Pediatric Living Donor Liver Transplantation

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27.1 History

The first deceased-donor liver transplant attempted by Thomas Starzl on March 1, 1963, involved a pediatric recipient with biliary atresia [1]. The next eight pediatric recipients operated by Starzl in 1967 had a 50 % 1-year survival rate. An immunosuppression regimen based on azathioprine, steroids, and antilymphocyte globulin was used in these patients. As pediatric cadaveric donors were exceedingly few in number, the concept of reduced liver transplantation was introduced in 1984 [2], wherein the remnant portion of the large liver graft was discarded. The first split liver transplantations, with one cadaveric donor used for two recipients, were done by Pichlmayr in Europe (1988) and Broelsch in the United States [3].

The improved understanding of liver anatomy and refinement of techniques of liver resection enabled the development of living-donor liver transplantation (LDLT) in 1989 [4]. The ethical considerations involved in a motivated parent donating a graft to a child were reasonably clear and without suspicion of coercion. The surgical risks involved in harvesting the left lobe or left lateral segment from a healthy donor were also surmountable. Development of LDLT has drastically reduced the number of pediatric patients with end-stage liver disease on the waiting list for DDLT [5]. In the United States, organ allocation system, the PELD (pediatric end-stage liver disease) score as well as the exceptions for certain indications tended to benefit the pediatric population over adult candidates using the MELD (Model for End-Stage Liver Disease) scoring system. Hence, LDLT for children has resulted in increasing the relative availability of grafts for adults with end-stage liver disease.

The first successful liver transplant from a brain-dead donor in Asia was performed in Taiwan in 1984. Pediatric liver transplants for biliary atresia and metabolic diseases were performed soon thereafter. The high endemic rates of viral hepatitis coupled with low organ donation rates due to sociocultural factors propelled the development of LDLT in East Asia. Pediatric LDLT was first performed in Taiwan in 1994. LDLT vastly improves the survival of children with end-stage liver disease, as it enables the availability of a matched size graft from a properly assessed healthy donor on an elective basis. Currently, pediatric LDLT is a significant component of most LDLT programs around the world.

27.2 Indications

Cholestatic diseases like biliary atresia are the most common indications for pediatric LDLT, unlike parenchymal diseases which are more common in adults (Table 27.1). Children with defects in the urea cycle and primary hyperoxaluria may require transplant despite the absence of cirrhosis, in order to manage the systemic effects of these metabolic diseases. More commonly, LDLT is done for end-stage liver disease or for congenital diseases refractory to medical management. The timing of transplantation should be optimal, in order to avoid the child falling off the growth curve.

27.2.1 Biliary Atresia

It is the most common cholestatic disorder of childhood and accounts for 50–75 % of pediatric LDLT in most centers [6]. It is characterized by a progressive inflammation of the extrahepatic bile ducts and if left untreated, inevitably leads to cirrhosis and death. A successful hepatic portoenterostomy (Kasai procedure) performed within the first 3 months of life has equivalent survival to liver transplantation performed within the first year [7]. Even then, the child may need a liver transplant at an older age due to increased frequency of cholangitis and failure to thrive. Patients with failed Kasai procedure and those presenting with complications of cirrhosis usually require liver transplantation before 2 years of age.

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Table 27.1 Indications for pediatric LDLT

Cholestatic diseases
Biliary atresia
Alagille syndrome
Familial intrahepatic cholestatic syndrome (Byler disease)
Primary sclerosing cholangitis
Idiopathic
Metabolic diseases
Wilson's disease
α1-Antitrypsin deficiency
Urea cycle defects
Primary hyperoxaluria
Glycogen storage diseases
Crigler-Najjar syndrome
Cystic fibrosis
Hemochromatosis
Familial hypercholesterolemia
Fulminant liver failure and cirrhosis
Neonatal hepatitis
Drug induced (e.g., acetaminophen)
Acute viral hepatitis
Autoimmune hepatitis
Other infectious hepatic failure (syphilis, toxoplasmosis, bacterial)
Idiopathic
Malignancy
Hepatoblastoma
Hepatocellular carcinoma
Hemangioendothelioma
Others
Budd-Chiari syndrome
Congenital hepatic fibrosis

27.2.2 Alagille Syndrome

The hepatic hallmark of this syndrome is the paucity of bile ducts. The cholestasis typically waxes and wanes, and ocular, cardiac, and skeletal manifestations besides hypercholesterolemia may be present. While biliary diversion and medical management may be beneficial in many, liver transplantation can provide a definitive cure in most patients with hepatic effects of this syndrome [8].

27.2.3 Wilson's Disease

This autosomal recessive disease is characterized by increased copper deposition, primarily in the liver and brain. Hepatic manifestations are more common than neurologic symptoms in children. It may present as acute hepatitis or may progress from chronic liver disease to end-stage liver disease. Liver transplant is a curative therapy, indicated for those with severe portal hypertension and those refractory to medical therapy [9].

27.2.4 α1-Antitrypsin Deficiency

This autosomal dominant deficiency in serum α1-antitrypsin is the most common genetic liver disease in children of Northern European descent and the most common metabolic cause of neonatal hepatitis. Children with end-stage liver disease benefit from liver transplantation.

27.2.5 Urea Cycle Defects

Deficiency of liver enzymes involved in metabolizing ammonia to urea results in hyperammonemia and neurologic sequelae. Liver transplantation before the onset of irreversible brain damage can be curative in these children.

27.2.6 Neonatal Hepatitis

It is predominantly caused by infections such as viral (enterovirus; herpes simplex virus; hepatitis A, B, C; cytomegalovirus, Epstein-Barr virus, rubella, etc.), bacterial (*Streptococcus pyogenes*, *Staphylococcus aureus*, tuberculosis, syphilis), toxoplasmosis, etc., although a significant proportion are of idiopathic origin. Other causes include inborn errors of metabolism, mitochondrial defects, adrenal insufficiency, Budd-Chiari syndrome, polycystic disease, etc.

27.2.7 Fulminant Hepatitis

Children of any age can be affected by acute liver failure. Other than the causes enumerated above for neonatal hepatitis, other causes like idiosyncratic or dose-related drug toxicity and autoimmune disease can also cause fulminant hepatitis necessitating liver transplantation.

27.2.8 Liver Tumors

Hepatoblastoma is the most common primary liver tumor in children. The majority of hepatoblastomas can be managed by liver resection and is preceded by chemotherapy if required. However, liver transplantation may be indicated for unresectable intrahepatic tumors. They comprise less than 3 % of pediatric LDLT. Other uncommon tumors like HCC with advanced cirrhosis, and benign tumors like adenoma or arteriovenous malformations replacing nearly all liver tissue, are also indications for liver transplantation.

27.3 Preoperative Evaluation and Management of Recipient

A potential recipient benefits from early referral to a transplant center for simultaneous evaluation and preoperative management by an experienced multidisciplinary team. The diagnosis, severity of disease, and need for liver transplant can be validated, and the evaluation protocol is initiated. The child is put on the waiting list for DDLT according to the regional guidelines. Management based on severity of liver disease, for the specific etiology, and for various complications can be started.

Close consultation among the transplant surgical team, pediatrician, hepatologist, anesthesiologist, radiologist, psychiatrist, nutritionist, social worker, and nursing team is essential. Depending upon coexisting morbidities, consultations from other specialties such as pulmonology, cardiology, nephrology, neurology, hematology, etc., may be required.

A thorough physical examination and investigations are carried out (Table 27.2).

Patients who are medically stable can be investigated on an outpatient basis, whereas those candidates with acute liver failure may need to be managed in an ICU setting. The PELD score was developed to assess the risk of mortality in children with chronic liver disease [10]. It is based on the principle that severity of liver disease is more when multiple hepatic functions such as protein synthesis, bile excretion, and metabolic and immunologic functions are compromised. The urgency for transplantation can thus be assessed using a formula based on the measurement of serum albumin, bilirubin, INR, and growth retardation.

$$\begin{aligned}\text{PELD Score} = 10 \times [&0.48 \times \log_e(\text{total bilirubin}) \\ &+ 1.857 \times \log_e(\text{INR}) - 0.687 \times \log_e(\text{Albumin})] \\ &+ 0.667 (\text{if height} < 2 \text{standard deviations for age}) \\ &+ 0.436 (\text{if age} < 1 \text{year})\end{aligned}$$

Fulminant liver failure (FHF) in children differs from that in adults in its etiology and time to progression. Some cases may resolve without transplantation, and the outcomes of transplantation for FHF are inferior to transplantation for chronic liver disease. Hence, the decision to proceed with LDLT is a difficult one. Prognostic scoring models like the King's College criteria [11], which is based on age, etiology, duration of jaundice, INR, and bilirubin, and the Clichy criteria (based on age and factor V levels) have been developed, but their positive predictive value for pediatric acute liver failure is low, which can possibly lead to higher transplantation rates [12].

At this stage of the evaluation, any possible contraindications for transplant are assessed. There are relatively few absolute contraindications to pediatric LDLT, such as uncontrolled sepsis or presence of extrahepatic malignancy.

Table 27.2 Investigations for potential pediatric recipient

Hematology
Complete blood count, blood typing and antibody screening, prothrombin time, INR (international normalized ratio)
HLA (human leukocyte antigen) typing and crossmatching with donor lymphocytes
Other laboratory investigations
Creatinine, blood urea nitrogen, eGFR (estimated glomerular filtration rate), albumin, bilirubin, liver enzymes (AST, ALT, alkaline phosphatase, γ-GT), electrolytes, ammonia
Arterial pH, serum lactate, phosphate, coagulation factors assay
HBsAg, HBsAb, HBeAg, HBeAb, HBcAb, HBV DNA
HCVAb, HCV genotype, and RNA
IgG, IgM, and antigens as required for CMV, HSV (herpes simplex virus), rubella, measles, EBV, varicella, hepatitis A, HIV, TB PCR
Autoimmune workup as required
Cholesterol, triglycerides, fat-soluble vitamins (A, D, E), iron, ferritin, thyroxine
α-Fetoprotein, CEA, CA 19-9, CA 125
Blood and venous catheter tip cultures
Ascitic fluid and urine examination
Radiology
Liver Doppler ultrasound
Chest X-ray and high-resolution CT
Liver CT angiography, MRCP
Others
ECG
EEG, brain CT
Endoscopy
Sputum and bronchial lavage studies
Workup for associated anomalies
Gene mutation analysis
Liver biopsy
Nutritional assessment

Massive brain injury or uncontrolled cerebral edema in metabolic diseases or fulminant liver failure, or progressive extrahepatic disease such as severe pulmonary hypertension with hypoxemia, also precludes liver transplantation. Technical factors such as associated anomalies or extensive portal thrombosis, presence of HIV infection, and developing multiorgan failure may be considered as relative contraindications for transplant.

It is vital that an excellent rapport is created between the child's family and the medical staff managing the patient. A long stay in the hospital involving complex treatment procedures and risk of numerous complications can strain relationships easily. The social worker can help identify logistic and financial issues besides social dynamics which can impact the management of the patient. At the same time, a psychosocial evaluation of the older child and making him aware about the illness and its management in an optimistic manner can be helpful.

The elective nature of LDLT permits optimization of the child's status before transplantation. A child with chronic liver disease may be mostly managed in an outpatient setting, while a child with acute liver failure may need aggressive treatment in an ICU.

Vaccination is more effective if given before transplantation and initiation of immunosuppression regimens [13]. An accelerated regimen of routine vaccines may be required considering the young age of many recipients. Achieving high levels of antibody to HBsAg by vaccination can help prevent de novo HBV infection after transplant [14].

Malnutrition is common with pediatric liver disease, and growth failure is one of the indications for transplantation. It is caused by multiple factors like increased catabolism, anorexia due to liver disease, and abdominal heaviness due to hepatosplenomegaly, malabsorption, cholestasis, and impaired parenchymal function. Preoperative malnutrition and sarcopenia can have significant negative impact on liver transplantation outcomes [15]. Anthropometric assessment and delayed milestones of development can guide nutritional therapy. Vitamin and medium-chain triglyceride supplements in normal diet, high-caloric-density preparations, nasogastric feeding, and parenteral nutrition may be required. Growth failure due to parenchymal disease cannot be corrected after a point by nutritional therapy, and hence, it is a strong independent indication for liver transplantation.

Coagulopathy in decompensated chronic liver disease or in acute liver failure is indicative of worsening condition. Management of coagulopathy before transplant can greatly improve surgical outcomes. It can also increase safety of invasive procedures such as liver biopsy or invasive intracranial pressure monitoring. Increased bleeding tendency in liver disease results from a decrease in both procoagulant and anticoagulant factors as well as due to factors like altered platelet activation, hemodynamic alterations of portal hypertension, endothelial dysfunction, sepsis, and renal failure. Correction of coagulopathy must hence focus on all these factors rather than simple replacement of depleted coagulation factors [16]. Hospital guidelines regarding transfusion of fresh frozen plasma, cryoprecipitate, platelets, recombinant factor VIIa, and plasmapheresis should be prepared, as the benefit of these measures is not broadly accepted.

Neonatal candidates for transplantation usually have acute liver failure, and pulmonary, renal, and cardiac dysfunction is common. Their small size makes management difficult, as interventional procedures such as hemofiltration are not easy to perform. They require hyperreduced size grafts, increasing the risk of surgical complications.

Survival outcomes of LDLT recipients weighing less than 10 kg are inferior to those with higher weights, and hence ideally LDLT should be done after the age of the child is at least 6 months old [17]. However, as liver failure results in growth retardation, LDLT may be required in children with low weights, if they are below the third percentile of the growth curve or if the severity of the liver disease so demands; hyperreduced size grafts are required in such cases.

27.4 Preoperative Evaluation of Donor

Donor evaluation is similar to that for LDLT in adults. Guidelines regarding degree of donor relationship and donor age are usually framed by the local health authority. For example, the Organ Transplant Act of Taiwan permits only adult relatives within fifth degree of consanguinity to be donors, whereas there is no provision for emotionally related donors. Donation should be voluntary, and the willingness of the donor should be thoroughly assessed in one-on-one psychosocial consultations. The donor should have an understanding of the potential risks associated with the surgery, especially as the donor may be an important caregiver for the recipient. Presence of social and family support systems for the donor and their comfort with the donor's decision should be assessed. Thus, a structured assessment and informed consent are of vital importance in donor surgery.

If there are multiple potential donors, then a basic screening is conducted to rule out contraindications for donation. Presence of active infection, malignancy, and systemic disease are obvious contraindications, whereas history of past infection or malignancy needs further assessment. Seropositivity for HBV, HCV, or HIV generally precludes organ donation, while LDLT with HBcAb-positive grafts may be done with pretransplant hepatitis B vaccination and if required, posttransplant antiviral agents [18].

ABO incompatibility is a major factor limiting the donor pool in LDLT. ABO-incompatible LDLT and DDLT have resulted in high rates of intrahepatic nonanastomotic biliary strictures, liver necrosis, and lower graft survival before the introduction of rituximab. On the other hand, outcomes of ABO-incompatible LDLT for recipients aged less than 1 year are similar to those of ABO-compatible LDLT, probably because the immune system is still developing [19]. In order to reduce the incidence and severity of reactions due to blood group incompatibility, various modalities like plasmapheresis to reduce blood group antibodies in serum, rituximab to reduce B cells via cytotoxic reaction, and local graft infusions of prostaglandins and steroids have been used. The outcomes for ABO-incompatible LDLT for older children are expected to improve as the immunosuppression protocols for ABO-incompatible LDLT in adults are being improved [20].

When inborn errors of metabolism are the indication for pediatric LDLT, there is a risk that the related donor may be affected by the same disease. Symptomatic donors are usually excluded during the evaluation process, but grafts from asymptomatic donors have been utilized without incident [21]. Many of these metabolic disorders are inherited in an

autosomal recessive manner, and hence, the recipient has homozygous affected genes, while the asymptomatic donor may have two normal genes or carry one affected gene. Alternative methods for investigating the donor for inheritable metabolic diseases include carrying out a metabolic loading test or taking a liver biopsy from the donor to accurately measure the target enzyme activity. Such methods may be particularly useful for ornithine transcarbamylase deficiency, an X-linked recessive inherited urea cycle defect, as even heterozygous female donors who carry the recessive gene may become symptomatic due to mosaicism [22].

Complete HLA matching is not a criteria for donor selection in liver transplants because of the tolerogenic nature of the liver and the paucity of donors, although it can lead to low rates of acute rejection and increased chances of developing operational tolerance after transplant (absence of graft rejection despite withdrawal of immunosuppression) [23]. Conventionally, the cytotoxic lymphocyte crossmatch between donor lymphocytes and recipient sera is performed to assess risk of graft rejection, although quantitative assays of donor-specific antibodies and DNA-based typing methods may be more accurate and efficient.

Normally, the main concern in liver transplantation is to avoid graft rejection (initiated when the recipient's immune system identifies graft antigens as foreign and initiates an immune response) rather than GVHD (graft versus host disease, where the lymphocytes in the graft recognize the recipient cells as foreign and initiate an immune response even though the recipient immune system is quiescent).

However, when a parent is the donor for a pediatric LDLT, the risk of GVHD has to be assessed. If the parent is homozygous for HLA allotypes and the child is heterozygous, then the recipient immune system tolerates the graft, but the graft lymphocytes may initiate a GVHD against the recipient's HLA allotypes. In such cases, an alternative donor may be needed. Preoperative identification of anti-HLA antibodies quantitatively and qualitatively may help in avoiding severe immune intolerance (e.g., by initiating immunosuppression regimens in the recipient similar to those for ABO incompatibility) and expand the donor pool [24].

27.5 Preoperative Operative Planning

Radiology and volumetry: The left lobe or left lateral segment is almost invariably used in pediatric LDLT. Numerous variations of size, shape, and anatomy can be encountered in both the donor and recipient in pediatric LDLT, and hence, good preoperative imaging is invaluable in preparing for the procedure. A left lobe graft leaves a safe remnant liver volume of more than 40 % of the standard liver volume in the donor. A graft-to-recipient weight ratio (GRWR) of 1–3 is ideal for pediatric recipients. Grafts may turn out to be small for size when a diminutive-sized donor is present for an adolescent or due to iatrogenic ischemia of a segment from a left or left lateral graft or due to portal hyperperfusion in advanced cirrhosis. More frequently in pediatric LDLT, there is the risk of having a large-for-size graft, if the donor is big or the child is too small. A GRWR greater than 5 predisposes to portal hypoperfusion, followed by graft ischemia and graft dysfunction. It is relatively straightforward to estimate the volume of a left lobe graft by CT volumetry. Estimation of the volume of a left lateral graft and a monosegment graft is more difficult and requires expert review. A fatty liver more than 30 % may not be preferred in most centers. It is also useful to estimate the volume of the spleen in the recipient, as the relative volumes of the liver and the spleen give an estimate of the portal hyperperfusion [25].

Apart from the graft volume, the dimensions of the graft and the abdominal cavity are also important. The anteroposterior diameter of the graft (the maximum distance between the anterior surface of the graft and the porta hepatis on CT imaging of the donor) should be accommodated inside the child's abdominal cavity (the distance from the vertebral body to the anterior abdominal wall on CT imaging of the recipient). A recipient with preoperative ascites or hepatomegaly may be able to receive a larger graft. While a difference of 2 cm between the graft size and the size of the abdominal cavity may be overcome due to the compliance of the pediatric chest wall and abdomen, any excessive disparity may require temporary abdominal wall closure using a prosthetic material, with its attendant risks [26].

Portal vein hypoplasia is common in patients with biliary atresia and so the portal vein size, portal flow velocity, and location of the splenomesenteric junction in relation to the pancreas and coronary vein should be assessed preoperatively. The coronary vein may be needed as a portal vein replacement or it may need to be ligated to increase portal perfusion. Early branching of P2 and P3 from the main portal vein, replacing the left portal vein is possible in the donor and should be looked for.

CT angiography of the donor liver gives important information about the arterial anatomy of the left side. An accessory hepatic artery or replaced left hepatic artery may arise from the left gastric artery and run through the lesser omentum. Unless it is extremely small, it is not sacrificed, but taken along with the graft. Adequate length of the hepatic artery may be obtained by dividing the left gastric artery proximally. The A4 may arise from the common, left or right hepatic artery and has to be carefully dissected for left lobe LDLT. The CT angiography gives information about the size of the hepatic arteries (which may be large in cases of biliary atresia with portal hypoplasia) and patency of the gastroduodenal and gastroepiploic artery (which is the nearest alternative inflow artery of suitable size and length if the recipient hepatic arteries cannot be used). The biliary anatomy is evaluated in the donor by

MRCP or three-dimensional reconstruction of high-resolution CT images. The left-sided graft more commonly has only a single bile duct.

A wide venous outflow reconstruction is crucial for obtaining good outcomes after LDLT. The middle hepatic vein (MHV) is usually taken along with the left lobe graft, and the middle and left hepatic veins usually form a single outflow tract. Occasionally, V2 and V3 may drain separately into the MHV instead of forming the LHV. When a hyperreduced size graft is required, preoperative imaging can guide the surgical technique, by delineating the vascular anatomy and estimating the volumes and dimensions of segments 2 and 3. Close coordination between the surgical teams operating on the donor and recipient ensures that no time is wasted and minimal graft ischemic times are achieved.

27.6 Donor Surgery

The left lobe hepatectomy for pediatric LDLT is similar to the adult donor hepatectomy. The common trunk of the MHV and LHV is exposed by suprahepatic dissection after dividing the falciform ligament. The left inferior phrenic vein is divided early in the dissection to prevent inadvertent bleeding. The gastrohepatic ligament is incised, taking care to preserve any accessory hepatic vessels running in the ligament. The Arantius duct is carefully transfixed where it enters the LHV and divided. This maneuver enables the common trunk of the MHV and LHV to be safely looped.

The gall bladder is mobilized away from its liver bed, and the cystic plate is separated from the hilar plate. Intraoperative cholangiography (IOC) is performed in left-sided grafts if there is history of previous biliary surgery in the donor or if the preoperative MRCP shows variations such as the right posterior sectoral duct arising from the left hepatic duct, trifurcation of the hepatic ducts, or branching of the left hepatic ducts within 1 cm of the confluence [27]. IOC is performed using an olive-tipped needle inserted into the infundibulum or the cystic duct. The gall bladder acts as a guide to the biliary and arterial anatomy of the hilum and is useful for retraction. Hilar dissection is started with the aim of exposing the left hepatic artery first. The A4 is identified if present. The left portal vein is looped after identifying and dividing its caudate branch(es). The arterial and portal inflow to the left lobe is temporarily occluded, and the left lobe demarcation is marked on the surface of the liver. The volume of the graft is estimated again by visual inspection.

If the caudate lobe is to be taken with the graft, then the caudate veins entering the IVC are carefully divided. It is wiser to suture rather than simply ligate the venous stumps on the anterior surface of the IVC. The caudate lobe is thus mobilized toward the right.

The parenchymal transection is started at the inferior border of the liver near the gall bladder fossa. The transection line follows the line of demarcation which is along the Cantlie's line. Inflow occlusion is not required. The aim is to preserve the MHV with the left lobe graft and ligate the V5 and V8 branches as they enter the MHV. Electrocautery is used to transect the liver capsule and superficial liver tissue. Further dissection is done using a combination of clamp fracture, ultrasonic dissector (CUSA®), bipolar electrocautery, and suture ligation. As the parenchymal transection approaches the hilar plate, the left hepatic duct, the Glissonian sheath, and the periductal tissue are encircled together. This complete hilar plate encircling ensures that the vascular supply of the graft left hepatic duct is preserved [28]. An IOC with the aid of a radiopaque marker over the left hepatic duct is useful to precisely delineate the biliary anatomy and the site of transection. The hilar plate is sharply divided (Fig. 27.1) and the peribiliary vessels are controlled with fine sutures.

A modified "hanging maneuver" facilitates faster and safer parenchymal transection. A Penrose drain or umbilical tape is passed between the RHV and MHV and along the anterior surface of the IVC. If the caudate lobe is not included in the graft, it is passed along the path of the Arantius duct. Inferiorly, it is brought up between the left hepatic vessels and the liver parenchyma. The tape is elevated before proceeding with the remaining parenchymal dissection.

Once the parenchymal transection is complete, heparin is administered intravenously, and the left hepatic artery (LHA) and accessory hepatic arteries are divided after applying vascular clamps. It is useful to mark the anterior surface of the left portal vein with a fine suture before division, to ensure that there is no twisting while performing the portal anastomosis in the recipient. The common trunk of the LHV and

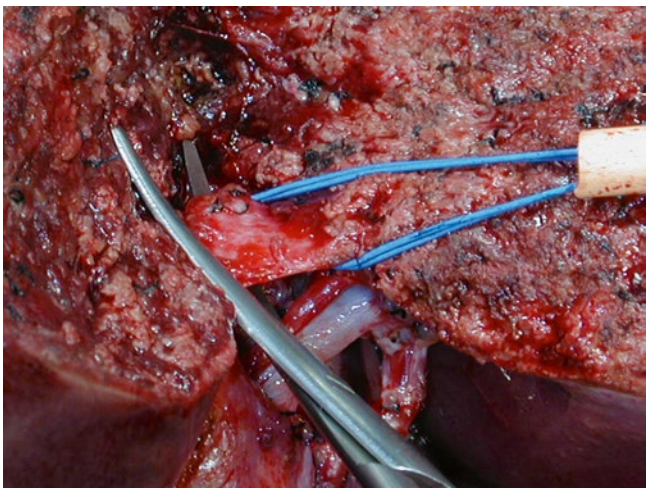

Fig. 27.1 Complete hilar plate encircling technique for left-side graft. The entire hilar plate and the hepatic duct, Glissonian sheath, and periductal tissue are dissected free, encircled, and sharply divided

MHV is clamped and divided. Inclusion of a thin cuff of the inferior vena cava (IVC) increases the size of the orifice and facilitates a wide outflow reconstruction in the recipient.

The graft is transferred to the back table and infused with chilled organ preservative solution (e.g., Custodiol®). A heparinized perfusate based on graft weight is used to reduce the risk of graft vessel thrombosis while also reducing the dosage of systemic heparinization of the donor [29]. On the backtable, the effluent should turn from hemorrhagic to clear. The outflow is observed, and venoplasty of the outflow orifices is performed if required.

The portal and hepatic vein stumps in the donor are closed with fine polypropylene or hexafluoropropylene-VDF (Pronova® – Ethicon US, LLC) sutures in a running fashion. Care must be taken to avoid a purse string effect while suturing which may result in vascular stenosis. The hepatic artery stump is sutured with fine polypropylene sutures. The stump of the left hepatic duct is sutured with polypropylene 4-0, and the patency of the common and right hepatic duct is confirmed by IOC. The hilar plate and the caudate process are examined for small bile duct openings, which are closed. Doppler ultrasound study is performed to confirm vascular patency in the remnant liver. Hemostasis is ensured and a closed drain is inserted into the hepatic fossa. The raw surface of the liver is examined for bile leaks and bleeding by keeping clean laparotomy pads. Abdominal wall closure is done.

When only the left lateral segment is to be harvested, then the technique of parenchymal transection is slightly different from that for a left lobe donor hepatectomy. The parenchymal transection is done in a plane slightly to the right of the falciform ligament. The intrahepatic segment 4 vasculobiliary pedicle is encountered early in the transection – it is kept as long as possible and marked with long suture before ligation and division, as it may be useful for canulating the portal vein intraoperatively if stenting is required [30]. An IOC is not routinely performed except for the conditions mentioned previously [27]. As the transection proceeds posteriorly, the union of the MHV and LHV is encountered. Occasionally, the V2 and V3 join the MHV separately, instead of forming the LHV. Such cases can be dealt in several ways – if the MHV is not the dominant outflow for the right lobe, then it may be harvested with the left lateral graft from the point where the V3 joins the MHV. This enables an easy outflow reconstruction in the recipient as V2 and V3 do not have to be dealt with individually, but it may cause congestion of the anterior sector in the donor.

If the MHV is of large caliber and carries significant drainage from the right lobe, then it is preserved. A patch of the MHV is taken along with the V2 and V3 which enables wide outflow reconstruction. The MHV in the donor is reconstructed in a tension-free manner to avoid stenosis (Fig. 27.2). Alternatively, the V2 and V3 may be divided separately, and a unification venoplasty may be done to form a single large orifice. A venous patch using cryopreserved vein or saphenous vein may be sutured to make the orifice even wider (Fig. 27.3).

If the left lateral segment graft is too big (GRWR more than 5) or too thick to fit inside the recipient's abdomen, then it may be reduced further. A reduced left lateral segment graft or a hyperreduced size monosegment graft can be fashioned by in situ transection [31]. For a hyperreduced size graft based on segment 2, the initial transection is done in a manner similar to that for a left lateral graft. Intraoperative Doppler ultrasound study is performed to identify the portal branches to segments 2 and 3, as well as the position of V2 and V3. The continuation of the hilar plate in the umbilical fissure is taken down to the left of the round ligament, with the intention of exposing the vasculobiliary pedicles supplying segment 3. Each individual pedicle can be occluded temporarily and the area of ischemia noted. In such a manner, the pedicles supplying segment 3 can be identified, ligated, and divided. The parenchymal transection to reduce the left lateral segment to a monosegment then follows the line of ischemia. The hepatic vein draining segment 2 is kept intact with a cuff of surrounding hepatic tissue up to its union with the LHV.

Laparoscopic donor hepatectomy is now being performed in increasing numbers. Left lateral resection is particularly amenable for laparoscopic resection [32]. Proper selection of cases is essential to avoid complications. Laparoscopic CUSA and vascular staplers are used to perform the parenchymal transection and vascular division.

27.7 Recipient Surgery

The abdominal cavity is exposed through a bilateral subcostal incision, sometimes with a midline extension (Mercedes incision). In infants, the superior flap of the incision can be retracted using sutures passed through the edge of the anterior abdominal wall and held in place with a Bookwalter retractor [33]. The round ligament is isolated and held with a long suture for exposure of the hilar region. The suprahepatic vena cava is approached by dividing the falciform ligament and carefully dissecting the dense fascia over the diaphragm and hepatic veins in this region, using a combination of electrocautery, suture ligation, and blunt dissection. Left triangular ligament is incised and opened. The left inferior phrenic vein is usually ligated and divided just before entering the inferior vena cava. The left coronary ligament is ligated and divided. The gastrohepatic ligament is opened, taking care to preserve any arteries supplying the liver. Once the caudate lobe is exposed, it is retracted to the right, and the caudate veins entering the vena cava are double ligated or transfixed and cut. The duct of Arantius is carefully transfixed and ligated before cutting it.

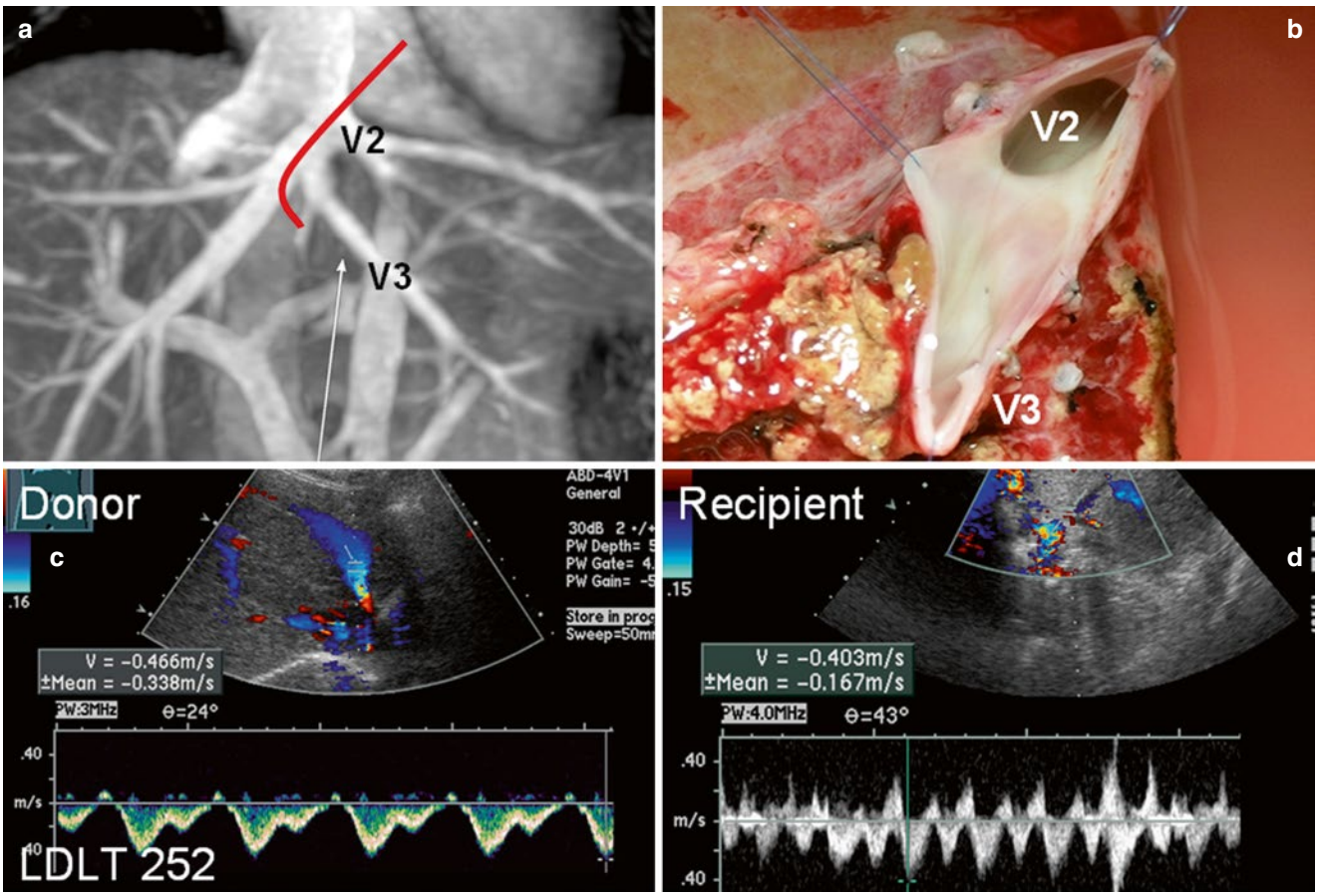

Fig. 27.2 (**a**) Separate V2 and V3. (**b**) When encountering widely separate V2 and V3, half of the MHV circumference containing both V2 and V3 is harvested. (**c**) Triphasic waveforms in the donor MHV years after donation. (**d**) Triphasic waveforms in the recipient hepatic veins after reconstruction

The right side of the liver is now mobilized. The retroperitoneal attachments to the kidney and adrenal tissues are cut, and hemostasis is achieved using electrocautery and sutures. The right triangular ligament is dissected, and the inferior vena cava is visualized. The right hepatic vein and the trunk of the middle and left hepatic vein are looped separately.

The hilar dissection is started by looking for the left hepatic artery after applying upward traction to the round ligament. It is followed down up to the common hepatic artery, dissected free from surrounding tissues, and encircled with a vascular loop. The left portal vein may be visible at this point in a deeper plane to the left hepatic artery. The cystic duct is divided to enable easier hilar dissection, and the gall bladder is left in situ. The right hepatic artery is identified at this point and dissected carefully. The portal vein is identified below the right hepatic artery and common bile duct and is dissected free and looped carefully. The hepatic arteries are dissected as high as possible and examined for quality of vessel wall and blood flow. They are occluded with atraumatic microvascular clamps before proceeding with further hilar dissection. The bile ducts are not dissected bare; the whole hilar plate containing the bile ducts, Glissonian sheath, and periductal tissues is kept intact and separated from the underlying portal veins. This hilar plate is traced as high as possible, and then the right and left hilar pedicles are cut separately. The vascularity, size, and number of bile duct openings are noted. A vascular clamp is used to prevent bleeding from the pedicles and also for retraction purposes. The cut end of the hilar plate on the hepatic side is sutured. The portal veins are now the sole vascular supply to the native liver.

Recipients with biliary atresia who have undergone Kasai procedure may have dense adhesions, and hilar dissection may be difficult in such cases. The Roux loop has to be taken down to complete the hilar dissection. Often, the atretic bile duct cannot be identified. The hepatic arteries may be large but fragile and must be handled delicately. The main portal vein may be sclerotic and hypoplastic and is traced down to the confluence of the splenic and superior mesenteric veins (splenomesenteric junction).

The bare area of the liver is a significant source of bleeding in the cirrhotic patient. While waiting for the graft to be

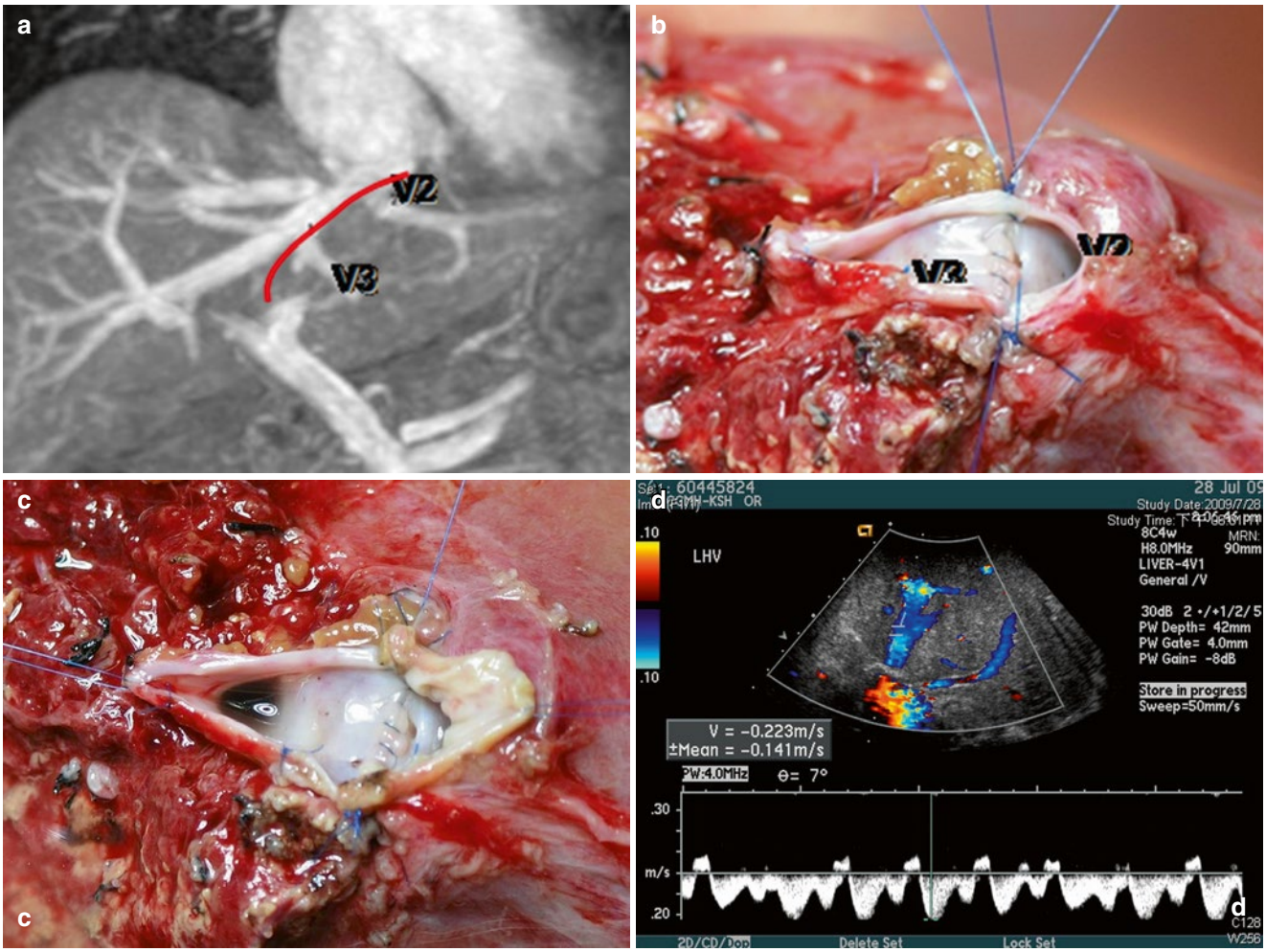

Fig. 27.3 (**a**) Separate V2 and V3. (**b**) V2 and V3 harvested individually and a graft venoplasty has been done. (**c**) A cryopreserved vein patch has been used. (**d**) Doppler ultrasound after reconstruction shows triphasic waveforms in the recipient hepatic veins

prepared, this area may be sutured and the peritoneal folds approximated to achieve hemostasis.

It is useful at this point to insert drains and connect them to suction tubing, to enable proper visualization of the surgical field.

The suprahepatic and infrahepatic vena cavae are dissected circumferentially to permit safe application of vascular clamps. In pediatric LDLT, a triple venoplasty (Fig. 27.4) utilizing the right, middle, and left hepatic vein orifices may be used to ensure a wide outflow [34]. Alternately, the venoplasty may be performed by extending the opening of the common trunk of middle and left hepatic veins to the right.

The main portal vein is clamped and the right and left portal veins are cut separately a short distance from the bifurcation. This ensures that the right, left, or main portal vein, or even a branch patch of the right and left portal vein, can be used, depending on the size of the graft portal vein. It is inspected for presence of thrombosis, and thrombectomy is done if required. It is important to keep the orientation of the portal vein in mind, in order to avoid torsion while making the vascular anastomosis. The vascular clamps are passed around the inferior vena cava, above and below the hepatic vein orifices, after communication with the anesthetist. A cross clamping time of 45 min to 1 h can be tolerated without significant hemodynamic compromise. The presence of extensive collaterals facilitates the performance of the procedure without using venovenous bypass. The hepatic veins are divided, leaving a short stump. The right hepatic vein orifice is sutured if it is not going to be included in the reconstruction. The common trunk of the LHV and MHV may be incised medially to make the opening wider and ensure adequate outflow from the graft. Although the orifice should be wide, the reconstructed hepatic vein should not be unduly long; otherwise, it might get kinked when the graft regenerates.

The graft is positioned inside the upper abdomen and oriented properly. Hepatic vein anastomosis to the IVC is done usually with 5-0 Pronova, similar to the technique in adult

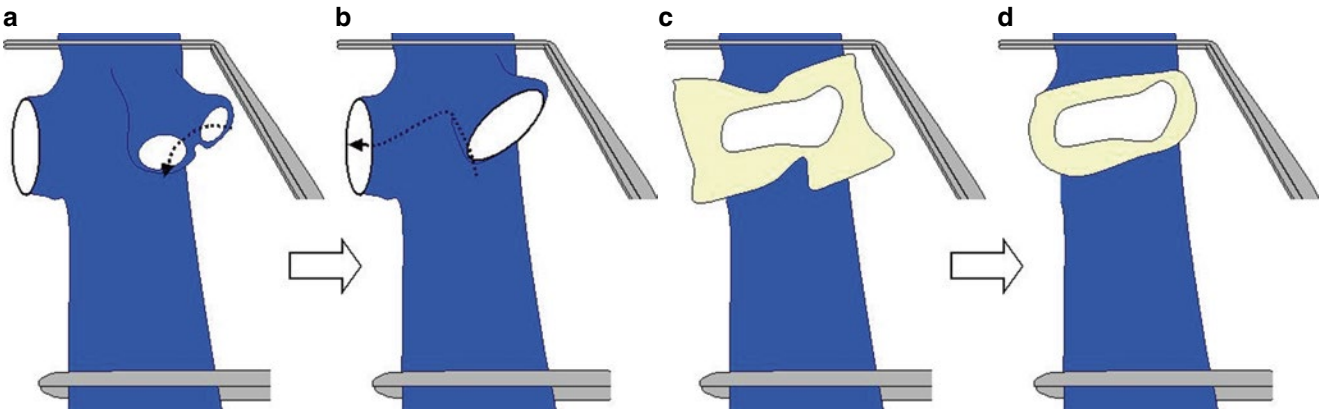

Fig. 27.4 Recipient triple venoplasty. (**a**) The septa between the middle and left hepatic veins is divided (*dotted arrow*) to perform a double venoplasty. (**b**) Triple venoplasty technique is performed by dividing all the intervening septa between the three hepatic veins (*dotted arrow*). (**c**) A single wide orifice is thus created. (**d**) The edges of the orifice-can then be suitably modified before anastomosis with the graft side outflow tract

LDLT. Portal infusion of lactated Ringer's solution is stopped after completing the anastomosis. Initial induction of immunosuppression with loading dose of methylprednisolone 10 mg/kg/day is kept ready.

The orifice of the recipient portal vein is now examined and adequate portal flow is confirmed. The reconstructed portal vein must not be redundant in order to avoid kinking. The main portal vein is flushed vigorously to remove thrombi, and anastomosis with the graft portal vein is commenced. Everted running polydioxanone (PDS® – Ethicon US, LLC) or polyglyconate (Maxon™ – Covidien AG) monofilament sutures are taken, and size disparity is managed. An "air knot" or growth factor equal to the diameter of the portal vein is kept in order to prevent purse string effect. Correct orientation is essential for avoiding stenosis.

The arterial anastomosis is ideally done using the operating microscope and microsurgical instruments by an experienced microsurgeon. The exposure of the surgical field, depth of the site of anastomosis, respiratory movements, and the mobile viscera are significant factors which are encountered in microvascular reconstruction. The size, quality, and orientation of the arteries are examined under the microscope. Usually, the arterial anastomosis is performed using interrupted 8-0 or 9-0 polypropylene sutures [35]. If the graft has two arteries, then the dominant artery is reconstructed first. The second artery is ligated if there is strong pulsatile backflow. If the recipient's hepatic artery is not suitable, then the gastric arteries, especially the right gastroepiploic artery, are suitable alternates, because of their diameter, presence in the same surgical field, and adequate length. A radial artery interposition graft can also be considered. Size disparity up to a factor of 2 can be managed by using a branch patch or obliquely cutting the artery [36].

The bile duct anastomosis is done routinely using the operating microscope at the author's center since 2006, using 6-0 polypropylene or polydioxanone interrupted sutures without a stent. A primary anastomosis of the graft bile duct with the recipient bile duct is preferable to a bilioenteric anastomosis except in cases of biliary atresia, where the Roux-en-Y loop is preferred. In cases where there are more than one bile duct openings in the graft, a ductoplasty or separate biliary anastomoses may be done, depending on the diameter of the bile duct openings and the distance between them [37].

An intraoperative Doppler ultrasound is performed after the arterial anastomosis. An ideal arterial anastomosis should demonstrate a peak flow velocity of more than 40 cm/s, a triphasic pulsatility pattern and a resistive index between 0.5 and 1. Unsatisfactory arterial flow may be due to thrombosis, stenosis at anastomosis site, kinking, etc., and may need a redo anastomosis or construction of a new inflow anastomosis. Ideally, the portal flow velocity should be more than 10 cm/s to rule out portal hypoperfusion, and the portal flow volume should be less than 250 ml/min/100 g graft weight to avoid portal hyperperfusion. If low portal flow is encountered, it is essential to rule out hypovolemia, hypotension, and outflow obstruction and perform maneuvers such as repositioning the graft, ligation of collateral veins, portal stenting under fluoroscopic guidance, and even redo of the anastomosis. A high portal flow may be managed by splenic artery ligation or splenectomy. However, it is unusual in pediatric recipients.

After the biliary anastomosis, hemostasis is checked. Areas such as the diaphragmatic surface, bare area of the liver, anterior surface of the IVC, site of the anastomoses, raw surface of the graft, etc., are specifically checked. The falciform ligament is fixed to the anterior abdominal wall for left-sided grafts, to prevent graft rotation. Abdominal incision is closed in layers. Doppler ultrasound is repeated after closure to check vascular flow. Patient is shifted to the ICU, usually without extubation.

Postoperatively, mechanical ventilation support is removed usually on the first postoperative day. Doppler

ultrasound study is performed daily for the first 2 weeks and more frequently if indicated. Anticoagulants and prostaglandins are started after stabilization and are continued in the first 2 weeks. Immunosuppression in the form of calcineurin inhibitors (cyclosporine or tacrolimus) and steroids is started with drug level monitoring. Proper ICU care with early enteral feeding, physical and pulmonary therapy, and early mobilization are essential for early recovery. Radiologic imaging, laboratory investigations, and liver biopsy as indicated are vital in diagnosing various complications in the early stage.

27.8 Complications

Various complications may lead to suboptimal outcomes after LDLT (Table 27.3). Surgical complications carry the highest relative risk with respect to long-term graft survival and patient survival [38].

Hepatic artery thrombosis (HAT) is especially likely when pediatric LDLT is associated with low body weight, small-caliber artery, and CMV infection. Incidence of HAT is above 10 % in some series [39]. It is necessary to confirm suspicious Doppler ultrasound findings by urgent CT angiography. Early HAT within 2 weeks of transplant is best managed by reexploration, revision of anastomosis, or creation of new anastomosis. Persistence of HAT or onset of graft necrosis implies need for urgent retransplantation. In the long term, HAT leads to graft dysfunction, septic complications, and ischemic biliary strictures [40].

Portal venous thrombosis (PVT) is less common than HAT (1–5 %) but is just as serious. Early PVT can be diagnosed on Doppler study, and treatment options include urokinase, transhepatic or transplenic stenting by radiologic guidance, and surgical revision. Late PVT presents with features of portal hypertension and is managed by endoscopic treatment of varices, medical therapy, and retransplantation if indicated.

Outflow obstruction due to kinking or stenosis of hepatic veins is more likely with smaller grafts and occurs in 1–2 % cases. It typically presents with ascites, altered LFT, and splenomegaly. Doppler ultrasound and CT angiography can confirm the diagnosis. Percutaneous or transjugular stenting or balloon dilatation may be curative.

Biliary complications are the most common cause of significant morbidity in the recipient, with incidence ranging from 5 to 20 % [37]. It could manifest as bile leaks or anastomotic stricture in the early postoperative phase. Bile leaks could be from the transection surface of the liver or the anastomotic site. Careful monitoring of drain output and liver function can help in deciding whether surgical exploration is warranted. Delayed biliary strictures are usually due to ischemic changes and manifest as cholangitis and jaundice. ERBD (endoscopic retrograde biliary drainage) and PTCD (percutaneous transhepatic cholangiographic drainage) are indicated to dilate and stent the biliary stricture. Surgical exploration or retransplantation may be required for long-standing biliary complications resulting in decompensated liver function.

Small-for-size syndrome results when the portal perfusion is more than 250 ml/min/100 g of functioning graft tissue and manifests as persistent jaundice and ascites for more than 2 weeks. It is associated with higher risk of morbidity and mortality. Intraoperative Doppler ultrasound study can help to alleviate the hyperperfusion by reducing the portal flow using splenic artery ligation or splenectomy. However, it is unusual in pediatric patients.

Large-for-size graft increases the chances of graft ischemia and primary graft dysfunction. This is more likely to occur with low-body-weight infants and can be ameliorated by using hyperreduced size grafts.

Biliary atresia patients have usually undergone previous surgeries and are behind in the growth curve. Their small size and dense adhesions predispose them to significant blood loss during recipient hepatectomy. Inadvertent enterotomies may occur due to the extensive bowel adhesions. If the flow in the recipient's main portal vein is unsatisfactory, then various alternative options need to be considered.

Graft portal vein could be anastomosed with:

- Recipient portal vein (if it is of adequate caliber). Large shunts such as the coronary vein may need to be ligated to achieve sufficient portal inflow.
- Recipient splenomesenteric junction. Care should be taken to avoid tension on the venous anastomosis.
- Interposition graft or venous patch on the splenomesenteric junction (if the splenomesenteric junction and the graft portal vein are distant from each other or the splenomesenteric junction is behind the pancreas).
- Coronary vein (if it is of large caliber, it can replace the native portal vein).

Patients with acute liver failure are at risk of encephalopathy, cerebral edema, coagulopathy, and sepsis. Hence, their perioperative management and anesthetic monitoring are extremely important. Similarly, patients undergoing retransplantation are extremely challenging. They carry higher risk of bleeding, bowel injury, poor wound healing, renal dysfunction, and infections such as CMV. They are also prone to PTLD, graft rejection, and lower survival rates [41].

Donor complications occur less frequently than with adult LDLT, because of the use of the left lobe or left lateral segment in pediatric LDLT rather than right lobe LDLT. Donor morbidity may be due to bile leak from the hilar plate or cut surface of the liver, as well as due to gastric stasis caused by adhesion of the stomach to the cut surface of the remnant

Table 27.3 Early and late complications after pediatric LDLT

Infection
Wound infection
Pneumonia
Surgical site infection
Cholangitis
Immunologic
Hyperacute rejection (rare)
Acute cellular rejection
Chronic rejection
Immunosuppression related
Renal insufficiency
Infections (Epstein-Barr virus, cytomegalovirus, etc.)
Posttransplantation lymphoproliferative disorder (PTLD)
Arterial
Hepatic artery thrombosis
Hepatic artery stenosis
Ischemic biliary strictures
Portal
Portal vein stenosis
Portal vein thrombosis
Hepatic vein
Outflow obstruction
Biliary
Bile leak
Biliary strictures – anastomotic and nonanastomotic
Others
Intra-abdominal bleeding
Primary graft nonfunction
Graft necrosis
Graft failure
Small-for-size graft (relative portal hyperperfusion)
Large-for-size graft (relative portal hypoperfusion)
Side effects of drugs (hypertriglyceridemia, obesity, diabetes, renal dysfunction)
Noncompliance to treatment

liver. Other causes of donor morbidity are similar to those described in adult LDLT.

27.9 Outcomes

The outcomes of pediatric LDLT are superior to those for adult LDLT in terms of survival and complication rates. Most indications for pediatric LDLT do not recur after transplantation. The regeneration of the liver graft ranges from 30 to 120 % of the original graft size within 6 months of transplant. It is significantly reduced in recipients with large-for-size grafts or low body weight.

The 5-year overall survival rate is above 90 % in some centers [42] and reported to be 75 % at 20 years [43]. The 5-year survival rate for biliary atresia children undergoing LDLT at the author's center is 98 % [6]. The survival rates for recipients aged less than 6 months when undergoing LDLT are reported to be inferior to those for older recipients [17]. The principal causes of late mortality include rejection due to noncompliance to immunosuppression regimens, PTLD, sepsis, and malignancy. The graft survival rates have improved over time, as the rates of technical complications and rejection have decreased with accumulated experience. Early retransplantation may be required due to hepatic artery thrombosis or primary graft nonfunction, while indications for late retransplantation include chronic rejection of the graft and biliary complications. Survival rates after retransplantation are inferior due to the complexity of the procedure and associated comorbid conditions.

Growth of the child after LDLT is accelerated due to optimal nutrition, anabolic effect of steroids, and treatment of liver disease. The child may get back on the normal growth curve, provided the transplant was done before the onset of severe malnutrition or growth failure. Ten to fifteen percent of recipients may have impaired cognitive functions and lag in psychosocial assessment compared to their peers. However, most children grow up and are able to study, work, marry, and have children [44]. The incidence of renal dysfunction and diabetes mellitus is less than in adults but along with the cardiovascular disease, contributes to significant morbidity by the time they reach adulthood.

Conclusion

The better long-term survival in pediatric LDLT is attributed to careful preoperative planning, better anesthesia management, meticulous surgical technique, and prompt detection and treatment of complications. The wise use of immunosuppression drugs and expert surgical management has resulted in excellent outcomes for children with end-stage liver diseases and metabolic diseases. Continuing innovations in surgical techniques and perioperative management can be expected to further improve the quality of life over the long run.

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