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Pediatric liver transplantation

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ABSTRACT

Considerable strides have been made over the last several decades toward improving outcomes in pediatric liver transplantation. Refinements in surgical technique has allowed for the use of living donor and deceased donor split-liver grafts, thus expanding the pool of available organs and reducing waitlist mortality. The use of a multidisciplinary team continues to be paramount in the care of the transplant recipient. With improvements in overall graft and survival, indications for liver transplantation have also broadened. Currently, pediatric transplant patients have a 5-year survival of over 85%. Long-term morbidity is mainly associated with complications from immunosuppression and chronic rejection. Here we review indications for liver transplantation in children, surgical considerations, post-operative complications, and long-term outcomes.

Introduction

Pediatric liver transplantation has evolved significantly over the last 40 years with current long-term survival rates of greater than 85% in most large volume pediatric transplant centers (Figure 1).[1] The development and refinement of techniques to procure split-liver grafts from deceased donors and living donors have increased the availability of organs and decreased waitlist mortality. Currently, approximately 90% of pediatric patients on the waitlist eventually undergo a liver transplant.[2,3] The care of a liver transplant recipient is optimized through the use of a multidisciplinary team. With excellent perioperative outcomes, clinical efforts have shifted from preventing mortality to improving the morbidity associated with the immunosuppressive regimen such as chronic kidney disease or post-transplant lymphoproliferative disease (PTLD). This review will highlight and focus on current indications and surgical considerations in pediatric liver transplant as well as clinical outcomes and future directions (Table).

Indications for liver transplantation

In general, liver transplant (LT) is indicated when the risk of mortality from the native liver disease outweighs the overall risk of transplantation. Indications for liver transplantation in children are comprised of malignant and non-malignant conditions that also typically have a bimodal distribution. These include: (1) extrahepatic cholestasis (e.g., biliary atresia); (2) intrahepatic cholestasis (e.g., progressive familial intrahepatic cholestasis, Alagille's syndrome, sclerosing cholangitis); (3) metabolic disorders (e.g., urea cycle defects, Wilson's disease, tyrosinemia, alpha-1 antitrypsin deficiency); (4) acute liver failure; and (5) primary liver malignancy. Here we will review some of specific considerations for the more common indications for pediatric liver transplantation.

Cholestatic liver disease

Biliary atresia is the leading diagnosis in approximately 30–50% of the pediatric transplant recipients.[2,4] The majority of patient with biliary atresia undergo Kasai portoenterostomy to improve biliary drainage, however, a significant proportion of patients continue to have progressive liver disease (20–40% over a 10 year period) and go on to require LT.[2,5] In order to facilitate the transplant hepatectomy, it is important to note that at the time of the portoenterostomy procedure, full mobilization of the liver from the diaphragm and retroperitoneum should be avoided and hilar dissection should be kept to the minimum necessary extent in order to perform the procedure safely. This will minimize adhesion vascular formation, thus making hepatectomy at the time of transplant easier and with less blood loss. The vast majority of the patients following Kasai portoenterostomy fall into 2 main groups: those that develop end-stage liver disease (ascites,

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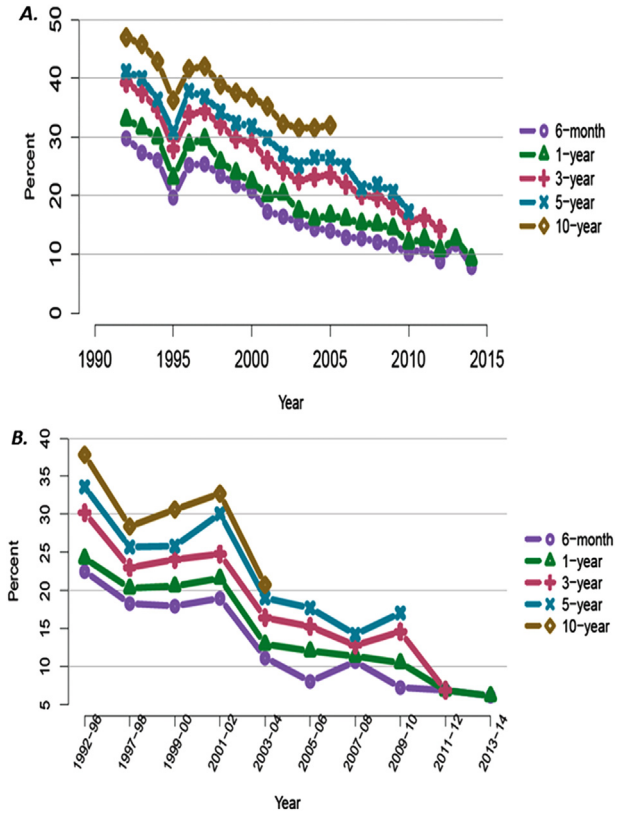

Fig. 1. (A) Patient survival among pediatric liver transplant recipients in the United States by age (2006–2010). (B) Graft survival among pediatric liver transplant recipients in the United States by age (2006–2010). Based on 2015 SRTR report.[17].

portal hypertension, and malnutrition) or recurrent cholangitis over the course of the first 1–2 years of life or those that have satisfactory biliary drainage but eventually develop cirrhosis and end-stage liver disease in late childhood or adolescence. A small cohort of patients may present with biliary atresia beyond 120 days of life and end-stage liver disease at which point portoenterostomy will not be of value and a primary transplant should be considered.

Alagille's syndrome (AS) is another cholestatic condition that may result in end-stage liver disease requiring LT. AS is an autosomal dominant disorder in which there is paucity of intrahepatic bile ducts.[6] While most patients can be medically managed by optimizing their nutrition, supplementation of fat soluble vitamins, and medical management of debilitating pruritis, some patients require external biliary diversion or an ileal bypass to divert biliary flow from the enterohepatic circulation for symptom management.[2] There is a cohort of patients that eventually develop end-stage liver disease and/or intractable pruritus and thus require LT.[6] It is important to note, however, that a thorough cardiac and renal evaluation is needed as anomalies of these organ systems is often associated with AS.

Progressive familial intrahepatic cholestasis (PFIC) is another inherited cholestatic disorder in which bile salt, phospholipid, or cholesterol transport genes are mutated such that protein function is either abnormal or absent.[7] PFIC accounts for up to 15% of neonatal cholestatic disorders and is therefore one of the more common indications for pediatric LT.[7] There are 4 subtypes of PFIC, the most common of which are PFIC 1 and 2, which typically present in early infancy and neonatal period, respectively. LT in patients with PFIC 1–3 has been reported. In a single center series of 23 pts of PFIC 2 or 3 patients, graft survival and overall survival were excellent at 89 and 100%, respectively.[8] Outcomes in PFIC 1 patients have not been as favorable secondary to aggravation of baseline high volume diarrhea, post-transplant steatosis, and eventual cirrhosis.[7]

Table
Indications for pediatric liver transplantation

Cholestatic disorders
Extra-hepatic biliary atresia
Intrahepatic biliary hypoplasia (Alagille disease)
Progressive familial intrahepatic cholestasis
Sclerosing cholangitis (primary and secondary)
Caroli disease
Congenital liver fibrosis
Langerhans cell histiocytosis
Metabolic disorders without cirrhosis
Urea cycle disorders
Cigler-Najjar syndrome
Hyperoxaluria
Gaucher's disease
Familial hypercholesterolemia
Glycogenosis type IA
Protein C deficiency
Organic academia
Wolman's disease
Metabolic disorders with cirrhosis
Alpha-1 antitrypsin deficiency
Cystic fibrosis
Wilson's disease
Tyrosinemia
Galactosemia
Neonatal hemochromatosis
Gestational alloimmune liver disease
Glycongenosis type IV
Niemann-Pick's disease
Acute liver failure
Hepatitis
Neonatal hepatitis
Hepatitis B
Hepatitis C
Hepatitis non-ABC
Autoimmune hepatitis
Primary liver tumors
Hepatoblastoma
Hepatocellular carcinoma
Hemangioendothelioma
Other
Budd–Chiari syndrome
Cryptogenic liver cirrhosis

Metabolic disorders

Patients with inherited metabolic disorders comprise a large subset of LT recipients. These disorders are typically a result of mutations that affect amino acid, metal, lipid metabolism, or mitochondrial function. Some metabolic diseases such as tyrosinemia, Wilson's disease or α1-antitrypsin deficiency can result in structural liver injury, acute liver injury, end-stage liver disease, or liver cancer. Other metabolic diseases such as urea cycle defects or Maple syrup urine disease (MSUD) result in systemic metabolic derangements with intact hepatic synthetic function. Patients with recurrent metabolic crises are at risk of severe neurologic injury and therefore LT is used to minimize the frequency and the risk of these crises. It should be noted that liver transplantation does not correct the enzyme deficiency in other organs and therefore, in certain metabolic disorders, ongoing metabolic derangement at the cellular level may continue to affect the nervous system. In general, LT in the setting of an inherited metabolic disorder is offered to those that can be cured or those patients whose medical management can be significantly facilitated with transplant.[9]