prevention of acidosis with bicarbonate supplements, and control of the bone biochemistry help considerably. Control of uraemia by encouraging a diet containing about 1 gram of protein/kg daily and a high carbohydrate intake will also contribute to good growth.

In young children, the problems are much greater. They are often extremely anorexic; most babies with severe CRF virtually do not feed, and only survive if tube fed for months or even years. Many also vomit excessively. Even when supplemented with tube feeds, very young children with CRF often remain small.

**Transplantation**

Renal transplantation (if it is available) from a living or deceased donor gives the best quality of life for children with end-stage renal failure.

### 5.7 Liver disorders

#### 5.7.A Acute liver failure

**BOX 5.7.A.1 Minimum standards**
- Vitamin K.
- IV glucose 10%.
- Oxygen.
- Lactulose.
- Blood transfusions and clotting factors.
- Ranitidine/antacids.
- Antibiotics and antifungal treatment.
- High-carbohydrate diet.
- N-acetylcysteine.
- Measurements of prolonged blood clotting times.

**Introduction**

In contradistinction to fulminant liver failure in adults, acute liver failure (ALF) in children may not be accompanied by encephalopathy, which tends to be a late feature, or if it occurs early in the course suggests a metabolic cause.

Prolonged prothrombin time (PT) or international normalised ratio (INR) indicates coagulopathy due to the absence of liver-synthesised coagulation factors, and is the basis of the definition of ALF. However, coagulopathy in the presence of liver dysfunction can also result from vitamin K deficiency (usually due to prolonged cholestasis) and consumption of coagulation factors due to disseminated intravascular coagulation (DIC).

**Definition**

Based on the above, ALF is present in children when coagulopathy accompanies liver disease but is not due to DIC or a lack of vitamin K (see Table 5.7.A.1). Administration of IV or IM vitamin K (300 micrograms/kg for children aged 1 month to 12 years: 10 mg for those over 12 years of age) ensures that remaining coagulopathy is due to failed production (liver failure) or excess consumption (DIC). Markers that suggest DIC, rather than ALF, include a low platelet count, compatible blood film (fragmented cells, schistocytes) and a serum bilirubin that is predominantly unconjugated.

**Diagnosis of ALF**

- The history may establish a recent episode of shock including severe dehydration, sepsis or heatstroke, evidence of ingestion of toxic mushrooms or drugs (including those bought over the counter or obtained from any non-conventional source), or exposure to infection such as *Salmonella typhimurium* (see Table 5.7.A.2).
- The possibility of bloodborne or other parenteral infection with hepatitis B up to 6 months previously should be explored.
- Examination may show features of acute portal hypertension with liver tenderness suggesting Budd–Chiari syndrome or a veno-occlusive disease, or lymphadenopathy suggesting malignancy.
- Urine should be tested for bilirubin, urobilinogen and reducing substances.
- Stools should be examined for colour.
- **Tests to establish many of the causes of ALF require sophisticated laboratory facilities which may not be available.**
- The cause may be diagnosed from local epidemiology.
- A blood film and an INR or prothrombin ratio should be measured.
- A full septic screen, **excluding lumbar puncture because of coagulopathy**, should be performed (including fungal cultures and chest X-ray).

**TABLE 5.7.A.1 Clinical features of ALF**

| 1. | Nausea and vomiting is a frequent early feature. |
| 2. | Bruising, petechiae and bleeding secondary to deranged clotting (INR > 4 is associated with 90% mortality). |
| 3. | Jaundice with tender hepatomegaly or a liver that is enlarged but reducing in size in days. |
| 4. | Encephalopathy latterly complicated by features of raised intracranial pressure. |
| 5. | Metabolic alkalosis from failure of the urea cycle associated with a low serum potassium concentration. |
| 6. | Failure to maintain normoglycaemia. |
### TABLE 5.7.A.2 Causes of acute liver failure

<table>
<thead>
<tr>
<th>Type</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infective Viral</td>
<td>Hepatitis A, B, C or D, HIV, parvovirus, herpes virus, enterovirus, adenovirus, echovirus varicella, yellow fever, Lassa fever, Ebola virus, Marburg virus, dengue</td>
</tr>
<tr>
<td>Bacterial, protozoal</td>
<td>Leptospirosis, typhoid, malaria</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Wilson’s disease, tyrosinaemia, urea cycle disorders, galactosaemia, mitochondrial disorders, haemochromatosis, Niemann–Pick disease type C</td>
</tr>
<tr>
<td>Drugs</td>
<td>Paracetamol, anti-TB drugs, halothane, carbamazepine, sodium valproate</td>
</tr>
<tr>
<td>Toxins</td>
<td>Amanita phalloides, heatstroke, shock (all causes)</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>Anti-smooth-muscle antibodies and anti-liver-kidney microsome (LKD) antibodies, antibody-positive giant cell hepatitis with haemolytic anaemia</td>
</tr>
<tr>
<td>Vascular</td>
<td>Budd–Chiari syndrome, veno-occlusive disease (may follow bush tea ingestion)</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>Non-A, non-B hepatitis</td>
</tr>
</tbody>
</table>

### Complications of ALF

These include the following:
- Encephalopathy and raised intracranial pressure, convulsions.
- Hepatorenal syndrome.
- High-output cardiac failure.
- Hepatopulmonary syndrome.
- Acid–base disturbance; initially alkalosis with hypokalaemia, followed by metabolic acidosis from multi-organ failure.
- Gastrointestinal bleeding, including early development of oesophageal varices.
- Pancreatitis.
- Bone-marrow aplasia.
- Sepsis, particularly Gram-negative and fungal, pulmonary (including aspiration) and septicaemia.

### Fluids in ALF

- Fluids in ALF should be restricted to two-thirds of normal maintenance (see Section 9 Appendix).
- When albumin needs to be infused, the dose is 5 mL/kg of 20% albumin, and for fresh-frozen plasma the dose is 10–20 mL/kg.
- Do not give any potassium if the patient is anuric.
- Treat hypoglycaemia in the usual way (see Section 5.8.B).

### Management of children with ALF

- In the absence of liver transplantation, conservative management relies on liver recovery, which will occur in many cases of ALF, taking place before irrecoverable damage occurs in another organ, particularly the brain. The best possible high-dependency care may improve the likelihood of this occurring.
- Refer the child to a specialised centre if one exists in that country. Undertake frequent reviews and clinical observations and high-dependency nursing.

- Blood tests for coagulation, electrolytes, blood glucose levels and blood count should be performed frequently (ideally 8-hourly).
- Hypoglycaemia and hypokalaemia must be detected and corrected.
  - Maintain blood glucose levels in the range 4–9 mmol/litre using a restricted fluid volume (two-thirds of maintenance) consisting of a minimum concentration of 10% glucose (given IV or orally); 20% glucose is the preferred solution, but is irritant to peripheral veins and is best given into a central vein or, better still, if tolerated, orally or via a nasogastric tube.
  - A metabolic alkalosis resulting from a failure of the urea cycle may cause hypokalaemia as a result of a shift of potassium into the cells. This hypokalaemia can worsen encephalopathy, and should be corrected enterally or IV.
- Children with encephalopathy should be nursed with their head elevated at 30 degrees above the horizontal and without neck flexion (to decrease intracranial pressure and minimise cerebral irritability). Children with agitated encephalopathy of grade II or III represent a major management problem, as they may pull out monitoring equipment and IV lines. Sedation will worsen their encephalopathy.
- Strict fluid balance is essential.
  - Allowance should be made for a hot climatic environment by giving 10–20% extra fluid, and 10% extra fluid should be given for each degree of fever.
  - Strict monitoring of urinary output and fluid balance is required. Aim for a urine output of not less than

### TABLE 5.7.A.3 Four grades of hepatic encephalopathy

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Irritable, inappropriate behaviour</td>
</tr>
<tr>
<td></td>
<td>Lethargy</td>
</tr>
<tr>
<td></td>
<td>Mildly depressed awareness</td>
</tr>
<tr>
<td></td>
<td>Tremor or flap (slow wave in outstretched extended hand)</td>
</tr>
<tr>
<td>Grade II</td>
<td>Aggressive outbursts, bad language</td>
</tr>
<tr>
<td></td>
<td>Unable to stay still</td>
</tr>
<tr>
<td></td>
<td>Pulling at IV cannulae, plaster, etc.</td>
</tr>
<tr>
<td>Grade III</td>
<td>Mood swings, irritable, odd behaviour</td>
</tr>
<tr>
<td></td>
<td>Not recognising parents</td>
</tr>
<tr>
<td></td>
<td>Photophobia</td>
</tr>
<tr>
<td>Grade IVa</td>
<td>Mostly sleeping, but rousable</td>
</tr>
<tr>
<td></td>
<td>Incoherent, sluggish pupils</td>
</tr>
<tr>
<td></td>
<td>Hypertonia with or without clonus and extensor spasm</td>
</tr>
<tr>
<td>Grade IVb</td>
<td>Absent reflexes</td>
</tr>
<tr>
<td></td>
<td>Irregular gasps with imminent respiratory failure</td>
</tr>
<tr>
<td></td>
<td>Bradycardia</td>
</tr>
<tr>
<td></td>
<td>Unresponsive to painful stimuli</td>
</tr>
</tbody>
</table>
0.5mL/kg/hour (determined by weighing nappies or measuring output).

- Daily weights are useful if the child can be moved, and will allow greater precision in fluid balance.

- If possible and appropriate, insert a central venous line and aim to provide a central venous pressure (CVP) of 6–10cmH₂O if necessary to give a normal blood pressure. Increased CVP may be required to compensate for an increased cardiac output, or to treat the reduced cardiac performance that is seen as liver failure progresses.

- Patients who require isotropes despite adequate central venous filling are developing multi-organ failure and have a very poor prognosis.

- Stop oral protein initially, and during recovery gradually reintroduce 0.5–1 gram/kg/day in oral or nasogastric feeding.

- A high-energy intake, predominantly of dietary carbohydrate, should be promoted to prevent protein catabolism with an increased serum ammonia level. In the absence of products such as Maxijul, uncooked cornstarch may be used as a source of carbohydrate. It may be given up to 2-hourly to provide predicted energy requirements, and may also help to maintain normoglycaemia.

- Lactulose, 5–10mL two to three times a day, is given to produce two to four soft and acid stools per day (it should be omitted if diarrhoea occurs).

- Maintain normothermia by environmental measures (but NOT with paracetamol, aspirin or ibuprofen).

- Give one dose of IV or IM vitamin K (300 micrograms/kg for children aged 1 month to 12 years: 10mg for those over 12 years of age) to attempt correction of prolonged clotting time.

- If there is frank bleeding (gastrointestinal or other), consider giving fresh blood, fresh-frozen plasma or cryoprecipitate at 10mL/kg IV.

- A prophylactic H₂-blocking agent (e.g. ranitidine 2mg/kg twice daily orally or IV) is given with oral antacid (e.g. sucralfate 250mg four times a day for children aged 1 month to 2 years, 500mg four times a day for those aged 2–12 years, 1 gram four to six times a day for those aged 12–18 years) to prevent gastric and/or duodenal ulceration.

- Treat any confirmed sepsis aggressively.

- Broad-spectrum antibiotics, such as a cephalosporin plus amoxicillin, or penicillin plus gentamicin, should be used prophylactically.

- Systemic fungal infection may require IV amphotericin (250 micrograms to 1mg/kg/day) or oral fluconazole (10mg/kg once daily).

- Give prophylactic oral nystatin mouthwashes (100000IU (1mL) four times a day).

- Manage hypotension with IV colloids and possibly dopamine and nor-adrenaline infusions if central venous access has been obtained (see Section 5.5.C).

### Paracetamol overdose

If paracetamol overdose is suspected or confirmed, N-acetylcysteine must be started immediately, whatever the time between the alleged overdose and the visit to the hospital. Histories after overdose are often misleading, with multiple administrations and other drugs not immediately admitted. N-acetylcysteine is given IV at 150mg/kg over 15 minutes as a loading dose, then 100mg/kg over 12 hours, then 100mg/kg/day as a continuous infusion until the INR is normal.

### Prognosis for ALF

The most important prognostic parameter for ALF is metabolic acidosis. Even in the presence of a very prolonged INR, a patient who is not acidic will have an 80% chance of survival. A plasma pH of < 7.25 (if blood gas measurement is available) indicates a 95% risk of mortality.

Other factors that predict a poor outcome are grade III or IV hepatic encephalopathy and oliguric renal failure (usually occurring 3–4 days after onset).

### Risk factors

- Age < 2 years.
- INR > 4 (associated with a mortality of > 90%).
- Serum bilirubin concentration > 350 micromol/litre.
- Grade III or IV encephalopathy.
- Non-A non-B hepatitis.
- Drug-induced ALF.

### Poisoning or toxic reactions associated with the development of ALF

These include the following:

- paracetamol
- mushrooms, particularly *Amanita phalloides* and similar species
- carbon tetrachloride
- copper
- iron
- halothane and other volatile anaesthetic agents
- sodium valproate
- carbamazepine
- phenytoin
- phenobarbitone
- isoniazid
- cytotoxic drugs
- irradiation.

### Galactosaemia

- A defect of galactose-1-phosphate uridyl transferase is revealed in the perinatal period when affected infants are first exposed to milk feeding.
- Infants present with vomiting, hepatitis, liver failure and DIC, often with sepsicaemia.
- Symptoms settle within 2–3 days when feeding with milk is discontinued.
- Hypoglycaemia is seen in the majority of cases.
- Cataracts may be detected.
- Fanconi’s nephropathy explains the presence of galactose in the urine giving the characteristic ‘Clinistix negative, Clinitest positive’ side-room test pattern when the infant is receiving feeds.
- Management consists of the removal of galactose from the diet and standard management of liver failure and sepsis.
5.7.B Chronic liver disease

**BOX 5.7.B.1 Minimum standards**
- Hepatitis B vaccine.
- Vitamin K.
- Fat-soluble vitamins (A, D, E and K).
- Cholestyramine.
- Specific nutritional support.

**Introduction**

The liver is anatomically strategically positioned between the gastrointestinal tract and the systemic circulation to perform its nutritional homeostatic role. Through the portal system, it filters organic and inorganic substances, microorganisms and their breakdown products, including endotoxins. It also stores and processes nutritional substrates and coordinates nutritional status through endocrine carrier proteins. The liver is therefore the major organ of nutritional homeostasis.

It can be helpful in diagnostic and prognostic terms to think of clinically evident liver dysfunction as having degrees of severity in three simultaneous dimensions: cholestasis, portal hypertension (with hypersplenism) and synthetic function (although homeostasis of ammonia and blood glucose levels may fit better into this synthetic group). The clinical features are summarised in Table 5.7.B.1.

**Clinical symptoms and signs of chronic liver disease (CLD)**

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Cholestasis</th>
<th>Portal hypertension</th>
<th>Cell dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice</td>
<td>Conjugated</td>
<td>–</td>
<td>Mixed if severe</td>
</tr>
<tr>
<td>Pruritis</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Leuchonychia</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fat-soluble vitamin deficiency</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Xanthomas</td>
<td>+*</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Cutaneous shunts</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Other cutaneous stigmata</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Hyersplenism</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Hepatopulmonary syndrome</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Oesophageal varices</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Ascites</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Dependent edema</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*Not in familial intrahepatic cholestasis.

**Jaundice**

Accompanied by dark urine and pale stools, jaundice is characteristic of cholestatic liver disease. The urine of infants should not contain significant colour or stain the nappy, and yellow urine strongly suggests bile obstruction. Yellow sclerae suggest cholestatic jaundice but are difficult to detect in small infants, and children with deep skin pigmentation may have some scleral pigmentation. There is no substitute for personal examination of stool and urine, as the history can be misleading. White stool, or stools the colour of cream cheese or uncooked pastry, are clearly abnormal, whilst pale yellow, pale green or pale brown stools may also raise concern about liver function. There is no substitute for personal examination of stool and urine, as the history can be misleading. White stool, or stools the colour of cream cheese or uncooked pastry, are clearly abnormal, whilst pale yellow, pale green or pale brown stools may also raise concern about liver function.

Comparison with a stool colour chart (www.yellowalert.org/file_download.aspx?id=7358) can be extremely helpful if there is doubt.

**Hepatomegaly**

Healthy infants may have up to 2 centimetres of liver edge palpable below the costal margin, but the texture is soft. An abnormally hard texture or irregular inferior margin strongly suggests established liver disease with fibrosis/cirrhosis. Changed liver conformation with prominence in the mid-line but an palpable right lobe suggests collapse, regeneration and the development of cirrhosis. Tenderness of a smoothly enlarged liver suggests a rapid recent increase in liver size (e.g. in acute hepatitis and also congestive cardiac failure).

**Splenomegaly**

Newborns may normally have a palpable spleen tip. Later palpable spleen suggests splenomegaly, possibly from portal hypertension, but as children get older a larger spleen can be accommodated beneath the ribs, so the sign becomes less sensitive.

**Coagulopathy**

With cholestasis, coagulopathy results from a failure of absorption of sufficient vitamin K. In infants this may present as haemorrhagic disease of the newborn, who should not...
normally suffer spontaneous bleeding. Routine vitamin K is given to newborns in some countries. Fresh blood from sites such as the umbilicus or nares should always prompt a search for evidence of vitamin K malabsorption or liver disease even when jaundice seems trivial.

In liver disease and coagulopathy unresponsive to vitamin K, but without consumptive coagulopathy, liver synthetic failure must be present. The degree of coagulopathy is the most sensitive index of liver impairment in children.

**Hypoglycaemia**

Hypoglycaemia may suggest a metabolic disease as a cause of liver dysfunction or profound failure of liver function.

**Encephalopathy**

More common in acute liver failure (see Section 5.7.A), chronic hepatic encephalopathy may be insidious, with educational failure, poor impulse control, bizarre behaviour and absences noted intermittently over months or years. Improvement may be associated with a low-protein diet reduced to 1 gram/kg/day, with lactulose to give acid stools and change the gut flora in favour of organisms that are less likely to produce the amines associated with encephalopathy.

**Investigations into CLD**

Consider liver dysfunction according to the following three categories (see Table 5.7.B.2):

- **cholestasis**: impairment of bile flow with a consequent reduction in intraluminal bile salt concentration and associated conjugated hyperbilirubinaemia and malabsorption
- **portal hypertension (PHT)** with associated hypersplenism and the effects of portosystemic shunting
- **hepatocellular impairment** (cell dysfunction) with failure of synthetic and homeostatic function, such as hyperammonaemia and hypoglycaemia.

Clinical findings (see Table 5.7.B.1) can be interpreted according to this classification, although some (e.g. ascites) are represented in more than one category. Serum albumin concentration reflects liver synthetic function but also depends on nutritional status and losses (e.g. via the gastrointestinal tract or kidneys). Thus it is necessary to consider all clinical features supported by basic laboratory parameters when possible to evaluate the severity of liver disease.

A precise diagnosis of the various causes of CLD is often not possible without specialised and expensive investigations, yet use of the above clinical assessment may allow a general if unconfirmed diagnosis.

**Ascites**

This is seen in advanced CLD, being a function of the balance between plasma oncotic pressure, which is mostly contributed by serum albumin, and hydrostatic pressure from portal hypertension.

**Cutaneous manifestations**

Pruritus, liver palms, cutaneous shunts, clubbing, white nails and xanthomas are well-recognised signs.

**Hepatopulmonary syndrome**

Progressive cyanosis occurs without lung disease, associated with low pulmonary artery pressure. Exertional dyspnoea is a frequent early feature. Type 1 implies pulmonary capillary vasodilatation and improves at least in part with inspired oxygen, whereas type 2 implies fixed intrapulmonary shunts without a response to oxygen.

**Other presentations**

Chronic liver disease may be present without detectable symptoms or signs. For example, chronic viral hepatitis B can be present for decades, proceeding to cirrhosis without any external evidence.

**TABLE 5.7.B.2 Laboratory features of CLD**

<table>
<thead>
<tr>
<th>Laboratory feature</th>
<th>Cholestasis</th>
<th>Portal hypertension</th>
<th>Cell dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum bilirubin</td>
<td>Conjugated</td>
<td>Normal</td>
<td>Normal or mixed</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>Normal</td>
<td>Normal</td>
<td>Low</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>High†</td>
<td>Normal</td>
<td>Low</td>
</tr>
<tr>
<td>Prothrombin time/ratio</td>
<td>Normal‡</td>
<td>Normal*</td>
<td>Prolonged if severe</td>
</tr>
</tbody>
</table>

* Implies minor prolongation seen in portal vein thrombosis.
† Except in familial intrahepatic cholestasis types 1 and 2.
‡ If there is adequate vitamin K.

**Outcome of CLD**

Although CLD can often only be cured in specialised centres in countries where transplantation is available (costs are over $120 000 per case), much can be done to relieve suffering in children with CLD, and most notably Wilson’s disease can be treated successfully for US$1–2 per day depending on the patient’s size and age.

**Cholestatic CLD: diagnosis and management**

Cholestasis is most frequently seen as a complication of the neonatal hepatitis syndrome. The commonest defined diagnosis is **biliary atresia**, an obliterative inflammatory condition of the intra- and extrahepatic biliary system exclusive to the perinatal period. Infants typically present with jaundice, pale stools and dark urine. If left untreated, biliary atresia progresses to biliary cirrhosis and death from complications of decompensated liver function within 2 years in 95% of cases. It is the commonest individual cause of severe liver disease in childhood in all populations, occurring in 1 in 9000 to 1 in 16 000 live births.

Causes of cholestatic CLD that are rare and difficult to treat include the following:

- **Alagille syndrome**: a condition characterised by...
cholestasis of variable severity associated with syndromic features.

- **Progressive familial intrahepatic cholestasis (PFIC):** a series of clinical syndromes of cholestasis representing impairment of bile salt transport or handling that may present as neonatal giant-cell hepatitis or drug- or viral-induced cholestasis.

- **Neonatal sclerosing cholangitis:** a rare condition which may mimic biliary atresia, although stools may show variable pigmentation.

The consequences of cholestasis include **pruritus**. This is a particularly troublesome symptom, resulting in disruption for the whole household, especially at night. Persistent scratching can be complicated by secondary infection of broken skin and bloodstaining of clothes and bedclothes. Early onset, before 7 months of age, implies profound cholestasis and a poor prognosis. Treatment is often difficult. First-line management is with **cholestyramine**, at a starting dose of 1 gram/day for under 1 year olds, 2 grams (sachets)/day for children under 6 years, or 4 grams (sachets)/day for those over 6 years, up to 6 sachets/day according to response, but not given within 4 hours of vitamins or other medicine. Second-line treatment is **rifampicin**, 2–4 mg/kg (maximum 300 mg) twice daily, and third-line treatment is **ursodeoxycholic acid**, 5–10 mg/kg two to three times a day up to 15 mg/kg two to three times a day.

Fat-soluble vitamin deficiencies (A, D, E and K) are frequently encountered in cholestasis unless patients receive prophylactic treatment. Clinical features of **rickets**, such as splayed epiphyses, especially swollen wrists, rickety rosary and craniotabes should be sought regularly. Metabolic bone disease should, if possible, be screened for by measurements of serum phosphate, calcium and parathormone levels and regular wrist X-rays. Prothrombin time or INR should be measured to ensure adequate vitamin K repletion.

Vitamin A replacement is **5000–10 000 units per day** or **100 000 units by deep IM injection every 2 to 4 months**. Vitamin D deficiency may be refractory to oral calciferol (vitamin D₃) tablets or cholecalciferol (vitamin D₃), but **10 000–25 000 units (250 micrograms) for 1–12 years and 10 000–40 000 for 12–18 years per day of either may help**. More water-soluble preparations such as 1-alpha-calcidol, 15–30 nanograms/kg for 1 month to 12 years and 250–500 nanograms for 12–18 years once daily, are more effective. **They may also cause hypercalcaemia.** Vitamin E deficiency is associated with hypotonia, peripheral neuropathy, developmental delay and haemolysis, and is the most frequently encountered vitamin deficiency in liver disease. The dose of vitamin E for all age groups is initially 100–200 mg/day adjusted according to response up to 200 mg/kg once daily, to increase until normal plasma levels are maintained. Vitamin K replacement for infants orally is 1 mg/day, and for children it is 5–10 mg/day.

Nutritional management applies to all three categories of CLD, and is discussed below.

### Portal hypertension (PHT): diagnosis and management

The complications of portal hypertension can be divided into:

- those related to the increased pressure (e.g. enteropathy, hypersplenism)
- those related to the anatomy of any collateral circulation (e.g. bleeding varices, haemorrhoids)
- those related to the effects of substances bypassing the liver by porto-systemic shunting (e.g. hepatic encephalopathy, hepatopulmonary syndrome, porto-pulmonary syndrome, hepatorenal syndrome). In this group complications may increase as shunting increases and portal pressure then falls.

The aetiology of PHT has conventionally been divided into the following:

- **pre-hepatic causes**, including portal vein thrombosis and other congenital and acquired portal vein anomalies, including arterioportal fistulae
- **hepatic causes**, including all causes of cirrhosis, especially cystic fibrosis and other biliary diseases, congenital hepatic fibrosis, and causes of non-cirrhotic portal hypertension, including portal vein sclerosis.
Hepatocellular liver disease: diagnosis and management

**Chronic viral hepatitis B, C and D**

**Hepatitis B**

Millions of children worldwide are infected with hepatitis B virus (HBV), and many ultimately die in adulthood from its complications, particularly decompensated cirrhosis and hepatocellular carcinoma. The population prevalence may exceed 10%, making HBV a major international public health problem. Spread may occur vertically at the time of birth or shortly afterwards, but also horizontally, especially in poor communities. Unlike HIV infection, surface contact with very small amounts of infected blood (e.g. as a result of sharing toothbrushes) can result in infection. A neonate exposed to HBV for the first time has more than a 90% risk of becoming chronically infected, a child has a 25% risk, and an adult has a 10% risk.

Risk factors associated with the development of cirrhosis and hepatocellular carcinoma include eAg+, a high level of HBV DNA, and male gender. Once infected, children have about a 15% probability per annum of reducing a high-risk state to a low-risk state as defined by eAg/antibody status.

Vaccines based on the antigenicity of the S Ag are highly efficacious in generating antibody response and providing protection. Protocols that involve three subcutaneous immunisations given at 0, 1 and 6 months give adequate antibody levels in 95% of individuals. In neonates, vaccination with the same dose, or half the dose for economy, at birth, 1 month, 3 months and 1 year achieves similar protection. Up to 5% of individuals will not mount an antibody response despite repeated vaccination, but it is not clear whether these are lifelong non-responders.

The WHO has recommended universal HBV vaccination. If such a policy was to be implemented it is highly likely that HBV would become a rare disease of children within less than 10 years, with a corresponding reduction in cirrhosis and hepatocellular carcinoma in one generation, representing one of the current great unsolved opportunities of international public health.

**Hepatitis C**

Hepatitis C virus (HCV) was responsible for at least 90% of post-transfusion hepatitis in early US studies. Around 5% of sexual partners may become infected. Around 4–5% of infants of viraemic mothers may become infected. The risk is related to the level of maternal viraemia, with HIV-positive mothers having the highest HCV viral loads and the highest risk of transmission. HCV is also a small but significant risk for healthcare workers.

Following exposure, viraemia in HCV occurs within 7 days, with antibody positivity appearing from 21–28 days. Less than 10% of affected individuals adequately remove the virus, and the remainder progress to chronic liver disease. The rate of progression to cirrhosis is unclear, but factors such as liver iron content, alcohol consumption and other viral infections (including hepatitis A) contribute. Around 5% of adults with HCV develop cirrhosis each year. The median timescale for developing cirrhosis in HCV is probably of the order of four decades.

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**Post-hepatic causes**, including hepatic venous outflow obstruction such as Budd–Chiari syndrome, various causes of veno-occlusive disease and problems of inferior vena caval flow or right heart function; particularly difficult to detect are constrictive pericarditis and IVC webs.

**Treatment of bleeding varices**

**Box 5.7.B.2 Minimum standards: oesophageal varices**

- Vitamin K.
- Blood transfusion (ideally fresh blood) and blood-clotting factors (if available).
- Propranolol.
- Antacids (aluminium hydroxide or magnesium carbonate).
- Ranitidine.

**Acute management**

1. Advise the parents not to panic, but to stay with the child.
2. Unless the CLD is very advanced, or the child is vitamin K deficient, the bleed will probably stop spontaneously, although the child may be shocked by that time.
3. Give oxygen by face mask.
4. Gain IV access and obtain cross-matched blood if possible. Resuscitation with 10–20 mL/kg boluses of Ringer-lactate or Hartmann’s solution is appropriate in the acute situation while waiting for blood for transfusion.
5. Give IV vitamin K slowly over 5 minutes 250–300 micrograms/kg up to a maximum of 10 mg or 1 mg for children under 1 year; 3 mg for those aged 1–4 years; 5 mg for those aged 5–12 years; 10 mg for those over 12 years). Repeat according to the results of clotting studies.
6. Start antacids (see below).
7. Arrange skilled endoscopy with sclerotherapy or banding (if available).

**Prevention**

- Propranolol is beneficial as primary and secondary prophylaxis for variceal bleeding, particularly when given early in the course of PHT. Give 500 micrograms/kg orally twice daily (adjust according to the heart rate; aim to reduce the rate by up to 25%). Around 30% of patients who receive propranolol have side effects, including wheeze and systemic vasoconstriction.
- Antacids. If there is a tendency to diarrhoea, use aluminium hydroxide (children aged 6–12 years: 5 mL three to four times a day between meals; children over 12 years: 10 mL three to four times a day). If there is a tendency toward constipation, use magnesium carbonate in the same dosage. The two may be used in combination.
- Avoid aspirin, ibuprofen and other gastric irritants.
- H2-receptor antagonists are of no proven value but are often used (ranitidine 1 mg/kg for 1–6 months, 2–4 mg/kg 6 months to 12 years, 150 mg 12–18 years ALL twice daily).
Hepatocellular carcinoma is a recognised complication of HCV and cirrhosis, following the latter by 5–15 years typically. Treatment is becoming rapidly more effective, including that for the more resistant genotypes I and IV. Children should be treated after the age of 5 years in order to avoid the neurotoxic effects of interferon.

**Wilson's disease**
This is an autosomal-recessive disorder caused by the accumulation of copper in the liver, brain, eyes, kidney and bone. The prognosis depends on the speed of diagnosis. Treatment with a low-copper diet and penicillamine is highly successful if started well before the onset of liver failure.

**Drugs and the liver**
Drugs are a major cause of liver dysfunction. Over 600 drug hepatopathies have been documented; common examples are given below. Drug clearance may be reduced in liver disease, and liver disease increases the risk of drug injury to the liver.

Acute/subacute hepatocellular toxicity is caused by paracetamol, aspirin, ibuprofen, iron, isoniazid, sodium valproate, carbamazepine, methotrexate and ketoconazole.

Cholestasis is caused by rifampicin, penicillins, erythromycin, oestrogens and anabolic steroids.

Progressive fibrosis is caused by azathioprine.

**HIV and the liver**
HIV is known to be associated with worsening of hepatitis due to other conventional causes and cholangiopathy, probably related to ascending infection with low-grade organisms such as Cryptosporidium or cytomegalovirus (CMV) infection (see Section 6.2.D). Hepatitis due to a conventional cause, especially CMV, may be particularly severe or progressive when associated with a low CD4 count.

**Metabolic liver diseases**
These are rare and difficult, if not impossible, to treat without liver transplantation or expensive diets. Advice from a specialist unit should be sought.

The management of nutrition in CLD
Malnutrition is a serious consequence of CLD. Thin limbs and a prominent abdomen are frequently seen, and malnutrition will be evident in anthropometric measurements. Triceps skinfold thickness tends to become reduced earlier in the course of progressive disease, followed by a reduction in mid upper arm circumference (MUAC). Stunting tends to occur later, unless severe rickets is present. Weight is affected by fluid balance abnormalities and organomegaly, and is therefore an insensitive indicator of nutritional state. Lean body mass, and skeletal muscle in particular, is prone to depletion as a result of progressive liver disease.

Anorexia is attributed to organomegaly or pressure effects of ascites, but may be equally due to a congested gastric mucosa or reduced gastrointestinal motility of portal hypertension or central effects of unidentified toxins. Malabsorption of long-chain fats, including those with polyunsaturated fatty acids (PUFAs), is dependent on intra-luminal bile acid concentration. Cholestasis may result in the intra-luminal bile acid concentration falling below that required for micelles to be formed. The resulting steatorrhoea creates faecal energy loss, but also risks essential fatty acid deficiency, with possible neurodevelopmental consequences, particularly in early life. Protein malabsorption may also result from functional pancreatic insufficiency with failure of protease activation by bile acids. Malabsorption may also result from bacterial overgrowth or other unspecified effects of portal hypertension; for example, congestion of the gut may cause impaired active or passive absorption.

Thus malnourished children with liver disease have high energy expenditure for their size. Target energy intake should be estimated from what the child's current weight for age should be.

Breast milk contains more PUFAs than typical formula milks. PUFAs are long-chain fats that are dependent on intraluminal bile acids for absorption, and are essential for normal cell membranes and for myelination, particularly in infancy. Breastfeeding is therefore important in children with CLD.

Treatment with intensive enteral feeding and high-dose enteral or parenteral vitamins can improve the quality of life of children who have malnutrition from their liver disease. In the absence of specialist feeds, a modular feed may be prepared using protein powder, carbohydrate polymer, MCT oil and long-chain fat oil, preferably with essential fatty acids from walnut oil or another similar source, to provide 4% of fat. Up to 4 grams/kg/day of protein, and 100–140 kcal/kg/day of energy, of which two-thirds is from carbohydrate and one third is from lipid as MCT, is an ideal target range.

Commercial liver formulas are extremely expensive, and their effect on the outcome of the liver disease is unproven. In the absence of the supplements described above, proprietary baby formula can be enriched with locally available oils and starches to give 140 kcal/kg/day, with half of the total formula energy as lipid and half as starch. Remember that if commercial formula is given at an increased concentration to increase protein intake, the electrolyte intake will increase proportionally, with a risk of sodium overload and fluid retention.