Clinical haematology

Clinical haematology is dedicated to the diagnosis and treatment of diseases of the blood and blood-forming tissues. Haematology diseases may involve blood cells disorder (red blood cells, white blood cells and platelets) or other blood components or include the hematopoietic organs (bone marrow, lymph nodes, spleen).

Anaemia

Anaemia is a reduction in the concentration of circulating haemoglobin or oxygen-carrying capacity of blood below the level expected for healthy persons of the same age and sex in the same environment.

Normal haemoglobin (and packed cell volume or PCV) levels are given in Table 2.1.

Anaemia exists if haemoglobin or PCV level is below the lower limit of normal for the particular age and sex.

Table 2.1: Normal levels of haemoglobin and packed cell volume

Age/Sex	Haemoglobin (g/dl)	PCV (%)
Adult males	13–17	40–50
Adult females (nonpregnant)	12–15	38–45
Adult females (pregnant)	11–14	36–42
Children, 6–12 years	11.5–15.5	37–46
Children, 6 months–6 years	11–14	36–42
Infants, 2–6 months	9.5–14	32–42
Newborns	13.6–19.6	44–60

The normal average haemoglobin level depends upon the age and sex of the individual and the environment. The difference in haemoglobin level between sexes is related to the **androgens** that have a stimulatory effect on erythropoiesis. The lower level of haemoglobin during pregnancy as compared to the no pregnant state is due to **haemodilution** caused by an **expansion of plasma volume**. The normal haemoglobin level in the newborn period is **highest**; subsequently, the haemoglobin level falls and reaches the minimum level by 2 months. Haemoglobin level reaches adult levels by **puberty**. Persons living at **high altitudes** exposed to low oxygen tensions have a higher haemoglobin concentration than persons living at sea level.

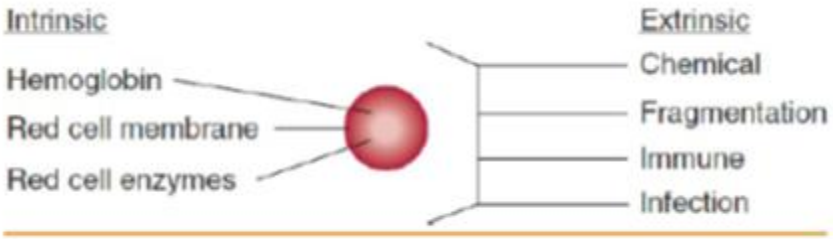


FIGURE 3.1 Intrinsic and extrinsic causes of hemolysis.

Cause of Anaemia

- **Nutritional deficiency**: Iron, folate, less commonly vitamin B12
- **Infections**: Tuberculosis, malaria, kala-azar, HIV infection/AIDS, hookworm
- **Inherited anaemias**: Thalassaemias, sickle cell disorders, glucose-6-phosphate dehydrogenase deficiency
- **Blood loss**: Obstetrical problems

Classification of Anemia

There are several classifications of anaemia.

1. **Morphological classification**: It is based on (1) **red cell size** (Normocytic, microcytic, or macrocytic), and (2) **degree of hemoglobinization,** reflected by the color of red cells (normochromic or hypochromic).
   - **Microcytic hypochromic anaemia** is characterized by red blood cells smaller than normal and the central pallor more than normal 1/3. It shows reduced MCV (< 80 fL) and reduced MCHC (30 gm/dL).
   - **Normocytic normochromic anaemia** is characterized by normal red cell size as well as central pallor. It shows a normal MCV (82-100 fL) and normal MCHC (33-36 gm/dL).
   - **Macrocytic normochromic anaemia** is characterized by red cells larger than normal. They have increased MCV (>100 fL) and normal MCHC due to defective maturation of erythroid precursors in the bone marrow.

2. Etiological classification: Based on the cause and the underlying mechanisms of production of anemia

Table 2.5: Morphological classification of anaemias

Macrocytic anaemias (MCV > 100 fl)	Microcytic anaemias (MCV < 80 fl)	Normocytic anaemias (MCV 80–100 fl)
Megaloblastic anaemia	Iron deficiency anaemia	Reticulocyte production normal
Nonmegaloblastic anaemia	Thalassaemias	• Recent blood loss
• Liver disease	Sideroblastic anaemia	• Haemolytic anaemia
• Haemolytic anaemia	Anaemia of chronic disease	Reticulocyte production deficient
• Alcoholism		• Aplastic anaemia
• Myelodysplastic syndrome		• Myelophthisic anaemia
• Hypothyroidism		• Chronic renal failure
		• Anaemia of chronic disease
		• Hypothyroidism

Table 2.3: Aetiological classification of anaemia

Anaemias due to impaired red cell production	
1. Anaemias due to deficiency of nutrients • Iron deficiency anaemia • Megaloblastic anaemia due to deficiency of folate or vitamin B_{12} 2. Anaemia of chronic disease 3. Sideroblastic anaemia 4. Aplastic anaemia and related disorders 5. Anaemia of chronic renal disease 6. Anaemia of liver disease 7. Anaemia in endocrine disorders 8. Myelophthisic anaemia (Anaemia due to replacement of marrow by metastatic carcinoma, leukaemia, lymphoma, infections, storage disorders, etc.) 9. Congenital dyserythropoietic anaemia	
Anaemias due to excessive red cell destruction (Haemolytic anaemias)	
Abnormality intrinsic to red cells	*Abnormality extrinsic to red cells*
1. **Defects in red cell membrane** • Hereditary spherocytosis • Hereditary elliptocytosis	1. **Immune haemolytic anaemias** • Autoimmune • Alloimmune • Drug-induced
2. **Defects in haemoglobin** • Quantitative: Thalassaemias • Qualitative: Sickle-cell disease; Haemoglobin D, E, or C disease	2. **Mechanical haemolytic anaemia** • Microangiopathic • Cardiac • March haemoglobinuria
3. **Defects in enzymes** • Glucose-6-phosphate dehydrogenase deficiency • Pyruvate kinase deficiency	3. **Direct action of physical, chemical, or infectious agents**
	4. **Hypersplenism**
Anaemias due to excess blood loss	

Table 2.4: Classification of anaemia according to the reticulocyte response

Reticulocyte response	Reticulocyte production index (Absolute reticulocyte count)	Causes
1. Appropriate for the degree of anaemia	≥ 2% (>100,000/µl)	Hyperproliferative anaemias (blood loss, haemolytic anaemias)
2. Inappropriately low for the degree of anaemia	< 2% (<75,000/µl)	Hypoproliferative anaemias (iron deficiency anaemia, megaloblastic anaemia, anaemia of chronic disease, thalassaemia, endocrine diseases, sideroblastic anaemia, aplastic anaemia, myelodysplasia)

Table 4.3 The reticulocyte count and causes of anemia

Reticulocytes <100,000/μL or Reticulocyte Index <2%	*Reticulocytes ≥100,000/μL or Reticulocyte Index ≥2%*
Hypoproliferative anemias	**Appropriate response to blood loss**
Iron deficiency anemia	
Anemia of acute inflammation	**Hemolytic anemias**
Anemia of renal disease	Hemoglobinopathies
Endocrine anemias	Membrane defects
Pure red cell aplasia	Enzyme defects
Bone marrow replacement	Mechanical causes
	Autoimmune hemolytic anemia
Maturation defects	Alloimmune hemolytic anemia
Folate deficiency	
B_{12} deficiency	
Sideroblastic anemia	

Table 2.6: Differential diagnosis of anaemias based on MCV and RDW

MCV	RDW	Causes
1. Low	Normal	Thalassaemia carrier, anaemia of chronic disease
2. Low	High	Iron deficiency anaemia, haemoglobin H disease, sickle-cell-β thalassaemia
3. High	Normal	Myelodysplastic syndrome, aplastic anaemia
4. High	High	Megaloblastic anaemia, immune haemolytic anaemia
5. Normal	Normal	Anaemia of chronic disease, sickle-cell trait, hereditary spherocytosis
6. Normal	High	Early iron deficiency or megaloblastic anaemia, sideroblastic anaemia, myelofibrosis, sickle-cell anaemia

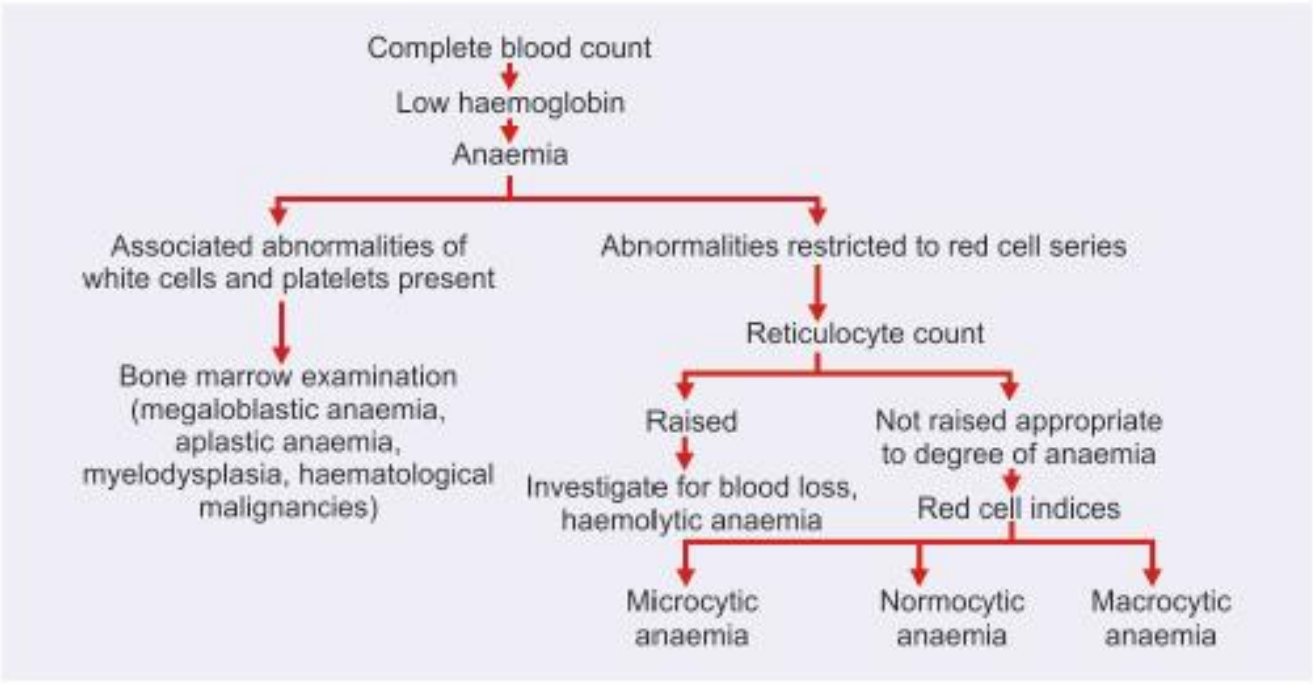


Figure 2.4: A simplified approach for evaluation of anaemia based on complete blood count

Clinical Features of Anemia

The symptoms depend on four main factors:

- **Speed of onset of anemia:** Rapidly progressive anemia causes more symptoms than that of gradual onset. This is because there is less time for adaptation in the cardiovascular system.
- **The severity of anemia:** Mild anemia produces no symptoms compared to significant symptoms in severe anemia.
- **Age of the patient:** Young patients can tolerate anemia better than elderly.
- **Underlying illness:** The disease which caused the anemia.

General clinical features are either due to tissue hypoxia or compensatory mechanisms.

1. **Due to tissue hypoxia:**

- *Nonspecific symptoms:* Weakness, malaise and easy fatigability due to hypoxia of muscles.
- *Dyspnea on mild exertion:* It is due to the lowered oxygen content of the circulating blood.
- *Pallor:* Patients appear pale due to deficiency of red coloured haemoglobin which is better appreciated in the conjunctiva, the mucous membrane of tongue and nail beds. Pallor associated with icterus is suggestive of hemolytic anemia.
- *CNS:* Patients with severe anemia may complain of headache, vertigo, tinnitus and lack of concentration.

2- Due to compensatory mechanisms:

- *Cardiac features:* Dyspnea on mild exertion, palpitation, tachycardia and cardiac murmur occur due to compensatory mechanisms. The resulting increase in the cardiac output may cause congestive cardiac failure.

Table 8.3 Signs and Symptoms of Anemia

Cardiovascular

- Tachycardia
- Palpitations
- Strong arterial pulses
- Cardiac enlargement
- Murmurs
- Bleeding in the retina

Respiratory

- Difficult or painful breathing (dyspnea)
- Problem with breathing when lying down (orthopnea)
- Increased depth and rate of respiration

Neuromuscular

- Headaches
- Dizziness (vertigo)
- Faintness
- Inability to concentrate
- Feeling of fatigue
- Sensitivity to cold
- Ringing in the ear (tinnitis)

Integumentary

- Paleness (pallor) of the skin, especially the mucous membranes and nailbeds
- Delayed wound healing

Gastrointestinal

- Anorexia
- Nausea
- Flatulence
- Constipation
- Diarrhea

Genitourinary

- Menstrual irregularity
- Amenorrhea
- Increased urination

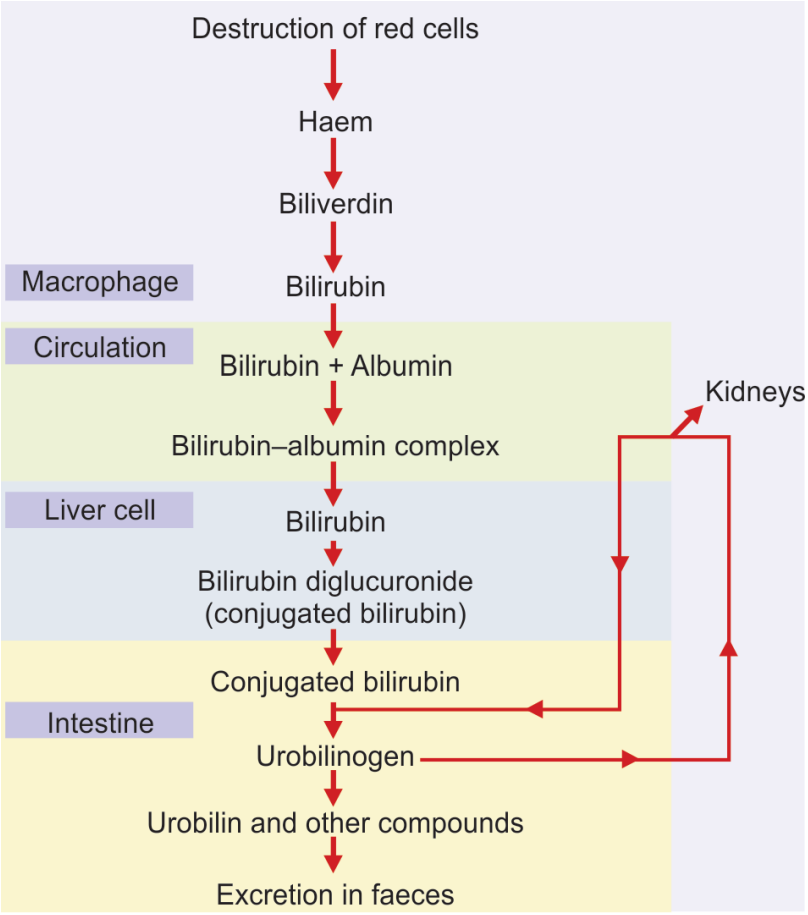
Some terminology for abnormal RBC shapes

- ***Normocytic normochromic:*** Red cells with normal size and colour (i.e. normal haemoglobin content); 7–8 μ size; pink with a small area of central pallor (1/3rd the diameter of the red cell)
- ***Anisocytosis:*** Significant variation in the size of red cells
- ***Poikilocytosis:*** Significant variation in shape of red cells; both aniso- and poikilocytosis are nonspecific features of a variety of anaemias
- ***Microcytic hypochromic:*** Red cells smaller than normal with increased area of central pallor due to deficiency of haemoglobin
- ***Macrocytic:*** Red cells larger in size than normal; may be round or oval

Tests to the presence of haemolysis

Red cell destruction can occur either **extra-or intravascularly**.

- **Extravascular destruction of red cells** by macrophages occurs mostly in spleen and liver.
- **Intravascular haemolysis** causes the release of haemoglobin in circulation. Free haemoglobin combines with haptoglobin in plasma, and this complex is then cleared from the circulation by hepatocytes.



Mechanism of extravascular haemolysis in macrophages of reticuloendothelial system with formation of bilirubin

Table 2.7: Comparison of extravascular and intravascular haemolysis

Parameter	Intravascular haemolysis	Extravascular haemolysis
1. Site of haemolysis	Within circulation	Macrophages of spleen, liver, bone marrow, etc.
2. Causes	Blackwater fever, incompatible blood transfusion, PNH, PCH	Haemoglobinopathies, hereditary haemolytic anaemias, autoimmune haemolytic anaemia
3. Splenomegaly	Absent	Present
4. Reticulocyte count	Increased	Increased
5. Indirect serum bilirubin	Increased	Increased
6. Plasma haemoglobin	Markedly increased	Mild to moderately-increased
7. Haemoglobin in urine	Present	Absent
8. Haemosiderin in urine	Present	Absent
9. Methaemalbumin (Schumm's test)	Positive	Negative
10.Serum haptoglobin	Decreased	Decreased
11. Serum LDH	Increased	Increased
PNH: Paroxysmal nocturnal haemoglobinuria; PCH: Paroxysmal cold haemoglobinuria		

- Free haemoglobin (haemoglobinaemia) appears in circulation once the plasma haptoglobin disappears. Free haem can bind albumin, leading to the formation of methaemalbumin (methaemalbuminaemia).
- Methaemalbumin can be detected by Schumm's test (detection of the distinctive absorption band of methaemalbumin at 558 nm on spectrophotometry). Free haemoglobin is also excreted by the kidneys resulting in haemoglobinuria. Benzidine or orthotoluidine test can be used for detection of haemoglobin in urine.

Estimation of serum Haptoglobin

The measurement of the serum haptoglobin level is another test to estimate the presence of increased hemolysis in the circulating blood. The normal level of serum haptoglobin is about 200mg/dL of blood. If that level drops sharply, it may indicate the presence of large amounts of free hemoglobin in the blood due to intravascular hemolysis.