INDICATIONS FOR LIVER TRANSPLANTATION IN CHILDREN

The indications for liver transplantation in children are shown in Table 1. This is not to be considered an all inclusive list. Unusual conditions, and very rare metabolic diseases in children continue to be added to the indications for liver transplant. There are four major categories:

1. cholestatic diseases

2. metabolic diseases

3. fulminant liver failure

4. chronic active hepatitis

Other indications include malignancy, Budd Chiari syndrome, parenteral nutrition induced cirrhosis, trauma, and Caroli's disease.

GENERAL LISTING CRITERIA

Children should be listed for liver transplantation when there is evidence that hepatic decompensation is (i) unavoidable (based on knowledge of the history of the disease itself), (ii) imminent, or (iii) has already occurred. The end points which determine that OLT is required in children can include one, or more of the following:

1. intractable cholestasis

2. portal hypertension with or without variceal bleeding

3. multiple episodes of ascending cholangitis

4. failure of synthetic function (coagulopathy, low serum albumin, low cholesterol)

5. failure to thrive and malnutrition

6. intractable ascites

7. encephalopathy

8. unacceptable quality of life e g. school failure, intractable pruritis

9. metabolic defects for which liver transplantation will reverse life-threatening illness and/or prevent irreversible central nervous system damage.

10. Life threatening complications of stable liver disease e.g. hepatopulmonary syndrome

The decision to place a child on a deceased donor liver waiting list must also address several other factors:

1. appropriate confirmation of a diagnosis correctable by OLT

2. knowledge of the average waiting time for an organ for the child's weight, blood type and geographic area

3. assessment of any contraindications to transplantation

SPECIAL LISTING CONSIDERATIONS BY DISEASE CATEGORY

Discussed below are examples of several special circumstances based on disease category which influence the time of listing. This is not intended as a definitive policy covering all circumstances but rather as a guide to the more common special circumstances in pediatric OLT.

Cholestatic liver disease

(i) Obstructive cholestasis: e.g. biliary atresia and sclerosing cholangitis

(ii) Intrahepatic cholestatis: e.g. Alagille's syndrome, Byler's disease, familial cholestatic syndromes

Biliary atresia: is the most common indication for liver disease transplant in children comprising 60-70% of all candidates.

Natural history:

(1) with Kasai: even with timely performance of a Kasai procedure about 75% of children with biliary atresia will require transplantation. Children should be listed when any one of the general indications for transplantation are identified, or if at the time of the Kasai procedure, the surgeon judges that the operation has a high probability of failure.

(2) without Kasai: death is inevitable usually before the second birthday. Children should be listed as soon as the diagnosis is made.

Intrahepatic cholestasis

The presentation may be highly variable. Mild forms may be characterized only by pruritis and mild cholestasis and do not necessarily require transplantation. However, pruritis alone may be so severe as to impact on normal development. The severe forms of intrahepatic cholestasis for which transplantation is indicated early include Byler's disease, which is characterized by early deterioration with cirrhosis and some familial cholestasis syndromes. Alagille's syndrome is important because frequently cardiovascular anomolies are associated which occasionally are severe precluding transplantation.

Metabolic diseases

It is essential that the metabolic defect is well characterized before OLT is considered, including tissue localization of the defective or missing enzyme, assessment of extrahepatic manifestations of the disease and whether liver replacement will prevent further deterioration or improve dysfunction in extrahepatic organs. OLT should be offered if:

1. the metabolic defect is exclusively located to the liver e.g. Crigler-Najjar syndrome

2. the enzyme defect is also located in extrahepatic tissues but the clinical impact of the extrahepatic defect does not include the central nervous system and will be overridden by a normally functioning liver e.g. tyrosinemia.

3. the extrahepatic manifestations of the metabolic defect do not preclude OLT e.g. Wilson ☐s disease.

Metabolic disorders for which liver transplantation alone is not indicated include disorders of lipid metabolism, e.g. Gauchers disease, and lysosomal storage diseases e.g. the mucopolysaccharidoses, which are characterized by a wide spread enzymatic defects. Progressive extrahepatic disease especially the degenerative CNS disease can be expected after transplantation. Liver transplantation alone is not indicated.

Urea Cycle Defects:

The risk of profound central nervous system damage secondary to hyperammonemia is so high, that listing for OLT should occur soon after the diagnosis is made.[1-3]

Although medical management of elevated ammonia can achieve temporary improvement, severe elevations in ammonia can occur unpredictably causing profound central nervous system damage. All hospitalized children with this indication should be given highest priority.

Crigler-Najjar

In Crigler-Najjar syndrome, Type I phototherapy and tin protoporhyrin treatment may control hyperbilirubinemia and delay the onset of kernicterus for the first few months of life.[4-5] Listing for transplantation should occur early before any evidence that the bilirubin is escalating.

Tyrosinemia

37% of children > 2 years of age can be expected to develop hepatocellular carcinoma.[6] Preemptive transplant before the second birthday regardless of other indications for liver transplantation is indicated.

Cystic fibrosis

Cirrhosis, associated with cystic fibrosis may cause life threatening complications in the face of relatively mild lung disease. If pulmonary function is relatively well preserved and infection controlled, liver transplant alone is indicated and has been shown to benefit pulmonary function without serious infectious complications. [7]

Fulminant Liver Failure

O'Grady's criteria [8] identified age 11 years as an increase risk factor for death from fulminant liver failure. Therefore children with this indication should be listed as soon as encephalopathy reaches stage 2 and/or bilirubin escalates, protime is >20 or factor 5 levels < 30%.

Chronic active hepatitis with cirrhosis

This is a relatively uncommon indication for transplantation in children compared to adults. Children should be listed when one or more of the general indications for OLT are met.

Malignancy

Hepatoblastoma is the most common primary liver malignancy in children. The natural history and prognosis is different to hepatocellular carcinoma, the most common liver tumor in adults. Hepatoblastoma is locally invasive with late distant metastases and a better long-term prognosis. [9] Children with hepatoblastoma should be immediately listed if the tumor is confined to the liver but unresectable, or if tumor recurs after an initial resection.

Re-transplantation

The most common reason for re-transplantation in pediatric liver transplantation is hepatic artery thrombosis. [10] Hepatic artery thrombosis may present very acutely as graft failure and require emergent re-transplantation. If there is evidence of rapid liver decompensation the candidate should be relisted as soon as the diagnosis is made. Other indications include intractable acute rejection (rare), delayed graft function or primary non-function (rare), chronic rejection (unusual) and recurrent disease (rare). The general criteria for liver transplantation, absolute and relative contraindications all apply to re-transplant listing

Multiple organ transplants including liver

Liver transplantation combined with another organ transplant is indicated in several circumstances in pediatric candidates. The most common is combined liver/small bowel transplantation. Other examples include liver/kidney transplantation for primary hyperoxaluria, liver/lung transplantation in cystic fibrosis, and liver/heart transplantation for familial hypercholesterolemia. Other unusual circumstances may also apply. Combined liver with other organ transplants require individual case-by-case evaluation to determine the appropriate time of listing. In general, the time of listing is guided by the organ showing the most rapid life-threatening complications.

Table 1: Summary of metabolic disease for which liver transplantation may be indicated

DISEASE	DEFECT	INHERITANCE	COMMENTS
a_1 <antitrypsin deficiency	9a_1 <antitrypsin serum levels	Codominant	OLT restores a_1 -AT serum levels to normal, prevents lung disease
Wilson's disease	9biliary copper excretion	Autosomal recessive	OLT improves or reverses neurologic manifestations
Tyrosinemia	fumarylacetoacetate hydrolase deficiency	Autosomal recessive	OLT for fulminant neonatal form or OLT at about 2 yrs to avoid hepatocellular carcinoma
Urea Cycle Defects	Ornithine trans carbamylase deficiency Carbamoyl phosphate synthetase deficiency Arginosuccinate synthetase deficiency	x linked dominant Autosomal recessive Autosomal recessive	OLT may be needed in neonatal period to prevent irreversible CNS damage Variants may present in later childhood
Galactosemia	Galactose 1 - phosphate uridyl transferase deficiency	Autosomal recessive	May develop cirrhosis and risk of hepatocellular carcinoma
Glycogen Storage Diseases Type 1A Type 1V	glucose 6 phosphatase deficiency Brancher enzyme deficiency	Autosomal recessive Autosomal recessive	Dietary management alone sometimes successful. Risk of hepatic adenoma. Cirrhosis often early Amylopectin accumulation liver, heart, muscle may not be completely reversed by OLT.
Familial Hyper-cholesterolemia Type IIA	LDL receptor deficiency	Autosomal recessive	Early OLT may avoid cardiac arteriosclerosis. May need heart and liver tx.
Gaucher's Disease	Glucocerebrosidase deficiency	Autosomal recessive	Widespread extrahepatic enzyme defect. OLT alone does not prevent reaccumulation of storage material. ? OLT combined with BMT.
Niemann-Pick Disease	Sphingomyelinase deficiency	Autosomal recessive	A
Wolman's Disease	Acid lipase deficiency	Autosomal recessive	A
Cholesterol Ester Storage			

Disease	Acid lipase deficiency	Autosomal recessive	A
Crigler Najjar Syndrome Type I	Uridine diphosphate glucuronyl transferase	Autosomal recessive	OLT indicated when outgrows efficacy of phototherapy. Avoid fatal kernicterus.
Cystic Fibrosis	Abnormality chloride ion transfer gene	Autosomal recessive	Progressive pulmonary disease and infection limit usefulness of OLT alone
Hyperoxaluria Type I	Alanine glyoxalate aminotransferase deficiency	Autosomal recessive	Combined liver-kidney tx usually indicated
Defects of Mitochondrial Function	Medium and long chain acyl CoA dehydrogenase deficiencies. Reye's Syndrome	Autosomal recessive	OLT unlikely to reverse neurologic manifestations
Mucopolysaccharidoses	Lysomal storage diseases	Autosomal recessive (usual)	OLT alone does not prevent or resolve neurologic sequelae. ? role of BMT.
Neonatal Iron Storage Disease	Unknown	Variable	OLT needed in infancy usually
Hemophilia A Hemophilia B	Factor VIII deficiency Factor IX deficiency	x-linked	OLT indicated if transfusion-related disease also present
Protein C Deficiency	Low undetectable Protein C level	Autosomal recessive	Normal protein C levels post OLT
Disorders of Bile Acid Synthesis (e.g. Byler's Disease)	Unknown	Variable	OLT only in selected cases with associated end stage liver disease

Abbreviations: OLT = orthotopic liver transplantation
Tx = transplantation
BMT = bone marrow transplantation

References

1. Todo S, Starzl TE, Tzakis A, Benkov KJ, Kalousek F, Saheki T, et al. Orthotopic liver transplantation for urea cycle enzyme deficiency. Hepatology 1992; 15: 419.

2. Esquivel CO, Mieles L, Marino IR, Todo S, Makowka L, Ambrosino G, et al. Liver transplantation for hereditary tyrosinemia in the presence of hepatocellular carcinoma. Transplant Proc 1989; 21: 2445.

3. Mieles L, Esquivel CO, Van Thiel DH, Koneru B, Makowka L, Tzakis A, et al. Liver transplantation for tyrosinemia. A review of 10 cases from the University of Pittsburgh. Dig Dis Sci 1990; 35: 153.

4. Shevell MI, Bernard B, Adelson JW, Doody DP, Laberge JM, Guttman FM. Crigler-Najjar syndrome type I: Treatment by home phototherapy followed by orthotopic hepatic transplantation. J Pediatr 1987; 110: 429.

5. Kaufman SS, Wood RP, Shaw BW, Markin R, Rosenthal P, Gridelli B, et al. Orthotopic liver transplantation for type I Crigler-Najjar syndrome. Hepatology 1986; 6: 1259.

6. Weinberg AG, Mize CE, Worthen HG. The occurrence of hepatoma in the chronic form of hereditary tyrosinemia. J Pediatr 1976; 88: 434.

7. Noble-Jamieson G, Valente J, Barnes ND, Friend PJ, Jamieson NV, Rasmussen A, et al. Liver transplantation for hepatic cirrhosis in cystic fibrosis. Arch Dis Child 19944; 71: 349.

8. O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989; 97: 439.

9. Koneru B, Flye MW, Busuttil RW, Shaw BW, Lorber MI, Emond JC, et al. Liver transplantation for hepatoblastoma. The American Experience. Ann Surg 1991; 213: 118.

10. D'Alessandro AM, Ploeg RJ, Knechtle SJ, Pirsch JD, Stegall MD, Hoffmann R, et al. Retransplantation of the liver--a seven-year experience. Transplantation 1993; 55: 1083.