding)
- Airway obstruction (stridor, difficulty-breathing) caused by mediastinal infiltration
- Meningeal leukemia (or leukemic meningitis) → headache, neck stiffness

### Diagnosis

- Bone marrow aspirate or biopsy: confirmatory diagnostic tests
  - AML: > 20% myeloblasts in the bone marrow
  - ALL: > 25% lymphoblasts in the bone marrow

## Prognostic features

Good prognostic factors	Poor prognostic factors
<ul style="list-style-type: none"> <li>French-American-British (FAB) L1 type</li> <li>common ALL</li> <li>pre-B phenotype</li> <li>low initial WBC</li> <li>del(9p)</li> <li><b>t(12;21)</b></li> </ul>	<ul style="list-style-type: none"> <li>FAB L3 type</li> <li>T or B cell surface markers</li> <li>Philadelphia translocation, t(9;22)</li> <li><b>t(8;14) the worst prognosis</b></li> <li>age &lt; 2 years or &gt; 10 years</li> <li>male sex</li> <li>CNS involvement</li> <li>high initial WBC (e.g. <math>&gt; 100 * 10^9/l</math>)</li> <li>non-Caucasian</li> </ul>

- The 8:14 chromosomal translocation** is associated with a particularly **poor prognosis**, and is found in approximately 1% of adults with ALL. The incidence of CNS involvement is very high at the point of diagnosis, and median event free survival after chemotherapy is only two months.

## Treatment

- Before ALL treatment with chemotherapy, if blast cells count is very high ( $> 100 * 10^9/l$ ) → the patient needs **Leukapheresis** to prevent sludge in of capillary beds, this can be life-saving.
- Philadelphia positive ALL:**
  - **Chemotherapy + rituximab + Tyrosine Kinase Inhibitor**
    - high dose chemotherapy** (usually UKALL 14 or hyper-CVAD), **together with** the anti-CD20 monoclonal antibody **rituximab** and a **tyrosine kinase inhibitor** in view of the BCR-ABL positivity.
- Central nervous system (CNS) therapy (intrathecal) is indicated in all patients with ALL
- Lumber puncture (LP) should be delayed until chemotherapy has begun**
- Allogeneic stem cell transplantation

## Chronic lymphocytic leukaemia (CLL)

CLL - treatment: Fludarabine, Cyclophosphamide and Rituximab (FCR)

CLL - immunophenotyping is investigation of choice

**CLL + anaemia with positive Coombs test → autoimmune haemolytic anaemia (AHA) → Prednisolone is the initial intervention of choice. rituximab is the second-line step.**

### Overview

- (CLL) is caused by a monoclonal proliferation of well-differentiated lymphocytes which are **almost always B-cells (99%)**

### Prevalence

- CLL is the **most common form of leukemia found in adults** in Western countries.
- generally, affects older populations (The median age at diagnosis is 72 years)

### Features

- often none

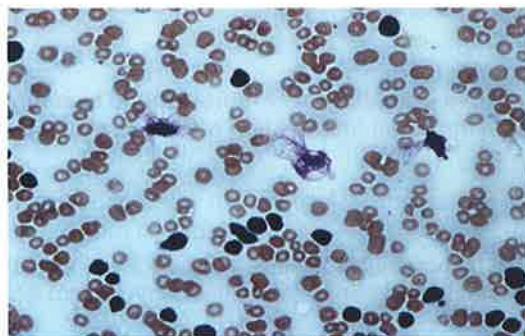
- constitutional: anorexia, weight loss
- bleeding, infections
- lymphadenopathy more marked than CML

### Complications

- **hypogammaglobulinaemia** leading to recurrent infections
  - **Infections are the most frequent complication causing death in patients with CLL.**
  - Although intravenous immunoglobulin prevents recurrent infections it does not prolong survival.
- **Autoimmune complications are common with CLL:**
  - **warm autoimmune haemolytic anaemia** in 10-15% of patients
    - the combination of spherocytes with a raised bilirubin, LDH and positive direct Coombs' test is consistent with an autoimmune haemolysis.
  - **immune thrombocytopenia (ITP)**
    - ❖ **the next step in management → Chemotherapy and intravenous immunoglobulin**
      - ⇒ In ITP, platelets would only be indicated for life threatening bleeding (or platelet count  $<10 \times 10^9/L$ )
- transformation to high-grade lymphoma (Richter's transformation)

### Investigations

- Blood film:
  - smudge cells (also known as **smear cells**)
    - smudge cells are the artifacts produced by the lymphocytes damaged during the slide preparation.
  - $\geq 5000$  monoclonal B lymphocytes/ $\mu l$ . The clonality of the circulating B lymphocytes needs to be confirmed by flow cytometry.
- **Immuno-phenotyping:**
  - **Peripheral blood flow cytometry is the most valuable test to confirm a diagnosis of CLL.**
  - will demonstrate the cells to be B-cells
    - **CD5, CD19 and CD23** are characteristically positive.
- Although a **bone marrow biopsy** is not required for diagnosis, it is recommended for the diagnostic evaluation of unclear cytopenias, or FISH or molecular genetics if peripheral blood cell lymphocytosis does not allow adequate immunophenotyping
- An extended **FISH** analysis is recommended before the start of therapy because the detection of additional cytogenetic abnormalities [del(11q) or trisomy 12] may have therapeutic consequences



Peripheral blood film showing smudge B cells

## Management

- observation policy is usual during the early stages of the disease.
- Indications for treatment
  - progressive marrow failure: the development or worsening of anaemia and/or thrombocytopenia
    - Bone marrow compromise (stage C disease).
  - Lymphocyte doubling time of less than 12 months
  - massive (>10 cm) or progressive lymphadenopathy
  - massive (>6 cm) or progressive splenomegaly
  - progressive lymphocytosis: > 50% increase over 2 months or lymphocyte doubling time < 6 months
  - Immune complications, for example, ITP, autoimmune haemolysis
  - systemic symptoms: (Disabling B symptoms)
    - weight loss > 10% in previous 6 months,
    - fever >38 C for > 2 weeks,
    - extreme fatigue,
    - night sweats
- Drugs
  - fludarabine, cyclophosphamide and rituximab (**FCR**) has now emerged as the **initial treatment of choice** for the majority of patients
  - monitoring by regular blood counts
  - **What antimicrobial prophylaxis should he receive before starting chemotherapy with fludarabine?**
  - ➔ **Co-trimoxazole**
    - Fludarabine is a purine analogue that is phosphorylated intracellularly.
    - All of the purine analogues cause myelosuppression, but there is a significantly **higher risk of patients developing Pneumocystis jirovecii pneumonia** while on treatment.
    - Use of prophylactic co-trimoxazole (Septrin) has dramatically reduced the frequency of this severe opportunistic infection in these patients.
    - Co-trimoxazole should be **continued after chemotherapy until the CD4 counts exceeds 200 cells/mm<sup>3</sup> (0.2 × 10<sup>9</sup>/L).**
  - Regular infusions of **immunoglobulin** to prevent infections
    - Recurrent infections are recognised in CLL due to hypogammaglobulinaemia and immune paresis; but are not an indication for disease control.

## CLL prognostic factors

### Poor prognostic factors (median survival 3-5 years)

- male sex
- age > 70 years
- lymphocyte count > 50
- prolymphocytes comprising more than 10% of blood lymphocytes
- lymphocyte doubling time < 12 months
- raised LDH
- CD38 expression positive
- deletions of part of the short arm of chromosome 17 (del 17p)

### Chromosomal changes

- deletion of the long arm of **chromosome 13** (del 13q) is the **most common** abnormality, being seen in **around 50%** of patients. It is associated with a **good prognosis**
- deletions of part of the short arm of **chromosome 17** (del 17p) are seen in **around 5-10%** of patients and are associated with a **poor prognosis**

**Differential diagnosis**

- **mantle cell lymphoma (MCL)**
  - These tumour cells express B-cell surface antigens and also expresses CD5, **but usually not CD23.**
  - For cases that express CD23, staining for cyclin D1 or SOX11 and fluorescence *in situ* hybridisation (**FISH**) for detecting a translocation (11;14) are useful for establishing the diagnosis of MCL.
- **small lymphocytic lymphoma (SLL)**
  - In the WHO classification, small lymphocytic lymphoma (SLL) and CLL are considered to be a single entity.
  - CLL is effectively the same disease as SLL except the disease is found mostly in the bone marrow or blood.
    - SLL is found mostly in lymph nodes
  - The diagnosis of SLL requires the presence of lymphadenopathy and/or splenomegaly with a number of B lymphocytes in the peripheral blood not exceeding  $5 \times 10^9/l$ .
  - SLL cells show the same immunophenotype as CLL.
  - The diagnosis of SLL should be confirmed by histopathological evaluation of a lymph node biopsy, whenever possible.
- **monoclonal B-lymphocytosis' (MBL)**
  - In absence of lymphadenopathy, organomegaly, cytopaenia and clinical symptoms, the presence of fewer than 5000 monoclonal B lymphocytes/ $\mu l$  defines 'monoclonal B-lymphocytosis' (MBL)
  - can be detected in 5% of subjects with normal blood count.
  - Progression to CLL occurs in 1%–2% of MBL cases per year.

**Acute myeloid leukaemia (AML)**

Acute myeloid leukaemia - poor prognosis: deletion of chromosome 5 or 7 .

Acute myeloid leukaemia - good prognosis: t(15;17)

- AML is the **most common form of acute leukaemia in adults.**
- It may occur as a primary disease or following a secondary transformation of a myeloproliferative disorder.
- **Acute leukemia is defined as an accumulation of more than 20 percent of immature blasts at the bone marrow.**
  - Chronic myeloid leukaemia often ends in acute blastic transformation after a mean duration of approximately four years.
- classically associated with **Down syndrome.**
- **Alkylating agents** is a chemotherapy drug class that increases the risk of developing AML.
- characterized by cells with positive cytoplasmic **staining for myeloperoxidase.**
- The median age of onset of AML is 65 years.

**Presentation**

- Vague and non-specific (flu-like symptoms)
- Due to pancytopenia (Infection, anaemia , bleeding)
- Splenomegaly may occur but typically mild and asymptomatic.
- LN swelling is rare.

- High total leucocyte count (TLC) leads to leucostasis and hyperviscosity → drowsiness and retinal vein dilatation.
- Blood film reveals white cells predominantly myeloblasts and promyelocytes.

### Poor prognostic features

**AML → Cytogenetics Karyotype is of most prognostic value.**

- > 60 years
- > 20% blasts after first course of chemo
- cytogenetics: deletions of chromosome 5 or 7
  - bone marrow cytogenetics are the **most important** aspect in determining prognosis in AML

### Good prognostic features

- Karyotype of bone marrow
  - patients with t(8;21) or chromosomes 16 inversion have a low risk of relapse

### Classification - French-American-British (FAB)

- M0 - undifferentiated
- M1 - without maturation
- **M2** - with granulocytic maturation
  - the **most common** (25% of adult AML)
  - associated with a t(8;21) translocation.
- **M3 - acute promyelocytic (APL)**
  - has the **best prognosis** of all the subtypes of AML.
  - Unlike the other AML subtypes, APL is treated with all-trans retinoic acid (ATRA).
  - t(15;17)
- M4 - granulocytic and monocytic maturation
  - associated with a t(16;16) translocation
- M5 - monocytic
- M6 - erythroleukaemia
- M7 – megakaryoblastic

AML (monocytic) **M5**: high count of circulating blasts → may lead to symptoms of cellular hyperviscosity (headache, confusion, fits, coma) and tissue deposits of leukaemia cells (gums hypertrophy) with cells stain positive with Sudan Black and myeloperoxidase plus NES.

**ALL** cells characteristically stain positive for **PAS** (Periodic acid-Schiff) and **NSE** (Non-specific Esterase).

**AML** cells characteristically stain positive for **Sudan Black** and **myeloperoxidase**, but **M4** and **M5** cells stain positive for **NSE**, while **M6** cells stain positive for **PAS**.

**Differentiating between ALL and AML**

	ALL	AML
Presence of auer rods in blood	None	Always present
Presence of lymphoblasts in blood	Always present	May or may not be present
Bone and joint pain	More common	Less common
Hepatosplenomegaly	More common	Less common
Organ infiltration	More common	Quite unusual

**Management**

- Combination chemotherapy including arabinosylcytosine after **apheresis**.
- Cytarabine and Anthracycline is considered the initial treatment of choice for patients with AML.

**Bone marrow transplantation**

- The aim would be to choose a fully matched sibling who was also CMV-negative.
- In general, **fully HLA matched, CMV matched, male donors are preferred over fully HLA matched, CMV matched female donors**. This is because of the **increased risk of graft versus host disease in stem cell donations from female donors to male recipients**.

**Acute promyelocytic leukaemia (APML)****Acute promyelocytic leukaemia - t(15;17)**

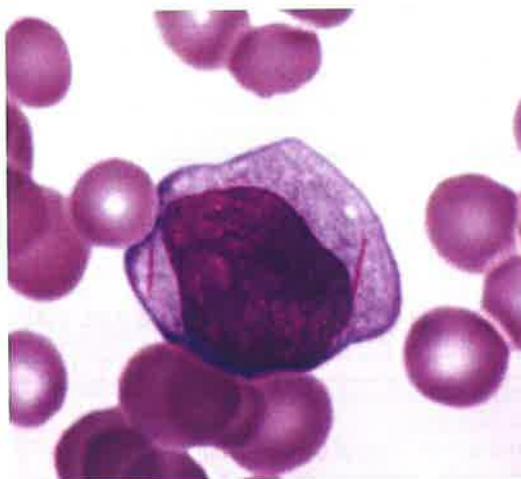
- APML, the M3 subtype of AML.
- The importance of identifying APML lies in both the presentation (classically disseminated intravascular coagulation) and management
- APML is associated with the t(15;17) translocation**
  - causes fusion of the PML and RAR-alpha genes.
  - In 95% of cases, retinoic acid receptor-alpha (RARA) gene on chromosome 17 is involved in a reciprocal translocation with the promyelocytic leukaemia gene (PML) on chromosome 15.
  - The mechanism underlying leukaemogenesis is **aberrant fusion of 2 genes PML and RARA**.

**Features**

- presents younger than other types of AML (average = 25 years old)
- DIC or thrombocytopenia often at presentation
- Auer rods** (seen with myeloperoxidase stain)
  - Auer rods are eosinophilic needle-like cytoplasmic inclusions found in blast cells
- good prognosis

**management**

- treatment of APML differs from that of all other AML forms
- the most appropriate initial treatment regimen: All trans retinoic acid (ATRA) a derivative of vitamin A., plus Anthracycline based chemotherapy**



The distinct elongated cytoplasmic structures are **Auer rods** which are pathognomonic for AML.

### **Retinoic acid syndrome** (or differentiation syndrome)

#### **Pathophysiology**

- thought to be the result of the release of cytokines and subsequent lung infiltration by the neutrophils created by the maturation of myelocytes in APML.
- The presence of CD13 expression on leukemic cells can be a predictor of the future development of this syndrome.

#### **Causes**

- after treatment of APML with all-trans retinoic acid (ATRA) (present within a week of treatment)
- after treatment of APML with arsenic trioxide.
- usually occurs during induction therapy

#### **Incidence**

- 14-16% of patients.

#### **Features**

- dyspnea, pulmonary edema and effusions, A chest X-ray shows interstitial infiltrates.
- fevers,
- hypotension,
- Other complications include pericardial effusion, renal insufficiency, and hypertension.

#### **treatment**

- Corticosteroids
- the drug is temporarily stopped, then started again at 50-75% of the earlier dose.  
Alternatively, arsenic therapy can be tried.

#### **prognosis**

- Without prompt treatment with glucocorticoids, patients with this disorder have a mortality rate as high as 30% due to brain edema or hypoxic respiratory failure.
- Fortunately, most patients improve markedly within 12 hours and their symptoms resolved completely within 24 hours.

## Chronic myeloid leukaemia (CML)

**Chronic myeloid leukaemia – imatinib = tyrosine kinase inhibitor**

**CML- Philadelphia chromosome = t(9:22)**

**Philadelphia translocation, t(9:22) – good prognosis in CML, poor prognosis in AML + ALL**

### **Pathophysiology**

- The Philadelphia chromosome is present in more than 95% of patients with (CML).
- It is due to a translocation between the long arm of chromosome 9 and 22 - t(9:22)(q34; q11). This results in part of the ABL proto-oncogene from chromosome 9 being fused with the BCR gene from chromosome 22. The resulting BCR-ABL gene codes for a fusion protein which has tyrosine kinase activity in excess of normal

### **Epidemiology**

- Sex: ♂ > ♀
- Peak incidence: 50–60 years

### **Etiology**

- Idiopathic (in most cases)
- Ionizing radiation (e.g., secondary to therapeutic radiation)
- Aromatic hydrocarbons (especially benzene)

### **Features**

- middle-age (40-50 years)
- anaemia,
- weight loss,
- splenomegaly may be marked → abdominal discomfort

### **Complications**

- may undergo blast transformation (AML in 80%, ALL in 20%)

### **Investigations**

- Peripheral blood
  - **spectrum of myeloid cells seen**
    - The blood film shows both mature (neutrophils) and immature forms in various stages of differentiation (myelocytes and metamyelocytes)
      - ❖ In acute myelogenous leukemia (AML) one would expect only immature blasts.
    - CML causes the most severe leukocytosis (> 500,000/ $\mu$ l) of all forms of leukemia
    - Increasing basophilia is a sign of acceleration!
- **Cytogenetic analysis of the patient's bone marrow**
  - the most useful test
  - most cases of CML are usually associated with BCR-ABL translocation, (Philadelphia chromosome)
  - Better than molecular analysis of peripheral blood
- **Molecular analysis of peripheral blood**
  - useful and least invasive for the patient

- BCR-ABL translocation ( $t[9;22]$ ) can be detected by **PCR**
- **however, in practice one would still eventually proceed to a bone marrow (BM) examination to assess morphology** and you would still also perform conventional cytogenetics on the bone marrow (this is done on a bone marrow sample rather than peripheral blood because the cellularity tends to be greater in the BM, giving lower failure rates of the test).
- Leukocyte alkaline phosphatase (LAP) → decreased
  - Low LAP is a distinct feature of CML that distinguishes it from all other forms of leukemia

### **WHO classification of the CML phases**

CML Phase	Blast count in peripheral blood and bone marrow
Chronic	< 10%
Accelerated	10–19%
Blast	≥ 20%

### **Management**

- Unlike (CLL), CML will progress to frank leukaemia quite rapidly, so treatment is needed.
- **imatinib** is now considered first-line treatment
  - inhibitor of the tyrosine kinase associated with the BCR-ABL defect
  - very high response rate in chronic phase CML
- If remission is not achieved with **imatinib**, then:
  - in a patient under 60-65 years, an allogeneic transplant would be considered if there was a matched sibling donor;
  - in a 50-year-old patient or younger a matched unrelated donor transplant would be considered too.
- If the patient had been in **blast crisis phase**, then AML-type chemotherapy as well as Glivec (**imatinib**) would be the choice.
- hydroxyurea
- interferon-alpha
- allogenic bone marrow transplant

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## **Allogenic bone marrow transplant**

### **Complication**

#### **Cytomegalovirus pneumonia**

- The microscopy shows owl's eye inclusion bodies, characteristic of CMV, but diagnosis is usually made by PCR of blood/lavage fluid.
- It is the commonest life-threatening complication following allogenic bone marrow transplant,
- usually occurring within the first 4 months following surgery.
- **the treatment of choice → Ganciclovir**
- Onset is rapid and mortality in the context of BMT is around 80%, even with antiviral therapy (ganciclovir).

## Hairy cell leukaemia

### Overview

- malignant proliferation disorder of **B cells**.
- Rare, about 2% of leukemias.
- more common in males (4:1)
- frequently occurs in **men in their fifth decade**.

### Features

- pancytopenia
- splenomegaly
- skin vasculitis in 1/3 patients
- 'dry tap' despite bone marrow hypercellularity
- tartrate resistant acid phosphatase (TRAP) stain positive
- characteristic hairy leukocyte on blood smear with a "fried egg" appearance
  - medium-sized lymphocytes with numerous spiky, peripheral, cytoplasmic projections.

### Management

- chemotherapy is **first-line**: **cladribine** (adenosine deaminase inhibitor), pentostatin
  - Cladribine**
    - Cladribine is a purine analog → inhibit DNA polymerase and cause DNA strand breaks.
    - SE → myelosuppression, nephrotoxicity, and neurotoxicity.
- immunotherapy is **second-line**: rituximab, interferon-alpha
  - Alpha interferon at 2 million U/m<sup>2</sup> subcutaneously three times a week for 12-18 months can be used to salvage relapsed or refractory hairy cell leukemia.

## Paraproteinaemia

### Causes of paraproteinaemia

- myeloma
- monoclonal gammopathy of uncertain significance (MGUS)
- benign monoclonal gammopathy
- Waldenstrom's macroglobulinaemia
- amyloidosis
- CLL, lymphoma
- heavy chain disease
- POEMS

### Benign monoclonal gammopathy

- non-lymphoid malignancy (e.g. colon, breast)
- infections (CMV, hepatitis)
- autoimmune disorders (RA, SLE)

## Multiple myeloma

classic symptoms of multiple myeloma: bone pain, pathological fracture, anaemia and hypercalcaemia (leading to thirst).

Multiple myeloma causes a **low anion gap**.

### Definition

- Multiple myeloma is a **neoplasm of the bone marrow plasma cells**.

### Epidemiology

- The peak incidence is patients aged 60-70 years.

- Multiple myeloma is the most common primary tumor of the bone in patients older than 50 years.
- equal sex ratio
- more common in Afro-Caribbean ethnic groups than in Caucasians

#### **Monoclonal products produced**

- IgG (50-60%)
- IgA (20-30%)
- light chain disease (20%)

#### **Association**

- **Type 2/Proximal renal tubular acidosis is a type of renal tubular acidosis associated with multiple myeloma.**

#### **Pathophysiology**

- Neoplastic proliferation of plasma cells
  - Bone marrow infiltration → suppression of hematopoiesis → leukopenia, thrombocytopenia, anemia
  - Cell proliferation → osteolysis → hypercalcemia
- Overproduction of monoclonal immunoglobulin and/or light chains
  - Non-functioning antibodies → functional antibody deficiency
  - ↑ Serum viscosity → hyperviscosity syndrome

#### **Clinical features**

- bone disease:
  - due to neoplastic plasma cells activating RANKL receptors on osteoclasts.
  - **bone pain**, (Bones commonly affected are the flat bones of the spine, and as such lower back pain is one of the most common presenting features)
  - osteoporosis + **pathological fractures (typically vertebral)**, osteolytic lesions
  - weakness and paresthesias in the lower extremities due to vertebral compression fractures
- anaemia
  - fatigue and malaise
  - **The most common presenting manifestations of multiple myeloma are those related to anemia.**
- infection
- hypercalcaemia → nausea, fatigue, confusion, polyuria, constipation
- hyperphosphataemia
  - due to **reduced renal excretion** which may be directly **due to renal impairment** or interference with excessive protein load.
- Foamy urine,
  - caused by Bence Jones proteinuria
- renal failure
  - the most common cause is from **light chain deposition**.
  - **Usually**, the renal damage in MM is **tubular**. Occasionally there may be glomerular damage with consequent albumin loss.
- amyloidosis e.g. Macroglossia, carpal tunnel syndrome; neuropathy; hyperviscosity
  - carpal tunnel syndrome - the most common peripheral neuropathy associated with multiple myeloma
- **Multiple myeloma may present with rouleaux formation on blood film and raised total protein (globulin component).**
  - The globulin level is markedly raised (albumin + globulin = total protein), suggesting the presence of a paraprotein.
    - (globulin level = total protein - albumin). A normal level should be below 36 g/L.
- **Hypercalcaemia in myeloma**
  - primary factor:

- due primarily to increased osteoclastic bone resorption caused by local cytokines (e.g. IL-1, tumour necrosis factor) released by the myeloma cells
- much less common contributing factors:
  - impaired renal function, increased renal tubular calcium reabsorption and elevated PTH-rP levels

**Which acid-base disorders may be found in an IgG multiple myeloma?**

➔ **Low anion-gap metabolic acidosis**

- IgG tends to be cationic, whereas IgA tends to be anionic. As a consequence, patients with IgG myeloma will tend to have a lower than normal serum anion gap.

**Diagnostic criteria** for multiple myeloma requires one major and one minor criteria or three minor criteria in an individual who has signs or symptoms of multiple myeloma.

- **Major criteria**
  - Plasmacytoma (as demonstrated on evaluation of biopsy specimen)
  - 30% plasma cells in a bone marrow sample
  - Elevated levels of M protein in the blood or urine
    - monoclonal proteins:
      - ❖ in the serum → (usually IgG or IgA)
      - ❖ in the urine (Bence Jones proteins)
    - ⇒ **there is Negative dipstick for protein and positive in biochemistry, because Bence jones proteins are not detected by dipstick**
- **Minor criteria**
  - 10% to 30% plasma cells in a bone marrow sample.
  - Minor elevations in the level of M protein in the blood or urine.
  - Osteolytic lesions (as demonstrated on imaging studies).
  - Low levels of antibodies (not produced by the cancer cells) in the blood.

**Investigations:** (NICE 2016)

1. **to confirm the presence of a paraprotein** indicating possible myeloma or (MGUS):
  - serum protein electrophoresis **and** serum-free light-chain assay
    - **(best initial test)** → serum protein electrophoresis
  - If serum protein electrophoresis is abnormal → use serum immunofixation
  - Do not use serum protein electrophoresis, serum immunofixation, serum-free light-chain assay or urine electrophoresis (urine Bence–Jones protein assessment) **alone** to exclude a diagnosis of myeloma.
    - The observation that serum free light chains can occur in the absence of a detectable monoclonal protein in the peripheral blood is the explanation why two tests must always be done when investigating possible myeloma: both serum electrophoresis and either serum or urinary free light chains.
    - **monoclonal free light chains are found in isolation in 20–30% of cases of myeloma**
2. **to confirm a diagnosis of myeloma:**
  - **bone marrow aspirate** and trephine biopsy
  - **the bone marrow aspirate would confirm the diagnosis irrefutably.**
    - morphology to determine plasma cell percentage
      - ❖ Bone marrow examination would reveal increased plasma cells (greater than 4% and usually greater than 30%).
    - flow cytometry to determine plasma cell phenotype
    - **bone marrow aspirate → dark red jelly-like material in the syringe (Plasma cells)**

**3. in a patient presenting with spinal cord compression:**

- the most appropriate initial investigation is → **Urgent MRI of her spine**
  - This should be done before investigation that used to confirm myeloma.
- skeletal survey → bone lesions

### Laboratory confirmation of Multiple Myeloma (NICE 2018)

**1. To confirm the presence of a paraprotein indicating possible myeloma or (MGUS):**

- **Two tests must always be done:** both serum electrophoresis **and either** serum or urinary free light chains
- **If serum protein electrophoresis is abnormal,** use serum immunofixation to confirm the presence of a paraprotein indicating **possible** myeloma or MGUS.
- **Do not use** serum protein electrophoresis, serum immunofixation, serum-free light-chain assay or urine electrophoresis (urine Bence-Jones protein assessment) **alone** to exclude a diagnosis of myeloma.
  - free light chains (20–30% of cases of myeloma) are found in the absence of a detectable monoclonal protein in the peripheral blood.

**2. To confirm a diagnosis of myeloma:**

- **Bone marrow aspirate** and trephine biopsy
  - Morphology to determine plasma cell percentage ( $\geq 10\%$ ).
  - flow cytometry to determine plasma cell phenotype.

### Treatment: general view

- The best initial treatment of multiple myeloma is **chemotherapy induction**.
- autologous bone marrow transplant in addition to chemotherapy has **better** results than chemotherapy alone.

- Asymptomatic patients: → watch and wait, unless patients have:
  - $\geq 60\%$  clonal cells,
  - excessive free light chains or
  - $\geq 1$  bone lesion
- Symptomatic patients
  - HCT eligible: induction therapy followed by autologous HCT
  - HCT ineligible: chemotherapy alone (e.g., dexamethasone and lenalidomide)
- Supportive therapy
  - Osteolysis and bone pain
    - Bisphosphonates
    - Radiation therapy of osteolytic regions
  - Pancytopenia with anemia and increased risk of infection
    - Blood transfusions
    - Granulocyte-colony stimulating factor (G-CSF) and erythropoietin (EPO)

**Patients with myeloma with high paraprotein levels and symptoms related to hyperviscosity should have urgent plasma exchange, chemotherapy needs to then be instituted promptly to control the disease process and prevent symptoms reoccurring.**

**Treatment**

- previously untreated multiple myeloma (newly diagnosed)
  - Patients who are eligible for high-dose chemotherapy with stem cell transplantation
    - bortezomib + dexamethasone,
    - or bortezomib + dexamethasone + thalidomide
  - if high-dose chemotherapy with stem cell transplantation is considered inappropriate
    - thalidomide + alkylating agent + corticosteroid
- People who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation:
  - bortezomib (a proteasome inhibitor) monotherapy
- People who have received two or more prior therapies:
  - lenalidomide + dexamethasone
    - lenalidomide → immunomodulatory derivatives (structural derivatives of thalidomide)
- People with untreated, newly diagnosed, myeloma-induced acute renal disease:
  - bortezomib + dexamethasone
  - If a bortezomib is unsuitable → thalidomide + dexamethasone
  - Do not perform plasma exchange for myeloma-induced acute renal disease.
- Preventing bone disease, managing non-spinal and spinal bone disease
  - bisphosphonates should be given routinely, even in the absence of hypercalcaemia.
  - Bisphosphonates reduce bony disease in myeloma, lowering the frequency of pathological fractures, modulate the disease and have some antitumor activity.
    - zoledronic acid or
    - disodium pamidronate, if zoledronic acid is contraindicated or not tolerated or
    - sodium clodronate, if zoledronic acid and disodium pamidronate are contraindicated, not tolerated or not suitable
  - surgical stabilisation followed by radiotherapy for non-spinal bones that have fractured or are at high risk of fractures.
  - Consider **radiotherapy** for people who need additional **pain relief**
- Managing peripheral neuropathy
  - If patient on bortezomib
    - switch to subcutaneous injections and/or
    - reduce to weekly doses and/or
    - reduce the dose.
  - if patient on other than bortezomib
    - Temporarily stop neuropathy-inducing myeloma treatments if people develop either of the following:
      - ❖ grade 2 neuropathy with pain
      - ❖ grade 3 or 4 neuropathy
- Managing fatigue
  - Erythropoietin analogues (adjusted to maintain a steady state of haemoglobin at 110–120 g/litre) to improve fatigue in people with myeloma who have symptomatic anaemia.
- Cord compression secondary to bony involvement of multiple myeloma:
  - I.V Steroids should be commenced **immediately**
    - Melphalan and dexamethasone both have a place in the treatment of myeloma but would not be of use as pain control.
  - However, the **treatment of choice is local radiotherapy**. NICE suggest localised radiotherapy should be the first point of call for urgent treatment.
    - **Radiotherapy is extremely effective as pain control in this situation and would be the ideal choice.**
  - **Vertebroplasty** is typically considered in patients of whom have evidence of metastatic changes in the spine but show no signs of spinal cord compression.

- **Surgical decompression:** is also considered if imaging suggests any form of spinal instability or structural defects, but often after steroids and radiotherapy has been administered.

#### Blood transfusion in myeloma may cause acute deterioration

- The plasma volume increases with increasing viscosity and may compromise cardiac function.
- They should not be transfused until the viscosity has been lowered as a rise in haematocrit can precipitate a serious worsening of their symptoms.

#### Thalidomide

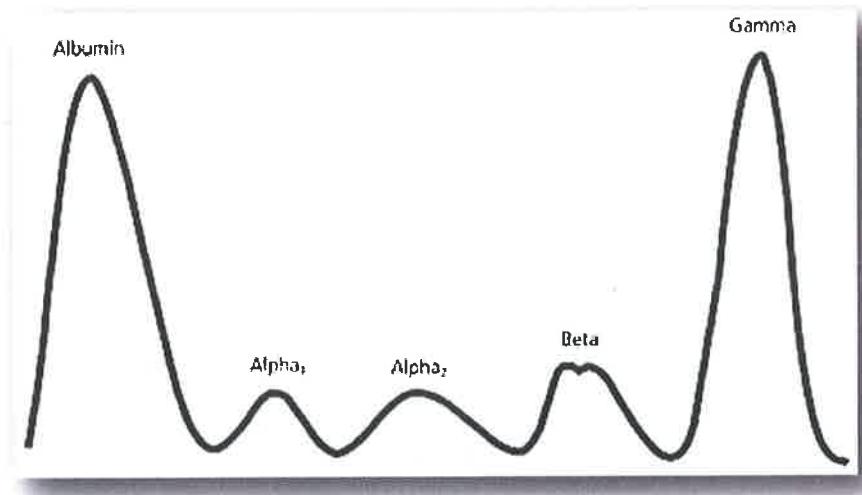
- Immunomodulatory drugs such as thalidomide and **lenalidomide** are now first line medications in the treatment of myeloma.
- The most common side effect of lenalidomide is myelosuppression, whereas somnolence, peripheral neuropathy and constipation are side effects of thalidomide.
- The inherent, serious issue that is applicable to both medications is the teratogenic potential - **all patients must be informed of this risk and advised regarding birth control** and avoidance of sharing of medications with any other person.
- It is not known whether lenalidomide is present in the semen of male patients receiving the drug. Therefore, males receiving lenalidomide must always use a latex condom during any sexual contact with females of childbearing potential even if they have undergone a successful vasectomy.

#### Myeloma: prognosis

- **B2-microglobulin is a useful marker of prognosis** - raised levels imply poor prognosis.
  - Beta-2-microglobulin has been shown to be predictive of risk of progression of disease in myeloma, myelodysplastic syndrome, and chronic myeloid leukaemia.
  - In myeloma it is an accurate estimate of total disease load, with guidelines suggesting that a beta-2-microglobulin level of  $>3.5 \text{ mg/L}$  is strongly associated with increased mortality and morbidity.
- Low levels of albumin are also associated with a poor prognosis
- Increased **lactate dehydrogenase** levels more than **double** the normal is considered a bad prognostic sign in multiple myeloma.

#### International prognostic index

Stage	Criteria	Median survival (months)
I	B2 microglobulin $< 3.5 \text{ mg/l}$ Albumin $> 35 \text{ g/l}$	62
II	Not I or III	45
III	B2 microglobulin $> 5.5 \text{ mg/l}$	29



**Abnormal serum protein electrophoresis pattern in a patient with multiple myeloma. Note the large spike in the gamma region.**

- In the interpretation of serum protein electrophoresis, most attention focuses on the gamma region(gamma-globulin zone), which is composed predominantly of antibodies of the IgG type.

### **Monoclonal gammopathy of undetermined significance (MGUS)**

- MGUS also known as benign paraproteinaemia and monoclonal gammopathy) is a common condition that causes a paraproteinaemia and is often mistaken for myeloma. Differentiating features are listed below.
- can be seen in >5% of people over 70 years of age.

#### **Risk of transmission to malignancy:**

- Around 10% of patients eventually develop myeloma at 5 years, with 50% at 15 years
- 1 percent per year develop multiple myeloma.

#### **Features**

- usually asymptomatic
- no bone pain or increased risk of infections
- around 10-30% of patients have a **demyelinating neuropathy**

#### **Differentiating features from myeloma**

- normal immune function
- normal beta-2 microglobulin levels
- lower level of paraproteinaemia than myeloma (e.g. < 30g/l IgG, or < 20g/l IgA)
- stable level of paraproteinaemia
- no clinical features of myeloma (e.g. lytic lesions on x-rays or renal disease)

feature	MGUS	myeloma
M protein concentration in serum	<30 g/l	>30 g/l
bone marrow plasma cells	<10 %	>10 %
organ and tissue impairment	no end organ damage including bone lesions	organ or tissue impairment (including bone lesions)

### Treatment

- **Observation**
- if there is neuropathy
  - MGUS patients are associated with osteoporosis and osteopenia. They may benefit from treatment with **bisphosphonates**
    - Bisphosphonates
      - ❖ pyrophosphate analogue
      - ❖ act by binding to hydroxyapatite in bone which leads to low osteoclastic activity.

**MRCPUK-part-2-March- 2017:** A 72-year-old man C/O persistent tiredness over the past 3 months. No other abnormality. Investigations reveals Albumin: 38 g/l, IgG paraprotein band: 14 g/l, Bone marrow: 7% plasma cells. Which of the following is the most appropriate intervention?

➔ **Observation**

- MGUS is defined by paraprotein (<30 g/l), bone marrow plasma cells <10% and the absence of myeloma-related organ or tissue damage (predominantly renal, skeletal or bone marrow impairment).
- **Annual overall progression to myeloma is 1%** and, as such, no intervention is required.

### Smoldering myeloma

- **Smoldering multiple myeloma** → multiple myeloma (M-protein >3g/dL or >10% plasma cells in bone marrow) + no end organ damage.
- **criteria for end-organ damage**, which are:
  - Serum calcium >11.5 mg/dL
  - Serum creatinine >2 mg/dL or estimated creatinine clearance <40 ml/min
  - Anemia with hemoglobin <10 g/dL
  - Bone lesions: osteolytic, pathological fracture; osteopenia
- **Treatment → Observe and monitor**

### Non-secretory myeloma

- Bone marrow clonal plasma cells =10%, Myeloma-related end-organ damage, No M protein in blood or urine

**Thymoma** are the most common tumour of the anterior mediastinum and is usually detected between the sixth and seventh decades of life.

#### Associated with

- myasthenia gravis (30-40% of patients with thymoma)
- red cell aplasia
- dermatomyositis
- also : SLE, SIADH

#### Causes of death

- compression of airway
- cardiac tamponade

## Tumour lysis syndrome (TLS)

Rasburicase - a recombinant version of urate oxidase, an enzyme that metabolizes uric acid to allantoin

- Tumour lysis syndrome (TLS) is a potentially deadly condition

**Causes:**

- treatment of high grade lymphomas and leukaemias.
- It can occur in the absence of chemotherapy but is usually triggered by the introduction of combination chemotherapy.

**Pathophysiology:**

- breakdown of the tumour cells and the subsequent release of chemicals from the cell.

**Features:**

- **high** potassium
- **high** phosphate
- **low calcium**.
- It should be suspected in any patient presenting with an **acute kidney injury** in the presence of a high phosphate and **high** uric acid level.

**Diagnosis:**

- From 2004 TLS has been graded using the Cairo-Bishop scoring system -
  - Laboratory tumor lysis syndrome: abnormality in **two or more of the following, occurring within three days before or seven days after chemotherapy**.
    - uric acid > 475umol/l or 25% increase
    - potassium > 6 mmol/l or 25% increase
    - phosphate > 1.125mmol/l or 25% increase
    - calcium < 1.75mmol/l or 25% decrease
- Clinical tumor lysis syndrome: laboratory tumor lysis syndrome plus one or more of the following:
  - increased serum creatinine (1.5 times upper limit of normal)
  - cardiac arrhythmia or sudden death
  - seizure

**Management of acute tumour lysis syndrome**

- **aggressive hydration, aiming for 3 L/m<sup>2</sup>** control of electrolyte disturbances (typically, hypocalcaemia, hyperphosphataemia, hyperkalaemia and uraemia)
- clearance of the increased metabolic load with **rasburicase**, a specific recombinant enzyme.

**Prevention:**

- Patients at high risk of TLS should be given IV allopurinol or IV rasburicase immediately prior to and during the first days of chemotherapy.
  - Rasburicase is a recombinant version of urate oxidase, an enzyme that metabolizes uric acid to allantoin. Allantoin is much more water soluble than uric acid and is therefore more easily excreted by the kidneys.
    - The commonest reported side effect of rasburicase is fever.
    - rasburicase overdose may lead to accumulation of hydrogen peroxide.
- patients at low risk → oral allopurinol during chemotherapy
- Other options for the management of tumour lysis syndrome include
  - Acetazolamide to drive urine alkalinisation.

## Waldenstrom's macroglobulinaemia

IgM paraproteinaemia - ?Waldenstrom's macroglobulinaemia

### Overview

- It is a lymphoplasmacytoid malignancy seen in older men, characterised by the secretion of a monoclonal IgM paraprotein,
- indolent B-cell lymphoma
- Also known as **Lymphoplasmacytoid lymphoma**
- most common in older white men

### Pathophysiology

- monoclonal IgM production by a malignant lymphoplasmacytic clone that can cause damage to multiple organs.
- The tumor cells in Waldenstrom macroglobulinemia are positive to CD20 markers.

### Features

- monoclonal IgM paraproteinaemia
- systemic upset: weight loss, lethargy
- **hyperviscosity syndrome** e.g.:
  - visual disturbance,
  - neurological symptoms such as headache, dizziness, and vertigo
  - raynaud phenomenon
- Bleeding is a possible complication as viscous serum causes defective platelet aggregation.
- hepatosplenomegaly
- lymphadenopathy
- cryoglobulinaemia e.g. Raynaud's

### Investigations

- protein electrophoresis → elevated IgM
- Bone marrow biopsy (the gold standard for the diagnosis)
  - Shows → abnormal plasma cells with **Dutcher bodies** (intranuclear inclusions of IgM deposits)
- **Plasma viscosity**
  - plasma viscosity measurement is essential to diagnose and initiate treatment. The initial treatment would be plasmapheresis followed by cytoreductive therapy.

### Differential diagnosis

- , multiple myeloma
  - usually presents with IgG or IgA secretion and lytic bone lesions.
- Waldenström's
  - **In an elderly patient found to have a large IgM-kappa paraprotein, which feature will help to decide whether it is related to Waldenström's macroglobulinaemia?**
    - **No isotype suppression**
      - ❖ Isotype suppression (normal IgG and IgA levels) is more a feature of myeloma than Waldenström's macroglobulinaemia and is therefore a good differentiator.

### Treatment

- Asymptomatic → Follow-up
  - treatment only indicated in symptomatic patients
- Causative: CD20 antibodies (e.g., rituximab)
- Hyperviscosity syndrome: plasmapheresis

**ECOG score**

- The ECOG score ( Eastern Cooperative Oncology Group (ECOG) score) is a 'performance status' scale, or a score that measures the functional status of a patient.
- It is **used to decide if a patient is a good or poor candidate for future oncological therapies.**
- Those with a poor functional status is a poor candidate for further chemotherapy.

0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

**Tumour markers**

Tumour markers may be divided into:

- monoclonal antibodies against carbohydrate or glycoprotein tumour antigens
- tumour antigens
- enzymes (alkaline phosphatase, neurone specific enolase)
- hormones (e.g. calcitonin, ADH)

It should be noted that tumour markers usually have a low specificity

**Monoclonal antibodies**

Tumour marker	Association
CA 125	Ovarian cancer <b>primary peritoneal cancer</b>
CA 19-9	Pancreatic cancer
CA 15-3	Breast cancer

## Tumour antigens

Tumour marker	Association
Prostate specific antigen (PSA)	Prostatic carcinoma
Alpha-feto protein (AFP)	Hepatocellular carcinoma, <b>teratoma</b> , non-seminomatous germ-cell tumours
Carcinoembryonic antigen (CEA)	Colorectal cancer
S-100	Melanoma, schwannomas
Bombesin	Small cell lung carcinoma, gastric cancer, neuroblastoma
$\beta$ -human chorionic gonadotrophin	choriocarcinomas, germ-cell tumours and lung cancers

- Bence Jones protein → specific for myeloma. false positives are rare, and therefore it is **more specific than the other markers**. **The most specific tumour marker**
- **Alpha-fetoprotein (AFP)**, **beta-hCG** and **PLAP** (placental like isoenzyme of alkaline phosphatase) are the major tumour markers in use for the monitoring of **testicular teratoma**.

Common tumor markers	
Tumor marker	Associated conditions
<b>Alpha fetoprotein (AFP)</b>	<ul style="list-style-type: none"> <li>• Hepatocellular carcinoma (HCC)</li> <li>• Hepatoblastoma</li> <li>• Yolk sac tumor of the ovary (endodermal sinus tumor)</li> <li>• Mixed germ cell tumor</li> </ul> <ul style="list-style-type: none"> <li>• Transient elevation during pregnancy</li> <li>• ↑ AFP: abdominal wall defects, neural tube defects</li> <li>• ↓ AFP: associated with trisomy 21, 18, and 13 (See prenatal diagnostics for details)</li> </ul>
<b><math>\beta</math>-HCG</b>	<ul style="list-style-type: none"> <li>• Testicular germ cell tumors (choriocarcinoma, embryonal cell carcinoma, mixed germ cell tumor, seminoma)</li> <li>• Ovarian cancer: choriocarcinoma (gestational trophoblastic disease)</li> </ul> <ul style="list-style-type: none"> <li>• If detectable in urine           <ul style="list-style-type: none"> <li>• Pregnancy marker</li> <li>• Molar pregnancy (hydatidiform mole)</li> </ul> </li> </ul>
<b>Carcinoembryonic antigen (CEA)</b>	<ul style="list-style-type: none"> <li>• Colorectal cancer</li> <li>• Pancreatic cancer</li> <li>• Breast cancer</li> <li>• Lung cancer (especially in non-small cell cancers)</li> </ul>

Common tumor markers	
Tumor marker	Associated conditions
	<ul style="list-style-type: none"> <li>• Gastric cancer</li> <li>• Endometrial cancer</li> <li>• Medullary thyroid cancer</li> <li>• Smokers</li> </ul>
Prostate-specific antigen (PSA)	<ul style="list-style-type: none"> <li>• Prostate cancer</li> <li>• Benign prostatic hyperplasia</li> <li>• Prostatitis</li> </ul>
Calcitonin	<ul style="list-style-type: none"> <li>• Medullary thyroid cancer</li> </ul>
Alkaline phosphatase	<ul style="list-style-type: none"> <li>• Metastases to bone or liver</li> <li>• Paget disease of the bone</li> </ul>
Lactate dehydrogenase (LDH)	<ul style="list-style-type: none"> <li>• Ovarian cancer (dysgerminoma)</li> <li>• Testicular germ cell tumors (both seminoma and nonseminoma)</li> <li>• Lymphomas</li> <li>• Ewing's sarcoma</li> <li>• Hepatitis</li> <li>• Hemolysis</li> <li>• Myocardial infarction</li> </ul>
Neuron specific enolase (NSE)	<ul style="list-style-type: none"> <li>• Small cell lung cancer</li> <li>• Neuroendocrine tumors</li> <li>• Neuroblastoma</li> <li>• NSE is released secondary to brain injury (e.g., stroke)</li> </ul>
CA 19–9	<ul style="list-style-type: none"> <li>• Pancreatic adenocarcinoma</li> </ul>
CA 15–3/CA 27–29	<ul style="list-style-type: none"> <li>• Breast cancer</li> </ul>
CA 125	<ul style="list-style-type: none"> <li>• Ovarian carcinoma(80–100%)</li> </ul>
Chromogranin A	<ul style="list-style-type: none"> <li>• Neuroendocrine tumors</li> <li>• Medullary thyroid cancer</li> </ul>
S-100 protein (S100A) and (S100B)	<ul style="list-style-type: none"> <li>• Malignant melanoma</li> </ul>
$\beta$ 2 microglobulin ( $\beta$ 2M)	<ul style="list-style-type: none"> <li>• Multiple myeloma</li> <li>• Chronic lymphocytic leukemia</li> <li>• Renal disease</li> </ul>
Thyroglobulin	<ul style="list-style-type: none"> <li>• Papillary thyroid carcinoma</li> <li>• Follicular thyroid carcinoma</li> </ul>
Monoclonal immunoglobulins	<ul style="list-style-type: none"> <li>• Multiple myeloma</li> <li>• Waldenstroms macroglobulinemia</li> <li>• Monoclonal gammopathy</li> <li>• Infections</li> <li>• Certain autoimmune conditions (e.g., rheumatoid arthritis)</li> </ul>

## Neutropenic sepsis (Febrile neutropenia)

### Definition

- Neutropenic sepsis is a relatively common complication of cancer therapy (chemotherapy).
- It most commonly occurs 7-14 days after chemotherapy.
- It may be defined as a **neutrophil count of  $< 0.5 \times 10^9$**  in a patient who is having anticancer treatment and has one of the following:
  - a temperature higher than 38 C or
  - other signs or symptoms consistent with clinically significant sepsis

### Causes

**Neutropenic patients should avoid cold meats, soft cheese and dairy products due to risk of listeriosis**

- in the majority of them identifying a source of the temperature can be impossible.
- **the most common pathogens are now gram-positive organisms.** such as **Staphylococcus epidermidis** or Streptococcus viridans (around 60% of cases)
- **Source of infection**
  - In neutropenic patients, almost any site can be the source.
  - Indwelling lines → Staph.epidermidis infection
  - mucositis or previous quinolone treatment → viridans streptococci

**Mucositis can be a source of neutropenic sepsis → Swab mouth ulcer**

### Risk factors

- Age > 65
- Albumin less than 35 g/l
- Hepatic dysfunction
- Baseline neutrophil less than  $1.5 \times 10^9$
- Planned relative dose intensity > 80%

### Prophylaxis

- if it is anticipated that patients are likely to have a neutrophil count of  $< 0.5 \times 10^9$  as a consequence of their treatment they should be offered a fluoroquinolone

### Management

- antibiotics must be started immediately, **do not wait for the WBC**,(N.B. after taking cultures).
- **First-step:**
  - NICE recommend starting empirical antibiotic therapy with **piperacillin with tazobactam** (Tazocin) immediately
    - **piperacillin with tazobactam with gentamicin** is the preferred first-line option according to Christies guidelines **for patient who are not allergic to penicillin** and have no significant renal impairment.
    - **If there is penicillin allergy** → meropenem 1g three times a day is an appropriate option
      - ❖ Dose adjustment may be needed where the GFR is less than 50 ml/min
  - many units add vancomycin if the patient has central venous access, but NICE do not support this approach
  - **assessment the patient at 48 hours, If they have improved and the temperature has settled** → **Convert patient to oral antibiotics and discharge**

- NICE does not recommend keeping patients in hospital whilst waiting for their neutrophil count to improve.
- **Second-step:**
  - **If patients are still febrile and unwell after 48 hours** an alternative antibiotic such as meropenem is often prescribed +/- vancomycin
- **Third-step:**
  - **If patients are not responding after 4-6 days** the Christie guidelines suggest ordering **investigations for fungal infections** (e.g. HRCT), rather than just starting antifungal therapy blindly
- there may be a role for G-CSF (filgrastim) in selected patients
  - if the neutropenic sepsis has **responded well to treatment, but is still neutropenic**, could be given **G-CSF to stimulate a neutrophilia** to help restore his cell counts quicker and reduce the chance of developing another episode of neutropenic sepsis.
  - Side-effect of G-CSF (filgrastim):
    - Filgrastim stimulates a white cell count which can increase far above the normal range, and **the white cell count will return to normal once it is stopped.**

**Neutropenic sepsis with no response to antibiotics at 48 hrs → possible fungal infection**

**Gram colony stimulating factor (G-CSF) can be used to boost neutrophil numbers in neutropenia**

**MRCPUK-part-1-May 2016 exam: When is the risk of febrile neutropenia thought to be highest following chemotherapy?**

→ **10 days in to treatment**

## Assessment of neutropenia

### Definition and classification

- absolute neutrophil count (ANC)  $<1500/\text{microlitre}$  or  $<1.5 \times 10^9/\text{L}$  is defined as neutropenia and graded as mild, moderate, severe, or very severe:
  - Mild:  $1000$  to  $1500/\text{microlitre}$  or  $1$  to  $1.5 \times 10^9/\text{L}$
  - Moderate:  $500$  to  $999/\text{microlitre}$  or  $0.5$  to  $0.99 \times 10^9/\text{L}$
  - Severe:  $200$  to  $499/\text{microlitre}$  or  $0.2$  to  $0.49 \times 10^9/\text{L}$
  - Very severe:  $<200/\text{microlitre}$  or  $<0.2 \times 10^9/\text{L}$ .
- As the ANC falls below  $1000/\text{microlitre}$  or  $1 \times 10^9/\text{L}$ , the risk of infection progressively increases.
- If the ANC falls below  $500/\text{microlitre}$  or  $0.5 \times 10^9/\text{L}$ , infections may be **life-threatening**.
  - However, there are some diseases, such as **autoimmune neutropenia (AIN)**, in which a low ANC does not confer an infection risk; **infections are rare in these patients despite the ANC often being  $<500/\text{microlitre}$  or  $<0.5 \times 10^9/\text{L}$ .**
- The ANC varies according to age and ethnicity.
  - It is lower in children than in adults.
  - Black people and some Arab populations display lower average values.
  - The normal range in black people has a lower limit of  $1400/\text{microlitre}$  or  $1.4 \times 10^9/\text{L}$ .

## Causes

- Infections (the most common causes of neutropenia in adults),
- drug-induced neutropenias
- Acquired bone marrow diseases such as the leukaemias, lymphomas, and aplastic anaemia
- nutritional deficiencies (vitamin B12, folate, copper)

## Systemic mastocytosis

Systemic mastocytosis results from a neoplastic proliferation of mast cells

### Features

- urticaria pigmentosa - produces a wheal on rubbing (Darier's sign)
- flushing
- abdominal pain
- monocytosis on the blood film

### Diagnosis

- raised serum tryptase levels
- urinary histamine

## Cervical cancer

- Cervical cancer is the most common cancer worldwide
- The incidence of cervical cancer peaks around the 6th decade.
- It may be divided into
  - squamous cell cancer (80%)
  - adenocarcinoma (20%)

### Features

- may be detected during routine cervical cancer screening
- abnormal vaginal bleeding: postcoital, intermenstrual or postmenopausal bleeding
- vaginal discharge

### Risk factors

- **human papilloma virus (HPV) 16,18 & 33 → the most common**
  - associated with HPV 16 and 18 in approximately 70% of cases.
  - New vaccines are currently available in the United Kingdom to help immunise against this virus and hopefully prevent future cases of cervical cancer.
- smoking
- human immunodeficiency virus
- early first intercourse, many sexual partners
- high parity
- lower socioeconomic status
- combined oral contraceptive pill\*
  - \*the strength of this association is sometimes debated but a large study published in the Lancet (2007 Nov confirmed the link

### Mechanism of HPV causing cervical cancer

- HPV 16 & 18 produces the oncogenes E6 and E7 genes respectively
- E6 inhibits the p53 tumour suppressor gene
- E7 inhibits RB suppressor gene

## Ovarian tumours

**Ovarian cancer screening is not recommended in the general population as no survival benefit from earlier diagnosis and therapy has been shown.**

- germ cell tumours
  - Patients are usually young.
    - most commonly seen in adolescents due to embryologic remnants
  - early pulmonary metastases
    - **The fact that this lady is young, and has early pulmonary metastases, make a germ cell tumour much more likely**
- The diagnosis is usually made on biopsy in the case of ovarian tumours.
- treatment usually consists of surgery followed by chemotherapy (BEP).
- Epithelial cell tumours
  - usually disseminate through the abdomen and peritoneum prior to metastasising to the lungs.
- Markers such as AFP,  $\beta$ -human chorionic gonadotropin (HCG) and lactate dehydrogenase (LDH) may be raised
  - **the most sensitive marker used for monitoring treatment efficacy and risk of relapse is AFP.**
- Treatment of ovarian cancer:
  - **Patients with low risk, early-stage ovarian cancer (stage I, grade 1 disease confined to one or both ovaries with an intact capsule and no ascites) after thorough surgical staging have a greater than 90% cure rate with surgery alone and close observation is required.**
  - Platinum-based therapy, such as intravenous carboplatin and paclitaxel, is warranted for high risk, early-stage ovarian cancer (stage IC or II, grade 3 tumour or clear cell histology).
  - Intraperitoneal chemotherapy is indicated for patients with stage III disease
  - **Debulking surgery followed by chemotherapy is proven to be the best treatment option in patients with peritoneal carcinomatosis from ovarian cancer.**
    - Intraperitoneal chemotherapy has less toxicity compared to IV chemotherapy and is better tolerated.
- **A young man with a germ cell tumour (raised  $\beta$ -HCG) can expect a greater than 95% cure rate, especially with seminomas.**
- **$\beta$ -HCG is the best tumour marker confers the best prognosis**

## Breast cancer

**The triple assessment of a breast lump is essential to diagnose a breast lump accurately. It involves;**

1. **physical examination,**
2. **mammography and then**
3. **ultrasound guided fine needle aspiration (FNA).**

## Risk factors

- **inherited BRCA-1 mutation (or BRCA-2)**
  - **the greatest risk**
  - ***BRCA1/2 carriers have a 40–70% chance of getting breast cancer by age 70, and a 10–70% chance of getting ovarian cancer by age 70.***
  - family history of breast cancer at a young age makes this more likely.
  - **What is the DNA repair mechanism by which the BRCA1 and BRCA2 proteins act?**
    - **Double strand DNA break repair**
    - ❖ **BRCA** involved in repair of double strand DNA breaks by homologous recombination.
- Early menarche
- late menopause
  - due to increased hormone exposure throughout life.
- Nulliparity
- Oral contraceptive use is also associated with a slight increase in risk of developing breast and also endometrial cancer.

What is **the best predictive factor for local recurrence of breast cancer after** surgery, chemotherapy and radiotherapy?

- **Age**
  - **Patients below the age of 40 are significantly more likely to develop local recurrence of a breast cancer than those aged 41+.**

## Screening

- Mammograms screening
  - sensitive in older (because of less dense breast tissue)
  - not sensitive in younger (because of denser breast tissue) → MRI and ultrasound are better in them.
  - **In young patients with a BRCA mutation, mammographic screening has a low sensitivity for detecting tumours**
- Mammographic screening of all women between the ages of 50 and 70 years can reduce mortality from breast cancer by 25%. There is no evidence for routine screening below this age.
- **mutation of BRCA1 or BRCA2 gene increases the risk of breast cancer** → should be screened at younger than 50 years.

**Breast MRI is used for patients with invasive breast cancer in the following circumstances:**

- if there is a discrepancy regarding the extent of disease from clinical examination, mammography and ultrasound assessment for planning treatment
- if breast density precludes accurate mammographic assessment
- to assess tumour size if breast conserving surgery is being considered for invasive lobular cancer

- Staging CT is not used routinely in primary breast cancer, only if there is suspicion of metastatic spread.

### Tumour marker

- CA15-3** tumour marker are used to assess disease activity in metastatic breast cancer

### Management

- Breast-conserving therapy**
  - lumpectomy with sentinel lymph node biopsy followed by breast irradiation
  - indicated for patients with focal disease
  - randomised clinical trials have shown that the survival rate for women undergoing breast-conserving therapy is equivalent to that of those who undergo mastectomy,
  - breast-conserving therapy resulting in improved cosmetic outcomes and less morbidity than mastectomy.
  - Most patients treated with lumpectomy without radiation therapy have a high risk for local recurrence.
  - Sentinel lymph node biopsy is safe and adequate for screening the axillary lymph nodes for metastases in women with small breast tumours.
- Mastectomy**
  - indicated in patients in whom complete excision cannot be achieved unless mastectomy is performed or radiation is contraindicated.
- Adjuvant radiotherapy** is recommended by (NICE) given after wide local excision of a breast tumour to reduce the risk of local recurrence.
  - There is growing evidence that adjuvant radiotherapy also increases survival for those patients at high risk of relapse.
  - There is however a risk of increased cardiovascular mortality after 15-20 years, which may be reduced with the use of modern techniques such as conformal radiotherapy and intensity-modulated radiotherapy.
  - Wound healing can be reduced after radiotherapy, and a period of at least a few weeks is usually given between surgery and initiation of radiotherapy.
- Prophylactic mastectomy is indicated only in patients with BRCA1 or BRCA2.

### Drug therapy

- Hormonal treatment is used to remove the proliferative stimulus of oestrogen from tumour cells.
- Tamoxifen** is used for adjuvant hormone treatment in **pre-menopausal** women **first line**.
  - Tamoxifen acts by blocking the binding of oestrogen to its receptor within the nucleus.
  - In patients with oestrogen receptor-positive tumours, tamoxifen therapy for five years in addition to lumpectomy decreases the risk of a new breast cancer event.
  - long-term use is associated with:
    - vaginal bleeding,
    - endometrial thickening and increased risk of endometrial cancer

- **thromboembolism.**
- The lack of oestrogen receptor staining suggests a poor response to hormonal therapy with tamoxifen.
- **Anastrozole** is used for adjuvant hormone treatment in **post-menopausal** women **first line**.
  - **aromatase inhibitor**
  - Three aromatase inhibitors are licensed for treatment of early oestrogen-receptor-positive breast cancer:
    1. anastrozole,
    2. exemestane,
    3. letrozole.
  - Aromatase inhibitors work by **preventing peripheral conversion of oestrogen** and therefore cause profound oestrogen deprivation in a post-menopausal woman.
  - This increases the risk of osteoporosis and fragility fractures.
  - **A DEXA scan must be done at the start of treatment** to identify those patients in whom a bisphosphonate must be considered for bone protection.
    - **Aromatase inhibitors can be continued** in a patient who has suffered **no fragility fractures** providing adequate measures are taken for bone protection, for example, **prescribing a bisphosphonate**.
    - **In patients who suffer a fragility fracture tamoxifen must be considered** as this does have a partial oestrogen agonist action on bone, reducing the risk of osteoporosis.
  - A common side-effect is **reduced bone mineral density**, and bone densitometry is therefore often carried out prior to and during treatment.
  - Anastrozole is currently indicated for early oestrogen-receptor-positive breast carcinoma at a dose of 1 mg daily for 5 years.
- **Fulvestrant** is a new pure anti-oestrogen agent which appears to be as effective as anastrozole. It is given by sub-cutaneous injection once every three weeks.
  - **mechanism of action** → **Selective oestrogen receptor down regulator**
  - has been shown to be equivalent to anastrazole in terms of efficacy.
  - Fulvestrant is the only endocrine agent currently available that can be given parenterally, which offers significant advantages to patients with swallowing difficulties.
  - Fulvestrant is not currently given first line in post-menopausal women but this may change in the near future.
- The positive C-erb B2 (**HER2/neu**) staining suggests that **trastuzumab** (Herceptin) may be effective.
  - Several randomised trials have demonstrated that 52 weeks of adjuvant trastuzumab therapy reduces the risk for breast cancer recurrence in women with HER2 overexpression by approximately 50% and may even reduce mortality by as much as 30%.

- the best test for monitoring the patient while she is receiving Herceptin (trastuzumab)?
  - Three monthly echocardiogram
    - ❖ Herceptin appears to be directly toxic to the cardiac muscle itself with relative sparing of the electrical conductivity of the heart.
    - ❖ As such regular echocardiograms are the best test to assess treatment safety, a reduction of greater than 10% in ejection fraction indicating the need to stop treatment.
- Bisphosphonate therapy
  - prevents skeletal complications resulting from osteolytic bone involvement in patients with breast cancer.
  - An intravenous bisphosphonate (eg: zoledronic acid) is indicated for treatment of lytic bone metastases.
    - The evidence demonstrating benefit of oral bisphosphonate therapy such as alendronate in the treatment of bone metastases is conflicting.

➔ oestrogen receptor (ER)-positive tumours + pre-menopausal women → Tamoxifen  
 ➔ oestrogen receptor (ER)-positive tumours + post-menopausal women → Anastrozole  
 ➔ ER-negative or are refractory to endocrine treatment → chemotherapy  
 ➔ Patients with HER2 overexpression → chemotherapy + trastuzumab.  
 ➔ patients with HER2-negative metastatic breast cancer → Bevacizumab

### Prognosis

- Poor prognostic factors include:
  - high-grade tumour,
  - positive lymph node status,
  - oestrogen-receptor-negative tumour,
  - progesterone-receptor-negative tumour,
  - young age (< 40 years),
  - premenopausal at diagnosis
  - increased tumour size.

### Paget's disease of the breast

- Overview
  - Paget's disease of the breast is a rare (1-4% of breast cancers) form of breast cancer that affects the nipple and areola.
  - underlying invasive breast cancer, or ductal carcinoma in situ (DCIS) almost always present
    - unlike Paget's disease of the vulva
  - Malignant cells infiltrate into the epidermis via the mammary duct epithelium, leading to thickening of the affected skin.
- Features
  - Presents with dermatitis or macular rash over nipple or areola
  - It presents insidiously and is similar in appearance to eczema; as such it often goes undiagnosed for several months.

- **Diagnosis**

- Skin biopsy with immunohistochemistry is the first line investigation.
- Investigations should also be done for underlying malignancy:
  - biopsy if a lump is palpable,
  - imaging if no lump is palpable.

- **Management**

- usually surgical with post-operative radiotherapy

- **Prognosis**

- high chance of recurrence.

### Radiotherapy

- External beam radiotherapy or use of targeted intraoperative radiotherapy does not render the patient radioactive. **No radiation precautions need to be taken**
- Use of brachytherapy methods can involve insertion of radioactive seeds or beads which may require some radiation protection precautions depending on the site.
- Use of an unsealed source, for example radio-iodine treatment of thyroid cancer, has substantial need for precautions and patients need to be **isolated in a lead-lined side room, often for several days**.

### Chemotherapy

- Adjuvant chemotherapy is commonly given in many cancers **to reduce** the risk of local or distant recurrence or **metastasis**.
- **multi-drug chemotherapy resistance**
  - **Upregulation of which protein is associated with multi-drug chemotherapy resistance? → P-glycoprotein**
    - P-glycoprotein, which is also known as multidrug resistance protein 1, is a member of the adenosine triphosphate (ATP)-binding cassette transporters which actively remove harmful substances from the cytoplasm.
    - If upregulated these proteins can pump chemotherapeutic agents out of tumour cells leading to drug resistance.

### Chemotherapy complications

- **Oral mucositis**
  - **Severe mucositis** is common with head and neck cancer treatment due to the combination of chemotherapy and external beam radiotherapy.
    - **Admit the patient for IV fluids and nutritional support**
      - ❖ Often patients require a PEG or RIG to provide adequate nutritional support during their potentially curative treatment.
  - Oral hygiene is the mainstay of treatment in prevention of mucositis however it will not treat an existing mucositis.
  - Chlorhexidine mouthwash can improve a grade 1-2 mucositis.

## Salivary Gland Tumors

- Most commonly occur in the **parotid gland**
  - generally **benign**
  - if the tumor involves a non-parotid gland it is more likely to be malignant
- Types
  - **pleomorphic adenoma**
    - **the most common benign salivary gland neoplasm.**
      - ❖ **70% to 80% of all benign salivary gland tumours.**
    - more common in **females** (middle-aged women > 40)
    - It is found mostly in the parotid gland (84%).
    - 90% of parotid gland pleomorphic adenomas arise lateral to the facial nerve.
    - benign with high rate of recurrence but may become malignant
    - Usually they **do not enhance** following intravenous contrast injection in CT.
    - The optimal treatment is superficial or total parotidectomy with facial nerve preservation
  - Warthin's tumor
    - benign
    - more common in **males**
    - **heterotopic salivary gland tissue located in a lymph node**
    - surrounded by lymphatic tissue
  - mucoepidermoid carcinoma
    - most common **malignant** tumor
      - note: muco = malignant
    - generally, involves **parotid** gland
    - combination of neoplastic **mucus** and **squamous** cells
- Physical exam
  - **painless, moveable mass found at the angle of the jaw**
    - pleomorphic adenoma
  - **disturbance in CN VII function**
    - more likely to be malignant pleomorphic adenoma

## Palliative care prescribing: pain

Metastatic bone pain may respond to NSAIDs, bisphosphonates or radiotherapy

**The breakthrough dose of short acting morphine should be 1/6th of the total 24-hour dose.**

### **WHO recommendations**

- Standard practice would be to follow the World Health Organization recommendations for the management of cancer pain, which suggest analgesia should be given:
  - By the mouth - that is, using the oral route for all drugs including morphine and other opioids unless patient is vomiting, semi-conscious, has dysphagia, etc.
  - By the clock - persistent pain requires preventative treatment and as needed (prn) analgesia only is not acceptable.
  - By the ladder - that is, the WHO analgesic ladder.
- The WHO analgesic ladder is as follows:
  - Step 1 - Non-opioid +/- adjuvants (e.g. paracetamol/NSAIDs)

- Step 2 - Weak opioid + non-opioid +/- adjuvants (e.g. co-codamol 30/500)
- Step 3 - Strong opioid + non-opioid +/- adjuvants (e.g. morphine, fentanyl, oxycodone).
- Nerve pain often also has a nociceptive opioid responsive element and hence **opioids (with a combination of nonsteroidal anti-inflammatory drugs [NSAIDs]) should be tried first** (eg: ibuprofen and tramadol) and used as part of the WHO analgesic ladder. Morphine would be tried next, followed by the other agents.

### Starting morphine

- Morphine is the opioid of choice for treating moderate to severe cancer pain.
- **Choices between morphine preparations**
  - when starting treatment, offer patients with advanced and progressive disease regular oral modified-release (**MR**) or oral immediate-release morphine(**IR**) (depending on patient preference), with oral immediate-release morphine for breakthrough pain
  - oral modified-release morphine should be used in preference to transdermal patches
  - **Immediate release preparations are used for titration** as they offer greatest flexibility. Most patients should be started on 5-10mg orally every 4-hours, with the same dose prescribed as a breakthrough (or 'rescue') dose wherever needed. **Once drug requirements are constant, the patient can be converted to modified-release morphine.**
  - Once a patient has been titrated on immediate release opioids these can be converted to the equivalent dose of a modified release preparation.
  - If a patient has good pain control on one drug, the modified release version of this drug should be used.
- **Morphine doses**
  - if no comorbidities use 20-30mg of MR a day with 5mg morphine for breakthrough pain. For example, 15mg modified-release morphine tablets twice a day with 5mg of oral morphine solution as required
  - When increasing the dose of opioids, the next dose should be increased by 30-50%.
  - **An appropriate starting dose of morphine sulphate immediate release (IR) should not be more than 10mg every 4 hours.** Alternatively, morphine sulphate modified release (MR) 30mg 12 hourly could be used.
- **Opioids Side effects:**
  - Constipation: laxatives should be prescribed for all patients initiating strong opioids
    - **Morphine causes constipation by enhancing intestinal ring contractions.** This results in hypersegmentation which in turn impairs peristalsis.
    - 90% of patients taking morphine require a laxative and a stimulant is the best choice (such as senna). **Senna is the most commonly used laxative for this indication**
  - Nausea: patients should be advised that nausea is often transient. If it persists then an antiemetic should be offered
  - drowsiness is usually transient - if it does not settle then adjustment of the dose should be considered

### Preferred opioids for patients with chronic kidney disease

Breakthrough dose = 1/6th of daily morphine dose

- **Opioids should be used with caution in patients with chronic kidney disease.**  
**Alfentanil, buprenorphine and fentanyl are preferred**
  - Fentanyl patches are difficult to titrate because they are used for 72 hours. therefore, only used once a patient has a stable opiate usage.
  - Fentanyl is a selective  $\mu$  receptor agonist.

- It has extensive first-pass metabolism so is not especially effective orally.
- However, buccal absorption is good so lozenges are an effective mode of administration and have a rapid onset of action (five minutes). This is therefore very useful for patients with "breakthrough pain".
- It is very useful in renal failure as it is metabolised mainly in the liver and it has inactive metabolites.

**What is the most appropriate opioid to prescribe for a syringe driver in renal failure?**

→ Alfentanil

#### Combination therapies antagonism

- Partial opioid agonists (for example, **buprenorphine**), when used in association with **morphine**, may **produce a reduction in the analgesic effect due to partial antagonism**.
- This is an aspect of pain management that needs to be considered when using combination therapies.

#### Oxycodone

- Oxycodone is often used as a **second line opioid** for patients who experience either inadequate analgesia or excessive side effects with morphine.
- It has similar analgesic properties to morphine but is twice as potent.
- It is available in immediate-release and modified-release oral preparations and can also be used parentally.
- Oxycodone can be used in moderate **renal failure**, but only as breakthrough pain relief. Modified release preparations should be avoided.
- **Parental oxycodone is twice as potent as oral oxycodone.**
- **The total daily dose of immediate and modified release oral oxycodone is the same.**
- causes less sedation, vomiting and pruritis than morphine but more constipation.

#### Opioid side-effects

Usually transient	Usually persistent
Nausea Drowsiness	Constipation

#### Conversion between opioids

- calculate the total daily dose of morphine salt, (include the doses of breakthrough pain) then convert it to the appropriate amount

From	To	Conversion factor
Oral codeine	Oral morphine	Divide by 10
Oral tramadol	Oral morphine	Divide by 10

From	To	Conversion factor
Oral morphine	Oral oxycodone	Divide by 1.5-2**

\*\*historically a conversion factor of 2 has been used (i.e. oral oxycodone is twice as strong as oral morphine). The current BNF however uses a conversion rate of 1.5

From	To	Conversion factor
Oral morphine	Subcutaneous morphine	Divide by 2
Oral morphine	Subcutaneous diamorphine	Divide by 3
Oral oxycodone	Subcutaneous diamorphine	Divide by 1.5

### Transdermal preparations:

The current BNF gives the following conversion factors for transdermal preparations

- **transdermal fentanyl**
  - a transdermal fentanyl 12 microgram patch equates to approximately 30 mg oral morphine daily
  - fentanyl 75 patch is equivalent to 180mg daily intake of morphine salt
  - fentanyl 100patch is equivalent to 240mg daily morphine salt.
- **transdermal buprenorphine**
  - transdermal buprenorphine 10 microgram patch equates to approximately 24 mg oral morphine daily.

### Diamorphine

- Diamorphine has a rapid onset so could be used for breakthrough pain **if the renal function is normal**.
- **Constipation is a characteristic sequel to treatment**
- Hallucinations also tend to occur.
- An aperient (laxative) should always be added to the treatment regime.
- Addiction is not a problem.
- An intramuscular injection is three times more effective than the same oral dose.
- **the best option for controlling pain associated with vomiting in palliative care → Subcutaneous diamorphine by continuous infusion** (able to effectively titrate the dose to achieve adequate analgesia)

### Codeine

- The analgesic effect of codeine depends on its conversion to morphine by the CYP2D6 hepatic enzyme. Up to 10% of Caucasians are CYP2D6 poor metabolisers and are unlikely to derive any analgesia from it.
- If hepatic metabolism is impaired for any other reason (drugs or hepatic impairment) patients are also unlikely to benefit from codeine.

### Methadone

- acts as a neuropathic agent by NMDA antagonism.
- Methadone can be used as a **third line** opioid for patients with complex pain that is poorly responsive to other opioids and adjuvants
- Opioids which are **safe in CKD 4 and 5** include fentanyl, buprenorphine and **methadone**.

### Incident pain

- defined as pain which comes on as a **result of an action or activity**, for example during personal care (pain throughout the day is otherwise well controlled).
- Treated with rapid onset and short-acting opioid such as:
  - Sublingual fentanyl
  - morphine sulphate immediate release liquid.
    - A breakthrough dose (1/6th of the total daily dose) of morphine **should be given 30 minutes prior to the activity** as indicated in the BNF.

**Other notes:**

- **Nifedipine**
  - relieves painful oesophageal spasm and tenesmus associated with gastrointestinal tumours and could be used to relieve odynophagia.
- **Corticosteroids**
  - used to treat pain from central nervous system tumours
- **Oxybutynin**
  - painful bladder spasm may be relieved by oxybutynin.
- **Hyoscine**
  - to reduce air way secretions in palliative care → Both hyoscine and atropine when given subcutaneously are thought to be equally appropriate for drying up secretions.
  - hyoscine s/c can be given up to three times per day in boluses of 10-20 mg.
- **Cyclizine**
  - Cyclizine is a commonly used antihistamine antiemetic and its primary site of action is the vomiting centre (which is rich in histamine and muscarinic cholinergic receptors).
  - **Cyclizine has a strong affinity for muscarinic receptors and therefore anticholinergic side effects (dry mouth, drowsiness, blurred vision, constipation, etc) are common**, especially in the first few days.
- **Gabapentin**
  - **Gabapentin** is a commonly used adjunctive agent for neuropathic pain.
  - mechanism of action: (**Activation of GABA inhibitory system**).
  - Four to six weeks of treatment are often needed before the patient experiences benefit.
- **Bisphosphonates**
  - inhibits osteoclastic bone resorption
  - useful for bone pain and the associated hypercalcaemia, especially in breast cancer and myeloma.
  - Whilst bisphosphonates have a role in bone metastases they are **not suitable for acute pain**.
  - **The risk of osteonecrosis of the jaw is much greater for patients receiving intravenous bisphosphonates in the treatment of cancer.**
    - All patients receiving bisphosphonates for cancer should have a dental check-up before bisphosphonate treatment.
    - other patients who are prescribed bisphosphonates should have a dental examination only if they have poor dental health.
  - The beneficial effect of bisphosphonates can be delayed for up to two weeks and can last for one month, and treatments are therefore usually given monthly (typically for 6 months).
  - increase analgesia while waiting for the bisphosphonates to work and review over the next few days to see whether you could reduce them again.

Acupuncture is playing an increasing role in pain management, **Which structures are involved in mediating the effects of acupuncture? Cerebral cortex and A beta nerve fibres.**

- The A beta nerve fibres are the path for fast transmission of sensation.
- Acupuncture also has a central effect.

## Opioid toxicity in palliative care

most opiates are renally excreted, leading to opiate toxicity. Fentanyl, buprenorphine and methadone are metabolised by the liver and are therefore safer in renal failure

Transdermal fentanyl absorption is increased by heat (e.g. hot water bottle) or pyrexia, potentially leading to opioid toxicity

- May be precipitated by:
  - Renal impairment with renally excreted opiates
  - increase transdermal fentanyl absorption by heat eg: fever
  - reduction in opioid requirement. This is a common occurrence in patients who have radiotherapy for bone metastases if their medication dose is not adjusted.
- Features:
  - Reduced conscious level, hallucinations, vomiting, myoclonic jerks and pinpoint pupils.
- Management
  - stop the long acting opioid temporarily to allow the excess drug to be excreted and then rely on short acting opioid for any breakthrough pain that might occur.
    - once the patient recovered, the long acting opioid can be reintroduced at a much-reduced dose.
  - Although the patient is opioid toxic, giving naloxone would not usually be the right thing to do.
    - Naloxone antagonises opioid receptors in the nervous system and this can cause patients significant pain and distress as their analgesia is reversed.
    - Unless the patient is in a peri-arrest situation where use of naloxone could be justified, it is better simply to withdraw the regular opioid until the patient recovers.

## Palliative care prescribing: nausea and vomiting

### Opiate induced nausea

- Haloperidol
  - 90% of patients taking morphine require antiemetics (morphine stimulates D2 receptors in the CTZ).
  - **Haloperidol is the first-choice antiemetic for opiate induced nausea in the palliative care setting.**
  - Haloperidol acts as a central dopamine (D2-receptor) antagonist. The chemoreceptor trigger zone (CTZ) is rich in dopaminergic receptors. Opioid related nausea is thought to be predominantly due to dopamine pathways in the CTZ.
  - **haloperidol → dopamine receptor antagonist (D2) activity → drug-induced parkinsonism (DIP).**

### Post-chemotherapy or radiotherapy induced nausea

- **Ondansetron** (5HT<sub>3</sub> antagonist) is mainly used in post-chemotherapy or radiotherapy induced nausea.
- In UK 5HT<sub>3</sub> antagonists are licensed only for post-chemotherapy and post-operative nausea.
- **Which antiemetics is most useful following treatment with a platinum-based chemotherapy? → Ondansetron**
  - Examples of platinum-based chemotherapies are cisplatin, carboplatin and oxaliplatin

**Nausea associated with cerebral disease (brain metastases)**

- If the patient's history raises the possibility of **brain metastases**, cyclizine would be the most appropriate first line agent.
  - It targets the dopamine and cholinergic receptors and is widely accepted as the best antiemetic for nausea associated with cerebral disease.

**Treatment of vomiting associated with breast cancer chemotherapy**

- modern palliative chemotherapy for breast cancer would be **unlikely to cause severe nausea and vomiting**.
- The patient may have **anticipatory vomiting** (before attending for treatment) almost certainly associated with anxiety about chemotherapy. Therefore, treatment with a **benzodiazepine as an anxiolytic as well as an antiemetic** would be the most logical.

**Palliative care prescribing: hiccups**

Hiccups in palliative care - chlorpromazine or haloperidol

**Management of hiccups**

- Metoclopramide is the first choice to treat hiccup as well as nausea.
- chlorpromazine is licensed for the treatment of intractable hiccups
- Other options include: baclofen, nifedipine, haloperidol, gabapentin
- dexamethasone is also used, particularly if there are hepatic lesions
  - In the presence of hepatic or cerebral cancer a trial of dexamethasone may induce some remission

**Palliative care prescribing: Constipation****Causes**

- Constipation is common in patients with advanced cancer, particularly in those taking opioid medication, with reduced oral intake and reduced mobility.
- Hypercalcaemia can cause constipation (**a constipation in cancer → do blood tests, including bone profile**)
  - Hypercalcaemia is a common problem in palliative care.
  - prostate cancer with bone metastasis is a frequent cause.

**Treatment**

- **Polyethylene glycol (Movicol) would seem the best choice in this scenario.**
  - It has an osmotic action and helps to retain water in the gut to aid faecal passage.
  - It is generally better tolerated than some other oral laxatives and has been shown to be more effective than lactulose in the management of chronic constipation.
- **Lactulose (an osmotic laxative) is usually avoided in palliative care**
  - as it can cause abdominal cramps and excessive flatulence.
  - Its sweet taste can be unpalatable for some patients
  - it needs to be consumed with large volumes of liquid which is sometimes not practical for palliative care patients.
- Co-danthramer is a combination of danthron (a stimulant laxative) and poloxamer (a stool softener) and is a popular choice for constipation in palliative care. It is **licensed only for use in patients with a terminal illness** and should not be given to those who are incontinent (of urine or faeces) due to the risk of developing a 'danthron burn' through prolonged contact with the skin.

## Palliative care prescribing: agitation and confusion

### Causes

- hypercalcaemia,
- infection,
- urinary retention
  - can even develop in patients who have not received any hydration for several days.
  - **Assessment for catheterisation should be one of the first management steps in a newly agitated patient.**
- medication.

### Management

- Treatment of underlying cause
- If specific treatments fail, then the following may be tried:
  - **first choice: haloperidol**
  - other options: chlorpromazine, levomepromazine
  - **Terminal agitation**
    - In the terminal phase of the illness then agitation or restlessness is best treated with midazolam
    - **Midazolam** is the drug suggested by the Liverpool Care Pathway (LCP) (starting dose of 2.5 - 5 mg sc PRN).
    - benzodiazepines are traditionally the first line for terminal agitation.

## Palliative care: Breathlessness

**Opioids** are the first line treatment to reduce the sensation of breathlessness in Palliative care

- Breathlessness is a significant problem in the palliative care setting and not just in patients with lung cancer.
- Palliation of breathlessness involves:
  - **First-line: Opioids**
    - **Opioids are very effective agents to reduce the sensation of breathlessness** - they reduce inappropriate respiratory drive.
    - They rarely cause respiratory depression when used correctly.
  - Second line: Benzodiazepines (effective agents after opioids).
  - Other therapies
    - Psychological support and physiotherapy
      - ❖ are very useful adjuncts to medications.
      - ❖ However, these take time and if the patient is distressed, they are not helpful in the immediate cases (unless breathing techniques have been taught).
    - Oxygen
      - ❖ has a small role in the management of breathlessness in palliative medicine, unless the patient is hypoxic.
      - ❖ It can be necessary when patients become psychologically dependent on supplementary oxygen.

## Palliative care: end of life care

- Glucocorticoids are prominent in end of life care
  - Benefits of steroids
    - Improve general feelings of wellbeing
    - Relieve fatigue and improve energy
    - Relieve nausea
    - Control of pain
      - ❖ 15% improvement in pain
      - ❖ If the patient is unable to obtain satisfactory pain relief despite an escalating opiate regimen → Commence trial with dexamethasone
      - ❖ One of the sources of pain associated with liver metastases is due to stretching and irritation of the liver capsule for which a trial of dexamethasone may provide an analgesic effect.
      - ❖ Liver capsule pain tends not to be opioid responsive, therefore increasing the modified or immediate release morphine would not be the correct option.
  - Dexamethasone is the usual agent of choice
- The most important aspect of management is to try to keep the patient calm and relieve distress with a large dose of midazolam (10mg).
  - In a massive terminal haemorrhage, a large dose of midazolam (10mg) can be given as part of 'crisis management' to relieve distress. Red or green towels or blankets should be available to soak up and mask the colour of blood

## Epstein-Barr virus: associated conditions

EBV: associated malignancies:

- Burkitt's lymphoma
- Hodgkin's lymphoma
- nasopharyngeal carcinoma
- Epstein-Barr virus infects B lymphocytes and squamous epithelial cells of the oropharynx. The virus can transform B cells and epithelial cells to produce tumors
- Malignancies associated with EBV infection
  - Burkitt's lymphoma (both African and sporadic Burkitt's)
  - Hodgkin's lymphoma
  - nasopharyngeal carcinoma
    - Epstein-Barr virus is detectable in over 90% of nasopharyngeal cancers
    - the most common type is the undifferentiated form.
  - HIV-associated central nervous system lymphomas
- The non-malignant condition hairy leukoplakia is also associated with EBV infection.

**September 2019 exam: What type of virus family is associated with nasopharyngeal carcinoma? Herpesvirus** (Epstein-Barr virus is one of the herpes viruses)

## T cell lymphoma (Adult T-cell lymphoma (ATLL))

- makes up about 10-20% of non-Hodgkin's lymphomas
- has a worse prognosis than B cell lymphoma.
- Adult T-cell leukaemia/lymphoma (ATLL) is a potentially aggressive type of mature T-cell non-Hodgkin lymphoma.
- It is linked to the viral infection, HTLV-1 (human T-cell lymphotropic virus 1).
- It is more prevalent in countries where infection with HTLV-1 is common, such as Japan, China, the Caribbean, South and Central America and West Africa.
- ATLL occurs in 2%-5% of people who are infected with the HTLV-1 virus.
- The HTLV-1 virus is a retrovirus, and is in the same class of virus as the HIV/AIDS virus. It is believed that the HTLV-1 virus is a key factor in the development of this rare lymphoma which is transmitted through sexual contact, exposure to contaminated blood or breastfeeding.
- slightly more common in men than in women,
- In **acute ATLL**, symptoms develop rapidly and include:
  - fatigue,
  - skin rash
  - enlarged lymph nodes
  - hypercalcaemia may also be present which can cause confusion, bone pain and severe constipation.
- **lymphomatous form of ATLL** presents with:
  - enlarged lymph nodes.
- **Chronic ATLL** is slow growing and frequently characterised by:
  - enlarged lymph nodes
  - Skin rash and
  - fatigue.
- Smouldering ATLL develops slowly and presents with very mild symptoms such as a few lesions on the skin.
- Patients with the chronic or smouldering types of ATLL can progress to the acute form in about 25% of cases.
- for the acute and lymphomatous types: Therapies include antiviral drugs, such as acyclovir and interferon, together with chemotherapy regimens

## Testicular cancer

The triad of a testicular lump, a mass on chest X-ray and a raised (3-HCG (human chorionic gonadotrophin) are suggestive of testicular seminoma

### Testicular mass

- ↑ LDH → pure seminomas germ cell tumor
- ↑ AFP → mixed non-seminomatous germ cell tumour

### Epidemiology

- Most common solid malignant tumor in young men in the US

### Classification:

- **germ cell tumors** (comprise more than 90% of all tumours and more commonly malignant)
  - Germ cell tumours are classified as either:
    - pure seminomas

- ❖ seminoma is the most common type of testicular germ cell tumor.
- ❖ ~ 40%
- ❖ Good radiosensitivity; slow growth, late metastases, and better overall prognosis compared to nonseminomas
- ❖ **Lactate dehydrogenase (LDH) is most likely to be elevated (in 40–60%)**
- ❖ A raised (3-HCG is found in around 15% of seminomas
- ❖ Orchidectomy with chemotherapy is curative in 90% of cases
- ❖ (3-HCG) levels may be a useful correlate with response to treatment
- mixed non-seminomatous germ cell tumours (NSGCTs)
  - ❖ **Elevated AFP levels are most consistent with NSGCT**
  - ❖ **Choriocarcinoma** is the most aggressive of the NSGCTs.
    - ⇒ Highly malignant and **most aggressive**
    - ⇒ Early hematogenous metastasis to the lungs or brain is common.
    - ⇒ Most testicular GCTs cause scrotal swelling, with a palpable mass, choriocarcinoma is different in that the local tumour may be small or nonpalpable.
    - ⇒ Beta-human chorionic gonadotropin (Beta-HCG) is usually markedly elevated in pure choriocarcinoma but is only elevated in 10-15% of seminomas.
    - ⇒ Gynecomastia occurs due to elevation of beta-hCG levels and is therefore common in choriocarcinoma, but only rarely seen in patients with a seminoma.
    - ⇒ On ultrasound scanning, choriocarcinoma is associated with haemorrhage and necrosis and may appear more cystic, inhomogeneous, and calcified than a seminoma. Calcifications and cystic areas are less common in seminomas than in nonseminomatous tumours.
  - can cause precocious puberty in boys.
  - Young men are more at risk for germ cell tumors.
  - teratoma is a testicular germ cell tumor that is benign in children and **malignant in adults**.
- **Non-germ cell tumors** (make up less than 10% of all testicular tumours)
  - Leydig cell tumours
    - golden brown color on morphology
    - Eosinophilic cytoplasmic inclusion bodies called Reinke crystals are found in Leydig cell type of testicular tumors.
  - Sertoli cell tumours,
  - gonadoblastomas.
- Testicular lymphoma is the most common testicular tumor in **older men**.
  - Most common testicular tumor in men > 60 years of age
  - Testicular lymphoma is a cancer that arises from metastasis from metastatic lymphoma to the testes.
  - Usually extranodal non-Hodgkin lymphoma

#### Risk factors

- Cryptorchidism
  - Patients with history of cryptorchidism have a 10- to 40-times increased risk of testicular cancer
  - this risk is greater for the abdominal versus inguinal location of undescended testis.
  - Orchidopexy does not reduce the risk of subsequently developing a malignancy.
  - An abdominal testis is more likely to be seminoma, while a testis surgically brought to the scrotum by orchidopexy is more likely to be non-seminomatous germ cell tumours (NSGCTs).

- family history
- infertility
- Klinefelter syndrome, Down syndrome (increased risk for germ cell tumors)

### Features

- testicular mass
  - Most commonly presents as a **hard, painless nodule on one testis** noticed by the patient or at a regular clinic examination.
- fatigue, weight loss,
- gynaecomastia
  - Rarely gynaecomastia can be the trigger by which a young man will seek medical attention; testicular examination should therefore be done in every case.
  - **What is the mechanism by which patients with testicular cancer develop gynaecomastia?**
  - ➔ **Raised oestrogen levels**
    - testicular cancers → ↑ $\beta$ -HCG → ↑oestrogen → stimulates hypertrophy of breast tissue.
- Testicular tumors metastasize early via the lymphatic system (drain to the para-aortic lymph nodes first) into the retroperitoneum, with the exception of early hematogenously metastasizing choriocarcinomas.

Until proven otherwise, a firm nodule on the testis should be considered cancer

### Investigation

**$\beta$ -hCG may be elevated in patients with seminomatous or nonseminomatous tumours,**

**AFP is increased only in patients with nonseminomatous tumours.**

- Ultrasound of the testis is 90% to 95% accurate in diagnosis.
- tumour markers
  - used for diagnosis and in monitoring the treatment response.
  - $\beta$  subunit of human chorionic gonadotropin ( $\beta$ -hCG):
    - may be elevated in patients with seminomatous or nonseminomatous tumours
  - **$\alpha$ -fetoprotein (AFP):**
    - **increased only in patients with nonseminomatous tumours**
    - Raised AFP in a boy with testicular swelling are highly suggestive of a yolk sac tumor.
  - **placental ALP**
    - increased in seminomas,
  - **Lactate dehydrogenase (LDH)**
    - LDH is elevated in **40–60%** of men with testicular germ cell tumours
    - may be the only tumour marker which is elevated in some men with seminomas.
    - It is neither sensitive nor specific as a marker for tumour recurrence, although the level at baseline does have prognostic value in men with advanced disease.
- Raised oestrogen levels
- transillumination test is negative in testicular germ cell tumors.

HCG is always elevated in cases of choriocarcinoma and sometimes in seminoma.

AFP is always elevated in yolk sac tumors.

In mixed germ cell tumors, both AFP and HCG may be elevated.

If testicular tumor is suspected, the testis is removed and sent to pathology without prior trans-scrotal biopsy

### Treatment

- **Radical orchectomy** to confirm histological diagnosis is **initial treatment** in most cases.
- followed by additional staging studies such as a CT scan of the abdomen and pelvis and radiograph of the chest.
- In **testicular cancer** the **BEP** combination is used: **Bleomycin, Etoposide and Cisplatin (Platinum)**.
  - **Etoposide**
    - works by inhibiting topoisomerase II and causing DNA degradation.
    - Etoposide is also used in the treatment of small cell lung cancer, leukemias, and lymphomas.
    - adverse effects: myelosuppression and alopecia.

### Prognosis

- ~95% cure is expected with treatment

The **rapid deterioration**, seen over the course of a few hours, is most suggestive of **haemorrhage into a metastasis**. Teratomas are well known to metastasise via haematogenous spread, including to liver, lung, bone and brain.

## Laryngeal cancer

### Treatment

- **Initial therapy for stages I and II is radiation therapy or surgery.**
  - early-stage disease could receive curative therapy with surgery or radiation alone.
  - **External beam radiation** is the curative and function sparing treatment for patient who prefer not to lose his ability to speak and he is willing to stop smoking immediately.
- Chemotherapy is not necessary in patient who has local and potentially curable disease.
- In the setting of lymph node-positive or locally advanced disease, the benefit of concurrent chemoradiotherapy is recommended.
- Cetuximab is a monoclonal antibody and is effective when combined with radiation, it has been found to improve local control and overall survival rates.

## Von Hippel-Lindau syndrome

### Definition

- VHL syndrome is an **autosomal dominant** condition predisposing to neoplasia.

### Aetiology

- due to an abnormality in the VHL gene located on short arm of **chromosome 3**
  - von-Hippel-Lindau= 3 words for chromosome 3.
- VHL gene normally act as a **tumor suppressor gene**
  - VHL gene normally is responsible for regulating the **hypoxia-inducible factor (HIF)**, a transcription factor.
  - In patients with VHL, there is constitutive expression of HIF resulting in angiogenesis and cancer development.

### Epidemiology

- it has over 90% penetrance by the age of 65.
- prevalence is 1 in 39,000.
- Mean age at presentation of 27 years.

### Types

- Type 1 VHL is associated with tumours in eye, brain, spinal cord, kidney and pancreas.
- Type 2 is associated with phaeochromocytoma:

### Features

- haemangioblastomas of the CNS (The most common presentation)
  - retinal haemangiomas: vitreous haemorrhage
  - **Retinal haemangioblastomas** is the initial presentation in 40% of patients.
  - **Annual ophthalmological exam for haemangioblastoma is the most appropriate screening investigation**
  - cerebellar haemangiomas is another common initial presentation.
    - CNS haemangioblastomas tend to be infratentorial.
    - cerebellar haemangiomas secretes erythropoietin-like substance, leading to a **secondary polycythaemia**.
    - haemangioblastomas are typically not cancerous, but they can compress the brain and spinal cord resulting in headaches, vomiting, paralysis, and ataxia.
- cysts in various organs (e.g., kidney, pancreas, liver)
  - renal cysts ( premalignant )
    - ↑ risk of developing **clear cell renal cell carcinoma**.
    - **Renal cell carcinoma** (Clear cell ) **is the commonest cause of death** (70% of patients having renal cysts and carcinomas by age of 60 years).
  - extra-renal cysts: epididymal, pancreatic, hepatic
- phaeochromocytoma
  - occurs in 20% of patients, although the incidence is much higher in those with von Hippel Lindau type 2
- endolymphatic sac tumours

### Diagnosis

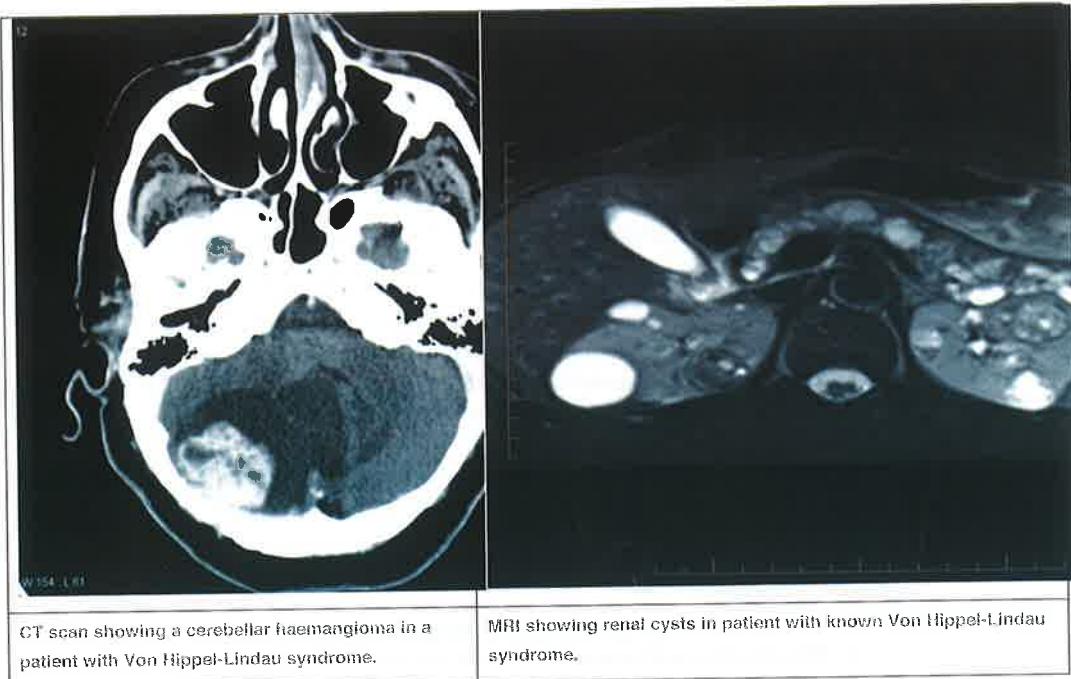
- genetic testing → mutations in the VHL gene.
  - Ideally, genetic testing in affected families should take place around the age of 5 years.

### Treatment

- Asymptomatic small haemangioblastomas → observation.
- Renal cell carcinoma → surgery.

### Monitoring

- Affected individuals require:
  - yearly urinalysis, catecholamine screening, fluorescein angiography
  - 3-yearly brain magnetic resonance imaging.



## Haemangiomas

- Hemangiomas are benign vascular tumors that lead to a messy clump of dilated blood vessels.
- **Hepatic hemangioma**
  - a benign liver tumor composed of masses of blood vessels
  - the most common benign tumor affecting the liver.
  - The most common site of hemangiomas in internal organs is the liver.
  - mesenchymal in origin and usually, are solitary
  - oral contraceptives and steroids may accelerate the growth of a hemangioma.
  - Investigations
    - biopsies are contraindicated because of the risk of bleeding.
    - A good way to determine if a structure is hypervascular is to look for IV contrast enhancement.
- **Capillary hemangioma**
  - **cherry hemangioma:**
    - also known as (Campbell de Morgan spots)
    - benign **capillary** hemangioma of the elderly that does not regress
    - benign skin lesions which contain an abnormal proliferation of capillaries.
    - frequency increases with age.
    - The most common benign capillary skin tumor found in elderly
    - affect men and women equally.
    - Features
      - ❖ erythematous, papular lesions
      - ❖ typically 1-3 mm in size
      - ❖ non-blanching
      - ❖ not found on the mucous membranes
    - As they are benign no treatment is usually required.



- Infants with large hemangiomas should have **ultrasonography** of the abdomen to rule out the presence of other hemangiomas in the viscera.
- **Propranolol is the first line of treatment** of hemangiomas causing disfigurement.

### Cytotoxic agents

The tables below summarises the mechanism of action and major adverse effects of commonly used cytotoxic agents.

#### Alkylating agents

Cytotoxic	Mechanism of action	Adverse effects
Cyclophosphamide	Alkylating agent - causes cross-linking in DNA	Haemorrhagic cystitis, myelosuppression, transitional cell carcinoma

#### Cytotoxic antibiotics

Cytotoxic	Mechanism of action	Adverse effects
Bleomycin	Degradates preformed DNA	<b>Lung fibrosis</b>
Doxorubicin	Stabilizes DNA-topoisomerase II complex inhibits DNA & RNA synthesis	Cardiomyopathy

**Antimetabolites**

Cytotoxic	Mechanism of action	Adverse effects
Methotrexate	Inhibits dihydrofolate reductase and thymidylate synthesis	Myelosuppression, mucositis, liver fibrosis, lung fibrosis
Fluorouracil (5-FU)	Pyrimidine analogue inducing cell cycle arrest and apoptosis by blocking thymidylate synthase (works during S phase)	Myelosuppression, mucositis, dermatitis
6-mercaptopurine	Purine analogue that is activated by HGPRTase, decreasing purine synthesis	Myelosuppression
Cytarabine	Pyrimidine antagonist. Interferes with DNA synthesis specifically at the S-phase of the cell cycle and inhibits DNA polymerase	Myelosuppression, ataxia

**Acts on microtubules**

Cytotoxic	Mechanism of action	Adverse effects
Vincristine, vinblastine	Inhibits formation of microtubules	<b>Vincristine:</b> Peripheral neuropathy (reversible), paralytic ileus <b>Vinblastine:</b> myelosuppression
Docetaxel	Prevents microtubule depolymerisation & disassembly, decreasing free tubulin. has a further action in blocking bcl-2	Neutropaenia

**Other cytotoxic drugs**

Cytotoxic	Mechanism of action	Adverse effects
Cisplatin	Causes cross-linking in DNA	Ototoxicity, peripheral neuropathy, hypomagnesaemia
Hydroxyurea (hydroxycarbamide)	Inhibits ribonucleotide reductase, decreasing DNA synthesis	Myelosuppression

Vincristine - peripheral neuropathy

## **Busulfan**

- alkylating antineoplastic agent,
- Busulfan was the mainstay of the chemotherapeutic treatment of chronic myeloid leukemia (CML) until it was displaced by the new gold standard, imatinib
- Busulfan is used in pediatrics and adults in combination with cyclophosphamide or fludarabine/clofarabine as a conditioning agent prior to bone marrow transplantation, especially in chronic myelogenous leukemia (CML) and other leukemias, lymphomas, and myeloproliferative disorders.
- **Busulfan lung**
  - **Busulfan lung is a form of drug-induced pulmonary toxicity with an idiopathic pulmonary fibrosis-like picture.**
  - It is clinically symptomatic in 5% of patients.
  - There are no predictors of toxicity and pulmonary function testing is not a useful "screening" test.
  - Withdrawal of busulfan is the key step in treatment.

## **Combinations of chemotherapeutic agents**

- what is the rationale behind using combinations of chemotherapeutic agents rather than single agents?
  - ➔ **Combination therapy decreases the chances of drug resistance developing**
    - There are two main reasons for using combinations of different chemotherapy agents:
      1. **Different drugs will exert their effects through different mechanisms**, so combining them will increase the number of tumour cells killed in each cycle.
      2. It also reduces the chances therefore of drug resistance developing.

## **Vinblastine**

- Vinblastine is an **M phase**-specific chemotherapeutic agent that works by **disrupting the assembly of microtubules via binding tubulin**.
- Cell death results because anaphase cannot commence without the formation of the mitotic spindle and kinetochore.
- **Which cellular event occurs in the same phase of the cell cycle at which vinblastine functions? ➔ Breakdown of the nuclear membrane**
- **Breakdown of the nuclear membrane** occurs during the prometaphase portion of mitosis.

Taxanes (e.g. Docetaxel) prevent microtubule disassembly

## **Cyclophosphamide**

Cyclophosphamide - haemorrhagic cystitis - prevent with mesna

- Cyclophosphamide is an **alkylating agent** used in the management of cancer and autoimmune conditions.
- It works by causing **cross-linking of DNA**
- Cyclophosphamide is **inactive unless metabolised by the liver to 4-hydroxyl cyclophosphamide**, which decomposes into alkylating species as well as to chloroacetaldehyde and acrolein

**Adverse effects**

- **haemorrhagic cystitis** (Acrolein causes **chemical cystitis**):
  - incidence reduced by the use of hydration and mesna
- myelosuppression
- transitional cell carcinoma
- premature ovarian failure ,
- **infertility** in both men and women.

**Mesna**

- 2-mercaptopropane sulfonate **Na**
- a metabolite of cyclophosphamide called **acrolein** is toxic to urothelium
- mesna binds to and inactivates acrolein helping to prevent haemorrhagic cystitis

**Cisplatin**

Cisplatin may cause peripheral neuropathy

Cisplatin is associated with hypomagnesaemia

- **Platinum**-based antineoplastic (end with: **-platin**)

**Mechanism of action**

- **Causes crosslinking in DNA** → makes it impossible for rapidly dividing cells to duplicate their DNA for mitosis.

**Side effects**

- Marrow toxicity
- **Ototoxicity**
  - Due to vestibulocochlear nerve damage (CNVIII)
  - Sodium Thiosulfate Prevents Cisplatin-Induced Hearing Loss in Children With Cancer
- Peripheral neuropathy
- Nephrotoxicity
  - The nephrotoxicity of platinum-class drugs seems to be related to reactive oxygen species
  - Hypocalcaemia, **hypomagnesaemia** and hypokalaemia may occur as a result of nephrotoxicity
  - Amifostine is an antidote for cisplatin treatment to counteract nephrotoxicity.
  - Adequate hydration and diuresis is used to prevent renal damage.
    - Chloride diuresis is a renal procedure that can be performed to prevent the nephrotoxicity caused by cisplatin.
- Alopecia,
- Changes in taste.
- Although optic neuritis is described it is not a typical side effect.

## Trastuzumab

Trastuzumab (Herceptin) - cardiac toxicity is common

A baseline echocardiogram to assess heart function is recommended prior to starting trastuzumab.

- Trastuzumab (Herceptin) is a monoclonal antibody directed against the HER2/neu receptor.
- It is used mainly in metastatic breast cancer although some patients with early disease are now also given trastuzumab.

### Adverse effects

- flu-like symptoms and diarrhoea are common
- **cardiotoxicity: associated with Dilated cardiomyopathy** in 2% to 7% of users
  - more common when anthracyclines have also been used(eg : **Doxorubicin**).
  - Toxic to cardiac muscle itself with relative sparing of the electrical conductivity of the heart
  - Studies have shown that activation of **Erb-b2** (also known as HER-2), the receptor blocked by trastuzumab (Herceptin), is important in preventing the development of cardiomyopathy
  - Mechanism
    - Anthracyclines → activate stress signal pathways within the heart → cardiac damage
    - HER2 activation is protective against the damage that this stress signaling induces
    - HER2 inhibition removes this layer of protection, leading to → dilated cardiomyopathy.
  - An echo is usually performed before starting treatment
  - **Regular echocardiogram (three monthly) is the best test to assess treatment safety**
  - Reduction of greater than 10% in ejection fraction indicating the need to stop treatment.

In which chemotherapeutic agents is the cumulative dose limited due to cardiotoxicity ?

- **anthracycline chemotherapeutic agents** (eg: Epirubicin )
  - Epirubicin and the other anthracycline chemotherapeutic agents are extremely potent but are **limited by dose constraints**.
  - Cumulative doses of over 900 mg/m<sup>2</sup> can lead to significant cardiac toxicity and heart failure.
  - Trastuzumab can cause direct myocardial damage and must be monitored with regular echocardiograms but it is not limited to a maximum lifetime dose.

## Erlotinib

- Erlotinib specifically targets the epidermal growth factor receptor (EGFR) tyrosine kinase (which is required for the conformational change) and binds in a reversible fashion to the adenosine triphosphate binding site.
- For the signal to be transmitted, two members of the EGFR family need to come together to form a homodimer. These then use the molecule of adenosine triphosphate (ATP) to autophosphorylate each other, which causes a conformational change in their intracellular structure, exposing a further binding site for binding proteins that cause a signal cascade to

the nucleus. By inhibiting the ATP, autophosphorylation is not possible and the signal is stopped.

- A key issue with EGFR-directed treatments is that **after a period of 8-12 months, the cancer cells become resistant to the treatment. This most commonly occurs due to a mutation in the ATP binding pocket of the EGFR kinase domain.** This prevents the binding of erlotinib (Tarceva).

### **Imatinib**

- **Belong to the class of → Signal transduction inhibitor**
- Imatinib is a **tyrosine kinase inhibitor** which is fairly specific for the bcr/abl protein. It blocks the active site, which has a number of downstream effects.
  - The result is reduced cell proliferation, reduced cell motility, decreased adhesion and increased apoptosis.
- **Indications**
  - accelerated or blast crisis phase of CML.
  - gastrointestinal stromal tumours.

### **Tamoxifen**

Tamoxifen is a selective estrogen receptor modulator (SERM) which acts as an oestrogen receptor antagonist and partial agonist. It is used in the management of oestrogen receptor positive breast cancer

#### **Adverse effects**

- menstrual disturbance: vaginal bleeding, amenorrhoea
- hot flushes
- venous thromboembolism
  - **Particularly during and immediately after major surgery or periods of immobility**
- endometrial cancer

Tamoxifen is typically used for 5 years following removal of the tumour.

Raloxifene is a pure oestrogen receptor antagonist, and carries a lower risk of endometrial cancer

### **UK licensed monoclonal antibodies**

Name	Target	Licensed indication
Infliximab	TNF- $\alpha$	Refractory Crohn's, Crohn's fistulas, refractory rheumatoid arthritis
Palivizumab	F protein on RSV	Prophylaxis, RSV in premature infants or bronchopulmonary dysplasia
Abciximab	Platelet glycoprotein IIb/IIIa	High risk coronary intervention
Rituximab	CD20	Refractory low grade or follicular B cell lymphoma
Basiliximab	IL-2 receptor $\alpha$ chain	Prophylaxis of acute rejection in allogeneic renal transplantation
Daclizumab	IL-2 receptor $\alpha$	As Basiliximab
Trastuzumab	HER 2 growth receptor	Relapsed HER2 (high) breast malignancy

IL-2, interleukin 2; TNF- $\alpha$ , tumour necrosis factor  $\alpha$ ; RSV, respiratory syncytial virus.

## Rituximab

- Rituximab binds to CD20, an antigen located on pre-B and mature B-lymphocytes
- The receptor is thought to mediate B-cell lysis and apoptosis
- After rituximab therapy, levels of B-lymphocytes appear suppressed for around 6 months, with levels slowly increasing after this time
- As well as for rheumatoid arthritis, rituximab is also used for the treatment of non-Hodgkin's lymphoma
- Infusion reactions associated with cytokine release occur in up to 15% of patients receiving rituximab, and the medicine is administered in a specialist centre for this reason

## Cetuximab

- Action → epidermal growth factor receptor (EGFR) inhibitor
  - Cetuximab works by blocking the extracellular domain of EGFR preventing ligand binding and therefore preventing downstream signal transduction.
- Cetuximab is a monoclonal antibody given by intravenous infusion
- The patient's tumour must express k-ras wild-type as k-ras mutated is constitutively active regardless of whether a ligand is attached or not.
  - Which histopathological subtypes is essential for successful treatment with cetuximab?
  - K-ras wild-type
    - ❖ Cetuximab and other EGFR inhibitors only work on tumors in which K-ras is not mutated
    - ❖ it has no effect in colorectal tumors with a K-ras mutation (this also applied to the EGFR antibody panitumumab).
    - ❖ genetic testing to confirm the absence of K-ras mutations (and so the presence of the K-ras wild-type gene), is now clinically routine before the start of treatment with EGFR inhibitors.
- Cetuximab is licensed by NICE in metastatic colorectal cancer for k-ras wild-type proven patients who require downstaging prior to surgical resection of liver metastatic disease.
  - 75% of patients with metastatic colorectal cancer have an **EGFR-expressing tumor** and are therefore considered eligible for treatment with cetuximab or panitumumab
- Side effect
  - acne type rash (the most important and serious SE).

## Capecitabine

- Capecitabine is the oral analog of 5-fluorouracil, a chemotherapeutic agent which is broken down, predominantly, by dihydropyrimidine dehydrogenase (DPD).
- Deficiency of dihydropyrimidine dehydrogenase (DPD) is autosomal recessive and will lead to a toxin buildup which in homozygous patients is usually fatal.

## Capecitabine versus 5-fluorouracil (5-FU)

- Advantages of capecitabine versus 5-fluorouracil (5-FU) → Can be orally administered
  - The major difference between capecitabine and 5-FU is that **capecitabine is an oral prodrug of 5-FU**.
  - **5-FU** is one of the most effective chemotherapeutic agents used in the treatment of advanced colorectal cancer, it is administered via IV infusion.
  - **Capecitabine** is orally administered chemotherapy, it is then metabolised to 5-FU.
  - The final step in metabolism to 5-FU is thymidine phosphorylase, higher activity of thymidine phosphorylase occurring in tumour tissues.
- Evidence suggests that efficacy of capecitabine versus 5-FU is broadly similar,

## **Chemotherapy side-effects: nausea and vomiting**

- Nausea and vomiting are common side-effects of chemotherapy.
- Risk factors for the development of symptoms include:
  - anxiety
  - age less than 50 years old
  - concurrent use of opioids
  - the type of chemotherapy used
- For patients at low-risk of symptoms then drugs such as metoclopramide may be used first-line.
- For high-risk patients, then **5HT3 receptor antagonists such as ondansetron** are often effective, especially if combined with dexamethasone

## **Adverse effects of other cancer treatment**

### **Purine analogue (eg: fludarabine) for CLL → Pneumocystis jirovecii infection**

- This cytotoxic agent affects T-cell function. Patients are therefore prone to opportunistic infections including pneumocystis infection.
- Patients therefore receiving purine analogues should also receive co-trimoxazole to reduce this risk.
- All patients who receive purine analogues are at risk of **transfusion-associated graft-versus-host disease** and therefore should receive irradiated blood products. The clinical features of transfusion associated graft-versus-host disease are:
  1. pancytopenia,
  2. liver dysfunction,
  3. diarrhoea and
  4. rash

### **Etoposide → secondary haematological malignancy**

- In patients who have received Etoposide, secondary haematological malignancy may develop in as little as 1-3 years.
- It is currently indicated for the treatment of small cell lung cancer and non-seminomatous testicular carcinoma.

## **Filgrastim**

- Action
  - granulocyte colony-stimulating factor (G-CSF)
- Mechanism
  - Filgrastim is similar to naturally occurring granulocyte colony-stimulating factor (G-CSF).
  - produced by recombinant DNA technology using genetic material of *Escherichia coli*.
  - stimulating the bone marrow to increase production of neutrophils.
- Indications
  - used to treat neutropenia caused by:
    - chemotherapy,
    - radiation poisoning,
    - congenital neutropenia
    - aplastic anemia
    - also used to increase white blood cells for gathering during leukapheresis.
- It is given either by injection into a vein or under the skin.
- side effects
  - The most commonly observed adverse effect is mild bone pain after repeated administration and local skin reactions at the site of injection
  - Severe side effects include splenic rupture and allergic reactions.
  - Other side effects include

- serious allergic reactions (including a rash over the whole body, shortness of breath, wheezing, dizziness, swelling around the mouth or eyes, fast pulse, and sweating),
- alveolar hemorrhage, acute respiratory distress syndrome, and hemoptysis.
- Severe sickle cell crises, in patients with sickle cell disorders.

## Sargramostim

- Action
  - granulocyte macrophage colony-stimulating factor (GM-CSF)
- It is produced in yeast
- stimulate other myeloid and megakaryocyte
- Indications
  - for myeloid reconstitution after bone marrow transplantation.
  - neutropenia induced by chemotherapy
- side effects
  - GM-CSF can cause more severe effects, including fever, arthralgias, and capillary damage with edema.
  - edema