Challenges in Pediatric Liver Transplant

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35.1 Introduction

Liver transplantation in pediatrics is a hard-won victory after the contribution from the advanced technologies and the surgical and medical expertise of the transplant team. However, considerable challenges still exist in terms of donor selection, complications following transplant and immunosuppressive barriers based on recipient's immune reactivity and immune tolerance. Creation of further improvised protocols and target-based strategies to deal early and delayed complications and to maintain long-term follow-up is still in a growing phase to meet the challenges of pediatric liver transplant. Besides robust infrastructure, advanced technologies, expertise in medical and surgical field, certain policies, protocols, and decisions need to be strengthened.

35.2 Journey till the Transplant

The child who is being taken as recipient due to an end stage liver disease embarks a unique journey from pre-transplant assessment to the post-transplantation. The first successful pediatric liver transplantation (LT) was done in 1967 by Starzl et al. [1]. Bismuth and Houssin were the first to describe the scope of reduced adult liver in the pediatric population. It was Strong who successfully transplanted the left lobe liver of the mother into her son (recipient). Since then, the science of living donor transplantation (LDLT) is ever growing crossing the obstacles one by one. With the advancement in surgical, anesthetic and medical techniques along with availability of newer immunosuppressive drugs - the outcome of LDLT have been improved worldwide. The most common form of LT performed in Asia, presently is LDLT. The factors which needs a meticulous consideration for this successful journey includes the following.

(a) Detection at the right time and timely referral.
(b) Risk identification and stratification.
(c) Donor Selection.
(d) Co-morbities management in the recipient.
(e) Technical and operational feasibilities.
(f) Successful graft uptake and survival.

35.3 Challenges in Pediatric Liver Transplant

The challenges in the pediatric liver transplant can be understood based on the age and the physiology of pediatric patients, transplanted liver

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{rejection, native liver disease, and surgical complications} post-transplant care (sepsis, drug toxicity) and those related to the underlying disease (recurrence of the primary disease in allograft) and many other contributing factors. Sometimes the weight of an adolescent child is more to fulfil the criteria to accept only a single lobe from one donor and hence dual donor are being selected for the two lobes of liver in the recipient to match the required graft recipient body weight ratio (GRWR).

The challenges include timely referral, selection criteria, small for size infant, nutritional status, vaccination status, difference in anatomy and size of vessels as compared to adults (portal vein, hepatic artery and hepatic vein), associated multisystem involvement (renal, brain, cardiac) operational feasibility, medical and surgical expertise, post-transplant intensive unit (ICU) care (including sepsis, immune suppression, post-surgical complications) post-transplant morbidity, longer life expectancy, physiological immaturity, adolescence issues, transition stage to adulthood, and quality of life as compared to the peers (Table 35.1).

1. Selection of pediatric LT candidates: The guidelines or the selection criteria of the pediatric LT candidates varies from center to center across the world. Although the guidelines given by North American Society for Pediatric Gastroenterology Hepatology and Nutrition (NASPGHAN) and American Association for the Study of Liver Diseases (AASLD) have clearly suggested regarding the evaluation and selection of the pediatric LT candidates. The factors such as age at diagnosis, other system involvement, metabolic liver disease, gender bias, distance from their native place to the specialized center, insurance types, and financial dilemmas besides other issues play key role in timely referral.

The commoner indications for LT for which the patient is being referred includes biliary atresia, metabolic liver disease, liver disease associated with other system anomalies like complex congenital heart disease, genetic causes of liver disease, inherited metabolic disease, and complex tumor of liver. The delay in referral not only worsens the ongoing disease but has a substantial impact on the vulnerable organs like brain development and overall growth, development and nutritional status of the child. Besides this pediatric population has lots of specificities which make them more vulnerable to the functional dis-

Table 35.1 Challenges

S. No.	Main challenges	Description
1.	Selection of patient and timely referral	Multiple factors affecting the selection criteria lack of understanding the value of in time referral
2.	Nutritional status	Malnutrition has a deleterious effect on post-transplant status
3.	Vaccination status	Vaccine preventable infections (VPI) are common post-transplant
4.	ABO incompatibility	Increased chances of rejection
5.	Operational feasibility	Advanced technology for assessment
6.	Medical and surgical expertise	Expertise in handling small for size children
7.	Post-transplant ICU care	Well-equipped pediatric ICU
8.	Post-surgical complications	Sepsis, rejection vascular, and biliary complications
9.	Immune suppression	Prolonged and severe side effects
10.	Post-transplant morbidity and mortality	Still higher rates of morbidity and mortality
11.	Physiological immaturity	Effect of metabolic and immune system on growth and development
12.	Adolescence issues	Delicate developmental period
13.	Transition stage to adult	Various psychosocial and socioeconomic issues
14.	Quality of life	Health related quality of life as compared to the peer group

abilities. The prognosis for pediatric LT is also challenging since the list of indications for the pediatric LT is vast but the sample size for the transplant is relatively small. The methods like PELD score to assess the morbidity and mortality of a child or extrapolating adult data to children are not the appropriate way to prognosticate as witnessed in many studies recently.

Despite the advancement in diagnosis and management of acute liver failure (ALF) in children, there is still inability to predict outcome in many cases. In a child presenting with ALF, the challenge is to determine whether the child has potentially treatable condition or LT is necessary and appropriate for the survival of the patient. The prognosis also depends upon the complications such as sepsis, cerebral edema, multiorgan failure, hepatic encephalopathy. Still there is a lack of robust criteria or tools to determine the survival or mortality in ALF. The existing scoring system such as King's College Hospital Criteria (KCHC) and Pediatric End Stage Liver Disease Score (PELDS) has its own limitations. KCHC is relevent only for acute liver failure patient whereas PELDS can be used for chronic liver disease in children. The two criteria KCHC & PELDS are not interchangable [2]. While our capacity to understand and deal with pediatric ALF is constantly improving it still remains a challenging entity. The short-term survival in ALF is good but the long-term survival remains poor as compared to the other indications. The timely referral to an experienced transplant center is the one of the most crucial factors altering the survival rates post-transplant [3]. LDLT with optimization of timing and less cold ischemia time has increased the survival rate.

The timely referral to LT centre is important. The process starts with Identification of patients by the referring unit in a standardized laid down manner. This will result in well timed transplantation and good outcome.

2. Nutritional Status of the child: Children with end stage liver disease offer a more complex challenge regarding the nutritional status, growth and development, cognition, psychosocial and neuro-development. Nutritional status at liver transplant is an important prognostic factor in outcome and survival. Almost 60% of children undergoing liver transplantation are found to be malnourished. The factors contributing to the poor nutrition list includes frequent admissions, nausea, recurrent vomiting, altered gustatory sensations, ascites, altered mental status, and many more. The metabolic factors responsible are increased metabolic rate, increased resting energy expenditure [4], increased fat oxidation, elevated leptin and TNF-alpha, insulin resistance, decreased insulin like growth factor and reduced glycogen store. A malnourished child undergoing liver transplantation is at increased risk of infections with increase in morbidity and mortality. High calorie diet with protein supplements is given orally. In case of poor oral acceptance occasionally nocturnal nasogastric feeding protocol [5] is followed. High doses of fat-soluble vitamin (A, D, E, K) must be added along with water soluble vitamins in cholestatic liver disease. Increasing the protein calorie malnutrition score (PCM score) pre-transplant increases the survival rates post-transplant.
3. Vaccination and its impact: The incidence of vaccine preventable infections (VPIs) is more in transplant child as compared to general population. In the first 5 years post-transplant the incidence of hospital admission is one in six transplant recipients resulting in significant morbidity, mortality, graft injury, and cost. NASPGHAN (North American Society for Pediatric Gastroenterology, Hepatology and Nutrition) and AASLD (American Association for the Study of Liver Disease) recommend in their joint practice guideline on evaluation of the pediatric patient for transplant that "completion of all age-appropriate vaccinations should occur prior to transplantation and ideally before the development of end stage liver disease [6] and those children who have not completed the necessary vaccine schedule can receive vaccinations on an accel-

erated schedule. Immunizations are a minimally-invasive, cost-effective approach to reducing the incidence of VPIs. The importance of vaccination in pre-transplant phase is crucial because of increased immunogenicity of the vaccines given before the initiation of immunosuppressive drugs. Live vaccines are not indicated due to the risk of acquiring the disseminated vaccine strain disease in an immunocompromised host. Ideally a transplant should not occur until at least 4 weeks [7] following live vaccine administration.

4. ABO incompatible liver transplantation (ABOi LT): It is also one of the challenges which is being optimally managed by breaking the ABO barrier before LT. The recognition of the blood group antigens by recipient immune system can cause complications and graft loss in unmatched liver. As the blood group antigens exist on bile ducts epithelium, the chances of progressive intrahepatic bile duct injury are more [8]. The development of anti--A/B antibody reducing immunosuppressive protocols including plasmapheresis, immunoglobulin, and use of immunomodulators such as rituximab which have made the outcome after living donor (LD) ABO incompatible LT equivalent to that achieved with LD ABO-compatible (ABO-c) [9] (Fig. 35.1).
5. Operational Feasibility: The availability of the latest imaging apparatus using the modern techniques is required to precisely assess the finer anatomical details of the vessels. An effective pre-operative imaging evaluation provides a broad understanding of the vascular size and anatomy of celiac axis, and portal vein, hepatic veins, inferior vena cava besides the parenchymal status and morphology of liver. The ultrasound doppler and CECT with arterial phase sequences provides the information regarding any anatomical variants and accurate vascular measurements. The diameter of portal vein can be measured at the probable anastomosis level which can help us in assessing the chances of portal vein stenosis.

The classification of hepatic artery anatomic variants given by Michel has 10 sub-types, the sub-types II, III, V and IX are most significantly associated [10] with LDLT. In children the multiple arterial feeders in the grafts can cause poor perfusion of the graft. This may require creation of an alternate interposition graft between aorta and hepatic artery for an alternate inflow. Hepatic artery variants usually do not affect liver transplant but only in case the right hepatic artery arises from the superior mesenteric artery which requires for bench reconstruction.

6. Medical and Surgical expertise: The innovative and advanced surgical techniques over the last few years have overcome the hurdles of finding the size matched donors especially in small children. There is tremendous improvement in the graft and patient survival at 1 year after liver transplantation of more than 85%. The long-term survival of these patients is due to fair graft function despite complications. The need for re-transplantation has been decreased significantly. Over the years the surgical skillful techniques of using split, reduced

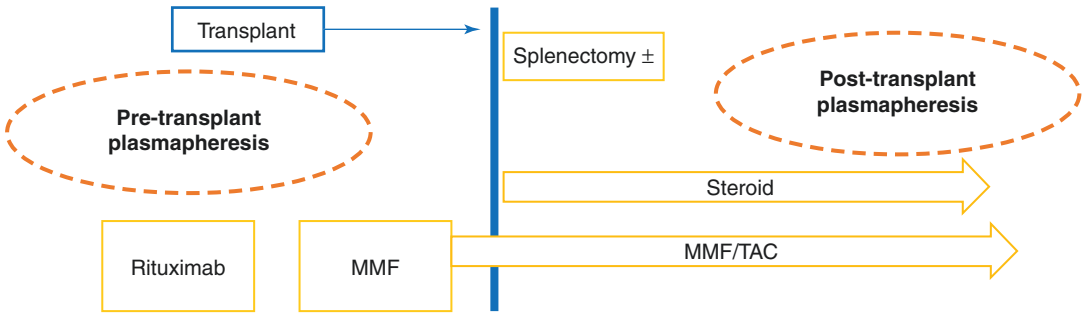

Fig. 35.1 ABO-Incompatible transplant

and living related transplantation have increased the pool and the survival of liver transplantation in children The surgical expertise has managed the technical challenges including vascular anatomy, sufficient volume for metabolic demands of the patient, and biliary drainage. The surgical skills in using the split liver from deceased donors and partial grafts from living donors has resulted in better and prolonged graft viability. The use of a left lateral segment graft (segments II and III) enables to do away the discrepancy of donor to recipient size ratio. For very small babies a further reduction of the left lateral segment is possible to provide a single segment graft (segment II or III). Early surgical interventions for post-operative bleeding, hepatic artery thrombosis or the hepatic or portal vein obstruction often needed for immediate surgical revascularization for salvaging the graft. The uncommon complications like bowel perforation and phrenic nerve injury may also require the surgical expertise for correction-although rarely required [11]. All the above surgical interventions are incomplete without the expert medical management under the guidance of the team headed by pediatric hepatologist.

7. ICU care post-transplantation: The surgery affects almost every system of the body. The patient is shifted to critical care unit immediately after the transplantation with or without tracheal intubation. The intensive critical unit stay is usually directly proportional to the time of extubating after surgery. The early weaning from ventilator is advocated if the patient is hemodynamically active. In patients of long-standing portal hypertension pulmonary vasodilatation results in shunting which leads to desaturation and hence hepatopulmonary syndrome which may require high positive end expiratory pressures keeping the target spo2 > 92% [12]. The other pulmonary complications include pulmonary edema, pleural effusion (right more than left), atelectasis, ventilator associated pneumonia, and very rarely acute respiratory distress syndrome.

Sepsis is the leading cause of morbidity post-transplantation. The infections probably result from donor, post-operative wounds, central venous catheter and intra-arterial catheter and lower respiratory tract from nosocomial sources. Sepsis is frequently encountered and one of the most dreaded complications which can increase the mortality rate. In suspected nosocomial infections hospital culture-based protocol is followed. Central catheters and fungal infection on prolonged antibiotics are also an issue for which vigilant protocols are followed. The feasibility between the immunosuppressant and antibiotics are to be tightly regularized. Serial CRP, procalcitonin, and blood culture plays the pivotal role in upgrading the antibiotics and antifungal drugs accordingly.

Another important parameter in children to be monitored is hemodynamic stability. The volume status of the child depending upon the total intake (oral and intravenous) and output (urine and abdominal drain or aspirates) is an important tool to assess the hemodynamic stability. The hemodynamic status can be measured using invasive to non-invasive methods. The invasive methods include intra-arterial blood pressure monitoring, cardiac output monitoring, and other methods which varies from center to center. The clinical states which may affect the urine output status of the child and indirectly affecting the hemodynamic stability includes hepatorenal syndrome and syndrome of inappropriate antidiuretic secretion (SIADH). To obtain the optimal hemodynamic status of the child requiring fluids, inotropes or vasopressors for optimum cardiac output, the clinical and advance hemodynamic monitoring guides to monitor the actual fluid status.

The electrolytes imbalance is very crucial and need a careful monitoring in post-transplant child. The common electrolyte disturbances seen in post-transplant child are as follows [12].

Electrolyte imbalance needs to be closely monitored and carefully addressed to avoid potential harmful effects like hemolysis, cerebral,

Table 35.2 Electrolyte disturbances

Electrolyte abnormality	Mechanism
Hyponatremia	Common in end staged liver disease. Fluid with high sodium resulting in rapid increase should be avoided
Hyperkalemia	Ischemia -perfusion process during transplant
Hypocalcemia	Citrate in blood products given during surgery chelates calcium
Hypophosphatemia	Increased uptake by regenerating hepatocytes, intracellular shifts
Transient hyperglycemia	Additional insulin infusion may be required

neuromuscular, and myocardial irregularity (Table 35.2).

The neurological complications account for 13–43% in post-transplant children observed in a 1 year follow-up study [13]. The complication usually occurs in first 2 weeks post-transplantation. The commonest manifestation is seizure which is frequently of generalized tonic-clonic variety. The probable causes include hypoglycemia, hypomagnesemia, hyponatremia. Cerebral infarction, hypertension, posterior reversible leukoencephalopathy syndrome (PRES), and adverse effects of immunosuppressive drugs. The modalities of investigations include electroencephalogram (EEG) and brain imaging. The differential diagnosis includes prolonged unconsciousness due to the use of benzodiazepines (Hepatic insufficiency prolongs half-life), intracranial hemorrhage, and meningitis. The antiepileptic of choice is levetiracetam [14] because it does not have liver metabolism and minimum drug interactions.

Another area of pediatric intensive unit care is gastrointestinal (gi) involvement in terms of high gastric aspirates or a paralytic ileus. Such complications sometimes might need re-exploration.

The nutrition of the child even post-transplantation is a big challenge. The aim of 120% of basal energy expenditure and protein supplementation in the range of 1.0–1.3 g/kg/day is fulfilled to promote good wound healing and hepatocyte recovery post-liver transplant [4]. Glucose infusion rate (GIR) should be around 2–3 gm/kg body weight per day of glucose with the frequent sugar monitoring and keeping the blood glucose range between 140 and 180 mg/dl [15]. The role of total parenteral nutrition (TPN) is reserved only in the cases where the cough and swallow reflexes are compromised. The enteral nutrition should be initiated within 12–24 h post-liver transplantation or as soon as possible to prevent the atrophy of intestinal cells and maintain the structural and the functional integrity of the gut. The other advantages of early enteral feeding include prevention of translocation of microorganisms, prevention of bile stasis, and stimulation of portal blood flow.

Late complications. Post-surgical complications:

(a) Early.

- Acute rejection: Acute cellular rejection as a complication usually occurs between 7 days and 6 weeks postoperatively. It is less common in infants (20%) but increases to 40–50% in older children. In majority of cases, it responds with increase in dose of immunosuppression and high dose of steroids.
- Sepsis: It is one of the dreaded complications following transplant. Bacterial infections are common soon after transplant and are related to pretransplant status of the patient, malnutrition and lowered immunity secondary to immunosuppression, malnutrition and pretransplant status of the patient. In suspected nosocomial infections, hospital-based culture protocols are followed. Fungal infection due to prolonged use of broad spectrum antibiotics and Catheral Related Blood Stream Infection (CRBSI) require stringent protocols.
- Vascular thrombosis and venous outflow obstruction: Portal vein thrombosis occurs in 10–40% in post-Kasai biliary atresia patients usually secondary to narrow fibrotic portal vein. Hepatic artery thrombosis is consid-

ered as one of the most devastating complications and it may cause graft loss with increased morbidity and mortality without immediate thrombectomy either by interventional radiology team or surgery [16]. Re-transplant may also be required in these cases. The smaller size of vessels in children make them more prone to this complication as compared to adults. The hepatic artery thrombosis may result in biliary necrosis secondary to ischemia leading to biliary strictures. Hepatic vein stenosis resulting in outflow tract obstruction may present with ascites.

- Biliary Complications Early biliary complications can occur anytime within 12 weeks of transplant. These complications can be biliary leaks, calculi, obstruction or strictures. These complications are commonly observed in reduced size graft recipients. Dysfunction of sphincter of oddi, although rare but is also a documented cause of biliary complications.
- Surgical complications: This includes sudden intra-abdominal hemorrhage due to a surgical cause like slipped ligature which requires re-exploration. Gut perforation may also be seen especially in previously operated patients of biliary atresia with peritonitis.

(b) Late:

- These fall into two categories related to allograft itself sand those related to immunosuppressive drug (IS). These include late biliary stricture, EBV infection, late hepatic artery or portal vein thrombosis, post-transplant lymphoproliferative disease (PTLD), de novo auto immune hepatitis. Nephrotoxicity, hyperlipidemia, obesity, diabetes, hypertension, and hirsutism may occur sequential to immunosuppressive drugs.
- Immunosuppression: This is the critical step in liver transplantation which achieves the balance between allograft rejection and infection. The physiological differences between children and adult makes the use of immunosuppression in children more challenging and more complex. The differences in children as compared to adults includes as follows.
  - Pharmacodynamic and pharmacokinetics of the drugs in children based on their physiology.
  - Lack of clinical trials in children.
  - Incomplete immunization status makes prone towards VPI.
  - Challenges regarding adherence and transition to adulthood.
  - Continuous and close monitoring for the adverse effects and appropriate management of intercurrent infections.
  - Longer exposure period needs continuous assessment of impact on growth and development. The commonly used drugs are steroids, tacrolimus, mycophenolate mofetil, and newer renal protective drugs like sirolimus and everolimus. Under-suppression may lead to rejection which is responsible for graft dysfunction and is being commonly reported in children. It has been observed most commonly within first 6 months of transplant and late acute rejection being observed with non-adherence.

9. A variety of factors contribute to the challenges of immunosuppressive medications in infants and young children. Dispensing medicines as compounded suspension for exact medication concentration, unpalatability of drugs (especially for infants and toddlers) and interaction between supplements, nutrition and immunosuppressive drugs are the most difficult issues to tackle. The common challenges with immunosuppressive drugs are being tabulated (Table 35.3).

Another challenge in children being more prone towards Epstein–Barr Virus (EBV) infection

Table 35.3 Drug dispensing

S. No.	Compounding factor
1.	Dispensing drug as liquid and matching exact concentration
2.	Co-administration of drugs with milk, antacids, and iron may cause chelation of drugs
3.	Presence of food may alter the rate and extent of absorption. Example: Mycophenolate (MMF) to be taken empty stomach for optimal effect
4.	Certain medication needs to be refrigerated and suspension should be shaken before giving like MMF
5.	Children needs 2.7–4.4 times higher dose per kg to reach the same serum concentration
6.	In case of refusal to drug in toddlers nasogastric tube is put to ensure drug delivery
7.	Bone marrow suppression, gastrointestinal disturbances, QTc prolongation, nephrotoxicity, bone disease, and photosensitivity with IS drugs are commoner in children
8.	On-going steroids may lead to short stature, diabetes, hypertension, cosmetic changes (cushingoid facies and striae), mood swings
9.	Gingival and hirsutism are commoner in children with the use of cyclosporine
10.	Neuropsychological deficits and lower cognitive function due to disease and prolonged exposure to immunosuppressive drugs

and more likelihood of PTLD which require alteration in immunosuppressive goals. Immunosuppression following LT is usually high in the initial 3–6 months and gradually tapered thereafter [17]. Development of immune tolerance requiring no immunosuppression is still a subject of understanding in liver transplantation [18].

10. Post-transplant morbidity and mortality: After transplant the currently reported survival rates are more than 95% at 1 year and 85% at 10 years. Children lead a near normal life style including attainment of puberty and development of secondary sexual characteristics and acceptable reproductive life. However, timely and regular follow-up with doctor and frequent blood sampling cannot be ignored. In a series of 200 paediatric transplant from author's center in India, 1-year and 5-year survival rate was 94% and 87% respectively with no statistical difference between the children weighing less or more than 10 kg [19, 20].

11–14. (Physiological Immaturity, Adolescent issues, Transition into adulthood, and Quality of life) The liver transplant recipients who were small children may have challenges once they reach adolescent age. The challenges are not only physical but also psychological, emotional, social, and financial. The main concerns faced in adolescence are mainly the distorted body images, a low feeling for below average academic performance. The mood swings are due to phases of anxiety and depression for the future. In children frequent hospital visits, everyday medication can lead to behavioural issues. This can result in strained parent peer relationship and non adherence to drug regime. Because of the incomplete education, low physical strength makes them seek low profile job which again is an area of disappointment for them.

These challenges are to be tackled by regular counseling of the recipient child and the family by the health care professional. The family including the child may be kept in follow-up of psychologist for timely consult on behavioral and other relevant issues. The government needs to frame policies to provide jobs to liver transplant recipients with a security and a handsome amount to meet the financial challenges of the treatment. Non-government organization should assist such patients in getting the financial support for the long-term medication and daily living. The Ministry of Health needs to take steps to make the non-affording children to complete their studies and create window of opportunities for the kids undergone liver transplant under 18 years. Social isolation due to learning disabilities should be condemned.

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