Paediatric Liver Transplantation

62

K. Sharif and A.J.W. Millar

Contents

62.1 Introduction

Liver transplantation is accepted as a life saving treatment for children with end stage liver disease. Until recently, treatment options for the debilitating effects of liver disease in children were limited to supportive therapy, anti-viral agents and immunosuppressive agents. With surgical conditions such as biliary atresia, some success has been achieved with timely diagnosis and early surgical intervention. However, in many cases even with expert management there was inevitable progression of liver disease. Liver transplantation offers the only chance of a cure for these unfortunate children. Although the first attempted human transplant was performed in 1963, it was not until 5 years later that long-term success was achieved. Advances in surgical technique, anaesthetic management, pre- and post-operative care and refinements in immunosuppression over the last 4 decades have resulted in a much improved outcome and wide acceptance of liver transplantation among paediatricians with an ever-increasing list of indications being identified.

The full story of liver transplantation for children is yet to be told but the current expected 5-year survival is now greater than 85% in major paediatric transplant centres. Excellent quality of life is the rule rather than the exception. The longest survivor is well more than 35 years after transplantation. Current anxieties are over organ donor scarcity, long-term side effects of the immunosuppressive therapy and some ethical issues. The focus of attention has now shifted from an initial target of early post-transplant survival to quality of life in the long-term. The transformation of a miserable jaundiced invalid into an active healthy child remains a powerful stimulant for paediatricians and transplant surgeons alike.

P. Puri and M. Höllwarth (eds.), *Pediatric Surgery: Diagnosis and Management*,
DOI: 10.1007/978-3-540-69560-8_62,

62.2 Indications

Liver disease has generally been underestimated as a cause of death in children. In general, liver transplantation should be considered as a therapeutic option in all cases of acute and chronic liver disease before the end stage liver disease is reached. The most common indications for paediatric liver transplantation are biliary atresia (43%), metabolic diseases (13%) and acute liver failure (11%) A list of conditions for which liver transplant has been performed is summarized in Table 62.1. For approximately 75% of children with acute hepatic failure, the cause is unknown. Among the worldwide accepted indications for liver transplantation, inherited metabolic disorders constitute a major portion. In some paediatric centres this indication runs second after extrahepatic biliary atresia. The aim of liver transplantation in inherited metabolic disorders is twofold: the first is to save a patient's life by addressing the immediate consequences of the pathologic defect and the second is to accomplish phenotypic and functional cure of disease. In some metabolic diseases, the manifestations are widespread and affect other organs as well. Examples are heamochromatosis, tyrosinemia, Wilson's disease, glycogen storage diseases and hyperoxaluria. With experience, certain disorders have moved from the list of contraindications to acceptable indication. One such example is hepatic respiratory chain disorders, although it is essential to exclude extra-hepatic disease before transplantation.

In recent years the outcome of the operation is so improved that indications for early transplant would be evidence of impaired synthetic function, including prolonged prothrombin time, reduced serum cholesterol levels and low serum albumin. Clinical indicators include presence of ascites, bleeding from oesophageal varices not controlled by endoscopic banding or sclerotherapy and poor response to nutritional resuscitation. Those with acute hepatic failure who develop encephalopathy, hypoglycaemia, a prothrombin time of greater than 50 s and a Factor V level of less than 20% should be considered for transplant, as almost all of these children die without transplantation. Timing of liver transplantation not only affects survival rate, but may also influence neurodevelopmental outcome.

Table 62.1 Indications for which liver transplantation has been performed in children

I Metabolic (inborn errors of metabolism).
(a) Alpha-1 antitrypsin
(b) Tyrosinaemia
(c) Glycogen storage disease type III and IV
(d) Wilson's disease
(e) Neonatal haemochromatosis
(f) Hypercholesterolaemia
(g) Cystic fibrosis
(h) Hyperoxaluria (+ renal transplant)
(i) Haemophilia A + B
(j) Protein C deficiency
(k) Crigler-Najjar syndrome
II Acute and chronic hepatitis
(a) Fulminant hepatic failure (viral, toxin or drug induced)
(b) Chronic hepatitis (B, C, etc. toxin, autoimmune, idiopathic)
III Intrahepatic cholestasis:
(a) Neonatal hepatitis
(b) Alagille syndrome
(c) Biliary hypoplasia
(d) Familial cholestasis
IV Obstructive biliary tract disease
(a) Biliary atresia
(b) Choledochal cyst with cirrhosis
V Neoplasia
(a) Hepatoblastoma
(b) Hepatocellular carcinoma
(c) Sarcoma
(d) Haemangioendothelioma
VI Miscellaneous
(a) Cryptogenic cirrhosis
(b) Congenital hepatic fibrosis
(c) Caroli's disease
(d) Budd-Chiari syndrome
(e) Cirrhosis from prolonged parenteral nutrition

62.2.1 Contraindications

There are few reasons for refusal for transplantation. These include disorders as listed in Table 62.2. Until recently, hypoxemia (hepato-pulmonary syndrome) was considered as a relative contraindication for liver transplantation.

Table 62.2 Contra-indications

1. Absolute:
Uncontrolled systemic infection
Malignancy outside the liver
Disease in other organs incompatible with quality survival
2. Relative:
Cyanotic pulmonary arteriovenous shunting with pulmonary hypertension
Hepatitis B, eAg positive, HIV positive
Psychosocial factors
Inadequate vascular supply

However it has been shown that liver transplantation can be successfully achieved in severely hypoxemic children and that postoperative correction of the right to left shunt is then obtained. HIV/AIDS as well as other major cardio-respiratory, neurological or renal disease, which would be incompatible with quality of life and long-term survival, are also considered as contraindications.

62.2.2 Assessment

Liver transplant assessment includes thorough evaluation of the child and family. This process allows detailed disease assessment and time for discussion of treatment options, to prepare for the transplant procedure and afterwards. This also provides opportunity to assess the family's commitment to sustain long-term compliance after transplantation and to put in place supportive strategies to ensure adherence to treatment regimens, which need to be lifelong. However, detailed assessment is not possible in children presenting with acute liver failure or those with acute deterioration of chronic liver disease. The pre-transplant assessment protocol from our center is summarized in Table 62.3.

(A) **Child assessment**: All children require initial confirmation of the diagnosis, intensive medical investigation and nutritional resuscitation to treat the complications of the liver disease, portal hypertension and nutritional deprivation. Disease assessment includes identification of contraindications.

Table 62.3 Pre-transplant assessment

Anthropometry:
- Height and Weight
- Head circumference—under 2 years of age (OFC)
- Mid-xyphisternal umbilical circumference (girth)
- Mid-arm circumference (MAC) & Triceps skin fold (TSF)

Routine Bloods:
- Blood group
- FBC
- PT,PTT, Fibrinogen
- AST, ALT, αGT, Alk. Phos, Cholesterol
- Total protein, Albumin
- Na, K, Urea, Creatinine, Calcium, Potassium, Magnesium Phosphate
- Vitamin A/E

N.B. Additional bloods may be required if Metabolic Liver Disease is suspected

Serology:
- EBV (IgG)
- CMV (IgG)
- Measles
- Varicella
- Hepatitis A (IgG)
- Hepatitis B (Hepatitis B sAg + Hep B core antibody – hepatitis B s antibody if previously vaccinated)
- Hepatitis C antibody
- HIV 1 and 2

Microbiology
- MRSA
- VRE – Pseudomonas—B cepacia screen if chronic patient or CF
- Blood C&S if indwelling catheter

Urine
- MC + S
- Protein/creatinine ratio
- Tubular re-absorption of phosphate

Assessment of severity of liver disease:
- Upper Gastrointestinal Endoscopy (if required)
- Liver biopsy (if indicated, otherwise obtain previous biopsy result)
- Paediatric hepatology scores (PHS and PELD)

Radiology:
- Chest X-ray
- Bone age for rickets or metabolic bone disease
- Abdominal ultrasound and Doppler study to evaluate diameter of portal vein and direction of flow, size of spleen, ascites, vascular anatomy, resistivity index if biliary atresia or reverse flow in portal vein
- MRI and/or angiography if vascular anatomy uncertain

Cardiology:
- ECG
- ECHO
- Cardiology opinion if needed
- Blood Pressure

Neurology:
- EEG
- Developmental Assessment

Renal Function:
- Chromium EDTA
- Calculated GFR (Schwartz index)
- Urine tubular phosphate re-absorption (TRP)
- Urine protein/creatinine ratio

Respiratory:
- Oxygen saturations (resting and on exercise)
- For children with cystic fibrosis:
- Pulmonary function tests
- Cough swab sputum for MC + S
- Lung perfusion study only if cyanosed

Immunisations:

Arrange pre-transplant immunisation as needed–Suspend from list for 2 weeks if live vaccine given.
- Check hand held record for routine DPT, polio, HIB, MenC and MMR
- Ensure live vaccines are given if time permits i.e. VZ, MMR (if over 6 months) plus advice on completing other vaccinations such as Prevenar®, Pneumovax II®, Hepatitis A and B, influenza.

(B) **Family assessment**: Transplant candidacy inevitably results in enormous emotional stress for parents while waiting for the appropriate donor. Family life may become disrupted especially for those who live afar. Compliance is more difficult to predict in children with acute hepatic failure, as time from presentation to decision to transplant is much shorter. Living related transplant includes extensive evaluation of the potential donors including both physical and psychological assessment.

62.3 Surgical Technique

(A) **Donor operation**: Age limits for suitable donors are being extended due to shortage of organs. Paediatric donors can be accepted from 1 month of age while livers procured from older children and even young adults can be transplanted into small children after ex-vivo reduction of the size of the graft. However, stable cadaver donors from patients with a short intensive care unit stay (less than 3 days), little requirement for inotropic support and normal or near normal liver function are preferred, with an expected < 5% incidence of impaired function after transplant. Liver biopsy is useful if steatosis is suspected. Viral screening of the donors is essential. This would include Hepatitis A, B & C, CMV, EBV and HIV screening. Core HBV antibody and HCV positive donors would only be considered in selected viral infected recipients.

Surgical techniques used for donor retrieval and recipient liver removal and engraftment have evolved over the last 30 years. The majority of donor livers are removed as part of a multi-organ procurement procedure, which would include various combinations of kidneys, liver, heart or heart and lungs, small bowel and pancreas. University of Wisconsin solution is widely used as the preservation solution of choice.

The two procurement techniques used are a careful dissection and excision technique or the so-called 'rapid' technique described by Starzl. A mid-line incision is made from the supra- sternal notch to the pubis and the sternum is opened. The abdominal part of the operation includes quick assessment of all the abdominal organs. Control of the aorta is achieved above the coeliac axis by incision of the right crus of the diaphragm. The inferior vena cava and aorta are identified, dissected and encircled with tapes below the renal vessels. After a careful search for any vascular abnormalities, the liver is mobilised by division of the left coronary ligament. An appropriate sized cannula is placed in the inferior mesenteric or superior mesenteric vein so that the tip lies at the junction with the splenic vein. A large bore cannula is placed in the aorta with the tip approximately opposite the renal arteries, the distal common iliac vessels are tied off and the donor is given a heparin (3 gm/kg). A large bore cannula may be placed in the inferior vena cava, which is connected to an away suction. Procurement commences with infusion of preservation solution through both the portal vein and aorta after cross clamping the aorta at the level of the diaphragm and incising the supra-hepatic vena cava within the pericardium. The porta hepatis is divided distal to the gastro duodenal artery, which is ligated and the portal vein is divided at the junction with the splenic vein. The proximal part of the superior mesenteric artery is defined and is dissected down to the aorta.

The liver is now removed with a patch of aorta including the base of the superior mesenteric and the celiac axis. The resected liver includes a cuff of diaphragm around the bare area along with the retrohepatic cava and part of the right adrenal gland, which is cut through. The infrahepatic inferior vena cava is divided above the renal veins. Once the organs have been removed, they are placed in a plastic bag and the liver is further perfused with 500 ml of preservation solution via the portal vein, hepatic artery and through the bile ducts. The liver then is placed in a further two plastic bags and packed in ice for transportation.

A major constraint has been the shortage of donor organs of appropriate size. The use of reduced size adult organs has partially alleviated this problem but the previous technique employed was limited to a donor to recipient body-weight disparity of not greater than 3:1. Innovative techniques have been described that allow safe transplantation with a donor to recipient weight ratio of greater than 15:1.using further of a left lateral segment graft to a monosegment, usually segment 3. Splitting the donor liver into two functioning units for two recipients is now routine in good donors.

(B) **The recipient operation**: The recipient operation commences with an upper abdominal transverse or curved subcostal laparotomy incision, which may be extended in the midline to the xiphoid process for extra exposure. The porta hepatis is dissected first and in children with biliary atresia, this requires the portoenterostomy to be taken down. The portal vein is dissected and isolated. The rest of the liver is carefully mobilised. This includes the

gastrohepatic ligament, the falciform and triangular ligaments together with the right retroperitoneal reflexion. Mobilisation of the liver off the inferior vena cava which is frequently preserved to facilitate reduced size transplantation or piggy-back engraftment should be done and is assisted by carefully dividing the vena cava ligament and ligating the right adrenal vein. The suprahepatic and infrahepatic vena cava are dissected and encircled with tape. Haemostasis of the retroperitoneum must be ensured with a combination of suture ligation and cautery. If the recipient inferior vena cava is to be preserved, this is simply done by carefully incising the diseased liver clear of the cava and when the liver has been removed, individually suturing all small areas of leakage from divided direct caudate lobe hepatic veins. The IVC is prepared for the donor liver by dividing the bridges between the separate hepatic veins. This creates a wide orifice for the hepatic vein to cava anastomosis. The inferior vena cava should be incised distally for approximately 1–2 cm to make a triangular orifice for the 'piggy-back' graft. Engraftment should begin with the upper caval anastomosis, which is usually performed with continuous posterior sutures of polypropolene and interrupted anterior sutures if a conventional transplant is being done. Prior to completion of the anastomosis, the liver is flushed clear of potassium rich preservation solution via the portal vein with either normal saline or a colloid solution. The lower cava anastomosis is then performed if required being sure not to cause any stricture or kinking, a growth factor of about a third of the diameter of the vessel is usually sufficient to prevent this occurring. The recipient portal vein is usually used for the anastomosis and in reduced size transplants where the donor liver is of large diameter, the bifurcation of the recipient portal vein is opened to create a trumpeted end for anastomosis. If the portal vein is hypoplastic, then the anastomosis is done at the level of the confluence of the splenic vein after careful dissection under the head of the pancreas. Another technique is to place a graft of donor iliac vein onto this area first during the anhepatic phase. The portal vein anastomosis is carefully performed using continuous posterior and interrupted anterior sutures or the use of a generous growth factor. In reduced size grafts, plenty of portal vein length should be left to avoid having any tension on the vein, which may result in stretching thus compromising flow. The donor hepatic artery is flushed with heparin saline to remove air and blood clots and an anastomosis is done to the recipient common hepatic artery. End to end microvascular techniques are preferred while others have used donor iliac artery vascular grafts to the infra-renal aorta or from the supra celiac aorta with success. The donor liver is usually revascularised with removal of the suprahepatic clamp followed by the infrahepatic clamp, portal vein and artery. After careful haemostasis of bleeding areas, either from the free edge of a reduced size liver or from any of the other major bleeding points, the operation is completed, by performing the biliary reconstruction. The bile duct is trimmed back such that good bleeding from the edges is obtained and the end is spatulated. In biliary atresia patients and those with a reduced size graft, a Roux-en-Y choledochojejunostomy is performed with fine absorbable sutures. Occasionally in paediatric cases, a duct-to-duct anastomosis may be performed with a whole liver graft in a recipient with a normal extrahepatic biliary system. Stents or T tubes are optional with some evidence of increased biliary complications associated with their use. The only real advantage is access to the biliary system during the postoperative period. Finally haemostasis is obtained and the wound closed with drainage to the suprahepatic and infrahepatic spaces. If there is any tension at sheath closure due to bowel oedema or graft size, it is wise to insert a temporary patch of gortex or other non-adherent material as a 'tight' abdominal closure is associated with an increased incidence of vascular thrombosis and graft dysfunction. It is usually possible to obtain skin closure over the patch without too much tension. The patch can be removed 5–10 days later (Fig. 62.1).

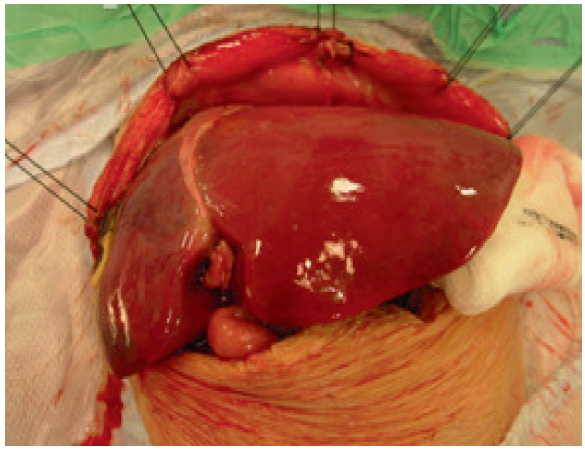

Fig. 62.1 This shows a reduced size liver (segments 2, 3 and part of 4) after transplantation before abdominal closure. In this case a silastic patch would be required to accommodate the large liver without any compression

62.4 Living Related Donors

Living related donation of the left lateral segment, first successfully performed by Strong, has become widely accepted as a method of acquiring a liver graft in the face of severe donor shortages, particularly in countries with cultural or religious reticence to accept brain death in a ventilated heart-beating donor. There are clear advantages in the planned nature of the procedure preferably before end stage liver disease in the recipient, the excellent quality of the graft and short ischaemic time. The use of a living donor also increases the availability of donor organs in general for other patients on the waiting list. The only advantage to the donor is a psychological one and there is a current morbidity of around 10% (wound sepsis, hernia, bile leak and adhesive bowel obstruction). There is also a reported mortality of around 0.2% although in Japan more than a 1,000 of these operations were done without donor mortality. There are ethical concerns, which appear justified, as with more widespread transplant activity increasing mortality and morbidity has been recorded. The donor should first undergo a thorough screening, both clinical and psychological without coercion and be given an option to withdraw from the procedure at any time before the transplant. It is important to recognize limitation of living related liver transplantation as the major source of organs for children. Parents usually approach living related liver transplantation with enthusiasm. They should be advised of the high chance of unsuitability, including the finding of significant pathology and complications, including death.

62.4.1 Split Liver Transplantation

The donor pool for children has been extended by the use of cut-down, split, living-related and, recently, non-heart-beating donor and isolated hepatocyte transplantation. In the split technique, the liver of the donor is divided into two functional units thus making maximum use of this very scarce resource. The procedure may be performed in-situ, which has been associated with less post-reperfusion bleeding from the cut surfaces and improved graft function. However, this technique is time-consuming and may not be feasible in many cases. Early results with ex-situ dissection on the back table were poor and this was in part due to a technical learning curve, prolonged preservation times and the use of grafts, for only those recipients in the worst condition. Recent results are much improved. Clearly the infrastructure must be in place to either perform two transplants simultaneously or alternatively one hemi-liver graft is exported to another centre. The in-situ technique is similar to a living related transplant. Cholangiography is essential as there is considerable variety in the intrahepatic biliary anatomy. Angiography is desirable but not essential. Some centres leave the hepatic artery with the right lobe making it more acceptable as an 'export'. The left lateral segment graft remaining is then used locally. Segment 4 should be used with the left graft if size is compatible; otherwise it is better to resect it prior to transplant as the segment 4 duct usually drains into the left hepatic duct. Likewise arterial anatomy is carefully examined and apportioned to each hemi-liver. There is usually a sufficient periductular vascular network to ensure adequate blood supply to the relevant duct systems so long as the main hepatic artery branch to each hemi-liver is preserved. Accessory arteries can be ligated if there is adequate 'back bleeding' after reperfusion.

62.5 Medical Management

62.5.1 Postoperative Care

Patients are monitored intensively postoperatively and usually require ventilation for a period of 24–48 h. Post-transplant protocol from our centre is summarised in Table 62.4.

1. Liver ultrasound with colour flow doppler is performed for the first 5 days and later as clinically indicated to confirm vascular patency and the absence of biliary dilatation.
2. Hypertension is almost universal in paediatric transplantation and can be initially managed with nifedipine sublingually in conjunction with diuretic agents. Subsequently calcium channel blockers may be given in appropriate dosage.
3. Aspirin 3 mg/kg given on alternate days is used as prophylaxis against arterial thrombosis and a proton pump inhibitor is given for gastric mucosal protection.
4. Nutritional and vitamin supplementation should

Table 62.4 Post-transplant management

Immediate management on arrival to ITU:

- Baseline measurements of FBC, U & E, Astrup, Ca, PT, PTT, chest X-ray, lactate.
- HB must be kept between 8 and 10 g/dl (or PCR < 0.35)
- Measurements of fluid, urine and drain output

Frequency of monitoring and investigations:

- **Hourly:**
  - BP, HR by ECG monitor, CVP, core/peripheral temperature difference, cutaneous oxygen saturation, fluid balance including colloid, wound drainage, urine output and drug volumes.
- **4 hourly for 24 h if required**:
  - Arterial blood gases, serum Na, K, Ca, blood glucose and lactate.
  - Gastric pH is recorded 6 hourly by nasogastric aspiration (aim to keep pH > 5).
- **Daily**:
  - Chest X-ray if indicated
  - FBC and clotting (PT, PTT)
  - Cyclosporin/Tacrolimus level
  - Urea, creatinine, calcium, phosphate, magnesium, total proteins, albumin, CRP
  - Full LFTs (bilirubin total & unconjugated, ALP, ALT, AST, GGT)

Culture: Wound swabs
Drain fluid
ETT aspirates if indicated

(i) Anti-microbials

1. Cefuroxime 25 mg/kg/dose tds for 48 h (max 750 mgs tds)
2. Amoxicillin 25 mg/kg/dose tds for 48 h (max 500 mgs tds)
3. Metronidazole 8 mg/kg/dose (maximum 500 mg) tds over 1 h (can give over 30 min) for 48 h
4. Cotrimoxazole: Up to 5 years 240 mgs od orally
   Over 5 years 480 mgs od orally
   Over 5 years 480 mgs od orally

(ii) Anti-virals

If the donor status for EBV and CMV is known, all transplanted children are to be started on antiviral prophylaxis.

If donor is EBV NEGATIVE

Recipient Status	Donor Status	Treatment
CMV –ve	CMV –ve Stop	Aciclovir
CMV +ve	CMV –ve	Stop Aciclovir
CMV +ve	CMV +ve	Continue Aciclovir
CMV –ve	CMV + ve	Continue Aciclovir

If donor is EBV POSITIVE

All to continue on aciclovir irrespective of recipient EBV/CMV status

(iii) **Anti-fungals**

Nystatin 100,000 units (= 1 ml) orally qds if > 10 kg
50,000 units (= 0.5 ml) orally qds if < 10 kg
Ambisome 3 mg/kg for 7–10 days

(iv) **Gastric acidity prophylaxis**

Ranitidine 3 mg/kg/dose (I/V) tds, if pH still < 5 use sucralfate PO/NGT 250–500 mg QDS and consider using omeprazole 0.5 mg/kg/bd iv or orally.

(v) **Immunosuppression**

Standard immunosuppression (i.e. first graft, no renal failure) begins post-operatively.

(a) **Daclizumab (3 doses)** 1 mg/kg in 50 ml of sodium chloride 0.9% over 15 min (in fluid restriction or in smaller patients dilute to 1 mg/ml).
Intra-operatively, Day 4 post transplant and Day 18 post transplant

(b) **Tacrolimus (Prograf)**
First dose 0.2 mg/kg/dose orally given within 6 h of transplant.
Then 0.1 mg/kg/dose bd orally to maintain levels of 10–15 nanogram/ml in first 2 weeks.
Subsequently adjust dosage to achieve:
7–11 ng/ml in 3rd/4th weeks
4–7 ng/ml in 2nd/3rd month
2–4 ng/ml thereafter

(c) **Steroids**

From Day 0: **Hydrocortisone IV OD *(First dose to be given as child reaches ITU)*:**

Weight kg	Dose
<20	50 mg bd
>20	100 mg bd

When oral diet is tolerated please commence oral steroids (maximum daily dose 40 mg):

(vi) **Anti—platelet treatment**

(a) **Aspirin *(if platelet > 75,000)*** 3 mg/kg/day OD orally/NGT
(maximum dose 75 mg)

(b) **Dipyridamole *(if platelets > 50,000)***
If patient weighs < 10 kg 25 mg tds orally, if weighs > 10 kg 50 mg tds orally

(vii) **Heparin infusion**

For vascular anastomosis at risk (complex vascular reconstruction or small diameter arteries or portal vein)

(viii) **Analgesia and sedation**

Analgesia is achieved with morphine in the routine transplant patient with reasonable graft function and is titrated against pain level

be commenced within 72 h of surgery and may be supplemented by nasogastric feeding or parenteral nutrition in the early phase if there is a delay in restoration of bowel function. Phosphate and magnesium deficiency is common and requires replacement therapy in nearly all patients.

62.5.2 Immunosuppression

There is considerable variation in the selection of immunosuppressive agents. Most protocols currently employ triple therapy with Tacrolimus, methylprednisolone and a monoclonal interleukin-2 inhibitor (CD 25) antibody. Some centres use steroid free immunosuppression. In addition, there are a number of other strategies in place to reduce the amount of nephrotoxicity, which is a toxic side effect to both calcineurin inhibitors. Thus, mycophenolate mofetil, an inosine monophosphate dehydrogenase inhibitor may be used instead from early on in what is called "nephron sparing immunosuppression". Rapamycin, a drug structurally similar to tacrolimus, which prevents proliferation of T cells but acts at a different stage of T cell activation than either cyclosporin or tacrolimus, has the advantage that it is not nephrotoxic and does not interfere with transcription and production of interleukin 2, rather it antagonises the action of interleukin 2 on its receptor. It has no adverse effects on liver function and may be synergistic with cyclosporin.

The methylprednisolone dosage is reduced over the 1st week to about 1 mg/kg/day for the first month and then reduced to a level of 0.3 mg/kg/day to 0.2 mg/kg as maintenance. This can be later reduced in some patients to alternate day therapy or even withdrawn completely. Both mycophenolate mofetil and rapamycin can be used as renal sparing should nephrotoxicity become evident. Use of humanised anti-CD25 monoclonal antibodies given before and during the 1st week of the transplant have reduced the incidence of acute rejection in the first 3 months by around 30% but long term graft survival is essentially the same as when these agents have not been used. The other polyclonal anti-lymphocyte immunoglobulins are rarely used.

62.5.3 Anti-Infection Agents

Immunosuppression naturally leads to susceptibility to bacterial, fungal and viral infections. Fungal infection (FI) is a major and potentially fatal complication in liver transplantation (LT).Fungal prophylaxis is given before the transplant as mycostatin orally to reduce Candida colonisation of the gut and after transplant as amphotericin and continued for a period of several months. From two to 3 weeks after the transplant, for at least the 1st year, trimethoprim-sulphamethoxazole is given at a dose of 6 mg/kg/day in two divided doses 3 days a week for prevention of pneumocystis carinii infection. Intravenous ganciclovir 5 mg/kg/dose 12 hourly is used as prophylaxis against cytomegalovirus (CMV) and Epstein Barr virus (EBV) infection, initially for 2 weeks and this may be extended for up to 3 months in high risk patients who have not previously been exposed to CMV or EBV but have received a donor graft with previous exposure. This considerably reduces the incidence of both cytomegalovirus disease and post transplantation lymphoproliferative disorder. Either hyper-immune cytomegalovirus globulin or immunoglobulin is also given to assist viral prophylaxsis. Leucocyte filtered blood products are used throughout to reduce CMV load. Prophylactic antibiotics are given with induction of anaesthesia and continued for 3–5 days. These are changed according to cultures taken of blood, secretions, sputum and urine. Anti-tuberculosis prophylaxis is given only if the reason for transplant is a reaction to anti-tuberculosis drugs with fulminant hepatic failure, where evidence of tuberculosis is found before surgery and if a close family contact has tuberculosis. Ofloxacin, rifampicin and ethambutol or ethionamide may be used in addition to isoniacid but very careful monitoring of liver function tests is required because all of these drugs may be hepatotoxic and particularly rifampicin may result in a decrease in cyclosporin or tacrolimus levels due to enzyme P450 induction with increased drug metabolism.

62.6 Surgical Complications

Surgical complications may be reduced to an absolute minimum with meticulous technique. These may present early and late as summarised in Table 62.5. Most common surgical complications are as follows.

(A) **Biliary complications** continue to be a significant problem with an overall incidence of between 10–20%, particularly in living related left lateral segment grafts. These complications include bile leak, anastomotic strictures, and non-anastomostic strictures of the donor bile duct with sludge formation. Most biliary complications (72%) occur

Table 62.5 Summary of common postoperative problems

1. **Biliary tract**
   (a) Stenosis or stricture
   (b) Anastomotic leak—often associated with hepatic artery thrombosis
   (c) Infection
2. **Rejection**
   (a) Acute
   (b) Chronic (vanishing bile duct syndrome)
3. **Infection**—bacterial, viral, (CMV, EBV, Herpes Zoster, hepatitis B). fungal (Candida, Aspergillus), parasitic (pneumocystis)
   (a) Abdominal (peri or intra-hepatic abscess)
   (b) Biliary tree
   (c) Pulmonary
   (d) Re-activated virus
   (e) Gastro-intestinal tract
   (f) Catheter associated (intravenous, urinary tract)
4. **Graft vascular injury (thrombosis, stenosis)**
   (a) Hepatic artery
   (b) Portal vein
   (c) Inferior vena cava (supra and infrahepatic)
   (d) Hepatic vein (left lateral segment grafts), Budd-Chiari recurrence
5. **Renal dysfunction**
   (a) Tacrolimus/Cyclosporin or other drug induced injury
   (b) Tubular necrosis due to hypoperfusion
   (c) Pre-existing disease (hepato-renal syndrome)
   (d) Hypertension
6. **Miscellaneous**
   (a) Encephalopathy (cyclosporin, tacrolimus, hypertensive, metabolic)
   (b) Bowel perforation (steroid, diathermy)
   (c) Diaphragm paresis/paralysis
   (d) Gastrointestinal haemorrhage (peptic ulceration, variceal)
   (e) Obesity (steroids)
   (f) Other drug side effects

in the first 2 weeks following transplantation. Ultrasound and cholangiography are the principle imaging modalities used for detection of these complications. Ultrasound is important in the post-operative surveillance of paediatric liver transplants, with cholangiography having a complementary role. It is imperative with all suspected biliary complications to ensure that the hepatic artery is patent using doppler ultrasound or angiography as hepatic artery thrombosis will cause ischaemia and necrosis of the biliary tree. Simple bile leaks are diagnosed in the early postoperative period by the presence of bile in drainage fluid or in percutaneous aspirate of fluid collections around the liver. Early biliary complications are best treated by immediate surgery and re-anastomosis if required. Late stricture formation may be satisfactorily dealt with by endoscopic or percutaneous balloon dilatation or stenting.

(B) **Graft ischaemia** either from hepatic artery thrombosis or portal vein thrombosis can be a devastating complication. Hepatic artery thrombosis (HAT) represents a significant cause of graft loss and mortality after pediatric orthotopic liver transplantation (OLT). The reported incidence of this complication is 7.8%. The incidence is much less frequent with the use of reduced size liver transplants and microsurgical techniques for living donor transplants. Most centres recommend routine Doppler ultrasound in the early post-operative period ranging from 3–7 days to confirm the patency of these vessels. Consequences of vascular thrombosis are graft necrosis, intrahepatic abscess, biliary necrosis and bile leakage. A massive rise in enzyme activity, particularly in the first few days after transplant, may be the first signs. Immediate intervention with thrombectomy and re-anastomosis may be successful if the diagnosis and treatment is carried out as soon as the complication is diagnosed. If thrombectomy fails, urgent re-transplant is required. Late thrombosis may be asymptomatic and if so can be ignored. Although technical factors usually account for most cases, it is advisable to maintain the haematocrit at around 30 to improve microvascular flow and most centres use aspirin and dipyrimidole as long term prophylaxis.

(C) **Portal vein thrombosis** usually presents with a degree of liver dysfunction with prolonged clotting and portal hypertension, which may be heralded by an oesophageal varicoele bleed. Immediate thrombectomy may be successful. Where graft thrombosis is established, a meso-portal (Rex) shunt, with a vein graft taken from the internal jugular vein of the patient or donor veins from vascular bank (if available) and interposed between the superior mesenteric vein and the left branch of the portal vein, may be curative. Significant risk factors for portal vein thrombosis are young age and weight at the time of LT, small portal vein, and emergency LT. Overall risk of portal vein thrombosis (PVT) is 2.2% in teams using aspirin with or without dipyridamole compared with 7.8% when no antiaggregative agents are given.

(D) **Bowel perforation** is a well-recognized complication following orthotopic liver transplantation (6.7%). Contributory factors include previous operation, steroid therapy and viral infection. The incidence is higher in children who underwent transplantation for biliary atresia after a previous Kasai portoenterostomy. Diagnosis may be difficult and a high index of suspicion is needed.

(E) **Post-operative fluid collections** arising from the cut surface of the liver has the reported incidence of 39% and 44% of which nearly 50% required intervention. These collections can be due to biliary anastomosis leaks or bowel perforation however the overall incidence of fluid collections are not increased by the use of reduced-size liver transplants. Late presentations may be less acute and typically present with gram-negative sepsis, liver abscess or biliary complications.

(F) **Inferior vena cava thrombosis** is now rare Thrombosis in the IVC may develop either in the immediate postoperative period presenting with ascites and lower body oedema or later on due to regeneration of the graft and twisting of the caval anastomosis. Thrombolytic therapy may be successful in late thromboses but should be avoided in early thromboses as uncontrollable bleeding may occur from raw surfaces particularly if a reduced/split liver was transplanted.

(G) **Hepatic venous outflow obstruction** is a more frequent complication. This can be due to redundancy of hepatic vein (when the graft hepatic vein is kept long) in reconstruction of a partial graft. The correction of the redundancy is made by pulling the graft caudally and to the left or right side of the abdominal cavity as determined by Doppler ultrasonography. It can also be suspected if there is persistence of ascites in the early post transplant period. This is usually confirmed either by angiography or by liver biopsy findings of congestion and red cell extravasation around central veins.

(H) **Diaphragmatic paresis and hernia** are rare complications of liver transplantation. The possible role of several contributing factors include cross clamping of the IVC at the level of the diaphragmatic hiatus, trauma at operation (dissection and diathermy) and diaphragm thinness related to low weight and malnutrition.

62.7 Late Medical Complications

Most patients can be discharged from the intensive care unit within the 1st week after transplantation. Complications of transplantation include bacterial, viral, fungal and opportunistic infections, renal function impairment, hypertension, rejection and particular concern is the post-transplant lymphoproliferative syndrome.

(A) **Infections:** The reported incidence of infection in the liver transplant population is 1.36 infection/patient. The most common sites of infection are bloodstream (36.5%) and abdomen (30%). Gram-positive bacteria (78%) predominated over gram-negative bacteria (22%). Detailed analysis of risk factors shows that age < 1 year, body weight < 10 kg, extrahepatic biliary atresia, intraoperative transfusion > 160 ml × kg(–1), mechanical ventilation > 8 days and PICU stay > 19 days are associated with higher risk of infection.

(B) **Acute rejection:** Despite the availability of potent immunosuppressive drugs, rejection after organ transplantation in children remains a serious concern, and may lead to significant morbidity, graft loss, and death of the patient. Diagnosis of rejection can be made on the basis of clinical, biochemical and histologic changes and usually presents in the first few weeks after transplant with fever, malaise, a tender graft and loose stools. Diagnosis is confirmed by liver biopsies performed using the Menghini technique (Hypafix needle (Braun), diameter 1.4 mm), unless biliary dilatation is observed on ultrasonography. Biopsies are also routinely assayed for viral and bacterial activity.The grade of rejection is assessed according to established histological criteria on a scale of 0–4. Some centres are trying to evaluate non-invasive tools to diagnose acute rejection such as radiologic findings on post-transplant Doppler ultrasound. Others are using Interleukin 5 (IL-5), it is produced in the liver and is a T cell-derived cytokine that acts as a potent and specific eosinophil differentiation factor in humans. During liver allograft rejection, intragraft IL-5 mRNA and eosinophilia have been observed. It may be a useful as a specific marker of allograft rejection. However once diagnosed acute rejection is treated with three doses of methyl prednisolone 10 mg/kg on successive days with adjusted baseline immunosuppression. Some patients

experience corticosteroid resistant acute rejection, the management of which is not standardized. Various agents used include the addition of mycophenolate mofetil or sirolimus. The use of antithymocyte globulins (ATG) or monoclonal anti-CD3 antibodies, muromonab CD3 (OKT3) is hampered by numerous adverse effects, including a significant risk of over-immunosuppression. These therapies are nowadays indicated in only few selected cases. Other treatments such as plasmapheresis and high dose immunoglobulins may be useful in difficult cases. In patients with refractory rejection despite therapeutic escalation, the risks of over-immunosuppression, including opportunistic infections and malignancies (especially the Epstein-Barr virus related post-transplant lymphoproliferative disease) have to be balanced with the consequences of graft loss due to rejection.

(C) **Late acute cellular rejection**: Although acute rejection is mostly encountered during the first 3 months after liver transplant, it may occur later on. Late cellular rejection in children is usually due to low or decreased immunosuppression and is associated with long-term complications. Prompt intervention to correct inadequate immunosuppression and careful follow-up to identify other treatable conditions is essential.

(D) **Chronic rejection** is an irreversible phenomenon which is chiefly intrahepatic and ductular rather than a vascular phenomenon in contrast to other organ transplants. This is usually manifested by disruption of bile duct radicals with development of the vanishing bile duct syndrome. The incidence seems less frequent with tacrolimus based immunosuppressive regimens as opposed to cyclosporin where an incidence of up to 10% has been recorded. Late chronic rejection may also be associated with a vasculopathy affecting larger arteries.

(E) **Chronic graft hepatitis** occurs in 20–30% children after liver transplantation but the prevalence and causes are not known. Serum liver associated autoantibodies are often positive. It is most frequently seen in children transplanted for cryptogenic cirrhosis (71%). However neither hepatitis C nor hepatitis G infection was associated. Management is with re-introduction or increase in steroid dose.

(F) **Cytomegalovirus (CMV) infection**: Cytomegalovirus (CMV) infection (seroconversion or virus isolation) and CMV disease (infection plus clinical signs and symptoms) have a reported incidence of 37% and 11.5% respectively with significant morbidity and mortality. The high prevalence of CMV infections supports the view that clinical signs alone are inadequate to direct investigations for CMV. Cytomegalovirus (CMV) infection is best monitored with PP65 antigen and polymerase chain reaction (PCR) measurement of the virus. Ganciclovir remains an important therapeutic option for the prevention and treatment of CMV disease in transplant recipients. Prophylactic treatment with ganciclovir appears the best strategy to implement in high risk patients. A rare association with cytomegalovirus (CMV) reactivation is Haemophagocytic syndrome (HPS). It is a rare event, which is often fatal. These patients are treated with a combination of antiviral agents, immunomodulatory and supportive therapy.

(G) **Epstein-Barr virus (EBV) and post-transplant lymphoproliferative disease (PTLD)**. EBV infection is the main cause of PTLD. Since many infants are EBV seronegative at the time of transplantation, PTLD is a major concern for these patients. Post transplantation lymphoproliferative disorder (PTLPD) presents from the first few weeks after transplant to several years later with a mean time of onset around 9 months. First manifestations of PTLD are adenoidal and/or tonsillar involvement. A typical presentation is usually with acute membranous tonsillitis and associated cervical lymphadenopathy, which is resistant to antibiotic therapy. It is important to remember that tonsillar enlargement in paediatric liver transplant patients does not necessarily imply a diagnosis of PTLD. Furthermore, the presence of increased numbers of EBV infected cells in tonsils from liver transplant recipients by itself does not indicate an increased risk of developing PTLD. However, the disease may be widespread and gastrointestinal and central nervous system involvement is common. Currently there are no tests to accurately identify paediatric liver transplant patients at risk for post-transplant lymphoproliferative disorder (PTLD). Attempts have been made to use cytokine polymorphisms and real-time quantitative polymerase chain reaction (qPCR) Epstein-Barr virus (EBV) viral load to identify patients at risk for PTLD development. Use of cytokine genotyping in conjunction with qPCR for EBV viral load can significantly improve the predictive value of diagnostic tests for identification of patients at high risk for

PTLD. Management strategies include reduction of immunosuppression, which may require complete withdrawal along with standard anti-lymphoma chemotherapy, particularly with the monoclonal type. Mortality varies from 20% to 70% or more. Prophylactic intravenous ganciclovir given for a prolonged period may be effective in preventing EBV activation which is the promoter of PTLD in most cases. Rituximab, an anti-CD 20 monoclonal antibody has been used with good effect. As B cells are largely ablated, replacement immunoglobulin therapy is required until B cell recovery has occurred.

(H) **Renal impairment**: A degree of renal impairment is almost inevitable in those patients suffering from chronic liver disease and with the additional burden of the use of nephrotoxic immunosuppressive drugs such as cyclosporin and tacrolimus with other neprotoxic antibiotics and antifungal agents may result in significant renal impairment of function in the long term. The importance of renal sparing strategies in immunosuppression is becoming increasingly evident as long-term survivors present with drug induced renal failure.

62.7.1 Re-Transplantation

Ten percent to 15% of patients may suffer graft failure at some time and need re-transplantation. Early indications may be primary non-function, early hepatic arterial thrombosis, severe drug resistant acute rejection and established chronic rejection. Early re-transplantation is technically a much less traumatic procedure than the original transplant, although the patient may be in a poorer condition. Outcome largely depends on the indication for re-transplantation and is quite good for technical causes but less satisfactory for rejection and infection. An increasingly poorer outcome can be expected after third and fourth re-transplants and the efficacy and ethics of these interventions are in question.

62.7.2 Longterm Survival and Quality of Life

One year survival of > 95% is being achieved in the best centres with predicted 10 year survivals of around 80–85%. Patients grafted for acute liver failure have done less well with a higher early death rate usually associated with cerebral complications and multi-organ failure. Excellent quality of life can be achieved and most children are fully rehabilitated. It is however increasingly evident that prolonged cholestatic jaundice and malnutrition in infancy may have late effects and despite good physical rehabilitation evidence of significant cognitive deficits, which present during early schooling as learning difficulties and attention deficit disorder, are common. Quality of life may not reach perfection, and depends also on the way society accepts these imperfections. As with any immunosuppressed patient, the incidence of neoplasia in a lifetime is greatly increased.

62.8 Conclusion

Careful planning, extensive preparation of personnel and a broad base of skills along with good teamwork between health professionals are required for the development of a successful paediatric transplant programme. Surgical technique, anaesthetic skills, and medical care of the highest order are essential. A patient with a liver transplant is a patient for life and requires complete commitment from the transplant medical and surgical team, which cannot be abrogated after discharge from hospital. Endemic viral and bacterial infections particularly HBV, CMV, EBV and PTLD, impact negatively on any programme. Extended hospital stay may be required and this, along with long-term therapy may be extremely expensive.

The need for paediatric liver transplants has been assessed at approximately 1–2 children per million per year. Thus transplant activity should be concentrated in specific centres preferably doing more than 12 transplants a year. The shortage of donor organs will continue and future efforts must be focused on maximum use of cadaver donors and increasing living related donation. Transplant activity is rapidly increasing throughout the developing world. This endeavour should be strongly supported as poor socio-economic status is not a contraindication to transplantation and we have frequently been impressed by how parents with relatively few material resources have been able to diligently care for their children. No child with end stage liver disease should be denied the opportunity of receiving appropriate treatment. As with any new development, knowledge and experience improve,

costs decline and success is ensured. These challenges must be met to offer any infant or child requiring liver replacement a chance of a life. The ultimate aim is to restore the child to normal health such that he/she can grow up into a productive healthy adult who can make his/her contribution to society and develop all of his/her human potential.

Further Reading

Baker A, Dhawan A, Heaton N (1998) Who needs a liver transplant? (new disease specific indications). Arch Dis Child 79(5):460–464

Cox KL, Berquist WE, Castillo RO (1999) Paediatric liver transplantation: indications, timing and medical complications. J Gastroenterol Hepatol 14(Suppl):S61–S66

de Ville de Goyet, J et al (1995) Standardized quick en bloc technique for procurement of cadaveric liver grafts for pediatric liver transplantation. Transpl Int 8(4):280–285

Muiesan P, Vergani D, Mieli-Vergani G (2007) Liver transplantation in children. J Hepatol 46(2):340–348

Otte JB (2004) Paediatric liver transplantation–a review based on 20 years of personal experience. Transpl Int 17(10): 562–573

Otte JB (2002) History of pediatric liver transplantation. Where are we coming from? Where do we stand? Pediatr Transpl 6(5):378–387

Puri P, Höllwarth M (2006) Pediatric Surgery. Springer, Berlin, Heidelberg

Shepherd RW (1998) The treatment of end-stage liver disease in childhood. Aust Paediatr J 24(4):213–216

Shneider BL (2002) Pediatric liver transplantation in metabolic disease: clinical decision making. Pediatr Transplant 6(1):25–29

Vilca-Melendez H, Heaton ND (2004) Paediatric liver transplantation: the surgical view. Postgrad Med J 80(948): 571–576