Chapter

35

Anaesthesia for Hepatobiliary Surgery, Including Transplantation, in Children

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Introduction

Liver disease is rare in children; however, its consequences may be devastating. Care for children with liver disease is usually provided in specialist liver units, but children may present to non-specialist centres, so it is important that all anaesthetists treating children should be aware of the principles of management for this group.

This chapter will consider normal hepatic function, the pathophysiology of liver disease, common conditions that present to the anaesthetist working in a specialist unit and a brief discussion of hepatic transplantation in children.

Anatomy

The liver is a large abdominal organ, typically 5% of the body weight of a neonate, falling to 2% by adolescence. It lies in the right-upper quadrant and is divided into left and right lobes and smaller caudate and quadrate lobes.

The blood supply to the liver consists of the portal vein and hepatic artery, which together comprise around 25% of the cardiac output. The portal vein provides two thirds of the liver blood flow, but hepatic artery flow can increase to compensate for reduced flow in the portal vein, even in the presence of advanced liver disease. The portal vein drains the intestines and receives flow from the superior mesenteric and splenic veins. Thus, the portal vein carries deoxygenated blood with the products of digestion at relatively low pressure, whereas the hepatic artery carries oxygenated blood at systemic pressure from the aorta via the celiac trunk. The hepatic artery has alpha- and beta-adrenergic receptors, thus arterial flow is in part modified by the autonomic nervous system. The vessels enter inferiorly via the porta hepatis and divide repeatedly within the liver along with the biliary tree; the Couinaud system divides the liver into eight functional segments according to the course of these vessels. The segments are not macroscopically apparent but are important in regional perfusion, and the implications of this arrangement for the venous and biliary drainage of the liver must be carefully considered during and after hepatic surgery.

The venous drainage of the liver is via the left, middle and right hepatic veins. These vessels are short, valveless and empty into the inferior vena cava (IVC). The bile ducts leave the liver at the porta hepatis; the left and right bile ducts join to form the common hepatic duct. The cystic duct from the gallbladder joins the common hepatic duct to form the common bile duct, which ultimately empties into the second part of the duodenum.

Microscopically, the liver is divided into lobules organised around small branches of the portal vein, hepatic artery and the bile ducts in the portal tracts. Blood perfuses the lobules via sinusoidal vessels that ultimately drain into the central hepatic veins.

Normal Liver Physiology and Pathophysiology of Liver Disease

Knowledge of normal liver physiology is essential for understanding the effects of liver disease. The liver is a complex organ with myriad functions; those that are important to anaesthetists include:

- Synthesis
- Catabolism and excretion
- Intermediary metabolism – carbohydrates, protein, lipid, vitamins and cholesterol
- Immunological functions

Synthesis

All coagulation factors except factor VIII/vWF (derived from vascular endothelium) are synthesised in the liver. Synthesis of factors II, VII, IX and X is dependent on vitamin K. Bile is necessary

for the absorption of the lipid-soluble vitamin K, and impaired bile flow into the small intestine leads to coagulopathy. The half-lives of factors V and VII are only a few hours, so coagulopathy can develop quickly.

Albumin forms the largest fraction of the protein output of liver. Albumin has a long half-life, around 20 days, so levels change slowly in response to changes in liver function. Albumin is an important acid-base buffer, has oncotic effects and is an important determinant of the free fraction of many drugs, but the consequences of low albumin level can be relatively minor. Other plasma proteins, including transport globulins and lipoproteins, are more crucial in maintaining health.

Bile and the bile salts also play an important role in digestion, particularly of lipids.

Catabolism and Excretion

Bilirubin is the breakdown product of haemoglobin. It is excreted in bile, and the appearance of jaundice can be the first sign of liver problems. Protein catabolism forms amino acids that provide a substrate for gluconeogenesis. Deamination of protein releases toxic ammonia, which is normally safely excreted via conversion to urea by the urea cycle enzymes. The accumulation of ammonia in acute liver failure leads to hepatic encephalopathy, raised intracranial pressure and coma.

Failure of protein catabolism can be very disruptive; for example, if insulin is not removed from the circulation, hypoglycaemia can result. Failure of regulation of other hormones can also be important.

Metabolism and excretion of xenobiotics, including drugs, are also vital. Most of these reactions are phase 1 reactions, carried out by cytochrome P-450 enzymes. Phase 2 reactions are conjugation processes, such as glucuronidation, to create water-soluble compounds that are then excreted in the urine. Some drugs, particularly larger molecules, are excreted in bile.

Intermediary Metabolism

Carbohydrates

The liver plays a key role in carbohydrate metabolism and glucose homeostasis. Insulin release after meals promotes hepatic glucose uptake; glucose monomers are phosphorylated to glucose-6-phosphate and then polymerised into glycogen. When energy supplies are low, liver glycogen can be broken down into glucose-6-phosphate and then into glucose that is released into the circulation; the process does not consume any energy as the glucose has already been phosphorylated. Seventy-five per cent of body glycogen is stored in muscle, but this is only for 'local' use; muscle does not contain glucose-6-phosphatase, so glucose cannot be released from muscle glycogen. The liver can store only a limited amount of glycogen, and liver failure rapidly impairs the ability to maintain plasma glucose levels.

Proteins

The liver is a major site of protein synthesis and catabolism. A wide range of essential proteins are synthesised, including albumin and the clotting factors, as described in the 'Synthesis' section.

Protein catabolism produces amino acids that can be used in energy production via gluconeogenesis or ketone body formation. The handling of dietary protein depends on the liver. End-stage liver disease is commonly associated with marked muscle wasting, and this can be impossible to prevent despite determined nutritional care.

Lipid and Cholesterol

The liver regulates the distribution of lipid and cholesterol by packaging these substances with apoproteins to form a range of lipoproteins that are essential for health. Lipids can be catabolised and the products directed into gluconeogenesis and the formation of ketone bodies.

Immunological Functions of the Liver

A sizeable fraction of the cells in the liver (Kupffer cells, pit cells) have immunological functions and are important for the control of pathogens and tumour surveillance.

FEATURES OF LIVER DISEASE

Acute Liver Failure

Acute liver failure is a condition resulting from the rapid decline in liver function in patients without evidence of previous liver disease. The presenting features are those of loss of hepatocyte function; there is no associated portal hypertension, and a marked coagulopathy is usual. There is a failure of

glucose homeostasis, and intravenous glucose supplementation is usually required, sometimes in large amounts. There is usually a metabolic acidosis with a high serum lactate. The clinical course is variable. Mild disease may recover completely or may progress slowly over some weeks. Conversely, deterioration may be extremely rapid, causing death within a few days if the patient does not undergo urgent liver transplantation. Acute liver failure is associated with high output cardiac failure, and acute renal failure is inevitable if the patient lives long enough. As encephalopathy progresses, it is accompanied by cerebral oedema and raised intracranial pressure. Ascites is generally mild, if present. Bilirubin rarely reaches the high levels seen in some of the chronic cholestatic conditions. Death is usually from cerebral herniation, overwhelming sepsis or circulatory failure.

Chronic Liver Disease

In chronic liver disease, there are repeated episodes of hepatic damage and regeneration, with fibrosis and eventual cirrhosis. This leads to portal hypertension and cholestasis, as well as loss of liver cell function. Cellular function is often well preserved until end-stage disease; the severity of portal hypertension and cholestasis may vary according to the aetiology of the liver disease and between individuals suffering from the same disease.

Portal Hypertension

Normal portal vein pressure is 5–10 cmH_2O. Increased pressure can lead to the formation of varices and variceal bleeding. There may be ascites and pleural effusions. Hypersplenism may cause thrombocytopenia or pancytopenia. Fluid shifts and other factors may contribute to the hepatopulmonary or hepatorenal syndromes.

Cholestasis

Obstruction to, or loss of bile ducts as a result of fibrosis will cause jaundice with a conjugated hyperbilirubinemia. Pruritus is common and may severely impair quality of life. Biliary obstruction may lead to cholangitis and systemic sepsis. The lack of bile flow into the gastrointestinal tract can cause malabsorption and steatorrhea, leading to depletion of lipid-soluble vitamins A, D, E and K; coagulopathy due to loss of vitamin K-dependent clotting factors; and accumulation of drugs that are eliminated in bile.

Hepatocellular Dysfunction

An early indicator of hepatocellular dysfunction is coagulopathy that is not fully corrected by vitamin K. Low albumin levels aggravate ascites, and peripheral oedema may develop. Drug volume of distribution and plasma protein binding may be altered. Drug metabolism may be impaired by the disturbance of either phase 1 or phase 2 conjugation processes. There may be loss of peripheral vascular resistance, causing a high-output low-pressure circulation. Encephalopathy is associated with raised ammonia levels, and there may be enhanced gamma-aminobutyric acid (GABA)-receptor effect and neuroinflammatory processes. Impaired immunity increases the likelihood and severity of sepsis.

Neonatal Jaundice

Establishing a diagnosis in a baby with jaundice is important as some conditions, such as biliary atresia, have a good prognosis if the baby receives early surgical treatment.

Physiological jaundice is common in neonates; it is worse in the breast-fed baby, but usually disappears by two weeks. Persistent or worsening jaundice requires investigation. Haemolytic disease of the newborn is rare in the developed world since the introduction of anti-D immunoglobulin.

The differential diagnosis of neonatal jaundice includes:

- Physiological jaundice
- Haemolytic disease
- Biliary atresia (or possible choledochal cyst, although this is often asymptomatic, at least initially)
- Neonatal hepatitis and other infections, such as TORCH
- Metabolic disorders (alpha-1-antitrypsin deficiency, galactosaemia, Crigler–Najjar syndrome, etc.)
- Drug reactions

Pale stools suggest bile is not entering the gut normally. Conjugated hyperbilirubinaemia, which causes dark urine, suggests biliary obstruction, whilst unconjugated hyperbilirubinaemia suggests physiological jaundice or haemolytic disease.

Liver Function Tests

The most important blood tests for assessment of liver function are the coagulation parameters and albumin levels, both indicators of synthetic function. Excretory function can be assessed by the serum bilirubin level; a high proportion of conjugated versus unconjugated fraction implies biliary obstruction; a high unconjugated fraction implies hepatic dysfunction, or that the conjugating capacity has been overwhelmed by haemolysis. The liver enzymes help to indicate the origin and nature of hepatocyte damage: aspartate transaminase (AST) is partially microsomal, whereas alanine transaminase (ALT) is exclusively cytosolic; a high AST/ALT ratio implies cell death (e.g. cirrhosis or tumour secondaries), whereas ALT will rise more in conditions where the cell membrane becomes 'leaky' (e.g. viral hepatitis). Alkaline phosphate (ALP) and gamma glutamyl-transferase (GGT) are both membrane bound and do not 'leak' out. GGT is a marker of enzyme induction, and both ALP and GGT rise when there is biliary obstruction.

Special Investigations and Imaging

The liver is effectively imaged by ultrasound, and structural abnormalities of liver parenchyma, biliary tree and vasculature can be readily identified. CT with or without contrast may be indicated to define the size of lesions and their relation to major vessels or to guide specific therapeutic options. MRI may provide greater resolution of subtle tissue differences.

Oesophagogastroendoscopy may be indicated to identify varices and thus portal hypertension. Percutaneous liver biopsy can be a valuable investigation, yielding diagnostic histology not available from liver function tests. It is a painful procedure and requires general anaesthesia in most children and carries a significant risk of bleeding. Transjugular liver biopsy maybe indicated in the presence of coagulopathy in acute liver failure. Endoscopic retrograde cholangiopancreatography (ERCP) may be required to diagnose biliary or pancreatic pathology. It usually requires general anaesthesia. Its therapeutic uses include stone extraction from the biliary tree, sphincterotomy of the sphincter of Oddi as well as dilatation or stenting of biliary strictures.

Anaesthesia for Children with Liver Disease

Some of the common conditions in children with liver disease are described in the following sections. The necessary procedures may be categorised as minor, intermediate and major. In general, a child with liver disease requires a higher intensity of care than a healthy child; even minor or moderate surgery may require invasive monitoring, active warming, fluid therapy and an intensity of perioperative care that might be provided for a major procedure in a normal child. Surgery is high risk in this population, and the child should be offered the best chance of a favourable outcome. If a child presents to a non-specialist unit, advice should be sought and transfer to a specialist unit considered.

Hepatobiliary Procedures

Hepatobiliary surgery can be divided into procedures for conditions of the biliary tree and for those of the liver itself, although there are obviously some features common to both.

Biliary Atresia

Biliary atresia is a rare condition of unknown aetiology affecting roughly 1:14,000 live births in the United Kingdom. Around 25% of cases are associated with other anomalies, typically abdominal situs inversus, polysplenia and atrial septal defect. Absence of extrahepatic and (to a variable degree) intrahepatic bile ducts leads to cholestasis, progressive fibrosis and cirrhosis.

The affected neonate is usually born at term. Jaundice and pale stools soon become apparent, and the infant fails to thrive. The presence of hepatomegaly suggests hepatic fibrosis. Investigation reveals a raised conjugated bilirubin, alkaline phosphatase and AST. Serum albumin and prothrombin times are usually normal in the early stages. Abdominal ultrasound reveals contracted or absent gallbladder, and a Tc trimethylbromoiminodiacetic acid (TEBIDA) scan demonstrates failure to excrete radioisotope from the liver into bowel. Liver biopsy demonstrates cholestasis and bile duct proliferation and plugging.

Definitive diagnosis is with an operative cholangiogram which fails to demonstrate bile ducts. Following confirmation of the diagnosis, the surgical team will proceed to the Kasai

portoenterostomy procedure. This involves excision of the fibrotic portion of the biliary tree and formation of a Roux-en-Y portoenterostomy to allow bile drainage. The Kasai procedure usually achieves biliary clearance in greater than 50% of infants, and over 40% avoid liver transplantation until at least 10 years of age. The outcomes are worse when performed in infants older than eight weeks of age or with advanced fibrosis or established cirrhosis.

Anaesthesia for the Kasai Procedure

A systematic approach to preoperative assessment is necessary for infants undergoing this operation. The full blood count may reveal anaemia, but the platelet count is usually normal, as portal hypertension is unusual at this stage. The prothrombin time is generally normal provided the child has received supplementary vitamin K. Standard starvation guidelines can be followed, but the risk of hypoglycaemia should be remembered, and intravenous glucose may be required.

Induction of anaesthesia may proceed according to the anaesthetist's preference. A non-depolarising muscle relaxant is administered, oral tracheal intubation is performed and a nasogastric tube is placed. Anaesthesia is maintained with a volatile agent in a mixture of oxygen and air.

Epidural analgesia has much merit as it offers good postoperative analgesia, promotes early feeding and avoids the risk of opioid accumulation; however, there are concerns about sepsis in the epidural space because of systemic sepsis secondary to ascending cholangitis. Epidural analgesia should be avoided in the presence of coagulopathy or thrombocytopenia.

A safer alternative may be local anaesthetic infiltration and continuous infusion via a subcutaneous catheter sited by the surgical team, in addition to intravenous opioid, using a nurse-controlled analgesia (NCA) pump.

When forming the anastomosis between the Roux-en-Y and the porta hepatis, the liver is retracted, potentially reducing venous return from the IVC. Thus, adequate venous access in the upper limbs is necessary; a central venous catheter may be useful for access, both intra- and postoperatively, and measurement of central venous pressure. Arterial cannulation is generally unnecessary in the absence of associated cardiac anomalies or haemodynamic instability.

As these patients are usually less than eight weeks of age, they are prone to hypothermia; this may be avoided using warmed intravenous fluids and external warming devices.

Extubation at the end of surgery and return to a high-dependency unit is usual. Antibiotic prophylaxis should be continued for five days to prevent postoperative cholangitis. Recurrent cholangitis, cirrhosis and portal hypertension may all occur despite adequate biliary drainage. Rotating courses of antibiotics are often necessary as prophylaxis for cholangitis and nutritional support is useful to help with growth, which may be impaired secondary to a degree of malabsorption.

In the United Kingdom, this surgery is performed in three designated centres, allowing monitoring and timely assessment for liver transplantation, should this become necessary.

Choledochal Malformations

Choledochal malformations are localised dilatations of the biliary tree. The aetiology is unknown, and the incidence is around 1:100,000 live births. Presentation in infancy is usually with obstructive jaundice, although it may have been detected as a chance finding on antenatal ultrasound. In older children, recurrent abdominal pain is the main feature, potentially with acute pancreatitis.

Choledochal malformations can lead to severe cholangitis, hepatic fibrosis and cirrhosis; there is a risk of malignancy later in life if left untreated. Surgical treatment is by excision of the malformation and formation of a Roux-en-Y anastomosis. Anaesthetic management is similar to that for infants with biliary atresia, but patients with choledochal malformations are generally older and more robust, and prognosis and recovery are usually very good.

Gallstone Disease

Although considered a disease of adult life, gallstones can affect children with haemoglobinopathies, where haemolysis leads to deposition of pigment stones, children with disorders of cholesterol metabolism and, increasingly, obese teenagers. It rarely affects infants. Presentation is most commonly with right-upper quadrant pain, intermittent jaundice and pancreatitis. Surgical treatment is cholecystectomy, often with intraoperative cholangiography to exclude biliary obstruction due to residual stones in the bile duct. Laparoscopic

cholecystectomy is popular because of reduced postoperative pain and shorter recovery time. This approach necessitates a significant pneumoperitoneum and often steep head-up tilt, which may cause some degree of haemodynamic compromise. Good venous access is required. Routine anaesthesia is used, avoiding nitrous oxide owing to its potential to diffuse into gas-filled cavities. Analgesia is usually with intravenous paracetamol, a non-steroidal anti-inflammatory agent, and morphine. Local anaesthetic infiltration to the sites of the laparoscope ports may be useful. Shoulder tip pain secondary to diaphragmatic irritation can be severe but is usually short lasting.

Laparoscopic cholecystectomy may be technically difficult and require conversion to an open procedure. Postoperative pain should be managed with opioid patient-controlled analgesia (PCA) and local anaesthetic infusion to the wound or transversus abdominis plane (TAP) block, or with epidural analgesia. The postoperative course may be complicated by pain, fluid shifts and ileus.

Hepatic Tumours

Hepatoblastoma is the most common liver tumour encountered in the paediatric population, with an incidence of around 0.77 per million. It is more common in boys. Hepatoblastoma is commonest in children under the age of four years and is associated with conditions such as Beckwith–Wiedemann syndrome and hemihypertrophy. It usually presents as an abdominal mass, which may have become quite large before it is discovered. Full blood count may reveal anaemia, but liver function tests are often normal. α-Fetoprotein (AFP) is a useful diagnostic test and monitor of treatment response. Abdominal ultrasound helps to differentiate hepatoblastoma from other abdominal tumours. CT and MRI scanning provide information about metastatic spread and the relationship of the tumour to vascular structures and thus staging and surgical resectability. Treatment is with chemotherapy (cisplatin and doxorubicin) and surgical resection as guided by the International Society of Paediatric Oncology (SIOPEL) regimen. Children with unresectable hepatoblastoma may be suitable for liver transplantation. Doxorubicin toxicity may lead to cardiomyopathy, and all children should be assessed by echocardiography.

Anaesthesia for liver resection shares many similarities with that for liver transplantation (described in the next section), particularly the risks of severe and rapid blood loss. Issues specific to hepatic resection are the risks of air embolus and hepatic insufficiency. In order to achieve clearance and reduce bleeding, surgical resection is usually by hemihepatectomy or segmentectomy using an ultrasonic scalpel or similar device to divide the liver parenchyma along the planes of the functional anatomical segments. Occasionally very peripheral tumours may be suitable for extra-anatomical resection. Entrainment of air into veins held open in the liver parenchyma can lead to air embolus; this may be minimised by meticulous surgical technique and adequate fluid loading. However, excessive administration of fluid leads to engorgement of the liver and increased bleeding. Fluid administration is therefore usually restricted until after the parenchymal resection is completed. A lower central venous pressure has been shown to reduce bleeding and reduce blood product transfusion. Systemic arterial blood pressure should be maintained with appropriate inotropes and vasopressors to preserve liver perfusion and postoperative liver function. Clamping the portal vein and hepatic artery or vascular exclusion with clamping of the vena cava may reduce bleeding. This has the advantage of increased speed of surgery and reduced blood loss but risks ischaemic damage to the remaining liver and postoperative hepatic dysfunction.

There is always the potential for massive blood loss in these children. Intra-arterial and central venous pressure monitoring and urinary output measurement are mandatory. A wide bore intravenous catheter, in addition to a multiple-lumen central venous catheter, will facilitate rapid infusion of intravenous fluid and blood products. The majority of these patients will have an existing Hickman catheter, which is not adequate for rapid transfusion.

Perioperative hepatic dysfunction is suggested by a progressive base deficit and lactic acidosis. Adequate cardiac output must be maintained. Clotting factors are sometimes needed to support coagulation. There is little evidence to support the use of N-acetylcysteine to aid residual liver recovery. Children with hepatic dysfunction are best managed in the intensive care unit.

For uncomplicated liver resection, epidural analgesia is effective and allows early extubation and return to the high-dependency unit. Epidural analgesia may be high risk in the presence of

coagulopathy due to postoperative hepatic dysfunction, so careful consideration should be given to the size of the tumour and expected difficulty of the resection. The infusion of local anaesthetic agents via tunnelled infiltration catheters in the surgical wound is an alternative technique which can provide good analgesia when combined with a morphine NCA.

Liver Transplantation

Liver transplantation may be a very effective treatment for children with acute or chronic liver disease. The first successful liver transplant was performed on a child with hepatoblastoma in 1967. However, it was not until the introduction of cyclosporin immunosuppression in the 1980s that the procedure became an established therapy for end-stage liver disease.

Children with chronic liver disease can expect a one-year survival of over 90% after liver transplantation. The outcomes for acute liver disease are generally not quite as good. Developments in anaesthesia and critical care, surgery and immunosuppression have greatly contributed to this success; however, the impact of improved nutrition, microbiology and nursing care should not be forgotten.

The variety of conditions causing paediatric liver disease, and their influence on symptoms, is remarkable. Table 35.1 lists some common indications for liver transplantation.

Table 35.1 Some commoner indications for liver transplantation at various ages

Disease	Typical age
Gestational alloimmune liver disease (GALD)/ neonatal haemochromatosis	Neonatal period
Biliary atresia	Infancy and onwards
Unresectable hepatoblastoma	Typically <3 years
Alagille syndrome	>4 years
Progressive familial intrahepatic cholestasis	>4 years
A-1-antitrypsin hepatitis	>6 years
Glycogen storage diseases	>6 years
Autoimmune hepatitis	>10 years
Wilson disease, tyrosinaemia	>10 years
Cystic fibrosis	Adolescence

Acute Liver Failure in Children

About 10% of liver transplants are performed in patients with acute liver disease. The features of acute liver failure are quite different from chronic disease, requiring urgent effective multidisciplinary treatment.

Acute liver failure is a complex illness which evolves following a severe insult to the liver. The aetiology and progression of acute liver failure vary with age. In the newborn, infection and gestational alloimmune liver disease (GALD), previously known as neonatal haemochromatosis, are frequent diagnoses; in older children, viral hepatitis, drugs and toxins are more likely, but often no cause is found.

Acute liver failure is an emergency with a high mortality, requiring rapid diagnosis and management. Early transfer to a specialist unit with transplantation facilities is essential. Children with moderate or severe encephalopathy should be admitted to the intensive care unit for ventilation and invasive monitoring. The high mortality rate in acute liver failure is mainly from circulatory collapse, neurological deterioration and sepsis; it is essential that close attention be paid to haemodynamics and neurology. Hypotension is common and must be treated aggressively due to impaired cerebral autoregulation.

Intravascular volume must be maintained to ensure adequate organ perfusion in the face of high cardiac output and low systemic vascular resistance. Inotropic support, usually noradrenaline, is often required to maintain adequate perfusion pressure. Acute renal failure is common, necessitating renal replacement therapy.

Survival in acute liver failure requires rapid diagnosis, coordinated management and timely liver transplantation if recovery is unlikely; the decision whether to transplant or wait for possible recovery may be extremely difficult. Actual or impending loss of cerebral perfusion, progressive circulatory failure unresponsive to inotropic support and multi-organ failure suggest a low likelihood of recovery, with or without transplantation.

Assessment of Children for Liver Transplantation

Most liver transplants in the United Kingdom are performed with grafts from cadaveric donors, thus

the time available for review and optimisation is limited. In most liver units, potential transplant candidates are fully assessed by a multidisciplinary team before listing. The anaesthetist has an important role as a part of this team assessing all aspects of preparation for liver transplantation. Particularly important features are the severity of the liver disease itself and the effects on other systems, with special regard to the cardiovascular, respiratory, renal and neurological systems.

Irrespective of aetiology and severity, some features of chronic end-stage liver disease and portal hypertension are commonly seen. Patients are often malnourished and display poor growth, reduced muscle mass and thin subcutaneous tissue. The abdomen may be distended due to ascites and hepatosplenomegaly. The skin may demonstrate jaundice, scratch marks from severe pruritis, bruising and dilated veins, particularly around the umbilicus.

Assessment of Cardiovascular Function

In end-stage liver disease, cardiac output is typically increased and systemic vascular resistance reduced. Fluid retention and peripheral oedema are common despite diuretic treatment. Electrocardiogram (ECG) and transthoracic echocardiography should be reviewed to exclude cardiac abnormalities such as pericardial effusion, cardiomyopathy and congenital cardiac anomalies. Moderate ventricular hypertrophy is reasonably common. Discovery of associated cardiac anomalies allows risk stratification, which includes the danger of paradoxical air embolus during surgery in cases where there is the potential for right-to-left intracardiac shunting. The decision to treat cardiac anomalies either surgically or by interventional cardiological techniques must be balanced by the extra risk of the procedure in a patient with liver disease; it may be difficult to decide which problem to treat first.

Respiratory Function

Moderate hypoxia and respiratory impairment are common and often secondary to ascites and hepatosplenomegaly, causing basal atelectasis. Pleural effusions are also common, as are lower respiratory tract infections.

The hepatopulmonary syndrome (HPS) is a condition characterised by abnormal blood oxygenation associated with intrapulmonary vascular dilatation in the presence of cirrhotic liver disease. The incidence is variable, and the condition is often insidious and not necessarily related to the severity of the liver disease. The children may demonstrate clubbing and marked hypoxia, particularly on standing. Investigation with contrast echocardiography or a Tc99 radiolabelled microalbumin scan may quantify the degree of shunting. Significant levels of shunting maybe discovered and supplemental oxygen therapy indicated. The outcome with liver transplantation for children with HPS is similar to those without the condition; however, the hypoxia may worsen acutely, necessitating higher inspired oxygen levels and prolonged postoperative ventilation. HPS usually resolves completely in the weeks and months following liver transplant.

Renal Function

Renal impairment is common in advanced liver disease as a consequence of sepsis, diuretic therapy and hypovolaemia. It may be most accurately assessed by measurement of serum cystatin C, the level of which is unaffected by muscle mass. The hepatorenal syndrome (HRS) is unusual in children.

Neurological Assessment

Hepatic encephalopathy is not always apparent or recognised but is a worrying sign and difficult to treat. The cause remains elusive, but raised serum ammonia, neurotoxins and neuro-inflammatory processes are implicated. Cirrhotic liver disease may result in portosystemic shunting, allowing potentially neurotoxic intestinal metabolites, normally removed by healthy hepatocytes, to be found in the circulation. There is a significant risk of hepatic encephalopathy following placement of transjugular intrahepatic portosystemic shunts to treat portal hypertension. There may be other causes of impaired consciousness in chronic liver disease, including hyponatraemia, hypoglycaemia, sepsis and impaired metabolism of sedative drugs. Table 35.2 describes the grading of hepatic encephalopathy.

Anaesthetic Management of Liver Transplantation

Start times for liver transplantation are difficult to predict, but preoperative fasting protocols should

Table 35.2 Grading of hepatic encephalopathy

Grade 0	Normal
Grade I	Minimal drowsiness but oriented; some impairment of cognitive functions or reversal of day/night sleep pattern
Grade II	Drowsy, confused, mood swings
Grade III	Very drowsy, unresponsive to speech
Grade IV	Comatose

allow most children to drink clear sugar containing fluids up to one hour before induction of anaesthesia. If hypoglycaemia is problematic, a glucose-containing infusion should be commenced.

Sedative premedication, typically oral midazolam, may be given to minimise anxiety, but delayed start times, impaired drug metabolism and fragile clinical state demand pragmatism and sound clinical judgement.

Coagulopathy should be corrected, or partially corrected, with fresh frozen plasma and platelet transfusion, but fluid overload should be avoided. Hyponatremia is common because of fluid retention and diuretics and is associated with increased mortality in those awaiting transplantation. A serum sodium of less than 126 mmol l^{-1} is concerning; lower values than this risk central pontine myelinolysis and should be treated.

After induction of anaesthesia, a higher than usual dose of non-depolarising neuromuscular blocking drug may be required, owing to increased volume of distribution in advanced liver disease and binding to acute phase proteins. Nasal intubation is avoided due to the risks of bleeding. The abdominal distension from ascites and hepatosplenomegaly often makes positive pressure ventilation difficult initially; positive end expiratory pressure (PEEP), high inflation pressures and high inspired oxygen levels may be needed. Ventilation usually improves following opening of the peritoneum and drainage of ascites, although surgical retractors may impede diaphragmatic excursion and make ventilation difficult.

Anaesthesia is maintained with isoflurane in a mixture of oxygen and air, supplemented with an opioid infusion. Neuromuscular blockade is usually maintained with an atracurium infusion.

Manipulation and clamping of the IVC may drastically reduce venous return, so IV cannulae and central catheters are sited in the upper body. Similarly, the infrarenal aorta may be clamped when forming an arterial conduit to the graft, so radial artery cannulation is preferred. Generally, one or two peripheral cannulae and a multiple-lumen central venous line for pressure monitoring and infusion of inotropes and other drugs is required. High risk cases warrant placement of a wide-bore catheter in a central vein to facilitate rapid fluid infusion. Coagulopathy and thrombocytopenia increase the risk of central venous cannulation, and ultrasound guidance is recommended.

Intraoperative hypothermia is common due to the small size of the patient, malnourished state and peripheral vasodilation, which may be exacerbated by rapid transfusion, loss of ascites and implantation of a cold liver graft. The ambient temperature should be raised, and a warming mattress and waterproof drapes used to reduce convection and prevent pooling of fluids and subsequent cooling. IV fluids and surgical wash should be warmed, and inspired gases humidified. Core and peripheral temperature should be monitored.

The major fluid shifts and alterations in cardiac output that occur during liver transplantation have profound haemodynamic effects, making cardiac output measurement useful. Pulmonary artery catheters are rarely used in small children. Transoesophageal echocardiography (TOE) offers a dynamic assessment of ventricular filling, stroke volume and ejection fraction, and it can be used even in small children, although there are concerns about the passage of such a device in the presence of oesophageal varices. Continuous cardiac output measurement by pulse contour analysis is increasingly popular in paediatric anaesthesia and critical care and may be useful during liver transplantation.

Fluid management is initially with crystalloids such as compound sodium lactate solution (Hartmann's or Ringer's solution) at maintenance rates; glucose infusion may be added if hypoglycaemia develops. Ascitic losses, bleeding and alterations in venous return may necessitate infusion of further crystalloid, colloid, and blood products. There is continued debate concerning the risks of hyperchloraemic acidosis and acute kidney injury (AKI) with 0.9% NaCl compared with more balanced solutions. Regular blood gas, glucose, electrolyte and haematocrit measurements can direct

the type of infused fluid or other physiological and therapeutic manoeuvres. Changes in coagulation occur as a result of transfusion, dilutional coagulopathy and loss of liver function. Transfusion of coagulation factors and platelets is guided by prothrombin time (PT), activated partial thromboplastin time (APTT) and point of care viscoelastic testing. These parameters change very quickly during transplantation and analysers should be situated in or very close to the theatre, to minimise delays in obtaining data to guide treatment.

Thromboelastography (TEG) is a point of care viscoelastic test used to measure coagulation. It measures the transmitted force from a rotating sample of warmed blood to a wire inserted into the sample. A computer displays these forces in real time as clot forms. Standardised values are produced: reaction time (R), maximum amplitude (MA), α angle and LY30. These results are interpreted to provide an assessment of rate of clot formation, clot strength and fibrinolysis. Thromboelastometry (ROTEM) is a refinement of the technique which employs additional assays to identify specific information about blood coagulation, particularly hyperfibrinolysis.

The liver transplant procedure is classically divided into three phases: dissection, anhepatic and reperfusion. The dissection phase is from skin incision to occlusion of the hepatic artery and portal vein, which is the start of the anhepatic phase. The anhepatic phase ends when blood first reperfuses the transplanted liver.

Dissection phase

Division of adhesions, venous collaterals and varices may result in considerable bleeding, and large volumes may also be lost as ascites. Transfusion should be guided by filling pressures, haematocrit and coagulation studies. Despite intensive preventive measures, hypothermia and coagulopathy are common. Manipulation of the liver may cause reduced flow in the IVC, reducing venous return and cardiac output. Hypocalcaemia may be aggravated by the citrate load secondary to fresh frozen plasma (FFP) transfusion and should be treated with an infusion of calcium ions; this should be done cautiously to avoid hypercalcaemia.

Intraoperative cell salvage and autologous blood transfusion reduces the requirement for allogenic blood, so reducing risks of donor blood transfusion and cost. There is growing confidence that its use is safe in liver transplantation for malignancy.

Anhepatic Phase

The anhepatic phase is characterised by sustained reduction of venous return and absence of liver function. Although surgical techniques vary, the IVC and portal vein are often clamped, which leads to reduced cardiac output and hypotension, often accompanied by a compensatory tachycardia. Treatment is with inotropic support and cautious fluid administration to avoid excessive right-sided filling pressures at reperfusion. Clamping the portal vein may lead to congestion of the intestines and can be associated with intestinal perforation and bacterial translocation.

Absent hepatic function leads to profound metabolic changes. Implantation of the ice-cold liver graft reduces core temperature, requiring adjustment of warming devices. Hypoglycaemia is common and often profound, necessitating adjustment of the glucose infusion. A progressive metabolic acidosis develops. Sodium bicarbonate or other acid-buffering solutions should be withheld unless the acidosis becomes so severe that it causes inotrope-resistant hypotension, hyperkalaemia or other dangerous effects. Severe hyperkalaemia at reperfusion carries a risk of cardiac arrhythmias; buffers, calcium, furosemide and dextrose/insulin may be needed.

Towards the end of the anhepatic phase, the liver graft is flushed to wash out potassium, preservation medium, heparin, metabolites, inflammatory mediators, cell debris and air. Crystalloid, colloid or the patient's blood may be used. Before reperfusion, careful attention should be paid to the serum potassium, calcium and acidosis, and fluid and inotrope infusions should be prepared.

Reperfusion Phase

Unclamping of the IVC leads to a sudden increase in venous return to the heart, so the portal vein is unclamped slowly. The characteristic features of reperfusion are systemic hypotension, increased cardiac output, pulmonary vasoconstriction and hyperfibrinolysis. The definition and characterisation of the post-reperfusion syndrome (PRS) have evolved over the years, and because of this its incidence varies in the literature. It can have a major effect on morbidity and mortality of liver

transplantation. Risk factors include increased donor age and prolonged cold ischaemia time for the graft. The pathogenesis of post-reperfusion syndrome is unclear, but endogenous mediators are implicated. Post-reperfusion syndrome is usually transient but may be profound and prolonged, requiring fluid and inotropic support, usually noradrenaline or adrenaline. Often the simplest and most successful strategy is to use the minimum therapy required to support viable circulation until the reperfusion phenomena start to wear off, which may be no more than a few minutes.

Reperfusion coagulopathy is common; thrombelastography (TEG)/rotational thrombelastography (ROTEM) often reveals hyperfibrinolysis, requiring treatment with clotting factors and tranexamic acid or aprotinin. Over-transfusion should be avoided to prevent congestion of the graft, excessive volume loading of the heart and worsening of bleeding. Additionally, there may be significant bleeding from the cut surface of a reduced or split liver graft. This situation can be challenging in the presence of abnormal coagulation.

The surgical team then commences arterialisation of the graft, which requires good systemic arterial blood pressure. In infants undergoing a split liver transplant, an aortic conduit is often required, necessitating temporary aortic clamping.

Following completion of the arterial anastomosis, the biliary anastomosis is performed (usually with a Roux-en-Y) and the abdomen closed. If primary abdominal closure is difficult due to a large donor liver graft, then delayed or staged closure may be required.

Following liver transplantation, the patient returns to the intensive care unit. During the early postoperative phase, vigilance is required; the patient is closely observed for any haemodynamic or respiratory changes, which are promptly acted upon. Abdominal drain losses, temperature and urine output are all monitored closely, along with assessment of graft function. Transabdominal doppler scanning is utilised to assess liver graft perfusion.

Types of Liver Grafts

The imbalance between the number of children awaiting liver transplantation and the availability of size-matched donor livers has led to innovative surgical techniques to provide more liver grafts and reduce waiting list times and mortality. Smaller grafts and split liver grafts allow adult cadaveric livers to be used even for small infants. Living related grafts have the advantage of allowing scheduling of the liver transplant operation and provision of a high-quality graft, but the risk of morbidity and mortality to the donor is a powerful disincentive.

Outcomes and Complications after Liver Transplantation

Liver transplantation is one of the most physiologically challenging procedures performed in children, and given the fact the children undergoing transplantation can be extremely sick, it is perhaps surprising that after an uncomplicated procedure, most children can be discharged from the intensive care within 24 hours and from the ward in 7–10 days or even fewer. However, disastrous complications can occur resulting in perioperative mortality. Five-year survival rates of 80–90% are achievable for chronic liver disease but nearer 60–70% for acute liver failure. With meticulous surgical technique and close attention to the treatment of coagulopathy, early returns to theatre for bleeding are rare. Complete normalisation of clotting parameters is not necessary and may even be undesirable; prothrombin time or internationa normalised ratio (INR) less than twice normal is generally acceptable.

- Early graft failure is rare and may necessitate urgent re-transplantation, often within 48 hours.
- Early graft loss (within the first few days or weeks) is usually due to vascular problems (hepatic artery or portal vein thrombosis).
- Graft perfusion may be compromised if abdominal closure is too tight (abdominal compartment syndrome), if the patient becomes hypovolaemic or if there is excessive use of vasoconstrictors.
- Grafts may be lost, or the patient may die, in the first month or two due to infective complications.
- Later complications include problems with immunosuppressive therapy leading to graft rejection or malignancy, particularly post-transplant lympho-proliferative disorder (PTLD). Problems with biliary or venous drainage may require further surgery or radiological intervention.

Overall a re-transplantation rate of about 10% can be expected. Re-grafts take longer, bleed more and

suffer worse outcomes from both mortality and morbidity, but success is still achievable, so they are definitely worth trying in most circumstances. Good communication and collaboration and an experienced multidisciplinary team can help achieve the best results. The rewards can also be great, as transplantation provides a realistic hope of near-normal growth and development for children who are desperately ill with end-stage liver disease.

Key Points

- Jaundice is relatively common in the neonatal period and is usually benign, but warrants investigation to detect serious but treatable conditions
- Chronic liver disease is characterised by portal hypertension, jaundice and relatively preserved synthetic function until end-stage
- Acute liver disease is characterised by hypoglycaemia, coagulopathy, acidosis, raised intracranial pressure and high-output, low-resistance circulatory failure
- Liver transplantation provides the hope of cure from the symptoms of liver disease with excellent survival for many indications.
- Significant liver disease is best treated in specialist units, and so prompt referral is recommended.