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PEDIATRICS

VOLUME 23





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Hot Topics

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4 Pediatric Liver Transplantation: Progress in India

Akshay Kapoor, Anupam Sibal

ABSTRACT

Liver transplantation is now well-established therapy for children with acute liver, end stage liver disease and a variety of metabolic disorders. The first successful pediatric liver transplant in India was performed in an 18-month-old child with biliary atresia in November 1998 at Apollo Hospitals, New Delhi, India. That child remains well 15 years post-transplantation. Over the years, the indications have expanded and successful living related liver transplantation has been reported for acute liver failure and metabolic disorders such as Crigler-Najjar syndrome. Age and size are no longer barriers as babies as young as 6 months have been transplanted. Excellent survival figures have been reported in children weighing less than 7.5 kg. Fathers have now started to come forward as donors. Children from different parts of India and more than 20 countries have been transplanted. The average cost of a pediatric transplant in India is 12–15 lakhs. This is only about 1/5th to 1/10th the cost in the West. With 5 year survival rates of 90%, India has now become a major center for LT for international patients as well because of the high quality-low cost value proposition. With increasing acceptance of LT amongst the medical community and the public at large, there is now potential for the number of liver transplants to increase significantly so as to offer hope to the thousands of children who suffer from liver failure.

Keywords: Complications, End-stage liver disease, Extra Extrahepatic hepatic biliary atresia, Immunosuppression, Hepatocyte transplantation, Liver transplant tolerance, Post-transplant metabolic syndrome.

INTRODUCTION

Pediatric liver transplantation (LT) is considered an epitome of medical and surgical expertise and excellence across the globe. The evolution of the procedure from an experimental desperate attempt to a stream-lined surgery has revolutionized the treatment of children with end stage liver disease, acute liver failure and metabolic liver disease.[1]

Long-term data from centers across the world have shown encouraging survival figures. Published data from the Japanese and Korean registries (predominantly living related programs) have consistently shown 10-year survival figures of above 90%.[2,3] Recent published data from India has mirrored the success of programs worldwide.[4]

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In the West, approximately 2–3 pediatric liver transplants per million population are performed annually. At that rate, around 2–3000 children will need liver transplants in India every year. This estimate is likely to be representative, since the incidence of EHBA (1/12,000–1/18,000), which is the most common indication for LT, is similar throughout the world.

HISTORY OF PEDIATRIC LIVER TRANSPLANTATION IN INDIA

The first successful pediatric LT in India was performed at Indraprastha Apollo Hospital, New Delhi, in November 1998.[5]

While the first successful LT provided a much-needed impetus to establish transplantation in India, the first few years were full of challenges. Many children requiring LT were often referred late, as guidelines regarding referral to a specialized center were not available. The majority of children, who merited a transplant belonged to the economically deprived strata of the society and were financially incapable of affording a LT. In addition, a well-entrenched bias against the girl child and lack of cadavers limited the number of transplants.

However, with the passage of time and increasing success rates of the transplant programs, acceptability increased. Both the medical fraternity and the public at large now recognize LT as established therapy. The paradigm shift was possible as multidisciplinary teams armed with extensive international experience were supported by hospital managements who wanted to revolutionize health care in the country. In addition, newer surgical techniques, better intensive care and availability of excellent immunosuppressants compounded the gains of LT.

Since the first transplant for extrahepatic biliary atresia (EHBA) in November 1998, several other firsts have been achieved. In 2008, the first successful transplant in India for Crigler-Najjar syndrome was performed.[6] Excellent results have also been reported in younger children. The 100% survivals for both graft and recipient in infants with weight less than 7.5 kg were reported in 2010.[7] The world's youngest domino liver transplant was reported from India in 2011.[8] Combined liver and kidney transplants (CLKT) are now being performed with regularity.

The last 7 years have shown a rapid growth in the number of pediatric LT recipients in India. There are six well-established pediatric LT programs in the country. Two programs perform above 30 predominantly living related liver transplants. The total pediatric liver transplants performed in India are in excess of 450.[9]

Philanthropic individuals and associations have come forward to support the cause of pediatric LT, pitching in with financial assistance and other resources to help the underprivileged. LT is also changing the social milieu, as was evidenced by fathers coming forward in greater numbers as donors.[9]

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INDICATIONS FOR PEDIATRIC LT

The indications are summarized in Table 4.1.

Acute Liver Failure (ALF)

Acute liver failure (ALF) has been defined in the consensus statement of Pediatric Gastroenterology Subspecialty chapter of the Indian Academy of Pediatrics (IAP) as follows:[10]

- Evidence of liver dysfunction within 8 weeks of onset of symptoms (neonates may have only deranged liver functions without overt symptoms)
- Uncorrectable (6–8 hours after administration of one dose of parenteral vitamin K) coagulopathy with International Normalized Ratio (INR) >1.5 in patients with hepatic encephalopathy, or INR > 2.0 in patients without encephalopathy
- No evidence of chronic liver disease either at presentation or in the past.

Table 4.1: Indications for pediatric LT

Indications	*Metabolic (primary hepatic)*	*Hepatocellular*
Cholestatic Biliary atresia	Alpha-1-antitrypsin deficiency*	Acute and subacute hepatic failure
Biliary hypoplasia (Alagille)	Tyrosinemia	Autoimmune liver disease (Type I and II)
Nonsyndromic biliary paucity	Wilson's disease	Chronic hepatitis B or C
Progressive familial	Neonatal hemochromatosis	Polycystic liver disease
Giant cell hepatitis/ neonatal hepatitis of unknown etiology	Glycogen storage disease type I, III, IV Cystic fibrosis	
	• Metabolic (Primary nonhepatic) • Crigler-Najjar syndrome Type I • Ornithine transcarbamylase (OTC) deficiency • Maple syrup urine disease (MSUD) • Familial hypercholesterolemia • Methylmalonic acidemia • Propionic acidemia • Citrin deficiency • Hyperoxaluria (combined liver and kidney transplant) • Atypical HUS (combined liver and kidney transplant)	
Nonresectable hepatic tumors		
Hepatoblastoma Hepatocellular carcinoma		

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ALF is a rapidly evolving, dynamic illness characterized by massive hepatic necrosis leading to an incapacitated liver which is incapable of performing its functions. LT is the only definitive therapy for ALF. It is, however, the timing of LT in the setting of ALF which is a topic of debate. Numerous prognostic and scoring systems are available for deciding the timing of LT in children with ALF. The King's College criteria and the Clichy's criteria have been accepted and validated as the most useful tools to establish the risk of death and need for LT among patients with ALF.[11] However, both these scores have the drawback of a low negative predictive value.[12] The IAP consensus statement recommends using an INR > 4 or factor V concentration of < 25% as the best available criteria for listing for LT. Contraindications for LT are active uncontrollable and untreatable sepsis, severe cardiopulmonary disease, multiorgan failure, mitochondrial disease and HE grade IV encephalopathy with severe neurological impairment.[13]

End Stage Liver Disease

The most common indication for pediatric LT in India and across the world is EHBA. To list a child with EHBA after hepatoportoenterostomy, the clinical course of the patient post-portoenterostomy must be taken into account. A Kasai operation is considered to have failed, if the bilirubin is more than 6 mg/dL, 3 months after the surgery. LT is indicated in babies with a failed Kasai who have developed synthetic dysfunction manifesting as hypoalbuminemia and deranged clotting. Recurrent cholangitis and bleeding secondary to portal hypertension are other indications. Early planning and preparation of the child for LT as soon as failure of the Kasai operation is established is necessary, with special attention to the prevention and correction of malnutrition and micronutrient deficiencies.

As many children with cirrhosis and portal hypertension have well compensated liver function it may be difficult to decide when to transplant. Useful indicators include:[14]

- Persistent rise in total bilirubin
- Prolongation of prothrombin time (INR >1.4)
- Fall in serum albumin < 3.5 g%
- Reduction in psychosocial development
- Failure to thrive despite nutritional intervention
- Chronic hepatic encephalopathy
- Refractory ascites
- Recurrent variceal bleeding despite optimal management
- Intractable pruritus
- Severe metabolic bone disease.

Metabolic Liver Disease

It includes a wide spectrum of disorders with variable effects on the liver and other organ systems of the body. They can be broadly classified into

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two subtypes. The first category includes diseases in which the primary defect is in the liver, and LT is performed primarily for hepatic complications (Wilson's disease, tyrosinemia, galactosemia, etc.). LT in such cases replaces the cirrhotic liver and also corrects the underlying metabolic defect.

The second category includes diseases wherein the liver is the source of the metabolic defect, but is structurally unaffected, i.e. there is absence of cirrhosis (Primary hyperoxaluria type 1, hypercholesterolemia, Crigler-Najjar syndrome, etc.). LT in such cases is done to correct the underlying gene defect. Combined or multivisceral transplantation might be required in such cases.

LT is usually performed for chronic Wilson's disease (WD), for decompensated cirrhosis refractory to medical therapy and for patients who present in ALF. A special prognostic score is available for children with WD and a score of 11 or more indicates high mortality, with 93% sensitivity and 98% specificity.[15] In tyrosinemia, LT is indicated, only if there is failure of NTBC therapy, ALF at presentation, hepatic dysplasia or hepatocellular carcinoma. In progressive familial intrahepatic cholestasis (PFIC), decision to transplant is taken, if there is established cirrhosis or intractable itching despite maximal medical therapy or surgical diversion.[16] In glycogen storage disorders type I, III and IV, LT is indicated if there is poor metabolic control, decompensated cirrhosis, or if multiple adenomas develop.

It is the diseases in the second subgroup that have expanded the ambit of indications for pediatric LT. LT prevents the onset of kernicterus in infants with Crigler-Najjar syndrome and prevents atherosclerosis and risk of sudden cardiac death in patients with hypercholesterolemia. CLKT is now the norm for patients suffering from hyperoxaluria and atypical hemolytic uremic syndrome.[17]

Contraindications to pediatric LT are detailed in Table 4.2.

Table 4.2: Contraindications to transplantation

Absolute contraindications
• Extrahepatic malignancy considered incurable by standard oncologic criteria
• *Sepsis:*
– Uncontrolled systemic infection
– Acquired immunodeficiency syndrome
• *Extrahepatic disease (incurable):*
– Irreversible massive brain injury
– Uncorrectable congenital anomalies affecting major organs
Relative contraindications
• Malignancy that is considered cured or curable by standard oncologic criteria
• *Sepsis:*
– Treatable infection
– Human immunodeficiency virus
• *Extrahepatic disease:*
– Progressive extrahepatic disease
– Substance abuse

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PRE-LIVER TRANSPLANT ASSESSMENT AND MANAGEMENT

Evaluation of a child for LT not only involves a detailed clinical and surgical assessment; it also involves a detailed socioeconomic assessment. Families need to be committed to the cause as a young child will need the support of a caregiver for the greater part of his childhood.

Aims of assessment for LT are to confirm the diagnosis and severity of disease, to define the patient's general medical status, to determine eligibility and priority for transplant and to arrange interim supportive care.

Table 4.3 highlights the pretransplant assessment tests (for the recipient) that are done as routine at our center.

MEDICAL MANAGEMENT OF CHILDREN AWAITING LT

Children with chronic liver failure (CLF) can have complex multisystem problems which need to be addressed prior to undergoing LT. This usually includes nutritional rehabilitation, completion of immunization and management of complications arising from liver failure (varices, ascites, hepatorenal and hepatopulmonary syndromes).

Table 4.3: Pretransplant assessment guidelines for recipient

- *Nutritional status:*
  - Height, weight, triceps skinfold, mid-arm muscle area
- *Identification of hepatic complications:*
  - Ascites, varices
- *Cardiac assessment:*
  - ECG, echo (contrast ECHO for HPS), chest X-ray
- *Respiratory function:*
  - Oxygen saturation, ventilation perfusion scan, lung function tests (in cystic fibrosis)
- *Neurological and developmental assessment:*
  - EEG, Development Assessment Scale for Indian Infants (DASII), Development Profile (DP- 2)
- *Renal functions:*
  - Urea, creatinine, electrolytes
  - Urinary protein/creatinine ratio
  - Cr EDTA (if available)
- Dental assessment
- *Radiology:*
  - Wrist X-ray for bone age and rickets
  - MRI/angiography (if portal vein anatomy equivocal)
- *Serology:*
  - Cytomegalovirus
  - Epstein-Barr virus
  - Varicella zoster
  - Herpes simplex
  - Hepatitis A, B, C
  - HIV
- *Hematology:*
  - Full blood count, platelets, blood group
- Immunization status

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Malnutrition in children with chronic liver disease has a multifactorial etiology (Fig. 4.1).

The severity of malnutrition correlates poorly with the degree of hepatic dysfunction as also with the micronutrient deficiencies. Various studies have shown that pretransplant nutritional status has a direct bearing on the success of LT, especially in children.[18] Therefore, modular feeds allowing protein (3 g/kg), carbohydrate (using glucose polymers) and fat (50% medium and 50% long chain triglycerides) contents to provide calories up to 150 kcal/kg along with fat soluble vitamins supplementation is recommended. Water soluble vitamin requirement is usually twice the recommended dietary allowance.

Immunization rates in children with CLF are universally low across the world. This statistic is more pronounced in India, where the competed immunization rate is 61% in normal healthy children under the age of 2 years.[19] Two-thirds of all prospective LT candidates referred to us were partially immunized. This is significant as the risk of infections increases significantly in the post-transplant period due to immunosuppressants. It is essential to make sure that routine immunizations are complete. Children undergoing LT should be immunized against measles, mumps, rubella, varicella, diphtheria, tetanus, *Haemophilus influenzae* type B, *Pneumococcus*, influenza, hepatitis A and B and polio. Vaccines should be given at least one month before LT to ensure seroconversion. If needed, the immunization schedule should be advanced.

Management of complications such as varices and ascites can be done by endoscopic ligation and adding diuretics. Coagulopathy is treated by giving enteral/parenteral vitamin K; active bleeding can be managed by giving fresh frozen plasma (FFP).

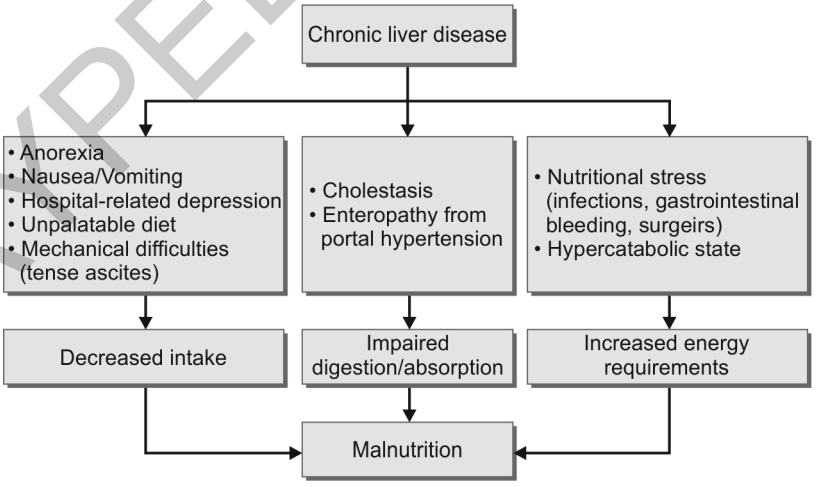

Fig. 4.1: Multifactorial etiology of malnutrition in chronic liver disease
Adapted from: Valeria R, Soriano HE, Ramalingam A, Klish William J. *J Pediatr Gastroenterol Nutr* 2000; 30:361-367.

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LIVER TRANSPLANT OPERATION

The liver graft can be obtained from either a cadaver or from a living donor. Cadaveric donation is common in the western world. Cadaver livers are retrieved from heart-beating donors that have fulfilled the criteria of brainstem death. Both the donor and recipient should have compatible ABO blood group. HLA matching is not necessary except to establish relationship between the recipient and donor.

The operation *per se* has three distinct steps:
1. The donor operation/native liver dissection
2. The back table operation/anhepatic phase
3. The recipient operation/revascularization.

The transplant procedure involves excision of the diseased liver by division of the common bile duct (or Roux loop, if there has been previous biliary surgery), hepatic artery, portal vein, and the inferior vena cava above and below the liver. The liver can be dissected to provide smaller grafts, based on the segmental anatomy of the liver as proposed by Couinad. Use of a left lateral segment graft (segments II and III) can overcome a donor to recipient size discrepancy of nearly 10:1. Use of the left or right lobes can overcome lesser degrees of size discrepancy. Further reduction of the left lateral segment is possible to provide a single segment graft (segment II or III) for very small babies. These hyper-reduced grafts have been used with successful outcomes.[20]

The following technical variants are in existence:
- *Split liver transplantation*: Split liver transplantation provides two grafts from a single donor, the left lateral segment for a child and the right lobe for an adult.
- *Monosegmental liver transplantation*: Reduced left lateral segment grafts and hyper-reduced left lateral segment grafts can be used in cases where the graft is too large to be fitted into the abdominal cavity without compromising its vascular pedicle.
- *Auxiliary partial liver transplantation*: This is a unique type of liver transplantation (the graft is placed with the diseased native liver *in situ*) that is performed where there is a possibility of native liver regeneration and immunosuppression withdrawal as in ALF. Careful, serial and meticulous follow-up with radiological screening and tapering of immunosuppression is required while the transplanted liver shrinks and degenerates and the native liver regenerates.

LIVING RELATED LIVER TRANSPLANTATION

Living related liver transplantation (LRCT) is the practical option in countries (including India) which do not frequently see cadaver donation. This has benefitted pediatric liver transplant programs immensely, as the left lateral

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segment can be safely taken from the parents without significant morbidity. The major advantages of LRLT over a cadaveric LT for the recipient are:

- Elective procedure
- Healthy donor
- Short cold ischemia time which reduces possibility of graft nonfunction
- Possible immunological advantage due to a related donor.

The donor must be a relative of the child and preferably have a compatible blood group. ABO incompatible liver transplants have also been performed successfully by using pretransplant conditioning with Rituximab and/or plasmapheresis.[21] All donors undergo a comprehensive medical and psychological assessment. Optimum health of the donor decreases post-transplant complications. A government committee scrutinizes both donor and recipient in person and gives the final approval for surgery. No organ transplant can be performed without prior approval of this authorization committee. The objective of the committee is to ensure that living donor transplants are performed as per Transplantation of Human Organs Act and Rules, 1994 and subsequent amendments made thereunder.

POSTOPERATIVE MANAGEMENT

The postoperative period is based on the cornerstones of ventilation, adequate tissue perfusion, management of sepsis and immunosuppression.[22]

Elective ventilation with adequate analgesia during the first 12–24 hours post-transplant helps the patient as well as the intensivist tide over metabolic derangements arising out of prolonged surgery. It also enables reliable radiological assessment of the new graft. Malnourished children and those with prior encephalopathy may require prolonged respiratory support.

Fluid shifts are the norm in liver transplant surgery. Children usually become hypovolemic during surgery, as they lose ascitic fluid and vasoconstrict due to intraoperative hypothermia and inotropes. Fluid replacement with colloids/crystalloids may be necessary to maintain a central venous pressure between 6–7 cm of water and an adequate urine output.

Prophylactic antibiotics with an adequate gram-positive, gram-negative and antifungal cover are started 24 hours preoperatively. Any change in the antibiotic is mandated either by the clinical condition or the surveillance cultures.

IMMUNOSUPPRESSION

The availability of potent immunosuppressants has contributed greatly to the success story of pediatric LT. While the initial treatment regimen of LT consisted of corticosteroids and azathioprine (AZT) with a graft survival of only 30%, the introduction of cyclosporin (CSA) in the early 1980s and

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tacrolimus (TAC) in the early 90s, revolutionized solid organ transplantation with 1-year graft and patient survival rates as high as 90%.[23]

The usual immunosuppressive regimen consists of TAC and prednisolone, with or without AZT or mycophenolate mofetil (MMF). Although cyclosporin has been successfully used safely and effectively in children, TAC-based immunosuppression is preferred because it has been associated with less acute rejection, less estimated corticosteroid-resistant acute rejection rates and fewer cosmetic side effects such as hirsutism. It also is associated with better long-term graft survival. There is no evidence for an increased risk of lymphoproliferative disease in children treated with TAC. However, TAC is associated with a greater incidence of *de novo* diabetes and gastrointestinal side effects as compared to CSA.[24]

Sirolimus is a macrocyclic triene antibiotic which prevents T-cell proliferation by inhibiting cytokine production in a manner different from TAC and CSA by interfering with the postreceptor signalling. It has a significant steroid sparing effect and considerably less nephro- and neurotoxicity.[25]

Interleukin-2 receptor antibodies are monoclonal antibodies, which selectively target the IL-2 receptors on activated T-cells, which is a key step in the development of cell-mediated immunity. Two antibodies are available, Basiliximab and Daclizumab, both of which are renal sparing and provide effective induction immunosuppression post-transplant in combination with a calcineurin inhibitor.[26] Long-term use including their incorporation into CNI sparing regimens in liver graft recipients with emerging nephrotoxicity or neurotoxicity has been validated. The emphasis is now to minimize immunosuppression at the earliest. Most centres advocate early steroid withdrawal by 3–6 months. Many recipients more than 2 years after LT maintain normal graft function (as determined by liver blood tests) on monotherapy with tacrolimus (levels < 6 ng/mL) or cyclosporine (levels < 100 ng/mL).

Despite the ability of current immunosuppressive agents to reduce the incidence of ACR, the long-term toxicity associated with current regimens now has become a major challenge for liver transplant recipients and is increasingly being perceived as an unmet clinical need. The most common side effects of these agents include increases in the incidence of bacterial and viral infections, nephrotoxicity with chronic renal impairment, *de novo* diabetes mellitus, hyperlipidemia, arterial hypertension, cardiovascular disease, osteoporosis, neurotoxicity, hematological toxicity, the development of *de novo* or recurrent solid organ cancers, and disease recurrence after LT.[27]

With the use of generic immunosuppressants and indigenous consumables, transplant programs such as ours have been able to substantially decrease costs and bring LT into the realm of affordability. At a cost of 12–15 lakhs, the pediatric LT cost is 1/10th of that being offered worldwide.

The immunosuppressant drugs and their dosing profiles are documented in Tables 4.4 and 4.5.

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Table 4.4: Immunosuppressant drug toxicities

Cyclosporin A	*Tacrolimus*	*MMF*	*Sirolimus*
Nephrotoxicity	Nephrotoxicity	Cytopenias	Hyperlipidemia
Neurotoxicity	Neurotoxicity	Gastrointestinal toxicity	Gastrointestinal—toxicity
Hypertension	Hypertension		Cytopenias
Hyperlipidemia	Hyperglycemia		
Hirsutism	Gastrointestinal toxicity		

Table 4.5: Dosage and monitoring

	*Dosage**	*Monitoring*
Cyclosporine A	4–6 mg/kg/dose twice daily	Trough levels (C0) 2 hours postdose (C2)
Tacrolimus	0.15 mg/kg/dose (within first 12 hours after abdominal closure), then 0.05 to 0.1 mg/kg/dose twice daily per oral	Trough level
Mycophenolate mofetil	15 mg/kg/dose twice daily or 600 mg/m^2 twice daily	• Trough levels (C0) • 1 hour postdose (C1)
Sirolimus weekly	15 mg/m^2 once daily	After 4 days of therapy, then C0 twice
		For 1st month, then weekly for 2nd month (Target: 5–15 μg/L)

* Recommended starting dose

COMPLICATIONS

The main causes of graft loss in the first week include primary graft nonfunction (PNF), thrombosis of the hepatic artery (HAT) or portal vein (PVT), overwhelming systemic sepsis, and multiorgan failure (<10%).[28]

Primary graft nonfunction of the graft is a rare but catastrophic complication of LT. It mostly requires re-transplantation. Causes include poor donor status, faulty organ preservation and retrieval, and technical or immunological complications in the recipient. Signs of poor graft function include hemodynamic instability, increasing lactate level, metabolic acidosis, and irreversible coagulopathy.

Early HAT has an estimated incidence of less than 10%. Risk factors include small recipient vessels, whole liver graft, right split liver graft, need for arterial grafting, prolonged cold ischemia time, and recipient ascites and hypercoagulable state. Endothelial damage due to arterial linking or liver edema is the principal pathology behind early HAT. Prompt recognition by judicious use of Doppler followed by thrombectomy and revision of arterial anastomosis might be lifesaving.

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Late HAT is often recognized as a missed early HAT wherein extensive collaterals saved the graft. Nonspecific transaminase elevations, *de novo* biliary complications, and a finding of parvus tardus could point towards late HAT. The graft dysfunction is minimal. It can be managed conservatively.

Portal vein thrombosis (PVT) has an incidence of 5% and is common in children with small hypoplastic veins. It can presents as graft dysfunction or unexplained *gastrointestinal* hemorrhage. A physiological shunt such as the Meso-Rex may be performed, if technically feasible.

Sepsis continues to be one of the leading complications in the post-transplant period. Pre-existing significant sepsis, insertion of central venous catheters, prolonged ventilation and poor graft function can all contribute to its increased incidence.

Acute cellular rejection (AR) is characterized by fever, irritability and vague abdominal pain. Since, the symptoms are nonspecific physicians have to rely on the biochemistry which shows an increased bilirubin level with transaminitis. AR may be seen in as many as 50% of the transplant recipients. Definitive diagnosis is made on liver biopsy, which is graded by the Banff criteria.[29] Characteristic changes include lymphocyte predominant portal infiltrates, cholangiolar damage, and endotheliitis. Treatment is with pulse methylprednisolone (20–40 mg/kg/day) intravenously over 2 or 3 days. If there is inadequate histological or biochemical response, treatment with methylprednisolone may be repeated but conversion to a more potent immunosuppressive drug may be required.

Chronic rejection (CR) is an uncommon complication in the pediatric setting. Its incidence is less than 5%. It can cause an insidious onset of graft fibrosis, ductopenia and eventual graft loss. Biochemical findings include an increasing bilirubin level and a raised GGTP in excess of ALT/AST. Treatment modalities include intensifying or changing the immunosuppressant regimen. Features of vanishing bile ducts on biopsy are characteristic. CR may result in need for re-transplantation.

Biliary complications are the most common structural post-LT complications and can occur at any time. They are easy to suspect as they lead to cholangitis and elevated GGTP levels on biochemistry. The strictures can be anastomotic or nonanastomotic. Anastomotic strictures can occur at the hepatico-jejunostomy site or at the ductal confluence. Nonanastomotic strictures are often the result of late HAT. Anastomotic strictures are short and respond well to endoscopic stenting, while nonanastomotic strictures are harder to manage. They can lead to progressive graft dysfunction.[20]

De novo autoimmune hepatitis (AIH) has been reported in the pediatric age group more commonly as compared to the adults. It is characterized by high circulating titres to the ANA antibody. Though controversy still persists of it being an alloimmune rather than autoimmune disorder, conventional treatment with steroids is the norm.

Certain diseases are known to recur in the allograft post-LT. Autoimmune hepatitis, hepatitis C (rarely an indication in children) and primary sclerosing

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cholangitis belong to this group. Continued use of steroids can decrease the rate of recurrence in children transplanted for autoimmune hepatitis. It is also important to note that patients who undergo LT for cystic fibrosis need continuous monitoring of other systems including the lung and heart.[30]

Cytomegalovirus (CMV) infection in a transplanted child can occur either as a *de novo* infection or due to reactivation of a previous infection. Primary CMV infection from a seropositive donor usually occurs early (1–3 months post-transplant) and is associated with invasive disease and increased mortality. Late CMV infections occur when pre-emptive chemoprophylaxis (ganciclovir) is withdrawn. They are milder in their clinical course and may manifest as a nonspecific viral syndrome or tissue-invasive disease. Nonspecific viral syndrome is characterized by fever and features of marrow depression (leukopenia, atypical lymphocytosis, and thrombocytopenia). Tissue-invasive CMV disease is manifested by visceral organ involvement (gastrointestinal tract, liver, and lungs). CMV has also been associated with rejection, fungal infection, and late patient and graft loss. Most centres give either intravenous ganciclovir or oral valganciclovir prophylaxis to CMV naïve recipients of CMV positive donors for a period ranging from 3–6 months. Established CMV disease characterized by *pp65* antigenemia and a positive PCR needs to be treated with intravenous ganciclovir till complete clearance is established by two negative reports two weeks apart. Alternate drugs like foscarnet and cidofovir should be given only in cases of suspected non response to conventional therapy.[31]

Epstein-Barr Virus (EBV) infection is known to cause a wide spectrum of disease ranging from an infectious mononucleosis such as presentation to post-transplant lymphoproliferative disease (PTLD). EBV infection should be suspected in post-transplant patients with prolonged fever and unexplained lymphadenopathy. A tissue biopsy should be performed for all cases in which the lesion can be identified on physical examination or CT/MRI scanning. EBV loads should also be monitored closely in such patients. Reducing immunosuppression is the first step in treating PTLD. Use of monoclonal antibodies such as CD20 antibody rituximab in conjunction with low dose corticosteroid therapy has been tried with variable success in EBV positive PTLD.[32]

Due to the use of calcineurin inhibitors (CNIs) such as TAC and CSA, the glomerular function of the recipient has been shown to decline. Renal dysfunction was reported at 30% in a cross-sectional study of studies of pediatric liver transplantation (SPLIT) and the Birmingham's group reported a 15% incidence in their >15 years survivors.[33] Children with pre-existing renal disease, e.g. those with Alagille syndrome, Caroli's syndrome and congenital hepatic fibrosis are more predisposed to renal dysfunction. Similarly, children with hepatorenal syndrome in the pretransplant period have a greater chance of renal dysfunction. LT centers are now more inclined to use renal sparing drugs such as IL-2R antibodies along with low dose CNIs.

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Using ACE inhibitors and Angiotensin II receptor blockers in children with concomitant hypertension and proteinuria has a protective effect on the eGFR.

The complications are summarized in Table 4.6.

LIFE AFTER LIVER TRANSPLANTATION

Most studies have shown an improvement in the health-related quality of life (HRQOL) of the children post-LT. However, the HRQOL is lower when compared to the general population. Children (< 7 years) who received hepatic grafts have progressed to puberty normally with normal linear growth and sexual maturation. Prepubertal children who underwent LT had impaired height velocities and sexual maturation. Parents of transplanted children have reported low scores for social interaction and scholastic performance, which picked up with time. Sexual maturation and fertility are achieved normally in pediatric liver recipients. Successful pregnancies have been reported with both CSA and TAC-based immunosuppression. Proactive family planning and contraception should thus be encouraged in all teenage transplant recipients to prevent sexually transmitted diseases.[34]

Issues of adherence and compliance to drug regimens and health check-ups remain important concerns. Studies have shown a more than four-fold incidence of noncompliance in children when compared to adults. Poor communication by transplant teams, low self-esteem in transplanted children, lengthy prescriptions and distance from the transplant center, all contribute in varying amounts to this serious issue.[35]

Another important facet is the threat of developing the post-transplant metabolic syndrome (PTMS). Diabetes, hyperlipidemia and obesity form the triumvirate of the metabolic syndrome. The use of steroids and CNIs has been ascribed to cause this lifestyle disease. However, poor-eating habits, sedentary lifestyle and lack of exercise contribute in equal measure. Madhwal et al found that the cardiovascular risk is increased by 64% in LT recipients.[36]

Table 4.6: Complications of pediatric liver transplantation

Early (< 1 month)	*Intermediate (1–3 month)*	*Late (> 3 month)*
PNF	Late HAT, PVT	Late PVT, Hepatic venous outflow obstruction
HAT, PVT	Biliary strictures	Chronic Rejection
Acute rejection	Late acute rejection	Steatohepatitis, Chronic fibrosis
Bile leak	Infections (Varicella, EBV, CMV)	Metabolic syndrome
Sepsis	PTLD	Infections (CMV, EBV)
Diarrhea	Decreasing GFR	Compliance and adherence issues
		Recurrence of disease activity
		De novo malignancies

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Study from Toronto has shown the risk incidence of PTMS to be 20% in the transplant group versus 3% in the general population. Prevention in the form of steroid restricted immunosuppression, exercise and good-eating habits can decrease the incidence of PTMS.[37]

ADVANCES IN PEDIATRIC LIVER TRANSPLANTATION

Tolerance

The ultimate goal of clinical transplantation is tolerance induction and acceptance of graft without need for life-long immunosuppression. Tolerance is defined as the lack of an immune response to the foreign antigens expressed by an organ allograft in the absence of ongoing immunosuppressive therapy. Mazariegos had shown that transplant recipients who were negative for donor specific antibodies (DSA) could be weaned of immunosuppression gradually versus those who were positive for DSA. Experience in LT recipients who have been poorly compliant with therapy or in whom immunosuppression has been withdrawn because of adverse effects suggests that it is possible in some cases to withdraw immunosuppression completely without precipitating graft rejection or loss.[38]

Hepatocyte Transplantation

Hepatocyte transplantation (HT) is a potentially promising alternative to whole organ liver transplantation so as to overcome the imbalance between patients and available organs. Clinical observations have demonstrated the safety of the procedure and of patients who have undergone (HT). However, most publications refer to clinical cases with no unanimity of criteria as to indications, methodology, cellular cryopreservation or assessment of the response to HT. The indications for HT include Crigler-Najjar syndrome, urea cycle defects, ALF, etc. The technique involves infusing ABO compatible cryopreserved hepatocytes manually into the recipient. The portal vein is usually chosen for children with metabolic disorders. Between 5 and 10% of the recipient's estimated theoretical liver cell mass is transfused. The portal pressure needs to be monitored consistently to prevent side effects.[39] Alternatively, the hepatocytes can be transfused into the splenic artery or the peritoneum. Immunosuppression protocols are similar to the ones used for conventional LT. The infusion of hepatocytes into the liver or spleen is a safe procedure which patients tolerate well. It has the advantage of not being a major surgical procedure. It has lower morbidity, mortality and cost and is a far less invasive therapy than conventional transplant, offering the possibility of maximizing resources because one single donor can be used for several recipients. Since the trials in HT are limited, there are still unresolved issues regarding appropriate therapeutic mass of hepatocytes and engraftment parameters which are yet to be standardized. Therefore, HT is yet to establish itself as a therapeutic alternative to LT.

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SUMMARY AND CONCLUSION

Pediatric LT is now a well and established therapy. Graft and patient survival have shown a continuous upward trend which can be attributed to medical, surgical, anesthetic management and ever-expanding immunosuppressant armamentarium. With the advent of LRLT and split liver grafts, the perennial shortage of organs is being addressed. Since procedure-related mortality is on the decline, the emphasis is on moderating and rationalizing immunosuppression and inducing a state of functional tolerance. The second area of concern is to identify lacunae in long-term post-transplant care, including prevention of kidney dysfunction, PTMS and *de novo* malignancies. LT programs in India have now come of age. Their success has shown that this model is reliable, replicable and affordable. Another welcome development is that our transplant centres have become referral centres for patients from across the globe.

KEY LEARNING POINTS

- LT is now an established therapy
- One-year and 5-year post-transplant survival rates are above 90% and 85%, respectively
- Success rate in children < 1 year of age and those weighing < 10 kg have improved
- EHBA and ALF are the most common indications for pediatric LT
- Expanding indications for LT include metabolic disorders and nonresectable tumors
- Hepatocyte transplant and liver assist devices are experimental
- Lifelong immunosuppression with regular monitoring of drug levels is required to prevent rejection
- Majority of transplanted children are able to lead a normal life with resumption of growth and participation in age-related activities.
- LT is now well established in India
- The first successful liver recipient from India has now completed 13 years of a normal life.

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