

Liver Transplantation for Children: Red Cross Children's Hospital Experience

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ABSTRACT

Background. The liver transplant program for infants and children at the Red Cross Children's Memorial Hospital is the only established pediatric service in sub-Saharan Africa. Since 1985, 250 infants and children have been assessed and 155 accepted for transplantation.

Methods. Since 1987, 76 children (range 6 months to 14 years) have had 79 liver transplants, with biliary atresia being the most frequent diagnosis. The indications for transplantation include biliary atresia (n = 44), metabolic (n = 7), fulminant hepatic failure (n = 10), redo transplants (n = 3), and other (n = 15). Three combined liver/kidney transplants have been performed. Forty-nine were reduced-size transplants with donor: recipient weight ratios ranging from 2:1 to 11:1, and 29 children weighed < 10 kg.

Results. Fifty-six (74%) patients survived 3 months to 12 years posttransplant. Cumulative 1- and 5-year patient survival data are 79% and 70%, respectively. However, with the introduction of prophylactic intravenous gancyclovir and the exclusion of hepatitis B virus (HBV) IgG core Ab-positive donors, the projected 5-year pediatric survival has been >80%. Early (<1 month) post-liver-transplant mortality was low, but included: primary malfunction (n = 1); inferior vena cava thrombosis (n = 1); bleeding esophageal ulcer (n = 1); and sepsis (n = 1). Late morbidity and mortality was mainly due to infections: de novo hepatitis B (5 patients, 2 deaths); Epstein-Barr virus (EBV)-related posttransplantation lymphoproliferative disease (12 patients, 7 deaths); and cytomegalovirus disease (10 patients, 5 deaths). Tuberculosis (TB) treatment in three patients was complicated by chronic rejection (n = 1) and TB drug-induced subfulminant liver failure (n = 1).

Conclusions: Despite limited resources, a successful pediatric program has been established with good patient and graft survival figures and excellent quality of life. Shortage of donors due to HBV and human immunodeficiency virus (HIV) leads to significant waiting list mortality and infrequent transplantation.

THE LIVER TRANSPLANT PROGRAM for infants and children at the Red Cross Children's Memorial Hospital is presently the only established pediatric service

in sub-Saharan Africa. The first pediatric transplant was performed on December 6, 1987 for end-stage liver disease, due to α 1-antitrypsin deficiency. Unfortunately,

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that patient died of complications in January 1988. The pediatric program was then put on hold until the adult program had become established at Groote Schuur Hospital and the pediatric program was restarted in November 1991.¹ Since 1985, 250 children have been referred to our unit for assessment for liver transplantation and 155 have been accepted into the program. These referrals come from most provinces within South Africa as well as from Namibia.

PATIENTS AND METHODS

Since 1987, 79 orthotopic liver transplants have been performed on 76 children and all are included in this retrospective review. The major indication for liver transplantation was biliary atresia (56%), followed by acute liver failure (13%). There were four combined liver/kidney transplants for primary hyperoxaluria (n = 3) and congenital hepatic fibrosis associated with polycystic kidneys. (n = 1)

Demographics

The age of the children ranged from 6 months to 14 years (mean 4.6 years) and included 36 boys and 40 girls. The ethnic distribution was as follows: 13 black; 32 mixed race; 4 Asian; and 27 white. Their weight ranged from 4 to 50 kg (mean 13 kg) and 29 children weighed <10 kg. Table 1 shows indications for liver transplantation.

Surgical Techniques

The surgical techniques used for donor retrieval and recipient liver removal and engraftment have been described previously in detail.¹⁻³ Forty-nine reduced-size grafts were used (28 left lateral segment, 17 left lobe, 4 right lobe). In all the reduced-size livers and in patients with biliary atresia, choledochojunostomy was used for biliary drainage without the use of stents or T tubes. The donor: recipient weight ratios varied between 2:1 and 11:1 (mean 3.4 to 1). One living related (mother-child) transplant was performed.

Anesthesia

The anesthetic time ranged from 7 to 16 hours (mean 10 hours) and the mean blood volume transfused was 2.5 blood volumes (range

0.5 to 5.7). Blood group crossmatch was identical in 61, compatible in 15, and incompatible in 3 (blood group B into blood group O).

Immunosuppression

Baseline immunosuppression consisted of triple therapy in the form of cyclosporine, Medrol, and azathioprine. Oral cyclosporine (5 mg/kg was given immediately before surgery and continued postoperatively initially intravenously; however, since 1997, it has been given orally as Neoral in a three-times-daily dosage, aiming for a trough level of 350 to 400 ng/mL initially and a 2-hour peak level of >1000 ng/mL.⁴ Methylprednisolone (10 mg/kg) and azathioprine (0.5 to 1 mg/kg) were given intravenously at the time of reperfusion of the graft, with the methylprednisolone dosage reduced in the first week to 1 mg/kg for the first month and then further reduced to 0.2 mg/kg as maintenance. Azathioprine was continued for approximately 6 months. Rejection episodes were managed with three or four daily pulses of methylprednisolone, but increasingly this has not been required with early conversion to tacrolimus and selective use of mycophenolate mofetil. Recently, anti-CD25 antibodies have been used (basiliximab at 20 mg per dose for weight >40 kg, 10 mg per dose for weight <20 kg; daclizumab 1 mg/kg per dose), both used as a two-dose regimen.⁵ Rapamycin was also used in two patients with chronic rejection and high Epstein-Barr virus (EBV) levels and associated posttransplant lymphoproliferative disease (PTLD).

Infection Prophylaxis

Intravenous ampicillin plus cephalosporin is presently given at anesthetic induction, repeated together with metronidazole at the time of biliary anastomosis and continued for 3 to 5 days perioperatively.⁶⁻¹⁰ Antifungals in the form of oral mycostatin and amphotericin lozenges are given and those patients with severe cholestasis and prolonged pretransplant inpatient treatment receive intravenous amphotericin perioperatively for ± 2 weeks. Cotrimoxazole 6 mg/kg per day in two divided doses is given 3 d/wk for prevention of *Pneumocystis carinii* and is continued for 6 months. Intravenous gancyclovir 5 mg/kg twice daily was previously given as viral prophylaxis against cytomegalovirus (CMV) and EBV infections, initially for 2 weeks; however, since 1996, this has been given for 3 months in children <3 years of age and in high-risk children not previously exposed to EBV, in an attempt to prevent posttransplant lymphoproliferative disease.¹¹ In addition, Polygam is given intravenously for the first 5 days posttransplant and all blood products are leukocyte-filtered. Tuberculosis (TB) prophylaxis is used in high-risk patients only.

RESULTS

Since 1987, 79 orthotopic liver transplants have been performed on 76 children. All patients have survived the procedure and currently 56 (74%) have survived 3 months to 12 years posttransplant. Fifty-one children have an excellent quality of life. The causes and timing of death are as follows:

- Early (≤ 1 month): sepsis (n = 1); bleeding esophageal ulcer (n = 1); primary nonfunction (n = 1); IVC thrombosis (n = 1).
- Intermediate (>1 to 6 months): rejection and associated sepsis (n = 1); portal vein thrombosis with variceal bleed (n = 1).

Table 1. Indications for Liver Transplantation

- Biliary atresia (44)
- Fulminant hepatic failure (10)
- Metabolic (7)
 - $\alpha 1$ -antitrypsin deficiency (4)
 - Primary hyperoxaluria (3)
- Redo transplants (3)
 - Chronic rejection (2)
 - Acute rejection (1)
- Other (15)
 - Autoimmune hepatitis (5)
 - Cryptogenic cirrhosis (2)
 - Neonatal hepatitis (3)
 - Budd-Chiari syndrome (1)
 - Alagille syndrome (2)
 - Congenital hepatic fibrosis (1)
 - Hepatoblastoma (1)

Number of patients in parentheses.

- Late (>6 months): bacterial, viral, and fungal infections (n = 5); PTLD (n = 7); and chronic rejection (n = 2).

Surgical Complications

Hepatic artery thrombosis occurred in two patients and portal vein thrombosis in three. In two patients, the portal vein thrombosis was successfully repaired and the third presented with an uncontrollable variceal bleed at 6 months posttransplant. IVC thrombosis occurred in two patients and this was treated with thrombolytic therapy, which was successful in one patient (6 months posttransplant), but the second patient died from bleeding and sepsis in the perioperative period. Bile leaks occurred in four patients: in two this was successfully managed with revision of the biliary anastomosis, and in two the biliary leak was associated with a reduced-size graft and settled spontaneously. Four patients developed postoperative gastrointestinal (GIT) bleeding requiring re-look laparotomies in two and revision of the Roux-en-Y anastomosis in one; the other patient was found to have bleeding from the cut-surface of the liver, which was cauterized. One patient had postoperative GIT bleeding, which settled spontaneously, and another patient presented with uncontrollable bleeding from a post-sclerotherapy esophageal ulcer.

Medical Complications

Tuberculosis (n = 3). Two children developed pulmonary tuberculosis and one patient a pleural effusion. TB drug treatment was complicated by chronic rejection in one patient and TB drug-induced subfulminant liver failure in another.

De novo hepatitis B (n = 5). Hepatitis B virus infection is endemic in South Africa with an HBsAg incidence of 5% to 20% and an HB IgG core Ab incidence of 40% to 80%. Forty percent of potential donors are HB IgG core Ab-positive. Prior to 1996, donors were screened only for HBsAg. Five children (6 to 14 months posttransplant) developed de novo hepatitis B. All had been HBsAg-negative pretransplant and the explanted liver showed no evidence of hepatitis B. Three of the children received organs from hepatitis B IgG core Ab-positive donors and sera were not available for testing in two. Two children have developed mild chronic hepatitis and two developed severe chronic hepatitis progressing to cirrhosis. DNA levels ranged from 1920 to 4800 pg/mL (mean 3556). All patients were treated initially with famcyclovir, then changed to lamivudine.¹²⁻¹⁴ Lamivudine resistance developed in two patients and two died as a result of progressive chronic hepatitis B and complications of cirrhosis. One died soon after diagnosis from TB drug-induced liver failure.

CMV infection and disease. CMV infection is endemic in our population and 90% donors were CMV-positive.¹⁵ CMV infection, as defined by the presence of fever together with a positive culture or positive pp65Ag, occurred in 12 patients and was treated successfully with intravenous gancyclovir. Ten patients developed CMV disease and the sites

of disease included the lung (n = 4), liver (n = 7), pancreas, and GIT (n = 1). Five of the 10 patients with CMV disease have died. Risk factors for CMV infection and disease include poor nutritional status, high-dose steroids, and pulsing. Since 1995, regular use of CMV pp65Ag monitoring has enabled earlier diagnosis and treatment of CMV infection and, consequently, less disease. At present, preemptive intravenous gancyclovir is given to all high-risk children and this has contributed to a decrease in the incidence of CMV disease.

EBV and posttransplant lymphoproliferative disease. EBV infection resulted in significant morbidity and mortality in the children studied. Twelve children developed PTLD, all of whom were <3 years of age, and the mean time to development of PTLD was 9.2 months (range 3 to 30 months posttransplant). Eight children had typical acute membranous tonsillitis with associated lymphadenopathy. Seven were EBV EBNA-positive at time of transplant and all were positive at the time of PTLD diagnosis. Sites of involvement included tonsils (n = 8), intestine (n = 6), mediastinum (n = 4), and CNS (n = 4). On histologic assessment, there were six monoclonal, two oligoclonal, and four polyclonal PTLD cases. Management of PTLD included the reduction of immunosuppression in all patients, with complete withdrawal in two patients.^{10,11}

Adenotonsillectomy was performed in seven patients and debulking surgery in four. Three patients received chemotherapy, but all three died within 10 weeks of diagnosis. Two patients received intravenous rituximab. Seven patients died as a result of PTLD and one required a retransplant for chronic ductopenic rejection. Overall, there has been a 15% incidence of PTLD in our program, with 58% mortality, despite the use of chemotherapy, reduction in immunosuppression, and use of rituximab.

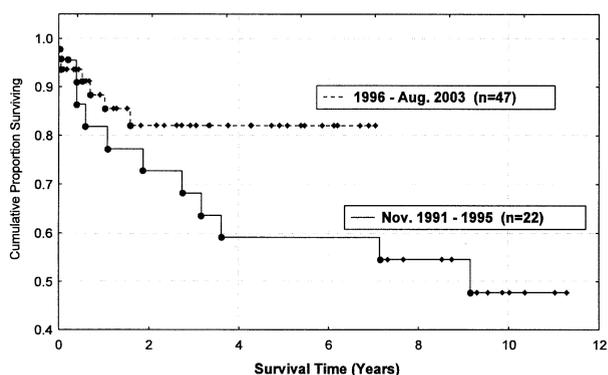


Fig 1. Pediatric liver transplantation. Cumulative proportion surviving (Kaplan-Meier), November 1991 to 1995 vs 1996 to 2003. The cumulative survival of patients transplanted since 1991 (n = 69) divided into those receiving transplants before 1996 and after. Current expected 5-year survival >80%. (●) Died; (◆) alive.

Survival

The overall cumulative 5-year patient survival is 70%. Since 1996, with the introduction of IVI gancyclovir for 3 months and the exclusion of HBV IgG core Ab-positive donors, the projected 5-year survival is >80% (Fig 1).

DISCUSSION

As the only established pediatric liver transplant center within South Africa, children are referred from all over South Africa and this dislocation from social support services, including family, friends, and the workplace, has major emotional and financial implications. In the early stages of our program, children were referred in a premorbid clinical state and frequently died while awaiting a liver transplant. However, with increasing public awareness and education of the medical fraternity, children are now increasingly being referred early on in the course of their liver disease. Still, successful outcomes to liver transplantation are dependent on both a committed family and committed medical support, particularly when the child returns home to a medical center in another province. Fortunately, current methods of electronic communication have greatly improved management and long-term follow-up of these patients.

Endemic viral and bacterial infections, particularly TB, CMV, EBV, and hepatitis B, have had a significant impact on our program.^{12,13,15-17} The recent ability to monitor CMV pp65 Ag and EBV PCR has enabled us to recognize viral infections earlier, treat appropriately, and decrease immunosuppression. The de novo hepatitis B in the five children was probably acquired as the result of using hepatitis B core Ab-positive donors.¹⁸ Two children have died as a result of chronic hepatitis B and two developed lamivudine resistance. Since 1996, hepatitis B IgG core Ab-positive donors have been excluded as potential liver donors and no further cases of de novo hepatitis B have occurred. The hepatitis B IgG core Ab-positive rate in the donor pool is approximately 40% and this, together with the increasing prevalence of HIV (current HIV infection rates in the 30 to 40-year age group estimated around 20% to 40%), has significantly decreased the number of potential donors.

With the introduction of aggressive antiviral prophylactic regimes and the exclusion of hepatitis B core Ab-positive donors since 1996, the predicted 5-year patient survival figures are now >80%, which is comparable to other reported series. Despite limited resources, diminishing manpower, and a decreasing donor pool, the Red Cross Children's Paediatric Liver program continues to be active, with survival figures comparable to those of larger centers. With increasing public awareness, the number of children

requiring transplantation will increase, although, at present, split-liver transplantation is beyond the capacity of our restricted manpower. Other options that need to be considered in expanding the donor pool include increasing the use of marginal donors and embarking on an active living-related donor program.

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