PERSONAL PRACTICE

Who needs a liver transplant? (new disease specific indications)

A Baker, A Dhawan, N Heaton

Department of
Paediatric Liver,
King's College
Hospital, Denmark
Hill, London SE5 9RS,
UK

A Baker
A Dhawan

Liver Transplantation
Unit, King's College
Hospital
N Heaton

Correspondence to:
Dr Baker.

Improvements in surgical techniques and the availability of reliable immunosuppression have produced excellent results for orthotopic liver transplantation (OLT). Eighty to 90% five year survival can be expected even for infants. The success of OLT has resulted in many more patients being considered, but with pressure to use OLT as a substitute for good clinical management of liver disease.

Results of OLT for children

Individual cases of successful OLT are currently alive and well with normal liver functions up to 24 years after the procedure, but significant cohorts did not survive until cyclosporin A became generally available in 1986. Survival curves have steadily improved but retain the same basic characteristics—most mortality in the first three months and the slope almost horizontal by one year; thereafter, annual graft and patient loss are less than 1% and 0.5% respectively. Thus, the long term prognosis appears to be good following OLT (table 1)¹⁻¹⁶ but factors such as nephropathy and malignancy may have a much greater influence later in the course of follow up than our current experience.

Pre-OLT factors influencing outcome include nutritional state, severity of decompensation of liver functions, and aetiology. Age appears only to be important for newborns. Timing of transplantation is important. If performed too early children may be denied a period of good quality life by death or graft function worse than the diseased liver, while transplantation in poor condition jeopardises the chance of recovery.¹¹

Chronic liver diseases and cirrhosis

Accepted non-disease specific indicators in children of need for OLT are derived from adult experience, including failure of synthetic function with a low serum albumin or prolongation of INR (international normalised ratio), or recurrent or uncontrollable variceal haemorrhage, deterioration of liver function after variceal haemorrhage, intractable ascites, or spontaneous bacterial peritonitis, hepatorenal or hepatopulmonary syndromes, and, rarely in children, chronic encephalopathy. Table 2 shows the criteria to define decompensation of cirrhosis. These indicators may themselves be disease specific—for example, conjugated serum bilirubin above 100 µmol/l is highly predictive of death within two years more than three months after Kasai portoenterostomy for biliary atresia, but it has no such predictive value in Alagille syndrome. Quality of life indicators such as intractable pruritus, extensive xanthomas, particularly if painful or restricting movement of hands or feet, and severe lethargy are also accepted. Failure of growth or to meet neurodevelopmental milestones due to liver disease are important.

In 1987, Malatck *et al* reviewed the outcome of patients with severe liver disease and developed a scoring system weighting factors to show high, medium or low risk of mortality within six months without OLT.¹⁷ Attempts to develop "quantitative" liver function tests of prognostic significance^{18 19} aimed at

Table 1 Outcome of liver transplantation

Reference	Patients (n)	Diagnosis (age/state)	Follow up	Survival (%)	
				Patient	Graft
1	38	FHF	Immediate	79*	—
2	28	FHF	Left hospital	79*	—
3	12	FHF	Median 18 months	67*	—
4	9	FHF < 3 months	Mean 22	55*	55
5	25	All < 1 year	4 months to 4 years	88†	—
6	12	AS	14 months to 5.5 years	91.7*	—
7	149	All < 1 year	1 year	81.9*	—
8	42	BA	1 year	80*	57
9	15	All < 1 year	1 year	91*	71
10	31	All > 1 year	3 years	70†	—
11	53	All	4 years	85†	76
12	100	BA elective emergency	4 years	60	53
13	76	High risk	4 years	49†	—
14	42	Low risk	4 years	90.5†	—
15	100	All	4 years	86†	72
16	103	All	5 years	77†	59
17	190	All	5 years	78†	76
18	64	BA	5 years	84†	69
19	76	All	8 years	77.3†	—
20	18	BA	8 years	82.3†	—

*Simple survival; †actuarial survival.

FHF, fulminant hepatic failure; BA, biliary atresia; AS, Alagille syndrome.

Table 2 Decompensation of cirrhosis

Coagulopathy—increased INR
Hypoalbuminaemia
Hyperbilirubinaemia
The development of ascites
The development of encephalopathy
Malnutrition—particularly with falling height standard deviation score

identifying children in need of OLT were unsuccessful, and the decision has remained a clinical one. It seems naive to believe that the same criteria could be applied to all diseases in the same way and with the same prognostic significance. This article aims to review published criteria for poor outcome in liver disease, and hence the need for OLT, to identify disorders that can be improved by medical management, and summarise current practice in our unit.

Biliary atresia (BA) is the most common cause of paediatric liver disease accounting for 40–50% of OLT in childhood. Kasai portoenterostomy is the preferred treatment and the emphasis remains on early diagnosis and surgery. Portoenterostomy should be viewed as complementary to, rather than competing with, OLT, which is reserved for children who fail to lose jaundice or who develop complications of cirrhosis. At least 30% of children will need OLT within two years of Kasai portoenterostomy because of a failure to excrete bile, leading to liver failure. Forty per cent of children undergoing portoenterostomy remain alive without transplantation at 10 years. Thus there is a group of about 30% of patients with BA aged 2–10 years who will come to OLT despite a “successful” Kasai operation. Moukartzel *et al* and Shepherd *et al* have shown separately that a height standard deviation score < -1 is associated with a significant increase in mortality, perioperative infections, and hepatic artery thrombosis after OLT.^{20–21} Short stature is probably associated with significant depletion of lean body mass with adverse consequences, particularly for the immune system. It is not clear if the increased risk can be reversed by intensive nutritional intervention. Impairment of height growth is, therefore, an indication for OLT.

Hepatopulmonary syndrome, a condition of central cyanosis due to lung perfusion abnormalities with normal or low pulmonary artery pressure associated with portal hypertension, is a progressive and ultimately fatal disorder. It has been associated with all cirrhotic conditions but particularly with BA splenic malformation anomaly,²² and it is completely reversed within three months following transplantation.²³ Older survivors with BA and portosystemic shunting (surgical or spontaneous) may develop chronic encephalopathy, taking the form of an insidious but progressive attention deficit disorder with disinhibition. Higher skills may be lost resulting in educational failure. The diagnosis may be proved using a behaviour diary and psychometric testing with a double blind trial of protein restriction versus administration. Rapid resolution is seen after OLT but our limited experience is that patients are left with an IQ in the range of 80–100. Recurrent life threatening ascending cholangitis is an uncommon complication of a successful Kasai operation. Liver function may be entirely normal between episodes although portal hypertension tends to progress. Investigations to exclude Roux loop stasis and intrahepatic collections are necessary. A trial of prolonged intravenous antibiotics given by

Hickman line is often successful, but should it fail OLT is indicated.

Acute decompensation may occur with apparently stable chronic liver disease leading rapidly to death, including in up to 6% of cases of BA. In progressive cirrhosis, portal vein flow may be reduced and the liver becomes increasingly dependent on the hepatic artery for its blood supply. As the cirrhotic liver becomes progressively stiffer, hepatic artery blood flow is reversed during diastole. This can be measured by ultrasound Doppler as the hepatic artery resistance index (RI) exceeding 1.0. Reduced hepatic artery systolic pressure due to dehydration or sepsis may then result in areas of liver infarction or ischaemic hepatitis. Children with RI > 1 have a median survival of about two months and should be considered as urgent candidates for OLT.²⁴

α_1 Antitrypsin deficiency is an infrequent cause of childhood liver failure, but the development of ascites, variceal bleeding or recurrence of jaundice herald rapid decompensation and require OLT.

Children presenting with autoimmune hepatitis may have decompensation of liver function, and require up to 12 months' treatment with immunosuppressive drugs to restore normal synthetic function. Expert management of immunosuppression will achieve earlier remission even of resistant cases. Once in remission, patients may be left with a stable cirrhosis and OLT may be deferred for many years.²⁵

A condition of unknown cause is giant cell hepatitis with Coomb's positive haemolytic anaemia. Initially it may respond to immunosuppression, particularly prednisolone and azathioprine. Liver failure ensues in more than 50% of cases. Following OLT, limited experience is that the disease always recurs within a short period of time.²⁶

Cystic fibrosis is relatively common and 40% of affected children will develop liver disease. Early fears that OLT would worsen lung infections in children with cystic fibrosis have proved to be unfounded, with nutritional status and lung function improving following OLT.^{27–28} The indications focus on the complications of portal hypertension rather than hepatocellular dysfunction. Anorexia and worsening malabsorption despite increasing administration of pancreatic supplements, abdominal bloating and pain, and failure to thrive despite nasogastric or gastrostomy feeding suggest an enteropathy related to portal hypertension. Patients with lung function at least 40% of normal can benefit from OLT. With increasing survival cystic fibrosis will become a more common indication, but heart, lung, and liver transplantation remains a high risk procedure.

Renal polycystic disease or medullary sponge kidney is associated with congenital hepatic fibrosis and bile duct ectasia (Caroli's disease). OLT is rarely indicated, but an infected biliary system will lead to rapid deterioration of liver function²⁹ with OLT required to control sepsis. Patients with Caroli's disease may require combined liver–

kidney transplantation despite stable liver function.

Acute liver failure

Acute liver failure is defined as the presence of coagulopathy despite parenteral administration of vitamin K and with intravascular coagulation excluded. In children, especially infants, encephalopathy is uncommon, occurs late, and is an ominous sign.¹ O'Grady *et al* showed that young age and a prothrombin time prolonged by more than 90 seconds were powerful indicators of likelihood of death, associated with a mortality in excess of 90%.³⁰ Badhuri and Mieli-Vergani showed that INR or prothrombin ratio above 4 at any point was associated with 92% mortality without OLT³¹ and is currently the criterion used for emergency listing of children. No specific diagnosis is possible before OLT in 40–50% of cases, which should not delay the procedure. Neonates with coagulopathy due to acute liver failure have a particularly poor prognosis. Early listing following the exclusion of contraindications is required.

Patients with liver failure from paracetamol overdose may survive with an INR > 4, but indications of a grave prognosis include grade III and IV encephalopathy, renal failure, and metabolic acidosis.³² A prognostic score for Wilson's disease has been developed by Mowat.³³ Scores < 6 are likely to be associated with full recovery following treatment with penicillamine and zinc. High scores > 9 are associated with inevitable death and indicate the need for urgent OLT. Children with scores of 6–9 may recover on treatment. The patients are listed for OLT and the score is repeated daily. A trend for the score to increase indicates the need for OLT.

Tyrosinaemia type I is an inborn error of metabolism that may present with acute liver failure in the first months of life. Liver transplantation was the only treatment available until the introduction of NTBC (2-(2-nitro-4-trifluoro-methylbenzoyl)-1,3-cyclohexanedione), an inhibitor of 4-hydroxyphenylpyruvate dioxygenase in the tyrosine degradation pathway.³⁴ Liver failure and renal dysfunction resolve and crises due to neurotoxicity of accumulated metabolites are abolished. The need for OLT in the acute phase is removed in all but the worst cases. It is not yet clear whether those left with cirrhosis will need OLT or whether there continues to be long term risk of hepatocellular carcinoma. NTBC does not prevent development of hepatocellular carcinoma in the knock-out mouse model of tyrosinaemia.³⁵

OLT is not indicated for patients with acute liver failure who already have strong evidence of permanent neurological damage secondary to cerebral oedema or intracranial haemorrhage, but grade IV encephalopathy is entirely recoverable. Patients with pupillary signs and borderline cerebral perfusion pressures have made good neurological recoveries. OLT is contraindicated if it will not correct the underlying disease, particularly if that disease also involves the neurological system or when the

original disease will rapidly and inevitably recur in the graft. Sodium valproate treatment has been described in association with acute liver failure. Patients may have previous soft neurological signs such as mild developmental delay or strabismus. Typically, coagulopathy is more prominent than jaundice at presentation. Some have a progressive encephalopathic illness, which may be a variant of Alper's syndrome.³⁶ The acute liver disease may have a better prognosis than suggested by INR alone but encephalopathy may be progressive, resulting in death over weeks or months, despite transplantation.

The most common condition causing acute liver failure involving organ systems outside the liver is haemophagocytic lymphohistocytosis (HLH). This condition of unknown aetiology is associated with immune deficiency and is characterised by histiocytic invasion of bone marrow, liver, and other tissues. Liver transplantation does not affect the underlying disease. Neiman-Pick C disease, an inborn error of cholesterol esterification, may present with acute liver failure in the first months of life. Patients have deposition of storage material in the liver, spleen, and bone marrow and most have it in the central nervous system.³⁷ Liver transplantation does not prevent progress of the neurological disease.

Management of symptoms

Alagille syndrome is a condition of biliary hypoplasia associated with cardiac defects and characteristic benign facial, eye, and spinal abnormalities that progresses to cirrhosis in up to 30% of patients. Cholestasis is the major complication associated with poor growth, severe itch, and fat soluble vitamin deficiency, significantly impairing the quality of life of the child and family. The most common cardiac lesion is peripheral pulmonary artery stenosis. When right heart pressures are significantly raised, risk of mortality at OLT appears to be up to 60%,³⁸ possibly because the heart is unable to increase output during liver reperfusion, and there is no cardiac reserve for any complication such as systemic sepsis. With milder cardiac disease, results of OLT are comparable with other indications.⁶ The cardiac effects of reperfusion may be simulated at cardiac catheterisation by infusion of dobutamine 10–30 µg/kg/min. A 50% increase in cardiac output may indicate sufficient cardiac reserve for OLT. Currently this forms our minimum requirement if the transplant is being performed for poor quality of life mainly because of the severity of the pruritis.

Tumours

Aggressive chemotherapy followed by resection has achieved 60%, two year survival in hepatoblastoma when previously it was less than 2%.³⁹ The key to long term survival appears to be removing the primary tumour. OLT is reserved for cases in which, after prolonged chemotherapy, the tumour remains unresectable. Living related donation may be preferable to permit OLT between courses of chemotherapy. Hepatocellular carcinoma is uncommon in

children. Tumours < 5 cm in diameter on contrast enhanced computed tomography are considered appropriate for OLT in adults. There is no long term published information on the outcome for children, but five year survival in selected adults is in excess of 60%.

Non-cirrhotic inborn errors of metabolism based in the liver

Metabolic conditions that are not associated with cirrhosis may have normal liver function and histology but cause severe and life threatening complications outside the liver. Important examples are Crigler-Najjar syndrome type I (CN1), primary hyperoxaluria type I (PH1), urea cycle disorders, homozygous familial hypercholesterolaemia, procoagulant conditions such as protein C and S and antithrombin 3 deficiency, and propionic and methylmalonic acidemias. In each of these, prolonged poor control of the underlying disease can result in complications that may persist despite successful OLT. Some resolution of neurological signs of CN1 can be expected but cerebral palsy and deafness will remain. In PH1, OLT can prevent the need for renal transplantation if it is undertaken when glomerular filtration is > 40 ml/min. Therefore, in all these conditions liver transplantation should be undertaken before complications have occurred, but families may be reluctant to allow a child to suffer the risks of OLT before symptoms are present.

Contraindications

Absolute contraindications to OLT are not stated unequivocally in the literature. Alpers's syndrome and HLH presenting with acute liver failure may be absolute contraindications, but individual patients with conditions such as HIV positivity, hepatic malignancies, Niemann-Pick C disease without neurological progression, and giant cell hepatitis with Coomb's positive haemolytic anaemia with good remission and low likelihood of recurrence in the graft may be considered for palliative OLT. Cerebral palsy is not an absolute contraindication if OLT will improve the child's and family's quality of life, and they appreciate that OLT will have no effect on neurological state. For ambiguous cases the discussion will focus on appropriate use of scarce donor organs as well as short and medium term outcome. At our institution the decision not to provide OLT is occasionally taken for individual patients, typically because the patient's clinical condition is so poor that survival is unlikely or a successful outcome would still imply an intolerably low quality of life. All such decisions are made after extensive discussion with the parents.

Conclusions

In 10 years OLT has progressed from a procedure in children only when they are about to die from their liver disease to one that can be offered for poor quality of life due to liver disease but without immediate risk of death. Early attempts to identify a point at which OLT is required using a single test have failed owing to

the diversity of the actions of the liver and hence manifestations of liver dysfunction. Clinical judgment—the mainstay of good medicine—has reasserted itself. Nevertheless, there are a lack of published data, even necessarily retrospective, on which to base clinical judgments. We need large collaborative studies, particularly of rare conditions, to determine the long term outcome of OLT compared with the prognosis of whatever conservative management is available.

- Rivera-Penera T, Moreno J, Skaff C, McDiarmid S, Vargas J, Ament ME. Delayed encephalopathy in fulminant hepatic failure in the pediatric population and the role of liver transplantation. *J Pediatr Gastroenterol Nutr* 1997;24:128–34.
- Castells A, Salmeron JM, Navasa M, et al. Liver transplantation for acute liver failure: analysis of applicability. *Gastroenterology* 1993;105:532–8.
- Tan KC, Mondragon RS, Vougas V, et al. Liver transplantation for fulminant hepatic failure and late-onset hepatic failure in children. *Br J Surg* 1992;79:1192–4.
- Bonatti H, Muiesan P, Connolly S, et al. Hepatic transplantation in children under 3 months of age: a single centre's experience. *J Pediatr Surg* 1997;32:486–8.
- Beath SV, Brook GD, Kelly DA, et al. Successful liver transplantation in babies under 1 year. *BMJ* 1993;307:825–8.
- Cardona J, Houssin D, Gauthier F, et al. Liver transplantation in children with Alagille syndrome—a study of twelve cases. *Transplantation* 1995;60:339–42.
- Inomata Y, Tanaka K, Okajima H, et al. Living related liver transplantation for children younger than one year old. *Eur J Pediatr Surg* 1996;6:148–51.
- Dunn SP, Weintraub W, Vinocur CD, Billmire DF, Falkenstein K. Is age less than 1 year a high-risk category for orthotopic liver transplantation? *J Pediatr Surg* 1993;28:1048–50.
- Chin SE, Shepherd RW, Cleghorn GJ, et al. Survival, growth and quality of life in children after orthotopic liver transplantation: a 5 year experience. *J Pediatr Child Health* 1991;27:380–50.
- Gauthier F, Chardot C, Branchereau S, et al. Urgent liver transplantation for biliary atresia: the experience in Bicetre. *Exp Med* 1997;181:129–38.
- Rodeck B, Melter M, Kardorff R, et al. Liver transplantation in children with chronic end stage liver disease. *Transplantation* 1996;62:1071–6.
- Yandza T, Gauthier F, Valayer J. Lessons from the first 100 liver transplantations in children at Bicetre Hospital. *J Pediatr Surg* 1994;29:905–11.
- Busuttil RW, Seu P, Millis JM, et al. Liver transplantation in children. *Ann Surg* 1991;213:48–57.
- Goss JA, Shackleton CR, Swenson K, et al. Orthotopic liver transplantation for congenital biliary atresia. An 11 year, single-center experience. *Ann Surg* 1996;224:276–87.
- Nagral S, Muiesan P, Vilca-Melendex H, et al. Liver transplantation for extra hepatic biliary atresia. *Exp Med* 1997;181:117–27.
- Eckhoff DE, D'Alessandro AM, Knechtle SJ, et al. 100 consecutive liver transplants in infants and children: an 8 year experience. *J Pediatr Surg* 1994;29:1135–40.
- Malatck JJ, Schaid DJ, Urbach AH, et al. Choosing a pediatric recipient for orthotopic liver transplantation. *J Pediatr* 1987;111:479–89.
- Burdelski M, Schutz E, Nolte-Buchholtz S, Armstrong VW, Oellerich M. Prognostic value of the monoethylglycineoxylidide test in pediatric liver transplant candidates. *Ther Drug Monit* 1996;18:378–82.
- Baker A, Balantine N, Girling A, Smith S, Kelly DA. The prognostic significance of caffeine half-life in saliva in children with liver disease. *J Pediatr Gastroenterol Nutr* 1995;20:196–201.
- Moukarzel AA, Najm I, Vargas J, McDiarmid SV, Busuttil RW, Ament ME. Effect of nutritional status on outcome of orthotopic liver transplantation in pediatric patients. *Transplant Proc* 1990;22:1560–3.
- Shepherd RW, Chin SE, Cleghorn GJ, et al. Malnutrition in children with chronic liver disease accepted for liver transplantation: clinical profile and effect on outcome. *J Paediatr Child Health* 1991;27:295–9.
- Davenport M, Savage M, Mowat AP, Howard ER. Biliary atresia splenic malformation syndrome: an etiologic and prognostic subgroup. *Surgery* 1993;113:662–8.
- Fewtrell MS, Noble Jamieson G, Revell S, et al. Intrapulmonary shunting in the biliary atresia/polysplenia syndrome: reversal after liver transplantation. *Arch Dis Child* 1994;70:501–4.
- Broide E, Baker A, Farrant P, et al. Increased hepatic artery resistance index predicts early death in children with biliary atresia. *Liver Transplant Surg* 1997;3:604–10.
- Gregorio GV, Portmann B, Reid F, et al. Autoimmune hepatitis in childhood: a 20-year experience. *Hepatology* 1997;25:541–7.
- Melendes HV, Rela R, Baker AJ, et al. Liver transplant for giant cell hepatitis with autoimmune haemolytic anaemia. *Arch Dis Child* 1997;77:249–51.

- 27 Noble-Jamieson G, Barnes ND. Liver transplantation for cirrhosis in cystic fibrosis. *J Pediatr* 1996;**129**:314.
- 28 Mack DR, Traystman MD, Colombo JL, *et al*. Clinical denouement and mutation analysis of patients with cystic fibrosis undergoing liver transplantation for biliary cirrhosis. *Am J Pediatr* 1995;**127**:881-7.
- 29 Starzl TE, Reyes J, Tzakis A, Micles L, Todo S, Gordon R. Liver transplantation for polycystic liver disease. *Arch Surg* 1990;**125**:575-7.
- 30 O'Grady JG, Alexander GSM, Hallyner KM, Williams R. Early prognostic indicators prognosis in fulminant hepatic failure. *Gastroenterology* 1989;**97**:439-45.
- 31 Badhuri BR, Mieli-Vergani G. Fulminant hepatic failure: pediatric aspects. *Sem Liver Dis* 1997;**4**:349-54.
- 32 Makin AJ, Wendon J, Williams R. A 7-year experience of severe acetaminophen-induced hepatotoxicity (1987-1993). *Gastroenterology* 1995;**109**:1907-16.
- 33 Mowat AP. *Liver disease in childhood*. 3rd ed. Oxford: Butterworths, 1994:327.
- 34 Lindstedt S, Holme E, Lock EA, Hjalmarson O, Strandvk B. Treatment of hereditary tyrosinaemia type I by inhibition of 4-hydroxyphenylpyruvate dioxygenase. *Lancet* 1992;**340**:813-17.
- 35 Grompe M, Lindstedt S, Al-Dhalimy M, *et al*. Pharmacological correction of neonatal lethal hepatic dysfunction in a murine model of hereditary tyrosinaemia type I. *Nat Genet* 1995;**10**:453-60.
- 36 Bicknese AR, May W, Hickey WF, Dodson WE. Early childhood hepatocerebral degeneration misdiagnosed as valproate hepatotoxicity. *Ann Neurol* 1992;**32**:767-75.
- 37 Kelly DA, Portmann B, Mowat AP, Sherlock S, Lake BD. Niemann-Pick disease type C: diagnosis and outcome in children, with particular reference to liver disease. *J Pediatr* 1993;**123**:242-7.
- 38 Tzakis AG, Reyes J, Tepetes K, Tzoracoleftherakis V, Todo S, Starzl TE. Liver transplantation for Alagille's syndrome. *Arch Surg* 1993;**128**:337-9.
- 39 Saxena R, Leake JL, Shafford EA, *et al*. Chemotherapy effect on hepatoblastoma. A histological study. *Am J Surg Pathol* 1993;**17**:1266-71.

Archives of Disease in Childhood—

[http:// www.archdischild.com](http://www.archdischild.com)

Visitors to the world wide web can now access the *Archives of Disease in Childhood* either through the BMJ Publishing Group's home page (<http://www.bmj.com>) or directly by using its individual URL (<http://www.archdischild.com>). There they will find the following:

- Current contents list for the journal
- Contents lists of previous issues
- Members of the editorial board
- Subscribers' information
- Instructions for authors
- Details of reprint services

A hotlink gives access to:

- BMJ Publishing Group home page
- British Medical Association web site
- Online books catalogue
- BMJ Publishing Group books

The web site is at a preliminary stage and there are plans to develop it into a more sophisticated site. Suggestions from visitors about features they would like to see are welcomed. They can be left via the opening page of the BMJ Publishing Group site or, alternatively, via the journal page, through "about this site".