REVIEW

Paediatric liver transplantation: the surgical view

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Liver transplantation is the accepted treatment for a wide variety of liver diseases in children. Over the past 10 years a number of innovative surgical techniques have been developed to overcome the shortage of size matched donors particularly in children less than 5 years of age. Graft and patient survival at one year after liver transplantation has continued to improve, and is now over 85% and higher for good risk cases. Complications are relatively common, but provided graft function is satisfactory, long term survival for these children is to be expected. The need for retransplantation has fallen significantly. Causes of early mortality include graft dysfunction and sepsis. Late mortality is due to sepsis, post-transplant lymphoproliferative disease, and non-compliance. Long term survival with good graft function and excellent quality of life is possible for the majority of children undergoing liver transplantation.

The success of liver transplantation in the management of children with liver disease is creating new challenges. The results of liver transplantation for good risk elective cases is approaching 95% at one year. Even for the treatment of acute liver failure, survival of 80% in children at one year post-transplantation is becoming the norm. The initial advances in immunosuppression, particularly the introduction of ciclosporin in the early 1980s, have continued, with new and more varied immunosuppressive agents coming into clinical practice. Organ preservation and perioperative and post-operative care has also improved hugely. The supply of donor liver grafts has been sustained by the use of reduced, split, and living related liver grafts, and these surgical techniques have now become routine transplant procedures.

This success has led to a growing cohort of children, the majority transplanted under the age of 5 years, being alive and well 10–15 years after transplantation. The challenge is whether these children can live a natural lifespan. The long term problems tend to be related to the complications of drug therapy and non-compliance, but psychosocial development, education, and employment are assuming great importance.

INDICATIONS FOR LIVER TRANSPLANTATION

Liver transplantation should be considered for any child with end stage liver disease with a predicted prognosis of less than one year. Timing of liver transplantation is critical to minimise the

risk of dying on the waiting list and to ensure that the child is in optimal condition to survive transplantation. The assessment and management of children with liver disease requires input from a large multidisciplinary team. A number of factors may influence the timing of transplantation, including the age of the child, aetiology of the underlying liver disease, their quality of life, and past medical and surgical history.

The majority of children (~60%) are aged <5 years at age of transplant. Age does not appear to significantly affect outcome, except in children <3 months of age.

Progressive liver failure (prolonged international normalised ratio (INR), low serum albumin, ascites), disordered metabolism (jaundice, encephalopathy, loss of muscle mass, osteoporosis), portal hypertension (variceal bleeding, intractable ascites), encephalopathy, profound lethargy, spontaneous bacterial peritonitis, recurrent cholangitis, and intractable pruritus may all be indications for transplantation.¹ Some children develop hepatorenal or hepatopulmonary syndrome, which will reverse after transplantation.² Pulmonary hypertension may be present in children with long standing chronic liver disease, and if unrecognised and severe (greater than median 50 mm Hg), may cause death in the early postoperative period. Developmental and/or growth retardation is common in children with chronic liver disease, and needs to be treated before and after liver transplantation.

Extrahepatic biliary atresia accounts for 50% of children referred for transplantation. Intrahepatic cholestasis and inborn errors of metabolism resulting in cirrhosis, such as α_1 -antitrypsin deficiency, constitute the second most common group. Other indications for transplantation in children are given in table 1. More recently, because of improved outcome, some children are being transplanted to improve their quality of life rather than for survival benefit.

Acute liver failure is rare in children but is associated with significant mortality. Causes include non-A, non-B hepatitis, drugs toxicity (antituberculous, non-steroidal anti-inflammatory drugs, antiepileptic drugs, and halothane), and paracetamol intoxication. Direct toxic injury may occur with carbon tetrachloride and *Amanita phalloides* poisoning. Other potential causes include Wilson's disease and congenital haemochromatosis. The indications for liver transplantation in a child with acute liver failure are not as clearly defined as for adults,³ but poor prognosis

Abbreviations: AST, aspartate aminotransferase; CMV, cytomegalovirus; INR, international normalised ratio; PVT, portal vein thrombosis

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Table 1 Indications for liver transplantation in children at King's College Hospital

Aetiology	Patients (%)	Patient survival (%)
Chronic liver disease (70%)		
Extrahepatic biliary atresia	48	87
Intrahepatic cholestasis	14	89
α_1 -Antitrypsin deficiency	10	95
Non-cirrhotic metabolic liver disease	10	90
Tumours (hepatoblastoma)	3	80
Others	15	
Acute liver failure (15%)		
Non-A, non-B hepatitis	70	70
Haemochromatosis	10	60
Wilson's disease	5	90
Paracetamol overdose	5	70
Others	10	
Retransplantation (15%)		
Hepatic artery thrombosis	50	67
Chronic rejection	50	60

is predicted by the presence of encephalopathy, INR greater than 4, severe metabolic acidosis, cardiovascular instability, a rapidly shrinking liver, and presence of renal failure.⁴ Prior to listing it is important to use bone marrow examination to exclude haemophagocytic lymphohistiocytosis.

DONOR ORGAN RETRIEVAL

The liver is generally obtained from a brainstem dead, heartbeating donor. Causes of brainstem death include head injury, spontaneous intracranial bleed, anoxia, meningitis, or primary brain tumour. Both donor and recipient should be ABO blood group compatible, but preferably an identical ABO matched graft is used. There is no upper age limit for liver donation, but livers from donors over 50 years of age tend to be used less commonly in children. Providing the donor liver is suitable for reduction or splitting, it can be used for a child. Although there is no lower age donor limit, the use of livers from donors under 6 months of age have been associated with a higher incidence of hepatic artery thrombosis.

Donor risk factors that increase the possibility of graft dysfunction or non-function include age over 50 years, prolonged cardiac or respiratory arrest, use of inotropes, hospital stay of greater than three days, and fatty infiltration of the liver. Isolated abnormalities of routine liver function tests do not by themselves predict early graft function and survival.⁵ Graft assessment by an experienced transplant surgeon remains the most reliable method of predicting graft function.

Donor livers are removed as part of multiorgan retrieval. Surgery is performed through a midline incision. The abdominal aorta and portal vein are isolated, the supra-diaphragmatic aorta is clamped, and University of Wisconsin solution is perfused through cannulas placed in the portal vein and aorta to preserve the liver and kidneys. The liver is excised with a cuff of vessels and bile duct, and stored in sterile plastic bags in an icebox. Liver preservation of up to 20 hours is practicable.

LIVER TRANSPLANTATION

There is a shortage of size matched liver grafts for children, but the use of surgical techniques such as reduced, split, and living related liver transplantation has increased the pool of available grafts to fulfil the current need of 90 children/year in the UK. Owing to this, waiting list mortality for children has fallen to <5%.

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. Orthotopic liver replacement using a whole size graft is accomplished by anastomosing the corresponding structures with the donor liver and achieving haemostasis (fig 1). Management of intraoperative coagulopathy is an essential component of the operation.

The liver can be cut down to provide smaller grafts, based on the segmental anatomy of the liver (fig 2). Use of a left lateral segment graft (segments II and III) will overcome a donor to recipient size discrepancy of 10:1. Use of the left or right lobes will 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) to treat very small babies.

Split liver transplantation provides two grafts from a single donor, the left lateral segment for a child and the right lobe for an adult, with excellent patient and graft one year survival rates (90% and 87% respectively) (fig 3).⁶ Living related liver transplantation uses the left lateral segment from a parent.⁷ Over 1500 cases have been performed worldwide, with two donor deaths reported and donor morbidity of 5%–10%. Recipient survival is over 90% at one year, and for countries lacking cadaveric donation, living donation liver transplantation represents an important surgical innovation.

Replacement of native hepatic artery, portal vein, or inferior vena cava has become routine, and any anatomical anomaly can be overcome. The temporary use of Silastic mesh to close the abdominal cavity preserves graft perfusion when "large" livers are used to transplant smaller children. The liver shrinks over 2–3 weeks and the abdomen can usually be closed before discharge from hospital.

IMMUNOSUPPRESSION

Calcineurin inhibitors, either ciclosporin or tacrolimus, form the mainstay of immunosuppression. In the first three months immunosuppression is augmented with steroids, which are rapidly weaned or withdrawn in the majority of children. Azathioprine or mycophenolate mofetil are used to augment immunosuppression, as steroid sparing agents, or to allow sparing of calcineurin inhibitors in the presence of nephrotoxicity.

Side effects of calcineurin inhibitors (ciclosporin and tacrolimus), include renal impairment, systemic hypertension,

Figure 1 Orthotopic liver transplantation.

Figure 2 Segmental anatomy of the liver.

neurotoxicity, gingival hyperplasia, hirsutism, and gastrointestinal toxicity. There is a need for long term monitoring to detect problems early. Renal sparing immunosuppression using either mycophenolate mofetil or sirolimus to avoid calcineurin inhibitor toxicity has become increasingly important. Overimmunosuppression may result in cytomegalovirus (CMV) infection, lymphoproliferative disease often related to Epstein-Barr virus infection, renal failure, and in the long term, skin cancer.

Non-compliance is also becoming a serious problem in adolescents and may result in chronic rejection, graft loss, and death.⁸ Retransplantation is the only therapeutic option.

Post-transplant complications

Early recognition and correction of post-transplant complication improves graft and patient survival. The majority of complications and deaths occur within the first three months.⁴⁻⁹

POOR GRAFT FUNCTION

Primary non-function of the graft is relatively rare (2%–5%) and inevitably needs retransplantation. Causes include donor status, organ preservation and retrieval, and technical or immunological complications in the recipient. Signs of poor graft function include haemodynamic instability and need for inotrope support, metabolic acidosis, and coagulopathy. INR >4 and first day aspartate aminotransferase (AST) levels >2000 IU/l reflect major cell damage, but even levels of 5000 IU/l may settle, with good long term graft function.

Postoperative bleeding

Postoperative bleeding occurs in 5%–10% of patients. Risk factors include poor graft function, renal failure, haemodialysis, and large intraoperative blood loss. Correction of coagulopathy or low platelet count will often lead to haemostasis. Bleeding from the cut surface of a “cut down” graft may reflect venous outflow obstruction. Exploratory laparotomy and haemostasis is often needed; however, no specific site of haemorrhage can be identified in 50% of cases.

Hepatic artery thrombosis

This is a major complication, which often leads to graft loss. The incidence varies (5%–15%) depending on the type of graft, being less common in cut down livers. Causes include poor surgical technique or kinking of the artery, endothelial injury (poor handling during retrieval or implantation), increased coagulability, or liver swelling during acute rejection. Factors such as high haematocrit and raised blood

Figure 3 Split liver transplantation.

viscosity, arterial hypotension, infection, or perfusion injury predispose to thrombosis.¹⁰ Early recognition and immediate surgical revascularisation may salvage the graft.

Late hepatic artery thrombosis presenting several years after transplantation may occur. Invariably, the intrahepatic arterial supply has been reconstituted by collateral vessels. Presentation is often subtle, with mild liver dysfunction, late biliary stricture, recurrent low grade cholangitis, bacteraemia, or changes in centrilobular cell fallout on liver biopsy. Most cases are managed successfully by conservative measures. Underlying procoagulant disorders such as the presence of anticardiolipin antibody have to be excluded. Occasionally a more aggressive course can be observed, with the development of intrahepatic biliary necrosis requiring retransplantation.¹¹

Portal vein thrombosis or stenosis

Portal vein thrombosis (PVT) occurs in approximately 4% of transplants, particularly in small children with hypoplastic portal veins. Technical complications and previous PVT account for other cases. Early PVT presents with graft dysfunction or gastrointestinal bleeding, and the diagnosis is confirmed by Doppler ultrasound and aortoportography. Measurement of splenic size is often a good guide as to the continuing presence or development of portal hypertension. Low platelet count and slight prolongation of the INR are also indirect indicators of portal hypertension. Early surgical intervention to restore portal venous flow will usually rescue the graft.

Late portal vein complications present with signs of portal hypertension such as variceal haemorrhage or splenomegaly. The underlying cause may be technical, but on occasions remodelling of a “cut down” liver causes stretching of the portal vein.

Venous outflow obstruction

This is uncommon and represents technical failure in anastomosing the graft to the hepatic veins or inferior vena cava. It may cause serious difficulty in controlling bleeding from the cut surface of the graft, or in the longer term, a clinical picture similar to Budd-Chiari syndrome.

Inferior vena cava complications

These complications are rare and usually due to technical shortcomings. Suprahepatic caval stenosis presents with bilateral leg and lower trunk oedema and signs of portal hypertension with ascites and renal impairment. Doppler ultrasound, cavography, and pressure measurements will

confirm the presence of a significant gradient across the stenosis, and dilatation may lead to resolution.

Biliary complications

Biliary leak and stricture are the most common technical complications occurring in 5%–30% of children. Biliary drainage is re-established by bile duct to bile duct anastomosis, or more commonly hepaticojejunostomy.¹²

Biliary leaks may occur from the anastomosis, T tube insertion site (if used), or from an unrecognised anomalous segmental bile duct. Patients present insidiously with fever or mild graft dysfunction, and if undiagnosed will progress to biliary peritonitis. Hepatic artery thrombosis must be excluded, and endoscopic or percutaneous cholangiography and stenting will usually lead to resolution.

Anastomotic biliary strictures occur in 5%–10% of cases, generally within a year of transplant. The clinical picture includes cholestasis, cholangitis, or features of biliary obstruction on liver function tests or histology. The γ -glutamyltransferase test remains the most sensitive indicator of developing bile duct complications. Dilatation of the biliary tree may be identified on liver ultrasound. Endoscopic or percutaneous transhepatic balloon dilatation, and if indicated placement of a biliary stent, leads to the resolution of the majority of early strictures. Surgical reconstruction (for example, hepaticojejunostomy) should be undertaken if the stricture does not resolve with repeated dilatations.

Non-anastomotic or diffuse biliary strictures are less frequent and tend to present late, often more than 12 months after transplantation. They are associated with hepatic artery thrombosis, preservation injury, and use of ABO incompatible grafts, and although some patients can be managed conservatively most require retransplantation.

Roux loop obstruction is a cause of late biliary complications, which can be diagnosed with nuclear medicine scanning.

Occasionally, extrinsic bile duct obstruction can be caused by bilomas, cystic duct mucocoeles, amputation neuromas, or post-transplantation lymphoproliferative disorder.

Other surgical complications

Bowel perforation is uncommon (6%), except in children with biliary atresia who have undergone previous surgery, when the incidence rises to over 10%.¹³ Paralysis of the right diaphragm due to a phrenic nerve crush injury at surgery may occasionally be the cause of failure to wean from the ventilator despite excellent gas exchange and a "normal" chest x ray.

Immunological complications

Acute rejection occurs in 40%–70% of children within the first month, usually between five and 15 days after transplant. Graft loss caused by acute rejection is relatively rare for liver in comparison to other organs. Fever and feeling unwell may accompany rejection; however, a rise in the serum AST is the most reliable test and the diagnosis is confirmed by liver biopsy. Typical histological features include a dense periportal cellular lymphocytic and eosinophilic infiltration with endothelitis and bile duct damage. Acute rejection is treated with methylprednisolone. Steroid resistant rejection is treated with antilymphocyte antibodies.

Chronic rejection has been a significant cause of graft loss, occurring in up to 10% of children, but the incidence is decreasing. Histological features include loss of bile ducts and graft arteriopathy; however, its pathophysiology is not properly understood. Most cases present within the first year with jaundice and pruritus. There is usually marked cholestasis with only mild to moderate elevation of the serum transaminase. Hepatic synthetic function is usually well preserved, out of proportion to the other laboratory

abnormalities. Early treatment with tacrolimus (serum bilirubin <250 μ mol/l) and/or sirolimus may reverse the changes in some children, but most cases progress to retransplantation.

Infection

The majority of children will have at least one episode of infection in the postoperative recovery period. Risk factors include poor graft function, prolonged intensive care unit stay, ventilator dependence, gut perforation, retransplantation, and the use of antilymphocyte antibodies to treat rejection.¹⁴ Gram negative septicaemia and systemic fungal infection carry a high mortality. Bacterial infections are common within the first 2–4 weeks, whereas viral infections, of which CMV is the most important, are common causes of late infection.

Bacterial pneumonia is the most common infection in the first week. Gram positive intravenous line infections occur from five days onwards, and venous access lines must be changed regularly. Gram negative sepsis is often associated with biliary leak, bowel perforation, or graft ischaemia. Immunosuppressive therapy may minimise clinical signs of sepsis. Late opportunistic bacterial infections including legionellosis, nocardiosis and tuberculosis may also occur, particularly in those children who have received higher levels of immunosuppression.¹⁵ Children from ethnic minorities may be at increased risk of developing tuberculosis.

Liver transplant recipients are at risk of fungal sepsis because of immunosuppression, invasive monitoring providing a port of entry, and the need for multiple courses of antibiotics. Fungal sepsis occurs in up to 40% of patients with acute liver failure. Risk factors include retransplantation, for graft dysfunction, hepatic artery thrombosis, bowel perforation, reintubation, and acute liver failure. The majority are due to candida species but infections with aspergillus, mucormycosis, coccidioidomycosis and cryptococcus species, while less common, may also occur and are associated with a high mortality. Fungal sepsis should be suspected in any transplant patient who presents with fever and high white blood count while receiving broad spectrum antibiotics. Amphotericin B is the main stay of treatment, but itraconazole has been effective for invasive aspergillosis. Fungal infections, particularly candida, respond to treatment with fluconazole or amphotericin B, but invasive aspergillosis is often fatal.

Herpes viruses form the most important viral pathogens post-transplant. Herpes simplex and varicella zoster infections occur within one or three months respectively after transplant, and both respond to early treatment with acyclovir. CMV infection occurs between two and 12 weeks after transplant, and is characterised by malaise, fever, leukopenia, thrombocytopenia, and arthralgia, and later hepatitis, enteritis, or pneumonitis. Other rare late CMV manifestations include myocarditis, vasculitis, and encephalomyelitis. Prophylaxis can delay or prevent the development of CMV infection,¹⁶ and high risk cases, for example CMV positive donor and negative recipient, should receive prophylactic ganciclovir. Monitoring of antigenaemia or CMV DNA has had a significant impact on recipient management.

Epstein-Barr viral infection can present with a spectrum ranging from a mononucleosis-like illness to malignant lymphoma. Clinical features include high fever, lymphadenopathy, positive faecal occult blood, and anaemia. Young Epstein-Barr virus negative children appear to be particularly at risk of developing Epstein-Barr virus related post-transplant lymphoproliferative disease (4% at one year). Treatment includes withdrawal of calcineurin inhibitors and administration of steroids. Rituximab should be given if the

tumour does not resolve.¹⁷ Chemotherapy should be reserved for unresponsive cases.

Hepatitis B and C infections are uncommon indications for transplantation in childhood, but may be a cause of late graft dysfunction and should be considered in the differential diagnosis of hepatitis. Hepatitis may be acquired from the donor graft, although with current donor testing this is rare.

Adenovirus infection may cause fulminant hepatitis or necrotising pneumonitis in the early post-transplantation period. Influenza A and B are common viral pathogens associated with upper and lower respiratory tract infections. Immunosuppressed patients should receive the trivalent inactivated influenza vaccine annually. Respiratory syncytial virus is the most common cause of lower respiratory tract infection in young children, but seldom causes life threatening complications.

RETRANSPLANTATION

Retransplantation is performed in 15% of children, although the incidence is falling rapidly. Hepatic artery thrombosis accounts for 50% of cases. Patient survival of 82% has been reported with elective retransplantation versus 46% with emergency retransplantation. Retransplantation for primary non-function or in cases of multiorgan failure has a survival rate of <20%.¹⁸ Retransplantation has made a significant contribution to overall recipient survival in children.

QUALITY OF LIFE

As increasing numbers of liver transplantation centres achieve one year patient survival in excess of 90%, attention is now turning to long term survivors and their quality of life. The impact on children and their family has not been studied in depth until recently. Quality of life is difficult to measure, especially in children, although attempts have been made to evaluate objective changes in lifestyle. An early study, of 44 children surviving less than one year after liver transplant, showed that although 13 subsequently died, most of the survivors were able to return to school.¹⁹ Quality of life depended on graft function and an absence of recurring complications requiring repeated hospital admission.

After the introduction of ciclosporin and the use of low dose steroids, it became apparent that children lost the physical stigma of chronic disease, had increased energy levels, and were able to return to school. Because of the shape of the survival curve with a plateau after one year, the majority of survivors should continue to do well. "Doing well" denotes more than just survival, as these children do appear to have significantly fewer hospitalisations after transplantation and fewer days per year in hospital. Prior to the introduction of ciclosporin, patients spent 39% of the first year and 5% of subsequent years in hospital. With ciclosporin immunosuppression, patients spent an average of eight days in hospital each year (2.3%). The most common cause for admission was viral illness, accounting for nearly 20% of cases, and mainly as a precaution rather than because of severe illness.

Liver function tests are significantly improved after transplantation. Good liver and kidney function results in loss of ascites, jaundice, and pruritus. Metabolic bone disease improves with long term resolution. Children who are unable to walk prior to transplantation because of rickets or pulmonary hypertrophic osteoarthropathy are able to do so independently within a year.²⁰

Children take fewer medications after than before transplantation and may only need to take ciclosporin and prednisolone or tacrolimus alone. Antihypertensives are the other most commonly taken medication.

More than three quarters of children are in age appropriate school classes or slightly behind.²¹ The most common reason for delay in educational progress is chronic illness prior to transplantation, which often results in emotional immaturity. Little effect has been noted on cognitive function; however, some motor developmental delay may be due to chronic illness. Parents often comment that their child is active, plays well, is able to do many things that were not possible pre-transplant, and participates in physical activities such as football. Overall behaviour, family interactions, and school behaviour also improve. Parents tend to view themselves as more relaxed and being able to apply more consistency and balance in discipline. Siblings behave in a more appropriate fashion, although they may remain resentful toward the recipient. For many families, however, there is difficulty in adjusting to the new situation after transplantation. There remains long term anxiety about the child's prognosis and wellbeing. It remains difficult for parents not to worry after nursing their child through deteriorating health and transplantation, and it is not possible to give an absolute assurance that the child will remain well. The family hierarchy is organised on the basis of having an ill child, and rearrangement after successful transplantation may cause marked disruption. The child is used to taking a disproportionate amount of the parents' time and attention, often to the detriment of other siblings, and trying to redress this balance can cause problems. Parents often report that their child's behaviour is not entirely normal. Behavioural immaturity often persists, and acts of defiance or aggression are sometimes seen, particularly in adolescents. Parents express persistent concerns, even in the long term, of fear of rejection, side effects of treatment, becoming overprotective, continuing medical and "social" expenses, and alteration of roles and identity within the family. Mothers, who have devoted most of their energy into the care of a chronically ill child and abandoned their professional life, often find it difficult to adjust to their new role within the family with a "well" child.²² Anxieties about children going to school and being separated from their parents after many years of dependence cause particular problems. Unfortunately, there are few detailed studies, and early reports tended to be overoptimistic and selective in the patients studied.

CONCLUSION

Long term survival is now achieved by significant numbers of children following liver transplantation. The initial obstacles to survival, particularly organ preservation, surgical technique, and immunosuppression have been addressed, but the psychological, social, and health problems produced by successful transplantation are only beginning to be recognised. We still have little idea of the life expectancy of these children and of the future problems we may have created. The goal remains transplantation without long term immunosuppression, and until donor specific tolerance can be safely produced there will continue to be complications from therapy. The quality of life enjoyed by the recipient and their family following successful transplantation requires further study. As the majority of children are under 5 years of age at transplant we must be prepared for their future needs, particularly during adolescence when compliance will become a significant issue.

Ensuring that these children complete their education, have employment, and are able to have families of their own is important, and in future may have a bearing on the timing of transplantation. The challenge is to ensure children undergoing liver transplantation can be restored to a normal life expectancy with the potential to enjoy life to the full.

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