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Liver transplantation can be considered for any child with end-stage liver disease due to acute or chronic liver disease. The most common indications are biliary atresia, metabolic diseases, alpha-1-antitrypsin deficiency, tyrosinemia, Wilson's disease, and chronic active hepatitis. Prospective recipients are evaluated with regard to growth and nutrition, hepatic encephalopathy, and metabolic disease. The MELD system adapted for the pediatric population, PELD assesses 1) age at listing, 2) albumin, 3) bilirubin, 4) INR, and 5) growth failure based on gender, height, and weight. Preoperative management includes medical therapy to correct metabolic abnormalities, correction of malnutrition, delivery of normal "well child" care, and vaccination. Surgical options include reduced-size liver grafts, split, and living-related grafts. In the early postoperative period, small children and infants are particularly liable to develop vascular problems and bile leaks.

Keywords: liver transplantation; biliary atresia; Crigler-Najjar syndrome

CRIGLER-NAJJAR SYNDROME

Unconjugated hyperbilirubinemia

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Currently 1- and 5-year survival for children undergoing liver transplantation equals or exceeds that of adults. For children, in particular, the refinements in surgical technique, immunosuppressive therapy, and nutritional support have led to expanded indications for liver transplantation while dramatically reducing death due to organ scarcity in the pediatric age group.

Nevertheless, there are considerable differences in outcomes for specific pediatric subgroups. Small infants, particularly those that are chronically ill and malnourished, have the highest risk for postoperative surgical and medical complications including hepatic artery or other vascular thrombosis, early and late biliary complications, and infection. Older children and teenagers have the best outcomes.

Indications for Liver Transplantation in Children

Liver transplantation can be considered for any child with end-stage liver disease due to acute or chronic liver disease. The common indications for orthotopic liver transplantation in children are listed in Table 1. In addition, liver transplantation may be indicated for children with inborn errors of metabolism that do not cause liver failure but which produce severe morbidity or mortality and are corrected by liver transplantation (for example, ornithine transcarbamylase deficiency or Crigler-Najjar syndrome). Children with chronic liver disease due to systemic illnesses (i.e., cystic fibrosis) or primary hepatic malignancies may be appropriate candidates.

Evaluation of Pediatric Candidates and Timing of Liver Transplantation

Children with acute or chronic liver disease will often come to transplantation for indications similar to those seen in adults, including fulminant liver failure, complications of cirrhosis, portal hypertension, variceal bleeding, and encephalopathy. Health care providers for children should be aware of the consequences of liver disease that are specific to the pediatric population and indicate the need for early listing for transplantation.

Growth and Nutrition:

- Growth failure is a significant complication of liver disease.
- Children with otherwise compensated cirrhosis may have poor weight gain and/or linear

Table 1 | **Primary Diagnosis of 395 Children Undergoing Liver Transplantation**

Primary Diagnosis	Number of Patients	Percentage
Biliary atresia	187	47
Metabolic diseases (all types)	78	19
Alpha-1-antitrypsin deficiency	46	12
Tyrosinemia	12	3
Wilson's disease	9	2
Glycogen storage disease	5	1
Cystic fibrosis	4	1
Other	2	< 1
Fulminant hepatic failure	21	5
Cryptogenic cirrhosis	17	4
Familial cholestatic syndromes (Alagille syndrome, Byler syndrome, etc.)	16	4
Chronic active hepatitis (infectious, autoimmune)	10	2
Primary sclerosing cholangitis	9	2
Neonatal hepatitis	8	2
Biliary obstruction	3	< 1
Tumors	11	3
Miscellaneous	13	3

Data were compiled from published and personal series.

TYROSINEMIA

Disorder of tyrosine metabolism caused by fumarylacetoacetate hydrolase (FAH) deficiency

growth often followed by declining school performance or cognitive development.

- If malnutrition cannot be reversed with supplemental tube feedings or other interventions, liver transplantation should be performed as soon as possible.
- Due to the serious nature of growth failure and resulting developmental and cognitive delay in children, these findings qualify a child for higher UNOS listing status for transplantation.

Hepatic Encephalopathy:

- Encephalopathy must be evaluated in an age-appropriate manner, and therefore experience in assessing pediatric cognitive skills and developmental milestones is of critical importance.
- Ammonia levels correlate very poorly with degree of encephalopathy.

Metabolic Diseases:

- Metabolic diseases causing primary hepatic injury are, as a group, a common indication for liver transplantation in childhood. Children may also benefit from special exceptions to standard listing criteria in these cases if additional end organ or malignant risks are involved. Diseases in this category include tyrosinemia, cystic fibrosis, and alpha-1-antitrypsin deficiency, for example.
- Tyrosinemia is a disorder of tyrosine metabolism caused by deficiency of fumarylacetoacetate hydrolase (FAH). The enzyme defect results in injury to multiple organs via the generation of abnormal metabolites. In the liver, the primary site of tyrosine metabolism, the block of tyrosine catabolism produces a large variety of toxic intermediates that result in a range of phenotypes extending from neonatal fulminant hepatic failure to chronic relapsing liver disease. In all forms of disease, there is a sharply increased rate of hepatocellular carcinoma, estimated at 13%-37% in various studies, occurring even as young as 2 years of age. Medical therapy composed of dietary restrictions and supplements designed to redirect the formation of toxic intermediates has been very successful in stabilizing liver function; however, development of hepatocellular carcinoma is still a problem. Liver transplantation restores liver function, reduces extrahepatic organ injury, and normalizes the hepatocellular cancer risk to that of the general transplant population.

- Metabolic diseases with primarily extrahepatic manifestations may be cured by liver transplantation despite otherwise normal hepatic function. These diseases are accepted indications for liver transplantation and an area eligible for exception status within the UNOS system. Children with urea cycle defects, Crigler-Najjar syndrome type I, or primary hyperoxaluria, for example, have automatic exceptions to standard listing practices.
- Inborn errors of the urea cycle (for example, ornithine transcarbamylase deficiency) lead to recurrent hyperammonemia and irreversible brain injury, despite aggressive medical therapy. Liver transplantation is curative; standard listing criteria are inappropriate, as all other hepatic functions are normal.
- Crigler-Najjar syndrome: CNS injury from unconjugated hyperbilirubinemia is virtually unavoidable in Crigler-Najjar syndrome type I despite medical therapies.
- Primary hyperoxyluria is an inborn error producing oxylate crystals throughout the body that ultimately causes renal failure and cardiac arrhythmia. Early liver transplantation can prevent renal failure and preclude the need for combined renal and hepatic transplantation.

PELD

System of allocation of livers to children

PELD

The MELD system used for allocation of livers to adults in the United States has been modified for children; the following variables are assessed:

- Age at listing
- Albumin
- Bilirubin
- INR
- Growth failure (based on gender, height and weight)

The score for an individual patient can be calculated on the UNOS Web site (www.unos.org). In addition to this scoring system, UNOS policy has several advantages for pediatric recipients. The pediatric advantages were granted in response to concern that the small number of children waiting for liver transplant would be overwhelmed by the huge number of adults with equivalent higher scores, causing increases in deaths and lengthy waiting times. Lengthy waiting time has a disproportionate negative effect on young infants and children due to the impact of chronic liver disease on physical, cognitive, and social development. For these reasons, pediatric donors (donors under 18 years of age) are offered to pediatric recipients at an equivalent status or score before potential adult recipients. Furthermore, standard UNOS exceptions exist for specific metabolic diseases, and additional exceptions may be granted by the regional review boards of UNOS on request.

Preoperative Management

- Medical therapy to correct metabolic abnormalities, coagulopathy, ascites, vitamin deficiencies, and malnutrition as much as is possible is a critical part of the management of any child with liver disease.
- Malnutrition requires special attention, as optimization of nutrition protects brain development prior to transplant and also improves outcome after surgery. Nutritional support can start with institution of a high-density caloric diet, but often infants and young children require supplemental tube feedings. The choice of formula is important; a partially hydrolyzed protein formula with increased medium-chain triglycerides is generally selected to optimize absorption in the face of cholestasis.
- Meticulous attention to the delivery of normal "well-child" care is crucial.
- Vaccination: children awaiting liver transplantation should receive all standard immunizations (polio, DPT, HIB, HBV, MMR, varicella), with particular attention given to live virus vaccines (which are generally not administered to immunosuppressed individuals). Furthermore, additional vaccinations (pneumococcus, influenza, etc.) are generally indicated. Serologic evaluation for prior virus infections (particularly varicella, CMV, and EBV) are also of great importance and have considerable impact on posttransplant management and monitoring.

Table 2 | **Deaths Awaiting Orthotopic Liver Transplantation in 1990, 1995, and 1999**

Age of Candidate	< 1 year	1-5 years	6-10 years	11-17 years
1990	268/34/540	265/17/197	100/7/212	161/18/455
1995	337/45/359	389/23/132	208/5/51.6	287/14/110
1999	548/54/234	425/22/92	254/7/48	454/22/80

Data are shown as Patients listed/Deaths/Death rate per 1000 patient years at risk. (Adapted from the UNOS Web site: www.unos.org.)

BILIARY ATRESIA

Inflammatory/obliterative process of the extrahepatic bile ducts

Surgical Issues and Options

- In the early era of liver transplantation, the severe shortage of size-matched donors for infants and young children limited the application of transplantation to pediatric patients. Although the death rate on the waiting list remains significant for children, the risk of dying while waiting for a liver allograft has considerably improved for pediatric patients as shown in data in Table 2.
- Innovative surgical techniques including reduced-size liver grafts, split, and living-related grafts has resulted in dramatic improvements in organ procurement for even very small infants, and waiting times and deaths have been proportionately reduced.
- Biliary atresia
  - –Biliary atresia is the result of an inflammatory/obliterative process of the extrahepatic bile ducts of unknown etiology. Left untreated, this process results in obstructive cholestasis, biliary cirrhosis, and death in 100% of children by age 2 years. Management with the Kasai procedure can restore bile flow in up to 80% of cases with the anastomosis of a bowel limb to the hepatic capsule. Despite the improvement in survival following the Kasai procedure, many of these children will develop complications of portal hypertension in late childhood or adolescence (variceal hemorrhage, ascites) and require transplantation at that time.
  - –Biliary atresia is the most frequent underlying diagnosis in pediatric liver transplant recipients (see Table 1).
  - –Since almost all of candidates undergoing liver transplantation for biliary atresia will have had a prior portoenterostomy, the biliary anastamosis is made to the existing or newly revised intestinal "Roux-en-Y" limb rather than to the native common duct (by definition absent in biliary atresia).
- Even children with intact extrahepatic biliary structures may require implantation of the bile duct into a Roux limb due to size limitations or multiple donor ducts in a partial graft. Use of a Roux limb is an important feature, as future biliary problems cannot be approached by ERCP. Direct visualization of the biliary system can only be achieved by percutaneous transhepatic cholangiogram in these patients.
- Children may require vascular grafts or microsurgical techniques for the vascular anastomoses, and the risks of thrombosis (particularly of the hepatic artery) are greatly increased for small infants. Vascular bypass is generally not required for children or infants and is rarely performed (then only in larger teenagers).

Early Postoperative Management

The immediate postoperative management of pediatric liver graft recipients is directed toward continued support of liver function, critical care issues, and detection of early surgical complications.

- Vascular problems: Small children and infants are particularly at risk for vascular thromboses, so the routine includes frequent Doppler ultrasound to evaluate flow. Pediatric recipients are routinely treated with intravenous Dextran to prevent thromboses in the perioperative period and then receive oral aspirin for 1 year after transplantation.

- Bile leaks: Reduced size, living related, or split liver grafts have increased risk of bile leak and/or bleeding from the cut surface.
- Nutrition: Feeding can be difficult in small children and infants with midline liver placement, and short-term transpyloric tube feeding may be needed.
- Immunosuppression: In general, immunosuppressive management is similar to that in adults, although the arguments for restricting corticosteroids are even greater. Drug dosages need be considered for the child's weight.

Subsequent Management

This is similar to that of adult recipients in terms of monitoring for and management of changes in liver function, rejection, late biliary complications, and infections, but there are a few important exceptions.

- Nutrition is again of utmost importance in recovery and rehabilitation, though a standard formula can generally replace the specialized feedings used pretransplant. Very young children and infants who received tube feedings pretransplant often have delayed oral-motor development and may require feeding therapy in order to accept oral feedings.
- Occupational or physical therapy may be necessary for children and infants with a lifetime history of chronic liver disease. Older children generally recover very quickly and are eager to return to school and normal activities, often much faster than their adult counterparts return to work.
- Infections: Prophylaxis and surveillance for viral infections, particularly in those young children who did not have primary infections with EBV and CMV pretransplant, is an ongoing issue.
- EBV naive children undergoing liver transplant are at high risk of developing chronic EBV infection and post transplant lymphoproliferative disease if the primary EBV infection occurs on immunosuppression. The use of new quantitative PCR analysis for EBV has improved the monitoring for EBV activity. PTLD is discussed in this issue in the article "Graft Dysfunction" by Geoffrey H. Haydon, in addition to the standard reduction or elimination of immune suppression and addition of ganciclovir or acyclovir antiviral therapy.
  - –CMV-negative children will often receive CMV-positive grafts (especially if they receive a partial graft from an adult donor) and are at risk of CMV infection.
  - –Exposure to other childhood viral illnesses is an ongoing issue for these children; varicella exposure, for example, is a frequent occurrence. Children should be vaccinated for varicella prior to transplant; however, the vaccine is less effective if given under 1 year of age. Varicella antibody negative children should receive varicella immune globulin within 48 hours of known exposure (ideally within 12-24 hours) and are treated with intravenous acyclovir if clinical chicken pox develops. Even after an episode of clinical infection, most of these children will not develop antibodies and they are therefore at risk for repeated infection with subsequent exposures.
  - –Live vaccine administration to immunosuppressed transplant recipients is controversial, with standard recommendations against immunization. Even in those centers where MMR and/or varicella immunizations are given posttransplant, reduced response to vaccination is observed.
- Compliance: Compliance with medical therapy is a major issue with teenage liver graft recipients, especially those transplanted in infancy or early childhood. Many of these teenagers do not remember their transplant experience and are entering a time of personality turbulence, testing of limits, and have acquired a general sense of invulnerability that extends from the usual adolescent risk-taking (experimentation with drugs of abuse, exploration of sexuality) to failure to take medications. The response to this behavior must be tailored to the individual child and family and must take into account the social and cultural background. Parents, social workers, school guid-

ance counselors, and other resources are important partners in the effort to sustain delivery of medical care through adolescence.

- The adolescent patient: Children entering adolescence experience a variety of endocrinologic, physical, and psychosocial changes. In most cases, these young adults will be best served at a pediatric center, but care should be transitioned to an adult transplant center when medically and psychosocially appropriate.

Suggested Reading

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