

## 5.10 Nutritional disorders

### 5.10.A Vitamin or mineral deficiencies

#### BOX 5.10.A.1 Minimum standards

- Adequate diet.
- Vitamins A, B, C, D and K.
- Folic acid.
- Zinc.
- Iodine.

#### Vitamin A deficiency (VAD)

##### Significance

- Vitamin A deficiency is the single most important cause of childhood blindness in resource-limited countries.
- It makes a significant contribution to morbidity and mortality from common childhood infections, even at subclinical levels of deficiency.
- A Cochrane review indicates that regular vitamin A supplementation reduces mortality by 24%.

##### Prevalence

- Vitamin A deficiency is endemic in at least 60 countries worldwide, especially in Africa, South and South-East Asia, some areas of South America and the Western Pacific.
- Around 250 million preschool children are at risk.
- It causes 250 000–500 000 cases of blindness per year.

**Good food sources** are red palm oil, mango, pawpaw, dark green leafy vegetables, unskimmed milk, eggs and liver.

##### Aetiological factors

- Persistent inadequate intake of vitamin A exacerbated by insufficient consumption of dietary fat, leading to ineffective absorption.
- Frequent infections, especially measles, gastroenteritis and respiratory infections, resulting in decreased food intake, malabsorption, increased urinary loss, and increased utilisation of vitamin A by the body resulting in depletion of liver stores. The decrease in vitamin A levels in the body in turn predisposes children to infection, and so a vicious cycle is set up.
- Vitamin A deficiency is common in the context of poverty, social under-development, hostile living environments, water shortage and food scarcity, and individual factors such as lack of breastfeeding, inappropriate weaning practices and increased physiological needs during periods of rapid growth.

##### Clinical effects

- Night blindness (decreased ability to generate rhodopsin in the retinal rod photoreceptors essential for vision in dim light).

- Compromised integrity of epithelial surfaces due to loss of mucus-producing goblet cells, leading to 'dry eye' (conjunctival xerosis), Bitot's spots, corneal xerosis, corneal ulceration, and irreversible damage to the eye (keratomalacia).
- Depressed immunity (both innate and adaptive immunity), which results in increased susceptibility, duration and severity of common infections (e.g. acute respiratory infection, diarrhoea, measles).
- Poor growth, apathy and slow development.

TABLE 5.10.A.1 Signs of vitamin A deficiency in the eyes

Sign	Description
Night blindness	Inability to see in dim light (e.g. at dawn or dusk). Often occurs in the later part of pregnancy
Conjunctival xerosis	The conjunctiva looks dry and slightly rough instead of smooth and shiny
Bitot's spots	White foamy patches on the conjunctiva. Not always present
<i>Active corneal lesions:</i> At this stage the condition can worsen within a few hours and complete or partial blindness can result	
Corneal xerosis	The cornea looks dry and cloudy
Ulcers on the cornea	Often on the edge of the cornea
Keratomalacia	The cornea is cloudy and soft like jelly. Rare

##### Assessment of vitamin A status

There are no simple tests for vitamin A deficiency, but it is likely to affect communities where vitamin-A-rich food is scarce and infection and/or malnutrition rates are high.

- Vitamin A deficiency becomes a public health problem when the following are prevalent in the child population:
  - night blindness (> 1%)
  - Bitot's spots (> 0.5%)
  - corneal xerosis with or without ulceration (> 0.01%)
  - corneal scarring (> 0.05%).

##### Prevention

- Encourage the use of local foods rich in vitamin A.
  - Provide dietary education about vitamin-A-rich foods (e.g. dark green leafy vegetables, carrots, mango, papaya, eggs, orange fruits, liver, red palm oil, fatty fish).
  - Treat the siblings and mother. Mothers are especially vulnerable to vitamin A deficiency, and should be supplemented in the first month of lactation.

- Give regular supplementation every 4 to 6 months as described in Table 5.10.A.2.
- Prevent recurrent infections by recommending the use of impregnated nets, deworming, using clean water and breastfeeding.

**TABLE 5.10.A.2 Vitamin A supplements to prevent vitamin A deficiency**

Target group	Immunisation contact	Vitamin A dose
Infants under 6 months who are not breast fed or breast fed infants whose mothers have not received vitamin A supplements.		50 000 IU
Infants aged 6–11 months	Measles vaccine contact	100 000 IU
Children aged 12–59 months	Booster doses Special campaigns Delayed primary immunisation doses	200 000 IU every 4 to 6 months

Regular vitamin A supplementation is advised for all children in resource-limited countries. It has been shown to reduce all causes of mortality, and especially mortality from diarrhoea.

If a child has malnutrition, severe diarrhoea or measles, give one high-dose vitamin A capsule, according to Table 5.10.A.3, unless they have received a dose in the previous month.

### Treatment

If there are any eye signs, give vitamin A as indicated in Table 5.10.A.3.

**TABLE 5.10.A.3 Doses of vitamin A for treatment of clinical deficiency**

Age	Day 1	Day 2	Two weeks later
< 6 months	50 000 IU	50 000 IU	50 000 IU
6–12 months	100 000 IU	100 000 IU	100 000 IU
> 12 months	200 000 IU	200 000 IU	200 000 IU

If there are ulcers or the eyes look soft or cloudy, instil atropine 0.1%, three times a day for 3–5 days, and a topical antibiotic. Cover the affected eye with a saline-soaked bandage.

Deep IM injection of vitamin A (retinyl palmitate) 50 000 IU for children under 2 years of age, and 100 000 IU for those over 2 years, should be given if severe stomatitis, persistent vomiting or malabsorption are present.

### Vitamin B<sub>1</sub> deficiency: beriberi

- This may occur in areas of severe nutritional deprivation where little more than polished rice is consumed. It is uncommon in Africa, as the staple is maize or wheat, which contains vitamin B<sub>1</sub>.

- It affects adults, children and breastfed infants of thiamine-deficient mothers.
- It is often mistaken for oedematous malnutrition (kwashi-orkor), nephritis, cerebral malaria, encephalopathy or septicaemia.
- It causes wet (cardiac) or dry (neurological) beriberi:
  - cardiac failure with breathlessness, oedema and tachycardia
  - peripheral neuritis, with tingling and burning of feet, and reduced tendon reflexes
  - acute encephalopathy and coma.
- An aphonic form is characterised by a noiseless cry due to laryngeal nerve paralysis.

### Beriberi is rapidly fatal.

- The initial dose is 50–100 mg thiamine hydrochloride. IM or orally. This is particularly effective in heart failure (facilities for treating anaphylaxis must be available).
- Continue with 10 mg/day for children under 2 years of age, 25 mg/day for those aged 2–12 years, and 50 mg/day for those over 12 years for 3–4 days.
- Patients with beriberi often have other B vitamin deficiencies.
- Good food sources of vitamin B<sub>1</sub> are pork, whole grain cereals, legumes, nuts and liver.

### Nicotinic acid (niacin) deficiency: pellagra

Nicotinic acid is synthesised from the essential amino acid tryptophan, and pellagra is found where the diet is deficient in either nicotinic acid or tryptophan. It is common where maize is the staple diet, as in many parts of Africa. Maize is deficient in tryptophan, and the nicotinic acid is bound and unavailable.

### Clinical features

- Dermatitis of parts of the skin exposed to sunlight, namely the neck (Casal's necklace), face and hands, usually seen in children over 5 years.
- Diarrhoea and malabsorption.
- Encephalopathy, which is rare in children.

### Treatment

- Nicotinic acid:
  - 10 mg three times daily for 7 days in children under 2 years of age
  - 25 mg three times daily for 7 days in children over 2 years. In severe cases give 100 mg IV.
- Treat other B vitamin deficiencies at the same time (thiamin and riboflavin).
- Improve the diet with protein and green vegetables, peanuts, wholegrain cereals, meat, fish, chicken and liver.

### Vitamin C deficiency: scurvy

This usually presents at the age of 4–10 months. Cow's milk is low in vitamin C.

- Vitamin C is needed for collagen formation (in bones, cartilage, teeth and capillary walls).
- It is important for the healing of wounds.
- It increases iron absorption.
- It is found in citrus fruits, vegetables and breast milk.

Very little vitamin C is present in cow's milk, especially if it is heated.

- Vitamin C deficiency is found in severe malnutrition and in children fed on very poor diets in institutions.

### Clinical features

- Spontaneous haemorrhages, especially from gums, and defective bone, cartilage and dentine formation.
- Local tenderness and swelling of the legs (due to subperiosteal haemorrhages), which may present as irritability when the child is picked up or moved.
- Pseudo-paralysis of the limbs.
- Haemorrhagic and spongy changes in the gums.
- Petechiae and ecchymoses around the eyes.
- Microscopic haematuria may be present.
- The anterior ends of the ribs swell.
- Mild anaemia.
- Increased risk of fractures.
- Poor healing of fractures and wounds.
- Characteristic X-ray appearance: loss of trabeculae in long bones gives a ground-glass appearance, dense lines of calcification in the epiphysis next to the epiphyseal plate and calcification of subperiosteal haemorrhages.

### Treatment

- **By mouth**
  - Child 1 month–4 years 125–250 mg daily in 1–2 divided doses
  - Child 4–12 years 250–500 mg daily in 1–2 divided doses
  - Child 12–18 years 500 mg–1 g daily in 1–2 divided doses.
- A subsequent improvement in diet is needed, with plenty of fresh fruit and vegetables.

### Vitamin D<sub>3</sub> deficiency: rickets

Vitamin D deficiency causes the following:

- rickets (failure of mineralisation of growing bone)
- hypocalcaemic tetany in infancy
- osteomalacia in adults.

Nutritional rickets is most prevalent in North Africa, the Middle East and Pakistan. Asian and Afro-Caribbean children are also at risk in the UK and other countries where there is limited sunshine. Vitamin D deficiency is unusual in African children over 18 months, as at this age they can walk and therefore go out into the sunshine. Older children in Africa with rickets must be investigated for causes of rickets other than vitamin D deficiency, such as dietary calcium deficiency or inherited forms of hypophosphataemic rickets.

### Biochemistry

- Vitamin D increases Ca<sup>2+</sup> absorption from the gut, reabsorption of Ca<sup>2+</sup> from the kidney, and a phosphate diuresis.
- Vitamin D deficiency reduces Ca<sup>2+</sup> and increases parathyroid hormone (which increases phosphate loss by the kidney), resulting in low Ca<sup>2+</sup> and low phosphate levels. Subsequently there is a rise in alkaline phosphatase and then the X-ray features of rickets occur.

### Aetiology

- Prolonged breastfeeding, especially if the mother is vitamin D deficient.
- Lack of vitamin-D-containing foods such as oily fish, eggs, butter and margarine.
- Lack of sunlight exposure (UV light) (black- and brown-skinned children living indoors or in countries where there is little sunlight are particularly at risk).
- An infant's diet contains only small amounts of vitamin D, so fortification of foods and vitamin D supplementation is recommended.
- If a child presents with rickets and has normal exposure to sunlight, consider a hypocalcaemic diet (reported in South Africa and Nigeria). Cereals can bind calcium and prevent its absorption.
- Rarely, there is a metabolic disorder such as familial hypophosphataemic rickets. Where consanguinity is common, renal tubular disorders can produce this.
- Vitamin D deficiency also occurs in chronic renal and liver failure.

### Clinical features

- 1,25-Dihydroxyvitamin D crosses the placenta, and the neonate generally has sufficient levels for the first few months of life.
- Disturbance of the normal growth of the epiphyseal plate leads to the formation of inadequately calcified new bone at the diaphysis edge of the plate (so-called osteoid tissue). The proliferating zone on the epiphyseal side of the plate enlarges excessively, producing a swelling of the plate. Osteoid tissue may also form subperiosteally. There is also demineralisation of the skeleton. The following features result from these abnormalities:
  - epiphyseal swelling (especially distal radii at the wrists, and also the ankles and knees)
  - craniotabes (soft areas of the skull bones, especially of the occiput, which when pressed gently are easily depressed)
  - rickety rosary (enlarged costochondral junctions)
  - delayed fontanelle closure
  - curvature of the shafts of the tibia and femur (may occur in severe cases)
  - bossing of the frontal and parietal skull bones due to osteoid formation
  - pigeon chest (pectus carinatum)
  - Harrison's sulci
  - deformities of the thoracic and lumbar spine can produce kyphoscoliosis and lumbar lordosis
  - pelvic bone deformities in female children can lead to subsequent birthing difficulties due to damage to the inlet and outlet of the birth canal
  - delayed dentition
  - delayed gross motor development with generalised muscle weakness and hypotonia
  - growth retardation
  - occasionally, especially in infants, symptoms of hypocalcaemia.

### Diagnosis

- Very elevated plasma alkaline phosphatase activity.
- Usually normal, but possibly slightly low, plasma calcium levels.
- Very low plasma phosphate levels.

- Lowered plasma levels of 25-hydroxyvitamin D<sub>3</sub>, but often this cannot be tested for.
- The best sites to radiologically assess for rickets are those where there is rapid bone growth, namely the wrists and knees.
  - Typical X-ray appearance: cupping and fraying of the distal ends of the long bones, such as the ulna and radius.
  - There is widening of the metaphyseal plate due to osteoid formation.
  - The periosteum may be raised.
  - There may be abnormal curvature of bones and generalised under-calcification.

### Prevention measures

- Exposure to sunlight and foods such as egg yolk, milk and fortified margarine.
- Vitamin D<sub>2</sub> (ergocalciferol) supplementation, 400–600 IU daily.

### Treatment

- Vitamin D<sub>3</sub> (colecalciferol) or vitamin D<sub>2</sub> (ergocalciferol) by mouth daily for 4 weeks: child aged 1–6 months 3000 IU, 6 months–12 years 6000 IU and 12–18 years 10 000 IU.
- If hypocalcaemia is present, calcium supplements may be added in the early stages of treatment.

### Vitamin K deficiency

- Vitamin K is a cofactor for the hepatic synthesis of clotting factors (prothrombin, and factors VII, IX and X).
- Sources are green leafy vegetables, meat, liver, cheese, and synthesis by gut flora.
- Deficiency may occur as a result of the lack of bile salts and the malabsorption of fats after the use of broad-spectrum antibiotics, or in the breastfed newborn whose gut is not yet colonised with bacteria and therefore does not produce vitamin K.
- Treat bleeding due to vitamin K deficiency with 250–300 microgram/kg (max 10 mg) IV; neonates 1 mg. Repeat doses every 8 hours if needed.
- Prevent haemorrhagic disease of the newborn by giving 1 mg vitamin K to all newborn infants either orally or IM (preterm 400 microgram/kg maximum dose 1 mg).

### Folic acid deficiency

- The most important issue here is that women who are deficient in folic acid at the time of conception and in early pregnancy are at increased risk of having a baby with a neural tube defect (spina bifida or anencephaly).
- Relative deficiency occurs in haemolytic anaemias and in preterm infants (see Section 3.3 and Section 5.11.C).
- Deficiency occurs in malabsorption syndromes such as coeliac disease and blind loop syndromes.
- Anticonvulsants such as phenytoin may interfere with the metabolism of folic acid.
- Consequences of folic acid deficiency include the following:
  - fetal abnormalities
  - megaloblastic anaemia, neutropenia and thrombocytopenia.
- Sources of folic acid include green leafy vegetables, oranges and other fruit, legumes, nuts, liver and yeast.

### Treatment

- All women who are anticipating pregnancy should be taking an additional 400 micrograms of folic acid per day before and throughout pregnancy.
- To treat deficiency, give infants 500 micrograms/kg once daily and children over 1 year of age 5 mg once daily.
- Treat for up to 4 months and exclude concomitant vitamin B<sub>12</sub> deficiency, which if untreated could result in neuropathy.
- For haemolytic anaemia, treat with 2.5–5 mg orally once a day for children aged 1 month to 12 years, and 10 mg once a day for those over 12 years of age.
- Neonates 50 micrograms once daily or 500 micrograms once weekly.
- Give preterm infants 100–200 micrograms orally per day.

### Iodine deficiency

Iodine deficiency in pregnancy causes maternal hypothyroidism and cretinism in the newborn.

- It is one of the commonest causes of disability worldwide.
- Clinical features of cretinism range from mild neuromuscular incoordination and cognitive deficit to severe mental retardation, spasticity and deafness, and severe stunting of growth.
- Iodine deficiency is endemic in mountainous regions far from the sea (e.g. the Andes, the Himalayas, Central Africa, Papua New Guinea) and areas where iodine is eluted from the soil by repeated flooding (e.g. Bangladesh).
- The prognosis is poor even after early recognition and treatment with thyroid hormone.
- Prevention is by salt iodination or a single oral dose of iodine in pregnancy.

### Zinc deficiency

- Zinc is an essential trace element required for maintaining cells, bone growth and immune function (it scavenges for free radicals).
- Deficiency often occurs in children living in resource-limited settings, and arises from either insufficient intake of zinc-containing foods or insufficient absorption.
- Foods high in zinc are of animal origin, such as meats, fish and dairy products.
- Dietary fibre and phytates found in cereals and legumes bind zinc and reduce its absorption.
- Zinc deficiency is difficult to diagnose, as serum zinc levels do not reflect total body zinc levels.
- Zinc deficiency is associated with stunting of growth, impaired immunity and increased risk and severity of diarrhoea and respiratory infections.
- Zinc deficiency is a feature of the rare disease acrodermatitis enteropathica, in which children present with peri-oral and peri-anal rashes.

**Therapeutic zinc supplementation is now recommended as an adjunct to oral rehydration therapy for treatment of diarrhoea. Routinely giving 10 mg per day to children under 6 months of age and 20 mg per day to those over 6 months of age for 10–14 days can reduce diarrhoea duration and severity and the likelihood of subsequent infections for 2 to 3 months.**

Zinc supplements of 2 mg/kg/day should be an essential component of the mineral mix used in the management of severe malnutrition.

### Useful website

World Health Organization (1997) *Vitamin A Supplements: a guide to their use in the treatment and prevention of vitamin A deficiency and xerophthalmia*, 2nd edn. <http://whqlibdoc.who.int/publications/1997/9241545062.pdf>

## 5.10.B Severe malnutrition

### BOX 5.10.B.1 Minimum standards

- Scales (accurate to 5 gram), metre length board, MUAC tapes, care charts.
- ReSoMal.
- Vitamin and mineral mixtures.
- Antibiotics.
- IV 10% glucose.
- Anthelmintic drugs.
- F-75 and F-100 feeds.
- Barrier skin cream.
- Sources of heat (blankets, hat, warm room, clothes).

### Introduction

Severe acute malnutrition (SAM) is characterised by oedema or wasting, often with anorexia and infection. The main immediate causes of death are infections, septic shock, hypoglycaemia, electrolyte imbalance, dehydration, hypothermia, cardiac failure and severe anaemia. Every physiological and metabolic function is impaired, so the children affected are extremely fragile, similar to the premature neonate.

In 2009 the WHO and UNICEF defined SAM for children aged 6–60 months as follows:

- 1 using new weight for length/height charts (see procedures) a cut-off of below minus 3 standard deviations
- 2 **and** the mid upper arm circumference (MUAC) less than 115 mm.

Two clinical pictures are seen, with much overlap between them.

- Marasmus (wasting) affects all ages, but young infants are particularly at risk. It is usually due to insufficient intake of growth nutrients after breastfeeding stops. It can also be due to chronic illness. The baby is extremely thin, with loss of subcutaneous fat, resulting in skin wrinkles and folds. Weight for length or height is less than 70% of the median (see Section 9), or the MUAC is less than 115 mm.
- Kwashiorkor (oedematous malnutrition) usually occurs in children aged 2–4 years. It is an acute illness that suddenly appears over a few days. It is thought to be due to a deficit in the antioxidant nutrients. It presents with sodium retention and oedema of various degrees (from pedal to generalised), and skin lesions that are like severe sunburn in a fair-skinned person. There is fatty liver, with low circulating levels of all hepatic export proteins. The hair may be de-pigmented (this has no relation to the prognosis, and should be ignored clinically), and the hair pulls out very easily and painlessly (which **is** related to the prognosis).

In severe malnutrition, biochemical abnormalities include the following:

- low urea
- severe hypoproteinaemia
- hypokalaemia and hypophosphataemia
- hypomagnesaemia
- hypoglycaemia (see below)
- anaemia (frequently present).

### Principles of treatment

Early identification and treatment is important, and children are often missed on the general admission wards or in outpatients because they are not measured. Screening using MUAC is helpful for identifying children if length measurement is not easily performed, or weight for height is not charted.

Treatment is much more successful if standard treatment protocols are followed than if clinical judgements are made on individual patients. This is because the illness itself changes the clinical presentation, signs and symptoms of common complications.

### Inpatient versus outpatient community management of acute malnutrition (CMAM)

Traditionally, care has been provided for all children in inpatient hospital units, ideally in a defined malnutrition ward. However, carers are less likely to be prepared to attend these until the child is unwell, so patients tend to present late. They also want the child to be discharged as soon as they are clinically stable, so often leave before nutritional deficits have been restored and the child has recovered. This predisposes to higher post-discharge mortality, which is rarely identified by the inpatient programme.

There has been a change to management of the malnourished child who is not unwell, through CMAM programmes. This is sometimes referred to as community-based therapeutic care (CTC). These programmes separate children into those with complications or severe oedema (complicated malnutrition), and those with uncomplicated malnutrition. Children with uncomplicated malnutrition have a reasonable appetite, and on formal testing are able to eat a portion of ready-to-use therapeutic food (RUTF). Children with fever, poor appetite, diarrhoea or dehydration, or who are not fully alert or have generalised oedema are identified and referred to inpatient care (a stabilisation centre), where initial management is delivered.

If a CMAM programme is operating in your area, children with complicated malnutrition will be sent to the hospital, and you may be able to direct those with uncomplicated malnutrition to the CMAM programme after hospital

admission for an illness, or if they present with complicated malnutrition, once they are stabilised and on phase II feeds (see later).

This subsection will deal with the care of children managed in an inpatient hospital unit.

## Inpatient management

The inpatient treatment of severe malnutrition is divided into two phases, which are separated by a transition phase.

### Phase I (initial treatment)

**Specific objectives:** return of normal homeostasis and treatment of complications.

- The immediate treatment of life-threatening complications: hypoglycaemia, hypothermia, heart failure, septic shock, infections and infestations, severe dehydration and very severe anaemia.
- The prevention of hypoglycaemia and hypothermia.
- Nutritional treatment based on a maintenance diet (total 100 kcal/kg/day), divided into frequent meals (eight meals per 24 hours).

**Transition phase:** the diet is gradually increased over 4–5 days.

### Phase II (rehabilitation or catch-up growth)

**Specific objectives:** promotion of rapid weight gain (10–20 g/kg/day) and preparation for discharge.

- A nutritional treatment based on a high energy intake (160–200 kcal/kg/day) divided into six meals a day.
- Emotional and physical stimulation.

The treatment in phase II can be given as ready-to-use therapeutic food (RUTF) in the community, or through an Outpatient Therapeutic Programme (OTP), either administered through a hospital clinic, or preferably in community-based clinics. If RUTF or an equivalent (such as a high-energy biscuit) is not available, children continue on F-100 until nutritional cure is achieved. This is usually defined as achieving 85% of median weight for height.

### Ongoing nutritional support

After discharge from this therapeutic programme, it is good practice to link the child to a supplementary feeding programme, which gives a food ration to the family for up to 4 months following discharge. This is a means of ensuring food security for the vulnerable child. Programmes with this safety-net provision often discharge children at 80% of median weight for height.

### Admission criteria

- Weight for height less than 70% of the median.
- Oedema (exclude nephritic syndrome and other clinical conditions).
- MUAC of less than 110 mm if the child is over 65 cm in length.

### Assessment of nutritional status and recovery

For practical procedures relating to nutrition measurement, see Section 9.

### Discharge criteria

These depend upon the quality of the follow-up services. If adequate follow-up services and a Supplementary Food Programme (SFP) are available, the discharge criteria are as follows:

- weight for height of more than 80% of the median for 3 days (85% if there is no SFP)
- **and** no oedema for 10 days
- **and** no medical complications.

### Medical and nutritional history and examination

The pro-forma history and examination sheet (see Appendix, Section 9) should be filled in by the admitting physician or an experienced nurse.

#### Key points in the history

- Recent intake of foods and fluids.
- Usual diet before current illness.
- Whether breastfeeding or not.
- Duration and frequency of diarrhoea and vomiting.
- Type of diarrhoea (watery/bloody).
- Appetite.
- Family circumstances.
- Previous attempts at treatment, local drugs and/or traditional medicines given.
- History of chronic cough or contact with TB.
- History of contact with measles.
- Potential HIV infection (including mother's status and whether parents are alive).

#### Key points on examination

- Oedema.
- Dehydration (this is very difficult to diagnose, and impossible in the oedematous child).
- Shock (often gives the appearance of dehydration in a child with oedema).
- Severe palmar pallor.
- Eye signs for vitamin A deficiency (dry eyes, Bitot's spots, corneal ulceration, keratomalacia) (see Section 5.10.A).
- Signs of local infection (ear, throat, skin, pneumonia).
- Signs of HIV (adenopathy, oral candida, chronic ear discharge) (see Section 6.2.D).
- Fever.
- Hypothermia (oral temperature < 35.5°C, axillary temperature < 35°C).
- Mouth ulcers, *Candida* or other oral problems.
- Skin changes of kwashiorkor (hypo- or hyperpigmentation, desquamation, ulceration, exudative lesions resembling burns, often with secondary infections such as *Candida*).

**Children with vitamin A deficiency are likely to be photophobic and will keep their eyes tightly closed. Examine their eyes carefully to prevent corneal rupture.**

### Laboratory tests

Laboratory tests are not needed to guide or monitor treatment. Electrolytes and haemoglobin are difficult to interpret and can easily be misleading. If haemoglobin is measured this should be done on admission only, and a transfusion should be given at this time if essential. The patient should not be given a blood transfusion after the first 48 hours

following admission. The haemoglobin level nearly always falls after admission due to haemodilution with expansion of the circulation during mobilisation of oedema and export of sodium from inside the cells in marasmus. At this time, with expansion of the circulation, there is such a grave danger of precipitating heart failure that a transfusion should rarely be given, even for very severe anaemia.

In endemic areas, a malaria smear or rapid test is useful if malaria treatment is not given as part of the routine management of all severely malnourished children.

In regions where HIV is prevalent, HIV testing (serology using two tests in children over 1 year of age, or serology and PCR for children under 1 year) is informative for ongoing care, initiating co-trimoxazole prophylaxis, and determining eligibility for antiretroviral (ARV) therapy. The

mother of a seropositive child is invariably HIV infected, and mothers of seropositive children should be offered an HIV test. Services vary, but would normally include counselling prior to voluntary HIV testing. Where testing is routinely offered, uptake is usually high. CD4 counts are not usually required for the initial management of severe acute malnutrition, as this follows the standard protocols, but may be relevant when considering initiating ARV therapy (see Section 6.2.D).

### Details of treatment

In Phase I (initial phase) the aim is to restore nutritional imbalances and metabolic function and treat complications. Phase II (catch-up growth) is a period of rapid weight gain. There is a 'transition phase' between these phases.

**TABLE 5.10.B.1 Phases of malnutrition treatment**

Phases of treatment		
Phase 1 (1–7 days)	Transition phase (3–4 days)	Phase 2 (usually 14–21 days)
Treat dehydration		Correct nutrient deficiencies
Treat hypoglycaemia		
Treat hypothermia		
Treat infection	Treat helminths	
Do not give iron	Do not give iron	Correct iron deficiency
Correct electrolyte problems		
Diet is maintenance intake	Diet is moderate intake	Diet is high intake
Stimulate the child	Stimulate the child	Stimulate the child
		Provide physical activities
		Prepare for discharge

- There are **routine measures** that are systematically implemented for all malnourished children, and additional routine treatments that are often included.
- **Specific treatments:** these include emergency management of life-threatening complications and of specific diseases.
- **General points:** on admission, severely malnourished children should be separated from those with infections and kept in a warm room (25–30°C) without draughts. Washing should be minimal and when possible with warm water, and the child immediately dried. The mother should be encouraged to stay with her child.

### Intravenous infusion and blood transfusion

Intravenous infusions are to be avoided whenever possible in all severely malnourished children. The risk of precipitating heart failure is very high because of their atrophic heart muscle and high intracellular sodium and electrolyte imbalance.

- The only indication for IV infusion in severely malnourished children is unconsciousness due to circulatory collapse or shock. This is a condition which is difficult to diagnose.
- The only indication for blood transfusion is when anaemia is present on admission and is life-threatening.
- Cannulas should not have IV fluids running after the prescribed treatment has been given. If flushed for IV treatment, they should be removed when not required.

Nasogastric tube feeding is recommended in cases of:

- anorexia with an intake of less than 70 kcal/kg (70% of phase I feed prescribed)
- severe dehydration with inability to drink
- inability to drink and eat because of weakness or clouded consciousness
- painful or severe mouth lesions (herpes, cancrum oris)
- repeated, very frequent vomiting.

Try to not tube-feed for more than 3–4 days. Always explain the reason to the mother.

Try to breastfeed or feed by mouth every time, and top up by nasogastric tube.

### Dehydration with severe malnutrition

Dehydration from diarrhoea is common in severely wasted children (with marasmus) on admission. The treatment of dehydration is not the same as in the non-malnourished child (with the exception of cholera).

This section does not apply to mild diarrhoea occurring during transition from one phase to another, which is a common event.

### Signs of dehydration in malnutrition

The normal signs used to assess dehydration are all unreliable in severe malnutrition.

Assume that all children with acute watery diarrhoea have some dehydration.

The interpretation of the signs relies on the history. The specific signs are as follows:

- history and observation of frequent **watery** diarrhoea
- history of recent sinking of the eyes; the eyes appear 'staring'
- history of not passing urine for 12 hours
- history and observation of thirst.

Reduced skin turgor and sunken eyes (that are long-standing symptoms) are features of malnutrition itself. It is not possible to adequately determine the degree of dehydration in the severely malnourished child.

The appearance of dehydration in children without watery diarrhoea or in those with oedema can be caused by a toxic shock with dilatation of the blood vessels. These patients should not be treated as if they have dehydration, but as cases of septic shock (see later).

**Note that** low blood volume can occur with oedema.

### Oral treatment of dehydration in malnutrition

Standard WHO oral rehydration solutions (ORS) have too high a sodium content and too low a potassium content for children with severe malnutrition.

ReSoMal (rehydration solution for malnutrition; see below) is a special solution for this situation.

**TABLE 5.10.B.2** Composition comparison of ReSoMal, standard WHO ORS and reduced-osmolality WHO ORS

Composition	ReSoMal (mmol/litre)	Standard ORS (mmol/litre)	Reduced-osmolality ORS (mmol/litre)
Glucose	125	111	75
Sodium	45	90	75
Potassium	40	20	20
Chloride	70	80	65
Citrate	7	10	10
Magnesium	3	–	–
Zinc	0.3	–	–
Copper	0.045	–	–
Osmolality (mOsm/litre)	300	311	245

### Children with watery diarrhoea in an adequate clinical state

At admission, give one dose of ReSoMal orally or by nasogastric tube and start to feed the child with the phase I diet. Feed smaller amounts more frequently if they are vomiting. Further ReSoMal can be given after each stool or vomit.

- Give a 50-mL dose for children less than 2 years or less than 85 cm in length.
- Give 100mL for children over 2 years or over 85 cm in length.

### Children with watery diarrhoea in a poor clinical state

Start rehydration with ReSoMal immediately. Give 10mL/kg/hour for the first 2 hours, and then 5mL/kg/hour until rehydration is complete.

This rate is slower than for normally nourished and dehydrated children.

### Completed rehydration

The rehydration is completed when the child is alert, no longer thirsty, and has passed urine. There should be less sunken eyes and fontanelle and improved skin turgor. **(Note that loss of sunken eyes in a severely wasted patient or the worsening of oedema can be a sign of over-hydration.)**

The diet should now be given.

### Monitoring

ReSoMal at 70mL/kg weight per day is usually enough to restore hydration. However, be careful, as **rehydration can quickly lead to fluid overloading, causing cardiac failure or sudden death**. Malnourished children do not excrete excess sodium well. The clinical state of the child should be reassessed every 30 minutes during the first 2 hours, and then every hour. The best way to monitor the child is by regularly measuring their weight; this gives 'fluid balance' directly and accurately, without having to measure any stool or vomit. The ReSoMal should be stopped immediately if:

- the body weight increases by 10% or more
- the respiratory rate or pulse rate increase
- the jugular vein becomes engorged
- oedema appears or the eyelids become puffy
- the liver enlarges by more than 2 cm (mark its position on the skin with marker pen at the onset of rehydration).

**Note:** It is common for malnourished children to pass many small unformed stools. This must not be confused with profuse watery stools, and does not require fluid replacement.

### Feeding and rehydration

- Breastfeeding should continue during rehydration.
- Phase I diet should start immediately when the child is alert.
- If the child has had severe dehydration, feeding should start as soon as the child is alert and the severe dehydration has been treated (2–3 hours).

### Rehydration solutions

If no commercial ReSoMal is available, a solution can be made. (Note that this is double the quantity of water normally used, i.e. 2 litres, so the solution is effectively half strength.)

To 2 litres of boiled filtered water add:

- 1 sachet of ORS (3.5 grams sodium chloride, 2.9 grams trisodium citrate dihydrate, 1.5 grams potassium chloride, 20 grams glucose)
- 50 grams of sugar
- 40mL of combined mineral mix\* (or commercial CMV if available).

\* See below for the recipe for the electrolyte/mineral solution. If this cannot be made up, use 45mL of potassium chloride solution (100 grams of KCl in 1 litre of water) instead.

### Formula for concentrated electrolyte/mineral solution

This is used in the preparation of starter and catch-up feeding formulas and ReSoMal. Sachets containing pre-mixed electrolytes and minerals are produced by some manufacturers. If these are not available or affordable, prepare the solution (2500 mL) using the ingredients shown in Table 5.10.B.3.



**TABLE 5.10.B.3 Electrolyte and mineral mixture**

Constituent	Grams	Concentration/20 mL
Potassium chloride (KCl)	224	24 mmol
Tripotassium citrate	81	2 mmol
Magnesium chloride	76	3 mmol
Zinc acetate	8.2	300 micromol
Copper sulphate	1.4	45 micromol

Water: make up to 2500 mL.

If available, also add selenium (0.028 grams of sodium selenate) and iodine (0.012 grams of potassium iodide) per 2500 mL.

- Dissolve the ingredients in cooled boiled water.
- Store the solution in sterilised bottles in the fridge to slow down deterioration. Discard if it turns cloudy.
- Make fresh solution each month.
- Add 20 mL of the concentrated electrolyte/mineral solution to each 1000 mL of milk feed.

If it is not possible to prepare this electrolyte/mineral solution, and pre-mixed sachets are not available, give potassium, magnesium and zinc separately. Make a 10% stock solution of potassium chloride (100 grams in 1 litre of water) and a 1.5% solution of zinc acetate (15 grams in 1 litre of water).

### Emergency IV treatment of severe dehydration with shock in severe malnutrition

IV infusion should be administered only in the case of circulatory collapse severe enough to reduce consciousness.

**Alert children should never be given an infusion.**

The main signs are as follows:

- cold hands and feet with increased capillary refill time > 3 seconds
- weak or absent radial pulse
- diminished consciousness.

Severe dehydration and septic shock are difficult to differentiate in children with severe malnutrition. They both present with signs of hypovolaemic shock. The following points help to differentiate them:

- Eyelid retraction associated with a history of diarrhoea is a sign of severe dehydration. The child with septic shock has eyelids that droop.
- If the child is unconscious (or asleep) without having the eyelids together (a sign of excess adrenaline), either dehydration or hypoglycaemia is present.
- Superficial veins are always constricted in severe dehydration, but may be dilated in septic shock.

### Treatment protocol for life-threatening dehydration with shock in severe malnutrition

Immediate treatment should be given as follows:

- 1 Give 15 mL/kg IV over 1 hour. The recommended solution is Ringer-lactate or Hartmann's solution, each with 5% glucose.
- 2 At the same time, insert a nasogastric tube and give ReSoMal at 10 mL/kg per hour.

- 3 Monitor carefully for signs of over-hydration, reassessing respiratory rate and heart rate every 15 minutes.

- **If after 1 hour the child is improving but still severely dehydrated**, continue nasogastric ReSoMal 10 mL/kg/hour for up to 5 hours.
- If after 1 hour the child has not improved (i.e. radial pulse is still weak), assume that they have septic shock and treat it accordingly (see below for treatment of septic shock). Since hypoalbuminaemia is likely also to be present, 4.5% albumin 5–15 mL/kg IV over 1 hour may also be helpful in intractable shock but this approach requires urgent research.

### Electrolyte problems in SAM

All severely malnourished children have deficiencies of potassium and magnesium that may take 2 weeks or more to correct. Oedema is partly a result of these deficiencies.

**Do not treat oedema with a diuretic.** Excess body sodium exists even though the plasma sodium levels may be low.

**Giving high sodium loads could kill the child.**

#### Treatment

- Give extra potassium (3–4 mmol/kg daily).
- Give extra magnesium (0.4–0.6 mmol/kg daily).
- The extra potassium and magnesium are present in commercial F-75 and F-100 feeds, but if making from ingredients locally should be added to the feeds during their preparation. See Table 5.10.B.3 for a recipe for a combined electrolyte/mineral solution. Add 20 mL of this solution to 2.5 litres of feed to supply the extra potassium and magnesium required.
- Prepare food without adding salt.

### Infections in SAM: treatment and prevention

All malnourished children must be assumed to have an infection. Because of the lack of an inflammatory response, clinical signs of infection may be entirely absent in a malnourished child with severe systemic infection. If untreated, this may cause mortality, morbidity and poor weight gain.

**All children with severe acute malnutrition should routinely be given broad-spectrum antibiotics.**

#### Protocol for treatment

##### Specific infections

Children with specific infections should receive the appropriate antibiotic according to local guidelines.

##### No specific infection and no suspected septic shock

The principle is to have a first-line treatment and a second-line treatment.

- **First-line treatment** is routinely given on admission to all severely malnourished children **without** complications such as septic shock, hypothermia, hypoglycaemia or a specific infection (skin, eyes). This is usually oral amoxicillin or co-trimoxazole.
- **Second-line treatment** is given after 48 hours to children who do not respond to the first-line treatment, and to all children with complications. This usually includes a parenteral antibiotic, although absorption of oral ciprofloxacin and chloramphenicol is excellent, so these can

be used orally once the child is stabilised. Some units routinely give metronidazole 7.5 mg/kg orally 8-hourly for 7 days in addition to the above.

The choice of the antibiotics used in first-line and second-line treatment is based on local guidelines, which are ideally informed by local resistance patterns. Factors such as route of administration, availability and cost of the drugs are all relevant. It should be a broad-spectrum antimicrobial agent, such as gentamicin 7.5 mg/kg IV once daily for 7 days, **in combination** with either ampicillin (50 mg/kg 6-hourly for 2 days IV) then oral amoxicillin (15 mg/kg/dose 8-hourly for 5 days) **or** ciprofloxacin (10 mg/kg 12-hourly IV or orally for 7 days). If the child fails to improve after 48 hours, add chloramphenicol 25 mg/kg 8-hourly (IV or oral) or ceftriaxone 100 mg/kg daily IV (or IM if this is not possible). These doses are correct for children over 1 year of age, but all doses should be checked against local guidelines, and for infants.

### **Septic shock: recognition**

Septic shock is a very common cause of deaths in these patients. The signs are as follows:

- clouding of consciousness
- rapid respiratory rate:
  - 50 breaths/minute for children aged 2–12 months
  - 40 breaths/minute for children aged 12 months to 5 years
- rapid pulse rate
- cold hands and feet with visible subcutaneous veins and prolonged capillary refill time > 3 seconds
- signs of dehydration but without a history of watery diarrhoea
- hypothermia or hypoglycaemia
- poor or absent bowel sounds
- an abdominal splash when the child is shaken.

It can be very difficult to distinguish between severe dehydration and septic shock.

### **Suspected septic shock: treatment**

- A broad-spectrum IV antibiotic treatment (ceftriaxone) is started immediately.
- Warm the child to prevent or treat hypothermia (see hypothermia below).
- Feeding and fluid maintenance should be undertaken by nasogastric tube or orally.
- Close monitoring of the vital signs (pulse, respiration and conscious level) is essential.

### **Circulatory collapse**

- Give high-flow oxygen through a face mask with reservoir.
- Give IV infusion as described in the case of circulatory collapse due to severe dehydration. However, as soon as the radial pulse becomes strong and the child regains consciousness, discontinue the infusion and start the diet orally or by nasogastric tube.

### **Hypothermia: prevention and treatment**

Malnourished children have a low metabolic rate. The thermoneutral temperature is 28–32°C. At 24°C they can become hypothermic. Those with infection or extensive skin lesions are at particular risk. A hypothermic malnourished child should always be assumed to have septicaemia.

### **Signs**

The signs of hypothermia are a core temperature (oral) < 35.5°C (with a low-reading thermometer). If the axillary temperature is < 35°C or does not register, assume hypothermia.

### **Routine prevention**

- Cover all children with clothes and blankets. They should wear a warm hat (most heat is lost from the head).
- Ensure that the mother sleeps alongside her child. **Do not leave a child alone in bed at night.**
- Keep the ward doors and windows closed to avoid draughts.
- Avoid wet nappies, clothes or bedding.
- Do not wash very ill children. Others can be washed quickly, ideally with warm water, and dried immediately.
- Make sure that the child is fed, so that metabolic heat can be produced. Ensure that feeds occur during the night.
- **Avoid medical examinations which leave the child feeling cold.**

### **Emergency treatment of hypothermia**

- Immediately place the child on the mother's bare chest or abdomen (skin to skin) and cover both of them. Give the mother a hot drink to increase her skin blood flow.
- If no adult is available, clothe the child thoroughly (including the head) and put them near a lamp or radiant heater.
- Immediately treat for hypoglycaemia (see below) and then start normal feeds.
- Give second-line antibiotics.
- Monitor the temperature every 60 minutes until it is normal (> 36.5°C).

### **Hypoglycaemia: prevention and treatment**

Severely malnourished children easily develop hypoglycaemia. This is associated with serious infection. If available, test blood glucose levels (< 2.5 mmol/litre), or if they are not measurable assume that hypoglycaemia is present.

### **Signs**

The main signs of hypoglycaemia are as follows:

- lethargy, limpness, loss of consciousness or convulsions
- drowsiness/unconsciousness with the eyelids partly open, or retraction of the eyelids
- low body temperature
- convulsions.

**Sweating and pallor do not usually occur in this situation.**

### **Routine prevention**

- Give frequent small feeds, day and night.
- Feeding should start while the child is being admitted.
- Treat any infections.

### **Emergency treatment**

If hypoglycaemia is suspected:

- **If the child can drink:** give therapeutic milk or 50 mL of glucose 10%, or 50 mL of drinking water plus 10 grams of sugar (one teaspoon of sugar in 3.5 tablespoons of clean water). Follow this with the first feed as soon as possible. If achievable, divide the first feed into four and

give half-hourly. If not, give whole feeds every 2 hours during the day and night for at least the first day.

- **If the child is unconscious or has convulsions:** give 5 mL/kg body weight of glucose 10% IV or by the intra-osseous (IO) route, or if neither of these routes is possible give 5 mL/kg of glucose 10% or sugar solution as described above by nasogastric tube.

Continue frequent feeding to avoid a recurrence.

Give second-line antibiotics.

If there are convulsions other causes must be excluded, including cerebral malaria, meningitis, encephalitis, thiamine deficiency and hypernatraemic/hyponatraemic dehydration (especially in hot dry climates).

If blood glucose levels are available and are low, repeat the finger or heel prick after 60 minutes.

## Congestive heart failure

This is a common and dangerous complication that usually occurs several days after admission. The heart muscle is atrophic (effectively there is a cardiomyopathy). During early recovery from severe malnutrition, sodium can be mobilised from the tissues before the kidney recovers sufficiently to excrete the excess. All blood transfusions must be done as soon as possible (in the first 2 days after admission), and should be rarely indicated.

Heart failure is usually caused by inappropriate treatment, including the following:

- misdiagnosis of dehydration with consequent inappropriate 'rehydration'
- very severe anaemia
- overload due to blood transfusion
- a high-sodium diet, using conventional oral rehydration solution, or excess ReSoMal
- inappropriate treatment that involves 're-feeding diarrhoea' with rehydration solutions.

## Signs

Excess weight gain is the most reliable sign, and daily weights should be taken for all malnourished children. Differentiate pneumonia and heart failure by weighing the child. If their weight has increased, particularly if by more than 5%, consider heart failure. If they have lost weight, consider pneumonia.

**First sign:** fast breathing:

- 50 breaths/minute for children aged 2–12 months
- 40 breaths/minute for children aged 12 months to 5 years.

**Later signs:**

- lung crepitations
- respiratory distress
- rapid pulse rate
- engorgement of the jugular vein
- cold hands and feet
- cyanosis or hypoxaemia diagnosed by pulse oximetry if available ( $\text{SaO}_2 < 94\%$  in air at sea level)
- liver enlarged by  $> 2$  cm from baseline.

## Emergency treatment of congestive cardiac failure

- **Give high-flow oxygen.**
- Stop all oral intake and IV fluid.

- The treatment of heart failure takes precedence over feeding of the child.
- No fluid at all should be given until the cardiac function improves, even if it takes 24–48 hours.
- Give a diuretic IV, usually furosemide (1 mg/kg). This is the only situation in which diuretics should be used: **diuretics should never be given to reduce oedema in malnourished children.**

## Measles: prevention and treatment

Measles is especially dangerous in severe malnutrition.

### Routine prevention

All children over 6 months of age who are admitted with malnutrition should be vaccinated against measles. This is often done weekly, but if measles is being transmitted locally, it should be done on admission. A second dose of vaccine in a previously immunised child is not harmful. A second dose should be given once recovered or at the normal time, where the prior vaccination state is uncertain or the child was not vaccinated before admission.

### Treatment of measles

If a case of measles is admitted:

- Isolate the individual and any suspected cases.
- Review the vaccination status of all patients in the ward, and ensure that all are immunised.
- Give two doses of vitamin A separated by 1 day.
- Treat for measles (see Section 6.2.E) as well as for malnutrition.

## Micronutrient deficiencies

All children with acute malnutrition will have these deficiencies. Commercial F-100 and RUTFs contains all of the required micronutrients in the correct amounts.

If not using these, give a daily multivitamin supplement, and add a mineral mix to the feeds. This should contain potassium, zinc, copper, magnesium and ideally selenium. Premixed sachets are available, or a solution can be made. It is important to **avoid** adding iron to milk-based feeds during the first 2 weeks, and until the child is gaining weight (RUTFs contain iron within the food, and this is safe to use for stable children and in CMAM programmes). After 2 weeks, iron is added to the F-100 feeds. In goitrous regions, potassium iodide should be added to the mineral mixture (12 mg/2500 mL), or else the child should be given Lugol's iodine, 5–10 drops per day.

## Vitamin A: prevention and treatment

### Routine preventive treatment

Oral vitamin A is particularly important for the severely malnourished child, and one dose should be given routinely to each child admitted with malnutrition.

**TABLE 5.10.B.4 Vitamin A dosage: preventive treatment**

Weight	Dose at admission
$< 6$ kg	50 000 IU once
6–10 kg	100 000 IU once
$> 10$ kg	200 000 IU once

### Treatment of xerophthalmia

If a child shows signs of vitamin A deficiency (xerophthalmia) or has measles, three doses of vitamin A treatment should be given.

**TABLE 5.10.B.5 Vitamin A dosage in xerophthalmia**

Weight	Dose on day 1	Dose on day 2	Dose on day 3
< 6 kg	50 000 IU	50 000 IU	50 000 IU
6–10 kg	100 000 IU	100 000 IU	100 000 IU
> 10 kg	200 000 IU	200 000 IU	200 000 IU

If the eyes show signs of inflammation or ulceration, give the following additional care to the affected eye(s) to prevent corneal rupture and extrusion of the lens:

- Instil chloramphenicol or tetracycline eye drops, 2- to 3-hourly as required for 7–10 days.
- Instil atropine eye drops, one drop three times daily for 3–5 days.
- Cover with sterile saline-soaked eye pads.
- Bandage the eye(s).

Note that **children with vitamin A deficiency are likely to be photophobic and have their eyes closed. It is important to examine their eyes very gently to prevent corneal rupture.**

### Treatment of anaemia

The majority of malnourished children have anaemia. This is due to the many deficiencies they have (iron, folic acid, riboflavin, pyridoxine, ascorbic acid, vitamin E, copper) and their inability to metabolise iron. **Iron should not be given until 2 weeks after the start of treatment.**

#### Routine treatment

##### Folic acid

Give 5 mg of folic acid on the day of admission, then 1 mg/day thereafter (in F-100 already).

##### Iron

**Iron should never be given during Phase I or during the transition phase.** In malnourished patients, iron is not properly metabolised and is therefore dangerous. The free iron enhances the production of free radicals that can damage cell walls. Excess free iron encourages systemic infection.

**Oral iron supplementation should start 14 days after admission.** This is best added to the F-100 milk diet at a dose of one crushed tablet of ferrous sulphate (200 mg) to 2 litres of therapeutic milk. Alternatively, it can be given as ferrous sulphate 3 mg/kg/day orally, which should be continued until anaemia has resolved clinically, or ideally on blood test. It is present in adequate amount in RUTF.

### Emergency treatment of very severe anaemia

Blood transfusion in malnourished children is potentially dangerous because it can precipitate heart failure. There are only two indications for considering blood transfusion, namely:

- the child with a haemoglobin concentration of < 4 grams/100 mL, especially if in shock

- the child with signs of heart failure due to anaemia (at immediate risk of death).

Give 10 mL/kg body weight of packed cells (or whole blood) slowly by partial **exchange** transfusion. Ideally, and if this can be achieved, use a carefully and continuously observed cannula in an artery or central vein. It is also possible in a vein in the antecubital fossa. First 2.5 mL/kg of anaemic blood is removed and then when 5 mL/kg of appropriately screened and cross-matched blood has been transfused, 2.5 mL/kg is again taken and the cycle is repeated. The child is closely monitored for signs of congestive heart failure.

If partial exchange is not possible and heart failure is present, give 10 mL/kg, ideally as packed cells, otherwise as whole blood. Transfuse over 4 hours and give IV furosemide 1 mg/kg at the start of the transfusion. Monitor carefully for worsening heart failure.

### Intestinal parasites

#### Routine treatment

Routine deworming treatment is given to all children over 1 year of age, but only in phase II or the transition phase.

For children over 1 year of age, give mebendazole 100 mg (1 tablet) twice daily for 3 days. Some countries use albendazole 200 mg (for children aged 12–24 months) or 400 mg (for those over 24 months of age) once.

### Dermatosis of kwashiorkor

Shedding of the skin in scales or sheets, desquamation, exfoliation, cracking of the skin surface, and ulceration of the genital or perianal areas are all common.

There can be widespread weeping skin lesions that resemble burns.

Zinc deficiency is usual in this situation, and oral zinc supplements improve the skin (give 2 mg/kg/day of elemental zinc).

#### Treatment

- Leave the exposed area open to dry during the day.
- Apply barrier cream (zinc and castor oil ointment) or petroleum jelly or tulle gras to the raw areas, and gentian violet or nystatin cream to the skin sores twice a day.
- These children should be on broad-spectrum antibiotics.
- Do not use plastic pants or disposable nappies for these children.

### Continuing diarrhoea

See also Section 5.12.B.

Diarrhoea should subside during the first week of treatment. In the rehabilitation phase, loose or poorly formed stools are normal and do not need treatment provided that weight is increasing.

#### Treatment

##### Giardiasis

Giardiasis and mucosal damage are common causes of continuing diarrhoea. Where possible, examine the stools by microscopy.

If cysts or trophozoites of *Giardia lamblia* are found, give metronidazole (7.5 mg/kg 8-hourly for 7 days). If not

detected but clinically *Giardia* is possible, give metronidazole anyway.

### Lactose intolerance

Diarrhoea is only rarely due to lactose intolerance. Only treat for lactose intolerance if the continuing diarrhoea is preventing general improvement. Starter F-75 is a low-lactose feed. In exceptional cases:

- Substitute milk feeds with yoghurt or a lactose-free infant formula.
- Reintroduce milk feeds gradually in the rehabilitation phase.

### Osmotic diarrhoea

This may be suspected if the diarrhoea worsens substantially with hyperosmolar F-75, and ceases when the sugar content and osmolality are reduced. In these cases:

- Use a lower osmolar cereal-based starter F-75 (for the recipe, see Table 5.10.B.7) or, if available, use a commercially prepared isotonic starter F-75.
- Introduce catch-up F-100 gradually.

## Malaria: treatment and prevention

In endemic areas, all malnourished children should have a rapid malaria smear or rapid test on admission. Where this is not possible, all malnourished children should receive antimalarial treatment according to local guidelines for the area. The parasitaemia is usually much lower than in normal children. In initially smear-negative children, there can be a recrudescence during nutritional replacement treatment, so consider malaria in children who develop fever.

Children and mothers should sleep under impregnated nets in the wards.

## Tuberculosis

In patients treated for malnutrition, tuberculosis (TB) can be a cause of failure to gain weight. In malnourished children, the diagnosis of tuberculosis is particularly difficult and misdiagnosis is common.

### How to diagnose pulmonary TB

The signs of TB in malnourished children are often not specific (e.g. anorexia, failure to thrive). Asymmetric chest signs or asymmetric lymph nodes are usually TB. Pneumonia in malnourished children affects both lungs, and HIV gives symmetrical lymphadenopathy.

Consider TB as a possible diagnosis in children who fail to gain weight during admission.

Sputum is rarely available. The Mantoux test can be negative in malnutrition. Undertake a chest X-ray if possible. A family history is often helpful. BCG offers protection against TB, but does not protect completely against infection.

### Treatment (see Section 6.1.N)

**Children with TB should not be isolated**, for the following reasons:

- Young children are not a source of transmission (as it is rarely a cavitating disease).
- Treatment quickly eliminates the risk of transmission.
- An isolated child is stigmatised and neglected in resource-limited settings.

Usually paediatric TB is acquired from a sputum-positive adult, so the TB infected carer is a much higher infection risk to the ward. Take note of the carer on the ward with cough, as they should have a chest X-ray.

## Malnutrition and AIDS

Basically, the initial stabilisation phase and nutritional treatment of HIV-infected patients is the same as for any other severely malnourished patient (see Section 6.2.D). They follow the same dietary and initial medical treatments. Many HIV-positive patients will respond well to the nutritional treatment and gain weight.

However, in units where HIV is prevalent, and particularly where there are programmes that offer additional nutritional support, co-trimoxazole, ARV treatment, PMTCT, and counselling on future pregnancies, there are excellent reasons why a carer would choose to have their child identified during admission as infected with HIV. Moreover, where this is routinely offered, such a policy is not found to be stigmatising.

The presentation of HIV-infected children is similar to that of the uninfected, so cannot be easily identified clinically, although there are some conditions that are more common. HIV-infected children are less likely to present with kwashiorkor than with marasmus. They are more likely to have oral candida, discharging ears, lymphadenopathy, chronic cough, persistent diarrhoea and dermatosis. They may have a family member with HIV, or be orphaned. They may present in infancy, while still breastfeeding, which is an uncommon time for presentation with severe acute malnutrition otherwise.

HIV testing should follow counselling, and be voluntary. It is usually done using two rapid ELISA serological tests. In infants under 1 year of age, serology reflects maternal status rather than infection in the infant. To diagnose infection in infants, a PCR test is required. All children identified as infected with HIV (or where PCR is not available as having indeterminate status) should be commenced on prophylactic co-trimoxazole. This has been shown to reduce long-term mortality.

In an HIV-infected infant, or one possibly infected with HIV and presenting with malnutrition, it is not sensible to stop breastfeeding during admission, as this will deprive the infant of an important source of nutrition. For children who are PCR negative, but exposed to HIV, the decision is less clear, although it will depend on the mother's likely viral load (check whether she is on ARV treatment), the food security of the family, the mother's ability to provide an alternate breast milk substitute, and her choice. There will usually be guidelines depending on local factors.

If the HIV-infected child is not responding well to malnutrition treatment, this may be because of unidentified infection. Non-typhoidal salmonella (NTS) is more common, as are organisms resistant to commonly used antibiotics. TB is a recognised co-infection, although it may be difficult to identify. Some children do not start gaining weight until ARV drugs are started.

It is not known when it is best to initiate ARV therapy in severe acute malnutrition, although it is generally accepted that children should be on phase II feeds. Some children do not meet the criteria for treatment clinically if they respond well to nutritional support with rapid weight gain. CD4 testing is helpful for determining who would benefit, as not

all HIV-infected children have severe immunodeficiency, because HIV can be related to malnutrition through food insecurity as well as illness. However, long-term follow-up of infected malnourished children has identified them as being at high risk of mortality, suggesting that earlier ARV treatment might be of greater help in reducing this.

On discharge it is important to ensure that the child is linked into HIV and nutrition support programmes which the family can access, that carers are aware of the ongoing needs of the child, and that the wider family is offered HIV testing.

## Dietary treatment of severe malnutrition

### Dietary treatment in Phase I

#### Objectives

The aim of this phase is progressive restoration of the electrolyte, metabolic and physiological balance by the frequent feeding of special formula milk.

#### Principles

Severely malnourished children are usually anorexic, and have thin bowel walls, damaged metabolism, and too much sodium in their bodies. Initially they require a low-salt and low-protein diet and are unable to tolerate large amounts of food because their **capacity is reduced**. Therefore initially a diet high in carbohydrate with low levels of sodium and iron and very modest protein content is given. This diet leads to restoration of metabolic and physiological function, but is insufficient for weight gain.

- Feeding should start quickly after admission.
- It should be divided into many small meals to stay within the absorptive and metabolic capacity of the child and to prevent hypoglycaemia and hypothermia.
- The child should be encouraged to eat, but not be forced to do so. Feeding a malnourished child requires time and patience. Use a cup, bowl, spoon or syringe to feed very weak children. If the child takes less than 70% of the prescribed diet, they should be fed by a nasogastric tube.
- Always continue breastfeeding, and encourage the mother to breastfeed. After the breastfeed give the scheduled amounts of starter formula first (see below).

The following guidelines are also useful:

- Give frequent small feeds of low osmolarity and low lactose content.
- Night feeds are essential.
- Give oral or nasogastric feeds (never parenteral preparations).
- Give 100 kcal/kg/day.
- Protein: give 1–1.5 grams/kg/day.
- Liquid: give 130mL/kg/day to all children, whether or not oedema is present.

**TABLE 5.10.B.6 A recommended schedule**

Days	Frequency	Volume/kg/ feed	Volume/kg/ day
1–2	2-hourly	11 mL	130 mL
3–5	3-hourly	16 mL	130 mL
6 onwards	4-hourly	22 mL	130 mL

**TABLE 5.10.B.7 Volumes of F-75 per feed**

Child's weight (kg)	2-hourly (mL/feed)	3-hourly (mL/feed)	4-hourly (mL/feed)
2.0	20	30	45
2.2	25	35	50
2.4	25	40	55
2.6	30	45	55
2.8	30	45	60
3.0	35	50	65
3.2	35	55	70
3.4	35	55	75
3.6	40	60	80
3.8	40	60	85
4.0	45	65	90
4.2	45	70	90
4.4	50	70	95
4.6	50	75	100
4.8	55	80	105
5.0	55	80	110
5.2	55	85	115
5.4	60	90	120
5.6	60	90	125
5.8	65	95	130
6.0	65	100	130
6.2	70	100	135
6.4	70	105	140
6.6	75	110	145
6.8	75	110	150
7.0	75	115	155
7.2	80	120	160
7.4	80	120	160
7.6	85	125	165
7.8	85	130	170
8.0	90	130	175
8.2	90	135	180
8.4	90	140	185
8.6	95	140	190
8.8	95	145	195
9.0	100	145	200
9.2	100	150	200
9.4	105	155	205
9.6	105	155	210
9.8	110	160	215
10.0	110	160	220

Mix the milk, sugar, oil and electrolyte/mineral solution to a paste, and then slowly add the warm boiled water. Make up to 1000mL. If available, use an electric blender or hand whisk.

#### What food to give

The special milk for phase I is called F-75. If it is not available, F-100 should be diluted to the same calorie strength as F-75 and given in its place. Alternatively, it can be made from ingredients using the recipe in Table 5.10.B.7 above.

**TABLE 5.10.B.8** Homemade recipes for re-feeding formulas F-75 and F-100

	F-75 <sup>ab</sup> (starter)	F-75 <sup>c</sup> (starter: cereal-based)	F-100 <sup>d</sup> (catch-up)
Dried skimmed milk (grams)	25	25	80
Sugar (grams)	100	70	50
Cereal flour (grams)	—	35	—
Vegetable oil (grams)	27	27	60
Electrolyte/mineral solution (mL)	20	20	20
Water: make up to (mL)	1000	1000	1000
<i>Contents per 100 mL</i>			
Energy (kcal)	75	75	100
Protein (grams)	0.9	1.1	2.9
Lactose (grams)	1.3	1.3	4.2
Potassium (mmol)	4.0	4.2	6.3
Sodium (mmol)	0.6	0.6	1.9
Magnesium (mmol)	0.43	0.46	0.73
Zinc (mg)	2.0	2.0	2.3
Copper (mg)	0.25	0.25	0.25
% energy from protein	5	6	12
% energy from fat	32	32	53
Osmolality (mOsm/litre)	413	334	419

<sup>a</sup> A comparable starter formula can be made from 35 grams of whole dried milk, 100 grams of sugar, 20 grams of oil, 20 mL of electrolyte/mineral solution, and water to make 1000 mL. If using fresh cow's milk, take 300 mL of milk, 100 grams of sugar, 20 mL of oil, 20 mL of electrolyte/mineral solution, and water to make 1000 mL.

<sup>b</sup> Isotonic versions of F-75 (280 mOsm/litre) are available commercially, in which maltodextrins replace some of the sugar, and in which all of the extra nutrients (potassium, magnesium and micronutrients) are incorporated. These are of lower osmolality and therefore less likely to cause osmotic diarrhoea.

<sup>c</sup> Cook for 4 minutes. This may be helpful for children with dysentery or persistent diarrhoea.

<sup>d</sup> A comparable catch-up formula can be made from 110 grams of whole dried milk, 50 grams of sugar, 30 grams of oil, 20 mL of electrolyte/mineral solution, and water to make 1000 mL. If using fresh cow's milk, take 880 mL of milk, 75 grams of sugar, 20 mL of oil, 20 mL of electrolyte/mineral solution, and water to make 1000 mL.

F-75 contains:

- 75 kcal/100 mL
- 0.9 grams of protein/100 mL (around 5% of kcal provided by protein)
- 2 grams of fat/100 mL (around 32% of kcal provided by fat)
- 13 grams of carbohydrate/100 mL (around 62% of kcal provided by carbohydrates).

### What quantity of food to give

Give 100 kcal/kg/day. The daily number of kcal should be divided by the number of meals given during the day (usually eight meals per day).

F-75: 133 mL = 100 kcal.

### Example

A child of 6 kg should receive a diet of 100 kcal/kg/day. The child will be given eight meals of F-75.

Number of kcal/day: 100 kcal × 6 kg = 600 kcal.  
Quantity of F-75 per day: 800 mL (798 exactly). Quantity per meal: 800/8 = 100 mL.

Do not exceed 100 kcal/kg/day in this initial phase. Diarrhoea should gradually decrease and oedematous children should **lose weight** as the oedema disappears. If diarrhoea continues, see above.

### Dietary treatment in the transition phase (for 48 hours)

#### What food to give

In the transition phase, full-strength F-100 is given in the same volume that was calculated for F-75 in phase I. There is no other change made in the transition phase.

F-100 contains:

- 100 kcal/100 mL
- around 2.6 grams of protein/100 mL (10% of kcal provided by protein)
- around 5.6 grams of fat/100 mL (50% of kcal provided by fat)
- around 9.8 grams of carbohydrate (40% of kcal provided by carbohydrate).

There are two forms of F-100.

### Commercial F-100

This therapeutic milk is prepared in a sachet. All that the nurse has to do is open the packet and dilute the contents in 2 litres of potable (boiled) water. The commercial F-100 has a lower osmolality to reduce 're-feeding' diarrhoea in the severely malnourished children.

**Home-made F-100**

This can be made from ingredients using the recipe shown in Table 5.10.B.8 above.

**Dietary treatment in phase II****Objectives**

The aim is catch-up growth of the child with rapid weight gain (10–20 g/kg/day). Usually the appetite has returned.

**Principles**

The child has re-established their physiological balance and should get enough food to gain weight as quickly as possible. They are given a high-energy diet with normal protein content.

- The intake is increased in quantity (to about 200 kcal/kg/day).
- Reduce meal frequency from eight to six meals per day.
- There should be no limit on the quantity of food given. The child is allowed to eat as much as they want, but must never be forced to eat.
- Breastfeeding continues. Breast milk must always be offered **before** the high-energy food is given.
- Aim for weight gain of more than 10 grams/kg/day.
- Remain alert for heart failure.

**What food to give**

The basic diet is composed of F-100 meals. However, when the child is gaining weight quickly, other foods can be introduced – for example:

- enriched porridges (1 mL contains 1 kcal/gram) as one to two meals a day
- enriched biscuits (useful for overnight feeding if phase II is conducted in a day-care centre) or RUTF (see below)
- local meal: composed of the usual food eaten in the area; this should be enriched in the pot with the addition of oil and CMV and sometimes DSM.

**Quantity of food to give**

Dispense and offer 200 kcal/kg of F-100 per kg of body weight per day.

**Example of calculation**

A child who weighs 9 kg should receive  $200 \text{ kcal} \times 9 = 1800 \text{ kcal}$  per day. The child will receive six meals per day, and each meal should provide  $1800 \text{ kcal}/6 = 300 \text{ kcal}$ .

The diet is composed of six meals of F-100. The enriched porridge or family meal is given **in addition** if the child wishes to take it.

- F-100 (1 mL of F-100 = 1 kcal): the child should receive 300 mL of F-100 per meal.

Older children and adolescents, when they are gaining weight rapidly, often do not want the milk and demand 'solid food'. This usually slows the rate of recovery. The solid food should always be enriched.

When developing local recipes the weight gain should be compared with that of children taking F-100 alone. If the weight gain is similar, the recipe for the porridge is adequate.

**Ready-to-use therapeutic foods (RUTFs)**

RUTFs have been developed to provide the same nutritional content as F-100, but in a peanut-butter-type paste that is not susceptible to pathogens growing in it, due to its low water content. These are usually based on a mix of

groundnuts, vegetable oil, dry skimmed milk, sugar and micronutrient mix. If this is available, children can be introduced to this when on phase II feeds, and if they have a good appetite, could be followed up after 1–2 weeks in an outpatient- or community-based malnutrition programme. This is referred to as an Outpatient Therapeutic Programme (OTP), CMAM or CTC (see Further Reading at the end of this subsection).

**Individual child monitoring****Phase I**

A daily medical and nutritional round of all the children in phase I should be done. The children should be carefully monitored every day for:

- oedema
- weight
- appetite: how the child is eating and the quantity eaten
- clinical state: consciousness, diarrhoea, vomiting, skin, etc.
- behaviour: apathetic, alert, crying, etc.
- temperature
- liver size, heart rate and heart sounds.

This information should be recorded every day on an individual chart.

**When to pass to the transition phase**

Children usually remain in phase I for 1–7 days. The child can pass to the transition phase when:

- they regain appetite
- they are lively and interested
- serious medical complications are under control
- oedema is decreasing (although it may be still present).

If after 5–7 days the child is not ready for the transition phase, they should be completely re-examined and investigated.

After 2 days in the transition phase without experiencing any problem, the child is ready to move to phase II. Oedema should be significantly improved, and the child must be stable, before progressing to phase II.

**Phase II**

The monitoring in phase II includes the following:

- a daily round by the nurse, who checks the general state of the child, including whether there is oedema, nausea or vomiting, and how the child is eating
- a physician round undertaken weekly if the child is stable
- measurement of the child's weight twice a week if they are well
- measurement of their height monthly or in each OTP clinic review.

This information should be recorded on the individual chart.

**If a child develops a complication in phase II, such as re-feeding diarrhoea or vomiting that requires passage of a nasogastric tube, rehydration solutions, transfusion, etc., they should be returned to phase I and subsequently the transition phase again. The above treatments must never be given to children while in phase II and taking very large amounts of F-100 diet.**

**When the child can be discharged**

Children remain in phase II until they meet the criteria for recovery. The average total length of stay is around 4 weeks



in traditional inpatient care, and longer if very severe complicated malnutrition, HIV, TB, or underlying disease or disability is present.

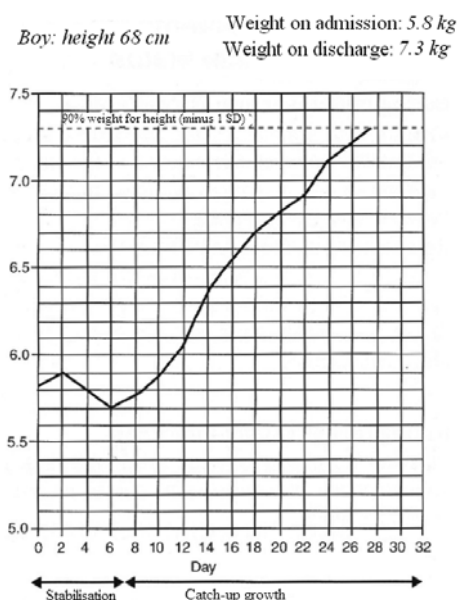
Figure 5.10.B.1 shows an example of a typical growth recovery chart.

When the child has reached their target weight and is in a good clinical state, they will be either referred to a supplementary feeding programme or sent directly home with arrangements made for follow-up. Children with long-term illness should be transferred to an appropriate community service.

## Failure to gain weight

If the child fails to gain weight they should be investigated. Weight gain is defined as poor if it is less than 5 grams/kg/day, moderate if it is 5–10 grams/kg/day, and good if it exceeds 10 grams/kg/day. The following are the most common reasons for failure to gain weight:

- Food prescription or food preparation (kitchen) is incorrect and the child has not received the right quantity of the right food.
- The child does not eat the amount of food prescribed (e.g. because they dislike the food, or the food is being eaten by other people).
- Suspect hidden acute infections (e.g. urinary tract infection, acute respiratory infection, otitis media, mouth candidiasis, giardiasis).
- There are chronic hidden infections (tuberculosis, HIV).
- Re-examine, do stool and urine microscopy, and take a chest X-ray.
- Look for poor feeding techniques, and check that night feeds are occurring.



**FIGURE 5.10.B.1** Weight catch-up chart for a boy weighing 5.8 kg on admission to hospital.

## Emotional and physical stimulation

The severely malnourished child is nearly always psychosocially deprived. The illness itself makes the child unresponsive, and so they do not cry or complain. Because mothers use a cry as the signal to give attention, these

children do not receive the attention they need to stimulate them. The neglect is not wilful on the part of the mother, but rather it is a failure of the two-way communication between the mother and her child.

Because they do not cry or complain, these children are often also neglected by nurses and staff. This greatly compounds the problems associated with being in a strange environment. It is essential to stimulate these children, particularly the unresponsive ones. The ward should be made as much like home as possible and children should sleep alongside their mothers.

- **In phase I** it is essential that the mother (or other carer) is present, feeds the child, comforts them, holds them, plays with them, and talks and sings to them.
- **In phase II** it is important to stimulate the child to move, and to play with other children. A play area should always be present. Staff should be identified who have a responsibility for providing (local) toys and encouraging play.

## The daily organisation of the activities

To organise the treatment of malnourished children, a schedule of activities (e.g. care, distribution of meals) must be established. An example is given below.

**TABLE 5.10.B.9** Daily organisation of activities

Time (24-hour clock)	Children in phase I and transition phase	Children in phase II (day care)
02.00	Milk distribution	
05.00	Milk distribution	
07.00	Team changeover (day shift)	
07.30	Temperatures	Arrival of children
08.00	Milk distribution and drugs	Milk distribution and drugs
09.00	Weight, oedema assessment	Weight, oedema assessment
09.30	Mother's meal	Medical round
10.00	Medical round	Milk distribution
11.00	Milk distribution	Mother's meal
12.00		Milk distribution and drugs
13.00	Dressings	Dressings
14.00	Milk distribution and drugs	
15.00		Porridge distribution
16.00	Mother's meal	Mother's meal
17.00	Milk distribution	Milk distribution
18.00	Medical round	Departure home with porridge and enriched biscuits for the night
19.00	Team changeover (night shift)	
20.00	Milk distribution and drugs	
21.00	Close windows, wrap child	
23.00	Milk distribution	

### Inappropriate practices

- Too much sodium, energy and protein given during phase I of treatment.
- No distinction made between phases I and II.
- Failure to monitor food intake.
- Lack of feeding at night.
- Lack of blankets and hats.
- No daily schedule organised.
- Diuretic given to treat oedema.
- Anaemia treated from time of admission with iron supplements.
- Intravenous fluids given for indications other than circulatory collapse.
- Use of high-sodium diet and standard oral rehydration solution.
- Routine antibiotics not given.
- No vitamin A given.
- No measles vaccine given.

### Problems with the management of severe malnutrition

A high level of care is needed. The treatment of a severely malnourished child requires intensive protocol-based care, like that for a premature neonate, with close monitoring, some complex medical care (severe or chronic infections), a diet well enriched in nutrients (F-100, etc.), and an emotionally stimulating, rich and physically warm environment.

**The resources are almost always limited.** The limited financial resources lead to difficulty in obtaining therapeutic milks and other fortified food, drugs and materials.

However, if staff follow the protocols advocated by the WHO, and described above, outcomes can improve. Staff need to be confident that they can follow the guidelines approved for their unit, and if they are unable to do so, be able to address these deficits in care provision. Nursing staff are often better at following the guidelines than doctors, who may try to individualise treatment as they would for other children. The recording charts, weight charts and pro forma are tools that greatly help in the management of these children.

Analysis has shown that the main reasons for death are inappropriate medical interventions, such as fluid overload from ORS, blood transfusion, and the use of

diuretics in oedema. Another reason is failure to adhere to the guidelines, due to either a lack of resources, or a lack of understanding of the differences in the care needs of this group of children. A significant and often unrecognised cause of death and relapse is inadequate discharge planning, or premature discharge.

However, perhaps the greatest problem is posed by the limited human resources on the malnutrition ward, with an insufficient number of skilled personnel, and constant movement of staff as soon as they are trained. The greatest resource that a unit can have is a motivated, trained and experienced staff, who have the basic resources to deliver the care described in this subsection.

### Further reading

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## 5.11 Haematological disorders

### 5.11.A Anaemia

#### BOX 5.11.A.1 Minimum standards

- Haemoglobin estimation facility.
- Blood transfusion.
- Drugs:
  - Haematinic agents: iron, folic acid.
  - Anthelmintic drugs: mebendazole, albendazole, pyrantel.
  - Antimalarial drugs.

#### 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 B<sub>12</sub> deficiency)
  - white blood cells: hypersegmented neutrophils (folate, vitamin B<sub>12</sub> 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 anthelmintic therapy in endemic areas (see Section 6.3.C).
- Give haematinics:

- 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).

### Iron medication

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

Age or weight (6 mg/kg elemental iron)	Ferrous sulphate 200 mg (60 mg/kg elemental iron)	Ferrous fumarate 60 mg per 5 mL (12 mg elemental iron/mL)
2–4 months (4–6 kg)	–	2 mL
4–12 months (6–10 kg)	–	2.5 mL
1–3 years (10–14 kg)	½ tablet	4 mL
3–5 years (14–19 kg)	½ tablet	5.5 mL
> 5 years (> 19 kg)	1 tablet	–

- Preterm 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.

### 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 35 days at 2–6°C or out of the fridge for more than 2 hours, or that is visibly spoiled (plasma must not be pink, and red cells must not be purple or black), or from a bag that is open or leaking.
- 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).

- Record the quantities given.

### 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) × 4 × desired rise in haemoglobin (grams/dL) **or**
- 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:

- It increases oxygen-carrying capacity.
- Plasma content improves circulating volume better than crystalloids.
- Clotting factors and platelets are beneficial in septic shock.

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 IV. A third-generation cephalosporin or a combination of gentamicin and a penicillin would be advisable. Flucloxacillin should be added if *Staphylococcus* is suspected (e.g. if there are boils or a known abscess). In suspected intra-abdominal sepsis, metronidazole should be added to cover anaerobic organisms.

### Transfusion reactions

See Section 1.7.

### Prevention of iron-deficiency anaemia

- Improve iron intake in infants:
  - breastfeeding for at least 6 months
  - give breastfeeding mothers iron
  - include vitamin-C-rich foods (citrus fruit juices) and/or meat, fish, beans and leafy vegetables by 6 months with cereals
  - low-birth-weight babies should receive oral iron 2 mg/kg daily from the age of 4 weeks, for 6 months.
- Prevent infections:
  - diarrhoea (breast milk)
  - measles (vaccination)
  - prevention and prompt treatment of malaria
  - routine deworming of children under 5 years every 3–6 months
  - malaria prophylaxis in sickle-cell patients.

## 5.11.B Sickle-cell disease

### BOX 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.

### Introduction

#### Genetic basis

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.

### 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.

### 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 ( $\alpha_2\beta_2$ ) 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

Finding	Pattern	Interpretation
HbF and HbA	FA	Normal baby
HbF, HbA and HbS	FAS	Sickle-cell trait
HbF, HbS and HbA	FSA	Sickle-cell beta <sup>+</sup> thalassaemia
HbF and HbA	FS	Sickle-cell disease (HbSS or HbS beta <sup>0</sup> thalassaemia)

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 5.11.B.1 Precipitants of sickle crises

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

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

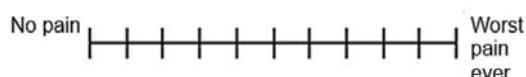
**TABLE 5.11.B.2 Management of an uncomplicated acute painful episode**

Treatment	Comment
Antibiotics and antimalarial drugs (see later)	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
Hydration	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)
Analgesia	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. <b>Do not use pethidine</b>
Severe anaemia	Consider transfusion if the haemoglobin concentration is very low (e.g. < 5 grams/dL) or has fallen by > 2 grams/dL from a known baseline level, or the child is clearly clinically compromised
Oxygen	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

- 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.

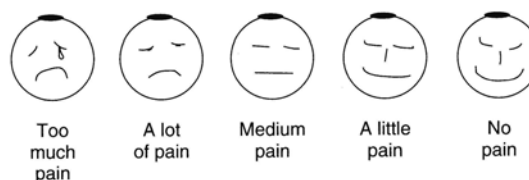
### The acute painful sickle episode

- 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.

**FIGURE 5.11.B.1** Visual analogue scale.

### Hydration and fluids in sickle-cell disease

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

**FIGURE 5.11.B.2** Faces scale.

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.

Fluids can be delivered by the oral, nasogastric or IV route (or a combination of these) and titrated against clinical response. Generally it is safe to start with hyperhydration (150% of normal), although this may be reduced to normal hydration in children who are less unwell.

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

Body weight (kg)	Fluids (mL/kg/day)
First 10 kg	150
11–20 kg	75
Subsequent kg over 20	30

### 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,

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

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

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 ceftriaxone 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.



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 parvovirus are extremely rare, as immunity to parvovirus is lifelong. Review other family members with sickle-cell disease, because they too may be infected with parvovirus.

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 PaO<sub>2</sub> 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 include the following:

- 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

around 20–30 mg/kg over slow subcutaneous infusion (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.

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

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

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

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

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 adeno-tonsillectomy. Treatment is as indicated for other children with upper airways obstruction (see Section 5.1.D).

- 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 flucloxacillin, 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 pigment 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

Congenital	Acquired
Haemoglobin defects: sickle-cell disease, thalassaemia	Infection: malaria, visceral leishmaniasis
Red cell enzyme defects: G6PD, pyruvate kinase deficiency	Alloimmune: haemolytic disease of the newborn, transfusion reactions
Red cell membrane defects: spherocytosis, elliptocytosis	Red cell fragmentation: haemolytic-uraemic syndrome
	Autoimmune infection (e.g. EBV, CMV, HIV, mycoplasma), malignancies (lymphomas, leukaemias), immune deficiencies
	Drugs
	Burns

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

With minor splenomegaly	With marked splenomegaly
G6PD deficiency	Sickle-cell disease
Autoimmune haemolytic anaemia	Beta-thalassaemia major
Haemolytic-uraemic syndrome	Hb E beta-thalassaemia
Beta-thalassaemia minor	Hereditary spherocytosis
Hb H alpha-thalassaemia syndrome	Hyper-reactive malarial splenomegaly (tropical splenomegaly)
	Visceral leishmaniasis (kala-azar)

### 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 life-long 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.

#### Treatment

This is the same as for spherocytosis.

#### 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.

#### Diagnosis

Blood film shows erythrocytes with a central mouth-like slit (stomatocytes).

#### Treatment

This is the same as for spherocytosis, but **splenectomy is ineffective and may be harmful**, leading to a thrombotic tendency.

#### 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.

**Diagnosis**

- Blood film shows 'blister' 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 (i.e. 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.

**Diagnosis**

- Blood film shows microcytosis, anisocytosis, and hypochromic and nucleated red cells.
- Haemoglobin electrophoresis: Hb F increased (10–90%), Hb A absent, Hb A<sub>2</sub> can be reduced, normal or occasionally elevated.
- Serum iron and ferritin levels are increased.
- Reticulocyte numbers are often lower than expected for the degree of anaemia.

**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 haematopoiesis, **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 desferrioxamine 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  $1.0 \times 10^9/\text{litre}$ , stop iron chelation and monitor recovery.
- If infection is present, the neutrophil count is less than  $0.5 \times 10^9/\text{litre}$  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).

- Hypersplenism.
- Secondary to infection: EBV, CMV, *Mycoplasma*, rarely HIV.
- Secondary to malignancies: lymphomas, leukaemias.
- Secondary to autoimmune diseases: SLE, rheumatoid arthritis.

#### 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

British Committee for Standards in Haematology. [www.bcshguidelines.com](http://www.bcshguidelines.com) (up-to-date guidelines on spherocytosis and infection risk in people who have had splenectomy).

## 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 embryonic 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.
- Anti-diarrhoeal 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

IV fluid therapy after initial rehydration compared with the previous standard WHO ORS solution. The new ORS also reduces the incidence of vomiting by 30% and stool volume by 20%.

In addition, zinc supplementation has been shown to significantly reduce the severity and duration of diarrhoea.

### Definition

Diarrhoea is the passage of loose or watery stools, usually at least three times in a 24-hour period. However, it is the consistency of the stools rather than the number that is most important. Mothers usually know when their children have diarrhoea, and may provide useful working definitions in local situations. The volume of fluid lost through the stools in 24 hours can range from 5 mL/kg (near normal) to 200 mL/kg, or more. Dehydration occurs when these losses are not replaced adequately and a deficit of water and electrolytes develops. The concentrations and amounts of electrolytes lost also vary. The total body sodium deficit in young children with severe dehydration due to diarrhoea is usually about 70–110 millimoles/litre of water deficit. Potassium and chloride losses are in a similar range.

The most common causes of diarrhoea are rotavirus, enterotoxigenic *E. coli* (ETEC) and, during epidemics, *Vibrio cholerae* O1 or O139.

### Classification of diarrhoea

- **Acute watery diarrhoea** (including cholera): this lasts from several hours to days. The main danger is dehydration, and malnutrition also occurs if feeding is not continued. If there is a current epidemic, cholera is likely and causes severe dehydration with a positive stool culture for *Vibrio cholerae* O1 or O139.
- **Acute bloody diarrhoea**, or dysentery (blood is mixed in with stool): the main dangers are intestinal damage, sepsis and malnutrition. Other complications, including dehydration, may also occur.
- **Persistent diarrhoea**: this is defined as passage of three or more loose watery stools in a 24-hour period, which lasts for 14 days or longer. The main danger is malnutrition and serious non-intestinal infection; dehydration may also occur (see Section 5.12.B).
- **Diarrhoea with severe malnutrition** (marasmus or kwashiorkor): the main dangers are severe systemic infection, dehydration, heart failure and vitamin and mineral deficiency (see Section 5.10.A).
- **Diarrhoea associated with a recent course of broad-spectrum oral antibiotics.**

### Assessment of the child with diarrhoea

- Fever, vomiting and loose stools are the common symptoms of acute gastroenteritis.
- If possible, rule out other serious illness (e.g. meningitis, malaria, bacterial sepsis).
- Assess for degree of dehydration, bloody diarrhoea, persistent diarrhoea, malnutrition and serious non-intestinal infections.

### History

Specific points to enquire about in the history include the following:

- duration of diarrhoea
- presence of blood in the stool

- local knowledge or reports of a cholera epidemic
- recent use of antibiotics
- the presence of fever, cough or other important problems (e.g. convulsions, measles)
- usual feeding practices
- the type and amount of fluids (including breast milk) and food taken during the illness
- drugs or other remedies taken
- immunisation history.

### Physical examination

First assess the patient for shock and treat this urgently as a priority if it is present. Children with shock will have reduced consciousness, a high and increasing heart rate, weak pulse, poor skin circulation time with prolonged capillary refill time (> 3 seconds), and low or even unmeasurable blood pressure.

**Children with shock require immediate resuscitation (ABC)**, including high concentrations of oxygen (if available) and an IV bolus of 10–20 mL/kg of either Ringer-lactate or Hartmann's solution given as rapidly as possible (see Section 5.5.B). If IV access is not possible (often the veins are collapsed), consider the intra-osseous route (see Section 8.4.B). If shock is not relieved by 20 mL/kg, give another bolus of 10–20 mL/kg, but watch very carefully for fluid overload and in particular pulmonary oedema (this is most likely if the patient is also severely anaemic and will be shown by increasing breathlessness, crepitations may be heard).

The examination includes measurement of vital signs together with clinical correlation. The degree of dehydration is graded according to signs and symptoms that reflect the amount of fluid lost (see Table 5.12.A.2). Infants with acute diarrhoea are more apt to dehydrate than are older children, because they have a higher body surface area to weight ratio, have a higher metabolic rate, and are dependent on others for fluid. Although the most accurate assessment of fluid status is acute weight change, the patient's premorbid weight is often not known.

In severe dehydration, prolonged skin retraction time and decreased perfusion are more reliably predictive of dehydration than a sunken fontanelle or the absence of tears. A good correlation has been reported between capillary refill time and fluid deficit. However, fever, ambient temperature and age can affect capillary refill time as well.

**In severe dehydration, shock and death soon follow if rehydration is not started quickly.**

Children with some dehydration or severe dehydration should be weighed without clothing when estimating their fluid requirements. If weighing is not possible, the child's age may be used to estimate their weight:

- Weight = (age in years + 4) × 2 for children less than 10 years old.
- For an infant up to 1 year old, birth weight doubles by 5 months and triples by 1 year.

**Treatment should never be delayed because facilities for weighing are not rapidly available.**

In addition:

- Look for an abdominal mass or abdominal distension.
- In an infant less than 1 week old, diarrhoea is sometimes a sign of neonatal sepsis (see Section 3.4). In an infant, blood in the stool may be due to an intussusception (see Section 5.19).

**Remember other diagnoses**, including typhoid, antibiotic-associated colitis and (rarely) inflammatory bowel disease (see Section 5.12.D).

### Investigations

Laboratory investigations are rarely needed at the outset. Serum electrolytes, especially sodium or potassium concentrations, are useful in severe dehydration and for monitoring progress, if available. Stool cultures should be undertaken if at all possible in dysentery (bloody diarrhoea), but are not needed to initiate treatment in the usual case of acute watery diarrhoea. Stool microscopy can be useful for diagnosing *Giardia lamblia*, *Cryptosporidium* and amoebic dysentery.

## Principles of case management

There are five essential elements of the management of all children with diarrhoea:

- **Resuscitation from shock, if present:** Give IV boluses of Hartmann's solution or Ringer-lactate solution. This needs to be done rapidly (caution is required in malnutrition and anaemia; see Section 5.10.B). Improvement in conscious level is a good indicator of response to circulatory shock treatment.
- **Rehydration therapy:** this should be done more slowly, so as not to cause rapid metabolic change.
- **Maintenance therapy:** this is to replicate the normal fluid needs and any ongoing extra losses.
- **Zinc supplementation.**
- **Continued feeding.**

### Calculating fluid requirements

WHO Plans A to C for gastroenteritis in children (see Appendix to this section) include estimates of total fluid requirements, and assume that most children will be drinking by 4 hours into treatment and thus able to 'self-regulate'. For patients for whom this is not the case, fluid management can be undertaken using the following guidelines.

### Estimating fluid requirements

The amount of fluid that the child needs over a 24-hour period needs to be calculated. It is the sum of:

$$\text{estimated fluid deficit} + \text{maintenance requirements} + \text{ongoing losses.}$$

### Deficit

**If an accurate recent pre-illness weight is available**, subtract the current weight to estimate lost fluid (1 kg = 1 litre of fluid).

For example, a child who weighed 9.2 kg is seen with diarrhoea and weighs 8.3 kg:

$$\text{estimated fluid loss is } (9.2 - 8.3) \text{ kg} = 0.9 \text{ kg} = 900 \text{ mL deficit, i.e. } 10\% \text{ dehydrated.}$$

**If no recent weight is available, or the recorded weight is considered to be unreliable**, assess the degree of dehydration as described in Table 5.12.A.2.

Weigh the child (or estimate their weight from their age as follows: weight (kg) =  $2 \times [\text{age (years)} + 4]$ ) if over one year.

Then use the following formula: percentage dehydration  $\times$  weight (kg)  $\times$  10 = deficit (in mL).

For example, a child whose weight is estimated to be 10 kg is 10% dehydrated.

$$\text{Their estimated fluid loss is } 10 \times 10 \times 10 = 1000 \text{ mL} \\ (40 \text{ mL/hour if replaced over 24 hours}).$$

## Maintenance

**TABLE 5.12.A.1 Estimated maintenance fluid requirements based on body weight for a child**

Body weight	Fluid needed per day	Fluid needed per hour
First 10 kg of body weight	100 mL/kg	4 mL/kg
Second 10 kg of body weight	50 mL/kg	2 mL/kg
Subsequent kg	20 mL/kg	1 mL/kg

### Ongoing losses

**For each diarrhoeal stool:**

- < 2 years of age: give 50–100 mL or 10 mL/kg
- $\geq$  2 years of age: give 100–200 mL or a cup or small glass if drinking or tolerating NG fluid.

**For each vomit:** use 2 mL/kg ORS, and give small frequent volumes (e.g. 5 mL/minute in a child) via a spoon, syringe or cup. Gradually increase the amount given and closely supervise this.

**For nasogastric tube aspirates:** replace volume for volume with either ORS or Ringer-lactate solution with 5% or 10% glucose or Hartmann's solution with 5% or 10% glucose.

### Signs of over-hydration

- Oedematous (puffy) eyelids.
- Heart failure (especially in severe malnutrition), chronic malnutrition or protein-losing enteropathy: look for tachycardia, tachypnea, crepitations at the lung bases, hepatomegaly or gallop rhythm (see Section 5.4.B).
- A chest X-ray may be helpful in showing pulmonary plethora or oedema.

Stop giving ORS, but give breast milk or plain water, and food.

Do not give a diuretic unless there is pulmonary oedema (lung crepitations), in which case give furosemide 1 mg/kg IV.

### Treatment phases in dehydration with shock

In the shock phase, the circulating volume must be improved sufficiently to perfuse vital organs, this will be identified by an improvement in conscious level, falling heart rate and stronger pulse volume.

- In the rehydration phase, the fluid deficit should be replaced and clinical hydration achieved.
- In the maintenance phase, adequate dietary and fluid intake should be maintained.
- In all phases, excess fluid losses must be replaced continuously.

**TABLE 5.12.A.2** Estimated degrees of dehydration with symptoms, signs and treatment

Degree of dehydration with diarrhoea	Symptoms and signs present	Treatment
No dehydration	None Increased thirst	<ul style="list-style-type: none"> <li>• Treat at home with extra fluids. WHO Treatment Plan A (see below)</li> <li>• Breastfeeding or standard diet must continue</li> <li>• Warn mother about danger signs of some or severe dehydration and when to return</li> <li>• Zinc supplements</li> </ul>
Some dehydration (5–9% fluid deficit)	Two or more of the following signs: <ul style="list-style-type: none"> <li>• Restless and irritable</li> <li>• Sunken eyes</li> <li>• Drinks eagerly/thirsty</li> <li>• Loss of skin turgor; tents when pinched and goes back slowly</li> </ul> Any one additional sign of severe dehydration below	<ul style="list-style-type: none"> <li>• Treat with WHO Treatment Plan B in hospital for at least 24 hours (if feasible)</li> <li>• Give ORS or ReSoMal if there is malnutrition</li> <li>• Breastfeeding or standard feeding to continue</li> <li>• Zinc supplements</li> </ul>
Severe dehydration (10% or greater)	Two or more of the following signs <ul style="list-style-type: none"> <li>• Prostration</li> <li>• Sunken eyes</li> <li>• Loss of skin turgor; tents when pinched and goes back very slowly (<math>\geq 2</math> seconds)</li> <li>• Not able to drink or drinks poorly</li> </ul> In addition may show: <ul style="list-style-type: none"> <li>• Rapid deep breathing from acidosis</li> <li>• Lack of urine output</li> </ul>	<ul style="list-style-type: none"> <li>• WHO Treatment Plan C</li> <li>• Rapid IV rehydration, giving ORS while IV cannula is put in place</li> <li>• Test for and treat any hypoglycaemia</li> <li>• Breastfeeding or standard feeding as soon as possible</li> <li>• Zinc supplements</li> </ul>
Shock	As above with: <ul style="list-style-type: none"> <li>• High and increasing heart rate; weak pulse volume</li> <li>• Poor skin circulation time (cool and poorly perfused extremities) with prolonged capillary refill time (<math>&gt; 3</math> seconds)</li> <li>• Low or even unmeasurable blood pressure</li> <li>• Very reduced conscious level or coma</li> </ul>	<ul style="list-style-type: none"> <li>• Urgent IV or intra-osseous access</li> <li>• Urgent IV/intra-osseous fluid bolus of 10 mL/kg Ringer-lactate or Hartmann's solution</li> <li>• Repeat 10 mL/kg boluses if remains shocked, up to a total of 40 mL/kg, then beware of fluid overload</li> <li>• Then rehydrate more slowly</li> <li>• Use NG or oral ORS/breast milk as soon as tolerated</li> </ul>

A child's fluid deficit can be estimated as follows:

- Mild or no signs of dehydration:  $< 5\%$  fluid deficit;  $< 50$  mL/kg.
- Some dehydration:  $5\text{--}10\%$  fluid deficit;  $50\text{--}100$  mL/kg.
- Severe dehydration:  $> 10\%$  fluid deficit;  $> 100$  mL/kg.

Rehydration therapy is based on degree of dehydration.

### Treatment with low-osmolality ORS

The formula for standard ORS and the latest low-osmolality ORS recommended by the WHO and UNICEF is given in Table 5.12.A.3. The quantities shown are for preparation of 1 litre of ORS, by adding one sachet of oral rehydration salts to 1 litre of clean water.

When prepared and given correctly, ORS provides sufficient water and electrolytes to correct the deficits associated with acute diarrhoea. Potassium is provided to replace the large potassium losses associated with acute diarrhoea, especially in infants, thus preventing serious hypokalaemia. Citrate (or bicarbonate) is provided to prevent or correct base deficit acidosis. Glucose is essential because, as it is absorbed, it promotes the absorption of sodium and water in the small intestine. This is true irrespective of the cause of the diarrhoea. Without glucose, ORS solution would be ineffective.

Healthcare workers and mothers criticised standard ORS because it did not reduce stool output or the duration of diarrhoea. Reduced-osmolality ORS is as effective as

standard ORS for preventing and treating diarrhoea, but it also reduces stool output/volume by 25%, reduces vomiting by almost 30%, and reduces the need for supplemental IV rehydration by 33%. This means that there is less need for hospital care, less disruption of breastfeeding, less use of needles and, where IV treatment is not available, less risk of dying from acute diarrhoea.

It is as effective as standard ORS in the treatment of cholera in adults, but may produce transient hyponatraemia. In children it appears to be as effective as standard ORS in cholera, but careful observations for hyponatraemia should be undertaken if possible.

### Use ReSoMal instead of low-osmolality ORS in

**TABLE 5.12.A.3** Composition by weight of WHO/UNICEF oral rehydration salts to be dissolved in boiled water to produce 1 litre

Ingredient	Original standard ORS (grams/litre clean water)	New and recommended low-osmolality ORS (grams/litre clean water)
Sodium chloride	3.5	2.6
Trisodium citrate dihydrate	2.9	2.9
Potassium chloride	1.5	1.5
Glucose anhydrous	20	13.5

**TABLE 5.12.A.4 Resulting molar concentration of components of standard and reduced-osmolarity WHO oral rehydration solutions**

ORS	Standard osmolarity (mEq/litre)	Reduced osmolarity (mEq/litre)
Glucose	111	75
Sodium	90	75
Chloride	80	65
Potassium	20	20
Citrate	10	10
Osmolarity	311* mOsm/litre	245 mOsm/litre

\* Hyperosmolar with respect to plasma osmolality (normal = 276–295 mOsm/litre).

If using bicarbonate ORS there are 30 mmol/litre of bicarbonate instead of citrate.

**children with severe malnutrition, as this product is specifically designed for such children.**

### Zinc supplementation

Zinc is an important micronutrient for children's overall health and development. It is lost in greater quantity during diarrhoea. Replacing the lost zinc is therefore important both for helping the child to recover and for keeping them healthy in the coming months. It has been shown that zinc supplements given during an episode of diarrhoea reduce the duration and severity of the episode, and lower the incidence of diarrhoea in the following 2–3 months. For these reasons, all patients with diarrhoea should be given zinc supplements as soon as possible after the diarrhoea has started. **Give 10 mg/kg for infants less than 6 months old and 20 mg/kg for older infants and children for 14 days.**

### Treatments for different degrees of dehydration with/without shock

Dehydration does not neatly fit into discrete categories, although texts such as this one and the WHO publications show practicality in this way for clarity and guidance. Similarly, it can be very difficult to distinguish severe dehydration from dehydration with shock, and the two 'categories' overlap. The essential point to understand is that each severely ill patient must be reassessed frequently to ascertain whether the treatment protocol is having the desired effect of reversing the life-threatening signs of fluid loss. Look for the following:

- increasing awareness and response to stimuli
- gradually strengthening pulse with a decreasing rate (however, a slow weak pulse is a pre-terminal sign).

### Children severely dehydrated with shock: shock treatment phase

**Children with shock will have a high and increasing heart rate, weak pulse, poor skin circulation time with prolonged capillary refill time (> 3 seconds), depressed conscious level, and low or even unmeasurable blood pressure.**

**These children require immediate resuscitation (ABC) and emergency treatment (see also Section 5.5.B).**

### Airway (if patient has a reduced conscious level)

- Use an opening manoeuvre if the airway is not open or

if it is partially obstructed. Then keep the airway open. If there is immediate improvement but the airway closes without active opening support, consider using airway adjuncts to support the airway.

- Suction if necessary, but not routinely.
- If the child is deeply unconscious (P or less on the AVPU scale), the airway may need to be secured by intubation using experienced senior help (if available).

### Breathing

- Give 100% oxygen (mask with reservoir and flow rate of at least 6 litres/minute) regardless of SpO<sub>2</sub> (this increases oxygen delivery as well as improving tissue oxygenation).
- For inadequate ventilation or depressed conscious level (as indicated by the AVPU score) with hypoventilation, respiration should be supported with oxygen via a **bag and mask**, and experienced senior help summoned (if available).

### Circulation

- Obtain vascular access to give boluses quickly. Insert an IV cannula and if facilities available send blood for a full blood count, urea and electrolytes blood glucose, cross-matching (if anaemic) and clotting. If peripheral veins are difficult to access an intra-osseous infusion (e.g. EZIO) is rapid and effective. In the absence of IO equipment, the **external jugular vein** or **long saphenous vein cut-down** are good alternatives (see Section 8.B for circulatory procedures). If a skilled operator is available, an internal jugular vein central line is ideal, once an initial rapid infusion has been given, if the patient is very severely shocked and likely to need ongoing high dependency care, as it can also allow CVP measurements (if available).
- Give an initial **rapid** bolus of 10 mL/kg of Ringer-lactate or Hartmann's solution and reassess. **Do not use 5% glucose or 0.18% saline/4% glucose solutions for resuscitation, as these can cause hyponatraemia and cerebral oedema.** Boluses should be manually pushed in using a 20- to 50-mL syringe (utilising a three-way tap and link to an IV giving set).
- The re-assessment after the first bolus allows the clinician to ascertain whether the child has any contraindications to large volume resuscitation. Assess for:
  - malnutrition (this should be obvious: see Section 5.10.B) severe anaemia or cardiac problem. **Rapid fluid infusion can be fatal in malnutrition, severe anaemia or cardiac problems. Stop the rapid infusion and proceed more slowly with reference to Sections 5.10.B malnutrition, 5.11.A anaemia and 5.4.B heart failure and consider a blood transfusion.**
- Further 10 mL/kg boluses with reassessment will usually be required if shock continues. In a child with shock from severe dehydration caused by diarrhoea, it would be very unusual to need more than 30–40 mL/kg to improve the child's circulation. Reconsider the diagnosis. For example:
  - surgical abdominal pathology (e.g. intussusception or volvulus) (see Section 5.19)
  - additional pathology e.g. septicaemia (see Section 5.5.C)
  - ongoing severe diarrhoea, particularly if there is a cholera epidemic.

- Once a **total** of 40 mL/kg of boluses have been given IV, complications such as pulmonary oedema may occur. If available, expert help (including CVP monitoring and facilities for positive pressure ventilation) is essential. If expert help is not available and there is ongoing severe diarrhoea, continue with fluid resuscitation until there is some improvement in conscious level.
- If a blood glucose shows hypoglycaemia (< 2.5 mmol/L) or glucose stick test has not been available, give a dose of 5 mL/kg of 10% glucose IV to any child who still has a depressed conscious level, as hypoglycaemia may be contributing to this problem. Increased alertness confirms hypoglycaemia (and see below).
- Keep the patient warm, but do not overheat them as this will cause peripheral vasodilatation and reduce the blood supply to vital centres. Hypothermia will exacerbate poor peripheral perfusion, acidosis and coagulation abnormalities.
- Elevate the legs (raise the foot of the bed).
- Give a 10 mL/kg bolus of fresh blood as soon as possible if severe anaemia is present, but watch for circulatory overload.
- Consider using broad-spectrum IV antibiotics.
- Monitor urine output.
- If the child has a reduced level of consciousness or has a convulsion, particularly if they are an infant or young child, hypoglycaemia may be present. Always measure the blood glucose level in this situation. However, if blood glucose measurement is not possible, always treat as for presumed hypoglycaemia and, in addition to the IV fluids given above, give 5 mL/kg of 10% glucose IV or, if there is no IV access, by intra-osseous needle.

As shock is being treated, reassess the child's vital signs: alertness, pulse, respiratory rate etc. after each bolus and at least every 15–30 minutes until signs of shock are improving. Increased alertness, lower pulse and respiratory rate are encouraging signs, but the easiest and most sensitive to recognise is the degree of responsiveness.

### Children severely dehydrated with shock: rehydration phase

The best route for rehydration is the oral or nasogastric one, but in children who were sick enough to require rapid IV boluses, further IV fluid is likely to be needed initially.

At this stage, also, there is a need to again consider hypoglycaemia (which may have been identified earlier on stick testing). See below.

### Fluid requirement for replacing in the rehydration phase

Fluid requirement falls into the three categories mentioned above:

- 1 Correction of deficit
  - Weigh the child again or estimate the weight as above
  - Re-assess the clinical signs of dehydration as shown in Table 5.12.A.2 and estimate the percentage of dehydration: fluid deficit in mL = weight in kg × % dehydrated × 10
  - e.g. a 6 kg child with a 5% dehydration will have 6 × 5 × 10 = 300 mL deficit.
- 2 Replacement of ongoing losses
  - For each diarrhoeal stool: < 2 years of age: give

50–100 mL or 10 mL/kg and ≥ 2 years of age: give 100–200 mL

- For each vomit: use 2 mL/kg ORS
- For nasogastric tube aspirates: replace volume for volume
- e.g. a 6 kg child of 7 months with 5 loose watery stools will need another 300 mL as replacement.

3 Maintenance fluids (see Table 5.12.A.5).

TABLE 5.12.A.5 IV maintenance fluids

Weight	Total fluid in 24 hours	Fluid/ hour
First 10 kg of body weight	100 mL/kg	4 mL/kg
Second 10 kg of body weight	50 mL/kg	2 mL/kg
Subsequent kg	20 mL/kg	1 mL/kg

The 6 kg child will need 600 mL in 24 hours for maintenance

Total fluid in 6 kg child with 5 loose watery stools who is 5% dehydrated is 300 + 300 + 600 mL = 1200 in 24 hours. The IV would be set to run at 50 mL/hr. initially. Adjustments to the volume will have to be made in the presence of further large watery stools or vomits or nasogastric aspirate. If available, a check on the plasma electrolytes is very useful at least daily to monitor response to treatment and to guide further therapy. Clinical observations should be done at least hourly and include looking for evidence of urine output.

### Choice of IV fluid

As described before, a solution such as **Ringers's lactate or Hartman's** solution is preferable to Normal (0.9%) Saline as it contains less chloride and contains potassium which is vital in diarrhoea treatment. If N saline must be used, add 10 mmol of potassium chloride to each 500 mL bag **once urine has been passed**. If Ringers's lactate or Hartman's solution are being used, add 5 mmol to each 500 mL bag **once urine has been passed**.

There is an advantage in managing these children with a urinary catheter as urine volume measurement is a useful guide to fluid need in the absence of cardiac failure but its use must be weighed against the risk of infection.

There is always a possibility of hypoglycaemia as the child is not eating (see below) so for this reason, add glucose to the infusion fluid.

To make a 5% solution of dextrose in Ringers's lactate, Hartman's solution or N saline, remove 50 mL from the 500 mL bag and replace with 50 mL of 50% dextrose

To make a 10% solution of dextrose in Ringers's lactate, Hartman's solution or N saline, remove 100 mL from the 500 mL bag and replace with 100 mL of 50% dextrose.

Start the rehydration fluid regime, review the child's vital signs at least hourly, including assessing urine output and looking for signs of fluid overload, such as puffy face or limbs or increased breathlessness. Also review if there is any change reported by the mother. Once the child is regaining a degree of responsiveness and has a gag reflex, consider introducing oral or nasogastric (enteral) fluids to replace the IV route.

### Re-introduction of enteral fluid

Re-assess the child's dehydration status by checking skin pinch, level of consciousness, and ability to drink, at least

every hour, in order to confirm that hydration is improving. Sunken eyes recover more slowly than other signs, and are less useful for monitoring.

As has been mentioned earlier, enteral fluid is the safest way to rehydrate the child. Enteral rehydration can be achieved when:

- The child is conscious enough to be fed by a nasogastric tube without aspiration i.e there is a gag reflex present OR
- The child is conscious enough to take sufficient fluid orally AND
- The child is not vomiting a significant volume of the fluid

The enteral rehydration fluid should be reduced osmolarity ORS (or ReSoMal if malnutrition is present). ORS should be introduced while the IV infusion is still running and the IV fluid volume reduced accordingly. Allow the child to breast feed whenever they want.

Once volumes approaching those required (see WHO Plan B in the Appendix to this section) are reached, the IV infusion can be discontinued and WHO Plan B rehydration continued alone.

All the WHO Plans for rehydration with details on prevention fluids, home fluids and advice for parents can be found in the Appendix to this section (see below).

### **Hypoglycaemia in diarrhoea (blood glucose < 2.5 mmol/L or < 45 mg/dL)**

If the child has a reduced level of consciousness or has a convulsion, particularly if they are an infant, hypoglycaemia may be present. Always measure the blood glucose level in this situation. However, if blood glucose measurement is not possible, always treat as for presumed hypoglycaemia. Give 2–5 mL/kg of 10% glucose IV or, if there is no IV access, by intra-osseous needle. If there is no circulatory access, while further attempts are made to access the circulation, any hypoglycaemia can be temporarily managed as below, if there are sufficient staff.

### **Sublingual sugar (sucrose) for treatment of hypoglycaemia**

- Sublingual sugar may be used as an immediate 'first-aid' measure for managing hypoglycaemia in an unconscious child in situations where IV administration of glucose may be impossible or delayed.
- Give 1 teaspoonful of sugar, moistened with 1–2 drops of water, under the tongue. More frequent repeated doses are needed to prevent relapse. Children should be monitored for early swallowing, which leads to delayed absorption, and in this case another dose of sugar should be given. If sublingual sugar is given, repeat doses at 20-minute intervals.
- Recheck the blood glucose concentration in 20 minutes, and if the level is low (< 2.5 mmol/litre or < 45 mg/dL) repeat the sublingual sugar.
- Clearly, once an IV or IO access has been established, glucose can be given into the circulation if necessary.

### **Electrolyte disturbances in dehydration from diarrhoeal illnesses**

Knowledge of the levels of serum electrolytes rarely changes the management of children with diarrhoea. Indeed, these values are often misinterpreted, leading to inappropriate

treatment. The disorders described below are usually adequately treated by oral rehydration therapy (ORT).

### **Hypernatraemia**

Some children with diarrhoea develop hypernatraemic dehydration, especially when given drinks that are hypertonic due to their sugar content (e.g. soft drinks, commercial fruit drinks) or salt. These draw water from the child's tissues and blood into the bowel, causing the concentration of sodium in extracellular fluid to rise. If the solute in the drink is not fully absorbed, the water remains in the bowel, causing osmotic diarrhoea.

Children with hypernatraemic dehydration (serum Na<sup>+</sup> > 150 mmol/litre) have thirst that is out of proportion to other signs of dehydration. Their most serious problem is convulsions, which usually occur when the serum sodium concentration exceeds 165 mmol/litre, and especially when intravenous therapy is given. Seizures are much less likely to occur when hypernatraemia is treated with ORS, which usually causes the serum Na<sup>+</sup> concentration to become normal within 24 hours.

**It is absolutely essential that intravenous rehydration does not lower the serum Na<sup>+</sup> too rapidly. Intravenous glucose solutions (5% glucose or 0.18% saline/4% glucose) are particularly dangerous and can result in cerebral oedema, which is usually fatal or permanently disabling.**

### **Hyponatraemia**

Children with diarrhoea who drink mostly water, or watery drinks that contain little salt, may develop hyponatraemia (serum Na<sup>+</sup> < 130 mmol/litre). Hyponatraemia is especially common in children with shigellosis and in severely malnourished children with oedema. It is occasionally associated with lethargy and (less often) with seizures. ORS is safe and effective therapy for nearly all children with hyponatraemia. An exception is children with oedema, for whom ORS may provide too much sodium. ReSoMal (see Section 5.10.B) may be helpful here.

### **Hypokalaemia**

Inadequate replacement of potassium losses during diarrhoea can lead to potassium depletion and hypokalaemia (serum K<sup>+</sup> < 3 mmol/litre), especially in children with malnutrition. This can cause muscle weakness, paralytic ileus, impaired kidney function and cardiac arrhythmias. Hypokalaemia is worsened when base (bicarbonate or lactate) is given to treat acidosis without simultaneously providing potassium. Hypokalaemia can be prevented, and the potassium deficit corrected, by using ORS for rehydration therapy and by giving foods rich in potassium during diarrhoea and after it has stopped (e.g. bananas, coconut water, dark green leafy vegetables).

It is also essential to check blood potassium levels, especially if the child has not passed urine, prior to replacing potassium IV, in order to avoid complications of hyperkalaemia secondary to pre-renal failure.

If it is necessary to give potassium intravenously (e.g. if serum K<sup>+</sup> is < 2.0 mmol/litre or there are ECG signs of hypokalaemia, namely ST depression, T-wave reduction and prominent U waves), great care must be taken. In acute depletion, an infusion at the rate of 0.2 mmol/kg/hour can be used and the serum K<sup>+</sup> level checked after 3 hours. The potassium for injection **must** be diluted before use and thoroughly mixed before being given. **The maximum**

concentration of potassium that can be given through a peripheral vein is 40 mmol/litre. The maximum infusion rate of potassium is 0.5 mmol/kg/hour. The recommended concentration is 20 mmol/litre.

**Note:** The injectable form of KCl usually contains 1.5 grams (i.e. 20 mmol of potassium in 10 mL), and can be given orally. The daily potassium requirement is 2.5–3.5 mmol/kg.

## Supportive treatments

### Dietary therapy

During diarrhoea, a decrease in food intake, lack of nutrient absorption and increased nutrient requirements combine to cause weight loss and failure to grow. In turn, malnutrition can make the diarrhoea more severe, more prolonged and more frequent, compared with diarrhoea in non-malnourished children. Therefore give nutrient-rich foods during the diarrhoea and when the child is recovering.

- Breastfed infants: continue feeding on demand.
- Bottle-fed infants: administer full-strength formulas immediately after rehydration (no longer than 4 hours). Lactose intolerance may develop and cause an exacerbation of diarrhoea with a lactose-containing formula. If this happens, temporarily reduce or remove lactose from the diet.
- Older children: continue their usual diet during diarrhoea. Recommended foods include starches, cereals, yoghurt, fruits and vegetables. Foods high in simple sugars and fats should be avoided. Excess fluid losses via vomiting or diarrhoea must be replaced with ORS (see above).

### Zinc treatment

Zinc is an important micronutrient which is lost in diarrhoeal illnesses. Replacement speeds recovery and reduces severity as well as reducing the frequency of diarrhoeal illnesses in the ensuing 2 to 3 months.

Dose under 6 months of age 10 mg (½ tablet) daily for 10–14 days; dose over 6 months of age 20 mg (1 tablet) daily for 10–14 days.

### Drug therapy: use of antimicrobial and ‘anti-diarrhoeal’ drugs

Antimicrobial drugs should not be used routinely. This is because, except as noted below, it is not possible to distinguish clinically episodes that might respond, such as diarrhoea caused by enterotoxigenic *E. coli*, from those caused by agents unresponsive to antimicrobials, such as rotavirus or *Cryptosporidium*. Moreover, even for potentially responsive infections, selecting an effective antimicrobial drug requires knowledge of the likely sensitivity of the causative agent, and such information is usually unavailable. In addition, use of antimicrobials adds to the cost of treatment, risks adverse reactions and enhances the development of resistant bacteria.

**Antimicrobial drugs are reliably helpful only for children with bloody diarrhoea (probable shigellosis), suspected cholera with severe dehydration, and serious non-intestinal bacterial infections such as pneumonia. Antiprotozoal drugs are rarely indicated except as described below when a definite diagnosis is available.**

## Antimicrobial drugs for acute diarrhoea

### Neonates

Diarrhoea and vomiting may be a symptom of septicaemia. If septicaemia is suspected, parenteral antibiotics are required (see Section 3.4).

### Bloody diarrhoea

- **Bacterial causes:** *Campylobacter jejuni*, *Shigella sonnei*, *Shigella flexneri* and *Shigella dysenteriae*, and less commonly *Salmonella*, *E. coli* 0157:117 and *Aeromonas*.
- May be accompanied by abdominal pain and rectal prolapse.
- As culture facilities may not be available, sick toxic children with bloody diarrhoea should be treated for shigella dysentery.
- Children with diarrhoea and blood in stool (dysentery) should be treated with ciprofloxacin as first-line treatment and ceftriaxone as second-line treatment if they are severely ill and local antimicrobial sensitivity is not known. Where local antimicrobial sensitivity is known, local guidelines should be followed:
  - ciprofloxacin: 20 mg/kg/dose twice daily for 5 days
  - ceftriaxone: 80 mg/kg IV or IM once daily for 5 days.
- Mild infections due to *Shigella sonnei* are usually self-limiting. *Shigella* in resource-limited countries is commonly resistant to co-trimoxazole and ampicillin. Nalidixic acid, ciprofloxacin, ceftriaxone **or the antibiotic of choice for the area** should be used for a 5-day course.
- In infants and young children, exclude surgical causes (e.g. intussusception) (see Section 5.19).

### Salmonella

If non-typhoidal *Salmonella* is suspected in infants under 1 year of age or in immunocompromised children, blood cultures should be undertaken. If these are positive or the infant is toxic, an appropriate parenteral antibiotic should be given (e.g. chloramphenicol, ceftriaxone or ciprofloxacin) for 7–10 days. Be alert for pneumonia or metastatic abscesses in bone, brain or elsewhere. Otherwise *Salmonella* gastroenteritis is not treated with antibiotics.

**Systemic *Salmonella* infection is common in malnutrition, HIV infection, sickle-cell disease and schistosomiasis.**

*Campylobacter jejuni* (and also *Shigella* and *Salmonella*) may cause severe abdominal pain, mimicking a surgical emergency. Otherwise the disease is self-limiting and does not require antibiotics. If treatment is considered appropriate, erythromycin (12.5 mg/kg four times daily) for 5 days is the antibiotic of choice.

### Other causes of diarrhoea that warrant antimicrobial treatment

- **Amoebic dysentery:** this is diagnosed by microscopy of fresh warm stool. Treatment is with metronidazole 10 mg/kg three times daily (maximum dose 2 grams) for 5–7 days.
- **Cholera:** this is usually only diagnosed during epidemics. If the child has severe watery diarrhoea, suspect cholera or enterotoxigenic *E. coli* (only diagnosed by specialist laboratories). Treatment for cholera is with tetracycline 12.5 mg/kg four times a day for 3 days in children aged over 8 years. The alternative for young children is chloramphenicol 25 mg/kg 8-hourly for 3 days. In addition to rehydration, give an antibiotic to which local



strains of *Vibrio cholerae* are sensitive. These include tetracycline, doxycycline, co-trimoxazole, erythromycin and chloramphenicol.

- **Giardiasis:** this is diagnosed by microscopy of stool, and is usually self-limiting or asymptomatic. If symptomatic in a malnourished child or the disease is prolonged, it is justified to treat with metronidazole for 5 days (as for amoebic dysentery). Tinidazole is an alternative (50–75 mg/kg once only (maximum dose 2 grams), a second dose may be given if necessary).
- *Clostridium difficile* usually occurs after a course of antibiotics for some other illness, and is associated with antibiotic-associated pseudomembranous colitis (there is a danger of bowel perforation). Antibiotics, especially clindamycin, may alter the flora of the gastrointestinal tract and allow overgrowth of *C. difficile*. The latter produces a toxin which causes damage to the gut mucosa, resulting in pseudomembranous colitis. Confirmation is by culture of *C. difficile* in the faeces. Treatment is with oral vancomycin for 7–10 days, which clears *C. difficile* from the gut. The doses are orally:
  - **Child 1 month–5 years:** 5 mg/kg 4 times daily for 10–14 days (increased up to 10 mg/kg 4 times daily if infection fails to respond or is life threatening)
  - **Child 5–12 years:** 62.5 mg 4 times daily for 10–14 days (increased up to 250 mg 4 times daily if infection fails to respond or is life threatening)
  - **Child 12–18 years:** 125 mg 4 times daily for 10–14 days (increased up to 500 mg 4 times daily if infection fails to respond or is life threatening).

### Symptomatic drugs

**‘Antidiarrhoeal’ drugs and anti-emetics have no practical benefits for children with acute or persistent diarrhoea. They do not prevent dehydration or improve nutritional status, which should be the main objectives of treatment. Some, like loperamide, have dangerous and sometimes fatal side effects. These drugs should never be given to children under 5 years of age.**

### Treatment of rectal prolapse

Gently push back any tissue that has come out of the anus using a surgical glove or wet cloth, or if it is oedematous and cannot be reduced, warm compresses of magnesium sulphate may reduce the oedema.

### Haemolytic–uraemic syndrome

If laboratory tests are not available, suspect this syndrome when purpura, pallor, altered level of consciousness and low or absent urine output are present. If laboratory tests are available, blood smear shows fragmented red cells and decreased or absent platelets. There will be an increase in blood urea and creatinine levels (see Section 5.6.A).

## Appendix

### WHO Treatment Plan A: home therapy to prevent dehydration and malnutrition

Children with no signs of dehydration need extra fluids and salt to replace their losses of water and electrolytes due to diarrhoea. If these are not given, signs of dehydration may develop.

Mothers should be taught how to prevent dehydration at home by giving the child more fluid than usual, how to

prevent malnutrition by continuing to feed the child, and why these actions are important. They should also know what signs indicate that the child should be taken to a health worker. *These steps are summarised in the four rules of Treatment Plan A.*

### Rule 1: Give the child more fluids than usual, to prevent dehydration

#### What fluids to give

Many countries have designated recommended home fluids. *Wherever possible, these should include at least one fluid that normally contains salt* (see below). Plain clean water should also be given. Other fluids should be recommended that are frequently given to children in the area, that mothers consider acceptable for children with diarrhoea, and that mothers would be likely to give in increased amounts when advised to do so.

#### Suitable fluids

Most fluids that a child normally takes can be used. It is helpful to divide suitable fluids into two groups:

##### Fluids that normally contain salt, such as:

- ORS solution
  - salted drinks (e.g. salted rice water or a salted yoghurt drink)
  - vegetable or chicken soup with salt.
- Insert

Teaching mothers to add salt (about 3 g/L) to an unsalted drink or soup during diarrhoea is also possible, but requires a sustained educational effort.

A home made solution containing 3 g/L of table salt (one level teaspoon) and 18 g/l of common sugar (sucrose) is effective but is not generally recommended because the recipe is often forgotten, the ingredients may not be available or too little may be given.

##### Fluids that do not contain salt, such as:

- plain water
- water in which a cereal has been cooked (e.g. unsalted rice water)
- unsalted soup
- yoghurt drinks without salt
- green coconut water
- weak tea (unsweetened)
- unsweetened fresh fruit juice.

#### Unsuitable fluids

A few fluids are potentially dangerous and should be avoided during diarrhoea. Especially important are drinks sweetened with sugar, which can cause osmotic diarrhoea and hypernatraemia. Some examples are:

- commercial carbonated beverages
- commercial fruit juices
- sweetened tea.

Other fluids to avoid are those with stimulant, diuretic or purgative effects, for example

- coffee
- some medicinal teas or infusions.

#### How much fluid to give

The general rule is: give as much fluid as the child or adult

wants until the diarrhoea stops. As a guide, after each loose stool, give:

- children under 2 years of age: 50–100 mL (a quarter to half a large cup) of fluid
  - children aged 2 up to 10 years: 100–200 mL (a half to one large cup)
  - older children and adults: as much fluid as they want.
- Insert

**Rule 2: Give supplemental zinc (10–20 mg) to the child every day for 10 to 14 days**

Zinc can be given as a syrup or as dispersible tablets, whichever formulation is available and affordable. By giving zinc as soon as diarrhoea starts, the duration and severity of the episode as well as the risk of dehydration will be reduced. By continuing zinc supplementation for 10–14 days, the zinc lost during diarrhoea is fully replaced and the risk of the child having new episodes of diarrhoea in the following 2 to 3 months is reduced.

**Rule 3: Continue to feed the child, to prevent malnutrition**

The infant's usual diet should be continued during diarrhoea and increased afterwards. Food should never be withheld, and the child's usual foods should not be diluted. Breastfeeding should always be continued. The aim is to give as much nutrient-rich food as the child will accept. Most children with watery diarrhoea regain their appetite after dehydration is corrected, whereas those with bloody diarrhoea often eat poorly until the illness resolves. These children should be encouraged to resume normal feeding as soon as possible.

When food is given, sufficient nutrients are usually absorbed to support continued growth and weight gain. Continued feeding also speeds the recovery of normal intestinal function, including the ability to digest and absorb various nutrients. In contrast, children whose food is restricted or diluted lose weight, have diarrhoea of longer duration, and recover intestinal function more slowly.

**What foods to give**

This depends on the child's age, food preferences and pre-illness feeding pattern; cultural practices are also important. In general, foods suitable for a child with diarrhoea are the same as those required by healthy children. Specific recommendations are given below.

**Milk**

- Infants of any age who are breastfed should be allowed to breastfeed as often and as long as they want. Infants will often breastfeed more than usual; this should be encouraged.
- Infants who are not breastfed should be given their usual milk feed (or formula) at least every three hours, if possible by cup. Special commercial formulas advertised for use in diarrhoea are expensive and unnecessary; they should not be given routinely. Clinically significant milk intolerance is rarely a problem.
- Infants below six months of age who take breast milk and other foods should receive increased breastfeeding. As the child recovers and the supply of breast milk increases, other foods should be decreased (if fluids other than breastmilk are given, use a cup, not a bottle).

This usually takes about 1 week. If possible, infants of this age should become **exclusively** breastfed.

There is no value in routinely testing the stools of infants for pH or reducing substances. Such tests are oversensitive, often indicating impaired absorption of lactose when it is not clinically important. It is more important to monitor the child's clinical response (i.e. weight gain, general improvement). Milk intolerance is only clinically important when milk feeding causes a prompt increase in stool volume and a return or worsening of the signs of dehydration, often with loss of weight.

**Other foods**

If the child is at least 6 months old or is already taking soft foods, he or she should be given cereals, vegetables and other foods, in addition to milk. If the child is over 6 months old and such foods are not yet being given, they should be started during the diarrhoea episode or soon after it stops.

Recommended foods should be culturally acceptable, readily available, have a high content of energy and provide adequate amounts of essential micronutrients. They should be well cooked, and mashed or ground to make them easy to digest; fermented foods are also easy to digest. Milk should be mixed with a cereal. If possible, 5–10 mL of vegetable oil should be added to each serving of cereal. (Most staple foods do not provide enough calories per unit weight for infants and young children. This is improved by adding some vegetable oil.) Meat, fish or egg should be given, if available. Foods rich in potassium, such as bananas, green coconut water and fresh fruit juice, are beneficial.

**How much food and how often**

Offer the child food every three or four hours (six times a day). Frequent small feedings are tolerated better than less frequent large ones.

After the diarrhoea stops, continue giving the same energy-rich foods and provide one more meal than usual each day for at least 2 weeks. If the child is malnourished, extra meals should be given until the child has regained normal weight for height.

**Rule 4: Take the child to a healthcare worker if there are signs of dehydration or other problems**

The mother should take her child to a healthcare worker if the child:

- starts to pass many watery stools
- has repeated vomiting
- becomes very thirsty
- is eating or drinking poorly
- develops a fever
- has blood in the stool
- does not get better in 3 days.

**WHO Treatment Plan B: oral rehydration therapy for children with some dehydration**

Children with some dehydration should receive oral rehydration therapy with ORS in a healthcare facility following the treatment plan described below.

Children with some dehydration should also receive zinc supplementation as described above.

**TABLE 5.12.A.6 Guidelines for treating children with some dehydration: approximate amount of ORS to give in the first 4 hours**

Age	< 4 months	4–11 months	12–23 months	2–4 years	5–14 years	15 years or older
Weight (kg)	< 5	5–7.9	8–10.9	11–15.9	16–29.9	30 kg or more
Volume (mL)	200–400	400–600	600–800	800–1200	1200–2200	2200–4000

**How much ORS is needed?**

Use Table 5.12.A.6 to estimate the amount of ORS needed for rehydration. If the child's weight is known, this should be used to determine the approximate amount of solution needed. The amount may also be estimated by multiplying the child's weight in kg by 75 mL. If the child's weight is not known, select the approximate amount according to the child's age.

The *exact* amount of solution required will depend on the child's dehydration status. Children with more marked signs of dehydration, or who continue to pass frequent watery stools, will require more solution than those with less marked signs or who are not passing frequent stools. *If the child wants more than the estimated amount of ORS, and there are no signs of over-hydration, give more.*

Oedematous (puffy) eyelids are a sign of *over-hydration*. They may be a sign of chronic malnutrition. If this occurs, stop giving ORS, but give breast milk or plain water, and food. Do not give a diuretic. When the oedema has gone, resume giving ORS or home fluids according to Treatment Plan A.

**How to give ORS**

A family member should be taught to prepare and give ORS. The solution should be given to infants and young children using a clean spoon or cup. Feeding bottles should *not* be used. For babies, a dropper or syringe (without the needle) can be used to put small amounts of solution into the mouth.

Children under 2 years of age should be offered a tea-spoonful every 1 to 2 minutes. Older children (and adults) may take frequent sips directly from the cup.

Vomiting often occurs during the first hour or two of treatment, especially when children drink the solution too quickly, but this rarely prevents successful oral rehydration, as most of the fluid is absorbed. After this time vomiting usually stops. If the child vomits, wait 5–10 minutes and then start giving ORS again, but more slowly (e.g. a spoonful every 2–3 minutes).

**Monitoring the progress of oral rehydration therapy**

Check the child from time to time during rehydration to ensure that ORS is being taken satisfactorily and that signs of dehydration are not worsening. If at any time the child develops signs of severe dehydration, switch to WHO Treatment Plan C.

**After 4 hours**, reassess the child fully, following the guidelines in Table 5.12.A.2. Then decide what treatment to give next:

- If signs of *severe dehydration* have appeared, intravenous (IV) therapy should be started following Treatment Plan C. This is very unusual, however, occurring only in children who drink ORS poorly and pass large watery stools frequently during the rehydration period.
- If the child still has signs indicating *some dehydration*, continue oral rehydration therapy by repeating Treatment Plan B. At the same time start to offer food, milk and

other fluids, as described in Treatment Plan A (see above), and continue to reassess the child frequently.

If there are *no signs of dehydration*, the child should be considered fully rehydrated. When rehydration is complete:

- the skin pinch is normal
- thirst has subsided
- urine is passed
- the child becomes quiet, is no longer irritable and often falls asleep.

Teach the mother how to treat her child at home with ORS and food following Treatment Plan A. Give the mother enough ORS sachets for 2 days. Also teach her the signs that mean she should bring her child back.

- Use the patient's age only when you do not know their weight. The approximate amount of ORS required (in mL) can also be calculated by multiplying the patient's weight in kg by 75.
- If the patient wants more ORS than is shown above, give more.
- Encourage the mother to continue breastfeeding her child.
- For infants under 6 months who are not breast fed, if using the old WHO ORS solution containing 90 mmol/L of sodium also give 100–200 mL clean water during this period. However, if using the new reduced (low) osmolality ORS solution containing 75 mmol/L of sodium, this is not necessary.

**Note:** During the initial stages of therapy, while still dehydrated, adults can consume up to 750 mL per hour, if necessary, and children up to 20 mL/kg body weight/hour.

**Meeting normal fluid needs**

While treatment to replace the existing water and electrolyte deficit is in progress, the child's normal daily fluid requirements must also be met. This can be done as follows:

- **Breastfed infants:** continue to breastfeed as often and for as long as the infant wants, even *during* oral rehydration.
- **Non-breastfed infants** under 6 months of age: if using the old WHO ORS solution containing 90 mmol/L of sodium also give 100–200 mLs clean water during this period. However, if using the new reduced (low) osmolality ORS solution containing 75 mmol/L of sodium, this is not necessary.
- **Older children:** throughout rehydration and maintenance therapy, offer as much plain boiled water to drink as they wish, in addition to ORS.

**If oral rehydration therapy must be interrupted**

If the mother and child must leave hospital before rehydration with ORS is completed:

- Show the mother how much ORS solution to give to finish the 4-hour treatment at home.

- Give her enough ORS packets to complete the 4-hour treatment and to continue oral rehydration for two more days, as shown in Treatment Plan A.
- Show her how to prepare ORS solution.
- Teach her the four rules in Treatment Plan A for treating her child at home.

### When oral rehydration fails

With the previous ORS, signs of dehydration would persist or reappear in about 5% of children. With the new reduced (low) osmolality ORS it is estimated that such treatment 'failures' will be reduced to 3% or less. The usual causes for these 'failures' are:

- continuing rapid stool loss (more than 15–20 mL/kg/hour), as occurs in some children with cholera
- insufficient intake of ORS due to fatigue or lethargy
- frequent severe vomiting.

Such children should be given ORS by nasogastric (NG) tube or Ringer Lactate Solution intravenously (IV) (75 mL/kg in four hours) usually in hospital. After confirming that the signs of dehydration have improved, it is usually possible to resume ORT successfully.

### Rarely, oral rehydration therapy should not be given. This is true for children with:

- abdominal distension with paralytic ileus, usually caused by opiate drugs (e.g. codeine, loperamide) and hypokalaemia
- glucose malabsorption (indicated by a marked increase in stool output, failure of the signs of dehydration to improve, and a large amount of glucose in the stool).

In these situations, rehydration should be given IV until the diarrhoea subsides; nasogastric therapy should *not* be used.

### Giving zinc

Begin to give supplemental zinc, as in Treatment plan A, as soon as the child is able to eat, following the four hour rehydration period.

### Giving food

Except for breast milk, food should not be given during the initial 4-hour rehydration period. However, children who are continued on Treatment Plan B for longer than 4 hours should be given some food every 3–4 hours as described in Treatment Plan A. All children older than 6 months of age should be given some food before being sent home. This helps to emphasise to mothers the importance of continued feeding during diarrhoea.

### WHO Treatment Plan C: intravenous rehydration therapy for patients with severe dehydration

The preferred treatment for children with severe dehydration is initial rapid intravenous rehydration following Treatment Plan C. If possible, the child should be admitted to hospital. Guidelines for IV rehydration are given in Table 5.12.A.7.

Children who can drink, even poorly, should be given ORS by mouth until the IV drip is running. In addition, all children should receive some ORS solution (about 5 mL/kg/hr) when they can drink without difficulty, which is usually within 3–4 hours for infants and 1–2 hours for older patients.

This provides additional base and potassium which may not be adequately supplied by the IV fluid.

### Monitoring the progress of intravenous rehydration

Patients should be reassessed every 15–30 minutes until a strong radial pulse is present. If it is not, the intravenous drip should be given more rapidly.

When the planned amount of intravenous fluid has been given (after 3 hours for older patients, or 6 hours for infants), the child's hydration status should be reassessed fully as in Table 5.12.A.2.

Look and feel for all the signs of dehydration

- If signs of *severe* dehydration are still present, **repeat** the intravenous fluid infusion as outlined in Treatment Plan C. This is very unusual, however, occurring only in children who pass large watery stools frequently during the rehydration period.
- If the child is improving (able to drink) but still shows signs of *some dehydration*, **discontinue** the intravenous infusion and give ORS for 4 hours, as specified in Treatment Plan B.
- If there are *no signs of dehydration*, follow Treatment Plan A. If possible, observe the child for at least six hours before discharge while the mother gives the child ORS, to confirm that she is able to maintain the child's hydration. Remember that the child will require therapy with ORS until the diarrhoea stops.

If the child cannot remain at the treatment centre, teach the mother how to give treatment at home following Treatment Plan A, give her enough ORS packets for two days and teach her the signs that mean she should bring her child back.

### What to do if intravenous therapy is not available

- If IV therapy is not available at the facility, but can be given nearby (i.e. within 30 minutes), send the child immediately for intravenous treatment. If the child can drink, give the mother some ORS and show her how to give it to her child during the journey.
- If IV therapy is not available nearby, healthcare workers who have been trained can give ORS by NG tube, at a rate of 20 mL/kg body weight per hour for 6 hours (total of 120 mL/kg body weight). If the abdomen becomes

**TABLE 5.12.A.7 Guidelines for intravenous treatment of children with severe dehydration**

Start IV fluids immediately. If the patient can drink give ORS by mouth until the drip is set up. Give 100 mLs/kg of Ringers Lactate Solution <sup>a</sup> divided as follows		
Age	First give 30 mL/kg in:	Then give 70 mL/kg in:
Infants under 12 months	1 hour <sup>b</sup>	5 hours
Older	30 minutes <sup>b</sup>	Over 2.5 hours

Reassess the patient every 1–2 hours. If hydration is not improving, give the IV drip more rapidly. After six hours (infants) or three hours (older patients), evaluate the patient using the assessment chart. Then choose the appropriate Treatment Plan (A, B or C) to continue treatment

- If Ringers Lactate Solution is not available, normal saline may be used
- Repeat once if radial pulse is still very weak or not detectable

swollen, ORS should be given more slowly until the abdomen becomes less distended.

- If NG treatment is not possible but the child can drink, ORS should be given by mouth at a rate of 20 mL/kg body weight per hour for 6 hours (total of 120 mL/kg body weight). If this rate is too fast, the child may vomit repeatedly. In this case, give ORS more slowly until the vomiting subsides.
- Children receiving NG or oral therapy should be reassessed at least every hour. If the signs of dehydration do not improve after 3 hours, the child must be taken immediately to the nearest facility where intravenous therapy is available. Otherwise, if rehydration is progressing satisfactorily, the child should be reassessed after

6 hours and a decision on further treatment made as described above for those given IV therapy.

- If neither NG nor oral therapy is possible, the child should be taken *immediately* to the nearest facility where IV or NG therapy is available.

### Further reading

World Health Organization (2005) *The Treatment of Diarrhoea: a manual for physicians and other senior health workers*, 4th revision. <http://whqlibdoc.who.int/publications/2005/9241593180.pdf>

World Health Organization and UNICEF (2013) *Ending Preventable Child Deaths from Pneumonia and Diarrhoea by 2025: the integrated Global Action Plan for Pneumonia and Diarrhoea (GAPPD)*. [http://apps.who.int/iris/bitstream/10665/79200/1/9789241505239\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/79200/1/9789241505239_eng.pdf)

## 5.12.B Post-infectious prolonged or persistent diarrhoea

### BOX 5.12.B.1 Minimum standards

- Low-osmolality ORS and ReSoMal in severely malnourished children.
- Ringer-lactate or Hartmann's solution with potassium: oral and IV.
- Antibiotics: amoxicillin, gentamicin.
- Vitamin A and zinc.
- Electrolyte and mineral mix.
- Folic acid.

### Introduction

#### Epidemiology

- Diarrhoeal episodes that start acutely and last for 7–14 days are usually labelled as prolonged diarrhoea, and may be associated with greater morbidity and more severe nutritional consequences.
- Persistent diarrhoea is commonly defined as diarrhoea that starts acutely, but lasts for more than 14 days and is associated with growth faltering.
- Most cases are thus post-infectious in origin, and other disorders such as inflammatory bowel disease and coeliac disease are therefore excluded.
- Around 4–20% of all episodes of diarrhoea in resource-limited countries become prolonged, with associated case-fatality rates that may exceed 50% in severe cases.
- In parts of sub-Saharan Africa, the association of persistent diarrhoea with HIV infection is often the terminal event.

#### Risk factors for prolonged and persistent diarrhoea

Appropriate case management of acute diarrhoea is key to the prevention of prolonged episodes.

**Specific pathogens:** although some studies have identified an association between persistent diarrhoea and infections with organisms such as entero-aggregative *E. coli* or *Cryptosporidium*, this is by no means pathognomonic, nor is there a particular pattern of small bowel microbial colonisation or overgrowth seen in most cases. In HIV-endemic parts of Africa an association of persistent diarrhoea with cryptosporidiosis is well recognised, but may

represent a manifestation of immunodeficiency. Evidence from Bangladesh does suggest that recurrent bouts of infection with bacterial pathogens such as *Shigella* lead to prolongation of the duration of successive diarrhoeal episodes, and thus there is a link between prolonged and persistent diarrhoea as an epidemiological continuum.

**Malnutrition:** persistent diarrhoea is commonly seen in association with significant malnutrition, and the relationship may be bidirectional. It is widely recognised that diarrhoeal episodes, especially if invasive, may become prolonged in malnourished children. The recent evidence of micronutrient deficiencies, especially of zinc and vitamin A in malnourished children with persistent diarrhoea, may indicate impaired immunological mechanisms for clearing infections, as well as ineffective mucosal repair mechanisms.

**Dietary risk factors:** although many children with persistent diarrhoea are lactose-intolerant, there is no role of specific dietary allergies in inducing and perpetuating enteropathy of malnutrition or post-infectious prolonged diarrhoea. Several studies have highlighted the high risk of prolonged diarrhoea with lactation failure and early introduction of artificial feeds in resource-limited countries.

**Inappropriate management of acute diarrhoea:** the association of prolongation of diarrhoea with food deprivation and inappropriately prolonged administration of parenteral fluids is well recognised. Unnecessary food withdrawal, and replacement of luminal nutrients, especially breast milk, with non-nutritive agents is prolonging the mucosal injury after diarrhoea. In particular, blanket administration of antibiotics and **any administration of anti-motility agents must be avoided**. Optimal management of acute diarrhoea episodes with ORS, zinc and appropriate diets is a key factor in reducing the risk of recurrence and prolongation of diarrhoeal episodes.

### Principles of management of persistent diarrhoea

In general, the management of persistent diarrhoea in malnourished children (see Figure 5.12.B.1) represents a blend of the principles of management of acute diarrhoea and malnutrition (see Section 5.12.A and Section 5.10.B).

Associated malnutrition may be quite severe in affected children, necessitating appropriate and rapid nutritional rehabilitation, sometimes in hospital. Given the chronicity of the disorder, prolonged hospitalisation may be quite problematic in resource-limited countries, and whenever possible the importance of ambulatory or home-based therapy must be emphasised.

The following represent the basic principles of management of persistent diarrhoea, and a suggested therapeutic approach is shown in Figure 5.12.B.1.

### Rapid resuscitation and stabilisation

- Most children with persistent diarrhoea and associated malnutrition are not severely dehydrated, and oral rehydration is adequate.
- However, acute exacerbations and associated vomiting may require brief periods of intravenous rehydration with Ringer-lactate solution.
- Acute electrolyte imbalance such as hypokalaemia and severe acidosis may require correction (see Section 5.6.A).
- Associated systemic infections (bacteraemia, pneumonia and urinary tract infections) are well recognised in severely malnourished children with persistent diarrhoea, and are a frequent cause of early mortality. These must be screened for at admission. In severely ill children requiring hospitalisation, it may be best to cover with

intravenous antibiotics at admission (usually ampicillin, IV 25 mg/kg three times daily up to a maximum of 4 grams/day, and gentamicin, IV 7.5 mg/kg once daily) while awaiting cultures. In other instances with suspected severe pneumonia, oral amoxicillin will suffice.

- It should be emphasised that there is little role for oral antibiotics in persistent diarrhoea, as in most cases the original bacterial infection that triggered the prolonged diarrhoea has disappeared by the time the child presents.

### Oral rehydration therapy

This is the preferred mode of rehydration and replacement of ongoing losses. Although in general the standard low-osmolality WHO oral rehydration solution (containing 75 mmol/litre of Na<sup>+</sup>) is adequate, some evidence indicates that the hypo-osmolar rehydration fluid ReSoMal (containing 45 mmol/litre of Na<sup>+</sup>) as well as cereal-based oral rehydration fluids may be advantageous in severely malnourished children. In general, replacing each stool with about 50–100 mL of ORS or ReSoMal is safe.

### Enteral feeding and diet selection

- Most children with persistent diarrhoea are not lactose intolerant, although administration of a lactose load exceeding 5 grams/kg/day is associated with higher rates of stooling and treatment failure. In general,

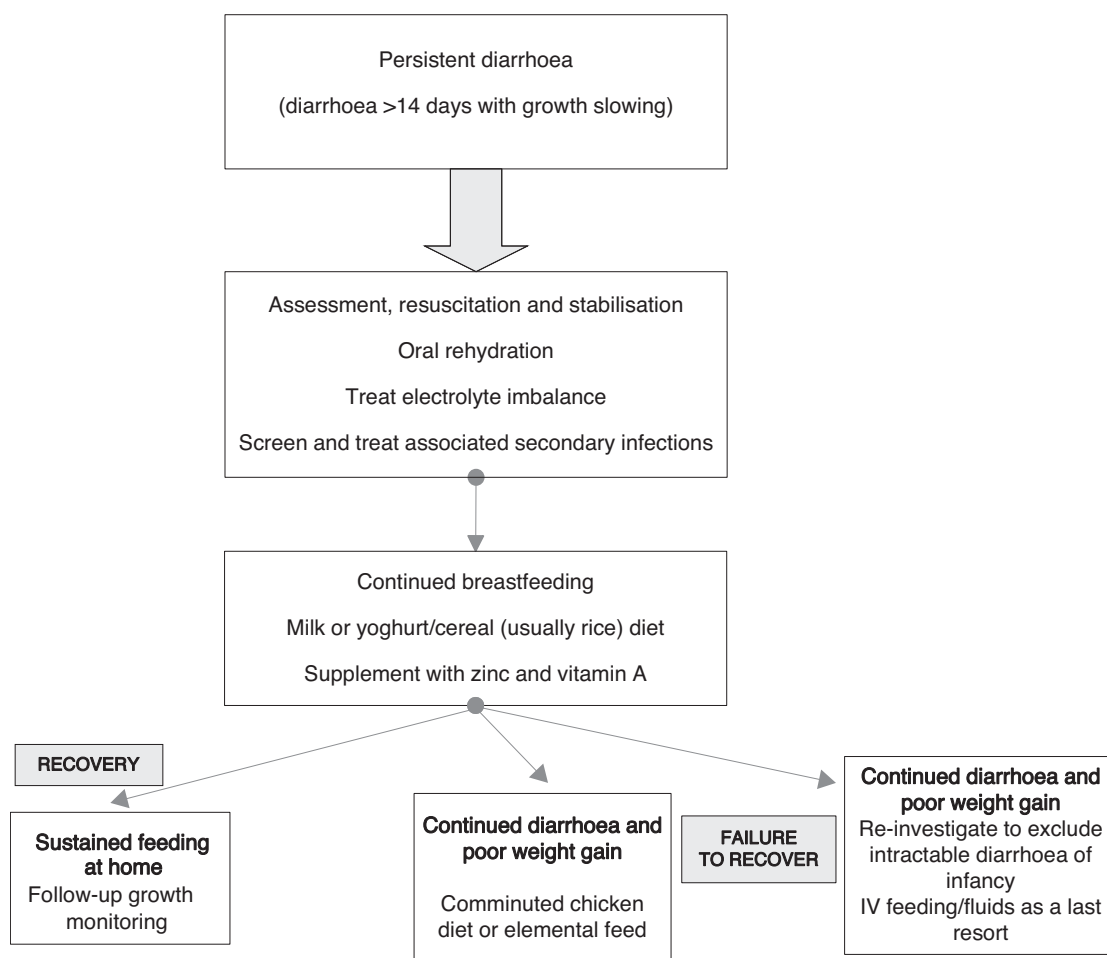


FIGURE 5.12.B.1 Management of persistent diarrhoea in malnourished children.

therefore, withdrawal of milk and replacement with specialised (and expensive) lactose-free formulations is unnecessary.

- Alternative strategies for reducing the lactose load in malnourished children with persistent diarrhoea include reducing the overall amount of milk intake, addition of lactose-free milk to cereals, and replacement of milk with fermented milk products such as yoghurt. These measures have now been extensively evaluated in successive studies of the management of persistent diarrhoea in South Asia, and found to be extremely effective.
- It is rare to find persistent diarrhoea in breastfed infants, and **it must be emphasised that breastfeeding must not be stopped under any circumstances.**
- Rarely, when dietary intolerance precludes the administration of cow's-milk-based formulations or milk, it may be necessary to administer specialised milk-free diets such as a comminuted or blenderised chicken-based diet or an elemental formulation. However, the latter may be almost unaffordable in most resource-limited countries. A choice of enteral diets and formulations is given in Table 5.12.B.2. It must be emphasised that this

is extremely rare, and most infants will recover with the approach outlined above.

- The usual energy density of any diet used for the therapy of persistent diarrhoea should be around 1 kcal/gram, aiming to provide an energy intake of at least 110 kcal/kg/day and a protein intake of 2–3 grams/kg/day (in meals given six times daily). Nasogastric feeding may be required during the first 2–3 days of care, particularly while infection is being treated.
- There should be at least 3 successive days of increasing weight before a response can be verified.
- Dietary failure is shown by an increase in stool frequency (> 10 watery stools/day) or a failure to establish a daily weight gain within 7 days.
- In selected circumstances when adequate intake of energy-dense food is problematic, the addition of amylase to the diet through germination techniques which increase the endogenous amylase content of foods may be helpful. The ready-to-use therapeutic foods (RUTFs) can be used in moderate amounts in children with severe malnutrition and persistent diarrhoea, and the diets below also offer a suitable alternative.

**TABLE 5.12.B.2 Suggested composition of selected diets in children with persistent diarrhoea**

Component	Khitchri (rice-lentils) (per 100 grams)	Home made version of F-75 diet (WHO) (per 1000 mL)	Comminuted chicken (per 100 grams)	Semi-elemental diet (per 100 mL)
Protein	Mung lentils, 30 grams	Dried skimmed milk, 25 grams	Protein, 8 grams	Protein, 2.25 grams (hydrolysed)
Fat	Oil, 2 grams	Vegetable oil, 27 grams	Fat, 4 grams	Fat, 1.65 grams (medium-chain triglycerides)
Minerals and micronutrients	Salt (to taste)	Vitamin mix, 140 mg Mineral mix, 20 mL	Electrolytes (sodium, 0.4 mmol; potassium, 1.3 mmol; calcium, 0.2 mmol; phosphorus, 1.5 mmol)	Electrolytes (sodium, 1.9 mmol; potassium, 2.3 mmol; calcium, 1.8 mmol)
Carbohydrate	Rice, 60 grams	Cereal flour, 35 grams Sugar, 70 grams		Caloreen, 5 grams

#### **First diet: a starch-based reduced milk concentration (low-lactose) diet**

The diet should contain at least 70 kcal/100 grams, provide milk or yoghurt as a source of animal protein, but no more than 3.7 grams of lactose/kg body weight/day, and should provide at least 10% of calories as protein. The following example provides 83 kcal/100 grams, 3.7 grams of lactose/kg body weight/day and 11% of calories as protein:

- full-fat dried milk: 11 grams (or whole liquid milk: 85 mL)
- rice: 15 grams
- vegetable oil: 3.5 grams
- cane sugar: 3 grams
- water to make up to 200 mL.

Of the children who do not improve on this first diet, more than 50% will improve when given the second diet, from which the milk has been totally removed and starch (cereals) partly replaced with glucose or sucrose.

#### **Second diet: a no-milk (lactose-free) diet with reduced cereal (starch)**

The second diet should contain at least 70 kcal/100 grams, and provide at least 10% of calories as protein (egg or chicken). The following example provides 75 kcal/100 grams:

- whole egg: 64 grams

- rice: 3 grams
- vegetable oil: 4 grams
- glucose: 3 grams
- water to make up to 200 mL.

Finely ground, cooked chicken (12 grams) can be used in place of egg to give a diet that provides 70 kcal/100 grams.

Of the children who do not improve on the first diet, more than 50% will improve when given the second diet, from which milk has been totally removed and starch (cereals) partly replaced with glucose or sucrose.

#### **Micronutrient supplementation**

Most malnourished children with persistent diarrhoea have associated deficiencies of micronutrients, including zinc, iron and vitamin A. This may be a consequence of poor intake and continued enteral losses. It is therefore important to ensure that all children with persistent diarrhoea and malnutrition receive an initial dose of vitamin A orally, or if that is not possible by deep intramuscular injection (< 6 months of age, 50 000 units; 6–12 months, 100 000 units; > 1 year, 200 000 units). They should also receive a daily intake of the following for the next 2 weeks:

- a multivitamin supplement

- folic acid, 250 micrograms/kg on day 1, then 75 micrograms/kg/day
- zinc, 3–5 mg/kg/day.
- copper, 0.3 mg/kg/day
- magnesium, 0.2 mmol/kg/day.

Although the association of significant anaemia with persistent diarrhoea is well recognised, iron replacement therapy should not be initiated until recovery from diarrhoea has started (ferrous sulphate 18 mg/kg/day, or 6 mg/kg/day of elemental iron in two divided doses).

### Follow-up and nutritional rehabilitation

Given the high rates of relapse in most children with persistent diarrhoea, it is important to address the underlying risk factors and institute preventive measures. These include appropriate feeding (breastfeeding, complementary feeding) and close attention to environmental hygiene and sanitation. This poses a considerable challenge in communities deprived of basic necessities such as clean water and sewage disposal.

By the time they return home, children should be receiving a diet that provides at least 110 kcal/kg/day (including milk and fresh fruit and well-cooked vegetables).

### Further reading

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## 5.12.C Constipation

### BOX 5.12.C.1 Minimum standards

- Movicol – osmotic laxative – softens
- Lactulose – osmotic laxative – softens
- Docusate sodium – softener and weak stimulant
- Senna or sodium picosulphate-stimulant laxative
- Glycerine suppositories – lubricant and rectal stimulant
- Small volume of phosphate enema (e.g. fleet enema)
- Sodium citrate enema (e.g. Micralax enema).

### Introduction

#### Definition

Constipation is defined as difficulty with, delay in or pain on defecation.

#### Normal defecation patterns

- Breastfed babies average three stools per day and formula-fed babies two stools per day. However, the range of normal stool frequency in breastfed babies is very wide, from one stool every few days to a stool with every feed.
- Children average one stool per day after 3 years, but the normal range is from once on alternate days to three times daily.

#### Pathophysiology

Most children with constipation have no underlying medical cause. An episode of constipation can be triggered by inadequate food or fluid intake, an intercurrent illness, or excessive intake of cow's milk.

#### Constipation cycle

The child passes a hard painful stool. On subsequent

occasions they try to withhold the stool in order to avoid experiencing pain (faecal holding). The stool remains in the rectum, becoming harder still, and so causing even more pain when it is eventually passed.

If this cycle is allowed to continue, eventually the rectum may become enlarged, resulting in a 'megarectum'. The child by this stage has lost the normal urge to defecate, and the large rectal mass of stool holds open the anal sphincter, which leads to soiling with liquid faeces. This is involuntary and should not be confused with encopresis, which occurs when the child voluntarily passes normal stools in unacceptable places.

### Diagnosis

Diagnosis can usually be made by taking a good history.

- On examination of the abdomen, faecal masses may be palpable. These are often in the left and right iliac fossae, but sometimes suprapubically. On inspection of the anus, anal tags and fissure may be seen in chronic constipation.
- On rectal examination, hard impacted faeces may be felt. Rectal examination is usually not necessary. If there is an anal fissure, rectal examination should be done with topical lignocaine jelly (1%) and terminated if it is too painful.
- Abdominal X-ray is not a useful examination for diagnosis of constipation.

#### Pathological causes

The vast majority of constipation is idiopathic, but there are a few uncommon causes that are important not to miss.



### Hirschsprung's disease

Suspect this when there is infancy-onset constipation and a delay of more than 48 hours in passing meconium at birth. In more advanced cases there will be abdominal distension and sometimes failure to thrive and vomiting. There may be alternating constipation and diarrhoea and surprisingly little soiling for the degree of constipation. On rectal examination an explosive gush of faeces occurs when the examining finger is withdrawn.

### Anal lesions that cause pain or create an obstruction

These include anal fissures, perianal skin infections and (rarely) congenital anterior anus and anal stenosis. One cause of painful anal lesions is sexual abuse, a rare but important cause which should not be missed.

### Endocrine conditions

Hypothyroidism, renal tubular acidosis, diabetes insipidus and hypercalcaemia can be associated with constipation. There should be a high level of suspicion for a metabolic or endocrine cause if constipation and failure to thrive coexist.

### Neurogenic constipation

Spinal cord lesions involving sensation in the rectum will cause neurogenic constipation. These can be excluded by a normal neurological and spinal examination.

### Management of idiopathic constipation

Parental understanding of the aetiology and sequence of events in developing chronic constipation is crucial to successful physical and psychological management (see Figure 5.12.C.1). Each and every element of this flow diagram should be addressed and treated if management is to be completely successful.

### Explanation

A careful and thorough explanation of the problem should be given to the parent and child. Emphasise that soiling

is not deliberate, and that the child needs support, not condemnation. Assess the need for psychological as well as physical treatment.

### Evacuation of hard impacted faeces

- 1 To soften and lubricate the retained faeces, initially give a softener. This could be a macrogol such as Movicol or another softening laxative such as docusate sodium. The dose will vary according to age.
- 2 Alongside the softener, in order to expel the retained mass, give a stimulant laxative (e.g. sodium picosulphate).
- 3 If sodium picosulphate is not available, a large dose of senna can be tried, but may need to be used for longer.
- 4 Only if the above fails give suppositories (glycerine) once daily (infant, 1 gram; child < 12 years, 2 grams; child > 12 years, 4 grams).
- 5 If the oral and suppository methods are unsuccessful, if excessive abdominal pain develops and/or there is vomiting, stimulant enemas will be required. Phosphate enemas should not be used in children under 2 years of age. For children aged 2–10 years give 60 mL (half a phosphate enema) and for those over 10 years of age give 120 mL (full enema). If phosphate enemas are not available, a small-volume sodium citrate enema (micro-enema) can be used. However, the use of enemas can add to the child's fear of defecation. **The child should never be forcibly held down to receive an enema.** Give enemas **once a day** in the morning. Most children need two or three enemas to clear a faecal mass.
- 6 If these measures fail, the child should undergo manual evacuation of faecal mass under general anaesthetic, **but only if this is available and can be done safely.**

### Maintenance laxatives to keep the stool soft, defecation pain-free and overcome faecal holding

- Softening agents such as Movicol or docusate sodium to keep the stool soft.
- Stimulant laxatives, usually senna or sodium picosulphate, to expel the soft stool. The aim is to produce

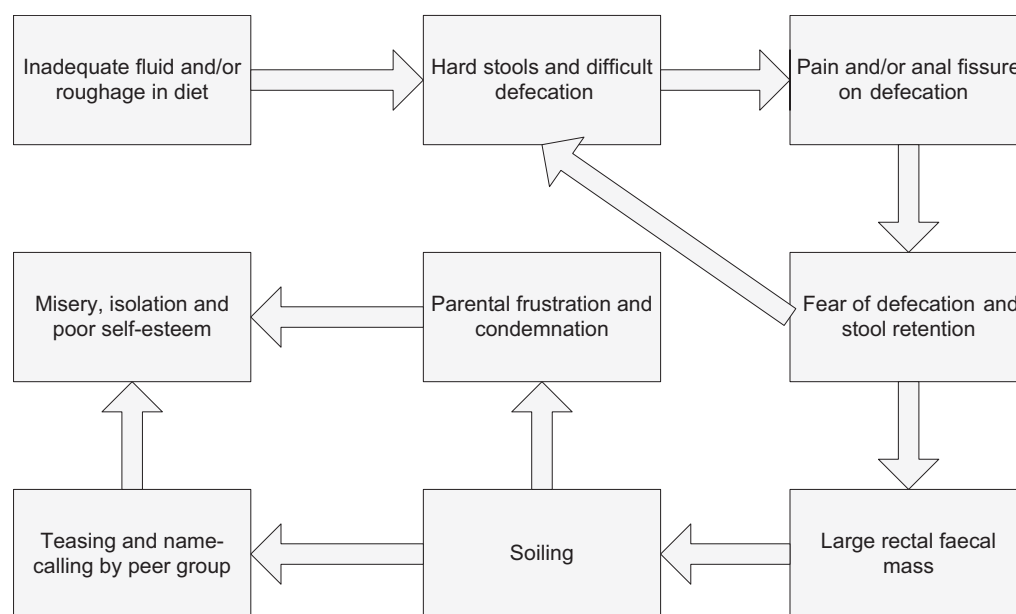


FIGURE 5.12.C.1 Sequence of events in faecal soiling.

loose stools initially and then subsequently reduce the dose to produce at least one soft stool per day. Often large doses will be required initially to overcome the child's faecal holding.

### Behaviour changes

- Encourage increased fluid intake and a high-roughage diet (fruit, vegetables and cereals).
- Give positive praise and encouragement for regular toileting, and for passage of stool into the toilet.

### Length of treatment

Children are likely to require several months of stimulant laxatives until their fear of defecation resolves, and often months to years of continuous or intermittent treatment with softening laxatives. A general rule of thumb is that the child will need laxatives for the same length of time that they were constipated before treatment started.

## 5.12.D Inflammatory bowel disease

### BOX 5.12.D.1 Minimum standards

- Aminosalicylates.
- Prednisolone.
- Methylprednisolone.
- Corticosteroid enemas.
- Blood transfusion.
- Polymeric diet.
- Metronidazole.

### Introduction

Inflammatory bowel disease (IBD) is uncommon in children in resource-limited countries, where abdominal tuberculosis is more common. However, in the UK about 18% of children with IBD are non-white, of whom most are of either Indian or Caribbean origin. Although IBD may present in younger children, the mean age in the UK is approximately 12 years. Crohn's disease is more than twice as common as ulcerative colitis. A family history is common.

### Diagnosis

- Clinical symptoms of ulcerative colitis are almost invariably bloody diarrhoea with predefecation abdominal pain and tenesmus. Crohn's disease may have a wide variety of symptoms, especially extra-intestinal ones. Iron-deficiency anaemia is common in both.

- The interval between onset of symptoms and diagnosis is often over 6 months in Crohn's disease, and may be 2–3 months in ulcerative colitis. Denial of symptoms is common, especially in adolescents.

### Investigations

- Growth parameters and investigations are a guide to the severity and duration of disease and the nutritional state of the child.
- Examination of the mouth and anus is essential.
- Stool examination is essential to exclude bacterial and parasitological causes of diarrhoea, especially before corticosteroids are prescribed.
- Normal investigations: acute-phase reactants (erythrocyte sedimentation rate or C-reactive protein), haemoglobin, platelet count, albumin; do not exclude ulcerative colitis, but normal blood tests would be very unusual in Crohn's disease.
- Children with ulcerative colitis often have little or no weight loss or growth failure.
- Children with Crohn's disease and severe involvement of the colon may present similarly to those with ulcerative colitis, but generally have larger haematological changes.

TABLE 5.12.D.1 Comparison between Crohn's disease and ulcerative colitis

Feature	Ulcerative colitis	Crohn's disease
Pathology	Mucosal disease	Transmural disease, skin lesions, strictures, fistulae
Site	Recto-colonic (rectum always involved). In children over 70% have a pancolitis	Panenteric disease is common in children: small bowel and colon, 50%; colon, 35%; ileum, 6%; upper gastrointestinal tract, 50%
Common presenting symptoms	Diarrhoea mixed with blood/mucus Pain (lower abdominal) Often no or little weight loss	Pain in the right iliac fossa Diarrhoea with or without blood Growth failure and weight loss Peri-anal and oral disease
Extra-intestinal features (finger clubbing, arthritis, skin disorders, fever)	Uncommon	Common

### General investigations

#### Stool

- Blood, mucus.

- Microscopy for *Entamoeba histolytica*, *Schistosoma*, *Trichuris trichiura*, *Giardia lamblia*.
- Culture for bacteria.

**Full blood count**

- Haemoglobin level decreased.
- White blood cell count increased.
- Platelet count increased.

**Acute-phase reactants**

- Erythrocyte sedimentation rate raised.
- C-reactive protein raised.

**Chemical pathology**

- Electrolytes (if diarrhoea severe).
- Ferritin (may be spuriously raised – acute-phase reactant).
- Albumin level low.

**Specific investigations**

Specific investigations depend on the availability of paediatric gastrointestinal facilities.

- Sigmoidoscopy is essential.
- Flexible endoscopy of the lower and upper gastrointestinal tract should ideally be undertaken.
- Barium enema (double contrast) is required in colitis **only** if colonoscopy is not available.
- Normal macroscopic appearance of the lower or upper gut **does not exclude IBD. Histology is essential.**
- 'Indeterminate colitis' is a term used to describe patients whose histology is not typical of ulcerative colitis or Crohn's disease. They are usually treated initially as having ulcerative colitis.

**TABLE 5.12.D.2 Specific investigations for Crohn's disease and ulcerative colitis**

Feature	Ulcerative colitis	Crohn's disease
Endoscopy*	Proctoscopy Sigmoidoscopy Colonoscopy	Lower gut Upper gut*
Radiological studies	Barium enema† (double contrast)	Barium meal and follow-through
White blood cell scan (technetium labelled)‡	Screening	Screening

\* Depending on availability.

† Only required if colonoscopy is unavailable.

‡ Only available in well-resourced countries.

**Management of ulcerative colitis**

- Initial management depends on severity.
- Follow-up: parents and older children should be taught so that they understand how to recognise and treat any relapse promptly.

**Management of active colitis (see Table 5.12.D.3)**

- **Mild disease:** less than four motions per day, intermittent blood, normal acute-phase reactants, no toxicity:
  - Aminosaliclates.
  - Mesalazine (1 g rectally) or corticosteroid (20 mg) enema until the bleeding stops, and then given alternate nights for 1 week.

– Corticosteroids given orally if there is no response within 2 weeks.

- **Moderate disease:** four to six motions per day, moderate blood, slight toxicity, anaemia and raised acute-phase reactants:

– As above plus oral steroids immediately. If there is a poor response, treat as for severe disease.

- **Severe disease:** more than six bloody motions per day, nocturnal stools, toxicity, fever, anaemia and hypoalbuminaemia:

– Intravenous pulse methylprednisolone or hydrocortisone dose for 3–5 days.

– Antibiotics (e.g. metronidazole) (benefit is not proven).

– Intravenous fluids and correction of electrolyte deficits.

– Blood transfusion if required.

– Intravenous cyclosporine (500 micrograms–1 mg/kg aged 3–18 years) or oral cyclosporine (2 mg/kg twice daily maximum 5 mg/kg aged 2–18 years) may be of value if there is no response to intravenous corticosteroids.

- **Toxic dilation:** if there is no response to intensive therapy by 12–24 hours, perform colectomy.

**Relapse**

Prompt commencement of rectal mesalazine or a corticosteroid enema is essential. If there is no response, give a course of oral corticosteroids.

**Maintenance**

- Aminosaliclic acid preparations are generally given lifelong. Mesalazine 10 mg/kg 2–3 times daily 5–12 years, 2 G once daily 12–18 years.
- If relapses occur when corticosteroids are reduced, give azathioprine for up to 3–5 years.

**TABLE 5.12.D.3 Drug dosages for ulcerative colitis**

<i>Corticosteroids</i>	
Prednisolone:	2 mg/kg/day (maximum 40 mg) for 3 weeks, then reduce by 5 mg/week
Methylprednisolone:	IV 1–1.5 mg/kg/day (maximum 60 mg)
Hydrocortisone:	IV 4 mg/kg 6-hourly
Prednisolone enema or foam (20 mg in 100 mL):	50–100 mL at night
<i>Aminosaliclates</i>	
Sulphasalazine: (tablets 10 mg and 50 mg)	10 mg/kg 4- to 6-hourly for acute episodes. Decrease the dose by half for maintenance as soon as possible. Urine and tears will turn orange. Report sore throat
Mesalazine: (oral tablets 500 mg)	Under 40 kg body weight aged 5–12 years give 10 mg/kg 2–3 times daily; over 40 kg body weight aged 12–18 years, give 2 G once daily
Mesalazine: rectal	Aged 12–18 years, 1 gram daily
Metronidazole: (orally)	7.5 mg/kg three times daily
Azathioprine: (orally)	1.5–2.5 mg/kg once daily

- Regular monitoring of the blood count (every 1 to 2 months) is important.

### Indicators for colectomy

- Toxic megacolon (see above), intractable disease and growth failure.
- The risk of cancer relates to the extent of disease and its duration. Good maintenance therapy is important for prevention. Two-yearly colonoscopy should be considered in those with pancolitis for 10 years after the commencement of disease.
- Colectomy and ileostomy would be the usual operation in resource-limited settings, and are curative symptomatically, but the patient then has the ileostomy for life.

## Management of Crohn's disease

- The key to management is to maintain growth and nutrition and control symptoms.
- Most children will have recurrent relapses.
- Many will require surgery at some stage.
- Nutritional treatment and support are essential.

### Polymeric diet

A polymeric diet can be any liquid nutritional preparation that is nutritionally complete. Examples would include PaediaSure/Ensure (Abbott Nutrition), Modulen IBD/Resource Junior (Nestle) and Alicalm/Fortini (Nutricia). Polymeric diet is effective in producing 70% remission in small bowel disease and 50% remission in colonic disease. The advantages over corticosteroids are the positive effect on growth and lack of side effects. The diet is given for 6 weeks, usually orally, during which time no other food is given (but the child can drink water), and then the normal diet is re-introduced.

Maintenance therapy with polymeric diet can also be used.

### Drug therapy

See Table 5.12.D.3 for drug dosages in ulcerative colitis.

- Prednisolone 2 mg/kg/day (maximum 40 mg/day) is effective in small and large bowel disease. Continue this dose for 3 weeks, then reduce it by 5 mg/week and then stop. If required to maintain remission, alternate-day therapy may have fewer side effects.
- Mesalazine but not sulphasalazine can be effective for maintaining remission in ileal as well as colonic disease (dose is aged 5–12 years 10–15 mg/kg orally 2–3 times daily, aged 12–18 years 2 G once daily).
- Azathioprine is effective in long-term maintenance and has steroid-sparing effects. It may be useful for healing perianal fistulae. It takes many months to act, and it should be continued for at least 4 years. Blood counts should be undertaken every 1–2 months.
- Metronidazole may be effective in controlling perianal disease and fistulae. It may also reduce small bowel overgrowth. Ciprofloxacin is an alternative.
- Infliximab is a very expensive monoclonal antibody that inhibits tumour necrosis factor alpha (TNF $\alpha$ ). It is used in severe Crohn's disease that is not responding to conventional treatment. It is administered IV at intervals. Because of its immunosuppressive effects there are real dangers from infection, especially **latent TB**. Other side effects include anaphylaxis, lymphoma and possibly demyelinating disorders.

### Surgery

Indications for surgery include failure of medical therapy, intestinal obstruction and growth failure. Strictureplasty may be an effective method of avoiding excision of bowel when strictures are present.

### Follow-up and support for IBD

Patients and their families require long-term understanding and support. Psychological therapy may be helpful in some cases.

## 5.12.E Upper gastroenterological disorders

### Introduction

Upper gastrointestinal disorders are not common complaints in the population presenting to hospitals in resource-limited countries. It may be that symptoms are under-reported or overlooked because of more common problems, such as gastroenteritis, persistent diarrhoea, intestinal helminths and malnutrition. However, certain life-threatening conditions do occur, including obstruction of the oesophagus due to a foreign body, strictures due to caustic soda poisoning, haematemesis due to peptic ulcer or portal hypertension, and volvulus due to malrotation.

In well-resourced communities, particularly where facilities for upper gastrointestinal paediatric endoscopy are available, similar symptoms to those that occur in well-resourced countries present. These include recurrent abdominal pain, epigastric and substernal pain, recurrent/persistent vomiting, dyspepsia and water-brash/heartburn.

### Gastro-oesophageal reflux

TABLE 5.12.E.1 Gastro-oesophageal reflux

Symptoms	Complications
Vomiting (regurgitation)	<i>In Infants</i>
Water-brash/heartburn	Apnoea
Nausea	Life-threatening event
Epigastric/retrosternal pain	<i>All ages</i>
	Failure to thrive*
	Aspiration pneumonia
	Haematemesis
	Anaemia
	Oesophageal stricture

\*Particularly in children with cerebral palsy.

Gastro-oesophageal reflux (GOR) is a normal physiological condition in infants, children and adults. If GOR is associated with complications (as below) then it is termed gastro-oesophageal reflux disease (GORD). GORD is common in children with cerebral palsy.

**Note:** Sandifer–Sutcliffe syndrome is dystonic posturing associated with GOR.

### Diagnosis

Often no investigations are needed and a diagnosis can be made by taking a good clinical history. The following investigations are helpful if they are needed and available:

- **Barium swallow:** This is often the only diagnostic facility available in resource-limited countries. It is a much less sensitive method for diagnosing reflux than pH monitoring, but will detect associated or other conditions such as oesophageal stricture, hiatus hernia, diaphragmatic hernia and malrotation.
- **Endoscopy and biopsy** (particularly looking for oesophagitis).
- pH monitoring: this grades the frequency and duration of exposure of the lower oesophagus to acid (pH < 4.0).

### Management

- Simple GOR in the thriving child: reassurance is all that is needed.
- Excessive regurgitation causing failure to thrive in an infant, or mild symptoms of oesophagitis: treatment by thickening feeds with Carobel (Cow & Gate) or an alginate preparation (e.g. Gaviscon) can be tried.
- Moderate to severe GOR with oesophagitis: H<sub>2</sub>-receptor antagonists, such as ranitidine (2–4 mg/kg twice daily, maximum 150 mg twice daily) or the proton pump inhibitor, omeprazole (700 micrograms to 3 mg/kg once daily) should be given. Motility stimulants such as domperidone (200–400 micrograms/kg every 4–8 hours) may be effective, particularly in children with cerebral palsy. However, proof of their efficacy is lacking.
- Surgery: Nissen fundoplication would be considered if, despite medical management, there **was** severe oesophagitis, failure to thrive or aspiration pneumonia. It is sometimes required in children with cerebral palsy and GOR.

### *Helicobacter pylori*

*Helicobacter pylori* is a ubiquitous bacterium that commonly infects the stomach (especially the antrum) of children in resource-limited countries from an early age. Child-to-child transmission is important. In developed countries up to 40–60% of adults are infected, probably mainly during childhood. Conditions associated with *H. pylori* include the following:

- **Chronic gastritis:** often asymptomatic; not a major cause of abdominal pain in children.
- **Duodenal ulcer:** *H. pylori* has a strong association with duodenal ulcer and must be eradicated to ensure healing.

### Diagnosis

Testing for *H. pylori* should only be undertaken if the child has symptoms of ulcer dyspepsia. Diagnostic tests (outlined

below) are rarely available as routine in resource-limited countries.

- Serology: this is good for epidemiological studies, but has reduced sensitivity in children under 7 years of age.
- Urea breath test (13C-UBT): this is sensitive and specific, especially in children over 6 years of age.
- Faecal antigen testing: this is sensitive and specific in both children and adults.
- Endoscopy: histological demonstration and culture of *H. pylori*.

### Management

Selection of optimal antibacterial agents is difficult because of the development of resistance.

### Suggested regimen

- 1 Omeprazole
  - Aged < 2 years 700 micrograms/kg to 3 mg/kg once daily up to a maximum of 20 mg.
  - Aged > 2 years, body weight 10–20 kg, give 10 mg once daily up to maximum 20 mg once daily.
  - Aged > 2 years, body weight > 20 kg, give 20 mg once daily up to a maximum of 40 mg once daily.
- 2 **plus** antibiotics, such as amoxicillin (< 1 year, 62.5 mg; 1–4 years, 125 mg; 5–12 years, 250 mg; > 12 years, 250–500 mg, three times daily)
- 3 **plus** clarithromycin (7.5 mg/kg twice daily) **or** metronidazole (7.5 mg/kg three times daily).

Treatment should be continued for 1–2 weeks. Strict compliance in order to avoid the development of resistance is imperative.

### Duodenal ulcer

Duodenal ulcers are uncommon in children, but can be life-threatening due to haematemesis, melaena and perforation.

There is often a family history. Common symptoms include epigastric pain that typically:

- is worsened by fasting
- is improved by eating or antacids
- causes **nocturnal waking**.

### Diagnosis

- Endoscopy, including biopsy for *H. pylori*, is the **optimal method**.
- Barium swallow: this is less sensitive for diagnosing acute ulceration and better at detecting scarring.

### Management

- Unless facilities to diagnose *H. pylori* are available, all children should be treated for eradication of presumed *H. pylori*.
- Give H<sub>2</sub> antagonists or a proton pump inhibitor for 6–8 weeks: ranitidine 2–4 mg/kg twice daily (maximum 150 mg twice daily); omeprazole 10 mg for 10–20 kg (can increase to 20 mg) and 20 mg for > 20 kg once daily (can increase to 40 mg).

## 5.12.F Gastrointestinal bleeding

### BOX 5.12.F.1 Minimum standards

- Full blood count.
- Stool examination, microscopy and culture, parasite identification.
- Ultrasound.
- Barium X-ray studies.
- Gastroscopy.
- Colonoscopy.

and clinical examination are essential and will indicate specific investigations.

- In haematemesis, it is important to exclude swallowed blood due to disorders of the nose and mouth.
- In children the commonest cause of fresh rectal bleeding is an anal fissure.
- Melaena has to be differentiated from dark stools associated with medication (e.g. iron preparations) and colouring from foods.
- A large bleed from the upper gastrointestinal tract may present as red blood at the anus because of rapid transit.

### Introduction

- The causes of bleeding from the gastrointestinal tract are many, and relate to the age of the child. A good history

TABLE 5.12.F.1 Causes of gastrointestinal haemorrhage

Site of bleeding	Clinical features/further information
<b>Upper gut</b>	
Poisoning with or treatment with salicylates	'Coffee-ground' vomit
Mallory–Weiss syndrome	
Oesophagitis, gastro-oesophageal reflux	See Section 5.12.E
Portal hypertension, oesophageal varices	See Section 5.7.B (liver disease) See Section 6.3.C.c (schistosomiasis)
<b>Midgut</b>	
Intussusception, volvulus	Infants (see Section 3.4 and 5.19)
Meckel's diverticulum	Often symptomless
<b>Colorectal</b>	
Infection (e.g. shigellosis, amoebiasis)	See Section 5.12.A and Section 6.3.B
Inflammatory bowel disease	Abdominal pain, diarrhoea, weight loss See Section 5.12.D
Milk protein intolerance	See Section 5.12.G
Polyps (single, multiple, Peutz–Jeghers syndrome)	Blood separate from normal stool
<b>Anus</b>	
Fissure	Infants, constipation, tags (see Section 5.12.C)
Crohn's disease	See Section 5.12.D
Miscellaneous	
Necrotising enterocolitis (see Section 3.4), Henoch–Schönlein purpura (see Section 5.13), AIDS (see Section 6.2.D)	
Any coagulation or blood malignancy disorder (see Section 5.11.D and Section 5.14)	

### Investigations

The investigations chosen will depend on the suspected site of bleeding and the clinical features.

See appropriate sections as indicated in the tables above.

It is important to consider the following:

- Stool:
  - Direct observation: blood, mucus.
  - Microscopy: *Cryptosporidium*, *Salmonella*, *E. coli*, *Shigella*, *Campylobacter*, ova, cysts and parasites.
  - Faecal occult blood.
- Full blood count, grouping and cross-matching.
- Serum ferritin and iron levels.
- Isotope scan: diagnosis of Meckel's diverticulum (30% false negative).
- Barium studies: diagnosis of malrotation.
- Ultrasound: diagnosis of intussusception.
- Upper endoscopy: diagnosis and treatment of oesophageal, gastric and/or duodenal bleeding.
- Colonoscopy: diagnosis and treatment of colitis and/or polyps.

**TABLE 5.12.F.2 Features of gastrointestinal bleeding**

History/examination	Looking for:
<i>History</i>	
Acute/chronic, amount of blood	Severity
Endemic area	Schistosomiasis
Haematemesis	Upper gastrointestinal disorder
Nose and mouth lesions	Swallowed blood
Site of any pain	Upper or lower gastrointestinal tract
<i>Stool:</i>	
Hard/loose	Constipation/diarrhoea
Blood mixed in stool	Inflammation/infection
Blood around or separate	Anal fissure/polyp

History/examination	Looking for:
Inflammatory bowel disease, family history	See Section 5.12.D
Bleeding tendency	Clotting disorder, malignancy
<i>Examination</i>	
Nose and mouth lesions	Swallowed blood
Pallor, capillary refill, blood pressure	Anaemia, shock
Petechiae, telangiectasia	Thrombocytopenia, hereditary telangiectasia
Abdomen	Tenderness, hepatosplenomegaly
Anus	Fissure, tags, infection

## 5.12.G Malabsorption, including coeliac disease

### Malabsorption

Malabsorption is an abnormality in absorption of food nutrients from the gastrointestinal tract.

Common causes of malabsorption and resultant failure to thrive in resource-limited countries include recurrent respiratory infection, persistent diarrhoea and HIV infection. None of these require bowel investigation. The main emphasis is on nutritional rehabilitation which regenerates the small bowel atrophy and the immune system (see management of persistent diarrhoea and severe malnutrition in Sections 5.12.B and 5.10.B, respectively). Only a limited response to nutritional support is expected in HIV infection, depending generally on the stage of disease and the response to antiretroviral (ARV) drugs.

### Types of malabsorption

- **Selective:** as seen in lactose intolerance.
- **Partial:** as observed in Crohn's disease and HIV infection.
- **Total:** as seen in coeliac disease.

### Pathophysiology

The gastrointestinal tract functions to digest and absorb nutrients (fat, carbohydrate, protein and fibre), micronutrients (vitamins and trace minerals), water and electrolytes. This is dependent on the proper processing of food by mechanical (chewing and gastric churning) and enzymatic (gastric, pancreatic, biliary or intestinal) means. The final products of digestion are then absorbed through the intestinal epithelial cells.

Malabsorption constitutes the pathological breakdown of the normal physiological sequence of digestion (i.e. intraluminal process), absorption (i.e. mucosal process) and transport (post-mucosal events) of nutrients.

### Clinical features

Symptoms can be intestinal or extra-intestinal, and include the following:

- diarrhoea/steatorrhoea: watery, diurnal and nocturnal, bulky, frequent stools

- bloating
- flatulence
- abdominal discomfort/cramping abdominal pain
- growth retardation
- weight loss
- failure to thrive
- delayed puberty
- swelling or oedema from loss of protein
- anaemia (vitamin B<sub>12</sub>, folic acid and iron deficiency)
- fatigue
- weakness
- muscle cramp
- osteomalacia and osteoporosis
- bleeding tendencies.

### Diagnosis

Investigation is guided by symptoms and signs. Since a range of different conditions can produce malabsorption, it is necessary to look for each of these specifically. Tests are also needed to detect the systemic effects of deficiency of the malabsorbed nutrients (e.g. anaemia with vitamin B<sub>12</sub> malabsorption).

Investigations may include the following:

- full blood count and blood film
- C-reactive protein and erythrocyte sedimentation rate
- serum albumin
- serum iron, ferritin and total iron-binding capacity (TIBC)
- serum folic acid
- serum cholesterol or triglyceride
- serum calcium, phosphate and alkaline phosphatase
- prothrombin time and activated partial thromboplastin time
- blood chemistry (electrolytes, glucose, HCO<sub>3</sub><sup>-</sup>, urea and creatinine)
- serum zinc levels
- stool studies, including cultures.

**TABLE 5.12 G.1 Common causes of malabsorption**

	Common causes of malabsorption
Due to infective agents	Intestinal tuberculosis
	HIV-related malabsorption
	Tropical sprue
	Traveller's diarrhoea
	Parasites, such as <i>Giardia lamblia</i> , fish tapeworm, roundworm, hookworm ( <i>Ancylostoma duodenale</i> and <i>Necator americanus</i> )
Due to structural defects	Blind loops
	Inflammatory bowel diseases (e.g. Crohn's disease)
	Intestinal hurry from surgical procedures (e.g. post-gastrectomy, gastro-jejunostomy)
	Fistulae, diverticulae and strictures
	Short bowel syndrome
Due to mucosal abnormality	Coeliac disease
	Cow's milk intolerance
	Soya milk intolerance
Due to enzyme deficiencies	Lactose intolerance (constitutional, secondary or rarely congenital)
	Sucrose intolerance
Due to digestive failure	Pancreatic insufficiencies
	Cystic fibrosis
	Chronic pancreatitis
	Bile salt malabsorption
	Terminal ileal disease
	Obstructive jaundice
	Bacterial overgrowth
Due to systemic diseases	Coeliac disease
	Hypothyroidism and hyperthyroidism
	Addison's disease
	Diabetes mellitus
	Hyperparathyroidism and hypoparathyroidism
	Malnutrition

**Serological studies**

The following specific tests are carried out to determine the underlying cause:

- IgA anti-transglutaminase antibodies
- IgA anti-endomysial antibodies.

**Radiological studies**

- Barium meal and follow-through.
- Barium enema.
- CT of the abdomen.

**Specialised tests (if available)**

- Biopsy of small bowel.
- Colonoscopy can be helpful in colonic and ileal disease.
- Endoscopic retrograde cholangiopancreatography (ERCP) will show pancreatic and biliary structural abnormalities.
- Glucose hydrogen breath test for bacterial overgrowth.

- Lactose hydrogen breath test for lactose intolerance.
- Magnetic resonance cholangiopancreatography (MRCP).

**Management**

Treatment is directed largely towards management of the underlying cause. In severe nutritional deficiency, hospital admission may be required for total parenteral nutrition (TPN). Subsequently, advice and support from a dietitian is vital.

**Coeliac disease****BOX 5.12.G.1 Minimum standards**

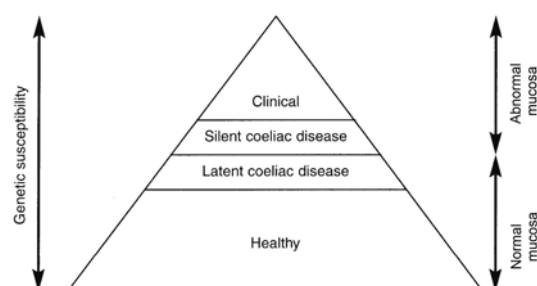
- Gluten-free diet.
- Full blood count and film.

Coeliac disease is an autoimmune disorder of the small intestine in genetically predisposed people of all ages from middle infancy onwards. It is caused by a reaction to gliadin, a gluten protein found in wheat and similar cereals. Therefore it is common among populations whose diet contains substantial amounts of wheat. Apart from people of European origin, in whom it commonly manifests, it is also frequently seen in North Africa, the Middle East, and the north of the Indian subcontinent where wheat is a staple diet. Other populations at increased risk for coeliac disease include children with Down's syndrome and Turner syndrome, type 1 diabetes and autoimmune thyroid disease, including both hyperthyroidism and hypothyroidism.

**Pathophysiology**

Upon exposure to gliadin, the enzyme tissue transglutaminase (tTG) modifies the immune system to cross-react with the small-bowel villous lining, causing an inflammatory reaction. This leads to villous atrophy, which interferes with the absorption of nutrients, minerals and the fat-soluble vitamins A, D, E and K.

Coeliac disease appears to be polyfactorial. Almost all people with coeliac disease have either the HLA-DQ2 or the HLA-DQ8 allele. However, additional factors are needed for coeliac disease to manifest besides the HLA risk alleles. Furthermore, around 5% of those people who do develop coeliac disease may not have typical HLA-DQ2 or HLA-DQ8 alleles.



**FIGURE 5.12.G.1** The spectrum of coeliac disease. Latent coeliac disease: positive anti-endomysial antibodies, normal small bowel, but risk of developing disease.



### Clinical features

Clinical features may range from severe to almost non-existent. Severe coeliac disease in young children leads to the characteristic symptoms of pale, loose and greasy stools (steatorrhoea) with weight loss or failure to gain weight. Adolescents and older children with milder coeliac disease may have symptoms that are much more subtle and occur in other organs rather than in the bowel itself.

**TABLE 5.12.G.2 Clinical features of coeliac disease**

Under 2 years of age	Over 2 years of age
Steatorrhoea	Short stature
Vomiting	Delayed puberty
Abdominal distension	Iron-resistant anaemia
Irritability	Rickets/osteomalacia
Anorexia	Behaviour problems
Growth failure	<i>With or without the gut disorders that occur in younger children</i>

### Diagnosis

The diagnosis of coeliac disease is based on two types of testing.

#### Serological blood tests

These are the first-line investigation and include the following:

- **IgA anti-tissue transglutaminase (tTG) antibodies:** this test is reported to have a high sensitivity (99%) and specificity (over 90%) for identifying coeliac disease. Therefore it should be done first. It is also an easier test to perform. An equivocal result on tTG testing should be followed by antibodies to endomysium.
- **IgA anti-endomysial antibodies:** this test has a sensitivity and specificity of 90% and 99%, respectively, for detecting coeliac disease.

It is important that the total serum IgA level is also checked, as coeliac patients with IgA deficiency may be unable to produce the antibodies on which these tests depend ('false-negative'). In such patients, IgG antibodies against transglutaminase (IgG-tTG) or IgG anti-gliadin antibodies (IgG-AGA) may be helpful in reaching a diagnosis.

#### Dudeno-jejunal biopsies

Because of the implications of a diagnosis of coeliac disease, guidelines recommend that a positive serological blood test may still be followed by a dudeno-jejunal biopsy. Similarly, a negative serology may still be followed by a recommendation for a biopsy if clinical suspicion remains high. Tissue biopsy is still considered the gold standard in the diagnosis of coeliac disease.

For this purpose, biopsies can be obtained using metal capsules attached to a suction device. The capsule is swallowed and allowed to pass into the small intestine. After X-ray verification of its position, suction is applied to collect part of the intestinal wall inside the capsule. Commonly used capsule systems are the Watson capsule and the Crosby-Kugler capsule. This method has now been largely replaced by fibre-optic endoscopy, which carries a higher sensitivity and a lower frequency of errors.

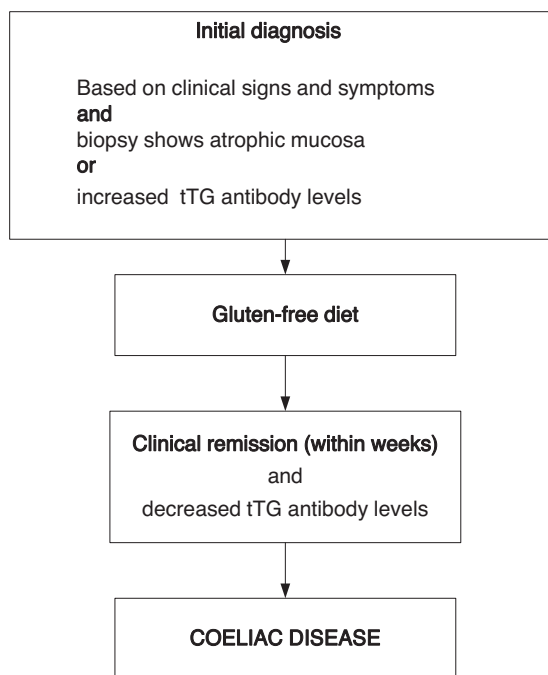
**TABLE 5.12.G.3 Investigations for malabsorption**

General	Specific
Full blood count plus film	Immunoglobulins IgA and IgG
Serum iron and ferritin	IgA tTG antibodies
Folate (red blood cell)	IgA anti-endomysial antibodies
Vitamin B <sub>12</sub> levels	IgA anti-gliadin (AGA)
Serum albumin	Small bowel biopsy:
Hydrogen breath test	<ul style="list-style-type: none"> <li>• Villous atrophy</li> <li>• Hyperplasia of crypts</li> <li>• Increased inflammatory cells</li> </ul>
Serum calcium, phosphate and alkaline phosphatase	
Serum T <sub>4</sub> and TSH	

There are several ways in which these tests can be used to assist in diagnosing coeliac disease. However, all tests become invalid if the patient is already taking a gluten-free diet. Intestinal damage begins to heal within weeks of gluten being removed from the diet, and antibody levels decline over a period of months. In such cases it may be necessary to perform a re-challenge with gluten-containing food over 2–6 weeks before repeating the investigations.

A histology compatible with coeliac disease on a gluten-containing diet, followed by a clinical improvement (i.e. gain in weight and height and resolution of symptoms) once the gluten is removed from the diet is often enough to establish the diagnosis. Most guidelines do not recommend a repeat biopsy unless there is no improvement in the symptoms on the gluten-free diet. In some cases a deliberate gluten challenge, followed by biopsy, may be conducted to confirm or refute the diagnosis. A normal biopsy and normal serology after the challenge indicates that the diagnosis may have been incorrect.

In resource-limited countries where facilities for biopsies may not exist, the same model can be used with serological tests. A positive serological test on a gluten-containing diet will revert to normal with clinical improvement once the patient is on a gluten-free diet.



**FIGURE 5.12.G.2** Diagnosis of coeliac disease.

**BOX 5.12.G.2 Gluten challenge**

Do a gluten challenge if:

- the diagnosis is in doubt
- there is a possibility of another diagnosis, especially in children under 2 years of age (e.g. milk protein intolerance, persistent diarrhoea, giardiasis)
- the response to a gluten-free diet is not clear-cut
- the subject is asymptomatic (e.g. first-degree relatives).

**Note:** Gluten challenge should preferably be undertaken when the child is over 6 years old and before puberty, to reduce the effects on dentition and growth.

**Treatment**

At present, the only effective treatment is a lifelong gluten-free diet. Strict compliance allows the intestines to heal, with resolution of symptoms in most cases. Early intervention and good compliance can eliminate the heightened risk of intestinal cancer and in some cases sterility.

Dietitian input can be helpful in ensuring that the patient is aware of which foods contain gluten, which foods are safe, and how to have a balanced diet despite the limitations. The diet can be cumbersome, and failure to comply may cause relapse.

The commonly implicated cereals include wheat (and its subspecies, such as spelt, semolina and durum), barley, rye and oats.

Other cereals, such as maize (corn), millet, sorghum, teff and rice, are safe for patients to consume. Similarly, non-cereal foods such as fruits, vegetables and foods derived from animal sources (i.e. milk, fish, poultry and other meat) can be used.

**Further reading**

Steele R (2011) Diagnosis and management of coeliac disease in children. *Postgraduate Medical Journal*, **87**, 19–25.  
*European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Guidelines for the Diagnosis of Coeliac Disease:*  
[http://espghan.med.up.pt/position\\_papers/Guidelines\\_on\\_coeliac\\_disease.pdf](http://espghan.med.up.pt/position_papers/Guidelines_on_coeliac_disease.pdf)

## 5.13 Rheumatology

**BOX 5.13.1 Minimum standards**

- Penicillin.
- Aspirin.
- Prednisolone.
- Haloperidol, diazepam and lorazepam.
- Anti-endocarditis measures.
- IV gamma globulin if at all possible.
- Non-steroidal anti-inflammatory drugs (NSAIDs).
- Sulphasalazine.
- Ocular steroids and mydriatics.
- Intra-articular steroids.
- Physiotherapy and family support.

**Introduction**

Making a diagnosis of a rheumatic disease in a child relies primarily on clinical skill and experience, as there are few diagnostic laboratory tests. Although these diseases are rare in children, symptoms that raise the possibility of rheumatic disease are common. Rheumatic symptoms may be relatively specific, such as joint swelling, or relatively non-specific, such as fever, lethargy, pallor, anorexia, failure to thrive, muscle weakness, musculoskeletal pain, rash, headache and abdominal pain. The interpretation of these clinical features requires a meticulous approach to characterising the nature of each feature and considering the overall pattern of all the clinical features in the individual patient. The aims of this section are to assist in the recognition of common patterns of clinical features, and to provide guidance for appropriate treatment and monitoring of rheumatic disease in children.

pGALS (paediatric Gait, Arms, Legs and Spine) is a simple quick approach to joint examination and helps to discern abnormal from normal joints; this is especially useful in the context of non-specific features such as limp or fever. pGALS includes incorporates a series of simple manoeuvres to assess all joints quickly (takes approximately 2–3 minutes). It has been validated in school-aged children (although can be performed in younger children) and has been shown to be effective when performed by non-specialists in detecting significant joint abnormalities in acute paediatric practice (including in Africa). The interpretation of pGALS requires knowledge of normal musculoskeletal development and the clinical context to facilitate a differential diagnosis ([www.arthritisresearchuk.org/health-professionals-and-students/video-resources/pgals.aspx](http://www.arthritisresearchuk.org/health-professionals-and-students/video-resources/pgals.aspx)).

**Rheumatic fever**

Rheumatic fever is an abnormal immune response to group A streptococcal infection in genetically susceptible individuals. It is most common between the ages of 6 and 16 years. Symptoms of acute rheumatic fever follow streptococcal pharyngitis after a latent period of approximately 3 weeks. The disease usually presents with joint pain, but may have an insidious onset, especially if carditis is the predominant feature. There is no definitive test, and diagnosis depends on recognition of clinical signs known as the Jones criteria.