5.11 Haematological disorders

5.11.A Anaemia

80X 5.11.A.1 Minimum standards
- Haemoglobin estimation facility.
- Blood transfusion.
- Drugs:
  - Haematinic agents: iron, folic acid.
  - Antihelmintic drugs: mebendazole, albendazole, pyrantel.
  - Antimalarial drugs.
- Genetic:
  - haemoglobinopathies (HbSS, thalassaemias)
  - glucose-6-phosphate dehydrogenase deficiency.
- Malignancy:
  - leukaemia
  - other types of malignancy.

Introduction

Definition of anaemia
Table 5.11.A.1 gives the World Health Organization (WHO) definition of haemoglobin concentrations below which anaemia is present at sea level.

| TABLE 5.11.A.1 Lower limit of normal haemoglobin concentrations |
|-------------|------------------|------------------|
| Age of child | Haemoglobin concentration (grams/dL) | Haematocrit (%) |
| 6 months to 4 years | 11 | 33 |
| 5–11 years | 11.5 | 34 |
| 12–14 years | 12 | 36 |

The problem of anaemia
- It is widespread in disadvantaged countries.
- It is common in young children under 5 years of age.
- More than one cause of anaemia is usually found in each anaemic child.
- Genetic causes of anaemia are common.
- It has significant deleterious effects on growth, health and development.

Main causes of childhood anaemia in resource-limited settings
- Low birth weight:
  - results in low iron and folate stores (0–2 years age group).
- Dietary:
  - diets tend to be low in iron
  - delayed weaning
  - poor maternal iron intake in breastfed infants
  - weaning on to non-fortified cow’s milk.
- Infections:
  - malaria (haemolysis)
  - hookworm (Ancylostoma duodenale and Necator americanus) (see Section 6.3.C)
  - whipworm (Trichuris species)
  - congenital infection (CMV, rubella)
  - HIV.
- Genetic:
  - haemoglobinopathies (HbSS, thalassaemias)
  - glucose-6-phosphate dehydrogenase deficiency.
- Malignancy:
  - leukaemia
  - other types of malignancy.

The child with iron-deficiency anaemia

Clinical features of anaemia
- Often asymptomatic until haemoglobin concentration is < 8 grams/dL.
- Breathless on exertion when haemoglobin concentration is < 6 grams/dL.
- Pallor:
  - nail beds (the best site)
  - palmar creases
  - mucous membranes.
- Suboptimal growth, delayed puberty.
- Congestive heart failure.

Investigations
The tests in bold listed below should always be done before a transfusion (to exclude causes other than iron deficiency):
- Haemoglobin concentration (cyanmethaemoglobin method or HemoCue B).
- Haematocrit or PCV (microcentrifuge).
- Blood film:
  - malarial parasites
  - red blood cells: hypochromia, microcytosis, anisocytosis target cells (iron deficiency, thalassaemia)
  - sickle cells
  - macrocytes (folate, vitamin B12 deficiency)
  - white blood cells: hypersegmented neutrophils (folate, vitamin B12 deficiency).
- Mean corpuscular volume (MCV) and reticulocyte count as the two principal criteria for the initial classification of anaemia.
- Haemoglobin electrophoresis: sickle cell, thalassaemia.
- Stool test: parasitic ova, blood.

Management of anaemia
- Establish the diagnosis, cause and severity of iron-deficiency anaemia.
- Treat malaria (oral route) (see malaria guidelines in Section 6.3.A.d).
- Give empirical antihelmintic therapy in endemic areas (see Section 6.3.C).
- Give haematinics:
Blood transfusion (see also Section 1.7)

Only undertake this if it is essential.

- Warm the blood first under the mother’s clothing, in contact with the skin, especially if it is to be given to an infant.
- Do not use blood that has been stored for more than 4 hours of removal from the fridge.
- Check that the blood is the correct group and that the patient’s name and number are identical on both label and form.
- Use a needle/catheter that is 22 gauge or larger, to prevent clotting.
- If there are signs of heart failure, give 1 mg/kg of furosemide IV at the start of transfusion unless hypovolaemic shock is also present.
- Record the baseline temperature and pulse rate.
- Each transfused unit must be completely used within 4 hours of removal from the fridge.
- Ideally, in infants or those with heart failure, control the flow with an in-line burette.
- Record observations every 30 minutes, looking for heart failure (shortness of breath) and transfusion reactions (fever and malaise).

Indications for transfusion

- Severe anaemia (haemoglobin concentration < 4 grams/dL).
- Impending or overt cardiac failure if the haemoglobin concentration is < 6 grams/dL.
- Hyperparasitaemia in malaria if the haemoglobin concentration is < 6 grams/dL.
- Children in congestive cardiac failure due to severe anaemia (consider partial exchange).
- Acute severe blood loss with shock that is unresponsive to 40 mL/kg of volume resuscitation given in 10 mL/kg aliquots, or where massive haemorrhage is continuing.

Volume of transfusion

- Use packed red cells where possible.
- Give whole blood: 20 mL/kg or:
  - required volume (mL) = weight (kg) × desired rise in haemoglobin (grams/dL)
  - Packed red cells: 10–15 mL/kg or
  - required volume (mL) = weight (kg) × 3 × desired rise in haemoglobin (grams/dL).
- In all cases, rate = 5–10 mL/kg/hour (usually over 3–4 hours unless shocked).
- Consider giving furosemide 1 mg/kg IV immediately in advance of transfusion to avoid precipitating cardiac failure (unless there is hypovolaemic shock) in cases of very severe anaemia.

Treatment of severely anaemic child with septic shock

The first priority will still be to call for help, and manage the airway, followed by breathing and then the circulation.

Call for help.

Airway

Assess the airway by the simple technique of asking the child ‘Are you all right?’

Any vocalisation, such as a reply or crying, indicates an open airway and some ventilation. In the absence of a response, formally open the airway with a head tilt/chin lift or a jaw thrust manoeuvre (see Section 1.12), and assess the breathing by looking, listening and feeling for its presence.

Breathing

All children with suspected shock must receive high-flow oxygen.

If possible, this should be given through a mask with a reservoir to achieve the higher concentrations.

In the absence of spontaneous breathing, give assisted ventilation with a bag-mask (see Section 1.13).

Circulation

Intravenous access with a short wide-bore venous cannula, or placement of an intra-osseous line (see Section 8.4.B), is vital. Severely anaemic children cannot tolerate rapid boluses of fluid as they are likely to be in heart failure and may also be malnourished. The fluid they need most is blood. When transfusing severely anaemic children we usually give packed cells, but in suspected septic shock, fresh whole blood has the following advantages:

**Iron medication**

**TABLE 5.11.A.2. Dosage of iron medications for iron-deficiency anaemia in childhood**

<table>
<thead>
<tr>
<th>Age or weight (6 mg/kg elemental iron)</th>
<th>Ferrous sulphate 200 mg (60 mg/kg elemental iron)</th>
<th>Ferrous fumarate 60 mg per 5 mL (12 mg elemental iron/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2–4 months (4–6 kg)</td>
<td>–</td>
<td>2 mL</td>
</tr>
<tr>
<td>4–12 months (6–10 kg)</td>
<td>–</td>
<td>2.5 mL</td>
</tr>
<tr>
<td>1–3 years (10–14 kg)</td>
<td>½ tablet</td>
<td>4 mL</td>
</tr>
<tr>
<td>3–5 years (14–19 kg)</td>
<td>½ tablet</td>
<td>5.5 mL</td>
</tr>
<tr>
<td>&gt; 5 years (&gt; 19 kg)</td>
<td>1 tablet</td>
<td>–</td>
</tr>
</tbody>
</table>

- Premature infants should start prophylactic iron (5 mg/day) from 4–6 weeks of age until mixed feeding is established.
- Treatment with iron injections may increase mortality (meningitis) and morbidity (respiratory infections, malaria) in infants.

**Antihelmintic drugs (see Section 6.3.C)**

- Albendazole (the drug of choice if available):
  - 400 mg as a single dose (200 mg if child is less than 2 years of age).
- Mebendazole (most effective against hookworm and whipworm):
  - For children over 1 year of age, 250 mg as a single dose (or 500 mg if the child is over 2 years). May be repeated after 2 or 3 weeks.

- folic acid: up to 5 years of age, 2.5 mg once daily; above 5 years, 5 mg once daily
- iron (see Table 5.11.A.2).
should be added to cover anaerobic organisms. In suspected intra-abdominal sepsis, metronidazole suspect(e.g. if there are boils or a known abscess). Of gentamicin and a penicillin would be advisable. IV. Consider partial exchange transfusion. Give antibiotics but it should be packed, or if the child is in heart failure, fresh whole blood is not available, give stored blood, Ringer-lactate solution, and then reassess the child. If at 20 mL/kg, give 10 mL/kg of Hartmann’s solution or While awaiting the blood, which should be transfused at 20 mL/kg, give 10 mL/kg of Hartmann’s solution or Ringer-lactate solution, and then reassess the child. If fresh whole blood is not available, give stored blood, but it should be packed, or if the child is in heart failure, consider partial exchange transfusion. Give antibiotics.

**5.11.B Sickle-cell disease**

### 5.11.B.1 Minimum standards
- Facility for haemoglobin estimation and electrophoresis.
- Analgesia: paracetamol, NSAIDs, opiates.
- Blood transfusion.
- Oxygen.
- Penicillin prophylaxis.
- Pneumococcal (PCV and Pneumovax), hepatitis B and Haemophilus influenzae vaccines.
- Oral rehydration solution (ORS).
- Antimalarial drugs.
- Iron chelation: desferrioxamine, deferasirox or deferiprone.

### Prognosis
In well-resourced countries, the life expectancy of individuals with sickle-cell disease has been continuously improving, and historic data suggest that it is now well beyond the fifth decade of life, with the overwhelming majority of children surviving into adulthood. The pattern of the disease and its complications is also changing in well-resourced countries, with a shift from being a fatal paediatric illness to a chronic disease associated with episodic painful crises and progressive deterioration and organ damage in later life.

However, in resource-limited countries, sickle-cell disease is still associated with a very high mortality and morbidity, particularly during childhood. Sickle-cell disease remains a major cause of mortality in children under 5 years of age, with estimates as high as 50–90% in some rural areas of Africa. The major causes of death are infection, especially malaria and invasive pneumococcal infection, and severe profound anaemia. For those who live with the condition, sickle-cell disease is the cause of a great burden of suffering for those affected and their families.

### Introduction
Sickle-cell disease is a recessively inherited disorder of haemoglobin synthesis. It occurs due to a point mutation at position 6 on chromosome 11 resulting in the substitution of valine for glutamic acid on the beta-globin chain. Those affected inherit two copies of the altered beta-globin gene and are therefore homozygous for HbS (HbSS). Alternatively, a single HbS may be inherited with another beta-chain mutation such as beta thalassaemia (HbSB+ or HbSB+) or HbC (HbSC).

A child who inherits two of the same trait genes, one from each parent, will be born with the disease. However, a child of two carriers has only a 25% chance of receiving two trait genes and developing the disease, and a 50% chance of being a carrier. Most carriers lead completely normal healthy lives.

The HbS mutation is common. It is estimated that up to 5% of the world population are healthy carriers of sickle gene, and this can rise to 25% in West Africans. Although the HbS mutation is most common in Africa, it occurs widely across many groups. It is estimated that each year 300,000 children are born with homozygous sickle-cell disease worldwide.

### Pathogenesis
The clinical manifestations of sickle-cell disease are due to vaso-occlusion and chronic haemolysis, often in response to triggers such as illness, hypoxia or dehydration.

The presence of abnormal HbS leads to the production of a haemoglobin tetramer (x2/β2) that is poorly soluble when deoxygenated, and polymerises readily into a rope-like fibre within the red blood cell. This leads to red cell distortion into the classic sickle shape, a reduction in red cell deformability, and red cell destruction through haemolysis, with consequent shortening of the red cell lifespan, and anaemia.

Vaso-occlusive episodes occur when blood vessels become clogged with sickle cells, causing pain, tissue oxygen deprivation and organ damage alongside altered cell adhesion and abnormal erythrocyte-endothelium...
interaction. In addition to vaso-occlusion, there is a chronic intravascular haemolysis leading to a compensated anaemia with functional nitric oxide (NO) dysregulation with chronic vascular endothelial damage. This means that polymerisation alone does not account for the pathophysiology of sickle-cell disease. Changes in red cell membrane structure and function, disordered cell volume control, and increased adherence to vascular endothelium also play an important role.

Clinical presentations
In children, the most common presentation of sickle-cell disease is with an acute crisis, usually as a painful episode. More recently, as more countries adopt a newborn screening programme, children may be diagnosed with sickle-cell disease before their first crisis.

Presentation includes the following:
- newborn screening
- a painful vaso-occlusive crisis
- infection and overwhelming sepsis
- severe anaemia
- acute chest syndrome (ACS)
- stroke.

Newborn screening programmes
The goal of any newborn screening programme for sickle-cell disease is to identify affected children as early as possible and thus reduce the morbidity and mortality of sickle-cell disease, especially from bacterial infections, through the early introduction of antibiotic prophylaxis. In well-resourced countries, the preferred option is the universal screening programme rather than selective screening of high-risk infants only.

Methodology of newborn screening
The methodology of screening can vary, but in principle involves the collection of a dried neonatal blood spot sample for transport and testing by haemoglobin electrophoresis, thin-layer isoelectric focusing, or HPLC. A second confirmatory test may be taken 1–2 weeks later for repeat testing by isoelectric focusing, HPLC, PCR techniques or DNA analysis by a reference laboratory. The tests used must have the capability to distinguish between HbF, HbS, HbA and HbC. As several of the sickle-cell disease syndromes can have similar results on electrophoresis or isoelectric focusing, examining the peripheral blood smear remains useful.

- Haemoglobin electrophoresis is the standard method for separating HbS from other haemoglobin variants.
- Thin-layer isoelectric focusing is a more complicated technique, which can distinguish some haemoglobins not seen on standard electrophoresis, as the bands are more sharply seen.
- High-performance liquid chromatography (HPLC) is a very precise and fully automated technique for identification and quantification of haemoglobins.
- Sickle solubility test. A positive sickle solubility test will detect the presence of HbS but will not identify whether the person is a carrier or has sickle-cell disease.

Results and patterns in the newborn period

<table>
<thead>
<tr>
<th>Finding</th>
<th>Pattern</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbF and HbA</td>
<td>FA</td>
<td>Normal baby</td>
</tr>
<tr>
<td>HbF, HbA and HbS</td>
<td>FAS</td>
<td>Sickle-cell trait</td>
</tr>
<tr>
<td>HbF, HbS and HbA</td>
<td>FSA</td>
<td>Sickle-cell beta thalassaemia</td>
</tr>
<tr>
<td>HbF and HbA</td>
<td>FS</td>
<td>Sickle-cell disease (HbSS or HbC beta thalassaemia)</td>
</tr>
</tbody>
</table>

In countries with limited resources, the combination of haemoglobin electrophoresis and a sickle solubility test will confirm the diagnosis of sickle-cell disease for most older children once the beta-chain production is fully developed beyond the newborn period.

Diagnosis
- Haemoglobin electrophoresis demonstrates the absence of HbA and either HbS (SS) or HbS and another haemoglobin such as HbC (SC).
- A positive sickle solubility test denotes the presence of sickle haemoglobin, but does not indicate whether the person is a carrier (Hb AS) or Hb SS.
- A full blood count shows severe (SS) to mild anaemia (SC).
- Examination of the peripheral blood shows sickled erythrocytes.

General principles of the management of an acute sickle crisis
Most children do not develop symptomatic disease in the first few months of life until adult haemoglobin production is established. The principles of managing any acute crisis are based on searching for, and actively treating, any precipitants (see Table 5.11.B.1). Any child presenting with an acute crisis should be considered at risk of sudden and life-threatening deterioration, and clinicians are advised to have an anticipatory approach.

Crisis precipitants include the following:
- infection
- dehydration
- extremes of temperature.

<table>
<thead>
<tr>
<th>Problem/precipitant</th>
<th>Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever and/or evidence of infection</td>
<td>Treatment dose of appropriate antibiotics</td>
</tr>
<tr>
<td>Child should be considered functionally asplenic and immunocompromised</td>
<td>Use of appropriate antimalarial drugs</td>
</tr>
<tr>
<td></td>
<td>Use of antipyretic drugs</td>
</tr>
<tr>
<td>Dehydration</td>
<td>Rehydration</td>
</tr>
<tr>
<td>Extremes of temperature and cold</td>
<td>Warmth and rest</td>
</tr>
</tbody>
</table>

Clinicians should be alert to signs suggesting the possibility of a sudden acute deterioration during a crisis. The following trigger list may be helpful for identifying children at increased risk of sudden or rapid deterioration:
- uncontrolled pain despite strong opiate analgesia
- increasing pallor, breathlessness or exhaustion
- marked fever (> 38°C)
- significant tachycardia, tachypnoea or hypotension
International Maternal & Child Health Care

- **Table 5.11.B.2** Management of an uncomplicated acute painful episode

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics and antimalarial drugs (see later)</td>
<td>Any fever should prompt the search for infection and active treatment. Oral antibiotic dosages should be administered at higher dose as per the immunocompromised child</td>
</tr>
<tr>
<td>Hydration</td>
<td>Dehydration occurs readily in children with sickle-cell disease, due to impairment of renal concentrating power. Fluids should be given at 150% maintenance (orally or IV)</td>
</tr>
<tr>
<td>Analgesia</td>
<td>Assess pain using an age-appropriate visual analogue scale (VAS) (see below). Use the VAS to assess response to analgesia with the goal of minimal pain allowing successful mobilisation. Manage pain with prompt administration of the most appropriate choice and dose from the analgesic ladder. Take into account previous drugs and dosages given at home. Children in severe pain may need early use of opiates orally or IV. <strong>Do not use pethidine</strong></td>
</tr>
<tr>
<td>Severe anaemia</td>
<td>Consider transfusion if the haemoglobin concentration is very low (e.g. &lt; 5 grams/dL) or has fallen by &gt; 2 grams/dL from a known baseline level, or the child is clearly clinically compromised</td>
</tr>
<tr>
<td>Oxygen</td>
<td>Provide oxygen if the saturations in air are below 95%. Falling saturations in air or a rising oxygen requirement should prompt re-evaluation and the search for an emerging complication of the crisis</td>
</tr>
</tbody>
</table>

- chest pain with or without signs of consolidation
- desaturation in air or a rising oxygen requirement to maintain saturations above 94%
- abdominal pain with or without distension
- severe diarrhoea and vomiting
- sudden profound pallor with or without jaundice
- parents reporting an enlarged spleen
- any abnormal neurological signs, including painless loss of function, headache and fitting.

**The acute painful sickle episode**
- This is also referred to as a painful or vaso-occlusive crisis, and is the most common presentation of sickle-cell disease in childhood, resulting from blockage of small vessels. The mainstay of treatment is effective and prompt pain control (see Section 1.15), alongside management of any precipitants.
- Approximately 40% of children with sickle-cell disease will have an episode of ‘hand–foot syndrome’ or dactylitis during early childhood, and this number rises to 50% of children under 2 years old who go on to develop symptomatic disease. Typically children present with vaso-occlusion and infarction of the metacarpals or metatarsals, which is evident as an overlying soft tissue reaction with swelling, redness and marked tenderness affecting either one or all of the hands and feet.
- By later childhood the most common sites of bony sickle-related pain include the long bones, thighs, hips, spine, ribs, shoulders and upper humerus, as well as the bones of the cranium, joints and muscles.

**Hydration and fluids in sickle-cell disease**
Dehydration occurs readily in children with sickle-cell disease, due to impairment of renal concentrating power.

**Diarrhoea and vomiting** are thus of particular concern. Rehydration calculations are therefore based on the assumption that children with sickle-cell disease have a higher fluid requirement than unaffected children.

**Table 5.11.B.3** Fluids in sickle-cell crises

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Fluids (mL/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First 10 kg</td>
<td>150</td>
</tr>
<tr>
<td>11–20 kg</td>
<td>75</td>
</tr>
<tr>
<td>Subsequent kg over 20</td>
<td>30</td>
</tr>
</tbody>
</table>

**Infection**
Infection is a common precipitating factor in painful or other types of sickle crises. All children with sickle-cell disease (regardless of type) should be considered to be immunocompromised.

**Bacteria**
Patients with sickle-cell disease are immunodeficient due to functional asplenia.

Functional asplenia occurs irrespective of spleen size in sickle-cell disease well before the age of 1 year in the majority of sufferers. Clinicians should therefore consider all patients to have increased susceptibility to infection,
Section 5.11

particularly with the encapsulated organisms listed below, all of which can cause life-threatening sepsis:
- *Pneumococcus*
- *Salmonella* species
- *Haemophilus*.

Any suspected bacterial infection should be managed with prompt institution of IV antibiotics to cover these organisms. Suggested choices are listed in Table 5.11.B 4 (note that these may vary according to region and local sensitivities). Persistent localised bone pain, swelling or fever should raise suspicion of osteomyelitis, which may require surgical treatment, and 6 weeks of antibiotic therapy.

### Specific infections

#### Osteomyelitis
This infection can be very difficult to distinguish from vaso-occlusive bone pain, which is commonly associated with localised swelling and joint effusions. Osteomyelitis should be considered in any child with persistent and localised pain who is systemically unwell.

The diagnosis of osteomyelitis in sickle-cell disease is more likely in the presence of:
- swinging pyrexia (fevers may not be persistent)
- severe systemic upset
- unusual swelling or pain
- positive blood cultures.

Few if any investigations are absolutely conclusive in making the diagnosis. Treatment is complex and may involve surgical intervention (rare) and a prolonged course of IV antibiotics (6 weeks). The oral route can be used to complete a course of antibiotics once the child is systemically well (i.e. fevers have settled) and any tests such as CRP have returned to normal. Antibiotic choices are broad, but may include the following:
- first line: IV ceftiraxone and clindamycin (consider flucloxacillin if no clindamycin available).
- second line: IV clindamycin.
- alternatives: meropenem, imipenem or ciprofloxacin.

#### Malaria
Studies confirm that sickle-cell trait (HbAS) is protective against severe complicated malaria, including cerebral malaria and severe anaemia related to malaria in children. By contrast, malarial infection in homozygous sickle-cell disease (HbSS) can be rapidly fatal, and requires prompt recognition and urgent treatment. Although children with sickle-cell disease are not at greater risk of complicated malaria infection, once infected they have a higher mortality, especially related to severe anaemia. In addition to drug treatment, transfusion may be required. Prevention should be emphasised (see Section 6.3.A.d).

#### Meningitis
Bacterial meningitis is more common in children with sickle-cell disease than in unaffected children, especially in the youngest age groups. The most frequent infecting organism is pneumococcus. Clinicians should maintain a high index of suspicion for this complication and treat it empirically.

#### Gastroenteritis/diarrhoea
Severe diarrhoea may precipitate sickling and crisis, including stroke. Hydration must therefore be maintained vigorously using ORS or IV fluid where necessary. Education relating to hand hygiene, clean water and prompt treatment should be given.

Children who are systemically unwell with a diarrhoeal illness may also be at higher risk of sepsis related to Gram-negative infection, and may require IV antibiotic treatment in addition to vigorous rehydration under such circumstances.

Children with diarrhoea who are also on the iron chelation medication desferrioxamine are at high risk of *Yersinia* or *Klebsiella* infection, and require prompt treatment with ciprofloxacin, alongside discontinuation of the desferrioxamine until they recover.

#### Viral infection
Children with sickle-cell disease are at particular risk of profound anaemia secondary to parvovirus B19 infection, which may trigger an aplastic crisis.

### TABLE 5.11.B.4 Antibiotic choices in sickle-cell crises

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rationale and comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Augmentin</td>
<td>Good activity against <em>Pneumococcus</em></td>
</tr>
<tr>
<td></td>
<td><em>Haemophilus</em> resistance is low</td>
</tr>
<tr>
<td></td>
<td>Suitable for use with clarithromycin for pneumonia</td>
</tr>
<tr>
<td></td>
<td>Does not mask <em>Salmonella</em> osteomyelitis</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Good activity against <em>Haemophilus</em></td>
</tr>
<tr>
<td></td>
<td>Pneumococcal resistance is low</td>
</tr>
<tr>
<td></td>
<td>Suitable for use with augmentin for pneumonia</td>
</tr>
<tr>
<td></td>
<td>Does not mask <em>Salmonella</em> osteomyelitis</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>Suitable for severe pneumonia with or without clarithromycin</td>
</tr>
<tr>
<td></td>
<td>Masks <em>Salmonella</em> osteomyelitis</td>
</tr>
<tr>
<td>Ceftriaxone and other third-</td>
<td>For suspected sepsis</td>
</tr>
<tr>
<td>generation cephalosporins</td>
<td>First-line treatment for suspected osteomyelitis (with clindamycin)</td>
</tr>
<tr>
<td></td>
<td>Second-line treatment for <em>Yersinia</em> if there is glucose-6-phosphate dehydrogenase (G6PD) deficiency</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>For use in patients on desferrioxamine with suspected <em>Yersinia</em> infection</td>
</tr>
<tr>
<td></td>
<td><strong>Stop iron chelation if suspected</strong></td>
</tr>
</tbody>
</table>

June 2015 © 2014 Maternal and Childhealth Advocacy International MCAI
Children with sickle-cell disease should also be protected from blood-borne viral infection, specifically HIV and hepatitis B infection. Routine immunisation against HBV must be undertaken in view of the probability that a child with sickle-cell disease may at some stage be a recipient of blood products or be started on a long-term transfusion programme.

**Severe anaemia in sickle-cell disease**

Children with sickle-cell disease are known to have a compensated anaemia, but are also at risk of events that may precipitate a sudden and potentially fatal drop in their haemoglobin levels. The main conditions to consider are as follows:
- acute sequestration events
- aplastic crisis
- infection with malaria.

**Acute sequestration events**

Sequestration events are characterised by pooling of red cells in an organ, most commonly the spleen, lungs and liver, and are associated with a sudden and potentially life-threatening fall in haemoglobin level, with shock and collapse alongside rapid (and often painful) expansion of the organ affected.

Sequestration events are often precipitated by infection or sepsis that requires vigorous antibiotic treatment. There is a high mortality. Any child who appears to be deteriorating during an acute painful crisis should be re-examined to exclude undiagnosed sequestration.

Treatment includes administration of antibiotics to manage any precipitating infection, and blood transfusion in children with cardiovascular compromise, or who have a haemoglobin level of < 5 grams/dL, or where there has been a sharp fall in haemoglobin level by > 2 grams/dL.

Urgent blood transfusion in children with sickle-cell disease is not uncommon, but does carry some risks. Clinicians should be cautious about over-transfusing beyond a target of 8 grams/dL (usually a maximum of 20 mL/kg) or at a higher rate than 5 mL/kg/hour, due to the risks of hyperviscosity associated with a sudden increase in haematocrit.

**Aplastic crisis**

Transient red cell aplasia caused by parvovirus B19 (with an associated reticulocytopenia) can lead to a sudden severe worsening of the patient’s anaemia. Ask about any recent viral prodromal illness, but classical erythema infectiosum (‘slapped cheek syndrome’) is uncommon. Second infections with parovirus are extremely rare, as immunity to parovirus is lifelong. Review other family members with sickle-cell disease, because they too may be infected with parovirus.

The differential diagnosis of a sudden fall in haemoglobin level includes sequestration crisis, and therefore abdominal palpation is mandatory in any acutely anaemic child to exclude this diagnosis.

Treatment includes use of blood transfusion in children who are cardiovascularly compromised, if the haemoglobin level is < 5 grams/dL, or if there has been a sharp fall in haemoglobin level by > 2 grams/dL.

See above for the risks of urgent blood transfusion.

**Acute chest syndrome (ACS)**

This is a major cause of morbidity and mortality in sickle-cell disease. It is strictly defined by evidence of new pulmonary infiltrates involving at least one complete lung segment consistent with the presence of alveolar consolidation, but excluding atelectasis. Clinically, patients have chest pain, a temperature of more than 38.5°C, tachypnoea, wheezing, or cough usually associated with arterial desaturation.

It is important to recognise that patients can be in the process of developing ACS and be severely ill before these strict criteria are met. Signs of lung consolidation, usually bilateral, generally start at the bases, but may be unilateral and impossible to distinguish from infection.

Chest X-ray signs may lag or be misleading. Early treatment may prevent further deterioration, so prompt action on clinical suspicion is essential.

Acute sickle chest syndrome is likely to be multifactorial in origin, with infection, thrombosis of pulmonary arteries and fat embolism all resulting in potentially similar clinical patterns. The diagnosis of this potentially life-threatening crisis must therefore be considered if there is a combination of desaturation in air, tachypnoea, pain and a high fever.

**Management of ACS**

- Anticipatory clinical approach.
- Effective analgesia to prevent basal atelectasis.
- Careful observations, including regular pulse oximetry.
- Chest X-ray:
  - upper lobe consolidation without basal changes suggests pneumonia rather than ACS.
  - Start dual IV antibiotics: treat pneumonia aggressively as it is often clinically indistinguishable.
  - High-flow oxygen.
  - Hyperhydration.
  - Arterial gases in air if the oxygen requirement is rising.
  - CPAP (if available) and saturations falling to the low 90s in air.
  - Exchange transfusion (if available) if PaO₂ in air is < 8 kPa or the child is deteriorating.
  - May require ventilation.
  - There is no role for diuretics.

**Neurological involvement in sickle-cell disease**

Sickle-cell disease is associated with several central nervous system complications and events, as outlined below. The most significant event is stroke, mainly infarction. The treatment approach is outlined in the next section.

**Neurological complications of sickle-cell disease**

- Infection: meningitis and malaria.
- Stroke: ischaemic stroke, subarachnoid haemorrhage and transient ischaemic attacks (TIAs).
- Silent infarcts.
- Convulsions.
- Neurocognitive decline: reduction in IQ, attention deficits.

**Stroke in sickle-cell disease**

Stroke is a potentially devastating complication of sickle-cell disease, most commonly occurring in (but not limited to) individuals with homozygous disease (HbSS). The
most common event is infarctive stroke, but haemorrhagic stroke can also occur with increasing frequency as children progress towards adulthood. Stroke can occur in any age group, but is most common in children under 10 years.

Predictive factors for stroke include a history of transient ischaemic attacks, a recent episode of acute chest syndrome, hypertension, or a low haemoglobin F percentage and/or low baseline haemoglobin levels. Any child with sickle-cell disease can have a stroke (even if they are apparently not ‘high risk’).

Precipitating factors for stroke include a recent history of fever, infection, dehydration and acute chest syndrome. However, some children will have a stroke without any identifiable precipitating event or risk factor.

Symptoms and signs of stroke can be broad, and range from the ‘classic’ presentation of a focal neurological deficit such as a hemiplegia (painless loss of function) to behavioural changes, severe headache, altered consciousness, convulsions or coma.

Historic data from the USA suggest that 11% of children with sickle-cell disease have a stroke episode by the age of 20 years. More recent data from well-resourced countries speculate that this figure is coming down with the advent of transcranial Doppler (TCD) screening to identify children at high risk of stroke and the aggressive use of regular long-term blood transfusion programmes as a primary prevention strategy.

Stroke is a major cause of mortality and morbidity in sickle-cell disease. On the long-term transfusion programme the risk of stroke falls to approximately 10%.

**Treatment of acute stroke**

Prompt treatment of an ischaemic stroke can potentially arrest a stroke in evolution. Children with a suspected stroke require:

- rehydration with fluids
- antibiotic treatment of any suspected infection, including malaria or meningitis
- treatment of any convulsions (see Section 5.16.D and E)
- exchange transfusion to reduce the circulating sickle percentage as rapidly as possible to less than 25%; this procedure is usually performed in a staged manner over 24–48 hours
- there is no role for aspirin in stroke related to sickle-cell disease.

In the absence of accessible exchange transfusion, it may be reasonable to consider a cautious top-up blood transfusion to maximise oxygen-carrying capacity and reduce the HbS percentage through a dilutional effect. Extreme care must be taken to avoid over-transfusion and the risk associated with increasing blood viscosity thus further contributing to the stroke. In either situation, the haematocrit should not exceed 0.4.

Most children make a good motor recovery from an initial stroke, but may be left with intellectual defects. If untreated, most of these children will suffer a second cerebrovascular accident, usually within 2–3 years of the first episode, as a result of which many of them will die and most will be seriously impaired. Transient ischaemic attacks may presage a more major event.

**Secondary prevention of stroke**

Because of the risk of a subsequent stroke, all children should be considered for the long-term transfusion programme to reduce their recurrence risk (although the risk is never fully eradicated). Most children require a top-up transfusion every 4 weeks for life, and this is a heavy burden for patients and their families.

The treatment goals of secondary prevention of stroke using the transfusion programme are as follows:

- to reduce and then maintain the pre-transfusion HbS% at below 30%
- to maintain the pre-transfusion haemoglobin level in the range 9–9.5 grams/dl
- in order to achieve these goals, the post-transfusion target is usually set no higher than 12.5 grams/dl
- to monitor and treat iron overload.

**Note that there is no role for co-administration of desferrioxamine during transfusions.**

**Risks of the long-term transfusion programme**

- transmission of bloodborne viral infection
- allo-immunisation to foreign red cell antigens
- iron overload.

In more well-resourced settings, some children may be able to receive alternatives to long-term top-up transfusions as outlined above. These alternatives include the use of manual or automated exchange transfusions to maintain a low HbS% without incurring iron overload states. These children may be able to go for longer periods between blood transfusions, although the risk of exposure to blood does not change.

Unfortunately, recent trials have indicated that there is little role for drugs such as hydroxyurea as an effective alternative to transfusion in the primary or secondary prevention of stroke.

**Transcranial Doppler (TCD) and primary prevention of stroke**

The use of annual TCD monitoring in more well-resourced countries is having a significant impact on the reduction of the incidence of stroke events in children with no prior apparent risk of stroke, and is now a routine screening tool in sickle-cell disease care.

Children are identified as at high risk of stroke if the recorded velocities on TCD persistently exceed 200 cm/second. The stroke risk can be significantly reduced from 40% in high-risk patients through the use of the long-term transfusion programme as outlined above. Unfortunately, once started, there is little evidence as to whether transfusions could ever be discontinued, as the data suggest that once transfusions are stopped the original stroke risk rapidly returns.

In areas where access to TCD machines and trained technicians may be limited, use of TCD may not be possible, particularly when weighing up the risks and benefits of the long-term transfusion programme.

**Prevention programmes**

**Iron overload and transfusions**

Children who are exposed to multiple and regular blood transfusions are likely to develop iron overload. The most widely available iron-chelating agent is desferrioxamine (Desferal), which is administered as a subcutaneous dose.
Splenectomy is not routinely undertaken in children with sickle-cell disease, although it does have a role in allowing the baseline haemoglobin to rise by approximately 2 grams/dL in children with evidence of hypersplenism. Splenectomy may also be indicated in children who have had an episode of life-threatening splenic sequestration.

As with all surgical procedures in sickle-cell disease, careful risk assessment should be undertaken before a planned procedure involving a general anaesthetic, due to the risk of post-operative sickling secondary to hypoxaemia and cold. Current advice suggests that children with sickle-cell disease undergoing moderate- or low-risk surgical procedures should be considered for a pre-operative transfusion to bring their haemoglobin level up towards (but not higher than) 10 grams/dL, to maximise oxygen-carrying capacity.

Growth

Growth failure and delayed puberty are common in children with sickle-cell disease, especially in those with hypersplenism or who have had multiple acute sickle crises. Weight tends to be affected more than height, and malnutrition is a major factor in determining whether children achieve their full growth potential.

Puberty may be delayed because of hypersplenism or malnutrition because of the hyper-metabolic state and inadequate nutrition.

Dietary advice, treatment of any chronic infections and possibly splenectomy (if hypersplenism is present) may be helpful. Occasionally, children may benefit from temporary use of the monthly transfusion programme to assist them into puberty.

Priapism

Priapism is a serious but under-reported complication of sickle-cell disease. If untreated, it can lead to fibrosis of the corpus cavernosa and impotence, a risk which appears to be lower in pre-pubertal boys. The duration of an episode predicts the overall outcome. Therefore prompt recognition and management are essential.

Patients typically present with an erect painful penis, which may be precipitated by a painful sickle crisis, fever, dehydration, use of recreational drugs, or sexual activity.

Acute fulminant priapism is characterised by a prolonged and sustained episode, more than 4 hours in

### TABLE 5.11.B.5 Drug treatments to reduce iron loading (iron chelation)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desferrioxamine</td>
<td>Well-understood safety profile through long-term use</td>
<td>Relatively poor iron chelation properties</td>
</tr>
<tr>
<td></td>
<td>Cheap</td>
<td>Poor patient compliance</td>
</tr>
<tr>
<td>Deferiprone</td>
<td>Oral administration</td>
<td>Requires close monitoring due to risk of sudden unexpected neutropenia and risk of overwhelming infection</td>
</tr>
<tr>
<td>Deferasirox (Exjade)</td>
<td>Oral once-daily administration</td>
<td>Expensive</td>
</tr>
<tr>
<td></td>
<td>Effective chelation agent</td>
<td>Long-term safety profile not yet fully understood</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Common side effects are deranged urea and electrolytes and gastrointestinal upset</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Requires some monitoring</td>
</tr>
</tbody>
</table>

Note: see Section 5.11.C for doses of newer iron chelation treatments

### Prevention of infection

Prevention of infection is the mainstay of reducing mortality and morbidity in sickle-cell disease.

- All children should receive immunisation against *Pneumococcus, Haemophilus influenzae*, meningococcus and hepatitis B, in addition to any standard immunisation schedule.
- Pneumococcal immunisation should be as broad as possible, including pneumococcal conjugate vaccine and Pneumovax. Pneumovax should be given from the age of 2 years, every 5 years for life.
- All children should receive prophylactic penicillin V (erythromycin or clarithromycin can be used as an alternative):
  - age up to 1 year: penicillin 62.5 mg twice a day
  - age up to 5 years: penicillin 125 mg twice a day
  - age 5 years or over: penicillin 250 mg twice a day into adulthood.
- All children should be protected from malaria infection (see Section 6.3.A.d).
- Families should be counselled about prevention, risks and signs of infection, so that they can seek prompt treatment.

### Prevention of crises

- Maintain good fluid intake, especially during gastroenteritis or other infections.
- Folic acid:
  - age up to 1 year: 1 mg daily
  - age up to 5 years: 2.5 mg daily
  - age 5 years or over: 5 mg daily into adulthood.
- Families should be taught how to feel their child's abdomen in order to identify the onset of a sequestration crisis.
- Hydroxyurea (hydroxycarbamide) may raise baseline haemoglobin levels by promoting fetal haemoglobin (HbF) production. This may reduce the frequency and severity of crises in children. However, it is myelosuppressive and should be used with caution and only where facilities for monitoring blood counts exist and the dose can be monitored carefully.

### Splenectomy (and surgery) in sickle-cell disease

Splenectomy is not routinely undertaken in children with (8–12 hours) for 5–7 nights per week. Many children become non-compliant with this regimen, and newer medications are available as outlined below.
duration. In stuttering priapism, episodes are repetitive and may be individually brief. Patients may have a combination of both of these events.

Treatment of acute priapism is still the subject of much debate. Current best practice suggests the initial use of warm baths, exercise, hydration and gentle sedation while preparing for a more definitive intervention. Subsequent definitive treatment choices include aspiration of blood from the corpus cavernosum followed by surgical washout using saline (irrigation) or adrenergic agonists, which can be performed under conscious sedation. The goal is rapid detumescence within 4–12 hours of the procedure. Ideally, treatment should start within 2 hours of an episode. After 12 hours the patient may require surgical intervention to achieve detumescence. Exchange transfusion (the target haemoglobin concentration is approximately 10 grams/dL, with a haematocrit no higher than 0.4) may be required.

There is still considerable debate about the best treatment options for stuttering priapism, and this is the subject of an ongoing international trial (PISCES). Currently patients with stuttering priapism can be advised to try gentle exercise and warm baths. A preventative approach may be needed, and the following options are available:
- Pseudoephedrine at 30 mg/kg/day, increasing to 60 mg/kg four times a day:
  - alternatively give etilefrine 0.25 mg/kg twice a day
  - both of these drugs are part of the ongoing PISCES trial (2011).
- Hydroxyurea at 10–30 mg/kg/day.
- Use of the long-term transfusion programme.

Other problems
- Around 30% of SS children suffer from sleep-related upper airways obstruction with consequent hypoxaemia. Nocturnal hypoxaemia has been increasingly identified as a risk factor for acute chest syndrome (and possibly an independent risk factor for stroke) in children with sickle-cell disease, and marked improvement can occur after adenotonsillectomy. Treatment is as indicated for other children with upper airways obstruction (see Section 5.1.1).
- Chronic pain resulting from damage caused by acute vaso-occlusive crises occurs, and other pain secondary to the haemolytic process can occur.
- Avascular necrosis of the hip or shoulder can occur as young as 6 years, although it is uncommon before adolescence. The initial presentation may be with the acute vaso-occlusive crisis, but once disintegration of the femoral head occurs, the pain is of a chronic osteoarthritic type, and should be managed as such.
- Leg ulcers that can become seriously infected are common, and their prevalence rises with age. Appropriate antibiotics such as erythromycin and flucloxacinil, wound cleaning and protection together with rest and elevation of the leg are helpful. Compression stockings may also be of benefit.
- Children develop a renal tubular concentrating defect by the age of 2 years. During adolescence, proteinuria, the nephrotic syndrome or chronic renal failure may develop.
- Renal papillary necrosis may produce haematuria, urinary tract infection and renal colic. Rarely the haematuria is severe and blood transfusion is required. Renal colic is treated with copious fluids and adequate analgesia.
- Many patients are chronically jaundiced with exacerbations. There is no treatment, and reassurance should be given that this rarely represents liver failure.
- Gallstones are common, due to pigmentation from haemolysis. The pain can mimic an acute painful crisis. Treatment is surgical. Antibiotic treatment of cholecystitis with amoxicillin and metronidazole may be required.

5.11.C Haemolytic anaemias

**BOX 5.11.C.1 Minimum standards**
- Folic acid.
- Screened blood for transfusion.
- Splenectomy.
- Iron chelation therapy: desferrioxamine.
- Pneumococcal vaccine/penicillin.
- Meningococcal vaccine.
- *Haemophilus influenzae* type B (HiB) vaccine.

**Definition**
Haemolytic anaemias are disorders characterised by a reduction in the lifespan of red blood cells, and may be congenital or acquired.

**Clinical features of haemolytic anaemia**
These include pallor, jaundice, splenomegaly and gallstones.

The degree of splenomegaly can be a useful clue to the cause of haemolytic anaemia.

**TABLE 5.11.C.1 The differences between congenital and acquired haemolytic anaemia**

<table>
<thead>
<tr>
<th>Congenital</th>
<th>Acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin defects:</td>
<td>Infection: malaria, visceral leishmaniasis</td>
</tr>
<tr>
<td>sickle-cell disease, thalassaemia</td>
<td></td>
</tr>
<tr>
<td>Red cell enzyme defects:</td>
<td>Allimmune: haemolytic disease of the newborn,</td>
</tr>
<tr>
<td>G6PD, pyruvate kinase deficiency</td>
<td>transfusion reactions</td>
</tr>
<tr>
<td>Red cell membrane defects: spherocytosis,</td>
<td>Red cell fragmentation:</td>
</tr>
<tr>
<td>elliptocytosis</td>
<td>haemolytic–uræmic syndrome</td>
</tr>
<tr>
<td>Autoimmune infection (e.g. EBV, CMV, HIV,</td>
<td></td>
</tr>
<tr>
<td>mycoplasma), malignancies (lymphomas,</td>
<td></td>
</tr>
<tr>
<td>leukaemias), immune deficiencies</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
</tr>
<tr>
<td>Burns</td>
<td></td>
</tr>
</tbody>
</table>

June 2015 © 2014 Maternal and Childhealth Advocacy International MCAI
Laboratory features of haemolytic anaemias: general
These include low haemoglobin, increased reticulocyte count, raised and predominantly unconjugated bilirubin, pink plasma after centrifuging of blood (due to free haemoglobin) in severe cases, reduced haptoglobin, and increased urinary urobilinogen.

Hereditary haemolytic anaemias
Red cell membrane defects (dominant inheritance)
Spherocytosis
This is the most common haemolytic anaemia due to a membrane defect. It may present at any time from birth to old age, and varies in severity from patients with haemoglobin concentrations of 4–5 grams/dL to asymptomatic individuals with normal haemoglobin levels. Acute haemolytic or aplastic crises may be triggered by viral infections. These usually last for 10–14 days, but may result in sudden severe anaemia requiring transfusion.

Diagnosis
- Along with a positive family history, the clinical features are mild jaundice, pallor and splenomegaly. Gallstones may occur in children.
- Laboratory features: blood film shows spherocytes, increased osmotic fragility of red cells, increased reticulocytes, negative antiglobulin (Coombs') test.

Treatment
- Folic acid 1 month–12 years 2.5–5 mg daily; 12–18 years 5–10 mg daily.
- Severely anaemic and symptomatic moderately anaemic children may benefit from splenectomy if the facilities available make this a low-risk procedure.
  - Splenectomy carries a major risk of lifelong increased vulnerability to infection with capsulated bacteria such as pneumococci, meningococci and Haemophilus influenzae type B. The risks and benefits need to be weighed up very carefully before splenectomy is undertaken.
  - Delay splenectomy until after the age of 5–10 years if possible.
- Administration of pneumococcal, meningococcal and HiB vaccine prior to splenectomy, and lifelong prophylactic oral penicillin thereafter (under 12 months of age, 62.5 mg twice daily; 1–5 years 125 mg twice daily; over 5 years 250 mg twice daily).

Elliptocytosis
This condition is less common than spherocytosis. It is rare in European populations, but is seen more often in West Africa. In South-East Asia there is a variant, South-East Asian ovalocytosis (SAO), which causes oval-shaped red cells and neonatal hyperbilirubinaemia, but little haemolysis later in life.

Diagnosis
- Blood film shows 25–90% of oval, elliptical or rod-shaped red blood cells.
- Homozygotes tend to have severe haemolytic anaemia from infancy.

Stomatocytosis
Hereditary stomatocytosis is rare, but it can be acquired in several conditions, especially liver disease. The hereditary form may cause neonatal oedema and ascites which resolves spontaneously.

Metabolic defects
Glucose-6-phosphate dehydrogenase deficiency (G6PD) (X-linked)
There are two types of normal G6PD enzymes (types A and B). Worldwide, there may be 100 million people with diminished red cell G6PD activity. G6PD A deficiency is common in black children, and their G6PD function is reduced to about 10% of normal. G6PD B deficiency (G6PD Mediterranean) is less common, and the enzyme activity is reduced to 1–3%; this and the Chinese variant of G6PD deficiency are the more severe forms of the disease.

Clinical features
Severe enzyme deficiency causes chronic haemolytic anaemia and jaundice.
Haemoglobinuria may occur with less than 10% enzyme activity, and severe episodes of haemolysis occur with oxidant stress:
- favism due to ingestion of the fava broad bean or inhalation of its pollen
- oxidant drugs such as antimalarial drugs, sulphonamides, high-dose aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), quinidine, quinine, nitrofurantoin, phenacetin and vitamin K analogues
- other chemicals, such as those in mothballs, can also trigger an episode.

TABLE 5.11.C.2 Degree of splenomegaly in haemolytic anaemias

<table>
<thead>
<tr>
<th>With minor splenomegaly</th>
<th>With marked splenomegaly</th>
</tr>
</thead>
<tbody>
<tr>
<td>G6PD deficiency</td>
<td>Sickle-cell disease</td>
</tr>
<tr>
<td>Autoimmune haemolytic anaemia</td>
<td>Beta-thalassaemia major</td>
</tr>
<tr>
<td>Haemolytic–uraemic syndrome</td>
<td>Hb E beta-thalassaemia</td>
</tr>
<tr>
<td>Beta-thalassaemia minor</td>
<td>Hereditary spherocytosis</td>
</tr>
<tr>
<td>Hb H alpha-thalassaemia syndrome</td>
<td>Hyper-reactive malarial splenomegaly (tropical splenomegaly)</td>
</tr>
<tr>
<td></td>
<td>Visceral leishmaniasis kala-azar</td>
</tr>
</tbody>
</table>

TABLE 5.11.C.1 Degree of splenomegaly in haemolytic anaemias

<table>
<thead>
<tr>
<th>With minor splenomegaly</th>
<th>With marked splenomegaly</th>
</tr>
</thead>
<tbody>
<tr>
<td>G6PD deficiency</td>
<td>Sickle-cell disease</td>
</tr>
<tr>
<td>Autoimmune haemolytic anaemia</td>
<td>Beta-thalassaemia major</td>
</tr>
<tr>
<td>Haemolytic–uraemic syndrome</td>
<td>Hb E beta-thalassaemia</td>
</tr>
<tr>
<td>Beta-thalassaemia minor</td>
<td>Hereditary spherocytosis</td>
</tr>
<tr>
<td>Hb H alpha-thalassaemia syndrome</td>
<td>Hyper-reactive malarial splenomegaly (tropical splenomegaly)</td>
</tr>
<tr>
<td></td>
<td>Visceral leishmaniasis kala-azar</td>
</tr>
</tbody>
</table>

TABLE 5.11.C.1 Degree of splenomegaly in haemolytic anaemias

<table>
<thead>
<tr>
<th>With minor splenomegaly</th>
<th>With marked splenomegaly</th>
</tr>
</thead>
<tbody>
<tr>
<td>G6PD deficiency</td>
<td>Sickle-cell disease</td>
</tr>
<tr>
<td>Autoimmune haemolytic anaemia</td>
<td>Beta-thalassaemia major</td>
</tr>
<tr>
<td>Haemolytic–uraemic syndrome</td>
<td>Hb E beta-thalassaemia</td>
</tr>
<tr>
<td>Beta-thalassaemia minor</td>
<td>Hereditary spherocytosis</td>
</tr>
<tr>
<td>Hb H alpha-thalassaemia syndrome</td>
<td>Hyper-reactive malarial splenomegaly (tropical splenomegaly)</td>
</tr>
<tr>
<td></td>
<td>Visceral leishmaniasis kala-azar</td>
</tr>
</tbody>
</table>
Diagnosis
- Blood film shows ‘blisters’ and ‘bite’ cells. Heinz bodies may be seen on unstained blood film.
- Enzyme assay (if available) is needed to make the diagnosis (but this may be normal if reticulocyte numbers are raised). It may be necessary to wait several weeks after an acute episode before measuring enzyme levels.

Treatment
- Avoid drugs that cause oxidant stress (e.g. chloroquine, primaquine, sulphonamides, nitrofurantoin, quinolones, dapsone, high-dose aspirin, phenacetin) or fava beans. If primaquine is necessary, this can be given weekly for 8 weeks.
- Patients usually recover spontaneously once the precipitating factors have been removed.
- Transfusion may be necessary if there is severe haemolysis.

Pyruvate kinase deficiency (autosomal recessive)
This is the second commonest enzyme defect of the glycolytic pathway, and affects mainly northern Europeans.

Clinical features
These are very variable.
- Neonates may have severe haemolysis and present with early jaundice (within 48 hours), anaemia and hyperbilirubinaemia.
- In older children, haemolysis is variable and may be asymptomatic or lead to poor growth, delayed puberty and the skeletal changes associated with chronic haemolysis, such as maxillary prominence and frontal bossing and an increased tendency to long bone fractures.

Diagnosis
- Blood film shows increased reticulocytes, Heinz bodies and mild macrocytosis.
- Enzyme assay for pyruvate kinase.

Treatment
- Folic acid (250 micrograms/kg once daily).
- Splenectomy (only if the facilities available make this a low-risk procedure).
- Transfusion if there is severe anaemia or an aplastic crisis.

Haemoglobin defects
- Abnormal variants: sickle (see Section 5.11.B), Hb C, Hb E, Hb D, etc.
- Defective synthesis: thalassaemias.
- Beta-thalassaemia major (autosomal recessive).

Beta-thalassaemia major
In this condition there is a complete or almost complete absence of the beta-globin chain synthesis. There is a high incidence of the beta-thalassaemia gene (1–15%) in southern Europe, the Middle East, India, Pakistan and South-East Asia.

Clinical features
- Anaemia, which becomes obvious by 3 months.
- Weakness and tiredness.

- Failure to thrive, intermittent fever and poor feeding.
- Cardiac failure may develop.
- Infections and splenomegaly.
- Stunted growth with skeletal changes (e.g. frontal bossing, maxillary hyperplasia, increased tendency to fractures).
- Increased skin pigmentation.
- Delayed puberty.

Management of beta-thalassaemia major
Management is by regular blood transfusion and iron chelation therapy to reduce iron deposition in tissues, especially the heart, liver and endocrine glands (transfusion haemosiderosis).

Blood transfusion
- Monitor haemoglobin levels, growth and development, and transfuse when the child stops developing or when the haemoglobin concentration is less than 7 grams/dL in the absence of infection.
- Blood should be ABO, rhesus (Dd, Cc, Ee) and Kell matched and filtered to avoid allo-immunisation and transfusion reactions.
- Immunise against hepatitis B prior to transfusion.
- Transfuse 20 mL/kg of filtered red cell concentrate over 2–3 hours.
- To monitor, calculate the transfused red cell concentrate in mL/kg yearly. If blood consumption is > 300 mL/kg, investigate the cause.
- Increased blood consumption may be due to large spleen, large liver, autoimmune haemolytic anaemia or multiple allo-antibodies.
- To prevent bone deformities, osteoporosis and extra-medullary haemopoiesis, aim for a pre-transfusion level of not less than 9 grams/dL.
- Pre-transfusion haemoglobin is mandatory. Post-transfusion haemoglobin is optional.
- As a rule, the haemoglobin level drops by 1 gram/week in splenectomised children, whereas in non-splenectomised patients it drops by 1.5 grams/week.
- Monitor serum ferritin levels (normal range is 7–200 micrograms/litre in children over 5 months old).

Iron chelation
- To avoid damage to the endocrine glands, liver and heart, iron chelation should be started when the serum ferritin level is around 1000 micrograms/litre.
  1. Desferrioxamine infusion IV or subcutaneous given slowly over 10–12 hours. The initial dose should not exceed 30 mg/kg desferrioxamine in 10 mL of water for injection, followed by maintenance doses of 20–50 mg/kg each over 10–12 hours on 3–7 nights a week.
  Too much desferrioxamine can cause growth,
hearing and eyesight problems. Give 100–200 mg vitamin C orally at the same time as desferrioxamine. This enhances iron excretion in the urine, but it should be given separately from food as it also enhances iron absorption from food. Desferrioxamine should not be given to children with cardiac dysfunction.

2. Oral chelation (Deferiprone or Deferasirox) may be used when desferrioxamine is not available or not tolerated. These drugs are much more acceptable to children than desferroxamine as they are oral rather than a long overnight infusion but they have significant side effects.

- Deferiprone by mouth: child 6–18 years 25 mg/kg 3 times daily (maximum 40 mg/kg daily).
- Deferasirox by mouth: child 2–18 years initially 10–30 mg/kg once daily according to serum-ferritin concentration. For maintenance, consult product literature.
- The most serious side effect is neutropenia.
- Monitor the neutrophil count every 2 weeks.
- If the neutrophil count is less than 1.0 × 10⁹/litre, stop iron chelation and monitor recovery.
- If infection is present, the neutrophil count is less than 0.5 × 10⁹/litre and there are symptoms, take blood cultures and treat with a broad-spectrum antibiotic to prevent septicaemia.
- Other side effects are joint pain, nausea, fluctuating liver enzymes and zinc deficiency.

**Monitoring treatment**
- Measure height and weight, plot height velocity and watch for delayed puberty.
- To avoid psychological trauma and ensure the development of secondary sexual characteristics, treat if no signs of sexual development have occurred by 16 years of age (see Section 5.8.C).
- Check the following at least twice yearly: serum ferritin (iron overload), liver function tests, calcium, phosphate, alkaline phosphatase (hypoparathyroidism, tetany).
- Undertake yearly screening for HCV and HIV infection.
- If HCV is positive, assess viraemia (serotype) if possible, perform a liver biopsy and give interferon with or without ribavirin to avoid cirrhosis and hepatoma.
- If HIV-positive, continue transfusions and give the latest available antiviral treatment.
- All blood donors should be tested for HCV and HIV.

**Acquired haemolytic anaemia**

**Immune mediated**

- Haemolytic transfusion reaction.
- Haemolytic disease of the newborn (see Section 3.4).

**Diagnosis**

- Anaemia with increased reticulocytes.
- Splenomegaly.
- Positive direct Coombs’ test.

**Management**

- Most secondary cases (70–80%) are transient, lasting about 3 months.
- Infants and older children may develop the chronic form.
- Treatment may not be needed if the symptoms are not severe.
- Transfusion may be necessary if there is severe haemolysis.
- Steroids: prednisolone 2 mg/kg/day (up to 6 mg/kg/day in severe cases) can be given if treatment is needed until the rate of haemolysis declines, and then stopped gradually.

**Malaria**

See Section 6.3.A.d.

**Secondary to organ disease**

Renal failure (see Section 5.6.C).
Liver disease (see Section 5.7.B).

**Burns**

See Section 7.3.I.b.

**Miscellaneous**

- Chemicals and drugs.
- Toxins (e.g. Haemophilus influenzae type B, staphylococcal, streptococcal, clostridial).
- Venoms (e.g. cobra, viper, rattlesnake, bee, wasp, yellow jacket).

**Reference**

5.11.D Blood clotting disorders

**BOX 5.11.D.1 Minimum standards**
- Regional/national centre.
- Prednisolone.
- Immunisation; hepatitis B.
- Blood clotting products.
- Desmopressin and tranexamic acid.

**Factor deficiencies**

The incidence of haemophilia is similar worldwide, at around 1 in 5000–10,000 male births. Major advances have been made in both separating haemophilia A (factor VIII deficiency) and haemophilia B (factor IX deficiency) and delivering safe therapeutic intervention with replacement therapy. However, this is only available to the 20% of haemophiliacs who live in well-resourced countries. For those in resource-limited countries, severe haemophilia continues to be a personal and social disaster, with affected boys becoming progressively crippled during childhood from spontaneous painful intractable haemorrhages into muscles and joints. These boys commonly die in childhood or early adulthood. Severe deficiencies of the other coagulation factors (X, XI, VII, V, XIII, fibrinogen and von Willebrand factor) are also associated with severe and sometimes life-threatening or fatal haemorrhage.

- The largest barrier to providing replacement therapy is its high cost.
- There are also non-financial barriers, including insufficient knowledge even among the medical community, lack of a proper healthcare structure, and low levels of literacy.
- In the last decade the WHO and the World Federation of Haemophilia (WFH) have made considerable progress in setting up programmes in resource-limited countries.
- The WHO has identified the following as core components:
  - training of care providers and the establishing of care centres
  - identification and registration of people with haemophilia
  - improving social awareness of haemophilia
  - prevention of haemophilia
  - providing safe therapeutic products
  - developing a programme of comprehensive care.

**How can delivery of haemophilia care be implemented in resource-limited countries?**

- National haemophilia societies are crucial. In addition to supporting affected families, they can lobby for support from the healthcare budget.
- The WHO and WFH have visiting teams that have contributed to education and improvement through these national groups. They include international haemophilia training fellowships, workshops and twinning programmes, in order to transfer knowledge and diagnostic expertise to these embryo services.
- It is important that those planning healthcare fully appreciate that provision of laboratory diagnostic services for haemophilia and the development of safe blood transfusion services to provide safe replacement therapy will benefit a wide range of medical services.

**How should the service be built and structured?**

- At least one national centre should be created where the laboratory, scientific and medical expertise exists to make an accurate diagnosis, which will then allow the appropriate counselling, including genetic counselling, of the patient’s family (similar to a national centre for cancer therapy with links to centres in well-resourced countries: see Section 5.14). With advances in molecular biology, carriers of haemophilia can currently be identified and antenatal diagnosis provided so that a choice can be made to prevent the birth of haemophiliac boys, particularly if treatment is not available.
- National registers should be set up for service planning.
- A clinical service involving paediatricians, dentists, orthopaedic surgeons and adult physicians needs to be set up. Safe replacement therapy, probably initially derived from donated plasma, should be developed.
- Donor screening and product treatment to remove the risk of at least HIV and hepatitis B and C infection must be provided.
- Haemophiliacs should be vaccinated at an early age against hepatitis B.

**What treatment should be given in the absence of replacement therapy?**

Spontaneous haemorrhages into muscles and joints can be extremely painful and will lead to progressive crippling deformities. The acute episode must be managed with bed rest. For bleeds such as those in the knees, splinting with a back slab to restrict movement may help. Analgesia for the pain is also required (see Section 1.15). Opiates may be needed to obtain adequate pain relief. Bleeding with loss of first dentition may be severe enough to warrant blood transfusion.

In mild to moderate cases, desmopressin (DDAVP) can be helpful.

- **By intravenous infusion over 20 minutes:** Child 1 month–18 years 300 nanograms/kg as a single dose immediately before surgery or after trauma; may be repeated at intervals of 12 hours if no tachycardia.
- **Intranasally:** Child 1–18 years 4 micrograms/kg as a single dose. For pre-operative use, give 2 hours before procedure.

Avoid drugs that impair haemostasis, such as aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) (e.g., ibuprofen).

**Platelet deficiencies: idiopathic thrombocytopenic purpura (ITP)**

- Isolated thrombocytopenia usually follows a viral infection 1–3 weeks previously.
- Boys and girls are equally affected, and the peak incidence is in those aged 2–4 years.
There is a 90% probability of complete remission, but those presenting over the age of 10 years are more likely to have chronic ITP. ITP that persists for 6 months is defined as chronic. Children with chronic ITP are more likely to have an underlying cause (e.g., autoimmune disease). Bleeding manifestations include petechiae, purpura, epistaxes, haematuria, gastrointestinal haemorrhage and (rarely) intracerebral haemorrhage. The child has no hepatosplenomegaly and is usually well. Other causes of thrombocytopenia must be excluded. If there is any doubt, a bone-marrow aspirate will show normal haematopoiesis with increased numbers of megakaryocytes in ITP.

**Management**
- Treatment is based on symptoms, not platelet count, and many patients require no treatment.
- Petechiae on the head and neck, and gastrointestinal and oral bleeding, are indicators for prednisolone (1–2 mg/kg/day after food in two divided doses for no more than 14 days or 4 mg/kg for no more than 4 days; reduce over 5 days and stop irrespective of the platelet count if the patient is asymptomatic). Prednisolone does not alter the course of the disease. The time to remission is very variable.
- Tranexamic acid can be useful in the treatment of mucosal bleeding. Give 10 mg/kg IV slowly over 10 minutes in children 6–18 years (maximum 1 gram) followed by 25 milligrams/kg orally (maximum 1.5 gram) three times daily for 2–8 days.
- Hormonal treatment can benefit girls with menorrhagia. In addition Tranexamic acid 1 gram orally 3 times daily for up to 4 days can help (initiate when menstruation starts).
- Chronic ITP with serious bleeding into the gastrointestinal tract or brain may require splenectomy. However, in resource-limited countries there is a high risk of infection following splenectomy, and long-term penicillin prophylaxis and pneumococcal vaccination are required.

**Reference**
Grainger JD, Rees JL, Reeves M et al. (2012) Changing trends in the UK management of childhood ITP. Archives of Disease in Childhood, 97, 8–11.

### 5.12 Gastrointestinal disorders

#### 5.12.A Acute diarrhoea

**Box 5.12.A.1 Minimum standards**
- Reduced-osmolarity ORS.
- ReSoMal for children with severe malnutrition.
- IV fluids: Hartmann’s or Ringer-lactate solution with glucose 5% or 10% to prevent hypoglycaemia.
- Potassium: oral and IV.
- ABC resuscitation for shock.
- Antibiotics: co-trimoxazole, amoxicillin, nalidixic acid, ciprofloxacin, cefotaxime, chloramphenicol, erythromycin, metronidazole, tetracycline, vancomycin, doxycycline.

**Important issues**
- Shock management, rehydration therapy and continued feeding are key strategies.
- Antibiotics are not given routinely, but they are indicated in bloody diarrhoea (probable Shigella infection) and suspected cholera.
- Antidiarrhoeal drugs and anti-emetics should never be given and can be dangerous in children.
- Zinc supplementation speeds recovery and helps to prevent further episodes.

**Introduction**
Diarrhoeal diseases are a leading cause of childhood morbidity and mortality in resource-limited countries. In 2001, an estimated 1.5 million children under 5 years of age died from diarrhoea, 80% of them in the first 2 years of life. Around 50% of these deaths are due to watery diarrhoea and occur either because of lack of access to oral rehydration solution (ORS) or because of incorrect case management. About one-third of deaths are caused by persistent diarrhoea and the remainder (approximately 15%) are caused by dysentery.

This section is primarily aimed at the management of the infant and child under 5 years as they are the most seriously affected. There are particular problems in managing children with severe co-morbidities: these include significant malnutrition and anaemia (Hb below 6 G/dL see Sections 5.10.B and 5.11.A). In these children, assessment is more difficult and there is likely to be an abnormal response to a fluid load because of poor cardiac function. Modifications to the management plans for these children largely involve slower shock management and rehydration, the careful use of blood transfusion and diuretics and very frequent re-assessment.

ORS has been a simple and effective solution, reducing morbidity and mortality in diarrhoeal illness. The new low-osmolarity ORS reduces by 33% the need for supplemental