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PAE 510

DISEASES OF THE BLOOD

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Course code: PAE 510

Course title: Diseases of the Blood

Course credit load: 2 Units

Series 1: The Haematopoietic System and Evaluation of Anaemia in Children

- **Part 1.1: The Haematopoietic System: Definition, Components, and Development**
  - Sub Part 1.1.1: Definition and components of the haematopoietic system
  - Sub Part 1.1.2: The bone marrow and haematopoiesis
  - Sub Part 1.1.3: Development of the haematopoietic system
- **Part 1.2: Evaluation of a Child with Haematologic Disorders**
  - Sub Part 1.2.1: General principles of evaluating a child with a suspected haematologic disorder
  - Sub Part 1.2.2: Key elements of history in suspected haematologic disorders
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- **Part 1.3: General Approach to Anaemia: History, Examination, and Laboratory Evaluation**
  - Sub Part 1.3.1: Definition of anaemia and relevant patient characteristics
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- **Part 1.4: Classification of Anaemia**
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  - Sub Part 1.4.2: Normocytic anaemia and reticulocyte response
  - Sub Part 1.4.3: Confirmatory testing

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Introduction

Picture a pale, tired eight year old brought to clinic by a concerned mother, with a full blood count returning a low haemoglobin, prompting the essential next question of exactly what type of anaemia this represents and why. Understanding the haematopoietic system and developing a structured, systematic approach to evaluating a child with anaemia forms the essential foundation

for this entire PAE 510 course, since the specific diseases of the blood discussed in later Series all ultimately present, at least in part, through their effects on this same system.

The aim of this Series is to equip you with an understanding of the haematopoietic system and its development, and a structured approach to evaluating a child with haematologic disorders, particularly anaemia.

This Series begins with the **definition, components, and development of the haematopoietic system**, before turning to the **evaluation of a child with haematologic disorders**. Next, we examine the **general approach to anaemia**, including history, examination, and laboratory evaluation, before concluding with the **classification of anaemia**.

Series Learning Outcomes

At the end of this Series, you should be able to:

- **SLO 1.1:** define the haematopoietic system and describe its components,
- **SLO 1.2:** describe the development of the haematopoietic system,
- **SLO 1.3:** describe the evaluation of a child with haematologic disorders,
- **SLO 1.4:** define anaemia and describe relevant patient characteristics, including age, sex, race, and ethnicity,
- **SLO 1.5:** describe the history and physical examination relevant to a child with anaemia,
- **SLO 1.6:** describe the laboratory evaluation of anaemia, including full blood count, RBC indices, blood smear, and reticulocyte count,
- **SLO 1.7:** describe the classification of anaemia by red cell size, and
- **SLO 1.8:** describe confirmatory testing in the evaluation of anaemia, including haemoglobin electrophoresis.

1.1 The Haematopoietic System: Definition, Components, and Development

1.1.1 definition and components of the haematopoietic system

A system responsible for producing every blood cell

The **haematopoietic system**, abbreviated **HS**, refers to the collective organs and tissues responsible for the production, maturation, and regulation of **blood cells**, and comprises three principal components: the **blood cells** themselves, the **bone marrow**, the primary site of blood cell production, or **haematopoiesis**, in postnatal life, and the **lymphoid organs**, including the

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spleen, **lymph nodes**, and **thymus**, which support **lymphocyte** development and immune function.

Blood cells are broadly classified into three main lineages: **red blood cells**, or **erythrocytes**, responsible for oxygen transport, **white blood cells**, or **leukocytes**, responsible for immune defence, further subdivided into **granulocytes**, **lymphocytes**, and **monocytes**, and **platelets**, responsible for **haemostasis**, and all three lineages ultimately arise from a common **haematopoietic stem cell** population within the bone marrow.

Fill in the blank: The haematopoietic system comprises blood cells, the bone marrow, and _____ organs.

1.1.2 the bone marrow and haematopoiesis

The **bone marrow** contains **haematopoietic stem cells**, capable of both **self-renewal** and **differentiation** into all the mature blood cell lineages, through a carefully regulated process involving specific **growth factors** and **cytokines**, such as **erythropoietin**, stimulating red cell production, and various **colony-stimulating factors**, stimulating white cell production, each acting on specific progenitor cell populations at different stages of maturation.

In children, **active bone marrow**, capable of producing blood cells, is distributed more widely throughout the skeleton than in adults, in whom active marrow becomes progressively confined to the **axial skeleton** and proximal long bones with increasing age, a normal developmental change with practical relevance to the interpretation of bone marrow biopsy findings and imaging at different ages.

Fill in the blank: Erythropoietin is a growth factor that stimulates _____ cell production.

1.1.3 development of the haematopoietic system

Haematopoiesis during **fetal development** occurs sequentially in different anatomical sites, beginning in the **yolk sac** in very early gestation, transitioning to the **liver** and **spleen** during mid-gestation, and finally to the **bone marrow**, which becomes the dominant site of haematopoiesis by **late gestation** and remains so throughout postnatal life, a sequential pattern reflecting the changing anatomical and physiological requirements of the developing fetus.

Understanding this normal developmental sequence has practical clinical relevance, since **extramedullary haematopoiesis**, the resumption of blood cell production in the liver or spleen outside the bone marrow, can occur **postnatally** in certain pathological states where bone marrow function is significantly compromised or overwhelmed, effectively representing a reversion to this earlier, fetal pattern of blood cell production.

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Fill in the blank: Extramedullary haematopoiesis is the resumption of blood cell production outside the _____ marrow.

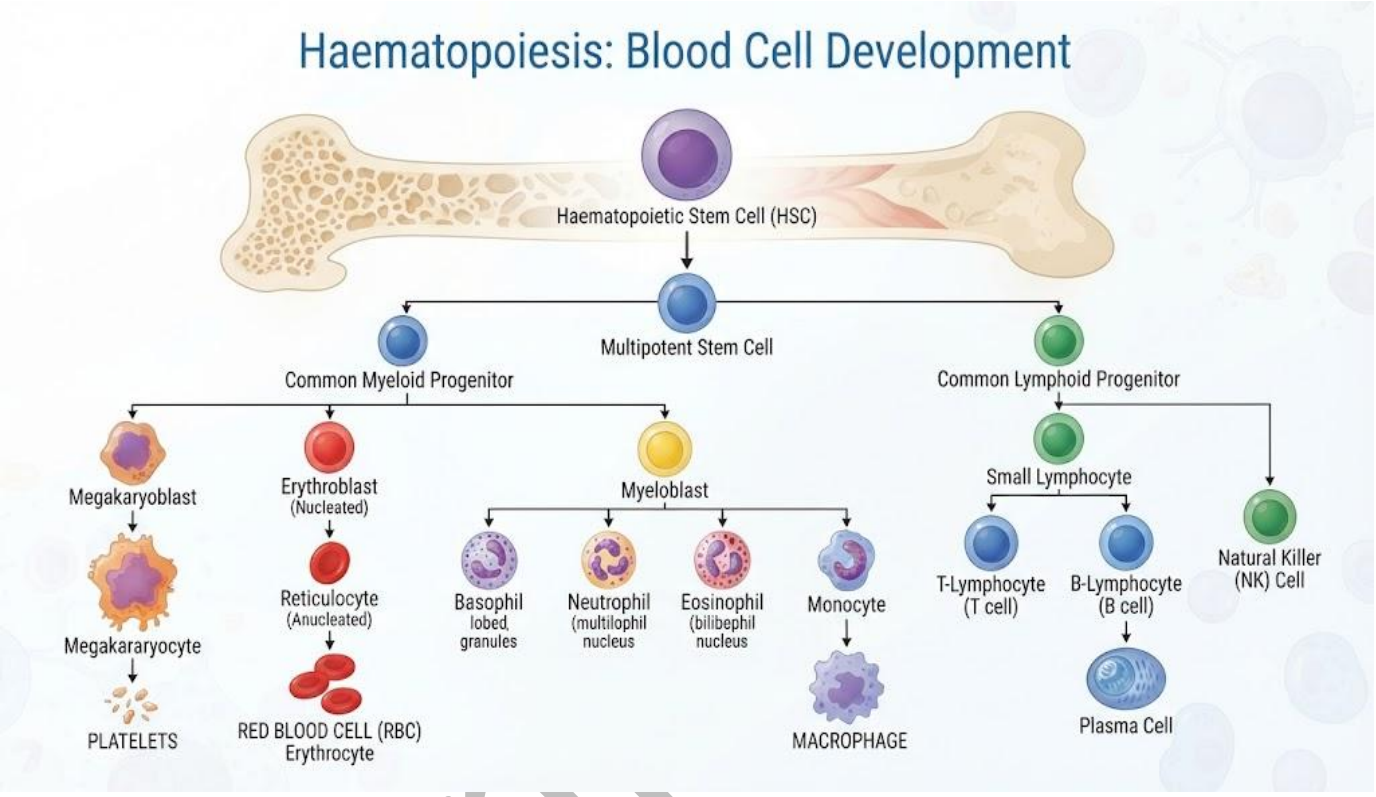

Figure 1.1: The lineages of blood cell development from a common haematopoietic stem cell.

Pilot questions 1.1

1. Define the haematopoietic system and list its three principal components. (Linked to SLO 1.1)
2. List the three main lineages of blood cells and their general function. (Linked to SLO 1.1)
3. Describe the role of erythropoietin and colony-stimulating factors in haematopoiesis. (Linked to SLO 1.1)
4. Describe the sequential sites of haematopoiesis during fetal development. (Linked to SLO 1.2)
5. Define extramedullary haematopoiesis and explain when it can occur postnatally. (Linked to SLO 1.2)

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1.2 Evaluation of a Child with Haematologic Disorders

1.2.1 general principles of evaluating a child with a suspected haematologic disorder

A structured approach across history, examination, and testing

Evaluation of a child with a suspected **haematologic disorder** requires a structured approach combining a detailed **history**, thorough **physical examination**, and appropriately selected **laboratory investigations**, since haematologic disorders can present with a genuinely wide range of clinical features, from entirely **asymptomatic** laboratory abnormalities identified incidentally, to significant, even life-threatening, acute presentations requiring urgent evaluation and management.

The specific **pattern** of presentation, together with relevant **patient characteristics**, discussed further in the next Part of this Series, meaningfully narrows the likely differential diagnosis before any laboratory testing is even performed, meaning careful, structured clinical assessment remains genuinely central to efficient, accurate evaluation rather than relying on laboratory testing alone to reach a diagnosis.

Fill in the blank: The specific pattern of presentation, together with relevant patient characteristics, meaningfully narrows the likely differential _____.

1.2.2 key elements of history in suspected haematologic disorders

A focused **history** should establish the **presenting symptoms**, such as **fatigue**, **pallor**, **bruising**, or **bleeding**, together with their **onset**, **duration**, and **progression**, and relevant **background history**, including **family history** of haematologic conditions, **dietary history**, particularly relevant to nutritional causes of anaemia, discussed further later in this Series, and any history of **chronic illness** or **medication use** that might contribute to a haematologic abnormality.

Birth history and **developmental history** are also relevant, particularly in younger children, given the potential for certain **congenital** or **inherited** haematologic conditions, discussed in detail in later Series of this course, to present from early infancy, and a thorough, systematic history genuinely helps distinguish between the many possible underlying causes of a given haematologic presentation before examination and testing even begin.

Fill in the blank: A focused history should establish presenting symptoms such as fatigue, pallor, bruising, or _____.

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1.2.3 physical examination in suspected haematologic disorders

Physical examination should include careful assessment for **pallor**, best assessed at the **conjunctivae**, **palms**, and **nail beds**, **jaundice**, suggesting possible **haemolysis**, **lymphadenopathy** and **hepatosplenomegaly**, which may suggest an underlying **malignant** or **infiltrative** process, and **bruising** or **petechiae**, suggesting a possible underlying **bleeding disorder**, discussed in detail in the final Series of this course.

Growth parameters should also be assessed, given the potential for chronic haematologic disease to affect growth, and a thorough, **systematic** examination, considering the whole child rather than focusing narrowly on a single presenting feature, remains essential, since haematologic disorders frequently have systemic manifestations extending well beyond the blood itself, reflecting the genuinely widespread physiological role of the haematopoietic system throughout the body.

Fill in the blank: Pallor is best assessed at the conjunctivae, palms, and _____.

Figure 1.2: A clinician examining a child's conjunctivae for pallor.

Pilot questions 1.2

1. Describe the general approach to evaluating a child with a suspected haematologic disorder. (Linked to SLO 1.3)
2. List three key elements of history relevant to a suspected haematologic disorder. (Linked to SLO 1.3)
3. Describe the key components of physical examination in a suspected haematologic disorder. (Linked to SLO 1.3)
4. Explain the clinical significance of lymphadenopathy and hepatosplenomegaly in this context. (Linked to SLO 1.3)
5. Explain why growth parameters should be assessed in a child with a suspected haematologic disorder. (Linked to SLO 1.3)

1.3 General Approach to Anaemia: History, Examination, and Laboratory Evaluation

1.3.1 definition of anaemia and relevant patient characteristics

Normal ranges shift meaningfully with age, sex, and background

Anaemia is defined as a **haemoglobin concentration** below the normal range for a child's **age** and **sex**, reflecting a reduced capacity of the blood to carry adequate oxygen to meet the body's metabolic needs, and normal haemoglobin ranges genuinely **vary** considerably by age, being relatively high at birth, falling to a **physiological nadir** around 2 to 3 months of age, before gradually rising again through childhood towards adult values.

Patient characteristics relevant to interpreting a haemoglobin result include **age**, given the age-related variation just described, **sex**, since normal ranges differ modestly between males and females, particularly from puberty onward, and **race and ethnicity**, since certain **haemoglobinopathies**, discussed in detail in a later Series of this course, and other haematologic conditions show recognised variation in prevalence between different population groups.

Fill in the blank: Normal haemoglobin falls to a physiological nadir around 2 to 3 months of age before gradually _____ again through childhood.

1.3.2 history and physical examination in anaemia

History in a child with suspected anaemia should establish the **onset** and **progression** of symptoms, **dietary history**, particularly **iron intake** and any **restrictive diet**, **family history**,

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given the relevance of inherited causes, and any history suggestive of **blood loss**, whether **gastrointestinal**, **menstrual** in older girls, or, in infants, related to **feeding practices** such as early, excessive **cow's milk** intake, a recognised, common contributor to iron deficiency in this age group.

Physical examination should assess for **pallor**, discussed in the previous Part of this Series, signs suggestive of the **underlying cause**, such as **glossitis** or **koilonychia**, spoon-shaped nails, in iron deficiency, and signs of **haemodynamic compromise**, such as **tachycardia** or, in severe cases, **cardiac failure**, which can occur with significant, longstanding anaemia given the heart's compensatory response to reduced oxygen-carrying capacity.

Fill in the blank: Early, excessive cow’s milk intake in infants is a recognised, common contributor to _____ deficiency.

1.3.3 laboratory evaluation of anaemia

Laboratory evaluation begins with a **complete blood count**, providing the **haemoglobin** and **haematocrit** concentration, together with **red blood cell indices**, including **mean corpuscular volume**, or **MCV**, reflecting average red cell size, **white blood cell count**, and **platelet count**, since abnormalities in other cell lines alongside anaemia can suggest a broader underlying process, such as bone marrow failure or malignancy, discussed in a later Series of this course.

A **peripheral blood smear**, examined microscopically, provides valuable additional information about **red cell morphology**, and the **reticulocyte count**, reflecting the bone marrow's current red cell production rate, helps distinguish anaemia resulting from **reduced production** from anaemia resulting from **increased destruction** or **loss**, a distinction of central importance discussed further in the final Part of this Series.

Fill in the blank: The reticulocyte count reflects the bone marrow’s current red cell _____ rate.

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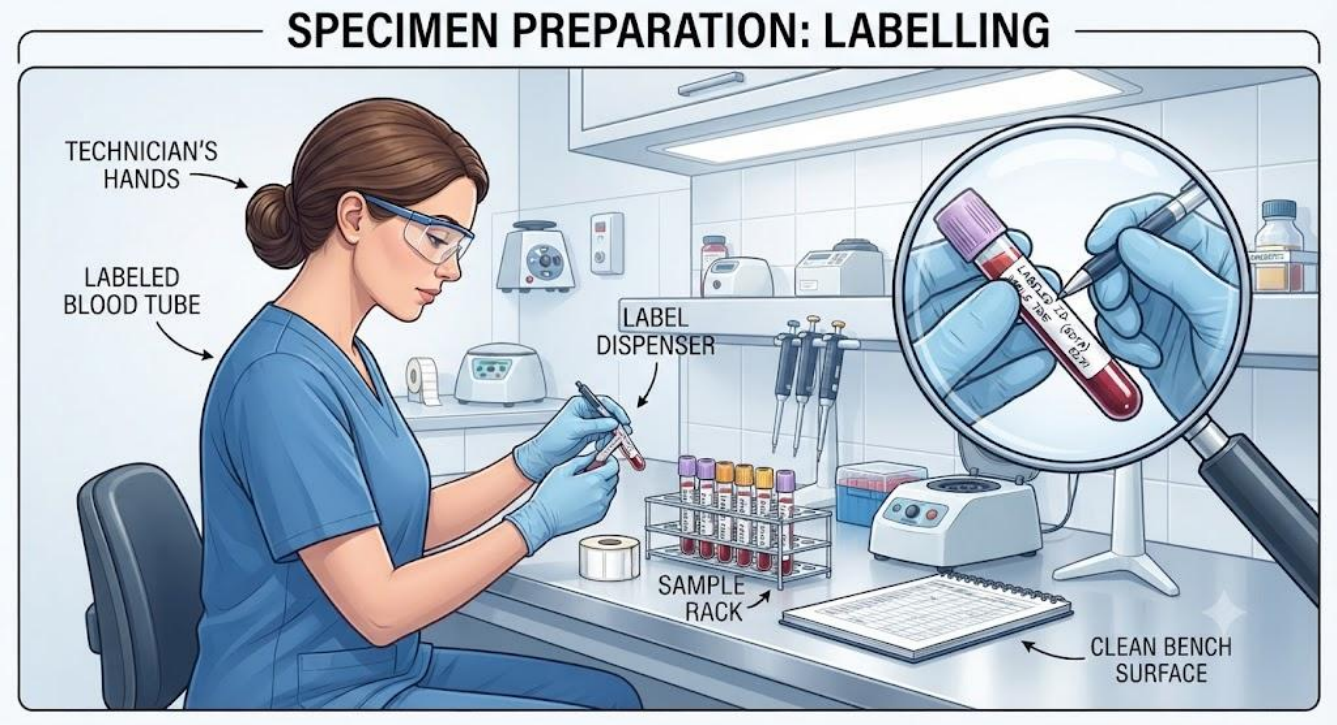

Figure 1.3: A laboratory technician preparing a blood sample for analysis.

Pilot questions 1.3

1. Define anaemia and explain why normal haemoglobin values vary with age. (Linked to SLO 1.4)
2. Explain the relevance of race and ethnicity to interpreting a haemoglobin result. (Linked to SLO 1.4)
3. Describe key elements of history relevant to a child with suspected anaemia. (Linked to SLO 1.5)
4. Describe key physical examination findings relevant to anaemia. (Linked to SLO 1.5)
5. List the components of a complete blood count relevant to evaluating anaemia. (Linked to SLO 1.6)

1.4 Classification of Anaemia

1.4.1 classification of anaemia by red cell size

MCV provides an immediate, practical starting point

Anaemia is conventionally classified according to the **mean corpuscular volume**, or **MCV**, into **microcytic anaemia**, with **small** red cells, **normocytic anaemia**, with **normal-sized** red cells,

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and **macrocytic anaemia**, with **large** red cells, and this classification provides a practical, widely used **starting point** for generating a focused differential diagnosis, since the underlying causes within each category differ considerably.

Microcytic anaemia most commonly results from **iron deficiency**, the most common cause of anaemia in children globally, or, less commonly, **thalassaemia**, discussed in detail in a later Series of this course, or, rarely, **anaemia of chronic disease**, while **macrocytic anaemia** is less common in children and can result from **vitamin B12** or **folate deficiency**, or certain **bone marrow disorders**.

Fill in the blank: Microcytic anaemia most commonly results from _____ deficiency, the most common cause of anaemia in children globally.

1.4.2 normocytic anaemia and reticulocyte response

Normocytic anaemia has a particularly broad differential diagnosis, including **acute blood loss**, **haemolysis**, discussed in detail in later Series of this course in the context of sickle cell disease, and **anaemia of chronic disease** or **bone marrow failure**, meaning the **reticulocyte count**, introduced in the previous Part of this Series, becomes particularly valuable in this specific category for further narrowing the differential diagnosis.

An **elevated reticulocyte count** in the context of anaemia suggests an **appropriate bone marrow response** to ongoing blood loss or destruction, pointing towards **haemolysis** or **acute blood loss** as the underlying cause, while a **low or inappropriately normal reticulocyte count** suggests **inadequate bone marrow production**, pointing towards **bone marrow failure**, **nutritional deficiency**, or **anaemia of chronic disease** as more likely explanations.

Fill in the blank: An elevated reticulocyte count in anaemia suggests an appropriate bone marrow _____ to ongoing blood loss or destruction.

1.4.3 confirmatory testing

Confirmatory testing, guided by the initial classification and clinical picture, may include **iron studies**, including **serum ferritin**, **serum iron**, and **total iron-binding capacity**, for suspected iron deficiency, **haemoglobin electrophoresis**, which separates and quantifies different haemoglobin types, essential for confirming **thalassaemia** or **sickle cell disease**, discussed in detail in the following two Series of this course, and, where indicated, **bone marrow examination** for suspected bone marrow failure or malignancy.

The overall diagnostic approach to anaemia, moving systematically from **classification by red cell size**, through **reticulocyte response**, to **specific confirmatory testing**, exemplifies the

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broader principle of **structured, stepwise clinical reasoning** that will continue to be applied throughout the remaining Series of this course as we turn to the specific diseases of the blood introduced in the Course Contents.

Fill in the blank: Haemoglobin electrophoresis separates and quantifies different _____ types.

Table 1.4: Classification of anaemia by red cell size with example causes.

Category	MCV	Example causes
Microcytic	Low	Iron deficiency, thalassaemia
Normocytic	Normal	Acute blood loss, haemolysis, chronic disease
Macrocytic	High	Vitamin B12 or folate deficiency, bone marrow disorders

Pilot questions 1.4

1. Describe the classification of anaemia by mean corpuscular volume. (Linked to SLO 1.7)
2. List two causes of microcytic anaemia. (Linked to SLO 1.7)
3. Explain how reticulocyte count helps narrow the differential diagnosis of normocytic anaemia. (Linked to SLO 1.7)
4. Describe the significance of a low reticulocyte count in a child with anaemia. (Linked to SLO 1.7)
5. Describe two examples of confirmatory testing used in the evaluation of anaemia. (Linked to SLO 1.8)

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Series Summary

This Series introduced the **haematopoietic system**, establishing its definition, three principal components of blood cells, bone marrow, and lymphoid organs, and the sequential pattern of its development from the yolk sac through the fetal liver and spleen to the bone marrow that ultimately becomes the dominant site of blood cell production for the remainder of life, before turning to the **structured evaluation of a child with haematologic disorders**, emphasising how careful, systematic history taking and physical examination meaningfully narrow the differential diagnosis before laboratory testing even begins.

We then examined the **general approach to anaemia**, including relevant patient characteristics, history, examination, and laboratory evaluation, before concluding with the **classification of anaemia** by red cell size and the role of confirmatory testing. Having worked through this Series, you should now have a solid foundation in the haematopoietic system and a structured approach to evaluating anaemia in children. The next Series turns to **sickle cell disease and other haemoglobinopathies**.

Glossary of Terms

- **Haematopoietic system:** the collective organs and tissues responsible for the production, maturation, and regulation of blood cells.
- **Haematopoiesis:** the process of blood cell production, occurring primarily in the bone marrow after birth.
- **Haematopoietic stem cell:** a self-renewing cell capable of differentiating into all mature blood cell lineages.
- **Extramedullary haematopoiesis:** blood cell production occurring outside the bone marrow, typically in the liver or spleen.
- **Anaemia:** a haemoglobin concentration below the normal range for a child's age and sex.
- **Mean corpuscular volume (MCV):** a red cell index reflecting average red cell size, used to classify anaemia.
- **Reticulocyte count:** a measure reflecting the bone marrow's current red cell production rate.
- **Microcytic anaemia:** anaemia with small red cells, most commonly caused by iron deficiency.
- **Macrocytic anaemia:** anaemia with large red cells, associated with vitamin B12 or folate deficiency.
- **Haemoglobin electrophoresis:** a laboratory test that separates and quantifies different haemoglobin types.
- **Koilonychia:** spoon-shaped nails, a physical sign associated with iron deficiency.

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- **Iron studies:** laboratory tests including serum ferritin and serum iron used to evaluate suspected iron deficiency.

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Concept Check Questions [Series 1]

Objective questions

1. The haematopoietic system comprises blood cells, the bone marrow, and _____ organs.
2. Extramedullary haematopoiesis is the resumption of blood cell production outside the _____ marrow.
3. Normal haemoglobin falls to a physiological nadir around 2 to 3 months of age before gradually _____ again through childhood.
4. Microcytic anaemia most commonly results from _____ deficiency, the most common cause of anaemia in children globally.
5. Haemoglobin electrophoresis separates and quantifies different _____ types.

Short-answer questions

6. List the three main lineages of blood cells and their general function.
7. List three key elements of history relevant to a suspected haematologic disorder.
8. Explain why normal haemoglobin values vary with age.
9. Describe the classification of anaemia by mean corpuscular volume.
10. Describe the significance of a low reticulocyte count in a child with anaemia.

Long-answer questions

11. Discuss the definition, components, and development of the haematopoietic system. (Linked to SLO 1.1, SLO 1.2)
12. Discuss the general approach to evaluating a child with a suspected haematologic disorder. (Linked to SLO 1.3)
13. Discuss the definition of anaemia and relevant patient characteristics. (Linked to SLO 1.4, SLO 1.5)
14. Discuss the laboratory evaluation of anaemia. (Linked to SLO 1.6)
15. Discuss the classification of anaemia and the role of confirmatory testing. (Linked to SLO 1.7, SLO 1.8)

Answers to Concept Check Questions [Series 1]

Objective questions

1. Lymphoid.

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2. Bone.
3. Rising.
4. Iron.
5. Haemoglobin.

Short-answer questions

6. Red blood cells transport oxygen, white blood cells provide immune defence, and platelets support haemostasis.
7. Presenting symptoms, family history, and dietary history are key elements of a relevant history.
8. Normal haemoglobin values are relatively high at birth, fall to a nadir around 2 to 3 months, then gradually rise through childhood.
9. Anaemia is classified as microcytic, normocytic, or macrocytic based on mean corpuscular volume.
10. A low reticulocyte count suggests inadequate bone marrow production, pointing towards bone marrow failure or nutritional deficiency.

Long-answer questions

11. **Basic response:** The haematopoietic system comprises blood cells, bone marrow, and lymphoid organs, developing sequentially from the yolk sac through the fetal liver and spleen to the bone marrow.

Value-added response: Extramedullary haematopoiesis can resume in the liver or spleen postnatally when bone marrow function is significantly compromised, reflecting a reversion to this earlier fetal pattern.

12. **Basic response:** Evaluation of a suspected haematologic disorder combines detailed history, thorough physical examination, and appropriately selected laboratory investigations.

Value-added response: The specific pattern of presentation and relevant patient characteristics meaningfully narrow the differential diagnosis before laboratory testing even begins.

13. **Basic response:** Anaemia is defined as haemoglobin below the normal range for age and sex, with relevant patient characteristics including age, sex, and race or ethnicity.

Value-added response: Normal haemoglobin ranges vary considerably with age, and certain haemoglobinopathies show recognised variation in prevalence between population groups.

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14. **Basic response:** Laboratory evaluation begins with a complete blood count providing haemoglobin, RBC indices, white cell, and platelet counts, supported by blood smear examination.

Value-added response: The reticulocyte count distinguishes anaemia from reduced production versus increased destruction or loss, a distinction of central diagnostic importance.

15. **Basic response:** Anaemia is classified by MCV into microcytic, normocytic, and macrocytic categories, each with characteristic example causes.

Value-added response: Confirmatory testing, such as iron studies or haemoglobin electrophoresis, is guided by the initial classification to reach a specific diagnosis.

Answers to Pilot Questions [Series 1]

Part 1.1

1. The haematopoietic system comprises blood cells, the bone marrow, and lymphoid organs.
2. Red blood cells transport oxygen, white blood cells provide immune defence, and platelets support haemostasis.
3. Erythropoietin stimulates red cell production, and colony-stimulating factors stimulate white cell production.
4. Haematopoiesis begins in the yolk sac, moves to the liver and spleen, and finally to the bone marrow.
5. It is the resumption of blood cell production outside the bone marrow, occurring when marrow function is significantly compromised.

Part 1.2

1. A structured approach combining detailed history, thorough examination, and appropriate laboratory investigations.
2. Presenting symptoms, family history, and dietary history are key elements of history.
3. Assessment for pallor, jaundice, lymphadenopathy, hepatosplenomegaly, and bruising or petechiae.
4. They may suggest an underlying malignant or infiltrative process.
5. Chronic haematologic disease can affect growth, making growth assessment clinically relevant.

Part 1.3

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1. Anaemia is haemoglobin below the normal range for age and sex; values vary because normal ranges change with age.
2. Certain haemoglobinopathies show recognised variation in prevalence between different population groups.
3. Onset and progression of symptoms, dietary history, and family history are relevant elements.
4. Pallor, glossitis, koilonychia, and signs of haemodynamic compromise are relevant findings.
5. Haemoglobin, haematocrit, RBC indices, white blood cell count, and platelet count are components of a CBC.

Part 1.4

1. Anaemia is classified as microcytic, normocytic, or macrocytic based on MCV.
2. Iron deficiency and thalassaemia are causes of microcytic anaemia.
3. It distinguishes appropriate bone marrow response, suggesting haemolysis or blood loss, from inadequate production.
4. It suggests inadequate bone marrow production, pointing towards bone marrow failure or nutritional deficiency.
5. Iron studies and haemoglobin electrophoresis are examples of confirmatory testing.

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- Orkin, S. H. et al. (2015). Nathan and Oski's Hematology and Oncology of Infancy and Childhood (8th ed.). Elsevier.
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- World Health Organization (2011). Haemoglobin Concentrations for the Diagnosis of Anaemia and Assessment of Severity. WHO Press.

Figures, Plates, Tables, and Boxes

- Figure 1.1: The lineages of blood cell development from a common haematopoietic stem cell. AI-generated using the prompt: "Create a professional educational diagram titled Haematopoiesis: Blood Cell Development, showing a haematopoietic stem cell branching into red blood cell, white blood cell, and platelet lineages. Clean clinical educational diagram style, single illustration, no text-heavy panels."
- Figure 1.2: A clinician examining a child’s conjunctivae for pallor. AI-generated using the prompt: "A calm, respectful clinical illustration of a clinician gently examining a child’s lower eyelid during an assessment, with a caregiver present nearby. Single clean medical illustration, soft clinical lighting, no text overlays, no multiple panels, sensitive and accurate depiction."
- Figure 1.3: A laboratory technician preparing a blood sample for analysis. AI-generated using the prompt: "A professional clinical illustration of a laboratory technician carefully labelling and preparing a blood sample tube at a clean laboratory bench. Single clean medical illustration, clinical lighting, no text overlays, no multiple panels, accurate and professional depiction."
- Table 1.4: Classification of anaemia by red cell size with example causes. AI-generated using the prompt: "Create a clean reference table titled Classification of Anaemia by Red Cell Size, listing category, MCV, and example causes. Simple clinical reference table style with outside border."

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Series 2: Sickle Cell Disease and Other Haemoglobinopathies

- **Part 2.1: Sickle Cell Disease: Definition, Epidemiology, and Pathogenesis**
    - Sub Part 2.1.1: Definition and epidemiology of sickle cell disease
    - Sub Part 2.1.2: Pathogenesis of sickle cell disease
    - Sub Part 2.1.3: Inheritance and genotypes
- **Part 2.2: Factors Enhancing Sickling and Haplotype**
    - Sub Part 2.2.1: Factors that enhance sickling
    - Sub Part 2.2.2: The clinical significance of avoiding known triggers
    - Sub Part 2.2.3: Haplotype
- **Part 2.3: Sickle Cell Crises I: Vaso-Occlusive Pain, Acute Chest Syndrome, and Stroke**
    - Sub Part 2.3.1: Vaso-occlusive pain episodes
    - Sub Part 2.3.2: Acute chest syndrome
    - Sub Part 2.3.3: Stroke in sickle cell disease
- **Part 2.4: Sickle Cell Crises II and Chronic Complications**
    - Sub Part 2.4.1: Hyper-haemolytic and aplastic crises
    - Sub Part 2.4.2: Sequestration crisis and priapism
    - Sub Part 2.4.3: Chronic complications of sickle cell disease

Introduction

In the last Series, we explored the haematopoietic system and the evaluation of anaemia. We now turn to sickle cell disease, the most common significant haemoglobinopathy encountered in Nigerian paediatric practice, and one of the most important chronic haematologic conditions affecting children in this region. Picture a seven year old with known sickle cell disease brought to the emergency unit with severe limb pain during a hot, dry period, a presentation representing just one of the many acute complications that can affect a child with this genuinely multisystem condition throughout their life.

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The aim of this Series is to equip you with the knowledge required to understand the epidemiology, pathogenesis, and factors influencing sickle cell disease, and to recognise the acute crises and chronic complications that affect children with this condition.

This Series begins with the **definition, epidemiology, and pathogenesis of sickle cell disease**, before turning to the **factors enhancing sickling and the concept of haplotype**. Next, we examine the **acute sickle cell crises**, including vaso-occlusive pain, acute chest syndrome, and stroke, before concluding with **further crises and chronic complications**.

Series Learning Outcomes

At the end of this Series, you should be able to:

- **SLO 1.1:** define sickle cell disease and describe its epidemiology,
- **SLO 1.2:** describe the pathogenesis and pathophysiology of sickle cell disease,
- **SLO 1.3:** describe the factors that enhance sickling,
- **SLO 1.4:** describe the concept of haplotype in sickle cell disease,
- **SLO 1.5:** describe vaso-occlusive pain episodes and acute chest syndrome in sickle cell disease,
- **SLO 1.6:** describe stroke and hyper-haemolytic crisis in sickle cell disease,
- **SLO 1.7:** describe aplastic crisis, sequestration crisis, and priapism in sickle cell disease, and
- **SLO 1.8:** describe the chronic complications of sickle cell disease, including osteomyelitis, avascular necrosis, sickle cell nephropathy, and hepatopathy.

2.1 Sickle Cell Disease: Definition, Epidemiology, and Pathogenesis

2.1.1 definition and epidemiology of sickle cell disease

A single amino acid substitution with genuinely major consequences

Sickle cell disease, abbreviated **SCD**, is an inherited **haemoglobinopathy** resulting from a **point mutation** in the **beta-globin gene**, producing an abnormal haemoglobin, **haemoglobin S**, or **HbS**, in place of normal **haemoglobin A**, and includes several genotypes, most importantly **homozygous sickle cell anaemia**, or **HbSS**, and **compound heterozygous** forms, such as **HbSC disease** and **sickle beta-thalassaemia**.

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Sickle cell disease is particularly common in individuals of **sub-Saharan African** ancestry, with Nigeria carrying one of the highest global burdens of the condition, reflecting the historical **selective advantage** conferred by carrying a single copy of the sickle gene, or **sickle cell trait**, against severe **falciparum malaria**, discussed in an earlier course, a genuinely important example of evolutionary selection pressure shaping the population-level prevalence of a genetic condition.

Fill in the blank: Sickle cell disease results from a point mutation in the _____-globin gene.

2.1.2 pathogenesis of sickle cell disease

Under conditions of **deoxygenation**, abnormal **haemoglobin S** molecules **polymerise**, forming rigid **polymer strands** within the red blood cell that distort the cell into the characteristic **sickle shape**, and this **sickling** process, initially reversible with **reoxygenation**, becomes progressively **irreversible** with repeated cycles, ultimately producing permanently sickled cells with reduced deformability and a markedly shortened lifespan.

These abnormally shaped, rigid **sickled cells** are prone to both **haemolysis**, contributing to chronic anaemia, and **vaso-occlusion**, obstructing small blood vessels and impairing local blood flow and oxygen delivery, and this dual pathophysiological process, combining **chronic haemolytic anaemia** with recurrent, unpredictable **vaso-occlusive events**, underlies the genuinely wide-ranging, multisystem clinical picture of sickle cell disease discussed throughout the remainder of this Series.

Fill in the blank: Sickled cells are prone to both haemolysis and _____, obstructing small blood vessels.

2.1.3 inheritance and genotypes

Sickle cell disease follows **autosomal recessive** inheritance, meaning a child requires **two abnormal beta-globin alleles** to be clinically affected, with **sickle cell trait**, a single abnormal allele, generally **asymptomatic** and not considered a disease state, though relevant for **genetic counselling**, discussed in an earlier course, given the recurrence risk when both parents carry the trait.

The specific **genotype**, whether **HbSS**, **HbSC**, or **sickle beta-thalassaemia**, meaningfully influences **disease severity**, with **HbSS** generally associated with the most severe clinical course, and **HbSC disease** generally, though not invariably, associated with a somewhat **milder** phenotype, meaning accurate genotype identification, discussed further in the context of confirmatory testing in the previous Series of this course, provides valuable prognostic information for an individual child.

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Fill in the blank: Sickle cell disease follows _____ recessive inheritance, requiring two abnormal alleles for clinical disease.

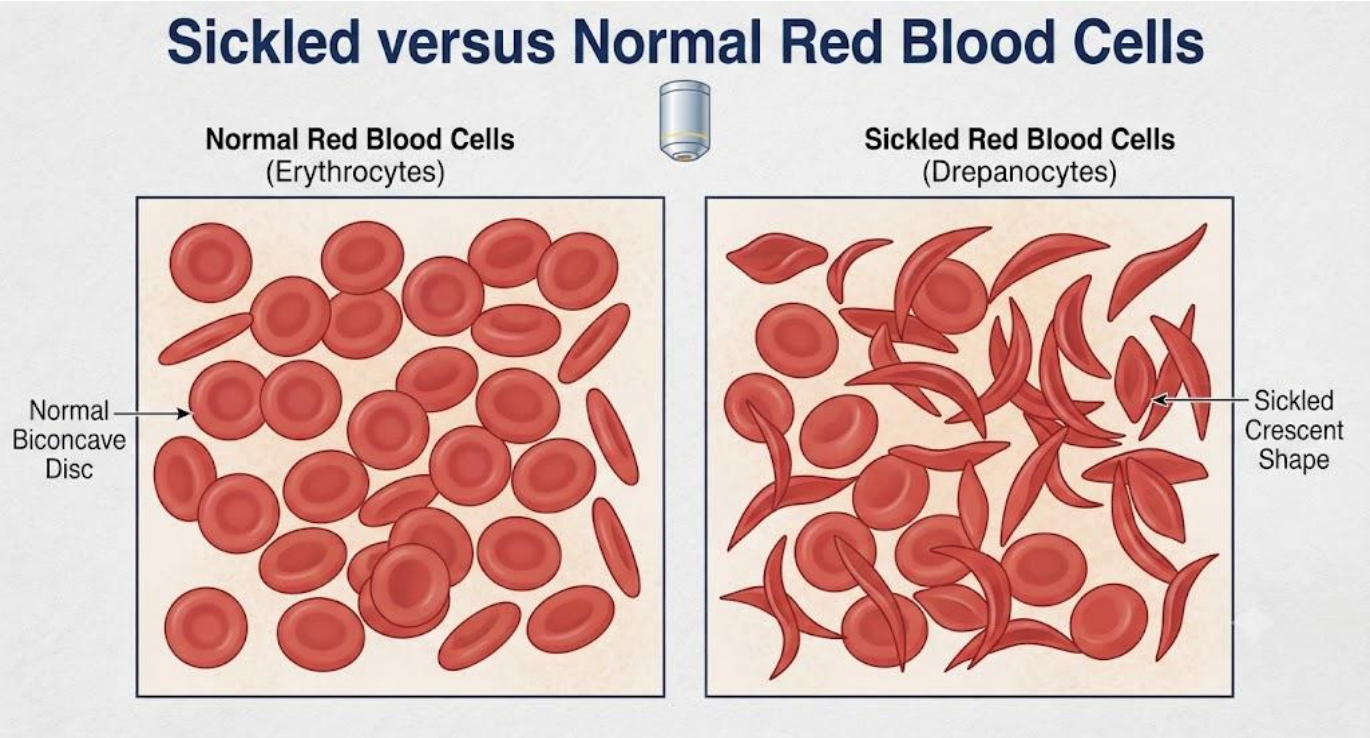

Figure 2.1: Sickled red blood cells alongside normal red blood cells under microscopy.

Pilot questions 2.1

- Define sickle cell disease and name its most common genotype. (Linked to SLO 2.1)
- Describe the epidemiology of sickle cell disease and its relationship to malaria. (Linked to SLO 2.1)
- Describe the process by which haemoglobin S causes red cells to sickle. (Linked to SLO 2.2)
- Explain how sickling contributes to both haemolysis and vaso-occlusion. (Linked to SLO 2.2)
- Describe the inheritance pattern of sickle cell disease and distinguish it from sickle cell trait. (Linked to SLO 2.3)

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2.2 Factors Enhancing Sickling and Haplotype

2.2.1 factors that enhance sickling

Everyday triggers can precipitate an acute crisis

Several factors enhance **sickling** and can precipitate an acute crisis in a child with sickle cell disease, including **hypoxia**, reducing oxygen tension and promoting haemoglobin S polymerisation, **dehydration**, increasing intracellular haemoglobin concentration and promoting polymerisation, **acidosis**, and **infection**, which can trigger sickling through several combined mechanisms, including fever, dehydration, and hypoxia.

Cold exposure, causing peripheral vasoconstriction and reduced blood flow, and **physical exertion** or **stress**, increasing metabolic demand and oxygen consumption, are also recognised precipitants, meaning practical, everyday advice to affected families regarding **adequate hydration**, **avoidance of extreme temperatures**, and **prompt treatment of infection** forms an important, genuinely accessible component of routine sickle cell disease care.

Fill in the blank: Dehydration enhances sickling by increasing intracellular haemoglobin concentration and promoting _____.

2.2.2 the clinical significance of avoiding known triggers

Understanding these precipitating factors allows both **affected families** and **healthcare providers** to actively anticipate and, where possible, **avoid or minimise** exposure to known triggers, and forms an essential component of **anticipatory guidance** provided to families at the time of diagnosis and during routine follow up, complementing the medical management of established crises discussed later in this Series.

During any **acute illness** or **surgical procedure**, proactive attention to maintaining adequate **hydration**, **oxygenation**, and **temperature regulation**, together with prompt treatment of any **precipitating infection**, meaningfully reduces the risk of triggering a significant sickle cell crisis, illustrating how understanding the underlying pathophysiological triggers directly translates into practical, preventive clinical care.

Fill in the blank: Proactive attention to hydration, oxygenation, and temperature regulation forms part of _____ guidance for families.

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2.2.3 haplotype

Haplotype refers to the specific combination of **genetic markers**, particularly within the **beta-globin gene cluster**, inherited together on a single chromosome, and several distinct sickle cell **haplotypes** have been identified, generally named after the **geographic region** in which they were first characterised, including the **Benin**, **Bantu**, **Senegal**, and **Cameroon** haplotypes, each showing somewhat different geographic distribution and clinical associations.

Haplotype is of clinical relevance since certain haplotypes are associated with differing levels of **fetal haemoglobin**, discussed further in relation to disease severity, since higher fetal haemoglobin levels generally correlate with a **milder** clinical course, meaning haplotype, alongside the specific genotype discussed in the previous Part of this Series, contributes to the genuinely considerable **variability** in disease severity observed between different individuals with sickle cell disease.

Fill in the blank: Certain sickle cell haplotypes are associated with differing levels of fetal _____, influencing disease severity.

Figure 2.2: A caregiver encouraging a child with sickle cell disease to drink water regularly.

Pilot questions 2.2

1. List four factors that enhance sickling and can precipitate an acute crisis. (Linked to SLO 2.3)
2. Explain why dehydration is a significant risk factor for sickling. (Linked to SLO 2.3)
3. Describe the practical importance of anticipatory guidance for families of children with sickle cell disease. (Linked to SLO 2.3)
4. Define haplotype in the context of sickle cell disease. (Linked to SLO 2.4)
5. Explain the clinical relevance of haplotype and fetal haemoglobin to disease severity. (Linked to SLO 2.4)

2.3 Sickle Cell Crises I: Vaso-Occlusive Pain, Acute Chest Syndrome, and Stroke

2.3.1 vaso-occlusive pain episodes

The most common, and often first, presentation of sickle cell disease

Vaso-occlusive pain episodes, the most common acute complication of sickle cell disease, result from **obstruction** of small blood vessels by sickled cells, causing **ischaemia** and significant **pain**, most commonly affecting the **long bones**, **back**, and **abdomen**, and, in young children specifically, the **hands and feet**, termed **dactylitis**, or **hand-foot syndrome**, often the first clinical presentation of sickle cell disease in infancy.

Management of vaso-occlusive pain includes **adequate analgesia**, following a **stepwise approach** according to pain severity, **hydration**, and identification and treatment of any **precipitating factor**, discussed in the previous Part of this Series, and prompt, adequate pain relief is genuinely important, since inadequately treated pain causes significant, avoidable suffering and can itself contribute to ongoing physiological stress that may prolong or worsen the crisis.

Fill in the blank: Dactylitis, or hand-foot syndrome, is often the first clinical presentation of sickle cell disease in _____.

2.3.2 acute chest syndrome

Acute chest syndrome is a serious, potentially life-threatening complication of sickle cell disease, presenting with **new pulmonary infiltrate** on chest radiograph together with

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respiratory symptoms, such as **chest pain**, **cough**, or **shortness of breath**, and **fever**, resulting from a combination of **infection**, **pulmonary vaso-occlusion**, and **fat embolism** from infarcted bone marrow, meaning the underlying cause is frequently multifactorial rather than a single, isolated process.

Acute chest syndrome requires **prompt recognition** and **aggressive management**, including **supplemental oxygen**, **analgesia**, **antibiotics** given the frequent infective component, and, in more severe cases, **blood transfusion**, since acute chest syndrome remains one of the **leading causes of death** in individuals with sickle cell disease, underscoring the genuine clinical urgency required whenever this specific complication is suspected.

Fill in the blank: Acute chest syndrome results from a combination of infection, pulmonary vaso-occlusion, and fat _____.

2.3.3 stroke in sickle cell disease

Stroke is a serious neurological complication of sickle cell disease, resulting from **vaso-occlusion** of major cerebral blood vessels, and can present with **sudden onset** of **focal neurological deficit**, such as **weakness**, **speech disturbance**, or **seizures**, and children with sickle cell disease carry a considerably **increased risk** of stroke compared with the general paediatric population, particularly during **childhood** itself.

Transcranial Doppler ultrasound screening, used to identify children at increased **stroke risk** based on measured cerebral blood flow velocities, allows **targeted preventive intervention**, most importantly **regular blood transfusion**, in identified high-risk children, representing an important example of proactive, structured screening meaningfully reducing the risk of a serious complication before it occurs, rather than simply treating stroke once it has already happened.

Fill in the blank: Transcranial Doppler ultrasound screening identifies children at increased stroke risk based on cerebral blood flow _____.

Table 2.3: Comparing major acute sickle cell crises.

Crisis	Key feature	Key management step
Vaso-occlusive pain	Pain, most often long bones, back, abdomen	Analgesia and hydration
Acute chest syndrome	New pulmonary infiltrate with respiratory symptoms	Oxygen, antibiotics, transfusion if severe
Stroke	Sudden focal neurological deficit	Urgent imaging and exchange transfusion

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Pilot questions 2.3

1. Describe vaso-occlusive pain episodes and their typical distribution. (Linked to SLO 2.5)
2. Define dactylitis and its clinical significance. (Linked to SLO 2.5)
3. Describe the clinical features and management of acute chest syndrome. (Linked to SLO 2.5)
4. Explain why acute chest syndrome is considered a leading cause of death in sickle cell disease. (Linked to SLO 2.5)
5. Describe the role of transcranial Doppler ultrasound in stroke prevention. (Linked to SLO 2.6)

2.4 Sickle Cell Crises II and Chronic Complications

2.4.1 hyper-haemolytic and aplastic crises

Two distinct mechanisms producing a similar, worsening anaemia

Hyper-haemolytic crisis refers to an **acute exacerbation** of the baseline chronic haemolysis present in sickle cell disease, presenting with worsening **anaemia**, **jaundice**, and an appropriately **elevated reticulocyte count**, reflecting ongoing, active bone marrow compensation, and is often triggered by an underlying **infection** or other acute illness.

Aplastic crisis, by contrast, results from **temporary bone marrow suppression**, most classically caused by infection with **parvovirus B19**, presenting with worsening anaemia but, critically, a **low reticulocyte count**, reflecting **inadequate** bone marrow compensation during this specific episode, a distinction that meaningfully differentiates it from hyper-haemolytic crisis and directly guides appropriate management, including consideration of blood transfusion during the temporary period of marrow suppression.

Fill in the blank: Aplastic crisis is most classically caused by infection with _____.

2.4.2 sequestration crisis and priapism

Splenic sequestration crisis is a potentially life-threatening complication, most common in **young children** before the spleen has undergone the process of **autoinfarction** typical of longstanding sickle cell disease, presenting with **sudden splenic enlargement**, **worsening**

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anaemia, and features of **hypovolaemic shock**, resulting from significant pooling of blood within the enlarged spleen, requiring urgent recognition and, frequently, **blood transfusion**.

Priapism, a prolonged, painful **erection** unrelated to sexual stimulation, results from vaso-occlusion within the **penile vasculature**, and requires **prompt medical attention**, since prolonged, untreated priapism carries a genuine risk of permanent **erectile dysfunction**, meaning affected boys and their families should be specifically educated about this complication and the importance of seeking urgent care should it occur.

Fill in the blank: Splenic sequestration crisis is most common in young children before the spleen has undergone _____.

2.4.3 chronic complications of sickle cell disease

Chronic complications of sickle cell disease reflect the cumulative effects of **recurrent vaso-occlusion** and **chronic haemolysis** over time, including **osteomyelitis**, with affected children at increased risk of infection with **Salmonella** species in addition to the more common **Staphylococcus aureus**, discussed in an earlier course, and **avascular necrosis**, particularly affecting the **femoral head**, resulting from chronic impaired blood supply to this specific site.

Further chronic complications include **sickle cell nephropathy**, encompassing a range of renal abnormalities including impaired urinary concentrating ability and, over time, progressive **chronic kidney disease**, discussed in an earlier course, and **sickle cell hepatopathy**, encompassing chronic liver dysfunction related to recurrent hepatic vaso-occlusion, together illustrating the genuinely wide-ranging, multisystem nature of long-term sickle cell disease that requires comprehensive, coordinated, lifelong follow up.

Fill in the blank: Children with sickle cell disease are at increased risk of osteomyelitis with Salmonella species in addition to Staphylococcus _____.

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Figure 2.4: A clinician reviewing a child's growth and health records during a routine sickle cell disease follow-up visit.

Pilot questions 2.4

1. Distinguish hyper-haemolytic crisis from aplastic crisis by reticulocyte response. (Linked to SLO 2.7)
2. Describe the typical cause of aplastic crisis. (Linked to SLO 2.7)
3. Describe splenic sequestration crisis and why it is most common in young children. (Linked to SLO 2.7)
4. Describe priapism and explain why it requires prompt medical attention. (Linked to SLO 2.7)
5. List four chronic complications of sickle cell disease. (Linked to SLO 2.8)

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Series Summary

This Series introduced **sickle cell disease**, beginning with its definition as an inherited haemoglobinopathy resulting from a point mutation in the beta-globin gene, its epidemiology and the evolutionary relationship between the sickle trait and protection against severe falciparum malaria, and the underlying pathogenesis by which deoxygenation-triggered polymerisation of haemoglobin S produces the characteristic sickled red cell, before turning to the **factors that enhance sickling**, including hypoxia, dehydration, and infection, and the concept of **haplotype** and its influence on disease severity through varying fetal haemoglobin levels.

We then examined the **acute sickle cell crises**, including vaso-occlusive pain episodes, acute chest syndrome, and stroke, before concluding with **hyper-haemolytic and aplastic crises, sequestration crisis, priapism, and the chronic complications** of sickle cell disease. Having worked through this Series, you should now be able to recognise and understand the management of the acute and chronic complications of sickle cell disease. The next Series turns to **thalassaemia**.

Glossary of Terms

1. **Sickle cell disease:** an inherited haemoglobinopathy resulting from a point mutation in the beta-globin gene, producing haemoglobin S.
2. **Haemoglobin S:** the abnormal haemoglobin that polymerises under deoxygenation, causing red cell sickling.
3. **Sickle cell trait:** the carrier state with a single abnormal beta-globin allele, generally asymptomatic.
4. **Vaso-occlusive pain episode:** the most common acute complication of sickle cell disease, caused by small vessel obstruction by sickled cells.
5. **Dactylitis:** hand-foot syndrome, often the first presentation of sickle cell disease in infancy.
6. **Acute chest syndrome:** a serious complication presenting with new pulmonary infiltrate and respiratory symptoms.
7. **Aplastic crisis:** temporary bone marrow suppression, most classically caused by parvovirus B19 infection.
8. **Splenic sequestration crisis:** sudden splenic enlargement with pooling of blood, most common in young children.

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9. **Priapism:** a prolonged, painful erection resulting from penile vaso-occlusion.
10. **Haplotype:** the specific combination of genetic markers inherited together, influencing sickle cell disease severity.
11. **Avascular necrosis:** bone death from impaired blood supply, particularly affecting the femoral head in sickle cell disease.
12. **Transcranial Doppler ultrasound:** a screening tool used to identify children with sickle cell disease at increased stroke risk.

Concept Check Questions [Series 2]

Objective questions

- Sickle cell disease results from a point mutation in the _____-globin gene.
- Sickled cells are prone to both haemolysis and _____, obstructing small blood vessels.
- Dactylitis, or hand-foot syndrome, is often the first clinical presentation of sickle cell disease in _____.
- Aplastic crisis is most classically caused by infection with _____.
- Children with sickle cell disease are at increased risk of osteomyelitis with Salmonella species in addition to Staphylococcus _____.

Short-answer questions

1. Describe the process by which haemoglobin S causes red cells to sickle.
2. List four factors that enhance sickling and can precipitate an acute crisis.
3. Describe the clinical features and management of acute chest syndrome.
4. Distinguish hyper-haemolytic crisis from aplastic crisis by reticulocyte response.
5. Describe priapism and explain why it requires prompt medical attention.

Long-answer questions

6. Discuss the definition, epidemiology, and pathogenesis of sickle cell disease. (Linked to SLO 2.1, SLO 2.2)
7. Discuss the factors that enhance sickling and the concept of haplotype. (Linked to SLO 2.3, SLO 2.4)
8. Discuss vaso-occlusive pain episodes, acute chest syndrome, and stroke in sickle cell disease. (Linked to SLO 2.5, SLO 2.6)

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9. Discuss hyper-haemolytic crisis, aplastic crisis, sequestration crisis, and priapism. (Linked to SLO 2.7)
10. Discuss the chronic complications of sickle cell disease. (Linked to SLO 2.8)

Answers to Concept Check Questions [Series 2]

Objective questions

11. Beta.
12. Vaso-occlusion.
13. Infancy.
14. Parvovirus B19.
15. Aureus.

Short-answer questions

16. Under deoxygenation, haemoglobin S polymerises into rigid strands that distort the red cell into a sickle shape.
17. Hypoxia, dehydration, acidosis, and infection are factors that enhance sickling.
18. Acute chest syndrome presents with new pulmonary infiltrate and respiratory symptoms, managed with oxygen, antibiotics, and transfusion if severe.
19. Hyper-haemolytic crisis shows an elevated reticulocyte count, while aplastic crisis shows a low reticulocyte count.
20. Priapism is a prolonged, painful erection; prompt treatment is needed to prevent permanent erectile dysfunction.

Long-answer questions

21. **Basic response:** Sickle cell disease results from a beta-globin gene mutation producing haemoglobin S, which polymerises under deoxygenation, causing sickling, haemolysis, and vaso-occlusion.

Value-added response: The condition is particularly common in sub-Saharan African populations, reflecting historical selective protection against severe falciparum malaria conferred by sickle cell trait.

22. **Basic response:** Hypoxia, dehydration, acidosis, infection, cold exposure, and exertion enhance sickling and can precipitate crises.

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Value-added response: Haplotype influences fetal haemoglobin levels and disease severity, alongside genotype, contributing to variability between individuals.

23. **Basic response:** Vaso-occlusive pain is the most common crisis, managed with analgesia and hydration, while acute chest syndrome and stroke are more serious complications requiring urgent management.

Value-added response: Transcranial Doppler screening identifies children at increased stroke risk, allowing preventive transfusion before a stroke occurs.

24. **Basic response:** Hyper-haemolytic crisis and aplastic crisis both cause worsening anaemia but are distinguished by reticulocyte response, while sequestration crisis and priapism represent other acute emergencies.

Value-added response: Aplastic crisis is classically caused by parvovirus B19, and sequestration crisis is most common in young children before splenic autoinfarction occurs.

25. **Basic response:** Chronic complications include osteomyelitis, avascular necrosis, nephropathy, and hepatopathy, reflecting cumulative vaso-occlusion and haemolysis over time.

Value-added response: These wide-ranging complications require comprehensive, coordinated, lifelong follow up given the genuinely multisystem nature of sickle cell disease.

Answers to Pilot Questions [Series 2]

Part 2.1

1. Sickle cell disease is an inherited haemoglobinopathy from a beta-globin mutation; HbSS is the most common genotype.
2. It is common in sub-Saharan Africa, reflecting historical protection conferred by sickle trait against severe malaria.
3. Deoxygenation causes haemoglobin S to polymerise, distorting the red cell into a sickle shape.
4. Sickled cells are fragile, causing haemolysis, and rigid, causing vaso-occlusion of small vessels.
5. It is autosomal recessive, requiring two abnormal alleles, unlike the generally asymptomatic single-allele trait.

Part 2.2

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6. Hypoxia, dehydration, acidosis, and infection are factors that enhance sickling.
7. Dehydration increases intracellular haemoglobin concentration, promoting polymerisation.
8. It helps families avoid known triggers and respond promptly to illness, reducing crisis risk.
9. Haplotype is the specific combination of genetic markers inherited together in the beta-globin gene cluster.
10. Certain haplotypes are associated with higher fetal haemoglobin, generally correlating with milder disease.

Part 2.3

11. Vaso-occlusive pain typically affects the long bones, back, and abdomen.
12. Dactylitis is hand-foot syndrome, often the first presentation of sickle cell disease in infancy.
13. Acute chest syndrome presents with new pulmonary infiltrate and respiratory symptoms, managed with oxygen and antibiotics.
14. It remains a leading cause of death due to its potentially rapid, serious progression.
15. It identifies children at increased stroke risk based on cerebral blood flow velocity, enabling preventive transfusion.

Part 2.4

1. Hyper-haemolytic crisis shows an elevated reticulocyte count; aplastic crisis shows a low reticulocyte count.
2. Parvovirus B19 infection is the classic cause of aplastic crisis.
3. Splenic sequestration is most common before splenic autoinfarction has occurred in young children.
4. Priapism is a prolonged, painful erection; delay risks permanent erectile dysfunction.
5. Osteomyelitis, avascular necrosis, sickle cell nephropathy, and sickle cell hepatopathy are chronic complications.

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References and Attributions [Series 2]

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2. Piel, F. B. et al. (2017). Sickle cell disease. New England Journal of Medicine, 376(16), 1561 to 1573.
3. National Heart, Lung, and Blood Institute (2014). Evidence-Based Management of Sickle Cell Disease: Expert Panel Report.
4. Adekile, A. D. and Ndugwa, C. (2004). Overview: sickle cell disease clinical outcomes in Africa. British Journal of Haematology, 125(4), 431 to 434.

Figures, Plates, Tables, and Boxes

1. Figure 2.1: Sickled red blood cells alongside normal red blood cells under microscopy. AI-generated using the prompt: "Create a professional educational scientific illustration titled Sickled versus Normal Red Blood Cells, showing crescent-shaped sickle cells alongside normal round red blood cells in a simple microscopy-style diagram. Clean clinical educational diagram style, single illustration, no text-heavy panels."
2. Figure 2.2: A caregiver encouraging a child with sickle cell disease to drink water regularly. AI-generated using the prompt: "A warm, respectful illustration of a caregiver handing a child a glass of water at a home kitchen table, both smiling gently. Single clean illustration, soft natural lighting, no text overlays, no multiple panels, warm and accurate depiction."
3. Table 2.3: Comparing major acute sickle cell crises. AI-generated using the prompt: "Create a clean reference table titled Comparing Major Acute Sickle Cell Crises, listing crisis, key feature, and key management step. Simple clinical reference table style with outside border."
4. Figure 2.4: A clinician reviewing a child's growth and health records during a routine sickle cell disease follow-up visit. AI-generated using the prompt: "A calm, respectful clinical illustration of a clinician reviewing a folder of health records with a caregiver and child during a routine follow-up consultation. Single clean medical illustration, soft clinical lighting, no text overlays, no multiple panels, respectful and accurate depiction."

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Series 3: Thalassaemia

- **Part 3.1: Thalassaemia: Definition, Epidemiology, and Pathogenesis**
  - Sub Part 3.1.1: Definition and epidemiology of thalassaemia
  - Sub Part 3.1.2: Pathogenesis of thalassaemia
  - Sub Part 3.1.3: Genetics of alpha- and beta-thalassaemia
- **Part 3.2: Classification and Diagnosis of Alpha- and Beta-Thalassaemia**
  - Sub Part 3.2.1: Classification of alpha-thalassaemia
  - Sub Part 3.2.2: Classification of beta-thalassaemia
  - Sub Part 3.2.3: Diagnosis of alpha- and beta-thalassaemia
- **Part 3.3: Clinical Manifestations of Thalassaemia**
  - Sub Part 3.3.1: Early clinical manifestations
  - Sub Part 3.3.2: Skeletal changes
  - Sub Part 3.3.3: Liver, gallbladder, and splenic manifestations
- **Part 3.4: Complications, Late Manifestations, and Management of Thalassaemia**
  - Sub Part 3.4.1: Splenectomy and its considerations
  - Sub Part 3.4.2: Renal and other late complications
  - Sub Part 3.4.3: Management of thalassaemia

Introduction

In the last Series, we explored sickle cell disease and other haemoglobinopathies. We now turn to thalassaemia, another important inherited haemoglobin disorder, resulting not from an abnormal haemoglobin structure as in sickle cell disease, but from reduced or absent production of a normal globin chain. Picture a two year old with progressive pallor, poor growth, and a gradually enlarging abdomen, findings that, together with a relevant family history, should raise suspicion for beta-thalassaemia major, one of the most severe forms of this genuinely varied group of conditions.

The aim of this Series is to equip you with the knowledge required to understand the epidemiology, pathogenesis, and classification of thalassaemia, and to diagnose, recognise the manifestations of, and manage alpha- and beta-thalassaemia in children.

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This Series begins with the **definition, epidemiology, and pathogenesis of thalassaemia**, before turning to its **classification and diagnosis**. Next, we examine the **clinical manifestations of thalassaemia**, before concluding with its **complications, late manifestations, and management**.

Series Learning Outcomes

At the end of this Series, you should be able to:

- **SLO 1.1:** define thalassaemia and describe its epidemiology,
- **SLO 1.2:** describe the pathogenesis of thalassaemia,
- **SLO 1.3:** enumerate the classification of thalassaemia,
- **SLO 1.4:** describe the diagnosis of alpha-thalassaemia and beta-thalassaemia,
- **SLO 1.5:** describe the early clinical manifestations of thalassaemia,
- **SLO 1.6:** describe the skeletal, hepatobiliary, and splenic manifestations of thalassaemia,
- **SLO 1.7:** list the complications and late manifestations of thalassaemia, and
- **SLO 1.8:** describe the management of thalassaemia.

3.1 Thalassaemia: Definition, Epidemiology, and Pathogenesis

3.1.1 definition and epidemiology of thalassaemia

A quantitative, rather than qualitative, globin defect

Thalassaemia is defined as a group of inherited disorders characterised by **reduced** or **absent synthesis** of one or more normal **globin chains**, in contrast to **sickle cell disease**, discussed in the previous Series of this course, which results from production of a **structurally abnormal** haemoglobin rather than a quantitative deficiency, a fundamental distinction between these two important groups of inherited haemoglobin disorders.

Thalassaemia is particularly common in populations originating from the **Mediterranean region**, the **Middle East**, **South Asia**, and **Africa**, including Nigeria, reflecting, similarly to sickle cell disease discussed in the previous Series, a likely historical **selective advantage** conferred by carrier status against **falciparum malaria**, meaning thalassaemia and sickle cell disease can, in some populations, occur together in the same individual or family.

Fill in the blank: Thalassaemia results from reduced or absent synthesis of one or more normal _____ chains.

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3.1.2 pathogenesis of thalassaemia

Normal adult haemoglobin consists of **two alpha-globin chains** and **two beta-globin chains**, and thalassaemia results from a genetic defect reducing or abolishing production of one of these chain types, causing an **imbalance** between alpha and beta chain production, with the **excess, unpaired chains** of the unaffected type becoming unstable and **precipitating** within the developing red blood cell precursor.

This **intracellular precipitation** of excess globin chains damages the red cell membrane, causing both **premature destruction** of red cell precursors within the bone marrow itself, termed **ineffective erythropoiesis**, and **shortened survival** of any mature red cells that do reach the circulation, together producing the characteristic **chronic anaemia** of thalassaemia through this combination of impaired production and increased destruction.

Fill in the blank: The intracellular precipitation of excess globin chains causes premature destruction of red cell precursors, termed ineffective _____.

3.1.3 genetics of alpha- and beta-thalassaemia

Alpha-thalassaemia results from deletion or, less commonly, mutation of one or more of the **four alpha-globin genes**, normally present as two copies on each chromosome 16, meaning the severity of alpha-thalassaemia correlates directly with the **number of affected genes**, ranging from the **silent carrier state**, with one affected gene, to the severe, generally fatal **haemoglobin Barts hydrops fetalis**, with all four genes affected.

Beta-thalassaemia, by contrast, results from mutations affecting the **two beta-globin genes**, normally present as a single copy on each chromosome 11, with **beta-thalassaemia minor**, or **trait**, resulting from one affected gene, and **beta-thalassaemia major**, the most clinically severe form, resulting from mutations affecting **both** beta-globin genes, a genetic distinction that directly explains the very different range of clinical severity discussed further later in this Series.

Fill in the blank: Alpha-thalassaemia severity correlates directly with the number of affected genes out of a normal total of _____.

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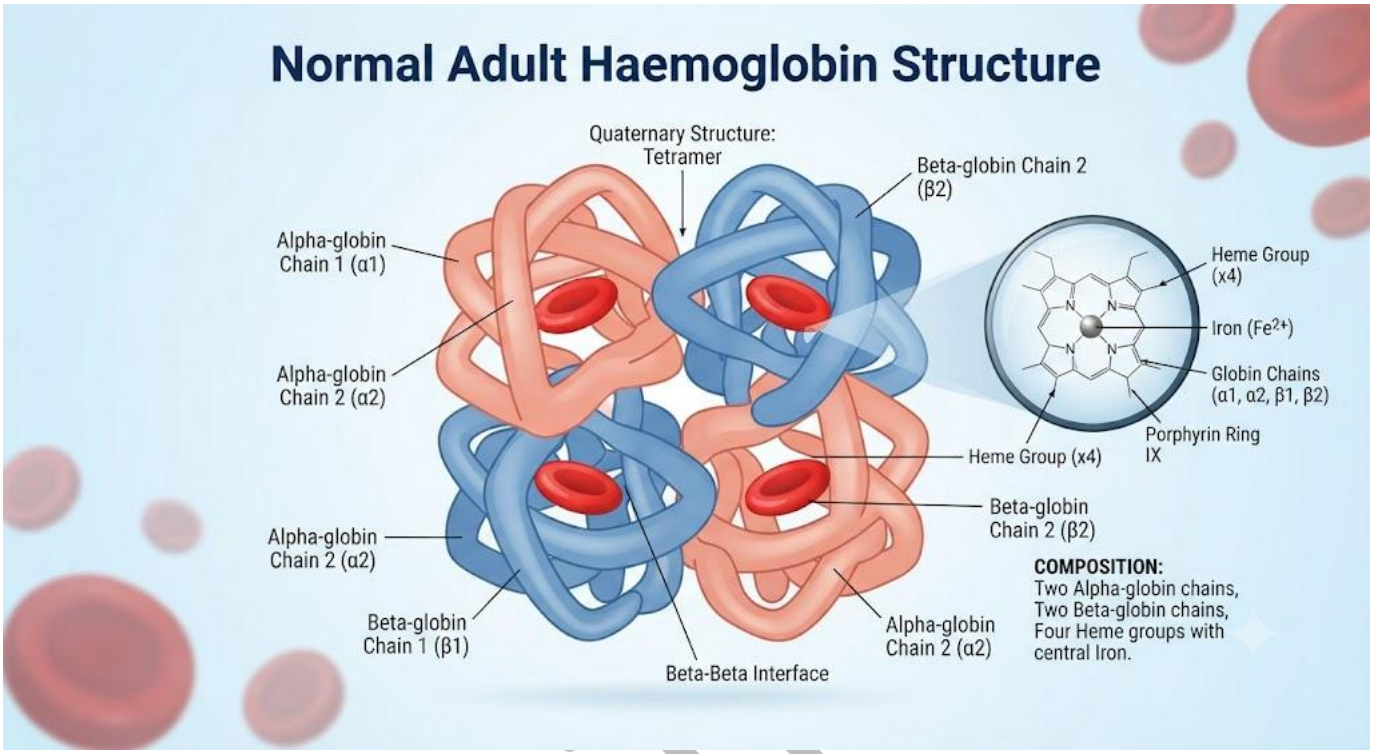

Figure 3.1: The normal structure of adult haemoglobin, showing alpha and beta globin chains.

Pilot questions 3.1

- Define thalassaemia and distinguish it from sickle cell disease. (Linked to SLO 3.1)
- Describe the epidemiology of thalassaemia and its relationship to malaria. (Linked to SLO 3.1)
- Describe the pathogenesis of anaemia in thalassaemia, including ineffective erythropoiesis. (Linked to SLO 3.2)
- Describe the genetic basis of alpha-thalassaemia and how severity relates to gene number. (Linked to SLO 3.3)
- Distinguish beta-thalassaemia minor from beta-thalassaemia major genetically. (Linked to SLO 3.3)

3.2 Classification and Diagnosis of Alpha- and Beta-Thalassaemia

3.2.1 classification of alpha-thalassaemia

A spectrum from entirely silent to incompatible with life

Alpha-thalassaemia is classified according to the number of affected genes into the **silent carrier state**, one affected gene, generally **asymptomatic** with normal or minimally reduced red

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cell indices, **alpha-thalassaemia trait**, two affected genes, causing **mild microcytic anaemia**, **haemoglobin H disease**, three affected genes, causing **moderate to severe** haemolytic anaemia, and **haemoglobin Barts hydrops fetalis**, all four genes affected, generally **incompatible with life** without intrauterine intervention.

This graded classification directly reflects the progressive reduction in **functional alpha-globin production** as increasing numbers of genes are affected, and understanding this spectrum is clinically valuable both for anticipating the likely clinical severity in an affected child and for appropriate **genetic counselling**, discussed in an earlier course, of families found to carry alpha-thalassaemia.

Fill in the blank: Haemoglobin Barts hydrops fetalis, with all four alpha-globin genes affected, is generally incompatible with _____.

3.2.2 classification of beta-thalassaemia

Beta-thalassaemia is classified into **beta-thalassaemia minor**, or **trait**, generally **asymptomatic** or associated with only mild anaemia, **beta-thalassaemia intermedia**, a clinically variable, intermediate severity form, and **beta-thalassaemia major**, the most severe form, presenting with **severe, transfusion-dependent anaemia** typically becoming apparent within the first **year of life**, once fetal haemoglobin production, which does not require beta-globin, has normally declined.

Beta-thalassaemia intermedia occupies a genuinely variable clinical position between minor and major forms, with some affected children requiring only **occasional** transfusion while others require more **regular** transfusion support, reflecting the considerable underlying genetic and clinical heterogeneity within this specific intermediate category.

Fill in the blank: Beta-thalassaemia major typically becomes apparent within the first year of life, once fetal _____ production has declined.

3.2.3 diagnosis of alpha- and beta-thalassaemia

Diagnosis of thalassaemia relies on **full blood count**, typically showing **microcytic**, **hypochromic** anaemia, often with a **disproportionately low MCV** relative to the degree of anaemia compared with iron deficiency, discussed in the first Series of this course, together with **haemoglobin electrophoresis**, which is particularly useful for **beta-thalassaemia**, typically showing **elevated haemoglobin A2** and, often, **elevated fetal haemoglobin**.

Alpha-thalassaemia is more challenging to diagnose using haemoglobin electrophoresis alone, since the electrophoresis pattern can appear relatively normal in milder forms, meaning **genetic**

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testing, directly identifying the specific alpha-globin gene deletions or mutations present, is often required for definitive diagnosis, particularly important for accurate genetic counselling regarding recurrence risk in affected families.

Fill in the blank: Beta-thalassaemia typically shows elevated haemoglobin A2 and, often, elevated fetal _____ on electrophoresis.

Table 3.2: Classification of alpha- and beta-thalassaemia by severity.

Type	Classification	Typical severity
Alpha-thalassaemia	Silent carrier (1 gene)	Asymptomatic
Alpha-thalassaemia	Haemoglobin H disease (3 genes)	Moderate to severe haemolytic anaemia
Beta-thalassaemia	Minor / trait (1 gene)	Asymptomatic or mild anaemia
Beta-thalassaemia	Major (2 genes)	Severe, transfusion-dependent anaemia

Pilot questions 3.2

1. Describe the four categories of alpha-thalassaemia and their relative severity. (Linked to SLO 3.4)
2. Describe the three categories of beta-thalassaemia and their relative severity. (Linked to SLO 3.4)
3. Describe the typical haemoglobin electrophoresis findings in beta-thalassaemia. (Linked to SLO 3.4)
4. Explain why genetic testing is often required to diagnose alpha-thalassaemia definitively. (Linked to SLO 3.4)
5. Distinguish the typical full blood count findings in thalassaemia from those of iron deficiency anaemia. (Linked to SLO 3.4)

3.3 Clinical Manifestations of Thalassaemia

3.3.1 early clinical manifestations

Severity of presentation mirrors the underlying genetic severity

Early manifestations of **severe thalassaemia**, particularly **beta-thalassaemia major**, include **progressive pallor**, **poor feeding**, and **failure to thrive**, typically becoming apparent within the **first year of life**, discussed in the previous Part of this Series, as fetal haemoglobin production

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declines and the underlying beta-globin production defect becomes clinically manifest, with affected infants requiring **regular blood transfusion** to sustain adequate growth and development.

Milder forms of thalassaemia, including **thalassaemia trait** and many cases of **thalassaemia intermedia**, may present later, or be identified **incidentally** through routine blood testing performed for another reason, or through **family screening** once a more severely affected relative has been diagnosed, meaning the age and circumstances of presentation vary considerably according to the specific underlying genetic severity.

Fill in the blank: Early manifestations of severe thalassaemia typically become apparent within the first _____ of life.

3.3.2 skeletal changes

Skeletal changes in inadequately transfused thalassaemia major result from **marked bone marrow expansion**, a compensatory response to chronic, severe anaemia, causing characteristic **facial changes**, termed **thalassaemic facies**, including **frontal bossing**, **maxillary hypertrophy**, and a resulting **prominent malar** appearance, together with generalised **skeletal thinning** and increased **fracture risk**.

These skeletal changes have become considerably **less common** and **less severe** in children receiving adequate, regular **transfusion therapy**, discussed further later in this Series, since consistent transfusion suppresses the excessive bone marrow expansion that otherwise drives these characteristic changes, illustrating how effective, consistent management directly modifies the clinical phenotype that might otherwise be expected based on the underlying genetic severity alone.

Fill in the blank: Skeletal changes in thalassaemia major result from marked bone marrow _____, a compensatory response to chronic anaemia.

3.3.3 liver, gallbladder, and splenic manifestations

Hepatosplenomegaly is a common finding in inadequately treated thalassaemia, resulting from a combination of **extramedullary haematopoiesis**, discussed in the first Series of this course, and **chronic haemolysis**, and **splenomegaly** can become sufficiently significant to cause **hypersplenism**, worsening anaemia and other cytopenias, sometimes prompting consideration of **splenectomy** in selected cases, discussed further in the next Part of this Series.

Gallstones, resulting from chronic haemolysis and the associated increased **bilirubin** production and biliary excretion, are common in thalassaemia, and the **liver** itself can be affected both by

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chronic haemolysis and, over time, by **iron overload**, discussed in the final Part of this Series, meaning hepatobiliary assessment forms an important, ongoing component of comprehensive thalassaemia follow up.

Fill in the blank: Gallstones in thalassaemia result from chronic haemolysis and increased _____ production.

Figure 3.3: A clinician assessing a child's growth as part of routine thalassaemia follow-up care.

Pilot questions 3.3

1. Describe the early clinical manifestations of severe beta-thalassaemia major. (Linked to SLO 3.5)
2. Explain why milder forms of thalassaemia may present later or be identified incidentally. (Linked to SLO 3.5)
3. Describe the skeletal changes seen in inadequately transfused thalassaemia major. (Linked to SLO 3.6)
4. Explain why regular transfusion reduces the severity of skeletal changes. (Linked to SLO 3.6)
5. Describe the cause and significance of gallstones and hepatosplenomegaly in thalassaemia. (Linked to SLO 3.6)

3.4 Complications, Late Manifestations, and Management of Thalassaemia

3.4.1 splenectomy and its considerations

A treatment for hypersplenism that carries its own specific risks

Splenectomy may be considered in thalassaemia where significant **hypersplenism**, discussed in the previous Part of this Series, is causing worsening anaemia or other cytopenias despite adequate transfusion, or where **massive splenomegaly** is causing significant mechanical discomfort, though the decision to proceed with splenectomy requires careful consideration of the specific **risks** involved.

Following splenectomy, children face an increased **lifelong risk of severe infection**, particularly from **encapsulated organisms** such as ***Streptococcus pneumoniae***, given the spleen's important role in immune defence against these specific organisms, meaning appropriate **vaccination**, discussed in an earlier course, and, in some cases, **prophylactic antibiotics**, are essential components of ongoing care following splenectomy.

Fill in the blank: Following splenectomy, children face an increased lifelong risk of severe infection from _____ organisms.

3.4.2 renal and other late complications

Renal involvement in thalassaemia can occur through several mechanisms, including the effects of chronic **anaemia** and **hypoxia** on renal function, and, in transfused patients, the effects of **chronic iron overload**, discussed further in the next sub-Part, meaning renal function should be monitored as part of comprehensive, ongoing thalassaemia follow up alongside the other organ systems already discussed throughout this Series.

Iron overload, resulting from both the **increased intestinal iron absorption** that occurs in thalassaemia, related to the underlying disordered erythropoiesis, and, particularly in transfusion-dependent children, the **cumulative iron load** from repeated blood transfusions, represents one of the most significant long-term complications of thalassaemia, since excess iron deposits progressively in multiple organs, including the **heart**, **liver**, and **endocrine glands**, causing significant, potentially life-limiting organ damage over time if not adequately managed.

Fill in the blank: Iron overload results from both increased intestinal iron absorption and the cumulative iron load from repeated _____.

3.4.3 management of thalassaemia

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Management of significant thalassaemia centres on **regular blood transfusion**, aiming to maintain an adequate haemoglobin level to suppress the excessive bone marrow expansion discussed earlier in this Series and support normal growth and development, together with **iron chelation therapy**, using specific medications to remove excess iron and prevent the organ damage associated with transfusion-related iron overload discussed in the previous sub-Part.

Curative treatment, in the form of **haematopoietic stem cell transplantation**, is available for selected children with severe thalassaemia, particularly where an appropriately matched donor, ideally a sibling, is available, and, more recently, **gene therapy** approaches have emerged as a further potential curative option, though access to both these curative approaches remains genuinely limited in many resource-constrained settings, including much of Nigeria, meaning supportive transfusion and chelation therapy remains the mainstay of management for the great majority of affected children in this setting.

Fill in the blank: Curative treatment for severe thalassaemia is available through haematopoietic stem cell _____.

Figure 3.4: A child receiving a routine blood transfusion as part of ongoing thalassaemia management.

Pilot questions 3.4

1. Describe the indications for splenectomy in thalassaemia and its main long-term risk. (Linked to SLO 3.7)

2. Describe the mechanisms contributing to iron overload in thalassaemia. (Linked to SLO 3.7)
3. Explain why iron overload is a significant long-term complication. (Linked to SLO 3.7)
4. Describe the general approach to management of significant thalassaemia. (Linked to SLO 3.8)
5. Describe the curative treatment options available for severe thalassaemia. (Linked to SLO 3.8)

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Series Summary

This Series introduced **thalassaemia**, beginning with its definition as a group of inherited disorders of reduced or absent globin chain synthesis, distinct from the structurally abnormal haemoglobin of sickle cell disease, its epidemiology and shared evolutionary relationship with malaria protection, and the underlying pathogenesis by which imbalanced globin chain production causes ineffective erythropoiesis and chronic haemolytic anaemia, before turning to the **classification and diagnosis** of alpha- and beta-thalassaemia, exploring how the number of affected genes in each type directly predicts the resulting clinical severity from entirely silent carriage through to transfusion-dependent disease.

We then examined the **clinical manifestations of thalassaemia**, including early presentation and skeletal, hepatic, and splenic changes, before concluding with its **complications, late manifestations, and management**, including splenectomy, iron overload, and both transfusion-based and curative treatment approaches. Having worked through this Series, you should now be able to classify, diagnose, and understand the management of thalassaemia. The next Series turns to **acute leukaemias in children**.

Glossary of Terms

1. **Thalassaemia:** a group of inherited disorders characterised by reduced or absent synthesis of one or more normal globin chains.
2. **Ineffective erythropoiesis:** premature destruction of red cell precursors within the bone marrow, characteristic of thalassaemia.
3. **Alpha-thalassaemia:** thalassaemia resulting from deletion or mutation of one or more of the four alpha-globin genes.
4. **Beta-thalassaemia major:** the most severe form of beta-thalassaemia, presenting with severe, transfusion-dependent anaemia.
5. **Haemoglobin Barts hydrops fetalis:** the most severe form of alpha-thalassaemia, generally incompatible with life without intrauterine intervention.
6. **Haemoglobin H disease:** a form of alpha-thalassaemia with three affected genes, causing moderate to severe haemolytic anaemia.
7. **Thalassaemic facies:** characteristic facial changes, including frontal bossing, resulting from marrow expansion in inadequately treated thalassaemia.
8. **Hypersplenism:** worsening cytopenias resulting from an enlarged, overactive spleen.

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9. **Iron chelation therapy:** medication used to remove excess iron and prevent organ damage from iron overload.
10. **Iron overload:** accumulation of excess iron from increased absorption and repeated transfusion, a significant long-term complication.
11. **Haematopoietic stem cell transplantation:** a curative treatment option for selected children with severe thalassaemia.
12. **Haemoglobin electrophoresis:** a laboratory test used to support the diagnosis of beta-thalassaemia by identifying elevated haemoglobin A2.

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Concept Check Questions [Series 3]

Objective questions

- Thalassaemia results from reduced or absent synthesis of one or more normal _____ chains.
- The intracellular precipitation of excess globin chains causes premature destruction of red cell precursors, termed ineffective _____.
- Beta-thalassaemia major typically becomes apparent within the first year of life, once fetal _____ production has declined.
- Following splenectomy, children face an increased lifelong risk of severe infection from _____ organisms.
- Curative treatment for severe thalassaemia is available through haematopoietic stem cell _____.

Short-answer questions

1. Distinguish beta-thalassaemia minor from beta-thalassaemia major genetically.
2. Describe the four categories of alpha-thalassaemia and their relative severity.
3. Describe the skeletal changes seen in inadequately transfused thalassaemia major.
4. Describe the mechanisms contributing to iron overload in thalassaemia.
5. Describe the general approach to management of significant thalassaemia.

Long-answer questions

6. Discuss the definition, epidemiology, and pathogenesis of thalassaemia. (Linked to SLO 3.1, SLO 3.2)
7. Discuss the classification and diagnosis of alpha- and beta-thalassaemia. (Linked to SLO 3.3, SLO 3.4)
8. Discuss the clinical manifestations of thalassaemia. (Linked to SLO 3.5, SLO 3.6)
9. Discuss splenectomy and iron overload as complications of thalassaemia. (Linked to SLO 3.7)
10. Discuss the management of thalassaemia, including curative options. (Linked to SLO 3.8)

Answers to Concept Check Questions [Series 3]

Objective questions

11. Globin.

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12. Erythropoiesis.
13. Haemoglobin.
14. Encapsulated.
15. Transplantation.

Short-answer questions

16. Beta-thalassaemia minor results from one affected gene, while beta-thalassaemia major results from mutations affecting both genes.
17. Silent carrier (asymptomatic), trait (mild anaemia), haemoglobin H disease (moderate to severe), and Barts hydrops fetalis (incompatible with life).
18. Marked bone marrow expansion causes frontal bossing, maxillary hypertrophy, and generalised skeletal thinning.
19. Increased intestinal iron absorption and cumulative iron load from repeated blood transfusions contribute to iron overload.
20. Regular blood transfusion combined with iron chelation therapy forms the mainstay of management.

Long-answer questions

21. **Basic response:** Thalassaemia results from reduced globin chain synthesis, causing imbalanced chain production, ineffective erythropoiesis, and chronic haemolytic anaemia.

Value-added response: Thalassaemia shares a similar evolutionary relationship with malaria protection as sickle cell disease, explaining its geographic distribution including parts of Nigeria.

22. **Basic response:** Alpha-thalassaemia is classified by the number of affected genes from one to four, while beta-thalassaemia is classified into minor, intermedia, and major forms.

Value-added response: Beta-thalassaemia diagnosis is supported by elevated haemoglobin A2 on electrophoresis, while alpha-thalassaemia often requires genetic testing for definitive diagnosis.

23. **Basic response:** Severe thalassaemia presents early with pallor and failure to thrive, with skeletal changes and hepatosplenomegaly developing if inadequately treated.

Value-added response: Regular transfusion suppresses excessive marrow expansion, reducing the severity of skeletal changes compared with inadequately treated disease.

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24. **Basic response:** Splenectomy may be considered for hypersplenism but carries an increased lifelong infection risk, while iron overload results from absorption and transfusion.

Value-added response: Iron overload causes progressive damage to the heart, liver, and endocrine glands if not managed with adequate chelation therapy.

25. **Basic response:** Management centres on regular transfusion and iron chelation therapy, with curative options including stem cell transplantation for selected children.

Value-added response: Access to curative treatment remains limited in resource-constrained settings, meaning supportive care remains the mainstay for most affected children.

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Answers to Pilot Questions [Series 3]

Part 3.1

1. Thalassaemia is reduced globin chain production, unlike sickle cell disease, which involves a structurally abnormal haemoglobin.
2. Thalassaemia is common in populations with historical malaria exposure, reflecting a similar selective advantage as sickle trait.
3. Excess unpaired globin chains precipitate, damaging red cell precursors and causing ineffective erythropoiesis.
4. Severity correlates with the number of affected alpha-globin genes, from one (silent) to four (incompatible with life).
5. Beta-thalassaemia minor has one affected gene; beta-thalassaemia major has both genes affected.

Part 3.2

6. Silent carrier, trait, haemoglobin H disease, and Barts hydrops fetalis, in order of increasing severity.
7. Minor (asymptomatic or mild), intermedia (variable), and major (severe, transfusion-dependent).
8. Elevated haemoglobin A2 and often elevated fetal haemoglobin are typical findings.
9. The electrophoresis pattern can appear relatively normal in milder alpha-thalassaemia forms.
10. Thalassaemia shows a disproportionately low MCV relative to the degree of anaemia compared with iron deficiency.

Part 3.3

11. Progressive pallor, poor feeding, and failure to thrive typically appear within the first year of life.
12. Milder forms have less severe globin chain imbalance, so symptoms are delayed or absent.
13. Frontal bossing, maxillary hypertrophy, and skeletal thinning result from marrow expansion.
14. Regular transfusion suppresses the excessive marrow expansion driving these changes.
15. Chronic haemolysis increases bilirubin production, causing gallstones, and contributes to hepatosplenomegaly.

Part 3.4

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1. Splenectomy is considered for significant hypersplenism; the main risk is increased lifelong infection risk from encapsulated organisms.
2. Increased intestinal iron absorption and cumulative transfusion load contribute to iron overload.
3. Excess iron deposits in the heart, liver, and endocrine glands, causing progressive organ damage.
4. Regular transfusion combined with iron chelation therapy forms the mainstay of management.
5. Haematopoietic stem cell transplantation and, more recently, gene therapy are curative options.

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References and Attributions [Series 3]

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4. Muncie, H. L. and Campbell, J. S. (2009). Alpha and beta thalassemia. American Family Physician, 80(4), 339 to 344.

Figures, Plates, Tables, and Boxes

1. Figure 3.1: The normal structure of adult haemoglobin, showing alpha and beta globin chains. AI-generated using the prompt: "Create a professional educational diagram titled Normal Adult Haemoglobin Structure, showing two alpha-globin chains and two beta-globin chains combined into a single haemoglobin molecule. Clean clinical educational diagram style, single illustration, no text-heavy panels."
2. Table 3.2: Classification of alpha- and beta-thalassaemia by severity. AI-generated using the prompt: "Create a clean reference table titled Classification of Alpha- and Beta-Thalassaemia by Severity, listing type, classification, and typical severity. Simple clinical reference table style with outside border."
3. Figure 3.3: A clinician assessing a child's growth as part of routine thalassaemia follow-up care. AI-generated using the prompt: "A calm, respectful clinical illustration of a clinician measuring a child's height using a stadiometer during a routine follow-up visit, with a caregiver present. Single clean medical illustration, soft clinical lighting, no text overlays, no multiple panels, sensitive and accurate depiction."
4. Figure 3.4: A child receiving a routine blood transfusion as part of ongoing thalassaemia management. AI-generated using the prompt: "A warm, respectful clinical illustration of a child sitting comfortably in a hospital chair receiving a blood transfusion, with a nurse checking the equipment and a caregiver present. Single clean medical illustration, soft warm lighting, no text overlays, no multiple panels, reassuring and accurate depiction, no graphic medical detail."

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Series 4: Acute Leukaemias in Children

- **Part 4.1: Acute Leukaemia: Classification of ALL and AML**
    - Sub Part 4.1.1: Definition and overview of acute leukaemia
    - Sub Part 4.1.2: Classification of acute lymphoblastic leukaemia
    - Sub Part 4.1.3: Classification of acute myeloid leukaemia
- **Part 4.2: Clinical Features of Acute Leukaemia**
    - Sub Part 4.2.1: Clinical features related to bone marrow failure
    - Sub Part 4.2.2: Clinical features related to organ infiltration
    - Sub Part 4.2.3: Diagnostic evaluation of suspected leukaemia
- **Part 4.3: Principles of Induction, Consolidation, and Maintenance Chemotherapy**
    - Sub Part 4.3.1: Induction chemotherapy
    - Sub Part 4.3.2: Consolidation chemotherapy
    - Sub Part 4.3.3: Maintenance chemotherapy
- **Part 4.4: Side Effects, Outcomes, and Prognostic Indices**
    - Sub Part 4.4.1: Side effects of chemotherapy in leukaemia treatment
    - Sub Part 4.4.2: Monitoring and management of treatment toxicity
    - Sub Part 4.4.3: Outcomes and prognostic indices

Introduction

In the last Series, we explored thalassaemia. We now turn to acute leukaemia, the most common childhood malignancy overall and one of the most important diagnoses to consider in a child presenting with unexplained pallor, bruising, and fatigue. Picture a five year old with several weeks of increasing tiredness, easy bruising, and low-grade fever, whose full blood count reveals an abnormal white cell count together with anaemia and thrombocytopenia, findings that demand urgent further evaluation given the possibility of acute leukaemia.

The aim of this Series is to equip you with the knowledge required to classify, recognise, diagnose, and understand the treatment and prognosis of acute leukaemia in children.

This Series begins with the **classification of acute lymphoblastic leukaemia and acute myeloid leukaemia**, before turning to the **clinical features of acute leukaemia**. Next, we

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examine the **principles of induction, consolidation, and maintenance chemotherapy**, before concluding with the **side effects, outcomes, and prognostic indices** of acute leukaemia.

Series Learning Outcomes

At the end of this Series, you should be able to:

- **SLO 1.1:** define acute leukaemia and distinguish acute lymphoblastic leukaemia from acute myeloid leukaemia,
- **SLO 1.2:** describe the classification of acute leukaemia, integrating morphology, cytochemistry, and cytogenetics,
- **SLO 1.3:** describe the clinical features of acute leukaemia,
- **SLO 1.4:** describe the diagnostic evaluation of a child with suspected leukaemia,
- **SLO 1.5:** describe the principles of induction chemotherapy,
- **SLO 1.6:** describe the principles of consolidation and maintenance chemotherapy,
- **SLO 1.7:** describe the side effects of chemotherapy used in leukaemia treatment, and
- **SLO 1.8:** describe the outcomes and prognostic indices in acute leukaemia.

4.1 Acute Leukaemia: Classification of ALL and AML

4.1.1 definition and overview of acute leukaemia

Uncontrolled proliferation of an immature clone

Acute leukaemia is a malignancy of the **haematopoietic system**, discussed in the first Series of this course, characterised by **uncontrolled proliferation** of an abnormal, **immature clone** of white blood cell precursors, or **blasts**, within the bone marrow, which progressively **replaces** normal marrow elements, impairing normal production of red cells, white cells, and platelets, and is the **most common childhood malignancy** overall.

Acute leukaemia is broadly classified into **acute lymphoblastic leukaemia**, abbreviated **ALL**, arising from **lymphoid precursor cells**, and **acute myeloid leukaemia**, abbreviated **AML**, arising from **myeloid precursor cells**, with **ALL** considerably **more common** in children overall, accounting for the great majority of childhood acute leukaemia cases, while **AML**, though less common, is generally associated with a somewhat **more challenging** treatment course.

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Fill in the blank: Acute leukaemia is characterised by uncontrolled proliferation of an abnormal, immature clone of white blood cell precursors, or _____.

4.1.2 classification of acute lymphoblastic leukaemia

ALL is classified according to the **cell of origin**, most commonly **B-cell precursor ALL**, the most common subtype in children, and, less commonly, **T-cell ALL**, which tends to present with somewhat different clinical features, including a greater likelihood of a **mediastinal mass**, discussed in an earlier course in the context of lymphoblastic lymphoma, given the close biological relationship between these two related conditions.

Modern classification of ALL integrates **morphology**, the microscopic appearance of the leukaemic blasts, **cytochemistry**, specific staining techniques that help distinguish lymphoid from myeloid lineage, **immunophenotyping**, identifying specific **cell surface markers** characteristic of the leukaemic cell population, and **cytogenetics**, identifying specific **chromosomal abnormalities**, each contributing complementary information that together provides a considerably more precise classification than morphology alone.

Fill in the blank: B-cell precursor ALL is the most common _____ of childhood acute lymphoblastic leukaemia.

4.1.3 classification of acute myeloid leukaemia

AML is classified according to the specific **myeloid lineage** and **stage of differentiation** of the leukaemic cells, using a combination of **morphology**, **cytochemistry**, particularly **myeloperoxidase staining**, which is characteristically **positive** in AML and helps distinguish it from ALL, and **cytogenetics**, with specific chromosomal abnormalities carrying important **prognostic significance**, discussed further in the final Part of this Series.

This integrated classification approach, combining **morphology**, **cytochemistry**, **immunophenotyping**, and **cytogenetics**, applies broadly to both ALL and AML, and reflects the genuinely important principle that accurate, precise subclassification of acute leukaemia meaningfully guides both **treatment intensity** and **prognosis**, rather than treating all cases of a given leukaemia type identically regardless of these specific underlying biological features.

Fill in the blank: Myeloperoxidase staining is characteristically positive in AML, helping distinguish it from _____.

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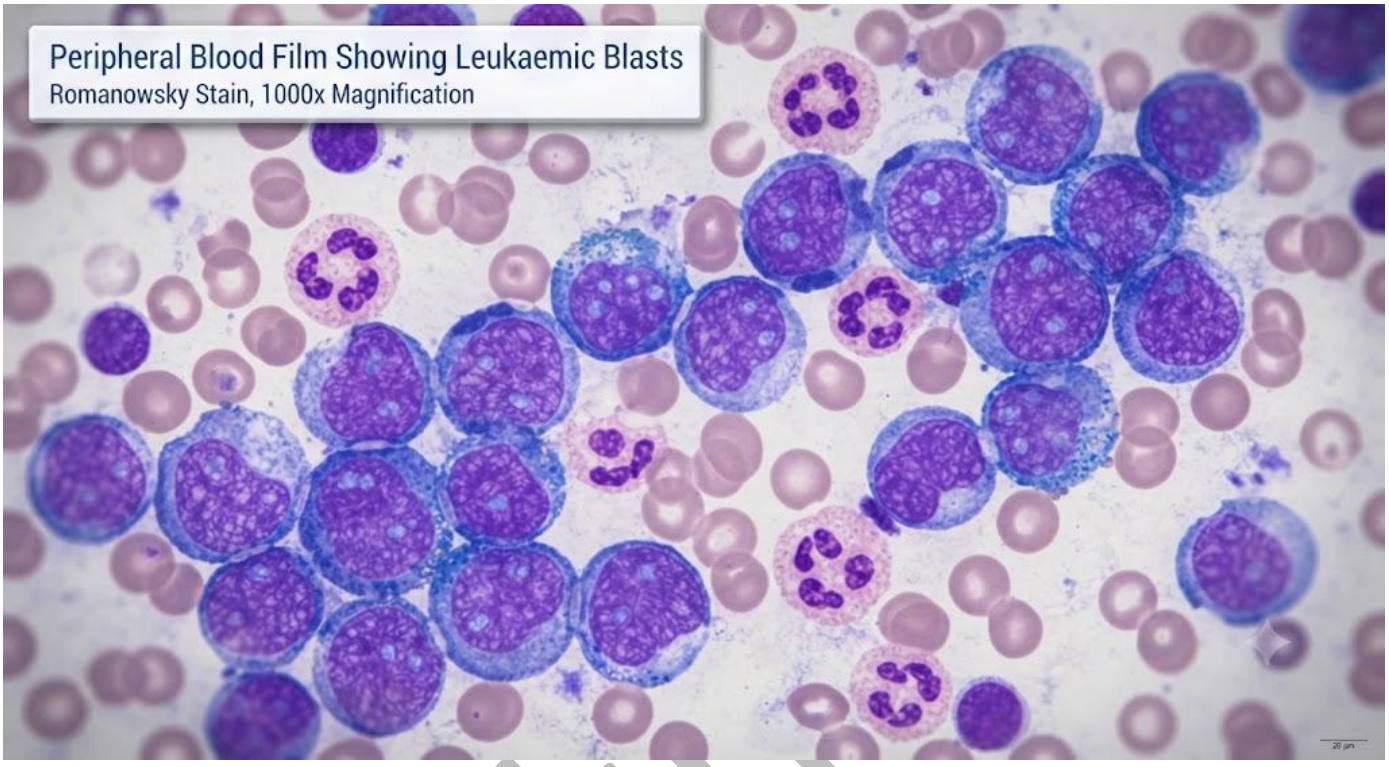

Figure 4.1: A peripheral blood film showing leukaemic blast cells among normal blood cells.

Pilot questions 4.1

- Define acute leukaemia and explain how it impairs normal blood cell production. (Linked to SLO 4.1)
- Distinguish ALL from AML by cell of origin and relative frequency in children. (Linked to SLO 4.1)
- Describe the subtypes of ALL and a distinguishing clinical feature of T-cell ALL. (Linked to SLO 4.2)
- List the four components of the integrated classification approach used for acute leukaemia. (Linked to SLO 4.2)
- Describe the role of myeloperoxidase staining in classifying acute leukaemia. (Linked to SLO 4.2)

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4.2 Clinical Features of Acute Leukaemia

4.2.1 clinical features related to bone marrow failure

Most presenting features reflect displaced normal marrow function

Most clinical features of acute leukaemia result directly from **bone marrow failure**, as leukaemic blasts progressively **replace** normal marrow elements, including **anaemia**, presenting with **pallor** and **fatigue**, **thrombocytopenia**, presenting with **bruising**, **petechiae**, or **bleeding**, and **neutropenia**, presenting with recurrent or severe **infection**, together representing the classic triad of presenting features that should prompt consideration of acute leukaemia.

Bone pain, resulting from **leukaemic infiltration** of the bone marrow itself, is also a common presenting feature, particularly in younger children, and can occasionally be mistaken for a musculoskeletal or infective cause, meaning acute leukaemia should be actively considered in the differential diagnosis of a child with unexplained, persistent bone pain, particularly when accompanied by other features suggestive of marrow failure discussed above.

Fill in the blank: Neutropenia in acute leukaemia presents with recurrent or severe _____.

4.2.2 clinical features related to organ infiltration

Organ infiltration by leukaemic cells can produce **lymphadenopathy**, **hepatosplenomegaly**, and, in some children, **testicular enlargement**, reflecting a recognised site of leukaemic infiltration in boys, and **central nervous system infiltration**, though less commonly a presenting feature, can occur, potentially causing **headache**, **vomiting**, or **cranial nerve palsies**, and is actively assessed for at diagnosis given its important treatment implications.

AML specifically can present with additional distinctive features, including **gum hypertrophy** and **skin infiltration**, termed **leukaemia cutis**, reflecting the specific tissue tropism of certain AML subtypes, and **disseminated intravascular coagulation**, a serious complication of coagulation activation, particularly associated with a specific AML subtype, **acute promyelocytic leukaemia**, requiring specific, urgent recognition and management given its genuine potential severity.

Fill in the blank: Acute promyelocytic leukaemia is particularly associated with disseminated intravascular _____.

4.2.3 diagnostic evaluation of suspected leukaemia

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Diagnostic evaluation of suspected acute leukaemia begins with a **full blood count** and **peripheral blood film**, which may show **circulating blasts**, together with variable abnormalities in the other cell lines already discussed, and **bone marrow aspiration and biopsy**, the definitive diagnostic investigation, providing sufficient material for **morphological**, **cytochemical**, **immunophenotypic**, and **cytogenetic** analysis, discussed in the previous Part of this Series.

Additional investigations include **lumbar puncture**, discussed in an earlier course, to assess for **central nervous system involvement**, and, importantly, given the risk of significant metabolic disturbance from a high burden of rapidly turning over leukaemic cells, assessment for **tumour lysis syndrome**, discussed in an earlier course in the context of Burkitt's lymphoma, which requires the same proactive, preventive management approach in acute leukaemia.

Fill in the blank: Bone marrow aspiration and biopsy is the definitive diagnostic investigation for suspected acute _____.

Pediatric Assessment: Clinical Examination of the Forearm.

Figure 4.2: A clinician examining a child for pallor and bruising during an assessment for suspected leukaemia.

Pilot questions 4.2

1. List the classic triad of presenting features resulting from bone marrow failure in acute leukaemia. (Linked to SLO 4.3)

2. Explain why bone pain can be a presenting feature of acute leukaemia. (Linked to SLO 4.3)
3. Describe organ infiltration features that can occur in acute leukaemia. (Linked to SLO 4.3)
4. Describe distinctive clinical features that can be seen specifically in AML. (Linked to SLO 4.3)
5. Describe the definitive diagnostic investigation for suspected acute leukaemia. (Linked to SLO 4.4)

4.3 Principles of Induction, Consolidation, and Maintenance Chemotherapy

4.3.1 induction chemotherapy

The critical first phase, aiming for rapid remission

Induction chemotherapy is the **initial, intensive phase** of leukaemia treatment, generally lasting **4 to 6 weeks**, with the specific goal of achieving **remission**, defined as elimination of detectable leukaemic blasts from the bone marrow and restoration of normal blood cell production, and typically uses a **combination** of several chemotherapy agents, discussed in an earlier course, to maximise the likelihood of achieving this initial remission.

Induction regimens differ somewhat between **ALL** and **AML**, reflecting their distinct underlying biology, with ALL induction commonly including agents such as **vincristine**, **corticosteroids**, and **asparaginase**, while AML induction typically uses a different combination, often including **anthracyclines** and **cytarabine**, and the **intensity** of induction chemotherapy, together with the resulting risk of significant treatment-related toxicity, is generally considerably **greater for AML** than for standard-risk ALL.

Fill in the blank: Induction chemotherapy aims to achieve _____, defined as elimination of detectable leukaemic blasts from the bone marrow.

4.3.2 consolidation chemotherapy

Consolidation chemotherapy follows successful induction, aiming to **eliminate residual leukaemic cells** not detectable by standard morphological examination but potentially still present at a **microscopic**, or **minimal residual disease**, level, since even a small number of

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residual leukaemic cells can eventually cause **relapse** if not adequately addressed following the initial induction phase.

Consolidation typically uses **different chemotherapy agents** or **combinations** from those used in induction, partly to reduce the risk of the leukaemic cell population developing **resistance** to a single, repeatedly used regimen, and, in **ALL** specifically, consolidation often includes specific attention to **central nervous system-directed therapy**, given the recognised tendency for leukaemic cells to persist within this specific anatomical **sanctuary site**, relatively protected from systemically administered chemotherapy.

Fill in the blank: Consolidation chemotherapy aims to eliminate residual leukaemic cells at a minimal residual _____ level.

4.3.3 maintenance chemotherapy

Maintenance chemotherapy, relevant particularly to **ALL** rather than AML, involves a **prolonged period**, typically **2 to 3 years**, of lower-intensity chemotherapy, commonly including **oral methotrexate** and **mercaptopurine**, given on an outpatient basis, aiming to further reduce the risk of **relapse** following the more intensive induction and consolidation phases already completed.

AML treatment generally does **not** include a prolonged maintenance phase comparable to ALL, instead relying on the intensity of induction and consolidation, sometimes combined with **haematopoietic stem cell transplantation** in higher-risk disease, discussed in an earlier Series of this course in the context of thalassaemia, reflecting a genuinely different overall treatment philosophy between these two related but biologically distinct forms of acute leukaemia.

Fill in the blank: Maintenance chemotherapy for ALL typically continues for 2 to _____ years.

Table 4.3: Phases of chemotherapy treatment for acute lymphoblastic leukaemia.

Phase	Approximate duration	General aim
Induction	4 to 6 weeks	Achieve remission
Consolidation	Several months	Eliminate residual disease, address CNS sanctuary site
Maintenance	2 to 3 years	Reduce relapse risk with lower-intensity therapy

Pilot questions 4.3

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1. Describe the goal and typical duration of induction chemotherapy. (Linked to SLO 4.5)
2. Describe the goal of consolidation chemotherapy and the concept of minimal residual disease. (Linked to SLO 4.6)
3. Explain why central nervous system-directed therapy is particularly relevant in ALL. (Linked to SLO 4.6)
4. Describe the goal and typical duration of maintenance chemotherapy in ALL. (Linked to SLO 4.6)
5. Explain why AML treatment does not generally include a prolonged maintenance phase. (Linked to SLO 4.6)

4.4 Side Effects, Outcomes, and Prognostic Indices

4.4.1 side effects of chemotherapy in leukaemia treatment

Toxicity requires the same proactive management as the malignancy itself

Side effects of leukaemia chemotherapy include the general acute side effects discussed in an earlier course, particularly significant **myelosuppression**, given the intensity of leukaemia treatment regimens, increasing the risk of serious **infection**, discussed in that earlier course in the context of febrile neutropenia, and requiring the same proactive supportive care approach throughout treatment.

Specific agent-related toxicities include **peripheral neuropathy** with **vincristine**, **hyperglycaemia** and other metabolic effects with **corticosteroids**, **pancreatitis** and **allergic reactions** with **asparaginase**, and **cardiotoxicity** with **anthracyclines**, discussed in an earlier course in the context of childhood lymphoma, each requiring specific monitoring throughout the relevant phase of treatment in which that particular agent is used.

Fill in the blank: Peripheral neuropathy is a specific side effect associated with the chemotherapy agent _____.

4.4.2 monitoring and management of treatment toxicity

Monitoring for treatment toxicity is an essential, ongoing component of leukaemia care throughout all phases of treatment, including regular **full blood count** monitoring to guide **dose adjustment** and identify significant myelosuppression, **cardiac monitoring** where anthracyclines are used, and specific, targeted monitoring for other known toxicities relevant to the specific agents included in a given child's treatment regimen.

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Supportive care, discussed in detail in an earlier course, remains genuinely essential throughout leukaemia treatment, including infection prevention and prompt management, transfusion support, and nutritional and psychosocial support, since successful treatment of acute leukaemia depends on the combination of both **effective anti-leukaemic therapy** and **comprehensive supportive care** working together throughout the often lengthy overall treatment course.

Fill in the blank: Successful treatment of acute leukaemia depends on the combination of effective anti-leukaemic therapy and comprehensive _____ care.

4.4.3 outcomes and prognostic indices

Outcomes for childhood **ALL** have improved dramatically over recent decades, with **cure rates** now exceeding **85 to 90 percent** in many settings with access to modern, comprehensive treatment, representing one of the most significant success stories in modern paediatric oncology, though **AML** outcomes, while also improved, generally remain somewhat **less favourable** than those for ALL, reflecting the more challenging underlying biology discussed earlier in this Series.

Prognostic indices for ALL include **age at diagnosis**, with children aged **1 to 9 years** generally having the most favourable prognosis, **initial white cell count**, with very high counts associated with poorer prognosis, and specific **cytogenetic abnormalities**, some conferring a **favourable** and others an **unfavourable** prognosis, together with **response to initial treatment**, assessed through **minimal residual disease** testing, discussed earlier in this Series, which has become an increasingly important, sensitive prognostic tool in contemporary practice.

Fill in the blank: Children with ALL aged 1 to _____ years generally have the most favourable prognosis.

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Figure 4.4: A child attending a follow-up clinic visit during leukaemia treatment.

Pilot questions 4.4

1. List three specific chemotherapy agents used in leukaemia treatment and a specific side effect of each. (Linked to SLO 4.7)
2. Describe the general approach to monitoring for treatment toxicity during leukaemia therapy. (Linked to SLO 4.7)
3. Explain why supportive care is essential alongside anti-leukaemic therapy. (Linked to SLO 4.7)
4. Describe the general outcome of childhood ALL with modern treatment. (Linked to SLO 4.8)
5. List three prognostic factors relevant to childhood ALL. (Linked to SLO 4.8)

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Series Summary

This Series introduced **acute leukaemia**, beginning with its definition as uncontrolled proliferation of immature blast cells that progressively replace normal bone marrow function, and the classification of ALL and AML using an integrated approach combining morphology, cytochemistry, immunophenotyping, and cytogenetics, before turning to the **clinical features of acute leukaemia**, exploring how most presenting features reflect either displaced normal marrow function, producing the classic triad of anaemia, bruising, and infection, or direct organ infiltration by leukaemic cells.

We then examined the **principles of induction, consolidation, and maintenance chemotherapy**, before concluding with the **side effects, outcomes, and prognostic indices** of acute leukaemia. Having worked through this Series, you should now be able to classify, recognise, diagnose, and understand the treatment and prognosis of acute leukaemia in children. The final Series of this course turns to **bleeding disorders, including coagulation, haemophilia, and von Willebrand disease**.

Glossary of Terms

1. **Acute leukaemia:** a malignancy characterised by uncontrolled proliferation of immature blast cells within the bone marrow.
2. **Acute lymphoblastic leukaemia (ALL):** the most common childhood leukaemia, arising from lymphoid precursor cells.
3. **Acute myeloid leukaemia (AML):** a less common but generally more challenging form of leukaemia arising from myeloid precursor cells.
4. **Immunophenotyping:** a laboratory technique identifying specific cell surface markers to classify leukaemic cells.
5. **Myeloperoxidase staining:** a cytochemical stain characteristically positive in AML.
6. **Remission:** elimination of detectable leukaemic blasts from the bone marrow following induction chemotherapy.
7. **Minimal residual disease:** a microscopic level of residual leukaemic cells not detectable by standard morphological examination.
8. **Sanctuary site:** an anatomical location, such as the central nervous system, relatively protected from systemic chemotherapy.
9. **Induction chemotherapy:** the initial, intensive phase of leukaemia treatment aiming to achieve remission.

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10. **Consolidation chemotherapy:** treatment following induction aiming to eliminate residual leukaemic cells.
11. **Maintenance chemotherapy:** a prolonged period of lower-intensity chemotherapy used particularly in ALL to reduce relapse risk.
12. **Acute promyelocytic leukaemia:** a specific AML subtype particularly associated with disseminated intravascular coagulation.

Concept Check Questions [Series 4]

Objective questions

- Acute leukaemia is characterised by uncontrolled proliferation of an abnormal, immature clone of white blood cell precursors, or _____.
- Myeloperoxidase staining is characteristically positive in AML, helping distinguish it from _____.
- Bone marrow aspiration and biopsy is the definitive diagnostic investigation for suspected acute _____.
- Consolidation chemotherapy aims to eliminate residual leukaemic cells at a minimal residual _____ level.
- Children with ALL aged 1 to _____ years generally have the most favourable prognosis.

Short-answer questions

1. Distinguish ALL from AML by cell of origin and relative frequency in children.
2. List the classic triad of presenting features resulting from bone marrow failure in acute leukaemia.
3. Describe the goal and typical duration of induction chemotherapy.
4. List three specific chemotherapy agents used in leukaemia treatment and a specific side effect of each.
5. List three prognostic factors relevant to childhood ALL.

Long-answer questions

6. Discuss the classification of ALL and AML, integrating morphology, cytochemistry, and cytogenetics. (Linked to SLO 4.1, SLO 4.2)
7. Discuss the clinical features and diagnostic evaluation of acute leukaemia. (Linked to SLO 4.3, SLO 4.4)

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8. Discuss the principles of induction, consolidation, and maintenance chemotherapy. (Linked to SLO 4.5, SLO 4.6)
9. Discuss the side effects of chemotherapy used in leukaemia treatment. (Linked to SLO 4.7)
10. Discuss the outcomes and prognostic indices of acute leukaemia. (Linked to SLO 4.8)

Answers to Concept Check Questions [Series 4]

Objective questions

11. Blasts.
12. ALL.
13. Leukaemia.
14. Disease.
15. 9.

Short-answer questions

16. ALL arises from lymphoid precursors and is more common; AML arises from myeloid precursors and is less common but more challenging.
17. Anaemia, bruising or bleeding, and infection are the classic triad from bone marrow failure.
18. Induction aims to achieve remission, typically lasting 4 to 6 weeks.
19. Vincristine (neuropathy), corticosteroids (hyperglycaemia), and anthracyclines (cardiotoxicity) are examples.
20. Age at diagnosis, initial white cell count, and cytogenetic abnormalities are prognostic factors.

Long-answer questions

21. **Basic response:** Acute leukaemia is classified into ALL and AML based on cell of origin, with integrated classification combining morphology, cytochemistry, immunophenotyping, and cytogenetics.

Value-added response: ALL is more common overall, with B-cell precursor ALL the most frequent subtype, while AML is generally associated with a more challenging treatment course.

22. **Basic response:** Clinical features result from bone marrow failure, causing anaemia, bruising, and infection, or organ infiltration causing lymphadenopathy and hepatosplenomegaly.

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Value-added response: Bone marrow aspiration and biopsy provides definitive diagnosis, supported by lumbar puncture and assessment for tumour lysis syndrome.

23. **Basic response:** Treatment proceeds through induction to achieve remission, consolidation to eliminate residual disease, and, in ALL, maintenance to reduce relapse risk.

Value-added response: CNS-directed therapy is particularly important in ALL given the sanctuary site phenomenon, and AML does not generally include a prolonged maintenance phase.

24. **Basic response:** Chemotherapy side effects include myelosuppression and specific agent-related toxicities such as neuropathy, cardiotoxicity, and metabolic effects.

Value-added response: Ongoing monitoring and comprehensive supportive care are essential alongside anti-leukaemic therapy throughout the treatment course.

25. **Basic response:** Outcomes for childhood ALL have improved dramatically, with cure rates now exceeding 85 to 90 percent, though AML outcomes remain somewhat less favourable.

Value-added response: Prognostic factors include age at diagnosis, initial white cell count, cytogenetic abnormalities, and response to treatment assessed by minimal residual disease testing.

Answers to Pilot Questions [Series 4]

Part 4.1

1. Acute leukaemia is uncontrolled proliferation of immature blasts, impairing normal blood cell production.
2. ALL arises from lymphoid precursors and is more common; AML arises from myeloid precursors and is less common.
3. B-cell precursor ALL is most common; T-cell ALL is more likely to present with a mediastinal mass.
4. Morphology, cytochemistry, immunophenotyping, and cytogenetics are the four components.

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5. Myeloperoxidase staining is characteristically positive in AML, helping distinguish it from ALL.

Part 4.2

6. Anaemia, thrombocytopenia (bruising or bleeding), and neutropenia (infection) are the classic triad.
7. Leukaemic infiltration of the bone marrow itself can cause bone pain.
8. Lymphadenopathy, hepatosplenomegaly, testicular enlargement, and CNS infiltration can occur.
9. Gum hypertrophy, leukaemia cutis, and disseminated intravascular coagulation can occur, particularly in specific AML subtypes.
10. Bone marrow aspiration and biopsy is the definitive diagnostic investigation.

Part 4.3

11. Induction aims to achieve remission, typically over 4 to 6 weeks.
12. Consolidation eliminates residual leukaemic cells at a minimal residual disease level not detectable morphologically.
13. Leukaemic cells can persist in the CNS as a sanctuary site relatively protected from systemic chemotherapy.
14. Maintenance uses lower-intensity therapy, typically for 2 to 3 years, to reduce relapse risk.
15. AML relies on intensive induction and consolidation, sometimes with transplantation, rather than prolonged maintenance.

Part 4.4

1. Vincristine causes neuropathy, corticosteroids cause hyperglycaemia, and anthracyclines cause cardiotoxicity.
2. Regular blood count and specific toxicity monitoring guide dose adjustment throughout treatment.
3. Successful treatment depends on the combination of effective anti-leukaemic therapy and comprehensive supportive care.
4. Cure rates for childhood ALL now exceed 85 to 90 percent in many settings with modern treatment.
5. Age at diagnosis, initial white cell count, and cytogenetic abnormalities are prognostic factors.

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References and Attributions [Series 4]

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3. Rubnitz, J. E. (2012). Current management of childhood acute myeloid leukemia. Paediatric Drugs, 14(1), 6 to 12.
4. Pui, C. H., Yang, J. J. and Hunger, S. P. (2015). Childhood acute lymphoblastic leukemia: progress through collaboration. Journal of Clinical Oncology, 33(27), 2938 to 2948.

Figures, Plates, Tables, and Boxes

1. Figure 4.1: A peripheral blood film showing leukaemic blast cells among normal blood cells. AI-generated using the prompt: "Create a realistic microscopy-style scientific illustration titled Peripheral Blood Film Showing Leukaemic Blasts, showing several large, immature blast cells among normal-appearing blood cells on a stained slide background. Clean scientific illustration style, single image, no text overlays."
2. Figure 4.2: A clinician examining a child for pallor and bruising during an assessment for suspected leukaemia. AI-generated using the prompt: "A calm, respectful clinical illustration of a clinician gently examining a child's arm during an assessment, with a caregiver present nearby. Single clean medical illustration, soft clinical lighting, no text overlays, no multiple panels, sensitive and accurate depiction, no graphic detail."
3. Table 4.3: Phases of chemotherapy treatment for acute lymphoblastic leukaemia. AI-generated using the prompt: "Create a clean reference table titled Phases of Chemotherapy for Acute Lymphoblastic Leukaemia, listing phase, approximate duration, and general aim. Simple clinical reference table style with outside border."
4. Figure 4.4: A child attending a follow-up clinic visit during leukaemia treatment. AI-generated using the prompt: "A warm, respectful clinical illustration of a clinician sitting with a caregiver and child during a routine follow-up consultation, reviewing notes together in a calm clinic room. Single clean medical illustration, soft natural lighting, no text overlays, no multiple panels, respectful and accurate depiction."

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Series 5: Bleeding Disorders: Coagulation, Haemophilia, and Von Willebrand Disease

- **Part 5.1: Coagulation: Mechanism of Clotting and Evaluation of Abnormal Coagulation Tests**
    - Sub Part 5.1.1: Mechanism of clotting
    - Sub Part 5.1.2: Evaluation of abnormal coagulation tests
    - Sub Part 5.1.3: Further coagulation testing
- **Part 5.2: Inherited Coagulation Disorders: Haemophilia A and B**
    - Sub Part 5.2.1: Definition and epidemiology of haemophilia
    - Sub Part 5.2.2: Clinical manifestations: age at first bleeding and initial site
    - Sub Part 5.2.3: Sites of bleeding in haemophilia
- **Part 5.3: Von Willebrand Disease and Clinical Manifestations of Bleeding Disorders**
    - Sub Part 5.3.1: Definition and epidemiology of von Willebrand disease
    - Sub Part 5.3.2: Clinical manifestations of von Willebrand disease
    - Sub Part 5.3.3: Laboratory evaluation of bleeding disorders
- **Part 5.4: Haemophilic Arthropathy, Inhibitors, and Diagnostic Evaluation**
    - Sub Part 5.4.1: Haemophilic arthropathy
    - Sub Part 5.4.2: Development of inhibitors
    - Sub Part 5.4.3: Diagnostic evaluation of a suspected bleeding disorder

Introduction

In the last Series, we explored acute leukaemias in children. We now turn to bleeding disorders, the final topic of this course, focusing on coagulation, haemophilia, and von Willebrand disease. Picture an eighteen month old boy with a swollen, painful knee following a relatively minor fall, with no history of trauma severe enough to explain the degree of swelling, prompting consideration of an underlying inherited bleeding disorder. Understanding the mechanism of normal clotting, and recognising and evaluating the inherited coagulation disorders that can disrupt it, is the focus of this final Series of the course.

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The aim of this Series is to equip you with the knowledge required to understand the mechanism of clotting, evaluate abnormal coagulation tests, and recognise, diagnose, and understand haemophilia A, haemophilia B, and von Willebrand disease.

This Series begins with **coagulation, the mechanism of clotting, and evaluation of abnormal coagulation tests**, before turning to **inherited coagulation disorders, haemophilia A and B**. Next, we examine **von Willebrand disease and the clinical manifestations of bleeding disorders**, before concluding with **haemophilic arthropathy, inhibitors, and diagnostic evaluation**.

Series Learning Outcomes

At the end of this Series, you should be able to:

- **SLO 1.1:** describe the mechanism of clotting and the coagulation cascade,
- **SLO 1.2:** describe the evaluation of abnormal coagulation tests,
- **SLO 1.3:** define haemophilia A and haemophilia B and describe their epidemiology,
- **SLO 1.4:** describe the clinical manifestations of haemophilia, including age at first bleeding and sites of bleeding,
- **SLO 1.5:** define von Willebrand disease and describe its epidemiology and clinical manifestations,
- **SLO 1.6:** describe the laboratory evaluation of bleeding disorders,
- **SLO 1.7:** describe haemophilic arthropathy and its development, and
- **SLO 1.8:** describe the development of inhibitors and the diagnostic evaluation of a child with a suspected bleeding disorder.

5.1 Coagulation: Mechanism of Clotting and Evaluation of Abnormal Coagulation Tests

5.1.1 mechanism of clotting

A cascade of sequential enzyme activation

Normal **haemostasis** involves a carefully coordinated sequence beginning with **primary haemostasis**, in which **platelets** adhere to and aggregate at a site of vessel injury, forming an initial **platelet plug**, followed by **secondary haemostasis**, the **coagulation cascade**, in which a sequential series of **clotting factors** are activated, ultimately converting soluble **fibrinogen** into insoluble **fibrin**, stabilising the platelet plug into a definitive clot.

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The coagulation cascade is conventionally described as two converging pathways, the **intrinsic pathway**, activated by contact with exposed subendothelial surfaces, and the **extrinsic pathway**, activated by **tissue factor** released from damaged tissue, both converging on a shared **common pathway**, ultimately generating **thrombin**, which converts fibrinogen to fibrin, with this conceptual model, though a simplification of the genuinely more complex and interconnected process occurring in vivo, remaining clinically useful for interpreting the specific coagulation tests discussed later in this Part.

Fill in the blank: Secondary haemostasis, the coagulation cascade, ultimately converts soluble fibrinogen into insoluble _____.

5.1.2 evaluation of abnormal coagulation tests

Prothrombin time, or **PT**, primarily assesses the **extrinsic** and **common pathways**, and is prolonged by deficiencies of factors within these specific pathways, while **activated partial thromboplastin time**, or **aPTT**, primarily assesses the **intrinsic** and **common pathways**, and is prolonged by deficiencies of factors within these pathways, including the specific factors deficient in **haemophilia A** and **haemophilia B**, discussed in detail in the next Part of this Series.

Interpreting a **prolonged aPTT** or **PT** requires a **mixing study**, in which the child's plasma is mixed with normal plasma, since **correction** of the prolonged time suggests a **factor deficiency**, which is corrected by the additional normal factors present in the mixed sample, while **failure to correct** suggests the presence of a circulating **inhibitor**, discussed further in the final Part of this Series, actively interfering with normal clotting function.

Fill in the blank: A mixing study helps distinguish a factor deficiency, which corrects, from a circulating _____, which does not.

5.1.3 further coagulation testing

Platelet count, assessed as part of a standard full blood count discussed in the first Series of this course, and **bleeding time**, or, increasingly, more specific **platelet function assays**, assess **primary haemostasis**, and abnormalities in this specific stage suggest a **platelet disorder** rather than a coagulation factor deficiency, an important distinction given the somewhat different underlying causes and management approaches for these two broad categories of bleeding disorder.

Specific factor assays, measuring the activity level of an individual clotting factor, provide **definitive confirmation** of a specific factor deficiency once suspected based on the screening tests discussed earlier in this Part, and, together, this structured, stepwise approach to coagulation

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testing, moving from initial screening tests through mixing studies to specific factor assays, allows accurate diagnosis of the specific underlying bleeding disorder in most affected children.

Fill in the blank: Specific factor assays provide definitive confirmation of a specific factor _____ once suspected.

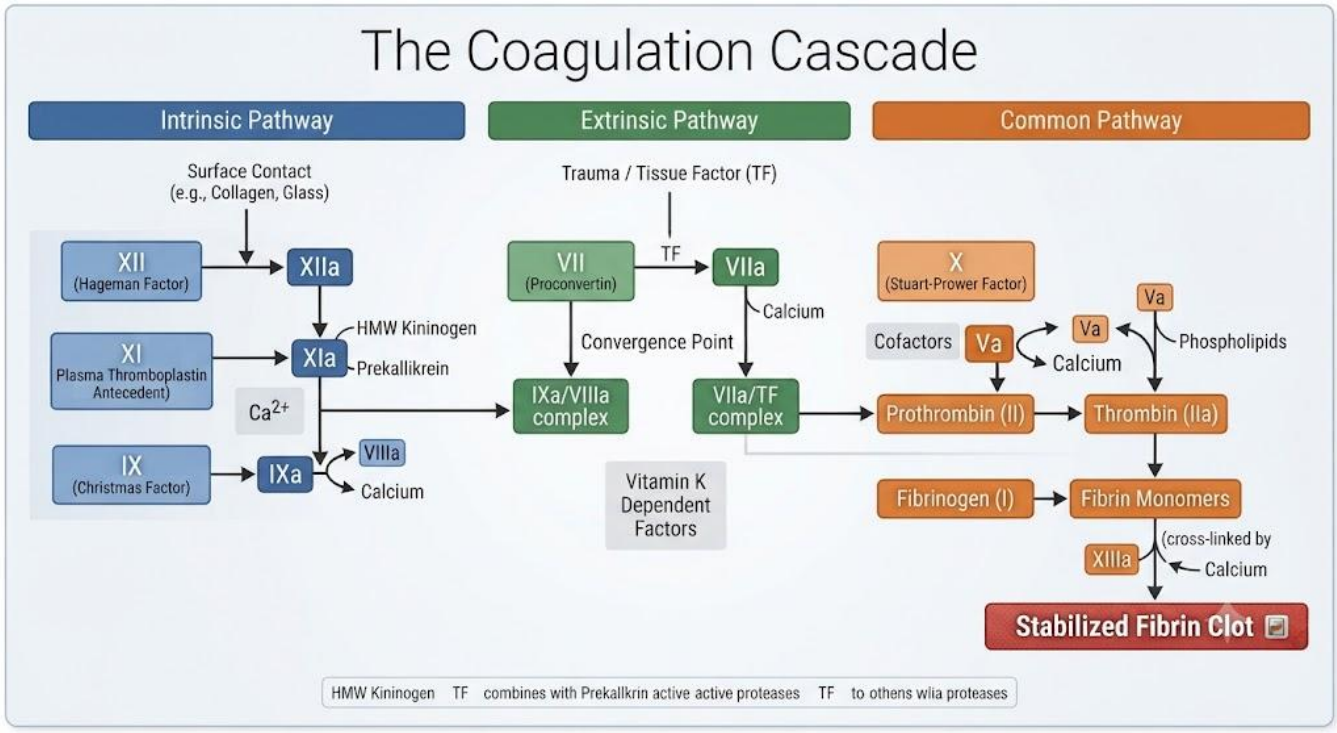

Figure 5.1: A simplified overview of the coagulation cascade.

Pilot questions 5.1

- Distinguish primary haemostasis from secondary haemostasis. (Linked to SLO 5.1)
- Describe the intrinsic, extrinsic, and common pathways of the coagulation cascade. (Linked to SLO 5.1)
- Describe what PT and aPTT each primarily assess. (Linked to SLO 5.2)
- Describe the purpose and interpretation of a mixing study. (Linked to SLO 5.2)
- Distinguish a platelet disorder from a coagulation factor deficiency based on initial screening tests. (Linked to SLO 5.3)

5.2 Inherited Coagulation Disorders: Haemophilia A and B

5.2.1 definition and epidemiology of haemophilia

X-linked disorders affecting boys almost exclusively

Haemophilia A results from **deficiency of factor VIII**, and **haemophilia B** results from **deficiency of factor IX**, with both conditions following **X-linked recessive** inheritance, meaning they predominantly affect **boys**, since females, having two X chromosomes, generally require both copies to be affected to be clinically symptomatic, though **carrier females** can occasionally have mildly reduced factor levels sufficient to cause some bleeding symptoms.

Haemophilia A is considerably **more common** than haemophilia B, accounting for approximately **80 to 85 percent** of haemophilia cases overall, and both conditions are classified by **severity**, based on measured **factor activity level**, into **severe**, **moderate**, and **mild** categories, with **severe haemophilia**, generally defined as factor activity below **1 percent**, associated with the most frequent and significant bleeding episodes.

Fill in the blank: Haemophilia A results from deficiency of factor _____.

5.2.2 clinical manifestations: age at first bleeding and initial site

Age at first bleeding in haemophilia correlates with **disease severity**, with **severe haemophilia** often presenting in **infancy**, sometimes with bleeding following **circumcision** or **intramuscular injection**, or, in older infants, with **joint** or **muscle bleeding** once the child becomes more physically active, while **mild haemophilia** may not become clinically apparent until **later childhood** or even adulthood, often first identified following a significant injury or surgical procedure.

The **initial site of bleeding** provides useful diagnostic and prognostic information, with **joints** and **muscles** the most common sites of spontaneous bleeding in significant haemophilia, discussed further in relation to haemophilic arthropathy in the final Part of this Series, though bleeding can occur at virtually **any site**, including sites discussed further in the following sub-Part.

Fill in the blank: Severe haemophilia often presents in infancy with bleeding following circumcision or intramuscular _____.

5.2.3 sites of bleeding in haemophilia

Intracranial bleeding, though relatively uncommon, represents one of the most serious potential complications of haemophilia, given the risk of significant, potentially fatal neurological injury, and any child with haemophilia presenting with **head trauma**, however apparently minor, or unexplained **neurological symptoms**, requires urgent evaluation and, generally, prompt **factor replacement** given the genuine severity of this specific potential complication.

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Other important sites of bleeding include **epistaxis**, **oral bleeding**, particularly following dental procedures or with tooth eruption, and **gastrointestinal bleeding**, and recognising this **wide range** of potential bleeding sites, extending well beyond the joints and muscles most classically associated with haemophilia, remains important for maintaining appropriate clinical vigilance across the full spectrum of presentations a child with haemophilia might experience.

Fill in the blank: Any child with haemophilia presenting with head trauma, however minor, requires urgent evaluation given the risk of intracranial _____.

Figure 5.2: A clinician gently examining a child's swollen knee joint.

Pilot questions 5.2

1. Define haemophilia A and haemophilia B by the specific factor deficiency in each. (Linked to SLO 5.3)
2. Describe the inheritance pattern of haemophilia and explain why it predominantly affects boys. (Linked to SLO 5.3)
3. Describe how age at first bleeding relates to haemophilia severity. (Linked to SLO 5.4)
4. List three sites of bleeding in haemophilia beyond joints and muscles. (Linked to SLO 5.4)
5. Explain why intracranial bleeding is considered particularly serious in a child with haemophilia. (Linked to SLO 5.4)

5.3 Von Willebrand Disease and Clinical Manifestations of Bleeding Disorders

5.3.1 definition and epidemiology of von Willebrand disease

The most common inherited bleeding disorder overall

Von Willebrand disease, resulting from **deficiency** or **dysfunction** of **von Willebrand factor**, a protein essential for normal **platelet adhesion** and also serving as a **carrier protein** for **factor VIII**, is the most common inherited **bleeding disorder** overall, considerably more common than haemophilia, though frequently **milder** in clinical severity and, as a result, sometimes **underrecognised**.

Unlike haemophilia, von Willebrand disease follows **autosomal** inheritance, meaning it affects **males and females** approximately **equally**, and is classified into several types, including **type 1**, a **partial quantitative deficiency**, the most common and generally mildest form, **type 2**, a **qualitative defect** with several further subtypes, and **type 3**, a **severe, complete deficiency**, considerably less common but associated with more significant bleeding symptoms.

Fill in the blank: Von Willebrand disease follows autosomal inheritance, affecting males and females approximately _____.

5.3.2 clinical manifestations of von Willebrand disease

Clinical manifestations of von Willebrand disease typically reflect the combined role of von Willebrand factor in **platelet function**, producing features characteristic of **mucocutaneous bleeding**, including **easy bruising**, **epistaxis**, **gum bleeding**, and, in older girls, **heavy menstrual bleeding**, or **menorrhagia**, often the presenting feature that first prompts clinical evaluation in an adolescent girl.

Unlike haemophilia, **spontaneous joint** and **muscle bleeding** are considerably **less common** in von Willebrand disease, except in the more severe **type 3** form, given the somewhat different underlying mechanism affecting primarily platelet function rather than the coagulation cascade itself, though bleeding following **surgery** or **dental procedures** can be significant across all types if the diagnosis is not recognised and appropriate precautions taken beforehand.

Fill in the blank: Menorrhagia, or heavy menstrual bleeding, is often the presenting feature of von Willebrand disease in older _____.

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5.3.3 laboratory evaluation of bleeding disorders

Laboratory evaluation of a suspected bleeding disorder should include **full blood count**, **PT**, **aPTT**, discussed earlier in this Series, together with **von Willebrand factor antigen** and **activity assays**, and **factor VIII level**, given its relationship with von Willebrand factor, discussed earlier in this Part, since von Willebrand disease can present with a **normal** or only **mildly prolonged** aPTT, meaning specific testing is required if clinical suspicion remains despite normal initial screening results.

Given the **considerable overlap** in clinical presentation between haemophilia and von Willebrand disease, particularly milder forms of each, and the genuine limitations of standard screening coagulation tests in reliably excluding either condition, a **low threshold** for specific factor and von Willebrand factor testing is appropriate in any child with a clinical history genuinely suggestive of an underlying bleeding disorder, rather than relying on normal screening results alone to exclude these possibilities.

Fill in the blank: Von Willebrand disease can present with a normal or only mildly prolonged _____.

Table 5.3: Comparing haemophilia A, haemophilia B, and von Willebrand disease.

Feature	Haemophilia A/B	Von Willebrand disease
Deficient factor	Factor VIII (A) or IX (B)	Von Willebrand factor
Inheritance	X-linked recessive	Autosomal
Sex predominantly affected	Male	Male and female equally
Typical bleeding pattern	Joint and muscle bleeding	Mucocutaneous bleeding

Pilot questions 5.3

1. Define von Willebrand disease and describe the role of von Willebrand factor. (Linked to SLO 5.5)
2. Distinguish the inheritance pattern of von Willebrand disease from haemophilia. (Linked to SLO 5.5)
3. Describe the typical clinical manifestations of von Willebrand disease. (Linked to SLO 5.5)
4. Explain why joint and muscle bleeding are less common in von Willebrand disease than in haemophilia. (Linked to SLO 5.5)
5. Describe the laboratory evaluation used to distinguish haemophilia from von Willebrand disease. (Linked to SLO 5.6)

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5.4 Haemophilic Arthropathy, Inhibitors, and Diagnostic Evaluation

5.4.1 haemophilic arthropathy

Recurrent joint bleeding causes cumulative, progressive damage

Haemophilic arthropathy refers to **chronic joint damage** resulting from **recurrent bleeding** into a joint, or **haemarthrosis**, most commonly affecting the **knees**, **elbows**, and **ankles**, with each bleeding episode causing **inflammatory** damage to the joint lining and, over repeated episodes, **progressive cartilage destruction** and, ultimately, **chronic arthritis** with significant pain and functional impairment.

A specific joint that has bled repeatedly, termed a **target joint**, becomes progressively more **vulnerable** to further bleeding, creating a genuinely self-perpetuating cycle of recurrent haemorrhage and cumulative joint damage, meaning **prompt, effective treatment** of joint bleeding episodes, together with, where appropriate, **prophylactic factor replacement** to prevent bleeding episodes before they occur, is essential to minimising the long-term development of haemophilic arthropathy.

Fill in the blank: A specific joint that has bled repeatedly is termed a _____ joint, becoming progressively more vulnerable to further bleeding.

5.4.2 development of inhibitors

Inhibitors are **antibodies** that develop against infused clotting factor, most commonly **factor VIII** in haemophilia A, representing a significant treatment complication since they **neutralise** the effect of standard factor replacement therapy, rendering bleeding episodes considerably more difficult to treat effectively using the child's previously established treatment approach.

Inhibitor development should be suspected when a child's bleeding episodes **fail to respond** adequately to standard factor replacement doses that have previously been effective, and confirmed through specific **inhibitor testing**, or the **Bethesda assay**, which quantifies the inhibitor level present, with management of established inhibitors requiring specialist input and often the use of **alternative haemostatic agents** that bypass the specific factor being inhibited.

Fill in the blank: Inhibitor testing, or the _____ assay, quantifies the level of inhibitor present.

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5.4.3 diagnostic evaluation of a suspected bleeding disorder

Diagnostic evaluation of a suspected bleeding disorder begins with a detailed **patient and family history**, including the **pattern**, **severity**, and **triggers** of bleeding episodes, together with a specific **family history** of bleeding disorders, given the inherited nature of the conditions discussed throughout this Series, since a positive family history considerably increases the likelihood of an underlying inherited bleeding disorder in an affected child.

Laboratory testing proceeds through **screening tests**, discussed earlier in this Series, **factor activity levels**, providing specific diagnosis and severity classification, and, increasingly, **genetic testing**, identifying the specific underlying **genetic mutation**, which can be valuable both for confirming diagnosis in genuinely ambiguous cases and for informing **genetic counselling**, discussed in an earlier course, regarding recurrence risk for affected families considering future pregnancies.

Fill in the blank: A positive family history considerably increases the likelihood of an underlying inherited bleeding _____.

Figure 5.4: A caregiver administering factor replacement therapy to a child at home.

Pilot questions 5.4

1. Define haemophilic arthropathy and describe how it develops. (Linked to SLO 5.7)
2. Define a target joint and explain its clinical significance. (Linked to SLO 5.7)

3. Describe inhibitors in haemophilia and when they should be suspected. (Linked to SLO 5.8)
4. Describe the Bethesda assay and its purpose. (Linked to SLO 5.8)
5. Describe the key components of diagnostic evaluation for a suspected bleeding disorder. (Linked to SLO 5.8)

Series Summary

This final Series examined **coagulation and bleeding disorders**, beginning with the mechanism of clotting, from the initial platelet plug of primary haemostasis through the intrinsic, extrinsic, and common pathways of the coagulation cascade to stable fibrin clot formation, and the structured, stepwise evaluation of abnormal coagulation tests using PT, aPTT, and mixing studies to distinguish a factor deficiency from a circulating inhibitor, before turning to the **inherited coagulation disorders**, haemophilia A and B, exploring their epidemiology, X-linked inheritance, and the wide range of clinical manifestations from age at first bleeding through to the many possible sites of bleeding beyond the classically associated joints and muscles.

We then examined **von Willebrand disease and the clinical manifestations of bleeding disorders**, before concluding with **haemophilic arthropathy, the development of inhibitors, and diagnostic evaluation**. Having worked through this Series, and indeed this entire course, you should now be equipped with a comprehensive foundation in the diseases of the blood covered throughout PAE 510, from the haematopoietic system and anaemia through sickle cell disease, thalassaemia, and acute leukaemia, to the coagulation disorders addressed in this final Series.

Glossary of Terms

1. **Primary haemostasis:** the initial formation of a platelet plug at a site of vessel injury.
2. **Coagulation cascade:** the sequential activation of clotting factors, ultimately producing a stable fibrin clot.
3. **Prothrombin time (PT):** a coagulation test primarily assessing the extrinsic and common pathways.
4. **Activated partial thromboplastin time (aPTT):** a coagulation test primarily assessing the intrinsic and common pathways.

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5. **Mixing study:** a test distinguishing a factor deficiency, which corrects, from a circulating inhibitor, which does not.
6. **Haemophilia A:** an X-linked recessive bleeding disorder resulting from factor VIII deficiency.
7. **Haemophilia B:** an X-linked recessive bleeding disorder resulting from factor IX deficiency.
8. **Von Willebrand disease:** the most common inherited bleeding disorder, resulting from deficiency or dysfunction of von Willebrand factor.
9. **Haemarthrosis:** bleeding into a joint, the most common site of spontaneous bleeding in significant haemophilia.
10. **Haemophilic arthropathy:** chronic joint damage resulting from recurrent haemarthrosis.
11. **Target joint:** a joint that has bled repeatedly and becomes progressively more vulnerable to further bleeding.
12. **Inhibitor:** an antibody that develops against infused clotting factor, neutralising the effect of factor replacement therapy.

Concept Check Questions [Series 5]

Objective questions

- Secondary haemostasis, the coagulation cascade, ultimately converts soluble fibrinogen into insoluble _____.
- Haemophilia A results from deficiency of factor _____.
- Von Willebrand disease follows autosomal inheritance, affecting males and females approximately _____.
- A specific joint that has bled repeatedly is termed a _____ joint, becoming progressively more vulnerable to further bleeding.
- Inhibitor testing, or the _____ assay, quantifies the level of inhibitor present.

Short-answer questions

1. Describe what PT and aPTT each primarily assess.
2. Describe how age at first bleeding relates to haemophilia severity.
3. Describe the typical clinical manifestations of von Willebrand disease.
4. Define a target joint and explain its clinical significance.
5. Describe the key components of diagnostic evaluation for a suspected bleeding disorder.

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Long-answer questions

6. Discuss the mechanism of clotting and the evaluation of abnormal coagulation tests. (Linked to SLO 5.1, SLO 5.2)
7. Discuss the definition, epidemiology, and clinical manifestations of haemophilia A and B. (Linked to SLO 5.3, SLO 5.4)
8. Discuss the definition, epidemiology, and clinical manifestations of von Willebrand disease. (Linked to SLO 5.5, SLO 5.6)
9. Discuss haemophilic arthropathy and its development. (Linked to SLO 5.7)
10. Discuss the development of inhibitors and the diagnostic evaluation of a suspected bleeding disorder. (Linked to SLO 5.8)

Answers to Concept Check Questions [Series 5]

Objective questions

11. Fibrin.
12. VIII.
13. Equally.
14. Target.
15. Bethesda.

Short-answer questions

16. PT assesses the extrinsic and common pathways; aPTT assesses the intrinsic and common pathways.
17. Severe haemophilia often presents in infancy, while mild haemophilia may not be apparent until later childhood or adulthood.
18. Mucocutaneous bleeding, including bruising, epistaxis, and heavy menstrual bleeding, are typical manifestations.
19. A target joint has bled repeatedly and becomes progressively more vulnerable to further bleeding, creating a self-perpetuating cycle.
20. Detailed patient and family history, screening coagulation tests, factor activity levels, and genetic testing.

Long-answer questions

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21. **Basic response:** Clotting proceeds from primary haemostasis, forming a platelet plug, through the coagulation cascade to stable fibrin clot formation, assessed using PT and aPTT.

Value-added response: A mixing study distinguishes a factor deficiency, which corrects with normal plasma, from a circulating inhibitor, which does not.

22. **Basic response:** Haemophilia A and B result from factor VIII and factor IX deficiency respectively, following X-linked recessive inheritance and predominantly affecting boys.

Value-added response: Age at first bleeding correlates with severity, and bleeding can occur at sites beyond joints and muscles, including intracranial bleeding, which is particularly serious.

23. **Basic response:** Von Willebrand disease results from deficiency or dysfunction of von Willebrand factor, following autosomal inheritance and typically presenting with mucocutaneous bleeding.

Value-added response: Unlike haemophilia, joint and muscle bleeding are uncommon except in severe type 3 disease, and diagnosis requires specific von Willebrand factor testing.

24. **Basic response:** Haemophilic arthropathy results from recurrent haemarthrosis causing progressive cartilage destruction, with target joints becoming increasingly vulnerable to further bleeding.

Value-added response: Prompt treatment and prophylactic factor replacement help minimise the long-term development of arthropathy.

25. **Basic response:** Inhibitors are antibodies against infused factor, suspected when bleeding fails to respond to previously effective treatment, confirmed by the Bethesda assay.

Value-added response: Diagnostic evaluation combines detailed history, screening and specific laboratory testing, and genetic testing to confirm diagnosis and inform genetic counselling.

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Answers to Pilot Questions [Series 5]

Part 5.1

1. Primary haemostasis forms an initial platelet plug; secondary haemostasis is the coagulation cascade forming stable fibrin.
2. The intrinsic and extrinsic pathways converge on a common pathway, generating thrombin and fibrin.
3. PT assesses the extrinsic and common pathways; aPTT assesses the intrinsic and common pathways.
4. A mixing study distinguishes a factor deficiency, which corrects, from a circulating inhibitor, which does not.
5. Platelet count and function assays being abnormal suggests a platelet disorder rather than a factor deficiency.

Part 5.2

6. Haemophilia A is factor VIII deficiency; haemophilia B is factor IX deficiency.
7. X-linked recessive inheritance predominantly affects boys, since females generally require both X chromosomes affected.
8. Severe haemophilia often presents in infancy, while mild haemophilia may not be apparent until later.
9. Epistaxis, oral bleeding, and gastrointestinal bleeding are sites beyond joints and muscles.
10. It carries a risk of significant, potentially fatal neurological injury.

Part 5.3

11. Von Willebrand disease results from deficiency or dysfunction of von Willebrand factor, essential for platelet adhesion.
12. Von Willebrand disease is autosomal, affecting males and females equally, unlike X-linked haemophilia.
13. Mucocutaneous bleeding, including bruising, epistaxis, and menorrhagia, are typical manifestations.
14. Von Willebrand factor primarily affects platelet function rather than the coagulation cascade itself.
15. Von Willebrand factor antigen and activity assays, plus factor VIII level, distinguish the two conditions.

Part 5.4

1. Recurrent haemarthrosis causes progressive cartilage destruction and chronic joint damage.
2. A target joint has bled repeatedly and becomes progressively more vulnerable to further bleeding.

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3. Inhibitors are antibodies against infused factor, suspected when bleeding fails to respond to standard treatment.
4. The Bethesda assay quantifies the level of inhibitor present.
5. Patient and family history, screening tests, factor levels, and genetic testing are key components.

References and Attributions [Series 5]

1. Kliegman, R. M., St Geme, J. W., Blum, N. J., Shah, S. S., Tasker, R. C. and Wilson, K. M. (2020). Nelson Textbook of Pediatrics (21st ed.). Elsevier.
2. Srivastava, A. et al. (2020). WFH guidelines for the management of hemophilia (3rd ed.). Haemophilia, 26(S6), 1 to 158.
3. Nichols, W. L. et al. (2008). von Willebrand disease (VWD): evidence-based diagnosis and management guidelines. Haemophilia, 14(2), 171 to 232.
4. Berntorp, E. and Shapiro, A. D. (2012). Modern haemophilia care. The Lancet, 379(9824), 1447 to 1456.

Figures, Plates, Tables, and Boxes

1. Figure 5.1: A simplified overview of the coagulation cascade. AI-generated using the prompt: "Create a professional educational diagram titled The Coagulation Cascade, showing the intrinsic and extrinsic pathways converging on a common pathway leading to fibrin clot formation. Clean clinical educational diagram style, single illustration, no text-heavy panels."
2. Figure 5.2: A clinician gently examining a child's swollen knee joint. AI-generated using the prompt: "A calm, respectful clinical illustration of a clinician gently examining a child's knee joint on an examination couch, with a caregiver present. Single clean medical illustration, soft clinical lighting, no text overlays, no multiple panels, sensitive and accurate depiction, no graphic detail."
3. Table 5.3: Comparing haemophilia A, haemophilia B, and von Willebrand disease. AI-generated using the prompt: "Create a clean reference table titled Comparing Haemophilia and Von Willebrand Disease, listing feature, haemophilia A/B, and von Willebrand disease. Simple clinical reference table style with outside border."
4. Figure 5.4: A caregiver administering factor replacement therapy to a child at home. AI-generated using the prompt: "A warm, respectful clinical illustration of a caregiver carefully administering a small intravenous infusion to a calm child at a clean home

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treatment table. Single clean medical illustration, soft warm lighting, no text overlays, no multiple panels, respectful and accurate depiction, no graphic medical detail."

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