Assessment and Preparation for Liver Transplantation in Children

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28.1 Introduction

Liver transplantation (LT) is now the standard of care for children with end-stage liver disease, liver-based metabolic defects, unresectable liver tumours and liver disorders leading to suboptimal quality of life. Multidisciplinary team assessment of liver transplant recipients is now becoming the standard of care (Fig. 28.1) [1]. The aims of the assessment process are to evaluate medical, infectious diseases (ID), psychosocial, surgical and anaesthetic risks to achieve best patient and graft outcomes. There is an increasing trend towards personalising immunosuppression induction and maintenance regimens. Unlike adults, parents play a major or sole role in decision-making and hence it is important for the evaluation team to ensure engagement of the whole family. The purview of this chapter will include these variations in preparation and evaluation of children for LT. The indications for transplantation and the long-term outcomes of LT are discussed in other chapters in this book.

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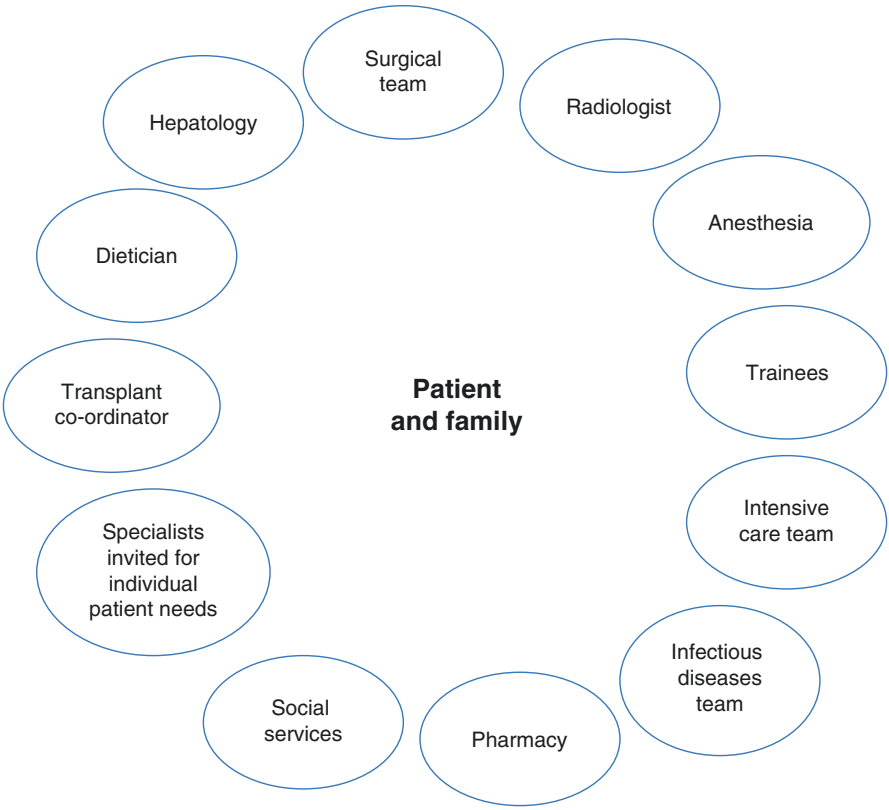

Fig. 28.1 Multidisciplinary team centred around the patient and the family

28.2 Evaluation and Preparation of a Child for LT

When a child is referred for LT, the assessment involves (i) establishing the indication for LT, (ii) a risk assessment to prepare for risk mitigation to achieve best graft and patient outcomes and (iii) a decision on the most appropriate timing for LT.

The assessment of the need for transplant starts with ensuring the confirmation of the diagnosis and indications for LT and medical optimisation to confirm that all medical options have been exhausted. Liver transplantation may be performed for the failure of synthetic and detoxification functions due to a decompensated chronic liver disease (CLD) or due to acute liver failure, unresectable liver tumours, non-cirrhotic liver-based metabolic disorders with extrahepatic manifestations or liver disease with suboptimal quality of life. Liver transplantation is usually offered when there is a high risk of death due to liver disease and its complications in the next 12 months, a risk of irreversible non-hepatic end-organ damage that can be prevented by liver transplantation, a reversible neurodevelopmental impairment due to liver disease, an unacceptable quality of life resulting from the consequences of

liver disease like refractory pruritus or when there is growth failure unresponsive to maximised medical treatment.

Risk assessment focuses on the co-morbidities and complications of the liver disease that will either preclude a liver transplant or which will need an optimisation before LT. Absolute contraindications, include overwhelming acute bacterial, acute fungal or acute viral extrahepatic infections, severe cardiovascular disease, active or recent extrahepatic malignancy or severe multisystemic involvement as in mitochondrial disorders with high risk of mortality after LT. Indications and contraindications are mostly determined by the transplant centre's experience.

The transplant coordinator plays a central role in ensuring a complete multidisciplinary assessment and preparation of a child for LT. The major tasks shouldered by a coordinator include developing a rapport with the family, educating them regarding the need for transplant, explaining the risk and process of transplant, collating documented clinical and management information regarding the child, ensuring an individualised and unified plan for preparation to LT and post-LT care by having open routes of communication between various care providers. The transplant coordinator also devises an individual education programme tailored to the needs of the family and the child.

The challenges of severe malnourishment in children, nutrition, vaccination, stabilisation in inherited metabolic disorders and congenital cardiac disorders are some unique issues that arise during assessment for LT.

28.2.1 Nutritional Assessment and Support

The nutritional status of a child with chronic liver disease who is listed for LT has a major bearing on survival while on the waiting list for LT and morbidity and mortality soon after LT. The growth and neurodevelopmental outcomes, infectious complications and wound healing after LT are closely linked to the nutritional status [2]. The poor nutrition in children with chronic liver disease (CLD) tends to be multifactorial [3, 4]. Some of the reasons for the malnutrition in CLD include the anorexia associated with the chronic disease, fat malabsorption resulting from cholestasis, the ascites and organomegaly that limits intake, salt and fluid restriction related to ascites management, protein loss from gastrointestinal (GI) bleeds and paracentesis, the increased catabolic rate, the inflammatory and metabolic stress imposed by the underlying condition and the inter-current infections. Most children lose subcutaneous fat and become sarcopenic. The effect of CLD on growth factor/insulin growth factor-1 (GF/IGF-1) axis affects height irrespective of the nutrition. Children with progressive end-stage liver disease less than 2 years of age with severe cholestasis and recurrent complications of liver disease (e.g. ascites and bleeding varices) are at higher risk of nutritional compromise. The impaired absorption of fat-soluble vitamins in cholestatic disease and impaired hydroxylation of vitamin D in the liver expose them to deficiency of these vitamins and also hepatic rickets. The metabolic stress also demands additional supplementation of the water-soluble vitamins.

Anaemia is most often a result of gastrointestinal blood loss due to portal hypertension, the chronic disease and hypersplenism.

Clinical and biochemical nutritional assessment and monitoring of children with CLD are not the same as in normal children. The hepatosplenomegaly, ascites and oedema make weight an unreliable parameter. Height is not useful in assessment of short-term changes in nutrition. Serial mid upper arm circumference and triceps skin fold thickness provide the most reliable way of monitoring nutritional status in these children that can be used in daily practice. Clinical evaluation for vitamin deficiencies should be supplemented by appropriate biochemical investigations. Children receiving vitamin D supplementation, especially those on parenteral supplementation, need to be monitored with vitamin D levels and serum calcium to avoid toxicity.

α-Tocopherol: Lipid ratio and not α-tocopherol levels should be used to diagnose vitamin E deficiency in cholestasis to avoid underestimation. Prothrombin time that is correctable by vitamin K is a sufficient reflection of deficiency and estimation of protein induced by vitamin k absence (PIVKA), reserved for research situations.

The nutritional management of children awaiting LT involves optimising the quantity and nature of nutrients delivered while paying attention to the mode of delivery. Energy intake need to be increased to 140–200% of estimated average requirements (EARs) to account for the increased calorie requirements. Concentrated medium-chain triglyceride (MCT)-containing formulas in infants and high calorie (1 kcal/mL) formula drinks in older children need to be supplemented in the form of nasogastric feeding if oral intake is inadequate. MCT increases calorie density while being easily absorbed without the need for micellar solubilisation and lymphatic absorption in cholestasis. While 30–50% of the total fat may be delivered as MCT formula or oil, very high MCT formulae risk essential fatty acid deficiency. Essential fatty acids should constitute 1–2% of energy intake in the form of walnut oil or fish. At least 2–3 g/kg/day of protein is delivered (up to 4 g/kg/day) without risk of encephalopathy. Protein restriction to 1.5 g/kg/day may be required during acute encephalopathy but should not be extended to long periods. There is insufficient evidence for routine use of branched-chain amino acid (BCAA)-enriched formulas. The enteral route is the best way to deliver nutrients as it is both physiological and cheaper. Nasogastric tubes may be used to supplement inadequate oral feeds but gastrostomy use is avoided in decompensated liver disease in view of the risk of stomal varices, infection and organomegaly. Night-time feeds are essential to avoid hypoglycaemia and protein catabolism. Continuous feeding may be required for improving feed tolerance. Total parenteral nutrition (TPN) use is complicated by catheter-associated bloodstream infections, gut bacterial overgrowth, bacterial translocation across the gut and long-term TPN-related liver injury. Yet, this may be necessary in those with malabsorption or feed intolerance. Standard preparations are used but with close attention to triglyceride levels. Vitamin A supplementation must be balance against the risk of hepatotoxicity with hypervitaminosis. Vitamin E being highly lipophilic is best administered as water-soluble tocopherol polyethylene glycol succinate which also enhances the absorption of other vitamins including

vitamin D. Parenteral administration of vitamin D may be required by those with significant malabsorption due to cholestasis or cystic fibrosis. Oral vitamin K is best administered as water-soluble Menadione even though intermittent parenteral administration may be needed in some.

Even though obesity is not a common problem in paediatric liver transplant recipients, when encountered, an attempt at resolving the obesity with dietary management is worthwhile in avoiding post-transplant obesity, metabolic syndrome and late transplant mortality.

28.2.2 Cardiopulmonary Assessment

Cardiac disease in children awaiting LT may be in the form of structural cardiac diseases, myocardial involvement in the form of cardiomyopathy which may be a part of metabolic and systemic diseases, cirrhotic cardiomyopathy or the effect of changes in pulmonary vasculature in the form of hepatopulmonary syndrome and portopulmonary hypertension. The minimal evaluation necessary in all patients is a 12-lead electrocardiogram, chest x-ray, Doppler echocardiography and saturated oxygen in arterial blood (SpO_2) in room air in the erect position. The anaesthetist may also request a venous or arterial blood gas.

Children with Alagille syndrome (AS) and biliary atresia (BA), especially biliary atresia splenic malformation syndrome, commonly have structural cardiac diseases [5, 6]. Children with complex cardiac diseases should have a formal assessment by a paediatric cardiologist and the decision to transplant such children is individualised. The most common problem associated with AS is the presence of peripheral pulmonary stenosis and right ventricular hypertrophy. During LT there is an increased delivery of fluids to compensate for caval clamping. The cardiac reserve may be limited to handle this fluid load in AS. After reperfusion, the pulmonary hypertension, systemic vasodilatation and increase in the central venous pressure impose a greater stress on the heart. Hence routine echocardiography is insufficient to evaluate the cardiac reserve under stress [7, 8]. Even though some centres reserve cardiac catheterisation studies in AS to patients with increased trans-stenotic gradient and a right ventricular pressure of >50% of the systemic pressures, the safest approach is that evolved by the King's College group. Children with AS undergo dynamic stress testing with dobutamine infusion which is an inotrope and also a vasodilator and partly mimics the stress during LT. A continuous infusion rate of 10 μg/kg/min is then increased to 20 μg/kg/min. The cardiac index, systemic vascular resistance and pulmonary vascular resistance index are monitored. Greater than 40% increase in cardiac output is accepted as sufficient for LT [9].

Glycogen storage disorders and mitochondrial disorders present with cardiomyopathy even though mitochondrial disorders are often contraindications for LT. Cirrhotic cardiomyopathy is a major concern in adults and presents with baseline increased cardiac output because of increased cardiac contractility and peripheral vasodilatation, myocardial hypertrophy, impaired diastolic relaxation, repolarisation abnormalities and attenuated response of the heart to direct beta

stimulation. There may not be manifest congestive heart failure unless exposed to high fluid load as in the peri-operative period. Even though 70% of children with BA listed for LT had abnormalities on echocardiography, the contribution of this to peri-operative outcomes in not entirely clear.

The highest frequency of hepatopulmonary syndrome in any liver disease across all age groups is in biliary atresia. It affects intra-operative and postoperative course by resulting in oxygen desaturation and need for intensive care. Children with a pulse oximetry saturation of 97% in room air, preferably in the erect position, should undergo contrast echocardiography with agitated saline to look for intra-pulmonary shunting. This cannot be done in children with structural cardiac left to right shunts. Appearance of bubbles in the left atrium after three cardiac cycles indicates an extracardiac shunt of possible pulmonary origin. The 99 m-Technetium-macroaggregated albumin perfusion lung scan provides a quantification of the shunt fraction. In patients with arterial oxygen pressure (PaO2) of less than 60 mmHg, computed tomographic (CT) pulmonary angiogram may be necessary to look for type 2 shunts that are amenable for coil closure before LT. In contrast, portopulmonary hypertension is not common in children.

Children with cystic fibrosis-associated liver disease referred for LT should undergo pulmonary function testing to assess the forcedexpiratory volume in one second (FEV1) and forced vital capacity (FVC) which has implications for the intra-operative and post-operative outcomes. Very compromised lung function or colonisation with multi-resistant organisms may be a contraindication or lead to consideration for combined liver/heart/lung transplant.

28.2.3 Renal Assessment

Renal involvement is common in children with Alagille syndrome, alpha-1-anti trypsin deficiency, tyrosinemia, propionic academia, Wilson disease, ciliopathies with renal involvement, history of chemotherapy and in those planned for retransplantation with previous prolonged exposure to high doses of calcineurin inhibitors. All children planned for LT should have a renal function assessment. Measured glomerular filtration rate (GFR) with exogenous agents is a cumbersome process which is difficult in children. Endogenous agents such as creatinine and cystatin C are more convenient to use. Plasma creatinine estimation is unreliable as a reflection of GFR as most of these children are sarcopenic, have a reduced conversion of creatine to creatinine in the liver and have elevated bilirubin which interferes with the picrate method of creatinine estimation. The modified Schwartz formula ($0.413 \times$ [serum Creatinine (mg/dL)/height (cm)] = GFR (mL/min/1.73 m^2) is based on the more reliable isotope dilution mass spectrometry. Cystatin C measured by immunoturbidimetric or nephelometric method standardised to an international calibrator is less influenced by muscle mass and is unaffected by the serum bilirubin levels. It does not undergo tubular

reabsorption and hence its level is more dependent on the GFR. Cystatin C levels which are higher in infancy reach normal adult levels (0.51–0.98 mg/L) by the age of 1 year. Cystatin C has been used to predict a GFR of <80 mL/min/1.73 m^2 in a cohort of both pre-transplant and post-transplant children and a level of 1.06 mg/L was shown to have a sensitivity and specificity of 91% and 81% [10]. A study in adult LT recipients using Cystatin C-based equation (CKD-EPI-CystC) to predict GFR has shown good reliability in predicting GFR but such an equation has not been validated in children with the newer methods of Cystatin measurement [11]. Serum bicarbonate estimation is necessary to look for renal tubular acidosis in children with Alagille syndrome, Wilson disease, tyrosinemia and ciliopathy. Children with acute liver failure may often present with acute kidney injury as part of the multi-organ dysfunction and may be on renal replacement therapy.

Children with ascites, low GFR and normal kidney parenchymal appearance on ultrasound where the aetiology of liver disease or nephrotoxic medication do not explain the kidney injury, should have their diuretics optimised and should receive albumin infusions before a diagnosis of hepato-renal syndrome is made. GI bleeds and infections should be adequately managed. Electrolytes should be closely monitored.

Children with low GFR or tubulopathy should be discussed in multidisciplinary meetings prior to LT to decide on a renal sparing induction regimen with Basiliximab and steroids so that tacrolimus can be initiated later after the transplant. Such children are usually maintained on lower serum levels of tacrolimus and adjuvant immunosuppression agents like Mycophenolate mofetil or Azathioprine. This decision is to be taken while listing such patients for transplant.

28.2.4 Anaesthesia Risk Stratification

It is now becoming a norm to have a designated paediatric anaesthetist who is well versed with transplant anaesthesia and peri-operative issues that arise with LT. An anaesthetist experienced in paediatric LT is preferred as many of the disorders in children present with multisystemic involvement including congenital cardiac, vascular and renal abnormalities. Conditions such as Alagille syndrome (cardiac, renal, vascular, neurovascular anomalies), biliary atresia splenic malformation syndrome (cardiac and vascular anomalies), ciliopathies (renal abnormalities) and metabolic disorders (cardiac and renal issues in primary hyperoxaluria, multisystem involvement in propionic academia) pose unique challenges that are best assessed by a paediatric LT anaesthetist. Biliary atresia, the commonest cause for paediatric LT, has the highest frequency of hepatopulmonary syndrome that can affect intra-operative and immediate post-operative outcomes. A complete renal, cardiac, pulmonary, hepatic, vascular, neurologic and haematological assessment by the anaesthetist is necessary.

28.2.5 Neurocognitive Assessment

Neurocognitive assessment of children in need of LT has two major goals—(i) Early identification of neurocognitive impairment resulting from the liver disease and poor nutrition that need early intervention and (ii) identification of neurocognitive features of a multisystem disorder that preclude liver transplantation.

Children with liver disease often have impaired nutritional status. The pre-transplant weight and growth parallel the neurodevelopmental and cognitive status of children who develop CLD early in life when the brain development is at its peak. Vitamin E deficiency in cholestatic liver diseases also affects neurological outcomes. These children tend to have impaired cognitive, gross motor and expressive language developmental outcomes. The severity of the liver disease also has a bearing on the neurocognitive outcomes. Early recognition of these problems and a close attention to nutrition can mitigate these problems.

Some disorders like mitochondrial hepatopathies and propionic academia are multisystemic and have neurocognitive implications. Severe neurocognitive impairment in propionic academia that has not been managed adequately by dietary interventions can be contraindications for LT. Most mitochondrial disorders are absolute contraindications for LT even with minimal neurocognitive impairment at the time of evaluation in view of these being multisystemic diseases. Exceptions include DNA polymerase subunit gamma (POLG-1) mutations in the context of valproate toxicity which used to be considered as absolute contraindications for LT. It is now known that the phenotype and genotype of POLG-1 mutations can determine whether LT should be offered during valproate-induced acute liver failure. The lack of cognitive impairment or other neurological features along with seizures, age greater than 10 years of age, absence of abnormalities on electroencephalogram (EEG) or neuroimaging and POLG-1 mutations involving non-critical clusters (clusters 2 and 5) are favourable factors that predict good long-term outcomes with LT [12–15].

28.2.6 Vascular Assessment

Assessment of vascular anatomy and patency involves (i) central venous access assessment and (ii) assessment of variations in hepatic vasculature and inferior venacava (IVC). Doppler ultrasound and magnetic resonance angiography (MRA) are used in evaluation. During caval clamping in LT, venous return is compromised and fluid delivery to maintain cardiac output is dependent on delivery via the superior vena cava. Hence, the assessment of patency of bilateral internal jugular and subclavian veins is essential. In cases where these veins are not patent, commonly as a result of prolonged TPN, the patency of the femoral-external iliac veins is to be confirmed. In such cases, the surgical technique needs to be modified to avoid caval clamping.

Information on the status of the portal veins, hepatic arteries and inferior cava before LT is important for the surgeon to anticipate problems and plan the vascular reconstruction. This is of utmost relevance in children in whom the portal vein can be absent, hypoplastic, of a smaller calibre or even thrombosed. Children with biliary atresia splenic malformation syndrome tend to have a pre-duodenal portal vein, absent IVC and other arterial abnormalities. Hepatic vein anatomy is a critical piece of information in children with Budd-Chiari syndrome. Accessory hepatic arteries are not uncommon. Children with reversed or absent flow in portal vein by Doppler ultrasound will need MRA for better delineation of the anatomy. MRA is also essential in children with biliary atresia splenic malformation syndrome. MRA is extremely reliable for evaluation of portal veins and is false negative in the detection of accessory hepatic arteries less than 1 mm in diameter. Imaging is also relevant in differentiating tumoural thrombosis from non-tumoural portal vein thrombosis in the case of malignancies [16, 17].

Simultaneous imaging evaluation for liver suspicious liver nodules may also be done along with the imaging for vascular assessment.

28.2.7 Surgical Risk Stratification

Based on the information available above, the surgeon reviews the child to ascertain the suitability for transplantation, the surgical issues anticipated based on the vascular anatomy, variations in the anatomy like in a patient with biliary atresia splenic malformation syndrome and the challenges posed by a repeat transplantation in a child who has had earlier liver transplantation. For the cadaveric allograft retrieval age and donor size, limits are suggested to accept the organ including family counselling about allografts obtained after cardiac death. Evaluation for severity of portosystemic shunts is also recommended as portal flow modulation may be required by obliteration of the preformed shunts.

28.2.8 Assessment for Infectious Diseases and Immunisation

Infections remain the major complication after transplant because of life-long immunosuppression. The pre-transplant infectious diseases evaluation is crucial, because it identifies the risks for post-transplant infections, which helps to individualise the preventive strategies, including post-transplant antimicrobial prophylaxis, treatment of existing infections and immunisation. The evaluation should be done by the experienced transplant infectious diseases (ID) specialist [18]. The assessment is focused on history of prior exposure of infections, distant exposures, laboratory screening tests for resistant organisms, serologic testing for latent infections and immunisation status [19, 20].

Current medications history should document whether the child has received multiple courses of antibiotics. Such treatment may predispose the patient to

infections with multidrug-resistant organisms (MDROs) or opportunistic fungal infections in early post-operative period. The social history can provide useful clues to the risk of latent infection. Patients should be queried regarding their city and country of origin as well as all prior sites of residence. Such information is useful to assess the likelihood of asymptomatic exposure to *Mycobacterium tuberculosis*, parasites and endemic fungi. A history of the child's contacts with tuberculosis in family or outside, animal exposure and hobbies may reveal other infection risks [20]. Many patients with acute liver failure are hospitalised in an intensive care unit where they may be colonised or infected with multidrug-resistant organisms (MDROs). Such patients require extra effort to obtain a detailed clinical history to avoid fatal complications with potentially treatable infectious diseases.

All transplant candidates should be tested for active infection and fully treated whenever possible. Transplant candidates who have resided in areas where tuberculosis is endemic should be closely assessed using available assays and radiologic screening. Latent infection with *M. tuberculosis* can be detected by skin testing with purified protein derivative (PPD), or by screening tests by interferon-gamma release assays [(QuantiFERON®-TB Gold test or enzyme-linked immunosorbent assay (ELISPOT)]. Both tests have been validated for screening in human immunodeficiency virus (HIV)-infected patients, the efficacy of such testing in patients who may be immunocompromised as a result of pre-transplant organ dysfunction is not well studied. Screening for viral pathogens such as HIV, hepatitis C virus (HCV), hepatitis B (HBV), Cytomegalovirus (CMV) and Epstein-Barr Virus (EBV) should be carried out. The results of cytomegalovirus and EBV screening of potential recipients are used to guide post-transplant antiviral prophylaxis. The CMV and EBV infection status of the child is assessed by serology. This is unreliable in children younger than 12 months of age due to the possibility of trans-placental transfer of antibodies and hence they are assumed to be naïve to the infection even if positive by serological tests. Children who are naïve to CMV infection and receive a CMV-positive donor liver are at the highest risk of CMV disease. The children who are CMV positive but receiving CMV naïve donor organs are at moderate risk, and associated with increased morbidity [21]. This group also should receive antiviral prophylaxis. Alternative strategy employed is close surveillance for infection and reactivation. Children with past CMV infection continue to have the risk of reactivation and in addition the risk of acquiring a disease from a different strain of CMV if the donor is also positive. Children naïve to EBV infection have the highest risk of post-transplant lymphoproliferative disorder (PTLD). Close surveillance of EBV viral titres is the only possible strategy for early diagnosis or prevention of PTLD.

Pre-Transplant Vaccination: Transplant candidate and recipients are at increased risk of vaccine preventable infections because of immunosuppression. However, it is not uncommon for children requiring transplantation to have received inadequate or no immunisations pre-transplant. Verifying immunisation status and updating vaccinations are important steps in the pre-transplant evaluation. It has been become a standard of practice. Every effort should be made to immunise transplant candidates, early in the course of their disease before placing them on the waiting list for transplantation according to recommended schedules Table 28.1.

Table 28.1 Indications and contraindications for liver transplantation

Indications
Decompensated chronic liver disease and its complications (ascites, encephalopathy, spontaneous bacterial peritonitis, hepatopulmonary syndrome or hepatorenal syndrome)
Acute liver failure fulfilling liver transplant criteria
Portal hypertension refractory to medical and endoscopic therapy
Refractory pruritus
Recurrent cholangitis in cholangiopathies
Severe growth failure/sarcopenia in chronic liver disease in spite of optimal nutritional management
Unresectable liver tumours
Liver-based non-cirrhotic metabolic defects
Contraindications
Overwhelming active extrahepatic acute multidrug-resistant bacterial, acute fungal or acute viral infections
Extrahepatic malignancy
Severe uncorrectable cardiopulmonary disease
Severe cerebral injury
Multisystemic progressive disorders such as mitochondrial diseases

The immune response is better before transplantation compared to after transplantation [22–24]. Following transplantation children are on immunosuppressive medications, which further decreases antibody titres compared to decrease in antibody titres of control populations. Live vaccines are not given after transplantation till further recommendations. Measles, mumps, rubella (MMR) and varicella can be given at age of 6 month onwards if patient is listed for transplant before 1 year of age assessment of immunity should be performed before and after transplantation [22]. For live vaccines, patient should be suspended from transplant list at least for 4 weeks. Complete the immunisation at least 4 weeks before transplantation. It is also important to immunise their household contacts and healthcare workers [24]. Liver transplant recipients will benefit from consistent immunisation practices and transplant centres are encouraged to be proactive, especially pre-transplant centres [24]. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity in post-transplant period. Live-attenuated vaccinations require further studies to determine safety of routine use after transplant. Appropriate timing of vaccination is important so patients may have the best opportunity to mount a robust immune response Table 28.2.

28.2.9 Dental Assessment and Care

All children require a pre-transplant dental assessment if possible by a paediatric dentist. It is not uncommon for children with CLD to have dental caries and this often parallels the severity of the underlying liver disease. Frequent and prolonged bottle feeding in these children contributes to the frequency of dental caries. Dental management is often compounded by the bleeding risk and sedation-related issues. Yet, early attention to dental disease in the form of dental caries, abscess and

Table 28.2 Recommended vaccine schedule in paediatric liver transplant candidate

Vaccine	LAV / or I Vaccines	Comments
DPT (diphtheria pertussis and tetanus)	I	Primary course of three doses at 1 month interval and two boosters
IPV (inactivated polio vaccine)	I	
Hib (*Haemophilus influenzae* b)	I	Three doses at monthly interval for less than 1 year, one dose recommended if given after 2 years of age
Rotavirus (RV)	LA	Two doses of RV vaccine (Rotarix) at 1 month interval for all infants. The maximum age for this vaccine is 6 month
Pneumococcal conjugate vaccine (PCV) 13 serotypes	I	Three doses before 1 year. In unimmunised children after 1 year, two doses are recommended. When children are behind on PCV13 schedule, minimum interval for doses given to children >2 years is 2 months
Pneumococcal polysaccharide vaccine (PPV) 23 serotypes	I	Immunogenic in children after 2 years of age. Should give PPV 8 weeks after PCV13 and to repeat dose after 5 years
Meningococcal B	I	Minimum age is 2 month. One dose is recommended if given after 1 year of age
Meningococcal C	I	Minimum age is 3 month. One dose is recommended if given after 1 year of age
Meningococcal ACWY	I	Recommended age 10–18 years
Inactivated influenza	I	Annual immunisation before start of influenza seasons
Hepatitis A	I	Two doses at 6 months interval, minimum age 1 year immunoglobulin prophylaxis is indicated for non-responders to active immunisation in case of high risk of exposure (e.g. travel to endemic areas, infection of contacts)
Hepatitis B	I	Antibody measurement should be done 1 month after the final dose. If anti-HBs <10 IU/L, additional double doses are recommended
Measles, mumps & rubella (MMR)[a]	LA	If listed for transplant at age less than 1 year, minimum age to give vaccine is 6 months. One should consider doing measles IgG levels, to rule out presence of maternal antibodies, which can interfere with immune response to vaccine. Complete immunisation at least 4 weeks before transplantation
Variciella zoster virus[a]	LA	
Human papillomavirus vaccine (HPV		Girls commencing HPV vaccine course before age of 15 years should follow two dose at 0, then 6–24 months schedule and at age 15 years and above should follow three dose 0, 1 and 4–6 months schedule

LAV Live attenuated, *I* Inactivated

[a]After administration of live viral vaccines, the period of viral replication and development of immunologic response is generally <3 weeks, so vaccination ≥4 weeks prior to immunosuppression (2 weeks prior for inactivated vaccines) will be safe

periodontitis avoids cancellations and postponement of LT which is not an uncommon scenario when dental care is not given due focus. It also attends to a potential source of infection and sepsis in the post-transplant period where immunosuppression can flare dental infections.

28.2.10 Psychosocial Assessment

A child or adolescent in need of a LT is more vulnerable than an adult and influenced by the family and social conditions in view of their dependence on their primary caregivers. The emotional status of the primary caregiver and the family has a huge impact on the disease management and post-transplant outcomes. Any adverse family issues need to be explored and addressed with a view to looking at family functioning and coping strategies. Lack of compliance to treatment is recognised as the most important reason for late graft loss. An adolescent's understanding of the disease, behavioural problems and lack of compliance have a major bearing on graft survival. Socio-economic problems including housing and transport need to be addressed before embarking on LT. Child safeguarding concerns related to physical abuse or substance abuse in parents need early recognition and intervention. The multitude of psychosocial issues that impact LT outcomes are best recognised and dealt with by coordination between the transplant coordinator, psychologist and social worker. The Paediatric Transplant Rating Instrument developed by Fung et al. is a comprehensive instrument that has a standardised interview format and rating system that tried to recognise all the major psychosocial determinants of LT outcomes [25]. The transplant team should be the advocate for the child where such issues are identified so that adequate support systems are constituted before LT.

28.3 Optimisation of Medical Management

Appropriate diuretic and dietary management of ascites may be necessary for ensuring quality of life while on waiting list, decreasing respiratory compromise and ensuring adequate nutritional intake. Albumin infusions and paracentesis may be required in case of tense ascites. Endoscopic management of varices decreases the morbidity and mortality due to bleed in those with high-risk varices or history of bleed. In conditions where a specific drug therapy is available for the liver disease, optimisation avoids rapid deterioration while awaiting LT. In diseases such as hepatitis C infection, treatment avoids recurrence after transplant. Adequate treatment of co-morbid extrahepatic disorders like inflammatory bowel disease may influence outcomes after transplant.

Drugs such as Phenobarbitone started for cholestasis or rifampicin for pruritus may need to be discontinued and replaced by alternate drugs to avoid stimulation of drug metabolising enzymes in the liver which can lead to low levels of immunosuppressive medications like calcineurin inhibitors and Sirolimus post-LT.

28.4 Education

Education of the parents and the child by methods appropriate to the mental age has a major influence on post-transplant compliance and patient/graft survival. This would include awareness of surgical procedure, understanding immunosuppression and drug administration, monitoring protocols, early recognition of infections and complications and long-term outcomes.

28.5 ABO Antibody Titres

In children in need of an urgent transplantation in the face of non-availability of ABO compatible organs, ABO incompatible liver transplantation (ABOILT) is an available option. The long-term outcomes tend to be better in children younger than 2 years of age receiving ABOILT. The ABO antibody titres guide the preparation of the patient. Strategies to decrease the antibody titres prior to LT include therapeutic plasmapheresis and Rituximab [26, 27].

28.6 Peri-Operative Stabilisation of Children at Risk of Metabolic Decompensation

Unlike in adults, metabolic disorders are not uncommon causes of LT. Preparation for LT in such patients involves discussion with the metabolic disorders physician managing the child. The peri-operative period is a phase of metabolic stress that has a potential to precipitate a metabolic crisis. The anticipated problems are different in different metabolic disorders. Disorders such as propionic academia and methyl malonic academia are multisystemic disorders that will need dietary restrictions and metabolic control even after LT. Primary hyperoxaluria may result in excessive bleeding during surgery due to oxalate deposition in the blood vessels that prevent vasoconstriction. Also conduction defects and cardiomyopathy are a concern in hyperoxaluria. Depending on the disorder, an individualised plan is made for each patient, including dextrose infusion during fasting, cardiac assessment, continuing routine medications, use of emergency drugs for metabolic crisis (e.g. sodium benzoate and phenylbutyrate), avoiding lactate containing fluids, avoiding albumin infusions in amino acid metabolism disorders and feeding protocols. The discussion of the details of management of individual metabolic disorders is beyond the purview of this chapter.

28.7 Conclusion

In summary, a thorough evaluation of a paediatric patient for liver transplantation is the cornerstone of good transplant outcomes. This is usually achieved only with the involvement of a multidisciplinary team that understands the unique challenges

posed by the variety of paediatric liver diseases and the issues specific to liver transplantation in children.

Key Points

- The key to a successful outcome in paediatric liver transplantation is a careful and thorough multidisciplinary team assessment of the child by team members who have expertise and experience in dealing with paediatric liver diseases and transplantation.
- The transplant coordinator plays a central role in bringing the team together and ensuring adequate assessment and preparation of the patient.
- Some of the key aspects of evaluation of paediatric liver transplant candidates include nutritional rehabilitation, adequate screening for active and latent infections, verifying immunisation status, updating vaccinations, understanding the unique cardiopulmonary and anatomical aspects of paediatric liver diseases/transplantation and also understanding the multisystemic involvement of some of the end-stage paediatric liver diseases and liver-based metabolic disorders.

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