Lecture_2

Presenting problem in hematology and Bone Marrow Failure and Aplastic anaemia

Fifth year students

By Dr Loma Al-Mansouri

Internist/Medical oncologist

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Investigation of diseases of the blood

The full blood count (FBC)

- anticoagulated blood is processed through automated blood analyser which can estimate :
  - no. of circulating cells
  - the haematocrit: the proportion of whole blood volume occupied by RBCs
  - the RBCs indices (mean cell volume, MCV), the amount of Hb present in the red cells (mean cell haemoglobin, MCH)
  - In addition differentiate types of WBCs and give automated counts of neutrophils, lymphocytes, monocytes, eosinophils and basophils.

Blood film examination

This requires manual examination blood samples prepared on a microscope slide which can often yield valuable information, Analysers cannot identify abnormalities of RBCs shape and content (e.g. Howell–Jolly bodies, basophilic stippling, malaria parasites) or fully define abnormal WBCs such as blasts

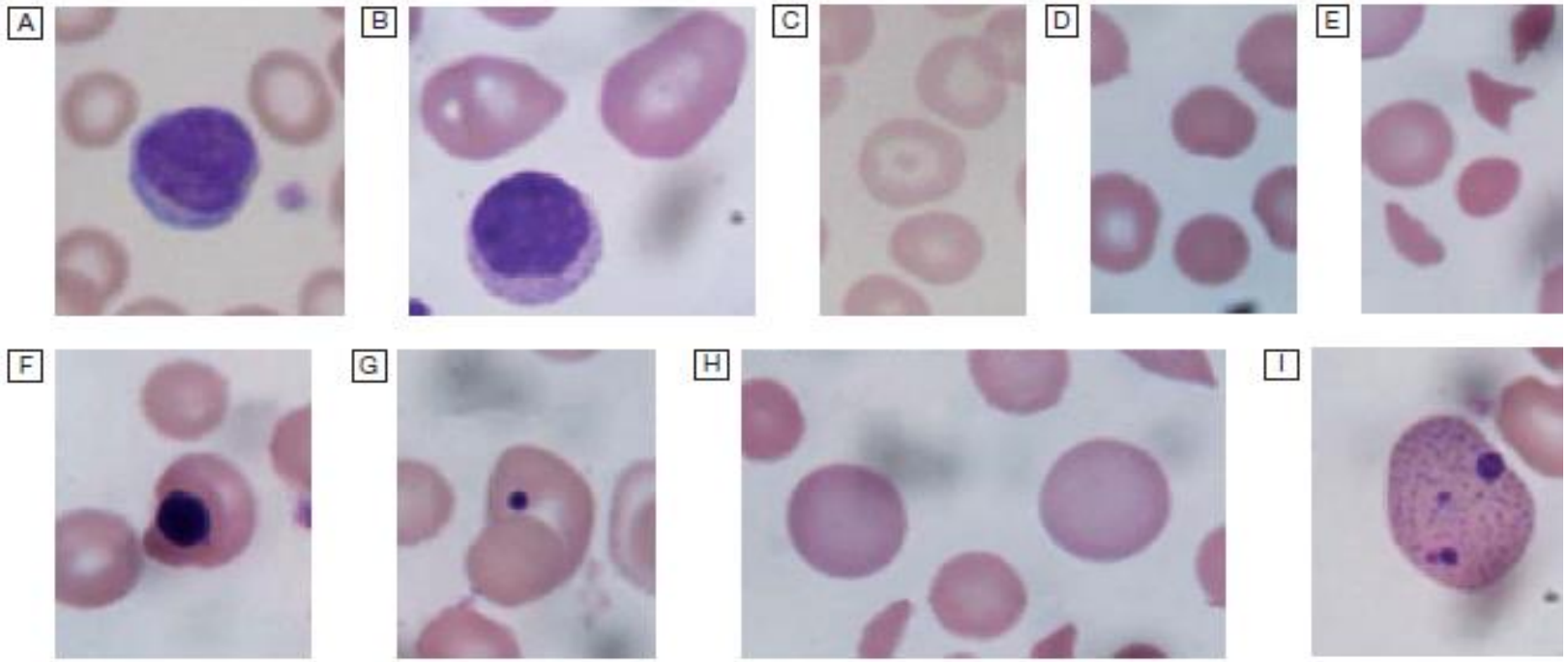
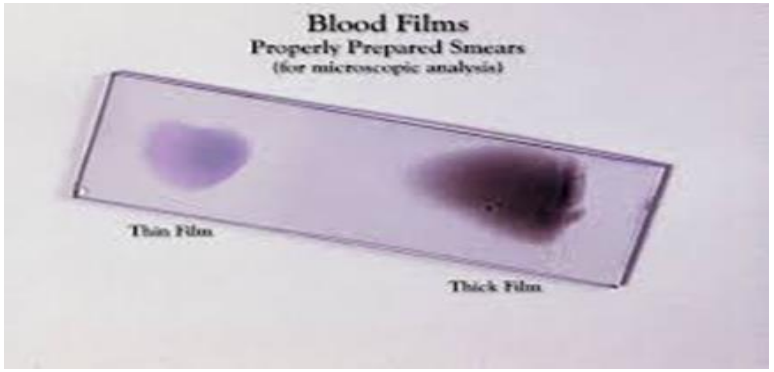


Fig. 23.8 **Appearance of red blood cells.** A Microcytosis. B Macrocytosis. C Target cells. D Spherocytes. E Red cell fragments. F Nucleate red blood cells. G Howell–Jolly bodies. H Polychromasia. I Basophilic stippling.



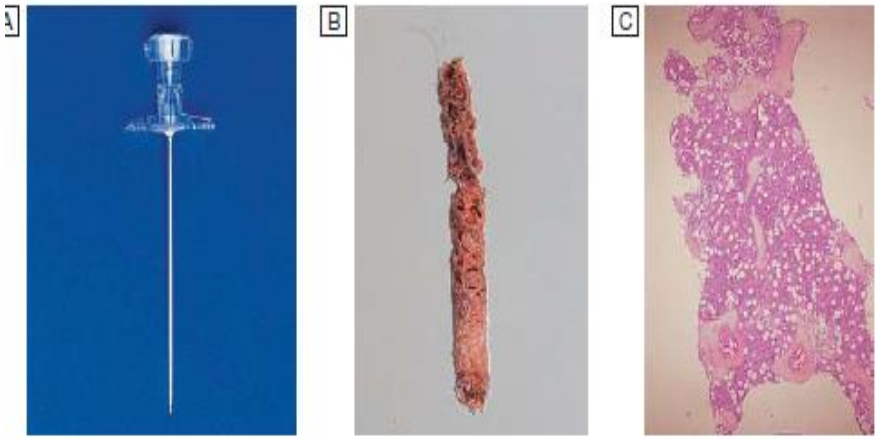
Bone marrow examination

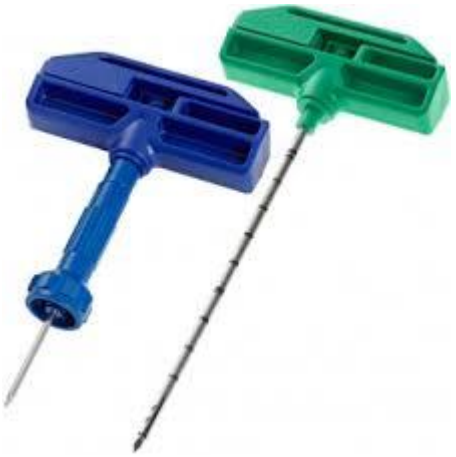
Site: posterior iliac crest under local anaesthetic, marrow can be sucked out from the medullary space, stained and examined under the microscope **(bone marrow aspirate).**

In addition, a core of bone may be removed **(trephine biopsy)**

BM aspirate is used to:

1) assess the composition and morphology of haematopoietic cells or abnormal infiltrates
2) cell surface marker analysis (immunophenotyping)
3) chromosome and molecular studies in malignant disease
4) marrow culture for suspected tuberculosis





- A trephine biopsy is superior for assessing:
  1) marrow cellularity
  2) marrow fibrosis
  3) infiltration by abnormal cells such as metastatic carcinoma

Polycythaemia Or erythrocytosis:

(high Hb) raised haematocrit (> 0.52 males, > 0.48 females)

a) True polycythaemia (or absolute erythrocytosis) ; excess RBCs
    - polycythaemia rubra vera (PRV)
b) ‘relative’, ‘apparent’ or ‘low-volume’ polycythaemia is due to a decreased plasma volume ex:
    - hypertension, smoking, alcohol and diuretic use (Gaisböck’s syndrome).

Leucopenia (low white cell count)

reduction in the total numbers of circulating WBC

1. **Neutropenia:** low neutrophil count ($< 1.5 \times 10^9$/L)

- Increased of bacterial infection
- Fever is the first manifestation of infection.
- Symptoms: sore throat, perianal pain or skin inflammation
- severe case with very low neutrophils can cause septicaemia and shocked within hours if immediate antibiotic therapy is not commenced

Causes of Neutropenia

1. Infection: viral, bacterial (e.g. Salmonella), protozoal (e.g. malaria)
2. Drugs: Cytotoxic, Gold, penicillamine, naproxen, carbimazole, propylthiouracil procainamide ,Captopril, nifedipine, penicillins, cephalosporins…etc
3. Autoimmune: connective tissue disease
4. Alcohol
5. Bone marrow infiltration: leukaemia, myelodysplasia
6. Congenital: Kostmann's syndrome
7. Constitutional: Afro-Caribbean and Middle Eastern descent

2) Lymphopenia

is absolute lymphocyte count of less than 1 × 109/L

- minor reductions may be asymptomatic
- deficiencies in cell-mediated immunity may result in infections (with fungi, viruses and mycobacteria)
- increase risk of lymphoid and other malignancies (particularly those associated with viral infections such as Epstein–Barr virus (EBV), human papillomavirus (HPV) and human herpesvirus 8 (HHV-8)). Lymphopenia without any obvious cause is common with advancing age

3) **Neutrophilia** :is an increase in the number of circulating neutrophils resulted from:
   - Infection: bacterial, fungal
   - Trauma: surgery, burns
   - myocardial infarct, pulmonary embolus, sickle-cell crisis
   - gout, rheumatoid arthritis, ulcerative colitis, Crohn's disease
   - solid tumours, Hodgkin lymphoma
   - polycythaemia, CML
   - Physiological: exercise, pregnancy

4) **lymphocytosis** is an increase in circulating lymphocytes greater than 3.5 × 109/L, the most common is viral infection, bacterial (e.g. Bordetella pertussis), CLL , lymphoma, Post-splenectomy

5) **Eosinophilia** is a high eosinophil count of more than 0.5 × 109/L is usually secondary to infection (especially parasites), allergy (e.g. eczema, asthma, reactions to drugs), immunological disorders (e.g. polyarteritis, sarcoidosis) or malignancy (e.g. lymphomas) and rarly in myeloproliferative disorders

Platelet abnormality

1. **Thrombocytopenia** is a reduced platelet count may arise by one of two mechanisms:
   - decreased or abnormal production (bone marrow failure and hereditary thrombocytopathies)
   - increased consumption following release into the circulation (immune-mediated, DIC or sequestration).
   - Spontaneous bleeding does not usually occur until the platelet count falls below 20 × 109/L, unless their function is also compromised

2) **Thrombocytosis (high platelet count)**
   - Either due to infection, inflammation, connective tissue disease, malignancy, iron deficiency,
   - Acute haemolysis or gastrointestinal bleeding

Presenting problems in blood disease

Anaemia

- Is a state in which the level of Hb in the blood is below the reference range appropriate for age and sex.
- Factors like pregnancy and altitude, also affect Hb levels and must be taken into account when considering whether an individual is anaemic.
- The clinical features of anaemia reflect diminished oxygen supply to the tissues. A rapid onset of anaemia (e.g. due to blood loss) causes more profound symptoms than a gradually developing anaemia.
- Individuals with cardiorespiratory disease are more susceptible to symptoms of anaemia

Clinical assessment

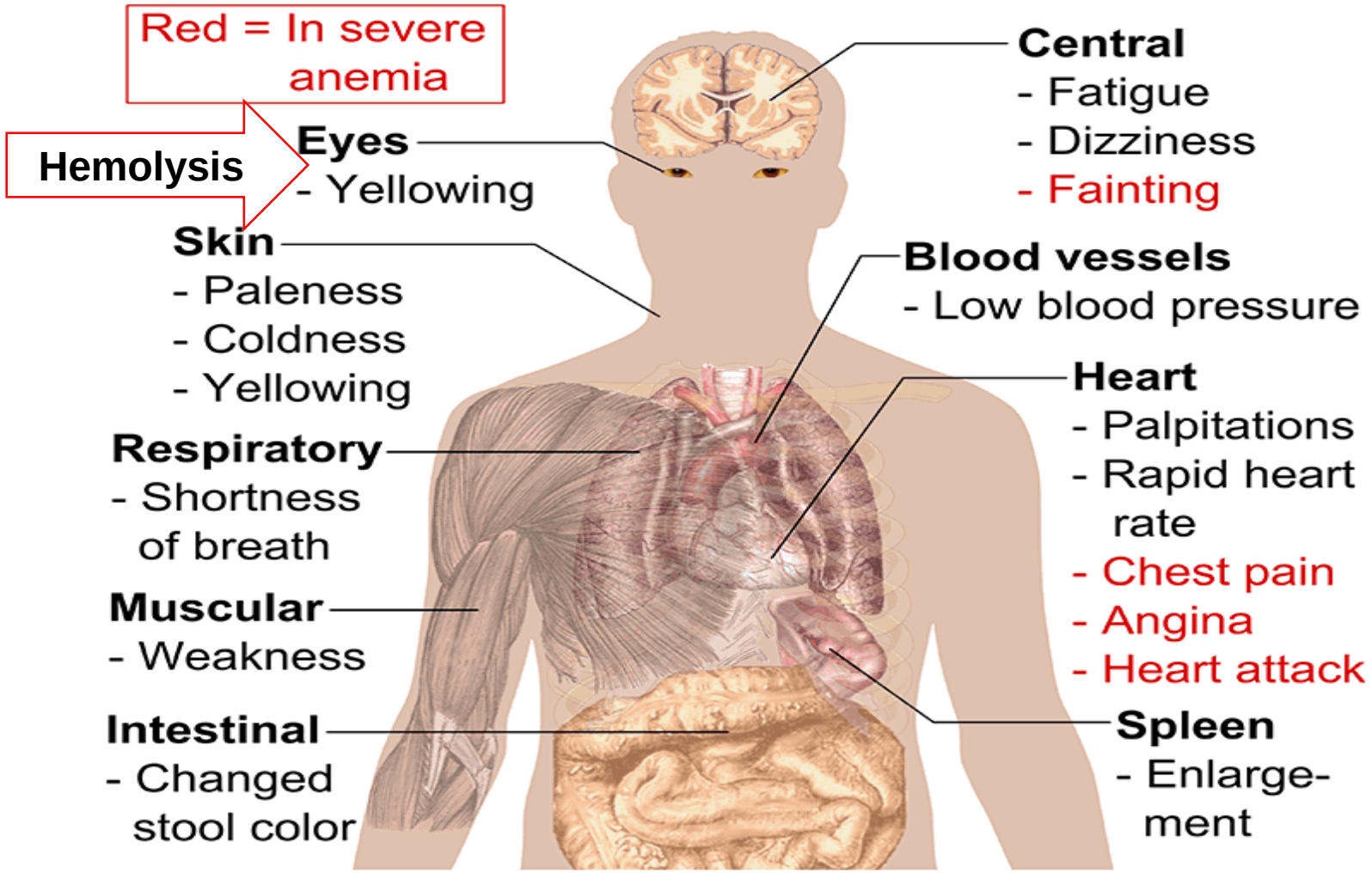
- *Iron deficiency anaemia* most common type of anaemia worldwide
- A thorough *GIT history* is important, symptoms of blood loss,
- *Menorrhagia* is a common cause of anaemia in pre-menopausal females
- A *dietary history* should assess the intake of iron and folate to assess deficiency (e.g. in pregnancy or during periods of rapid growth
- Medical history of chronic disease as: rheumatoid arthritis (anaemia of chronic disease), or previous surgery (e.g. resection of the stomach or small bowel, which may lead to malabsorption of iron and/or vitamin B12

- *Family history and ethnicity*: haemoglobinopathies and hereditary spherocytosis
- Pernicious anaemia may also run in families but is not associated with a clear Mendelian pattern of inheritance.
- *A drug history*: drugs that cause blood loss (e.g. aspirin and NSAIDs), hemolysis (e.g. sulphonamides) or aplasia (e.g. chloramphenicol)

On examination:

- general physical findings of anaemia (see figure)
- specific findings
  - for example, a right iliac fossa mass in case of caecal carcinoma,
  - jaundice in hemolytic anaemia,
  - Vitamin B12 deficiency may be associated with (peripheral neuropathy, dementia and signs of subacute combined degeneration of the cord)

Anemia Clinical Manifestations



- **Investigations**

  - A normal MCV (normocytic anaemia)
    - acute blood loss
    - anaemia of chronic disease, also known as the anaemia of inflammation (ACD/AI)

  - A low MCV (microcytic anaemia)
    - iron deficiency
    - Thalassaemia

  - A high MCV (macrocytic anaemia)
    - Vitamin B12 or folate deficiency
    - Myelodysplasia

23.2 How to interpret red cell appearances

Microcytosis (reduced average cell size, MCV <76 fL) A

- Iron deficiency
- Thalassaemia
- Sideroblastic anaemia

Macrocytosis (increased average cell size, MCV >100 fL) B

- Vitamin B_{12} or folate deficiency
- Liver disease, alcohol
- Hypothyroidism
- Myelodysplastic syndromes
- Drugs (e.g. zidovudine, trimethoprim, phenytoin, methotrexate, hydroxycarbamide)

Target cells (central area of haemoglobinisation) C

- Liver disease
- Thalassaemia
- Post-splenectomy
- Haemoglobin C disease

Spherocytes (dense cells, no area of central pallor) D

- Autoimmune haemolytic anaemia
- Post-splenectomy
- Hereditary spherocytosis

Red cell fragments (intravascular haemolysis) E

- Microangiopathic haemolysis, e.g. haemolytic uraemic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP)
- Disseminated intravascular coagulation (DIC)

Nucleated red blood cells (normoblasts) F

- Marrow infiltration
- Severe haemolysis
- Myelofibrosis
- Acute haemorrhage

Howell–Jolly bodies (small round nuclear remnants) G

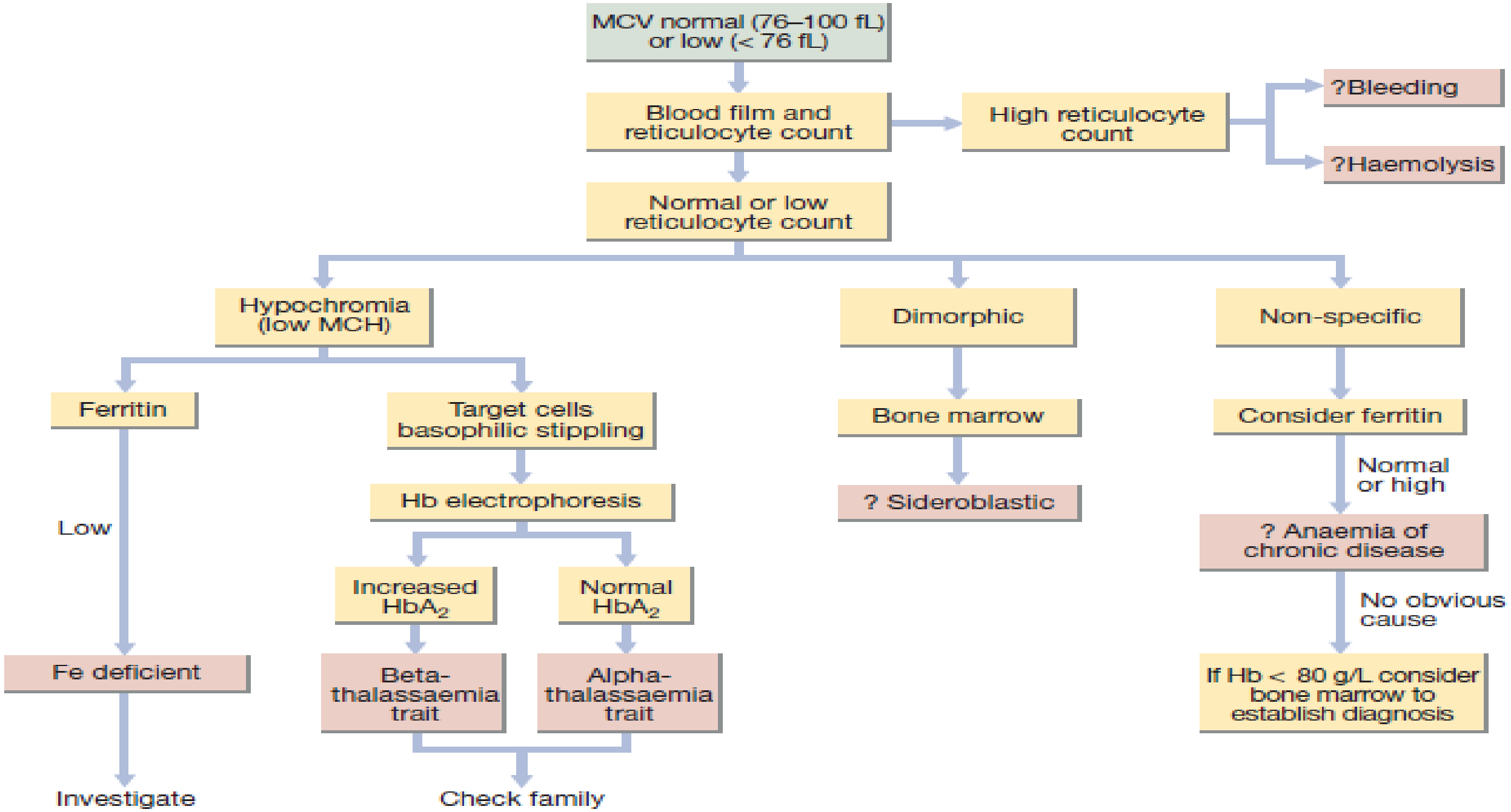
- Hyposplenism
- Post-splenectomy
- Dyshaematopoiesis

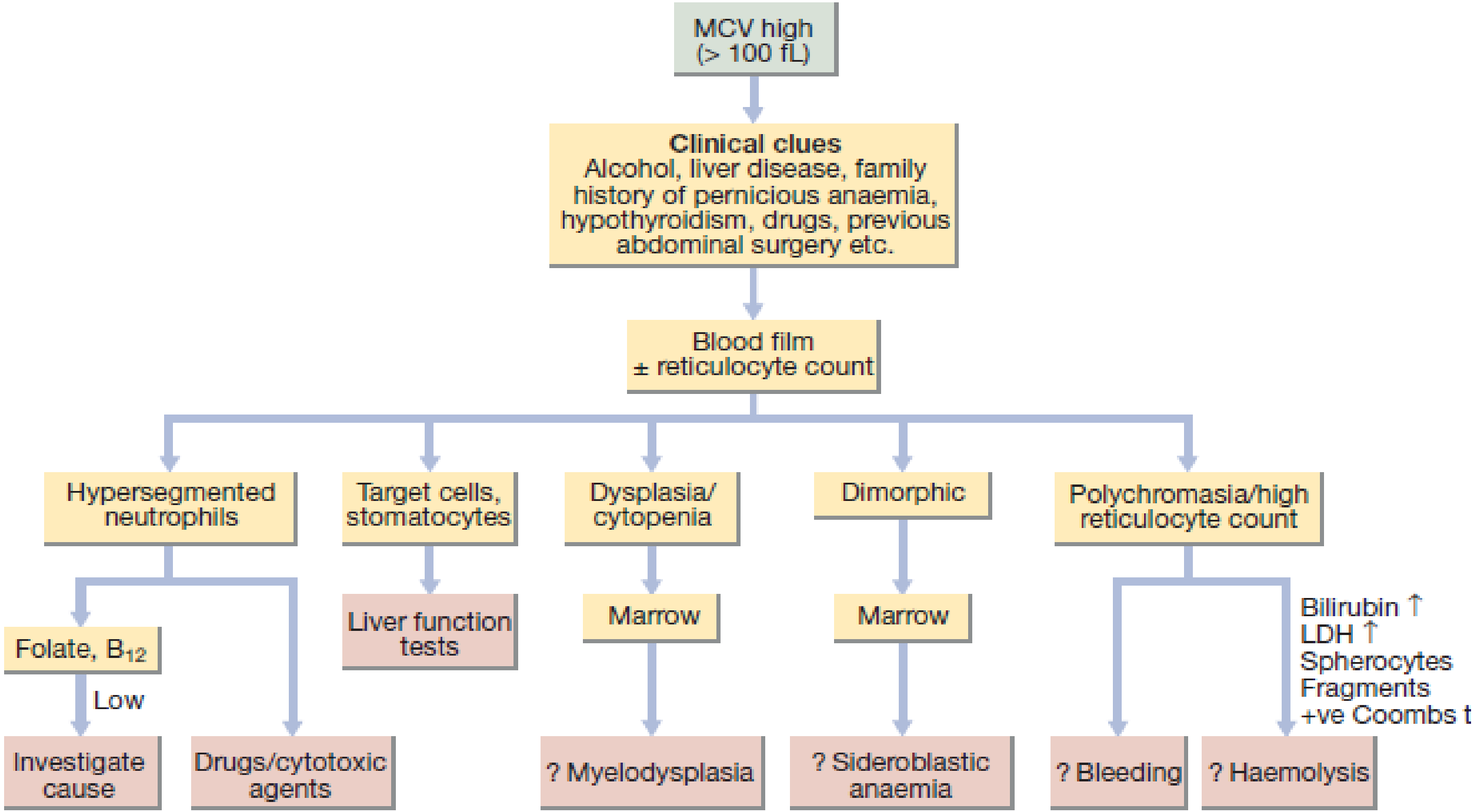
Polychromasia (young red cells – reticulocytes present) H

- Haemolysis, acute haemorrhage
- Increased red cell turnover

Basophilic stippling (abnormal ribosomal RNA appears as blue dots) I

- Dyshaematopoiesis
- Lead poisoning


MCV normal (76–100 fL) or low (< 76 fL)
Blood film and reticulocyte count
High reticulocyte count
?Bleeding
?Haemolysis
Normal or low reticulocyte count
Hypochromia (low MCH)
Dimorphic
Non-specific
Ferritin
Target cells basophilic stippling
Bone marrow
Consider ferritin
Low
Hb electrophoresis
? Sideroblastic
Normal or high
? Anaemia of chronic disease
Increased HbA2
Normal HbA2
No obvious cause
Fe deficient
Beta-thalassaemia trait
Alpha-thalassaemia trait
If Hb < 80 g/L consider bone marrow to establish diagnosis
Investigate
Check family


MCV high
(> 100 fL)
Clinical clues
Alcohol, liver disease, family history of pernicious anaemia, hypothyroidism, drugs, previous abdominal surgery etc.
Blood film
± reticulocyte count
Hypersegmented neutrophils
Target cells, stomatocytes
Dysplasia/ cytopenia
Dimorphic
Polychromasia/high reticulocyte count
Folate, B12
Low
Investigate cause
Drugs/cytotoxic agents
Liver function tests
Marrow
? Myelodysplasia
Marrow
? Sideroblastic anaemia
? Bleeding
Bilirubin ↑
LDH ↑
Spherocytes
Fragments
+ve Coombs t
? Haemolysis

23.7 Causes of anaemia

Decreased or ineffective marrow production

- Lack of iron, vitamin B_{12} or folate
- Hypoplasia/myelodysplasia
- Invasion by malignant cells
- Renal failure
- Anaemia of chronic disease

Normal marrow production but increased removal of cells

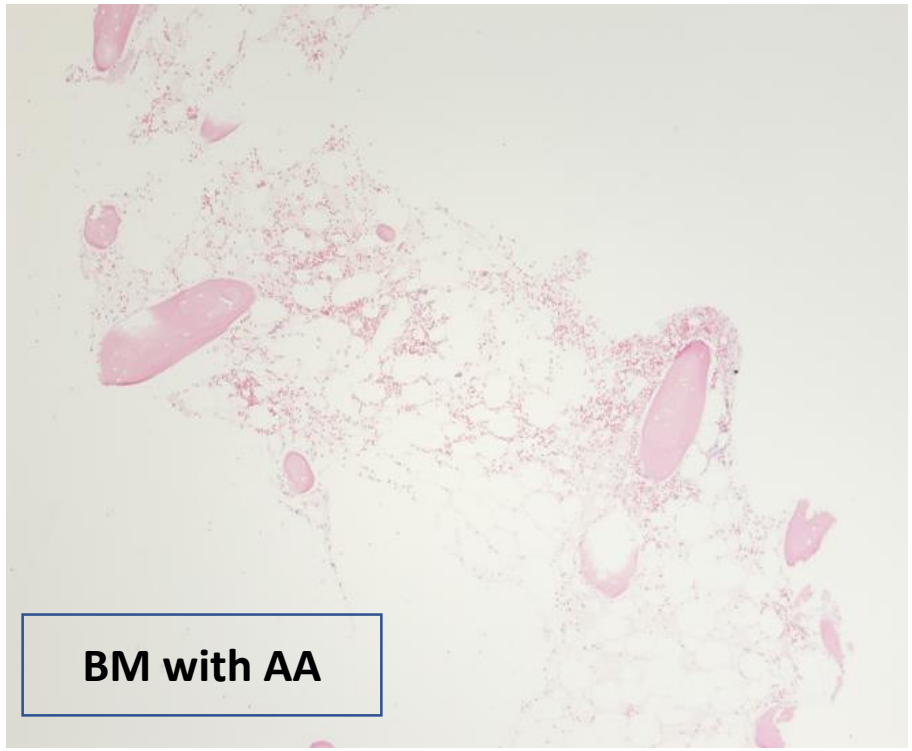
- Blood loss
- Haemolysis
- Hypersplenism

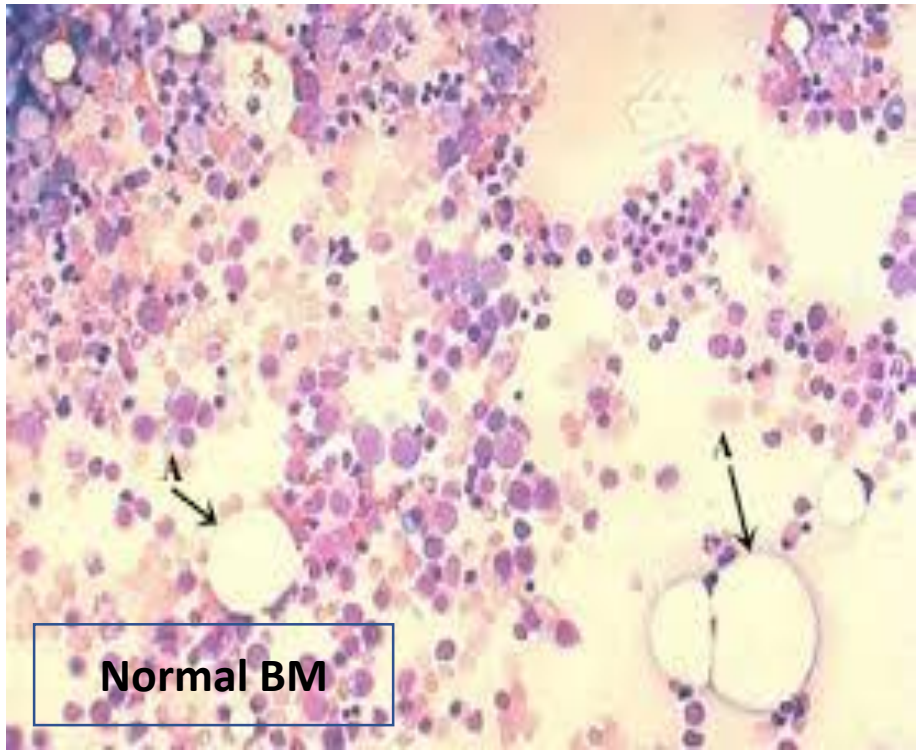
The bone marrow failure syndromes

- are disorders of the hematopoietic stem cell that can involve either 1 cell line or all of the cell lines (erythroid for red cells, myeloid for white blood cells, megakaryocytic for platelets), The lymphocytes, which are involved in lymphoproliferative disorders, are usually spared
- BM failure can be either inherited or acquired.
- The inherited BM failure syndromes include: Fanconi anemia, dyskeratosis congenita, Diamond-Blackfan anemia, and other genetic disorders.
- The most common cause of acquired bone marrow failure is aplastic anemia

Aplastic anemias

Def: is a syndrome of BM failure characterized by peripheral pancytopenia and marrow hypoplasia (see the image below). Although the anaemia is often normocytic, mild macrocytosis can also be observed in association with stress erythropoiesis and elevated foetal haemoglobin levels





- **Primary idiopathic acquired aplastic anaemia**
- **Secondary aplastic anaemia**

Primary idiopathic acquired aplastic anaemia

- rare disorder in Europe and North America
- with 2–4 new cases / million population annually
- much more common in east Asia
- There is failure of the pluripotent stem cells because of an autoimmune attack, producing BM hypoplasia with a pancytopenia
- The diagnosis required exclusion of other causes of secondary aplastic anaemia and rare congenital causes, such as Fanconi’s anemia

Clinical features

The onset is insidious, and the initial symptom is frequently related to **anaemia** or **bleeding**, **fever or infections** at presentation

- Specific signs and symptoms of aplastic anaemia may include the following:
  1. **Anemia**: May manifest as pallor, headache, palpitations, dyspnea, fatigue, or foot swelling
  2. **Thrombocytopenia**: May result in mucosal and gingival bleeding or petechial rashes
  3. **Neutropenia**: May manifest as overt infections, recurrent infections, or mouth and pharyngeal ulcerations

- Findings of LAP or organomegaly(enlarged liver or spleen) should suggest an alternative diagnosis

- In any case of suspected aplastic anemia, look for physical stigmata of inherited marrow-failure syndromes, such as the following:

  - Abnormal skin pigmentation
  - Short stature
  - Renal, cardiac, and gastrointestinal (GI) abnormalities
  - Microcephaly
  - Microphthalmos
  - Hypogonadism
  - Skeletal anomalies

Investigations:

- FBC : pancytopenia, low reticulocytes and macrocytosis ??
- Bone marrow aspiration and trephine : hypocellularity
- Hb electrophoresis and blood-group testing
- Biochemical profile (RFT, LFT, TFT, S electrolyte, B12 and Folate level…etc)
- Serology

- The severity of aplastic anaemia is graded according to the Camitta criteria

Camitta criteria

Severe AA (SAA)

- Marrow cellularity < 25% (or 25–50% with < 30% residual haematopoietic cells), plus at least two of:
  Neutrophils < 0.5 × 109/L
  Platelets < 20 × 109/L
  Reticulocyte count < 20 × 109/L

Very severe AA (VSAA)

- As for SAA but neutrophils < 0.2 × 109/L

Non-severe AA (NSAA)

- AA not fulfilling the criteria for SAA or VSAA

- **Management**
- Supportive with blood product support
- aggressive management of infection
- The prognosis of severe aplastic anaemia with the supportive care is poor
- > 50% of patients die in the first year
- The curative treatment for patients under 35 years of age with severe idiopathic aplastic anaemia is allogeneic HSCT if there is an available sibling donor
- Older patients (35–50) may be candidates if they have no comorbidities .
- Allogeneic HSCT can achieve long-term cure in 75–90

- In older patients and those unfit for HSCT , immunosuppressive therapy (IST)
  - Anti-thymocyte globulin (ATG)
  - ciclosporin
- IST is the treatment of choice and gives 5-year survival rates of 75%
- The thrombopoietin receptor agonist Eltrombopag has produced trilineage responses in patients who fail IST

Secondary aplastic anaemia

is a syndrome of BM failure with peripheral pancytopenia and marrow hypoplasia secondary to an underlying abnormality

- In some cases the cytopenia is more selective and affects only one cell line, ex: neutropenia.
- The clinical features and methods of diagnosis are the same as for primary idiopathic aplastic anaemia.
- An underlying cause should be treated or removed, but otherwise management is as for the idiopathic form.

Causes of secondary aplastic anaemia

Drugs:

Cytotoxic drugs
Antibiotics – chloramphenicol, sulphonamides
Antirheumatic agents – penicillamine, gold, phenylbutazone, indometacin
Antithyroid drugs – carbimazole, propylthiouracil
Anticonvulsants
Immunosuppressants – azathioprine

- **Chemicals:**

Benzene, toluene, solvent misuse – glue-sniffing
Insecticides – chlorinated hydrocarbons (DDT), organophosphates and carbamates

- **Radiation**
- **Viral hepatitis**
- **Pregnancy**
- **Paroxysmal nocturnal hemoglobinuria**

Thank you