Outcomes after Paediatric Liver Transplantation

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Overview

Children are a unique cohort as they have a longer life span post LT when compared to adults. With improved survival post LT, the focus is much on the problems they would face as adults, which would include social and economic setback due to disease and frequent hospitalization apart from medical problems that affect the graft and host. Pretransplant factors such as the underlying aetiology of liver disease, associated congenital malformation, impact of disease severity on other end organs involved etc. can impair the normal physical growth and neurodevelopment of children. During post LT, graft health, host health and complications due to long-term drug intake determine the long-term outcome. When it comes to host health, apart from physical well-being, other aspects such as mental well-being, education and family functioning have to be looked into. Anticipating and addressing these issues would help in long-term physical and mental well-being apart from mere survival.

30.1 Introduction

Liver transplantation (LT) has dramatically improved outcomes of children with end-stage liver disease and acute liver failure. Though the first LT and the first successful LT were performed on children, paediatric LT was overshadowed by adult LT due to their sheer numbers. Over the years, transplantation has evolved with technical refinements and a better understanding of the transplant immunology

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leading to improved outcomes [1]. Outcome after LT is based on the complex interplay between graft health, recipient health and effect of underlying disease aetiology. While each factor per se can affect the outcome, these three factors can variably interact with each other, compounding the morbidity.

30.2 Factors Influencing Long-Term Post-LT Outcomes

In children, the aetiologies, surgical techniques and immunosuppression regimes are different across age groups and weight categories. This makes comparative studies difficult and extrapolation of adult literature inaccurate. Surgical complications, infectious complications and the quality of allograft affect both short- and long-term outcomes. Going beyond patient and graft survival outcomes, physical and mental developmental domains remain critical metrics in assessing transplant outcomes in the paediatric population. Given the fact that the allograft has to survive more cumulative years in children than adults undergoing LT, optimizing modifiable risk factors will have a greater impact on the paediatric recipient. Factors which affect post LT outcomes could be broadly grouped into three categories, factors that affects graft, aetiology of underlying disease and recipients' general health.

30.2.1 Factors Affecting Graft Health

Surgical complications which compromise graft vascularity or biliary drainage adversely affect allograft function.

30.2.1.1 Surgical Complications

Hepatic Artery Thrombosis (HAT)

HAT rates have been variable with several series reporting an incidence of up to 11.5%. In general, arterial thrombosis occurring within 21 days of transplant is referred to as early HAT. Risk factors for HAT include age of recipients (higher in infants), low donor weight and technical complexity [2]. Early HAT is associated with drastically elevated liver enzymes and a rapid decline in liver function. Based on the extent of thrombus, degree of liver failure and patient stability, the recipient may need to undergo urgent revascularization or even re-transplantation. Since bile ducts primarily depend on the hepatic artery for their blood supply, HAT is likely to be associated with cholangiocyte death, which could result in cholangitic abscesses and non-anastomotic strictures in the long term [3]. Late onset HAT can happen over any time frame. The aetiology is unclear and could be related to technical or immunological causes. Spontaneous arterialization of the graft through collaterals in surviving grafts is well described. However, there have been reported cases of graft loss due to late HAT even 11 years after LT.

The long-term outcome for children with HAT, in whom the graft was salvaged with surgical or radiological revascularization remains unclear. Waaren et al. showed

that the five-year patient survival after failed intervention and re-transplantation was 40%, and it was 70% in those who had a primary re-transplantation for HAT. Ackermann et al. suggested no difference in 20-year patient survival between these subgroups, and outcomes were comparable to those without HAT [4, 5]. Definite evidence of the true impact of hepatic artery revascularization is lacking, though we have found increased incidence of biliary complications in these patients over medium-term follow-up.

Portal Vein Thrombosis (PVT)/Portal Vein Stenosis

PVT after LT is more common in the paediatric population, particularly in those with biliary atresia (BA) due to a small and often atretic portal venous anatomy [6]. The identified risk factors for PVT include a portal vein diameter less than 5 mm, graft recipient weight ratio (GRWR) >4 and hypercoagulable states. PVT within the first month of transplant is referred to as early PVT and manifests as raised liver enzymes, unsettled INR and gastrointestinal bleed from acute portal hypertension. Chronic PVT is more insidious and usually identified on evaluation for portal hypertension. Figure 30.1 shows chronic PVT with pre- and post-stenotic dilatation. Waits et al. have reported decreased long-term survival of patients with PVT when compared to non-PVT recipients [7]. Significant stenosis at the anastomotic site may predispose one to thrombosis and cause portal hypertension. These can usually be managed by portal vein stenting. However, a close follow-up is needed in the post-stenting period to observe for re-occlusions.

▶ **Tips** Principles of management in these two types of PVT differ. In early PVT, the aim is re-establishing hepatopetal portal flow while relieving portal hypertension is the primary goal in chronic PVT.

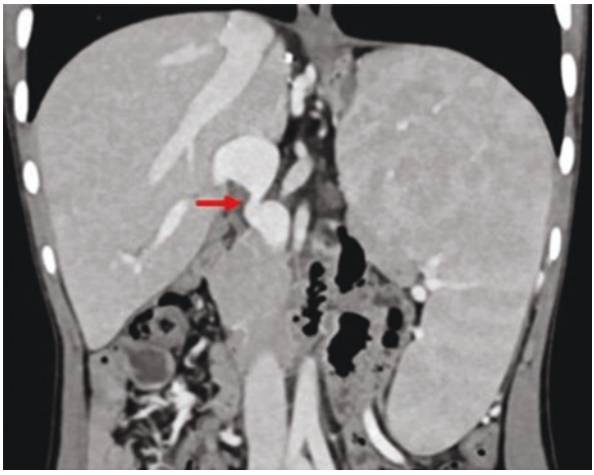

Fig. 30.1 Coronal CT image showing portal vein stenosis (red arrow) with pre & post stenotic dilatation and splenomegaly

Hepatic Venous Outflow Obstruction (HVOO)

The reported incidence of HVOO in the paediatric population ranges from 1% to 3.3% [8]. Persistent large volume ascites and worsening portal hypertension raises the suspicion of HVOO [9]. HVOO could be due to anastomotic stricture, graft torsion or thrombosis due to procoagulant pathology (Budd-Chiari syndrome). While it in more common in the early postoperative period, HVOO may also occur several years after LT [8]. Persistent congestion of the allograft due to a secondary Budd-Chiari syndrome-like picture will ultimately lead on to graft failure. Redo anastomosis/re-positioning of the graft using tissue expanders has been described for HVOO occurring early after transplant. Balloon angioplasty, stent placement and TIPSS have been described in the management of chronic HVOO.

Biliary Complications

Paediatric LT biliary complications range from 15 to 40% [10]. Early biliary complications predominantly consist of cut surface and anastomotic bile leaks. Long-term complications include anastomotic and non-anastomotic strictures, which may lead on to graft loss. Risk factors for late biliary complications are bile leaks in the early postoperative period, ischemic/hypoxic insult due to inappropriate bile duct anastomotic techniques and disrupted blood supply to the bile ducts. A high degree of suspicion is required as late biliary complications remain silent with normal serum bilirubin levels, normal morphology on ultrasound imaging and minimally elevated liver enzymes, with only a liver biopsy or MRCP showing an obstructive pattern. Late biliary complications may lead to graft fibrosis and graft loss [11]. Biliary anastomosis in paediatric LT is more often using a roux-loop rather than a duct to duct anastomosis. Anastomotic stricture dilatation in Roux-en-Y hepaticojejunostomy usually requires a percutaneous transhepatic cholangiography (PTC) approach. PTC has been shown to successfully treat these complications in 70 to 90% of cases [12]. Non-anastomotic strictures are usually multiple and present as a late complication of HAT or immunological graft injury. These are usually refractory to treatment and are likely to require re-transplantation. No significant differences have been observed in patients or graft survival in cohorts with and without biliary complications in LT. They do however lead to repeated hospitalization and poor quality of life [12].

30.2.1.2 Immune-Mediated Complications

Rejection

Acute cellular rejection (ACR) is a histological diagnosis based on the presence of inflammation affecting graft interlobular bile ducts and vascular endothelia, including portal vein and hepatic venules and occasionally the hepatic artery and its branches [13]. It is usually associated with elevated aminotransferases and when associated with increase in bilirubin, it indicates severe rejection. It is graded from mild to severe based on the severity of lymphocytic infiltration of portal tracts and damage to the vascular and biliary endothelium. Late-ACR is defined as rejection after 3 months of LT. This subtype of ACR may show features overlapping with chronic rejection (bile duct loss etc.). Late-ACR tends to lead to chronic rejection

unless it is diagnosed and treated early. In a small cohort of 20 children from King's College Hospital with late-ACR, 75% had low levels of immunosuppression [14]. Early histological changes in chronic rejection are characterized by necrotic inflammation in the central lobule and portal area, damage to the inter-lobular bile duct, central perivenulitis and perisinusoidal fibrosis. These changes may progress to obliterative arteriopathy and ductopenia [15]. Feng et al. showed that in a group of paediatric recipients with normal liver function followed up for over 6 years, 20% had interface activity, correlating with genes that regulate T-cell-mediated rejection (TCMR) [16]. Children with chronic rejection on cyclosporine-based immunosuppression may benefit from a switch to tacrolimus. Addition of anti-proliferative agents (Mycophenolate Mofetil) has also been shown to ameliorate chronic rejection. More recent publications have shown beneficial effects with mTOR inhibitors in reversing features of chronic rejection in children [17].

Antibody-Mediated Rejection (AMR)

AMR, though uncommon in liver transplantation, has been well documented. The consensus statement on AMR has proposed graft dysfunction, tissue injury, presence of immune complex c4d or immunoglobulin and circulating donor-specific antibodies (DSA) at the time of tissue biopsy as the diagnostic criteria for AMR in solid organ transplantation [18]. These criteria were proposed for kidney and heart transplant recipients, and their application in liver transplantation remains uncertain. AMR is difficult to treat and requires the use of B-cell depleting agents such as rituximab and plasmapheresis. Despite treatment, the disease can progress, resulting in graft loss. AMR decreases graft survival and reported graft loss is around 33% at the end of 21 months of follow-up [19].

De Novo Autoimmune Hepatitis (DAIH)

This condition presents as elevated liver enzymes, with circulating auto- and allo-antibodies. Histological findings of interface hepatitis and plasma-cell infiltrates in the liver in a patient who did not have prior autoimmune liver disease are diagnostic of DAIH. In a large multicentric study on children with DAIH, the incidence was 1.7% at a median follow-up of 5.3 (range 1.2–14.9) years after LT [20]. These children were followed up for a median (range) of 7 years (1.6–15 years) from the diagnosis of DAIH. Despite treatment, one-third of the children continued to have elevated amino transferases. Persistent immunological damage of the graft may lead to bile duct injury, progressive fibrosis and portal hypertension, necessitating re-transplantation.

30.2.1.3 Late Graft Hepatitis and Fibrosis

Protocol biopsies done on children with normal liver biochemistry at 1, 5 and 10 years have shown graft hepatitis and fibrosis on histology [21]. These findings become more prevalent with time and majority of those who did not have graft fibrosis at 1 year post-LT had fibrosis at the end of 10 years. Studies have shown that some form of abnormality exists in 70–90% of allografts in asymptomatic children. In a series of 158 asymptomatic children who underwent serial protocol biopsies at

1, 5 and 10 years following LT, Evan et al. showed that at the end of 10 years, nearly 64% had chronic hepatitis and 91% had graft fibrosis on histology [22]. The aetiology of chronic hepatitis in this setting remains unknown and has been labelled as 'idiopathic posttransplant hepatitis'. Based on the fact that increasing immunosuppression decreases the activity, it is postulated that this hepatitis represents a form of chronic rejection [21].

30.2.1.4 Disease Recurrence

A subgroup of patients tends to develop recurrence of disease due to de novo alloimmune activity. This phenomenon in seen when transplants are done between Glutathione-S-transferase T1 (GSTT1)-negative recipients and a GSTT1-positive donor or in a bile salt exporter pump (BSEP)-deficient recipient receiving their liver from a BSEP-positive donor. Anti-GSTT1 antibodies and anti-BSEP antibodies have been demonstrated in the sera of these patients and immunostaining has shown disappearance of the BSEP receptors. The distinction between alloimmune and autoimmune activity does blur as years progress after transplantation. It has been postulated that while episodes of ACR are MHC-restricted and epitope-specific, the consequent graft damage exposes other antigens that are non-MHC-restricted. Once self-tolerance is lost, auto-immune response is triggered [23]. Disease recurrence of up to 40% has been seen in patients undergoing LT for type 2 autoimmune hepatitis, especially in a background of cyclosporine and steroid withdrawal [24].

30.2.2 Effect of Underlying Disease Aetiology on Outcome

The primary aetiology for LT plays an important role in influencing long-term post LT outcomes. Non-BASM—BA is one such disease, where a majority do not have any extrahepatic malformation and post-transplant survival remains excellent. On the other hand, genetic diseases such as Alagille syndrome are associated with multiple extrahepatic congenital anomalies that can adversely affect long-term outcomes.

30.2.2.1 Biliary Atresia (BA)

BA is one of the most common indications for LT and post-transplant outcomes for this indication have been used as a standard to compare post-transplant outcomes for other diseases (genetic or malignant). Overall patient survivals in a cohort of 280 children over a period of 10 years at 1, 5 and 10 years were 85, 82 and 82%, respectively, and the corresponding overall graft survival rates were 77, 73 and 71% [25]. Majority of recipients had normal scholastic levels at 10 years post-LT. BASM (biliary atresia splenic malformation) and perioperative surgical complications have however shown to adversely affect outcomes. There have been concerns of increased perioperative complications in post-Kasai portoenterostomy children undergoing LT. This is in most part due to the presence of vacularized bowel adhesions and loss of anatomical tissue planes. Our own experience suggests that primary LT and LT after KPE provide equivalent results [26].

30.2.2.2 Progressive Familial Intrahepatic Cholestasis (PFIC)

PFIC is a genetic disorder defined by an impairment of bile flow into the biliary canaliculi. Several subtypes have been described under this spectrum for which post-transplant long-term data are available for types 1, 2 and 3. Familial intrahepatic cholestasis protein-1 (FIC1) disease also known as PFIC type 1 is a multisystem disease with the absence of/defective expression in the membrane of cells of the small intestine, kidney and pancreas apart from the liver. These children have severe cholestasis, growth failure, rickets and fat malabsorption. The primary defect in PFIC type 2 is bile salt exporter pump (BSEP) deficiency and in type 3 it is multidrug resistance protein 3 (MDR3) deficiency. Both these proteins are expressed only in the liver and unlike PFIC type 1 their deficiency does not have any extrahepatic effects.

Due to its multisystem effect, PFIC type 1 recipients have problems with increased stool frequency and steatohepatitis in the post-transplant period [27]. Figure 30.2 shows progressive allograft steatosis at 2 and 4 years post LT for PFIC type 1. The new allograft liver produces normal bile and the intestine of the FIC1-deficient patient, which has never been exposed to high loads of bile acids, is unable to cope, causing high volume osmotic diarrhoea. Kasahara et al. have shown that this may be circumvented by total internal biliary diversion (TIBD) at the time of LT [28]. Total internal biliary diversion decreases not only diarrhoea but also steatohepatitis by interrupting the enterohepatic circulation. PFIC types 2 and 3 do not have any extrahepatic complication. However, recurrence of disease due to formation of the anti-BSEP antibody is a well-known complication of PFIC type 2, which decreases the graft survival.

30.2.2.3 Metabolic Liver Disease (MLD)

MLD can be broadly divided into cirrhotic MLD (the specific enzyme is deficient in the liver and causes liver cirrhosis) and non-cirrhotic MLD (the specific enzyme is

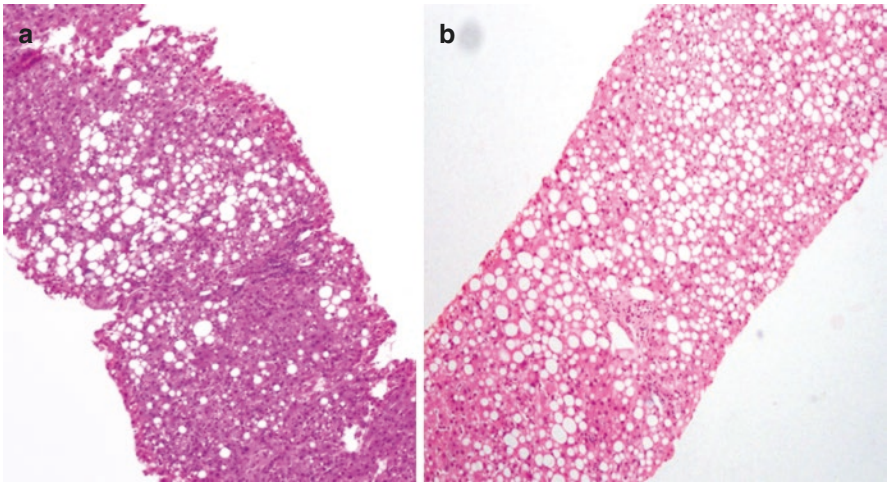

Fig. 30.2 Progressive allograft steatosis at two (**a**) and 4 years (**b**) post LT for PFIC type 1

deficient in the liver without causing cirrhosis). LT in cirrhotic MLD is for hepatic decompensation and/or tumour formation (e.g., Wilson's disease (WD), Tyrosinemia etc.) while LT in non-cirrhotic MLD is to prevent extrahepatic complication of enzyme deficiency. Overall graft and patient survival outcomes are better in LT for non-cirrhotic MLD as compared to those for cirrhotic MLD. Outcomes for MLD with extrahepatic manifestation like hyperoxaluria are affected by the extent of end-organ damage. Primary hyperoxaluria with deranged renal function had a lower post-LT 1- and 5-year survival of 90 and 71% as compared to LT for urea cycle defect, which had 93% and 90% survival over the same period [29]. With improved patient survival following LT, the focus in noncirrhotic MLD is now towards early transplantation to minimize neurological damage due to repeated metabolic crises [30].

Auxiliary partial orthotopic LT (APOLT) is indicated for selected noncirrhotic MLD and has the added advantage of the normally functioning native liver reducing the systemic effect of graft dysfunction, which gives the patient and the graft an opportunity to recover [31]. Graft failure is also not an immediate threat to the patient's life as in the case of OLT. This is particularly advantageous in children with propionic acidemia where graft dysfunction after OLT can precipitate severe metabolic stress and decompensation. Though technically more complex, it may be better than OLT due to lesser physiological stress and a smoother postoperative period. Shanmugam et al. showed 100% graft and patient survival followed up for a median of 32 months in a group of children who underwent APOLT for MLD [30].

30.2.2.4 Wilson's Disease (WD)

WD can present as acute liver failure, chronic liver disease or with neurological features. A long-term study from the European registry of 338 children showed post- LT survival of 87% (1-year), 84% (5-year), and 81% (10-year) [32]. Guillaud et al. showed a similar patient survival of 87% at 5, 10 and 15 years post-transplant in a series of 121 patients (adults and children) [33]. The prognosis was worse when the indication for transplant was fulminant or sub-fulminant disease. Post-transplant ceruloplasmin normalizes in the first month, urinary copper excretion normalize in 6–9 months and Kayser–Fleischer (KF) ring resolves at least partially in 100% of the recipients [34]. More recently, with the generous use of pre-transplant plasmapheresis, renal replacement therapy and good intensive care support, post-transplant survival has improved.

Neurologic manifestations associated with WD improve or stabilize in 70–90%. However, 1–30% may have varying degrees of exacerbation after LT [35–37]. New onset neuropsychiatric manifestations, extrapyramidal symptoms or seizures can occur after LT, most commonly as a side effect of calcineurin inhibitors (CNI) [38]. There was no difference in the time for normalization of metabolic parameters or long-term outcomes after living donor liver transplantation (LDLT) in WD [39].

30.2.2.5 Tumours

Hepatoblastoma is the most common malignant hepatic tumour in children. Majority of the tumours become resectable with neoadjuvant chemotherapy and have

excellent survival outcomes. Unresectable tumours such as PreTEXT stage 3—central tumours and pre-TEXT stage 4 tumours however require LT. Though rising alfa fetoprotein (AFP) before LT is not an absolute contraindication, it has shown to be associated with a poorer long-term outcome [40]. In a group analysis of 292 patients from 29 different publications, overall survival post-LT for hepatoblastoma was 76% [41].

Hepatocellular carcinoma (HCC) is the second most common paediatric malignant liver tumour. Chronic hepatitis B or underlying metabolic liver disease such as Tyrosinemia are the main background aetiologies for this tumour. In a retrospective multicentre study by Vinayak et al. over a period of 35 years, it was noted that the patient survival was 50%, which is similar to that seen in adults who were transplanted for HCC [42]. Incidental HCCs are tumours which are detected on explant histopathology. Survival rates are similar to those of individuals who underwent LT for biliary atresia. LT for other rare paediatric tumours such as embryonal tumours and metastatic neuroendocrine tumours has a better survival rate than those for HCC. Unlike adults where rigid transplant criteria exist for HCC, there are no well-defined selection parameters for LT. This is due to the underlying aetiology being different and that good outcomes are seen even in large tumours treated with LT [43].

▶ **Tip** Primary LT for large borderline resectable hepatoblastomas has better outcomes as compared to salvage LT following attempted resection. Improved surgical techniques and decreased waiting time also have an impact on long-term survival.

30.2.3 Effect of General Health on Long-Term Outcomes

The underlying disease per se and the post-LT medication can influence long-term survival. Issues commonly encountered are kidney injury, delay in growth and development, post-transplant lymphoproliferative disease (PTLD), cardiovascular issues and non-alcoholic steatohepatitis of allograft and psychosocial issues.

30.2.3.1 Kidney Injury

CNI, which are used as the first-line immunosuppressants, can affect renal function. Pre-existing kidney problems and renal insult during the perioperative period (e.g., drugs, septic shock, etc.) also have an adverse impact on long-term renal function [44]. Given the fact that children have a long-life expectancy, their kidneys are more prone to cumulative CNI toxicity. While measurement of the actual glomerular filtration rate (GFR) is cumbersome, the estimated-GFR (eGFR) is less accurate in children and underestimates the extent of impaired renal function. Cystatin C is a better surrogate marker of renal dysfunction. Current practice guidelines on monitoring kidney function in non-renal solid organ transplantation (SOT) suggest use of serum creatinine and cystatin C as screening tools. Blood pressure and proteinuria should be monitored regularly. Blood pressure values >95th percentile for age, microalbumin/creatinine ratio >32.5 mg/g (3.7 mg/mmol) creatinine and/or GFR

<90 mL/min/1.73 m^2 should be assessed further [45]. Around 11% children develop one or more kidney cysts along with low GFR at 10 years of follow-up [46]. Maintaining low serum levels of CNI using adjuvant mycophenolate mofetil (MMF) or azathioprine and switching tacrolimus to sustained release of a single daily dose, thereby decreasing the drug c-max levels, are few strategies used to decrease the renal toxicity of CNI. In patients who are found to be having renal impairment, swapping tacrolimus to a newer m-Tor inhibitor has been shown to aid in the recovery of renal function in children [47].

30.2.3.2 Catch-Up Growth

Severity of cholestasis in cirrhosis affects growth and bone health. Insulin-like growth factor- 1 (IGF-I) and its major binding-proteins, IGFBP-1, -2 and -3 are produced by the liver and are essential for linear growth. In cirrhosis, low prior growth and IGF-1 lead to compensatory secretion of the growth hormone (GH), resulting in relative GH resistance [48]. Linear growth and weight tend to catch up within the first 2 years of LT, after which it begins to plateau. Up to 25% of recipients may not reach the long-term final height, especially when catch-up growth has not occurred in the first 2 years [49]. Nutritional status before transplant, severity of cholestasis and long-term usage of steroids have been shown to adversely impact long-term growth.

30.2.3.3 Post-LT Malignancy

The risk of cancer in paediatric recipients is two to three times greater than in the general population [50]. The increased risk is attributed to impaired immunosurveillance, proliferation of oncogenic viruses [e.g., Epstein–Barr virus (EBV)] and direct damage of the host DNA [50]. The younger age of the recipient and consequently longer duration of immunosuppression with more intense immunosuppression are associated with increased incidences of malignancies. The incidences of de novo malignancy are 20% and 30%, respectively, after 10 and 20 years of transplantation [50]. Post-transplant lymphoproliferative disease (PTLD) is the most malignant complication after paediatric SOT, accounting for 50% of all tumours [51]. Skin cancers (squamous cell carcinoma, basal cell carcinoma, Kaposi sarcoma, malignant melanoma and Merkel cell tumours) are the second most frequent tumours in SOT recipients (20% of all tumours), with melanoma and cancers of the lip seen more commonly than in adults [51]. The risk of aerodigestive, gastrointestinal, genitourinary and gynaecologic malignancies is also increased [52].

PTLD consists of a spectrum ranging from polyclonal hyperplasia of the lymphoid system to monoclonal non-Hodgkin lymphoma [53]. There are four major categories: early lesions, polymorphic PTLD, monomorphic PTLD, and Hodgkin's disease/Hodgkin-like PTLD [53]. There is a bimodal distribution with those occurring within 1 year (early PTLD) after transplantation mostly associated with EBV. These frequently present with extranodal or graft organ involvement as compared to those occurring in the second to third year (late PTLD) [53]. The incidence after LT varies between 5 and 15%, with most being early PTLD (2,4). Risk factors for PTLD include an EBV seronegative child receiving a seropositive organ

(four-fold risk) and intense immunosuppression. Management consists of immunosuppression withdrawal and rituximab for low-grade disease and additional chemotherapy [e.g., cyclophosphamide, hydroxydaunorubicin, oncovin/vincristine, prednisone (CHOP)] for high-grade lymphoma [51, 53]. The prognosis of PTLD in paediatric recipients is better than in adults with an overall 2-year survival of over 70% [51].

EBV screening should be done regularly in all LT recipients. As ultraviolet radiation is an important risk factor in the pathogenesis of skin malignancies and exerts a field cancerization mutagenic effect in exposed areas of the skin, protection against prolonged sun exposure is advised [52]. The intensity of immunosuppression needs to be titrated to the lowest possible level to achieve stable graft function. Regular follow-up and monitoring allows for early detection and treatment of these lesions.

▶ **Tip** Quantitative measurement of EBV at regular intervals during the early post-transplant period helps in proactively decreasing the tacrolimus target levels.

30.2.3.4 Neurodevelopment

Paediatric LT recipients are at higher risk of neurocognitive impairment with several pre- and post-transplant factors being implicated. Long-term follow-up data are not conclusive regarding the incidence, proportion or severity of neurocognitive impairment. Early age of onset, severe malnutrition, severe liver disease with prolonged ICU and hospital stay are few of the factors associated with poor long-term neurocognitive outcomes [54]. Children with metabolic disorders (aminoacidopathy, urea cycle defects, tyrosinemia) are at higher risk of neurodevelopmental delay. Post-transplant medications (immunosuppressive agents/corticosteroids) can cause cumulative injury to the developing brain [54]. Children with malignancies receiving ototoxic medications may develop impaired hearing post-transplant. Differential impairment of language and verbal skills has been noted in several studies [54, 55]. LT recipients had more difficulties in executive functioning, particularly in self-regulation, planning and organization, problem-solving and visual scanning as compared to siblings or the normal population. Defects in these skills can hamper a child academically, socially and emotionally. Children who had undergone LT under the age of 5 years displayed twice the rate of intellectual delay and three times the rate of learning disability compared to the general population at early school age [55]. No difference was noted in intellect, cognition, academic function, memory and learning in LT recipients when compared to their siblings 10 years after LT [54]. Increased incidence of attention deficit hyperactivity disorder has also been reported [56, 57].

Paediatric LT recipients require close follow-up with clinical monitoring of neurocognitive function in the long term. Early detection can help identify children who will benefit from educational interventions and special support services. Children with significant delay pre-transplant should be initiated on rehabilitation immediately after transplantation.

30.2.3.5 Metabolic Syndrome and Cardiovascular Effects after LT

Paediatric LT recipients are at a higher risk for diabetes, hyperlipidaemia, hypertension, obesity and metabolic syndrome as long-term complications of immunosuppressive medications (CNI, steroids, MMF) [58]. Hypertension is an independent risk factor of renal insufficiency in LT recipients, and children with hypertension have a 2.5 times higher risk of developing hypertension in adulthood [59]. Analysis of the Studies in Paediatric Liver Transplantation (SPLIT) database of 815 recipients older than 5 years at 5–10 years post-LT showed that 15–20% were receiving treatment for hypertension or had elevated BP measurements [59]. Factors associated with increased risk were of age at transplant >1 year, had steroid use and a cGFR <90 mL mL/min/1.73 m^2 [59]. Analysis of the SPLIT database also showed that hypercholesterolaemia and hypertriglyceridaemia were seen in 7% and 10%, respectively, of children surviving beyond 5 years [60]. LT recipients are more likely to have lower HDL cholesterol levels as compared to normal controls [61]. In a large study, 13% had evidence of diabetes mellitus and 5% were receiving either insulin or antihyperglycaemic medications at 5-year follow-up [60]. Children receiving tacrolimus were at a higher risk of having blood sugar values in the diabetic range [60]. The odds of impaired glucose tolerance doubles every 7.5 years on CNI therapy [61]. Up to 30% of paediatric recipients may have impaired glucose tolerance (IGT) at 5-year follow-up [61].

Analysis of 1706 paediatric LT recipients showed that 18% were obese at 1 and 3 year follow-up [62]. The incidence of obesity in these recipients was much higher than in the general paediatric population though interestingly, at 5 years post-LT it was comparable to the general population [62, 63]. LT recipients who were obese at transplant were 10 times more likely to be obese after the transplant [62].

The overall prevalence of metabolic syndrome after paediatric LT was 14–19% [61, 63]. The increased risk of cardiovascular complications necessitates vigorous surveillance, early recognition and prompt referral for strategies targeting early prevention, lifestyle modifications, treatment and educating patients and caregivers.

30.2.3.6 Adolescent Health Issues Affecting Outcome

Non-adherence to medications among paediatric transplant recipients can be as high as 65%, which becomes more common in the adolescent population at the time of transition to adult services [64]. Low self-esteem, social adjustment problems, behavioural difficulties, financial difficulties, dysfunctional family status and medication side effects lead to nonadherence. Noncompliance results in rejection, graft loss, mortality and increased health care utilization rates [65]. Measures advocated to improve compliance include dedicated psychoeducational service, presence of a designated healthcare transition coordinator, simplifying immunosuppressive medication regimens and promoting self-management [64, 65]. Self-management includes the promotion of health education, communication skills, decision-making and problem-solving skills and self-care in the context of meaningful social support [64, 65].

Adolescents of age 15–19 years acquire 50% of all new sexually transmitted infections and have pregnancy rates varying from 10 to 69 births per 1000 females. In an immunocompromised patient, any infection is more serious, with significant complications compounding the risks involved in teenage pregnancy. In sexually active adolescents, fetotoxic medications (e.g., MMF) may need to be substituted. All adolescents should receive health guidance regarding responsible sexual behaviour and should have an annual preventive service visit. The promotion of healthy and responsible sexual decision-making is one of the most important goals of counselling. Counselling should include discussion about the prevention of STIs, effective contraceptive methods and safe sexual practices.

30.3 Conclusion

Dramatic improvements in technology, surgical techniques and medications have ensured that LT is no longer an experimental procedure with long-term survival becoming the norm. Despite small numbers and lack of randomized trials, the wealth of experience gained over the past four decades has given a fair insight into the unique problems and solutions encountered in paediatric LT. The initial obstacles to survival, particularly organ preservation, surgical technique, and immunosuppression have been addressed, but the psychological, social and health problems produced by successful transplantation are only beginning to be recognized. As the majority of children are under 5 years of age at transplant, we must be prepared for their future needs, particularly during adolescence when compliance will become a significant issue. The challenge is to ensure that these children complete their education, have employment and are able to have families of their own.

Key Points

- Longevity of the allograft is influenced by various factors such as surgical, immunological, immunosuppression compliance, etc.
- Apart from just survival, we expect these children to grow up and have meaningful lives that is, be economically self-sufficient, have a family life and become functional members of society.
- Immunosuppression has to be individually tailored so that it has a minimum effect on their growth and development.
- Graft dysfunction/loss due to poor drug compliance is an important issue during the transition period from adolescence to adult.
- Life style disorders such as obesity, diabetes and hypertension can affect the graft adversely.
- Regular follow-up is essential to identify complications early and address them.

References

1. Haddad EM, et al. Cyclosporin versus tacrolimus for liver transplanted patients. Cochrane Database Syst Rev. 2006;4:CD005161.
2. Ziaziaris WA, et al. Reducing the incidence of hepatic artery thrombosis in pediatric liver transplantation: Effect of microvascular techniques and a customized anticoagulation protocol. Pediatr Transplant. 2017;21(4)
3. Krajicek E, et al. Ischemic cholangiopathy 11 years after liver transplantation from asymptomatic chronic hepatic artery thrombosis. ACG Case Rep J. 2018;5:e75.
4. Waarnaar N, et al. Long-term results of urgent revascularization for hepatic artery thrombosis after pediatric liver transplantation. Liver Transpl. 2010;16(7):847–55.
5. Ackermann O, et al. The long-term outcome of hepatic artery thrombosis after liver transplantation in children: role of urgent revascularization. Am J Transplant. 2012;12(6):1496–503.
6. Chardot C, et al. Portal vein complications after liver transplantation for biliary atresia. Liver Transpl Surg. 1997;3(4):351–8.
7. Waits SA, et al. Portal vein thrombosis and outcomes for pediatric liver transplant candidates and recipients in the United States. Liver Transpl. 2011;17(9):1066–72.
8. Galloux A, et al. Diagnosis, treatment and outcome of hepatic venous outflow obstruction in paediatric liver transplantation: 24-year experience at a single Centre. Pediatr Radiol. 2018;48(5):667–79.
9. Fukuda A, et al. Modified triangular hepatic vein reconstruction for preventing hepatic venous outflow obstruction in pediatric living donor liver transplantation using left lateral segment grafts. Pediatr Transplant. 2018;22(3):e13167.
10. Kling K, Lau H, Colombani P. Biliary complications of living related pediatric liver transplant patients. Pediatr Transplant. 2004;8(2):178–84.
11. Tanaka H, et al. Biliary reconstruction in pediatric live donor liver transplantation: duct-to-duct or roux-en-Y hepaticojejunostomy. J Pediatr Surg. 2010;45(8):1668–75.
12. Feier FH, et al. Analysis of factors associated with biliary complications in children after liver transplantation. Transplantation. 2016;100(9):1944–54.
13. Thangarajah D, O'Meara M, Dhawan A. Management of acute rejection in paediatric liver transplantation. Paediatr Drugs. 2013;15(6):459–71.
14. D'Antiga L, et al. Late cellular rejection in paediatric liver transplantation: aetiology and outcome. Transplantation. 2002;73(1):80–4.
15. Tannuri AC, et al. Prognostic factors for the evolution and reversibility of chronic rejection in pediatric liver transplantation. Clinics (Sao Paulo). 2016;71(4):216–20.
16. Feng S, et al. Evidence of chronic allograft injury in liver biopsies from long-term pediatric recipients of liver transplants. Gastroenterology. 2018;155(6):1838–1851.e7.
17. Ueno T, et al. Everolimus rescue treatment for chronic rejection after pediatric living donor liver transplantation: 2 case reports. Transplant Proc. 2018;50(9):2872–6.
18. Takemoto SK, et al. National conference to assess antibody-mediated rejection in solid organ transplantation. Am J Transplant. 2004;4(7):1033–41.
19. Del Bello A, et al. Histological long-term outcomes from acute antibody-mediated rejection following ABO-compatible liver transplantation. J Gastroenterol Hepatol Foundation. 2017;32(4):887–93.
20. Ekong UD, et al. Long-term outcomes of de novo autoimmune hepatitis in pediatric liver transplant recipients. Pediatr Transplant. 2017:**21**(6).
21. Scheenstra R, et al. Graft fibrosis after pediatric liver transplantation: ten years of follow-up. Hepatology. 2009;49(3):880–6.
22. Evans HM, et al. Progressive histological damage in liver allografts following pediatric liver transplantation. Hepatology. 2006;43(5):1109–17.
23. Lohse AW, Weiler-Norman C, Burdelski M. De novo autoimmune hepatitis after liver transplantation. Hepatol Res. 2007;37(Suppl 3):S462.

24. Chai PF, et al. Childhood autoimmune liver disease: indications and outcome of liver transplantation. J Pediatr Gastroenterol Nutr. 2010;50(3):295–302.
25. Fouquet V, et al. Long-term outcome of pediatric liver transplantation for biliary atresia: a 10-year follow-up in a single center. Liver Transpl. 2005;11(2):152–60.
26. Safwan M, et al. Living donor liver transplantation for biliary atresia—an Indian experience. Pediatr Transplant. 2016;20(8):1045–50.
27. Hori T, et al. Living-donor liver transplantation for progressive familial intrahepatic cholestasis. World J Surg. 2011;35(2):393–402.
28. Mali VP, et al. Total internal biliary diversion during liver transplantation for type 1 progressive familial intrahepatic cholestasis: a novel approach. Pediatr Transplant. 2016;20(7):981–6.
29. Hoppe B, Langman CB. A United States survey on diagnosis, treatment, and outcome of primary hyperoxaluria. Pediatr Nephrol. 2003;18(10):986–91.
30. Shanmugam NP, et al. Auxiliary partial orthotopic liver transplantation for monogenic metabolic liver diseases: single-centre experience. JIMD Rep. 2018;
31. Rammohan A, et al. Auxiliary partial Orthotopic liver transplantation for selected noncirrhotic metabolic liver disease. Liver Transpl. 2019;25(1):111–8.
32. Pfister ED, et al. Predictive factors for survival in children receiving liver transplants for Wilson's disease: a cohort study using European liver transplant registry data. Liver Transpl. 2018;24(9):1186–98.
33. Guillaud O, et al. Long term results of liver transplantation for Wilson's disease: experience in France. J Hepatol. 2014;60(3):579–89.
34. Catana AM, Medici V. Liver transplantation for Wilson disease. World J Hepatol. 2012;4(1):5–10.
35. Lankarani KB, et al. Fourteen years of experience of liver transplantation for Wilson's disease; a report on 107 cases from shiraz, Iran. PLoS One. 2016;11(12):e0167890.
36. Laurencin C, et al. Liver transplantation in Wilson's disease with neurological impairment: evaluation in 4 patients. Eur Neurol. 2017;77(1–2):5–15.
37. Stracciari A, et al. Effect of liver transplantation on neurological manifestations in Wilson disease. Arch Neurol. 2000;57(3):384–6.
38. Erol I, et al. Neurologic complications of liver transplantation in pediatric patients with the hepatic form of Wilson's disease. J Child Neurol. 2008;23(3):293–300.
39. Wang XH, et al. Living donor liver transplantation treatment of Wilson's disease complicated with neuropathy. Zhonghua Yi Xue Za Zhi. 2003;83(18):1569–71.
40. Isono K, et al. Pretransplant trends in α-fetoprotein levels as a predictor of recurrence after living donor liver transplantation for unresectable hepatoblastoma: a single-institution experience. Pediatr Transplant. 2018;22(5):e13221.
41. Trobaugh-Lotrario AD, et al. Pediatric liver transplantation for hepatoblastoma. Transl Gastroenterol Hepatol. 2016;1:44.
42. Vinayak R, et al. Pediatric liver transplantation for hepatocellular cancer and rare liver malignancies: US multicenter and single-center experience (1981-2015). Liver Transpl. 2017;23(12):1577–88.
43. Ismail H, et al. Liver transplantation in children with hepatocellular carcinoma. Do Milan criteria apply to pediatric patients? Pediatr Transplant. 2009;13(6):682–92.
44. Wilkinson A, Pham PT. Kidney dysfunction in the recipients of liver transplants. Liver Transpl. 2005;11(Suppl 2):S47–51.
45. Filler G, Melk A, Marks SD. Practice recommendations for the monitoring of renal function in pediatric non-renal organ transplant recipients. Pediatr Transplant. 2016;20(3):352–63.
46. Calvo-Garcia MA, et al. Acquired renal cysts after pediatric liver transplantation: association with cyclosporine and renal dysfunction. Pediatr Transplant. 2008;12(6):666–71.
47. Basso MS, et al. Sirolimus as renal and immunological rescue agent in pediatric liver transplant recipients. Pediatr Transplant. 2011;15(7):722–7.
48. Maes M, Sokal E, Otte JB. Growth factors in children with end-stage liver disease before and after liver transplantation: a review. Pediatr Transplant. 1997;1(2):171–5.

49. Renz JF, et al. Posttransplantation growth in pediatric liver recipients. Liver Transpl. 2001;7(12):1040–55.
50. Karakoyun M, et al. Post-transplant malignancies in pediatric liver transplant recipients: experience of two centers in Turkey. Turk J Gastroenterol. 2018;29(1):89–93.
51. Mynarek M, et al. Posttransplant lymphoproliferative disease after pediatric solid organ transplantation. Clin Dev Immunol. 2013;2013:814,973.
52. Mukthinuthalapati PK, Gotur R, Ghabril M. Incidence, risk factors and outcomes of de novo malignancies post liver transplantation. World J Hepatol. 2016;8(12):533–44.
53. Khedmat H, Taheri S. Lymphoproliferative disorders in pediatric liver allograft recipients: a review of 212 cases. Hematol Oncol Stem Cell Ther. 2012;5(2):84–90.
54. Krull K, et al. Neurocognitive outcome in pediatric liver transplant recipients. Pediatr Transplant. 2003;7(2):111–8.
55. Sorensen LG, et al. Cognitive and academic outcomes after pediatric liver transplantation: functional outcomes group (FOG) results. Am J Transplant. 2011;11(2):303–11.
56. Ee LC, et al. Academic potential and cognitive functioning of long-term survivors after childhood liver transplantation. Pediatr Transplant. 2014;18(3):272–9.
57. Robertson CM, et al. Neurocognitive outcomes at kindergarten entry after liver transplantation at <3 yr of age. Pediatr Transplant. 2013;17(7):621–30.
58. Varo E, et al. Cardiovascular risk factors in liver allograft recipients: relationship with immunosuppressive therapy. Transplant Proc. 2002;34(5):1553–4.
59. McLin VA, et al. Blood pressure elevation in long-term survivors of pediatric liver transplantation. Am J Transplant. 2012;12(1):183–90.
60. Ng VL, et al. Outcomes of 5-year survivors of pediatric liver transplantation: report on 461 children from a north american multicenter registry. Pediatrics. 2008;122(6):e1128–35.
61. Perito ER, Lustig RH, Rosenthal P. Metabolic syndrome components after pediatric liver transplantation: prevalence and the impact of obesity and immunosuppression. Am J Transplant. 2016;16(6):1909–16.
62. Sundaram SS, et al. Obesity after pediatric liver transplantation: prevalence and risk factors. J Pediatr Gastroenterol Nutr. 2012;55(6):657–62.
63. Rothbaum Perito E, et al. Posttransplant metabolic syndrome in children and adolescents after liver transplantation: a systematic review. Liver Transpl. 2012;18(9):1009–28.
64. Fredericks EM. Nonadherence and the transition to adulthood. Liver Transpl. 2009;15(Suppl 2):S63–9.
65. Burra P, et al. Adherence in liver transplant recipients. Liver Transpl. 2011;17(7):760–70.